

The year in cardiovascular medicine 2020: arrhythmias

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Introduction

The Year in Cardiovascular Medicine: Arrhythmias 2020 reviews the most relevant studies in the field of arrhythmias and pacing. The past year has shown a significant progress: landmark clinical trials in atrial fibrillation (AF) and implantable defibrillator (ICD) therapy, new guidelines, integrated care, life style and arrhythmias, His bundle pacing, risk prediction in sudden cardiac death, and advances in cardiogenetics.

New guidelines

The guidelines on supraventricular tachycardia (SVT) and AF brought many new insights and recommendations (1, 2). The former dealt with SVT ablation as an early strategy and invasive risk assessment in ventricular preexcitation. Its focus also was on what-to-avoid in management of SVT (2). The new guidelines on AF promote the slogan 'CC to ABC', indicating that electrical Confirmation of AF is mandatory together with in-depth Characterisation of AF (*Figure 1*) (1). For management the AF guidelines advise to follow the Atrial fibrillation Better Care (ABC) pathway, which represents care to

- avoid stroke,
- better symptom control, and
- take care of co-morbidities and cardiovascular risk factors.

Despite the lack of data to show clinical effectiveness, AF

screening is advocated saying that once AF is detected outcome worsens. It is also recommended to measure the 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 to manage AF-associated heart failure and may be applied after one antiarrhythmic drug failure including failure on beta-blockade.

The CC to Atrial fibrillation Better Care paradigm in the latest European Society of Cardiology (ESC) guidelines provides a comprehensive and holistic approach towards diagnosis and management of atrial fibrillation. CC stands for Confirmation (first C) and Characterisation (second C) of atrial fibrillation according to the structured 4S-AF scheme including assessment of stroke risk, symptom severity, severity of atrial fibrillation burden, and substrate severity. Reproduced with permission from Ref 1.

Randomized trials on integrated care in atrial fibrillation

Interesting randomized trials on integrated AF management included the ALL-IN trial, a cluster randomized trial in elderly AF patients in primary care, which showed that integrated care delivered by practice nurses su-

