Godina 2016. u kardiologiji: aritmije i srčani implantabilni elektronički uređaji

The year in cardiology 2016: arrhythmias and cardiac implantable electronic devices

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RECEIVED:
February 27, 2017

ACCEPTED:
February 28, 2017

CITATION: Cardiol Croat. 2017;12(5-6):240-253. | https://doi.org/10.15836/ccar2017.240

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Uvod

Godinu 2016. obilježavaju brojna važna dostignuća u području aritmija srca. U ovome članku donosimo selekciju izdvojenih članaka koji donose informacije koje se čine potencijalno važne za svakodnevnu kliničku praksu.

Aritmije i kateterska ablacija

SUPRAVENTRIKULSKA TAHIKARDIJA: DIJAGNOZA I LIJEČENJE

Supraventrikulske aritmije (SVPT) i dalje su čest razlog prijma u hitnoj službi. U studiji REVERT evaluirana je najbolja i najučinkovitija strategija akutnoga zbrinjavanja SVPT-a te su uspoređivani različiti položaji tijela (podizanje donjih udova te nakon toga ležanje, oboje u trajanju od po 15 sekundi) sa standardiziranim naprezanjem pri Valsalvinu manevra (npr. tlak od 40 mm Hg koji

Preamble

The year 2016 was characterized by numerous relevant contributions in cardiac arrhythmias. A selected group of articles providing information with potential impact in daily practice has been identified by the authors and is reported in the present article.

Cardiac arrhythmias and catheter ablation

SUPRAVENTRICULAR TACHYCARDIA: DIAGNOSIS AND TREATMENT

Supraventricular tachycardia (SVT) continues to be a frequent cause of emergency hospital admission. The REVERT study evaluated the best and most efficient acute treatment strategy for SVT and compared postural modification (leg elevation and supine positioning applied

se održava u trajanju od 15 sekundi forsiranim izdisajem, a mjeri se aneroidnim manometrom koji ispitivaču pokazuje ciljni tlak).[1] Utvrđeno je da modificirani pristup prekida SVPT u znatno većeg udjela pacijenata (43 % od 214) negoli primjena konvencionalnih manevara (17 % od 214; P < 0,0001). Posljedično tomu, mnogo manji broj pacijenata uključenih u studiju zahtijevao je primjenu adenozina (50 % prema 69 %) ili akutnu primjenu antiaritmika radi prekida novonastalih aritmija[1], dok nije registriran utjecaj na vrijeme otpusta iz bolnice nije registriran. Rezultati spomenute studije mogu znatno utjecati na svakodnevnu kliničku praksu i smanjiti nuspojave povezane s primjenom lijekova za hitno zbrinjavanje pacijenta sa SVPTom. Potpuni pregled najnovijega pristupa dijagnozi i liječenju SVPT-a može se pogledati u EHRA/ESC zajedničkom dokumentu iz 2016. godine (Katritsis *et al.*, EHJ 2016 u tisku).

FIBRILACIJA ATRIJA: PATOFIZIOLOGIJA, ČIMBENICI RIZIKA, MOGUĆNOSTI LIJEČENJA I NOVE SMJERNICE EUROPSKOGA KARDIOLOŠKOG DRUŠTVA

Intenzivna znanstvena rasprava o patofiziologiji fibrilacije atrija (FA) i napose o pokretaču progresije FA-a upotpunjena je i potaknuta zanimljivim eksperimentima i kliničkim ispitivanjima o remodeliranju atrija.[2] Pokazano je da se masno tkivo u atriju, koje je ranije identificirano kao važan rizičan čimbenik za razvoj FA-a, progresivno zamjenjuje vezivnim tkivom koje čini supstrat za progresiju FA-a.[2] Nadalje, ti podatci mogu objasniti povezanost između debljine i AF-a, nedavno opisanog u kliničkim studijama.[3] Naime, te su studije također pokazale da se gubitkom tjelesne težine znatno smanjuje opterećenje AF-a. Također je predmet istraživanja pitanje je li strukturno remodeliranje povezano s opterećenjem sFA-a (**Slika 1**). Otkrivanje i kvantifikacija fibroze oslikavanjem s pomoću magnetne rezonancije osigurava mogućnost za dokumentiranje promjena tijekom vremena, a u budućnosti može dati daljnji uvid u taj važan aspekt patofiziologije AF-a (**Slika 2**).[4] Međutim, različiti metodološki pristupi moraju biti tek prevladani, prije svega zbog tanke stijenke atrija te su nužni odgovarajući protokoli. Kontrola frekvencije srca najčešća je primjenjiva opcija u liječenju pacijenta s FA-om diljem svijeta. Podatci o najboljoj medikamentnoj opciji koja podržava smanjenje simptoma kontrolom frekvencije srca, i smanjuje

for 15 sec at the end of 15 sec) with standardized strain Valsalva manoeuvre (i.e. pressure of 40 mm Hg sustained for 15 s by forced expiration measured by aneroid manometer with the target pressure visible to the treating team).[1] The modified treatment was found to terminate SVTs in a significantly larger proportion of patients (43% of 214) than using conventional manoeuvres (17% of 214; $P < 0.0001$). As a consequence, significantly less patients in the study arm required adenosine (50% vs. 69%) or emergency anti-arrhythmic treatment (57% vs. 80%) to terminate the incident arrhythmia[1] and no differences in time to discharge from hospital. This finding may considerably affect daily practice and reduce drug-related patient discomfort at time of emergency treatment in patients with SVT. The full scope of up-to-date diagnosis and treatment of SVTs can be reviewed best in 2016 EHRA/ESC consensus document on SVT management (Katritsis *et al.*, EHJ 2016 in press)

ATRIAL FIBRILLATION: PATHOPHYSIOLOGY, RISKS, TREATMENT OPPORTUNITIES, AND THE NEW ESC AF GUIDELINES

The intense scientific discussion about the pathophysiology of atrial fibrillation and particularly the drivers for AF progression was enriched and stimulated by a very interesting experimental and clinical study on atrial remodeling.[2] It was shown that atrial adipose tissue, which has been previously identified as a strong risk factor for AF development, is progressively replaced by fibrotic tissue that serves as the substrate for AF progression.[2] These data may further explain the link between obesity and AF recently described in clinical studies.[3] However, those studies also showed a significant reduction of AF burden with weight loss and it is now of particular interest whether or not the reduction in AF burden may coincide with reversed structural re-modelling—and vice versa (**Figure 1**). MRI-based fibrosis detection and quantification holds some promise to document the substrate changes over time and may give further insights into this important aspect of AF pathology in the future (**Figure 2**).[4] However, various methodological hurdles need to yet be overcome, mainly due to the thin wall of the atria, and appropriate protocols are indispensable. Rate control is the most frequent treatment options chosen for and by AF patients world-wide. Data

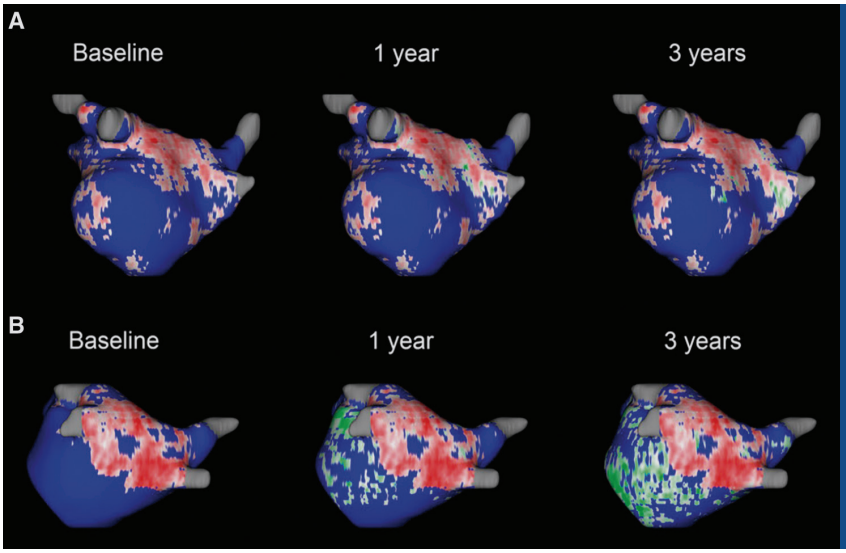

FIGURE 1. Different dynamics of scar progression with progressive fibrosis over a time period of 3 years in the years after atrial fibrillation ablation. Panel (*A*) depicts a patient with little to no increase in cardiac fibrosis while panel (*B*) depicts a patient with massive increase in cardiac fibrosis at 1 year and 3 years (green colour) coinciding with multiple AF recurrences.

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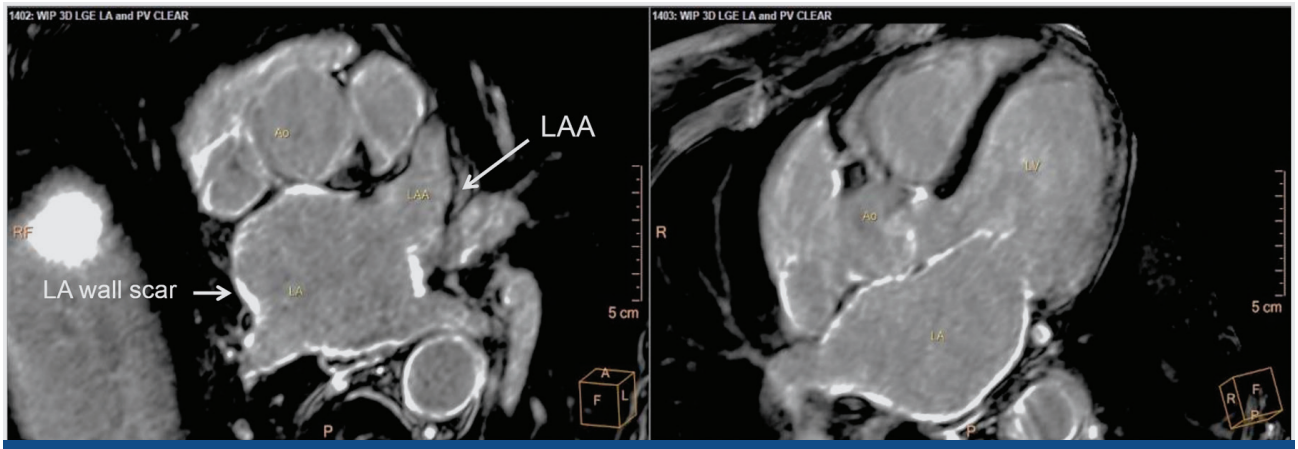

FIGURE 2. MRI-based imaging of atrial wall fibrosis. MRI cross section at the level of the left atrium (left side) and 5-chamber view (right side). Atrial fibrosis can be detected in various regions of the atrial wall (white spots). Only the left atrial appendage (LAA) is largely free of scar.

