

# Godina 2020. u kardiovaskularnoj medicini: aritmije

## The year in cardiovascular medicine 2020: arrhythmias

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### Uvod

Članak „Godina 2020. u kardiovaskularnoj medicini: aritmije“ nudi pregled najvažnijih istraživanja u području aritmija i elektrostimulacije srca. U protekloj godini zabilježen je značajan napredak: ključne kliničke studije u području liječenja fibrilacije atrijske (AF) i liječenja implantabilnim kardioverterskim defibrilatorima (ICD), nove smjernice, integrirana skrbi, životni stil i aritmije, elektrostimulacije srca putem Hisova snopa, predviđanje rizika u iznenadnoj srčanoj smrti i napredci u kardiogenetici.

### Introduction

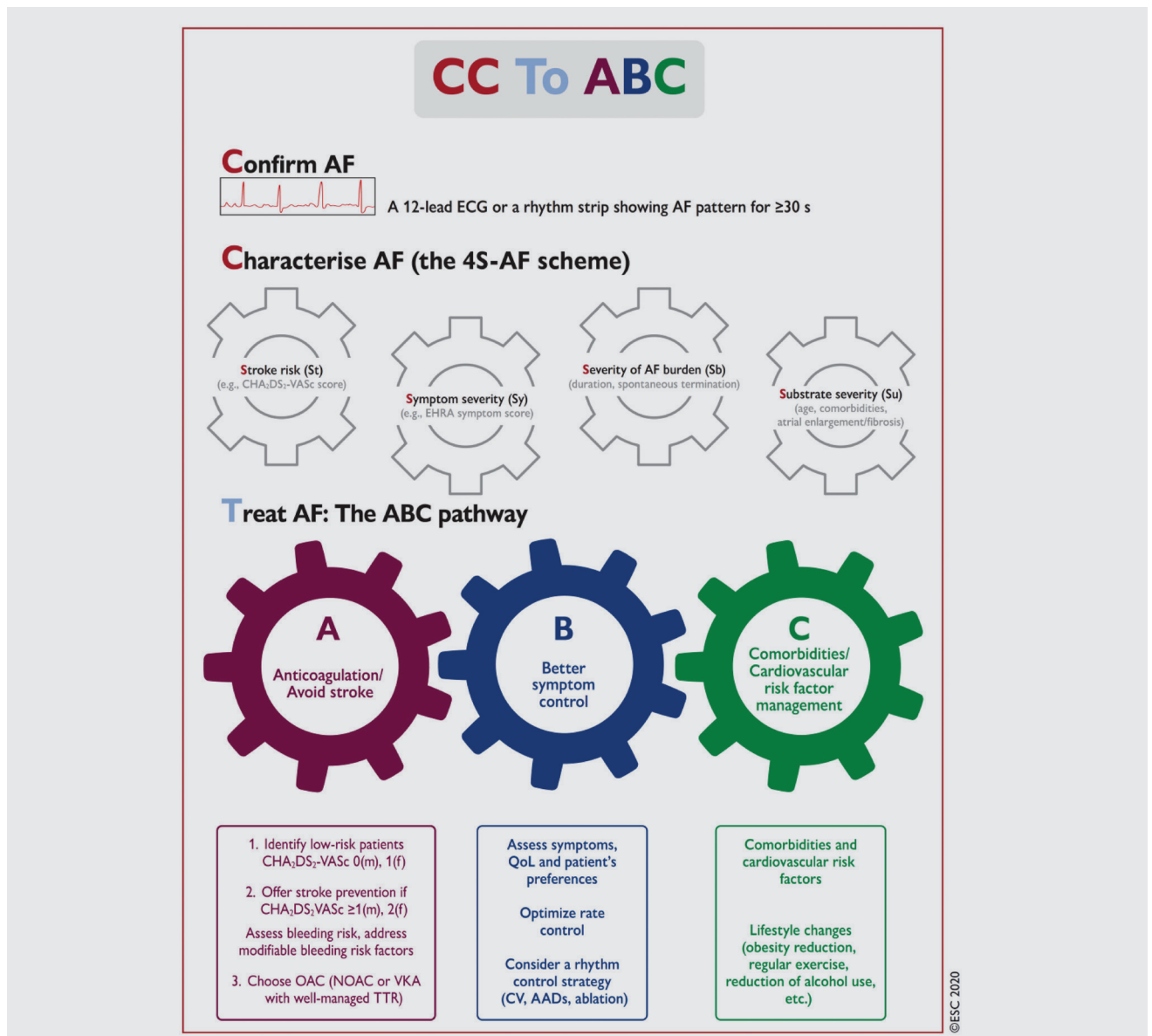
The Year in Cardiovascular Medicine: Arrhythmias 2020 reviews the most relevant studies in the field of arrhythmias and pacing. The past year has shown a significant progress: landmark clinical trials in atrial fibrillation (AF) and implantable defibrillator (ICD) therapy, new guidelines, integrated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

