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Cardiac arrhythmias and pacing*

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Atrial fibrillation

Clinical trials. In the last two years, a number of landmark clinical trials have been published which further our understanding and clinical management of patients with atrial fibrillation (AF). Two of the major goals in the treatment of this condition include reducing progression or recurrence of the arrhythmia and decreasing the risk of cardiovascular events, thereby improving quality of life and decreasing morbidity. Following on from a large body of evidence from pre-clinical studies, small clinical trials and meta-analyses suggesting that blockade of the renin-angiotensin system has beneficial effects on the pathophysiology of AF,[1] two large multi-centre, placebo-controlled, randomised trials were conducted to determine the effects of angiotensin II- receptor blockers (ARBs) on AF. The first of these trials, published in 2009, tested the hypothesis that the ARB valsartan could reduce the recurrence of AF in patients with underlying cardiovascular disease, diabetes or left atrial enlargement and a history of documented AF, in addition to established therapies.[2] A total of 1442 patients were enrolled into the study-722 assigned to the valsartan group (target dose 320 mg) and 720 to the placebo group. The investigators found that treatment with valsartan had no significant effect on AF recurrence (AF recurred 51.4% in the valsartan group and 52.1% in the placebo group, $p = 0.73$) over a relatively short follow up-period of one year. The second large ARB randomised-controlled trial published this year evaluated whether irbesartan would reduce the risk of cardiovascular events in patients with AF.[3] Patients with a history of risk factors for stroke and a systolic blood pressure of at least 110 mmHg were randomly assigned to receive either irbesartan (target dose of 300 mg once daily) or placebo. Patients for this study were already enrolled in one of two other AF trials looking at clopidogrel plus aspirin versus aspirin alone or versus oral anticoagulants. Essentially, the investigators found that irbesartan did not reduce cardiovascular events or hospitalization rates for AF (total of 9016 enrolled with a mean follow up of 4.1 years) and that, not surprisingly, more patients in the irbesartan group had symptomatic hypotension and renal dysfunction compared with the placebo group. Although the main findings from both of these large RCTs were negative, it should be noted that they were secondary prevention studies, i.e. patients already had established AF, and also had more advanced stages of disease (over 80% of patients in both studies had a history of persistent or permanent AF), implying that the substrate for AF

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was already well established in both study populations. It could be argued that blockade of the renin-angiotensin system may be a more effective strategy if performed earlier during the natural history of the disease or even before AF develops (i.e. primary prevention), since angiotensin-converting enzyme inhibitors and ARBs may prevent, but not necessarily reverse, the electrical and structural remodelling that leads to the development and progression of the arrhythmia. In support of this, a smaller randomised single-centre study of 62 patients with lone AF, with no history of hypertension or heart disease, presenting to the emergency department reported that patients given ramipril (5 mg per day) had significantly fewer AF relapses during a 3-year follow up period compared with patients given placebo.[4]

A significant new addition to the pharmacological options available for treating AF has been the emergence of dronedarone, a multichannel blocker with similar structural and electrophysiological properties to amiodarone with the main exception being removal of iodine and the addition of a methane-sulfonyl group.[5] These structural changes result in decreased lipophilicity, shortened half-life (to approximately 24 hours), reduced tissue accumulation and theoretically fewer side-effects compared with those associated with amiodarone. The ATHENA (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of Hospitalization or death from any cause in patients with atrial fibrillation/ flutter) trial was a ground breaking study published in early 2009 evaluating the effect of dronedarone on cardiovascular events in patients with AF.[6] In this trial, 4628 patients with AF (paroxysmal or persistent) or atrial flutter who had an additional risk factor for death (age ≥70 years, diabetes, history of stroke/ TIA, systemic embolism, left atrial diameter ≥50 mm and ejection fraction ≤40%) were randomly assigned to receive dronedarone (400 mg twice daily) or placebo. Over a mean follow-up of 21 ± 5 months, the investigators found that patients in the dronedarone group had significantly lower primary outcome of first hospitalization due to cardiovascular events or death compared with the placebo group [734 (32%) *vs.* 917 (39%), respectively, p <0.001]. Mortality from cardiac arrhythmias was significantly lower in the dronedarone group, although there was no overall difference in all-cause mortality. Interestingly, there was also a small but statistically significant reduction in acute coronary syndromes in the dronedarone group- the exact reason for this remains unclear. Patients taking dronedarone had higher rates of bradycardia, QT-prolongation, nausea, diarrhea, rash and increased serum creatinine compared with placebo. There were no significant differences in rates of thyroid- and pulmonary-related adverse events between the two groups, although, as acknowledged by the investigators in their discussion, the follow up period of 21 months may have been too short to detect such adverse effects, which may take more than 2 years to develop, as is often observed with amiodarone. In the original ATHENA trial and also a subsequent post-hoc analysis,[7] there was no evidence of harm in patients with heart failure or those with a low ejection fraction and NYHA class II or III symptoms. This contrasts with results from the earlier ANDROMEDA (ANtiarrhythmic trial with DROnedarone in Moderate to severe congestive heart failure Evaluating morbidity DecreAse) study, which was terminated early due to excess mortality in the dronedarone group.[8] The reason for this difference may be attributed to the exclusion of patients with NYHA class IV symptoms in the ATHENA study and the fact that the ANDROMEDA study also included patients with a recent exacerbation of heart failure. Nonetheless, in view of the results from the ANDROMEDA study, the authors warned against use of dronedarone in patients with severe heart failure and left ventricular dysfunction. This is reflected in the latest European and American guidelines, which propose that dronedarone can be used as a first line pharmacological option in patients with symptomatic AF, including those with structural heart disease, coronary artery disease, hypertensive heart disease and stable heart failure with NYHA class I or II symptoms, but should not be used in patients with NYHA class III or IV symptoms or recently unstable heart failure.[9,10] A number of post-hoc analyses of the ATHENA trial have been published providing further evidence for several beneficial effects of dronedarone. These include a reduction in stroke risk from 1.8% per year to 1.2% per year,[11] and favourable effects on rhythm and rate control.[12]