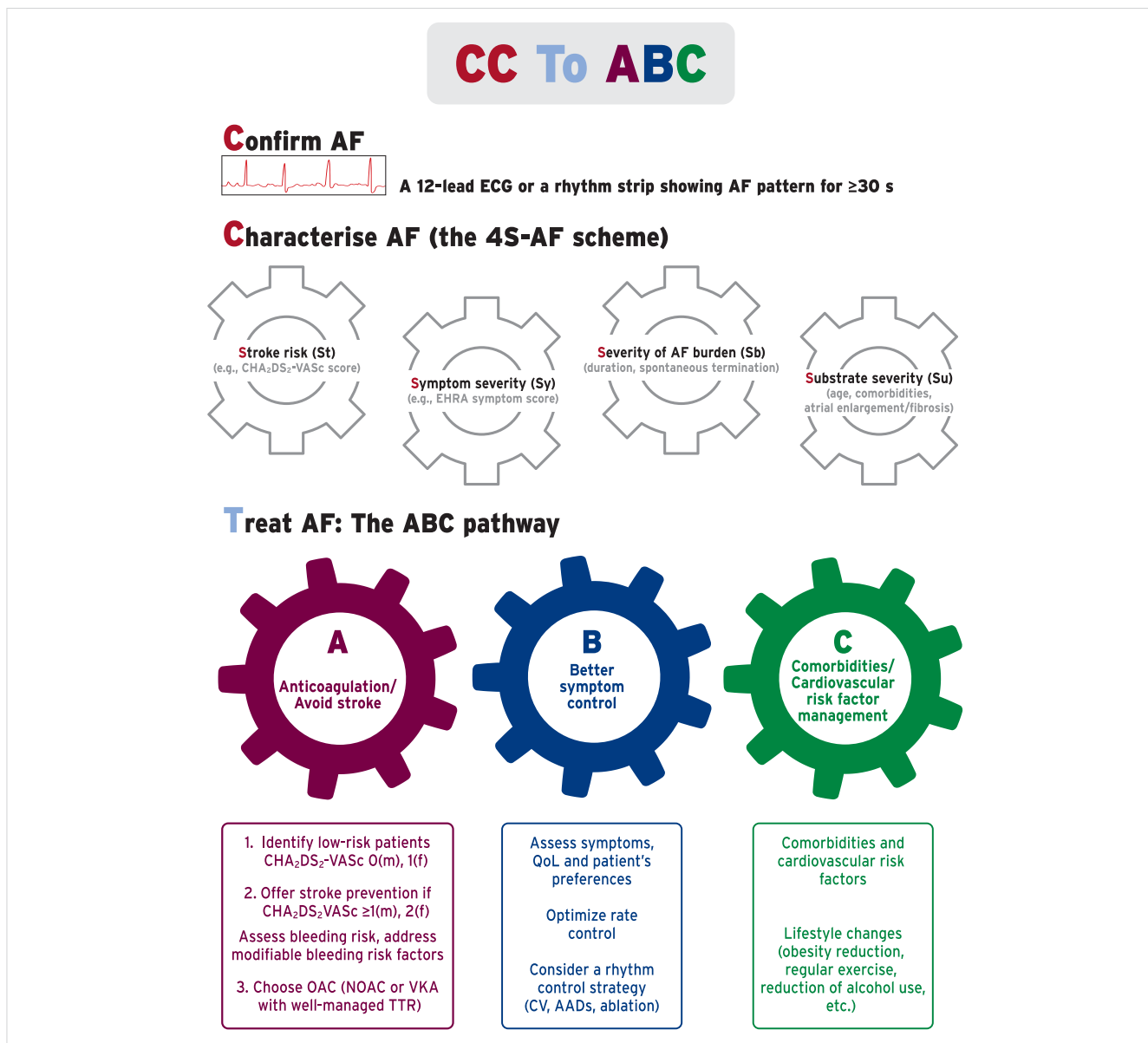


FIGURE 1. The CC to Atrial fibrillation Better Care paradigm in the latest European Society of Cardiology (ESC) guidelines provides a comprehensive and holistic approach towards diagnosis and management of atrial fibrillation. CC stands for Confirmation (first C) and Characterisation (second C) of atrial fibrillation according to the structured 4S-AF scheme including assessment of stroke risk, symptom severity, severity of atrial fibrillation burden, and substrate severity. Reproduced with permission from Ref. (1)

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pervised by general practitioners reduced all-cause mortality by 45% compared to usual-care (3). This is impressive and highlights the power of ‘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 responsibilities between primary care, anticoagulation clinics, cardiologists, and patients. Similarly, RACE 4 reported that nurse-led, information and communication technology

(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 (4). 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. Recent mHealth solutions include TeleCheck-AF (5, 6) and a mobile AF application incorporating the ABC pathway (Figure 1) (7). The mAFA II trial reported a sig-

nificant reduction in all-cause death and adverse cardiovascular events compared to routine management in high-risk AF (7). Notably, single elements of integrated care such as application of a clinical decision support system (8), an educational (9) or a motivational (10) intervention to improve anticoagulation or introduction of shared decision-making (11) improve the 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. 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 (12). Also, a randomized trial provided proof-of-concept data to support alcohol cessation as secondary prophylaxis against AF in regular drinkers (13). 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 (14).

Randomized trials on rhythm control in atrial fibrillation

The EAST-AFNET 4 trial compared a rhythm with a rate control strategy in patients with early AF lasting <1 year. It showed that rhythm control therapy, i.e. antiarrhythmic drugs and ablation, in early AF reduced cardiovascular outcomes without increasing time spent in-hospital, and without safety concerns (15). The results are at odds with older trials, which may relate to earlier intervention, safer use of antiarrhythmic drugs, and safe application of catheter ablation. In accordance with the AF Guidelines (1, 16–18), rhythm control was applied on top of cardiovascular prevention. Like previous trials (19–21), EAST-AFNET4 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 (22). EAST-AFNET4 included recently detected AF, which seems crucial since most events occur in the first year after AF detection (23, 24). Early intervention is supported by two recent trials showing that cryoballoon ablation as initial therapy is superior to drug treatment (25, 26). Therefore, initial AF care should be supervised by cardiologists rather than non-cardiologists since 1-year mortality and morbidity are lower if newly diagnosed AF is managed under cardiology care compared to non-cardiology care (27, 28).

