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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 resynchronisation therapy (CRT) for the treatment of patients with heart failure. Following the publication of major landmark randomised 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 favourable 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 haemoglobin (HbA1c) and poor glycaemic control,[1] coeliac disease,[2] rheumatoid arthritis[3] and psoriasis,[4] use of non-aspirin, non-steroidal anti-inflammatory drugs (NSAIDs),[5] and increased height.[6] 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 hospitalised with AF.[7] In another substudy of the Cardiovascular Health Study, investigators found that higher baseline circulating concentrations of total long chain n-3 polyunsaturated fatty acids (PUFA) were associated with a lower risk of incident AF.[8]

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,[9] and a community based study of 3220 patients which showed that new AF in patients with no history of AF before a

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myocardial infarction increased mortality in patients with myocardial infarction.[10] In a large Swedish registry study of 100 802 patients with AF, Friberg et al[11] found that ischaemic 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,[12] and among healthy women new onset AF was found to be independently associated with all cause cardiovascular and non-cardiovascular mortality.[13]

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 ≤80 beats/min) had a better quality of life and fewer symptoms than those whose AF was uncontrolled.[14] 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.[15] 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 hospitalisations 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).[16] 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[17] and that lenient rate control did not have an adverse effect on atrial and ventricular remodelling compared with strict rate control (although female gender was independently associated with significant adverse cardiac remodelling).[18] 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).[19] 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, randomised, open label trial of pharmacological cardioversion in patients with persistent AF, Yamase et al compared amiodarone with bepridil in 40 consecutive subjects.[20] 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 randomised controlled trials involving 1955 patients found that PUFA supplementation had no significant effect on AF prevention.[21] In the FORWARD trial (Randomised 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.[22] 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, randomised 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.[23] In contrast, another randomised, double blind, placebo controlled trial involving 199 patients who received either PUFA (2 g/day) or placebo for 4 weeks before direct current (DC) cardio-

version found that patients who received PUFA were more likely to be in sinus rhythm at 1 year follow-up compared with control patients.[24]

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 tachyarrhythmias in 261 patients (10.1%).[25] 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.[26,27] 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.[28] 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.[29] 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.[30] 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 randomised 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.[31] The investigators found no significant difference between the ablation and drug therapy groups in the cumulative burden of AF (90th 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 randomised study of AF ablation in patients with persistent AF, advanced heart failure and severe left ventricular (LV) systolic dysfunction, MacDonald et al[32] 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.[33]

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[34] who reported long term clinic outcomes of 83.6% (480 out of 574 patients) with a mean follow-up of 27±14 months using an extensive PV isolation approach in patients with both paroxysmal and persistent AF.[34] 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, randomised 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.[35] 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[36] and left atrial fibrosis as assessed by measuring echocardiograph derived calibrated integrated backscatter,[37] pericardial fat,[38] plasma biomarkers (such as plasma B-type natriuretic peptide values[39]), renal dysfunction,[40] and the metabolic syndrome.[41] 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.[42] In a small randomised 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).[43] 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 postoperative AF and decrease in-hospital stay in a multicentre, double blind, randomised trial of 336 patients.[44] In an interesting small randomised 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.[45]

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.[46] Factors associated with a higher risk of complications and/or 30-day readmission following an AF ablation were older age, female sex, prior AF hospitalisations, and recent hospital procedure experience. In another retrospective study of 565 patients, both the CHADS2 and CHA2DS2-VASc scores were found to be useful predictors of adverse events following AF ablation.[47]

The first randomised clinical trial comparing the efficacy and safety of catheter ablation of AF with surgical ablation involved 124 patients with drug refractory AF.[48] 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.[49]

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, randomised clinical trials comparing their efficacy with conventional vitamin K antagonists.[50-53] A meta-analysis of 12 studies totalling 54 875 patients showed a significant reduction of intracranial haemorrhage with these novel anticoagulants compared with vitamin K antagonists, and a trend toward reduced major bleeding.[54] 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 (Randomised 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.[55]

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,[56-58] although one study suggested an increased risk of bleeding and thromboembolic complications with dabigatran compared with warfarin.[59] A prospective randomised 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,[60] especially in patients at high risk of haemorrhage or stroke, unless international normalised ratio (INR) control with warfarin is already excellent.[61]

Another strategy to decrease thromboembolic events in patients with AF that is gaining favour 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.[62] 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 peri-device 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 peri-device flow who discontinued warfarin.[63] 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.[64] 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 resynchronisation therapy