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rizike vezane za FA, ograničeni su i donekle kontroverzni.[5] U nedavnoj studiji iz Tajvana ispitivani su dugotrajni učinci beta-blokatora, blokatora kalcijevih kanala i digitalisa primjenjivanih za kontrolu frekvencije srca kod FA-a na smrtnost.[6] Nakon usklađivanja temeljnih razlika, utvrđeno je da je rizik smrtnog ishoda bio značajno niži u 43 879 pacijenata koji su primali beta-blokatore i u 18 466 pacijenata koji su primali blokatore kalcijevih kanala negoli u kontrolnoj skupini od 168 678 pacijenata koji nisu primali nijedan lijek za kontrolu frekvencije srca. S druge strane, pacijenti na digoksinu imali su viši rizik od smrtnog ishoda. Posebno je zanimljiv utjecaj beta-blokatora jer nedavna metaanaliza o učinku tih lijekova na kontrolu frekvencije srca nije pokazala takav pozitivan učinak beta-blokatora.[7] Ti rezultati pridonose postojećoj kontroverziji o utjecaju lijekova za kontrolu frekvencije srca na rizik od ukupne smrtnosti u pacijenata sa kroničnom FA i zahtijevaju buduća randomizirana ispitivanja koja će odgovoriti na ta važna pitanja.

Pacijenti s aortnom stenozom (AS) u trenutku dijagnoze imaju često već prisutnu FA, koja može biti neotkrivena ili se tek razvija (tzv. novonastala FA) rano nakon kardiokirurške operacije ili transfemoralne zamjene aortne valvule (TAVI). Doista, kada se uspoređuju s pacijentima u sinusnom ritmu, pacijenti s FA i AS-om podvrgnuti kardiokirurškom zahvatu ili postupku ugradnje TAVI-ja imaju veći rizik od razvoja moždanog udara i krvarenja te višu ukupnu smrtnost.[8] Nedavno ažurirani klinički podatci o toj temi istaknuli su da je incidencija novonastale FA manja kod TAVI-ja u usporedbi s kirurškom zamjenom valvule.[8] Međutim, još nije jasno koja je optimalna strategija liječenja takvih bolesnika u smislu kontrole frekvencije srca ili ritma. U budućim kliničkim studijama i ispitivanjima trebalo bi ispitati uloge amiodarona u periproceduralnoj prevenciji razvoja FA-a i kontroli ritma te ulogu kateterske ablacije u strategiji kontrole ritma. Drugo područje kontroverzi odnosi se na optimalnu primjenu antikoagulacijskog liječenja, posebice u bolesnika s TAVI-jem: jesu li pogodni kandidati za primjenu NOAC-a ili su antagonisti vitamina K bolji izbor? Iako postoje dobri argumenti u prilog primjeni NOAC-a nakon transfemoralne zamjene aortnog zalistka, podatci iz specifičnih, velikih kliničkih ispitivanja još uvijek nisu dali odgovore na ovo važno pitanje.[9]

about the best medication to support rate control therapy by symptom relief and reducing AF-related risks are limited and somewhat controversial.[5] A recent nationwide study from Taiwan investigated the long-term effects of beta-blockers, calcium-channel blockers or digitalis given for the rate control in ongoing atrial fibrillation on mortality.[6] After adjustment for baseline differences, the risk of mortality was found to be significantly lower in the 43 879 patients receiving beta-blockers and in the 18 466 patients receiving calcium-channel blockers than in a control population of 168 678 patients not receiving any rate-control drug. On the contrary, patients receiving digoxin had a higher risk of mortality. Especially the effects observed for beta-blockers are interesting as a recent meta-analysis on rate control medications did not show such beneficial effects for beta-blockers.[7] These findings contribute to the ongoing controversy about the impact of rate-control drugs on the risk of all-cause death in patients with ongoing AF and prompt for the need of future randomized trials to address this relevant question.

Patients with aortic stenosis often also have pre-existing AF which may be 'silent' or develop AF (so-called 'new-onset AF') early after surgical or transfemoral aortic valve replacement (TAVI). Indeed, when compared with patients in sinus rhythm, patients with AF undergoing surgical or TAVI interventions have been shown to be at higher risk for stroke and bleeding but also for having a higher total mortality.[8] A recent clinical update on this topic pointed out that the incidence of new-onset AF may be lower with TAVI as compared with surgical valve replacement.[8] However, the optimal treatment strategy of such patients with respect to rhythm or rate control is still unclear. Particularly the role of amiodarone both for the peri-procedural prevention of AF and for classical rhythm control as well as the role of catheter ablation as a rhythm control strategy needs further evaluation in clinical studies and trials. Another field of controversy relates to the optimal anticoagulation regimen especially for TAVI patients: are AF patients after TAVI eligible for NOAC therapy or are vitamin K antagonists the better choice? While there are good arguments in favour of NOACs after TAVI convincing data from specific and large clinical trials are still lacking to answer this important question.[9]

Kateterska ablacija paroksizmalne FA: pitanje je spaliti ili smrznuti? Do sada nisu bili uspoređivani rezultati kateterske „point-by-point" radiofrekventne ablacije i balonske krioablacije u liječenju paroksizmalne FA. O navedenoj se temi mnogo raspravljalo tijekom godina. Sada se zna da obje ablacijske tehnike rezultiraju jednakom kontrolom ritma te da imaju slični postotak komplikacija.[10]

U međunarodnom, multicentričnom ispitivanju *FIRE AND ICE* 762 bolesnika s paroksizmalnom FA predviđena za izolaciju plućnih vena nasumično je bilo raspoređeno za radiofrekventnu ablaciju (RF) ili krioablaciju. Tijekom razdoblja praćenja od godinu i pol dana nisu utvrđene razlike između dviju skupine u postablacijskim kliničkim ishodima (npr. vraćanje FA, pojavi undulacije atrija ili atrijske tahikardije, uporabi antiaritmijskih lijekova ili ponavljanju ablacije): 34,6 % u skupini s krioablacijom te 35,9 % u grupi s RF ablacijom. Dokazano je da su te dvije tehnike podjednako sigurne, s jednakom ukupnom incidencijom smrti, cerebrovaskularnih događaja ili ozbiljnih događaja vezanih za postupak od 10,2 % i 12,08 %, kako je navedeno (P = NS). Relativno visoka incidencija događaja vezanih za postupak u skladu su sa ranijim prospektivnim podatcima provedenima u istraživanoj populaciji. Obje skupine pacijenata u studiji imale su sličnu kvalitetu života nakon ablacije. U kasnijem su istraživanju isti autori izvijestili da je u skupini s krioablacijom tijekom praćenja uočena niža stopa ponovljenih ablacija, kardioverzija i hospitalizacija zbog svih uzroka.[11] Slično tomu, u studiji *Freeze AF* u koju je bilo uključeno 315 pacijenta s paroksizmalnom AF dokazano je da rezultati krioablacije nisu inferiorni rezultatima RF ablacije.[12] Rezultati spomenutih dviju studija, karakterizirani ograničenim usvajanjem najnovijih tehničkih dostignuća u RF skupinama, pridonijet će prihvaćanju krioablacije kao važne alternative RF ablaciji paroksizmalne FA. Ipak još uvijek je potrebno istražiti mogu li ablacijske strategije zasnovane na supstratu u bolesnika s paroksizmalnom FA i niskovoltažnim područjima biti korisne za uspostavu sinusnog ritma nakon primjene RF ablacijskih tehnika.[13]

U studiji STAR AF II, koja je obuhvaćala pacijente s perzistentnom FA, bila je ispitivana učinkovitost izolacije plućnih vena (PVI) kateterom primjenjujući RF struju i uspoređena s PVI-jem s dodatnim ablacijskim linijama te s PVI-jem s ablacijom frakcioniranih atrijskih signala (CFAE).[14] U studiju je bilo uključeno 589 pacijenata koji su nasumično randomizirani u tri skupine prema omjeru 1 : 4 : 4, pri čemu nisu pronađene razlike u postotku pacijenta koji su bili bez pojave AF-a u razdoblju praćenja nakon 18 mjeseci (59 %, 49 %, 46 %). Ti su rezultati u suprotnosti s nedavno objavljenim rezultatima metaanalize[15] temeljene na ograničenoj seriji podataka. U njoj se govori o 51 %-tnoj redukciji relativnog rizika za povrat FA-a u pacijenta u kojih je primjenjivan PVI s dodatnim ablacijskim linijama u usporedbi s pacijentima u kojih je učinjen samo PVI. Razlike u podatcima između tih dviju studija ističu potrebu za novim randomiziranim studijama, a u svrhu potvrđivanja nalaza iz prethodnih studija primjenom manje rigoroznih metodologija. Utvrđivanje važnosti jednostavnih procedura kao prve linije ablacije u pacijenata s perzistentnom AF može imati znatan klinički utjecaj, s naglaskom na pacijentovu sigurnost. Potrebne su nove studije kojima bih se potvrdili dosadašnji nalazi, istražile nove ablacijske tehnike i utvrdila najbolja strategija u pacijenata s perzistentnom AF u kojih nije uspjela prva linija liječenja.