Early rhythm control in recent-onset AF in the emergency room was tested in another randomized study comparing procainamide and rescue electrical cardioversion if needed with immediate electrical cardioversion (29). Both strategies were clinically highly effective, but the authors suggested that immediate cardioversion be

preferred since less burdensome for patients and the hospital.

Catheter ablation may be particularly useful in heart failure with AF (21, 30), to improve quality of life (31, 32) as well as to save costs (33). One interesting observational study suggested that catheter ablation compared to drug treatment is associated with a lower incidence of vascular dementia (34). To support or circumvent catheter ablation, recent reports advocated add-on renal denervation (35) or low level vagus stimulation (36). In CASA-AF (37, 38), 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 quite limited and surgical learning curve effects may have affected outcome.

Postoperative atrial fibrillation

The risk of stroke and other adverse outcomes after postoperative AF (POAF) was reported from the combined datasets of the randomized POISE trials on the effects of metoprolol vs. placebo, aspirin vs. placebo, and clonidine vs. placebo (39). Patients with cardiovascular disease were undergoing non-cardiac surgery. POAF within 30 days after surgery was seen in 404 of 18 117 patients and was associated with 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 2*). Risk reduction strategies still need to be investigated. This knowledge gap was unfortunately not filled by a recent randomized trial testing the sedative dexmedetomidine against placebo to reduce new-onset POAF as well as delirium in 798 patients undergoing cardiac surgery (40). The incidence of new POAF (~32%) and delirium (~15%) did not differ between study groups.

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

The year 2020 saw an exponential increase in interest for His bundle (HBP) and left bundle branch area pacing (LBBAP) in cardiac resynchronization therapy (CRT). The number of implants in the USA of the most commonly used lead (Medtronic 3830), showed an increase from 2000 in 2016 to 10 000 in 2018. The number of HBP related publications increased from 5 in 2014 to 75 in 2018 (41). Worldwide sales of the 3830 lead increased nine-fold between 2014 and 2018. The Twitter '#dontdisthehis' attracted almost 1200 users within 2.5 years (42). 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

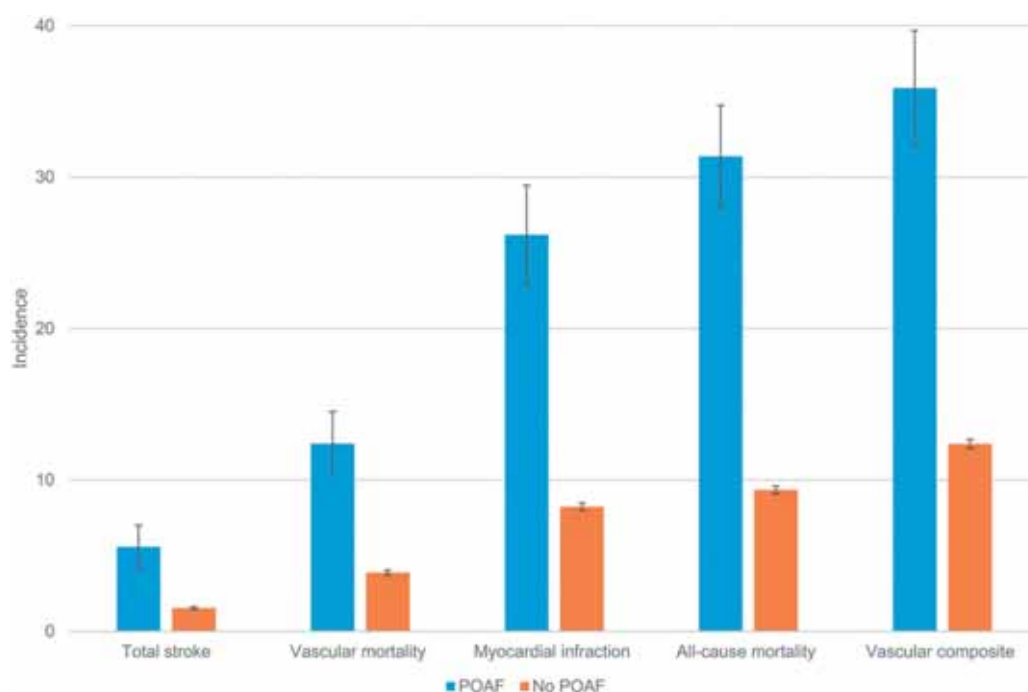


FIGURE 2. Adverse events per 100 patient-years follow-up in patients with cardiovascular disease after non-cardiac surgery indicate that postoperative atrial fibrillation is associated with a significantly elevated incidence of cardiovascular adverse events. Reprinted with permission from Ref. (39)

