

The Year in Cardiology 2020 – Arrhythmia and pacing

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This Year in Cardiology article reviews the most relevant and interesting studies in the field of arrhythmias and pacing. The past year has shown a significant progress in the arrhythmia field, in particular: landmark clinical trials in atrial fibrillation (AF) and implantable defibrillator (ICD) therapy, new guidelines, integrated care, life-style and arrhythmias, the emerging field of His bundle and left bundle area pacing, risk prediction in sudden cardiac death and molecular advances in cardiogenetic.

Guidelines on supraventricular tachycardia and atrial fibrillation

The new guidelines on supraventricular tachycardia (SVT) and atrial fibrillation brought many new insights and recommendations.^{1,2} The SVT guidelines dealt with SVT ablation as an early strategy (especially so in tachycardiomyopathy) and invasive risk assessment in ventricular preexcitation. They also focused on what-to-avoid in management of SVT.² The new guidelines on AF were presented at the ESC congress August 2020.¹ They promote the slogan 'CC to ABC', indicating that electrical confirmation of the AF diagnosis is mandatory together with in-depth characterisation of AF using a newly proposed unified 4S-AF scheme. For further management the AF guidelines advise to follow the 'simple and holistic' Atrial fibrillation Better Care (ABC) pathway which represents integrated care to avoid stroke (A), better symptom control (B) and take care of co-morbidities and cardiovascular risk factors (C), Figure 1. Despite the lack of data to show clinical effectiveness of AF screening, the Guidelines advocate both opportunistic and systematic screening for AF (saying that once AF is detected outcome worsens) and stress the importance of an effective structured management platform to confirm AF (if detection was by plethysmography) and for further management of newly found AF. Interestingly, the 4S-AF scheme represents a multi-domain characterisation of AF and contains not only actionable diagnostic elements essential for management but also emerging tools which will mature over time like molecular biomarkers, genetics risk scores and magnetic resonance imaging of the atria. In this way, the Guidelines not only aim to directly improve AF care but - by stressing future-proof infrastructure - also structured analysis. The latter promotes uniform collection of cutting-edge data which facilitates big data analysis of care pathways and patient outcomes, not only for scientific discovery but also value based health care. Related to this, it is recommended to measure quality of care over time and when needed improve care in an iterating cycle of improvement. The guidelines also highlight the importance of longitudinal rather than one-time cross-sectional assessment of stroke and bleeding risks since patients may outgrow their low risk status quite rapidly over time. Catheter ablation is advocated to ameliorate AF symptoms and treat AF associated electrical heart failure with reduced ejection fraction and may be applied after one antiarrhythmic drug failure including failure on beta-blockade. Because of later publication, the new guidelines could not incorporate the results from the EAST trial which suggests that rhythm control - including catheter ablation - may be beneficial irrespective of presence of AF symptoms.³

Randomised trials related to integrated care in atrial fibrillation

A number of interesting randomised trials on integrated management of AF were published. The ALL-IN trial was a cluster randomized trial in elderly AF patients in primary care in The Netherlands which showed that integrated care delivered by practice nurses supervised by general practitioners reduced all-cause mortality by 45% compared to usual-care.⁴ This is extremely impressive and highlights the power of our current “simple” interventions if deployed systematically. The integrated care pathway included quarterly AF check-ups by the practice nurse, case management of antithrombotic treatment and easy-access consultation of a cardiologist. This represents patient-centered shared care and responsibility between primary care, anticoagulation clinics, cardiology care and the patients with patient-empowerment through education and shared decision making (Figure 2). Another Dutch multicentre trial, RACE 4 reported that nurse-led, ICT-supported and physician-supervised integrated care reduces morbidity and mortality in experienced centres but not in less-experienced centres, and emphasized the importance of training in an integrated environment.⁵

Key elements of integrated care in these trials were the multidisciplinary team approach, education and empowerment of patients and where possible application of decision support technology or e-Health. Interesting recent mHealth solutions include TeleCheck-AF^{6,7} and a mobile AF application incorporating the ABC pathway⁸. The latter was applied in the mAFA II trial that reported a significant reduction of all-cause death and other major adverse cardiovascular events compared to routine management in high risk AF patients. Notably, recent studies investigating single elements of integrated care such as application of a clinical decision support system⁹, an educational¹⁰ or a motivational¹¹ intervention to improve anticoagulation or introduction of shared decision making¹², all improved level of care but not prognosis.