## Nove smjernice

Smjernice za zbrinjavanje supraventrikularne tahikardije (SVT) i AF-a donijele su mnoge nove spoznaje i preporuke.<sup>1,2</sup> Prve govore o ablaciji SVT-a kao ranoj strategiji i invazivnoj procjeni rizika u ventrikularnoj preekscitaciji. Fokus im je također i na onome što valja izbjeći pri zbrinjavanju SVT-a.<sup>2</sup> Nove smjernice za zbrinjavanje AF-a zagovaraju upotrebu slogana „CC do ABC“, naglašavajući da je električna potvrda (C – od engl. *Confirmation*) AF-a obvezna zajedno s detaljnijom karakterizacijom (C – od engl. *Characterisation*) AF-a (slika 1).<sup>1</sup> Za zbrinjavanje AF-a savjetuje se slijediti put za bolje zbr-

## New guidelines

The guidelines on supraventricular tachycardia (SVT) and AF brought many new insights and recommendations.<sup>1,2</sup> 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.<sup>2</sup> 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).<sup>1</sup> For management the AF guidelines advise to follow the Atrial fibrillation Better Care (ABC) pathway, which represents care to (i) avoid stroke,



**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.<sup>1</sup>

(from Crijns HJGM, Prinzen F, Lambiase PD, Sanders P, Brugada J. The year in cardiovascular medicine 2020: arrhythmias. Eur Heart J. 2021 Feb 1;42(5):499-507. <https://doi.org/10.1093/eurheartj/ehaa1091>, by permission of OUP on behalf of the ESC)

njavanje AF-a (ABC pristup – od eng. *Atrial fibrillation Better Care*), koji označuje skrb za izbjegavanje moždanog udara, bolju kontrolu simptoma te skrb o komorbiditetima i čimbenicima kardiovaskularnog rizika. Unatoč manjku podataka koji bi pokazali kliničku učinkovitost, zagovara se probir AF-a uz navod kako, jednom kada se otkrije AF, dolazi do pogoršanja ishoda. Također se preporučuje mjeriti kvalitetu skrbi kroz vrijeme i, kada je potrebno, poboljšati skrb primjenom ponavljajućeg ciklusa poboljšanja. Smjernice također ističu važnost longitudinalne (a ne jednokratne presječne) procjene rizika od moždanog udara i krvarenja jer bolesnici mogu „prerasti“ svoj mali rizik prilično brzo tijekom vremena. Zagovara se primjena kateterske ablacije da bi se ublažili simptomi AF-a i radi zbrinjavanja zatajavanja srca povezanog s AF-om, a koja se može primijeniti nakon neuspjeha primjene jednog antiaritmijskog lijeka, uključujući neuspjeh beta-blokade.

### Randomizirana istraživanja o integriranoj skrbi u fibrilaciji atrijske

Zanimljiva randomizirana istraživanja o integriranoj skrbi u AF-u uključuju i istraživanje *ALL-IN*, klaster randomiziranu studiju u starijih bolesnika s AF-om u primarnoj skrbi, koja je pokazala da je integrirana skrb koju su provodile medicinske sestre uz nadzor liječnika obiteljske medicine smanjila sveukupnu smrtnost za 45 % u usporedbi s uobičajenom skrbi.<sup>3</sup> Ovo je impresivno i naglašava snagu „jednostavnih“ intervencija ako se provode sustavno. Put integrirane skrbi uključuje tromjesečne kontrole AF-a koje provodi medicinska sestra, zbrinjavanje slučajeva koji zahtijevaju antitrombotsko liječenje i osiguranu dostupnost u slučaju potrebe za kardiološkom konzultacijom. To (u sklopu skrbi usmjerene na bolesnika) znači dijeljenje odgovornosti između primarne skrbi, ambulante za antikoagulantno liječenje, kardiologa i bolesnika. Slično ovomu, rezultati istraživanja *RACE 4* pokazali su da integrirana skrb koju vodi medicinska sestra uz podršku informacijskih i komunikacijskih tehnologija (ICT) i nadzor što ga provodi liječnik smanjuje poboljšanje i smrtnost u iskusnim centrima, no ne i u manje iskusnim centrima, naglašavajući važnost obrazovanja/usavršavanja u integriranom okruženju.<sup>4</sup> Ključni elementi integrirane skrbi u ovim istraživanjima bili su pristup multidisciplinarnog tima, obrazovanje i osnaživanje bolesnika i, gdje je bilo moguće, primjena tehnologija koje podupiru odlučivanje.