Another newly emerging drug that may have a role to play in the pharmacological cardioversion of AF is the atrial-selective anti-arrhythmic drug vernakalant (RSD1235).[13] Vernakalant is one of several new agents that have been designed to target atrial-specific ion channels and in doing so, theoretically reduce or limit the risk of ventricular proarrhythmia. In an open label trial assessing the efficacy of vernakalant in the cardioversion of AF, the intravenous agent was found to convert 50.9% of patients with AF (out of a total of 236) to sinus rhythm with a median time to conversion of 14 minutes among responders.[14] There were no episodes of ventricular arrhythmias and the drug was relatively well tolerated, apart from 10 patients (4.2%) having to discontinue treatment due to side effects (most commonly hypotension). In a more recent small randomized trial of 254 patients with recent onset AF (3 to 48 hours duration), vernakalant (10 min infusion of 3 mg/kg followed by a second 10 minutes infusion of 2mg/kg if patient was still in AF after a 15 min observation period) was compared with intravenous amiodarone (5 mg/kg over 60 min followed by 50 mg maintenance infusion over 60 mins).[15] A greater number of patients achieved the primary endpoint of conversion to sinus rhythm within 90 minutes in the vernakalant group compared with the amiodarone group (60 of 116 [51.7%] compared with 6 of 116 [5.2%], p <0.0001, respectively). The median time of cardioversion in the vernakalant patients that responded was 11 minutes and this was associated with a higher rate of symptom relief compared with amiodarone. Both drugs were well tolerated in this study and there were no cases of ventricular arrhythmias.

A small randomized study of 61 patients with heart failure and persistent AF contributed additional useful data towards the ongoing issue of rate versus rhythm control in patients with heart failure and AF.[16] Patients in this study were randomly assigned to a rhythm control strategy (oral amiodarone and electrical cardioversion) or rate control with beta-blockers and/ or digoxin

(target heart rate <80 bpm at rest and <110 bpm after walking). The investigators found that restoration of sinus rhythm in patients with AF and heart failure improved quality of life and left ventricular function compared with a strategy of rate control (66% in the rhythm control group were in sinus rhythm at one year and 90% in the rate control group achieved the target heart rate). For patients with AF in whom a rate control strategy has been decided upon, the optimal target heart rate has remained controversial. Guidelines have previously recommended strict rate control, although this was not based on clinical evidence. In an attempt to address this issue, a prospective, multicentre, randomised trial was conducted to test the hypothesis that lenient rate control was not inferior to strict rate control in preventing cardiovascular events in patients with permanent AF.[17] The investigators found that of the 614 patients recruited into the study, the frequencies of symptoms and adverse events were similar between patients assigned to a lenient rate-control strategy (resting heart rate <110 bpm) compared to those assigned to a strict rate-control strategy (resting heart rate <80b pm and heart rate during moderate exercise <110 bpm). A lenient- control strategy was easier to achieve as more patients in this group attained their heart rate target compared with the strict-control group (97.7% *vs.* 67.0%, p <0.001).

Despite some promising results from pre-clinical experiments and observational studies in humans,[18-20] the potential beneficial effects of polyunsaturated fatty acids (PUFA) in atrial fibrillation have not been confirmed from the results of several prospective randomised trials reported recently. The largest and most comprehensive study to date designed to address this issue involved a prospective, multicentre, randomised controlled trial of 663 patients with confirmed paroxysmal (n = 542) or persistent (n = 121) AF, with no substantial structural heart disease and in sinus rhythm at baseline.[21] Patients were randomly assigned to take prescription PUFA (8 g/day) or placebo for the first 7 days, followed by PUFA (4 g/day) or placebo thereafter for 24 weeks. Despite the assigned treatment being relatively well tolerated in both groups and plasma levels of eicosapentaenoic and docosahexaenoic acid being significantly higher in the prescription group than in the placebo group at weeks 4 and 24, the investigators found no reduction in AF recurrence over 6 months between the two groups. Two smaller prospective, placebo-controlled, randomised studies investigating the effects of PUFA in patients after electrical cardioversion of AF[22] and post-cardiac surgery[23] have failed to demonstrate a beneficial action of PUFA in decreasing the recurrence or incidence of AF.

Strategies to decrease thromboembolism

Important advances have been made in the area of stroke prevention in patients with AF over the last two years, which are likely to have a significant impact on future clinical management. In the RE-LY study (Randomized Evaluation of Long-term anticoagulation therapY), two fixed doses (110 mg or 150 mg twice daily) of a new oral direct thrombin inhibitor, dabigatran, were compared with warfarin in over 18,000 patients with AF and at least 1 additional risk factor for stroke.[24] The investigators found that patients taking the 110 mg dose of dabigatran experienced similar rates of stroke and systemic embolism compared with those on warfarin, but had lower rates of major haemorrhage, while subjects taking the 150 mg dose had *lower* rates of stroke and systemic embolism, with similar rates of major haemorrhage. Results from this study have been so impressive, that dabigatran has since been incorporated into the latest European and American guidelines on AF as an alternative to warfarin for the prevention of stroke and systemic embolism in patients with paroxysmal and permanent AF.[9,25] As 80% of the active drug is excreted by the kidneys and patients with a creatinine clearance of <30 ml/min were excluded from the RE-LY trial, dabigatran should be used with caution in patients with significant renal impairment. The dose of dabigatran approved by the US Food and Drug Administration in October 2010 was 150 mg bd in patients with non-valvular AF with a reduced dose of 75 mg bd for those mild renal impairment (creatinine clearance of 15 to 30 mL/min). There are currently no dosing recommendations for patients with a creatinine clearance below 15 ml/min or those on dialysis. In addition to the superiority of dabigatran (150 mg twice daily) over warfarin with regards to stroke and systemic embolism, another major advantage is that there is no need for INR monitoring. However, disadvantages include the lack of a specific antedote (its half-life is 12 - 17hours) and a slightly increased risk of non-haemorrhagic side effects, including dyspepsia. How this promising new oral anticoagulation will be incorporated into current local practices around the world will require future evaluation and consideration. For example, there may be little to be gained from switching patients already on warfarin and excellent INR control to dabigatran, while patients with poor INR control or those who are newly started on oral anticoagulation may derive greater benefit. Local standards of care with regards to anticoagulation control and follow up may also be an important consideration, as concluded in a sub-analysis of the RE-LY study in which the investigators found that sites with poor INR control and greater bleeding from warfarin may experience greater benefit from dabigatran 150 mg twice daily.[26] Other sub-studies following on from the original RE-LY trial have demonstrated that the benefits of dabigatran are similar between patients who have never been on a vitamin K antagonist (VKA-naive patients) and VKA-experienced patients,[27] and that dabigatran can be used as a safe alternative to warfarin in patients requiring cardioversion.[28]

