The year in cardiology: arrhythmias and pacing

The year in cardiology 2019

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Preamble

During this last year, there has been much progress with regard to anticoagulant and ablation therapy for atrial fibrillation (AF). Apart from recently issued European Society of Cardiology Guidelines for the management of patients with supraventricular arrhythmias, there has been little progress in research in this field. Ventricular arrhythmias and device therapy have seen modest progress.

Supraventricular tachycardias

This year has seen several publications on the ECG diagnosis of supraventricular tachycardia (SVT) 1–4 and interest in new consumer-led discovery of supraventricular arrhythmias. 5 EP mapping technology has provided better mapping of SVT. 6 There has been a surprising interest in new antiarrhythmic drugs for SVT, ranging from intranasal etripamil (an L-type calcium antagonist) for termination of SVT 7,8 and nifekalant to increase the refractoriness of accessory pathways and reduce the rate of pre-excited supraventricular arrhythmias. 9

Guidelines

2019 saw new European Society of Cardiology guidelines for the management of patients with SVT 10 which had previously been in 2003. However, there was little which was very new. The guidelines insisted that ablation was the best initial management for most re-entrant atrial and AV junctional tachycardia. However atrial tachycardia occurring after ablation for AF should not be considered for ablation until at least 3 months after the AF ablation procedure. The guidelines stressed that ablation for AV nodal re-entrant tachycardia could be achieved in almost all without risk of AV block. An invasive EP risk assessment of Wolff–Parkinson–White syndrome was recommended even in patients who are asymptomatic but have high-risk occupations or are competitive athletes. The guidelines recommend ablation in high risk or symptomatic WPW patients but stop short of recommending ablation of all accessory pathways. It is pointed out that SVT may cause tachycardia mediated cardiomyopathy and that ablation may not only eliminate the tachycardia but restore ventricular function.

There are strong Class III recommendations—what not to do, mostly related to antiarrhythmic drug therapy (Figure 1).

Atrial fibrillation risk assessment and treatment decisions

Various studies have highlighted new developments in the risk assessment for the development of AF and its complications, as well as the use of the non-vitamin K antagonist oral anticoagulants (NOACs) as thromboprophylaxis.

Risk assessment

Numerous clinical factors associated with incident AF have been described 11 but a simple, practical and reliable approach to identifying patients at risk of incident AF is needed.

Clinical factors such as change in body mass index have been associated with an increased risk of AF, 12 as has disordered sleep pattern. 13 Various clinical risk scores for identifying incident AF have been described, and as with most clinical scores, all have modest predictive value for identifying high-risk patients and until recently, have been complex models derived from multivariate analyses. The C2HEST score was derived and validated in Asia and has recently
been externally validated in a French post-stroke cohort and the Danish nationwide registries.\textsuperscript{14,15} This would facilitate targeted intensive screening for AF, for example, in the post-stroke population with AF, where oral anticoagulation (OAC) as secondary prevention is well established. In contrast, two randomized trials in embolic stroke of unknown source (ESUS) using NOACs failed to show a significant reduction in recurrent stroke, while one trial (NAVIGATE-ESUS) showed an excess of bleeds.\textsuperscript{16,17}

Screening for AF has attracted much attention, with population-based approaches and new technologies.\textsuperscript{18} The Apple Watch study investigated if a smartwatch-based irregular pulse notification algorithm identified possible AF, and reported that among participants who received notification of an irregular pulse, 34\% had atrial fibrillation AF on subsequent ECG patch readings and 84\% of notifications were concordant with AF.\textsuperscript{19} The Huawei Heart Study also showed the usefulness of photoplethysmographic (PPG) -based technology in population screening for AF, with the positive predictive value of PPG signals being 91.6\% and leading to improved anticoagulation use (\textges\%80).\textsuperscript{20}

