Godina 2015. u kardiologiji: aritmije i elektroničke naprave

The year in cardiology 2015: arrhythmias and device therapy

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Uvod

Godina 2015. također je bila ispunjena uzbudljivim i važnim novim otkrićima u polju invazivne elektrofiziologije i srčanih elektroničkih naprava. Ta otkrića uključuju tehničke inovacije, nove molekularne i stanične uvide i predstavljanje rezultata velikih randomiziranih kliničkih ispitivanja, kao i važnih registara s podatcima iz kliničke prakse. Osim toga, tijekom 2015. Godine objavljeno je nekoliko novih smjernica, uključujući one za liječenje ventrikulskih aritmija i sprječavanje iznenadne srčane smrti. Gotovo je nemoguće obuhvatiti sve nove napretke koji su vrijedni rasprave u ovakvoj vrsti pregleda; stoga su autori morali napraviti odabir i usredotočiti se na nekoliko važnih razvoja s izravnim posljedicama na svakodnevnu kliničku praksu.

Preamble

The year 2015 was once more filled with exciting and important novel developments in the field of invasive electrophysiology and implantable cardiac devices. These include technical innovation, novel molecular and cellular insights, and presentation of large randomized clinical trials as well as important 'real-world' registries. In addition, several new guidelines surfaced in 2015, including those for the treatment of ventricular arrhythmias and prevention of sudden cardiac death. It is virtually impossible to cover all novel developments that would merit discussion in this type of overview; as a result, the authors had to make a selection, focusing on several important developments with direct implications for daily clinical practice.

Srčane aritmije i kateterska ablacija

FIBRILACIJA ATRIJA

Kateterska ablacija fibrilacije atrija (FA) ostala je u središtu kliničkih ispitivanja i velikih studija. Uporaba tehnologije ablacijskih katetera, čini se, poboljšava pojavu dugotrajnih lezija atrija i znat-

Cardiac arrhythmias and catheter ablation

ATRIAL FIBRILLATION

Catheter ablation of atrial fibrillation (AF) remained in focus of clinical studies and large-scale trials. The use of force-sensing ablation catheter technologies seems to improve the

no smanjuje učestalost povrata FA nakon kateterske ablacije u metaanalizi većinom sastavljenoj od nerandomiziranih studija.[1] Ova će tehnologija postati standard za katetersku ablaciju FA u budućnosti. Ipak, sve je više dokaza da primjena samo ekstenzivne ablacije atrija ne poboljšava ishode vezane za ritam nakon kateterske ablacije FA. Studija *Minimax* usporedila je dvije strategije ablacije za izolaciju plućnih vena (IPV) u 234 pacijenta koji su podvrgnuti kateterskoj ablaciji paroksizmalne FA: postupak cirkumferencijalne antralne IPV ("minimalna ablacija") uspoređen je s IPV-om s intravenskom ablacijom grebena da bi se postigla individualna IPV ("maksimalna ablacija"). Nakon prosječnoga praćenja od 17 ± 8 mjeseci, odsutnost FA nakon ograničene (minimalne) ablacije nije bilo lošije u usporedbi s opsežnijom (maksimalnom) ablacijom (70 prema 62 %; *P* = 0.25).[2] Prethodni su podatci upućivali da se adenozinom potpomognuta detekcija neaktivne rekondukcije pulmonalne vene i daljnja reizolacija vena mogu uspješno primijeniti da bi se poboljšao ishod kateterske ablacije FA.[3] Međutim, mnogo veća randomizirana studija objavljena u časopisu *European Heart Journal* ispitivala je korisnost adenozinskog testiranja: u japanskoj UNDER-ATP studiji, 2113 pacijenata je nasumično podijeljeno u skupine testiranja adenozinom ili u kontrolnu skupinu, no nije registrirana nikakva razlika u recidivu FA nakon praćenja od 1 godine.[4] Za sada nisu jasni razlozi objavljenih kontradiktornih rezultata ovih dviju multicentričnih randomiziranih studija pa ovo zaslužuje daljnje istraživanje. Rezultati EAST AF studije dokazali su da primjena antiaritmika nakon kateterske ablacije smanjuje recidiv FA u razdoblju od 90 dana nakon kateterske ablacije, međutim, nakon jedne godine nije registrirana razlika u povratu aritmije između skupine koja se koristila antiaritmikom i kontrolne skupine.[5] Ovi su rezultati u skladu s podatcima iz studije *AmioCat*[6] u kojoj su pacijenti bili randomizirani u skupine na amidaronu ili placebu tijekom osam tjedana nakon kateterske ablacije FA. I dok je liječenje amiodaronom smanjilo učestalost hospitalizacija i kardioverzije tijekom praćenja od tri mjeseca nakon ablacije, nakon šest mjeseci praćenja nije bilo razlike u učestalosti povrata FA (39 prema 48 %; *P* = 0,18). Stoga primjena antiaritmika može spriječiti rani recidiv FA nakon ablacije, no ne potiče bolje remodeliranje atrija koje bi rezultiralo višim stupnjem sinusnog ritma tijekom praćenja. Podatci iz petogodišnjega praćenja iz MANTRA-PAF studije izneseni su tijekom kongresa Europskoga kardiološkog društva (ESC) u Londonu. Studija MANTRA-PAF uspoređivala je učinke radiofrekventne kateterske ablacije FA kao prve linije liječenja u usporedbi s primjenom antiaritmika. Nakon dvogodišnjeg praćenja nije bilo razlike u kumulativnom opterećenju FA-om između ablacijske skupine i skupine na antiaritmicima, no opterećenje FA bilo je znatno smanjeno u ablacijskoj skupini (90. percentil, 9 prema 18 %, *P* = 0.007).[7] Međutim, tijekom petogodišnjeg praćenja učestalost pacijenata bez povrata FA bila je češća u ablacijskoj skupini nego u skupini koja je primala antiaritmike (86 prema 71 %; *P* = 0.001). Također, opterećenje FA bilo je niže u ablacijskoj skupini u usporedbi sa skupinom koja je primala antiaritmike (*P* = 0,003), dok je učinak na kvalitetu života bio sličan u objema skupinama. Ovi podaci pokazuju da se dobrobit kateterske ablacije može povećati tijekom vremena; međutim, važno je razumjeti da je MANTRA-PAF studija bila premala da bi procijenila ikakve učinke ablacije ili antiaritmika na važne varijable ishoda poput moždanog