Nedavna rješenja mZdravlja uključuju *TeleCheck-AF*<sup>5,6</sup> i mobilnu aplikaciju za AF koja u sebi uključuje ABC pristup (**slika 1**).<sup>7</sup> Istraživanje *mAFA II* pokazalo je znatno smanjenje ukupne smrtnosti i nepovoljnih kardiovaskularnih događaja u odnosu prema rutinskoj skrbi u visokorizičnih bolesnika s AF-om.<sup>7</sup> Važno je napomenuti da pojedinačni elementi integrirane skrbi poput primjene kliničkog sustava potpore odlučivanju,<sup>8</sup> edukacijske<sup>9</sup> ili motivacijske<sup>10</sup> intervencije za poboljšanje antikoagulacije ili uvođenje zajedničkog donošenja odluka<sup>11</sup> poboljšavaju razinu skrbi, ali ne i prognozu.

U integriranoj skrbi promjene životnog stila što ih je poduzeo bolesnik koje su usmjerene prema pretilosti, konzumaciji alkohola i kontroli vrijednosti arterijskoga tlaka važne su prije postizanja kontrole ritma kateterskom ablacijom. U velikoj kohorti od 402 406 osoba iz *UK Biobank*, redovita tjelesna aktivnost bila je povezana s manjom pojavnošću AF-a (posebno u žena) i ventrikularnih aritmija, ali ne i bradiaritmija.<sup>12</sup> Također, randomizirano istraživanje pružilo je podatke o dokazu koncepta koji podržava prestanak konzumacije alkohola

(ii) better symptom control, and (iii) 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.

### 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 supervised by general practitioners reduced all-cause mortality by 45% compared to usual-care.<sup>3</sup> 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.<sup>4</sup> 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*<sup>5,6</sup> and a mobile AF application incorporating the ABC pathway (**Figure 1**).<sup>7</sup> The *mAFA II* trial reported a significant reduction in all-cause death and adverse cardiovascular events compared to routine management in high-risk AF.<sup>7</sup> Notably, single elements of integrated care such as application of a clinical decision support system,<sup>8</sup> an educational<sup>9</sup> or a motivational<sup>10</sup> intervention to improve anticoagulation or introduction of shared decision-making<sup>11</sup> 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.<sup>12</sup> Also, a randomized trial provided proof-of-concept data to support alcohol cessation as secondary prophylaxis against AF in regular drinkers.<sup>13</sup> 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.<sup>14</sup>

kao sekundarne profilakse pojave AF-a u osoba koje redovito konzumiraju alkohol.<sup>13</sup> Priroda istraživanja, koje se fokusiralo na jedan element životnog stila, nalaže nužnost razmatranja sveobuhvatnije višerazinske modifikacije čimbenika rizika kako bi se smanjili rizici od AF-a u svakodnevnom životu.<sup>14</sup>

## Randomizirana istraživanja o kontroli ritma u fibrilaciji atrijske

U istraživanju *EAST-AFNET 4* uspoređene su strategije kontrole ritma i kontrole frekvencije u bolesnika s AF koja traje <1 godine. Pokazalo se da strategija kontrole ritma, tj. primjena antiaritmikskih lijekova i ablacije, u ranoj fazi AF-a smanjuje kardiovaskularne ishode bez povećanja vremena provedena u bolnici i bez briga o sigurnosti.<sup>15</sup> Spomenuti rezultati nisu u skladu s onima iz prethodnih istraživanja, a uzrok tomu mogu biti ranije intervencije, sigurnija uporaba antiaritmikskih lijekova i sigurna primjena kateterske ablacije. U skladu sa Smjernicama za AF,<sup>1,16-18</sup> strategija kontrole ritma bila je primijenjena povrh kardiovaskularne prevencije. Kao i pri prethodnim istraživanjima,<sup>19-21</sup> u *EAST-AFNET 4* provedena je procjena strategije, a ne jednostavna usporedba dvaju načina liječenja namijenjena održavanju sinusnog ritma ili zadržavanje odgovarajuće kontrole frekvencije poput one u istraživanju *CABANA*.<sup>22</sup> U istraživanju *EAST-AFNET 4* uključeni su bolesnici s nedavno otkrivenom AF, što se čini presudnim jer se većina događaja zbiva u prvoj godini nakon otkrivanja AF-a.<sup>23,24</sup> Ranu intervenciju podržavaju dva nedavna ispitivanja koja pokazuju da je ablacija kriobalonom kao početna terapija superiornija od liječenja lijekovima.<sup>25,26</sup> Stoga bi početno zbrinjavanje AF-a trebalo radije biti pod nadzorom kardiologa nego nekardiologa, jer su jednogodišnja smrtnost i poboljšanje ako se novodijagnosticirana AF zbrinjava pod kardiološkom skrbi u usporedbi s nekardiološkom skrbi.<sup>27,28</sup>

Rana kontrola ritma u AF-u u hitnoj službi istražena je u drugom randomiziranom istraživanju uspoređujući primjenu prokainamida i spašavajuće električne kardioverzije po potrebi s trenutnom električnom kardioverzijom.<sup>29</sup> Objje su strategije bile klinički vrlo učinkovite, ali su autori pokazali da se preferira trenutna kardioverzija jer je to manje opterećujuće za bolesnike i bolnicu.