Recent research in the area of cardiac resynchronisation therapy (CRT) has looked at the long term effects of CRT pacing on LV and right ventricular (RV) function and further into which subgroups of patients may derive greatest benefit from CRT pacing. A favourable 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.[65] Following the landmark MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronisation 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,[66] 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[67] and atrial arrhythmias,[68] identification of additional factors that are associated with improved response to CRT[69,70] and with a super-response (defined by patients in the top quartile of LVEF change),[71] factors associated with greatest improvement in quality of life,[72] and information on optimal lead positioning of the LV lead.[73,74]

In a prospective, randomised controlled study to address whether ventricular dyssynchrony on echocar-

diography 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.[75] 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.[76] 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).[77]

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, randomised, multicentre study involving 186 patients.[78] 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, hospitalisation 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).[79] CRT mode and echo-optimised CRT were found to be the only independent protective factors against nonresponse (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.[80]

Heart block and pacemakers

The long term survival of older patients (average age 75±9 years) with Mobitz I second degree AV block was examined in a retrospective cohort study of 299 patients.[81] 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.[82]

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 randomised multicentre ISSUE-3 trial (Third International Study on Syncope of Uncertain Aetiology) 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.[83] 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.[84] A randomised, multicentre trial of the potential benefit of the ATP test in elderly patients (mean age 75.9±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%).[85] 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.[86] 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.[87] Patients

who were admitted with syncope had significantly increased all cause mortality, cardiovascular hospitalisation, recurrent syncope and stroke event rates and were more likely to have a pacemaker or ICD inserted later.

CIED related infection

CIED infection is recognised 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 analysed in a prospective cohort study using data from the International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCE) involving 61 centres in 28 countries.[88] 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.[89] 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 bacteraemia was present in 38% of late LAE but only 8% of early LAE.[90] 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 recognised risk in patients following myocardial infarction. In a study analysing 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.[91] 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.[92] 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 subgroups. 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.[93] 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%).[94] In another nationwide study on the incidence of SCD in persons aged 1-35 years, 7% of all deaths were attributed to SCD.[95] 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 ethnicity (African Americans having a higher risk) as well as traditional risk factors.[96]

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

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.[105-108] 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.[109] 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 noncardiovascular 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.[110] 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 ischaemic heart disease who had an ICD inserted for primary prevention were assessed in a retrospective cohort study of 900 patients.[111] 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 after 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.[112] 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.[113] 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 (≥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.[114] 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 personalised 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 characterise 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 ischaemic cardiomyopathy who received an ICD for primary prevention and in whom CMR with late gadolinium enhancement had been performed before ICD implantation.[115] 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.[116] 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 ≤30%, while in patients with LVEF ≤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.[117] 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 ischaemia 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.[118]

Reports on the complications and negative aspects of ICDs include problems associated with the Sprint Fidelis ICD leads[119-121] and potential psychological impact and phobic anxiety among ICD recipients.[122] 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.[123] 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.[124] 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.[125] 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,[126] and changes in ICD programming with a prolonged delay in therapy for tachyarrhythmias of ≥200 beats/min or higher, as demonstrated in the MADIT-RIT (MADIT-Reduction in Inappropriate Therapy) trial.[127] Increasing clinical experience is also being gained in the use of subcutaneous ICDs,[128,129] 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 ≤1 ICDs per year) were more likely to die or experience cardiac complications compared with operators who frequently performed ICD implantation.[130] 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%).[131]

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.[132,133] 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.[134] 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).[135] 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).[136] Hospital characteristics associated with improved patient outcomes following OHCA were analysed from the Victorian Ambulance Cardiac Arrest Registry of 9971 patients over an 8 year period.[137] 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.[138] The incidence of paediatric OHCA was 9.0 per 100 000 paediatric person-years (95% CI 7.8 to 10.3), whereas the incidence of paediatric 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 paediatric 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 randomised 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 favourable neurologic outcomes, although subgroup analyses suggested that chest compression first may be beneficial for cardiac arrests with a prolonged response time.[139] 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 favourable neurological outcomes compared with conventional CPR measures (chest compression and rescue breathing).[140] 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.[141,142]

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 association 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 remodelling. 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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REFERENCES