In the ACTIVE A study, the ACTIVE (AF clopidogrel trial with irbesartan for prevention of vascular events) investigators evaluated whether the addition of clopidogrel to aspirin would reduce the risk of vascular events compared with aspirin alone in patients for whom a vitamin K antagonist was considered unsuitable.[29] The ACTIVE W trial had previously demonstrated that the combination of aspirin and clopidogrel was inferior to oral anticoagulation for the prevention of vascular events in patients with AF at high risk of stroke.[30] In the ACTIVE A study, involving 7554 and a median follow up of 3.6 years, the investigators found that the combination of both anti-platelet agents reduced the risk of major vascular events, especially

stroke, compared with aspirin alone but at the price of increased risk of major haemorrhage. The clinical implication of the ACTIVE A and ACTIVE W trials are that oral anticoagulation is superior to the combination of aspirin and clopidogrel in stroke prevention in AF patients, but for patients that are unsuitable for oral anticoagulation, the combination of antiplatelets is superior to aspirin alone, although the risk of major haemorrhage is also greater. This reinforces the need for appropriate counselling and risk stratification of patients when deciding upon the most suitable strategy to lower the risk of vascular events in AF patients. Another important randomised controlled clinical trial involving patients who are not suitable for a vitamin K antagonist involved the use of new oral direct and competitive inhibitor of factor Xa, apixaban.[31] The AVERROES (Apixaban versus acetylsalicylic acid to prevent stroke in AF patients who have failed or are unsuitable for vitamin K antagonist treatment) study involved the random assignment of 5599 patients with AF (involving 522 centres in 36 countries) to apixaban (5 mg twice daily) or aspirin (81 to 324 mg per day).[32] In this study, patients with AF were 50 years or older and had to have at least one risk factor for stroke in addition to being unable to take a vitamin K antagonist, either because it was already demonstrated to be unsuitable or deemed to be unsuitable. The investigators found that apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of bleeding or intracranial haemorrhage and also reduced the risk of a first hospitalization for a cardiovascular cause.

Recent studies in the field of novel mechanical approaches to stroke prevention in AF include the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF) study.[33] In this non-inferiority study, the efficacy and safety of a novel percutaneous left atrial appendage (LAA) closure device was compared with warfarin treatment in 707 patients with non-valvular AF. Study participants had to have at least one risk factor for stroke (in addition to AF) and were assigned in a 2:1 ratio to receive LAA-closure device and subsequent discontinuation of warfarin or warfarin alone (with a target INR of between 2.0 and 3.0). The LAA-closure device was successfully implanted in 88% of subjects assigned to the intervention group. After a mean follow-up of 18 ± 10 months, the primary efficacy event rate of stroke (ischaemic or haemorrhagic) was 3.0 per 100 patient-years (95% CI: 1.9 - 4.5) in the intervention group and 4.9 per 100 patient-years (95% CI: 2.8 - 7.1) in the control group. Primary safety events were more frequent in the intervention group than in the control group, mainly related to peri-procedural complications (pericardial effusion in 4.8%, major bleeding in 3.5% and peri-procedural ischaemic stroke in 1.1%). This important study demonstrates that the Watchman (Atritech, Plymouth, Minnesota, USA) LAA-closure device might provide an alternative strategy to oral anticoagulation for the prevention of stroke in high risk patients with non-valvular AF and at high thromboembolic risk, although the trade-off is an increased risk of peri-procedural complications related to device implantation. As with all new interventional procedures, safety of the Watchman LAA-closure device is likely to improve with increased operator experience and familiarity with the new technology.[34] Longer-term follow-up data with an earlier percutaneous LAA-closure device, PLAATO (Percutaneous left atrial appendage transcatheter occlusion) system,[35] suggests that such devices can lower the annualized risk of stroke/ transient ischaemic attack (TIA) compared with the anticipated stroke/ TIA risk assessed using the CHADS2 score (3.8% per year and 6.6% per year, respectively), although event rates still remain significant.[36]

