The Year in Cardiology 2013: arrhythmias

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The Year in Cardiology ‘arrhythmias’ presents an update on the latest studies and innovations published in the field within the last 12 months. Recent advances in the management of atrial fibrillation and novel treatment strategies and technologies are presented. New consensus documents to improve the diagnosis and treatment of patients with inherited cardiac arrhythmias and for paediatric patients with cardiac arrhythmias are summarized. Great progress has also been made in the field of cardiac implantable electronic devices: improvements in implantation techniques and novel technologies have been introduced and successfully applied. In addition, novel data on prevention of implantable cardioverter defibrillator-shocks and cardiac resynchronization therapy will certainly help to improve the quality of care for patients with cardiac arrhythmias and heart failure.

Introduction

In the field of cardiac arrhythmias and electrophysiology, we are looking back to a busy and very successful year: Significant progress has been made in the various fields of diagnosis and treatment of cardiac arrhythmias. New concepts to better understand the pathophysiology of arrhythmias have been introduced, and novel technologies have been developed and are successfully being applied. While waiting for large-scale trials to substantiate these findings, several of these concepts have the potential to become breakthrough innovations in the field.

Advances in atrial fibrillation management

As atrial fibrillation (AF) develops into the most prevalent arrhythmia worldwide and the leading cause of ischaemic stroke and heart failure, its increasing burden on the healthcare system has lead to a focus on reducing associated morbidity and mortality, which remains high despite all efforts so far. After significant developments in 2012 in the anti-arrhythmic and anti-thrombotic management of AF and the subsequent publication of the focussed update of the ESC guidelines, 2013 saw several secondary analyses of large Phase 3 trials, particularly of the novel anti-coagulants apixaban, dabigatran, and rivaroxaban. These studies looked beyond ischaemic embolic events and bleeding risk, and assessed the impact of these agents on hospitalizations, quality of life, mortality, and ultimately AF-related healthcare costs. Further analysis of the AVERROES1 and ARISTOTLE2,3 trials demonstrated superiority of apixaban over aspirin and vitamin K antagonists in reducing both cardiovascular and non-cardiovascular hospitalizations—the strongest-independent predictor of death, and thus overall healthcare burden. In addition, apixaban proved superior to warfarin in patients with atrial fibrillation and reduced renal function.3 Since the publication of the 2012 guidelines, apixaban has been approved for use. SAMe-TT2R24 is a new score formulated to predict patients who will benefit from Vitamin K antagonists compared with novel anti-coagulants. However, the score needs to be validated further before its use in clinical practice can be recommended.

The COMPARE trial5 demonstrated that continuation of vitamin K antagonists throughout AF ablation reduced peri-procedural stroke and bleeding. The novel anti-coagulants have also been shown to have comparable safety and efficacy profiles, and a change towards uninterrupted oral anti-coagulation therapy during AF ablation is likely to become standard of care. Due to the ongoing acquisition of new data on these agents, the European Heart Rhythm Association (EHRA) has published an executive summary of a practical guide to assist physicians in managing the different novel anti-coagulants.5 This guide provides advice on the use of these agents in specific

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tate the effectiveness of atrial fibrillation expert programmes. The

The arrhythmogenic mechanisms conveying sudden death in these
diseases also contribute to the occurrence of atrial fibrillation

Localized triggers, in most cases originating from the pulmonary
veins, initiate AF. AF due to one or a few re-entrant drivers is also
considered to be part of this type of AF

Acute factors: inflammation, surgical trauma, high sympathetic
tone, electrolyte changes, and volume overload, potentially
interacting with a chronic predisposition

The concept addressed the question why progression of AF is significantly
variable among different patients with AF. While some patients with
AF show a rapid progression from paroxysmal to persistent AF; others
seem to have a slower progression and few AF patients may
even have no AF progression. This concept of an independent
disease process promoting the progression of AF deserved further
evaluation but may have an important implication for future AF
treatment strategies (Table 1).

Data from the SARA Trial, the first multicentre, prospective,
randomized trial comparing catheter ablation with anti-arrhythmic
drug therapy in patients with persistent atrial fibrillation, showed a
superiority of catheter ablation over medical therapy for rhythm
control. A total of 146 patients were randomized to undergo cath-
eter ablation or treatment with various anti-arrhythmic drugs.

