Approaching the comprehensive management of atrial fibrillation: evolution or revolution?

Royal College of Physicians of Edinburgh
Thursday 1–Friday 2 March 2012
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ACKNOWLEDGEMENTS

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All invited contributors (speakers, chairmen, panel, authors of background papers, authors of poster abstracts and members of the organising committee) have been asked to make comprehensive declarations of interests as they relate to the Consensus Conference. The RCPE receives these declarations in good faith. Sight of the declarations can be requested by delegates on application. The Consensus Panel had access to the declarations during the preparation of the consensus statement.

The full RCPE UK Consensus Conference on Atrial Fibrillation supplement is available at:
http://www.rcpe.ac.uk/journal/supplements/atrialfibrillation/supplement-18.php

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The abnormal heart rhythm, atrial fibrillation (AF), is a common and serious condition. However, despite its importance, it is often not detected or recognised, and even when it is diagnosed often the treatments provided are suboptimal. The evidence base guiding practice for screening and for treatment is rapidly evolving. As a result it is difficult for the average clinician to keep up-to-date.

Against this background, the Royal College of Physicians of Edinburgh Consensus Conference Committee convened the AF Conference in Edinburgh in March 2012 to address four particularly pertinent questions relevant to AF.

• How can we best detect AF?
• Should the treatment of AF be targeted towards control of rhythm, rate or both?
• What is the most effective and safest delivery of thromboprophylaxis in AF?
• What are the differences between physician and patient expectations with regard to the management of AF?

It is hoped that the consensus statement will be of use to many groups and individuals, both nationally and internationally. The guidance given is sometimes specific and definitive, and at other times more general. It is hoped that this statement will lead to improved detection of AF, and that when this arrhythmia is detected, effective thromboprophylaxis is offered. If this could be achieved, this could lead to a substantial reduction in stroke burden. Guidance is also given on rate and rhythm control where the relief of symptoms is the primary aim.

Thanks must be given to the many people who have contributed to this statement. These include the organising committee, authors of the background manuscripts, manuscript reviewers, chairmen and speakers at the conference, poster presenters and sponsors. The 11 members of the Consensus Panel worked together very efficiently and constructively to produce the statement. As in all Consensus Conferences, the audience were pivotal in shaping the draft statements. Thanks also must be given to the expert administrative support received from Margaret Farquhar, Christine Berwick and Sue Cartwright.

In the end there was a remarkable level of agreement (consensus!) within the Consensus Panel about the content of the statement. It is sincerely hoped that the information provided in this supplement will be of great value in ongoing attempts to detect and treat atrial fibrillation so as to limit the impact that this arrhythmia has on the lives of so many people.
## Membership of the Consensus Panel

<table>
<thead>
<tr>
<th>Name</th>
<th>Position and Affiliation</th>
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<tr>
<td>Dr Richard Dewar</td>
<td>Consultant Physician in General and Elderly Care Medicine, Cwm Taf Health Board, Royal Glamorgan Hospital, Glamorgan</td>
</tr>
<tr>
<td>Professor Clifford Garratt</td>
<td>Professor of Cardiology, Manchester Heart Centre, Manchester</td>
</tr>
<tr>
<td>Dr Kathryn Griffith</td>
<td>General Practitioner, University Health Centre, York University, York</td>
</tr>
<tr>
<td>Dr Nick Harding</td>
<td>General Practitioner, Handsworth Wood Medical Centre, Birmingham</td>
</tr>
<tr>
<td>Dr Martin James</td>
<td>Immediate Past President BASP and Consultant Stroke Physician/Clinical Senior Lecturer, Royal Devon and Exeter Hospital/Peninsula Medical School, Exeter</td>
</tr>
<tr>
<td>Dr Deirdre Lane</td>
<td>Lecturer in Cardiovascular Health, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham</td>
</tr>
<tr>
<td>Dr Duncan Petty</td>
<td>Lecturer Practitioner, University of Leeds, Leeds</td>
</tr>
<tr>
<td>Dr Paul Smith</td>
<td>Consultant Cardiologist, Bradford Hospitals NHS Trust, Bradford</td>
</tr>
<tr>
<td>Ms Margaret Somerville</td>
<td>Director of Advice and Support, Chest, Heart &amp; Stroke, Scotland</td>
</tr>
<tr>
<td>Professor David J Stott (Chair)</td>
<td>David Cargill Professor of Geriatric Medicine, University of Glasgow, Glasgow</td>
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<tr>
<td>Ms Jennifer Trueland</td>
<td>Freelance Writer</td>
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## Membership of the Organising Committee

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<thead>
<tr>
<th>Name</th>
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<tr>
<td>Professor John Camm</td>
<td>Professor of Clinical Cardiology, St George’s University of London</td>
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<tr>
<td>Dr Derek Connelly</td>
<td>Consultant Cardiologist, Glasgow Royal Infirmary and Golden Jubilee National Hospital, Glasgow</td>
</tr>
<tr>
<td>Dr Matthew Fay</td>
<td>General Practitioner, Westcliffe Medical Centre, Shipley</td>
</tr>
<tr>
<td>Mrs Margaret Farquhar</td>
<td>Consensus Conference Coordinator, RCPE</td>
</tr>
<tr>
<td>Professor Gregory Y H Lip (Chair)</td>
<td>Professor of Cardiovascular Medicine, University of Birmingham</td>
</tr>
<tr>
<td>Mrs Trudie Lobban MBE</td>
<td>Founder and CEO, Syncope Trust And Reflex anoxic Seizure Group; Founder and Trustee, Arrhythmia Alliance, the Heart Rhythm Charity; Founder and CEO, Atrial Fibrillation Association</td>
</tr>
<tr>
<td>Dr Gillian Mead</td>
<td>Reader in Geriatric Medicine, University of Edinburgh and Honorary Consultant Physician, NHS Lothian</td>
</tr>
<tr>
<td>Dr Scott Ramsay</td>
<td>Consultant Physician, St John’s Hospital, Livingston, RCPE Lead for Consensus Conferences</td>
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Atrial fibrillation (AF) is a common and serious condition, affecting at least 1.8% of the population, rising to over 6% in people aged above 65 years. As the population ages, prevalence is increasing. People with AF are five times more likely to have a stroke and have an increased risk of premature death, resulting in enormous personal, social and economic cost. Prevention of stroke is the main aim of management. Standard treatment involves oral anticoagulant (OAC) drugs – usually warfarin but there are new drugs available. AF is under-diagnosed and the use of OACs is inadequate. There is an urgent need to improve diagnosis and to encourage better uptake and adherence to OACs.

**Our key recommendations are:**

- Detection of AF must be improved; a national screening programme should be introduced.
- Uptake of OAC must be increased and methods of engaging patients in their AF management should be improved.
- Aspirin should not be used for stroke prevention in AF.
- In relation to rate and rhythm control for AF, relief of symptoms should be the goal of treatment.

**How can we best detect AF?**

- Detection and thromboprophylaxis of AF should be a NHS priority for the prevention of disabling cardioembolic stroke with all its consequences for individuals and for health and social care resources.
- Screening for AF in people of 65 or older satisfies the UK National Screening Committee criteria for a screening programme and such a national screening programme should be undertaken in the UK.
- The most cost-effective method for the detection of AF in primary care is by opportunistic screening of people aged 65 years or older by radial pulse checking followed as soon as practicable by a 12-lead ECG for those with an irregular pulse.
- Use of a single lead ECG recording at the time of symptoms can help in diagnosis but does not replace the need for a 12-lead ECG.
- Diagnostic ECGs should be analysed by a competent individual supported by audit and feedback.
- Where clinical suspicion of paroxysmal AF exists, including after ischaemic stroke or transient ischaemic attack (TIA), longer ECG monitoring periods (at least 24 hours) or event recorders should be used.

**Should the treatment of AF be targeted towards control of rhythm, rate or both?**

- In relation to rate and rhythm control for AF, relief of symptoms should be the goal of treatment. The risks and benefits of individual treatments should be considered and discussed with the patient.
- Drug therapy with a beta-blocker remains the standard first-line treatment for relief of symptoms. For patients with persistent AF, treatment should aim to achieve a resting heart rate of <100 beats per minute. Patients who remain symptomatic should be referred to a specialist for consideration of other antiarrhythmic strategies.
- Elective electrical cardioversion is useful in selected patients but the recurrence rate of AF is high. OAC should be continued post-cardioversion dependent upon calculated stroke risk.
- Procedures, such as left atrial catheter ablation, should be considered in patients who remain symptomatic despite anti-arrhythmic drug treatment.
- Currently there is not enough evidence that ablation improves prognosis (e.g. reduces stroke or mortality) to recommend it as first-line treatment, or in asymptomatic patients. There is a need for further evidence in this area.
- There is evidence that ablation has a higher success rate in maintaining normal heart rhythm in patients who are younger or who have paroxysmal AF.
Consensus statement

• AF may recur after ablation; OAC should be continued post-ablation dependent upon the calculated stroke risk.

WHAT IS THE MOST EFFECTIVE AND SAFEST DELIVERY OF THROMBOPROPHYLAXIS IN AF?

• All patients with AF should have a formal stroke risk assessment using a scoring tool such as CHA2DS2-VASc.
• Low risk patients (CHA2DS2-VASc=0) should not receive long-term thromboprophylaxis.
• Patients with paroxysmal, persistent or permanent AF who are over the age of 65 or who have any risk factor for stroke should be considered for OAC.
• Women under 65 years with AF and no other stroke risk factors have a relatively low stroke risk and thromboprophylaxis would not usually be recommended for this group.
• Aspirin should not be used for stroke prevention in AF as it is ineffective; patients who are taking aspirin solely for this purpose should be reviewed.
• The combination of aspirin plus clopidogrel reduces ischaemic stroke risk in AF but this is offset by a risk of serious bleeding. Therefore this combination is not recommended for thromboprophylaxis in AF.
• Before starting an OAC it is important to assess the risks and benefits of treatment, including an assessment of cognition and comorbidities. Use of the HAS-BLED tool can help identify modifiable bleeding risks which need to be addressed but should not on its own be used to exclude patients from OAC therapy.
• Anticoagulation should be with either well-controlled warfarin (currently standard treatment) or one of the new OACs.
• Newer OACs (direct thrombin and factor Xa inhibitors) are an option for patients who cannot tolerate, have an allergy to, or who cannot achieve satisfactory anticoagulant control on warfarin.
• All patients with AF should have the risks and benefits of OAC assessed annually.

• All providers of anticoagulation services should provide annual data of TTR (time in therapeutic range) as a means of quality improvement.
• Anticoagulant control may be improved by near patient testing and engaging patients in their own care; patient education should be supported at every stage.
• High risk patients in whom all OACs are contraindicated may be considered for a left atrial appendage occlusion device.

WHAT ARE THE DIFFERENCES BETWEEN PHYSICIAN AND PATIENT EXPECTATIONS WITH REGARD TO THE MANAGEMENT OF AF?

• Doctors under-prescribe OAC often assuming patients are not willing or able to take these drugs safely. This should be addressed.
• Patients presenting with AF should have their beliefs and expectations about the condition and treatments fully explored.
• Patients should be allowed time to consider the treatment options, having been given appropriate written and verbal information, before a decision to treat or not is made.
• If a patient declines a recommended treatment, consideration should be given to revisit the decision in the future.
• Patients and carers should be provided with appropriate information and education and involved in shared decision making.
• More research with healthcare professionals and patients is required to better understand and overcome the barriers to optimal use of OAC.
• We recommend the development of decision support aids involving professionals, patients and patient organisations. This should facilitate the discussion of the risks and benefits of OACs with patients and their families/carers.
How can we best detect atrial fibrillation?

K Harris, D Edwards, J Mant
1Academic Clinical Fellow; 2Clinical Research Associate; 3Professor; General Practice & Primary Care Research Unit, Strangeways Research Laboratory, University of Cambridge, Cambridge, UK

ABSTRACT
Atrial fibrillation (AF) is an arrhythmia of increasing prevalence associated with a reducible risk of stroke. We conducted a systematic review to address five questions relating to how we can best detect AF:

1. Are there useful screening tests to determine who should have a 12-lead electrocardiogram (ECG)? Potential screening tests, all with acceptable sensitivity, include pulse palpation, single-lead ECG and newer technologies such as modified sphygmomanometers or a finger probe device. Pulse palpation has a high number of false positives, but is the cheapest method.

2. Is it more effective to offer 12-lead ECGs to the whole population (or specific sub-groups) or only to those who screen positive for AF? The cost-effectiveness of new devices, such as a modified blood pressure monitor, needs to be assessed. It is more cost-effective to opportunistically screen people rather than to offer a 12-lead ECG to everybody.

3. How accurate are different healthcare professionals and interpretative software at diagnosing AF on ECG? Definitive diagnosis of AF should be by 12-lead ECG, interpreted by someone with appropriate expertise. Computer software is not currently sensitive enough to be used alone to diagnose AF on ECG. Primary care practitioners may not accurately detect AF on ECG, but consistently high accuracy can be achieved by healthcare professionals with adequate training.

4. How best can we diagnose paroxysmal atrial fibrillation (PAF)? In patients in whom PAF is suspected, longer periods of monitoring will detect more cases of PAF.

5. What is the impact of the use of different ECG monitoring strategies (e.g. Holter monitoring, serial ECGs, continuous ECG) on AF detection rates post-stroke? In patients post-stroke, a single ECG will miss cases of PAF which can be detected by longer duration monitoring such as Holter monitoring, cardiac event recorders and serial ECGs. Further research into the cost-effectiveness of these methods, the duration of monitoring required and the clinical significance of the PAF detected is needed.

DECLARATION OF INTERESTS Professor Mant has received consultancy fees (lapsed personal; current non-personal) from Boehringer Ingelheim. Dr Harris and Dr Edwards have no interests to declare.

INTRODUCTION
Atrial fibrillation (AF) is an arrhythmia present in around 1% of the population. It is characterised by an irregular heartbeat and is associated with symptoms such as palpitations, chest pain, breathlessness and dizziness. On an electrocardiogram (ECG) AF is characterised by an absence of consistent P waves. The prevalence is strongly associated with age, with over 8% of people aged 65 or over in AF. Indeed, 85% of people in AF are aged 65 or over. AF is becoming more common, not only in association with an ageing population, but also as a result of an increase in age-specific incidence, likely to be due to improved survival of people with ischaemic heart disease, which is linked to the majority of cases of AF. The presence of AF is associated with a five-fold increased risk of stroke, independent of other risk factors but it is often asymptomatic and the first presentation may be with a stroke. If AF is detected, the risk of stroke can be substantially reduced by oral anticoagulation, whether with vitamin K antagonists (VKA) or with one of the newer anticoagulants such as dabigatran.

The chronic forms of AF can be divided into paroxysmal AF (more than one episode with spontaneous termination within seven days, but usually within 48 hours); persistent AF (not self-terminating, or lasting more than seven days) and permanent AF (not terminated, terminated but relapsed or no cardioversion attempt made). Silent or asymptomatic AF may occur in any of...
these temporal forms, and carries a similar prognosis to symptomatic AF. About a quarter of AF is paroxysmal, which carries a similar prognosis to permanent AF.

The accepted investigation for diagnosing permanent AF is a 12-lead ECG. This will only pick up paroxysmal AF if the test is performed while a paroxysm is in progress. How best to detect AF may be operationalised into a number of different research questions:

1. Are there useful screening tests to determine who should have a 12-lead ECG? Potential such tests include pulse palpation, single-lead ECGs or new technologies such as finger probes or modified blood pressure monitors.
2. Is it more effective to offer 12-lead ECGs to the whole population (or specific sub-groups) or only to those who screen positive for AF?
3. How accurate are different healthcare professionals and interpretative software at diagnosing AF on ECG?
4. How best can we diagnose paroxysmal AF?
5. What is the impact of the use of different ECG monitoring strategies (e.g. Holter monitoring, serial ECGs, continuous ECG) on AF detection rates post-stroke?

METHODS

This narrative literature review uses papers cited in the 2006 National Institute for Health and Clinical Excellence (NICE) guidance on AF and a systematic search of Medline and Embase using the MeSH terms ‘atrial fibrillation’ and ‘sensitivity and specificity’ and ‘electrocardiography’ or ‘pulse’ or ‘electrocardiography, ambulatory’ or ‘diagnostic techniques, cardiovascular’ or ‘sphygmomanometers’, limiting our search to English language publications from 2006 onwards. After identifying all potentially relevant papers we then reviewed their references to find additional publications. We excluded from our search papers considering incidental detection of AF by devices such as pacemakers.

DESCRIPTION OF STUDIES

1. Are there useful screening tests to determine who should have a 12-lead ECG?
   a) Pulse palpation

   We found four relevant studies which were all set in UK general practices and involved pulse palpation by a practice nurse (Table 1). When the assessment was for any pulse irregularity, pulse palpation was reasonably sensitive (87%–97%), but not very specific (70%–81%). The largest study, which involved 25 general practices and is probably the most representative of clinical practice, found the lowest sensitivity. In the general population, the majority (70–87%) of people with any pulse irregularity will not have AF; as demonstrated by the low positive predictive values. Morgan et al found that specificity could be improved (and correspondingly, positive predictive value) if continuous pulse irregularity was sought, but at the cost of a big drop in sensitivity (from 91% to 54%).

   b) Single-lead ECGs

   A single-lead ECG avoids the need for the patient to remove clothing and is quicker to perform than a 12-lead ECG. However, inevitably some information is lost which may lead to a reduced ability to detect AF. Our search revealed four relevant studies which are summarised in Table 2. When interpreting such studies, it is important to distinguish between the effect of using a simpler ECG, and the effect of using (as would usually be the case in clinical practice) a non-expert to interpret the trace. Who reads the ECG appears to be a much more important factor than how the reading was obtained. Thus, in the study by Mant et al the relatively poor results of single-lead ECGs (sensitivity of 83–85% and specificity of 87–89% when interpreted by GPs) were similar to the results obtained for 12-lead ECGs when read by GPs (Table 3). In contrast, Doliwa et al and Somerville et al found high sensitivity (92% and 96%) and high specificity (96% and 98%) when a bipolar ‘thumb’ ECG was read by a cardiologist, and a bipolar ECG was read by an experienced GP, respectively.

   c) New technologies

   We found four relevant studies that considered two devices which could be used for screening for AF in the general population. The studies are summarised in Table 3. The device described by Lewis et al is a finger probe similar to that used in general practice for pulse oximetry which uses the principle of photoplethysmography. The two studies by Wiesel et al and that by Stergiou et al consider a modified blood pressure monitor similar to those used by patients to monitor their blood pressure at home. This could either be used by people monitoring their own blood pressure to self-screen for AF or by primary care professionals to opportunistically screen patients. These devices benefit from the ability to modify thresholds of detection in order to achieve maximum sensitivity to optimise their value as screening devices.

   In general, a screening test needs to have high sensitivity so it doesn’t miss cases. The higher the specificity, the fewer people who need to have the reference standard investigation. The reference standard test in diagnosing AF, a 12-lead ECG, is readily available, non-invasive and relatively inexpensive. Its main drawbacks are that it is...
time consuming to use and requires some degree of privacy to perform. With regard to potential screening tests for AF, the simplest is pulse palpation. With a sensitivity of approximately 90%, this is a reasonable screening test. The specificity is only moderate, with the result that in community settings, for every case of AF that is diagnosed, a further four people will have had an ECG that does not show AF. Thus, there is potential interest in screening tests with higher specificity, such as ‘cut down’ versions of 12-lead ECGs. Ignoring the issue of who reads the ‘cut down’ ECG, such tests are more specific than pulse palpation. Somerville et al\textsuperscript{17} for example found a specificity of 98% using a bipolar ECG. This would translate to a positive predictive value of 77% in a population with a 7% prevalence of AF if the test sensitivity was 90% (i.e. three cases of AF would be diagnosed for every four 12-lead ECGs performed as a result of a positive bipolar ECG). However, in practice, who reads the ECGs needs to be taken into account as well. The study by Gregg et al\textsuperscript{22} found that interpretative

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Reference standard</th>
<th>Method being tested</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
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<tbody>
<tr>
<td>Morgan et al (2001)\textsuperscript{14}</td>
<td>1,099 patients aged over 65 randomly selected from four general practices. Prevalence of AF 6.1%.*</td>
<td>Single lead (lead II) rhythm strip interpreted by the first author, who is a GP</td>
<td>Nurse pulse assessment of any pulse irregularity</td>
<td>91 (82–97)</td>
<td>74 (72–77)</td>
<td>19 (15–23)</td>
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<td></td>
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<td>Nurse pulse assessment of frequent or continuous pulse irregularity</td>
<td>72 (59–82)</td>
<td>94 (93–96)</td>
<td>44 (35–54)</td>
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<td></td>
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<td>Nurse pulse assessment of continuous pulse irregularity</td>
<td>54 (41–66)</td>
<td>98 (97–99)</td>
<td>61 (47–73)</td>
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<td>Sudlow et al (1998)\textsuperscript{19}</td>
<td>916 patients aged over 65 from nine GP practices in Northumberland. Prevalence AF 4.6%.*</td>
<td>Limb-lead ECG</td>
<td>Nurse pulse assessment of any pulse irregularity</td>
<td>95 (85–98)*</td>
<td>70 (67–73)*</td>
<td>13</td>
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<td>Somerville et al (2000)\textsuperscript{17}</td>
<td>86 patients selected from a single GP practice by inviting all patients aged over 65 with recorded AF and an equal number of patients over 65 without a diagnosis of AF. Prevalence of AF 30%.</td>
<td>12-lead ECG interpreted by a cardiologist</td>
<td>Nurse pulse assessment of any pulse irregularity</td>
<td>97</td>
<td>79</td>
<td>68+</td>
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<td>Hobbs et al (2005)\textsuperscript{13}</td>
<td>2,578 randomly selected people aged over 65 from 25 GP practices taking part in the SAFE randomised control trial between 2001 and 2003. Prevalence of AF 8.5%.</td>
<td>12-lead ECG interpreted by two independent cardiologists with a third cardiologist arbitrating if they were in disagreement</td>
<td>Nurse pulse assessment of any pulse irregularity</td>
<td>87</td>
<td>81</td>
<td>30</td>
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</table>

* Extra information from review by Cooke et al.\textsuperscript{14}  
+ Note the population used in this study had a much higher prevalence of AF than in the other studies.
software applied to 'cut down' ECG only led to a sensitivity of 84–88%, no better than pulse palpation. Studies evaluating newer technologies such as finger probes and modified blood pressure readings suggest that a sensitivity of greater than 90% could be achieved while maintaining reasonable specificity (84%–92%)

