News from EHRA Europace 2013

Dr James Rosengarten reports highlights from the European Heart Rhythm Association (EHRA) Europace 2013 meeting held recently in Athens, Greece.

Encouraging news on anticoagulants

With the number of patients with atrial fibrillation (AF) set to double by 2050, appropriate anticoagulation for this growing condition was highlighted in a special session at the meeting – a 'State of The Art Lecture'. Professor Stefan H Hohnloser (JW Goethe University, Frankfurt, Germany) described how stroke in Europe costs an estimated €38 billion per year, with 20% attributable to AF. Yet a decade ago, around 40% of AF patients did not receive appropriate anticoagulation. Of those receiving therapy, only around 50% of time in therapeutic range (TTR) is seen. With this in mind, novel oral anticoagulants (NOACs) are non-inferior to warfarin at reducing stroke risk, but also remove many of the therapeutic difficulties seen with oral anticoagulant therapy. The benefits of NOACs are seen even in those with previous stroke or impaired renal function.

Many of the difficulties with vitamin K antagonists (VKAs), such as warfarin, were seen in the past as good reason to avoid anticoagulation in all but the highest risk patients. Professor Gregory Y H Lip (University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham) believes we need to change the culture of under-prescribing thromboprophylaxis in AF. The focus has been on identifying those highest risk patients in whom benefits were believed to outweigh risks. However, a culture change is needed. NOACs now represent a more convenient and, in many respects, a safer option to VKA for stroke prophylaxis. The 2012 focussed update of the European Society of Cardiology (ESC) guidelines for the management of atrial fibrillation[1] recommend all but the lowest risk patients are indicated for oral anticoagulation. Attention should now be focussed on identifying these truly low risk individuals, scoring 0 or 1 on the CHA_2DS_2-VASc score.

Professor Lip also considered bleeding risk: the HAS-BLED score is a now well-validated score to identify those at risk of bleeding with oral anticoagulation. A score >3 is indicative of regular review and follow up, but should not be used as a reason for avoiding anticoagulation. In fact, patients with a high HAS-BLED score derive a higher net clinical benefit when balancing ischaemic stroke and intracranial bleeding.

Once you have identified your patient is at risk of stroke, which anticoagulant should you choose? The ESC guidelines recommend either a VKA with a high TTR, or a NOAC. A new scoring system – SAMe-TT_2R_2 (Sex female, Age less than 60, Medical history, Treatment strategy [rhythm control], Tobacco use [doubled] and race [doubled]) – can predict those who will do well with a VKA (a score of 0-1) or those who are likely to have poor anticoagulation control with a VKA (a score ≥2) and where a NOAC could be a better option.[2]

It is acknowledged that licensed indications and experience develops more quickly than guidelines can be updated. For this reason EHRA has published a Practical Guide on the use of NOACs in patients with non-valvular AF.[3] This addresses many of the practical concerns relating to these novel agents, including initiation and follow up, drug interactions, dosing issues, bleeding and administration in patients requiring urgent surgery, or suffering with acute coronary events, or stroke.

PREFER AF

Data on the trends in management of patients with AF in five European countries were presented in a Late Breaking Clinical Trials session at the meeting. PREFER AF (Prevention of Thromboembolic Events – European Registry in Atrial Fibrillation) found that oral anticoagulation is now used in over 85% of patients with AF eligible for therapy. PREFER AF provides a 'snapshot' of clinical practice across five European countries taken in 2012. It revealed that NOACs are now used

by 6.1% of AF patients and that use of rhythm control interventions and catheter ablations have increased.

"PREFER AF illustrates changes in management of patients with AF since the last ESC guidelines. The registry shows that oral anticoagulant therapy is now much more widely used than in the German Competence Network on Atrial Fibrillation (AFNET) and the Euro Heart Survey registries on AF and suggests that European clinicians are using guidelines well. The rapid uptake of new oral anticoagulants suggests that these drugs are filling a therapeutic gap," said Professor Paulus Kirchhof (School of Clinical and Experimental Medicine, University of Birmingham).

The investigators believe the study represents the largest European registry on AF to date. The ESC guidelines for the management of AF, published in 2010, incorporated several 'evolutionary' changes in the management of AF. These included the concept of active AF screening to initiate therapy before complications had occurred and, furthermore, emphasised that continuous oral anticoagulation was indicated for the majority of AF patients since almost all are at increased risk of stroke.