1. Huxley RR, Alonso A, Lopez FL, et al. Type 2 diabetes, glucose homeostasis and incident atrial fibrillation: the Athero-

sclerosis Risk in Communities study. Heart 2012;98:133-8.
2. Emilsson L, Smith JG, West J, et al. Increased risk of atrial fibrillation in patients with coeliac disease: a nationwide cohort study. Eur Heart J 2011;32:2430-7.
3. Lindhardsen J, Ahlehoff O, Gislason GH, et al. Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. BMJ 2012;344:e1257.
4. Ahlehoff O, Gislason GH, Jorgensen CH, et al. Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish Nationwide Cohort Study. Eur Heart J 2012;33:2054-64.
5. Schmidt M, Christiansen CF, Mehnert F, et al. Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case-control study. BMJ 2011;343:d3450.
6. Rosenberg MA, Patton KK, Sotoodehnia N, et al. The impact of height on the risk of atrial fibrillation: the Cardiovascular Health Study. Eur Heart J 2012;33:2709-17.
7. Ball J, Carrington MJ, Stewart S. Mild cognitive impairment in high-risk patients with chronic atrial fibrillation: a forgotten component of clinical management? Heart 2013;99:542-7.
8. Wu JHY, Lemaitre RN, King IB, et al. Association of plasma phospholipid long-chain omega-3 fatty acids with incident atrial fibrillation in older adults: the Cardiovascular Health Study. Circulation 2012;125:1084-93.
9. Bansal N, Fan D, Hsu Cy, et al. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. Circulation 2013;127:569-74.
10. Jabre P, Jouven X, Adnet Fdr, et al. Atrial fibrillation and death after myocardial infarction: a community study. Circulation 2011;123:2094-100.
11. Friberg L, Benson L, Rosenqvist M, et al. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. BMJ 2012;344:e3522.
12. Avgil TM, Jackevicius CA, Rahme E, et al. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. JAMA 2012;307:1952-8.
13. Conen D, Chae CU, Glynn RJ, et al. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. JAMA 2011;305:2080-7.
14. Steg PG, Alam S, Chiang CE, et al. Symptoms, functional status and quality of life in patients with controlled and uncontrolled atrial fibrillation: data from the RealiseAF cross-sectional international registry. Heart 2012;98:195-201.
15. Camm AJ, Breithardt G+, Crijns H, et al. Real-life observations of clinical outcomes with rhythm- and rate-control therapies for atrial fibrillation: RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation). J Am Coll Cardiol 2011;58:493-501.
16. Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 2010;362:1363-73.
17. Groenveld HF, Crijns HJGM, Van den Berg MP, et al. The effect of rate control on quality of life in patients with permanent atrial fibrillation: data from the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) study. J Am Coll Cardiol 2011;58:1795-803.
18. Smit MD, Crijns HJGM, Tijssen JGP, et al. Effect of lenient versus strict rate control on cardiac remodeling in patients with atrial fibrillation: data of the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) study. J Am Coll Cardiol 2011;58:942-9.
19. Saksena S, Slee A, Waldo AL, et al. Cardiovascular outcomes in the AFFIRM trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management): an assessment of individual antiarrhythmic drug therapies compared with rate control with propensity score-matched analyses. J Am Coll Cardiol 2011;58:1975-85.
20. Yamase M, Nakazato Y, Daida H. Effectiveness of amiodarone versus bepridil in achieving conversion to sinus rhythm in patients with persistent atrial fibrillation: a randomised trial. Heart 2012;98:1067-71.
21. Liu T, Korantzopoulos P, Shehata M, et al. Prevention of atrial fibrillation with omega-3 fatty acids: a meta-analysis of randomised clinical trials. Heart 2011;97:1034-40.
22. Macchia A, Grancelli H, Varini S, et al. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) trial. J Am Coll Cardiol 2013;61:463-8.
23. Mozaffarian D, Marchioli R, Macchia A, et al. Fish oil and postoperative atrial fibrillation: the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) randomized trial. JAMA 2012;308:2001-11.
24. Nodari S, Triggiani M, Campia U, et al. n-3 Polyunsaturated fatty acids in the prevention of atrial fibrillation recurrences after electrical cardioversion: a prospective, randomized study. Circulation 2011;124:1100-6.
25. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med 2012;366:120-9.
26. Ritter MA, Kochhauser S, Duning T, et al. Occult atrial fibrillation in cryptogenic stroke: detection by 7-day electrocardiogram versus implantable cardiac monitors. Stroke 2013;44:1449-52.
27. Mittal S, Movsowitz C, Steinberg JS. Ambulatory external electrocardiographic monitoring: focus on atrial fibrillation. J Am Coll Cardiol 2011;58:1741-9.
28. Roten L, Schilling M, Haberlin A, et al. Is 7-day event triggered ECG recording equivalent to 7-day Holter ECG recording for atrial fibrillation screening? Heart 2012;98:645-9.
29. Charitos EI, Stierle U, Ziegler PD, et al. A comprehensive evaluation of rhythm monitoring strategies for the detection of atrial fibrillation recurrence: insights from 647 continuously monitored patients and implications for monitoring after therapeutic interventions. Circulation 2012;126:806-14.
30. Deftereos S, Giannopoulos G, Kossyvakis C, et al. Estimation of atrial fibrillation recency of onset and safety of