<table>
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<tr>
<th>Study</th>
<th>Population</th>
<th>Reference standard</th>
<th>Method being tested</th>
<th>Sensitivity % (95% confidence interval where known)</th>
<th>Specificity % (95% confidence interval where known)</th>
<th>Positive predictive value % (95% confidence interval where known)</th>
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<tr>
<td>Somerville et al (2000)</td>
<td>86 patients selected from a single GP practice by inviting all patients aged 65 or over with recorded AF and an equal number of patients over 65 without a diagnosis of AF.</td>
<td>12-lead ECG interpreted by a cardiologist</td>
<td>Bipolar ECG interpreted by a cardiologist</td>
<td>96 (80–100)</td>
<td>98 (91–100)</td>
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<td>Bipolar ECG interpreted by a nurse</td>
<td>94</td>
<td>92.5</td>
<td>84</td>
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<td>Gregg et al (2008)</td>
<td>1,785 ECGs randomly selected from teaching hospital database.</td>
<td>12-lead ECG interpreted by a cardiologist</td>
<td>12-lead ECG with leads V1-V6 reconstructed from V2,V5 interpreted by interpretative software</td>
<td>84 (76–90)</td>
<td>99 (98–99)</td>
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<td></td>
<td>12-lead ECG with leads V1-V6 reconstructed from V1,V4 interpreted by interpretative software</td>
<td>88 (81–93)</td>
<td>99 (98–99)</td>
<td>85</td>
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<td>Doliwa et al (2008)</td>
<td>100 patients with AF, atrial flutter or sinus rhythm from cardiology clinic.</td>
<td>12-lead ECG interpreted by a cardiologist</td>
<td>Bipolar 'thumb' ECG interpreted by a cardiologist</td>
<td>92</td>
<td>96</td>
<td>96</td>
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<tr>
<td>Mant et al (2007)</td>
<td>2,595 randomly selected people aged 65 or over from 25 practices taking part in the SAFE randomised controlled trial between 2001 and 2003.</td>
<td>12-lead ECG interpreted by two independent cardiologists with a third cardiologist arbitrating if they were in disagreement</td>
<td>Single-lead thoracic placement ECG interpreted by a GP</td>
<td>84.8 (78.7–91.0)</td>
<td>86.4 (84.6–88.3)</td>
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<td>Single-lead limb lead ECG interpreted by a GP</td>
<td>82.5 (74.8–88.7)</td>
<td>88.5 (86.9–90.2)</td>
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<td></td>
<td>Single-lead thoracic placement ECG interpreted by a nurse</td>
<td>68.7 (60.1–76.4)</td>
<td>82.8 (80.7–84.8)</td>
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<td></td>
<td>Single-lead limb lead ECG interpreted by a nurse</td>
<td>72.0 (63.9–80.1)</td>
<td>83.4 (81.4–85.4)</td>
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+ Cases of atrial flutter were included in detection rates for AF in this study
In considering the potential role of these screening tools, the added costs of the screening needs to be set against the value of the detection of new cases of AF. A cost-effectiveness analysis comparing the use of a 12-lead ECG or ‘cut down’ ECGs found that the incremental cost per new case identified was similar. However, given that a 12-lead ECG would be indicated in someone who is in AF (a cost not taken into account in the cost-effectiveness analysis), this would raise the relative cost of a strategy that screened for AF using simplified ECGs. Nevertheless, there would be a potential advantage in using a device that detected AF while

<table>
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<tr>
<th>Study</th>
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<th>Reference method</th>
<th>Method being tested</th>
<th>Sensitivity % (95% confidence interval where known)</th>
<th>Specificity % (95% confidence interval where known)</th>
<th>Positive predictive value % (95% confidence interval where known)</th>
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<tr>
<td>Lewis et al (2010)</td>
<td>594 patients aged over 60-years-old attending hospital outpatient clinics or inpatients at two hospitals in South Wales or New York.</td>
<td>12-lead ECG interpreted by a cardiologist</td>
<td>Finger probe with threshold set after reference standard results available so sensitivity 100% with highest possible coexisting specificity</td>
<td>100</td>
<td>91.1</td>
<td></td>
</tr>
<tr>
<td>Wiesel et al (2004)</td>
<td>125 cardiology outpatients seen between April and August 2002.</td>
<td>12-lead ECG</td>
<td>Modified blood pressure monitor, single reading with threshold set after reference standard results available so sensitivity 100% with highest possible coexisting specificity</td>
<td>100</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>450 cardiology outpatients seen between April and August 2002.</td>
<td>12-lead ECG</td>
<td>Modified blood pressure monitor, single reading</td>
<td>100</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Modified blood pressure monitor, two readings where final result irregular if both readings are irregular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wiesel et al (2009)</td>
<td>405 cardiology outpatients in two cardiology departments in New York.</td>
<td>12-lead ECG interpreted by a cardiologist</td>
<td>Modified blood pressure monitor, single reading</td>
<td>95.3 (92.8–97.6)</td>
<td>86.4 (84.3–97.6)</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Modified blood pressure monitor, three readings where final result irregular if two out of three readings are irregular</td>
<td>96.8 (91–99)</td>
<td>88.8 (85–92)</td>
<td>72</td>
</tr>
<tr>
<td>Stergiou et al (2009)</td>
<td>73 patients aged over 35 with known AF or other arrhythmias and controls with sinus rhythm from an outpatient hypertension clinic, patients admitted to a medical ward and healthy volunteers.</td>
<td>12-lead ECG interpreted by an author and verified by a cardiologist</td>
<td>Modified blood pressure monitor, single reading</td>
<td>93 (74–99)</td>
<td>89 (76–96)</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Modified blood pressure monitor, three readings where final result irregular if two out of three readings are irregular</td>
<td>100 (94–100)</td>
<td>89 (75–96)</td>
<td></td>
</tr>
</tbody>
</table>
performing another function (e.g. measuring blood pressure), since there will be minimal additional time costs. We did not identify any cost-effectiveness analyses of the use of such devices.

2. Is it more effective to offer 12-lead ECGs in the whole population (or specific sub-groups) or only to those who screen positive for AF?

Given that the reference standard test (12-lead ECG) is relatively straightforward to perform, an important question to address is whether screening should simply be carried out with this tool, without using any prior investigations. A related question is whether screening should be systematic (i.e. invite all people over a certain age for screening or in a particular sub-group) or opportunistic (i.e. screen for AF when a patient attends the general practice for another reason). These questions are linked as systematic screening is likely to be with a 12-lead ECG, and opportunistic screening with one of the approaches discussed above.

We found two studies that addressed this question (Table 4). The largest of these, the SAFE study, involved randomisation of 50 practices to either screening or no screening. Within the 25 practices randomised to screening, there was further randomisation at an individual patient level to opportunistic or systematic screening. In the opportunistic arm, a ‘flag’ (paper or electronic) was placed in the patient record to prompt a member of the primary care team to take the patient’s pulse if they attended the practice. If the pulse was found to be irregular, then a 12-lead ECG was offered. In the systematic screening arm, patients were invited to attend the practice for a 12-lead ECG. The detection rate of new cases of AF in the screening arm 1,099 (73.3%) patients had pulse assessments and 439 (29.2%) patients in the opportunistic arm. In the screening arm 67 (4.5%) patients had AF compared to 19 (1.3%) in the opportunistic arm, with a difference in percentage detected of 3.2% (95% confidence interval 2.0–4.4). In 82% of those detected in the systematic screening arm AF had previously been recorded somewhere in their notes.

The second study randomised patients from four practices to systematic or opportunistic screening. In contrast to the SAFE study, this found systematic screening to be more effective than opportunistic screening. The take-up of opportunistic screening in this study was lower than in SAFE (29% over a six-month period vs 69% over a year), and the take-up of systematic screening higher (73% vs 53%). The clinical implications of
### TABLE 5 Studies of the accuracy of GPs, practice nurses and interpretive software in diagnosing atrial fibrillation on electrocardiogram.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Method being tested</th>
<th>Sensitivity % (95% confidence interval where known)</th>
<th>Specificity % (95% confidence interval where known)</th>
<th>Positive predictive value % (95% confidence interval where known)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mant et al (2007)</td>
<td>2,595 randomly selected people aged 65 or over from 25 practices taking part in the SAFE randomised control trial between 2001 and 2003.</td>
<td>Two independent cardiologists with a third cardiologist arbitrating if they were in disagreement</td>
<td>ECG interpretation by GPs</td>
<td>80 (71–87)</td>
<td>92 (90–93)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ECG interpretation by practice nurses</td>
<td>77 (67–85)</td>
<td>85 (83–87)</td>
<td>27.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ECG interpretation by interpretive software</td>
<td>83</td>
<td>99</td>
<td>89.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Either positive: 92, Both positive: 91</td>
<td></td>
<td></td>
<td>42.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99.8</td>
<td></td>
<td></td>
<td>95.9</td>
</tr>
<tr>
<td>Somerville et al (2000)</td>
<td>86 patients selected from a single GP practice by inviting all patients aged over 65 with recorded AF and an equal number of patients over 65 without a diagnosis of AF.</td>
<td>Single cardiologist</td>
<td>ECG interpretation by GP</td>
<td>100 (87–100)</td>
<td>98 (91–100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ECG interpretation by practice nurses</td>
<td>97</td>
<td>88</td>
<td>79.0</td>
</tr>
<tr>
<td>Poon et al (2005)</td>
<td>4,297 consecutive inpatient or outpatient ECGs from a teaching hospital.</td>
<td>One of two independent cardiologists with the second checking any ECGs where the first cardiologist disagreed with the initial computer interpretation</td>
<td>ECG interpretation by interpretive software</td>
<td>90.8</td>
<td>98.9</td>
</tr>
</tbody>
</table>
the second study are less clear, since the majority of patients identified through systematic screening (82%) already had a diagnosis of AF in their records, as compared to only 59% of the opportunistically screened group.

An integral part of determining screening strategy is to decide what population to include. Both these studies involved people aged 65 or over. SAFE also included a sub-study of the potential impact of screening in ‘high-risk’ people over the age of 65, i.e. those with a previous diagnosis of heart failure, hypertension, rheumatic heart disease, ischaemic heart disease, hyperthyroidism, or stroke/TIA. A strategy of opportunistic screening of all people was both more effective and cost less than a strategy of systematic invitations to people in these sub-groups.

3. How accurate are different healthcare professionals and interpretative software at diagnosing AF on ECG?

A systematic review by Salerno et al in 2003 of ECG interpretation accuracy studies found that both physicians and computer software frequently made errors compared to expert electrocardiographers, however there was also frequent disagreement in interpretation between experts.

Our search identified four studies which are summarised in Table 5. The largest study, by Mant et al investigated the ability of 42 general practitioners and 41 practice nurses to detect AF on ECGs generated during the SAFE study. Overall, primary care practitioners could not detect AF on an ECG with sufficient accuracy to guide therapy (GP sensitivity 80%; specificity 92%; practice nurse sensitivity 77%; specificity 85%). Interpretative software was found to be highly specific (99%), but insufficiently sensitive (83%). In practice, most ECG machines have interpretative software, but combining interpretative software with GP interpretation only improved the sensitivity to 92%.

In contrast, Somerville et al found much higher sensitivity (100%) and specificity (98%) in their study of the performance of a single general practitioner. This is consistent with the findings of Mant et al in that some GPs in this study did perform as well as this (though the majority did not). This suggests that GPs can detect AF on ECGs accurately, with appropriate training. Indeed, it is of interest that the two cardiologists in the SAFE study, who independently read 2,592 ECGs, only disagreed on the presence of AF in seven (0.27%) cases.

The accuracy of interpretative software will of course depend upon the diagnostic algorithm that it uses. In the study by Mant et al all the ECGs were read using the same computer software. The two other studies that evaluated the accuracy of computer software for detecting AF found similar results to Mant et al even though different software was employed, suggesting that there may be some consistency between the algorithms used. Interpretative software is probably not yet good enough to be a diagnostic gold standard, but it is conceivable that improvements in the diagnostic algorithms in the future may make this possible.

These studies suggest that quality control of the interpretation of ECGs is an important aspect of diagnosis of AF in primary care. Two potential strategies to address this are to provide training to healthcare professionals who regularly read ECGs for AF, or to have ECGs centrally read. Of note with regard to the latter strategy, Anh et al found that in the case of incorrect computer diagnosis, cardiologists corrected the ECGs more often than other specialists when they had ordered the ECG (94% vs 71%). However, when cardiologists had no patient contact and were presumably re-reading multiple ECGs, they corrected significantly less incorrect AF diagnoses than when they were the ordering physician (72 vs 94%).

4. How best can we diagnose paroxysmal atrial fibrillation?

While a 12-lead ECG is the accepted reference standard for diagnosing permanent AF, it will only pick up some cases of paroxysmal AF, since the ECG recording is made at a fixed point in time which may or may not coincide with an episode of AF. Many patients with AF do not experience symptoms and there is not always a good correlation between symptoms and episodes of AF. We found no studies evaluating multiple-moment-in-time ECG monitoring in the asymptomatic general population. We found two studies where patients had been referred for suspected arrhythmias because of symptoms (usually palpitations, Table 6). Both studies compare the use of Holter monitoring (over 24–48 hours) with longer term monitoring (up to 90 days).

Reiffel et al found that the use of memory loop recorders for 30 days detected significantly more cases of AF than a 24-hour Holter monitor did, and that automatic memory loop recorders detected more AF than standard memory loop recorders. This study involved a retrospective review of records, so it is possible that there was indication bias (i.e. the clinician may have used memory loop recorders in patients where they thought there was a higher likelihood of detecting AF).

Kinlay et al performed a randomised crossover trial comparing the use of Holter monitoring for 48-hours against the use of a trans-telephonic post-event recorder, a handheld device that the patient activates when symptoms occur. The event monitors detected eight clinically important arrhythmias (including two cases of AF) in 43 patients, while Holter monitoring detected none.
5. What is the impact of the use of different ECG monitoring strategies on AF detection rates post-stroke?

In contrast to the relative lack of studies on the detection of paroxysmal AF in the general population, we found several studies looking at detection rates of AF following stroke (Table 7). Performing an ECG on admission is standard practice but will miss some cases of PAF. The detection rates in these studies vary widely from 0% to 45%. This variation reflects differences in study population, method of ECG monitoring used (e.g. serial ECGs, Holter monitors, continuous ECG monitoring, cardiac event recorders), minimum duration of AF required for diagnosis and length of time that the ECG monitoring was carried out. It is therefore difficult to draw any firm conclusions, other than that the longer the monitoring is carried out, the more cases of AF are detected (Figure 1). Newer technologies are emerging in this rapidly developing field. For example, implantable cardiac event monitors can be used which potentially allow for long-term detection of AF. Before firm recommendations can be made on the optimal strategy for detecting AF post-stroke, stronger evidence is needed on the utility of detection of these additional cases of AF. While there is evidence that paroxysmal AF carries a similar prognosis to permanent AF, data are required to confirm that AF detected using these novel approaches carries the same risk. Recently, Healey et al found that subclinical atrial tachyarrhythmias lasting at least six minutes detected by implanted devices were associated with an increased risk of ischaemic stroke or systemic embolism (hazard ratio: 2.5, 95% CI 1.3–4.9), but this is lower than that associated with clinical AF. It should be noted that several of the studies listed in Table 7 defined AF using time periods considerably shorter than six minutes. Comparative evidence of the cost-effectiveness of the different monitoring strategies is required, ideally from randomised controlled trials.

TOWARDS A STRATEGY TO DETECT AF

It is likely to be cost-effective to opportunistically screen patients aged over 65 annually for AF. This means...
### TABLE 7 (continued) Studies of the detection rates of atrial fibrillation in acute stroke/transient ischaemic attack (TIA) patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Method being tested</th>
<th>Time to starting measurement</th>
<th>Definition of paroxysmal atrial fibrillation</th>
<th>Detection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu et al (2009)</td>
<td>Retrospective study of 96 patients admitted to a teaching hospital with ischaemic stroke, excluding those with known AF from January 2003 to December 2005.</td>
<td>24-hour Holter monitor</td>
<td>During admission</td>
<td></td>
<td>9.4</td>
</tr>
<tr>
<td>Alhadramy et al (2010)</td>
<td>Retrospective study of 413 patients diagnosed with stroke or TIA, excluding those with history of AF, at a university stroke clinic between September 2005 and September 2006.</td>
<td>Holter ECG, average 22.6 hours</td>
<td>From a few days to three months</td>
<td>Any duration</td>
<td>9.2</td>
</tr>
<tr>
<td>Lazzaro et al (2010)</td>
<td>133 patients admitted to a teaching hospital with ischaemic stroke or TIA between June 2007 and December 2008, excluding those with a history of AF or AF on admission ECG.</td>
<td>Holter ECG, mean duration 29.8 hours</td>
<td>During admission</td>
<td>&gt;30 seconds</td>
<td>6.0</td>
</tr>
<tr>
<td>Barthelemy et al (2003)</td>
<td>55 patients admitted to a university hospital with stroke or TIA, excluding those with AF detected on two admission ECGs between January and December 1998.</td>
<td>24-hour Holter ECG</td>
<td>During admission</td>
<td>&gt;30 seconds</td>
<td>5.5</td>
</tr>
<tr>
<td>Jabaudon et al (2004)</td>
<td>139 patients admitted with suspicion of acute stroke or TIA, to a university hospital, excluding those with haemorrhagic stroke or recent history of AF or AF detected on initial ECG, between February and December 2002.</td>
<td>24-hour Holter ECG</td>
<td>Median 8 days (range 1–29)</td>
<td>5.0 (confidence interval 2.3–10.2)</td>
<td></td>
</tr>
<tr>
<td>Koudstaal et al (1986)</td>
<td>Retrospective study of 100 patients admitted to a teaching hospital with a TIA who had a Holter monitor.</td>
<td>24-hour Holter ECG</td>
<td>Mean 15.2 days from onset of symptoms</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Method being tested</td>
<td>Time to starting measurement</td>
<td>Definition of paroxysmal atrial fibrillation</td>
<td>Detection rate (%)</td>
</tr>
<tr>
<td>-------</td>
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<td>-------------------</td>
</tr>
<tr>
<td>Stahenber et al(^{\text{a}}) (2010)</td>
<td>224 patients presenting with suspected stroke/TIA to an Emergency Department between March 2009 and February 2010 excluding those with AF on baseline ECG.</td>
<td>24-hour Holter ECG (average of seven 24-hour records)</td>
<td>Median 5.5 hours after admission</td>
<td>&gt;30 seconds</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48-hour Holter ECG (average of six 48-hour records)</td>
<td>Median 5.5 hours after admission</td>
<td>&gt;30 seconds</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seven day Holter ECG</td>
<td>Median 5.5 hours after admission</td>
<td>&gt;30 seconds</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;10 beats in a row</td>
<td>43.8</td>
</tr>
<tr>
<td>Rem et al(^{\text{b}}) (1985)</td>
<td>151 patients with acute stroke or TIA admitted to a stroke unit, excluding those with a history of arrhythmia or detected on admission ECG or 48-hour cardiac monitoring, between January and December 1983.</td>
<td>24–48-hour Holter ECG</td>
<td></td>
<td></td>
<td>3.9</td>
</tr>
<tr>
<td>Hornig et al(^{\text{c}}) (1996)</td>
<td>261 patients with acute focal brain ischaemia, excluding those in AF on admission ECG.</td>
<td>24-hour Holter ECG</td>
<td></td>
<td></td>
<td>3.8</td>
</tr>
<tr>
<td>Shafqat et al(^{\text{d}}) (2003)</td>
<td>Retrospective study of 194 patients admitted to a teaching hospital with acute ischaemic stroke, excluding those with AF on admission ECG.</td>
<td>24-hour Holter ECG</td>
<td></td>
<td></td>
<td>2.6</td>
</tr>
<tr>
<td>Rizos et al(^{\text{e}}) (2010)</td>
<td>120 patients aged over 60 presenting with acute stroke or TIA at a university hospital, excluding those with history of AF or AF shown on admission ECG or continuous ECG in first 24 hours, between July 2008 and March 2009.</td>
<td>24-hour Holter ECG</td>
<td>Median 49 hours</td>
<td>&gt;30 seconds</td>
<td>2.5</td>
</tr>
<tr>
<td>Schuchert et al(^{\text{f}}) (1999)</td>
<td>82 patients with acute ischaemic stroke, excluding those with a history of AF or AF on resting ECG.</td>
<td>24-hour Holter ECG</td>
<td>2–3 weeks</td>
<td>&gt;60 seconds</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48-hour Holter ECG</td>
<td></td>
<td>&gt;60 seconds</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>72-hour Holter ECG</td>
<td></td>
<td>&gt;60 seconds</td>
<td>6.1</td>
</tr>
<tr>
<td>Gunap et al(^{\text{g}}) (2006)</td>
<td>26 patients presenting with acute stroke and an ischaemic lesion &gt;3 cm, excluding those with a rhythm disturbance on admission ECG and those taking certain medications.</td>
<td>Three ECGs taken at six hourly intervals</td>
<td>Six hours after admission ECG</td>
<td></td>
<td>11 (n=3)</td>
</tr>
<tr>
<td>Kamel et al(^{\text{h}}) (2009)</td>
<td>Retrospective study of 2,504 patients with acute stroke in the placebo arms of four randomised control trials, excluding those with a history of AF or AF on their admission ECG.</td>
<td>Serial ECGs up to 90 days</td>
<td>All patients enrolled within 12 hours of onset of symptoms, ECGs started on admission</td>
<td></td>
<td>6.9</td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Method being tested</td>
<td>Time to starting measurement</td>
<td>Definition of paroxysmal atrial fibrillation</td>
<td>Detection rate (%)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>---------------------------------------------</td>
<td>---------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Douen et al(^a) (2008)</td>
<td>Retrospective review of 126 patients admitted to a stroke unit, excluding those with intra-cerebral haemorrhage and those with a history of AF or AF detected on admission ECG during an 8.5 month period in 2005.</td>
<td>Serial ECGs in first 72 hours after admission</td>
<td></td>
<td></td>
<td>6.3(^a)</td>
</tr>
<tr>
<td>Gaillard et al(^b) (2010)</td>
<td>Retrospective study of 98 patients with acute stroke or TIA admitted to a stroke unit between December 2003 and January 2006 with a negative Holter ECG who had a trans-telephonic ECG.</td>
<td>Trans-telephonic ECG monitoring (patients self-recorded at least one ECG each day for one month and transmitted the results by telephone to a cardiology centre)</td>
<td>Within six months of presentation</td>
<td></td>
<td>9.2</td>
</tr>
<tr>
<td>Rizos et al(^c) (2010)</td>
<td>136 patients aged over 60 presenting with acute stroke or TIA at a university hospital, excluding those with a history of AF or AF shown on admission ECG between July 2008 and March 2009.</td>
<td>Continuous bedside ECG monitoring, median duration 97 hours (interquartile range [IQR] 82–144) with confirmation 12-lead ECG of suspected episodes</td>
<td>Immediately on admission to ward</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Rem et al(^d) (1985)</td>
<td>160 patients with acute stroke or TIA admitted to a stroke unit, excluding those with a history of arrhythmia or one detected on admission ECG between January and December 1983.</td>
<td>48-hour bedside cardiac monitoring</td>
<td></td>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td>Lazzaro et al(^e) (2010)</td>
<td>133 patients admitted to a teaching hospital with ischaemic stroke or TIA between June 2007 and December 2008, excluding those with a history of AF or AF on admission ECG.</td>
<td>Continuous bedside cardiac telemetry, mean duration 73.6 hours with nurse review every eight hours or if abnormal rate/rhythm detected by device</td>
<td>During admission</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Barthelemy et al(^f) (2003)</td>
<td>52 patients admitted to a university hospital with stroke or TIA, excluding those with AF detected on two admission ECGs or on Holter ECG between January and December 1998.</td>
<td>Automatic self-analysing cardiac event recorders, mean duration 70.1 hours</td>
<td>Mean 10 +/- 2 days</td>
<td></td>
<td>7.7</td>
</tr>
<tr>
<td>Tayal et al(^g) (2008)</td>
<td>Retrospective study of 56 patients admitted to hospital with TIA/stroke without clear cause between January 2006 and May 2007, excluding those with a history of AF or AF on admission ECG or 24-hour Holter ECG.</td>
<td>21 day mobile cardiac outpatient telemetry monitoring (auto-triggered device which transmits possible AF events to a physician for review)</td>
<td>Median 20 days from onset symptoms</td>
<td></td>
<td>5.3</td>
</tr>
</tbody>
</table>

opportunistically checking the patient’s pulse when they attend the GP surgery for an unrelated reason (e.g. an appointment with the practice nurse for a flu jab) and arranging an ECG if the pulse is irregular. This strategy would have the potential to detect AF in the estimated 97% of patients aged over 65 who see a member of the general practice team at least once annually. Given that the prevalence of AF is over 8% in this age group and average consultation rates are over seven consultations per person-year, it would also be good practice to consider checking the pulse for irregularity whenever the opportunity arises.

