Almanah 2011.: srčane aritmije i elektrostimulacija. Časopisi nacionalnih društava predstavljaju odabrana istraživanja koja predstavljaju napredak u kliničkoj kardiologiji

Almanac 2011: cardiac arrhythmias and pacing. The national society journals present selected research that has driven recent advances in clinical cardiology

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Fibrilacija atrija

Klinička istraživanja

U posljednje dvije godine objavljen je niz važnih kliničkih istraživanja koje produbljuju naše razumijevanje i kliničko liječenje pacijenata s fibrilacijom atrija (FA). Dva glavna cilja liječenja, smanjenje progresije ili ponavljanja aritmije te smanjenje rizika kardiovaskularnih događaja, imaju za cilj poboljšanje kvalitete života i smanjuje smrtnosti. Prateći mnoštvo dokaza iz predkliničkih studija, manjih kliničkih studija i meta-analiza koji ukazuju da blokada renin-angiotenzinskog sustava ima korisne učinke na patofiziologiju FA,[1] dvije velike multicentrične, placebom-kontrolirane, randomizirane studije su provedene kako bi se utvrdili učinci blokatora receptora angiotenzina II (ARB) na FA.

Prva od ovih studija, objavljena 2009. godine, testirala je hipotezu da bi valsartan, lijek iz skupine ARB, pored uobičajene terapije, mogao smanjiti ponavljanje FA kod pacijenata s već prisutnom kardiovaskularnom bolesti, dijabetesom ili povećanjem lijevog atrija te s anamnestičkim podacima o prethodno dokumentiranoj FA.[2] Ukupno 1.442 pacijenta bilo je uključeno u studiju — 722 je dodijeljeno u skupinu s valsartanom (ciljna doza 320 mg) i 720 u skupinu na placebu. Istraživači su ustanovili da liječenje valsartanom nije imalo značajan učinak na ponavljanje FA (51,4% u valsartan skupini i 52,1% u placebo skupini, p=0,73) tijekom relativno kratkog razdoblja praćenja u trajanju od jedne godine.

Druga velika randomizirana studija sa sartanima, objavljena ove godine, procjenjivala je smanjuje li irbesartan rizik od kardiovaskularnih događaja kod pacijenata s FA.[3] Pacijenti s anamnezom rizičnih čimbenika za moždani udar i sistoličkim tlakom od najmanje 110 mmHg bili su randomizirani na primanje ili irbesartana (ciljna doza od 300 mg jednom dnevno) ili placeba. Ispitanici ove studije bili su već uključeni u jednu od druge dvije studije s FA koje su analizirale učinak klopidogrela i acetilsalicilne kiseline (ASK) naspram same ASK ili naspram oralnih antikoagulansa. Istraživači su ustanovili da irbesartan nije smanjio kardiovaskularne događaje ili učestalost hospitali-

Atrial fibrillation

Clinical trials

In the past two years, a number of landmark clinical trials have been published which further our understanding and clinical management of patients with atrial fibrillation (AF). Two of the major goals in the treatment of this condition include reducing progression or recurrence of the arrhythmia and decreasing the risk of cardiovascular events, thereby improving quality of life and decreasing morbidity. Following on from a large body of evidence from preclinical studies, small clinical trials and meta-analyses suggesting that blockade of the renin-angiotensin system has beneficial effects on the pathophysiology of AF,[1] two large multicentre, placebo-controlled, randomised trials were conducted to determine the effects of angiotensin II receptor blockers (ARBs) on AF.

The first of these trials, published in 2009, tested the hypothesis that the ARB valsartan could reduce the recurrence of AF in patients with underlying cardiovascular disease, diabetes or left atrial enlargement and a history of documented AF, in addition to established treatments.[2] A total of 1,442 patients were enrolled into the study-722 assigned to the valsartan group (target dose 320 mg) and 720 to the placebo group. The investigators found that treatment with valsartan had no significant effect on AF recurrence (AF recurrence 51.4% in the valsartan group and 52.1% in the placebo group, p=0.73) over a relatively short follow-up period of one year.

The second large ARB randomised controlled trial (RCT) published this year evaluated whether irbesartan would reduce the risk of cardiovascular events in patients with AF.[3] Patients with a history of risk factors for stroke and a systolic blood pressure of at least 110 mmHg were randomly assigned to receive either irbesartan (target dose of 300 mg once daily) or placebo. Patients for this study were already enrolled in one of two other AF trials looking at clopidogrel plus aspirin versus aspirin alone or versus oral anticoagulants. The investigators found that irbesartan did not reduce cardiovascular events or hospitalisation rates for AF (total of 9016 enrolled with a mean follow-up of

zacije zbog FA (ukupno 9.016 uključenih sa srednjim praćenjem od 4,1 godine) te da je, što nije iznenađujuće, više pacijenata u irbesartan skupini imalo simptomatsku hipertenziju i renalnu disfunkciju od onih u placebo skupini.

Iako su glavni nalazi iz oba velika randomizirana istraživanja bili negativni, trebalo bi napomenuti da su to bile studije sekundarne prevencije, odnosno, pacijenti su već imali ustanovljenu FA te su također imali naprednije stupnjeve bolesti (preko 80% pacijenata u obje studije je imalo anamnestičke podatke o perzistentnoj ili permanentnoj FA), što ukazuje da je podloga za FA već bila dobro utemeljena u obje skupine ispitanika. Moglo bi se razmišljati da blokada renin-angiotenzinskog sustava može biti učinkovitija strategija ako se započne ranije tijekom bolesti ili čak prije no što se FA razvije (tj. primarna prevencija), budući da ACE inhibitori i ARB mogu spriječiti, no ne nužno neutralizirati, električno i strukturalno remodeliranje koje dovodi do razvoja i progresije aritmije. Kao potpora ovoga, manja randomizirana studija s uključenih 62 pacijenta iz jednog centra koji su imali FA bez anamnestičkih podataka o hipertenziji ili srčanim bolestima, a bili su zaprimljeni u hitnu službu, je izvijestila da su pacijenti koji su liječeni ramiprilom (5 mg/dan) imali znatno rjeđe ponovno javljanje FA tijekom razdoblja praćenja od tri godine od pacijenata koji su primili placebo.[4]

Značajan novi dodatak farmakološkim opcijama dostupnima za liječenje FA je pojava dronedarona, multikanalnog blokatora sa sličnim strukturalnim i elektrofiziološkim svojstvima amiodaronu uz glavnu iznimku uklanjanja joda i dodatka metan-sulfonil skupine.[5] Ove strukturalne promjene rezultiraju smanjenom lipofilnosti, skraćenim poluživotom (na otprilike 24 sata), smanjenom akumulacijom u tkivima i teoretski manjim brojem nuspojava u usporedbi s amiodaronom.

