The year in cardiology 2014: arrhythmias and device therapy

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Abstract

This review looks back at important and clinically relevant new developments in the fields of invasive electrophysiology and device therapy in 2014. Many findings do not only apply to pure electrophysiologists, but also to every clinical cardiologist’s practice. The authors have extracted the key findings of studies with potential guideline impact and put those into a clinical perspective. Looking back at the achievements of 2014 may instil enthusiasm for further scientific endeavours in the years to come!

Introduction

Electrophysiology remains a growing part of modern cardiology. While technical innovation is a key determinant in invasive electrophysiology, both for ablation and device therapy, understanding the mechanisms, natural course, and evaluation of arrhythmias is the cornerstone of progress. The year 2014 noticed many new insights, from which the authors had to make a distinct selection. While the 2013 overview mainly focussed on technical innovation, we opted to zoom in more on clinically relevant new developments from 2014 that apply to every clinical cardiologist’s practice. Multiple large-scale studies and trials with potential guideline relevance have been published in various fields related to cardiac arrhythmias. Below follows an excerpt of the key findings of these studies and an assessment of their clinical relevance.

Cardiac arrhythmias and catheter ablation

Atrial fibrillation
Epidemiology and risk factors

There has been a long-standing interest into the relationship between endurance sports activity and atrial fibrillation (AF). Swedish investigators analysed data from a national database looking for arrhythmia-related hospitalizations in 52,755 participants of a popular 90 km cross-country skiing race.1 Those who completed the highest number of races had significantly higher risk of AF [HR 1.29] and bradyarrhythmias (HR 2.10). A similar association was seen for those who had the fastest relative finishing times. There was no association with other supraventricular tachycardias or ventricular arrhythmias (Figure 1). The data corroborate the concept that while mild-to-moderate exercise lowers the risk for AF (most likely mainly through a reduction of cardiovascular risk factors), those with the most extensive athlete’s heart remodelling may be predisposed to a brady-tachycardic presentation.2 Whether reduction of sports activity in those who have developed AF should be part of the therapeutic approach remains unproven, however.

Although randomized trials like GISSI-AF3 and ANTIPAF4 could not confirm the role of ACE inhibitors (ACEi) or angiotensin-receptor blockers (ARB) as upstream therapy to prevent development or progression of AF, the upstream place of specific drug classes has been brought back for consideration by the analysis of a population-wide Danish registry.5 By matching hypertensive individuals (and having no other concomitant AF promoting disease) on ACEi or ARB monotherapy with those receiving beta-blockers, diuretics, or calcium antagonists, the authors found that the use of ACEis and ARBs compared with beta-blockers and diuretics was associated with a reduced risk of AF, but not stroke. There was no difference in the incidence rates of AF under ACEi/ARB or calcium antagonists. The analysis suggests that controlling activation of the renin—angiotensin system or interfering with calcium handling, in addition to controlling blood pressure, is associated with a reduced risk of AF. The findings may re-open investigations into which patient groups could be best suited for such early upstream therapy to prevent AF.

Based on an echo substudy of the ENGAGE AF-TIMI 48 trial looking into indices of left atrial structure and function, investigators found that not only LA structure and function were increasingly abnormal in patients with a greater AF burden and higher CHADS2 risk score, but also LA dysfunction was present despite normal LA size in those in sinus rhythm.6 Therefore, assessment...
of LA function may add important incremental information in the evaluation of patients at risk of AF and should be further explored in detecting those at risk.