cardioversion using NTproBNP levels in patients with unknown time of onset. Heart 2011;97:914-17.
31. Cosedis Nielsen J, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med 2012;367:1587-95.
32. MacDonald MR, Connelly DT, Hawkins NM, et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. Heart 2011;97:740-7.
33. Hunter RJ, McCready J, Diab I, et al. Maintenance of sinus rhythm with an ablation strategy in patients with atrial fibrillation is associated with a lower risk of stroke and death. Heart 2012;98:48-53.
34. Miyazaki S, Kuwahara T, Kobori A, et al. Long-term clinical outcome of extensive pulmonary vein isolation-based catheter ablation therapy in patients with paroxysmal and persistent atrial fibrillation. Heart 2011;97:668-73.
35. Mun HS, Joung B, Shim J, et al. Does additional linear ablation after circumferential pulmonary vein isolation improve clinical outcome in patients with paroxysmal atrial fibrillation? Prospective randomised study. Heart 2012;98:480-4.
36. Chao TF, Sung SH, Wang KL, et al. Associations between the atrial electromechanical interval, atrial remodelling and outcome of catheter ablation in paroxysmal atrial fibrillation. Heart 2011;97:225-30.
37. den Uijl DW, Delgado V, Bertini M, et al. Impact of left atrial fibrosis and left atrial size on the outcome of catheter ablation for atrial fibrillation. Heart 2011;97:1847-51.
38. Wong CX, Abed HS, Molaee P, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. J Am Coll Cardiol 2011;57:1745-51.
39. Hussein AA, Saliba WI, Martin DO, et al. Plasma B-type natriuretic peptide levels and recurrent arrhythmia after successful ablation of lone atrial fibrillation. Circulation 2011;123:2077-82.
40. Tokuda M, Yamane T, Matsuo S, et al. Relationship between renal function and the risk of recurrent atrial fibrillation following catheter ablation. Heart 2011;97:137-42.
41. Mohanty S, Mohanty P, Di Biase L, et al. Impact of metabolic syndrome on procedural outcomes in patients with atrial fibrillation undergoing catheter ablation. J Am Coll Cardiol 2012;59:1295-301.
42. Lee G, Kalman JM, Vohra JK, et al. Dissociated pulmonary vein potentials following antral pulmonary vein isolation for atrial fibrillation: impact on long-term outcome. Heart 2011;97:579-84.
43. Deftereos S, Giannopoulos G, Kossyvakis C, et al. Colchicine for prevention of early atrial fibrillation recurrence after pulmonary vein isolation: a randomized controlled study. J Am Coll Cardiol 2012;60:1790-6.
44. Imazio M, Brucato A, Ferrazzi P, et al. Colchicine reduces postoperative atrial fibrillation: results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) atrial fibrillation substudy. Circulation 2011;124:2290-5.
45. Pokushalov E, Romanov A, Corbucci G, et al. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. J Am Coll Cardiol 2012;60:1163-70.
46. Shah RU, Freeman JV, Shilane D, et al. Procedural complications, rehospitalizations, and repeat procedures after catheter ablation for atrial fibrillation. J Am Coll Cardiol 2012;59:143-9.
47. Chao TF, LIN YJ, TSAO HM, et al. CHADS2 and CHA2DS2-VASc scores in the prediction of clinical outcomes in patients with atrial fibrillation after catheter ablation. J Am Coll Cardiol 2011;58:2380-5.
48. Boersma LVA, Castella M, van Boven W, et al. Atrial Fibrillation Catheter Ablation Versus Surgical Ablation Treatment (FAST): a 2-center randomized clinical trial. Circulation 2012;125:23-30.
49. Pison L, La Meir M, van Opstal J, et al. Hybrid thoracoscopic surgical and transvenous catheter ablation of atrial fibrillation. J Am Coll Cardiol 2012;60:54-61.
50. Lopes RD, Al-Khatib SM, Wallentin L, et al. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. Lancet 2012;380:1749-58.
51. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.
52. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92.
53. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
54. Dentali F, Riva N, Crowther M, et al. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. Circulation 2012;126:2381-91.
55. Nagarakanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. Circulation 2011;123:131-6.
56. Maddox W, Kay GN, Yamada T, et al. Dabigatran versus warfarin therapy for uninterrupted oral anticoagulation during atrial fibrillation ablation. J Cardiovasc Electrophysiol 2013;24:861-5.
57. Bassiouny M, Saliba W, Rickard J, et al. Use of dabigatran for periprocedural anticoagulation in patients undergoing catheter ablation for atrial fibrillation. Circ Arrhythm Electrophysiol 2013;6:460-6.
58. Kim JS, She F, Jongnarangsin K, et al. Dabigatran vs warfarin for radiofrequency catheter ablation of atrial fibrillation. Heart Rhythm 2013;10:483-9.