A push for personalized therapy in AF was the focal point of dis-
cussion at the 4th Consensus Conference of the AFNET/EHRA. As we
gain better understanding of the pathophysiology of the different
subtypes of AF, individualized management based on mechanism
and investigations aim to improve outcomes (Figure 1). In particular,
electrocardiogram assessment for complexity and asymptomatic AF
episodes may guide anti-arrhythmic and anti-coagulation therapy,
and studies such as the Early treatment of Atrial fibrillation for
Stroke prevention Trial are currently recruiting. Other brain and
cardiac imaging techniques, as well as genetic and biomarkers have
shown promise but require further validation.

The goal of better treatment of AF patients over Europe was
addressed in a proposal for interdisciplinary, nurse-coordinated
atrial fibrillation expert programmes as a way to structure daily
practice. The proposal outlined the need for systematization of
medical care for patients with AF, specific education, coordination
of care and also introduced potential outcome measures to evalu-
ate the effectiveness of atrial fibrillation expert programmes. The
urgent need for an improved quality of AF treatment was also high-
lighted by novel data on specific causes of death and their predic-
tors from the RE-LY trial: the mortality benefit in the patient
group treated with dabigatran was almost solely due to a reduction
in vascular mortality (embolism and haemorrhage related).

However, cardiac deaths which accounted for 38% of all deaths
were similar in both treatment groups. These results emphasize
the significance and the need for better approaches to reduce
cardiac mortality in patients with AF.

<table>
<thead>
<tr>
<th>AF type</th>
<th>Clinical presentation</th>
<th>Possible pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defined types of AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monogenic AF</td>
<td>AF in patients with inherited cardiomyopathies including channelopathies</td>
<td>The arrhythmogenic mechanisms conveying sudden death in these diseases also contribute to the occurrence of atrial fibrillation</td>
</tr>
<tr>
<td>Focally induced AF</td>
<td>Patients with repetitive atrial runs and frequent, short episodes of paroxysmal atrial fibrillation. Often highly symptomatic, younger patients with distinguishable atrial waves (coarse AF), atrial ectopy, an d/or atrial tachycardia deteriorating in AF</td>
<td>Localized triggers, in most cases originating from the pulmonary veins, initiate AF. AF due to one or a few re-entrant drivers is also considered to be part of this type of AF</td>
</tr>
<tr>
<td>Post-operative AF</td>
<td>Atrial fibrillation occurring after cardiac/pulmonary surgery in patients who were in sinus rhythm before surgery and had no prior history of AF</td>
<td>Acute factors: inflammation, surgical trauma, high sympathetic tone, electrolyte changes, and volume overload, potentially interacting with a chronic predisposition</td>
</tr>
<tr>
<td>Complex types of AF</td>
<td></td>
<td></td>
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<tr>
<td>Valvular AF</td>
<td>Atrial fibrillation manifesting before senescence (e.g. &lt;80 years) in patients with mitral stenosis or patients after mitral valve surgery</td>
<td>Left atrial pressure (stenosis) and volume (regurgitation) load contributes to atrial enlargement and structural atrial damage in these patients</td>
</tr>
<tr>
<td>AF in the elderly</td>
<td>AF which first manifests at an age &gt;80 years</td>
<td>Ageing of the atria (possibly including accelerated ageing), interstitial fibrotic infiltration, loss of cardiomyocytes, increased arterial and myocardial stiffness contribute to this type of AF</td>
</tr>
<tr>
<td>Polygenic AF</td>
<td>This type of AF is defined by the presence of common gene variants which are associated with early onset AF in the population</td>
<td>Currently under study, possibly including shortening of the left atrial action potential and/or left atrial cardiomyocytes with abnormal automaticity</td>
</tr>
<tr>
<td>Unclassified AF</td>
<td>AF which does not fulfill any of the other definitions. These forms of AF may be rather common, illustrating the need for a better classification</td>
<td>Shortening of atrial refractoriness (e.g. tachycardia-induced atrial remodelling or enhanced parasympathetic tone) or localized conduction disturbances due to atrial fibrosis induced by structural heart disease may contribute to this type of AF</td>
</tr>
</tbody>
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Table 1 A new classification of clinical types of atrial fibrillation as proposed by the Consensus Conference of AFNET/European Heart Rhythm Association (from Kirchhof et al. 7)

A new look on the pathophysiology of human atrial fibrillation was introduced with the concept of fibrotic atrial cardiomyopathy as a potential main driver of atrial fibrillation progression. This novel concept addressed the question why progression of AF is significantly variable among different patients with AF. While some patients with AF show a rapid progression from paroxysmal to persistent AF; others seem to have a slower progression and few AF patients may even have no AF progression. This concept of an independent disease process promoting the progression of AF deserved further evaluation but may have an important implication for future AF treatment strategies (Table 1).