Istraživanje ATHENA (placebom kontrolirana, dvostruko slijepa, studija s paralelnim skupinama za procjenu učinkovitosti 400 mg dronedarona dva puta dnevno u svrhu prevencije hospitalizacije ili smrti od bilo kojeg uzroka kod pacijenata s fibrilacijom/undulacijom atrija) je bila važna studija objavljena 2009. godine koja je procjenjivala učinak dronedarona na kardiovaskularne događaje kod pacijenata s FA.[6] U toj studiji, 4.628 pacijenata s FA (paroksizmalna ili perzistentna) ili undulacijom atrija koji su imali dodatni čimbenik rizika za smrtni ishod (dob ≥70 godina, dijabetes, anamnestički podatak o moždanom udaru/tranzitornoj ishemijskoj ataci, sistemska embolija, promjer lijevog atrija ≥50 mm i ejekcijska frakcija ≤40%) bili su randomizirani na dronedaron (400 mg dva puta dnevno) ili placebo. Tijekom srednjeg vremena praćenja od 21±5 mjeseci, istraživači su ustanovili da su pacijenti u dronedaronskog skupini imali znatno manju učestalost primarnih ishoda (prva hospitalizacija zbog kardiovaskularnog događaja ili smrtnog ishoda) od skupine na placebu (734 (32%) nasuprot 917 (39%), p<0,001). Mortalitet od srčanih aritmija je bio značajno niži u dronedaronskoj skupini, iako nije bilo razlike u ukupnoj smrtnosti. Interesantno je da je došlo do malog, no statistički značajnog smanjenja akutnih koronarnih sindroma u dronedaronskoj skupini, a točan razlog za ovo ostaje nejasan. Pacijenti koji su liječeni dronedaronom imali su višu učestalost bradikardije, prolongacije QT-intervala, mučnine, proljeva, osipa i povišene vrijednosti serumskog kreatinina od onih koji su

4.1 years) and that, not surprisingly, more patients in the irbesartan group had symptomatic hypotension and renal dysfunction than those in the placebo group.

Although the main findings from both of these large RCTs were negative, it should be noted that they were secondary prevention studies-that is, patients already had established AF, and also had more advanced stages of disease (over 80% of patients in both studies had a history of persistent or permanent AF), implying that the substrate for AF was already well established in both study groups. It might be argued that blockade of the renin-angiotensin system may be a more effective strategy if performed earlier during the natural history of the disease or even before AF develops (ie, primary prevention), since ACE inhibitors and ARBs may prevent, but not necessarily reverse, the electrical and structural remodelling that leads to the development and progression of the arrhythmia. In support of this, a smaller randomised single-centre study of 62 patients with lone AF, with no history of hypertension or heart disease, presenting to the emergency department reported that patients given ramipril (5 mg/day) had significantly fewer AF relapses during a 3-year follow-up period than patients given placebo.[4]

A significant new addition to the pharmacological options available for treating AF has been the emergence of dronedarone, a multichannel blocker with similar structural and electrophysiological properties to amiodarone with the main exception being removal of iodine and the addition of a methane-sulphonyl group.[5] These structural changes result in decreased lipophilicity, shortened half-life (to approximately 24 h), reduced tissue accumulation and theoretically fewer side effects than associated with amiodarone.

The ATHENA (A placebo-controlled, double-blind, parallel-arm Trial to assess the efficacy of dronedarone 400 mg twice daily for the prevention of Hospitalisation or death from any cause in patients with Atrial fibrillation/flutter) trial was a ground-breaking study published in early 2009 evaluating the effect of dronedarone on cardiovascular events in patients with AF.[6] In this trial, 4.628 patients with AF (paroxysmal or persistent) or atrial flutter who had an additional risk factor for death (age ≥70 years, diabetes, history of stroke/transient ischaemic attack (TIA), systemic embolism, left atrial diameter ≥50 mm and ejection fraction ≤40%) were randomly assigned to receive dronedarone (400 mg twice daily) or placebo. Over a mean follow-up of 21±5 months, the investigators found that patients in the dronedarone group had significantly lower primary outcome of first hospitalisation due to cardiovascular events or death than the placebo group (734 (32%) vs 917 (39%), respectively, p<0.001). Mortality from cardiac arrhythmias was significantly lower in the dronedarone group, although there was no overall difference in all-cause mortality. Interestingly, there was also a small but statistically significant reduction in acute coronary syndromes in the dronedarone group-the exact reason for this remains unclear. Patients taking dronedarone had higher rates of bradycardia, QT-prolongation, nausea, diarrhoea, rash and increased serum creatinine than those receiving placebo. There were no significant differences in rates of thyroid- and pulmonary-related adverse events between the two groups, although, as acknowledged by the investi-

primali placebo. Između dvije skupine nije bilo značajne razlike u učestalosti neželjenih događaja koji su se odnosili na štitnjaču i pluća, iako je, sukladno onom što su potvrdili istraživači u svojem razmatranju, razdoblje praćenja od 21 mjesec možda bilo prekratko kako bi se otkrili takvi štetni učinci, za čiju manifestaciju treba i do dvije godine, kao što se to često opažalo s amiodaronom.