Risk assessment continues to evolve, with availability of new data showing stroke risks associated with AF patients with hypertrophic cardiomyopathy\textsuperscript{21} and imaging-documented significant coronary artery lesions.\textsuperscript{22} There has been much interest into use of sophisticated methods such as machine-learning, even predicting incident AF from a simple 12-lead ECG.\textsuperscript{23} More complex risk assessment approaches improve AF stroke risk prediction (at least statistically) but need to be balanced against simplicity and practical application. For now, an independent Patient Cantered Outcome Research Institute (PCORI)-sponsored systematic review and evidence appraisal identified that amongst the commonly used risk stratification schemes in patients with AF, the CHA\textsubscript{2}DS\textsubscript{2}-VASc and HAS-BLED scores were the best predictors for stroke and bleeding risks, respectively.\textsuperscript{24} Bleeding risk prediction only focused on modifiable bleeding risk factors is an inferior strategy to a formal risk assessment using the HAS-BLED score.\textsuperscript{25,26}

Stroke and bleeding risk assessments incorporating biomarkers have been proposed based on highly selected anticoagulated clinical trial cohorts but ‘real-world’ studies have not shown the usefulness of such schemes. One study showing sequential addition of biomarkers did not improve the usefulness of stroke and bleeding risk prediction.\textsuperscript{27} Also, there are no data across the patient pathway, when first diagnosed and non-anticoagulated, or on aspirin—and following the initiation of OAC. Of note, many risk factors are based on baseline risk assessment but do not remain static and changes with age and incident risk factors.\textsuperscript{28} Thus, AF assessment is not a ‘one off’ item and needs to be reassessed at regular intervals, e.g. every 4–6 months.\textsuperscript{29}

Non-vitamin K antagonist oral anticoagulants and atrial fibrillation management in clinical practice

The NOACs have changed the landscape of stroke prevention in AF. These drugs are now the preferred OAC option in most guidelines, but challenges remain in its use amongst high-risk subgroups that were under-represented in clinical trials, as well as its adherence and persistence.

Clinical trial cohorts are selected populations and may be at lower risk compared to ‘real-world’ clinical practice data.\textsuperscript{30} The year also saw the first publications of real-world data for edoxaban, which was the fourth NOAC to enter the market.\textsuperscript{31} Increasing data for the NOACs in the elderly have been published,\textsuperscript{32,33} clearly showing their effectiveness and safety even in very elderly subjects, aged \textges\,80. Additional data emphasize the importance of using the appropriate label-adherent dosing to ensure best outcomes, as well as persistence data with the NOACs, for example, with dabigatran.\textsuperscript{34} One trial,
AEGEAN showed high adherence and persistence with apixaban (~90%) but did not show additional benefit from interventions to improve adherence/persistence.35

Also, studies of NOAC use in extremes of renal function, both severe renal impairment and supranormal renal function. The latter is pertinent given that all three Factor Xa inhibitors showed numerically more ischaemic strokes in the subgroup with CrCl >95 mL/min when compared with warfarin in their pivotal trials, although this is not apparent in real-world observational data.36 In end-stage renal failure, observational data show better safety for apixaban over warfarin.37

The last year has seen new trials with NOACs in catheter ablation (CA) for AF, and in the setting of AF patients presenting with an ACS or undergoing PCI/stenting. For CA, an uninterrupted NOAC-based strategy appears to be a safer option compared to a warfarin-based strategy.38-40 In AF/ACS/PCI patients, the publication to AUGUSTUS and ENTRUST-AF PCI completes the trials of NOACs in this clinical setting.41,42 These trials suggest that when OAC is used, a NOAC-based regime or a dual therapy (i.e. OAC plus a P2Y12 inhibitor) is associated with less major bleeding.43 Of the overall thrombotic or ischaemic outcomes, there is little difference between a triple therapy or dual therapy approach, or a NOAC-based strategy compared to a warfarin-based strategy. However, a dual therapy approach may be associated with an excess of stent thrombosis and myocardial ischaemic events, thus patients who are at high risk of such outcomes may merit a short period of triple therapy at the start. In stable coronary disease, OAC alone is associated with better outcomes compared to dual therapy, in the AFIRE trial.44