CONCLUSION

Existing guidelines are summarised in Table 8. The following conclusions may be drawn from this review of the evidence base for the detection of AF:

1. In the general population (Figure 2):
   - Opportunistic screening is more cost-effective than systematic screening.
   Considerations of whom to screen opportunistically will depend on an understanding of the epidemiology of AF. Prevalence of AF and the risk of stroke rise significantly with age, so both potential yield and potential benefit from treatment increases in older age groups. The evidence base for screening is largely in people aged 65 and over:
   - A number of methods may be employed to screen opportunistically. The cheapest of these is pulse palpation. The cost-effectiveness of newer technologies such as modified blood pressure monitors need to be assessed.
   - 12-lead ECG remains the standard investigation, but the accuracy of this investigation falls if it is read by someone without adequate training.

2. In the symptomatic population (e.g. post-stroke or with symptoms such as palpitations):
   - If a 12-lead ECG fails to show AF, then a number of different technologies are available that allow for longer term ECG monitoring. The relative cost-effectiveness of these technologies needs to be evaluated before a firm recommendation can be made in favour of any specific approach.

### Table 7 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Method being tested</th>
<th>Time to starting measurement</th>
<th>Definition of paroxysmal atrial fibrillation</th>
<th>Detection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elijovich et al (2009)</td>
<td>Retrospective study of 21 patients with stroke or TIA without clear cause admitted to a university stroke centre or seen in outpatient stroke clinic from June 2006 to March 2007 who were referred for 30-day cardiac event monitor.</td>
<td>30-day ambulatory cardiac event monitor (auto-triggered and patient-triggered recordings were sent to a cardiologist for review)</td>
<td>&gt;30 seconds</td>
<td>Using a cardiology for review</td>
<td>20 (n=4)</td>
</tr>
<tr>
<td>Jabaudon et al (2004)</td>
<td>88 patients admitted with suspicion of acute stroke or TIA to a university hospital, excluding those with haemorrhagic stroke or a recent history of AF or AF detected on initial ECG or 24-hour Holter monitoring and those that refused the test between February and December 2002.</td>
<td>Seven day event loop recording device with auto-triggered and patient-triggered recording</td>
<td>Median 55 days</td>
<td>5.7 (confidence interval 2.1 to 12.9)</td>
<td></td>
</tr>
<tr>
<td>Dion et al (2010)</td>
<td>24 patients diagnosed with cryptogenic stroke or TIA who had normal 12-lead ECG, 24-hour Holter monitoring and echocardiography.</td>
<td>Implantable loop recorder, mean duration 14.5 months</td>
<td>Within four months of diagnosis</td>
<td>Any duration</td>
<td>4.2 (n=1)</td>
</tr>
</tbody>
</table>

*The serial ECG detection rate has been calculated from the data available in the paper; it was not possible to calculate the detection rate for Holter ECG excluding those already detected on ECG or history.*
TABLE 8 Summary of current guidance.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC/AHA/ESC Guidelines for the management of patients with atrial fibrillation (2006)</td>
<td>The diagnosis of AF requires ECG documentation by at least a single-lead ECG recording during the dysrrhythmia, which may be facilitated by a review of emergency department records, Holter monitoring, or trans-telephonic or telemetric recordings. A portable ECG recording tool may help establish the diagnosis in cases of paroxysmal AF and provide a permanent ECG record of the dysrrhythmia. If episodes are frequent, then a 24-hour Holter monitor can be used. If episodes are infrequent, then an event recorder, which allows the patient to transmit the ECG to a recording facility when the arrhythmia occurs, may be more useful.</td>
</tr>
</tbody>
</table>
| NICE Atrial fibrillation guidelines: national clinical guideline for management in primary and secondary care (2006) | In patients presenting with any of the following: breathlessness/dyspnoea, palpitations, syncope/dizziness, chest discomfort, stroke/transient ischaemic attack (TIA):  
- Manual pulse palpation should be performed to assess for the presence of an irregular pulse that may indicate underlying AF.  
- An ECG should be performed in all patients, whether symptomatic or not, in whom AF is suspected because an irregular pulse has been detected.  
In patients with suspected paroxysmal AF undetected by standard ECG recording:  
- A 24-hour ambulatory ECG monitor should be used in those with suspected asymptomatic episodes or symptomatic episodes less than 24 hours apart.  
- An event recorded ECG should be used in those with symptomatic episodes more than 24 hours apart. |
### TABLE 8 (continued) Summary of current guidance.

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIGN Cardiac arrhythmias in coronary heart disease (2007)</td>
<td>No specific guidance on how to detect AF.</td>
</tr>
<tr>
<td>SIGN Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention (2008)</td>
<td>Guidelines recommend frequent ECG monitoring in the acute phase post-stroke, but does not mention anything specific about detecting AF.</td>
</tr>
<tr>
<td>European Stroke Organisation: Guidelines for management of ischaemic stroke and transient ischaemic attack (2008)</td>
<td>It is recommended that all acute stroke and TIA patients should have a 12-lead ECG. In addition, continuous ECG recording is recommended for ischaemic stroke and TIA patients. It is recommended that for stroke and TIA patients seen after the acute phase, 24-hour Holter ECG monitoring should be performed when arrhythmias are suspected and no other causes of stroke are found.</td>
</tr>
<tr>
<td>NICE stroke guidance: National clinical guideline for diagnosis and initial management of acute stroke and transient ischaemic attack (TIA) (2008)</td>
<td>No specific guidance on how to detect AF.</td>
</tr>
</tbody>
</table>
  - In patients with suspected AF, an attempt to record an ECG should be made when symptoms suggestive of AF occur.  
  - In patients with suspected symptomatic AF, additional ECG monitoring should be considered in order to document the arrhythmia.  
  - Additional ECG monitoring should be considered for detection of ‘silent’ AF in patients who may have sustained an AF-related complication. |
| Canadian Cardiovascular Society Atrial fibrillation guidelines 2010: prevention of stroke and systematic thromboembolism in atrial fibrillation and flutter | No specific guidance on how to detect AF.                                                                                                                                                                                                                                                                                               |
| Canadian Cardiovascular Society Atrial fibrillation guidelines 2010: etiology and initial investigations | Does not deal specifically with the detection of AF but does advise that a 12-lead ECG should be part of the baseline evaluation for all patients with AF.                                                                                                                                                                                      |
| AHA/ASA Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack (2011) | No specific guidance on how to detect AF.                                                                                                                                                                                                                                                                                               |
FIGURE 2 Summary of an evidence-based strategy for the detection of atrial fibrillation in the general population

- Opportunistic screening
  - Pulse palpation for any irregularity
    - If negative
      - Return to opportunistic screening
    - If positive
      - Modified BP monitor or finger probe: new technologies look promising but need further evaluation
  - Symptoms of atrial fibrillation or recent stroke
    - 12-lead electocardiogram (ECG) read by someone appropriately trained
      - If negative
        - High index suspicion atrial fibrillation e.g. because of symptoms or recent stroke
          - No
          - Yes
            - Consider longer electrocardiogram (ECG) monitoring e.g. Holter monitor/event recorder/other devices
              - If negative
              - If positive
                - AF diagnosed

Main diagnostic pathway
Possible diagnostic pathway
REFERENCES


K Harris, D Edwards, J Mant


Atrial fibrillation: the rate versus rhythm management controversy

AJ Camm, I Savelieva
Professor of Clinical Cardiology; Senior Research Fellow; St. George’s Hospital Medical School University of London, London, UK

ABSTRACT The fundamental management strategy for atrial fibrillation (AF) is still debated. There is no doubt that those patients at risk of thromboembolic events should be offered anticoagulant therapy. However, it is uncertain whether rhythm control (restoration and maintenance of sinus rhythm) or rate control (adjustment to a physiological ventricular rate while allowing AF to continue) is the preferred primary treatment option for the reduction of symptoms and major cardiovascular (CV) outcomes associated with AF.

Several well conducted trials comparing the two strategies led to the conclusion that there was little to choose between them. However, guidelines leaned towards recommending rate control as the initial strategy, and reserved rhythm control for those who remained symptomatic. Recently this status quo is being increasingly challenged by the clear demonstration that left atrial catheter ablation is effective at suppressing AF resistant to traditional antiarrhythmic drugs, such as those that failed to demonstrate any superiority when compared with rate control. Also, recently introduced antiarrhythmic therapy may have superior efficacy with regard to reducing unexpected CV hospitalization, CV mortality and stroke. In addition, there is a growing perception that atrial remodelling should be best prevented by early rhythm control rather than delaying until rate control has proven unsatisfactory.

For these reasons the results of large randomised clinical trials, which recruit patients soon after the presentation of AF and compare ‘aggressive’ modern rhythm control against the guideline approach of primary rate control, are eagerly awaited. In the meantime the pendulum of clinical opinion has begun to swing towards a rhythm control strategy.

DECLARATION OF INTERESTS Professor Camm has consulted and spoken on behalf of Sanofi, Merck, Menarini, Medtronic and Boston Scientific. Dr Savelieva has spoken on behalf of Sanofi.

INTRODUCTION Atrial fibrillation (AF) is an increasingly prevalent arrhythmia, affecting close to 2% of the general population. It accounts directly for over 15% of all strokes; many cryptogenic strokes may also be due to this arrhythmia. Hospitalizations for the management of AF itself, acute coronary syndrome and for heart failure are increased when AF is present. Exercise tolerance is generally reduced and quality of life is impaired, especially in symptomatic patients.

AF occurs in conjunction with almost every cardiac or vascular disease and may also complicate diseases of the chest. It may result from aging alone; most of the patients with this arrhythmia are relatively old and have underlying cardiac or pulmonary pathology. In younger patients, structural congenital cardiac disease or an association with channelopathies (QT abnormalities and Brugada syndrome), or familial cardiomyopathy (e.g. hypertrophic cardiomyopathy) may be responsible. The majority of younger patients however have no apparent cardiovascular cause for their AF, other than mild hypertension (without left ventricular hypertrophy) or possible cardiac autonomic dysfunction. Other elements may also be responsible for the arrhythmia, including genetic factors, a history of an inflammatory illness preceding the first episode, or toxic causes (e.g. alcohol, thyroid conditions, etc.).

While elderly patients, especially when sedentary and inactive, may be relatively asymptomatic from AF, younger patients (who are usually more active) find AF to be a very symptomatic and debilitating disease. Older patients may blame their symptoms on ‘getting old’ and accommodate by lowering their expectations and adjusting their lifestyle to the limitations imposed by the disease. Younger patients tend to expect a full eradication of the disease or at least complete suppression of their symptoms.
AF is typically divided into three types (paroxysmal, persistent and permanent) based on its presentation, duration, and response to therapy (if applicable).\(^{13}\) Paroxysmal AF is a self-terminating arrhythmia; although the duration of paroxysms may vary greatly (with the upper limit arbitrarily set at seven days) the majority will end within 48 hours. The 48-hour time period is clinically important because after this the likelihood of spontaneous conversion is low and anticoagulation must be considered prior to any attempt to cardiovert the arrhythmia, irrespective of the underlying thromboembolic risk profile. If AF lasts longer than seven days or requires pharmacological or electrical cardioversion, it is referred as persistent. When AF does not convert spontaneously and is refractory to cardioversion or other rhythm control interventions, or if the physician or the patient chooses not to pursue the rhythm control strategy and allow AF to remain, the term permanent (‘accepted’) AF is applied. AF lasting more than one year (or six months according to recent statements from regulatory authorities [MULTAQ]) is deemed to be ‘permanent’ but if a rhythm control strategy is to be pursued with cardioversion or catheter ablation the AF may be designated as ‘long-standing persistent’.

When AF is first detected, it may be a single non-recurrent event secondary to a reversible or transient cause, or it may evolve into recurrent paroxysmal or persistent AF. The onset of AF however may be asymptomatic and the first detected episode should not be regarded as necessarily the true onset of the arrhythmia. AF episodes may or may not terminate spontaneously. There is usually a progression of the disease from paroxysmal to persistent and eventually permanent (or accepted) AF.\(^{13}\) Progression from first diagnosed or recurrent paroxysmal AF to persistent or permanent AF occurs on average at the rate of 5% to 15% per year, depending on a number of factors, such as age at presentation and the presence of underlying heart disease (Table 1).\(^{13}\)

**RATE VERSUS RHYTHM CONTROL STRATEGIES**

AF is due to very rapid atrial excitations, caused and sustained by a combination of re-entry and automaticity mechanisms,\(^ {14}\) which effectively paralyze atrial mechanical function. These excitations are conducted (to a limited extent) to the ventricles and induce a rapid and irregular ventricular rate response. There are two fundamentally different clinical approaches to the arrhythmia:\(^ {13}\)

**Rate control:** Slowing the ventricular rate to a level which is physiologically appropriate. It is not clear exactly what this rate should be, but most clinicians settle for rates at rest below 100 beats per minute. In clinical trials specific definitions have been applied.

**Rhythm control:** Suppressing the rapid excitation of the atrium and restoring sinus rhythm. Antiarrhythmic drugs (ion channel blockers) are most commonly used for this purpose, but occasionally autonomic manipulation, with beta blockers for example, may also prove effective. Successful rhythm control may eliminate or reduce recurrent AF or slow its progression.

Patients who are not severely symptomatic could be considered for treatment using either strategy. Both patients and physicians have taken part in clinical trials in which these patients were randomised to receive either rate control or rhythm control treatment. Patients who have severe and disabling symptoms often demand a more aggressive approach towards restoring and maintaining sinus rhythm: rate versus rhythm control trials would therefore be difficult, and have never been undertaken.

Rhythm control appears to be a more attractive treatment option, as it offers physiologic rate control, normal atrial activation and contraction, the correct sequence of atrioventricular (AV) activation and normal haemodynamic and AV valve function. It also theoretically eliminates one (stasis) or more (endothelial abnormality or increased thrombogenic blood constituents) of Virchow’s triad of elements that encourage thrombosis within the atria and embolization of blood clots to potentially critical parts of the circulation. Advantages of the rate control approach on the other hand include avoiding the potential toxicity of antiarrhythmic drugs or the risks and discomfort associated with electrical cardioversion or invasive left atrial ablation for recurrences of AF.

Sinus rhythm with normal AV conduction may however not be an alternative treatment for AF since sinus node disease may be the underlying problem and chronotropic incompetence may be present. Atrial conduction and mechanical function may be seriously impaired due to existing AF, or underlying pathophysiologies such as left ventricular (LV) cavity dilatation, LV hypertrophy, hypertension, mitral valve disease, etc. Atrial contraction may not contribute much to cardiac output. AV conduction may be impaired because of associated structural disease, channelopathy or antiarrhythmic drug therapy. AV valve function may be structurally abnormal or functionally disturbed on a permanent basis because of dilatation of the atrium and AV valve annulus. AF which is not fully suppressed is likely to cause some symptoms which, when contrasted to asymptomatic periods of sinus rhythm, may make intermittent AF more troublesome than sustained AF.

It is not unusual for patients to be relieved of their symptoms when AF is established and becomes permanent. Often the only symptoms that remain are a minor limitation to exercise tolerance and a subtle
TABLE 1 Rates of progression of paroxysmal atrial fibrillation to persistent or permanent atrial fibrillation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Age, years</th>
<th>Type of AF</th>
<th>Follow-up, years</th>
<th>Progression of AF, %</th>
<th>Predictors of progression (risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Heart Survey, 2010</td>
<td>1219</td>
<td>64 ± 13</td>
<td>Paroxysmal; lone AF: 17%</td>
<td>1</td>
<td>15</td>
<td>Age &gt; 75 years (1.57), heart failure (2.22), hypertension (1.52), stroke/TIA (2.02), COPD (1.51)</td>
</tr>
<tr>
<td>RECORD-AF, 2011</td>
<td>2137</td>
<td>65.1 ± 12</td>
<td>Recent onset paroxysmal</td>
<td>1</td>
<td>15</td>
<td>Heart failure (2.2), hypertension (1.5), rate control (3.2). In subgroup with rhythm control as the initial strategy: heart failure (1.9), hypertension (1.8), heart rate (1.01)</td>
</tr>
<tr>
<td>Sakamoto (Tokyo), 1995</td>
<td>137</td>
<td>No progression: 62.4 ± 11 With progression: 70.1 ± 8.2</td>
<td>First detected paroxysmal</td>
<td>1</td>
<td>Sustained AF ≥ 6 months: 22</td>
<td>Age ≥ 65 years, heart failure, CTR ≥ 50%, diabetes, LA ≥ 38 mm, LVEF ≤ 0.76, f waves in V, ≥ 2 mm</td>
</tr>
<tr>
<td>Abe (Osaka), 1997</td>
<td>122</td>
<td>61 ± 12</td>
<td>Paroxysmal; lone AF: 21%</td>
<td>2.16</td>
<td>Sustained AF ≥ 6 months: 11.5</td>
<td>LA size, abnormal P-signal-averaged ECG</td>
</tr>
<tr>
<td>Fauchier (Tours), 2010</td>
<td>2167</td>
<td>71 ± 14</td>
<td>Paroxysmal</td>
<td>2.6</td>
<td>14.1</td>
<td>Age &gt; 75 years, heart failure, hypertension, COPD, number of electrical cardioversions, dilated cardiomyopathy, prosthetic valve</td>
</tr>
<tr>
<td>UK GPRD, 2005</td>
<td>418</td>
<td>Men: 67 ± 11, Women: 73 ± 10</td>
<td>First detected paroxysmal; no co-morbidity: 32%</td>
<td>2.7</td>
<td>11 at 1 year 17 at 2.7 years</td>
<td>Valvular heart disease (2.7), moderate to high alcohol intake (3.0)</td>
</tr>
<tr>
<td>Al-Khatib (Durham), 2010</td>
<td>231</td>
<td>60 ± 13</td>
<td>Paroxysmal; lone AF: 41.6%</td>
<td>4</td>
<td>8 at 1 year 18 at 4 years</td>
<td>Age (1.82 per decade), AF at presentation (3.56)</td>
</tr>
<tr>
<td>Pappone (Milan), 2008</td>
<td>106</td>
<td>57.5 ± 11.5</td>
<td>First detected paroxysmal; lone AF: 51%</td>
<td>5</td>
<td>Recurrent paroxysmal: 52.8 Persistent: 53.3 Persistent: 35.5 In subgroup with lone AF: 3.7 (persistent), 1.8 (permanent)</td>
<td>Age (1.19), heart failure (11.2), diabetes (17.3), drug therapy vs ablation</td>
</tr>
<tr>
<td>Rostagno (Florence), 1995</td>
<td>106</td>
<td>63 ± 11</td>
<td>First detected paroxysmal lone AF</td>
<td>6</td>
<td>Recurrent paroxysmal: 55.6 Sustained: 4.7%</td>
<td>–</td>
</tr>
<tr>
<td>Takahashi (Tokyo), 1980</td>
<td>94</td>
<td>60</td>
<td>First detected paroxysmal; lone AF: 24.5%</td>
<td>&gt; 6</td>
<td>Sustained AF ≥ 6 months: 20.2–25.3</td>
<td>Rheumatic valvular disease; frequency of paroxysms</td>
</tr>
</tbody>
</table>

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The difficulties in rhythm control management, principally the high AF recurrence rate and concern about the serious adverse effects associated with antiarrhythmic drug therapy, led to rate versus rhythm control studies.

### THE RATE VERSUS RHYTHM CONTROL TRIALS

The Atrial Fibrillation Follow up Investigation of Rhythm Management (AFFIRM) trial, the RAte Control versus Electrical cardioversion (RACE) trial, and most recently the Atrial Fibrillation Congestive Heart Failure (AF CHF) trial are the major studies in this area.\(^{15-18}\) (Table 2). There have also been a series of small or pilot studies, including the Pharmacological Intervention in Atrial Fibrillation (PIAF), Strategies of Treatment of Atrial Fibrillation (STAF), and How to Treat Chronic Atrial Fibrillation (HOT CAFÉ) among others.\(^{18-20}\)

All of these randomised clinical trials directly and prospectively compared the effects of rhythm control treatment strategies with rate control strategies on a variety of endpoints ranging from exercise tolerance to all-cause mortality. Generally, no consistent differences between the strategies have been demonstrated, except for more hospitalizations and the costs associated with rhythm control. However, the trials highlighted a trend toward improved survival and less serious cardiovascular adverse events in patients treated with a rate rather than rhythm control strategy.

The AFFIRM study of 4,060 AF patients aged 65 years or older, with at least one risk factor for stroke, was the only trial designed to assess, as a primary endpoint, all-cause mortality benefit from these different strategies for AF management.\(^{15}\) The mean follow-up was 3.5 years, with a maximum of six years. There was no difference in the primary endpoint of all-cause mortality or quality of life and functional status between rate and rhythm control.
TABLE 2 Clinical outcomes in rhythm versus rate control studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>PIAF</th>
<th>STAF</th>
<th>HOT CAFÉ</th>
<th>RACE</th>
<th>AFFIRM</th>
<th>AF-CHF</th>
<th>CRRAFT</th>
<th>J-RHYTHM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>252</td>
<td>200</td>
<td>205</td>
<td>522</td>
<td>4060</td>
<td>1376</td>
<td>144</td>
<td>823</td>
</tr>
<tr>
<td>Follow-up, years</td>
<td>1</td>
<td>1.6</td>
<td>1.7</td>
<td>2.3</td>
<td>3.5</td>
<td>3.1</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Symptom improvement</td>
<td>ACM, CV events, CPR, TE</td>
<td>ACM, TE, bleeding</td>
<td>CV death, hospitalization for CHF, TE, bleeding, pacemaker, AAD adverse effects</td>
<td>ACM</td>
<td>CV mortality</td>
<td>Clinical improvement</td>
<td>ACM, TE, bleeding, hospitalization for CHF, adverse effects</td>
</tr>
<tr>
<td>Difference in primary endpoint RhyC vs RC</td>
<td>Symptoms improved in 70 vs 76 pts (p=0.317)</td>
<td>5.5%/yr vs 6.0%/yr (p=0.99)</td>
<td>No difference (OR, 1.98; 95% CI, 0.28–22.3; p &gt;0.71)</td>
<td>22.6% vs 17.2% (HR, 0.73; 90% CI, 0.53–1.01; p=0.11)</td>
<td>23.8% vs 21.3% (HR, 1.15; 95% CI, 0.99–1.34; p=0.08)</td>
<td>27% vs 25% (HR, 1.06; 95% CI, 0.86–1.3; p=0.59)</td>
<td>Significant improvement with RhyC</td>
<td>15.3% vs 22% (p=0.0128)</td>
</tr>
<tr>
<td>ACM RhyC vs RC</td>
<td>Not assessed</td>
<td>2.5%/yr vs 4.9%/yr</td>
<td>3 (2.9%) vs 1 (1%)</td>
<td>6.8% vs 7%</td>
<td>As above</td>
<td>32% vs 33% (p=0.68)</td>
<td>0 vs 5 (p=0.023)</td>
<td>4 (1%) vs 3 (0.7%)</td>
</tr>
<tr>
<td>TE RhyC vs RC</td>
<td>Not assessed</td>
<td>3.1%/yr vs 0.6%/yr</td>
<td>3 (2.9%) vs 1 (1%)</td>
<td>7.9% vs 5.5%</td>
<td>RhyC vs RC</td>
<td>Stroke: 7.1% vs 5.5% (p=0.79)</td>
<td>3% vs 4% (p=0.32)</td>
<td>1 vs 0</td>
</tr>
<tr>
<td>CHF RhyC vs RC</td>
<td>Not assessed</td>
<td>Better with RC</td>
<td>No difference</td>
<td>4.5% vs 3.5%</td>
<td>2.7% vs 2.1% (p=0.58)</td>
<td>28% vs 31% (p=0.17)</td>
<td>Functional class improved in 60% vs 17.5% (p=0.0014)</td>
<td>0.5% vs 1.5%</td>
</tr>
<tr>
<td>Hospitalization RhyC vs RC</td>
<td>69% vs 24% (p=0.001)</td>
<td>54% vs 26% (p &lt;0.001)</td>
<td>74% vs 12% (p &lt;0.001)</td>
<td>More in RhyC</td>
<td>80% vs 73% (p &lt;0.001)</td>
<td>46% vs 39% (p=0.0063)</td>
<td>8.9% vs 15% (p=0.51)</td>
<td>Not reported</td>
</tr>
<tr>
<td>QoL RhyC vs RC</td>
<td>No difference</td>
<td>No difference</td>
<td>Not reported</td>
<td>No difference</td>
<td>No difference</td>
<td>Not yet available</td>
<td>Improved in 86.7% vs 50% (p=0.033)</td>
<td>Better with RhyC</td>
</tr>
</tbody>
</table>

Abbreviations: AAD = antiarrhythmic drugs; ACM = all-cause mortality; AF = atrial fibrillation; AF-CHF = Atrial Fibrillation and Congestive Heart Failure; AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; CHF = congestive heart failure; CI = confidence intervals; CPR = cardiopulmonary resuscitation; CRRAFT = Control of rate versus rhythm in rheumatic study in Rheumatic Atrial Fibrillation Trial; CV = cardiovascular; HOT CAFÉ = HOw to Treat Chronic Atrial Fibrillation; HR = hazard ratio; OR = odds ratio; PIAF = Pharmacological Intervention in Atrial Fibrillation; QoL = quality of life; RACE = Rate Control versus Electrical Cardioversion; RC = rate control; RhyC = rhythm control; RR = relative risk; STAF = Strategies of Treatment of Atrial Fibrillation; TE = thromboembolic event; a = including hospitalization for cardioversion

Source: Savelieva et al

However, this and other trials did not include younger, active or highly symptomatic patients, initial rate control could not have been easily applied to their management.