induction of durable atrial lesions and was shown to significantly reduce AF recurrence rate after catheter ablation in a meta-analysis mainly made of non-randomized trials.[1] This technology will become standard for AF catheter ablation in the future. A word of caution: there is growing evidence that more extensive ablation in the atria does not *per se* improve the rhythm outcome after AF catheter ablation. The Minimax Trial compared two ablation strategies for pulmonary vein isolation (PVI) in 234 patients who underwent catheter ablation of paroxysmal AF: circumferential antral PVI alone ('minimal') vs. PVI with intravenous ridge ablation to achieve individual PVI ('maximal'). After a mean follow-up of 17 ± 8 months, freedom from AF after limited 'minimal' ablation was not worse compared with more extensive 'maximal' ablation (70 vs. 62%; *P* = 0.25).[2] Previous data indicated that adenosine-guided detection of dormant pulmonary vein re-conduction and subsequent re-isolation of the veins can be successfully applied to improve outcome of AF catheter ablation.[3] However, a much bigger randomized trial published in *European Heart Journal* now questioned the usefulness of adenosine testing: in the Japanese UNDER anti-tachycardia pacing (ATP) Trial, 2113 patients were randomized to either adenosine challenge or control and no difference in AF recurrence rate was shown at 1 year.[4] The reasons for the contradictory results reported from these two multi-centre, randomized trials are unclear at present and deserve further investigation. Treatment with anti-arrhythmic drugs after catheter ablation was shown to reduce the AF recurrence 90 days after catheter ablation in the EAST AF trial, however, at 1 year there was no difference in arrhythmia recurrence between treatment and control group.[5] These results are quite in line with the data of the AmioCat Trial.[6] In AmioCat patients were randomized to amiodarone or placebo for 8 weeks after AF catheter ablation. While amiodarone treatment reduced hospitalizations and cardioversions in the 3-month post-ablation blanking period, there was no difference in AF recurrence rate at 6-month follow-up (39 vs., 48%; *P* = 0.18). Thus, anti-arrhythmic drugs may prevent early AF recurrences after ablation but may not promote a better atrial re-modelling resulting in a higher sinus rhythm rate during follow-up. The 5-year follow-up data of the MANTRA-PAF Trial were reported during the ESC Congress in London: MANTRA-PAF evaluated the comparative effects of first-line radiofrequency catheter ablation of AF with anti-arrhythmic drug therapy. At 2-year follow-up, there was no difference in cumulative AF burden between the ablation and anti-arrhythmic drug group, while the burden of AF was significantly lower in the ablation group (90th percentile, 9 vs. 18%; *P* = 0.007).[7] However, at 5-year follow-up, there was a significantly higher rate of AF-free patients in the ablation compared the anti-arrhythmic drug treatment group (86 vs. 71%; *P* = 0.001). Also, AF burden was lower in the ablation compared with the drug group (*P* = 0.003). Interestingly, the effects on quality of life were similar in both groups. These data indicate that the rhythm benefit resulting from catheter ablation may increase over time; however, it is important to understand that MANTRA-PAF was too small to evaluate any effect of ablation or anti-arrhythmic drugs on hard outcome parameters such as stroke and/or mortality. These questions will be open until data from the EAST Trial (endpoint: composite of death, stroke, and heart failure) and CABANA Trial (endpoint:

udara i/ili smrtnosti. Ova će pitanja ostati neodgovorena dok podatci studije EAST (zajednički ishodi: smrtnost, moždani udar i srčano popuštanje) i studije CABANA (zajednički ishodi: smrtnost, ozbiljno krvarenje, onesposobljavajući moždani udar i srčani arest) ne postanu dostupni.[8,9] Strategija ablacije perzistentne FA ni tijekom 2015. godine nije bila dovoljna za pojavu konsenzusa o liječenju. Rotablacija s pomoću mapiranja kontaktnom fazom dovodi se u pitanje,[10] a CAFÉ ablacija nije dovoljno specifična da bi bila uvjerljiva, kao što je pokazano velikom metaanalizom.[11] U usporedbi s navedenim, promjena životnog stila, poput gubitka tjelesne težine, pokazala se kao učinkovita u smanjenju opterećenja FA (gubitak težine od 10 % rezultira šesterostrukim smanjenjem opterećenja FA) i u poticanju reverznog remodeliranja veličine lijevog atrija i debljine septuma lijeve stijenke.[12]

PREVENCIJA MOŽDANOG UDARA

Na temelju objavljenih rezultata velikih kliničkih ispitivanja i stajališta u trenutačnim smjernicama ESC-a primjena novih oralnih antikoagulansa (NOAK) izbor je liječenja za prevenciju moždanog udara kod nevalvulne FA.[13] Edoksaban, četvrti NOAK, odobren je tijekom 2015. godine u mnogim zemljama, uključujući SAD, Švicarsku i Europu na osnovi rezultata studije ENGAGE AF-TIMI 48.[14] Tijekom 2015. godine pojavilo se nekoliko analiza podgrupa velikih studija s lijekovima iz skupine NOAK, uključujući zbrinjavanje krvarenja i ishode s apiksabanom,[15] uporabu rivaroksabana u kateterskoj ablaciji kod FA (studija VENTURE-AF)[16] i ishode liječenja amiodaronom u pacijenata koji primaju edoksaban[17]. Gotovo sve podgrupe velikih studija s NOAK pokazuju postojanu dobrobit i sigurnost ove skupine lijekova što potvrđuje ukupnu superiornost u usporedbi s varfarinom. To je poduprto važnim podatcima iz svakodnevne kliničke prakse (uključujući i podatke iz prospektivnog registara s rivaroksabanom, XANTUS)[18] koji upućuju na učinkovitost i sigurnost u skladu s podatcima izrandomiziranih kliničkih studija.