U originalnoj studiji ATHENA te također u naknadnim *post hoc* analizama,[7] nije bilo dokaza o štetnosti kod pacijenata sa zatajivanjem srca (ZS) ili onima s niskom ejekcijskom frakcijom i simptomima koji odgovaraju NYHA II. ili III. stupnju. Ovo nije u skladu s rezultatima ranije studije ANDROMEDA (antiaritmijska studija s dronedaronom kod umjerenog do teškog kongestivnog ZS u kojoj se procjenjivalo smanjenje morbiditeta), koja je prekinuta ranije zbog više smrtnosti u skupini s dronedaronom.[8] Razlika je nastala zbog isključivanja pacijenata sa simptomima NYHA IV. stupnja u studiji ATHENA i činjenici da je studija ANDROMEDA također uključivala pacijente s nedavnim pogoršanjem ZS. No ipak, u pogledu rezultata studije ANDROMEDA, autori su bili protiv korištenja dronedarona kod pacijenata s teškim stupnjem ZS i disfunkcijom lijeve klijetke. Ovo se odražava u najnovijim europskim i američkim smjernicama koje predlažu da se dronedaron koristi kao farmakološka opcija na prvoj liniji kod pacijenata sa simptomatskom FA, uključujući one sa strukturalnom bolesti srca, koronarnom bolesti srca, hipertenzivnom bolesti srca i stabilnim ZS sa simptomima NYHA I. ili II. stupnja, no ne bi se trebao koristiti kod simptoma NYHA III. ili IV. stupnja ili kod nedavnog nestabilnog ZS.[9,10] Objavljen je niz *post hoc* analiza studije ATHENA koje su dale dokaze o nekoliko korisnih učinaka dronedarona. Među njima su smanjenje rizika od moždanog udara s 1,8% godišnje na 1,2% godišnje[11] te pozitivni učinci na kontrolu ritma i frekvencije.[12]

Još jedan novi lijek koji bi mogao imati ulogu u farmakološkoj kardioverziji FA je atrioselektivan antiaritmijski lijek vernakalant (RSD1235).[13] Vernakalant je jedan od nekoliko novih lijekova koji su dizajnirani da ciljaju na atrijski specifične ionske kanale te pri tome teoretski smanjuju ili ograničavaju rizik od ventrikularne proaritmije. U otvorenoj studiji koja je procjenjivala učinkovitost vernakalanta u kardioverziji FA, pokazalo se da je intravenozni lijek konvertirao u sinusni ritam 50,9% pacijenata s FA (od ukupnih 236) sa srednjim vremenom konverzije kod pacijenata koji su reagirali na lijek od 14 minuta.[14] Nije bilo epizoda ventrikulskih aritmija i lijek je bio relativno dobro podnošljiv, osim kod 10 pacijenata (4,2%) koji su morali prekinuti liječenje zbog nuspojava (najčešće hipotenzije). U novijoj manjoj randomiziranoj studiji sa 254 pacijenta s novonastalom FA (trajanje 3-48 sati), vernakalant (10 minutna infuzija 3 mg/kg nakon čega je slijedila druga 10 minutna infuzija od 2 mg/kg ako je pacijent, nakon 15 minuta razdoblja praćenja, još uvijek bio u FA) je uspoređen s intravenoznim amiodaronom (5 mg/kg tijekom 60 minuta nakon čega je slijedila infuzija tijekom 60 minuta).[15] Veći broj pacijenata u skupini koja je uzimala vernakalant u usporedbi sa skupinom na amiodaronu (60/116 (51,7%) naspram 6/116 (5,2%), p<0,0001) je ostvario primarni ishod konverzije u sinusni ritam unutar 90 minuta. Srednje vrijeme kardioverzije kod pacijenata koji su primali vernakalant i koji su regirali na terapiju je iznosilo 11 minuta,

gators in their discussion, the follow-up period of 21 months might have been too short to detect such adverse effects, which may take more than two years to develop, as is often observed with amiodarone.

In the original ATHENA trial and also a subsequent *post hoc* analysis,[7] there was no evidence of harm in patients with heart failure (HF) or those with a low ejection fraction and New York Heart Association (NYHA) class II or III symptoms. This contrasts with results from the earlier ANDROMEDA (ANtiarrhythmic trial with DROnedarone in Moderate to severe congestive heart failure Evaluating morbidity DecreAse) study, which was terminated early owing to excess mortality in the dronedarone group.[8] The reason for this difference may be attributed to the exclusion of patients with NYHA class IV symptoms in the ATHENA study and the fact that the ANDROMEDA study also included patients with a recent exacerbation of HF. Nonetheless, in view of the results from the ANDROMEDA study, the authors warned against use of dronedarone in patients with severe HF and left ventricular dysfunction. This is reflected in the latest European and American guidelines, which propose that dronedarone can be used as a first-line pharmacological option in patients with symptomatic AF, including those with structural heart disease, coronary artery disease, hypertensive heart disease and stable HF with NYHA class I or II symptoms, but should not be used in patients with NYHA class III or IV symptoms or recently unstable HF.[9,10] A number of post hoc analyses of the ATHENA trial have been published providing further evidence for several beneficial effects of dronedarone. These include a reduction in stroke risk from 1.8% a year to 1.2% a year,[11] and favourable effects on rhythm and rate control.[12]

Another newly emerging drug that may have a role in the pharmacological cardioversion of AF is the atrial-selective antiarrhythmic drug vernakalant (RSD1235).[13] Vernakalant is one of several new agents that have been designed to target atrial-specific ion channels and in doing so, theoretically reduce or limit the risk of ventricular proarrhythmia. In an open-label trial assessing the efficacy of vernakalant in the cardioversion of AF, the intravenous agent was found to convert 50.9% of patients with AF (out of a total of 236) to sinus rhythm with a median time to conversion of 14 min among responders.[14] There were no episodes of ventricular arrhythmias and the drug was relatively well tolerated, apart from 10 patients (4.2%) who had to discontinue treatment owing to side effects (most commonly hypotension). In a more recent small randomised trial of 254 patients with recent onset AF (3-48 h duration), vernakalant (10 min infusion of 3 mg/kg followed by a second 10 min infusion of 2 mg/kg if patient was still in AF after a 15 min observation period) was compared with intravenous amiodarone (5 mg/kg over 60 min followed by 50 mg maintenance infusion over 60 min).[15] A greater number of patients achieved the primary end point of conversion to sinus rhythm within 90 min in the vernakalant group compared with the amiodarone group (60/116 (51.7%) compared with 6/116 (5.2%), p<0.0001, respectively). The median time of cardioversion in the patients receiving vernakalant who responded was 11 min and this was associated with a higher rate of symptom relief than with amiodarone. Both drugs were well tolerated

a to je povezano s češćim nestankom simptoma nego s amiodaronom. Oba lijeka su se dobro podnosili u ovoj studiji te nije bilo slučajeva ventrikulskih aritmija.

