Pregledni rad / Review article

Almanac 2013.: aritmije i elektrostimulacija srca

Almanac 2013: cardiac arrhythmias and pacing

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SAŽETAK: U posljednjih nekoliko godina učinjen je značajan napredak u području kliničke elektrofiziologije i elektrostimulacije srca. Znanstvenici i liječnici bolje razumiju patofiziološke mehanizme fibrilacije atrija (FA) što je rezultiralo poboljšanjem dijagnostičkih metoda, stratifikaciji rizika i liječenja. Uvođenje novih oralnih antikoagulansa omogućilo je liječnicima alternativne mogućnosti zbrinjavanja bolesnika s FA kod umjerenog ili visokog rizika tromboembolije te su dostupni i novi podaci za uporabu kateterske ablacije u liječenju bolesnika sa simptomatskom FA. Drugo područje intenzivnog istraživanja aritmija i elektrostimulacije srca vezano je uz primjenu kardijalne resinkronizacijske terapije (CRT) u liječenju bolesnika sa zatajivanjem srca. Po objavi najznačajnijih randomiziranih kontroliranih istraživanja koja dokazuju da CRT poboljšava šanse za preživljavanje kod bolesnika s teškim stupnjem zatajivanja srca te da ublažava simptome, provedene su mnoge studije vezane uz probir bolesnika za liječenje primjenom CRT i evaluirani su klinički znaci povezani s povoljnom reakcijom na terapiju. Također, nastavljeno je aktivno istraživanje područja iznenadne srčane smrti i implatibilnih kardioverter defibrilatora s važnim novim epidemiološkim i kliničkim podacima poglavito o metodama izbora, stratifikacije rizika i skrbi bolesnika. Ovaj pregledni rad prikazuje najznačajniji napredak na područjima aritimija i elektrostimulacije srca.

SUMMARY: Important advances have been made in the past few years in the fields of clinical cardiac electrophysiology and pacing. Researchers and clinicians have a greater understanding of the pathophysiological mechanisms underlying atrial fibrillation (AF), which has transpired into improved methods of detection, risk stratification, and treatments. The introduction of novel oral anticoagulants has provided clinicians with alternative options in managing patients with AF at moderate to high thromboembolic risk and further data has been emerging on the use of catheter ablation for the treatment of symptomatic AF. Another area of intense research in the field of cardiac arrhythmias and pacing is in the use of cardiac resynchronisation therapy (CRT) for the treatment of patients with heart failure. Following the publication of major landmark randomised controlled trials reporting that CRT confers a survival advantage in patients with severe heart failure and improves symptoms, many subsequent studies have been performed to further refine the selection of patients for CRT and determine the clinical characteristics associated with a favourable response. The field of sudden cardiac death and implantable cardioverter defibrillators also continues to be actively researched, with important new epidemiological and clinical data emerging on improved methods for patient selection, risk stratification, and management. This review covers the major recent advances in these areas related to cardiac arrhythmias and pacing.

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FIBRILACIJA ATRIJA

Epidemiologija fibrilacije atrija

Brojne velike epidemiološke studije koje koriste podataka iz registara i prospektivne kohorte podatka ponovno su ukazale na povezanost između fibrilacije atrija (FA) i ostalih netradicionalnih čimbenika rizika za FA. To uključuje povećani rizik od pojave FA kod bolesnika s visokom razinom HbA1c i lošom kontrolom glikemije[1], celijaklijom[2], reumatoidnim artritisom[3] i psorijazom[4], s uporabom nesteroidnih antireumatika[5] i visokih ljudi[6]. Druga zanimljiva veza je otkriće iz pod-

ATRIAL FIBRILATION

Epidemiology of atrial fibrillation

A number of large scale epidemiological studies using registry databases and prospective cohort data have reported novel associations between atrial fibrillation (AF) and other non-traditional risk factors for AF. These include an increased risk of incident AF in patients with high glycosylated haemoglobin (HbA1c) and poor glycaemic control[1], coeliac disease[2], rheumatoid arthritis[3] and psoriasis[4], use of non-aspirin, non-steroidal antiinflammatory drugs (NSAID)[5], and

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studije SAFETY (Standard versus Atrial Fibrillation SpecificManagement Study) u kojoj je kod 260 bolesnika s kroničnom FA otkrivena visoka zastupljenost blagih kognitivnih poremećaj kod starijih, visoko rizičnih bolesnika hospitaliziranih s FA[7]. U podstudiji Cardiovascular Health Study otkrivena je povezanost povišenih koncentracija ukupnih dugolančanih n-3 polunezasićenih masnih kiselina (PUFA) u cirkulaciji s niskim rizikom od pojave FA[8].

Druge nedavne epidemiološke studije o FA ukazuju na povećanje incidencije FA u bolesnika s povećanim rizikom od razvoja terminalne faze kronične bubrežne bolesti kod preegzistirajuće kronične bolesti bubrega[9]. Studija provedena kod 3.220 bolesnika je pokazala da je novonastala FA kod bolesnika s infarktom miokarda bez prethodnih anamnestičkih podataka o FA povezana s povećanom smrtnosti[10]. U velikoj švedskoj studijii s podacima od 100.802 bolesnika s FA uključenih u registar, *Friberg i sur.*[11] su utvrdili da su ishemijski moždani udari bili češći u žena nego u muškaraca, čime se podržava stav da se ženski spol treba uzeti u razmatranje prilikom donošenje odluke o antikoagulacijskom liječenju. Nadalje, kod starijih bolesnika primljenih s nedavno dijagnosticiranom FA, rizik od moždanog udara se čini većim kod žena nego kod muškaraca, bez obzira na uporabu varfarina[12], a među zdravim ženama novonastala FA se smatra neovisnim čimbenikom povezanim s ukupnom kardiovaskularnom i ne-kardiovaskularnom smrtnosti[13].

Medikamentozno liječenje fibrilacije atrija

Podaci iz međunarodne, opservacijske, presječne studije RealiseAF s bolesnicima s anamnestičkim podatkom o FA tijekom prethodne godine, ukazuju da su bolesnici kod kojih je FA "bila kontrolirana" (definirana kao sinusni ritam ili FA s frekvencijom srca u mirovanju ≤80/min) imali bolju kvalitetu života i manje simptoma nego oni kod kojih je FA bila nekontrolirana[14]. Ipak, čak i bolesnici s kontroliranom FA imaju često simptome poput nepodnošljivosti napora, promjene kvalitete života i kardiovaskularne događaje, pa su stoga važni kontinuirani napori u razvoju novog i boljeg liječenja kod FA. Registar RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation) je bila svjetska, prospektivna opservacijska studija o liječenju FA temeljena na neselektivnoj kohorti tijekom razdoblja od 12 mjeseci[15]. Kod 5.171 bolesnika, čiji su podaci bili dostupni, terapijski uspjeh (kontrola FA) ostvaren je u 54% svih bolesnika (kontrola ritma u 60% nasuprot kontrole frekvencije u 47%). Na kliničke ishode (koji su uglavnom bili potaknuti hospitalizacijama zbog aritmije i drugih kardiovaskularnih uzroka) nije utjecao izbor strategije kontrole srčane frekvencije ili ritma, iako je izbor kontrole ritma smanjio vjerojatnost napredovanja FA.

Studija RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation) je bila prva službena procjena drugačijih ciljeva u kontroli frekvencije u FA te je po prvi put pokazano da strategija blaže kontrole frekvencije (ciljna srčana frekvencija u mirovanju <110/min) nije inferiorna u odnosu na strategiju "stroge kontrole frekvencije" (ciljna srčana frekvencija u mirovanju <80/min i tijekom umjerenog vježbanja <110/min)[16]. Dvije naknadne pod-studije istraživanja RACE II su dokazale da stroga kontrola frekvencije nije imala značajan učinak na kvalitetu života u bolesnika s trajnom FA[17] te da blaža kontrola frekvencije nije imala negativan utjecaj na atrijsko i ventrikulsko remodeliranje u usporedbi sa strogom kontrolom frekvencije (iako je ženski spol bio neovisno povezan sa značajnim negativnim srčanim remodeliranjem)[18]. U drugoj

increased height[6]. Another interesting association is the finding from a substudy of 260 patients with chronic AF from the SAFETY trial (Standard versus Atrial Fibrillation Specific Management Study) that mild cognitive impairment is highly prevalent among older, high risk patients hospitalised with AF[7]. In another substudy of the Cardiovascular Health Study, investigators found that higher baseline circulating concentrations of total long chain n-3 polyunsaturated fatty acids (PUFA) were associated with a lower risk of incident AF[8].

Other interesting recent epidemiological studies on AF include the association of incident AF with an increased risk of developing end stage renal disease in patients with chronic kidney disease[9], and a community based study of 3,220 patients which showed that new AF in patients with no history of AF before a myocardial infarction increased mortality in patients with myocardial infarction[10]. In a large Swedish registry study of 100,802 patients with AF, *Friberg et al.*[11] found that ischaemic strokes were more common in women than in men, supporting the notion that female gender should be taken into consideration when making decisions about anticoagulation treatment. Furthermore, among older patients admitted with recently diagnosed AF, the risk of stroke appears to be greater in women than in men, regardless of warfarin use[12], and among healthy women new onset AF was found to be independently associated with all cause cardiovascular and non-cardiovascular mortality[13].

Medical management of atrial fibrillation

Data from the RealiseAF study, an international, observational, cross-sectional survey of patients with any history of AF in the previous year, suggested that patients in which their AF was 'controlled' (defined as sinus rhythm or AF with a resting heart rate ≤80 beats/min) had a better quality of life and fewer symptoms than those whose AF was uncontrolled[14]. Nonetheless, even patients with controlled AF experienced frequent symptoms, functional impairment, altered quality of life and cardiovascular events — hence the importance of ongoing efforts to develop novel and better treatments for AF. The RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation) registry was a worldwide, prospective observational survey of AF management in an unselected, community based cohort over a 12 months period[15]. The investigators found that in 5,171 patients whose data were available, therapeutic success (driven by control of AF) was achieved in 54% overall (rhythm control 60% vs rate control 47%). The choice of rate or rhythm strategy did not affect clinical outcomes (which were driven mainly by hospitalisations for arrhythmia and other cardiovascular causes), although the choice of rhythm control reduced the likelihood of AF progression.

The RACE (Rate Control Efficacy in Permanent Atrial Fibrillation) II trial was the first formal assessment of alternative rate control goals in AF and demonstrated for the first time that a 'lenient rate control' strategy (target resting heart rate <110 beats/min) was non-inferior to a 'strict rate control' strategy (target resting heart rate <80 beats/ min and heart rate during moderate exercise <110 beats/min)[16]. Two subsequent sub-studies of the RACE II trial showed that the stringency of rate control had no significant effect on the quality of life in patients with permanent AF[17] and that lenient rate control did not have an adverse effect on atrial and ventricular remodelling compared with strict rate control (although female gender was independently associated with significant adverse cardiac remodelling)[18]. In another sub-

podstudiji iz AFFIRM istraživanja (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) u kojoj su razmatrani kardiovaskularni ishodi, istraživači su otkrili da je ukupna smrtnost ili bolničko liječenje radi kardiovaskularnih događaja bilo bolje prilikom odabira kontrole frekvencije nego kontrole ritma (uporabom amiodarona ili sotalola)[19]. Nekardiovaskularna smrt i boravak u jedinici intenzivne skrbi su bili učestaliji kod bolesnika na terapiji amiodaronom uz kraće vrijeme boravka u bolnici zbog kardiovaskularnog događaja. U prospektivnoj, randomiziranoj, otvorenoj studiji, Yamase i sur.[20] su u bolesnika s perzistentnom FA uspoređivali farmakološku kardioverziju amiodaronom nasuprot bepridilom u 40 uzastopnih ispitanika. Bepridil je bio superioran u odnosu na amiodaron kod konverzije u sinusni ritam (85% naspram 35%; p< 0,05) i održavanja sinusnog ritma nakon prosječnog praćenja od 14,7 mjeseci (75% naspram 50%).