In integrated care patient-driven life-style changes targeting obesity, alcohol and blood pressure control is important before performing rhythm control with catheter ablation . Two new studies related to life-style and AF appeared in 2020. In a large cohort of 402,406 individuals from the UK Biobank, regular physical activity was related with a lower incidence of AF (especially in women) and ventricular arrhythmias but not of bradyarrhythmias.¹³ Also, a randomised trial provided proof-of-concept data to support alcohol cessation as secondary prophylaxis against AF in regular drinkers.¹⁴ Per nature of the trial, it focused on one element of life-style whilst a more comprehensive multi-level modification of AF risk factors may be needed to abrogate risks of AF in daily life.¹⁵

Randomised trials on rhythm control in AF: the importance of early intervention

The EAST-AFNET 4 trial showed that rhythm control therapy, i.e. antiarrhythmic drugs and ablation, in early AF reduced cardiovascular outcomes in patients with AF and cardiovascular conditions without increasing time spent in-hospital, and without safety concerns.³ The trial’s findings may change clinical practice towards rhythm control therapy early after the diagnosis of AF. Other reports support the notion of early rhythm control.¹⁶⁻²⁰ In contrast, current Guidelines typically recommend restricting rhythm control to AF patients with persistent symptoms while on otherwise effective rate control.¹ The results of EAST-AFNET 4 are at odds with older rhythm versus rate control trials which may be explained by the early intervention, safer use of antiarrhythmic drugs (also avoiding amiodarone as much as possible and using the newer drug dronedarone) and application of catheter ablation besides antiarrhythmic drugs. Catheter ablation indeed deserves a more prominent place, even in heart failure with AF^{21,22}, to improve quality of life^{23,24} as well as to save costs.²⁵ Above all and in accordance with current and previous AF Guidelines,^{1,26-28} in EAST-AFNET 4 rhythm control therapy was applied on top of patients being optimally protected by cardiovascular primary prevention therapies. It is important to understand that, like several previous rhythm versus rate control trials^{22,29,30}, EAST was a *strategy evaluation* and not a simple comparison of two treatment

modalities meant to either maintain sinus rhythm or keeping adequate rate control like the CABANA trial.³¹ In this respect, the concept of ‘cross-over’ from one modality to the other is pointless since failing rhythm or rate control may all be the outcome of an otherwise perfectly executed strategy. Had CABANA compared rhythm with rate *strategy* it would certainly have tested positive for rhythm control. EAST included first- or recently-detected AF which seems crucial since most events occur in the first year after AF detection probably because of heretofore concealed cardiovascular conditions.^{32, 33} In that respect, the initial cardiologist’s care may be warranted. A recent study indeed suggested that initial AF care should be supervised by cardiologists rather than non-cardiologists since 1-year mortality and morbidity were lower if patients with newly diagnosed AF were managed under cardiology care compared to non-cardiology care.^{34, 35} Early rhythm control in recent-onset AF in the emergency room was tested in a randomised study comparing procainamide and rescue electrical cardioversion if needed with immediate electrical cardioversion.³⁶ Both strategies were clinically highly effective. Although the study did not compare early with delayed cardioversion³⁷, the authors suggested that early cardioversion be preferred since it would be less burdensome for patients and the hospital than delayed cardioversion. However, delayed cardioversion does not take more time, it distracts less from overall needs of patients such as anticoagulation, and provides the patients the opportunity to experience self-termination which may enhance self-confidence and self-management.³⁸ Interestingly, to support or circumvent catheter ablation, recent reports advocated add-on renal denervation³⁹ or low level tragus stimulation.⁴⁰ In CASA-AF^{41, 42} single procedure thoracoscopic surgical left atrial posterior wall isolation was not superior to extensive point-by-point posterior wall isolation plus right and left isthmus ablation, and came with higher costs and less gain in QALYs. However, the surgical lesion set was far less extensive and surgical learning curve effects may have affected outcome. The Achilles’ heel of surgical ablation may be circumvented only if arrhythmia surgeons turn into dedicated ablationists.