Catheter ablation of paroxysmal AF: burn it down or freeze it? The comparative effect of catheter-based point-by-point radiofrequency ablation and balloon-based cryo-ablation for the treatment of paroxysmal AF was unknown and had been intensely debate over years. We now know that both ablation techniques result in the same rhythm outcome and have similar complication rates.[10] In the FIRE AND ICE international, multicentre, clinical trial 762 patients with paroxysmal AF were randomly assigned to undergo pulmonary vein isolation with RF-ablation or cryo energy. During 1.5 years of follow-up, no differences were found between the two groups in the incidence of post-ablation clinical failure (i.e. recurrence of AF, occurrence of atrial flutter or atrial tachycardia, use of anti-arrhythmic drugs, or repeat ablation): 34.6% in the cryo-balloon arm and 35.9% in the RF arm. The two techniques also proved similarly safe, with an aggregate incidence of death, cerebrovascular events, or serious treatment-related adverse events of 10.2% and 12.8%, respectively (*P* = ns). This relatively high incidence of side effects is in line with previous data of prospectively investigated populations. Quality-of-life assessment post-ablation did not differ between the two study arms. In a subsequent study, the same authors reported a lower incidence of repeat ablations, direct-current cardioversions, and all-cause rehospitalization during follow-up in the cryo-balloon study arm.[11] Similarly, a non-inferiority of cryo-balloon-assisted vs. RF-assisted ablation was also documented in the Freeze AF study which randomized 315 patients with paroxysmal AF.[12] The results of these two studies, which are characterized by a limited adoption in the RF arm of the most recently introduced technologies, will contribute to establish cryoballoon-assisted ablation as a valuable alternative to RF-assisted ablation of paroxysmal AF. However, it still needs to be evaluated whether substrate-based ablation strategies in patients with paroxysmal AF and low-voltage areas may add benefits with respect to rhythm outcome after RF-based ablation techniques.[13]

In patients with persistent AF, the efficacy of catheter-based PVI using RF current was comparatively assessed with that of PVI plus linear ablation and that of PVI plus complex fractionated atrial electrogram (CFAE) ablation in the STAR AF II study.[14] In the 589 study patients randomly assigned to the three study arms according to a 1:4:4 randomization ratio, no differences were found in the proportion of patients who were free from recurrent AF after 18-month follow-up (59%, 49%, 46%). These results diverge with those reported in a recent meta-analysis[15] on limited series showing a 51% relative risk reduction in the incidence of recurrent AF in patients receiving linear ablation in addition to PVI when compared with patients receiving PVI only. The discrepancy of findings between these two studies highlights the value of performing randomized studies in order to validate findings from previous studies using less rigorous methodology. Establishing on a large scale the role of a simpler procedure as the first ablation step in patients with persistent AF may have relevant clinical implications with regard to patient safety. New studies are required to confirm the present findings, investigate new ablation designs and identify the best strategy in patients with persistent AF who failed the first one.

The optimal antiarrhythmic management following ablation also still remains to be determined. In the Efficacy of Antiarrhythmic Drugs Short-Term Use After Catheter Ablation for

U budućnosti treba odrediti optimalnu antiaritmijsku terapiju nakon ablacije jer ona nije poznata. U ispitivanju *Efficacy of Antiarrhythmic Drugs Short-Term Use After Catheter Ablation for Atrial Fibrillation* ukupno je 2038 ispitanika nasumično randomizirano za primjenu antiaritmijskih lijekova za kontrolu FA-a nakon RF kateterske ablacije paroksizmalne, perzistentne i dugotrajne FA.[16] Rizik od recidiva atrijske tahiaritmije bio je manji u grupi s antiaritmijskim lijekovima tijekom razdoblja praćenja od 3 mjeseca, ali bez učinka na klinički ishod u kasnijem tijeku.

Ima li kateterska ablacija FA ikakva utjecaja na učestalost moždanih udara i/ili smrtnost? *Friber i sur.* ocjenjivali su mogući utjecaj ablacije FA na kliničke ishode na osnovi podataka prikupljenih u 361 913 pacijenata iz multicentričnog registra u Švedskoj.[17] Koristeći se metodom podudarnosti, formirane su dvije kohorte podjednake veličine, od kojih je jedna liječena ablacijom FA, a druga nije. Obje su grupe imale slične rezultate u 51 varijabli. Ablacija FA bila je povezana s mnogo nižom incidencijom ukupne smrtnosti (HR = 0,50; 95 % CI = 0,37 – 0,62) i ishemijskih moždanih udara (HR = 0,69; 95 % CI = 0,51 – 0,93). Najizraženije smanjenje rizika od ishemijskoga moždanog udara bilo je u podgrupi s CHA2DS2VASc bodovnim sustavom ≥ 2 (HR = 0,39; 95% CI = 0,19–0,78) i u pacijenata koji nisu bili podvrgnuti novoj kardioverziji unutar 6 mjeseci od ablacije. Ovakvi su rezultati ohrabrujući i traže odgovor koji randmomizirane studije adekvatne veličine mogu pružiti u ovoj kontraverznoj temi u budućnosti. Međutim, toliko dugo dok nema takvih ispitivanja i potpunih kliničkih izvještaja, potrebno je u visokorizičnih pacijenata prema CHADS-VASc bodovnom sustavu nastaviti s doživotnom antikoagulantnom terapijom – sukladno stajalištu koje je čvrsto zauzeto u smjernicama Europskoga kardiološkog društva o FA-u iz 2016. godine.[5]

Nove smjernice o FA-u ističu individualni te precizno upravljani pristup pacijentu s FA-om. Još važnije, u njima su intenzivno opisane uloge novih čimbenika rizika za razvoj FA-a, važnost promijene životnog stila u svrhu smanjenja opterećenja FA te potencijalno smanjenje rizika povezanih s FA-om. Prednosti koje proizlaze iz cjelokupne brige o FA-u, specijaliziranih timova za FA i suodlučivanje bolesnika o liječenju specifične su akcije koje se preporučuju za najbolju skrb o bolesnicima s FA-om.

PREVENCIJA MOŽDANOG UDARA

Zanimljiva činjenica nazvana „paradoksom pretilih" nedavno je objavljena u podanalizi istraživanja *ARISTOTLE*.[18] Od 17 913 bolesnika uključenih u istraživanje, 7159 bolesnika svrstano je u kategoriju pretilih, dok su 6702 bila prekomjerne, a 4052 normalne tjelesne težine. Tijekom 1,8 godina praćenja povišena je tjelesna težina bila povezana s nižim rizikom od ukupne smrtnosti (prekomjerna tjelesna težina HR = 0,67; 95% CI = 0,59 – 0,78; pretilost, HR = 0,63; 95% CI = 0,54 – 0,74). Navedena se dobrobit odnosila na rizik od moždanog udara u žena (P = 0,048), ali ne i u muškaraca. Nijedan stupanj povećanja tjelesne težine nije bio povezan s različitim rizikom od krvarenja. Jedno od mogućih objašnjenja navedenih rezultata jest ranija i rigoroznija uporaba dodatnih lijekova, promjena životnoga stila[19] te bolja metabolička rezerva[20] koja u konačnici može utjecati na srednjoročnu prognozu u pretilih bolesnika.

Još jedna zanimljiva činjenica zabilježena je u nedavnoj podanalizi *Engage AF-TIMI 48* istraživanja.[21] U navedenom je

Atrial Fibrillation trial, a total of 2038 patients were randomly assigned to antiarrhythmic drug therapy of control following radiofrequency catheter ablation for paroxysmal, persistent, or long-lasting AF.[16] The risk of recurrent atrial tachyarrhythmias was reduced in the antiarrhytmic drug therapy group during the treatment period of 3 months, however without an effect on clinical outcomes at later time points.

Does catheter ablation of AF have any effect on stroke rate and/or mortality? In a recent nationwide Swedish Patient Register identifying 361 913 patients, Friberg et al. evaluated the possible influence of AF ablation on clinical outcome.[17] Using propensity score matching, two cohorts of equal size (2836 patients each) were extracted of which one had received AF ablation and one not. The two cohorts presented similar characteristics in 51 dimensions. After adjustment for known confounders AF ablation was found to be associated with a significantly lower incidence of all-cause mortality (HR = 0.50; 95% CI = 0.37–0.62) and ischemic stroke (HR = 0.69; 95% CI = 0.51–0.93). Reduction in the risk of ischemic stroke by means of AF ablation was most pronounced in sub-groups with CHA2DS2VASc score ≥ 2 (HR = 0.39; 95% CI = 0.19–0.78) and among patients without a new cardioversion beyond 6 months after ablation (HR = 0.68; 95% CI = 0.48–0.97). These results are encouraging and prompt for the implementation that adequately sized randomized studies may provide to this controversial topic in the next future. Until those trials have arrived and fully reported clinical practice should include continuing life-long anticoagulation after ablation in at risk patients according to the CHADS-VASc Score—a point of view which is strongly supported by the 2016 ESC AF management guidelines.[5]

The new AF guidelines strengthen a personalized, precision driven approach to patients with atrial fibrillation. Importantly, the role of new AF risk factors and the importance of life style changes for reduction of AF burden and potentially for reduction of AF related risks is intensely described. Moreover, the benefits resulting from integrated AF care, AF heart teams and patient engagement for shared decision-making are presented and specific action is recommended to deliver the best care for AF patients.[5]

STROKE PREVENTION

An interesting finding referred to as the 'obesity paradox' was recently reported in a sub-analysis from the ARISTOTLE trial.[18] Out of 17 913 patients enrolled in this study, 7159 were categorized as obese, 6702 overweight and 4052 normal. During 1.8 years follow-up, higher body masses were associated with a lower risk of all-cause mortality (overweight, HR = 0.67; 95% CI = 0.59–0.78; obese, HR = 0.63; 95% CI = 0.54–0.74). Such benefit extended to the risk of stroke in the female (*P* = 0.048), but not in the male gender. No measure of adiposity was associated with a different risk of bleeding. Among possible explanations for this finding are an earlier more rigorous use of co-medications and life-style modification[19] and better metabolic reserve,[20] which may ultimately affect intermediate-term prognosis in obese patients.