Between January 2012 and January 2013, the PREFER AF registry enrolled consecutive patients with AF from 461 centres in France, Germany, Italy, Spain and UK. Altogether 42% of patients were office based and

53% hospital based, with 89% treated by cardiologists. "Since practice patterns can be influenced by the type of physicians, we felt it was important to recruit patients from a number of different settings," said Professor A Kirchhof. Results showed that of the 7,243 evaluable patients enrolled, 30% had paroxysmal AF, 24% persistent AF, 7.2% long-standing persistent AF, and 38.8% had permanent AF.

When medications were examined it was found that 66.3% of patients (4,799) received a VKA as monotherapy; 9.9% of patients (720) received VKA and an antiplatelet agent in combination; and 6.1% received NOACs (dabigatran, rivaroxaban or apixaban). Furthermore, antiplatelet agents alone were given to 11.2% of patients (808) while 6.5% of patients (474) received no antithrombotic therapy at all. Altogether, 78.6% of patients were adequately rate controlled, using a mean heart rate of 60 to 100 bpm as the definition.

Rhythm control therapy was deployed in 66.7% of patients, consisting of DC cardioversion in 18.1% of patients; pharmacological conversion in 19.5%; amiodarone in 24.1%; flecainide in 10.5%; sotalol in 5.5%; dronedarone in 4.0%; other antiarrhythmic drugs in 3.1%; and catheter ablation in 5.0%.

Over 80% of patients still suffered from AF symptoms despite good rate control. "We were surprised and puzzled by the high number of patients who suffer from AF despite good rate control," said Professor Kirchhof. "This indicates that we have more work to do to develop tools to better prevent AF and possibly to better maintain sinus rhythm in the future." The ongoing EAST (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) study (www.easttrial.org) is currently testing whether early use of rhythm control therapy can prevent adverse cardiovascular outcomes in patients with AF compared to usual care.

Depression screening in AF clinics recommended

Patients with paroxysmal AF rate their heath-related quality of life (HRQoL) lower than their physicians do, according to results from the ANTIPAF (Angiotensin II Antagonist in Paroxysmal Atrial Fibrillation) trial. The study found these patients show signs of depression, sleeping disorders and low levels of physical activity even in the absence of significant concomitant cardiac disease.

Researchers led by Professor Karl Ladwig (Helmholtz Centre, Munich, Germany) analysed data from patients enrolled in the ANTIPAF trial, which examined discordance between AF patients and their doctors. Between February 2004 and September 2008, 334 patients (41% female and 59% male) with paroxysmal AF, without significant concomitant heart disease, and their physicians from 43 participating centres were asked to rate the patients' HRQoL.

Results show physicians rated their patients' HRQoL higher than patients, both for the mental component score and physical component score. In the regression analyses, depression was significantly associated with discord in the mental component score and the physical component score. Furthermore, sleeping disorders were associated with discord in the mental component score and physical activity with discord in the physical component score.

"Electrophysiologists (EPs) generally decide whether to take a more or less aggressive treatment approach according to the patient's disease burden. Here, not only physical symptoms need to be taken into consideration, but also the patient's mental health and quality of life in general. If EPs don't know that their patients are suffering from depression they may not be offering them optimum treatments," said Professor Ladwig. "Good communication between physicians and patients is of paramount importance for adherence to medications and long term prognosis," he added.

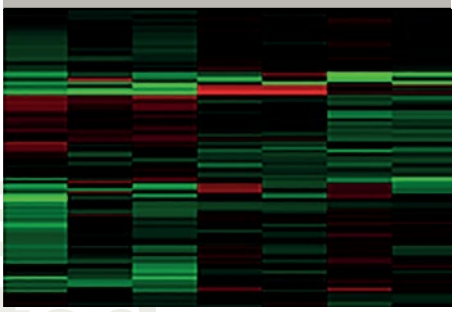
AF patient website launched

A website for AF patients *AFib Matters* (www.afibmatters.org) was introduced by the EHRA at the meeting.

The site outlines what AF is, symptoms, complications, types of drugs, and the need for stroke prevention. A section is devoted to frequently asked questions.

Professor Gregory YH Lip, who was Chairman of the Task Force responsible for the development of the website, said:

Figure 1. Protein cluster map demonstrating differential protein expression



"Patients with AF often have questions or misconceptions about their condition, such as whether they can travel, should they avoid certain foods, what can interact with their medication, and what is the risk of treatments. All of these questions are answered on the website."