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2020, a few studies indicated that HBP may be equal or superior to conventional biventricular pacing (BVP) with regard to acute hemodynamic improvement, reverse remodeling and clinical outcome (43–45).

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 1). Compared to HBP, LBBAP lead implantation is easier and pacing thresholds are lower (46). Some investigators aim at capturing the left bundle branch itself (45), but others are less critical and accept any ‘LV septal’ lead position (44). In 2020, a number of small single and multicenter studies appeared. Hou et al. (46) performed a study in 56 patients with bradyarrhythmias and LVEF >55%. 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-complex (QRS) duration in combination with a larger increase in LV ejection fraction (45, 47, 48).

Salden et al. (44) compared the acute hemodynamic and electrophysiological effects of ‘LV septum pacing’

with that of BVP and HBP. The three pacing modes were comparable with regards to increase in $LVdP/dt_{max}$, whilst HBP and LV septum pacing tended to provide better electrical resynchronization. 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. To show feasibility, safety (including lead extraction) and clinical effectiveness of these new pacing modalities, randomized studies are required comparing LBBP with HBP and BVP. A prospective randomized study is currently performed in China (49).

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

A novel approach to the diagnosis of Brugada syndrome (BrS) described the utilization of autoantibody screening for α -cardiac actin, α -skeletal actin, keratin, and connexin-43. In total, 18/18 BrS subjects demonstrated this autoantibody profile vs. 0/8 normal controls and 0/20 cardiomyopathy cases, which included arrhythmogenic right ventricular cardiomyopathy (ARVC), hypertrophic cardiomyopathy (HCM), and dilated cardiomyopathy (DCM) patients (50). In a subgroup of BrS patients, each of these proteins and the sodium chan-