Post hoc analysis of the AFFIRM trial, after correction for any mismatch of baseline characteristics, has demonstrated that being in sinus rhythm was an advantage, but that the use of the then available antiarrhythmic drugs was associated with an increased risk of death.  

In the AF-CHF trial, rate and rhythm control strategies were compared specifically in 1376 patients with an ejection fraction of 35% or less and a New York Heart Association (NYHA) classification of II to IV heart
failure. Amiodarone was the drug of choice (used in 82% of cases) for AF suppression and sinus rhythm maintenance, but sotalol and dofetilide were also used in select cases. The study showed no benefit to using rhythm control in addition to optimal medical therapy with regard to the primary endpoint (cardiovascular mortality) and pre-specified secondary endpoints (including total mortality, worsening heart failure, stroke, and hospitalization). Rhythm management was also found to be more expensive than rate control. Unlike the AFFIRM trial, the results of the AF-CHF trial did not confirm an advantage to using sinus rhythm in treating a population of elderly patients with heart failure (Figure 1).

The similar primary endpoint results from using the rhythm and rate control strategies may have been due to a general failure to achieve a clear difference with respect to rhythm and rate status in the two arms of the trials. Ideally the rhythm control arm should have included patients who were in sinus rhythm, whereas the rate control arm should have consisted mostly of patients in AF. This was not however typically the case; in the AFFIRM trial for example, only 60% of the rhythm control arm were maintained in sinus rhythm, while 40% of the rate control arm had reverted spontaneously to sinus rhythm.

The generally neutral results of the rate versus rhythm control trials were broadly accepted by the clinical community. They were interpreted to imply that rate control therapy should be the primary therapeutic option for patients with recurrent forms of AF. The reasons for this are not entirely clear but mostly relate to a belief that rate control is logistically easier than rhythm control, to the well-documented reduction in hospitalizations associated with rate control, and to the trend towards better major cardiovascular outcomes in favour of rate control (seen particularly in the AFFIRM and RACE trials). There was therefore a major shift towards the use of rate control and this was reinforced by the guidelines from the ACC, AHA and ESC published in 2001 and 2006. The advice from the 2006 guideline regarding rate versus rhythm control for patients with paroxysmal AF is summarised in Figure 2.

However, these interpretations (i.e. initial treatment with rate control agents and later, and therefore delayed, treatment with rhythm control drugs only if symptoms persisted) were not accepted by the arrhythmia and electrophysiology community who were treating younger, more symptomatic patients. This was primarily because these patients had not been included in the relevant trials, and also because the treatment of recurrent AF was beginning to change dramatically at that time. A new antiarrhythmic agent was about to emerge, paroxysmal AF and some persistent AF were increasingly treated with direct left atrial ablation (such as pulmonary vein isolation) and the idea that interventional treatment would be much more successful and might even be ‘curative’ if adopted early in the course of the disease was spreading.

<table>
<thead>
<tr>
<th>AFFIRM</th>
<th>AF-CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SR AFFIRM</strong></td>
<td><strong>SR AF-CHF</strong></td>
</tr>
<tr>
<td>Warfarin use</td>
<td>Warfarin use</td>
</tr>
<tr>
<td>Digoxin use</td>
<td>Digoxin use</td>
</tr>
<tr>
<td>AAD use</td>
<td>AAD use</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>Stroke/TIA</td>
</tr>
</tbody>
</table>

**FIGURE 1** Sub-group analyses of AFFIRM and RACE illustrating discrepant results with regard to the presence of sinus rhythm

**Abbreviations:** AAD = antiarrhythmic drugs; AF = atrial fibrillation; CAD = coronary artery disease; NYHA = New York Heart Association; SR = sinus rhythm; TIA = transient ischaemic attack

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AJ Camm, I Savelieva
**TABLE 3** Randomised controlled studies of pulmonary vein ablation versus antiarrhythmic drug therapy in atrial fibrillation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Type of AF</th>
<th>Previous use of AAD</th>
<th>Crossed to ablation in the ADD Group</th>
<th>AF free at one year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krittayaphong et al, 2003</td>
<td>30</td>
<td>Paroxysmal, persistent</td>
<td>≥1</td>
<td>Not stated</td>
<td>79% Ablation 40% AAD</td>
</tr>
<tr>
<td>Wazni et al, 2005 (RAAFT)</td>
<td>70</td>
<td>Mainly paroxysmal</td>
<td>No</td>
<td></td>
<td>49% Ablation 87% AAD 37%</td>
</tr>
<tr>
<td>Stabile et al, 2005 (CACAF)</td>
<td>137</td>
<td>Paroxysmal, persistent</td>
<td>≥2</td>
<td>57%</td>
<td>56% Ablation 9%</td>
</tr>
<tr>
<td>Oral et al, 2006</td>
<td>146</td>
<td>Persistent</td>
<td>≥1 (mean 2.1 ± 1.2)</td>
<td>77%</td>
<td>74% Ablation 4%</td>
</tr>
<tr>
<td>Pappone et al, 2006 (APAF)</td>
<td>198</td>
<td>Paroxysmal</td>
<td>≥2 (mean 2 ± 1)</td>
<td>42%</td>
<td>86% Ablation 22%</td>
</tr>
<tr>
<td>Jais et al, 2008 (A4 study)</td>
<td>112</td>
<td>Paroxysmal</td>
<td>≥1</td>
<td>63%</td>
<td>89% Ablation 23%</td>
</tr>
<tr>
<td>Forleo et al, 2008</td>
<td>70</td>
<td>Paroxysmal, persistent</td>
<td>≥1</td>
<td>Not stated</td>
<td>80% Ablation 43%</td>
</tr>
<tr>
<td>Wilber et al, 2009 (Thermocool)</td>
<td>167</td>
<td>Paroxysmal</td>
<td>≥1 (mean 1.3)</td>
<td>59%</td>
<td>66% Ablation 16%</td>
</tr>
<tr>
<td>Packer et al, 2010 (STOP-AF)</td>
<td>245</td>
<td>Paroxysmal</td>
<td>≥1</td>
<td>79%</td>
<td>69.9% Ablation 7.3%</td>
</tr>
</tbody>
</table>

**Abbreviations:** AAD = antiarrhythmic drugs; AF = atrial fibrillation; APAF = Ablation for Paroxysmal Atrial Fibrillation study; A4 = Atrial fibrillation Ablation versus AntiArrhythmic drugs; CACAF = Catheter Ablation for the Cure of Atrial Fibrillation study; RAAFT = Radiofrequency Ablation Atrial Fibrillation Trial; STOP-AF = Sustained Treatment of Paroxysmal Atrial Fibrillation; ’ = after 1 year

Source: Camm AJ et al.50

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**FIGURE 2** Illustration of the default ‘rate control’ strategy adopted in guidelines issued by professional societies.45

- Recurrent paroxysmal atrial fibrillation
  - Minimal or no symptoms
    - Anticoagulation and rate control as needed
  - Disabling symptoms in atrial fibrillation
    - Anticoagulation and rate control as needed
  - No drug for prevention of atrial fibrillation
    - Antiarrhythmic drugs (AAD) therapy
  - Atrial fibrillation if AAD treatment fails
The results of rate versus rhythm control studies highlighted the limitations of the therapies at that time to achieve and maintain sinus rhythm. Long-term maintenance of sinus rhythm has proven difficult to achieve in patients with persistent AF, and the strategy is time-consuming and expensive due to the costs of the antiarrhythmic drugs and the increased need for hospitalization. Little was known about the criteria for adequate and safe rate control. A study from the AFFIRM database, and another comparing the results of AFFIRM (strict rate control) to RACE (lenient rate control) suggested that a lenient approach to rate control is at least as effective as a strict rate control procedure. This conclusion was confirmed by a recent prospective randomised trial comparing strict control (<80 beats/minute at rest and <110 beats/minute on moderate exercise) with lenient control (<110 beats/minute at rest). Strict rate control was associated with more bradycardia and pacemaker implantation. These developments imply that the therapeutic emphasis on rate control may be tempered or even reversed if safer and more effective rhythm control therapies were to become available.

The use of left atrial ablation to isolate triggers, most often by pulmonary vein isolation, and/or to break up the substrate for AF by creating lines of block or eradicating areas of critical slow conduction, have proved successful in reducing the recurrence of AF (Table 3). This is particularly true in patients with paroxysmal AF of short duration, normal left atrial anatomy and size, and normal left ventricular function. The results with persistent AF, or with AF which would otherwise be designated as permanent, are also encouragingly positive, even when significant left ventricular systolic dysfunction is present. Often more than one procedure is needed, particularly in the complex cases mentioned above. There is also some concern about long-term recurrence which is now recognised to be about 5% per annum even in patients who remain arrhythmia-free for the first year or so. The recurrences tend to be short in duration however and relatively infrequent. Further ablation procedures may be needed and are often successful (Table 4).

Dronedarone is a new antiarrhythmic drug, structurally similar to amiodarone, but it does not contain iodine and is not lipophilic. Significant cutaneous or thyroid effects have not been seen. The electrophysiological spectrum of the drug also differs significantly from that of amiodarone – it is a more powerful sodium, calcium and acetylcholine-dependent K current (IKACh) blocker. This drug is an effective antiarrhythmic agent, also shown to reduce hospitalizations for AF and AF related co-morbidities, such as heart failure, and acute coronary syndrome in patients with recurrent forms of AF (Table 5). Dronedarone, however, appears not to be safe to use in patients with severe heart failure or permanent AF, especially in the presence of heart failure. There is some concern over severe liver toxicity, which has been

### Table 4: Long-term results of pulmonary vein ablation for atrial fibrillation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Number</th>
<th>Ablation strategy</th>
<th>Follow-up, months (±SD)</th>
<th>Arrhythmia free survival, %</th>
<th>Complications, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaita et al, 2008</td>
<td>Randomised 1:1 PVI vs PVI + LL</td>
<td>204</td>
<td>PVI/PVI+LL</td>
<td>41.4 ± 6.2/39.7 ± 5.5</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>Fiala et al, 2008</td>
<td>Randomised 1:1 segmental PVI vs circumferential PVI</td>
<td>110</td>
<td>PVI</td>
<td>48 ± 8</td>
<td>56</td>
<td>1</td>
</tr>
<tr>
<td>Bertaglia et al, 2009</td>
<td>Observational</td>
<td>177</td>
<td>PVI/PVI+LL</td>
<td>49.7 ± 13.3</td>
<td>58</td>
<td>Not reported</td>
</tr>
<tr>
<td>Bhargava et al, 2009</td>
<td>Observational</td>
<td>1404</td>
<td>PVI/PVI+LL</td>
<td>59 ± 16</td>
<td>73</td>
<td>3</td>
</tr>
<tr>
<td>Tsou et al, 2010</td>
<td>Observational</td>
<td>123</td>
<td>PVI</td>
<td>71 ± 18</td>
<td>71</td>
<td>Not reported</td>
</tr>
<tr>
<td>Wokhu et al, 2010</td>
<td>Observational</td>
<td>774</td>
<td>PVI/PVI+LL</td>
<td>36 ± 22.8</td>
<td>64</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ouyang et al, 2010</td>
<td>Observational</td>
<td>161</td>
<td>PVI</td>
<td>57.6</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td>Weerassooiya et al, 2011</td>
<td>Observational</td>
<td>100</td>
<td>PVI/PVI+LL</td>
<td>60</td>
<td>32</td>
<td>6</td>
</tr>
</tbody>
</table>

**Abbreviations:** LL = left lines; PVI = pulmonary vein isolation; SD = standard deviation

*only patients free from AF one year after ablation were included; in a total of 239 patients who underwent AF ablation, the success rate after 71 ± 18 months was only 36.4%**
### TABLE 5 Summary of clinical studies of dronedarone in atrial fibrillation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Dose of dronedarone</th>
<th>Placebo controlled</th>
<th>Primary endpoint</th>
<th>Follow-up, months</th>
<th>Outcome of dronedarone vs placebo for amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAFNE</td>
<td>199</td>
<td>Persistent AF post cardioversion</td>
<td>400 mg bid 600 mg bid 800 mg bid</td>
<td>Yes</td>
<td>Time to first AF recurrence</td>
<td>6</td>
<td>Median time to first AF recurrence: 400 mg bid: 60 vs 5.3 days (relative risk reduction, 55%; 95% CI, 28–72%; p=0.001). The effect was less apparent at higher doses. Treatment discontinuation due to adverse effects: 3.9%, 7.6%, 22.6% on 400, 600, 800 bid. vs 0%</td>
</tr>
<tr>
<td>EURIDIS</td>
<td>615</td>
<td>Paroxysmal and persistent AF post cardioversion</td>
<td>400 mg bid</td>
<td>Yes</td>
<td>Time to first AF recurrence</td>
<td>12</td>
<td>Median time to first AF recurrence: 96 vs 41 days, p=0.01</td>
</tr>
<tr>
<td>ADONIS</td>
<td>630</td>
<td>Paroxysmal and persistent AF post cardioversion</td>
<td>400 mg bid</td>
<td>Yes</td>
<td>Time to first AF recurrence</td>
<td>12</td>
<td>Median time to first AF recurrence: 158 vs 59 days, p=0.002</td>
</tr>
<tr>
<td>EURIDIS and ADONIS combined</td>
<td>1237</td>
<td>Paroxysmal and persistent AF post cardioversion</td>
<td>400 mg bid</td>
<td>Yes</td>
<td>Time to first AF recurrence</td>
<td>12</td>
<td>Median time to first AF recurrence: 116 vs 53 days. Recurrence at 12 months: 64.1% vs 75.2% (HR, 0.75; 95% CI, 0.65–0.87; p &lt;0.001)</td>
</tr>
<tr>
<td>EURIDIS and ADONIS post-hoc</td>
<td>1237</td>
<td>Paroxysmal and persistent AF post cardioversion</td>
<td>400 mg bid</td>
<td>Yes</td>
<td>All-cause mortality and hospitalization</td>
<td>12</td>
<td>All-cause mortality and hospitalizations: 22.8% vs 30.9% (HR, 0.73; 95% CI, 0.57–0.93; p = 0.01)</td>
</tr>
<tr>
<td>ERATO</td>
<td>630</td>
<td>Permanent AF with ventricular rates &gt;80 bpm on rate controlling therapy</td>
<td>400 mg bid</td>
<td>Yes</td>
<td>Mean 24-hour ventricular rate at two weeks</td>
<td>1</td>
<td>11.7 bpm lower on dronedarone (p&lt;0.0001) 24.5 bpm lower on dronedarone during maximal exercise (p&lt;0.0001)</td>
</tr>
<tr>
<td>ANDROMEDA</td>
<td>617</td>
<td>Congestive heart failure; EF &lt;0.35</td>
<td>400 mg bid</td>
<td>Yes</td>
<td>All-cause mortality and hospitalization for heart failure</td>
<td>2 (median)</td>
<td>Stopped early because of excess mortality in the dronedarone arm: 8.1% vs 3.8% (HR, 2.13; 95% CI, 1.07–4.25; p=0.03) Primary endpoint: 17.1% vs 12.6% (HR, 1.38; 95% CI, 0.92–2.09; p=0.12)</td>
</tr>
<tr>
<td>ATHENA</td>
<td>4628</td>
<td>Paroxysmal or persistent AF with risk factors</td>
<td>400 mg bid</td>
<td>Yes</td>
<td>All-cause mortality and hospitalization for cardiovascular events</td>
<td>1.7 (range, 1–2.5)</td>
<td>Primary endpoint: 31.9% vs 39.4% (HR, 0.76; 95% CI, 0.69–0.84; p&lt;0.001). Hospitalization: 29.3% vs 36.9% (HR, 0.74; 95% CI, 0.67–0.82; p&lt;0.001). All-cause mortality: 5% vs 6% (HR, 0.84; 95% CI, 0.66–1.08; p=0.18).</td>
</tr>
</tbody>
</table>
documented in rare cases but detailed post-approval studies have so far failed to confirm the concern. Unlike other drugs, dronedarone has not been associated with any pro-arrhythmia other than mild bradycardia.

Both dronedarone and left atrial ablation are recommended in recent guidelines for the management of patients with recurrent AF. The focused update incorporated into the ACC, AHA and HRS guidelines (2011)\(^6\) give a class I level recommendation for ablation of paroxysmal AF in optimal circumstances, and the ESC guidelines (2010)\(^5\) give a class 2a level recommendation for ablation of both paroxysmal and persistent AF and a 2b level recommendation for ablation of paroxysmal AF without the need to demonstrate failure with previous antiarrhythmic drug therapy. This guideline also supports (class 2b) ablation of AF in patients with systolic heart failure. Both guidelines recommend the use of dronedarone within its licensed indications. The ESC guideline no longer recommends that there should always be an attempt to control symptoms with rate control before considering the adoption of a rhythm control strategy. Early rhythm control may be important if the strategy is to stand any chance of long-term success.

New ‘rate versus rhythm control’ trials are urgently needed because younger, more active and more symptomatic patients should be studied. Better therapies than the older antiarrhythmic drugs used in the previous rate versus rhythm trials are now available. Left atrial ablation, and/or possibly dronedarone, might be used to provide safer and more effective rhythm control.

It is suggested that rhythm control should be timed much earlier during the course of the disease in order to prevent the progression of AF.\(^6\) Left atrial ablation or antiarrhythmic agents might be used to isolate or suppress triggers of AF or modify the substrate for example. If given early in the course of the disease, before substantial atrial remodelling has taken place due to the AF itself (‘AF begets AF’) or due to the haemodynamic stress associated with underlying diseases.

### TABLE 5 Summary of clinical studies of dronedarone in atrial fibrillation.

<table>
<thead>
<tr>
<th>Study</th>
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<th>Outcome of dronedarone vs placebo for amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIONYSOS</td>
<td>504</td>
<td>Persistent AF</td>
<td>400 mg bid</td>
<td>No; amiodarone used as an active comparator</td>
<td>AF recurrence (including unsuccessful direct current cardioversion [DCC]) or drug discontinuation; secondary safety endpoints</td>
<td>12 (median, 7)</td>
<td>Primary endpoint: 75.1% vs 58.8% (HR, 1.59; 95% CI 1.28–1.98; p&lt;0.0001). AF recurrence: 36.5% vs 24.3%. Main safety endpoint: 39.3% vs 44.5% (HR, 0.80; 95% CI, 0.60–1.07; p=0.129).</td>
</tr>
<tr>
<td>PALLAS</td>
<td>3149</td>
<td>Permanent AF with risk factors</td>
<td>400 mg bid</td>
<td>Yes</td>
<td>MACE (cardiovascular death, myocardial infarction, stroke, systemic embolism) or unplanned cardiovascular hospitalization and all-cause mortality</td>
<td>12 (median, 7)</td>
<td>Stopped early because of excess co-primary endpoints in the dronedarone arm. Major adverse cardiac events (MACE): 2% vs 0.9% (HR, 2.3; p=0.009). All-cause mortality and unplanned hospitalization: 7.5% vs 5.1% (HR, 1.5; p = 0.006). Death: 1% vs 0.4% (HR, 2.3; p=0.065).</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADONIS = American-Australian-African trial with DronedarONe In atrial fibrillation or flutter for the maintenance of Sinus rhythm; AF = atrial fibrillation; ANDROMEDA = ANtiarrhythmic trial with DROnedarone in Moderate to severe heart failure Evaluating morbidity Decrease; 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; bpm = beats per minute; DAfne = Dronedarone Atrial Fibrillation study after Electrical cardioversion; DIONYSOS = Double blind trial to evaluate efficacy and safety of drOnedarone (400 mg bid) versus amiodarone (600 mg qd for 28 days, 200 mg qd thereafter) for at least six months for the maintenance of Sinus rhythm in patients with atrial fibrillation; EF = ejection fraction; ERATO = Efficacy and Safety of Dronedarone for the Control of Ventricular Rate; EURIDIS = EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm; PALLAS = Permanent Atrial fibrillation outcome Study
such as hypertension and heart failure (which themselves can be aggressively managed), the recurrence of AF may be averted. Such considerations are the basis for large trials such as EAST (Early Atrial fibrillation Stroke Prevention Trial, NCT01288352) and CABANA (Catheter ABlation versus AnTiarrhythmic drug therapy for Atrial fibrillation, NCT00911508).

CONCLUSIONS

For the majority of patients with recurrent AF there is abundant and largely consistent randomised clinical trial evidence that the best initial strategy is rate control; rhythm control should only be considered if symptoms remain troublesome. However, little or no such evidence exists in younger, active and highly symptomatic patients. There is good evidence that left atrial ablation is considerably better than conventional antiarrhythmic drug therapy for the prevention of paroxysmal AF recurrences, although no trials have yet investigated whether ablation techniques result in a long-term reduction of major cardiovascular outcomes. Nonetheless, the clinical pendulum of rate versus rhythm control is swinging towards rhythm control. Results from large scale randomised clinical trials are urgently needed to evaluate whether a rhythm control strategy in the modern era can surpass rate control in terms of slowing the progression of AF, improving quality of life, and reducing cardiovascular consequences, including mortality.

REFERENCES


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**What is the most effective and safest delivery of thromboprophylaxis in atrial fibrillation?**

GYH Lip  
Professor of Cardiovascular Medicine, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK

**ABSTRACT** The presence of atrial fibrillation (AF) increases the risk of stroke five-fold, but the risk is dependent upon the presence of stroke risk factors. The challenge is defining patients who would best benefit from thromboprophylaxis, and how to deliver it in the most effective and safe way. The objective of this brief overview is to address this question. Previously, attention has been directed towards identifying high-risk patients who could be subjected to an inconvenient (and potentially dangerous) drug, warfarin. Aspirin has been increasingly recognised as an inferior choice for stroke prevention, and may not be any safer than warfarin in terms of major bleeding, especially in the elderly. Thus, the focus more recently has been directed towards identifying truly low-risk patients who do not need any antithrombotic therapy, and all others with ≥1 stroke risk factors should be considered for oral anticoagulation therapy (whether as well-controlled warfarin or one of the new oral anticoagulant drugs), as the most effective means of reducing the risk of stroke and thromboembolism in AF.