Nedvojbeno najuzbudljivija novost na polju NOAK-a dolazi od razvoja specifičnih reverznih lijekova (antidota). U studiji faze 1 na zdravim muškarcima monoklonsko protutijelo idarucizumab (specifično za dabigatran) dobro se podnosilo, nisu registrirane neočekivane ili klinički relevantne nuspojave, a njegova je primjena povezana s trenutačnim, potpunim i postojanim obratom antikoagulacije izazvane dabigatranom.[19] U studiji faze 3 pokazalo se da idarucizumab učinkovito i trenutačno poništava antikoagulacijski učinak dabigatrana u pacijenata s ozbiljnim krvarenjem ili u pacijenata koji su trebali hitno liječenje.[20] Stoga je američka *Food and Drug Administration* odobrila taj lijek u listopadu 2015. godine, a *Committee for Medicinal Products for Human Use* pri *European Medicines Agency* također je nedavno objavio pozitivno mišljenje te se do kraja 2015. ili rano tijekom 2016. godine očekuje i njihovo odobrenje. Značajno je da idarucizumab nije učinkovit protiv inhibitora Xa, a umjesto njega razvijaju se drugi antidoti s izravnim djelovanjem, uključujući andeksanet alfa i PER977. Prvi su rezultati s ovim lijekovima također pozitivni, a velike se kliničke studije očekuju tijekom 2016. godine. Dok su ti lijekovi svakako važan dodatak našem izboru lijekova, mnogi se aspekti njihove uporabe u praksi još uvijek moraju ustvrditi, uključujući i one za koje ih skupine pacijenata i stacomposite of death, serious bleeding, disabling stroke, and cardiac arrest) are available.[8,9] Persistent AF ablation strategy has never been mature enough for a consensus to emerge, neither in the past nor in 2015. Rotor ablation using contact phase mapping has been questioned,[10] and CAFÉ ablation is not specific enough to be convincing as demonstrated by a large meta-analysis.[11] In contrast, lifestyle modification such as weight loss is remarkably effective in reducing AF burden (10% loss translates into a six-fold AF burden reduction) and in inducing reverse remodelling on left atrial size and left ventricular septal thickness.[12]

STROKE PREVENTION

Due to the results from large-scale clinical trials, the non-vitamin K antagonist oral anticoagulants (NOACs) are the preferred treatment for stroke prevention in non-valvular AF, as reflected in current ESC guidelines.[13] As the fourth NOAC, edoxaban has been approved in 2015 in many countries including the USA, Switzerland, and Europe based on the results of the ENGAGE AF-TIMI 48 trial.[14] During the year 2015, several subgroup analyses of the large NOAC trials have surfaced, including bleeding management and outcome with apixaban,[15] the management of rivaroxaban around catheter ablation for AF (VENTURE-AF),[16] and the outcome of amiodarone co-medication in patients receiving edoxaban,[17] to name just a few. Virtually, all subgroups of the large NOAC trials indicate a consistent benefit and safety of these drugs compared with warfarin, further underlining their overall superiority. This is supported by important real-world data (including those from a prospective registry with rivaroxaban, XANTUS)[18] indicating efficacy and safety, which is in line with that observed in the randomized clinical trials.

Arguably, the most exciting novelty in the field of NOACs comes from the development of specific reversal agents ('antidotes'). In a Phase 1 study in healthy men, the monoclonal antibody idarucizumab (specific for dabigatran) was well tolerated with no unexpected or clinically relevant safety concerns, and was associated with immediate, complete, and sustained reversal of dabigatran-induced anticoagulation.[19] Moreover, in a Phase 3 study, idarucizumab was demonstrated to effectively and immediately reverse the anticoagulant effect of dabigatran in patients presenting with serious bleeding or requiring an urgent procedure.[20] As a result, the US Food and Drug Administration has approved the drug in October 2015; the Committee for Medicinal Products for Human Use of the European Medicines Agency has also recently issued a positive opinion, and approval is expected by the end of this year or early 2016. Importantly, idarucizumab is ineffective against Xa-inhibitors; instead, different directly acting antidotes are being developed, including andexanet alfa and PER977. First results are also positive with these agents, and larger-scale clinical trials are anticipated within the year 2016. While these drugs clearly represent an important addition to our portfolio, many aspects in the practical use remain to be determined, including the type of patients and conditions requiring reversal and the time of reinstitution of anticoagulation. These and other issues are elegantly described in the 2015 updated version of the European Heart Rhythm

nja treba rabiti te vrijeme ponovnog uvođenja antikoagulansa. Ovi i drugi problemi odlično su opisani u ažuriranoj verziji praktičnog vodiča *European Heart Rhythm Association* iz 2015,[21] koja je uslijedila nakon velikog uspjeha prve inačice objavljene 2013. godine.[22]

Hoće li kateterska ablacija FA imati utjecaja na rizik od moždanog udara? Novi podatci iz opsežnog danskog registra upućuju na vrlo nizak rizik od moždanog udara za pacijente nakon kateterske ablacije.[23] Međutim, ti se podaci trebaju potvrditi u budućim randomiziranim studijama prije no što se može mijenjati klinička praksa za razdoblje nakon kateterske ablacije.[24]

VENTRIKULSKA ARITMIJA I IZNENADNA SRČANA SMRT

Kateterska ablacija ventrikulske tahikardije (VT) jedno je od najbrže rastućih polja intervencijske elektrofiziologije[25]. Važnost dijagnosticiranja i pravilne trijaže VT-a, pogotovo onih koje su lako podložne kateterskoj ablaciji (**slika 1**), izazov je s kojim se kardiolozi redovito suočavaju. Mnogobrojne važne studije objavljene u prethodnih 12 mjeseci dokumentirale su važnost i povećanu uporabu ablacije kod VT-a. Unatoč nekolikim iznimnim tehničkim i tehnološkim napredcima i inovacijama, poput primjene slikovne integracije,[26] novih ablacijskih elektroda,[27,28] tehnologija očitavanja sile[29] ili mapiranja

Association practical guide,[21] following the great success of its first version published in 2013.[22]

Will catheter ablation of AF have an impact on stroke risk? Novel data from a large Danish registry suggest a very low risk of stroke for patients after catheter ablation.[23] However, these data do require validation in a prospective randomized trial before clinical practice for oral anticoagulation after catheter ablation may be changed.[24]

VENTRICULAR ARRHYTHMIAS AND SUDDEN CARDIAC DEATH

Catheter ablation of ventricular tachycardia (VT) is one of the fastest growing fields in interventional electrophysiology[25]; the importance of diagnosing and correctly triaging VTs, particularly those easily amenable to catheter ablation (**Figure 1**), is a challenge faced by cardiologists on a regular basis. Multiple important studies have been reported within the last 12 months documenting the importance and increased utilization of VT ablation. Despite several remarkable technical and technological improvements and innovations such as use of image integration,[26] novel ablation electrodes,[27,28] force-sensing technologies,[29] or ultra-high density mapping,[30] the relatively high recurrence rate of any VT after catheter ablation in patients with VT and structural heart disease remains a key challenge. As evident from recent multi-centre data, non-