Another interesting finding was observed in a recent subanalysis from the Engage AF-TIMI 48 trial.[21] In this study, a higher degree of protection from all-cause mortality vs. vitamin K antagonist (VKA) therapy was found in the edoxaban 30 mg arm (HR = 0.87; 95% CI = 0.79–0.96, *P* = 0.006) than in the

istraživanju pronađen viši stupanj zaštite od ukupne smrtnosti nasuprot antagonistima vitamina K (VKA) u terapijskome kraku od 30 mg edoksabana (HR = 0,87; 95% CI = 0,79 – 0,96, p = 0,006) u usporedbi s terapijskim krakom s edoksabanom od 60 mg (HR = 0,92; 95% CI = 0,83 – 1,01, p = 0,08). Ova je prednost bila prisutna unatoč evidentnom povećanju rizika od ishemijskog moždanog udara (HR = 1,41; 95% CI = 1,19 – 1,67, P < 0,001), pri nižoj dozi edoksabana, koja nije bila prisutna pri višoj dozi (HR = 1,00; 95 % CI = 0,83 – 1,19, p = 0,97). Ukupna manja smrtnost u grupi s edoksabanom bila je prije svega posljedica mnogo niže stope fatalnih krvarenja u skupinama s edoksabanom, a posebno u podskupini s nižom dozom. Ovakvi rezultati naglašavaju osjetljivu ravnotežu između rizika i koristi povezanu s primjenom oralnih antikoagulansa te pomiču primarni cilj njihove uporabe s prevencije tromboembolijskih događaja na ukupni kardiovaskularni morbiditet. Osim toga, dodatne su analize pokazale jasnu neto kliničku djelotvornost i sigurnost edoksabana u drugim visokorizičnim podskupinama, kao što su starije osobe[22] i bolesnici pod povišenim rizikom od pada,[23] potvrđujući poziciju lijeka kao valjanu alternativu u paleti lijekova za prevenciju moždanog udara u FA.

Nedavno randomizirano kontrolirano istraživanje (*Ensure AF*)[24] pokazalo je kako 60 mg oralno primijenjenog edoksabana jednom na dan ima sličnu učinkovitost i sigurnost kao VKA, kada se primjenjuje periproceduralno pri kardioverziji FA. Tijekom 30 dana praćenja nakon rane ili odgođene strategije kardioverzije 1095 pacijenata u skupini na edoksabanu imalo je 0,5 %-tnu incidenciju neželjenih događaja (moždanih udara, infarkta miokarda, periferne embolije ili kardiovaskularne smrtnosti) nasuprot 1,0 % koliko je uočeno u 1104 pacijenta u skupini s VKA-om (OR 0,46; 95 % CI = 0,12 – 1,43). Niske incidencije periproceduralnih znatnijih krvarenja (0,3 % i 0,5 %) registrirane su u objema prije navedenim skupinama (OR 0,61; 95 % CI = 0,09 – 3,13). Ovi rezultati nalik su onima koje su nedavno objavili *Cappato i sur.* u studiji *X-VeRT* koja je uspoređivala oralnu primjenu rivaroksabana prema VKA-u u sličnim kliničkim uvjetima.[25] Nijedno od istraživanja nije imalo dovoljno ispitanika za testiranje hipoteze o neinferiornosti. Međutim, visoka reproducibilnost te primarna učinkovitost i sigurnost u dvjema studijama čine navedene NOAK-e vrijednom alternativom VKA-u u takvih pacijenata.

Nakon odobrenja i puštanja u promet triju od četiriju novih oralnih antikoagulansa (NOAK-a), prethodno istraživanih u velikim istraživanjima faze III., objavljen je poprilično broj postautorizacijskih studija koje pružaju dokaze iz stvarnog života o efikasnosti i sigurnosti tih, novih lijekova. Istražujući sigurnost i efikasnost rivaroksabana u stvarnom životu, *Camm i sur.* izvijestili su kako je u vrijeme jednogodišnjega praćenja incidencija velikih krvarenja (2,1 na 100 pacijenata – godina) i cerebralnih zbivanja (0,7 na 100 pacijenata – godina) bila niska te nadograđuje one zabilježene u studiji *Rocket AF*.[26,27] Posljednji su objavljeni rezultati triju studija koje su se koristile ovim bazama podataka kao izvorom.[28-30] U registru *REVISIT-US*[28] mjera kliničke dobrobiti promatrana je putem skupne procjene moždanog udara i intrakranijalnog krvarenja u ispitivanoj populaciji. Liječenje rivaroksabanom i apiksabanom u kliničkoj je praksi je povezano s 39 % (HR 0,61; 95 % CI = 0,45 – 0,82) i 37 % (HR 0,63; 95% CI = 0,35 – 1,12) smanjenim rizikom u skupnoj incidenciji moždanih udara i intrakranijalnih krvarenja, izračunano na 22 822 i na 8166 pacijenata. Isti su autori nedavno dokazali sličnu dobrobit dabigatrana u usporedbi s VKA-om.

edoxaban 60 mg arm (HR = 0.92; 95% CI = 0.83–1.01, *P* = 0.08). This benefit occurred in spite of an evident increased risk of ischemic stroke (HR = 1.41; 95% CI = 1.19–1.67, *P* < 0.001) at the lower edoxaban dose, which was not found at the higher dose (HR = 1.00; 95% CI = 0.83–1.19, *P* = 0.97). The fewer total deaths observed with edoxaban were predominantly due to a significantly lower rate of fatal bleeding in the edoxaban groups and particularly in the low dose group. These findings raise our attention on the delicate balance between risk and benefit associated with administration or oral anticoagulants and shift the objective of their use from thromboembolic events to cardiovascular morbidity as a whole. In addition, further subgroup analyses were able to demonstrate a consistent net clinical efficacy and safety of edoxaban in other high risk subgroups such as the elderly[22] and patients at increased risk of falls,[23] hence establishing the drug as a valuable alternative in our armamentarium for stroke prevention in AF.

A recent randomized controlled study (Ensure AF)[24] showed that oral edoxaban 60 mg once daily presented similar efficacy and safety outcomes as VKAs when administered during the peri-procedural phase on cardioversion of atrial fibrillation. In the 30 days following cardioversion using either an early or delayed strategy, 1095 patients assigned to edoxaban presented a 0.5% incidence of aggregate stroke, myocardial infarction, peripheral embolism or cardiovascular death vs. a 1.0% observed in 1104 patients assigned to VKA therapy (OR 0.46; 95% CI = 0.12–1.43). Similarly low incidences of periprocedural major bleeding (0.3% and 0.5%) were observed in the two arms (OR 0.61; 95% CI = 0.09–3.13). These results are similar to those recently reported by Cappato et al. in the X-VeRT trial investigating oral rivaroxaban vs. VKA therapy in the same clinical setting.[25] Both trials were not numerous enough to test a non-inferiority hypothesis. However, the high reproducibility of primary efficacy and safety outcomes in the two studies make these NOACs a valuable alternative to VKAs in these patients.

After the authorization for market release of three of the four novel oral anti-coagulants (NOACs) previously investigated in large phase III trials, a number of post-authorization studies have been published providing real-life evidence for efficacy and safety of these new drugs. In a previous registry investigating the real-life efficacy and safety of rivaroxaban, Camm et al. had shown that during about 1-year follow-up, the incidences of major bleeding (2.1 per 100 patient-years) and stroke events (0.7 per 100 patient-years) were low and superimposable to those observed in Rocket AF.[26,27] Most recently, the results from three studies using claims database as data source were reported.[28-30] In the REVISIT-US registry,[28] a measure of net clinical benefit was inferred by the aggregate estimate of ischemic stroke and intracranial haemorrhage reported in the investigated populations. Real life treatment with rivaroxaban and apixaban was associated with a 39% (HR 0.61; 95% CI = 0.45–0.82) and a 37% (HR 0.63; 95% CI = 0.35–1.12) risk reduction in the aggregate incidence of ischemic stroke and intracranial haemorrhage as calculated in 22 822 patients and in 8166 patients, respectively. More recently, results showing a similar benefit of dabigatran vs. VKA were presented by the same authors.

Another real world analysis performed a propensity-matched analysis comparing apixaban (15 390 patient), dabigatran (28 614 patients), and rivaroxaban (32 350 patients)

Još jedna analiza primjene u kliničkoj praksi usporedila je apiksaban (15 390 pacijenata), dabigatran (28 614 pacijenata) i rivaroksaban (32 350 pacijenata), svaki s varfarinom u *Optum Labs Data Warehouse* (OLDW).[29] Pronašli su sličan rizik od ishemijskoga moždanog udara vezan za uzimanje dabigatrana u usporedbi s varfarinom (HR 0,98, 95 % CI 0,76 – 1,26; P = 0,98) i za rivaroksaban nasuprot varfarinu (HR 0,93, 95 % CI 0,72 – 1,19; P = 0,56) te niži rizik vezan za apiksaban prema. varfarinu (HR 0,67, 95 % CI 0,46 – 0,98; P = 0,04). Rizik od znatnog krvarenja bio je sličan pri uzimanju rivaroksabana prema varfarinu (HR 1,04, 95 % CI 0,90 – 1,20; P = 0,60) i niži za dabigatran prema varfarinu (HR 0,79, 95 % CI 0,67 – 0,94; P < 0,01), kao i za apiksaban prema varfarinu (HR 0,45, 95 % CI 0,34 – 0,59; P < 0,001).