**DECLARATION OF INTERESTS** Professor Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS Pfizer, Boehringer Ingelheim and Sanofi-Aventis.

**INTRODUCTION**

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, and has attracted much attention due to the strong and consistent relationship to stroke and thromboembolism. The presence of AF increases the risk of stroke five-fold, but the risk is dependent upon the presence of stroke risk factors, such as hypertension, diabetes, heart failure, etc.\(^1\)

The challenge is in defining patients who would best benefit from thromboprophylaxis, and how to deliver it in the most effective and safe way. The objective of this brief overview is to address this question.

**PATHOPHYSIOLOGY OF THROMBOEMBOLISM IN ATRIAL FIBRILLATION**

AF fulfils components of Virchow’s triad for thrombo-embolism, with evidence of abnormalities of blood flow (atrial stasis), abnormalities of vessel wall (with structural heart disease, endothelial damage, etc.) and abnormalities of blood constituents (with abnormal coagulation and fibrinolysis).\(^2\) Pathophysiologically, the composition of thrombus in AF is fibrin-rich (i.e. red clot) justifying oral anticoagulation (OAC) therapy, in contrast to thrombus in acute coronary syndromes (ACS) where the thrombus is platelet-rich (i.e. white clot), justifying antiplatelet therapy in the latter condition.

**WHAT DO THE EARLY TRIALS TELL US?**

Many clinical trials have shown the benefit of OAC therapy – essentially, the vitamin K antagonist (VKA) class of drugs (e.g. warfarin) for reducing stroke and thromboembolism in AF. In the meta-analysis by Hart et al.,\(^3\) the use of OAC significantly reduces stroke by 64% and all-cause mortality by 26%, compared to placebo. When compared to antiplatelet therapy, OAC reduces stroke by nearly 50%. In many of the early trials, strokes in the patients randomised to OAC usually occurred when patients were either not taking assigned therapy or had suboptimal anticoagulation. In contrast, antiplatelet therapy reduces stroke by 22% compared to placebo, a treatment effect size consistent with that seen for antiplatelet therapy in reducing stroke when given to patients with vascular disease.\(^4,5\) Given that AF commonly coexists with vascular disease, it is perhaps unsurprising that this small effect on stroke is seen. When confined to aspirin-only trials, aspirin non-significantly reduces stroke by 19% and all-cause mortality by 14%, compared to placebo. This 19% risk reduction with aspirin compared to placebo is driven by data from one single positive trial, the SPAF-I trial,\(^6\) which compared aspirin 325 mg daily with placebo. There was an important internal inconsistency for the aspirin effect between anticoagulation-eligible (94% risk reduction) and anticoagulation-ineligible (8% risk reduction, not significant) patients, which was

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**Declaration of Interests**

Professor Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS Pfizer, Boehringer Ingelheim and Sanofi-Aventis.

**Background paper**

http://dx.doi.org/10.4997/JRCPE.2012.S04
The individual patient meta-analysis by van Walraven et al. showed clearly that the risk of stroke starts to rise from age 65 onwards, and as patients got older, the absolute benefit of OAC increased while the absolute benefit of aspirin declined markedly. The risk of serious bleeding increased slightly with age, with a small absolute increase with antithrombotic therapy (either aspirin or warfarin) but the absolute increase in serious bleeding was far outweighed by the dramatic reduction in ischaemic stroke and cardiovascular events with warfarin.

**Low-risk patients**

Patients with AF at low risk do not derive any benefit from OAC compared to aspirin, and in the Japanese AF Stroke trial, there was no significant difference between aspirin and control for the reduction of the primary endpoint (stroke, thromboembolism etc.), with a trend to more bleeding and ICH events with aspirin. Unsurprisingly, aspirin is not even recommended for low-risk patients in the Japanese treatment guidelines for AF.

**ALTERNATIVE PHARMACOLOGICAL STRATEGIES TO THERAPEUTIC DOSE ADJUSTED VKA THERAPY**

Despite the effectiveness of OAC, warfarin is inconvenient and requires regular monitoring and dose adjustment. The VKAs have significant drug interactions as well as diet and alcohol restrictions. Serial INRs are also poorly predictive of bleeding risk.

Thus, other alternative strategies to OAC therapy have been tested, with the use of fixed or low intensity warfarin with or without aspirin, or other antiplatelet drugs (e.g. indobufen, triflusal).
The trials with fixed or low intensity OAC, whether in combination with aspirin or not showed that such a strategy was ineffective compared to therapeutic dose adjusted warfarin. One small trial (SIFA) suggested that the antiplatelet drug indobufen was associated with a similar rate of stroke to warfarin, but had less bleeding; however, this drug has never been tested in further trials in AF.

The antiplatelet drug triflusal was tested in combination with OAC in the NASPEAF trial, where combined antiplatelet plus moderate-intensity anticoagulation therapy significantly decreased the vascular events compared with OAC alone, with no significant difference in bleeding. No further trials with triflusal in AF have been performed.

**Aspirin-clopidogrel**

Aspirin-clopidogrel combination therapy has been tested against warfarin in the ACTIVE-W trial, and against aspirin monotherapy in the ACTIVE-A trial which was conducted in patients who were deemed unsuitable or had refused warfarin. The ACTIVE-W trial was stopped early due to a perception that the patient was unsuitable’ for warfarin (approximately 2%). Also, patients in ACTIVE-A were included on the basis of ‘physician perception that the patient was unsuitable’ for warfarin (50%) and patient preferences or refusal to take it in 26%, with contraindications at baseline (e.g. uncontrolled blood pressure) in 23% of patients.

In the ACTIVE-A trial, there was a significant 28% reduction in ischaemic stroke with combination therapy versus aspirin. However, aspirin-clopidogrel was associated with a rate of major bleeding that was broadly similar to that seen with warfarin (approximately 2%). Also, patients in ACTIVE-A were included on the basis of ‘physician perception that the patient was unsuitable’ for warfarin (50%) and patient preferences or refusal to take it in 26%, with contraindications at baseline (e.g. uncontrolled blood pressure) in 23% of patients.

**New OACs**

Given the various limitations of the VKA class of drugs, great efforts have been directed towards the development of new OACs that overcome the dosility of VKAs. These new OACs fall into two broad categories: the oral direct thrombin inhibitors (DTIs) and oral Factor Xa (FXa) inhibitors. Four large Phase 3 trials with new OACs have been published (RELY, ROCKET-AF, ARISTOTLE, AVERROES) and one is still ongoing (ENGAGE-AF, with edoxaban).

The first DTI, ximelagatran was tested against warfarin in the SPORTIF Ill and V trials, which showed non-inferiority of ximelagatran to warfarin. However, the drug has since been withdrawn due to liver toxicity. The next DTI, dabigatran was tested in two doses (110 mg twice a day [bid] and 150 mg bid) against warfarin in the huge RE-LY trial. The latter trial showed that dabigatran 110 mg bid was non-inferior to warfarin for the primary efficacy endpoint of reducing stroke and systemic embolism, with a significant 20% reduction in major bleeding events. Dabigatran 150 mg bid showed superiority (by 35%) over warfarin, with a similar rate of major bleeding events. Dabigatran 150 mg bid also resulted in significantly fewer ischaemic stroke events versus warfarin. Both doses of dabigatran were associated with significantly less haemorrhagic strokes and intracranial haemorrhage. There was a borderline reduction in all-cause mortality and a significant reduction in cardiovascular mortality. Total bleeding events (i.e. the composite of major plus minor bleeds) were significantly reduced with both doses of dabigatran, compared to warfarin. However, dabigatran 150 mg bid was associated with more gastrointestinal bleeds and both doses of dabigatran were associated with a non-significant numerical increase in myocardial infarction (MI) events. There was a significant excess of dyspepsia with dabigatran compared to warfarin.

The next new OAC with published Phase 3 data was the oral FXa inhibitor, rivaroxaban, tested against warfarin in the ROCKET-AF trial, which targeted high-risk patients with AF for inclusion. In this trial, rivaroxaban was non-inferior to warfarin for the primary efficacy endpoint of stroke and systemic embolism, although there was a significant reduction in haemorrhagic strokes. When tested on a more conservative intention to treat analysis, rivaroxaban was not superior to warfarin, although an on-treatment analysis did suggest that superiority to warfarin was achieved (by 12%) for reducing stroke and systemic thromboembolism. Rivaroxaban was non-inferior to warfarin for the primary efficacy endpoint of major plus clinically relevant non-major bleeds, with no significant difference in major bleeds, but an increase in gastrointestinal bleeding events. There was no excess of MI events compared to warfarin, and no significant difference in all-cause mortality or cardiovascular mortality.

The FXa inhibitor apixaban was tested against warfarin in the ARISTOTLE trial, which showed a superiority over warfarin in reducing stroke and systemic thromboembolism (by 21%), driven by a 50% reduction in haemorrhagic stroke and no significant difference in ischaemic stroke. Major bleeding was significantly less with apixaban (by 31%), as was total bleeding (major plus minor), with no excess of MI events. All-cause mortality was significantly reduced (by 11%) but there was no significant reduction in cardiovascular mortality. Apixaban was also tested against aspirin in a second Phase 3 trial, AVERROES, which included AF patients who had failed or refused VKA therapy. This trial was stopped early, due to a clear superiority of apixaban over aspirin 81 mg – 324 mg daily, and the rate of major bleeding or ICH was not significantly different between apixaban and aspirin. Apixaban was also significantly better tolerated (as reflected by treatment discontinuations) compared to aspirin or warfarin.
Patients with severe renal failure, defined as a creatine clearance of <30, were excluded from the trials with the new OACs. This is particularly relevant for dabigatran, which has a high renal excretion. Therefore, a dose adjustment with a lower dose (15 mg once daily [od]) used in patients with moderate renal impairment, where outcomes have been shown to be broadly similar to that seen with the 20 mg od dose used for other patients.\textsuperscript{38,39} In ARISTOTLE and AVERROES, there was a dose adjustment, with the use of the lower dose (2.5 mg bid) for patients with two out of three criteria (reduced BMI, age >80 and moderate renal impairment).

The new OACs have clearly changed the approach to thromboprophylaxis for stroke prevention in AF. Given the benefits of efficacy and safety, one Markov decision analysis model balancing the relative hazard of ischaemic stroke against the relative hazard of ICH concluded that the threshold for treatment with a new OAC (using the RELY data in the model) was an annual stroke rate of 0.9%, while the threshold for warfarin was 1.7%.\textsuperscript{35} Previously the strategy was to identify high-risk patients with AF so that these patients could be targeted for an inconvenient (and potentially dangerous) drug, warfarin. These new OACs offer convenience (no need for INR monitoring) and overcome the diet, drug and alcohol restrictions associated with warfarin. Various studies have also confirmed that these new drugs are cost-effective, given their safety and efficacy.\textsuperscript{34–36}

However, the fact still remains that these drugs are powerful anticoagulants and would work well if the patients are compliant and clinicians prescribe the drug correctly to appropriate patients. For example, elderly patients (age >80) are recommended dabigatran 110 mg bid given the significant age interaction with bleeding.\textsuperscript{35} While there is no necessity for anticoagulation monitoring for dose adjustment (unlike warfarin), coagulation tests such as the activated partial thromboplastin time (aPTT), ecarin clotting time (ECT) and thromboplastin time (TT) can be used to test for an anticoagulation effect with (for example) dabigatran.\textsuperscript{35,37} As there is no specific antidote for dabigatran, measures to manage bleeding are still largely supportive although haemodialysis is a possibility. One recent study suggested that the anticoagulation effect of rivaroxaban can be reversed with prothrombin complex concentrates (PCC), although this was a study in relatively young healthy individuals where effects on various coagulation tests were studied, with no relation to bleeding per se.\textsuperscript{40}

In summary, a paradigm shift has occurred to improve our ability to identify truly low-risk patients with AF who do not need any antithrombotic therapy, and those with one or more stroke risk factors who can be considered for OAC therapy, whether with well-controlled warfarin or one of the new OAC drugs.\textsuperscript{42} Hence, an important consideration is to improve our ability to comprehensively assess stroke risk in patients in AF.

**STROKE RISK STRATIFICATION**

While AF increased the risk of stroke five-fold, the risk is not homogeneous. The Stroke Risk in AF Working Group\textsuperscript{41} performed a systematic review of stroke risk factors, largely driven by data from non-VKA arms of the early clinical trials, and showed that prior stroke, hypertension, diabetes and female gender were significant predictors of stroke, as was moderate-severe systolic dysfunction on echocardiography, while history of heart failure and coronary artery disease were not significant risk factors. However, risk factors based on data from early trials had some inconsistency in definitions of some stroke risk factors and not all were systematically looked for nor recorded. The trial data therefore needed to be supplemented by additional evidence from epidemiological and cohort studies.\textsuperscript{44}

The simple CHADS\textsubscript{2} score is the most commonly used stroke risk stratification scheme, and has been validated in many studies (Table 1). This score is an amalgamation of two risk schemes from trial cohorts (the AF Investigators and the SPAF scheme) derived from the original early trials.\textsuperscript{46} As discussed above, the applicability of the early (now historical) trials to the general population has also been debated, given that only a minority of the patients screened (<10%) were randomised. In a recent systematic review and meta-analysis, the pooled c statistic and calibration analysis suggested only minimal clinical utility of CHADS\textsubscript{2} in predicting ischaemic stroke across all risk strata, and even concluded that further validation of CHADS\textsubscript{2} should perhaps be undertaken.\textsuperscript{46} While simple, the many advantages and disadvantages of the CHADS\textsubscript{2} score have been debated.\textsuperscript{47}

Various studies have shown that female patients with AF are at increased risk of stroke compared to men.\textsuperscript{48–50} Also, the presence of peripheral artery disease is a major risk factor for stroke and mortality, in the presence of AF.\textsuperscript{51–53} As mentioned above, the study by van Walraven et al\textsuperscript{13} clearly shows that age is an important driver for stroke risk, with the risk rising from age 65 upwards. Other cohort studies have clearly shown an increase in stroke risk at age 65–74 years,\textsuperscript{53–56} compared to younger subjects (age <65) and among these younger subjects, independent predictors of subsequent stroke were prior stroke, vascular disease and heart failure.\textsuperscript{59}
Older guidelines have divided stroke risk into low, moderate and high-risk categories, whereby high-risk patients could be targeted for warfarin, low-risk patients given aspirin and moderate-risk patients given aspirin or warfarin.55,56 This was in the era prior to the availability of new OACs with demonstrable efficacy over warfarin, and even better safety (and possibly, tolerability) over aspirin and warfarin, as well as the increasing recognition that aspirin had minimal beneficial impact on stroke prevention and may not be any safer. As mentioned above, the Japanese guidelines have removed aspirin from their stroke prevention guidelines for AF.19

Stroke risk is a continuum, and numerous studies assessing the predictive value of categorising AF patients into low, moderate and high-risk strata have shown that such an artificial classification only has modest predictive value for high-risk patients who subsequently suffer strokes.57,58 Many physicians would prescribe antithrombotic therapy in broadly similar proportions irrespective of the three strata.59,60 Given the shift towards getting better at identifying truly low-risk patients with AF (who do not need any antithrombotic therapy), rather than focusing on identifying high-risk patients, a major paradigm shift has been directed towards being more inclusive (rather than exclusive) of common stroke risk factors as part of any comprehensive stroke risk assessment.

The 2010 European Society of Cardiology (ESC) guidelines61 de-emphasises the artificial categorisation into low, moderate and high-risk strata, and recommends a risk factor based approach. The latter is based on defining major and clinically relevant non-major stroke risk factors (see Table 1) and these risk factors are within a new stroke risk score, CHA2DS2-VASc.62 This has consistently been shown to outperform the CHADS2 score in identifying truly low-risk patients with AF and at least as good as, and possibly better53,63 than the CHADS2 score in identifying high-risk patients who subsequently sustain a thromboembolic event. One recent analysis based on a large nationwide cohort dataset showed that there was a

### TABLE 1 The CHADS2, CHA2DS2-VASc and HAS-BLED scores for assessing stroke and bleeding risk (adapted from European Society of Cardiology Guidelines 2010).

<table>
<thead>
<tr>
<th><strong>CHADS2</strong></th>
<th><strong>Score</strong></th>
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<tbody>
<tr>
<td>Congestive cardiac failure (moderate to severe systolic left ventricular [LV] dysfunction, defined arbitrarily as left ventricular ejection fraction [LVEF] ≤40%)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension (blood pressure consistently &gt;140/90 mmHg or treated hypertension on medication)</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/transient ischaemic attack/thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td><strong>Maximum score</strong></td>
<td><strong>6</strong></td>
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<table>
<thead>
<tr>
<th><strong>CHA2DS2-VASc</strong></th>
<th><strong>Score</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive cardiac failure (moderate to severe systolic left ventricular [LV] dysfunction, defined arbitrarily as left ventricular ejection fraction [LVEF] ≤40%)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/transient ischaemic attack/thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (previous myocardial infarction [MI], peripheral arterial disease or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65–74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (i.e. female)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Maximum score</strong></td>
<td><strong>9</strong></td>
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<table>
<thead>
<tr>
<th><strong>HAS-BLED</strong></th>
<th><strong>Score</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (e.g. systolic &gt;160 mmHg)</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding tendency or predisposition</td>
<td>1</td>
</tr>
<tr>
<td>Labile International Normalized Ratio (INR) (only if on warfarin)</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (e.g. age &gt;65)</td>
<td>1</td>
</tr>
<tr>
<td>Drug (i.e. concomitant aspirin or non-steroidal anti-inflammatory drugs [NSAIDs]) or alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td><strong>Maximum score</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>
negative net clinical benefit analysis with warfarin, balancing ischaemic stroke against ICH only with a CHA2DS2-VASc score = 0, reflecting the truly low-risk status of these patients.64

The new ESC guidelines recommended use of the CHA2DS2-VASc score to complement the CHADS2 score, since those with a CHADS2 score of ≥2 were clearly high-risk and OAC is recommended (Table 2). In patients with a CHADS2 score of 0–1, more comprehensive stroke risk assessment was necessary, so components of the CHA2DS2-VASc score should be taken into consideration. Once truly low-risk patients (defined as CHA2DS2-VASc score = 0) were identified, no antithrombotic therapy is needed, and those patients with ≥1 stroke risk factors should have OAC as the preferred option, whether given as well-controlled warfarin or one of the new OAC drugs.

Given that guidelines should be applicable for >80% of the time, for >80% of the patients, the ESC guideline stroke risk assessment approach covers most of the patients we commonly see in everyday clinical practice, and considers the common stroke risk factors in such patients. The ESC guidelines61 also stress that antithrombotic therapy is necessary in all patients with AF unless they are age <65 and truly low-risk. Thus, some patients with female gender only as a single risk factor (still a CHA2DS2-VASc score = 1) would not need anticoagulation, if they fulfil the criteria of age < 65 and lone AF.

**BLEEDING RISK ASSESSMENT**

Decision-making for thromboprophylaxis needs to balance the risk of stroke against the risk of major bleeding, especially ICH. Until recently, bleeding risk assessment tools were based on complex formulae and/or derived from cohorts of general anticoagulated patients, rather than specifically from AF patients. Also, many risk factors for bleeding are also risk factors for stroke.45–47 Hence, guidelines from 2006 did not recommend the use of any bleeding risk score, and many clinicians were simply informally assessing bleeding risk in their patients, although it has been shown that physician risk assessment is poor.48

More recently, a simple bleeding risk score (HAS-BLED, Table 1) has been proposed69 and used in the ESC61 and Canadian70 guidelines. The latter guidelines recommend formal bleeding risk assessment, and in patients with a HAS-BLED score of ≥3, caution and regular review is recommended. The HAS-BLED score allows clinicians to make an informed assessment of bleeding risk (rather

<table>
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<tr>
<th>Risk category</th>
<th>CHA2DS2-VASc score</th>
<th>Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>One major or ≥2 clinically relevant non-major risk factors</td>
<td>≥2</td>
<td>OAC, given as well-controlled VKA (INR 2.0–3.0) or dabigatran*</td>
</tr>
<tr>
<td>One clinically relevant non-major risk factor</td>
<td>1</td>
<td>OAC or antiplatelet therapy† Preferred: OAC</td>
</tr>
<tr>
<td>No risk factors</td>
<td>0</td>
<td>Either antiplatelet therapy or no antithrombotic therapy** Preferred: no antithrombotic therapy**</td>
</tr>
</tbody>
</table>

**CHA2DS2-VASc**: cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 and sex category (female)  
**OAC**: oral anticoagulation, such as a vitamin K antagonist (VKA) dose-adjusted to an intensity range of INR 2.0–3.0 (target 2.5), or dabigatran  
**VKA**: vitamin K antagonist  
**INR**: international normalized ratio

*Dabigatran 150 mg bd if a patient is at low risk of bleeding (e.g. HAS-BLED score of 0–2) or dabigatran 110 mg bd considered if a patient is age ≥80, takes concurrent acting drugs (e.g. verapamil) or has a measurable risk of bleeding (e.g. HAS-BLED score of ≥3). When formally licensed, alternatives to dabigatran are as follows: (i) rivaroxaban 20 mg od, except in moderate renal impairment (creatinine clearance 30–49), 15 mg od; or (ii) apixaban 5 mg bid, except in patients with two of three criteria (BMI <20, age >80 and moderate renal impairment) whereby apixaban 2.5 mg bid should be used. The final labelling will determine the recommended doses of rivaroxaban and apixaban, when licensed.

†Antiplatelet therapy is given as aspirin-clopidogrel (if not at high bleeding risk) or less effectively, aspirin 75–300 mg.

In patients with one clinically relevant non-major stroke risk factor (i.e. CHA2DS2-VASc score = 1), dabigatran 110 mg bid may be considered (in view of a similar efficacy with VKA in the prevention of stroke and systemic embolism but lower rates of intracranial haemorrhage and major bleeding compared with the VKA and [probably] aspirin).

**Female patients with gender only as a single risk factor (i.e. CHA2DS2-VASc score = 1) would not need anticoagulation, if they would otherwise clearly fulfil the criteria of age <65 and lone AF (i.e. truly low-risk).’
than guesswork) and importantly, makes clinicians think of the correctable risk factors for bleeding, for example, uncontrolled blood pressure, concomitant use of aspirin/NSAIDs, labile INRs, etc.

In the net clinical benefit analysis by Olesen et al., patients with a high HAS-BLED score had a greater net clinical benefit with warfarin, given that higher risk individuals would have a much greater absolute reduction in stroke risk with warfarin, which would outweigh the small absolute increase in major bleeding events. This work has been extended by modelling these ‘real world’ data for net clinical benefit data balancing ischaemic stroke against intracranial haemorrhage in patients with non-valvular AF, for dabigatran, rivaroxaban and apixaban on the basis of recent clinical trial outcome data for these new OACs. This analysis showed that in patients with CHADS2 = 0 but at high bleeding risk, apixaban and dabigatran 110 mg bid had a positive net clinical benefit. At CHA2DS2-V ASc ≥ 1, apixaban and both doses of dabigatran (110 mg and 150 mg bid) had a positive net clinical benefit, while in patients with CHADS2 score ≥ 1 or CHA2DS2-V ASc ≥ 2, all three new OACs were superior to warfarin for net clinical benefit, irrespective of bleeding risk.71

CONCLUSION

What is the most effective and safest delivery of thromboprophylaxis in AF? Given recent developments in the field, the focus has been directed to improve our identification of truly low-risk patients who do not need any antithrombotic therapy, while those with one or more stroke risk factors should be recommended OAC, whether this is with well-controlled warfarin or one of the new OACs. Of the stroke risk schemes, the CHA2DS2-V ASc consistently outperform the CHADS2 score in identifying truly low-risk patients with AF; and is at least as good as, and possibly better than the CHADS2 score in

CHA2DS2-V ASc: cardiac failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 and sex category (male).