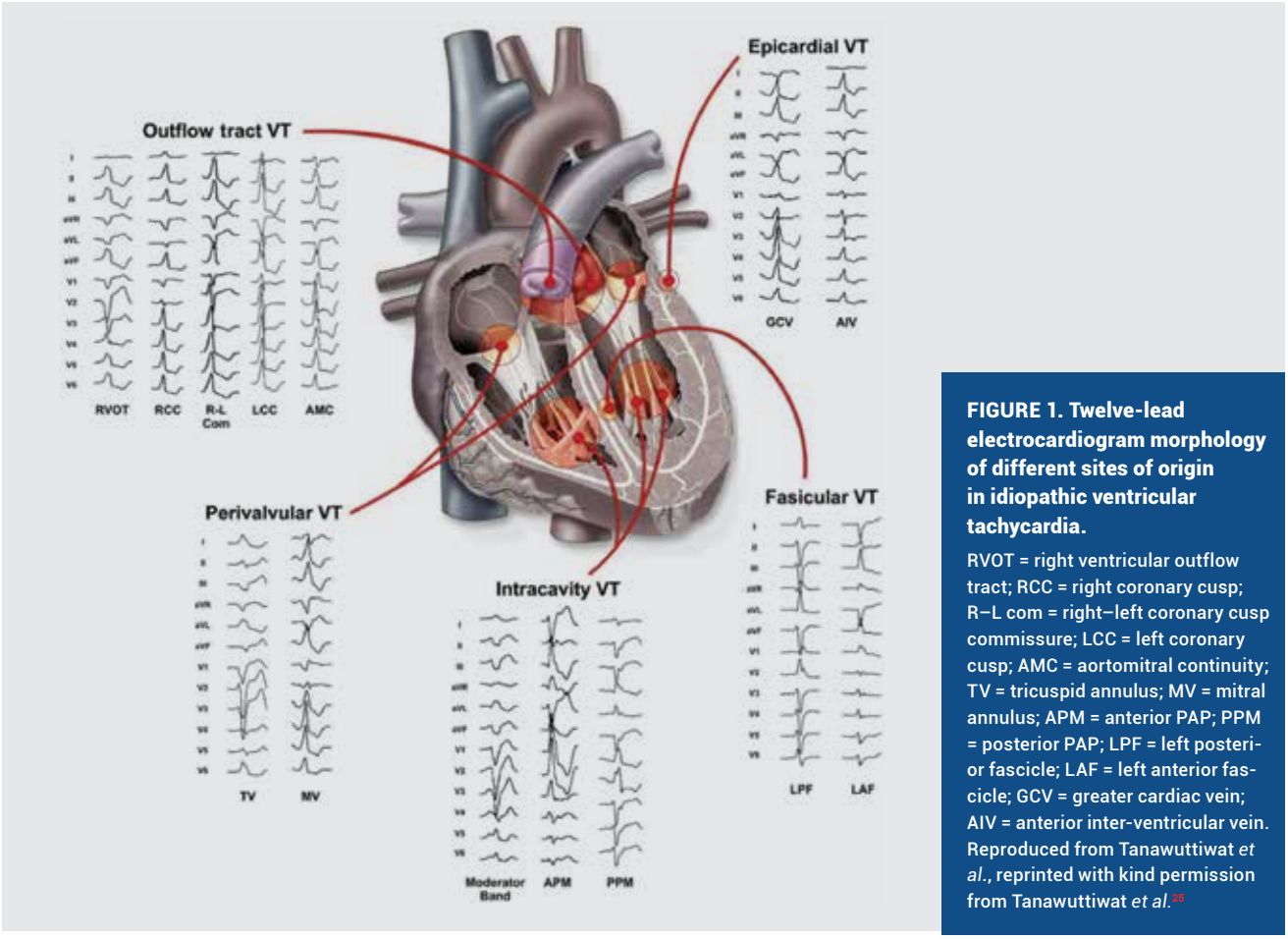

FIGURE 1. Twelve-lead electrocardiogram morphology of different sites of origin in idiopathic ventricular tachycardia.

RVOT = right ventricular outflow tract; RCC = right coronary cusp; R–L com = right–left coronary cusp commissure; LCC = left coronary cusp; AMC = aortomitral continuity; TV = tricuspid annulus; MV = mitral annulus; APM = anterior PAP; PPM = posterior PAP; LPF = left posterior fascicle; LAF = left anterior fascicle; GCV = greater cardiac vein; AIV = anterior inter-ventricular vein. Reproduced from Tanawuttiwat *et al.*, reprinted with kind permission from Tanawuttiwat *et al.*[25]

ultravisokom gustoćom,[30] relativno visok stupanj recidiva VT-a nakon kateterske ablacije u pacijenata s VT-om i strukturnom bolesti srca ostaje važan izazov. Kao što je vidljivo iz nedavno objavljenih podataka iz multicentričnih studija, neinducibilnost VT-a na kraju ablacije vjerojatno je najbolji ishod postupka i trebala bi biti njegov cilj.[31] Usto, kada je neinducibilnost podržana uklanjanjem abnormalnih potencijala, također može utjecati na preživljenje.[32,33] Najfascinantnije je izvješće o uspješnoj "ablaciji" Brugadina sindroma. Hipoteza o liječenju pacijenata s Brugadinim sindromom s rizikom od iznenadne srčane smrti postupkom ablacije potkrijepljena je nedavnim izvješćima Brugade *i sur.*[34] U njihovoj je seriji 13 pacijenata bilo podvrgnuto mapiranju epikarda i u svih je njih utvrđen abnormalni elektrokardiogram desne klijetke. Kateterska je ablacija normalizirala EKG i poništila prethodno postojeće tipične promjene u EKG-u izazvane flekainidom. Međutim, unatoč svom entuzijazmu, nije jasno utječu li te ablacije na spontanu pojavu VT / ventrikulske fibrilacije (VF) i/ili na rizik od iznenadne srčane smrti. Nove smjernice za liječenje ventrikulskih aritmija i prevenciju iznenadne srčane smrti predstavljene su tijekom kongresa ESC-a u Londonu.[35] Te smjernice pružaju najnoviji i najsuvremeniji sažetak trenutačnoga znanja i najboljih postupaka u liječenju na ovom polju.