Postoperative atrial fibrillation

Conen et al. reported on the risk of stroke and other adverse outcomes after post-operative AF in the combined datasets of the randomised POISE trials on the effects of metoprolol vs. placebo, aspirin vs. placebo, and clonidine vs. placebo.⁴³ Patients with cardiovascular disease were undergoing non-cardiac surgery. Postoperative AF (POAF) within 30 days after surgery was seen in 404 of 18117 patients and was associated with a 1-year stroke incidence of 5.6% compared to 1.5% in no POAF patients. also risk of death (31.3 vs 9.3%) and myocardial infarction (26.2 vs. 8.2) were increased (Figure 3). Risk reduction strategies still need to be investigated. This gap was unfortunately not filled by a recent randomised trial testing the sedative Dexmedetomidine against placebo to reduce new onset POAF as well as delirium in 798 patients undergoing cardiac surgery.⁴⁴ The incidence of new POAF (approx. 32%) and delirium (approx. 15%) did not differ between study groups.

Resynchronisation therapy, including His bundle, septal and left bundle pacing

In the field of pacing and Cardiac Resynchronization Therapy (CRT), 2020 was the year of exponential increase in interest for His bundle (HBP) and left bundle branch area pacing (LBBAP). The number of implants in the United States of the Medtronic 3830 lead, the lead that is most commonly used for HBP and LBBAP, showed an increase from 2,000 in 2016 to 10,000 in 2018. The number of HBP related publications increased from 5 in 2014 to 75 in 2018.⁴⁵ Worldwide sales of the 3830 lead increased 9-fold between 2014 and 2018. The Twitter account “dontdisthehis” attracted almost 1200 users within 2,5 years.⁴⁶ The increased interest in HBP is likely due to the availability of better guiding catheters and the evidence that HBP is also suitable for CRT. In 2020, a few studies indicated that HBP may be equal or superior to conventional biventricular pacing (BVP) with regards to acute hemodynamic improvement, reverse remodeling and clinical outcome.⁴⁷⁻⁴⁹

In 2020 LBBAP was only 3 years old but attracted already considerable interest. For LBBAP the 3830 lead is introduced transvenously and subsequently screwed through the interventricular septum until the tip of the lead is (almost) at the left ventricular (LV) endocardium (figure 4). Compared to HBP, LBBAP lead implantation is easier and pacing thresholds are lower.⁵⁰ Some investigators aim at capturing the left bundle branch itself⁴⁹, but others are less critical and accept any “LV septal” lead position.⁴⁸ In 2020 a number of small single and multicenter studies appeared. Hou et al. performed a study in 56 patients with bradyarrhythmias and LVEF>55%.⁵⁰ These authors found that permanent LBBAP is safe and feasible. A better maintenance of synchrony of contraction, determined using SPECT MPI phase analysis, was observed when the left bundle branch was captured.

Three studies comprising a total of 116 patients with LBBAP, 49 with HBP and 75 with BVP consistently showed a larger reduction in QRS duration in combination with a larger increase in LV ejection fraction.^{49, 51, 52}

Salden et al. compared the acute hemodynamic and electrophysiological effects of “LV septum pacing” with that of BVP and HBP.⁴⁸ The three pacing modes were comparable with regards to increase in LVdP/dtmax, while HBP and LV septum pacing tended to provide better electrical resynchronization (based on measurement of QRSarea and standard deviation of activation times, ECG belt technique). An important finding was also that similar effects were observed when pacing the LV septum at the basal, equatorial and apical part of the septum.

