

## REVIEWS

# Almanac 2013: cardiac arrhythmias and pacing—an editorial overview of selected research that has driven recent advances in clinical cardiology\*

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**Abstract:** Important advances have been made in the past few years in the fields of clinical cardiac electrophysiology and pacing. Researchers and clinicians have a greater understanding of the pathophysiological mechanisms underlying atrial fibrillation (AF), which has transpired into improved methods of detection, risk stratification, and treatments. The introduction of novel oral anticoagulants has provided clinicians with alternative options in managing patients with AF at moderate to high thromboembolic risk and further data has been emerging on the use of catheter ablation for the treatment of symptomatic AF. Another area of intense research in the field of cardiac arrhythmias and pacing is in the use of cardiac resynchronization therapy (CRT) for the treatment of patients with heart failure. Following the publication of major landmark randomized controlled trials reporting that CRT confers a survival advantage in patients with severe heart failure and improves symptoms, many subsequent studies have been performed to further refine the selection of patients for CRT and determine the clinical characteristics associated with a favorable response. The field of sudden cardiac death and implantable cardioverter defibrillators also continues to be actively researched, with important new epidemiological and clinical data emerging on improved methods for patient selection, risk stratification, and management. This review covers the major recent advances in these areas related to cardiac arrhythmias and pacing.

## ATRIAL FIBRILLATION

### Epidemiology of atrial fibrillation

A number of large scale epidemiological studies using registry databases and prospective cohort data have reported novel associations between atrial fibrillation (AF) and other non-traditional risk factors for AF. These include an increased risk of incident AF in patients with high glycosylated hemoglobin (HbA1c) and poor glycemic control<sup>1</sup>, coeliac disease<sup>2</sup>, rheumatoid arthritis<sup>3</sup> and psoriasis<sup>4</sup>, use of non-aspirin, non-steroidal anti-inflammatory drugs (NSAIDs)<sup>5</sup>, and increased height<sup>6</sup>. Another interesting association is the finding from a substudy of 260 patients with chronic AF from the SAFETY trial (*Standard versus Atrial Fibrillation Specific Management Study*) that mild cognitive impairment is highly prevalent among older, high risk patients hospitalized with AF<sup>7</sup>. In another substudy of the *Cardiovascular Health Study*, investigators found that higher base-line circulating concentrations of to-

tal long chain n-3 polyunsaturated fatty acids (PUFA) were associated with a lower risk of incident AF<sup>8</sup>.

Other interesting recent epidemiological studies on AF include the association of incident AF with an increased risk of developing end stage renal disease in patients with chronic kidney disease<sup>9</sup>, and a community based study of 3220 patients which showed that new AF in patients with no history of AF before a myocardial infarction increased mortality in patients with myocardial infarction<sup>10</sup>. In a large *Swedish registry study* of 100 802 patients with AF, Friberg et al<sup>11</sup> found that ischemic strokes were more common in women than in men, supporting the notion that female gender should be taken into consideration when making decisions about anticoagulation treatment. Furthermore, among older patients admitted with recently diagnosed AF, the risk of stroke appears to be greater in women than in men, regardless of warfarin use<sup>12</sup>, and among healthy women new onset AF was found to be independently

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associated with all cause cardiovascular and non-cardiovascular mortality<sup>13</sup>.

### Medical management of AF

Data from the RealiseAF study, an international, observational, cross-sectional survey of patients with any history of AF in the previous year, suggested that patients in which their AF was 'controlled' (defined as sinus rhythm or AF with a resting heart rate  $\leq 80$  beats/min) had a better quality of life and fewer symptoms than those whose AF was uncontrolled<sup>14</sup>. Nonetheless, even patients with controlled AF experienced frequent symptoms, functional impairment, altered quality of life and cardiovascular events-hence the importance of ongoing efforts to develop novel and better treatments for AF. The RECORDAF (*Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation*) registry was a worldwide, prospective observational survey of AF management in an unselected, community based cohort over a 12 months period<sup>15</sup>. The investigators found that in 5171 patients whose data were available, therapeutic success (driven by control of AF) was achieved in 54% overall (rhythm control 60% vs rate control 47%). The choice of rate or rhythm strategy did not affect clinical outcomes (which were driven mainly by hospitalizations for arrhythmia and other cardiovascular causes), although the choice of rhythm control reduced the likelihood of AF progression.

The RACE (*Rate Control Efficacy in Permanent Atrial Fibrillation*) II trial was the first formal assessment of alternative rate control goals in AF and demonstrated for the first time that a 'lenient rate control' strategy (target resting heart rate  $< 110$  beats/min) was non-inferior to a 'strict rate control' strategy (target resting heart rate  $< 80$  beats/min and heart rate during moderate exercise  $< 110$  beats/min)<sup>16</sup>. Two subsequent sub-studies of the RACE II trial showed that the stringency of rate control had no significant effect on the quality of life in patients with permanent AF<sup>17</sup> and that lenient rate control did not have an adverse effect on atrial and ventricular remodeling compared with strict rate control (although female gender was independently associated with significant adverse cardiac remodeling)<sup>18</sup>. In another sub-study looking at cardiovascular outcomes in subjects from the original AFFIRM trial (*Atrial Fibrillation Follow-Up Investigation of Rhythm Management*), investigators found that the composite outcome of mortality or cardiovascular hospital stays was better in rate compared with rhythm control strategies (using amiodarone or sotalol)<sup>19</sup>. Non-cardiovascular death and intensive care unit hospital stay were