Srčane elektroničke naprave

ELEKTROSTIMULATORI BEZ ELEKTRODA

Jedan od glavnih trendova u srčanim napravama tijekom 2015. godine bio je daljnji pomak prema napuštanju intravaskularnih elektroda. Nakon prvotno tegobnog početka, jednokomorni elektrostimulatori bez elektroda napokon su ušli u svakodnevnu kliničku uporabu. Rani rezultati u 140 pacijenata koji su liječeni Medtronic MICRA sistemom elektrostimulatora bez elektroda pokazali su pogodnu učinkovitost i sigurnosni profil.[36] Tijekom srednjega praćenja od 1,9 ± 1,8 mjeseci (tj. pokrivajući prije svega perioperativno i rano postoperativno razdoblje), nisu registrirane ozbiljne nuspojave u radu naprave, uključujući njezino pomicanje, a zabilježen je samo jedan slučaj perikardnog izljeva bez razvoja tamponade (koji je rezultirao duljom hospitalizacijom). Značajno je da se ovo, posljednje zbilo u pacijenta u kojega je napravu bilo potrebno opetovano repozicionirati (18 puta). U većine pacijenata (81 %), međutim, naprava je pravilno smještena bez potrebe za repozicioniranjem ili sa samo jednim repozicioniranjem. Tijekom pregleda, električne vrijednosti, uključujući prag stimulacije, impedanciju i očitavanje ostali su stabilni i povoljni, što je rezultiralo očekivanom trajanju baterije od 12,6 godina (raspon 8,6 – 14,4).[36] Stoga je u ljeto 2015. godine MICRA sistem dobio oznaku CE, nakon čega je uslijedilo pažljivo uvođenje u odabrane centre i u praksu operatera nakon što su prošli kroz opsežnu *in vivo* i *ex vivo* edukaciju. Ti su se pozitivni rezultati također odrazili i u većoj skupini od 725 pacijenata, od kojih je 719 (99,2 %) podvrgnuto uspješnom implantiranju.[37] Električne vrijednosti (prag, očitavanje i impedancija) bili su povoljne u 292 od 297 pacijenata s uparenim 6-mjesečnim podatcima. Primijećeno je 28 velikih komplikacija u 25 od 725 pacijenata [4,0 %, uključujući 11 (1,9 %) traumatskih kardioloških perfora-

inducibility of any VT at the end of the ablation is probably the best endpoint for the procedure and should be targeted.[31] In addition, non-inducibility when supported by elimination of abnormal potentials may also have an impact on survival as well.[32,33] Most fascinating is the report of successful 'ablation' of Brugada syndrome. The idea to treat Brugada patients at risk of sudden cardiac death with an interventional ablation procedure is further advanced by a recent report from Brugada *et al.*[34] In their series, 13 patients underwent epicardial mapping and right ventricular abnormal electrograms were identified in all of them. Catheter ablation normalized the ECG and abolished pre-existing typical ECG changes induced by flecainide. However, despite all enthusiasm, it is unclear whether or not these ablation effects have an impact on spontaneous VT/ventricular fibrillation (VF) and/or risk of sudden cardiac death. The new ESC Guidelines for the treatment of ventricular arrhythmias and prevention of sudden cardiac death were presented during the ESC congress in London.[35] These guidelines provide up-to-date state-of-the-art summary of current knowledge and best practice treatment in this field.

Cardiac electronic devices

LEADLESS PACEMAKERS

One of the main trends for cardiac devices in the year 2015 was the continued movement towards the abandonment of intravascular leads. After an initially tedious start, leadless single-chamber pacemakers have finally arrived in daily clinical practice. Early results from the 140 patients receiving the Medtronic MICRA leadless pacemaker system demonstrated a favourable efficacy and safety profile.[36] During a mean follow-up of 1.9 ± 1.8 months (i.e. covering primarily the perioperative and early postoperative period), no unanticipated serious adverse device events were observed, including no device dislodgement and only one pericardial effusion without tamponade (resulting in prolonged hospitalization). Of note, the latter occurred in a patient in whom the device needed to be repeatedly repositioned (18×). In the majority of patients (81%), however, the device was properly placed with no or only one repositioning. During follow-up, electrical values including pacing thresholds, impedance, and sensing remained stable and favourable, resulting in an anticipated battery longevity of 12.6 years (range 8.6–14.4).[36] As a result of these findings, the MICRA system received CE mark in the summer of 2015, followed by careful rollout to selected centres and operators after undergoing comprehensive *in vivo* and *ex vivo* training. These positive initial results were mirrored in a larger group of 725 patients, of whom 719 (99.2%) underwent successful implantation.[37] Electrical values (threshold, sensing, and impedance) were favourable in 292 of 297 patients with paired 6-month data. There were 28 major complications in 25 of 725 patients [4.0%, including 11 (1.9%) traumatic cardiac perforation or effusion and 1 death (0.1%)]. These numbers compared favourably with historic controls undergoing transvenous pacemaker implantation. Importantly, no device dislodgements were observed.[37] Results of the second available single-chamber transcatheter pacing system, the Nanostim

cija ili izljeva i jedan smrtni ishod (0,1 %)]. Ovi su brojevi povoljni u usporedbi s ranijim kontrolama pacijenata kojima su implantirani transvenski elektrostimulatori. Važno je da nije zamijećeno pomicanje naprava.[37] Rezultati drugog dostupnog jednokomornog transkateterskog stimulacijskog sistema, *Nanostim* (St Jude Medical), također su predstavljeni i objavljeni ove godine.[38] Od prvih 526 pacijenata kojima je sistem implantiran, postupak je bio uspješan u 504 pacijenta (95,8 %). Od 300 pacijenata koji su dovršili šestomjesečno praćenje, primarni ishod učinkovitosti (prihvatljive električne vrijednosti) postignut je u 90 % pacijenata. Od čitave skupine od 526 pacijenata, ozbiljni neželjeni događaji vezani za napravu zbili su se u 6,5 % pacijenata te su uključivali kardiološku tamponadu u 5 pacijenata (1,0 %), pomicanje naprave u šest pacijenata (1,5) i pomicanje naprave tijekom implantiranja zbog nedostatne fiksacije u dva pacijenta (0,4 %). Daljnje iskustvo s oba sistema elektrostimulatora bez elektroda pokazat će nam kakvi su u usporedbi s većim kontrolnim skupinama i u svakodnevnim kliničkim postupcima.