Since there is currently no evidence that the physiological LBBAP is inferior to HBP, LBBAP may become the preferred pacing mode, possibly replacing conventional RV pacing in bradytherapy, BVP in CRT and HBP in both. However, in order to achieve this, randomized studies are required comparing LBBP with HBP and BVP with regards to feasibility, safety (including lead extraction) and clinical outcome. A prospective randomized study is currently performed in China.⁵³

Inherited cardiac conditions, risk assessment, implantable defibrillators and sudden death

There have been a number of provocative papers in the inherited arrhythmia field this year. The prediction of Brugada syndrome (BrS) positive sodium channel blocker response to make the diagnosis in concealed forms remains a challenge in addition to the holy grail of risk prediction. A tangential approach described the utilisation of autoantibody screening for α -cardiac actin, α -skeletal actin, keratin, and connexin-43. In total, 18/18 BrS subjects demonstrated this autoantibody profile versus 0/8 normal controls and 0/20 cardiomyopathy cases which included ARVC, HCM and DCM patients.⁵⁴ In a subgroup of BrS patients, each of these proteins and the sodium channel protein type 5 alpha subunit (Nav1.5) aggregated in the sarcoplasm of myocardial cells. The mechanism as to why antibodies to these proteins identified BrS cases is unclear but could relate to sarcolemmal membrane damage either due to a myocarditic process in the disease course or abnormal cell adhesion resulting in an immune response. The novelty of this study is the utilisation of a serological test to identify BrS subjects which can be challenging given the transient nature of the ECG pattern. This needs to be verified in larger cohorts as well as other cardiomyopathies and also serological screening’s utility in predicting risk will be a key determinant of its wider utilisation. This paper is complemented by a study utilising polygenic risk scores (PRS) of ECG markers to predict a positive ajmaline response.⁵⁵ PRS for BrS, baseline QRS duration, presence of Type II or III BrS ECG at baseline, and family history of BrS were independently associated with the occurrence of a Type I BrS ECG, with good predictive accuracy (optimism-corrected C-statistic 0.74). This provides the first data to enable the combination of genetic and clinical screening to predict ajmaline responses and has implications for risk stratification.

The management of catecholaminergic polymorphic VT (CPVT) remains controversial as it is recognised that beta blockade and flecainide can effectively suppress VT/VF and patients can suffer ICD complications including inappropriate shocks. In a provocative paper by van der Werf et al, no survival benefit from ICDs was shown in young CPVT patients surviving cardiac arrest.⁵⁶ There are a number of caveats to this study including its relatively small nature, non-randomised design, lack of statistical power to prove reduced mortality without ICD, pre-selection of patients to receive medical versus ICD therapy, and inadequate beta blockade in ICD non-survivors. However, the main learning point was that such patients can be treated without an ICD but maximal medical therapy with nadolol with or without flecainide should be employed as these were highly effective in suppressing VT/VF and preventing sudden death.

The evidence base for minimally invasive sudden death prevention is expanding. PRAETORIAN is a landmark randomised controlled trial which compared the transvenous and subcutaneous ICD in 849 in patients >18 years with a class I or IIa indication for ICD therapy for primary or secondary prevention and who followed for a median of 49.1 months.⁵⁷ S-ICD demonstrated non-inferiority of the composite primary end-point of device related complications and inappropriate shocks. The key finding provides the first randomised trial evidence that the S-ICD is as effective and safe as TV-ICD in preventing SCD for patients not requiring brady-pacing, anti-tachycardia VT pacing or CRT. These data are supported by the subsequent UNTOUCHED study of primary indication patients for sudden cardiac death prevention, LVEF \leq 35%, without pacing indication, compared to the MADIT RIT population. Primary endpoint results showed an inappropriate shock-free rate of 95.9%, exceeding the performance goal of 91.6%. Patients with a history of AF, non-ischemic aetiology, and lower ejection fraction, were more likely to experience inappropriate shocks. These data indicate the ability of new SMART PASS filter technology and appropriate high rate S-ICD programming to minimise inappropriate shocks in S-ICD recipients.⁵⁸ Two primary prevention ICD trials in contemporary heart failure with reduced ejection fraction showed beneficial results but differed concerning efficacy in women.^{59, 60}