59. Lakkireddy D, Reddy YM, Di Biase L, et al. Feasibility and safety of dabigatran versus warfarin for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation: results from a multicenter prospective registry. J Am Coll Cardiol 2012;59:1168-74.
60. Kansal AR, Sorensen SV, Gani R, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in UK patients with atrial fibrillation. Heart 2012;98:573-8.
61. Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. Circulation 2011;123:2562-70.
62. Munkholm-Larsen S, Cao C, Yan TD, et al. Percutaneous atrial appendage occlusion for stroke prevention in patients with atrial fibrillation: a systematic review. Heart 2012;98:900-7.
63. Viles-Gonzalez JF, Kar S, Douglas P, et al. The clinical impact of incomplete left atrial appendage closure with the watchman device in patients with atrial fibrillation: a PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) substudy. J Am Coll Cardiol 2012;59:923-9.
64. Mahajan R, Brooks AG, Sullivan T, et al. Importance of the underlying substrate in determining thrombus location in atrial fibrillation: implications for left atrial appendage closure. Heart 2012;98:1120-6.
65. Leong DP, Hoke U, Delgado V, et al. Right ventricular function and survival following cardiac resynchronisation therapy. Heart 2013;99:722-8.
66. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329-38.
67. Goldenberg I, Hall WJ, Beck CA, et al. Reduction of the risk of recurring heart failure events with cardiac resynchronization therapy: MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). J Am Coll Cardiol 2011;58:729-37.
68. Brenyo A, Link MS, Barsheshet A, et al. Cardiac resynchronization therapy reduces left atrial volume and the risk of atrial tachyarrhythmias in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). J Am Coll Cardiol 2011;58:1682-9.
69. Goldenberg I, Moss AJ, Hall WJ, et al. Predictors of response to cardiac resynchronization therapy in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011;124:1527-36.
70. Pouleur AC, Knappe D, Shah AM, et al. Relationship between improvement in left ventricular dyssynchrony and contractile function and clinical outcome with cardiac resynchronization therapy: the MADIT-CRT trial. Eur Heart J 2011;32:1720-9.
71. Hsu JC, Solomon SD, Bourgoun M, et al. Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: the MADIT-CRT (multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy) study. J Am Coll Cardiol 2012;59:2366-73.
72. Veazie PJ, Noyes K, Li Q, et al. Cardiac resynchronization and quality of life in patients with minimally symptomatic heart failure. J Am Coll Cardiol 2012;60:1940-4.
73. Singh JP, Klein HU, Huang DT, et al. Left ventricular lead position and clinical outcome in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) trial. Circulation 2011;123:1159-66.
74. Kutyifa V, Zareba W, McNitt S, et al. Left ventricular lead location and the risk of ventricular arrhythmias in the MADIT-CRT trial. Eur Heart J 2013;34:184-90.
75. Diab IG, Hunter RJ, Kamdar R, et al. Does ventricular dyssynchrony on echocardiography predict response to cardiac resynchronisation therapy? A randomised controlled study. Heart 2011;97:1410-16.
76. Foley PWX, Patel K, Irwin N, et al. Cardiac resynchronisation therapy in patients with heart failure and a normal QRS duration: the RESPOND study. Heart 2011;97:1041-7.
77. Zareba W, Klein H, Cygankiewicz I, et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011;123:1061-72.
78. Brignole M, Botto G, Mont L, et al. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. Eur Heart J 2011;32:2420-9.
79. Brignole M, Botto GL, Mont L, et al. Predictors of clinical efficacy of ablate and pace therapy in patients with permanent atrial fibrillation. Heart 2012;98:297-302.
80. Chan JY-S, Fang F, Zhang Q, et al. Biventricular pacing is superior to right ventricular pacing in bradycardia patients with preserved systolic function: 2-year results of the PACE trial. Eur Heart J 2011;32:2533-40.
81. Coumbe AG, Naksuk N, Newell MC, et al. Long-term follow-up of older patients with Mobitz type I second degree atrioventricular block. Heart 2013;99:334-8.
82. van Geldorp IE, Delhaas T, Gebauer RA, et al. Impact of the permanent ventricular pacing site on left ventricular function in children: a retrospective multicentre survey. Heart 2011;97:2051-5.
83. Brignole M, Menozzi C, Moya A, et al. Pacemaker therapy in patients with neurally mediated syncope and documented asystole: third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. Circulation 2012;125:2566-71.
84. Deharo JC, Mechulan A, Giorgi R, et al. Adenosine plasma level and A2A adenosine receptor expression: correlation with laboratory tests in patients with neurally mediated syncope. Heart 2012;98:855-9.
85. Flammang D, Church TR, De Roy L, et al. Treatment of un-