more frequent in patients on amiodarone, and time to cardiovascular hospital stay was shorter. In a prospective, randomized, open label trial of pharmacological cardioversion in patients with persistent AF, Yamase et al compared amiodarone with bepridil in 40 consecutive subjects<sup>20</sup>. The investigators found that bepridil was superior to amiodarone in achieving sinus conversion (85% vs 35%;  $p < 0.05$ ) and maintaining sinus rhythm after an average follow-up of 14.7 months (75% vs 50%).

The issue of whether PUFA have any beneficial effects on AF remains a topical one. A large meta-analysis of 10 randomized controlled trials involving 1955 patients found that PUFA supplementation had no significant effect on AF prevention<sup>21</sup>. In the FORWARD trial (*Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation*), 586 outpatient participants with confirmed symptomatic paroxysmal AF who required cardioversion or had at least two episodes of AF in the preceding 6 months were randomly assigned to receive placebo or PUFA (1 g/day) for 12 months<sup>22</sup>. The investigators found that PUFA supplementation did not reduce the recurrence of AF or have any beneficial effects on the other prespecified end points (all cause mortality, non-fatal stroke, non-fatal acute myocardial infarction, systemic embolism or heart failure). In a large placebo controlled, randomized clinical trial involving 1516 patients in 28 centres, perioperative supplementation of PUFA, although well tolerated, was not shown to reduce the risk of postoperative AF<sup>23</sup>. In contrast, another randomized, double blind, placebo controlled trial involving 199 patients who received either PUFA (2 g/day) or placebo for 4 weeks before direct current (DC) cardioversion found that patients who received PUFA were more likely to be in sinus rhythm at 1 year follow-up compared with control patients<sup>24</sup>.

### Monitoring and assessment of AF

The detection of paroxysmal AF can be difficult with current methods and technology; hence ongoing efforts are being made to improve methods for detection and diagnosis. The association between subclinical AF and cryptogenic stroke has gained increasing prominence with more careful monitoring of patients using invasive and non-invasive methods. In a nice study of 2580 patients aged 65 years or older with a pacemaker or defibrillator recently implanted and no history of AF, investigators detected subclinical atrial tachyarrhythmia in 261 patients (10.1%)<sup>25</sup>. Over a mean follow-up of 2.5 years, patients with subclinical atrial tachyarrhythmias were found to have an increased risk of clinical

AF and of ischaemic stroke or systemic embolism (HR 2.49, 95% CI 1.28 to 4.85;  $p=0.007$ ). In patients who do not have pacemakers or defibrillators who present with cryptogenic stroke, longer term ambulatory ECG monitoring using external or implantable devices may be worth considering to help confirm a diagnosis of subclinical AF<sup>26,27</sup>. In a study of 100 patients being screened for AF, investigators compared the effectiveness of using 7-day triggered ECG monitoring with 7-day continuous Holter ECG monitoring for detection of AF<sup>28</sup>. An arrhythmia was recorded in 42 subjects (42%) with continuous ECG recordings versus 37 subjects (32%) with triggered monitoring ( $p=0.56$ ). The sensitivity of triggered ECG monitoring was found to be lower than that of continuous ECG monitoring, mainly due to a shorter effective monitoring duration, although qualitative triggered ECG analysis was less time consuming than continuous ECG analysis. In another larger study of 647 patients with implantable continuous monitoring devices, intermittent rhythm monitoring was found to be significantly inferior to continuous monitoring for the detection of AF and was not able to identify AF recurrence in a great proportion of patients at risk<sup>29</sup>. In an interesting study investigating the use of N-terminal pro B-type natriuretic peptide (NT-proBNP) values to estimate the recency of AF onset and safety of cardioversion, investigators separated 86 patients presenting with presumed recent onset AF into two groups (43 in each group), based on NTproBNP concentrations above and below a cut-off value, and subjected all subjects to transoesophageal echocardiography<sup>30</sup>. NT-proBNP concentrations below the cut-off value were found to be the most powerful predictor of the presence of thrombus, suggesting that a short term increase in NT-proBNP after AF onset might be useful in assessing the recency of onset of the AF episode, if unknown, and might be potentially used to help determine the safety of cardioversion.

### Catheter ablation of AF

Although antiarrhythmic drugs (AADs) and catheter ablation are the main treatment options available to maintain sinus rhythm in symptomatic patients with AF, many clinicians and patients still opt for an initial conservative strategy and consider catheter ablation only after one or more AADs have been tried and found to be ineffective. The question of whether catheter ablation of AF is an effective initial therapy for paroxysmal AF was addressed in a small randomized study in which 294 patients (with no history of AAD use) were randomly assigned to an initial strategy with

radiofrequency catheter ablation or therapy with a class 1c or III AAD<sup>31</sup>. The investigators found no significant difference between the ablation and drug therapy groups in the cumulative burden of AF (90<sup>th</sup> centile of arrhythmia burden 13% and 19%, respectively;  $p=0.10$ ) in the initial 18 months. However, at 24 months, AF burden was significantly lower in the ablation group compared with the drug therapy group (9% vs 18%;  $p=0.007$ ) and more patients in the ablation group were free from symptomatic AF (93% vs 84%;  $p=0.01$ ). In the drug therapy group, 54 patients (36%) subsequently underwent ablation.