Epidemiology and genetics of AF

Epidemiological studies have shed further light to the mechanisms underlying AF and identified novel risk factors. Using data from the Framingham Heart Study, investigators identified a prolonged PR interval (greater than 200 ms) as a predictor of incident AF, pacemaker implantation and all-cause mortality in 7575 individuals (mean age 47 years; 54% women).[37] This study contradicts the previously held belief that first-degree heart block is benign[38] and raises further questions as to the mechanism of how a prolonged PR interval might increase the risk of developing AF. In another study using 4764 participants from the Framingham Heart Study, a novel risk score was developed aimed to predict an individual's absolute risk for developing AF.[39] Age, sex, body-mass index, systolic blood pressure, treatment for hypertension, PR interval, clinically significant cardiac murmur, and heart failure were all found to be associated with AF (p <0.05, except body-mass index p = 0.08). When incorporated in a risk score, the clinical model C statistic was 0.78 (95% CI: 0.76 - 0.80). In a subsequent study, the same investigators looked at the relation between a number of plasma biomarkers and incident AF using the Framingham cohort and found that B-type natriuretic peptide (BNP) was a predictor of incident AF and improved risk stratification, increasing the C-statistic from 0.78 (95% CI: 0.75 – 0.81) to 0.80 (95% CI: 0.78 – 0.83).[40] In another community-based population study of older adults (n = 5445) who participated in the Cardiovascular Health Study, NT-proBNP was found to predict new-onset AF, independent of any other previously described risk factor.[41] Similar findings have now been reported in a Finnish cohort.[42] The potential role of biomarkers may extend beyond predicting incident AF- a recent study reporting that the kinetics of plasma NT-proBNP release in patients presenting acutely with AF provides a potential means of determining its time of onset and the safety of cardioversion.[43] There therefore appears to be a promising role for novel biomarkers in predicting incident AF, which may help guide clinicians as to which individuals are most at risk of developing AF and who may benefit from prophylactic therapies. Other studies looking at population data in women have reported body-mass index[44] and birth weight[45] to be associated with incident AF. Furthermore, recent data from 34,722 participants of the Women's Health Study provided evidence that new-onset AF in initially health women was independently associated with all-cause and cardiovascular mortality.[46]

The last two years have seen important advances in our understanding of the genetics and heredity of AF. Following the landmark discovery using genome-wide association studies on subjects from European and Chinese descent that two sequence variations on chromosome

4q25 are associated with an increased risk of developing AF,[47] two novel AF susceptibility signals have been identified on the same chromosome.[48] A meta-analysis of four independent cohorts of European descent (the Framingham Heart Study, Rotterdam Study, Vanderbilt AF Registry and German AF Network) confirmed a significant relationship between AF and intergenic regions on chromosome 4.[49] Interestingly, genetic variants in the chromosome 4q25 region also appear to modulate the risk of AF recurrence after catheter ablation[50] and are associated with the develop of AF following cardiac surgery.[51,52] Whether genetic sequencing of chromosome 4q25 will prove useful in risk stratification for the development of AF after catheter ablation or cardiac surgery remains to be determined- at present, this remains and distinct and promising possibility. In line with the newly emerging genetic data on AF, studies on population-based cohorts have also provided evidence for a heredity component. Using data from the Framingham Heart Study, investigators found that familial AF occurred in 1185 (26.8%) and premature familial AF occurred among 351 (7.9%) participants out of 4421 participants (11,971 examinations) during the period 1968 - 2007.[53] The association was not attenuated by adjustment for AF risk factors or reported AF-related genetic variants. Racial factors and ancestry also appear to be related to the risk of AF. Data from white and African-American subjects enrolled in the Cardiovascular Health Study (CHS) and Atherosclerosis Risk in Communities (ARIC) study suggest that European ancestry is a risk factor for incident AF.[54]

Catheter ablation of AF

In a large prospective, multicentre trial involving 19 centres, the use of catheter ablation was compared with antiarrhythymic drug therapy.[55] A total of 167 patients with paroxysmal AF who had failed at least one antiarrhythmic drug and experienced at least 3 AF episodes in the preceding 6 months were randomised (2:1) to undergo catheter ablation or medical treatment. After a 9 month follow-up period, the investigators found that catheter ablation resulted in a longer time to treatment failure and significantly improved quality of life scores. Major 30-day treatment-related adverse events occurred in 5 of 103 patients (4.9%) treated with catheter ablation and 5 of 57 patients (8.8%) treated with antiarrhythmic medication. An improvement in the quality of life was also demonstrated in a prospective follow-up study of 502 symptomatic subjects who underwent AF ablation.[56] The improvement in quality of life was sustained at 2 years in patients with and without recurrence of AF, although the change was greatest in patients who remained free of AF and off antiarrhythmic drugs.

Several well-respected, high volume centres have recently published their long term outcomes following catheter ablation for AF. The Bordeaux group reported their 5 year follow-up data on 100 patients (86% male; age 55.7 ± 9.6 years; 63% paroxysmal AF; 36% with structural heart disease).[57] Arrhythymia-free survival rates after a *single* catheter ablation procedure were 40%, 37% and 29% at 1, 2 and 5 years, respectively (most recurrences occurred over the first 6 months). A total of 175 procedures were performed with a median of 2 per patient (51 patients underwent a second procedure and 17 a third). There were no peri-procedural deaths although major complications (cardiac tamponade requiring drainage) occurred in 3 patients (3%), and minor complications (AV fistula, femoral pseudoaneurysm and asymptomatic pulmonary vein stenosis) occurred in another 3 patients. The important point to note from this study is that even in experienced hands with a selected AF population (patients who are referred for AF ablation tend to be younger and have fewer co-morbidities), there is a steady decline in arrhythmia-free survival with recurrences observed up to 5 years post-ablation, although the majority occur within the first 6 to 12 months. An experienced German centre also recently reported on their long term follow-up data of catheter ablation in 161 patients (75% male; age 59.8 ± 9.7 years) with symptomatic paroxysmal AF and normal left ventricular function.[58] They found that 75 patients (46.6%) were in sinus rhythm after the initial procedure during a median follow-up period of 4.8 years (0.33 to 5.5 years). A second procedure was performed in 66 and a third procedure in 12 patients. One patient suffered from an aspiration pneumonia that was successfully treated and two developed a sterile pericardial effusion that did not require drainage (there were no other procedural complications noted). There was a low rate of progression to chronic AF during the follow-up period, which was observed in only 4 patients (2.4%). A group from London, UK, similarly reported their long term results following catheter ablation for AF in 285 patients [75% male; mean age 57 (SD 11) years; 53% paroxysmal AF; 20% with structural heart disease] undergoing a total of 530 procedures.[59] During a mean follow-up of 2.7 years (0.2 to 7.4 years), freedom from AF/atrial tachyarrhythmia was 86% for patients with paroxysmal AF and 68% for those with persistent AF. Complications included 3 strokes/ TIAs. Late recurrence was 3 per 100 years of follow-up after >3 year. The investigators also found that targeting complex fractionated atrial electrograms (CFAE) during the ablation procedure improved outcome in patients with persistent AF. However, this was not observed in a randomised study performed by another group in which 119 patients with persistent AF were randomised to additional CFAE ablation following pulmonary vein isolation or no additional ablation.[60] In summary, the reports on long term success rates following catheter ablation for AF demonstrate that the procedure is effective in a selected group of symptomatic AF patients, although a significant proportion require more than one ablation procedure, there are risks of peri-procedural complications and AF recurrence remains a possible problem, even after follow-up periods as long as 5 years. It should be noted that reported outcomes from the different centres cannot be directly compared, since there are differences in patient population (e.g. percentage of paroxysmal and permanent AF patients, patients with structural heart disease), techniques used (segmental pulmonary vein isolation versus wide area circumferential ablation), length of follow-up and methods employed to detect AF recurrence.