"The website also highlights the latest developments in the treatment and management of AF including the new oral anticoagulant drugs, ablation and devices. It is the authoritative website on AF and will be updated at regular intervals with relevant and timely information," Professor Lip added.

Biomarkers may help stratify sudden cardiac death risk

Details of two biomarker discovery programmes were presented by myself and other colleagues from Southampton. The early results were generated by our team, headed by Professor John Morgan, and build on several years of collaboration between cardiologists at the University Hospitals Southampton and scientists at the University of Southampton. The work hopes to advance sudden cardiac death risk stratification and ultimately move towards a more personal selection of interventions, such as implantable defibrillators.

Traditional risk stratification markers, such as left ventricular function or QRS width, fail to identify those at greatest risk, or merely demonstrate those with advanced heart failure who will go on to die regardless of what intervention is offered. This variation in response may, in part, be due to the

genetic variability and response to, for example, ischaemic insult. Measuring this variability is challenging: gene expression does not accurately reflect functional protein expression. Proteomics is an emerging field in which this protein fingerprint can be sequenced directly.

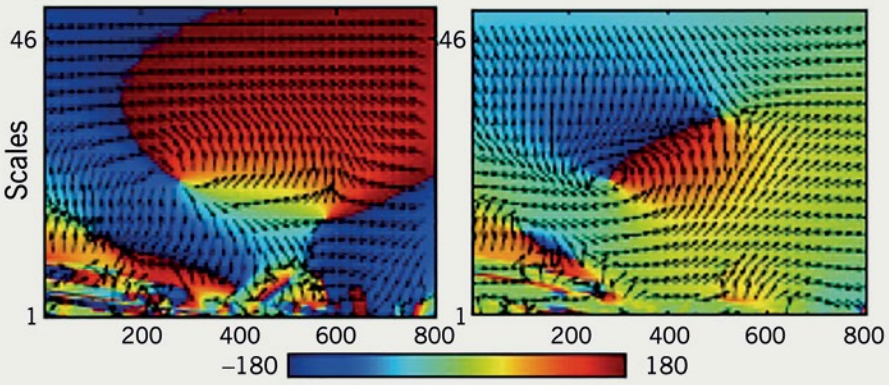
Our team have exploited these techniques, most frequently used in cancer sciences where solid tissue is readily available, to look for differences in protein expression of the whole serum proteome. We have taken serum samples from 243 patients with implantable cardiac devices, who were followed-up for 40 months for the occurrence of death, ventricular arrhythmia or survival without arrhythmia.[4] Following pooling and sample preparation, mass spectrometry was used to demonstrate differential expression between groups (**figure 1**), generating over 90 proteins that were associated with arrhythmia and not survival.

Generating candidate biomarkers in this fashion means that whole panels of proteins can be rapidly selected for testing. Usually, serum biomarkers are chosen based upon only a limited understanding of cellular mechanisms, whereas this technique enables unbiased selection without preconceptions.

An emerging risk stratification tool in recent years has been the use of cardiac magnetic resonance imaging (MRI) to quantify myocardial scar. Although the association between myocardial scar and ventricular arrhythmogenesis has been well reported, cardiac MRI is resource and time limited, making it unsuitable as a screening tool.

Our Southampton group looked at whether the resting ECG could be a surrogate for myocardial scar but found traditional ECG parameters were poor at detecting scar accurately.[5] Manual assessment of the ECG is time consuming and limited to those parameters that can be visually appraised. We know that the ECG signal contains much more information but extracting that data and processing large volumes requires a fresh approach. By working with biomedical signal engineers, the team sought to develop a novel algorithm that was capable of classifying scar. Standard 12-lead ECGs were recorded from over 150 patients undergoing cardiac MRI with scar assessment. Time, frequency and phase domain features were then 'extracted' from the digitally acquired signal and used in a 'machine learning' experiment to train the algorithm to classify ECGs with known scar burden (see **figure 2**). This classifier was then tested on the ECGs of over 80 patients; the algorithm correctly identified scar with 81% sensitivity and 73% specificity.

Figure 2. ECG image giving an example of a classification parameter: wavelet phase coherence. Left panel shows scar beat; right panel shows no scar



As more data are processed this type of approach can be endlessly refined. The classifier could be valuable in population screening before referral for more costly complex investigations, such as MRI scanning.