In another small randomized study of AF ablation in patients with persistent AF, advanced heart failure and severe left ventricular (LV) systolic dysfunction, MacDonald et al<sup>32</sup> found that catheter ablation was successful at restoring sinus rhythm in 50% of patients, although the procedure was associated with a significant complication rate of 15%. In addition, catheter ablation did not improve LV ejection fraction (LVEF) (as measured using cardiovascular magnetic resonance) or other secondary outcomes, calling into question the risk/benefit ratio of performing AF ablation in patients with persistent AF and LV dysfunction. An international multicentre registry study of 1273 patients undergoing AF ablation suggested that maintenance of sinus rhythm through catheter ablation was associated with a lower risk of stroke and death compared with a control group consisting of medically treated patients with AF in the *Euro Heart Survey*<sup>33</sup>.

Several studies have recently been reported which increase our understanding of the factors associated with success or failure following AF ablation. The importance of pulmonary vein (PV) isolation was further reinforced by Miyazaki et al<sup>34</sup> who reported long term clinic outcomes of 83.6% (480 out of 574 patients) with a mean follow-up of  $27\pm14$  months using an extensive PV isolation approach in patients with both paroxysmal and persistent AF<sup>34</sup>. Late recurrences (defined as 6–12 months following the initial AF ablation procedure) was associated with PV reconnection in all patients, while very late recurrences (>12 months after the procedure) were associated with non-PV triggers in 85.7% of cases. The added benefit of performing additional linear ablation lines after PV isolation on improving outcomes following AF ablation has been further questioned in a prospective, randomized study of 156 patients with paroxysmal AF who were randomly assigned to undergo PV isolation only, PV isolation and a roof line, or PV isolation, roof line and



a posterior inferior line<sup>35</sup>. The investigators found no improvement in clinical outcome in the patients who received the additional lines while, unsurprisingly, the addition of the linear ablations significantly prolonged procedure times. A number of investigators have found that many factors are predictive of or adversely related to outcome following AF ablation in addition to well established factors, such as type of AF (paroxysmal or persistent), left atrial size, and presence of LV dysfunction. These novel factors include cardiac related factors, such as atrial electromechanical interval on pulse wave Doppler imaging<sup>36</sup> and left atrial fibrosis as assessed by measuring echocardiograph derived calibrated integrated backscatter<sup>37</sup>, pericardial fat<sup>38</sup>, plasma biomarkers (such as plasma B-type natriuretic peptide values<sup>39</sup>), renal dysfunction<sup>40</sup>, and the metabolic syndrome<sup>41</sup>. Interestingly, the presence of dissociated PV potentials, often used as a marker of successful PV isolation, was not found to predict AF recurrence in a study of 89 consecutive patients over a mean follow-up of 21±8 months<sup>42</sup>. In a small randomized controlled study of 161 patients, a 3 month course of colchicine (0.5 mg twice daily) was found to decrease early AF recurrence after PV isolation, probably due to a reduction in inflammatory mediators, including interleukin 6 (IL-6) and C reactive protein (CRP)<sup>43</sup>. Colchicine (1.0 mg twice daily initially followed by a maintenance dose of 0.5 mg twice daily for 1 month) was also found to reduce the incidence of post-operative AF and decrease in-hospital stay in a multicentre, double blind, randomized trial of 336 patients<sup>44</sup>. In an interesting small randomized study of PV isolation with and without concomitant renal artery denervation in 27 patients with refractory symptomatic AF and resistant hypertension, Pokushalov et al showed that renal artery denervation reduced systolic and diastolic blood pressure and reduced the recurrence of AF during 1 year follow-up<sup>45</sup>.

Another area of research in the field of AF ablation has been on the factors associated with increased complications from the procedure. Using data from the *California State Inpatient Database*, Shah et al found that among 4156 patients who underwent an initial AF ablation procedure, 5% had periprocedural complications (most commonly vascular) and 9% were readmitted within 30 days<sup>46</sup>. Factors associated with a higher risk of complications and/or 30-day readmission following an AF ablation were older age, female sex, prior AF hospitalizations, and recent hospital procedure experience. In another retrospective study of 565 patients, both the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores

were found to be useful predictors of adverse events following AF ablation<sup>47</sup>.

The first randomized clinical trial comparing the efficacy and safety of catheter ablation of AF with surgical ablation involved 124 patients with drug refractory AF<sup>48</sup>. The investigators found that the primary end point (freedom from left atrial arrhythmia >30 s without AADs after 12 months) was 36.5% for the catheter ablation group and 65.6% for the surgical group (p=0.0022), but patients in the surgical group experienced significantly greater adverse effects (driven mainly by procedural complications) compared to the catheter ablation group. Pison et al reported relatively high 1 year success rates (93% for paroxysmal AF and 90% for persistent AF) with a combined transvenous endocardial and thorascopic epicardial approach for a single AF ablation procedure in a small cohort of 26 patients with AF<sup>49</sup>.