Pacijenti s tipičnom indikacijom za jednokomorni elektrostimulator, tj. trajna FA sa simptomatskom bradikardijom i/ili AV blokom trenutačno čine primarnu skupinu za elektrostimulatore bez elektroda. Buduće studije i iskustvo iz kliničke prakse pokazat će nam kako se ove naprave ponašaju tijekom duljeg razdoblja (uključujući novi sistem senzora koji se prilagođuje ritmu), a prva su osobna iskustva ohrabrujuća. Razvoj je naprednijih sistema u tijeku, a uključuje dvokomorne elektrostimulatore, terapiju srčane resinkronizacije i komunikaciju s potkožnim implantiranim kardioverterskim defibrilatorom (ICD).

LIJEČENJE IMPLANTIRANIM KARDIOVERTERSKIM DEFIBRILATOROM I TELEMONITORIRANJE IMPLANTIRANIM UREĐAJIMA

Testiranje implantiranih kardioverterskih-defibrilatora više nije potrebno tijekom rutinskih i nekompliciranih ICD implantacija: 1077 pacijenata u studiji *Nordic ICD* bilo je nasumično podvrgnuto prvoj implantaciji ICD-a s testiranjem (n = 540) i bez testiranja (n = 537) praga defibrilacije.[39] Učinkovitost defibrilacije nije bila različita u tim dvjema skupinama tijekom praćenja. Slično tomu, u studiji SIMPLE učinjenoj na 2500 pacijenata rutinsko testiranje defibrilacije nije rezultiralo smanjenjem aritmijske smrti tijekom prosječnoga praćenja od 3,1 godine.[40]

Gotovo svi elektrostimulatori i defibrilatori koji su trenutačno dostupni imaju tehničku opciju za udaljeni nadzor.[41] Prethodni rezultati randomiziranih kliničkih studija i analiza velikih skupina podataka upućuju na to da ove tehnologije mogu imati povoljan učinak ako se prikladno primijene.[42] Međutim, nedavni podatci iz studije *Optilink HF* izneseni na kongresu ESC-a u Londonu pokazali su poražavajuće rezultate: 1002 pacijenta sa srčanim popuštanjem i indikacijom za implantaciju ICD-a bilo je randomizirano u skupine s omogućenom udaljenom automatiziranom obavijesti o plućnoj kongestiji (n = 505) i onoj onemogućenoj (n = 497). Nakon 18 mjeseci praćenja nije bilo značajne razlike između skupina u primarnome ciljnom ishodu, koji je uključivao ukupnu smrtnost i kardiovaskularne hospitalizacije. Nešto više obećavajući podatci dobiveni su praćenjem podataka iz studije CHAMPION koja ja procje-

(St Jude Medical), were equally presented and published this year.[38] In the first 526 patients undergoing implantation, the system was successfully implanted in 504 (95.8%). Of the 300 patients who completed 6-month follow-up, the primary efficacy outcome (acceptable electrical values) was reached in 90%. Of the total cohort of 526 patients, serious device-related adverse events occurred in 6.5% of patients, including cardiac tamponade in 5 (1.0%), device dislodgement in 6 (in 1.5%), and device migration during implantation owing to inadequate fixation in 2 patients (0.4%). Further experience with both leadless pacing systems will show how they compare in even larger populations and in daily clinical practice.

Patients with a typical single-chamber pacemaker indication currently represent the primary population for leadless pacers, i.e. permanent AF with symptomatic bradycardia and/or AV block. Future studies and real-world experience will show how these device behave long term (including the novel rate-adaptive sensor system); first personal experiences are encouraging. The development for more advanced systems is ongoing, including dual-chamber pacemakers, cardiac resynchronization therapy, and communication with the subcutaneous implantable cardioverter defibrillator (ICD).

IMPLANTABLE CARDIOVERTER DEFIBRILLATOR THERAPY AND IMPLANT-BASED TELEMONITORING

Implantable cardioverter defibrillator testing is no longer necessary during routine and uncomplicated ICD implantation: in the Nordic ICD Trial, 1077 patients were randomly assigned to first time ICD implantation with (*n* = 540) or without (*n* = 537) testing of defibrillation threshold.[39] Defibrillation efficacy was not different between both groups during follow-up. Similarly, in the SIMPLE trial of 2500 patients, routine defibrillation testing did not result in a reduction in arrhythmic deaths during a mean follow-up of 3.1 years.[40]

Almost all pacemakers and defibrillators that are currently available have the technical option for remote monitoring.[41] Previous results from randomized clinical trials and analysis from big data sets indicated that these technologies may have beneficial effects when applied appropriately.[42] However, recent data from the Optilink HF Trial reported at the ESC Congress in London showed disappointing results: the trial randomized 1002 patients with heart failure and an indication for ICD implantation to remote automated pulmonary congestion alert 'on' (*n* = 505) or 'off' (*n* = 497). After 18 months of follow-up, there was no significant difference between groups in primary endpoint, which was a composite of all-cause death and cardiovascular hospitalizations. More promising data are derived from the follow-up report of the CHAMPION Trial that assessed the efficacy of automatic pulmonary pressure measurement in heart failure patients to guide and optimize heart failure therapy.[43] The superiority of the treatment group over the control group previously reported was maintained for an additional 13 months to the end of the Randomized Access Period with a significant reduction of heart failure-related hospitalizations by 33% and of all-cause hospitalizations by 16%. Second, the good results in the treatment group were maintained during an Open Ac-

njivala učinkovitost automatskoga mjerenja plućnog tlaka u pacijenata sa srčanim popuštanjem za vođenje i optimizaciju terapije za srčano popuštanje.[43] Prethodno izvještena superiornost liječene skupine nad kontrolom održala se daljnjih 13 mjeseci do kraja razdoblja randomiziranoga pristupa sa značajnim smanjenjem hospitalizacija povezanih sa srčanim popuštanjem za 33 % i hospitalizacija zbog svih uzroka za 16 %. Nadalje, dobri rezultati liječene skupine održali su se i tijekom razdoblja slobodnoga pristupa od daljnjih 12 mjeseci, tijekom kojih nije zamijećena veća učestalost bolničkog liječenja. Nakon što su podaci o tlaku u plućnoj arteriji postali dostupni, iskorišteni su za vođenje terapije tijekom razdoblja slobodnoga pristupa, a hospitalizacije zbog srčanog popuštanja i one zbog svih drugih uzroka u prethodno kontrolnoj skupini bile su znatno smanjene za 48 % i 21 %. Prema tome, udaljeni nadzor čini se veoma obećavajućim za potrebe podržavanja terapije pri srčanom popuštanju te je samo pitanje vremena kada će hemodinamski senzori biti kombinirani s elektrostimulatorima, defibrilatorima i napravama za kardiološku resinkronizaciju.