Pitanje ima li PUFA pozitivan učinak na FA i dalje ostaje jedno od tema. U velikoj meta-analizi koja uključuju 1.955 bolesnika iz 10 randomiziranih kontroliranih istraživanja utvrđeno je da dodatak PUFA nije imao značajan učinak na prevenciju FA[21]. U istraživanju FORWARD (Randomised Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) 586 ambulantnih ispitanika s dokazanom simptomatskom paroksizmalnom FA koja je zahtijevala kardioverziju ili koji su imali najmanje dvije epizode FA u prethodnih 6 mjeseci je nasumično, podijeljeno na liječenje placebom ili PUFA (1 g/dan) tijekom 12 mjeseci[22]. Dodatak PUFA nije smanjio recidive FA niti je bilo dobrobiti kod drugih prethodno definiranih zajedničkih ishoda (ukupna smrtnost, ne-fatalni moždani udar, ne-fatalni akutni infarkt miokarda, sistemske embolije ili zatajivanje srca). U velikom placebo kontroliranom, randomiziranom kliničkom istraživanju koje je uključivalo 1.516 bolesnika u 28 centara, perioperativni dodatak PUFA nije dokazao smanjenje rizika od postoperativne FA, iako se dobro podnosio[23]. Nasuprot tome, u drugom randomiziranom dvostruko slijepom placebom kontroliranom istraživanju koje je uključilo 199 bolesnika koji su primali PUFA (2 g/dan) ili placebo tijekom razdoblja od 4 tjedna prije elektrokardioverzije, utvrđeno je tijekom jednogodišnjeg praćenja da će se u sinusnom ritmu vjerojatnije zadržati bolesnici koji su primali PUFA[24].

Praćenje i procjena fibrilacije atrija

Dijagnosticiranje paroksizmalne FA dostupnim dijagnostičkim metodama i tehnologijom i danas može biti otežano te se čine stalni napori u cilju poboljšanja metoda za detekciju i dijagnosticiranje. Pažljivijim praćenjem bolesnika i uporabom invazivnih i neinvazivnih metoda postoji sve značajnija povezanost subkliničke FA i moždanog udara nejasne etiologije. U studiji provedenoj kod 2.580 bolesnika u dobi od 65 godina ili više, s nedavno ugrađenim elektrostimulatorom ili defibrilatorom i bez anamnestičkog podatka o FA, otkrivene su subkliničke atrijske tahiaritmije kod 261 bolesnika (10,1%)[25]. Tijekom prosječnog praćenja od 2,5 godine, otkriveno je da bolesnici sa subkliničkim atrijskim tahiaritmijama imaju povećan rizik od razvoja kliničke FA, ishemijskog moždanog udara ili sistemske embolije (HR 2.49, 95% CI 1.28 do 4.85; p=0,007). Kod bolesnika bez elektrostimulatora ili defibrilatora koji su razvili moždani udar nejasne etiologije, trebalo bi razmotriti dugoročno ambulantno praćenje elektrokardiograma vanjskim ili implantabilnim uređajima radi dijagnosticiranja subkliničke FA[26,27].

U studiji provedenoj kod 100 pacijenata radi detekcije FA, istraživači su uspoređivali učinkovitost primjene 7-dnevnog

study looking at cardiovascular outcomes in subjects from the original AFFIRM trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management), investigators found that the composite outcome of mortality or cardiovascular hospital stays was better in rate compared with rhythm control strategies (using amiodarone or sotalol)[19]. Non-cardiovascular death and intensive care unit hospital stay were more frequent in patients on amiodarone, and time to cardiovascular hospital stay was shorter. In a prospective, randomised, open label trial of pharmacological cardioversion in patients with persistent AF, Yamase et al.[20] compared amiodarone with bepridil in 40 consecutive subjects. The investigators found that bepridil was superior to amiodarone in achieving sinus conversion (85% vs 35%; p<0.05) and maintaining sinus rhythm after an average follow-up of 14.7 months (75% vs 50%).

The issue of whether PUFA have any beneficial effects on AF remains a topical one. A large meta-analysis of 10 randomised controlled trials involving 1,955 patients found that PUFA supplementation had no significant effect on AF prevention[21]. In the FORWARD trial (Randomised Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation), 586 outpatient participants with confirmed symptomatic paroxysmal AF who required cardio-version or had at least two episodes of AF in the preceding 6 months were randomly assigned to receive placebo or PUFA (1 g/day) for 12 months[22]. The investigators found that PUFA supplementation did not reduce the recurrence of AF or have any beneficial effects on the other prespecified end points (all cause mortality, non-fatal stroke, non-fatal acute myocardial infarction, systemic embolism or heart failure). In a large placebo controlled, randomised clinical trial involving 1,516 patients in 28 centres, perioperative supplementation of PUFA, although well tolerated, was not shown to reduce the risk of postoperative AF[23]. In contrast, another randomised, double blind, placebo controlled trial involving 199 patients who received either PUFA (2 g/day) or placebo for 4 weeks before direct current (DC) cardioversion found that patients who received PUFA were more likely to be in sinus rhythm at 1 year follow-up compared with control patients[24].

Monitoring and assessment of atrial fibrillation

The detection of paroxysmal AF can be difficult with current methods and technology; hence ongoing efforts are being made to improve methods for detection and diagnosis. The association between subclinical AF and cryptogenic stroke has gained increasing prominence with more careful monitoring of patients using invasive and non-invasive methods. In a nice study of 2,580 patients aged 65 years or older with a pacemaker or defibrillator recently implanted and no history of AF, investigators detected subclinical atrial tachyarrhythmias in 261 patients (10.1%)[25]. Over a mean follow-up of 2.5 years, patients with subclinical atrial tachyarrhythmias were found to have an increased risk of clinical AF and of ischaemic stroke or systemic embolism (HR 2.49, 95% CI 1.28 to 4.85; p=0.007). In patients who do not have pacemakers or defibrillators who present with cryptogenic stroke, longer term ambulatory ECG monitoring using external or implantable devices may be worth considering to help confirm a diagnosis of subclinical AF[26,27].

In a study of 100 patients being screened for AF, investigators compared the effectiveness of using 7-day triggered ECG monitoring with 7-day continuous Holter ECG monito-

događajima uvjetovanog praćenja elektrokardiorama sa 7-dnevnim kontinuiranim praćenjem holterom EKG[28]. Aritmija je zabilježena u 42 ispitanika (42%) na holteru u odnosu na 37 ispitanika (32%) s događajima uvjetovanim praćenjem elektrokardiograma (p=0,56). Osjetljivost događajima uvjetovanog praćenja elektrokardiograma je niža od one praćenjem holterom, uglavnom zbog kraćeg trajanja praćenja, iako je kvalitativna analiza događajima uvjetovanog praćenja zahtjevala manje vremena. U drugoj studiji od 647 bolesnika s implantabilnim uređajima za kontinuirano praćenje, utvrđeno je da je isprekidano praćenje inferiornije u odnosu na kontinuirano praćenje i nije u stanju prepoznati recidiv FA kod velikog broja rizičnih bolesnika[29]. U zanimljivoj studiji u kojoj se istražuje uporaba NT-proBNP radi ocijene nedavnog nastupa FA i sigurnosti kardioverzije, istražitelji su podijelili 86 bolesnika s pretpostavljenim nedavnim nastupom FA u dvije skupine (43 u svakoj skupini) na temelju vrijednosti NTproBNP iznad i ispod granične vrijednosti te su svi ispitanici bili pregledani transezofagealnom ehokardiografijom[30]. Normalne vrijednosti NT-proBNP bile su najjači prediktor prisutnosti tromba, što ukazuje da bi kratkoročni porast NT-proBNP nakon početka FA mogao biti koristan u ocjeni nedavnog nastupa epizode FA, ako je nepoznat, a može se potencijalno koristiti radi utvrđivanja sigurnosti kardioverzije.

Kateterska ablacija fibrilacije atrija

Iako su antiaritmici i kateterska ablacija izbori liječenja dostupni za održavanje sinusnog ritma kod simptomatskih bolesnika s FA, mnogi liječnici i bolesnici ipak inicijalno pribjegavaju konzervativnom pristupu i razmatraju katetersku ablaciju tek nakon što isprobaju jedan ili više antiaritmika te utvrde njihovu neučinkovitost.

Pitanje je li kateterska ablacija FA učinkovita kao početna terapija paroksizmalne FA je ispitana u maloj randomiziranoj studiji u kojoj je 294 bolesnika (bez da su prethodno koristili antiaritmike) randomizirano te je započeto liječenje radiofrekventnom kateterskom ablacijom ili antiaritmicima I.c ili III. skupine[31]. Nisu ustanovljene značajne razlike između skupina u kumulativnom opterećenju FA (90. centila opterećenja aritmije 13% i 19%, odnosno, p=0,10) u prvih 18 mjeseci. Međutim, nakon 24 mjeseca opterećenje FA je bilo značajno niže u skupini s ablacijom u usporedbi s onom na antiaritmicima (9% naspram 18%; p=0,007) te je manje bolesnika u skupini s ablacijom imalo simptomatsku FA (93% naspram 84%; p=0,01). U skupini koja je liječena lijekovima, 54 bolesnika (36%) je naknadno podvrgnuto ablaciji.

U maloj randomiziranoj studiji ablacije FA kod bolesnika s perzistentnom FA, uznapredovalim zatajivanjem srca i teškom sistoličkom disfunkcijom lijeve klijetke (LV), MacDonald i sur. su otkrili su da je kateterska ablacija bila uspješna u uspostavi sinusnog ritma u 50% bolesnika, iako je postupak bio povezan sa značajnom stopom komplikacija (15%)[32]. Kateterska ablacija također nije poboljšala sistoličku funkciju lijeve klijetke (mjereno kardiovaskularnom magnetskom rezonancijom) ili neke druge sekundarne ishode te je dovela u pitanje omjer rizik/korist za ablaciju kod bolesnika s perzistentnom FA i disfunkcijom lijeve klijetke. U Euro Heart Survey (međunarodni multicentrični registar) je kod 1.273 bolesnika podvrgnutih ablaciji FA uspostava sinusnog ritma kateterskom ablacijom bila povezana s nižim rizikom od moždanog udara i smrti u usporedbi s kontrolnom skupinom liječenom farmakološki[33].

ring for detection of AF[28]. An arrhythmia was recorded in 42 subjects (42%) with continuous ECG recordings versus 37 subjects (32%) with triggered monitoring (p=0.56). The sensitivity of triggered ECG monitoring was found to be lower than that of continuous ECG monitoring, mainly due to a shorter effective monitoring duration, although qualitative triggered ECG analysis was less time consuming than continuous ECG analysis. In another larger study of 647 patients with implantable continuous monitoring devices, intermittent rhythm monitoring was found to be significantly inferior to continuous monitoring for the detection of AF and was not able to identify AF recurrence in a great proportion of patients at risk[29]. In an interesting study investigating the use of N-terminal pro B-type natriuretic peptide (NT-proBNP) values to estimate the recency of AF onset and safety of cardioversion, investigators separated 86 patients presenting with presumed recent onset AF into two groups (43 in each group), based on NTproBNP concentrations above and below a cut-off value, and subjected all subjects to transoesophageal echocardiography[30]. NT-proBNP concentrations below the cut-off value were found to be the most powerful predictor of the presence of thrombus, suggesting that a short term increase in NT-proBNP after AF onset might be useful in assessing the recency of onset of the AF episode, if unknown, and might be potentially used to help determine the safety of cardioversion.