Konačno, nedavna analiza Američke agencije za hranu i lijekove provedena je u 52 240 ispitanika na dabigatranu i u 66 651 na rivaroksabanom koji su bili u dobi ≥65 godina. Medicare pacijenti imali su trend nižeg rizika od tromboembolijskih moždanih udara s rivaroksabanom u usporedbi s dabigatranom (HR, 0,81; 95 % CI, 0,65 – 1,01; P = 0,07).[30] Međutim, istodobno, intrakranijalna krvarenja (HR, 1,65; 95 % CI, 1,20 – 2,26; P = 0,002), kao i velika ekstrakranijalna krvarenja (HR, 1,48; 95 % CI, 1,32 – 1,67; P < 0,001) bila su češća u bolesnika na rivaroksabanu u usporedbi s dabigatranom, s tendencijom prema povećanoj ukupnoj smrtnosti (HR, 1,15; 95 % CI, 1,00 – 1,32; P = 0,051).

Dok su usporedbe velikih studija faze III. i mjere postautorizacijskih ishoda preporučene, međusobne statističke usporedbe NOAK-a trebalo bi obeshrabriti. Dostupni dokazi pokazuju kako sve analize iz kliničke prakse dolaze s brojnim mogućim ograničenjima, uključujući pristranost, kratko vrijeme praćenja, odabrane populacije pacijenata, nedosljednost mjerama ishoda (npr. definicija velikih krvarenja), manjak vanjskih kontrola i nepotpuno praćenje i time ograničena objektivnost podataka za usporedbu. Primarni i vjerojatno jedini zaključak koji može biti izveden iz podataka postautorizacijskih studija jest kako su njihove spoznaje u skladu sa sigurnošću i efikasnošću NOAK-a primijećenih u velikim randomiziranim kliničkim istraživanjima nakon što su prihvaćeni u svakodnevnoj praksi u većini medicinske zajednice širom svijeta. Slijedom toga, trenutačne smjernice za liječenje atrijske fibrilacije iz 2016. preporučuju uporabu NOAK-a kao prvu liniju terapije u pacijenata koji upravo započinju antikoagulantno liječenje zbog AF-a, s preporukom razine I., razredom dokaza A.[5] Nasuprot tomu, acetilsalicalatna kiselina je dobila razinu preporuke III. (moguće štetno djelovanje) s obzirom na njezinu ograničenu djelotvornost i često podcijenjen rizik od krvarenja.

VENTRIKULARNE ARITMIJE I IZNENADNA SRČANA SMRT

Kateterska ablacija ventrikularnih tahikardija važna je tehnika zbrinjavanja bolesnika s rekurentnom VT (**Slika 3**).[31] Međutim, randomizirana su klinička istraživanja koja ocjenjuju moguću prednost kateterske ablacije nad antiaritmičnom terapijom lijekovima oskudna. Nedavno objavljeno istraživanje VANISH bolesnike s ishemijskom kardiomiopatijom i ugrađenim defibrilatorom uz ventrikularnu tahikardiju koja ne reagira na lijekove randomiziralo je u skupinu onih s kateterskom ablacijom VT-a i nastavkom osnovne antiaritmične terapije nasuprot onima s postupnim pojačanjem antiaritmične terapije.[32] U potonjoj je skupini uveden amiodaron ako je prije bio

each with warfarin in OptumLabs Data Warehouse (OLDW).[29] They found a similar risk for ischemic stroke for dabigatran vs. warfarin (HR 0.98, 95% CI 0.76–1.26, *P* = 0.98) and for rivaroxaban vs. warfarin (HR 0.93, 95% CI 0.72–1.19, *P* = 0.56), and a lower risk for apixaban vs. warfarin (HR 0.67, 95% CI 0.46–0.98, *P* = 0.04). The risk of major bleeding was similar for rivaroxaban vs. warfarin (HR 1.04, 95% CI 0.90–1.20], *P* = 0.60), and lower for dabigatran vs. warfarin (HR 0.79, 95% CI 0.67–0.94, *P* < 0.01) as well as apixaban vs. warfarin (HR 0.45, 95% CI 0.34–0.59, *P* < 0.001).

Finally, a very recent FDA analysis in 52 240 dabigatran- and 66 651 rivaroxaban-treated elderly (≥ 65 years). Medicare patients revealed a trend for lower risk of thromboembolic stroke with rivaroxaban compared with dabigatran (HR, 0.81; 95% CI, 0.65–1.01; *P* = 0.07).[30] At the same time, however, intracranial haemorrhage (HR, 1.65; 95% CI, 1.20–2.26; *P* = 0.002) as well as major extracranial bleeding (HR, 1.48; 95% CI, 1.32–1.67; *P* < 0.001) were increased with rivaroxaban compared with dabigatran, with a trend towards an increased all-cause mortality (HR, 1.15; 95% CI, 1.00–1.32; *P* = 0.051).

While comparisons between large phase III study and post-authorization outcome measures are recommended, statistics on 'head-to-head' comparison among NOACs should clearly be discouraged. The available evidence, in fact, demonstrates that any 'real world' analysis equally comes with a number of possible limitations, including residual confounding, short follow-up, selected patient populations, inconsistency of outcome measures (i.e. major bleeding definition), lack of external adjudication, and incomplete follow-up, hence limiting the generalizability of such comparative data. The primary—and likely the only—conclusion that can be drawn from data from post-authorization studies is that their findings are consistent with the safety and efficacy of NOACs observed in the large-scale randomized clinical trials after their adoption in daily practice by large segments of the medical community across the world. As such, the current 2016 guidelines for the management of atrial fibrillation recommend the use of NOACs as first line therapy in patients who newly start anticoagulation treatment for AF, with a Class I recommendation, level of evidence A.[5] In contrast, the use of aspirin newly received a class III recommendation (possible harm) given its limited efficacy and frequently underestimated bleeding risk.

VENTRICULAR ARRHYTHMIAS AND SUDDEN CARDIAC DEATH

Catheter ablation of ventricular tachycardia (VT) is an important technique to manage patients with recurrent VT (**Figure 3**).[31] However, randomized clinical trials evaluating the potential benefits of catheter ablation as compared with antiarrhythmic drug therapy are scarce. The recently published VANISH trial randomized patients with drug refractory ventricular tachycardia in the setting of ischemic cardiomyopathy and defibrillator protection to VT catheter ablation with continuation of baseline antiarrhythmic medications vs. escalated antiarrhythmic drug therapy.[32] In the latter group, amiodarone was initiated if another drug had been used previously. The dose of amiodarone was increased up to 300 mg/day and mexiletine was added thereafter, if clinically required. During 27-month follow-up, significantly more deaths, VT storm events or appropriate ICD shocks were reported in the 127 patients assigned to the escalated therapy arm than

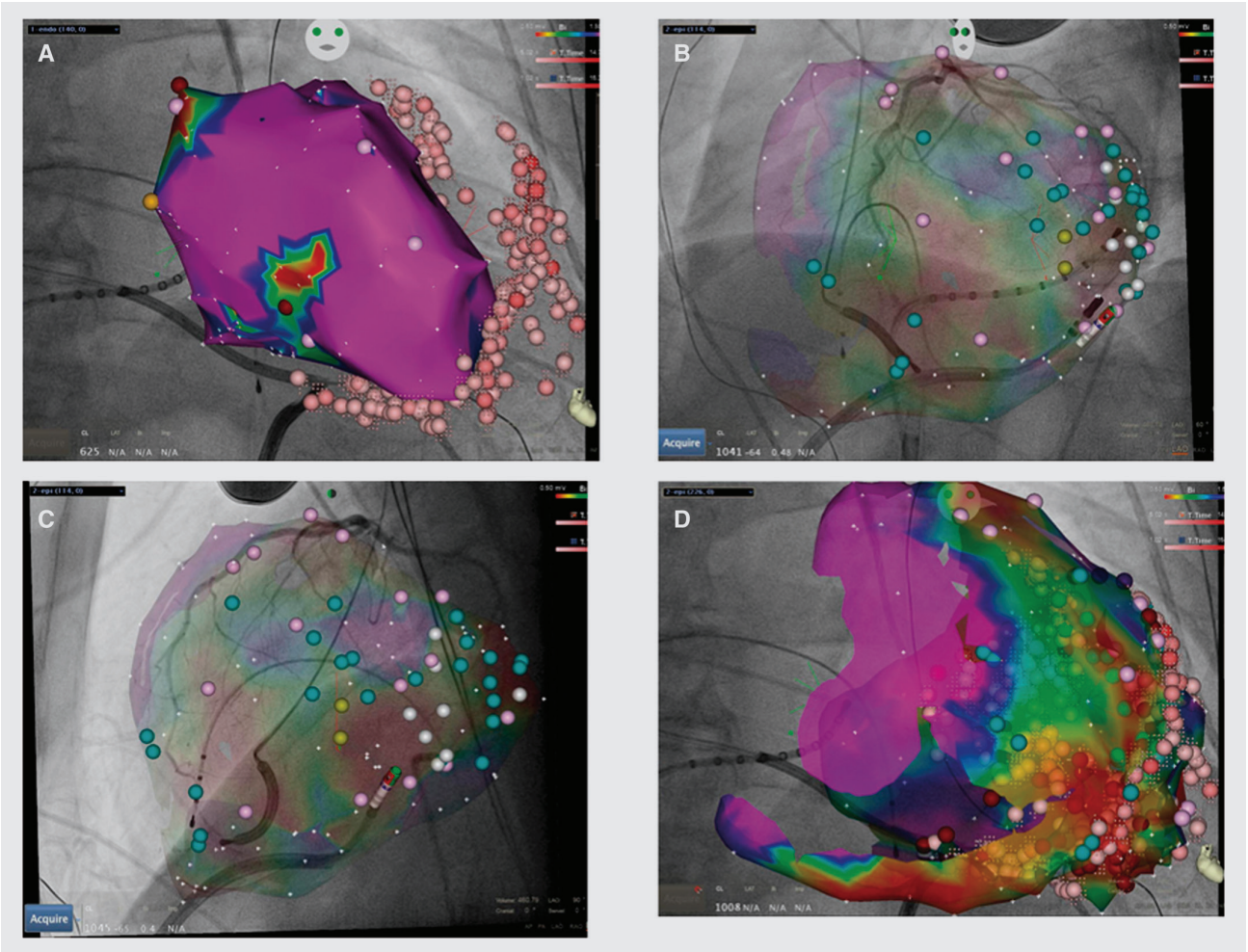

FIGURE 3. Endo- and epicardial VT ablation. Three-dimensional mapping of the left ventricular endocardial surface (*A*) as well as the epicardium (*B–D*), with superimposed coronary angiograms to detect the epicardially located coronary arteries. While only a small area of low-voltage is detectable on the endocardium (*A*, red area), the epicardial surface shows extensive fibrosis (*D*). Pink points denote sites of ablation.