While the concept of integrated AF management has been proposed, its application and implementation in a simple user-friendly manner have not been previously validated. Integrated care has been associated with reduced mortality and hospitalization.45 One integrated and holistic approach to AF management, streamlining the decision-making management approaches that would be uniformly applicable across the whole AF patient pathway, starting with primary care and linking with secondary care (including cardiologist/non-cardiologists), and understandable for the AF patients per se, is the ABC (Atrial fibrillation Better Care) pathway: Avoid stroke; Better symptom management with patient-centred symptom directed decisions on rate or rhythm control; Cardiovascular and risk factor optimisation, including lifestyle changes.46 (Figure 2). The ABC pathway approach has now been shown in independent studies to be associated with a reduction in mortality, hospitalization and adverse outcomes, as well as reduced healthcare costs, when compared to ‘non-ABC’ adherent management.47-50 The ABC pathway was tested in a cluster randomized trial showing improved clinical outcomes with an ABC pathway management based on an interactive App that included risk assessments, patient decision aids, educational materials and dynamic tracking of risk (mAFA-II trial51; presented as Late Breaking Science at the ESC congress, September 2019).

### Ablation

#### Clinical outcomes

A number of publications have described AF CA outcomes and impact on prognosis. Probably the most eagerly awaited was the CABANA study.52 This multicentre study randomized 2204 patients to CA or drug therapy. As designed, intention to treat, the study was neutral for CA impacting on the primary composite endpoint of death, disabling stroke, serious bleeding, or cardiac arrest. This type of study is incredibly difficult to recruit for because the clinicians most likely to recruit are seeing a patient referred for a CA, so even if
they are prepared to enter the study, the cross-over rate is likely to be high from drug to ablation, as it was in this study (27.5%). When analysing by treatment, there was a prognostic benefit, but this subverts the principle of randomization and increases bias.

The cerebral micro-emboli associated with AF CA do not appear to have much impact and CA itself may improve cognitive impairment as in 308 patients studied and followed for 1 year.52 Most electrophysiologists continue to tell patients that the primary goal of AF ablation is quality of life (QOL). The first randomized controlled trials (RCT) of AF CA vs drugs to examine QOL as the primary endpoint was published in 2019 and favoured CA.53 While this was a small study, 155 patients, it does open the way for double-blind RCTs of AF CA with QOL as the primary outcome.

The use of cryoablation for AF has accumulated more evidence this year: it is faster than RF CA,54 associated with lower risk of pericardial effusion,55,56 and has superior outcomes54,55 regardless of centre volume.57 Several large registries have published this year. The Swedish registry reveals CA procedure complications and death were low and that AF, ventricular tachycardia (VT), and premature ventricular complex (PVC) CA numbers increased with AF having the highest repeat procedure rate (41%).58 A European registry demonstrated that cryoablation is as effective for female patients but is associated with higher complication rates.59 The Danish registry confirmed that success rates for AFL ablation were 90% but that AF is a common presentation (13%) within 2 years after.60 The German Helios registry showed that pericardial effusion rates were 0.9% in 21 141 AF CA, and was more likely in low volume centres, but only if RF was used rather than cryo.55

CA of VF storm after myocardial infarction was reported in a multicentre study of 110 patients.61 In-hospital mortality (27%) and 2-year follow-up mortality (36%) were high and associated with the time taken to perform CA.

A retrospective study of 110 patients demonstrated CA of recurrent VT in patients with arrhythmogenic ventricular cardiomyopathy is no more effective than drugs but is more likely to be successful if both epicardial and endocardial approaches are used.62

New mapping technologies
It is recognized that the primary reasons for failure of CA in complex arrhythmia are a lack of understanding of the mechanism. There continues to be huge effort to solve this. This year ripple mapping has been used successfully used in persistent AF (18 months 53% vs. 39% conventional),64 atrial tachycardia,65 and VT in arrhythmogenic right ventricular cardiomyopathy (ARVC).66 Non-contact mapping is returning to clinical practice with an observational trial showed good outcomes for persistent AF CA at 12 months (59%).67 The STAR mapping system (Figure 3), presented its feasibility clinical trial of 35 patients showing freedom from AF after persistent AF CA guided by STAR of 80% at 18 months.68 It remains to be seen whether any of these make it to widespread clinical use.