explained syncope: a multicenter, randomized trial of cardiac pacing guided by adenosine 50 -triphosphate testing. Circulation 2012;125:31-6.
86. Brignole M, Deharo JC, De Roy L, et al. Syncope due to idiopathic paroxysmal atrioventricular block: long-term follow-up of a distinct form of atrioventricular block. J Am Coll Cardiol 2011;58:167-73.
87. Ruwald MH, Hansen ML, Lamberts M, et al. Prognosis among healthy individuals discharged with a primary diagnosis of syncope. J Am Coll Cardiol 2013;61:325-32.
88. Athan E, Chu VH, Tattevin P, et al. Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices. JAMA 2012;307:1727-35.
89. Deharo JC, Quatre A, Mancini J, et al. Long-term outcomes following infection of cardiac implantable electronic devices: a prospective matched cohort study. Heart 2012;98:724-31.
90. Greenspon AJ, Prutkin JM, Sohail MR, et al. Timing of the most recent device procedure influences the clinical outcome of lead-associated endocarditis: results of the MEDIC (Multicenter Electrophysiologic Device Infection Cohort). J Am Coll Cardiol 2012;59:681-7.
91. Ye S, Grunnert M, Thune JJ, et al. Circumstances and outcomes of sudden unexpected death in patients with high-risk myocardial infarction: implications for prevention. Circulation 2011;123:2674-80.
92. Soliman EZ, Prineas RJ, Case LD, et al. Electrocardiographic and clinical predictors separating atherosclerotic sudden cardiac death from incident coronary heart disease. Heart 2011;97:1597-601.
93. Marijon E, Tafflet M, Celermajer DS, et al. Sports-related sudden death in the general population. Circulation 2011;124:672-81.
94. Eckart RE, Shry EA, Burke AP, et al. Sudden death in young adults: an autopsy-based series of a population undergoing active surveillance. J Am Coll Cardiol 2011;58:1254-61.
95. Winkel BG, Holst AG, Theilade J, et al. Nationwide study of sudden cardiac death in persons aged 1–35 years. Eur Heart J 2011;32:983-90.
96. Bertoia ML, Allison MA, Manson JE, et al. Risk factors for sudden cardiac death in post-menopausal women. J Am Coll Cardiol 2012;60:2674-82.
97. Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008;358:2016-23.
98. Tikkanen JT, Anttonen O, Junttila MJ, et al. Long-term outcome associated with early repolarization on electrocardiography. N Engl J Med 2009;361:2529-37.
99. Derval N, Simpson CS, Birnie DH, et al. Prevalence and characteristics of early repolarization in the CASPER registry: cardiac arrest survivors with preserved ejection fraction registry. J Am Coll Cardiol 2011;58:722-8.
100. Nunn LM, Bhar-Amato J, Lowe MD, et al. Prevalence of J-point elevation in sudden arrhythmic death syndrome families. J Am Coll Cardiol 2011;58:286-90.
101. Gourraud JB, Le Scouarnec S, Sacher F, et al. Identification of large families in early repolarization syndrome. J Am Coll Cardiol 2013;61:164-72.