**Ablation therapy**
Several important clinical trials on catheter ablation of AF have recently been presented: the RAAFT 2 trial reported about the efficacy of ablation when compared with antiarrhythmic drug therapy as a first-line treatment. A total 127 patients were randomly assigned to receive either ablation therapy or antiarrhythmic drugs. Catheter ablation proved superior to antiarrhythmic drug treatment, although the difference between both groups measured as recurrence of AF or atrial tachycardia was lower than expected (54% after catheter ablation vs. 72% on antiarrhythmic drugs). The SARA trial has shown that catheter ablation also in patients with persistent AF leads to a higher degree of freedom from recurrent AF compared with antiarrhythmic drugs. During a Hotline session at the 2014 ESC meeting, the STAR AF 2 trial was presented, showing that the addition of linear lines or ablation of fragmented electrograms did not improve the outcome beyond what could be achieved by pulmonary vein (PV) isolation only. Although another Hotline presentation on the AMIO-CAT trial \( (n = 212) \) reported that 8 weeks of oral amiodarone treatment following ablation for paroxysmal or persistent AF did not significantly reduce recurrence of atrial tachyarrhythmias at the

**Figure 1** Atrial fibrillation related to fitness? The best trained participants to a popular 90 km cross-country skiing race in Sweden have a higher risk for arrhythmia. The figure shows the cumulative incidence of any arrhythmia by finishing time group in per cent of winning time (top) and by number of completed skiing races (bottom). (From Andersen et al.)
6-month follow-up, it more than halved atrial arrhythmia-related hospitalizations (RR 0.43; 95% confidence interval 0.23–0.77; \( P = 0.006 \)) and cardioversions (RR 0.36; 95% CI 0.20–0.62; \( P = 0.0004 \)) during the initial 3 months.\(^{10} \) Nevertheless, recurrence of AF or atrial tachycardia during the 3-month blanking period predicted recurrence of atrial arrhythmia at 6 months. Although the rationale for the short-term amiodarone treatment to reduce the long-term outcome is questionable, the findings support the concept that early PV reconduction is the main mechanism for later recurrences (and hence that durable PV isolation is essential), and at the same time open up the discussion whether a continued hybrid strategy should be considered in some patients with persistent AF undergoing ablation in whom more widespread atrial disease is present. To improve on durability of PV isolation, both technical and procedural improvements were presented in 2014. The SMART-AF trial confirmed earlier data on reduced AF recurrence when ablation points can be delivered with good contact-force,\(^{11} \) while the ADVICE investigators have reported that additional ablation in the case of adenosine-revealed dormant conduction after apparent pulmonary vein isolation increases the proportion of patients free from symptomatic AF after a single ablation procedure.\(^{12} \)

The ESC co-ordinated Atrial Fibrillation Ablation Pilot Study reported on the 1-year follow-up of 1300 patients who underwent atrial fibrillation ablation in 72 centres in 10 European countries.\(^{13} \) Registry data are important to observe deviation from best-practice recommendations and indicate opportunities for improvement. Success without antiarrhythmic drugs was achieved in 40.7% of patients (43.7% in paroxysmal AF; 30.2% in persistent AF; 36.7% in long-standing persistent AF) (Figure 2). The explanation for the deviation of these results from randomized trials (usually showing a \( \geq 70\% \) success rate in paroxysmal AF patients after a single procedure) needs further research. Interestingly, only 57.4% of the population underwent repeated long-duration (\( \geq 24 \) h) electrocardiographic monitoring, in contrast to HRS/EHRA/ECAS consensus recommendations. Knowing that 26% of recurrences were asymptomatic, this may hint to an even higher recurrence rate. A second ablation was required in 18%. There was a 1.7% major perioperative complication rate that must be weighed against the potential benefits when considering AF ablation in patients with mild symptoms.

Despite the advent of non-fluoroscopic mapping technology and even development of ablation procedures under full magnetic resonance guidance, fluoroscopy remains the cornerstone of imaging in most interventional electrophysiological procedures. A new EHRA Practical Guide discusses easy-to-implement ways to reduce radiation dose for patients and staff alike.\(^{14} \) Moreover, it recommends the use of effective dose estimates (derived from the dose-area product displayed by the X-ray equipment, with conversion factors that are age and gender specific) to compare patient exposure with different technology in the literature and as part of the clinical ablation report in the patient chart. Such direct feedback will motivate EP teams to further optimize their radiation practices.