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upotrebljavan neki drugi lijek. Doza amiodarona povećavana je do 300 mg/dan te je nakon toga dodavan meksiletin ako je to klinički bilo potrebno. U vrijeme 27-mjesečnog praćenja bilo je mnogo više prijavljenih smrti, VT oluja ili neadekvatnih ICD šokova u 127 pacijenata dodijeljenih skupini s postupnim pojačanjem antiaritmične terapije nego u 132 pacijenta u ablacijskoj skupini (69 % prema 59 %; HR = 0,72; 95 % CI = 0,53 – 0,98). Ipak, iako su takvi poželjni učinci na povrat VT-a registrirani u ablacijskoj skupini, nije bilo razlike u ukupnome preživljenju, što upućuje na to kako dodatni čimbenici, kao što su napredak strukturne bolesti srca i progresivno zatajivanje srca, mogu imati važnu ulogu u prognozi ovakvih pacijenata.

Rekurentne ventrikularne tahikardije u bolesnika s korigiranom Fallotovom tetralogijom važan su čimbenik rizika za iznenadnu srčanu smrt. Liječenje kateterskom ablacijom kompliciranо je zbog kompleksne anatomije nakon kardiokirurškog liječenja. No, kako je nedavno pokazano, detaljna elektroanatomska rekonstrukcija i mapiranje provodnih osobina u operiranim područjima učinkovito pronalazi kritičan provodni istmus koji je odgovoran za VT.[33] U jednoj od najvećih serija pacijenata s Fallotovom tetralogijom i VT-om do

in the 132 patients assigned to the ablation arm (69% vs. 59%; HR = 0.72; 95% CI = 0.53–0.98). However, although such beneficial effects on VT recurrence could be observed in the ablation group there was no difference in overall survival indicating that additional factors such as progression of structural heart disease and progressive heart failure may also play an important role for the prognosis of these patients.

Recurrent ventricular tachycardia in patients with repaired tetralogy of Fallot is a significant risk factor for sudden cardiac death. Treatment with catheter ablation is difficult due to the complex anatomy after surgical repair. However, as recently shown detailed electroanatomical reconstruction and mapping of the conduction properties in the operated areas effectively identifies critical conduction isthmus that promotes VT.[33] In one of the largest patient series of Fallot patients with VT reported so far it could be shown that discrete ablation of the isthmus results in VT termination and rendered VT non-inducible in the majority of patients. In patients with effective ablation VT recurrence was very low proving the benefits of this approach.

sada, prikazan je prekid VT-a diskretnom ablacijom istmusa te neinducibilna VT u većine bolesnika. U pacijenata s učinkovitom VT ablacijom ponovna je pojavnost bila vrlo niska, što dokazuje prednost ovakvoga pristupa.

U nedavnom su istraživanju *Kudenchuck i sur.* usporedili parenteralni amiodaron, lidokain i placebo primjenom fiziološke otopine, zajedno sa standardnim pristupom, u odraslih s izvanbolničkim srčanim zastojem, ventrikularnom fibrilacijom rezistentnom na primjenu elektrošoka ili VT-om bez pulsa nakon barem jednog elektrošoka.[34] Od 3026 uključenih pacijentata 974 su randomizirana na amiodaron, 993 na lidokain i 1059 na placebo. Nisu registrirane razlike u preživljenju do otpusta iz bolnice (24 %, 24 % i 21 %) ili u neurološkom ishodu između triju skupina. Zanimljivo, primjena lijeka povezana je s većom stopom preživljenja među bolesnicima sa srčanim zastojem koji je vidio očevidac (P = 0,05), ali ne i među onima bez očevidaca. Ove spoznaje nude ozbiljan argument protiv primjene intravenskih antiaritmika u bolesnika bez očevidaca izvanbolničkoga srčanog zastoja, ali ostavljaju otvorena vrata za moguću upotrebu u slučaju aresta s očevidcem.

Srčani elektronički uređaji

LIJEČENJE IMPLANTABILNIM KARDIOVERTERSKIM DEFIBRILATORIMA

Komu koristi liječenje implantabilnim kardioverterskim defibrilatorom (ICD), a komu ne koristi? Konačna preporuka u vezi s ovim pitanjem još nije donesena. U randomiziranoj studiji sa 1116 bolesnika sa simptomatskim zatajivanjem srca koje nije uzrokovano koronarnom bolesti srca (DANISH studija), *Kober i sur.* nedavno su dokazali kako liječenjem ugradnjom ICD uređaja uz uobičajenu skrb nije postignuta znatna zaštita u smislu smanjenja ukupne smrtnosti u usporedbi sa samo uobičajenom skrbi tijekom dugotrajnog praćenja (68 mjeseci).[35] U toj studiji važnost 50 %-tnog (visoko značajno) relativnog smanjenja iznenadne srčane smrti u bolesnika kojima je ugrađen ICD uređaj bila je umanjema većim udjelom bolesnika u istoj skupini koji su umirali zbog drugih kardiovaskularnih uzroka i, iznad svega, drugih nekardiovaskularnih uzroka smrti. Sve krivulje koje su prikazivale vrijeme do događaja razilazile su se u korist populacije bolesnika kojima je ugrađen ICD uređaj tijekom prvih 5 godina praćenja, a na kraju konvergiraju jedna prema drugoj. Ovi rezultati znatno pridonose raspravi koja traje o korisnosti liječenja ugradnjom ICD uređaja radi primarne profilakse u bolesnika s neishemijskom kardiomiopatijom.[36,37] Relativno viša životna dob pri uključenju (64 godine) i dugo razdoblje od trenutka postavljanja dijagnoze zatajivanja srca do uključenja (19 godina) učinili su istraživanu populaciju visoko odabranom i skupinom s relativno niskim očekivanim trajanjem života (ejekcijska frakcija pri ulasku u studiju bila je 25 %). No, analiza podskupine koja se fokusirala na dob bolesnika pokazala je značajnu statističku interakciju, pri čemu su mlađi bolesnici (< 59 godina) imali korist od ugradnje ICD uređaja u smislu cjelokupne smrtnosti koja nije bila očita u skupini starijih bolesnika. Dodatno, različitost zabilježenih kardiomiopatija čini istraživanu populaciju prilično heterogenom. Potrebne su daljnje studije koje će istražiti zaštitni učinak liječenja ugradnjom ICD uređaja u bolesnika u kojih je dijagnoza neishemijske kardiomiopatije postavljena u mladoj dobi i u kojih je indikacija za primarnu profilaksu postavljena u relativno kratkom vremenskom in-

In a recent study, Kudenchuck et al. compared parenteral amiodarone, lidocaine, and saline placebo, along with standard of care, in adults with out-of-hospital cardiac arrest, shock refractory ventricular fibrillation (VF) or pulseless VT after at least one shock.[34] Of 3026 enrolled patients, 974 were assigned to amiodarone, 993 to lidocaine and 1059 to placebo. No differences in survival to hospital discharge (24%, 24% and 21%, respectively) or neurologic outcome were found among the three groups. Interestingly, active drug administration was associated with a higher survival rate among patients with by-stander witnessed cardiac arrest (P = 0.05), but not among those with unwitnessed cardiac arrest. These findings offer a serious argument against the administration of intravenous antiarrhythmic drugs in unwitnessed out-of-hospital cardiac arrest victims, but leave the door open for their possible use in by-stander witnessed victims.

Cardiac electronic devices

IMPLANTABLE DEFIBRILLATOR THERAPY

Who benefits from an ICD and who does not? The final jury is not out on this ever moving target. In a randomized study of 1116 patients with symptomatic systolic heart failure not caused by coronary artery disease (the DANISH trial), Kober et al recently showed that implantable cardioverter defibrillator (ICD) therapy in addition to usual care did not confer a significant protection from all-cause mortality as compared with usual care only during long-term follow-up (68 months).[35] In this study, the 50% (highly significant) relative reduction of sudden death risk in patients assigned to an ICD was offset by a larger proportion of patients in this same group presenting with deaths caused by other cardiovascular causes and, above all, by non-cardiovascular death. All time-to-event curves tended to diverge in favour of the ICD population during the first 5 years of follow-up and then to converge. These results contribute significantly to the ongoing debate on the usefulness of ICD therapy for the primary prophylaxis of patients with non-ischemic cardiomyopathy.[36,37] The relatively old age at entry (64 years) and the long duration from time to diagnosis of heart failure to enrolment (19 years) make the investigated population of this study a highly selected one and one with a relatively low life-expectancy (ejection fraction at entry, 0.25). Indeed, a subgroup analysis focusing on patient age revealed a significant statistical interaction, with younger patients (< 59 years old) deriving a benefit from ICD in terms of all-cause mortality which was not evident in the elderly patients. In addition, the variety of reported cardiomyopathies makes the investigated population rather heterogeneous. Further studies are needed to evaluate the protective efficacy of ICD therapy in patients in whom a non-ischemic dilated cardiomyopathy is diagnosed at a younger age and whose eligibility for primary prophylaxis is raised at a relatively short time interval from diagnosis of heart failure. Previous studies investigating such a population were not numerous enough to test a superiority hypothesis by the ICD system vs. pharmacological therapy only.[38] In summary, the results of the DANISH trial are important, but in the end reinforce clinical practice which should ideally already be in place—i.e. to take into consideration competing risk and modes of death, particularly non-cardiovascular as well as pump failure, when deciding

tervalu od postavljanja dijagnoze zatajivanja srca. Prethodne studije koje su istraživale takvu populaciju nisu bile dovoljno brojne da bi testirale hipotezu o superiornosti ugradnje ICD uređaja u usporedbi s primjenom samo farmakološke terapije.[38] Zaključno treba reći da su rezultati studije DANISH važni, no u konačnici osnažuju kliničku praksu koja bi u idealnim uvjetima već trebala biti svakodnevica – npr. uzimajući u obzir međusobne rizike i vrste smrti, osobito nekardiovaskularne i one povezane sa zatajivanjem, kada se donosi odluka o ugradnji ICD uređaja, posebice u bolesnika s neishemijskom bolesti srca.