Mala randomizirana studija sa 61 pacijentom sa ZS i perzistentnom FA je donijela korisne podatke za nastavak teme o kontroli frekvencije naspram kontrole ritma kod pacijenata sa ZS i FA.[16] Pacijenti u ovoj studiji su randomizirani na strategiju kontrole ritma (oralni amiodaron i elektrokardioverziju) ili kontrolu frekvencije s beta-blokatorima i/ili digoksinom (ciljna frekvencija <80/min tijekom mirovanja i <110/min nakon hodanja). Istraživači su ustanovili da je obnova sinusnog ritma kod pacijenata s FA i ZS poboljšala kvalitetu života i funkciju lijeve klijetke u usporedbi sa strategijom kontrole frekvencije (66% u skupini za kontrolu ritma je bilo u sinusnom ritmu nakon 1 godine, a 90% u skupini za kontrolu frekvencije je postiglo ciljnu frekvenciju). Za pacijente s FA za koje je odabrana strategija kontrole frekvencije, optimalna ciljna frekvencija srca je ostala dvojbena. Smjernice su prethodno preporučale strogu kontrolu frekvencije, iako ovo nije bilo temeljeno na kliničkim dokazima. U pokušaju preispitivanja ovog problema, provedena je prospektivna, multicentrična, randomizirana studija kako bi se ispitala hipoteza da blaga kontrola frekvencije nije inferiorna strogoj kontroli frekvencije kod prevencije kardiovaskularnih događaja kod pacijenata s permanentnom FA.[17] Istraživači su ustanovili da je od 614 pacijenata koji su uključeni u studiju učestalost simptoma i neželjenih događaja bila slična između pacijenata kojima je dodijeljena blaga (frekvencija u mirovanju <110/min) i onih na strogoj strategiji kontrole ritma (frekvencija u mirovanju <80/min i pri umjerenoj vježbi <110/min). Strategiju blaže kontrole ritma je bila jednostavnije ostvariti u usporedbi sa strogom kontrolom ritma (97,7% naspram 67,0 %, p<0,001).

Unatoč obećavajućim rezultatima iz predkliničkih ispitivanja i opservacijskih studija na ljudima,[18-20] potencijalne dobrobiti polinezasićenih masnih kiselina (PUFA) kod FA nisu potvrđene u rezultatima nekoliko nedavnih prospektivnih randomiziranih studija. Do sada najveća i najiscrpnija studija dizajnirana da preispita ovu tematiku je prosektivna, multicentrična, randomizirana studija sa 663 pacijenta s potvrđenom paroksizmalnom (n=542) ili perzistentnom (n=121) FA, bez značajne strukturalne bolesti srca i u sinusnom ritmu na početku.[21] Pacijenti su bili randomizirani na uzimanje PUFA (8 g/dnevno) ili placeba u prvih 7 dana, nakon čega je slijedilo uzimanje PUFA (4 g /dan) ili placeba u trajanju od 24 tjedna. Unatoč tome što se dodijeljena terapija relativno dobro podnosila u obje skupine i razine eikosapentaenoične i dokosaheksaenoične kiseline u plazmi su nakon 4 i 24 tjedna bile značajno više u aktivnoj nego u placebo skupini, a istraživači nisu ustanovili smanjenje ponavljanja FA između obje skupine tijekom 6 mjeseci. Dvije manje prospektivne, placebom kontrolirane, randomizirane studije koje su ispitivale učinke PUFA kod pacijenata nakon elektrokardioverzije FA[22] i nakon operacije srca[23] nisu pokazale korist od PUFA kod smanjenja ponavljanja ili učestalosti FA.

Strategije za smanjenje učestalosti tromboembolija

Tijekom posljednje dvije godine je došlo do važnog napretka u prevenciji moždanih udara kod pacijenata s FA, koji će vjerojatno imati značajan utjecaj na buduće kliničin this study and there were no cases of ventricular arrhythmias.

A small randomised study of 61 patients with HF and persistent AF contributed additional useful data towards the continuing topic of rate versus rhythm control in patients with HF and AF.[16] Patients in this study were randomly assigned to a rhythm control strategy (oral amiodarone and electrical cardioversion) or rate control with β-blockers and/or digoxin (target heart rate <80 bpm at rest and <110 bpm after walking). The investigators found that restoration of sinus rhythm in patients with AF and HF improved quality of life and left ventricular function compared with a strategy of rate control (66% in the rhythm control group were in sinus rhythm at 1 year and 90% in the rate control group achieved the target heart rate). For patients with AF for whom a rate control strategy has been decided upon, the optimal target heart rate (HR) has remained controversial. Guidelines have previously recommended strict rate control, although this was not based on clinical evidence. In an attempt to examine this issue, a prospective, multicentre, randomised trial was conducted to test the hypothesis that lenient rate control was not inferior to strict rate control in preventing cardiovascular events in patients with permanent AF.[17] The investigators found that of the 614 patients recruited into the study, the frequencies of symptoms and adverse events were similar between patients assigned to a lenient rate control strategy (resting HR <110 bpm) and those assigned to a strict rate control strategy (resting HR <80 bpm and HR during moderate exercise <110 bpm). A lenient-control strategy was easier to achieve as more patients in this group attained their HR target compared with the strict-control group (97.7% vs 67.0%, p<0.001).