A number of studies have been performed to search for novel non-invasive parameters which may help predict AF recurrence following catheter ablation. These factors

include renal impairment,[61] novel echo parameters such as the atrial electromechanical interval,[62] atrial fibrosis assessed with echo[63] or magnetic resonance imaging[64] and B-type natriuretic levels.[65]

Ventricular arrhythmias and sudden cardiac death

Ventricular arrhythmias post myocardial infarction. To further understand the significance of the occurrence and timing of ventricular arrhythmias in the context of primary percutaneous coronary intervention (PCI), a secondary analysis of the APEX AMI (Assessment of PEXelizumab in Acute Myocardial Infarction) trial was undertaken.[66] Of the 5745 patients with ST-elevation myocardial infarction presenting for primary PCI (across 296 hospitals in 17 countries), VT/VF (ventricular tachycardia/ ventricular fibrillation) occurred in 329 (5.7%). Clinical outcomes and 90 day mortality were found to be worse in those with VT/VF compared with those without. Furthermore, outcomes were worse if the VT/VF occurred late (after the end of cardiac catheterisation) rather than early (before the end of cardiac catheterisation). The occurrence of ventricular arrhythmias remained associated with a significantly increased mortality after adjustment for potential confounders, although whether they were casually related to a poorer prognosis or simply a reflection of more severe heart disease is not yet clear. In the Occluded Artery Trial-Electrophysiological Mechanisms (OAT-EP) study, PCI to open a persistently occluded infarct-related artery after the acute phase of an AMI was compared with optimal medical therapy alone to determine which strategy reduced markers of vulnerability to ventricular arrhythmias.[67] There were no significant differences in heart rate variability, time-domain signal-averaged ECG, or T-wave variability parameters (all surrogate markers of ventricular instability) between either group at 30 days and one year after the AMI, which is consistent with the lack of clinical benefit from PCI in stable patients post AMI with persistently occluded infarct-related arteries in the main OAT study. The Cardiac Arrhythmias and Risk Stratification After Myocardial Infarction (CARISMA) trial was designed to investigate the incidence and prognostic significance of arrhythmias detected by an implantable cardiac monitor among post AMI patients with impaired LV function.[68] A total of 297 patients (out of 5969 initially screened) who had suffered a recent AMI and had reduced LVEF (≤40%) received an implantable loop recorder within 11 ± 5 days of the AMI and were followed up every 3 months for an average of 1.9 ± 0.5 years. The investigators detected a clinically significant number of brady- and tachyarrhythmias in these patients (28% new onset AF, 13% non-sustained VT, 10% high-degree AV block, 7% significant sinus bradycardia, 3% sinus arrest, 3% sustained VT and 3% VF). In particular, intermittent high-degree AV block was associated with a very high risk of cardiac death. The arrhythmogenic substrate for ventricular arrhythmias following reperfusion therapy for AMI was investigated in a study of 36 AMI survivors referred for catheter ablation of VT (13 ± 9 years after the AMI).[69] Of these, 14 patients had early reperfusion during AMI, while 22 were non-reperfused. The investigators found that scar size and pattern were different between VT patients with and without reperfusion during AMI using detailed electroanatomical mapping, with early reperfusion and less confluent electroanatomic scar being associated with faster VTs.

Risk stratification for sudden cardiac death and ICDs

An ongoing area of active research in relation to ventricular arrhythmias and sudden cardiac death (SCD) is in improved methods of risk stratification and selection of appropriate implantable cardioverter defibrillator (ICD) recipients.[70] A number of non-invasive cardiovascular tests have recently been evaluated among patients with an increased risk of SCD (e.g. AMI survivors and patients with coronary artery disease and cardiomyopathies) with promising results. These include T-wave alternans,[71,72] single-photon emission computed tomography (SPECT) myocardial perfusion imaging,[73] sympathetic nerve imaging with 123-iodine metaiodobenzylguanidine (123-I MIBG),[74] and late-gadolinium enhancement on cardiac MRI.[75] In addition, plasma biomarkers, such as serum collagen levels which reflect extracellular matrix alterations that may be involved with the generation of the arrhythmogenic substrate,[76] may have a future role to play in risk stratification. Genetic markers may also be relevant, as suggested by the observation from a combined population of 19,295 black and white adults from the Atherosclerosis Risk In Communities Study and the Cardiovascular Health Study that sequence variations in the nitric oxide synthase 1 adaptor protein (NOS1AP) were associated with baseline QT interval and the risk of SCD in white (but not black) US adults.[77,78]