Data from the SARA Trial, the first multicentre, prospective, randomized trial comparing catheter ablation with anti-arrhythmic drug therapy in patients with persistent atrial fibrillation, showed a superiority of catheter ablation over medical therapy for rhythm control. A total of 146 patients were randomized to undergo catheter ablation or treatment with various anti-arrhythmic drugs. A total of 146 patients were randomized to undergo catheter ablation or treatment with various anti-arrhythmic drugs. Primary end point of the study was recurrence of AF lasting >24 h. At 12 months follow-up, more patients in the catheter ablation group were free of the primary end point and had also less recurrence of any AF and required less cardioversions.

A push for personalized therapy in AF was the focal point of discussion at the 4th Consensus Conference of the AFNET/EHRA. As we
STOP-AF trial described the safety and efficacy of the cryo-balloon from the visually guided laser ablation catheter are promising. The simplify and improve success rates. The first multicentre results tion, several novel devices have been developed in an attempt to ary vein isolation (PVI) with conventional radiofrequency (RF) abla-

be safe without requiring warfarin transition and will likely to lead of patients ineligible for vitamin K antagonist therapy, it is shown to from the Protect-AF trial. Particularly beneficial in the subgroup into this novel single-shot device compared with conventional RF ablation. The reMARQable clinical study is currently recruiting in the USA for assessment of the novel multi-electrode spiral RF ablation catheter.

The development of several new mapping tools has further shown that stable rotors may drive AF once triggered. The CONFIRM trial first demonstrated the efficacy of the Focal Impulse and Rotor Modulation guided ablation. Further evaluation of rotors using several non-invasive activation mapping systems may lead to novel targets and improved ablation outcomes, with a potential step away from primarily PVI in the management of AF. Other emerging technologies attempting to reduce radiation risk for physicians and improve catheter stability and procedural success include remote magnetic navigation and remote robotic navigation systems. The Man and Machine Trial has recently finished recruiting, and results will be finalized and published in the coming year. The novel contact force catheter in conjunction with the VisiTag Module also shows promise in improving catheter-to-myocardial tissue contact and catheter stability. Another impressive innovation in the field of cardiac mapping and ablation with potential implications for ablation of AF using magnetic resonance imaging (MRI) interventional suites was also introduced (Figure 1).

**Inherited primary ventricular arrhythmia syndromes**

2012 saw several developments in the genetic classification of inherited sudden cardiac death, in an attempt to find a predictive test for clinical risk determination. Conflicting results from studies in this area, for instance in the role of programmed electrical stimulation or internal defibrillator implantation, has lead to the publication of the 2013 HRS/EHRA/APHRS executive summary expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes, which summarizes the diagnosis, classification, risk stratification, genetic testing and guidelines for the medical and device management of not only patients with primary arrhythmias, but for family members.

Beyond genotype, phenotypic analysis has produced insights into specific high-risk subgroups. Like many Mendelian disorders, long QT syndrome (LQTS) is an autosomally inherited disorder with incomplete penetrance. Crotti et al. determined that patients diagnosed with the LQTS1 genotype with a faster heart rate reduction after exercise conferred a higher risk for sudden cardiac death, independent of beta-blocker therapy, and recommends intense exercise training increasing vagal reflexes should be avoided. A US study analysed the natural history of early repolarization, and concluded that the prevalence was significantly higher than previous estimates in asymptomatic young adults, and the majority regressed by middle age.