Ovi su rezultati u suglasju s nedavnim velikim prospektivnim, multicentričnim registrom bolesnika u kojih je ugrađen uređaj za srčanu resinkronizacijsku terapiju (CRT). U sveukupno 1705 uzastopnih bolesnika u kojih je ugrađen ili CRT-P uređaj (535 bolesnika) ili CRT-D uređaj (1170 bolesnika), prilagođeni rizik od mortaliteta bio je 1,54 u bolesnika u kojih je ugrađen CRT-P uređaj u odnosu prema onima u kojih je ugrađen CRT-D uređaj (interval pouzdanosti – CI 1,07 – 2,21, P = 0,0209).[39] No ipak, 95 % prekomjerne smrtnosti u bolesnika u kojih je ugrađen CRT-P uređaj bilo je zbog povećanja u nenagloj srčanoj smrti, naglašavajući važnost individualizirane analize rizika prije odabira ispravnog uređaja za svakog bolesnika.

U nedavnom izvještaju *Vehmemeijer i sur.* napravili su iscrpan pregled i metaanalizu indikacija, učinkovitosti i sigurnosti liječenja ugradnjom ICD uređaja u odraslih bolesnika s kongenitalnom srčanom bolesti.[40] Sveukupno, 2162 bolesnika (66 % muškog spola) srednje dobi od 37 godina pri ugradnji bila su uključeno iz 24 studije. Uređaji su bili ugrađeni radi primarne prevencije u 53 % bolesnika (95 %-tni interval pouzdanosti CI = 43,5 – 62,7%), s nepostojanom VT koja je činila najčešću indikaciju, a potom su slijedile oslabljena funkcija LV-a, inducibilna VT, sinkopa, palpitacije ili presinkopa. Najčešće greške bile su Fallotova tetralogija, a nakon nje slijedile su transpozicija velikih arterija, kongenitalna ispravljena transpozicija velikih arterija, ventrikulski ili atrijski septalni defekt i druge. Tijekom praćenja u razdbolju od 3,6 godina 24 % bolesnika primilo je prikladne i 22 % neprikladne intervencije ICD uređaja, uključujući šok i/ili antitahikardijsku elektrostimulaciju. Sveukupni mortalitet zabilježen je u 10 % bolesnika. Ovi podatci daju uporište u pomnom razmišljanju vezanom za relativno visoku stopu komplikacija i neprikladnih ICD terapija u ovakvih bolesnika.

SUPKUTANI IMPLANTABILNI KARDIOVERTERSKI DEFIBRILATORI

U nedavnoj studiji *Friedman i sur.* evaluirali su trendove i unutarbolničke ishode povezane s ranim usvajanjem primjene S-ICD-a u SAD-u.[41] Kod 393 734 ugradnje ICD-a prijavljenih u *National Cardiovascular Data Registry ICD Registry* podatak o ugradnji ICD uređaja u razdoblju između rujna 2012. (vrijeme odobrenja ugradnje S-ICD uređaja od Američke agencije za hranu i lijekove) i ožujka 2015. god. istraživači su učinili 1 : 1 : 1 analizu 5760 bolesnika kako bi usporedili unutarbolničke ishode u bolesnika u kojih je ugrađen S-ICD uređaj u usporedbi s bolesnicima u kojih je ugrađen jednokomorni i dvokomorni ICD uređaj. Učestalost bolesnika u kojih je ugrađen S-ICD uređaj u odnosu prema svim bolesnicima s ugrađenim ICD uređajem u ispitivanom razdoblju bila je 0,9 %. U usporedbi s jednokomornim i dvokomornim ICD uređajima, bolesnici

to opt for ICD implantation, especially in patients with non-ischemic heart disease.

These results are in line with a recent large prospective, multicentre registry of patients with cardiac resynchronization therapy (CRT). In a total of 1705 consecutive patients implanted with either a CRT-P (535 patients) or CRT-D (1170 patients), the adjusted morality hazard 1.54 in CRT-P vs. CRT-D (CI 1.07–2.21, *P* = 0.0209).[39] However, 95% of the excess mortality in CRT-P recipients was due to an increase in non-sudden cardiac death, hence re-iterating the importance of an individualized 'competing risk' analysis prior to the right device for each patient.

In a recent report, Vehmemeijer et al. performed a comprehensive review and meta-analysis on the indications, efficacy and safety of ICD therapy in adults with congenital heart disease.[40] Overall, 2162 patients (66% males) with a mean age of 37 years at implant were included from 24 studies. The devices were implanted for primary prevention in 53% of patients (95% CI = 43.5–62.7%), with non-sustained VT representing the most frequent indication, followed by impaired LV function, inducible VT, syncope, and palpitations or presyncope. The most frequent substrate was tetralogy of Fallot, followed by transposition of great arteries, congenitally corrected transposition of great arteries, ventricular or atrial septal defects and others. During 3.6-year follow-up, 24% of patients received an appropriate and 22% an inappropriate ICD intervention, inclusive of shock and/or anti-tachycardia pacing. All-cause mortality occurred in 10% of patients. These data offer the rationale for a thoughtful decision process concerning the relatively high rate of complications and inappropriate ICD therapy in these patients.

SUBCUTANEOUS IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

In a recent study, Friedman et al. evaluated the trends and in-hospital outcomes associated with early adoption of the S-ICD in USA.[41] Out of 393 734 ICD implants reported to the National Cardiovascular Data Registry ICD Registry between September 2012 (US Food and Drug Administration S-ICD approval date) and March 2015, the investigators performed a 1:1:1 propensity-matched analysis of 5760 patients to compare in-hospital outcomes among patients with S-ICD with those of patients with single chamber (SC)-ICD and dual chamber (DC)-ICD. The proportion of patients receiving an S-ICD among all ICD patients during the investigated period was 0.9%. Compared with SC-ICD and DC-ICD, patients receiving an S-ICD were younger, more prevalently female, black, undergoing dialysis and survivors of cardiac arrest. Interestingly, many patients presented with a high number of co-morbidities. DFT testing resulted in a successful defibrillation in 99.7% of 2629 patients undergoing induction of ventricular arrhythmias at time of implant. In-hospital complication rates associated with an S-ICD were low (1.1%), similar to those associated with a SC-ICD (1.0%), and lower than those associated with a DC-ICD (1.2, $P < 0.001$). These figures provide an initial perspective of the impact of S-ICD in daily practice and offer an encouraging view on their safety at implant.

Another, preliminary report on the use of a subcutaneous ICD in a limited population of young patients (mean age, 34 years) with congenital heart disease recently showed a 100% success rate of device implant, and a 100% conversion rate

kojima je ugrađen S-ICD uređaj bili su mlađi, češće ženskog spola, crne rase, na dijalizi i oni koji su preživjeli srčani arest. Zanimljivo, brojni bolesnici imali su velik broj komorbiditeta. DFT testiranje rezultiralo je uspješnom defibrilacijom u 99,7 % od 2629 bolesnika kojima je inducirana ventrikulska aritmija tijekom implantacije. Unutarbolničke stope komplikacija povezane s ugradnjom S-ICD uređaja bile su niske (1,1 %), slične onima povezanima s ugradnjom jednokomornih ICD uređaja (1,0 %), i niže od onih povezanih s ugradnjom dvokomornih ICD uređaja (1,2 %, P < 0,001). Ovi brojevi daju inicijalnu perspektivu važnosti S-ICD uređaja u svakodnevnoj praksi i nude ohrabrujući pogled na njihovu sigurnost tijekom ugradnje.

Drugo, preliminarno izvješće o upotrebi supkutanog ICD uređaja u ograničenoj populaciji mladih bolesnika (srednja dob 34 godine) s kongenitalnom srčanom bolesti nedavno je pokazalo 100 %-tni uspjeh ugradnje uređaja i 100 %-tnu stopu konverzije induciranih aritmija sa ≤ 80 J.[42] Potrebne su randomizirane studije kako bi potvrdile ove rezultate i procijenile kliničku važnost S-ICD uređaja tijekom dugoročnog praćenja.[43] Još uvijek mlada tehnologija S-ICD uređaja istodobno se ubrzano razvija. Novi filtar (*SmartPass*, dostupan za Gen 2 i Gen 2,5 EMBLEM S-ICD uređaja) uveden je ove godine kako bi smanjio rizik od pojave *T-wave oversensinga* u bolesnika s ugrađenim S-ICD uređajima (*Theuns i sur.,* prikazano na HRS 2016). Modeliranje neprikladnih šoknih epizoda koje je zabilježeno u velikom EFFORTLESS registru pokazalo je smanjenje neprikladnih šokova za 81 % u usporedbi s prvom generacijom S-ICD uređaja.