Despite some promising results from preclinical experiments and observational studies in humans,[18-20] the potentially beneficial effects of polyunsaturated fatty acids (PUFA) in AF have not been confirmed from the results of several prospective randomised trials reported recently. The largest and most comprehensive study to date designed to examine this subject was a prospective, multicentre, RCT of 663 patients with confirmed paroxysmal (n=542) or persistent (n=121) AF, with no substantial structural heart disease and in sinus rhythm at baseline.[21] Patients were randomly assigned to take prescription PUFA (8 g/day) or placebo for the first 7 days, followed by PUFA (4 g/day) or placebo thereafter for 24 weeks. Despite the assigned treatment being relatively well tolerated in both groups and plasma levels of eicosapentaenoic and docosahexaenoic acid being significantly higher in the prescription group than in the placebo group at weeks 4 and 24, the investigators found no reduction in AF recurrence over 6 months between the two groups. Two smaller prospective, placebo-controlled, randomised studies investigating the effects of PUFA in patients after electrical cardioversion of AF[22] and after cardiac surgery[23] have failed to demonstrate a beneficial action of PUFA in decreasing the recurrence or incidence of AF.

Strategies to decrease thromboembolism

Important advances have been made in stroke prevention in patients with AF over the past two years, which are likely to have a significant impact on future clinical mana-

ko liječenje. U studiji RE-LY, dvije fiksne doze (110 mg ili 150 mg dva puta dnevno) novog oralnog izravnog inhibitora trombina, dabigatrana, su uspoređene s varfarinom kod više od 18.000 pacijenata s FA i bar još jednim dodatnim čimbenikom rizika za moždani udar.[24] Istraživači su ustanovili da su pacijenti koji su uzimali dozu od 110 mg dabigatrana imali sličnu učestalost moždanih udara i sistemskih embolija kao i oni koji su primali varfarin, uz manju učestalost krvarenja, dok su pacijenti koji su uzimali dozu od 150 mg imali nižu učestalost moždanih udara i sistemskih embolija, uz sličnu učestalost značajnijih krvarenja. Rezultati ove studije su bili tako impresivni da je od tada dabigatran uključen u najnovije europske i američke smjernice o FA kao alternativa varfarinu u prevenciji moždanih udara kod sistemskih embolija kod pacijenata s paroksizmalnom i permanentnom FA.[9,25]

Obzirom da se 80% aktivnog lijeka izlučuje preko bubrega, pacijenti s klirensom kreatinina od <30 ml/min bili su isključeni iz studije RE-LY; dabigatran bi trebalo koristiti oprezno kod pacijenata sa značajnim bubrežnim oštećenjem. Doza dabigatrana koju je u listopadu 2010. odobrila Američka administracija za hranu i lijekove iznosi 150 mg dva puta dnevno kod pacijenata s nevalvularnom FA i reducirana doza od 75 mg dva puta dnevno za one s blagim oštećenjem bubrega (klirens kreatinina od 15-30 ml/min). Ne postoje preporuke za doziranje u pacijenata s klirensom kreatinina <15 ml/min ili one koji su liječeni dijalizom. Uz superiornost dabigatrana (150 mg dva puta dnevno) u usporedbi s varfarinom za liječenje moždanog udara i sistemske embolije, još jedna velika prednost jest da nema potrebe za nadzor vrijednosti INR. Nedostaci uključuju nedostatak specifičnog antidota (njegov poluvijek iznosi 12-17 sati) i blago povišen rizik od drugih nuspojava osim krvarenja, uključujući dispepsiju. Trebat će daljnja procjena i razmatranje o tome kako će ovaj obećavajući novi oralni antikoagulantni lijek biti uključen u kliničku praksu diljem svijeta. Pacijenti liječeni varfarinom uz izvrsnu kontrolu INR vjerojatno bi imali malu dodatnu korist od prelaska na dabigatran, dok bi oni s lošom kontrolom vrijednosti INR ili pak oni koji su nedavno započeli oralnu antikoagulantno liječenje mogu imati najviše koristi. Lokalni standardi skrbi za antikoagulantnu kontrolu i praćenje mogu također biti važni za razmatranje, kao što je to zaključeno u podanalizi studije RE-LY, u kojoj su istraživači ustanovili da bi ispitanici s lošom kontrolom vrijednosti INR i većim rizikom krvarenja na varfarin mogli imati više koristi od primjene 150 mg dabigatrana dva puta dnevno.[26] Druge podstudije koje su proizašle iz originalne studije RE-LY su pokazale da je korist od dabigatrana slična između pacijenata koji nisu nikad primali antagonist vitamina K i od onih koji to jesu[27] te da se dabigatran može koristiti kao sigurna alternativa varfarinu kod pacijenata kojima je potrebna kardioverzija.[28]

Istraživači studije ACTIVE A procjenjivali su da li bi dodatak klopidogrela uz ASK mogao smanjiti rizik od vaskularnih događaja u usporedbi sa ASK kod pacijenata za koje su se antagonisti vitamina K smatrali neprimjerenim.[29] Studija ACTIVE W je već prije ukazala da je kombinacija ASK i klopidogrela inferiorna oralnoj antikoagulantnoj terapiji za prevenciju vaskularnih događaja kod pacijenata s FA uz visoki rizik od moždanog udara.[30] U studiji ACTIVE A, koja je uključivala 7.554 pacijenata uz srednje vrijeme

gement. In the RE-LY study (Randomised Evaluation of Long-term anticoagulation therapY), two fixed doses (110 mg or 150 mg twice daily) of a new oral direct thrombin inhibitor, dabigatran, were compared with warfarin in over 18, 000 patients with AF and at least one additional risk factor for stroke.[24] The investigators found that patients taking the 110 mg dose of dabigatran had similar rates of stroke and systemic embolism to those receiving warfarin, but had lower rates of major haemorrhage, while subjects taking the 150 mg dose had lower rates of stroke and systemic embolism, with similar rates of major haemorrhage. Results from this study were so impressive that dabigatran has since been incorporated into the latest European and American guidelines on AF as an alternative to warfarin for the prevention of stroke and systemic embolism in patients with paroxysmal and permanent AF.[9,25]