### Strategies to decrease thromboembolism

The use of novel oral anticoagulants to decrease the risk of stroke and systemic thromboembolism in patients with AF has gained increasing use and acceptance over the past several years following the publication of a number of landmark multicentre, randomized clinical trials comparing their efficacy with conventional vitamin K antagonists<sup>50-53</sup>. A meta-analysis of 12 studies totaling 54 875 patients showed a significant reduction of intracranial hemorrhage with these novel anticoagulants compared with vitamin K antagonists, and a trend toward reduced major bleeding<sup>54</sup>. These novel oral anticoagulants may also have a role in patients undergoing DC cardioversion. A sub-study of patients with AF who underwent cardioversion in the RE-LY (*Randomized Evaluation of Long-Term Anticoagulation Therapy*) trial showed that dabigatran (at two doses of 110 and 150 mg twice daily) is a reasonable alternative to warfarin, with low frequencies of stroke and major bleeding within 30 days of cardioversion<sup>55</sup>.

These novel oral anticoagulants may also have a role to play in the periprocedural anticoagulation of patients undergoing radiofrequency ablation for AF. Several registry and observational studies have suggested that dabigatran is as safe as periprocedural warfarin in patients undergoing AF ablation<sup>56-58</sup>, although one study suggested an increased risk of bleeding and thromboembolic complications with dabigatran compared with warfarin<sup>59</sup>. A prospective randomized controlled trial is required to definitively address the issue as to whether these novel oral anticoagulants can be used in place of warfarin for periprocedural anticoagulation in patients

undergoing AF ablation. Economic evaluation of these novel oral anticoagulants suggest that they may be cost effective as a first line treatment for the prevention of stroke and systemic embolism<sup>60</sup>, especially in patients at high risk of hemorrhage or stroke, unless international normalized ratio (INR) control with warfarin is already excellent<sup>61</sup>.

Another strategy to decrease thromboembolic events in patients with AF that is gaining favor involves the use of mechanical left atrial appendage (LAA) occlusion devices. In a systematic review of 14 studies, implantation of LAA occlusion devices in patients with AF was successful in 93% of cases, with periprocedural mortality and stroke rates of 1.1% and 0.6%, respectively; the overall incidence of stroke among all studies was 1.4% per annum<sup>62</sup>. A substudy of the PROTECT AF (*Percutaneous Closure of the LAA versus Warfarin Therapy for Prevention of Stroke in Patients with AF*) study reported that 32% of implanted patients had some degree of peridevice flow at 12 months on transoesophageal echocardiography, although this did not appear to be associated with an increased risk of thromboembolism compared to patients with no peridevice flow who discontinued warfarin<sup>63</sup>. A systematic review aimed at determining which subgroups of patients would benefit most from LAA closure devices looked at the location of atrial thrombi in patients with AF in a total of 34 studies<sup>64</sup>. The investigators concluded that patients with non-valvular AF may derive greater benefit from LAA closure devices – 56% of patients with valvular AF had atrial thrombi located outside the LAA, 22% in mixed cohorts and 11% in non-valvular AF patients.

## CARDIAC RESYNCHRONISATION THERAPY AND PACING

### Cardiac resynchronization therapy

Recent research in the area of cardiac resynchronization therapy (CRT) has looked at the long term effects of CRT pacing on LV and right ventricular (RV) function and further into which sub-groups of patients may derive greatest benefit from CRT pacing. A favorable RV functional response to CRT appears to be associated with improved survival in patients with CRT devices, and RV function was found to be an independent predictor of long term outcome after CRT insertion in a study of 848 CRT recipients<sup>65</sup>. Following the landmark MADIT-CRT (*Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy*) study, which demonstrated that CRT combined with implantable cardioverter defibrillator (ICD, CRT-D)

decreased the risk of heart failure events in relatively asymptomatic patients with a low ejection fraction and wide QRS complexes<sup>66</sup>, a number of subsequent analyses have provided further interesting information. This includes data on the benefits of CRT in reducing the risk of recurring heart failure events<sup>67</sup> and atrial arrhythmias<sup>68</sup>, identification of additional factors that are associated with improved response to CRT<sup>69,70</sup> and with a super-response (defined by patients in the top quartile of LVEF change)<sup>71</sup>, factors associated with greatest improvement in quality of life<sup>72</sup>, and information on optimal lead positioning of the LV lead<sup>73,74</sup>.

In a prospective, randomized controlled study to address whether ventricular dyssynchrony on echocardiography predicted response to CRT, Diab et al found that the presence of echocardiographic dyssynchrony identified patients who derived the most improvement from CRT, although patients without dyssynchrony also showed more benefit and less deterioration with CRT than without. The authors concluded that the latter group of patients should not be denied CRT<sup>75</sup>. CRT appeared to produce some benefits in patients with heart failure and a normal QRS duration, with patients experiencing an improvement in symptoms, exercise capacity and quality of life, although there was no difference in total or cardiovascular mortality in patients who received CRT compared with those receiving optimal pharmacological management<sup>76</sup>. Among patients with heart failure and prolonged QRS duration who received a CRT device, those with a left bundle branch block (LBBB) morphology derived greater benefit (lower risk of ventricular arrhythmias and death and improved echocardiographic parameters) compared with patients who had a non-LBBB QRS pattern (right bundle branch block (RBBB) or intraventricular conduction disturbances)<sup>77</sup>.