Catheter ablation of atrial fibrillation

Although antiarrhythmic drugs (AADs) and catheter ablation are the main treatment options available to maintain sinus rhythm in symptomatic patients with AF, many clinicians and patients still opt for an initial conservative strategy and consider catheter ablation only after one or more AADs have been tried and found to be ineffective.

The question of whether catheter ablation of AF is an effective initial therapy for paroxysmal AF was addressed in a small randomised study in which 294 patients (with no history of AAD use) were randomly assigned to an initial strategy with radiofrequency catheter ablation or therapy with a class 1c or III AAD[31]. The investigators found no significant difference between the ablation and drug therapy groups in the cumulative burden of AF (90th centile of arrhythmia burden 13% and 19%, respectively; p=0.10) in the initial 18 months. However, at 24 months, AF burden was significantly lower in the ablation group compared with the drug therapy group (9% vs 18%; p=0.007) and more patients in the ablation group were free from symptomatic AF (93% vs 84%; p=0.01). In the drug therapy group, 54 patients (36%) subsequently underwent ablation.

In another small randomised study of AF ablation in patients with persistent AF, advanced heart failure and severe left ventricular (LV) systolic dysfunction, MacDonald et al.[32] found that catheter ablation was successful at restoring sinus rhythm in 50% of patients, although the procedure was associated with a significant complication rate of 15%. In addition, catheter ablation did not improve LV ejection fraction (LVEF) (as measured using cardiovascular magnetic resonance) or other secondary outcomes, calling into question the risk/benefit ratio of performing AF ablation in patients with persistent AF and LV dysfunction. An international multicentre registry study of 1,273 patients undergoing AF ablation suggested that maintenance of sinus rhythm through catheter ablation was associated with a lower risk of stroke and death compared with a control group consisting of medically treated patients with AF in the Euro Heart Survey[33].

Nekoliko nedavno objavljenih studija je unaprijedilo naše razumijevanje čimbenika povezanih s uspjehom ili neuspjehom nakon ablacije FA. *Miyazaki i sur.* su dodano naglasili važnost metode izolacije plućnih vena (PV) u bolesnika s paroksizmalnom i perzistentnom FA i povezanosti s dugoročnim kliničkim ishodima kod 83,6% (480 od 574) bolesnika tijekom prosječnog praćenja od 27±14 mjeseci[34]. Kasni recidivi (6-12 mjeseci nakon prvog postupka ablacije FA) su bili povezani u svih bolesnika s ponovnom rekonekcijom PV, dok su vrlo kasni recidivi (>12 mjeseci nakon zahvata) bili nevezani s PV kod njih 85,7%. Prednost izvođenja dodatnih linearnih ablacijskih linija nakon izolacije PV na poboljšanje ishoda ablacije dodatno je ispitano u prospektivnoj, randomiziranoj studiji od 156 bolesnika s paroksizmalnom FA koji su randomizirani na izolaciju PV, izolaciju PV i krovne linije ili izolaciju PV, krovne i stražnje inferiorne linije[35]. Nije registrirana dodatna dobrobit mjerena kliničkim ishodom kod bolesnika s učinjenom izolacijom dodatnih linija, koja je značajno produžila vrijeme trajanja postupka. Veliki broj istraživača utvrdio je da su mnogi čimbenici predvidivi i utječu na negativan ishod nakon ablacije pored već poznatih čimbenika: vrste FA (paroksizmalna ili perzistentna), veličine lijeve pretklijetke te prisustva disfunkcije lijeve klijetke. Od novih čimbenika to su oni povezani sa srcem — atrijski elektromehanički interval mjeren pulsnim doplerom i ehokardiografski nalaz fibroze lijevog atrija mjeren kalibriranim integriranim povratnim raspršenjem (cIB)[37], perikardijalno masno tkivo[38], biomarkeri plazme (npr. B-tipa natriuretskog peptida)[39], disfunkcija bubrega[40] i metabolički sindrom[41]. Prisutnost disociranih potencijala PV, često korišten pokazatelj uspješne izolacije PV, nije predviđao recidiv FA u studiji s uključenih 89 uzastopnih bolesnika prosječno praćenih 21±8 mjeseci[42]. U maloj randomizirano kontroliranoj studiji sa 161 bolesnika utvrđeno je da tromjesečno uzimanje kolhicina (2 x 0,5 mg) smanjuje rani recidiv FA nakon izolacije PV, vjerojatno zbog smanjenja upalnih medijatora, uključujući interleukin 6 i C reaktivni protein[43]. U multicentričnom dvostruko slijepom randomiziranom istraživanju s 336 bolesnika utvrđeno je da kolhicin (2 x 1 mg na početku, potom doza održavanja od 2 x 0,5 mg tijekom mjesec dana) smanjuje učestalost postoperativne FA i skraćuje duljinu hospitalizacije[44]. U interesantnoj randomiziranoj studiji izolacije PV s i bez popratne denervacije renalne arterije kod 27 bolesnika s refraktornom simptomatskom FA i perzistentnom arterijskom hipertenzijom, Pokushalov i sur. su dokazali da je denervacija renalne arterije smanjila sistolički i dijastolički arterijski tlak te recidiv FA tijekom praćenja od godine dana[45].

Drugo polje istraživanja u području ablacije FA bili su čimbenici povezani s povećanim komplikacijama zbog postupka. Analizom podataka iz bolničke baze podataka države Kalifornije, *Shah i sur.* su otkrili da je među 4.156 bolesnika koji su bili podvrgnuti početnom postupku ablacije FA, 5% imalo periproceduralne komplikacije (najčešće vaskularne), a 9% ih je ponovno primljeno u roku od 30 dana[46]. Čimbenici koji su bili povezani s povećanim rizikom od komplikacija i/ili ponovnim prijemom u roku od 30 dana nakon ablacije FA su starija dob, ženski spol, prethodne hospitalizacije radi FA te nedavni bolnički postupci. Prema rezultatima retrospektivne studije s uključenih 565 bolesnika ljestvice CHADS2 i CHA2DS2-VASc predstavljaju korisne prediktore nuspojava nakon ablacije FA[47].

Prvo randomizirano kliničko istraživanje u kojem se uspoređivala učinkovitost i sigurnost kateterske ablacije s kirurškom ablacijom je uključivalo 124 bolesnika s FA refraktornom na lijekove[48]. Istraživači su otkrili da je primarni ishod (bez aritmije dulje od 30 sekundi porijekla iz lijeve pretkli-

Several studies have recently been reported which increase our understanding of the factors associated with success or failure following AF ablation. The importance of pulmonary vein (PV) isolation was further reinforced by *Miyazaki et al.* who reported long term clinic outcomes of 83.6% (480 out of 574 patients) with a mean follow-up of 27±14 months using an extensive PV isolation approach in patients with both paroxysmal and persistent AF[34]. Late recurrences (defined as 6-12 months following the initial AF ablation procedure) was associated with PV reconnection in all patients, while very late recurrences (>12 months after the procedure) were associated with non-PV triggers in 85.7% of cases. The added benefit of performing additional linear ablation lines after PV isolation on improving outcomes following AF ablation has been further questioned in a prospective, randomised study of 156 patients with paroxysmal AF who were randomly assigned to undergo PV isolation only, PV isolation and a roof line, or PV isolation, roof line and a posterior inferior line[35]. The investigators found no improvement in clinical outcome in the patients who received the additional lines while, unsurprisingly, the addition of the linear ablations significantly prolonged procedure times. A number of investigators have found that many factors are predictive of or adversely related to outcome following AF ablation in addition to well established factors, such as type of AF (paroxysmal or persistent), left atrial size, and presence of LV dysfunction. These novel factors include cardiac related factors, such as atrial electromechanical interval on pulse wave Doppler imaging[36] and left atrial fibrosis as assessed by measuring echo-cardiograph derived calibrated integrated backscatter[37], pericardial fat[38], plasma biomarkers (such as plasma B-type natriuretic peptide values[39], renal dysfunction[40], and the metabolic syndrome[41]. Interestingly, the presence of dissociated PV potentials, often used as a marker of successful PV isolation, was not found to predict AF recurrence in a study of 89 consecutive patients over a mean follow-up of 21±8 months[42]. In a small randomised controlled study of 161 patients, a 3 month course of colchicine (0.5 mg twice daily) was found to decrease early AF recurrence after PV isolation, probably due to a reduction in inflammatory mediators, including interleukin 6 (IL-6) and C reactive protein (CRP)[43]. Colchicine (1.0 mg twice daily initially followed by a maintenance dose of 0.5 mg twice daily for 1 month) was also found to reduce the incidence of postoperative AF and decrease in-hospital stay in a multicentre, double blind, randomised trial of 336 patients[44]. In an interesting small randomised study of PV isolation with and without concomitant renal artery denervation in 27 patients with refractory symptomatic AF and resistant hypertension, Pokushalov et al showed that renal artery denervation reduced systolic and diastolic blood pressure and reduced the recurrence of AF during 1 year follow-up[45].

Another area of research in the field of AF ablation has been on the factors associated with increased complications from the procedure. Using data from the California State Inpatient Database, *Shah et al.* found that among 4,156 patients who underwent an initial AF ablation procedure, 5% had periprocedural complications (most commonly vascular) and 9% were readmitted within 30 days[46]. Factors associated with a higher risk of complications and/or 30-day readmission following an AF ablation were older age, female sex, prior AF hospitalisations, and recent hospital procedure experience. In another retrospective study of 565 patients, both the CHADS2 and CHA2DS2-VASc scores were found to be useful predictors of adverse events following AF ablation[47].

The first randomised clinical trial comparing the efficacy and safety of catheter ablation of AF with surgical ablation involved 124 patients with drug refractory AF[48]. The investigators found that the primary end point (freedom from left at-

jetke u osoba bez antiaritmika nakon 12 mjeseci) bio 36,5% za skupinu s kateterskom ablacijom i 65,6% za skupinu koja se podvrgava operaciji (p=0,0022). U skupini bolesnika podvrgnuti operaciji registrirano je znatno više nuspojava (uglavnom zbog komplikacija tijekom postupka operacije) u odnosu na skupinu s kateterskom ablacijom. *Pison i sur.* su kod 26 bolesnika s FA objavili relativno visoke stope uspjeha u prvoj godini (93% za paroksizmalnu i 90% za perzistentnu FA) primjenom kombiniranog transvenoznog endokardijalnog i transtorakalnog epikardijalnog pristupa za prvi postupak ablacije FA[49].