POTKOŽNO UGRADIVI KARDIOVERTERSKI DEFIBRILATORI

Sve od njihova odobrenja 2009. godine, potkožno ugradivi ICD sistemi (S-ICD) zadobili su pozornost i zanimanje stručne kardiološke javnosti. Potpuni izostanak intravaskularnih elektroda potencijalno se povezuje sa znatnim smanjenjem pobola (i smrtnosti) zbog mogućih komplikacija povezanih s elektrodama kod klasičnih transvenskih ICD sistema koji se trenutačno uporabljuju. Godine 2015. odobren je novi EMBLEM S-ICD sistem čija je glavna odlika u usporedbi s prethodnim S-ICD sistemom da je 20 % tanji, a očekivani tijek trajanja mu je 40 % dulji. U isto vrijeme razvijaju se novi algoritmi kako bi se svladao rizik od nedostatne ispostave elektrošoka.[44,45] Nedavno objavljeni rezultati iz registara upozorili su na smanjen rizik od komplikacija, suboptimalnog programiranja i (u manjoj mjeri) nedostatne dostave elektrošoka kao posljedice rastućeg iskustva i broja postupaka.[46] Usto, spomenuti su registri pokazali visoku učinkovitost u zaustavljanju VT-a i VF-a, s učestalošću prekida od 90,1 % (100/111) događaja s pomoću jednog elektrošoka i 98,5 % (109/111) zaustavljenih događaja nakon dostupnih pet elektrošokova.[47] Kao rezultat ovakvih povoljnih podataka, uporaba S-ICD prvi put je uključena u smjernice za prevenciju iznenadne srčane smrti kao indikacija IIa (razina dokaza C) kao alternativa standardnoj ugradnji ICD-a u pacijenata bez indikacije za stimulaciju bradikardije, kardiološke resinkronizacije ili antitahikardne elektrostimulacije (ATP).[35] Usto, S-ICD se može uzeti u obzir (IIb, C) za pacijente s otežanim venskim pristupom, nakon uklanjanja transvenskog ICD-a zbog infekcija ili kod mlađih pacijenata s dugoročnom indikacijom za ICD terapiju.[35] Nedostatak mogućnosti ATP-a ili stimulacije bradikardije ostaje najvažniji nedostatak trenutačnih S-ICD naprava. Kombinacija S-ICD i elektrostimulatora bez elektroda bilo bi jedno od najočitijih rješenja ovoga problema. Međutim, programiranjem zasnovanim na dokazima (zone otkrivanja visoke stope ili duljeg trajanja), cjelokupna količina dostavljenog ATP-a najvjerojatnije će se smanjiti kao rezultat spontanog zaustavljanja VT-a i pojavljivanja VT-a ispod granice opažanja. U tijeku je prospective Period of another 12 months, during which no increase in hospitalizations was observed. Most importantly, heart failure-related hospitalizations and all-cause hospitalizations in the former control group were reduced significantly by 48 and 21%, respectively, after pulmonary artery pressure information became available to guide therapy during the Open Access Period. Thus, implant-based remote telemonitoring seems highly promising to support heart failure therapy and it will be just a matter of time when haemodynamic sensors will be combined with pacemakers, defibrillators, and cardiac resynchronization devices.

SUBCUTANEOUS IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

Ever since its approval in 2009, the subcutaneous ICD (S-ICD) system has increasingly gained attention and attraction. Indeed, its complete lack of intravascularly placed electrodes is potentially associated with a substantial reduction in morbidity (and mortality) due to lead complications associated with currently used 'classical' transvenous ICD systems. In 2015, the new generation EMBLEM S-ICD System was approved, the main feature of which is its 20% thinner size combined with a 40% longer life expectancy when compared with the previous S-ICD system. At the same time, novel algorithms are being developed to overcome the risk of inadequate shock deliveries.[44,45] Recently published registry results have indicated a decreasing risk of complications, suboptimal programming, and (to a lesser degree) inadequate shock deliveries with increasing experience and volume.[46] In addition, the same registries demonstrated a high efficacy for the termination of VT and VF, with 90.1% of events (100/111) terminated with one shock and 98.5% (109/111) terminated within the available five shocks.[47] As a result of these favourable data, the use of the S-ICD has, for the first time, been incorporated into the guidelines for the prevention of sudden cardiac death as a IIa indication [level of evidence (LoE) C] as an alternative to standard ICD for patients without an indication for bradycardia pacing, cardiac resynchronization, or ATP.[35] Also, the S-ICD may be considered (IIb, LoE C) in patients with difficult venous access, after the transvenous ICD removal for infections or in young patients with a long-term indication for ICD therapy.[35] Indeed, the lack of possibility to deliver ATP or bradycardia pacing remains the most important shortcoming of current S-ICD devices. Combination of the S-ICD with leadless pacers clearly would be one of the most obvious possible solution to this problem. However, with evidence-based programming (high-rate or long-duration detection zones), the overall amount of delivered ATP will likely be decreasing as a result of both spontaneous VT termination and VTs occurring below the detection limit. A prospective, randomized trial (PRAETORIAN) comparing currently available transvenous and subcutaneous ICDs (i.e. without the possibility of ATP) has been initiated and is currently ongoing.

WEARABLE CARDIOVERTER DEFIBRILLATOR

Also for the first time, the new 2015 guidelines for the prevention of sudden cardiac death give recommendations for the use of the wearable cardioverter defibrillator (WCD; **Figure 2**). With a class IIa recommendation (LoE C), WCD be considered

pektivna, randomizirana studija (PRAETORIAN) koja uspoređuje trenutačno dostupne transvenski i potkožno implantirane ICD-ove (tj. bez mogućnosti ATP-a).