Prediction of arrhythmic death in coronary artery disease patients remains a key area. The PREDETERMINE investigators integrated an ECG risk score with conventional cardiovascular parameters including ejection fraction. A high-risk ECG score incorporating contiguous Q waves, left ventricular hypertrophy, QRS duration, and JTc prolongation was more strongly associated with sudden arrhythmic death (SAD) than non-SAD mortality (adjusted hazard ratios = 2.87 vs. 1.38 respectively; P for delta = 0.003) and the proportion of deaths due to SAD was greater in the high vs. low risk groups (24.9% vs. 16.5%, P for delta = 0.03). Similar findings were observed in the validation cohort.⁶¹ The addition of ECG markers to a clinical risk factor model inclusive of LVEF improved discrimination and reclassification, including correct reclassification of 28% of patients in the validation cohort [net reclassification improvement 28 (7–49%), P = 0.009]. The strength of this approach is the utilisation of simple bedside derived biomarkers to determine management.

Legend to Figures

Figure 1. The CC to ABC paradigm in the latest ESC guidelines provides a comprehensive and holistic approach towards diagnosis and management of atrial fibrillation. Reproduced with permission from¹

Figure 2. Chronic integrated care for atrial fibrillation should be delivered by a multidisciplinary team. It may be driven by a nurse specialist^{5, 62, 63}, a general practitioner⁴ or a cardiologist^{8, 64}, and it may be supported by a clinical decision support system and electronic/mobile health technology, and it involves several specific types of specialist care. Reprinted with permission from¹

Figure 3. Adverse events per 100 patient-years follow-up indicate that POAF is associated with a significantly elevated incidence of cardiovascular adverse events. reprinted with permission from⁴³

Figure 4. Schematic representation (upper right) and X-ray and CT images (lower right) of positioning the pacing lead at the left side of the septum. Left panels show the ECG during intrinsic rhythm of a patient with atrial fibrillation that received a pacemaker. Middle row of ECGs show signals when pacing the lead at its initial position at the right of the septum and right row shows signals during pacing at final position. Note almost normalization of signals, WRD duration and QRS area during LBB pacing.