Strategije smanjenja tromboembolije

U posljednjih nekoliko godina je u porastu primjena novih oralnih antikoagulansa u bolesnika s FA s ciljem smanjenja rizika od moždanog udara i sistemske tromboembolije te se povećava njihova prihvaćenost nakon objavljivanja brojnih značajnih multicentričnih randomiziranih kliničkih studija u kojima se uspoređuje njihova učinkovitost s uobičajenim antagonistima vitamina K[50-53]. Meta-analiza 12 studija s ukupno uključenih 54.875 ispitanika je pokazala značajno smanjenje intrakranijskog krvarenja s novim antikoagulansima u usporedbi s antagonistima vitamina K, kao i trend smanjenja velikih krvarenja[54]. Novi oralni antikoagulansi mogu imati određenu ulogu kod bolesnika podvrgnutih elektrokardioverziji. Podstudija istraživanja RE-LY (Randomised Evaluation of Long-Term AnticoagulationTherapy) u kojoj su bolesnici s FA bili podvrgnuti kardioverziji je pokazala da je dabigatran (u dozama od 2 x 110 ili 2 x 150 mg) razumna alternativa varfarinu, s niskim zastupljenošću moždanog udara i velikih krvarenja u roku od 30 dana nakon kardioverzije[55].

Novi oralni antikoagulansi također mogu imati određenu ulogu u periproceduralnoj antikoagulaciji bolesnika podvrgnutih radiofrekventnoj ablaciji FA. Nekoliko studija dokazalo je da je dabigatran periproceduralno u bolesnika podvrgnutih ablaciji FA jednako siguran kao i varfarin[56-58], iako je jedna studija pokazala povećan rizik od krvarenja i tromboembolijskih komplikacija[59]. Da bi se definitivno razjasnilo pitanje mogu li se novi oralni antikoagulansi koristiti umjesto varfarina za periproceduralnu antikoagulaciju bolesnika podvrgnutih ablaciji FA potrebno je prospektivno randomizirano kontrolirano istraživanje. Ekonomska evaluacija novih oralnih antikoagulansa ukazuju na to da mogu biti isplativi kao prva linija liječenja za prevenciju moždanog udara i sistemske embolije[60], osobito u bolesnika s visokim rizikom od krvarenja ili moždanog udara, osim u slučaju da je kontrola INR s varfarinom bila izvrsna[61].

Druga opcija za smanjenje učestalosti tromboembolijskih događaja u bolesnika s FA koja sve više postaje značajnom je uporaba mehaničkih okluzijskih uređaja za zatvaranje aurikule lijevog atrija (LAA). U analizi 14 studija, implantacija okluzijskih uređaja za zatvaranje LAA u bolesnika s FA bila je uspješna u 93% slučajeva, s periproceduralnom smrtnošću i učestalosti moždanog udara od 1,1% i 0,6%; ukupna učestalost moždanog udara među svim studijama je bila 1,4% godišnje[62]. Podstudija studije PROTECT AF (Percutaneous Closure of the LAA versus Warfarin Therapy for Prevention of Stroke in Patients with AF) objavila je da je 32% bolesnika s ugrađenim uređajima na transezofagijskoj ehokardiografiji imalo određeni stupanj protoka oko uređaja u razdoblju od 12 mjeseci, iako se ne čini da je to povezano s povećanim rizikom od tromboembolije u odnosu na one bez protoka nakon ugradnje uređaja koji su prekinuli uzimanje varfarina[63]. Analiza 34 studije pažnju je usmjerila na utvrrial arrhythmia >30 s without AADs after 12 months) was 36.5% for the catheter ablation group and 65.6% for the surgical group (p=0.0022), but patients in the surgical group experienced significantly greater adverse effects (driven mainly by procedural complications) compared to the catheter ablation group. *Pison et al* reported relatively high 1 year success rates (93% for paroxysmal AF and 90% for persistent AF) with a combined transvenous endo-cardial and thorascopic epicardial approach for a single AF ablation procedure in a small cohort of 26 patients with AF[49].

Strategies to decrease thromboembolism

The use of novel oral anticoagulants to decrease the risk of stroke and systemic thromboembolism in patients with AF has gained increasing use and acceptance over the past several years following the publication of a number of landmark multicentre, randomised clinical trials comparing their efficacy with conventional vitamin K antagonists[50-53]. A meta-analysis of 12 studies totalling 54,875 patients showed a significant reduction of intracranial haemorrhage with these novel anticoagulants compared with vitamin K antagonists, and a trend toward reduced major bleeding[54]. These novel oral anticoagulants may also have a role in patients undergoing DC cardioversion. A sub-study of patients with AF who underwent cardioversion in the RE-LY (Randomised Evaluation of Long-Term Anticoagulation Therapy) trial showed that dabigatran (at two doses of 110 and 150 mg twice daily) is a reasonable alternative to warfarin, with low frequencies of stroke and major bleeding within 30 days of cardioversion[55].

These novel oral anticoagulants may also have a role to play in the periprocedural anticoagulation of patients undergoing radiofrequency ablation for AF. Several registry and observational studies have suggested that dabigatran is as safe as periprocedural warfarin in patients undergoing AF ablation[56-58], although one study suggested an increased risk of bleeding and thromboembolic complications with dabigatran compared with warfarin[59]. A prospective randomised controlled trial is required to definitively address the issue as to whether these novel oral anticoagulants can be used in place of warfarin for periprocedural anticoagulation in patients undergoing AF ablation. Economic evaluation of these novel oral anticoagulants suggest that they may be cost effective as a first line treatment for the prevention of stroke and systemic embolism[60], especially in patients at high risk of haemorrhage or stroke, unless international normalised ratio (INR) control with warfarin is already excellent[61].

Another strategy to decrease thromboembolic events in patients with AF that is gaining favour involves the use of mechanical left atrial appendage (LAA) occlusion devices. In a systematic review of 14 studies, implantation of LAA occlusion devices in patients with AF was successful in 93% of cases, with periprocedural mortality and stroke rates of 1.1% and 0.6%, respectively; the overall incidence of stroke among all studies was 1.4% per annum[62]. A substudy of the PROTECT AF (Percutaneous Closure of the LAA versus Warfarin Therapy for Prevention of Stroke in Patients with AF) study reported that 32% of implanted patients had some degree of peridevice flow at 12 months on transoesophageal echocardiography, although this did not appear to be associated with an increased risk of thromboembolism compared to patients with no peridevice flow who discontinued warfarin[63]. A systematic review aimed at determining which subgroups of patients would benefit most from LAA closure devices looked at the location of atrial thrombi in patients with

đivanje koje podskupine bolesnika bi imale najviše koristi od uređaja za zatvaranje LAA analizirajući lokalizaciju atrijskih tromba kod bolesnika s FA[64]. Zaključili su da bolesnici s nevalvularnom FA mogu imati veću dobrobit od zatvaranja LAA; 56% bolesnika s valvularnom FA su imali trombe u atriju smještene izvan LAA, 22% u mješovitim kohortama i kod 11% bolesnika s nevalvularnom FA.

RESINKRONIZACIJSKA TERAPIJA I ELEKTROSTIMULACIJA

Resinkronizacijska terapija

U nedavnom istraživanju iz područja resinkronizacijske terapije (CRT) proučavali su se dugoročni učinci CRT elektrostimulacije na funkciju lijeve klijetke (LV) i desne klijetke (DV) i koje podskupine bolesnika mogu imati najveću dobrobit od liječenja primjenom CRT. Čini se da je povoljni odgovor DV na CRT povezan s većom učestalosti preživljavanja kod bolesnika s CRT uređajima; a i utvrdilo se u studiji od 848 bolesnika koji su primili CRT da je funkcija DV neovisan prediktor dugoročnog ishoda[65]. Nakon važne MADIT-CRT studije (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronisation Therapy) koja je pokazala da je CRT u kombinaciji s implantabilnim kardioverter-defibrilatorom (ICD, CRT-D) smanjio rizik od zatajivanja srca kod relativno asimptomatskih bolesnika s niskom sistoličkom funkcijom i širokim QRS kompleksom[66], veliki broj naknadnih analiza je donio dodatne zanimljive informacije. To uključuje podatke o utjecaju CRT na smanjenje broja epizoda srčanog zatajivanja[67] i atrijskih aritmija[68], utvrđivanje dodatnih čimbenika koji su povezani s poboljšanim odgovorom na CRT[69,70] i s izvrsnim odgovorom (definiranog gornjim kvartilom promjene sistoličke funkcije LV)[71], čimbenike povezane s najboljim poboljšanjem kvalitete života[72], kao i informacije o optimalnom pozicioniranju elektrode u LV[73,74].

U prospektivnoj, randomiziranoj kontroliranoj studiji *Diab i sur.*[75] su utvrdili da bolesnici s prisustvom ehokardiografski utvrđene disinkronije klijetki imaju najbolji terapijski odgovor na CRT, iako su i bolesnici bez disinkronije s ugrađenim CRT također imali veću korist u odnosu na one bez ugradnje. Autori su zaključili da se posljednje spomenutoj skupini bolesnika CRT također ne bi trebao uskratiti. Čini se da CRT dovodi do određenog poboljšanja kod bolesnika sa zatajivanjem srca i normalnim trajanjem QRS kompleksa, pri čemu bolesnici navode poboljšanje simptoma, bolju toleranciju napora i kvalitetu života, iako nije bilo razlike u ukupnoj ili kardiovaskularnoj smrtnosti između skupina s CRT i onih s optimalnom medikamentoznom terapijom[76]. Među bolesnicima sa zatajivanjem srca i produljenim trajanjem QRS kompleksa koji su dobili CRT uređaj, veću su korist (manji rizik od ventrikulskih aritmija i smrti te poboljšane ehokardiografske varijable) imali bolesnici s morfologijom bloka lijeve grane u usporedbi s onima koji nisu imali takav oblik QRS kompleksa (blok desne grane ili poremećaje intraventrikularnog provođenja)[77].

U prospektivnoj randomiziranoj multicentričnoj studiji provedenoj sa 186 bolesnika ispitivalo se da li je u bolesnika s permanentnom FA i ablacijom atrioventrikularnog čvora (AV) terapija primjenom CRT superiorna u odnosu na konvencionalnu elektrostimulaciju DV u smanjenju epizoda zatajivanja srca[78]. Tijekom prosječnog praćenja od 20 mjeseci (IQR 11 do 24 mjeseci) u skupini sa CRT manje je bolesnika (11%) razvilo primarni ishod (smrt, hospitalizacija ili pogoršanje zatajivanja srca) u usporedbi sa skupinom na elek-

AF in a total of 34 studies[64]. The investigators concluded that patients with non-valvular AF may derive greater benefit from LAA closure devices — 56% of patients with valvular AF had atrial thrombi located outside the LAA, 22% in mixed cohorts and 11% in non-valvular AF patients.

CARDIAC RESYNCHRONISATION THERAPY AND PACING

Cardiac resynchronisation therapy

Recent research in the area of cardiac resynchronisation therapy (CRT) has looked at the long term effects of CRT pacing on LV and right ventricular (RV) function and further into which subgroups of patients may derive greatest benefit from CRT pacing. A favourable RV functional response to CRT appears to be associated with improved survival in patients with CRT devices, and RV function was found to be an independent predictor of long term outcome after CRT insertion in a study of 848 CRT recipients[65]. Following the landmark MADIT-CRT (Multi-center Automatic Defibrillator Implantation Trial-Cardiac Resynchronisation Therapy) study, which demonstrated that CRT combined with implantable cardioverter defibrillator (ICD, CRT-D) decreased the risk of heart failure events in relatively asymptomatic patients with a low ejection fraction and wide QRS complexes[66], a number of subsequent analyses have provided further interesting information. This includes data on the benefits of CRT in reducing the risk of recurring heart failure events[67] and atrial arrhythmias[68], identification of additional factors that are associated with improved response to CRT[69,70] and with a super-response (defined by patients in the top quartile of LVEF change)[71], factors associated with greatest improvement in quality of life[72], and information on optimal lead positioning of the LV lead[73,74].