Kateterska ablacija može biti osobito korisna pri zatajavanju srca s AF<sup>21,30</sup> radi poboljšanja kvalitete života<sup>31,32</sup>, kao i zbog smanjenja troškova.<sup>33</sup> Jedna zanimljiva opservacijska studija sugerirala je da je kateterska ablacija u usporedbi s primjenom lijekova povezana s manjom pojavnosću vaskularne demencije.<sup>34</sup> Da bi se podržala ili zaobišla primjena kateterske ablacije, nedavna izvješća zagovaraju dodatno denervaciju bubrežnih arterija<sup>35</sup> ili niskorazinsku stimulaciju tragusu.<sup>36</sup> U istraživanju *CASA-AF*<sup>37,38</sup> pojedinačni postupak torakoskopske kirurške izolacije stražnje stijenke lijevog atrijske nije bio superiorniji od opsežne „točka-po-točka“ izolacije stražnje stijenke plus ablacija desnog i lijevog istmusa i praćeni su višim troškovima i manjim dobitcima u QALY-ima. Međutim, set kirurških lezija bio je prilično ograničen, a i učinak kirurške krivulje učenja mogao je utjecati na ishod.

## Postoperativna fibrilacija atrijske

Rizik od moždanog udara i drugih nepovoljnih ishoda nakon postoperativne AF (POAF) zabilježen je u kombiniranim skupovima podataka randomiziranog istraživanja *POISE* o učincima metoprolola prema placebo, acetilsalicilatne kise-

## Randomized trials on rhythm control in atrial fibrillation

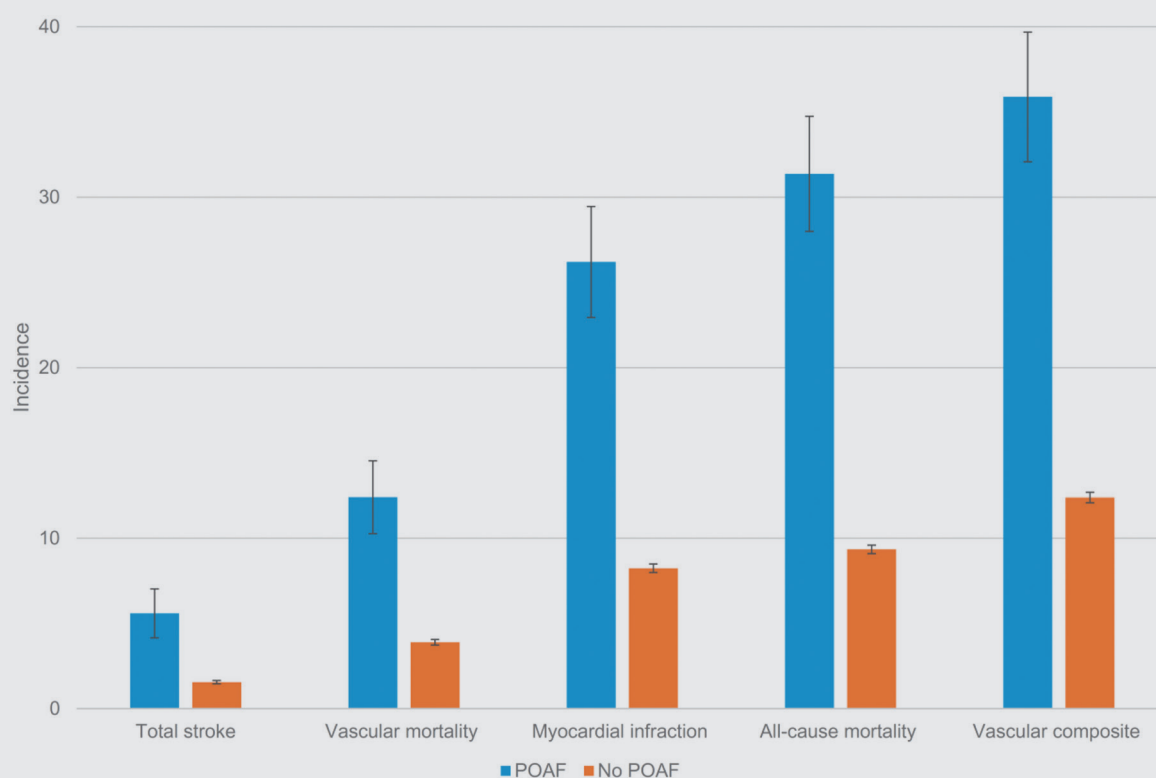
The *EAST-AFNET 4* trial compared a rhythm with a rate control strategy in patients with early AF lasting <1 year. It showed that rhythm control therapy, i.e. antiarrhythmic drugs and ablation, in early AF reduced cardiovascular outcomes without increasing time spent in-hospital, and without safety concerns.<sup>15</sup> 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,<sup>1,16-18</sup> rhythm control was applied on top of cardiovascular prevention. Like previous trials,<sup>19-21</sup> *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.<sup>22</sup> *EAST-AFNET4* included recently detected AF, which seems crucial since most events occur in the first year after AF detection.<sup>23,24</sup> Early intervention is supported by two recent trials showing that cryoballoon ablation as initial therapy is superior to drug treatment.<sup>25,26</sup> 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.<sup>27,28</sup>