The issue of whether CRT in patients undergoing atrioventricular (AV) junction ablation for permanent AF was superior to conventional RV pacing in reducing heart failure events was addressed in a prospective, randomized, multicentre study involving 186 patients<sup>78</sup>. Over a median follow-up of 20 months (IQR 11-24 months) fewer patients in the CRT group (11%) experienced primary end point events (death from heart failure, hospitalization due to heart failure or worsening heart failure) compared with patients in the RV group (26%; CRT vs RV group: sub-hazard ratio (SHR) 0.37, 95% CI 0.18 to 0.73;  $p=0.005$ ). Total mortality was similar in both groups. In a follow-up analysis looking at the predictors of clinical improvement after the 'ablate

and pace' strategy, more patients in the CRT group responded to treatment (83% vs 63% in the RV group)<sup>79</sup>. CRT mode and echo-optimized CRT were found to be the only independent protective factors against non-response (HR=0.24, 95% CI 0.10 to 0.58,  $p=0.001$  and HR=0.22, 95% CI 0.07 to 0.77,  $p=0.018$ , respectively). In the PACE (*Pacing to Avoid Cardiac Enlargement*) trial, RV pacing in patients with bradycardia and preserved LVEF was associated with adverse LV remodelling and deterioration of systolic function at the second year, which was prevented by biventricular pacing<sup>80</sup>.

### Heart block and pacemakers

The long term survival of older patients (average age  $75 \pm 9$  years) with Mobitz I second degree AV block was examined in a retrospective cohort study of 299 patients<sup>81</sup>. The investigators found that 141 patients (47%) had a cardiac implantable electronic device (CIED) inserted during the follow-up period, of which 17 were ICDs. Patients with a CIED had greater cardiac comorbidity than those without a CIED, although CIED implantation was associated with a 46% reduction in mortality (HR 0.54, 95% CI 0.35 to 0.82;  $p=0.004$ ). In another observational study of the impact of the ventricular pacing site on LV function in children with AV block, van Geldrop et al found that LV fractional shortening was significantly higher with LV pacing than with RV pacing<sup>82</sup>.

Further research on the topic of whether cardiac pacing is beneficial in patients with neurally mediated syncope suggests that dual chamber pacing may be useful in patients with severe asystolic forms. In the randomized multicentre ISSUE-3 trial (*Third International Study on Syncope of Uncertain Etiology*) patients with syncope due to documented asystole on an implantable loop recorder were randomly assigned to dual chamber pacing with rate drop response or to sensing only<sup>83</sup>. Those assigned to dual chamber pacing had fewer syncopal episodes during follow-up (32% absolute and 57% relative reduction in syncope). A positive test with intravenous adenosine 50-triphosphate (ATP) has been shown to correlate with a subset of patients with neurally mediated syncope<sup>84</sup>. A randomized, multicentre trial of the potential benefit of the ATP test in elderly patients (mean age  $75.9 \pm 7.7$  years) with syncope of unknown origin reported that active dual chamber pacing in those with a positive ATP test reduced syncope recurrence risk by 75% (95% CI 44% to 88%)<sup>85</sup>. Long term outcome data on a distinct form of AV block, paroxysmal AV block, which cannot be explained by currently known mechanisms, suggest that these patients

have a long history of recurrent syncope and may benefit from cardiac pacing, although in a small series of 18 patients (followed up for up to 14 years), no patient had permanent AV block<sup>86</sup>. The prognosis among healthy individuals admitted with their first episode of syncope was studied in a Danish nationwide registry involving 37 017 patients with syncope and 185 085 age and sex matched controls<sup>87</sup>. Patients who were admitted with syncope had significantly increased all cause mortality, cardiovascular hospitalization, recurrent syncope and stroke event rates and were more likely to have a pacemaker or ICD inserted later.

### CIED related infection

CIED infection is recognized as a significant cause of morbidity, mortality, and increased healthcare costs. The clinical characteristics, outcome, and health care implications of CIED related infections and endocarditis was analyzed in a prospective cohort study using data from the *International Collaboration on Endocarditis-Prospective Cohort Study* (ICE-PCE) involving 61 centres in 28 countries<sup>88</sup>. CIED infection was diagnosed in 177 out of 2760 patients (6.4%). In-hospital and 1 year mortality rates were 14.7% (95% CI 9.8% to 20.8%) and 23.2% (95% CI 17.2% to 30.1%), respectively. The rate of concomitant valve infection was high (found in 66 patients, 37.3%, 95% CI 30.2% to 44.9%) and early device removal was associated with improved survival at 1 year. In an attempt to assess the long term outcomes and predictors of mortality in patients treated according to current recommendations for CIED infection, Deharo et al conducted a two-group matched cohort study of 197 cases of CIED infection<sup>89</sup>. Long term mortality rates were similar between cases and matched controls (14.3% vs 11.0% at 1 year and 35.4% vs 27.0% at 5 years, respectively; both  $p=NS$ ). Independent predictors of long term mortality were older age, CRT, thrombocytopenia, and renal insufficiency. In another study examining whether the timing of the most recent CIED procedure influenced the clinical presentation and outcome of lead associated endocarditis (LAE), investigators found that early LAE presented with signs and symptoms of local pocket infection, whereas a remote source of bacteremia was present in 38% of late LAE but only 8% of early LAE<sup>90</sup>. In-hospital mortality was low (early 7%; late 6%).