In a prospective, randomised controlled study to address whether ventricular dyssynchrony on echocardiography predicted response to CRT, *Diab et al*[75] found that the presence of echocardiographic dyssynchrony identified patients who derived the most improvement from CRT, although patients without dyssynchrony also showed more benefit and less deterioration with CRT than without. The authors concluded that the latter group of patients should not be denied CRT. CRT appeared to produce some benefits in patients with heart failure and a normal QRS duration, with patients experiencing an improvement in symptoms, exercise capacity and quality of life, although there was no difference in total or cardiovascular mortality in patients who received CRT compared with those receiving optimal pharmacological management[76]. Among patients with heart failure and prolonged QRS duration who received a CRT device, those with a left bundle branch block (LBBB) morphology derived greater benefit (lower risk of ventricular arrhythmias and death and improved echocardiographic parameters) compared with patients who had a non-LBBB QRS pattern (right bundle branch block (RBBB) or intraventricular conduction disturbances)[77].

The issue of whether CRT in patients undergoing atrioventricular (AV) junction ablation for permanent AF was superior to conventional RV pacing in reducing heart failure events was addressed in a prospective, randomised, multicentre study involving 186 patients[78]. Over a median follow-up of 20 months (IQR 11-24 months) fewer patients in the CRT group (11%) experienced primary end point events (death from heart failure, hospitalisation due to heart failure or worsening

trostimulaciji DV (26%; CRT naspram DV skupine: SHR 0.37, 95% CI 0.18-0.73; p=0,005). Ukupna smrtnost je bila slična u obje skupine. U analizi praćenja koja se bavila prediktorima kliničkog poboljšanja nakon strategije '"ablirati i elektrostimulirati", više je bolesnika u CRT skupini reagiralo na liječenje (83% naspram 63% u DV skupini)[79]. Utvrđeno je su CRT mod i eho-optimizirani CRT uređaj jedini nezavisni protektivni čimbenici protiv lošeg odgovora (HR=0.24, 95% CI 0.10-0.58, p=0.001 i HR=0.22, 95% CI 0.07-0.77, p=0,018). U istraživanju PACE (Pacing to Avoid Cardiac Enlargement), elektrostimulacija DV je u bolesnika s bradikardijom i očuvanim sistoličkom funkcijom LV bila povezana s nepovoljnim remodeliranjem LV i pogoršanjem sistoličke funkcije u drugoj godini, što se sprječavalo biventrikularnom elektrostimulacijom[80].

Srčani blokovi i elektrostimulatori

U retrospektivnoj kohortnoj studiji s 299 bolesnika ispitivalo se preživljavanje bolesnika starije životne dobi (prosječna dob 75±9 godina) s AV blokom II. stupnja tip Mobitz I.[81]. Tijekom razdoblja praćenja srčani implantabilni elektronički uređaji (CIED) bili ugrađeni u 141 bolesnika (47%), od čega je bilo 17 ICD. Bolesnici s CIED su imali veći kardiološkii komorbiditet u odnosu na one bez, iako je ugradnja CIED bila povezana s 46% smanjenjem smrtnosti (HR 0.54, 95% CI 0.35-0.82; p=0,004). Van Geldrop i sur.[82] su u opservacijskoj studiji o utjecaju mjesta ventrikulske elektrostimulacije na funkciju LV u djece s AV blokom, otkrili da je frakcija skraćenja LV veća kod elektrostimulacije LV nego DV[82].

Daljnja istraživanja na temu da li je elektrostimulacija srca korisna u bolesnika s neurološki posredovanom sinkopom upućuju na to da dvokomorna elektrostimulacija može biti korisna u bolesnika s teškim asistolijom. U randomiziranom multicentričnom istraživanju ISSUE-3 (Third International Study on Syncope of Uncertain Aetiology) bolesnici sa sinkopom zbog asistolije dokumentirane implantabilnim loop rekorderom nasumično su raspodjeljeni u skupine s dvokomornim elektrostimulatorom reprogramiranim na program za nagli pad frekvencije ili samo na "osjećanje" (engl. sensing)[83]. Oni s dvokomornom elektrostimulacijom su imali manji broj epizoda sinkopa tijekom razdoblja praćenja (32% apsolutno i 57% relativno smanjenje sinkopa). Pokazalo se da pozitivan test s intravenozno primjenjenim adenozin 50-trifosfatom korelira s podskupinom bolesnika s neurološki posredovanom sinkopom[84]. Randomizirano multicentrično istraživanje potencijalne koristi testa adenozin 50-trifosfatom u starijih bolesnika (prosječna dob 75,9±7,7 godina) sa sinkopom nepoznatog podrijetla pokazalo je da je aktivna dvokomorna elektrostimulacija kod onih s pozitivnim testom smanjila rizik od recidiva sinkope za 75% (95% CI 44%-88%)[85]. Podaci na malom uzorku od 18 bolesnika s recidivirajućim sinkopama o dugoročnom ishodu (praćenje do 14 godina) glede različitih tipova AV blokova, pri čemu niti jedan bolesnik nije imao stalni ili paroksizmalni AV blok koji se ne može objasniti trenutno poznatim mehanizmima, ukazuju na to da ovi bolesnici mogu imati koristi od elektrostimulacije srca[86]. Na temelju podataka danskog nacionalnog registra koji je uključio 37.017 bolesnika sa sinkopom i 185.085 kontrola usklađenih prema dobi i spolu, proučavani su ishodi kod zdravih osoba primljenih zbog prve epizode sinkope[87]. Bolesnici koji su bili primljeni zbog sinkope su imali značajno veću ukupnu smrtnost, učestalije kardiovaskularne hospitalizacije, recidive sinkopa i moždane udare te su im kasnije češće ugrađivani elektrostimulatori ili ICD.

heart failure) compared with patients in the RV group (26%; CRT vs RV group: sub-hazard ratio (SHR) 0.37, 95% CI 0.18 to 0.73; p=0.005). Total mortality was similar in both groups. In a follow-up analysis looking at the predictors of clinical improvement after the 'ablate and pace' strategy, more patients in the CRT group responded to treatment (83% vs 63% in the RV group)[79]. CRT mode and echo-optimised CRT were found to be the only independent protective factors against nonresponse (HR=0.24, 95% CI 0.10 to 0.58, p=0.001 and HR=0.22, 95% CI 0.07 to 0.77, p=0.018, respectively). In the PACE (Pacing to Avoid Cardiac Enlargement) trial, RV pacing in patients with bradycardia and preserved LVEF was associated with adverse LV remodelling and deterioration of systolic function at the second year, which was prevented by biventricular pacing[80].

Heart block and pacemakers

The long term survival of older patients (average age 75±9 years) with Mobitz I second degree AV block was examined in a retrospective cohort study of 299 patients[81]. The investigators found that 141 patients (47%) had a cardiac implantable electronic device (CIED) inserted during the follow-up period, of which 17 were ICDs. Patients with a CIED had greater cardiac comorbidity than those without a CIED, although CIED implantation was associated with a 46% reduction in mortality (HR 0.54, 95% CI 0.35 to 0.82; p=0.004). In another observational study of the impact of the ventricular pacing site on LV function in children with AV block, van Geldrop et al. found that LV fractional shortening was significantly higher with LV pacing than with RV pacing[82].

Further research on the topic of whether cardiac pacing is beneficial in patients with neurally mediated syncope suggests that dual chamber pacing may be useful in patients with severe asystolic forms. In the randomised multicentre ISSUE-3 trial (Third International Study on Syncope of Uncertain Aetiology) patients with syncope due to documented asystole on an implantable loop recorder were randomly assigned to dual chamber pacing with rate drop response or to sensing only[83]. Those assigned to dual chamber pacing had fewer syncopal episodes during follow-up (32% absolute and 57% relative reduction in syncope). A positive test with intravenous adenosine 50-triphosphate has been shown to correlate with a subset of patients with neurally mediated syncope[84]. A randomised, multicentre trial of the potential benefit of the ATP test in elderly patients (mean age 75.9±7.7 years) with syncope of unknown origin reported that active dual chamber pacing in those with a positive ATP test reduced syncope recurrence risk by 75% (95% CI 44% to 88%)[85]. Long term outcome data on a distinct form of AV block, paroxysmal AV block, which cannot be explained by currently known mechanisms, suggest that these patients have a long history of recurrent syncope and may benefit from cardiac pacing, although in a small series of 18 patients (followed up for up to 14 years), no patient had permanent AV block[86]. The prognosis among healthy individuals admitted with their first episode of syncope was studied in a Danish nationwide registry involving 37,017 patients with syncope and 185,085 age and sex matched controls[87]. Patients who were admitted with syncope had significantly increased all cause mortality, cardiovascular hospitalisation, recurrent syncope and stroke event rates and were more likely to have a pacemaker or ICD inserted later.

Infekcija povezana sa srčanim implantabilnim elektroničkim uređajima

Infekcije povezana sa CIED su prepoznate kao značajan uzrok morbiditeta, mortaliteta i povećanih zdravstvenih troškova. Prospektivno kohortno istraživanje International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCE) uključilo je 61 centar u 28 zemalja, a analizirane su kliničke značajke, ishod i utjecaj infekcija povezanih sa CIED i endokarditisa[88]. Bolničke i jednogodišnje stope smrtnosti su bile 14,7% (95% CI 9.8%-20.8%) i 23,2% (95% CI 17,2%-30,1%). Učestalost istodobne infekcije zaliska je bila visoka (kod 66 bolesnika, 37.3%, 95% CI 30.2%-44.9%), a rano uklanjanje uređaja je bilo povezano s poboljšanjem preživljavanja u razdoblju od jedne godine. U pokušaju da se ocjene dugoročni ishodi i prediktori smrtnosti kod bolesnika liječenih prema važećim preporukama za infekciju povezanu s CIED, *Deharo i sur.*[89] su proveli kohortnu studiju na dvije podudarne skupine sa 197 slučajeva infekcije povezane s CIED. Dugoročna učestalost smrtnosti su bile slične među skupinama (14,3% naspram 11,0% u razdoblju od jedne godine i 35,4% naspram 27,0% u petogodišnjem razdoblju; obje p=NS). Neovisni prediktori dugoročne smrtnosti su starija dob, CRT, trombocitopenija i bubrežno zatajenje. U drugoj studiji u kojoj se istraživalo da li je vrijeme novog postupka ugradnje CIED utjecalo na kliničku sliku i ishod endokarditisa povezanog s implantiranom elektrodom, istraživači su otkrili da je rani endokarditis povezan s elektrodom popraćen znacima i simptomima lokalne infekcije džepa, dok je udaljeni izvor bakteremije bio prisutan u 38% kasnih endokarditisa povezanih s elektrodom, ali samo 8% ranih[90]. Bolnička smrtnosti je bila niska (rana 7%; kasna 6%).