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.<sup>29</sup> 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,<sup>21,30</sup> to improve quality of life<sup>31,32</sup> as well as to save costs.<sup>33</sup> One interesting observational study suggested that catheter ablation compared to drug treatment is associated with a lower incidence of vascular dementia.<sup>34</sup> To support or circumvent catheter ablation, recent reports advocated add-on renal denervation<sup>35</sup> or low level tragus stimulation.<sup>36</sup> In *CASA-AF*,<sup>37,38</sup> 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.<sup>39</sup> 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



**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.<sup>39</sup>**

(from Crijns HJGM, Prinzen F, Lambiase PD, Sanders P, Brugada J. The year in cardiovascular medicine 2020: arrhythmias. *Eur Heart J*. 2021 Feb 1;42(5):499-507. <https://doi.org/10.1093/eurheartj/ehaa1091>, by permission of OUP on behalf of the ESC)

line prema placebo i klonidina prema placebo.<sup>39</sup> Bolesnici s kardiovaskularnom bolesti bili su podvrgnuti neekardijalnom operativnom zahvatu. POAF unutar 30 dana nakon operativnog zahvata zabilježen je u 404 od 18 117 bolesnika i bila je povezana s jednogodišnjom učestalošću moždanog udara od 5,6 % u odnosu prema 1,5 % u bolesnika bez POAF. Također su bili povišeni rizik od smrti (31,3 % prema 9,3 %) i infarkta miokarda (26,2 % prema 8,2 %) (slika 2). Strategije smanjenja rizika još treba istražiti. Nažalost, ovaj jaz u znanju nije bio popunjen nedavnim randomiziranim istraživanjem u kojem se ispitivao učinak sedativa deksmedetomidina u usporedbi s placeboom kako bi se smanjila novonastala POAF kao i delirij u 798 bolesnika koji su podvrgnuti kardiokirurškom zahvatu.<sup>40</sup> Incidencija novonastale POAF (~32 %) i delirija (~15 %) nisu se razlikovali između ispitivanih skupina.

### Srčana resinkronizacijska terapija, uključujući elektrostimulaciju srca putem Hisova snopa, septuma i lijeve grane snopa

Godina 2020. zabilježila je eksponencijalni porast interesa za elektrostimulaciju srca putem Hisova snopa (HBP) i područja grane lijevoga snopa (LBBAP) u srčanoj resinkronizacijskoj terapiji (CRT). Broj implantacija najčešće korištene elektrode u SAD-u (Medtronic 3830) pokazao je porast s 2000 u 2016. g. na 10 000 u 2018. godini. Broj publikacija povezanih s HBP-om po-

surgery.<sup>40</sup> 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.<sup>41</sup> Worldwide sales of the 3830 lead increased nine-fold between 2014 and 2018. The Twitter '#dontdisthehis' attracted almost 1200 users within 2.5 years.<sup>42</sup> 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 regard to acute hemodynamic improvement, reverse remodeling and clinical outcome.<sup>43-45</sup>