Another important area requiring further clarification is the optimal timing of ICD insertion among AMI survivors who are deemed to be at greatest risk of SCD. The landmark DINAMIT study (Defibrillation in Acute Myocardial Infarction Trial), which did not show any mortality benefit from prophylactic ICD insertion in patients post-AMI if the device was inserted within 40 days of the index event,[79] has been used to guide current recommendations on ICD insertion among AMI survivors. A recent secondary analysis of this trial confirmed the original findings that the reduction in sudden death in ICD patients was offset by an increase in non-arrhythmic deaths, which was greatest in those who received ICD shocks.[80] A post-mortem study looking at 105 autopsy records of patients from the VALIANT (VALsartan In Acute myocardial infarctioN Trial) study who had died suddenly revealed that recurrent myocardial infarction or cardiac rupture accounted for a high proportion of sudden death in the early period after an AMI, thereby partly explaining the lack of benefit of early ICD insertion on overall mortality.[81] Arrhythmic death was more likely to occur later on (after 3 months), which is consistent with the findings of improved survival among ICD recipients from other major ICD trials in which the devices were inserted at a later stage. It should be noted however that 20% of sudden deaths in the first month post-AMI were presumed arrhythmic as there was no specific post-mortem evidence of any additional abnormality that could have caused the sudden death. A significant

proportion of patients who suffer an AMI therefore appear to continue to die suddenly in the early post-infarction period from cardiac arrhythmias. These patients are not included in current international guidelines for ICD insertion and remain a group for which ongoing research is required. Another group of patients who are not covered by current primary prevention ICD guidelines are those with relatively preserved LVEF following an AMI. Although these patients are at lower risk of SCD compared with those with poor LVEF, they represent a larger proportion of AMI survivors. Data from a multi-centre Japanese study suggests that in the era of primary PCI there is a low incidence of SCD among AMI survivors (overall mortality was 13.1% and SCD 1.2% over an average follow-up period of 4.2 years among 4122 patients).[82] The risk was highest for those with poor LVEF (<30%), although the absolute number at risk was greatest in those with relatively preserved LVEF (>40%).

The Intermediate Risk Stratification Improves Survival (IRIS) trial published in 2009 further tested the hypothesis that early implantation of an ICD soon after an AMI could improve survival compared with optimal medical therapy.[83] This was a randomised, prospective, multicentre trial which enrolled 898 patients, 5 to 31 days after their AMI, who met the following clinical criteria: LVEF ≤40% and a heart rate ≥90bpm on the first available ECG or non-sustained VT (≥150 bpm) during Holter monitoring. The main difference between this study and DINAMIT was a contemporary patient population (70% had undergone PCI and the majority were on optimal long term medication) and additional non-invasive criteria to identify a potentially higher risk population. However, the investigators did not find that ICD therapy reduced overall mortality after a mean follow-up of 37 months. Consistent with the findings from DINAMIT, the reduced incidence of SCD among ICD recipients in the IRIS study was offset by an increased incidence of non-sudden cardiac death.

Catheter ablation of ventricular arrhythmias

The VTACH (Ventricular Tachycardia Ablation in Coronary Heart disease) study, involving 16 centres in four European countries, assessed the potential benefit of catheter ablation of VT *before* ICD implantation in patients with a history of VT, myocardial infarction and LVEF ≤50%.[84] Patients (n = 110) were randomly allocated to receive catheter ablation and an ICD or ICD alone and followed-up for a mean period of 22.5 months (SD 9.0). The investigators found that prophylactic VT ablation before ICD implantation prolonged the time to VT recurrence from 5.9 months (IQR 0.8 - 26.7) in the ICD only group to 18.6 months (lower quartile 2.4 months; upper quartile could not be determined) in the ablation and ICD group. Complications related to the ablation procedure occurred in two patients. This study is in accordance with an earlier prospective randomised study of 128 patients which demonstrated that prophylactic catheter ablation of the ventricular arrhythmogenic substrate reduced the incidence of ICD therapy in patients with a history of myocardial infarction and previous ventricular arrhythmias.[85] It should be noted that VT ablation was performed in experienced centres in both of these trials and that there was no significant effect of catheter ablation on overall mortality. Whether VT ablation should routinely be performed prior to ICD insertion for secondary prevention of SCD in stable patients with previous myocardial infraction remains to be determined.

There has been an increase in number of publications on epicardial ablation for VT over the past few years in view of the realisation that not all VTs can be successfully eliminated via an endocardial-only approach.[86,87] In a retrospective study of 156 epicardial ablations for VT (out of a total of 913 VT ablations) in three tertiary centres evaluating the safety and mid-term complications of epicardial VT ablation, the risk of major acute (epicardial bleeding, coronary stenosis) and delayed (pericardial inflammatory reaction, delayed tamponade, coronary occlusion) complications related to epicardial access was found to be 5% and 2%, respectively.[88] Therefore, although this technique can be effective in some cases, especially where endocardial ablation has failed, it is associated with significant morbidity and should only be performed in centres experienced with this technique.

The prognostic significance of frequent premature ventricular contractions (PVCs) and effect of catheter ablation of these ectopics has received further attention recently. In a study of 239 asymptomatic patients with structurally normal hearts and frequent PVCs (>1000/day) from the right or left ventricular outflow tract, a significant negative correlation between PVC prevalence and ▫LVEF and positive correlation with ▫LV diastolic diameter was observed over a 5.6 (SD 1.7) year period.[89] In addition to PVC burden, other factors such as longer PVC duration, presence of non-sustained VT, multiform PVCs and right ventricular PVCs may be associated with a decline in LV function.[90,91] Although it is well known that catheter ablation of frequent PVCs can improve and restore LV function in some patients, the potential benefits of ablation in patients with normal LV function has been less well studied. A prospective study of 49 patients with frequent PVCs and normal baseline LVEF demonstrated that catheter ablation can improve the subtle LV dysfunction detected pre-ablation using speckle tracking imaging analysis.[92] However, unanswered questions remain, including benefits of catheter ablation on hard end-points (especially mortality) and when ablation should be performed (degree of PVC burden, LV function, after a trial of anti-arrhythymic medication?).