As 80% of the active drug is excreted by the kidneys, patients with a creatinine clearance of <30 ml/min were excluded from the RE-LY trial; dabigatran should be used with caution in patients with significant renal impairment. The dose of dabigatran approved by the US Food and Drug Administration in October 2010 was 150 mg twice daily in patients with non-valvular AF with a reduced dose of 75 mg twice daily for those with mild renal impairment (creatinine clearance of 15-30 ml/min). There are no dosing recommendations for patients with a creatinine clearance <15 ml/min or those undergoing dialysis. In addition to the superiority of dabigatran (150 mg twice daily) over warfarin for treatment of stroke and systemic embolism, another major advantage is that there is no need for international normalisation ratio (INR) monitoring. However, disadvantages include the lack of a specific antidote (its half-life is 12-17 h) and a slightly increased risk of non-haemorrhagic side effects, including dyspepsia. How this promising new oral anticoagulant drug will be incorporated into current local practices around the world will require future evaluation and consideration. For example, there may be little to be gained from switching patients already receiving warfarin and with excellent INR control to dabigatran, while patients with poor INR control or those who have newly started oral anticoagulation may derive greater benefit. Local standards of care for anticoagulation control and follow-up may also be an important consideration, as concluded in a subanalysis of the RE-LY study, in which the investigators found that sites with poor INR control and greater bleeding from warfarin may receive greater benefit from dabigatran 150 mg twice daily.[26] Other substudies following on from the original RE-LY trial have shown that the benefits of dabigatran are similar between patients who have never received a vitamin K antagonist (VKA-naive patients) and VKA-experienced patients,[27] and that dabigatran can be used as a safe alternative to warfarin in patients requiring cardioversion.[28]

In the ACTIVE A study, the ACTIVE (AF Clopidogrel Trial with Irbesartan for prevention of Vascular Events) investigators evaluated whether the addition of clopidogrel to aspirin would reduce the risk of vascular events compared with aspirin alone in patients for whom a VKA was considered unsuitable.[29] The ACTIVE W trial had previously demonstrated that the combination of aspirin and clopidogrel was inferior to oral anticoagulation for the prevention of vascular events in patients with AF at high risk of stroke.[30] In the ACTIVE A study, involving 7,554 patients and a

praćenja od 3,6 godina, istraživači su ustanovili da kombinacija oba antitrombocitna lijeka smanjuje rizik od velikih vaskularnih događaja, naročito moždanog udara, u usporedbi sa samom ASK, no uz cijenu povećanja rizika od većih krvarenja. Klinička implikacija studija ACTIVE A i ACTIVE W jest da je oralna antikoagulantna terapija bolja od kombinacije ASK i klopidogrela za prevenciju moždanih udara kod pacijenata s FA, no za pacijente za koje je oralna antikoagulantna terapija neprikladna, kombinacija antitrombocitnih lijekova je bolja od same ASK, iako je rizik od većih krvarenja također viši. Potrebno je odgovarajuće savjetovanje i stratifikacija rizika pacijenata s FA kada se odlučuje o najprimjerenijoj strategiji za smanjenje rizika od vaskularnih događaja.

Još jedna važna randomizirana kontrolirana klinička studija koja je uključivala pacijente kod kojih antagonisti vitamina K nisu bio odgovarajući, uključivala je uporabu apiksabana — novog oralnog izravnog i kompetitivnog inhibitora faktora Xa.[31] Studija AVERROES je uključivala randomizaciju 5.599 pacijenata s FA (u 522 centra iz 36 zemalja) na apiksaban (5 mg dvaput dnevno) ili ASK (81-324 mg dnevno).[32] U toj su studiji pacijenti s FA bili u dobi ≥50 godina te su morali imati bar jedan čimbenik rizika za moždani udar uz nemogućnost uzimanja antagonista vitamina K koji su se već pokazali neprikladnim ili su smatrani neprikladnim. Istraživači su ustanovili da je apiksaban smanjio rizik od moždanog udara i sistemske embolije bez značajnog povećanja rizika od krvarenja ili intrakranijalne hemragije te je također smanjio rizik od prve hospitalizacije zbog kardiovaskularnih uzroka.

Nedavno objavljene studije na području novih mehaničkih pristupa prevenciji moždanih udara kod FA uključuju i istraživanje PROTECT FA.[33] U ovoj studiji neinferiornosti, učinkovitost i sigurnost novog perkutanog uređaja za zatvaranje aurikule lijevog atrija (LAA) je uspoređena s terapijom varfarinom kod 707 pacijenata s nevalvularnom FA. Ispitanici su morali imati bar jedan čimbenik rizika za moždani udar (uz FA) te su u odnosu 2:1 uključeni u intervencijsku skupinu na primanje uređaja za zatvaranje LAA i potom prekida uzimanja varfarina nasuprot skupine koja je liječena samo varfarinom (uz ciljni INR između 2,0 i 3,0). Uređaj za zatvaranje LAA je uspješno implantiran kod 88% pacijenata dodijeljenih u intervencijsku skupinu. Nakon srednjeg praćenja od 18±10 mjeseci, primarna učinak — učestalost moždanih udara (ishemijskih ili hemoragijskih) iznosila je 3,0 na 100 pacijent-godina (95% CI 1,9 do 4,5) u intervencijskoj skupini i 4,9 na 100 pacijent-godina (95% CI 2,8 do 7,1) u kontrolnoj skupini. Primarni sigurnosni događaji su bili češći u intervencijskoj nego u kontrolnoj skupini te su većinom bili povezani s periproceduralnim komplikacijama (perikardijalni izljev kod 4,8%, značajna krvarenja kod 3,5% i periproceduralni ishemijski moždani udar kod 1,1%). Ova važna studija ukazuje da Watchman uređaj za zatvaranje LAA (Aritech, Plymouth, Minnesota, SAD) možda može pružiti alternativnu strategiju oralnim antikoagulansima za prevenciju moždanih udara kod pacijenata s visokim rizikom i nevalvularnom FA te s visokim tromboembolijskim rizikom, iako je implantacija uređaja povezana s povišenim rizikom od periproceduralnih komplikacija. Kao i sa svim novim intervencijskim postupcima, sigurnost Watchman uređaja za zatvaranje LAA će se najvjerojatnije poboljšati povećanjem iskustva i upoznavanjem operatora s novom tehnologijom.[34] Rezul-