102. Haruta D, Matsuo K, Tsuneto A, et al. Incidence and prognostic value of early repolarization pattern in the 12-lead electrocardiogram. Circulation 2011;123:2931-7.
103. Bastiaenen R, Behr ER. Early repolarisation: controversies and clinical implications. Heart 2012;98:841-7.
104. Junttila MJ, Sager SJ, Tikkanen JT, et al. Clinical significance of variants of J-points and J-waves: early repolarization patterns and risk. Eur Heart J 2012;33:2639-43.
105. Bastiaenen R, Behr ER. Sudden death and ion channel disease: pathophysiology and implications for management. Heart 2011;97:1365-72.
106. Nunn LM, Lambiase PD. Genetics and cardiovascular disease-causes and prevention of unexpected sudden adult death: the role of the SADS clinic. Heart 2011;97:1122-7.
107. Corrado D, Basso C, Pilichou K, et al. Molecular biology and clinical management of arrhythmogenic right ventricular cardiomyopathy/dysplasia. Heart 2011;97:530-9.
108. Napolitano C, Bloise R, Monteforte N, et al. Sudden cardiac death and genetic ion channelopathies: long QT, Brugada, short QT, catecholaminergic polymorphic ventricular tachycardia, and idiopathic ventricular fibrillation. Circulation 2012;125:2027-34.
109. Jamshidi Y, Nolte IM, Dalageorgou C, et al. Common variation in the NOS1AP gene is associated with drug-induced QT prolongation and ventricular arrhythmia. J Am Coll Cardiol 2012;60:841-50.
110. van Noord C, Sturkenboom MCJM, Straus SMJM, et al. Non-cardiovascular drugs that inhibit hERG-encoded potassium channels and risk of sudden cardiac death. Heart 2011;97:215-20.
111. van Rees JB, Borleffs CJW, van Welsenes GH, et al. Clinical prediction model for death prior to appropriate therapy in primary prevention implantable cardioverter defibrillator patients with ischaemic heart disease: the FADES risk score. Heart 2012;98:872-7.
112. Haines DE, Wang Y, Curtis J. Implantable cardioverter-defibrillator registry risk score models for acute procedural complications or death after implantable cardioverter-defibrillator implantation. Circulation 2011;123:2069-76.
113. Barsheshet A, Moss AJ, Huang DT, et al. Applicability of a risk score for prediction of the long-term (8-year) benefit of the implantable cardioverter-defibrillator. J Am Coll Cardiol 2012;59:2075-9.
114. Bilchick KC, Stukenborg GJ, Kamath S, et al. Prediction of mortality in clinical practice for Medicare patients undergoing defibrillator implantation for primary prevention of sudden cardiac death. J Am Coll Cardiol 2012;60:1647-55.
115. de Haan S, Meijers TA, Knaapen P, et al. Scar size and characteristics assessed by CMR predict ventricular arrhythmias in ischaemic cardiomyopathy: comparison of previously validated models. Heart 2011;97:1951-6.
116. Klem I, Weinsaft JW, Bahnson TD, et al. Assessment of