Cardiac resynchronisation therapy and pacing

Two pivotal cardiac resynchronisation therapy (CRT) clinical trials have been published in the last two years that potentially expand the indications for CRT in heart failure patients to those in NYHA class I and II symptoms. MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-CRT) compared the use of ICD alone with CRT-D (CRT with a defibrillator component) in patients with asymptomatic or mildly symptomatic heart failure symptoms (NYHA class I or II), LVEF ≤30% and QRS duration of ≥130 ms.[93] During an average follow-up of 2.4 years, fewer patients in the CRT-D group experienced the primary composite end point (all cause mortality and heart failure events) compared with the ICD group (17.2% compared with 25.3%, respectively, $p = 0.001$). Although these

results appear very impressive at first glance, closer examination of the data reveals that the main superiority of CRT-D was in reducing the rate of hospitalisation for heart failure and that there was no significant difference in mortality between the two groups (which was 3% annually). Furthermore, the study failed to show that NYHA class I patients fulfilling the enrolment criteria benefited from CRT-D. In RAFT (Resynchronisation-Defibrillation for Ambulatory Heart Failure Trial), CRT-D was compared to ICD alone in patients with NYHA class II or III heart failure, LVEF ≤30%, intrinsic QRS duration ≥120 ms or a paced QRS duration of ≥200 ms.[94] The investigators found that over a mean period of 40 months, the primary outcome (all-cause mortality or heart failure hospitalisation) occurred in fewer patients in the CRT-D group (33.2% compared with 40.3% in the ICD group, p <0.001). Unlike MADIT-CRT, RAFT demonstrated that CRT-D significantly reduced overall mortality and cardiovascular mortality compared with ICD alone, although more adverse device-related events were also seen in the CRT-D group. Possible reasons for mortality benefit observed in RAFT, but not MADIT-CRT, are that RAFT included patients with more advanced disease (and a higher proportion with ischaemic heart disease) and follow-up was longer and more complete.

A number of sub-analyses of MADIT-CRT have since been conducted to provide further information on the findings. One sub-analysis demonstrated that women experienced significantly greater reductions in all-cause mortality and heart failure compared with men, which was accompanied by greater echo evidence of reverse cardiac remodelling.[95] Another sub-analysis looking specifically at the echo parameters and performance between the two groups found that CRT resulted in significant improvement in cardiac size and performance compared with the ICD-only strategy, which probably accounted for the outcomes benefit in the CRT-D group.[96] Other studies have also provided additional echo evidence that CRT in mild heart failure (NYHA class I/II) results in major structural and functional reverse remodelling which may prevent disease progression.[97,98] The PACE (Pacing to Avoid Cardiac Enlargement) study explored whether biventricular pacing was superior to right ventricular (RV) apical pacing in preventing adverse cardiac remodeling in patients with bradycardia and *normal* ventricular function at baseline.[99] In this small randomised study of 177 patients followed-up over a 12-month period, the investigators found that the mean LVEF was significantly lower in the RV-pacing group than in the biventricular-pacing group (54.85 ± 9.1% *vs.* 62.2% ± 7.0%, p <0.001), with an absolute difference of 7.4 percentage points. However, the beneficial effects of biventricular pacing on echo parameters in this group of patients were not accompanied by any clinical benefit.

Other important and on-going areas of investigation in the field of CRT are issues of how best to select candidates who are most likely to respond to CRT and how to optimise response. Parameters that have recently been studied to improve patient selection include QRS morphology in MADIT-CRT (LBBB, rather than non-LBBB, patterns appears to remain the predominant morphology that is related to response),[100] baseline LV radial dyssynchrony, discordant LV lead position, and myocardial scar in the region of the LV pacing lead,[101] and pre-pacing systolic dyssynchrony measured by tissue Doppler imaging (TDI) velocity.[102] Consistent with existing knowledge, LV lead positioning has been re-confirmed to be important in MADIT-CRT patients[103] and patients with non-ischaemic dilated cardiomyopathy.[104] The prospective, randomised SMART-AV (SmartDelay determined AV optimisation: a comparison to other AV delay methods used in CRT) study compared three different methods of AV optimisation (fixed empirical AV delay of 120ms, echo-optimised AV delay, or AV optimisation with an ECG-based algorithm) in 980 patients with a CRT device to determine if any method was superior.[105] The study found that neither echo- or ECG-based AV optimisation was superior to a fixed AV delay of 120 ms and therefore concluded that the routine use of AV optimisation techniques was not indicated. However, the data did not exclude the possibility that AV-optimisation may have a role to play in selected patients who do not respond to CRT with empirical settings.

The potential deleterious effects of chronic RV pacing on cardiac function were revisited in the context of 103 patients with isolated congenital AV block. Long term pacing was not found to be associated with the development of heart failure or deterioration of ventricular function in patients who were negative for antinuclear antibody, although patients who tested positive for the antibody were more likely to develop heart failure.[106] Pacing in hypertrophic cardiomyopathy (HCM) was also recently revisited in a single-centre study which found some evidence of benefit from dual chamber pacing in HCM patients with NYHA III-IV symptoms, rest gradients of >50 mmHg and who were refractory to other medication, after follow-up periods of up to 10 years.[107] Another group of patients in which the role of pacing has remained controversial are patients with carotid sinus hypersensitivity (CSH) with syncope. In a double-blind, placebo-controlled, cross-over study, 34 patients (aged over 55 years) with CSH and ≥3 unexplained falls in the preceding 6 months were randomised to receive a dual-chamber pacemaker with rate-drop response programming which was switched on or off.[108] The investigators found that pacing intervention had no effect on the number of falls and concluded that the role of pacing for this group of patients remains controversial. A similar conclusion was reached in a multicentre study of 141 patients (mean age 78 years) with cardioinhibitory CSH.[109]