**Arrhythmias in the paediatric population**

2013 saw the publication of the first comprehensive EHRA and AEPC-Arrhythmia Working Group joint consensus statement on the pathophysiology, non-pharmacological, pharmacological, and interventional management of the full extent of arrhythmias in the paediatric population. This focussed on specific considerations; in particular, arrhythmias more associated in this population, in congenital heart disease, size, long-term implications of medications, radiation and non-flouroscopic ablation strategies, and devices. The specific issue of implanted defibrillator leads in children with
Congenital heart disease was addressed in the multicentre PLEASE study. The study showed a relatively high incidence of lead complications and identified implantation age and lead type as predictors for lead failure.

Cardiac pacemakers, implantable cardioverter defibrillators, and cardiac resynchronization therapy

Implantation techniques and novel device technologies

The Bruise Control trial reported the superiority of uninterrupted warfarin as compared with heparin bridging for implantation of pacemaker and defibrillator for patients at high risk of thromboembolic events. Significant pocket haematoma, the primary outcome parameter of the study, was observed in 3.5% of 343 patients on continued warfarin and in 16% of 338 patients with a bridging regimen. New data from a large patient cohort were reported for the completely subcutaneous implantable cardioverter defibrillator (ICD) supporting the efficacy of the technology, demonstrating a very high termination rate of induced ventricular tachyarrhythmias and an acceptably low complication rate. Thus, the subcutaneous implantable cardioverter defibrillator may be a viable alternative to transvenous systems among patients who do not require pacing therapy for heart failure, bradycardia, or ventricular tachycardia. Fluoroscopy exposure and associated risks for patients and medical staff remain a crucial issue in the field of CRT implantation. A new 4D non-fluoroscopic tracking technology was introduced for CRT implantation and showed a significant reduction of fluoroscopy exposure.

Advanced ICD programming and remote follow-up

The enormous value of optimized ICD programming was shown in the MADIT RIT trial: 1500 patients with an ICD were randomly assigned to three different ICD programming strategies. At 1.4 years of follow-up high rate therapy (ICD therapies for tachyarrhythmias of ≥200 b.p.m. or higher) or with prolonged delay in therapy as compared with conventional programming was associated with a significant reduction in inappropriate ICD therapies but also reduced all-cause mortality. There was also a significantly higher rate of inappropriate ICD therapies in the conventional group as compared with high rate therapy or delayed therapy groups, respectively. The results of this important trial should have a direct impact on device programming in clinical practice.

The REFORM trial investigated feasibility and safety of remote monitoring of implantable cardioverter defibrillators. In this prospective, multicentre study patients with a primary prevention indication for a defibrillator were randomized to routine 3-monthly in-office follow-up or yearly follow-up guided by home monitoring technology. Home monitoring proved safe and effective and significantly reduced the total number of in-office visits from 3.85 to 1.60 per patient year.

Figure 2 Analysis from the MADIT-CRT trial showing the cumulative probability of death for patients with an appropriate shock for VT/VF as compared with patients with inappropriate ICD shocks: appropriate shocks but not inappropriate shocks were associated increased risk of subsequent mortality (reproduced with permission from Sood et al.30).
New data on cardiac resynchronization

Two landmark studies addressed burning questions in the field of cardiac resynchronization therapy: Block HF and Echo CRT.28,29 In the Block HF Trial, 691 patients with Class I–III heart failure and left ventricular ejection fraction of <50% were randomized to right ventricular and biventricular stimulation after implantation of a cardiac pacemaker or cardioverter defibrillator because of atrio-ventricular block. Patients randomly assigned to biventricular pacing did better and had a significantly lower incidence of the primary study outcome parameter which was time to death, urgent care visit for heart failure requiring i.v. therapy, or a >15% decrease in LV volume end-systolic index.28


The association between myocardial substrate, implantable defibrillator shocks and mortality was analysed from the MADIT-CRT data.30 In this study, the 4-year cumulative probability of shocks was 13% for appropriate shocks and 6% for inappropriate shocks. Patients with appropriate shocks had a significantly higher risk of mortality as compared with patients who never received shocks (Figure 2). However, there was no association of inappropriate shocks and appropriate or inappropriate anti-tachycardia therapy with increased mortality.

Conclusions

Several important findings have surfaced in the field of arrhythmias and electrophysiology during the past year, both regarding cardiac devices. While some of these concepts have already been assessed in large-scale clinical studies, similar studies are eagerly awaited for some of the other potential breakthrough innovations. The results of these trials are likely to change clinical decision making and improve the quality of care for patients with cardiac arrhythmias.

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References