Cardiac implantable electronic device related infection

CIED infection is recognised as a significant cause of morbidity, mortality, and increased healthcare costs. The clinical characteristics, outcome, and health care implications of CIED related infections and endocarditis was analysed in a prospective cohort study using data from the International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCE) involving 61 centres in 28 countries[88]. CIED infection was diagnosed in 177 out of 2760 patients (6.4%). In-hospital and 1 year mortality rates were 14.7% (95% CI 9.8% to 20.8%) and 23.2% (95% CI 17.2% to 30.1%), respectively. The rate of concomitant valve infection was high (found in 66 patients, 37.3%, 95% CI 30.2% to 44.9%) and early device removal was associated with improved survival at 1 year. In an attempt to assess the long term outcomes and predictors of mortality in patients treated according to current recommendations for CIED infection, *Deharo et al.*[89] conducted a two-group matched cohort study of 197 cases of CIED infection. Long term mortality rates were similar between cases and matched controls (14.3% vs 11.0% at 1 year and 35.4% vs 27.0% at 5 years, respectively; both p=NS). Independent predictors of long term mortality were older age, CRT, thrombocytopenia, and renal insufficiency. In another study examining whether the timing of the most recent CIED procedure influenced the clinical presentation and outcome of lead associated endocarditis (LAE), investigators found that early LAE presented with signs and symptoms of local pocket infection, whereas a remote source of bacteraemia was present in 38% of late LAE but only 8% of early LAE[90]. In-hospital mortality was low (early 7%; late 6%).

VENTRIKULSKE ARITMIJE I IZNENADNA SRČANA SMRT

Epidemiologija iznenadne srčane smrti

Iznenadna smrt je čest i dobro poznat rizik u bolesnika nakon infarkta miokarda. U studiji u kojoj su se analizirali podaci 1.067 bolesnika iz istraživanja VALIANT (Valsartan in Acute Myocardial Infarction Trial) koji su doživjeli iznenadnu smrt, istraživači su otkrili da se visok udio smrtnih slučajeva dogodio kod kuće, iako su se bolnički ishodi dešavali ranije[91]. Bolesnici koji su zaspali najverojatnije su imali ovakve neosvjedočene događaje. Iako iznenadna srčana smrt (SCD) i koronarna bolest srca (KBS) imaju mnogo zajedničkih čimbenika rizika, neki klinički i elektrokardiografski parametri mogu biti korisni u izdvajanju ova dva stanja. Primjerice, iz podataka studije ARIC (Atherosclerosis Risk in Communitiesi) i Cardiovascular Health Study s 18.497 sudionika, Soliman i sur.[92] su utvrdili da su, nakon prilagodbe uobičajenih čimbenika rizika za KBS, hipertenzija, povišena srčana frekvencija, produljenje QTc intervala i abnormalno invertirani T valovi značajniji prediktori visokog rizika SCD. U usporedbi s tim, povišena visina ST-segmenta (mjereno na točci J i 60 ms nakon J točke) jači prediktor visokog rizika za KBS.

Više istraživanja o SCD je također bilo provedeno u drugim podskupinama. U francuskom prospektivnom nacionalnom istraživanju SCD u sportu provedenom od 2005. do 2010. godine, koje je uključivalo ispitanike od 10 do 75 godine života, istraživači su utvrdili da je ukupno opterećenje od iznenadne smrti u godinu dana iznosi 4.6 na milijun osoba, sa

VENTRICULAR ARRHYTHMIAS AND SUDDEN CARDIAC DEATH

Epidemiology of sudden cardiac death

Sudden death is a frequent and well recognised risk in patients following myocardial infarction. In a study analysing data from 1,067 patients from VALIANT (Valsartan in Acute Myocardial Infarction Trial) who had sudden death, investigators found that a high proportion of the deaths occurred at home, although in-hospital events were more common early on[91]. Patients who were asleep were more likely to have unwitnessed events. Although sudden cardiac death (SCD) and coronary artery disease (CAD) have many risk factors in common, certain clinical and electrocardiographic parameters may be useful to help separate out the two risks. For example, in a study of 18,497 participants from the ARIC (Atherosclerosis Risk in Communities) study and the Cardiovascular Health Study, Soliman et al.[92] found that after adjusting for common CAD risk factors, hypertension, increased heart rate, QTc prolongation, and abnormally inverted T waves were found to be stronger predictors of high SCD risk. In comparison, elevated ST segment height (measured at both the J point and 60 ms after the J point) was found to be more predictive of high incident CAD risk.

More research has also been performed on SCD in other subgroups. In a prospective, national survey of sports related sudden death performed in France from 2005 to 2010, involving subjects 10-75 years of age, investigators found that the overall burden of sudden death was 4.6 per million population per year, with 6% of cases occurring in young

6% slučajeva kod mladih profesionalnih sportaša. Više od 90% slučajeva se javlja u rekreativnom sportu[93]. Početna kardiopulmonalna reanimacija (CPR) od strane prolaznika i defibrilacija bili su najjači neovisni prediktori za preživljavanje do otpusta iz bolnice, iako je CPR od prolaznika pokrenut tek u jednoj trećini slučajeva.

U retrospektivnoj studiji u kojoj su provedene obdukcije na 902 mlade osobe (prosječne dobi 38±11 godina) koji su preboljeli netraumatsku iznenadnu smrt, uzrok iznenadne smrti se pripisao srčanoj patologiji kod 715 (79,3%) i neobjašnjivom uzroku kod 187 osoba (20,7%)[94]. U drugoj nacionalnoj studiji o učestalosti SCD kod osoba u dobi od 1 do 35 godina, 7% svih smrtnih ishoda se pripisivalo SCD[95]. Pojava SCD kod mladih procijenjena na 2,8% na 100.000 osoba-godina i viša je nego što se je ranije navodilo. Čimbenici rizika za SCD kod žena u postmenopauzi mogu uključivati više novih varijabli, kao što su viši puls, viši omjer struk-bokovi, povišen broj leukocita i etnička pripadnost (afrički Amerikanci imaju veći rizik), kao i tradicionalne čimbenike rizika[96].

Provedeno je intenzivnije istraživanje u različitim okruženjima o sindromu rane repolarizacije budući da su značajne studije pokazale vezu s idiopatskom ventrikularnom fibrilacijom i iznenadnom smrti[97,98]. One su uključivale studije o sindromu rane repolarizacije kod preživjelih sa srčanim zastojem i očuvanom sistoličkom funkcijom[99], u obiteljima sa sindromom iznenadne aritmogene smrti[100] i drugim obiteljima s obrascem rane repolarizacije u EKG[101] te u azijskim populacijama[102]. Međutim, još uvijek postoje kontroverze o točnom kliničkom značaju i posljedicama tih EKG nalaza[103,104].

Nasljedna srčana stanja i činjenica kako određeni genotipovi mogu dovesti do kliničkih manifestacija bolesti i dalje privlače veliki interes te utječu na zbrinjavanje i shvaćanje rizika SCD[105-108]. Rezultati studije DARE (Drug-induced Arrhythmia Risk Evaluation), u kojoj je ispitano 167 pojedinačnih polimorfizma nukleotida koji obuhvaćaju gen NOS1AP, kod 58 ispitanika bijele rase koji su imali QT prolongaciju induciranu lijekovima i 87 kontrolnih ispitanika bijele rase, pokazali su da su uobičajene varijacije gena NAS1AP bile povezane sa značajnim povećanjem učestalosti sindroma dugog QT induciranog lijekovima[109]. To će imati kliničke posljedice za buduće farmakogenomsko testiranje kod bolesnika koji imaju rizik od lijekovima induciranog sindroma produljenja QT intervala. U drugoj studiji u kojoj se ocjenjuje da li su nekardiovaskularni hERG (human Ether a go-go-Related Gene) blokatori kanala povezani s povećanim rizikom od SCD u općoj populaciji, istražitelji su usporedili 1.424 slučajeva SCD sa 14.443 slučaja u kontrolnim skupinama[110]. Utvrđeno je da je korištenje hERG blokatora kanala bilo povezano s povećanim rizikom od SCD; lijekovi s visokom sposobnošću inhibiranja hERG kanala su imali viši rizik za SCD nego oni za niskom sposobnošću inhibiranja.

Impantibilni kardioverter defibrilatori

U retrospektivnoj studiji s 900 bolesnika ocjenjivani su klinički parametri povezani uz smrt bolesnika s ishemijskom bolesti srca prije terapije ICD s onima kojima je implantiran ICD zbog primarne prevencije[111]. Istraživači su utvrdili da su značajni nezavisni prediktori smrti bolesnika bez odgovarajuće terapije s ICD; funkcijska klasa NYHA ≥III, poodmakla dob, šećerna bolest, istisna frakcija LV ≤25% i prethodno pušenje, uz napomenu da ove informacije mogu olakšati procjenu rizika kod bolesnika. Drugi algoritam za predviđanje akutnih proceduralnih komplikacija ili smrti nakon ugradnje ICD koristi 10 dostupnih varijabli dobivenih nakon

competitive athletes and more than 90% of cases occurring in the context of recreational sports[93]. Bystander cardiopulmonary resuscitation (CPR) and initial use of cardiac defibrillation were the strongest independent predictors for survival to hospital discharge, although bystander CPR was only initiated in one third of cases.

In a retrospective autopsy study of 902 young adults (mean age 38±11 years) who had suffered non-traumatic sudden death, the cause of sudden death was attributed to a cardiac condition in 715 (79.3%) and unexplained in 187 (20.7%)[94]. In another nationwide study on the incidence of SCD in persons aged 1-35 years, 7% of all deaths were attributed to SCD[95]. The incidence of SCD in the young, estimated to be 2.8% per 100,000 person-years, was higher than previously reported. Risk factors for SCD in post-menopausal women may include more novel parameters, such as higher pulse, higher waist-to-hip ratio, elevated white blood cell count, and ethnicity (African Americans having a higher risk) as well as traditional risk factors[96].

More intense research has been conducted in a variety of settings on the early repolarisation syndrome (ERS) since landmark studies showed a link with idiopathic ventricular fibrillation and sudden death[97,98]. These include studies on ERS on cardiac arrest survivors with preserved ejection fraction[99], in families with sudden arrhythmic death syndrome[100] and other families with an early repolarisation pattern on the ECG[101], and in Asian populations[102]. However, there is still some controversy over the exact clinical significance of these ECG findings and what the implications are[103,104].

The genetics of inherited cardiac conditions and how specific genotypes can lead to clinical manifestations of disease, affect SCD risk or guide management continues to attract intense interest[105-108]. Results from the DARE (Drug-induced Arrhythmia Risk Evaluation) study, in which 167 single nucleotide polymorphisms spanning the NOS1AP gene, were evaluated in 58 Caucasian patients who had experienced drug induced QT prolongation and 87 Caucasian controls, demonstrated that common variations in the NOS1AP gene were associated with a significant increase in drug induced long QT syndrome[109]. This may have clinical implications for future pharmacogenomics testing in patients at risk of drug induced long QT syndrome and safer prescribing. In another study assessing whether non-cardiovascular hERG (human Ether a go-go-Related Gene) channel blockers are associated with an increased risk of SCD in the general population, investigators compared 1,424 cases of SCD with 14,443 controls[110]. Use of hERG channel blockers was found to be associated with an increased risk of SCD and drugs with a high hERG channel inhibiting capacity had a higher risk of SCD than those with a low hERG channel inhibiting capacity.

Implantable cardioverter defibrillators

The clinical parameters associated with death before appropriate ICD therapy in patients with ischaemic heart disease who had an ICD inserted for primary prevention were assessed in a retrospective cohort study of 900 patients[111]. The investigators found that New York Heart Association (NYHA) functional class ≥III, advanced age, diabetes mellitus, LVEF ≤25%, and a history of smoking were significant independent predictors of death without appropriate ICD therapy, and suggested that this information may facilitate a more patient tailored risk estimation. Another risk score for predicting acute procedural complications or death after ICD

268.701 implantacija te je napravljen kako bi se osigurale korisne informacije liječnicima u selekciji bolesnika i određivanju intenziteta skrbi nakon ugradnje[112]. U studiji MADIT-II[113] kod 11.981 bolesnika je primijenjena procjena rizika usmjerena na predviđanje dugoročne (8 godišnje) koristi ugradnje ICD-a u primarnoj prevenciji. Bolesnici s niskim i srednjim rizikom (0 ili 1-2 čimbenika rizika) imali su više koristi od ugradnje ICD u usporedbi s bolesnicima s visokim rizikom (≥3 čimbenika rizika) koji su imali višestruke komorbiditete i kod kojih nije bilo značajne razlike u osmogodišnjem preživljavanju između onih s implantiranim ICD i onima bez njega.