## VENTRICULAR ARRHYTHMIAS AND SUDDEN CARDIAC DEATH

### Epidemiology of sudden cardiac death

Sudden death is a frequent and well recognized risk in patients following myocardial infarction. In a study analyzing data from 1067 patients from VALIANT (*Valsartan in Acute Myocardial Infarction Trial*) who had sudden death, investigators found that a high proportion of the deaths occurred at home, although in-hospital events were more common early on<sup>91</sup>. Patients who were asleep were more likely to have unwitnessed events. Although sudden cardiac death (SCD) and coronary artery disease (CAD) have many risk factors in common, certain clinical and electrocardiographic parameters may be useful to help separate out the two risks. For example, in a study of 18 497 participants from the ARIC (*Atherosclerosis Risk in Communities*) study and the *Cardiovascular Health Study*, Soliman et al found that after adjusting for common CAD risk factors, hypertension, increased heart rate, QTc prolongation, and abnormally inverted T waves were found to be stronger predictors of high SCD risk<sup>92</sup>. In comparison, elevated ST segment height (measured at both the J point and 60 ms after the J point) was found to be more predictive of high incident CAD risk.

More research has also been performed on SCD in other sub-groups. In a prospective, national survey of sports related sudden death performed in France from 2005 to 2010, involving subjects 10-75 years of age, investigators found that the overall burden of sudden death was 4.6 per million population per year, with 6% of cases occurring in young competitive athletes and more than 90% of cases occurring in the context of recreational sports<sup>93</sup>. Bystander cardiopulmonary resuscitation (CPR) and initial use of cardiac defibrillation were the strongest independent predictors for survival to hospital discharge, although bystander CPR was only initiated in one third of cases. In a retrospective autopsy study of 902 young adults (mean age 38±11 years) who had suffered non-traumatic sudden death, the cause of sudden death was attributed to a cardiac condition in 715 (79.3%) and unexplained in 187 (20.7%)<sup>94</sup>. In another nationwide study on the incidence of SCD in persons aged 1-35 years, 7% of all deaths were attributed to SCD<sup>95</sup>. The incidence of SCD in the young, estimated to be 2.8% per 100 000 person-years, was higher than previously reported. Risk factors for SCD in post-menopausal women may include more novel parameters, such as higher pulse, higher waist-to-hip ratio, elevated white blood cell count, and ethni-

city (African Americans having a higher risk) as well as traditional risk factors<sup>96</sup>.

More intense research has been conducted in a variety of settings on the early repolarization syndrome (ERS) since landmark studies showed a link with idiopathic ventricular fibrillation and sudden death<sup>97,98</sup>. These include studies on ERS on cardiac arrest survivors with preserved ejection fraction<sup>99</sup>, in families with sudden arrhythmic death syndrome<sup>100</sup> and other families with an early repolarization pattern on the ECG<sup>101</sup>, and in Asian populations<sup>102</sup>. However, there is still some controversy over the exact clinical significance of these ECG findings and what the implications are<sup>103,104</sup>.

The genetics of inherited cardiac conditions and how specific genotypes can lead to clinical manifestations of disease, affect SCD risk or guide management continues to attract intense interest<sup>105-108</sup>. Results from the DARE (*Drug-induced Arrhythmia Risk Evaluation*) study, in which 167 single nucleotide polymorphisms spanning the NOS1AP gene, were evaluated in 58 Caucasian patients who had experienced drug induced QT prolongation and 87 Caucasian controls, demonstrated that common variations in the NOS1AP gene were associated with a significant increase in drug induced long QT syndrome<sup>109</sup>. This may have clinical implications for future pharmacogenomics testing in patients at risk of drug induced long QT syndrome and safer prescribing. In another study assessing whether non-cardiovascular hERG (*human Ether à go-go-Related Gene*) channel blockers are associated with an increased risk of SCD in the general population, investigators compared 1424 cases of SCD with 14 443 controls<sup>110</sup>. Use of hERG channel blockers was found to be associated with an increased risk of SCD and drugs with a high hERG channel inhibiting capacity had a higher risk of SCD than those with a low hERG channel inhibiting capacity.