median follow-up of 3.6 years, the investigators found that the combination of both antiplatelet agents reduced the risk of major vascular events, especially stroke, compared with aspirin alone but at the price of increased risk of major haemorrhage. The clinical implications of the ACTIVE A and ACTIVE W trials are that oral anticoagulation is better than the combination of aspirin and clopidogrel in stroke prevention in patients with AF, but for patients for whom oral anticoagulation is unsuitable, the combination of antiplatelet agents is better than aspirin alone, although the risk of major haemorrhage is also greater. This reinforces the need for appropriate counselling and risk stratification of patients when deciding upon the most suitable strategy to lower the risk of vascular events in patients with AF.

Another important randomised controlled clinical trial including patients for whom a VKA was not suitable involved the use of new oral direct and competitive inhibitor of factor Xa, apixaban.[31] The AVERROES (Apixaban vs acetylsalicylic acid to prevent stroke in patients with AF who have are unsuitable for vitamin K antagonist treatment or for whom this treatment has failed) study involved the random assignment of 5,599 patients with AF (involving 522 centres in 36 countries) to apixaban (5 mg twice daily) or aspirin (81-324 mg/day).[32] In that study, patients with AF were aged ≥50 years and had to have at least one risk factor for stroke in addition to being unable to take a VKA, either because it had already been shown to be unsuitable or was deemed to be unsuitable. The investigators found that apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of bleeding or intracranial haemorrhage and also reduced the risk of a first hospitalisation for a cardiovascular cause.

Recent studies in the field of new mechanical approaches to stroke prevention in AF include the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF) study.[33] In this non-inferiority study, the efficacy and safety of a new percutaneous left atrial appendage (LAA) closure device was compared with warfarin treatment in 707 patients with non-valvular AF. Study participants had to have at least one risk factor for stroke (in addition to AF) and were assigned in a 2:1 ratio to receive the LAA-closure device and subsequent discontinuation of warfarin or warfarin alone (with a target INR of between 2.0 and 3.0). The LAA-closure device was successfully implanted in 88% of subjects assigned to the intervention group. After a mean follow-up of 18±10 months, the primary efficacy event rate of stroke (ischaemic or haemorrhagic) was 3.0 per 100 patient-years (95% CI 1.9 to 4.5) in the intervention group and 4.9 per 100 patient-years (95% CI 2.8 to 7.1) in the control group. Primary safety events were more common in the intervention group than in the control group, and were mainly related to periprocedural complications (pericardial effusion in 4.8%, major bleeding in 3.5% and periprocedural ischaemic stroke in 1.1%). This important study demonstrates that the Watchman (Atritech, Plymouth, Minnesota, USA) LAA-closure device may provide an alternative strategy to oral anticoagulation for the prevention of stroke in patients at high risk with non-valvular AF and at high thromboembolic risk, although the trade-off is an increased risk of periprocedural complications related to device implantation. As with all new interventional procedures, safety of the Watchman LAA-closure device is likely to improve with increased

tati dugoročnog praćenja s prethodnim perkutanim uređajem za zatvaranje LAA, sustavom PLAATO (perkutana transkatateraska okluzija aurikule lijevog atrija),[35] ukazuju da takvi uređaji mogu sniziti godišnji rizik od moždanog udara/TIA u usporedbi s očekivanim rizikom od moždanog udara/TIA procijenjen ljestvicom CHADS2 (3,8% odnosno 6,6% godišnje), iako je učestalost događaja i dalje ostala značajna.[36]

Epidemiologija i genetika fibrilacije atrija

Epidemiološke studije su dodatno rasvijetlile inherentne mehanizme FA i identificirale nove čimbenike rizika. Koristeći podatke iz *Framingham Heart Study*, istraživači su identificirali produljeni PR interval (>200 ms) kao prediktora nadolazeće FA, implantacije elektrostimulatora i smrtnosti od svih uzroka kod 7575 ispitanika (srednje dobi od 47 godina, 54% žena).[37] Ova studija osporava ranija vjerovanja da je AV blok prvog stupnja benigan[38] te postavlja daljnja pitanja o mehanizmima kojima produljeni PR interval može povisiti rizik od nastanka FA. U drugoj studiji sa 4.764 sudionika iz *Framingham Heart Study*, nastala je nova ljestvica rizika kojoj je cilj predviđanje pojedinačnog apsolutnog rizika nastanka FA.[39] Ustanovljeno je da su dob, spol, indeks tjelesne mase, sistolički arterijski tlak, antihipertenzivna terapija, PR interval, klinički značajan šum srca i ZS povezani s FA (p<0,05, izuzet indeks tjelesne mase p=0,08). Kad su uključeni u ljestvicu rizika, C statistika kliničkog modela je iznosila 0,78 (95% CI 0,76 do 0,80).