Izrađen je algoritam za predviđanje smrtnosti kod bolesnika kojima je implantiran ICD u primarnoj prevenciji na korisnicima Medicare od 17.991 bolesnika uz potvrdu na skupini od 27.893 bolesnika[114]. Tijekom prosječnog praćenja od 4 godine, 6.741 (37,5%) bolesnika u kontrolnoj i 8.595 (30,8%) bolesnika u promatranoj skupini je umrlo. Sedam kliničkih relevantnih prediktora smrtnosti je utvrđeno i korišteno za izradu modela kod određivanja onih bolesnika s najvećim rizikom od smrti nakon ugradnje ICD. Odabir bolesnika za implantaciju ICD u primarnoj prevenciji se u budućnosti stoga mora promijeniti te se osobno prilagoditi omjer rizik/koristi za pojedinog bolesnika, a ne se prema preporukama važećih smjernica uglavnom voditi sistoličkom funkcijom LV.

Ostala istraživanja, poput oslikavanja srca magnetskom rezonancom (CMR) radi utvrđivanja i definiranja ožiljka na miokardu mogu biti koristan dodatak u budućem odabiru bolesnika za ugradnju ICD u primarnoj prevenciji. U studiji od 55 bolesnika s ishemijskom kardiomiopatijom kojima je ugrađen ICD u primarnoj prevenciji ispitivana je mogućnost predviđanja ventrikulskih aritmija na temelju karakteristika ožiljka utvrđenog pomoću CMR i primjene gadolinija prije ugradnje uređaja[115]. Utvrđeno je da se sve utvrđene karakteristike ožiljaka oslikavanjem CMR mogu smatrati prediktorima nastanka ventrikulskih aritmije, potvrđujući potencijalnu korist ovih slikovnih modaliteta u stratifikaciji rizika i boljoj selekciji bolesnika za ugradnju ICD. Ovaj rezultat je dodatno podržan prospektivnom studijom od 137 bolesnika evaluiranih CMR prije ugradnje ICD za primarnu prevenciju[116]. Utvrđeno je da je ožiljak miokarda vidljiv primjenom CMR neovisan prediktor negativnih ishoda. Bolesnici sa značajnim ožiljkom (>5% lijeve klijetke) s ejekcijskom frakcijom LV >30% su imali sličan rizik kao i oni s ≤30%, dok je u onih s EF ≤30% minimalni ožiljak ili bez ožiljka bio povezan s manjim rizikom, slično onima s EF >30%.

Dodatna je pažnja usmjerena na uporabu intrakardijalnih ICD varijabli u procjeni rizika. U prospektivnoj multicentričnoj studiji sa 63 bolesnika s implantiranim ICD, utvrđeno je da su varijabilnosti alterirajućeg i ne-alterirajućeg T vala (TWA/V) statistički značajnije prije epizoda ventrikulske tahikardije/ventrikulske fibrilacije nego li tijekom bazičnog ritma[117]. Istraživači su zaključili da kontinuirano mjerenje TWA/V na intrakardijalnom elektrogramu ICD može biti koristan parametar u otkrivanju predstojeće VT/VF te omogućiti da uređaj pokrene terapijsku elektrostimulaciju radi sprječavanja ventrikulskih aritmija. Nasuprot tome, rana analiza prospektivne jednocentrične studije o korištenju ICD u praćenju ishemije u kliničkoj skrbi i zbrinjavanju bolesnika ukazala je na to da ovaj parametar nije bio klinički koristan i zapravo je povećao broj nepredviđenih ambulantnih posjeta kod bolesnika s ovom opcijom na ICD naspram onih bez te opcije[118].

Izvješća o komplikacijama i negativnim aspektima ICD uključuju probleme povezane s Sprint Fidelis ICD elektroda-

implantation using 10 readily available variables from 268 701 ICD implants was developed to provide useful information in guiding physicians on patient selection and determining the intensity of post-implant care required[112]. A risk score aimed at predicting the long term (8 years) benefit of primary prevention ICD implantation was applied to 11,981 patients from the MADIT-II trial[113]. The investigators found that patients with low and intermediate risk (0 or 1-2 risk factors, respectively) benefitted more from ICD implantation, compared with patients with high risk (≥3 risk factors) who had multiple comorbidities, in which there was no significant difference in 8 years survival between ICD and non-ICD recipients.

Another risk score for the prediction of mortality in Medicare beneficiaries receiving ICD implantation for primary prevention was developed from a cohort of 17,991 patients and validated in a cohort of 27,893 patients[114]. Over a median follow-up of 4 years, 6,741 (37.5%) patients in the development cohort and 8595 (30.8%) patients in the validation cohort died. Seven clinically relevant predictors of mortality were identified and used to develop a model for determining those patients at highest risk for death after ICD implantation. Future selection of ICD recipients for primary prevention ICDs may therefore be refined and more personalised to the individual patient's risk/benefit profile with the use of such models, rather than being based predominantly on LVEF, as is recommended by current guidelines.

Other investigations, such as cardiac magnetic resonance (CMR) imaging to identify and characterise myocardial scar, may be a useful addition to future risk stratification of patients for primary prevention ICD implantation. The ability of scar characteristics assessed on CMR to predict ventricular arrhythmias was evaluated in a study of 55 patients with ischaemic cardiomyopathy who received an ICD for primary prevention and in whom CMR with late gadolinium enhancement had been performed before ICD implantation[115]. All CMR derived scar tissue characteristics were found to be predictive for the occurrence of ventricular arrhythmias, supporting the potential use of this imaging modality to help refine risk stratification of patients and improve selection for ICD implantation. This finding was further supported by a prospective study of 137 patients evaluated with CMR before ICD implantation for primary prevention[116]. Myocardial scarring on CMR was found to be an independent predictor of adverse outcomes. Patients with significant scarring (>5% of the left ventricle) with LVEF >30% had a similar risk to those with LVEF ≤30%, while in patients with LVEF ≤30%, minimal or no scarring was associated with low risk, similar to those with LVEF >30%.

The use of intracardiac ICD parameters to assess risk has also received further attention. In a prospective, multicentre study of 63 ICD patients, T wave alternans and non-alternans variability (TWA/V) was found to be significantly greater before ventricular tachycardia/ventricular fibrillation (VT/VF) episodes than during baseline rhythm[117]. The investigators suggested that continuous measurements of TWA/V from the intracardiac ICD electrograms may be a useful parameter to detect impending VT/VF and allow the device to initiate pacing therapies to prevent the ventricular arrhythmias from occurring. In contrast, an early analysis of a prospective, single centre study on the use of ICD based ischaemia monitoring on clinical care and patient management reported that this parameter was not clinically useful and actually increased the number of unscheduled outpa-

ma[119-121] i potencijalnim psihološkim učinkom i pojavom anksioznosti među primateljima ICD[122]. Istraživači su u studiji provedenoj u 117 talijanskih centara na 3.253 bolesnika koji su podvrgnuti *de novo* implantaciji CRT-D uređaja, utvrdili su da su događaji povezani uz uređaje češći u primatelja CRT-D nego kod onih koji su primili samo ICD (jednokomorni ili dvokomorni), iako ti događaji nisu bili povezani s lošijim kliničkim ishodom[123]. U multicentričnoj longitudinalnoj kohortnoj studiji sa 104.049 bolesnika koji su primili jednokomorne ili dvokomorne ICD, ugradnja dvokomornog uređaja je bila češća, ali je bila povezana s povećanim periproceduralnim komplikacijama i bolničkom smrtnošću u usporedbi s jednokomornim ICD[124]. U retrospektivnoj jednocentričnoj kohortnoj studiji kod 334 bolesnika s hipertrofičnom kardiomiopatijom je objavljeno da je skupina bolesnika s ICD imala značajnu kardiovaskularnu smrtnost i bila izložena čestim neprimjerenim šokovima i komplikacijama implantata[125]. Nepovoljni događaji vezani za ICD (neprimjereni šokovi i/ili komplikacije impantanta) su zabilježeni kod 101 bolesnika (30%; 8,6% godišnje), bolesnici s CRT-D imali veću vjerojatnost za razvoj komplikacija vezanih uz implantante u odnosu na one s jednokomornim ICD te su imali višu stopu kardiovaskularne smrtnosti u 5-godišnjem razdoblju.

Strategije za smanjenje komplikacija vezanih uz ICD i neprimjerenih šokova uključuju korištenje posebnih dijagnostičkih ICD algoritama za utvrđivanje potencijalnih ranih problema[126] s elektrodom te promjene u programiranju ICD s produljenom odgodom u terapiji tahiaritmije s ≥200/min ili više, kao što je prikazano u studiji MADIT-RIT (MADIT-Reduction in Inappropriate Therapy)[127]. Sve veće kliničko iskustvo se stječe i u uporabi subkutanog ICD koji ima veliki potencijal u smanjenju nekih vrsta komplikacija povezanih s ICD, iako se prvo treba prevladati početna krivulja učenja[128,129]. Klinički podaci o ugradnji ICD i korištenju pokazuju da bolesnici koje zbrinjavaju operateri s malim brojem zahvata (liječnici koji ugrađuju ≤1 ICD godišnje) imaju veću vjerojatnost od smrtnog ishoda ili srčanih komplikacija u usporedbi s operatorima koji imaju veći volumen[130]. Druga strategija smanjenja komplikacija vezanih s ICD je unaprijediti proces odabira onih bolesnika koji bi doista imali koristi od tih uređaja. U opservacijskoj studiji ishoda kod uzastopnih ispitanika upućenih u regionalnu ambulantu za naslijeđena srčana stanja zbog nekog rođaka koji je imao naglu neočekivanu smrt, utvrđeno je da je broj ugrađenih ICD kao rezultat pregleda specijaliste bio vrlo mali (2%)[131].

Vanbolnički srčani zastoj

Čini se da je preživljavanje vanbolničkog srčanog zastoja poraslo u posljednjih nekoliko godina, vjerojatno kao posljedica bolje vanbolničke skrbi (rano prepoznavanje, učinkovitija kardiopulmonalna reanimacija (CPR), brža reakcija hitne službe) i napredka u bolničkom zbrinjavanju bolesnika nakon zastoja[132-133]. Podaci iz Londonskog registra hitne službe od 2007. do 2012. godine su pokazali poboljšanje u preživljavanju osoba s vanbolničkim srčanim zastojem tijekom razdoblja od pet godina[134]. U opservacijskoj studiji švedskog registra sa 7.187 bolesnika s vanbolničkim srčanim zastojem tijekom razdoblja od 18 godina, utvrđeno je da je CPR od strane prolaznika porasla sa 46% na 73% (95% CI za OR 1,060-10,081 godišnje), rano preživljavanje se povećalo sa 28% na 45% (95% CI 1,044-1,065) te jednomjesečno preživljavanje s 12% na 23% (95% CI 1,058-1,086)[135]. Značajni prediktori ranog i kasnog preživljavanje su bili kratak interval od kolapsa do defibrilacije, CPR od strane prolaznika, ženski spol i mjesto kolapsa. Velika prospektivna kohortna studi-

tient visits in patients with this feature on their ICD compared with patients with ICDs without this capability118.