Energy sources
High power short-duration RF may make point-by-point AF CA faster and, at least so far, not being associated with worse
outcomes.\textsuperscript{63} Electroporation is also showing promise as a novel energy source that is highly effective with low complication rates.\textsuperscript{69} The use of radiotherapy to treat intractable VT is an exciting innovation, showing promising results in a small prospective study of 19 patients.\textsuperscript{70}

**Guidelines and consensus statements**

A number of guidelines have been published this year and while these are useful reviews of the literature, the temptation to accept them as dogma has to be resisted given that they are often driven by consensus of a well-intentioned writing group rather than hard data. CA of ventricular arrhythmia (VA) guideline suggests that programmed electrical stimulation may come back into fashion as a method for prognostic prediction, this time in patients with frequent PVCs and structural heart disease, and also recommends use of ICE for VA ablation although much of the world does not use ICE without any apparent compromise to their outcomes.\textsuperscript{71} The sex differences in arrhythmia consensus highlighted that although outcomes may be different, this should not influence provision of CA for females.\textsuperscript{72}

**Ventricular arrhythmias**

**Arrhythmogenic cardiomyopathy**

This has been an exciting year in arrhythmogenic cardiomyopathy (ACM). There are major publications to be aware of. The first is the Heart Rhythm Society Consensus Document on Arrhythmogenic Cardiomyopathy.\textsuperscript{73} This document, which was led by McKenna and Towbin redefines ACM as a condition that presents with symptomatic and/or asymptomatic arrhythmias in association with some degree of cardiac dysfunction. This ‘big tent’ approach includes classic ARVC, the more recently described arrhythmogenic left ventricular cardiomyopathy, as well as other subgroups of patients. Included within ACM are sarcoidosis, Chagas disease, myocarditis, and a large number of inherited cardiomyopathies. This is a comprehensive and provocative article that is important to be aware of. One of the writing groups’ goals was to encourage having patients present with arrhythmias and a cardiomyopathy to a specialized centre that perform comprehensive evaluation, arrange for genetic testing, and determine a patient’s arrhythmic risk and need for an ICD.\textsuperscript{74}

Another important publication was authored by Cadrin-Tourigny et al.\textsuperscript{74} Through the combined efforts of five international ARVC registries, an ARVC risk calculator was developed to help estimate arrhythmic risk and inform decisions regarding ICD implantation (www.ARVCrisk.com). More than 500 ARVC patients from five registries in North America and Europe were enrolled. During 5 years of follow-up, 28% experienced sustained VT, sudden death, or received an appropriate ICD therapy. A prediction model to estimate annual arrhythmic risk was developed (Figure 4). The variables at baseline included in the model are recent syncope, age, gender, non-sustained VT, the number of PVCs in 24 h, and right ventricular ejection fraction. And a final paper by Chatterjee et al.\textsuperscript{75} investigated the diagnostic value of an anti-Desmoglein-2 antibody in diagnosing ARVC. An antibody to DSG-2 was identified in 12/12 and 25/25 ARVC cohorts and 7/8 borderline subjects. The antibody was absent in 11/12 and 20/20 control cohorts. The authors concluded that anti-DSG-2 antibodies are a sensitive and specific marker for ARVC. Before this test can be used clinically, it will need to be tested in more control populations including those with cardiac sarcoidosis.

**Cardiac arrest**

Sondergaard et al.\textsuperscript{76} examined the use of bystander CPR among patients who experience out of hospital cardiac arrest in Denmark. More than three-fourths of cardiac arrests occurred in residential
locations. Bystander CPR increased between 2001 and 2004 from 36% to 84% in public locations and from 16% to 61% in residential locations. Not surprisingly, the increased use of CPR resulted in an increased 30-day survival from 6% to 25% for arrests in public locations and from 3% to 10% in residential locations.