**Stroke prevention**

The fifth phase-3 non-VKA oral anticoagulant (NOAC) trial for stroke prevention in AF, ENGAGE-AF, reported on the efficacy and safety of edoxaban.\(^{15} \) The major strength of the trial is the extensive dose range studied, with prespecified dose adaptations. The results have puzzled physicians and regulators alike with findings like lower cardiovascular and total mortality in those with the lower dose regimen, although that regimen was associated with a (just not significant) higher number of ischaemic and total strokes. Further analysis will have to clarify the dose adaptation aspects.

![Figure 2](image-url) Recurrence of atrial fibrillation after catheter ablation: real-world data from 72 European centres (from Arbelo et al.\(^{13} \)).
A number of substudies from the NOAC trials have further expanded the scope of knowledge on indications and clinical use of NOACs. It is clear that AF patients with mechanical heart valves remain an important exclusion from NOAC therapy, as the results of the RE-ALIGN trial have shown that the use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications compared with warfarin. Findings included the fact that, just like with VKA therapy, there is an optimal plasma concentration of dabigatran (and likely for every NOAC) to obtain the best clinical outcome, i.e. combining low stroke rate with low bleeding rates. Although this insight has contributed to a discussion on the (in)appropriateness of plasma-level monitoring, the main message is that an optimal dosing should be determined for the individual patient, taking into account both clinical factors like age, weight and renal function and some drug–drug interactions as was already discussed in the EHRA Practical Guide. Moreover, follow-up of factors impacting on plasma levels (mainly renal function) is mandatory, and should be organized for every patient.

There is high anticipation of specific NOAC reversal agents. Nevertheless, bleeding under NOAC therapy not only was less common in the ARISTOTLE trial, it was also associated with a more benign clinical outcome, including lower mortality. Moreover, a large German registry of daily care patients (the Dresden NOAC Registry) showed that rates of rivaroxaban-related major bleeding were lower and that the outcome is similar or better than that of major VKA bleeding in historical controls. On the other hand, in NOAC patients from this Registry undergoing interventional procedures, heparin bridging did not reduce cardiovascular events, but led to significantly higher rates of major bleeding complications. Therefore, continuation or short-term interruption of NOACs, without bridging, seems to be the safest strategies for most invasive procedures.

A first prospectively randomized trial comparing NOAC with VKA for patients requiring elective cardioversion for AF of >48 h duration has been reported. The X-Vert trial showed similarly low stroke rates with rivaroxaban and VKA, also in patients with TEE-confirmed freedom of LAA thrombus and cardioversion within 1 to 5 days of administration of OAC therapy. Although reassuring, the trial was underpowered to detect significant differences. In a secondary analysis, rivaroxaban was associated with a significantly shorter time to cardioversion compared with VKAs in those in whom at least 3 weeks of well-maintained therapy was required (‘delayed strategy’, P < 0.001). Similar studies with the other NOAC drugs are underway.

An important clinical dilemma remains the best management of patients with a combined indication for antiplatelets and anticoagulation therapy, like those with AF requiring a percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS). An ESC consensus group published its recommended approach in a document that was also endorsed by HRS and APHRS. Like the prior EHRA Practical Guide, it calls for cautious combination, with triple therapy as short as possible, suggesting the possibility for dual therapy from early on after PCI or ACS, and calling for monotherapy with anticoagulants in patients with stable coronary disease (like from 1 year after PCI or ACS), unless specific increased risk. Non-VKA oral anticoagulants and VKA are put at the same level concerning combination therapy, based mainly on extrapolation of findings but without direct evidence. A number of trials are currently ongoing to investigate this further. Another consensus document reappraised the current state-of-the-art of left atrial occlusion therapy as an alternative or adjunct of OAC therapy.