Reports on the complications and negative aspects of ICDs include problems associated with the Sprint Fidelis ICD leads[119-121] and potential psychological impact and phobic anxiety among ICD recipients[122]. In a study of 3,253 patients from 117 Italian centres who underwent de novo implantation of a CRT-D device, investigators found that device related events were more frequent in patients who received CRT-D devices compared with those who received ICDs only (single or dual chamber), although these events were not associated with a worse clinical outcome[123]. In a multicentre, longitudinal cohort study of 104,049 patients receiving single and dual chamber ICDs, dual chamber device implantation was more common, but was associated with increased periprocedural complications and in-hospital mortality compared with single chamber ICDs[124]. A retrospective, single centre cohort study of 334 hypertrophic cardiomyopathy patients with ICDs reported that this group of patients had significant cardiovascular mortality and were exposed to frequent inappropriate shocks and implant complications[125]. Adverse ICD related events (inappropriate shocks and/or implant complications) were seen in 101 patients (30%; 8.6% per year), and patients with CRT-D were more likely to develop implant complications than those with single chamber ICDs and had a higher 5-year cardiovascular mortality rate.

Strategies to reduce ICD complications and inappropriate shocks include using special diagnostic ICD algorithms to identify potential lead problems early[126], and changes in ICD programming with a prolonged delay in therapy for tachyarrhythmias of ≥200 beats/min or higher, as demonstrated in the MADIT-RIT (MADIT-Reduction in Inappropriate Therapy) trial[127]. Increasing clinical experience is also being gained in the use of subcutaneous ICDs[128,129], which holds great potential in reducing some types of ICD related complications, although an initial learning curve needs to be overcome first. Real world data of ICD implantation and use show that patients treated by very low volume operators (physicians who implanted ≤1 ICDs per year) were more likely to die or experience cardiac complications compared with operators who frequently performed ICD implantation[130]. Another strategy to reduce ICD complications is to improve the selection process of those patients who would truly benefit from these devices. In an observational outcome study of consecutive subjects referred to a regional inherited cardiac conditions clinic because of a relative who had sudden unexpected death, the number of ICDs inserted as a result of specialist assessment was found to be very small (2%)[131].

Out-of-hospital cardiac arrest

Survival from out-of-hospital cardiac arrest (OHCA) appears to have increased over the past several years, probably as a result of better pre-hospital care (early recognition, more effective CPR, faster emergency services response) and advances in the hospital management of patients following OHCA[132,133]. Data from the London Ambulance Service's cardiac arrest registry from 2007 to 2012 showed an improvement in OHCA survival over the 5 year study period[134]. In an observational Swedish registry study of 7,187 patients with OHCA over an 18 year period, bystander CPR was found to increase from 46% to 73% (95% CI for OR 1.060 to 10.081 per year), early survival increase from 28% to 45% (95% CI 1.044 to 1.065), and survival to 1 month increase from 12% to 23% (95% CI 1.058 to 1.086)135. Strong predictors of

ja vanbolničkih srčanih zastoja kod odraslih u Sjevernoj Americi koja je uključivala 12.930 ispitanika (2.042 na javnom mjestu, 9.564 kod kuće) je pokazala da je preživljavanje do otpusta iz bolnice bilo bolje za zastoje koji su se dogodili na javnim mjestima s dostupnim automatskim vanjskim defibrilatorima (AED) koje primjenjuju prolaznici u odnosu na preživljavanja kod kuće (34% naspram 12%; prilagođeni OR 2,49, 95% CI 1,03-5,99, p=0,04)[136]. Bolničke karakteristike povezane s poboljšanim ishodima bolesnika nakon vanbolničkog srčanog zastoja bili su analizirani u Registru srčanog zastoja hitne službe Victoria kod 9.971 bolesnika tijekom razdoblja od 8 godina[137]. Utvrđeno je da je ishod bio znatno poboljšan u bolnicama s 24-satnim kardiološkim intervencijskim službama (OR 1,40, 95% CI 1,12-1,74; p=0,003) i prijmom bolesnika između 8 i 17 sati (OR 1,34, 95% CI 1,10-1,64, p=0,004). Vanbolnički srčani arest u djece je bio evaluiran u prospektivnoj studiji temeljenoj na podacima mlađih od 21 godina života[138]. Incidencija pedijatrijskog vanbolničkog srčanog zastoja je bila 9,0 na 100.000 pedijatrijskih osoba-godina (95% CI 7,8-10,3), dok je incidencija srčanog zastoja zbog srčanih uzroka iznosila 3,2 (95% CI 2,5-3,9). Autori su zaključili da vanbolnički srčani zastoj čini značajan udio u pedijatrijskoj smrtnosti, iako je velika većina onih koji su preživjeli imala nepromijenjen neurološki status.

Studije o optimalnom slijedu CPR mjera za uporabu kod bolesnika s vanbolničkim srčanim zastojem su objavile različite rezultate. U meta-analizi četiri randomizirana kontrolirana klinička istraživanja s 1.503 ispitanika, nije utvrđena značajna razlika u uspostavi spontane cirkulacije, preživljavanja do otpusta iz bolnice ili povoljnih neuroloških ishoda između početne kompresije prsnog koša u odnosu na defibrilaciju. Analize podskupina ukazale su da početak s kompresijom prsnog koša može donijeti dobrobit kod zastoja s produljenim vremenom reakcije[139]. U novijoj, japanskoj opservacijskoj studiji s bolesnicima s vanbolničkim srčanim zastojem koji su imali doživjeli zastoj i bili defibrilirani sa javno dostupnim AED, utvrđeno je da je CPR sa samo kompresijama prsnog koša povezana sa značajno višim jednomjesečnim preživljavanjem i povoljnijim neurološkim ishodima u usporedbi s konvencionalnim CPR (kompresija prsnog koša i disanje usta na usta)[140]. Međutim, za djecu i mlađe osobe s vanbolničkim srčanim zastojem zbog nekardijalnih uzroka, kao i osoba kod kojih je došlo do odgode u započinjanju CPR, ostale studije su pokazale da je konvencionalna CPR povezana s boljim ishodima od samih kompresija prsnog koša[141,142].

Zaključci

U posljednjih nekoliko godina postignut je važan napredak u našem razumijevanju osnovne i kliničke elektrofiziologije srca čime je unaprijeđeno i poboljšano zbrinjavanje bolesnika s poremećajima srčanog ritma. Veliki broj studija su ukazale na povezanost između FA i različitih sistemskih stanja te novih čimbenika rizika. U ovim studijama se naglašava važnost i složenost ove važne aritmije te se ukazuje da je FA sistemsko stanje. Iako se pokazalo da mnogi čimbenici nisu uzrok, mogu biti klinički korisni u budućim alatima za stratifikaciju rizika za dijagnosticiranje i liječenje FA. Potrebno je provesti više istraživanja kako bi poboljšali naše razumijevanje temeljnih mehanizama odgovornih za razvoj i napredovanje FA te kod kojih podskupina bolesnika će biti najviše koristi od određenih oblika liječenja ili različitih opcija antikoagulacije.

early and late survival were a short interval from collapse to defibrillation, bystander CPR, female gender, and place of collapse. A large prospective cohort study of OHCA in North American adults involving 12,930 subjects (2,042 occurring in a public place and 9,564 at home) also found that the rate of survival to hospital discharge was better for arrests in public settings with automated external defibrillators (AEDs) applied by bystanders compared to those that occurred at home (34% vs 12%, respectively; adjusted OR 2.49, 95% CI 1.03 to 5.99; p=0.04)[136]. Hospital characteristics associated with improved patient outcomes following OHCA were analysed from the Victorian Ambulance Cardiac Arrest Registry of 9,971 patients over an 8 year period[137]. Outcome following OHCA was found to be significantly improved in hospitals with 24 h cardiac interventional services (OR 1.40, 95% CI 1.12 to 1.74; p=0.003) and patient reception between 8.00 and 17.00 h (OR 1.34, 95% CI 1.10 to 1.64; p=0.004). OHCA in children was assessed in a prospective, population based study of victims younger than 21 years of age[138]. The incidence of paediatric OHCA was 9.0 per 100,000 paediatric person-years (95% CI 7.8 to 10.3), whereas the incidence of paediatric OHCA from cardiac causes was 3.2 (95% CI 2.5 to 3.9). The authors concluded that OHCA accounts for a significant proportion of paediatric mortality, although the vast majority of OHCA survivors have a neurologically intact outcome.

Studies on the optimal sequence of CPR measures to use in OHCA patients have reported varying results. In a meta-analysis of four randomised controlled clinical trials enrolling 1,503 subjects with OHCA, no significant difference was found between chest compression first versus defibrillation first in the rate of return of spontaneous circulation, survival to hospital discharge or favourable neurologic outcomes, although subgroup analyses suggested that chest compression first may be beneficial for cardiac arrests with a prolonged response time[139]. In a more recent, nationwide, population based observational study involving OHCA patients in Japan who had a witnessed arrest and received shocks with public access AED, compression only CPR was found to be associated with a significantly higher rate of survival at 1 month and more favourable neurological outcomes compared with conventional CPR measures (chest compression and rescue breathing)[140]. However, for children and younger people who have OHCA from non-cardiac causes, and in people in whom there was a delay in starting CPR, other studies have suggested that conventional CPR is associated with better outcomes than chest compression only CPR[141,142].

Conclusions

Important progress has been made over the past few years in our understanding of basic and clinical cardiac electrophysiology which have advanced and improved the management of patients with heart rhythm disorders. Multiple studies have demonstrated an association between AF and various systemic conditions and novel risk factors. These studies highlight the importance and complexity of this complex arrhythmia and further support the notion that AF is a systemic condition. Although many of these associations have not been shown to play a causal role, they may nonetheless prove useful clinically in future risk stratification scores for the diagnosis or treatment of AF. More research is still needed to increase our understanding of the underlying mechanisms responsible for the development and progression of AF and which patient subgroups will benefit most from specific treatments or the different options for anticoagulation.

U posljednjih nekoliko godina također je je vrlo brzo napredovalo područje implantacije CRT i elektrostimulacije s naglašenim interesom za definiranjem optimalnih kliničkih parametara u odabiru bolesnika, predviđanja reakcije i nepovoljnog remodeliranja. Također, odabir podobnih kandidata za implantaciju ICD postaje precizniji kako se naše razumjevanje patološkog supstrata za ventrikulske aritmije i iznenadnu srčanu smrt poboljšalo. Istraživanje komplikacija povezanih s implantabilnim kardijalnim uređajima, poput infekcije povezanih s uređajem i neprimjereni šokovi iz ICD postaju značajnim, jer se indikacije za implantaciju uređaja i dalje šire i sve se više bolesnika s postojećim uređajima podvrgava postupcima zamjene uređaja.

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The field of CRT and pacing has also progressed rapidly over the past few years with a lot of interest in the optimal clinical parameters for selection of patients, prediction of response, and adverse remodelling. Similarly, as our understanding of the substrate responsible for ventricular arrhythmias and SCD improves, the selection of suitable candidates for ICD therapy is becoming more refined. Research into the complications associated with implantable cardiac devices, such as device infection and inappropriate shocks from ICDs, remains important as indications for device implantation continue to expand and more and more patients with existing devices undergo device replacement procedures.

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