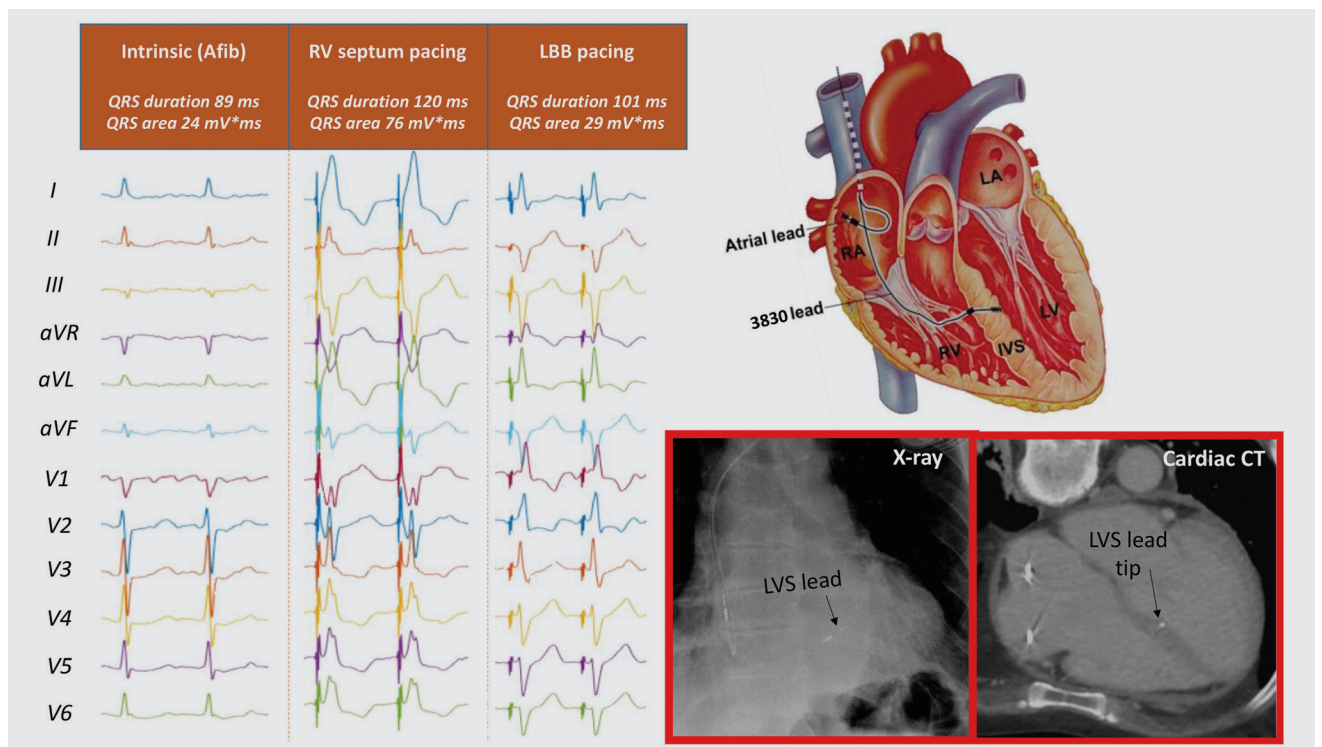
In 2020, LBBAP was only 3 years old but attracted already considerable interest. For LBBAP, the 3830 lead is introduced transvenously and subsequently screwed through the inter-ventricular septum until the tip of the lead is (almost) at the

većao se s 5 u 2014. na 75 u 2018. godini.<sup>41</sup> Širom svijeta prodaja elektrode 3830 povećala se devet puta između 2014. i 2018. godine. Twitter hashtag "#dontdisthehis" privukao je gotovo 1200 korisnika unutar 2,5 godina.<sup>42</sup> Povećani interes za HBP vjerojatno je rezultat dostupnosti boljih katetera za uvođenje i dokaza da je HBP također prikladan za CRT. Tijekom 2020. godine nekoliko je istraživanja pokazalo da bi HBP mogao biti jednako dobar ili superiorniji od konvencionalne biventrikularne elektrostimulacije (BVP) s obzirom na akutno hemodinamsko poboljšanje, reverzno remodeliranje i klinički ishod.<sup>43-45</sup>

Godine 2020. LBBAP je imao samo 3 godine, ali je već privukao znatan interes. Za LBBAP elektroda 3830 uvodi se transvenski te se nakon toga postavlja s pomoću vijka kroz interventrikulski septum dok vrh elektrode nije (gotovo) na endokardu lijeve klijetke (LV) (slika 3). U usporedbi s HBP-om, LBBAP implantacija elektrode je lakša i pragovi elektrostimulacije su niži.<sup>46</sup> Neki istraživači imaju za cilj „hvatanje“ same grane lijevog snopa,<sup>45</sup> ali su drugi manje kritični i prihvaćaju bilo koju „LV septalnu“ poziciju elektrode.<sup>44</sup> U 2020. godini pojavio se niz malih studija, provedenih u pojedinačnim centrima, ali i multicentričnih. Hou i sur.<sup>46</sup> proveli su istraživanje u 56 bolesnika s bradiaritmijama i LVEF-om >55 %. Spomenuti su autori otkrili su da je trajni LBBAP siguran i izvediv. Bolje održavanje sinkronosti kontrakcije, utvrđeno analizom SPECT MPI faze, primijećeno je kad je „uhvaćen“ lijevi snop

left ventricular (LV) endocardium (Figure 3). Compared to HBP, LBBAP lead implantation is easier and pacing thresholds are lower.<sup>46</sup> Some investigators aim at capturing the left bundle branch itself,<sup>45</sup> but others are less critical and accept any 'LV septal' lead position.<sup>44</sup> In 2020, a number of small single and multicenter studies appeared. Hou *et al.*<sup>46</sup> 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.<sup>45,47,48</sup>