Longer ECG follow-up will detect more AF; this adage has now also been proved true in patients with cryptogenic stroke. The CRYSTAL-AF trial showed that an implantable loop recorder results in more than 7-fold increased AF detection rate than usual care. It remains to be shown however that such detection efforts, and institution of OAC based on it, is an effective and cost-effective strategy. The IMPACT trial, presented at the ACC meeting in March 2014, had to be terminated because even in a population of 2718 ICD patients it seemed futile to show that an OAC intervention based on remote monitoring (RM) of atrial arrhythmias would have an effect on stroke rates. Moreover, a sub-analysis from the ASSERT study, following 2580 hypertensive device patients without a history of AF, showed that although AF detection was associated with a 2.5-fold increased risk of stroke or systemic embolism, only 4 out of 51 patients (8%) had an AF episode within 30 days before the event.

### Ventricular arrhythmias and sudden death

Several psychotropic drugs used are associated with an increased risk of sudden cardiac death. While the absolute risk of drug-induced life-threatening arrhythmia may be relatively low, even small increments in risk of SCD may have a major health impact, considering that millions of patients are treated with such drugs. Moreover, some patient populations may be at increased risk. Since clear clinical recommendations within the field are lacking, it is unclear to many psychiatrists and cardiologists alike on how to deal with patients in need for psychotropic drugs. A Danish mixed working group from the Danish Cardiac Society and Society of Psychiatry has suggested an algorithm to reduce the risk of malignant arrhythmia in such patients, which may also serve as a starting point for further clinical investigations and refined international recommendations (Figure 3).

How effective is catheter ablation of ventricular tachycardia (VT) in patients with structural heart disease? Dinov et al. reported one of the largest series of patients with VT post myocardial infarction (n = 164) or in non-ischaemic cardiomyopathy (n = 63). Notably, almost half of the patients had an electrical storm with multiple episodes of VT shortly before catheter ablation. The clinical VT could be successfully ablated in >80% of patients and all inducible VT were successfully treated in >70% of patients. Recurrence rate of any VT within 1 year after ablation was high: 40% of the ischaemic VT and 60% of non-ischaemic VT patients developed at least one recurrence of any VT. Thus, although many clinical VTs could be successfully ablated, which was potentially lifesaving for a significant number of patients treated, the high recurrence rate underlines the need for technical and technological improvements for VT ablation in patients with structural heart disease, but also indicates the volatile nature of arrhythmia substrates in such patients.

In an elegant new approach to localize the critical isthmus of VT circuits, De Chillou et al. presented their experience with pacemapping maps during sinus rhythm, which adds to voltage mapping and pace-mapping during VT itself. Their technique has been developed in well-tolerated postinfarct VTs. Additional studies are required to
validate these findings in patients with unmappable VT and non-ischaemic cardiomyopathy, which would be a worthwhile addition in the armamentarium to localize and ablate such circuits.

**Cardiac implantable electronic devices: pacemakers, defibrillators, and resynchronization therapy**

The nationwide Danish pacemaker and defibrillator registry reported the peri-implant complications in 5918 patients implanted between May 2010 and April 2011. This Danish registry is very solid as all implantations performed nationwide were included. Complications occurred in 562 patients (9.5%) and were more frequent than expected based on previous studies. Female gender, implantation of a dual-chamber ICD or CRT-defibrillator, system upgrade or lead revision, and emergency implantation identified subgroups at higher risk. In addition, implantation centre experience and operator experience were shown to be important as complication rates were significantly higher at sites with a small or moderate implantation volume. Similar findings in a nationwide German pacemaker registry with more than 430,000 implantations were presented during a Hotline session at the ESC meeting 2014 in Barcelona.

Previous studies have reported the deleterious effects of permanent right ventricular stimulation in pacemaker and defibrillator patients. The ANSWER trial addressed this issue and assessed the effects of a new pacemaker algorithm capable of minimizing ventricular pacing on clinical outcome parameters in 650 patients with a pacemaker indication due to sinus node dysfunction or advanced atrio-ventricular block. After a follow-up of 3 years, ventricular pacing was significantly reduced in the advanced algorithm study arm when compared with DDD-paced controls (11.5 vs. 93.6%, \(P\), 0.0001). However, no difference was found regarding the co-primary composite of hospitalizations for heart failure, AF, or cardioversion. In addition, all-cause mortality was not different between both groups. On the other hand, the secondary endpoints of composite heart failure hospitalizations or cardiac death and cardiovascular hospitalizations were significantly reduced in the advanced algorithm study group. Further research is certainly warranted to identify specific patient populations that may benefit most from such advanced pacing algorithms.