myocardial scarring improves risk stratification in patients evaluated for cardiac defibrillator implantation. J Am Coll Cardiol 2012;60:408-20.
117. Swerdlow C, Chow T, Das M, et al. Intracardiac electrogram T-wave alternans/variability increases before spontaneous ventricular tachyarrhythmias in implantable cardioverter-defibrillator patients: a prospective, multi-center study. Circulation 2011;123:1052-60.
118. Forleo GB, Tesauro M, Panattoni G, et al. Impact of continuous intracardiac ST-segment monitoring on mid-term outcomes of ICD-implanted patients with coronary artery disease. Early results of a prospective comparison with conventional ICD outcomes. Heart 2012;98:402-7.
119. Hauser RG, Maisel WH, Friedman PA, et al. Longevity of Sprint Fidelis implantable cardioverter-defibrillator leads and risk factors for failure: implications for patient management. Circulation 2011;123:358-63.
120. Birnie DH, Parkash R, Exner DV, et al. Clinical predictors of Fidelis lead failure: report from the Canadian Heart Rhythm Society Device Committee. Circulation 2012;125:1217-25.
121. Parkash R, Thibault B, Sterns L, et al. Sprint Fidelis lead fractures in patients with cardiac resynchronization therapy devices: insight from the Resynchronization/ Defibrillation for Ambulatory Heart Failure (RAFT) study. Circulation 2012;126:2928-34.
122. Cho EYN, von Känel R, Marten-Mittag B, et al. Determinants and trajectory of phobic anxiety in patients living with an implantable cardioverter defibrillator. Heart 2012;98:806-12.
123. Landolina M, Gasparini M, Lunati M, et al. Long-term complications related to biventricular defibrillator implantation: rate of surgical revisions and impact on survival: insights from the Italian Clinical Service Database. Circulation 2011;123:2526-35.
124. Dewland TA, Pellegrini CN, Wang Y, et al. Dual-chamber implantable cardioverter-defibrillator selection is associated with increased complication rates and mortality among patients enrolled in the NCDR implantable cardioverter-defibrillator registry. J Am Coll Cardiol 2011;58:1007-13.
125. O'Mahony C, Lambiase PD, Quarta G, et al. The long-term survival and the risks and benefits of implantable cardioverter defibrillators in patients with hypertrophic cardiomyopathy. Heart 2012;98:116-25.
126. Swerdlow CD, Sachanandani H, Gunderson BD, et al. Preventing overdiagnosis of implantable cardioverter-defibrillator lead fractures using device diagnostics. J Am Coll Cardiol 2011;57:2330-9.
127. Moss AJ, Schuger C, Beck CA, et al. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 2012;367:2275-83.
128. Olde Nordkamp LRA, Dabiri Abkenari L, Boersma LVA, et al. The entirely subcutaneous implantable cardioverter-defibrillator: initial clinical experience in a large Dutch cohort. J Am Coll Cardiol 2012;60:1933-9.
129. Jarman JWE, Lascelles K, Wong T, et al. Clinical experience of entirely subcutaneous implantable cardioverter defibrillators in children and adults: cause for caution. Eur Heart J 2012;33:1351-9.
130. Lyman S, Sedrakyan A, Do H, et al. Infrequent physician use of implantable cardioverter-defibrillators risks patient safety. Heart 2011;97:1655-60.
131. Caldwell J, Moreton N, Khan N, et al. The clinical management of relatives of young sudden unexplained death victims; implantable defibrillators are rarely indicated. Heart 2012;98:631-6.
132. Perkins GD, Brace SJ, Smythe M, et al. Out-of-hospital cardiac arrest: recent advances in resuscitation and effects on outcome. Heart 2012;98:529-35.
133. Nolan JP, Lyon RM, Sasson C, et al. Advances in the hospital management of patients following an out of hospital cardiac arrest. Heart 2012;98:1201-6.
134. Fothergill RT, Watson LR, Chamberlain D, et al. Increases in survival from out-of-hospital cardiac arrest: a five year study. Resuscitation 2013;84:1089-92.
135. Adielsson A, Hollenberg J, Karlsson T, et al. Increase in survival and bystander CPR in out-of-hospital shockable arrhythmia: bystander CPR and female gender are predictors of improved outcome. Experiences from Sweden in an 18-year perspective. Heart 2011;97:1391-6.
136. Weisfeldt ML, Everson-Stewart S, Sitlani C, et al. Ventricular tachyarrhythmias after cardiac arrest in public versus at home. N Engl J Med 2011;364:313-21.
137. Stub D, Smith K, Bray JE, et al. Hospital characteristics are associated with patient outcomes following out-of-hospital cardiac arrest. Heart 2011;97:1489-94.
138. Bardai A, Berdowski J, van der Werf C, et al. Incidence, causes, and outcomes of out-of-hospital cardiac arrest in children: a comprehensive, prospective, population-based study in the Netherlands. J Am Coll Cardiol 2011; 57:1822-8.
139. Meier P, Baker P, Jost D, et al. Chest compressions before defibrillation for out-of-hospital cardiac arrest: a meta-analysis of randomized controlled clinical trials. BMC Med 2010;8:52.
140. Iwami T, Kitamura T, Kawamura T, et al. Chest compression-only cardiopulmonary resuscitation for out-of-hospital cardiac arrest with public-access defibrillation: a nationwide cohort study. Circulation 2012;126:2844-51.
141. Kitamura T, Iwami T, Kawamura T, et al. Conventional and chest-compression-only cardiopulmonary resuscitation by bystanders for children who have out-of-hospital cardiac arrests: a prospective, nationwide, population-based cohort study. Lancet 2010;375:1347-54.
142. Ogawa T, Akahane M, Koike S, et al. Outcomes of chest compression only CPR versus conventional CPR conducted by lay people in patients with out of hospital cardiopulmonary arrest witnessed by bystanders: nationwide population based observational study. BMJ 2011;342:c7106.