**Cardiac devices**

What is the evidence behind current guideline recommendations for primary prevention ICD implantation in our present day and age? Can patient populations, background therapies and treatment algorithms, particular in heart failure, underlying trials conducted well over a decade ago be extrapolated to current daily clinical practice? (Figure 5) According to a large analysis from the French-British-Swedish-Czech CRT Network, death due to progressive heart failure remains the leading cause of death for the majority of patients. Moreover, increasing evidence indicate left ventricular (LV) remodelling as a main driver or arrhythmogenic events leading to sudden cardiac death (SCD), which may be reduced by modalities aimed at preventing (or even reversing) these processes, i.e. neurohormonal blockade and cardiac resynchronization therapy (CRT). These concepts and findings call into question the validity of the available randomized clinical trial evidence underlying current recommendations for primary prevention ICD implantation in heart failure patients. On a conceptual level, they additionally raise the question if trials should generally come with a ‘due date’ after which they would require re-validation. On the flipside, however, device therapies have advanced over the last decades, including better algorithms to detect ventricular arrhythmias and to prevent inadequate shocks, as well as the development of extravascular systems such as the S-ICD and the extravascular (EV-) ICD. Indeed, even entirely leadless CRT systems appear to be feasible. If proven safe and effective in the (ongoing) large RCTs, these novel modalities will come with a substantially reduced system-related morbidity, which may again tip the scale towards device-based SCD prevention. Indeed, inadequate shocks, as well as infections, remain the most devastating complications of current ICD systems, which come along with a substantial impact on quality of life, morbidity, and mortality.

In addition, better means of risk prediction for SCD above and beyond left ventricular ejection fraction (LVEF) are desperately needed in order to better protect those patients who need it (and prevent those who do not from unnecessary device implantation). One such risk prediction model for patients post-myocardial infarction with preserved LVEF has recently been put forward using electrocardiographic non-invasive risk factors (PVCs, non-sustained VT, late potentials, prolonged QTc, increased T-wave alternans, reduced heart rate variability, and abnormal deceleration capacity with abnormal turbulence) combined with programmed ventricular stimulation. The algorithm yielded an excellent sensitivity and negative predictive value (arguably the most important parameter) of 100%, as well as a specificity of 93.8%; on the downside, positive predictive value was only 22%. Modern imaging modalities such as MRI may...
further yield added value in identifying patients at increased risk of ventricular arrhythmias who may benefit from ICD implantation. Similar algorithms are being developed also for rarer disease entities such as arrhythmogenic right ventricular cardiomyopathy (ARVC). If proven positive in randomized clinical outcome trials, these concepts may move the field closer to venturing beyond the current (suboptimal) standard of LYVEF for risk stratification. Until such outcome trials are available, however, it may be prudent to stick to the currently available evidence and guideline recommendations; at the same time, recruitment into ongoing trials is encouraged in order to generate the next level of evidence that may potentially alter current clinical practice.

Cardiac resynchronization therapy remains an important treatment modality for heart failure patients to induce reverse LV remodeling and to improve morbidity and mortality. However, the rate of so-called ‘non-responders’ remains in the order of 20–30%, depending on definitions and cut-offs. The MORE-CRT MPP trial investigated the effect of stimulating the LV from two sites instead of one to reduce the number of non-responders. Five hundred and forty-four patients classified as non-responders (defined as an LV end-systolic volume reduction by <15%) 6 months after CRT implantation were randomized to receive the ‘Multipoint™ algorithm turned on (MPP ON) or off (standard of care group). While the conversion rate to ‘responders’ was no different between the two groups (31.8% vs. 33.8%) patients in the MPP group programmed to a wide electrode distance were significantly more likely to convert to responders than those programmed to other vector combinations (45.6% vs. 26.2%, P = 0.006). Although interesting and biologically plausible, these findings have to be viewed as hypothesis-generating in view of the negative primary endpoint.

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References