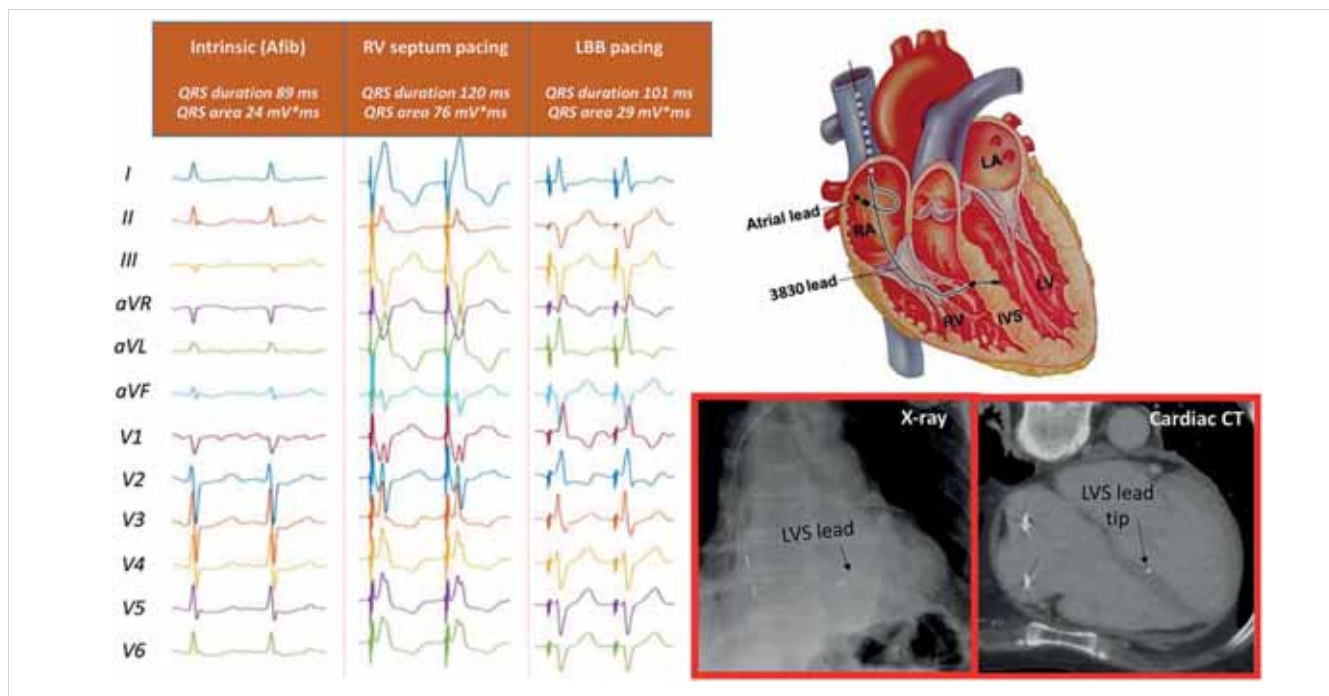


FIGURE 3. Schematic representation (upper right) and X-ray and computed tomography images (lower right) of positioning the pacing lead at the left side of the septum. Left panels show the electrocardiogram (ECG) during intrinsic rhythm of a patient with atrial fibrillation that received a pacemaker. Middle row of ECGs shows 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, QRS duration, and QRS area during LBB pacing

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nel 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 electrocardiogram (ECG) pattern. This paper is complemented by a study investigating polygenic risk (PRS) of ECG markers to predict a positive ajmaline response (51). 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.

A combined clinical and electrophysiological mapping study showed that SCN5A mutation carriers exhibit more pronounced epicardial electrical abnormalities and a more aggressive clinical presentation than non-carriers (52).

Recent data support the use of drug therapy to man-

age patients with catecholaminergic polymorphic VT (CPVT). In a provocative paper by Van der Werf et al. (53), no survival benefit from ICDs was shown in young CPVT patients surviving cardiac arrest. There are a number of caveats to this study, but the main learning point was that such patients can be treated without an ICD.

PRAETORIAN compared transvenous and subcutaneous ICDs in 849 patients >18 years with a class I or IIA indication for ICD therapy for primary or secondary prevention, followed for 49.1 months (54). S-ICD demonstrated non-inferiority of the composite primary endpoint of device-related complications and inappropriate shocks. This provides the first multicentre trial evidence that the S-ICD is as effective and safe as transvenous ICD in preventing SCD for patients not requiring bradypacing, anti-tachycardia VT pacing, or CRT, but challenges remain including longevity of leads and ICD, and inappropriate shocks. Concerning the latter, the UNTOUCHED study of primary prevention ICD therapy supports the PRAETORIAN data by showing an inappropriate shock-free rate of 95.9%, suggesting that the new SMART PASS filter technology and appropriate high rate S-ICD programming may minimize inappropriate shocks in S-ICD recipients (55).

Two primary prevention ICD registries applying propen-

sity scoring showed beneficial effects but differed concerning efficacy of ICD in women and elderly (56, 57). To predict sudden arrhythmic death (SAD) in coronary artery disease, the PRE-DETERMINE investigators integrated an ECG risk score with conventional cardiovascular parameters. A high-risk ECG score incorporating contiguous Q waves, LV hypertrophy, QRS duration, and JTc prolongation was more strongly associated with SAD than non-SAD (adjusted hazard ratios 2.87 vs. 1.38) and the proportion of deaths due to SAD was greater in the high vs. low risk groups (24.9% vs. 16.5%) (58). The addition of ECG markers to a clinical risk factor model including LVEF improved discrimination and reclassification, including correct reclassification of 28% of patients in the validation cohort. The strength of this approach is the utilization of simple bedside biomarkers to determine management, but it needs clinical validation in a randomized trial. To conclude, The Year in Cardiovascular Medicine 2020 – Arrhythmias shows significant progress in the field, much of it incremental, some of it attention gathering, and some of it clearly needing further work. Conflict of interest: none declared.

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