** Female patients with gender only as a single risk factor (i.e. CHA2DS2-V ASc score = 1) would not need anticoagulation, if they would otherwise clearly fulfil the criteria of age <65 and lone AF (i.e. truly low-risk).*

† If HAS-BLED score ≥ 3, caution and regular review is recommended, including management of correctable risk factors for bleeding. Regular review of risk factors for stroke is essential.

* OAC: oral anticoagulation
† At time of publication, only dabigatran is licensed for this indication as a new oral anticoagulant.
‡ Aspirin/clopidogrel combination or (less effectively for stroke prevention) aspirin.
identifying high-risk patients who subsequently sustain a thromboembolic event. Assessment of bleeding risk should also be mandated as part of the approach to thromboprophylaxis, and where relevant, the lower dose of new OACs (for example, dabigatran 110 mg bid), should be used. The HAS-BLED score is simple, well-validated and recommended in international guidelines. A suggested approach to stroke and bleeding risk assessment is shown in Figure 1.

REFERENCES
32 Eckman MH, Singer DE, Rosand J et al. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. CIRCOUTCOMES.110.958108


What are the differences between physician and patient expectation with regard to the management of atrial fibrillation?

1MR Fay, 2C Montaña
1General Practitioner, Westcliffe Medical Practice, Shipley, West Yorkshire, UK; 2Research Fellow, Leeds Institute of Health Sciences, The University of Leeds, Leeds, West Yorkshire, UK

ABSTRACT

Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with approximately 840,000 people suffering from it nationally. People with AF have an increased risk of stroke which can be mitigated effectively with the use of anticoagulant therapy. Nevertheless, evidence suggests that less than 50% of eligible patients are receiving this form of intervention.

Method: A comprehensive literature search was undertaken to assess the published evidence in order to understand why clinicians and patients underutilize an effective intervention such as anticoagulation in favor of the less effective antiplatelet agents.

Results: The decision to use anticoagulant drugs in patients with AF involves a consideration of the potential benefits versus the risks, inconveniences, and costs. There is however widespread variation in the importance placed on these factors across primary care practices, individual doctors and between and within different patient groups. There is a paucity of literature designed to examine patient expectations. Available studies suggest that patients are prepared to be placed at a higher risk of bleeding than their prescribing doctors would be prepared to accept. Given that this judgement depends on a range of factors, it is not surprising that attempts to understand clinician’s barriers to prescribing take precedence.

Conclusion: The barriers to anticoagulation can be identified, but we still don’t understand the importance that clinicians and individuals give them. These barriers continue to limit the use of anticoagulation therapy, a potentially beneficial treatment. Due to these limitations it is unclear what impact the increased range of oral anticoagulants and the alteration to the Quality and Outcomes Framework (QoF) will have on the incentive to primary care physicians to anticoagulate those at risk.

DECLARATION OF INTERESTS Dr Fay has served as a consultant for Boehringer Ingelheim, Bayer, Bristol Myers Squibb and Sanofi-Aventis. Despite evidence showing the benefit of anticoagulants, observational studies have consistently reported an overuse of antiplatelet agents and an apparent under-use of anticoagulant drugs in these patients. The available data show that of those patients with AF and no contraindications to warfarin therapy, only 15% to 44% are prescribed warfarin. The unpublished Guidance on Risk Assessment and Stroke Prevention for Atrial Fibrillation (GRASP-AF) data shows this to be 15–64% in England.

Reviews of patient records frequently reveal that only around 25% of patients meeting the criteria for anticoagulation are actually receiving it. Around 55% of these patients would still not be considered for anticoagulation even after a review, due to perceived contraindications. Another 20% of patients indicated for treatment are not currently receiving it. A review of patient records can often trigger changes to their treatment.
LITERATURE OVERVIEW

A comprehensive review of barriers to warfarin use in AF published by Ingelgard et al in 2006 captures much of what is currently known about factors influencing prescribing decisions. They identified, coming mainly from the USA, Australia, Canada and mainland Europe. Known barriers can be described under four main themes including: 1) medical characteristic factors; 2) patient ability to take the treatment and adhere to monitoring requirements; 3) patient preferences; and 4) healthcare system barriers. The barriers to prescribing in the UK may be the same but this is not known for certain.

It is clear that the decision to use anticoagulant drugs in patients with AF involves a consideration of the potential benefits versus the risks, inconveniences, and costs. There is however widespread variation in the importance placed on these factors across primary care practices, individual doctors and between and within different patient groups. There is also a lack of agreement on the legitimacy of cited contraindications to prescribing, such as risk of falls or age of patients.

The extent to which each or all of these factors influence prescribing decisions and treatment is not known, although assessment of risk (haemorrhage or bleeding episode) is a key factor. However, there are wide variances in the thresholds for assessment of risk both between and within studies. Physicians who see higher numbers of patients with AF are prepared to take more risks regarding anticoagulation although more experienced practitioners, i.e. cardiologists, overestimate the benefit of using anticoagulation drugs in low-risk patients. Increased experience as a registered medical practitioner however is generally related to poorer performance on classifying patients according to risk of stroke. GPs in the UK tend to overestimate both the number of their patients who meet eligibility thresholds for anticoagulant therapy and also the number of their patients currently receiving warfarin.

At the same time, attempts to change prescribing practices, for example the introduction of quality indicators, education including knowledge and skills training, computerised feedback (although this has been criticised as consultation outcomes often need to vary from the decision support software’s recommendations), risk reduction strategies such as patient-specific information aids to help prescriber decision-making i.e. Mini Mental State Examination (MMSE) to help with cognition rating and shared decision-making, paced information with the opportunity to check understanding at a later time, and the introduction of practice-specific protocols all show some success, although they are often limited to the specific setting, with little sustainability or generalisability.

One possible reason for these difficulties is that perhaps we do not fully understand the behavioural determinants (constructs which affect behaviour) prior to initiating interventions aimed at behavioural change, or even know that the constructs are amenable to change; hence the intervention may not be delivered through the most relevant behaviour change technique available.

Perhaps we will see improvements in the proportion of eligible patients receiving anticoagulants now that alternatives to warfarin exist. Two licensed agents are now available in the form of the direct thrombin inhibitor, dabigatran and the factor Xa inhibitor rivaroxaban, and a further Xa inhibitor, apixaban will soon come to market. All three agents have been shown to be non-inferior to warfarin however all have also demonstrated a lower intracerebral bleed rate. These drugs will be more convenient in clinical use as there is no need for regular assessment of their anticoagulant effect and have set dosing (although some advice is required for dose adjustment if given for impaired renal function and extreme age). However they are not without risk if not used correctly and dabigatran in particular is very expensive. Most healthcare organisations across the UK have produced guidelines to encourage cost beneficial use. There is good reason therefore to believe that most of the impetus for management (or lack of management) of atrial fibrillation comes from GPs and hospital doctors; whether patients are offered treatment or not depends largely on their skills and abilities. We know that patients find this decision complex and there are reasons why they might justifiably avoid an effective treatment; however, many inappropriate variations in practice cannot be explained by patient expectations. We need to obtain a better understanding of how we can encourage more doctors to offer anticoagulants as a treatment option.

The literature is not presented in a way that facilitates current understanding of why and how patients remain under-treated. Previous research attempts have focused on identifying the barriers to warfarin use and preferences for treatment options, while widespread consultation with key prescribers and patients on how to improve warfarin use and its day-to-day management is lacking. Research to date mainly consists of retrospective cohort analysis and observational studies, prospective observational studies, point-prevalence studies, literature reviews and medical record and chart reviews, patient quality of life surveys and cross-sectional postal surveys and questionnaires (many of which involve the use of clinical vignettes). However, asking prescribers (usually doctors) whether they would apply barriers to specific case examples, or asking them about the reluctance to prescribe if a barrier is theoretically present, are artificial scenarios and respondents give answers that are expected. We do not know how these barriers are applied in real life scenarios. There is some evidence supporting the idea that intention varies from actual
A systematic review published earlier this year focuses on the attitudes of physicians towards anticoagulation but relies on self-reported practice and fails to include qualitative literature within their scope. It could be argued based on these studies, that it is only when we speak to GPs about specific patients that are eligible but not given warfarin that we begin to understand the interplay between known barriers and treatment decisions.

**QUALITATIVE LITERATURE**

**Summary**

**GP interviews**


Lipman et al were interested in how GPs with an active interest in research and evidence-based medicine make decisions about anticoagulation in patients with AF. They conducted semi-structured interviews with 11 GPs. A constructivist approach was taken to analysis and interpretation. Two key themes materialised: evidence and professional role. Key findings were:

- There is wide variation in perception of the evidence, which is influenced by experience, attitudes and variable knowledge of the literature.
- Shared decision-making with the patient is paramount and this often results in antagonism towards prescriptive clinical guidelines.
- Hospital doctors have a strong influence on decision-making, and they are often seen as difficult to challenge and poor at communicating.


Short et al were interested in developing and designing a computerised decision support system for the management of stroke patients. The same 15 GPs in the study above underwent a second qualitative interview and questionnaire after having access to the support system. Hypothetical patient vignettes were used and it was determined that GPs were more certain about their decision-making, which was more in line with national guidelines. However, it is still not clear how this support system would be used in a real life scenario, although GPs felt that it would improve their dialogue with patients.


Oswald and Bateman observed the process of practitioners assimilating research evidence. In this study, lead GPs from six different practices provided information on the practicalities of agreeing a practice protocol and implementing it. Key findings include:

- Judgement over what constitutes a ‘key source’ to which reference must be made before a protocol is developed varies between practices and practitioners. The amount of time required to access information and the confidence in the appraisal of research papers also differs; the applicability of evidence to individuals under their care varies; the level of confidence in the lack of harm was different for everyone. There were also doubts about the durability of current research evidence. Harmonising with guidance from local specialists was also a challenge. GPs also rated published research evidence differently.
- There were variations in the assessment of risk, particularly for aspirin (doctors may have a lower threshold of what constitutes risk than that documented in studies). GPs believe that the decision is explicitly at the doctor’s discretion. There was disagreement over the criteria for referral for specialist opinion. The explicit involvement of patients and carers in decision-making was also a topic of debate.
- There were practical difficulties in maintaining momentum and doubts about the value of the enterprise and the sustainability of the proposed protocol.
- Reasons for not prescribing warfarin for patients were included, although their patient samples were not typical of under-warfarinisation rates reported in other studies, i.e. in this study three-quarters of those eligible were being given warfarin:
  - Prior medical knowledge of physicians.
  - Opinions of patients and others (i.e. local specialists).
  - A practitioner’s opinions around quality of life issues and whether individuals are covered by the protocols.

**Secondary care interviews**


Anderson et al were interested in understanding physicians’ behaviour and attitudes in decision-making about AF and the use of antithrombotics. They used a semi-qualitative questionnaire and an interview-based approach with 14 senior clinicians, and analysed the results using grounded theory (although closer inspection of the article reveals that the term is used loosely for the purposes of this study). Each participant was presented with five clinical vignettes illustrating a range of risks and
benefits to antithrombotic treatment choices for AF and stroke prevention. There was marked variation in levels of uncertainty and doubt about risks versus benefits, concerns about knowledge, and the role of the patient in decision-making. However, the level of information given in the vignettes was often not enough for clinicians to make an informed decision, a criticism that has been levied at other studies using similar methods.16

Group interviews


Bajorek et al were interested in identifying health professionals, patients and their carer’s views on strategies to improve the use and management of warfarin in older patients with AF. They used group interviews involving 14 patients, six community pharmacists, nine hospital pharmacists, three carers, 12 specialists, eight GPs and 11 nurses. Key barriers to use and management included:

- Appropriateness of guidelines to GP caseloads.
- Support services for GPs and patients, including dissemination of evidence to GPs and enlisting allied health professionals in patient management.
- Availability and appropriateness of information for patients.


Bajorek et al explored the barriers to warfarin use from the perspective of nurses working in elderly care. A semi-structured group interview was conducted with 11 nurses, and the results underwent a thematic analysis. Five main themes were identified: perceived patient attitude towards warfarin, barriers to the use of warfarin, expressed lack of confidence in the processes involved, nurses’ role in warfarin use, and strategies to improve warfarin use. They concluded that nurses feel that they have limited capacity to intervene and that they are a potentially underutilised resource for both patient support and prescribers.

Patient interviews

1 Dantas GC, Thompson BV, Manson JA et al. Patients’ perspectives on taking warfarin: Qualitative study in family practice. BMC Fam Pract 2004; 5:15.46

This study used face-to-face interviews with 21 older patients who had been taking warfarin for a minimum of six months. Participants were patients at a family practice clinic situated in a large, tertiary care teaching hospital. A semi-structured interview guide covering four main thematic areas was used: decision-making, knowledge/education, impact and satisfaction. Data were analysed according to the principles of content analysis. Main findings include:

- Patients tended to have minimal input into the decision to initiate warfarin therapy, instead relying largely on the physicians’ expertise.
- There appeared to be low retention of information about the therapy; half the patients in the sample had only a superficial level of understanding of the risks and benefits.
- Patients reported a high level of satisfaction with the care provided and a low level of impact on their day-to-day lives.

BEHAVIOURAL DETERMINANTS

Factors such as knowledge, level of skills, social/professional role and identity and beliefs about capabilities are well-documented in qualitative literature. Awareness of guidelines and recommendations is not enough to influence practice. There are a number of elements that influence what GPs think about the evidence e.g. attitude, credibility, beliefs in the extent to which it should influence behaviour and compatibility with professional standards and identity. There are also differences in how GPs view the consequences of treatment to themselves and their patients (and their beliefs about patient capabilities). Social influences such as power and hierarchy within the healthcare system must also be considered. There is a lack of clarity over the influential nature of different professionals within the entire system: hospital doctors have ‘power’ over GP prescribing decisions; nurses with ill-defined and variable roles within warfarin management plans.

The environmental context and resources available are also issues i.e. time constraints and lack of systems for monitoring and reviewing patients (although the extent to which these factors influence prescribing is also influenced by the GP’s attitude/beliefs about priorities for their patient). It has been suggested that computerised decision-making tools may help to focus GP/patient dialogue within the reality of time constraints, although the inflexibility inherent within these systems limits behaviour. Inability to work closely with other colleagues and competing time constraints are also a factor; likewise a reluctance to send more patients to attend hospital clinics and a lack of resources to assist with practice-based supervision are also important issues.

The applicability and appropriateness of information available for patients (how the GP conveys this information, the accuracy of it and/or the patient’s understanding) will also influence treatment. Information on patient resistance to treatment is rarely referred to within the present literature, indicating that this may be
lacking (although this was not a search parameter for our purposes). Devereaux et al demonstrated that patients at high risk of AF place more value on the avoidance of stroke and less value on the avoidance of bleeding than the physicians who treat these patients, thus indicating that even if risk factors are known, the patient’s knowledge and belief about these risk factors is as important as the doctor’s beliefs to the management outcome. Shared decision-making is seen as necessary within the literature although we are not clear about what factors facilitate and/or hinder this process in warfarinisation.

The motivation for and the aims of preventative medicine are rarely discussed within the literature, particularly in terms of how little benefit GPs can see from their efforts. Any harm on the other hand remains visible and carries practical consequences for the doctor and patient. In the Oswald study, 27 patients could be prescribed warfarin, preventing 1–2 strokes per year. Even if the full benefit from anticoagulation were felt within her/his population, a GP’s application of evidence will prevent a few strokes, of which, by definition he/she will be unaware. Finally, assessment of risk is a key factor that many patients give them. These barriers continue to limit the use of anticoagulation therapy, a potentially beneficial treatment.

WHAT IS NOT KNOWN

Barriers to anticoagulation therapy are known, but not the extent to which each applies.

- Where the barriers are found is not known, e.g. do they lie primarily with GPs or hospital doctors. There may be unknown obstacles that apply to healthcare management in the NHS, such as lack of ownership of the problem by primary or secondary care.

- Hospital specialists are often included in research into barriers, examination of the level of congruence/divergence between hospitals and GPs in terms of treatment is missing (although the scoping work search did not necessarily include studies from secondary care at this stage).

- We do not know how the barriers apply to real life scenarios.

- We lack data on patient objections to being prescribed warfarin, although their preference is a key determinant. Differences in preferences are difficult to predict, vary in direction and magnitude and are often specific to a particular condition.

- We have yet to see the impact that recently introduced prescribing indicators has on prescribing practice.

- We don’t know the extent to which a stroke risk stratification algorithm is actually used in practice.

- There may be differences and similarities between barriers to initiating prescription and unsuccessful dose maintenance.

- The extent to which patient samples in clinical trials represent clinical caseloads of GPs is not known.

- Research on cultural/ethnic barriers to prescribing is also required.

- Studies of patients recently prescribed warfarin are missing from the literature.

CONCLUSION

Despite a large amount of evidence showing the link between AF and ischaemic stroke, steadily increasing evidence regarding the benefits of anticoagulation and the development of tools to stratify risk, the uptake in those who would benefit from anticoagulation therapy remains poor.

The barriers to anticoagulation can be identified, but we still don’t understand the importance that clinicians and individuals give them. These barriers continue to limit the use of anticoagulation therapy, a potentially beneficial treatment.

REFERENCES


51% of patients at high risk (CHADS2 >1) were care trusts in more than 47,000 patients with AF; only applied nationally in over 310 practices in 48 primary care trusts. The CHADS2 score in identifying patients at low risk of hospital with AF, showing its superiority to the traditional CHA2DS2VASc score among patients admitted to AF. Anticoagulation uptake remains poor in high risk patients. BMJ 2011; 342:d1153.12


Other references retrieved that may contribute to development of quantitative method


Olesen et al validate the predictive value of the CHA2DS2VASc score among patients admitted to hospital with AF, showing its superiority to the traditional CHADS2 score in identifying patients at low risk of stroke.44 However, even among patients with identified AF and identifiable risk factors, the uptake of anticoagulation in the UK continues to be worryingly low.

A primary care database interrogation tool developed by the West Yorkshire Cardiac Network was used to calculate CHADS2 score among patients with AF. It was applied nationally in over 310 practices in 48 primary care trusts in more than 47,000 patients with AF; only 51.4% of patients at high risk (CHADS2 >1) were receiving warfarin. A cohort of 228,000 patients in York Primary Care Trust were assessed for contraindications to warfarin. Only 27% of the untreated high-risk population had absolute contraindications to warfarin. The most common reason for not giving warfarin to them was the reluctance of physicians to prescribe it. Thus the barrier to prescribing anticoagulants even to high-risk patients must be overcome. Typically, the current iteration of the Quality and Outcomes Framework for AF does not indicate the value of any risk stratification. Even among high-risk patients, it rewards treatment with aspirin or warfarin equally, despite considerable evidence of the superiority of warfarin at no excessive risk of bleeding.44 The undoubted value of a CHA2DS2VASc score in detecting patients at low-risk should not deflect from the main task of appropriately treating high-risk groups, however they are identified.


Introduction and objectives: Whenever new GP-led anticoagulant clinics were planned to take over the care of well-controlled patients who had previously obtained their supply of warfarin from a pharmacy-led hospital anticoagulant clinic, it was found that the lists of patients

Differences between physician and patient expectation

Purpose: The objective of this study was to quantify the association between optimal warfarin anticoagulation, as determined by time in therapeutic range, and the incidence of stroke in patients newly diagnosed with AF in the natural setting of clinical practice.

Methods: We conducted a population-based cohort study with a nested case-control analysis within the United Kingdom’s General Practice Research Database population. The cohort included all patients at least 18 years of age with a first ever diagnosis of AF between 1 January 1993 and 31 December 2008. During follow-up, all subjects who experienced a stroke were identified as cases. Up to ten controls selected from the cohort were matched to each case based on year of birth, sex, date of cohort entry, and duration of follow-up. A new algorithm, incorporating both international normalised ratios (INR) and warfarin prescription information, was created to categorize patients according to their time in therapeutic range. Conditional logistic regression was used to estimate rate ratios (RR) of stroke associated with the use of warfarin and time spent in different levels of anticoagulation. All RRs were adjusted for CHADS2 score and other relevant confounders, which included body mass index, excessive alcohol use and smoking status.

Results: The cohort comprised 74,095 patients newly diagnosed with AF, of whom 5,996 experienced a stroke during a mean follow-up of 3.8 years. The overall stroke rate was 21.3 per 1,000/year. Patients currently exposed to warfarin were at a decreased risk of stroke compared with patients who were never exposed to warfarin (adjusted RR: 0.63, 95% CI: 0.58, 0.68). When current warfarin users were categorised according to their level of anticoagulation, only those within therapeutic range (INRs between 2 and 3) were at a decreased risk of stroke (adjusted RR: 0.61, 95% CI: 0.52, 0.72), while no association was found for those below or above therapeutic range (adjusted RR: 0.85, 95% CI: 0.68, 1.06 and adjusted RR: 0.93, 95% CI: 0.69, 1.25, respectively).

Conclusions: The results of this large population-based study provide further evidence that warfarin therapy decreases the risk of stroke in patients with AF. However, this decreased risk was only observed in patients within the recommended therapeutic range.

investigated to determine if the practice had highlighted
record (used to generate repeat prescriptions) was
‘repeat template’ prescribing field of the electronic
discharge letters and outpatient clinic letters. The main
warfarin in the form of consultant discharge summaries,
and registered information sent by the hospital about
check was made to confirm that practices had received
referral by the hospital to the pharmacy-led clinic. A
period of at least four weeks following each new patient
records either in hospital or at the GP practice after a
Method:

The audit involved accessing GP electronic
records either in hospital or at the GP practice after a
period of at least four weeks following each new patient
referral by the hospital to the pharmacy-led clinic. A
check was made to confirm that practices had received
and registered information sent by the hospital about
warfarin in the form of consultant discharge summaries,
discharge letters and outpatient clinic letters. The main
‘repeat template’ prescribing field of the electronic
record (used to generate repeat prescriptions) was
investigated to determine if the practice had highlighted
that warfarin was being provided by a third party and
that the record relating to anticoagulation was
comprehensive. This included checking that the practice
was aware of the duration of anticoagulant therapy and
in patients taking aspirin, determining if this had stopped
or continued to be prescribed.

Results and discussions: From a sample of 84 referrals
by the hospital to the pharmacy clinic, 51 patients
belonged to GP practices using SystmOne. From this
latter group, there was only one instance where hospital
communications had not been scanned onto the
electronic record by a GP practice. Nevertheless, in 25
cases (49%), warfarin had not been entered on the
repeat template, possibly because the GP was not being
asked to prescribe the drug. This meant that as details of
warfarin use were consigned to less frequently accessed
sections of the electronic record, the GP might easily
overlook that anticoagulation had begun. Information
about the duration of warfarin treatment was invariably
absent. There were 18 cases where patients had remained
on aspirin unintentionally and two instances where the
hospital had not indicated if it should stop. Overall,

identified in each GP practice as taking anticoagulants
were different to those held by the hospital. GPs were
not sure which of their patients took warfarin. When
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They attempt to measure physicians’ reluctance to prescribe warfarin because it is already being provided in hospital, then there is a risk that their practice records about anticoagulation may remain incomplete. Retinoids, certain drugs for metabolic diseases and oral chemotherapy may also exclusively be supplied by hospitals, and possibly GPs may similarly not always be aware of their use. Anticoagulant clinic pharmacists could themselves correct the GP electronic record, but this was not a solution for those practices with no electronic link to the hospital. Instead a form was introduced for GPs formally to acknowledge that warfarin was recorded on their patient’s repeat template as being supplied by the hospital.

