

2014: A Year in AF

AF Association:

A summary of current research and developments in the management of AF

- Risk factors
- Drugs
- Intervention
- UK developments
- Screening and monitoring
- NICE activities in 2014
- UK drug research
- Tools to support management of AF
- Educational events
- AF in Parliament



Providing information,
support and access to established,
new or innovative treatments
for atrial fibrillation

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Atrial fibrillation (AF) remains the most common clinical arrhythmia and continues to increase in prevalence worldwide. In the UK alone, AF-related NHS admissions have risen by 60% over the last 20 years, costing the NHS £2.2bn a year. This figure is projected to double by 2050.

AF is a complex condition to treat and as such there is abundant research in this area. 2013 - 2014 produced much interesting work to increase our knowledge.

We aim to summarise these findings in this article, whilst addressing developments relevant to AF at a more national level.

Risk factors

The management of AF traditionally encompasses three key strategies: rate control, rhythm control and prevention of thromboembolism. 2013 brought a further dimension into the equation, namely AF-related stroke prevention. In an elegantly designed single centre randomised control trial, patients on the waiting list for AF ablation were randomised to either a physician-led weight loss programme (intervention group) or were provided with standard care alongside general lifestyle counselling (control group). Associated cardiometabolic risk factors in both groups were intensively managed. The results showed that compared with the control group, patients in the physician-led program lost weight, had reduced symptom burden and severity, and had reduced need for antiarrhythmic drug (AAD) use. More importantly, there were significant reverse remodelling effects observed using echocardiography in the intervention group with regression of left ventricular hypertrophy and reduction in left atrial size.

The results from this study were impressive but not wholly surprising: The key message is perhaps that AF should be viewed as part of the cardiometabolic spectrum and that proactive systemic cardiac risk modification in terms of weight loss with tighter control of hypertension and diabetes should be pursued in these patients to improve AF-related morbidity¹.

Drugs

As new oral anticoagulants (NOACs) exemplified by dabigatran, rivaroxaban and apixaban impact on clinical practice gradually but powerfully, the ENGAGE AF-TIMI 48 study, detailing the new kid on the block, edoxaban, was presented at the American Heart Foundation in Dallas this year. Edoxaban was found not only to be non-inferior to warfarin with respect to stroke and thromboembolism, but it also showed statistically lower rates of bleeding and cardiovascular mortality².

A subsequent meta-analysis of the key NOAC studies published thus far, RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48, incorporating data from all four NOACs, was published in the Lancet and reported data obtained from 71,683 participants. It concluded that the NOACs offered a favourable balance between efficacy and safety compared to warfarin, consistent across a wide range of AF patients with high risk for both ischaemic and bleeding events. Most importantly, they offered significant reductions in stroke, intracranial haemorrhage and mortality³.



Intervention

The MANTRA-PAF studied 294 drug naïve paroxysmal AF patients who had been randomly allocated to ablation or AAD (IC or III)⁴. The primary endpoint was AF burden, measured as both cumulative and per-follow-up visit burden (3, 6, 12, 18 and 24 months with 7-day Holter monitoring). AF burden was not significantly different between patients treated with ablation and those receiving AADs up to 18 months, but was significantly lower in the ablation arm at 24 months (90th percentile 9% vs. 18%, respectively; $P = 0.007$).

These results, though positive, do not highlight a significant advantage with ablation compared with drugs, as previous studies of this nature have. The results, however, should be interpreted with caution. There were inconsistencies in ablation technique, use of non-contemporary ablation equipment, and inexplicably, lack of confirmation of pulmonary vein isolation. Furthermore, there was a high complication rate in the ablation arm such that ablation had similar complication rates as AAD therapy (17% vs. 15%). These issues seem to explain the suboptimal ablation results and high complication rates in the ablation arm.

Although this study demonstrated superiority of ablation, the magnitude of this effect was modest compared to previous studies of this nature. Therefore further studies would be needed to better define differences. While the authors conclude that these data support the general recommendation to reserve AF ablation for those whose condition has not improved on at least one antiarrhythmic drug, additional studies are still needed to interpret differences in cost, healthcare utilisation, and long-term cardiovascular outcomes in order to inform that decision more fully.

The ARC-HF study looked at a major clinical problem; that of patients who demonstrate evidence of both AF and heart failure⁵. 52 patients were randomised either to ablation or to rate control drugs. At 12 months, an impressive 88% of the patients receiving ablation were in sinus rhythm (68% single procedure success) with the primary endpoint of peak O_2 consumption significantly higher in the ablation arm compared with rate control. Ablation also improved heart failure quality of life scores (Minnesota 'Living with Heart Failure' Questionnaire), B-type natriuretic peptide levels and six-minute walking distance. This small, randomised control study highlights the importance of sinus rhythm for patients with heart failure achieved through an AF ablation procedure. These results support the findings from a previous study which had demonstrated superiority of AF ablation versus AV node ablation and biventricular pacing in this same population.

In one further exemplar study, an extension of the original PROTECT-AF study with longer term follow-up (mean 2.3 +/- 1.1 years) was published⁶. The original study randomised over 700 AF patients to the left atrial appendage occlusion device (Watchman) versus warfarin. In keeping with the original results, in which the device was found to be non-inferior to warfarin for the combined endpoint of stroke, systemic embolism and cardiovascular death, this effect was maintained at longer follow-up.