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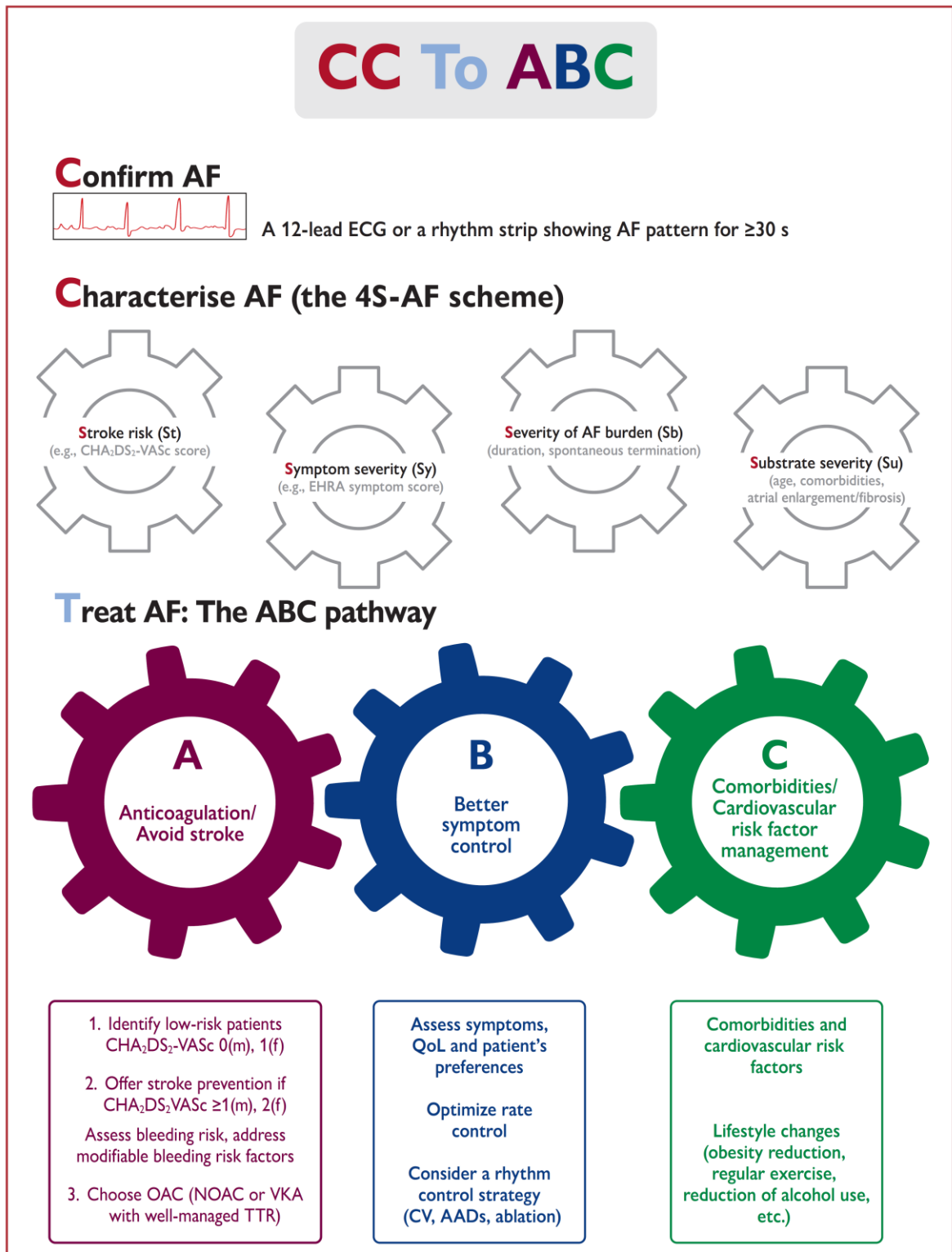
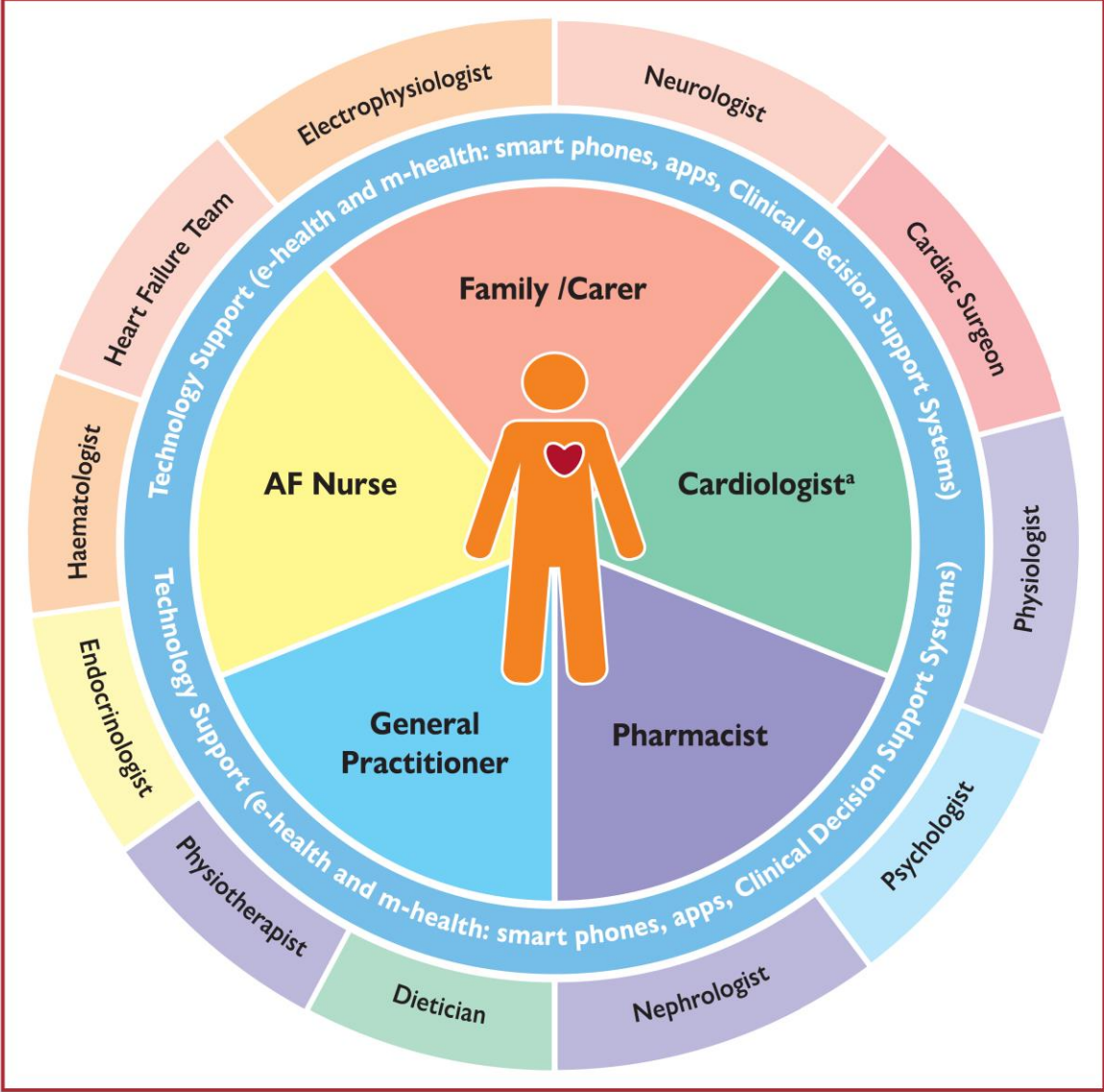