**ANNEX B**

Critique of Ingelgard et al’s paper

- This paper provides a useful summary of known barriers to warfarin use, although I suspect very little of the literature reviewed was UK-based.
- The authors identify 41 barriers, discussed under four broad themes: 1) patient medical characteristics; 2) healthcare system factors; 3) patient capability and 4) patient preference.
- The extent to which each of the identified themes influenced prescribing decisions was measured at two levels by 35 physicians; physician level (10 point likert scale listing identified barriers) and patient level (barriers scaled as non-critical to critical).
- They attempt to measure physicians’ reluctance to prescribe on a general level and their actual behaviour with respect to anticoagulant prescriptions in their own AF patients, which should provide for a better understanding of attitudes vs. reality. However, there are several problems with their method that make the interpretation of their results difficult:
  - They contextualise the limitations of previous studies i.e. non-structured approaches for eliciting barriers and use of clinical vignettes without the use of patient-level data. However, they use clinical vignettes in their measures (i.e. doctors are asked questions on the reasons for not prescribing warfarin based on AF patient medical records provided by the research team).
  - Less than half of their sample (n=35 physicians; 15) provided data about their AF patients. This was stated as two per physician although only 24 cases were recorded. Does this mean that there were actually 12 physicians or that some physicians had only one patient on their caseload with AF (and would this be typical?).
  - The factor that most strongly influenced physicians decisions not to prescribe was severe bleeding <3 months ago (N= 30, don’t know what happened to other five) while the most prevalent critical barriers (not sure what is meant by this or how this was perceived by physicians) in specific AF patients was patient unwilling to undergo repeat testing (N= 24, only 68% of sample, again don’t know why number reduced).
  - It is not clear how many of the responses to patient level data were to actual physicians’ own patients or those generated by the research team – so cannot tell if this data is dominated by responses to clinical vignettes.
  - In patient-level data, a bleeding episode >3 months ago is reported as a barrier as often there is difficulty in getting to monitoring appointments. It is difficult to understand how a medical characteristic would be just as influential as a transport issue in a prescribing decision. It may be that wide variation in physicians’ prior experiences accounts for these different barriers seemingly having equal precedence. Interestingly, severe bleeding episode within the past three months was reported less frequently (3, 12.5%) as a critical barrier compared to patients unwillingness to undergo repeat testing (7, 29.2%). This may be because physicians recognised their patient characteristics in the scenarios.
  - They state that physicians say they work around healthcare system barriers. This was because none of these barriers appeared among the 15 barriers of most concern to clinicians. These barriers were thought to be rare (e.g. lack of reimbursement for phone follow-up with a patient and increased office workload) and were unlikely to prevent a patient from receiving warfarin. It is difficult to consolidate this with findings from other studies where these barriers are instrumental in prescribing decisions for patients. At the same time, they list lack of experience and training in managing warfarin therapy as a barrier that physicians work around, and it is difficult to see how a physician lacking the knowledge and skill would be able to initiate a prescription, or openly admit to lack of competence in this area (particularly when they have volunteered to take part in the study).
  - There are wide variations in individual clinicians’ rating across all barriers.
  - State that there are 15 barriers of most concern, although only 14 are listed.
  - Don’t state how other barriers rated in relation to the 14 concerned.
  - Some of the categorisation of barriers may be different in the UK. For example, they list
difficulty in getting to warfarin monitoring or lab appointments as a patient capability; in the UK this may be seen as a healthcare system factor. Likewise, other capabilities may really be related to the costs incurred to the patient in non-UK healthcare systems.

» They list ‘patient unwilling to undergo repeat testing’ as a patient preference, but again this may be related to costs incurred to the patient.

» I am not certain which patient medical characteristics are actual contraindications or imposed by the physicians (fear of litigation may influence categorisation for example). They also list stroke prophylaxis as not being a primary concern in patients’ overall treatment goals (this must be influenced by the nature of the relationship with the patient).

» Physician characteristics may be biased. For example, the reported percentage of AF patients receiving warfarin was 68.8% (SD 19.5). However literature indicates that up to 60% of patients indicated for warfarin do not receive it. Their percentages of patients using different medications are erroneous (102%).

» They state that one of their aims is to understand underlying reasons for several abstract barriers in the literature such as non-compliance, age and dementia. However they do not address this in their results and discussion. Age is believed to be an independent barrier and not fully explained by barriers already on the list – not sure what they mean by this.

» The authors conclude that patient preference is a major factor limiting warfarin use. Precise reasons for this were not explored, and it is not clear to what extent these barriers exist within our healthcare system.
**OVERVIEW: EPIDEMIOLOGY, SCREENING AND HIGH RISK POPULATIONS**

J Mant
Addenbrooke's Hospital, Cambridge, UK

**EPIDEMIOLOGY OF AF**

AF is present in about 1% of the population. The prevalence rises with age, with over 8% of people aged 65 and over in AF. In this age group, which accounts for about 85% of the total number of cases of AF, the incidence of new cases is about 1.5% per annum. Much AF is associated with underlying cardiac disease. The prevalence of AF is expected to rise both as a result of improved survival of people with ischaemic heart disease and demographic shift. It is associated with a five-fold increase in stroke risk and reduced survival.

**SCREENING AND DETECTION OF AF**

Feeling the pulse is moderately sensitive (87–97%), but not very specific. 70–87% of people with an irregular pulse do not have AF. New devices such as modified sphygmomanometers and finger probes are more accurate than feeling the pulse, but their cost-effectiveness is uncertain. It is more cost-effective to opportunistically screen than systematically screen for AF. The reference standard for diagnosing AF is the ECG interpreted by someone with appropriate expertise. Computer software is not currently sufficiently accurate. Consistently high accuracy can be achieved by healthcare professionals with appropriate training. If paroxysmal atrial fibrillation is suspected, longer periods of monitoring will detect more cases of AF. Further research is needed on the cost-effectiveness of long-term monitoring devices and the clinical significance of AF detected in this way.

**WHO IS ‘HIGH-RISK’?**

Several factors have been identified that increase the risk of stroke in AF. These have been aggregated into risk scores, such as CHADS\(_2\), and CHA\(_2\)DS\(_2\)-VASc, which can classify people according to risk. The relatively poor performance of these scores suggests that they might be best used as binary scales (high risk – yes/no), with for example all people aged 75 or over, or with a history of stroke/TIA being regarded as high-risk.

**References**

1 Fitzmaurice DA 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. [http://dx.doi.org/10.1136/bmj.39280.660567.55](http://dx.doi.org/10.1136/bmj.39280.660567.55)


**COST AND ECONOMIC BURDEN OF ATRIAL FIBRILLATION**

TP van Staa
London School of Hygiene & Tropical Medicine, London, UK

Atrial fibrillation (AF) is the most common sustained disorder of cardiac rhythm. Various new anticoagulation and antiarrhythmic treatments are being investigated for the treatment of AF. Before novel treatments can be used widely in actual clinical practice, the cost-effectiveness of such novel treatments may need to be determined. We have evaluated the resource utilisation for AF and control patients in the General Practice Research Database (GPRD). GPRD currently includes data on over 10 million patients and has been shown to be representative of the UK population and has been linked to hospital data. Consistent with other studies, AF patients had significantly higher resource utilisation than controls. Resource utilisation increased with greater NICE stroke risk strata (graded as low, moderate or high based on associated risk factors). Both current warfarin and aspirin users had higher resource utilisation than control patients. Resource utilisation remained high amongst AF patients who discontinued therapy. The mortality rate was significantly higher in AF patients than controls, deaths due to circulatory system disease were increased four-fold and cancer deaths were doubled. All-cause and circulatory mortality rates, as well as rates of clinical outcomes, were related to the NICE stroke risk schema. There was large heterogeneity in resource utilisation between AF patients. Higher resource utilisation was evident in patients at higher risk of stroke, and remained where antithrombotic therapy was discontinued. The mortality risk in AF was increased substantially, both for cardiovascular and non-cardiovascular causes of death, indicating a large unmet medical need.

**PREVENTING PRECURSORS OF ATRIAL FIBRILLATION**

P Kirchhof
University of Birmingham, Birmingham, UK and University Hospital, Münster, Germany

Atrial fibrillation (AF) is the most common sustained arrhythmia, and its impact on health is growing in ageing populations. Current therapy, even if done within trials, results in high residual rates of stroke (1.5% per year in trials), death (3–4% per year), and unplanned hospitalizations (up to 20% per year\(^2\)). Furthermore, all current AF therapies carry risks, e.g. bleeding, proarrhythmia, bradycardia, or procedural complications. Current rhythm control therapies target known factors that cause AF, such as electrical remodeling, structural remodeling, and pulmonary vein ectopy."
Clinical conditions

Atrial damage predisposing to AF occurs before AF is diagnosed. The causes of this damage offer opportunities to prevent AF. Established conditions causing AF are age, male gender, hypertension, valvular heart disease, heart failure, diabetes mellitus, and overt coronary artery disease. In addition, height, obesity, kidney disease, lung disease, and thyroid dysfunction may also contribute.

Genetic factors

Most of the genetically conferred cardiomyopathies also cause AF. Furthermore, several genome-wide analyses associate AF in the population with genetic modifications on chromosome 4q25, close to the pitx2 gene. Pathophysiological studies confirmed that pitx2 dysfunction contributes to AF and to ‘loss of leftness’ in the left atrium. These observations call for further research.

Early therapy of AF

The concept of atrial remodeling has an established role in the maintenance of AF (‘AF begets AF’). Hence, an early initiation of rhythm control therapy may help to prevent recurrent AF. This hypothesis requires validation in trials.

In summary, several clinical conditions predispose to AF while additional, genetically conferred precursors of AF will be characterised in the near future. The concept of early rhythm control therapy appears attractive to stop the vicious circles that maintain AF. This concept is currently tested in the EAST trial (www.easttrial.org).

References


SESSION 2 – SHOULD THE TREATMENT OF AF BE TARGETED TOWARDS CONTROL OF RHYTHM, RATE OR BOTH?

RATE VERSUS RHYTHM – WHO SHOULD DECIDE AND HOW SHOULD WE DO IT?

N Sulke
Eastbourne District General Hospital, Eastbourne, UK

The answer to the rate versus rhythm debate in atrial fibrillation (AF) has occupied the medical profession for several decades. Successful rate or rhythm control does provide symptomatic relief for most patients. Instinctively the maintenance of sinus rhythm (SR) would seem preferential over rate control alone, however the current available rhythm control technologies are far from perfect incurring significant risks to the patients with moderate long-term success rates. It is not certain whether further benefits are gained, beyond symptom control, from the achievement of AF extinction. Attempting rhythm control is therefore not appropriate in all patients and the risks and benefits for each individual need to be assessed and discussed.

Rate control methods include medication, pacemakers and AV node ablation and risks are easy to define. These techniques usually entail low iatrogenic risk and achieve good symptomatic success and protects against tachycardia related cardiomyopathy. However the patient’s AF remains and the arrhythmia burden is likely to progress with time. The consequences of this are not clear and the stroke risk remains undiminished.

Defining the risk-benefit ratio for rhythm control is more complex due to varying study methodologies for achieving sinus rhythm, varying AF types and varying study endpoints. Anti-arrhythmic drugs with pro-arrhythmic side-effects and long-term toxicity, D/C cardioversion (DCCV) with poor long-term efficacy and AF ablation with moderate success but high procedural risks are all options. Large early studies, such as AFFIRM, compared attempts to control rate versus attempts at control of rhythm for all AF types using medication and DCCV. There was no additional benefit from rhythm control strategies, however interpretation of this data to an individual patient in 2012 is difficult. Other analyses comparing the presence of AF to the successful elimination of arrhythmia is open to the bias that fitter patients maintain SR and hence do better than the less fit patients in whom the arrhythmia persists.

More recent studies are more specific in their methods and endpoints. Registry data that has been retrospectively compared to matched controls suggests a favourable
outcome for patients undergoing AF ablation. Large randomised trials are needed to confirm these findings. Current guidelines imply that if SR can be achieved at a low risk then rhythm control should be used but if not then it should not be attempted. A scoring system to predict the success rate of a rhythm control strategy would be desirable. Currently available markers include age, gender, fitness, AF phenotype, AF cycle length, left atrial size and functional markers and left atrial fibrosis volume. Predictors of disease progression and associated morbidity and mortality such as the HATCH score may prove helpful.

As novel techniques and targeted anti-arrhythmic drugs become available the risk-benefit balance may swing in favour of rhythm control in a higher proportion of patients with AF.

**IS ELECTROPHYSIOLOGY THE ANSWER?**

R Schilling
St Bartholomews & The Royal London Hospital, London, UK

Elimination of AF (rhythm control) using drugs and direct current cardioversion have been shown to have no impact on prognosis and have actually been implicated in a worsening of prognosis when compared to simple heart rate control.1 There were probably two reasons for these results, firstly a low number of patients actually remained AF free in the rhythm control arms of these trials, secondly anticoagulation was stopped prematurely and AF recurrence was therefore associated with stroke. The cost of AF on healthcare providers and the poor performance of conventional treatments has led to a huge investment in both money and resources focused on developing new therapies. Implantable devices have demonstrated that AF is often asymptomatic even in patients who have clear symptoms during AF on other occasions. This has proven that absence of symptoms does not mean absence of AF. Many new implantable devices now have facilities to allow remote follow-up. This new technology has allowed earlier intervention when AF is detected by devices thus potentially allowing anticoagulation or prevention of inappropriate shocks.2 While these technologies have potential to correlate AF burden to prognosis (because they accurately record AF continually) such studies have not yet been published. Therefore whether absence of AF on implantable devices is associated with reduced risk of embolic stroke is not known and so implantation of devices to prevent stroke is not a currently accepted indication. Catheter ablation of AF has been shown in many randomised studies to be superior to drugs and cardioversion in restoring and maintaining sinus rhythm.3 There remain concerns about the cost-effectiveness of these therapies but some data suggest that ablation is cost-effective compared to drug therapy when used for paroxysmal AF, particularly when this is performed early in the disease or as first line therapy.4 There is increasing evidence that catheter ablation is also associated with an improvement in prognosis and reduction in stroke risk5 but randomised trials specifically designed to prove this will not report for at least another two years. Therefore at the present time catheter ablation remains the most effective therapy for patients with symptomatic AF. Whether it should be used for patients who are not symptomatic remains unknown.

**References**


**IS THE ENDPOINT SYMPTOM CONTROL, DEATH OR HOSPITALISATION?**

J Camm
St George’s Medical School, London, UK

It is relevant with any drug that is intended to supress or prevent atrial fibrillation that formal clinical trials document that it does. Similarly drugs that are intended to slow the ventricular rate during ongoing atrial fibrillation must be shown to do this. Until recently that was the extent of our medical curiosity. It is now realised that this is the equivalent to demonstrating that an antihypertensive drug reduces blood pressure. However, it is more important to know if these effects are clinically valuable. Important clinical endpoints include improvement of symptomatic status, restoration of quality of life and reduction of major cardiovascular events such as all cause, cardiovascular and arrhythmic mortality, stroke, acute coronary syndrome and heart failure events.

During the development of a drug to treat atrial fibrillation its immediate effect on the arrhythmia must be documented and thereafter its clinical value must be assessed. Very few drugs have been introduced in recent years, but the development programme of dronedarone
has set new standards which are widely recognised by clinical scientists and regulators. Essentially the relatively small, but pivotal trials that demonstrate antiarrhythmic or electrophysiological efficacy, perhaps in conjunction with quality of life estimates, must be followed by relatively large trials which are powered to show useful clinical effectiveness with regard to major cardiovascular outcomes.

These standards for drug development must also be applied to trials designed to assess left atrial ablation, AV nodal ablation and device based trials, particularly when the therapy is intended to compete with rate or rhythm control drug treatments. Comparison between drugs and other interventions, and between strategies, for example to compare rate and rhythm control must address similar endpoints.

**SESSION 3 – WHAT IS THE MOST EFFECTIVE AND SAFEST DELIVERY OF THROMBOPROPHYLAXIS IN AF?**

**THROMBOPROPHYLAXIS FOR AF – ANTICOAGULATION, ANTIPLATELETS OR COMBINATIONS?**

L Kalra  
London School of Medicine, King’s College Hospital, London, UK

AF is a common arrhythmia, the incidence of which increases with age. AF is also associated with a 5-fold increase in the risk of stroke. Cardioembolic strokes due to AF are known to have higher recurrence, mortality, disability and costs of care compared with other stroke aetiologies. AF is a thrombogenic state and cardioembolic strokes due to AF are preventable. A vast body of literature shows that a high proportion of AF patients at stroke risk, up to 50% in some series, do not receive adequate thromboprophylaxis. The key to optimum stroke prevention in AF is, firstly, to identify those patients who are at high risk and, secondly, to target the most appropriate antithrombotic treatment to individual patients based on their personal risk of having a stroke. This has been facilitated in recent years by the availability of several easy to undertake scoring systems such as CHADS2 and CHADS-VASC, which can be used to determine eligibility for treatment and the most appropriate antithrombotic agent to use. Despite the known benefits of anticoagulation for AF patients at high risk of stroke, treatment may remain suboptimal because of concerns about bleeding risk. Quite often this risk is exaggerated in older people, who have the most to gain from adequate stroke prevention. Scoring scales such as the HAS-BLED score offer an objective assessment of this risk which can be balanced against benefits. The arrival of newer oral anticoagulant agents has revolutionised stroke prevention in AF. These agents are simpler to use and have lower bleeding risks than warfarin, thus presenting new opportunities in eligible patients in whom International Normalised Ratio (INR) control with warfarin may be suboptimal or in those where warfarin use presents logistical challenges. Despite the greater recognition of the stroke risk in AF in recent years, advances in warfarin monitoring and the availability of newer anticoagulation agents, stroke prevention in AF remains a challenge for individual clinicians and healthcare systems.

**NON-PHARMACOLOGICAL APPROACH VERSUS NEW ORAL ANTICOAGULANTS FOR STROKE PREVENTION, ATRIAL FIBRILLATION**

P Rose  
South Warwickshire Foundation Trust, Coventry, UK

Approximately 20% of stroke cases are associated with atrial fibrillation (AF). To date warfarin has proved to be the most effective medication in stroke prevention for patients with AF. Standards of warfarin management remain highly variable as seen in clinical trials monitoring the time in treatment range (TTR). Outside clinic trials AF prophylaxis is considerably poorer with Canadian Stroke Network reporting only 40% of stroke patients with AF to be taking warfarin with 75% of these patients having sub-therapeutic INR levels at time of stroke. Only 10% of AF patients in the study had a therapeutic INR. Compliance with new oral anticoagulant agents is yet to be established, however, in the absence of laboratory monitoring to prompt compliance and the short half-life of these agents, the safety in routine practice is yet to be established. Furthermore, there is no simple method of reversing anticoagulant effect.

Studies of non-pharmacological interventions aimed at left atrial appendage (LAA) closure via percutaneous transcatheter approach to reduce stroke in AF are ongoing. In transoesophageal echocardiographic studies more than 90% of thrombi in AF patients are found in the left atrial appendage and the results of closure of the LAA have been reported in the PROTECT–AF study. LAA using the Watchman device is reported to be non-inferior to routine long-term warfarin management in AF patients (mean CHADS, 1.8) for a combined endpoint of all cause stroke and mortality. In this study haemorrhagic stroke risk is significantly reduced while early safety issues with pericardial effusion are reported. For patients where compliance with anticoagulation is likely to be an issue the results from longer-term follow-up with these devices may provide support for non-pharmacological reduction of stroke risk in AF.

**References**

With regard to the management of atrial fibrillation (AF), for thromboprophylaxis, doctors and between and within different patient groups. There is a paucity of literature designed to examine patient perspectives on atrial fibrillation, for thromboprophylaxis and rhythm control.

Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with approximately 840,000 people suffering from it nationally. People with AF have an increased risk of stroke which can be mitigated effectively with anticoagulant therapy. Nevertheless, evidence suggests that less than 50% of eligible patients are receiving this form of intervention.

Method: A comprehensive literature search was undertaken to assess the published evidence in order to understand why clinicians and patients underutilise an effective intervention such as anticoagulation in favor of the less effective anti-platelet agents.

Results: The decision to use anticoagulant drugs in patients with AF involves a consideration of the potential benefits versus the risks, inconveniences, and costs. There is however widespread variation in the importance placed on these factors across primary care practices, individual doctors and between and within different patient groups. There is a paucity of literature designed to examine patient expectations. Available studies suggest that patients are prepared to be placed at a higher risk of bleeding than their prescribing doctors would be prepared to accept. Given that this judgement depends on a range of factors, it is not surprising that attempts to understand clinicians’ barriers to prescribing take precedence.

Conclusion: The barriers to anticoagulation can be identified, but we still don’t understand the importance that clinicians and individuals give them. These barriers continue to limit the use of anticoagulation therapy, a potentially beneficial treatment. Due to these limitations it is unclear what impact the increased range of oral anticoagulants and the alternation to the Quality and Outcomes Framework (QoF) will have on the incentive to primary care physicians to anticoagulate those at risk.

Specific ‘problem’ patients
TG Robinson
Leicester Royal Infirmary, Leicester, UK

Atrial fibrillation is a leading cause of ischaemic stroke, where it is associated with significant mortality and long-term functional disability. Whilst long-term anticoagulant therapy with vitamin K antagonists is recommended for atrial fibrillation patients at risk of stroke, there is often poor uptake. Specific ‘problem’ patients include the elderly, and patients with cognitive impairment, and at risk of falls. In addition, other patients present common clinical dilemmas, for example the timing of the introduction of anticoagulation following acute ischaemic stroke, or the use of anticoagulation in patients with evidence of increasingly recognized as an inferior choice for stroke prevention in AF, and may not be any safer than warfarin in terms of major bleeding, especially in the elderly.

What is the most effective and safest delivery of thromboprophylaxis in AF? Given recent developments in the field, the focus has been directed to improve our identification of truly low-risk patients who do not need any antithrombotic therapy, while those with one or more stroke risk factors should be recommended effective stroke prevention with an oral anticoagulant (OAC), whether this is with well-controlled warfarin or one of the new OACs. Of the stroke risk schemes, the CHA2DS2-VASc consistently outperform the CHADS2 score in identifying ‘truly low-risk’ patients with AF, and is at least as good as – and possibly better than – the CHADS2 score in identifying high-risk patients who subsequently sustain a thromboembolic event. Assessment of bleeding risk should also be mandated as part of the approach to thromboprophylaxis, and where relevant, the lower dose of new OACs (for example, dabigatran 110 mg bid), should be used. The HAS-BLED score is such a simple and well-validated score, and recommended in international guidelines.
microbleeds on neuroimaging. The presentation will discuss the evidence-base for the treatment of such patients, and highlight ongoing trials and outstanding research questions.

References


Antithrombotic agents, particularly anticoagulants, are a cornerstone of stroke prevention in patients with atrial fibrillation. All antithrombotic treatment decisions must balance the benefit of reducing occlusive events against the small risk of bleeding. Antithrombotic-related intracerebral haemorrhage (ICH) has very high mortality, which could offset the benefit of treatment in some patient groups. Magnetic resonance imaging (MRI) can be used to identify the presence of cerebral small vessel diseases, including cerebral amyloid angiopathy and hypertensive arteriopathy: the importance of these disease processes is that they may predispose to ICH in patients treated with antithrombotic agents. Potential MRI biomarkers of small vessel diseases include cerebral microbleeds (CMBs) on gradient-recalled echo (GRE) T2*-weighted MRI; and leukoaraoisis (white matter changes). CMBs in particular, as a marker bleeding-prone small vessels, could be valuable in understanding causes and mechanisms of antithrombotic-related bleeding ICH, and in identifying those at highest risk.

Cross-sectional case-control or case-case comparisons have consistently shown that CMBs are associated with antithrombotic-related ICH, with an apparently stronger link to anticoagulants than antiplatelet agents. There are few high quality prospective studies available, but these also suggest an increased risk of future ICH associated with baseline CMBs, particularly for ICH.