NOSIVI KARDIOVERTERSKI DEFIBRILATOR

Također prvi puta, nove smjernice iz 2015. godine za prevenciju iznenadne srčane smrti preporučuju uporabu nosivih kardioverterskih defibrilatora (WCD; **slika 2**). S preporukom klase IIa C, primjenu WCD-a na ograničeno razdoblje treba se razmotriti u pacijenata sa smanjenom EF kojima prijeti iznenadna smrt zbog aritmije, ali koji trenutačno ne mogu dobiti ICD, uključujući i one s infekcijama nakon uklanjanja elektroda, s aktivnim miokarditisom i one s aritmijama u ranom oporavku nakon infarkta miokarda.[35] U odsutnosti randomiziranih kliničkih studija, ova se preporuka većinom zasniva na rezultatima iz velikih registara poput onih nedavno objavljenih iz prospektivnog registra koji prati ishode 2000 pacijenata koji koriste WCD (WEARIT-II) tijekom medijana primjene od 90 dana.[48] U tom registru, 120 postojanih ventrikulskih tahiaritmija (VT/VF) bilo je registrirano kod 41 pacijenta. Od ovih pacijenata, njih 54 % primilo je odgovarajuće WCD elektrošokove, dok u 10 pacijenata (0,5 %) WCD nije primijenio odgovarajuću terapiju.

Zaključak

Tijekom 2015. godine pojavile su se mnoge zanimljive studije na polju invazivne elektrofiziologije i srčanih elektroničkih naprava, od kojih bi mnoge mogle imati (ili već imaju) važne implikacije u svakodnevnoj kliničkoj praksi. Potvrđivanje i proširivanje ovih podataka iskustvima iz sadašnje kliničke prakse bit će ključni za potvrđivanje njihove učinkovitosti i sigurnosti u svakodnevnom radu. U jednom preglednom članku nije moguće obuhvatiti sve novosti te su neke metode i tehnologije morale biti izostavljene, uključujući neke preliminarne rezultate uporabe *multisite* pacing-a i usporedbe *point-by-point* i *single shot* ablacije. Ako se nastavi ovaj tempo i kvaliteta inovacija, 2016. godina nesumnjivo će biti uspješna godina na polju aritmija.

for a limited time period for patients with reduced EF who are at risk of sudden arrhythmic death, but who currently cannot receive an ICD, including patients post-lead removal for infection, patients with active myocarditis, and patients with arrhythmias in the early post-myocardial infarction phase.[35] In the absence of a randomized clinical trial, this recommendation was based mainly on large registries such as the recently published prospective registry of patients using the wearable defibrillator (WEARIT-II), which followed 2000 recipients of the WCD with a median wear time for 90 days.[48] In this registry, a total of 120 sustained ventricular tachyarrhythmias (VT/VF) were observed in 41 patients. Of these patients, 54% received appropriate WCD shocks, while only 10 patients (0.5%) received inappropriate WCD therapy.

Importantly, at the end of the individual time frame of WCD use, an ICD was implanted in only 840 patients (42%), with an improvement in EF being the most frequent reason for withholding ICD implantation. Given the potential cost saved for *de novo* ICD implantation as well as (potentially) associated follow-up cost and cost of complications, this strategy may in addition also turn out cost-effective, but comprehensive analyses in this regard are currently lacking.

Final thoughts

In the year 2015, many interesting studies have surfaced in the field of invasive electrophysiology and cardiac devices, most of which may have (or do already have) important implications for daily clinical practice. Ongoing confirmation and expansion of these data with experience from the real world will be crucial to substantiate their efficacy and safety in the 'real world'. Coverage of all of the exciting developments in one concise review is impossible; as such, various methods and technologies had to be omitted for the time being, including some preliminary results on the use of multi-site pacing and comparisons of point-by-point vs. single shot ablation. If the rate and quality of innovation persists, undoubtedly the year 2016 will equally be a successful one in the field of arrhythmias.

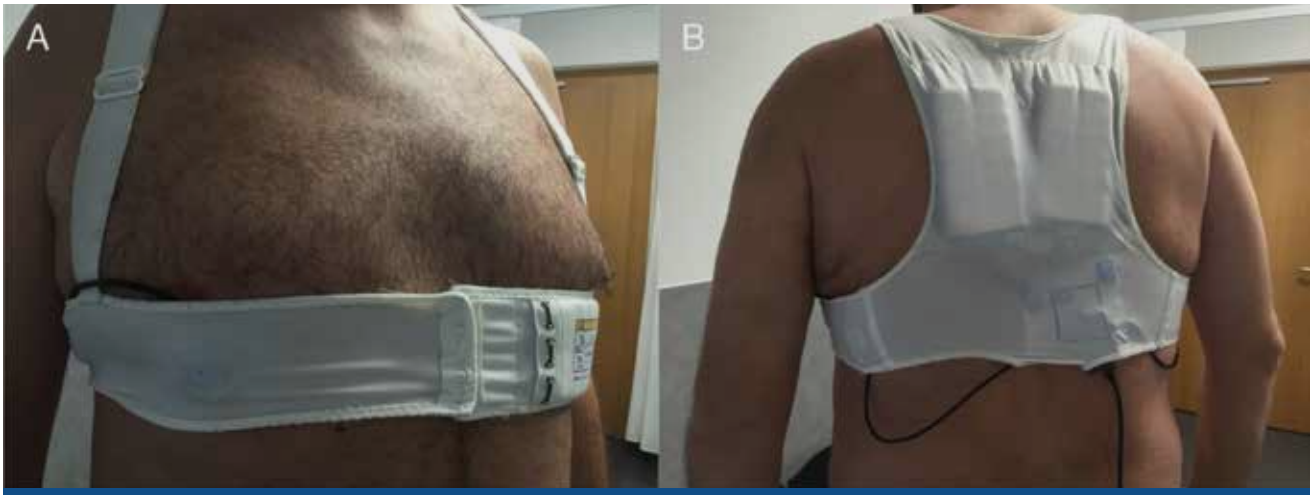

FIGURE 2. Wearable cardioverter defibrillator. Model of a wearable cardioverter defibrillator (images courtesy of J.S., reprinted with kind permission and patient consent).

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