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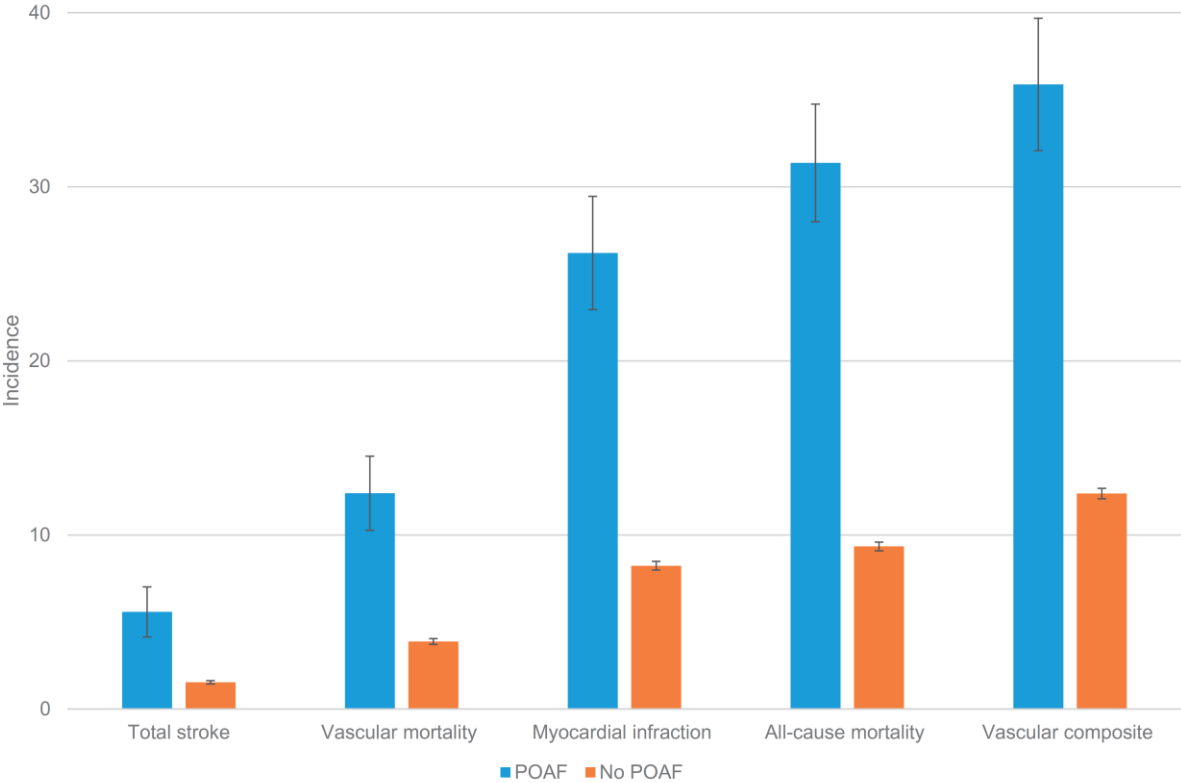
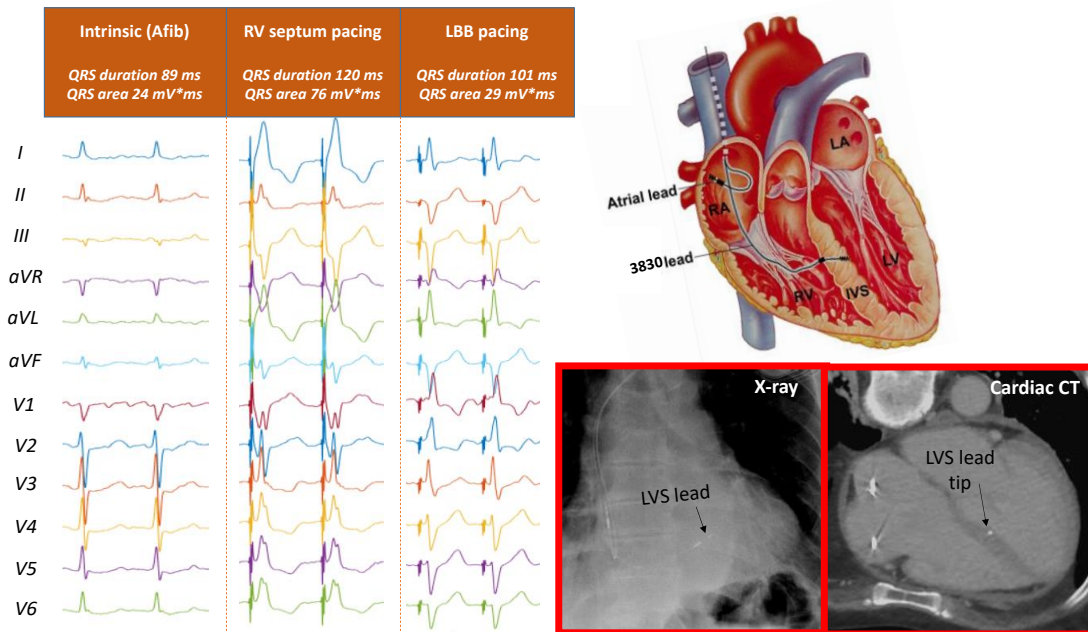


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