### Implantable cardioverter defibrillators

The clinical parameters associated with death before appropriate ICD therapy in patients with ischemic heart disease who had an ICD inserted for primary prevention were assessed in a retrospective cohort study of 900 patients<sup>111</sup>. The investigators found that *New York Heart Association* (NYHA) functional class ≥ III, advanced age, diabetes mellitus, LVEF ≤25%, and a history of smoking were significant independent predictors of death without appropriate ICD therapy, and suggested that this information may facilitate a more patient tailored risk estimation. Another risk score for predicting acute procedural complications or death af-

ter ICD implantation using 10 readily available variables from 268 701 ICD implants was developed to provide useful information in guiding physicians on patient selection and determining the intensity of post-implant care required<sup>112</sup>. A risk score aimed at predicting the long term (8 years) benefit of primary prevention ICD implantation was applied to 11 981 patients from the MADIT-II trial<sup>113</sup>. The investigators found that patients with low and intermediate risk (0 or 1-2 risk factors, respectively) benefitted more from ICD implantation, compared with patients with high risk ( $\geq 3$  risk factors) who had multiple comorbidities, in which there was no significant difference in 8 years survival between ICD and non-ICD recipients.

Another risk score for the prediction of mortality in Medicare beneficiaries receiving ICD implantation for primary prevention was developed from a cohort of 17 991 patients and validated in a cohort of 27 893 patients<sup>114</sup>. Over a median follow-up of 4 years, 6741 (37.5%) patients in the development cohort and 8595 (30.8%) patients in the validation cohort died. Seven clinically relevant predictors of mortality were identified and used to develop a model for determining those patients at highest risk for death after ICD implantation. Future selection of ICD recipients for primary prevention ICDs may therefore be refined and more personalized to the individual patient's risk/ benefit profile with the use of such models, rather than being based predominantly on LVEF, as is recommended by current guidelines.

Other investigations, such as cardiac magnetic resonance (CMR) imaging to identify and characterize myocardial scar, may be a useful addition to future risk stratification of patients for primary prevention ICD implantation. The ability of scar characteristics assessed on CMR to predict ventricular arrhythmias was evaluated in a study of 55 patients with ischemic cardiomyopathy who received an ICD for primary prevention and in whom CMR with late gadolinium enhancement had been performed before ICD implantation<sup>115</sup>. All CMR derived scar tissue characteristics were found to be predictive for the occurrence of ventricular arrhythmias, supporting the potential use of this imaging modality to help refine risk stratification of patients and improve selection for ICD implantation. This finding was further supported by a prospective study of 137 patients evaluated with CMR before ICD implantation for primary prevention<sup>116</sup>. Myocardial scarring on CMR was found to be an independent predictor of adverse outcomes. Patients with significant scarring ( $>5\%$  of the left

ventricle) with LVEF  $>30\%$  had a similar risk to those with LVEF  $\leq 30\%$ , while in patients with LVEF  $\leq 30\%$ , minimal or no scarring was associated with low risk, similar to those with LVEF  $>30\%$ .

The use of intracardiac ICD parameters to assess risk has also received further attention. In a prospective, multicentre study of 63 ICD patients, T wave alternans and non-alternans variability (TWA/V) was found to be significantly greater before ventricular tachycardia/ventricular fibrillation (VT/VF) episodes than during baseline rhythm<sup>117</sup>. The investigators suggested that continuous measurements of TWA/V from the intracardiac ICD electrograms may be a useful parameter to detect impending VT/VF and allow the device to initiate pacing therapies to prevent the ventricular arrhythmias from occurring. In contrast, an early analysis of a prospective, single centre study on the use of ICD based ischemia monitoring on clinical care and patient management reported that this parameter was not clinically useful and actually increased the number of unscheduled outpatient visits in patients with this feature on their ICD compared with patients with ICDs without this capability<sup>118</sup>.

Reports on the complications and negative aspects of ICDs include problems associated with the Sprint Fidelis ICD leads<sup>119-121</sup> and potential psychological impact and phobic anxiety among ICD recipients<sup>122</sup>. In a study of 3253 patients from 117 Italian centres who underwent de novo implantation of a CRT-D device, investigators found that device related events were more frequent in patients who received CRT-D devices compared with those who received ICDs only (single or dual chamber), although these events were not associated with a worse clinical outcome<sup>123</sup>. In a multicentre, longitudinal cohort study of 104 049 patients receiving single and dual chamber ICDs, dual chamber device implantation was more common, but was associated with increased peri-procedural complications and in-hospital mortality compared with single chamber ICDs<sup>124</sup>. A retrospective, single centre cohort study of 334 hypertrophic cardiomyopathy patients with ICDs reported that this group of patients had significant cardiovascular mortality and were exposed to frequent inappropriate shocks and implant complications<sup>125</sup>. Adverse ICD related events (inappropriate shocks and/or implant complications) were seen in 101 patients (30%; 8.6% per year), and patients with CRT-D were more likely to develop implant complications than those with single chamber ICDs and had a higher 5-year cardiovascular mortality rate.