The results of the BIOPACE trial were presented for the first time during the ESC congress in Barcelona. BIOPACE randomized 1810 patients with an indication for pacemaker implantation due to...
atrio-ventricular block to receive a dual-chamber pacemaker or a biventricular pacemaker. Left ventricular ejection fraction was 55 ± 12%. The primary endpoint of the study was a combination of time-to-death or first hospitalization for heart failure. After a mean follow-up of 5.6 years, there was no significant difference between both groups, although a trend in favour of cardiac resynchronization was reported (HR 0.87, 95% CI 0.75–1.01). Interestingly, the curves started to diverge in favour of resynchronization after only 4 years. Thus, it seems possible that longer follow-up is necessary to gain significant benefit from cardiac resynchronization therapy in the patient population studied. For the time being, the results of BIOPACE favour dual-chamber pacing rather than first-line biventricular pacing as treatment standard in patients with AV-block and preserved ejection fraction. Full publication of this important trial and the study subgroups is awaited early in 2015.

Is cardiac pacing moving into a new era of leadless devices? The technology for leadless pacing has been introduced in first clinical feasibility studies. Pacing devices as small as 5 mm in diameter and 35 mm in length can be completely implanted in the RV to provide cardiac stimulation in patients with severe bradycardia (Figure 4). Remarkably, the battery longevity of these small pacemakers should exceed 7 years. It is expected that these devices will significantly reduce lead-related complications such as lead fracture, infections, and endocarditis. Reddy et al.36 reported the results of the Leadless Trial in which 33 patients underwent implantation of a leadless pacemaker. The implantation was successful in 31 of 33 patients and sensing, impedance, and pacing thresholds proved good and stable during short-term follow-up. However, one patient died after implantation-related cardiac perforation and cardiac tamponade. Meanwhile, this complication has also been observed in few other patients that underwent implantation of a leadless pacemaker. Thus, as with all new technologies, careful assessment of the risk to benefit profile is necessary and further controlled clinical studies need to be done to prove the safety of leadless pacing and to assess whether the expected benefits become reality. However, if the results of these trials meet the expectations, leadless pacing

**Figure 4** A new era in cardiac pacing? Leadless stimulation has arrived in the clinical setting. The pacemaker is mounted on a delivery catheter introduced via the femoral vein (A). The delivery catheter is deflected and the pacemaker is advanced through the tricuspid valve (B) and placed at an apical–septal site in the right ventricle (C). After fixation of the pacemaker with a helix at the tip, the device is released from the delivery system (D). Figure courtesy of University Leipzig/Heart Center, reprinted with kind permission of Sergio Richter, MD.
may be expanded to dual-chamber application and cardiac resynchronization devices in the foreseeable future.

The role of telemedicine to improve the outcome of patients with advanced heart failure has been very controversial for many years. Now, we have new and important data from the field of telemonitoring in heart failure: The InTime trial reported a significant improvement of the clinical status of patients in whom therapy was supported by implant-based multiparameter telemonitoring. In the InTime trial, a total of 660 patients with an indication for ICD or CRT-ICD implantation were randomized to receive optimal medical therapy or optimal medical therapy plus device-based multiparameter telemonitoring. After 12 months of follow-up, significantly less patients in the telemonitoring group showed worsening of heart failure (as evident from the modified Packer score). In addition, total mortality, which was a secondary outcome measure of the trial, was significantly lower in the telemonitoring arm of the study (3.6%) when compared with the control group (8.4%). Interestingly, this benefit was shown both for patients implanted with ICD and with a CRT-D.