New 'user friendly' guidelines on pacing and CRT

The 2013 ESC Guidelines on Cardiac Pacing and Cardiac Resynchronisation Therapy[6] developed in collaboration with the EHRA, were launched at the meeting and also published simultaneously in the *European Heart Journal* and *EP Europace*. They have been redesigned to offer a more accessible format with greater emphasis on a practical 'how to' approach, which is targetted at generalists, including general practitioners and geriatricians, as well as cardiologists and electrophysiologists.

"By taking this user friendly approach we hope to get our messages out to the wider medical community, which ultimately should allow more patients to benefit from the latest evidence-based medicine," explained Professor Michele Brignole (Ospedali del Tigullio, Italy), Chairperson of the Guidelines on Cardiac Pacing and Cardiac Resynchronisation Therapy Task Force.

The guidelines explore:

- indications for pacing in patients who have cardiac arrhythmias
- indications for cardiac resynchronisation therapy (CRT) in heart failure
- indications for pacing in specific conditions, such as acute MI, pacing after cardiac surgery, transcatheter aortic valve implantation (TAVI) and heart transplantation, and pacing in children and individuals with congenital heart diseases
- complications of pacing and CRT implantation
- management considerations, such as re-implantation after device explantation for infection, MRI in patients with implanted cardiac devices, emergency (transvenous) temporary pacing and remote management of arrhythmias and devices.

The Guidelines take into account whether the patient has a persistent or intermittent problem, and whether it has been documented with electrocardiographic evidence (ECG documented) or not (ECG-undocumented).

The new ESC Guidelines have also created a new classification system for bradyarrhythmias according to mechanisms rather than aetiology.

Until now, guidelines have classified bradyarrhythmias according to aetiology,

for example whether the problem has been caused by sinus node dysfunction, MI, or bundle branch block.

"One of the big innovations of these guidelines is the development of a logical decision tree displaying the different pacing modes according to different clinical situations. In effect these guidelines take the clinician by the hand and lead them through a series of three or four questions," explained Professor Perry Elliott (The Heart Hospital, London), a member of the Guidelines Committee.

Pacemaker or ICD?

With over 90 major studies on pacing and resynchronisation published since the last guidelines, the Task Force went to considerable efforts to integrate the latest research. In areas where evidence is open to more than one interpretation, the guidelines provide information to help clinicians make a decision. For example, in patients with heart failure and poorly controlled symptoms, where choices have to be made between CRT pacemakers and CRT defibrillators, trials have had little to add to the decision-making process. "Clinicians have to consider factors such as expected life expectancy and comorbidities when choosing between pacemaker and defibrillator therapy," said Professor Elliott

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References

1. Camm AJ, Lip GY, De Caterina R *et al*. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012; 14:1385-413. http://dx.doi.org/10.1093/europace/eus305

2. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control amongst atrial fibrillation patients on warfarin: the SAMe-TT2R2 (Sex female, Age less than 60, Medical history, Treatment strategy [rhythm control], Tobacco use [doubled], Race [doubled]) score. *Chest* 2013; http://dx.doi.org/10.1378/chest.13-0054

3. Heidbuchel H, Verhamme P, Alings M *et al*. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013;15:625-51. http://dx.doi.org/10.1093/europace/eut083

4. Rosengarten JA, Scott PA, Larkin SE *et al*. High resolution multidimensional proteomics detects candidate arrhythmia biomarkers. Presented at Europace 2013, Athens, Greece. *Europace* 2013;**15**(suppl 2):ii11. http://dx.doi.org/10.1093/europace/eut194

5. Rosengarten JA, Dima SM, Panagiotou C *et al*. Novel non-invasive detection of arrhythmia substrate using supervised learning support vector machine. Presented at Europace 2013, Athens, Greece. *Europace* 2013;**15**(suppl 2):ii118. http://dx.doi.org/10.1136/heartjnl-2013-304019.72

6. Brignole M, Auricchio A, Baron-Esquivias G *et al*. for the Task Force on cardiac pacing and resynchronisation therapy of the European Society of Cardiology. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronisation therapy *Eur Heart J* 2013; http://dx.doi.org/10.1093/eurheartj/eht150 and *Europace* 2013; http://dx/doi.org/10.1093/europace/eut206