Strategies to reduce ICD complications and inappropriate shocks include using special diagnostic ICD algorithms to identify potential lead problems early<sup>126</sup>, and changes in ICD programming with a prolonged delay in therapy for tachyarrhythmias of  $\geq 200$  beats/min or higher, as demonstrated in the MADIT-RIT (*MADIT-Reduction in Inappropriate Therapy*) trial<sup>127</sup>. Increasing clinical experience is also being gained in the use of subcutaneous ICDs<sup>128,129</sup>, which holds great potential in reducing some types of ICD related complications, although an initial learning curve needs to be overcome first. Real world data of ICD implantation and use show that patients treated by very low volume operators (physicians who implanted  $\leq 1$  ICDs per year) were more likely to die or experience cardiac complications compared with operators who frequently performed ICD implantation<sup>130</sup>. Another strategy to reduce ICD complications is to improve the selection process of those patients who would truly benefit from these devices. In an observational outcome study of consecutive subjects referred to a regional inherited cardiac conditions clinic because of a relative who had sudden unexpected death, the number of ICDs inserted as a result of specialist assessment was found to be very small (2%)<sup>131</sup>.

### Out-of-hospital cardiac arrest

Survival from out-of-hospital cardiac arrest (OHCA) appears to have increased over the past several years, probably as a result of better pre-hospital care (early recognition, more effective CPR, faster emergency services response) and advances in the hospital management of patients following OHCA<sup>132,133</sup>. Data from the London Ambulance Service's cardiac arrest registry from 2007 to 2012 showed an improvement in OHCA survival over the 5 year study period<sup>134</sup>. In an observational Swedish registry study of 7187 patients with OHCA over an 18 year period, bystander CPR was found to increase from 46% to 73% (95% CI for OR 1.060 to 10.081 per year), early survival increase from 28% to 45% (95% CI 1.044 to 1.065), and survival to 1 month increase from 12% to 23% (95% CI 1.058 to 1.086)<sup>135</sup>. Strong predictors of early and late survival were a short interval from collapse to defibrillation, bystander CPR, female gender, and place of collapse. A large prospective cohort study of OHCA in North American adults involving 12 930 subjects (2042 occurring in a public place and 9564 at home) also found that the rate of survival to hospital discharge was better for arrests in public settings with automated external defibrillators (AEDs) applied by bystanders compared to

those that occurred at home (34% vs 12%, respectively; adjusted OR 2.49, 95% CI 1.03 to 5.99;  $p=0.04$ )<sup>136</sup>. Hospital characteristics associated with improved patient outcomes following OHCA were analyzed from the *Victorian Ambulance Cardiac Arrest Registry* of 9971 patients over an 8 year period<sup>137</sup>. Outcome following OHCA was found to be significantly improved in hospitals with 24 h cardiac interventional services (OR 1.40, 95% CI 1.12 to 1.74;  $p=0.003$ ) and patient reception between 08.00 and 17.00 h (OR 1.34, 95% CI 1.10 to 1.64;  $p=0.004$ ). OHCA in children was assessed in a prospective, population based study of victims younger than 21 years of age<sup>138</sup>. The incidence of pediatric OHCA was 9.0 per 100 000 pediatric person-years (95% CI 7.8 to 10.3), whereas the incidence of pediatric OHCA from cardiac causes was 3.2 (95% CI 2.5 to 3.9). The authors concluded that OHCA accounts for a significant proportion of pediatric mortality, although the vast majority of OHCA survivors have a neurologically intact outcome.

Studies on the optimal sequence of CPR measures to use in OHCA patients have reported varying results. In a meta-analysis of four randomized controlled clinical trials enrolling 1503 subjects with OHCA, no significant difference was found between chest compression first versus defibrillation first in the rate of return of spontaneous circulation, survival to hospital discharge or favorable neurologic outcomes, although subgroup analyses suggested that chest compression first may be beneficial for cardiac arrests with a prolonged response time<sup>139</sup>. In a more recent, nationwide, population based observational study involving OHCA patients in Japan who had a witnessed arrest and received shocks with public access AED, compression only CPR was found to be associated with a significantly higher rate of survival at 1 month and more favorable neurological outcomes compared with conventional CPR measures (chest compression and rescue breathing)<sup>140</sup>. However, for children and younger people who have OHCA from non-cardiac causes, and in people in whom there was a delay in starting CPR, other studies have suggested that conventional CPR is associated with better outcomes than chest compression only CPR<sup>141,142</sup>.

### CONCLUSIONS

Important progress has been made over the past few years in our understanding of basic and clinical cardiac electrophysiology which have advanced and improved the management of patients with heart rhythm disorders. Multiple studies have demonstrated an associa-

tion between AF and various systemic conditions and novel risk factors. These studies highlight the importance and complexity of this complex arrhythmia and further support the notion that AF is a systemic condition. Although many of these associations have not been shown to play a causal role, they may nonetheless prove useful clinically in future risk stratification scores for the diagnosis or treatment of AF. More research is still needed to increase our understanding of the underlying mechanisms responsible for the development and progression of AF and which patient subgroups will benefit most from specific treatments or the different options for anticoagulation.

The field of CRT and pacing has also progressed rapidly over the past few years with a lot of interest in the optimal clinical parameters for selection of patients, prediction of response, and adverse remodeling. Similarly, as our understanding of the substrate responsible for ventricular arrhythmias and SCD improves, the selection of suitable candidates for ICD therapy is becoming more refined. Research into the complications associated with implantable cardiac devices, such as device infection and inappropriate shocks from ICDs, remains important as indications for device implantation continue to expand and more and more patients with existing devices undergo device replacement procedures.

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