Jedno od (percipiranih) glavnih ograničenja trenutačnih S-ICD sustava jest nedostatak mogućnosti elektrostimulacije, što ograničava njihovu uporabu u bolesnika s poznatom monomorfnom VT ili indikacijom za elektrostimulaciju bradikardija. Ove je godine prvi put na životinjskom modelu pokazano da je moguća komunikacija S-ICD uređaja sa srčanim elektrostimulatorom bez elektrode, što je dovelo do adekvatnog prekida monomorfne VT i normalne VVI funkcije srčanog elektrostimulatora bez elektrode.[44] Ovi su podatci su visoko ohrabrujući na putu daljnjih poboljšanja trenutačnih S-ICD sustava.

SRČANI ELEKTROSTIMULATOR BEZ ELEKTRODE

Elektrostimulacija bez elektrode bila je u središtu pozornosti u području elektrostimulacije bradikardija zadnjih godina i važni novi podatci objavljeni su u 2016. godini. Primarni rezultati studije Micra u 725 bolesnika objavljeni su rano te godine,[45] a pokazali su povoljne električne vrijednosti (prag podražaja, sensing, impedancija) u 292 od 297 bolesnika s uparenim podatcima nakon 6 mjeseci. Otprilike 28 većih komplikacija dogodilo se u 25 od 725 bolesnika (4,0 %), uključujući 11 (1,9 %) srčanih perforacija ili perikardijalnih izljeva i jednu smrt (0,1 %). Ovakvi pozitivni rezultati dodatno su ojačani produženim razdobljem praćenja, a koji su bili prikazani na kongresu *CARDIOSTIM*, uz prosječno trajanje praćenja od 7,7 ± 3,9 mjeseci. Nije zabilježen određeni signal uz vrlo mali broj dodatnih kliničkih događaja; a najvažnije, nije zabilježena makrodislokacija ili embolizacija. Uz sada više od 2000 Micra elektrostimulatora koji su ugrađeni, navedeno se oslikava i u „stvarnome svijetu" izvan kliničke studije, dodatno naglašavajući osobito sigurnost uređaja.

NOSIVI KARDIOVERTERSKI DEFIBRILATORI

Nekoliko studija dokumentiralo je učinkovitost i sigurnost nosivih kardioverterskih defibrilatora.[46-48] U velikome njemačkom

with ≤ 80J of induced arrhythmias.[42] Randomized trials are required to confirm these results and evaluate the clinical impact of S-ICD during long-term follow-up.[43] The still young technology of the S-ICD is at the same time evolving rapidly. A novel high pass filter (SmartPass, available for Gen 2 and Gen 2.5 of the EMBLEM S-ICD) was introduced this year designed to reduce the risk of T-wave oversensing in S-ICD patients (Theuns et al., presented at HRS 2016). Modelling of inappropriate shock episodes recorded in the large EFFORTLESS registry demonstrated a reduction in inappropriate shocks by 81% compared with the first generation S-ICD.

One of the (perceived) major limitations of current S-ICD systems is the lack of pacing capability, hence limiting its use in patients with known monomorphic VT or an indication for bradycardia pacing. This year it was demonstrated for the first time in an animal model that communication of an S-ICD with a leadless cardiac pacemaker is possible, resulting in adequate termination of a monomorphic VT as well as in normal VVI functionality of the leadless pacer.[44] These data are highly encouraging on the way to a further improvement of the current S-ICD system.

LEADLESS PACEMAKER

Leadless pacing has taken centre stage in the field of bradycardia pacing for the last years, and important new data surfaced during the year 2016. The primary results of the Micra experience in 725 patients, published in print early in the year,[45] demonstrated favourable electrical values (threshold, sensing, impedance) in 292 of 297 patients with paired 6-month data. About 28 major complications occurred in 25 of 725 patients (4.0%), including 11 (1.9%) cardiac perforation or effusion and 1 death (0.1%). These positive results were reinforced by additional follow-up which were presented at Cardiostim, with an average follow-up duration of 7.7 ± 3.9 months. There was no signal apparent with very few additional clinical events; most importantly, no macro dislodgement and no embolization occurred. With now over 2000 Micra pacemakers implanted, the latter is also mirrored in the 'real world' outside the clinical trial, hence reinforcing particularly the safety of the device.

WEARABLE CARDIOVERTER DEFIBRILLATORS

Several studies have documented the efficacy and safety of wearable cardioverter defibrillators.[46-48] In a large German registry, 94 patients (1.6%) were treated by the WCD due to ventricular tachyarrhythmias, an incidence of 8.4 (95% confidence interval, 6.8–10.2) per 100 patient-years (German life vest Circulation 2016). About 112 of the 120 (93%) shocked patients survived 24 h after treatment, whereas asystole was observed in two patients (0.03%) with one resulting death. Taking together the available data, a recent science advisory from the American Heart Association,[49] suggested a list of conditions for which this therapy may be recommended, which is in great parts similar to the ESC guidelines for the prevention of sudden cardiac death.[50] Among them are the following circumstances: (**i**) as a bridging therapy in situations associated with risk of death in which ICDs have been shown to reduce sudden cardiac death but not overall mortality such as within 40 days of myocardial infarction; (**ii**) when there is a clear indication for an implantable device accompanied by a transient contraindication or need for interruption in ICD care such as infection; (**iii**) when there is concern about a heightened risk

registru, 94 bolesnika (1,6 %) liječena su nosivim kardioverterskim defibrilatorom (WCD) zbog ventrikulskih tahiaritmija, uz incidenciju od 8,4 (95%-tni interval pouzdanosti, 6,8 – 10,2) na 100 bolesnika/godina (German life vest, Circulation 2016.). Oko 112 od 120 (93 %) bolesnika koji su primili šokove preživjelo je 24 h nakon liječenja, a asistolija je zabilježena u dvaju bolesnika (0,03 %) s jednom koja je dovela do smrti. Promatrajući zajedno dostupne podatke, nedavno znanstveno savjetovanje *American Heart Association*,[49] uputilo je na listu stanja za koja se ovo liječenje može preporučiti, što je u velikom dijelu slično Smjernicama Europskoga kardiološkog društva za prevenciju iznenadne srčane smrti.[50] Neka su od njih navedena u sklopu sljedećih okolnosti: (**i**) „bridging" liječenje u situacijama povezanima s rizikom od smrti u kojima je primjena ICD uređaja pokazala da smanjuje učestalost iznenadne srčane smrti, no ne i ukupni mortalitet npr. unutar 40 dana od infarkta miokarda; (**ii**) kada postoji jasna indikacija za ugradnju ICD uređaja uz istodobnu prisutnost prolazne kontraindikacije ili potrebe za prekidom liječenja upotrebom ICD uređaja poput infekcije; (**iii**) kada postoji zabrinutost oko povišenog rizika od iznenadne srčane smrti koji se može razriješiti tijekom vremena ili uz liječenje disfunkcije lijeve klijeke, npr. kod ishemijske bolesti srca uz nedavnu revaskularizaciju, uz novopostavljenu dijagnozu neishemijske dilatacijske kardiomioatije u bolesnika koji počinju medikamentnu terapiju sukladno Smjernicama, ili sekundarne kardiomiopatije (posredovane tahikardijom ili poremećajem rada štitaste žlijezde) u koje je osnovna bolest potencijalno reverzibilna; (**iv**) kao premoštenje do boljega terapijskog rješenja poput transplantacije srca. U svjetlu nedefinitivne prirode studija koje se provode u ovom području, autori prepoznaju činjenicu da njihov dokument daje mogući okvir koji pomaže u donošenju odluka o primjeni sve češće upotrebljavanih terapija za zaštitu od iznenadne srčane smrti tijekom prolazne kliničke faze, no daljnje su studije potrebne kako bi poduprle ove preporuke.

of sudden cardiac death that may resolve over time or with treatment of left ventricular dysfunction, e.g. in ischemic heart disease with recent revascularization, newly diagnosed non-ischemic dilated cardiomyopathy in a patient starting guideline-directed medical therapy, or secondary cardiomyopathy (tachycardia mediated and thyroid mediated) in which the underlying cause is potentially reversible; (**iv**) as a bridge to more definitive therapy such as cardiac transplantation. In light of the non-definitive nature of the studies conducted in this field, the authors recognize that their document provides a tentative framework to assist in decision-making of an increasingly used therapy for the protection from sudden cardiac death during a transient clinical phase, but further studies are required to support these recommendations.

CONFLICT OF INTEREST: R.C. has acted as a consultant to Abbott, Bayer, Biosense Webster, Boehringer Ingelheim, Boston Scientific, Daiichi Sankyo, ELA Sorin, Medtronic, Pfizer and St. Jude; participated in speakers' bureaus for Abbot, BARD, Bayer, Biosense Webster, Boehringer Ingelheim, Boston Scientific, Medtronic, Sanofi and St. Jude; acted as a study investigator for Abbott, BARD, Bayer, Biosense Webster, Cameron Health, Medtronic, Pfizer and Sanofi; received grants from BARD, Biosense Webster, Boston Scientific, ELA Sorin, Medtronic, St. Jude; and holds equity and intellectual property rights in Cameron Health. G.H. Research grants from Biotronik, Boston Scientific and St. Jude Medical through the University Leipzig/Heart Center. J.S. has received consultant and/or speaker fees from Amgen, Astra-Zeneca, Atricure, Bayer, Biosense Webster, Biotronik, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cook Medical, Daiichi Sankyo, Medtronic, Novartis, Pfizer, Roche, Sanofi-Aventis, Sorin, St. Jude Medical and Zoll. J.S. is co-director of CorXL. He has received grant support through his institution from Bayer Healthcare, Biosense Webster, Biotronik, Boston Scientific, Daiichi Sankyo, Medtronic, und St. Jude Medical.

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