The topography of CMBs may reflect the underlying microangiopathy: strictly lobar CMBs may relate to CAA, whilst deep lesions reflect hypertensive arteriopathy. The risk of recurrent bleeding after symptomatic ICH seems to be higher for lobar ICH (often presumed due to CAA). Lobar CMBs may thus be a stronger risk factor for antithrombotic-related ICH than deep CMBs, but data are lacking, and large high quality prospective studies are needed to address this question.

This presentation will discuss the available evidence on CMBs and leukoaraoisis in the context of antithrombotic treatments, especially regarding their role as a predictor of future ICH risk after stroke.

**Selected references**


The past decade has substantiated the suspicion that many episodes of atrial fibrillation are asymptomatic (‘silent AF’), resulting in the mention of the diagnostic dilemmas caused by silent AF in the recent European Society of Cardiology (ESC) guidelines. This consideration is supported by a large body of trial data using systematic electrocardiogram (ECG) monitoring. Hence, in controlled trials in AF, systematic rhythm monitoring is recommended. Even intensified monitoring will, however, miss many AF episodes: When 12 consecutive 24-hr Holter ECG recordings show consistent sinus rhythm in a patient with paroxysm AF, the negative predictive value of this test battery for ‘recurrence of AF’ is only 30–50%.

This has obvious clinical relevance for the claim, based on rhythm control trials with incomplete ECG monitoring, that AF did not reoccur. It has other, possibly more relevant implications for the clinically relevant attempts to establish a diagnosis of AF e.g. in patients who survived a stroke or a TIA, or in other patients at risk for stroke. Clinical studies are ongoing to investigate how much ECG monitoring may be needed in such situations.

The relevance of AF burden for rhythm control therapies in clinical practice is less well-defined, mainly because of the fact that the main motivation to maintain sinus rhythm at present is driven by improving symptoms, rendering little need for ECG monitoring in asymptomatic patients with AF. Several large trials are ongoing that will establish the value of rhythm control therapy to improve outcomes in AF patients, such as EAST and CABANA. The outcome of these trials has the potential to change the need for rhythm monitoring for the adjustment of rhythm control therapy.

**References**


3. Jabaudon D, Szajezel J, Sievert K et al. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. Stroke 2004; 35: 1647–51. [http://dx.doi.org/10.1161/01.STR.0000131269.69502.d9](http://dx.doi.org/10.1161/01.STR.0000131269.69502.d9)

Atrial fibrillation (AF) is defined and detected electrophysiologically, namely by an electrocardiogram (ECG). However, it appears to be a marker for a wider clinical syndrome that has significant consequences for patients and physicians. The importance of AF as a risk factor for the development of cerebrovascular disease is finally being widely recognised. Recent progress in risk stratification and strategies for preventing stroke is encouraging. It is crucial to continue to accelerate efforts to tackle the non-electrophysiological implications of AF. Similarly, research continues to offer new insights into upstream determinants of the development of AF. This provides glimpses at therapeutic targets for the primary prevention of AF.

However, for the large number of people affected by symptoms of AF, there is a real need to prevent or treat the arrhythmia itself. The wide range of therapies currently available for this indication is a disappointing reflection on the absence of a truly effective, safe, standard treatment.

The electrophysiological definition of AF, though, implies an electrophysiological answer to the problem of symptomatic AF. Antiarrhythmic drugs (AADs) can be effective and well-tolerated in some, but have risks and side-effects that limit their use. Progress in the development of new, superior AADs is slow. In contrast, the rapid expansion in catheter ablation of AF has been accompanied by novel techniques and technologies. This has provided fresh insights into the electrophysiological mechanisms of AF, creating a virtuous cycle that directly benefits current patients.

Only a small proportion of AF patients will get access to AF ablation techniques. Although catheter ablation of AF is not the answer to everything, it is symbolic of the key role of electrophysiology in providing clinical benefit to the large and increasing number of people with AF. Electrophysiology will ultimately provide both the answer to treating the symptoms of, and potentially curing AF.

Speaker abstracts


IS ELECTROPHYSIOLOGY THE ANSWER TO EVERYTHING?

N Sulke
Eastbourne District General Hospital, Eastbourne, UK
SESSION 7 – NEW DEVELOPMENTS

IMPORTANT CLINICAL CONUNDRUMS IN THE MANAGEMENT OF ATRIAL FIBRILLATION

J Camm  
St George’s Medical School, London, UK

When considering the management of atrial fibrillation both patients and physicians now face new problems such as: should new oral anticoagulant (NOAC) therapy displace aspirin and warfarin in patients with atrial fibrillation, and should antiarrhythmic therapy (drugs or ablation) be advocated for improved survival (reduced likelihood of stroke, hospitalisations or cardiovascular mortality). Several case histories will be presented that explore these contentious issues.

STROKE PREVENTION IN AF: THE PRINCIPAL ROLE OF PRIMARY CARE: A DISCUSSION ON THE GROWING ROLE OF PRIMARY CARE IN RISK STRATIFICATION AND ANTICOAGULATION AS REFLECTED IN GUIDELINES AND THE ENGLISH QOF

Dr Matthew Fay,  
Westcliffe Medical Centre, Shipley

Background: Cardiovascular disease prevention is a multifaceted, with many significant stakeholders with interventions ranging from the government’s decisions on cigarette packaging to third sector groups supporting people in hard to reach populations. Primary care has generally had the more significant role in population management when it comes to therapeutics than other tiers of the medical profession. In the area of stroke prevention in atrial fibrillation the role of primary care to date has been that of case identification rather than initiating significant intervention.

Changes: The primary care contract in England has been negotiated with significant changes now coming into effect as regards the role of primary care in atrial fibrillation. The Quality and Outcome Framework (QoF) has now been altered to ensure that people identified with atrial fibrillation now need to undergo risk stratification using the CHADS2 schema on an annual basis. There is also an obligation to demonstrate the number of people who have a CHADS2 schema score of equal to, or greater than 1 who are on antplatelet agents and anticoagulants and those with a score in excess of 1 who are on anticoagulants.

This should bring a change to how general practitioners should perceive this area so that the decision-making process moves in to primary care to consider and initiate anticoagulants in the atrial fibrillation.

Discussion: There is a question raised at this stage to ask if the clinicians of primary care have the clinical experience and/or skill mix to be able to undertake this role. If the changes to the QoF are not to just cause confusion in the pathways of care what support is required for primary care to enable them to undertake this role. If this role is to move from secondary and tertiary care what support is required to support clinicians in this setting accepting decisions from primary care.
PB01
DETECTION OF ASYMPTOMATIC ATRIAL FIBRILLATION IN DUAL CHAMBER PACE-MAKERS: SINGLE CENTRE RETROSPECTIVE OBSERVATIONAL STUDY

P Garg, H Douglas
1 Northern General Hospital, Sheffield, UK; 2 University Hospital Aintree, Liverpool, UK

Background: Modern dual chamber pacemakers (PM) provide enough atrial sensing data to appreciate if a patient is having atrial fibrillation (AF) or not. Hence the need to study prevalence and presence of AF in asymptomatic patients who have had atrial sensing PM because of sino-atrial node or atrial-ventricular node diseases.

Purpose: Our aim was to identify patients with asymptomatic AF with atrial sensing pacemakers.

Methods: We studied all patients who had PM implanted between 2007 and 2008. We included patients who had atrial sensing PMs (DDD or AAI). All patients who had any past medical history of AF were excluded from study. Also, patients with VVI PM and Generator Box changes were excluded from study. Each patient's case notes were reviewed for past medical history, echocardiography findings, social habits history, PM implantation details, PM clinic follow-up. We studied PM yearly follow-up data to access Atrial High Rate Events (AHRE) and automatic mode switch (AMS). If PM data revealed that a patient had spent time in mode switch or AHRE more than five minutes in one episode, it was termed AF.

Results: We identified 169 patients who had PM implanted. From these, 75 patients had DDD/AI PM. 56 patients met inclusion criteria. Prevalence of asymptomatic AF was approximately 18% (n=10) over a period of two years (until 2010).

PB02
ANTITHROMBOTIC THERAPY AND ATRIAL FIBRILLATION IN SCOTLAND: RESULTS OF A NATIONAL AUDIT

J Simpson, I Findlay, M Denvir, D Murdoch
on behalf of NHS Quality Improvement Scotland

GP practices across Scotland were invited to participate in an audit of the management of atrial fibrillation (AF) as part of NHS Quality Improvement Scotland (QIS) National Audit of Clinical Standards in Heart Disease. A primary care database interrogation tool was developed to identify patients with AF, extract relevant data and calculate a CHADS2 score.

Results: 248 practices, with a total practice population of 1,376,834 contributed data. 19,470 patients with AF were identified (prevalence 1.4%) including 18,165 patients with non-valvular AF. Formal stroke risk assessment was rarely calculated a CHADS2 score.

<table>
<thead>
<tr>
<th>Stroke risk</th>
<th>No. of patients with AF (% of total)</th>
<th>No. on anti-platelet (% of group)</th>
<th>No. on warfarin (% of group)</th>
<th>No. on warfarin and anti-platelet</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2 =0</td>
<td>3136 (16%)</td>
<td>1019 (32%)</td>
<td>791 (28%)</td>
<td>78 (3%)</td>
</tr>
<tr>
<td>CHADS2 =1</td>
<td>5338 (28%)</td>
<td>2039 (38%)</td>
<td>1829 (35%)</td>
<td>211 (4%)</td>
</tr>
<tr>
<td>CHADS2 =2</td>
<td>9691 (56%)</td>
<td>3778 (39%)</td>
<td>3967 (41%)</td>
<td>567 (6%)</td>
</tr>
</tbody>
</table>

TABLE 1 Results

recorded in primary care (<1%). 79% of patients with AF were prescribed some form of antithrombotic therapy, either anti-platelet or warfarin (Table 1).

Conclusion: In Scotland, patients with AF are not receiving thromboprophylaxis according to guidelines. Patients at high risk of stroke are undertreated with warfarin and those at low risk of stroke are overprescribed warfarin. Strategies to improve appropriate anticoagulant use in this group include routine use of simple stroke risk stratification and regular GP practice audit and feedback.

PB03
WHAT IS THE PREVALENCE OF CO-MORBID ATRIAL FIBRILLATION AND ATHEROSCLEROSIS AND THE IMPLICATION FOR STROKE PREVENTION?

MA Lambert, R MacWalter, A Doney
Ninewells Hospital, Dundee, UK

Introduction: Approximately 20% of ischaemic strokes are caused by cardioembolism. Some patients have potentially both a cardioembolic, such as atrial fibrillation, and an atherembolic source. While oral anticoagulation therapy is most efficacious in reducing the incidence of ischaemic stroke in those with likely cardioembolism and antiplatelet therapy is best in those with an atheroembolic source it is unclear from current evidence whether combination therapy is best for those with both cardioembolic and atheroembolic sources.

Methods: Patients admitted to the acute stroke unit in Ninewells Hospital, Dundee undergo a comprehensive assessment of risk factors for stroke including carotid artery duplex scanning and detection of AF to determine the most likely source of emboli using the TOAST criteria. We used our electronic stroke database to determine how many patients admitted to the stroke unit over the past three years had both a cardioembolic and atheroembolic source.

Results: 518 (31%) patients with ischaemic stroke had a cardioembolic source. Of these 343 (66%) had a carotid scan performed. 180 (35%) of those with a cardioembolic source also had significant carotid disease.
Conclusions: A significant proportion of patients with ischaemic stroke have both a cardioembolic and atheroembolic source. Further studies are needed to show which therapy or combination of therapies is most efficacious for stroke prevention and safest in these patients.

PB04
WHEN SHOULD AN ATRIAL FIBRILLATION PATIENT RECEIVE ANTICOAGULANTS FOLLOWING INTRACRANIAL HAEOMRHRAGE?
1R Flynn, 1T MacDonald, 1AM Choy, 1G Murray, 1A Doney
1Medicines Monitoring Unit, University of Dundee, Dundee, UK; 1Division of Community Health Sciences, Edinburgh, UK

Background: The use of oral anticoagulants (OACs) following intracerebral haemorrhage (ICH) is perceived as contraindicated. There is little evidence to guide prescribers treating atrial fibrillation (AF) in patients with ICH.

Objectives: 1) To assess the risks of recurrent ICH from the Tayside Stroke Cohort; 2) to see if this remains constant with time; and 3) to examine the benefits of anticoagulation in these patients.

Methods: The rates of secondary events following ICH were calculated as annualised event rates assuming a Poisson distribution. As a measure of the benefits of anticoagulation, we compared these rates with annualised stroke rates based on the CHADS2 score.

Results: There were 417 patients with radiologically confirmed primary ICHs, with a total follow-up time of 1,478 patient-years. There were 14 recurrent ICHs. The annualised rate of recurrent-ICH in the six months post-discharge was 3.6% (95% CI 1.49–7.62%) whilst for the remainder of follow-up it was 0.54% (95% CI 0.22–1.12%). For AF patients with CHADS2 scores of 0 to six the annual risk of follow-up it was 0.54% (95% CI 0.22–1.12%). For AF was 3.69% (95% CI 1.49–7.62%) whilst for the remainder of patient-years. There were 14 recurrent ICHs. The annualised confirmed primary ICHs, with a total follow-up time of 1,478

PB05
MANAGEMENT OF STROKE RISK IN ATRIAL FIBRILLATION IN THE DIABETIC CLINIC IN FORTH VALLEY
1L Macdonald, 1S McKee, 1L Buchanan, 1C Labinjoh
1Department of Cardiology; 1Department of Diabetes; Forth Valley Royal Hospital, Larbert, UK

Background: Healthcare Improvement Scotland recently highlighted serious shortcomings in the anticoagulation of patients with atrial fibrillation (AF) at risk of stroke (CHADS2 score ≥2). AF has a prevalence of 0.9% in the general population but is increased in patients with diabetes (3.5%) or heart failure (13%). We speculated that in our clinics AF in diabetics would be underreported and, where CHADS2 score is ≥2, anticoagulation rates would be low compared to heart failure clinic patients.

Methods: Our diabetes and heart failure databases were interrogated.

Results: 4.7% of Forth Valley residents have diabetes. AF was documented in 55/13,618 (0.4%) (predicted 3.5%, 476/13,618) of our diabetic population. All of these had CHADS2 score ≥2 with warfarin prescribed in 66%. By comparison, warfarin was prescribed in 90% of heart failure patients with AF.

Discussion: Presence of AF is not adequately recorded in our diabetes database. However, because diabetics in AF are highly likely to require anticoagulation with warfarin this information is vitally important. Stroke prophylaxis is addressed better in our heart function clinics than in diabetic clinics within Forth Valley. We should drive the detection, recording and management of AF in our hospital diabetic population and seek to learn lessons from a comparable long-term condition, heart failure, to improve anticoagulation in diabetics with AF at risk of stroke.

PB06
AN AUDIT OF DELAYED OR CANCELLED CARDIOVERSION FOR ATRIAL FIBRILLATION
1SA Bodie, 1B Ford, 1S Hartley, 1J Luckit
1St George’s University International Medical School, Grenada, West Indies; 1Cardiology Department, North Middlesex University Hospital, London, UK; 1Haematology Department, North Middlesex University Hospital, London, UK

We conducted a retrospective audit of 69 patients with atrial fibrillation (AF) scheduled for cardioversion over a one-year period from September 2010 in a DGH. 31 were already anticoagulated and excluded from analysis.

We assessed the time from referral by a cardiologist to commencement of anticoagulation, time to achieving suitable International Normalised Ratio (INR) for cardioversion, and time from referral to cardioversion.

The average time from referral to anticoagulation was 21.92 days (range 5–74). The average time to stable INR was 115.66 days (range 39–378) and the average time from referral to cardioversion was 137.98 days (range 59–479). Sixteen patients (42.1%) had their cardioversion at first scheduled attempt whilst 22 (57.9%) had their procedure cancelled, 15 (39.5%) because of unsuitable INRs. Further cardioversion was scheduled for these 22 patients and, during this period, 10 more were cancelled due to...
PB07
FACTORS AFFECTING QUALITY OF WARFARIN ANTICOAGULATION IN PATIENTS WITH ATRIAL FIBRILLATION: INSIGHTS FROM AFFIRM

S Apostolakis, RM Sullivan, B Olshansky, GYH Lip
University of Birmingham, Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; Division of Cardiovascular Medicine, University of Iowa, Hospitals and Clinics, Iowa City, Iowa, USA

Introduction: The efficacy of warfarin anticoagulation in atrial fibrillation patients at risk for stroke is related to time in therapeutic range (TTR) with an International Normalised Ratio (INR) 2.0–3.0. Factors predisposing to low TTR have not been investigated comprehensively.

Methods: This post hoc analysis of the AFFIRM trial included patients with at least five INR values. ‘Optimal’ anticoagulation was defined as TTR ≥75%; above this level, adjusted-dose warfarin offers the same prognostic benefits as new oral anticoagulants. Binary regression analysis identified independent variables associated with TTR. The impact of TTR on outcomes was assessed further through Cox regression analysis.

Results: Of 4,060 patients recruited in AFFIRM, sufficient echo data were available in 2,433 patients (60%). Multivariate analysis showed that moderate-severe LV hypertrophy (IVS diastolic dimension >1.2 cm for women, >1.3 cm for men) was associated with all cause mortality (hazard ratio [HR] 1.45, 95% confidence interval [CI] 1.13–1.86, p=0.003). Concentric LV hypertrophy was associated with the worst outcome (p=0.008 vs. normal geometry). In a multivariate model, including established clinical, demographic and echo risk factors, moderate-severe LV hypertrophy assessed by IVS thickness was the strongest echo predictor of stroke (HR 2.2, 95%CI= 1.3–3.7, p=0.002).

Conclusion: In the AFFIRM Trial, LV hypertrophy assessed by gender-adjusted IVS thickness is an important risk factor for ischaemic stroke in patients with AF. LV hypertrophy assessed by gender-adjusted IVS thickness is associated with increased all cause mortality in AF patients.

PB09
NURSE LED RAPID ACCESS ATRIAL FIBRILLATION CLINIC

M Dunn
Cardiology Nurse Specialist, Hairmyres Hospital, East Kilbride, Scotland, UK

The Nurse Led Rapid Access Atrial Fibrillation Clinic was established in March 2010. Atrial fibrillation is the most common and sustained cardiac arrhythmia. It
occurring in about 1–2% of the population. Atrial fibrillation has frequent and severe consequences in affected patients. The main ones are: death, stroke, hospitalisation, quality of life and left ventricular function. Their prevention is the main therapeutic goal of management of atrial fibrillation.

The nurse led rapid access AF clinic was set up to address these by:

- Reducing the number of strokes, by addressing the need for antiplatelet/antithrombolytic therapy, using the CHADS2 score.
- Improve the patients’ quality of life by ensuring prompt initiation of medication, tailored to the patients’ symptoms and lifestyle.

Nurse led protocols were developed by the nurse specialist using Scottish Intercollegiate Guidelines Network (SIGN) and National Institute of Health and Clinical Excellence (NICE) guidelines as well as other current research. The service was then established at one Lanarkshire site on a pilot basis.

The audit results suggest that this is a safe and efficient pathway for patients with new onset atrial fibrillation. It ensures that patients are seen quickly and safely, reducing the propensity for stroke. Patients certainly valued the standard of the care delivered at the clinic.

One hundred per cent of patients received the suitable cardiac investigation as listed in the Quality Improvement Scotland (QIS) standards for management of atrial fibrillation.

After a year, 100% of patients referred were formally assessed for the risk of stroke, 42% were commenced on warfarin, 58% on aspirin. They were formally risk stratified using the CHADS2 scoring system.

Methods/Design: 27 clinical consultations were assessed using the OPTION tool to quantify the quality of the decision-making process. Patients were selected where there was a decision to be made regarding the treatment of their AF.

Results: Mean OPTION score was 25 (52%). This compares favourably with other published data in cardiac and other disease, but still leaves room for improvement. In particular patient expectations were not fully taken into account in 59% of consultations.

Discussion: This audit shows that shared decision-making was demonstrated to a good standard in these AF consultations, with physicians being particularly good at listing the treatment options, their pros and cons and encouraging questions. However, the study has highlighted areas for improvement, especially eliciting the patient’s preferred level of involvement in decision-making and how they would like to receive information. Interestingly, eliciting the patient’s ideas regarding treatment was another weakness, highlighting the differences in patient and physician expectations as a key issue for further study.

Reference
1 Lord S, Shepherd E, Langseth, M. Shared decision making and patient perceptions after tertiary care referral for cardiac electrophysiological disease management. 2010.

PB11
A THEORY-BASED EDUCATIONAL INTERVENTION FOR PATIENTS WITH ATRIAL FIBRILLATION TO IMPROVE ADHERENCE TO ORAL ANTICOAGULATION AND ITS ASSOCIATED LIFESTYLE RECOMMENDATIONS

DE Smith, GYH Lip, DA Lane
University of Birmingham Centre for Cardiovascular Science, City Hospital, Birmingham, UK

Background: Atrial fibrillation (AF) patients with a high risk of stroke are recommended to receive oral anticoagulation (OAC) with warfarin. Patient knowledge of AF and OAC therapy are poor which can impact on OAC control. An educational intervention may improve patients’ understanding of AF and OAC, and OAC control.

Methods/Design: Warfarin-naïve AF patients were randomised to either the intensive educational intervention or usual care. Intervention consists of one group session (2–6 patients) with information about the risks and benefits of OAC therapy, lifestyle modifications, importance of OAC monitoring and control. Interactive sessions comprise an ‘expert-patient’ focussed DVD, revised educational booklet, patient worksheets, and feedback session. The intervention was evaluated by assessment of the primary endpoint (time spent within therapeutic International Normalised Ratio [INR] target
range), secondary endpoints (Quality of Life [AF-QoL-18], Anxiety and Depression [HADS], Knowledge of AF and Anticoagulation, Beliefs about Medication [BMQ], Illness representations [IPQ-R] and clinical outcomes [bleeding, stroke and mortality]); at baseline, one, two and six months.

**Expected results:** To improve OAC control, AF-related quality of life, anxiety and depression (HADS), knowledge of AF and OAC and changes in patient's beliefs about medication and illness representations, based on the theoretical constructs used to design the intervention.

**Current stage of work:** The TREAT study results will be available in 2012.

**Discussion:** Results will provide an evaluation of a theory-based intervention that has the potential to be used by a range of educators and can be adapted for use with other medications and patient groups.

**PB12**

**A 2-YEAR STUDY OF THE EPIDEMIOLOGY AND MANAGEMENT STRATEGIES FOR PRIMARY ACUTE ATRIAL FIBRILLATION PRESENTING TO THE EMERGENCY DEPARTMENT**

1A Hamilton, 1A Cragg, 2D Clark, 3A Gray

1University of Edinburgh, Edinburgh, UK; 2Specialty Trainee in Emergency Medicine, Southeast Scotland training scheme; 3Consultant in Emergency Medicine Department of Emergency Medicine Royal Infirmary of Edinburgh, Edinburgh, UK

A retrospective consecutive analysis of all patients presenting to the emergency department with atrial fibrillation between 1 July 2009 and 30 June 2011.

Patients were categorised into the following groups by using all routinely available electronic hospital data: Primary atrial fibrillation (onset within seven days, first episode or paroxysm), persistent or permanent atrial fibrillation, secondary atrial fibrillation (precipitated by another illness e.g. infection); incidental finding (atrial fibrillation unrelated to current presentation).

The following data were recorded for these patients: routine demographics (age, sex), presentation characteristics, comorbidity, routine medications, acute treatments, presumptive diagnosis, admission, length of stay and outcome. Data was managed and analysed in secure MS Excel 2003 databases held on the hospital shared drive. Descriptive statistics were used to report key data.

There is a complete lack of emergency department epidemiological data around this patient group and the UK ED management. This study aims to investigate the epidemiology and ’real life’ management of patients with acute AF presenting to a UK emergency department.