Salden *et al.*<sup>44</sup> 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/dtmax, 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 compar-



**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.

(from Crijns HJGM, Prinzen F, Lambiase PD, Sanders P, Brugada J. The year in cardiovascular medicine 2020: arrhythmias. *Eur Heart J.* 2021 Feb 1;42(5):499-507. <https://doi.org/10.1093/eurheartj/ehaa1091>, by permission of OUP on behalf of the ESC)

grane. Tri studije koje su obuhvaćale ukupno 116 bolesnika s LBBAP-om, 49 s HBP-om i 75 s BVP-om dosljedno pokazuju veće smanjenje trajanja QRS-kompleksa u kombinaciji s većim porastom ejectionске frakcije LV-a.<sup>45,47,48</sup>

Salden *i sur.*<sup>44</sup> uspoređivali su akutne hemodinamske i elektrofiziološke učinke „elektrostimulacije LV septuma“ s učincima BVP-a i HBP-a. Tri načina elektrostimulacije bila su usporediva s obzirom na povećanje u LVdP/dtmax, dok su elektrostimulacija HBP-a i LV septuma imale tendenciju davati bolju električnu resinkronizaciju. Važno je otkriće bilo i da su slični učinci primijećeni pri elektrostimulaciji septuma LV-a na bazalnom, ekvatorijalnom i apikalnom dijelu septuma. Da bi se pokazale izvedivost, sigurnost (uključujući ekstrakciju elektrode) i klinička učinkovitost ovih novih modaliteta elektrostimulacije, potrebne su randomizirane studije za usporedbu LBBP-a s HBP-om i BVP-om. Trenutačno je u tijeku prospektivno randomizirano istraživanje u Kini.<sup>49</sup>

## Nasljedne bolesti srca, procjena rizika, implantabilni kardioverterski defibrilatori i iznenadna smrt

Novi pristup dijagnozi Brugada sindroma (BrS) opisao je uporabu probira autoantitijela na  $\alpha$ -srčani aktin,  $\alpha$ -skeletalni aktin, keratin i koneksin-43. Ukupno 18/18 BrS ispitanika imalo je ovaj profil autoantitijela u odnosu prema 0/8 normalnih kontrola i 0/20 slučajeva kardiomiopatije, koji su uključivali aritmogenu kardiomiopatiju desne klijetke (ARVC), hipertrofijsku kardiomiopatiju (HCM) i bolesnike s dilatacijskom kardiomiopatijom (DCM).<sup>50</sup> U podskupini bolesnika s BrS-om, svaki od ovih proteina i protein natrijeva kanala tipa 5 alfa-podjedinica (Nav1.5) agregirali su u sarkoplazmi stanica miokarda. Mehanizam zbog kojeg protutijela na te proteine identificiraju slučajeve BrS-a nije jasan, ali bi mogao biti povezan s oštećenjem sarkolemalne membrane bilo zbog miokarditičnog procesa u tijeku bolesti ili zbog abnormalnog prijanjanja stanica, što rezultira imunskim odgovorom. Novost ove studije jest uporaba serološkog testa za identificiranje osoba s BrS-om, što može biti izazov s obzirom na prolaznu prirodu specifičnog obrasca elektrokardiograma (EKG). Ovaj je rad dopunjen istraživanjem koje ispituje poligenski rizik (PRS) EKG biljega za predviđanje pozitivnog odgovora na ajmalin.<sup>51</sup> PRS za BrS, početno trajanje QRS-a, prisutnost tipa II. ili III. BrS EKG uzorka na početku i obiteljska anamneza BrS-a bili su neovisno povezani s pojavom tipa I. BrS-a u EKG-u, s dobrom prediktivnom točnošću ( $C$ -statistika 0,74 – optimistično korigirana). Ovo pruža prve podatke koji omogućuju kombinaciju genetskog i kliničkog probira za predviđanje odgovora na ajmalin i ima implikacije za stratifikaciju rizika.