Implementation of RM of device patients requires investment and reorganization of care by physicians and hospitals. The EuroEco trial was a randomized, prospective, multicentre, health economic trial in 312 ICD patients from 5 European countries, studying the total follow-up (FU)-related cost for physicians and hospitals.38 It showed that RM freed up physician time, with FU work taking over by specialized nurses and technicians. For all patients as a whole, FU-related costs for providers were not different when FU was based on RM vs. purely in-office. However, country analysis showed an important impact of reimbursement provisions on the net benefit for providers, illustrating the need for proper reimbursement to incentivise effective remote FU implementation. Interestingly, the costs for the payer of health care did not increase, even with RM FU reimbursement present, due to a (numerically) lower rate of hospitalization days and related costs. Therefore, EuroEco provides data to come to balanced reimbursement decisions that benefit both payers, providers, and patients alike.

The first large-cohort real-world multicentre data on the efficacy and safety of the subcutaneous implantable cardioverter (SICD) de-fibrillator were reported from the EFFORTLESS registry.39 A total of 472 patients implanted with the SICD were followed for a mean of 558 days. The device proved highly effective with a first shock conversion rate of 88% and an overall successful conversion rate of 100%. System- or implantation-related complications requiring an intervention occurred in 6.4% of patients. Inappropriate shocks mainly due to cardiac oversensing were observed in 7% of patients. Overall, the registry data provide further evidence that the SICD is an effective and safe alternative for the prevention of sudden cardiac death.

New data on the effects of vagal nerve stimulation for the treatment of heart failure with reduced ejection fraction were reported as ‘late breakers’ during the ESC meeting in Barcelona: Nectar HF and ANTHEM-HF.40,41 Nectar HF was the first sham controlled randomized trial evaluating vagal nerve stimulation in 92 patients. Primary end point was end-systolic left ventricular diameter, secondary endpoints included peak VO2 and pro-BNP levels, all assessed at baseline and 6-month follow-up. The study was negative: neither endpoint changed significantly in the therapy (n = 63) and control (n = 22) arm.40 ANTHEM-HF randomized left (n = 31) vs. right (n = 29) vagal nerve stimulation. For both groups combined, a significant increase in left ventricular ejection fraction was seen compared with baseline, without major differences between left- or right-sided stimulation.41 However, there was no control group in this study and the effects observed may be at least partially due to placebo effects and expectation bias. Both studies together clearly did not constitute a major breakthrough for vagal stimulation as a new therapy option for patients with heart failure and reduced ejection fraction.

Final thoughts

Arrhythmias 2014 — what’s the taste? Was 2014 a ‘good’ year? Certainly yes! A number of clinically highly relevant questions could be answered on the basis of novel data that have been presented and published. This is particularly evident in the fields of AF (ablation and stroke prevention) and cardiac implants (BIOPACE, InTime). In addition, new and fascinating technologies such as leadless pacing have been introduced and first clinical data have been reported. However, despite all these achievements, further intense research in the field of arrhythmias is warranted. In particular, concerning catheter ablation of VT or risk stratification and prevention of sudden cardiac death we are still facing significant unresolved problems and challenges. Thus, we should further strengthen our efforts with hard work and dedication to make 2015 also a ‘good’ year in arrhythmias . . . or maybe even a better one.

Conflict of interest: H.H. was Coordinating Clinical Investigator for the Biotronik-sponsored EuroEco study on health economics of remote device monitoring, has been a member of the scientific advisory boards, and/or lecturer for Siemens Medical Solutions, Boehringer-Ingelheim, Bayer, Bristol-Myers Squibb, Pfizer, Daichis-Sankyo, Cardiome and Sanofi-Aventis, received unconditional research grants through the University of Leuven from St Jude Medical, Medtronic, Biotronik and Boston Scientific, and received contract research funding through the University of Leuven from Siemens Medical Solutions. G.H.’s institution received grants and travel support from St Jude Medical, Boston Scientific, Biotronik and Biosense.

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