Inherited arrhythmogenic diseases

Major advances have been made in our understanding of the basic mechanisms, genetics and clinical features of the inherited arrhythmogenic diseases (IADs) over the last two years. Since these cannot all be covered in this short overview, only some of the major studies with important implications to general cardiologists will be mentioned. The rapid expansion in our knowledge of the genetic basis of the IADs and rise in commercially-available clinical genetic services has brought with it an additional dimension on how we manage these conditions. The reader is referred to a number of useful recently published reviews that address these issues in more detail.[110-112]

Sudden cardiac death without morphological evidence of heart disease accounted for 23% of cases in a recent

pathological study of UK athletes.[113] Potential causes of unexplained cardiac arrest were systematically evaluated in a prospective study involving 63 patients in 9 centres across Canada.[114] The tests, which included cardiac MRI, signal-averaged ECG, exercise testing, drug challenge and selective EP testing, resulted in a specific diagnosis (IAD, early repolarisation, coronary spasm and myocarditis) in 35 patients (56%). The remaining 28 patients were considered to have idiopathic VF. Subsequent genetic testing performed in 19 patients found evidence of causative mutations in 9 (47%) of these. Family screening of 64 family members of the 9 patients with causative mutations led to the discovery of mutations in 15 individuals (24%) who were subsequently treated. This study provides evidence that targeted genetic testing may play a role in helping diagnose genetically mediated arrhythmia syndromes, which may result in successful family screening.

An important study that investigated the presence of genetic factors or modifiers that could partly explain the phenomenon of incomplete penetrance seen in congenital long QT syndrome (LQTS) identified the nitric oxide synthase 1 adaptor protein (NOS1AP) as one such candidate.[115] This protein was chosen on the basis of previous studies that have demonstrated an association between genetic variants of NOS1AP with small quantitative increases in the QT interval and an increased risk of death in a general population.[116,117] In the study involving a South African LQTS population (500 subjects, 205 mutation carriers), NOS1AP variants were found to be significantly associated with the occurrence of symptoms, clinical severity (including cardiac arrest and SCD) and a greater likelihood of having a QT interval in the top 40% of values among all mutation carriers. In another study involving 901 patients enrolled in a prospective LQTS registry, three NOS1AP marker single nucleotide polymorphisms (SNP rs4657139, rs16847548, and rs10494366) were genotyped to assess the effect of variant alleles on QTc and on the incidence of cardiac events.[118] The investigators found that variant alleles tagged by SNPs rs4657139 and rs16847548 were associated with an average QTc prolongation of 7 and 8 ms, respectively, whereas rs4657139 and rs10494366 were associated with increased incidence of cardiac events. Furthermore, the rs10494366 minor allele as an independent prognostic marker among patients with QTc <500 ms, but not in the entire cohort. These two studies demonstrate that genetic testing for variants in the NOS1AP and tagged SNPs may be clinically useful for risk stratification of patients with congenital LQTS and potentially guide the choice of therapeutic strategies.

The FINGER (France, Italy, Netherlands, GERmany) registry, one of the largest series on Brugada syndrome (BrS) patients so far, involved 1029 consecutive individuals (745 men; 72%) with BrS (with a spontaneous or drug-induced type I ECG) who were followed up for a median period of 31.9 months.[119] The cardiac event rate per year was 7.7% in patients with aborted SCD, 1.9% in patients with syncope, and 0.5% in asymptomatic patients. This study provides important information that the event rate among asymptomatic patients with a Brugada ECG (which comprised 64% of subjects in the registry) is low. In addition, symptoms and a spontaneous type 1 ECG were predictors of arrhythmic events, whereas gender, familial history of SCD, inducibility of ventricular tachyarrhythmias during EP study, and the presence of an SCN5A mutation were *not* predictive of arrhythmic events. In an interesting mechanistic study of BrS, *in vivo* high-density mapping using non-contact mapping array was performed in the RV of 18 BrS patients and 20 controls.[120] The investigators identified marked regional endocardial conduction delay and heterogeneities in repolarisation in BrS patients and proposed that the slow-conduction zones may play a role the initiation and maintenance of ventricular arrhythmias. In line with these findings, an outstanding study was subsequently performed in which 9 symptomatic patients with BrS who had recurrent VF episodes underwent endocardial and epicardial mapping of the RV. Ablation at unique abnormal low voltage sites (clustering exclusively in the anterior aspect of the RVOT epicardium) rendered VT/VF non-inducible in 7 of the 9 patients, with no recurrence of ventricular arrhythmias in all patients over a follow up period of 20 ± 6 months. Interestingly, normalisation of the Brugada ECG pattern was observed in 8 patients post-ablation. This important proof-of-concept study lends further support to the notion that the underlying EP mechanism in patients with BrS is delayed depolarisation in the RVOT (specifically over the anterior epicardial region) and demonstrates for the first time that substrate-modification may be an effective strategy in symptomatic BrS patients with recurrent VF episodes.

Flecainide has recently emerged as a promising new treatment for catecholaminergic polymorphic ventricular tachycardia (CPVT). In a mouse model of CPVT, flecainide was found to prevent arrhythmias by inhibiting cardiac ryanodine receptor- mediated calcium release.[121] In the same publication, flecainide also completely prevented CPVT in two patients who had remained highly symptomatic on conventional drug therapy. In a clinical study of 33 patients who had received flecainide because of exercised-induced ventricular arrhythmias despite conventional therapy, flecainide was found to either partially or completely reduce the arrhythmias in 76% of cases.[122]

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