Kombinirano istraživanje kliničkog i elektrofiziološkog mapiranja pokazalo je da nosioci mutacija SCN5A pokazuju izraženije epikardijske električne abnormalnosti i agresivniju kliničku prezentaciju nego nenosioci.<sup>52</sup>

Noviji podatci podupiru primjenu terapije lijekovima za zbrinjavanje bolesnika s katekolaminergičnom polimorfnom VT (CPVT). U provokativnom radu Van der Werf *i sur.*<sup>53</sup> nije bilo dobrobiti u smislu preživljavanja od ugradnje ICD-a u mladih CPVT bolesnika koji su preživjeli srčani arrest. Iako su ograde u ovoj studiji brojne, glavna poruka bila je ta da se takvi bolesnici mogu liječiti bez ICD-a.

U istraživanju *PRAETORIAN* uspoređeni su transvenski i potkožni ICD u 849 bolesnika u dobi >18 godina s indikaci-

ing LBBP with HBP and BVP. A prospective randomized study is currently performed in China.<sup>49</sup>

## 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  $\alpha$ -cardiac actin,  $\alpha$ -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 arrhythmic right ventricular cardiomyopathy (ARVC), hypertrophic cardiomyopathy (HCM), and dilated cardiomyopathy (DCM) patients.<sup>50</sup> 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 electrocardiogram (ECG) pattern. This paper is complemented by a study investigating polygenic risk (PRS) of ECG markers to predict a positive ajmaline response.<sup>51</sup> 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.<sup>52</sup>

Recent data support the use of drug therapy to manage patients with catecholaminergic polymorphic VT (CPVT). In a provocative paper by Van der Werf *et al.*,<sup>53</sup> 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.<sup>54</sup> 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 brady-pacing, 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.<sup>55</sup>

jom klase I. ili IIa. za ICD terapiju za primarnu ili sekundarnu prevenciju, uz razdoblje praćenja od 49,1 mjesec.<sup>54</sup> Primjena S-ICD-a pokazala je neinferiornost u zajedničkom primarnom ishodu koji se sastojao od komplikacija povezanih s uređajima i neprikladnih šokova. To istraživanje pruža prvi multicentrični dokaz da je S-ICD jednako učinkovit i siguran kao transvenski ICD u prevenciji SCD-a za bolesnike koji nemaju potrebu za elektroterapijom zbog bradikardije, antitahikardijske VT elektrostimulacije ili CRT, ali izazovi ostaju, uključujući dugovječnost elektroda i ICD te neprikladne šokove. Što se tiče potonjeg, rezultati istraživanja *UNTOUCHED* (primarne prevencije ICD terapijom) podupiru podatke iz studije *PRAETORIAN* pokazujući učestalost slobode od neprikladnih šokova od 95,9 %, što upućuje na to da nova tehnologija filtra SMART PASS i odgovarajuće programiranje terapijskih zona visoke frekvencije S-ICD može smanjiti neprikladne šokove u S-ICD primatelja.<sup>55</sup>

Dva registra primarne prevencije ICD-a koja primjenjuju bodovanje sklonosti pokazali su korisne učinke, ali su se razlikovali u pogledu učinkovitosti ICD-a u žena i starijih osoba.<sup>56,57</sup>

Radi predviđanja iznenadne aritmijske smrti (SAD) kod koronarne bolesti srca, istraživači su u studiji *PRE-DETERMINE* integrirali EKG ocjenu rizika s konvencionalnim kardiovaskularnim parametrima. EKG ocjena visokog rizika koja uključuje susjedne Q-valove, hipertrofiju lijeve klijetke, trajanje QRS-a, i produljenje JTc bilo je jače povezano sa SAD-om nego s ne-SAD-om (prilagođeni HR 2,87 prema 1,38) i udio smrtnih slučajeva zbog SAD-a bio je veći u skupinama s visokim u odnosu prema niskom riziku (24,9 % prema 16,5 %).<sup>58</sup> Dodavanje EKG biljega kliničkom modelu čimbenika rizika, uključujući LVEF, poboljšalo je diskriminaciju i reklasifikaciju, uključujući pravilnu reklasifikaciju 28 % bolesnika u validacijskoj kohorti. Snaga je ovakvog pristupa korištenje jednostavnim kliničkim biomarkerom kako bi se odredilo zbrinjavanje, ali je potrebna klinička validacija u randomiziranom ispitivanju.

Zaključno, 2020. godina u kardiovaskularnoj medicini – aritmije pokazuje značajan napredak na ovom području: u većem dijelu asinkrono, u jednom dijelu privlači pozornost, a jedan dio jasno zahtijeva daljnji rad.

Two primary prevention ICD registries applying propensity scoring showed beneficial effects but differed concerning efficacy of ICD in women and elderly.<sup>56,57</sup>

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%).<sup>58</sup> 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.

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