UK developments

With the long awaited update of NICE AF guidelines due to be published in June 2014, it is now largely agreed that improving the management of AF and the pursuit of better patient outcomes has to be a national priority.

Innovation and technological advancement, not least in the UK, is supporting each step in the pathway, although any advances will continue to rely on greater awareness, ongoing education, real life data and evidence to support how each of the new options can be most effective in practice.

In January 2014, Mark Drakeford, Minister for Health and Social Services (Wales), concluded: "The choice is not between change and no change; it's about the sort of change we want to have and how we go about it."

Screening and monitoring

The national screening committee will report this summer following consultation. While noting the value of screening, the draft report queried the value of screening for AF in an adult population of 65 years+ when appropriate prescribing of anticoagulation remained so poor. The final recommendation will be published in June 2014, and while there is universal agreement that there is a need to improve the current management of already known AF patients, it is questionable whether this alone should preclude an AF screening programme. The most recent UK data suggest that in the first year of the AF QOF changes (April 2013), anticoagulation rates rose to nearly 66% excluding exception reporting.

NICE has approved the WatchBP blood pressure monitor as well as the AliveCor iPhone / Samsung heart monitor smartphone case, both of which now have a growing base of data to support effective and efficient on-the-spot screening within the home, medical practice or pharmacy, and they can facilitate ongoing monitoring.

NHS England: Pharmacies are now being 'called to action' as a frontline service, including screening for AF.

See this link for more important information:

<http://www.england.nhs.uk/ourwork/qual-clin-lead/calltoaction/pharm-cta/>

NICE activities in 2014

- March 2014 Scoping workshop for edoxaban undertaken, with recommendations on this new oral anticoagulant.
- June 2014 Updated AF Guidelines due to be published
- June 2014 Guidance due to be published on Point-of-Care INR self-testing monitors
- October 2014 Multi-Technical Appraisal (MTA) will be considered for newer oral anticoagulants



UK drug research

October 2013: The Cambridge based biopharmaceutical company, Xention Ltd., specialising in the discovery and development of ion channel-modulating drugs for AF, and Servier, the leading French pharmaceutical company, announced that they had entered into a joint development and commercialisation of XEN-Do103, a selective Kv1.5 modulator discovered and developed by Xention for the treatment of AF. XEN-Do103 is a potent and selective blocker of Kv1.5, a potassium channel blocker in the atria, which represents an exciting new target for atrial fibrillation. Xention's unique ion channel and cardiovascular development capabilities were critical for the discovery and development of this innovative compound, which has been shown to be safe and well tolerated in phase 1 clinical development.

Tools to support management of AF

AF revalidation tool for GPs: free online resource

<http://www.afrevalidation.org/>

AF stroke risk online calculator

<http://www.preventafstrokecrisis.org/calculator/>

Heart Rhythm Specialist website database; free to register and search

<http://www.heartrhythm-specialists.org/>

Primary Care Commissioning support for GPs

http://www.pccic.org.uk/sites/default/files/articles/attachments/business_rules_v26_summary_guide.pdf

NICE Quality Standards website

<http://www.nice.org.uk/guidance/qualitystandards/QualityStandardsLibrary.jsp>

Educational events

Regional Cardiac Update Meetings

<http://www.atrialfibrillation.org.uk/files/file/Events/140128-bh-FINAL-Cardiac%20OUUpdate%20Brochure.pdf>

October 2014: Heart Rhythm Congress, Birmingham, UK

<http://www.heartrhythmcongress.com/>

AF in Parliament

All-Party Group on Atrial Fibrillation (APGAF): Meetings and summary reports

<http://www.atrialfibrillation.org.uk/parliamentary-focus/westminster.html>

A summary of recent parliamentary questions on AF can be found on

<http://www.theyworkforyou.com/debates/?id=2014-01-14b.693.3&s=Glyn+davies+Atrial#g693.4>

Westminster Hall debate on AF, 12 March 2014

<http://www.atrialfibrillation.org.uk/parliamentary-focus/westminster.html>



Regular updates

Heart of AF – a 'one stop' healthcare professionals' website for AF. Features include the following:

- Service models
- Teaching tools
- Reports, papers and articles
- Events
- Daily news updates

www.heartofaf.org.uk

References

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2. Ruff C.T., Giugliano R.P., Antman E.M., et al, Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNTicoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). *American Heart Journal*, 2010; 160:635-41
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4. Cosedis Nielsen J., Johannessen A., Raatikainen P., et al, Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation, *The New England Journal of Medicine*, 2012;367:1587-95
5. Reddy V., Doshi S., Sievert H., et al, Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2-3 year follow-up of the PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in patients with Atrial Fibrillation) trial. *Circulation (AHA)* 2013;127:720-9
6. Jones, D.G, Haldar S.K., Hussain W., et al, A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *Journal of the American College of Cardiology*, 2013;61:1894-903

Additional references

NICE AF Guidelines update, draft, full document
<http://guidance.nice.org.uk/CG/Waveo/638/Consultation/Latest>

Screening in AF consultation document
<http://www.screening.nhs.uk/atrialfibrillation>

NICE INR self-testing monitors, June 2014
<http://www.nice.org.uk/guidance/index.jsp?action=folder&o=66490>