U kasnijoj studiji, isti istraživači su proučili vezu između niza plazmatskih biomarkera i incidentne FA koristeći kohortu iz studije Framingham te su ustanovili da je BNP prediktor incidentne FA koji poboljšava stratifikaciju rizika, povećavajući rezultat C statistike sa 0,78 (95% CI 0,75 do 0,81) na 0,80 (95% CI 0,78 do 0,83).[40]

U drugoj studiji osoba starije dobi (n=5.445) koji su sudjelovali u *Cardiovascular Health Study (CHS)*, ustanovljeno je da NT-proBNP predviđa novonastalu FA, neovisno o bilo kakvim drugim prethodno opisanim čimbenicima rizika.[41] Slične rezultati su ustanovljeni i u finskoj kohorti.[42] Potencijalna uloga biomarkera je možda veća od predviđanja atake FA — nedavna studija izvještava da kinetika otpuštanja NT-proBNP-a u plazmi kod pacijenata s akutnom FA daje potencijalni način određivanja njegovog vremena pojavnosti i sigurnosti kardioverzije.[43] Čini se da stoga postoji obećavajuća uloga novih biomarkera u predviđanju atake FA, što može pomoći u svakodnevnoj praksi u indentifikaciji pojedinaca koji imaju najveći rizik od nastanka FA i koji bi mogli imati najviše koristi od profilaktičkog liječenja. Druge studije koje su proučavale populacijske podatke za žene su izvijestile da su indeks tjelesne mase[44] i porođajna masa[45] povezani s atakom FA. Nadalje, nedavni podaci od 34.722 sudionika *Women's Health Study* su pokazali da je pojava novonastale FA kod početno zdravih žena neovisno povezana sa smrtnošću od svih uzroka i kardiovaskularnim mortalitetom.[46]

U posljednje dvije godine registrirali smo važne napretke u razumijevanju genetike i nasljeđivanja FA. Nakon važnog otkrića, primjenom studija povezivanja na genomu osoba europskog i kineskog porijekla, da se dvije varijacije niza na kromosomu 4q25 povezuju s povećanim rizi-

operator experience and familiarity with the new technology.[34] Longer-term follow-up data with an earlier percutaneous LAA-closure device, PLAATO (percutaneous left atrial appendage transcatheter occlusion) system,[35] suggest that such devices can lower the annualised risk of stroke/TIA compared with the expected stroke/TIA risk assessed using the CHADS2 score (3.8% a year and 6.6% a year, respectively), although event rates still remain significant.[36]

Epidemiology and genetics of AF

Epidemiological studies have shed further light on the mechanisms underlying AF and identified new risk factors. Using data from the Framingham Heart Study, investigators identified a prolonged PR interval (>200 ms) as a predictor of incident AF, pacemaker implantation and all-cause mortality in 7,575 individuals (mean age 47 years; 54% women).[37] This study contradicts the previously held belief that first-degree heart block is benign[38] and raises further questions about the mechanism by which a prolonged PR interval might increase the risk of developing AF. In another study using 4,764 participants from the Framingham Heart Study, a new risk score was developed aimed at predicting an individual's absolute risk for developing AF.[39] Age, sex, body mass index, systolic blood pressure, treatment for hypertension, PR interval, clinically significant cardiac murmur and HF were all found to be associated with AF (p<0.05, except body mass index p=0.08). When incorporated in a risk score, the clinical model C statistic was 0.78 (95% CI 0.76 to 0.80).

In a subsequent study, the same investigators looked at the relation between a number of plasma biomarkers and incident AF using the Framingham cohort and found that B-type natriuretic peptide (BNP) was a predictor of incident AF and improved risk stratification, increasing the C statistic from 0.78 (95% CI 0.75 to 0.81) to 0.80 (95% CI 0.78 to 0.83).[40]

In another community-based population study of older adults (n=5445) who participated in the Cardiovascular Health Study (CHS), NT-proBNP was found to predict new-onset AF, independently of any other previously described risk factor.[41] Similar findings have now been reported in a Finnish cohort.[42] The potential role of biomarkers may extend beyond predicting incident AF-a recent study reporting that the kinetics of plasma NT-proBNP release in patients presenting acutely with AF provides a potential means of determining its time of onset and the safety of cardioversion.[43] There therefore appears to be a promising role for new biomarkers in predicting incident AF, which may help guide clinicians as to which individuals are most at risk of developing AF and who may benefit from prophylactic treatments. Other studies looking at population data in women have reported body-mass index[44] and birth weight[45] to be associated with incident AF. Furthermore, recent data from 34,722 participants of the Women's Health Study provided evidence that new-onset AF in initially healthy women was independently associated with all-cause and cardiovascular mortality.[46]

The past 2 years have seen important advances in our understanding of the genetics and heredity of AF. Following the landmark discovery using genome-wide association studies on subjects from European and Chinese de-

kom od razvoja FA,[47] na istom kromosomu su identificirana dva nova signala podložnosti FA.[48] Meta-analiza četiri neovisne kohorte europskog porijekla (Framingham Heart Study, Rotterdam Study, Vanderbilt FA Registry i German AF Network) je potvrdila značajnu vezu između FA i intergenskih regija na kromosomu 4.[49] Čini se da genske varijacije u regiji kromosoma 4q25 moduliraju rizik od ponavljanja FA nakon kateterske ablacije[50] te se povezuju s nastankom FA nakon kardiokirurškog zahvata.[51,52] Da li će se gensko sekvencioniranje kromosoma 4q25 pokazati korisnim kod stratifikacije rizika za razvoj FA nakon kateterske ablacije ili operacije srca treba tek vidjeti, no trenutno ovo ostaje upečatljiva i obećavajuća mogućnost. U skladu s novim genskim podacima o FA, studije na kohortama baziranima na populaciji su također donijele dokaze o komponenti nasljednosti. Koristeći podatke iz Framingham Heart Study, istraživači su ustanovili da se nasljedna FA pojavila kod 1.185 (26,8%) i preuranjena nasljedna FA kod 351 (7,9%) sudionika od 4.421 sudionika (11.971 pregleda) tijekom razdoblja od 1968. do 2007. god.[53] Povezanost nije smanjena prilagođavanjem za čimbenike rizika FA ili genske varijacije povezane s FA. Čini se da su rasni faktori i porijeklo također vezani za rizik od FA. Podaci od bijelaca i afriko-amerikanaca koji su u bili uključeni u CHS i studiju *Atherosclerosis Risk in Communities* (ARIC) ukazuju da je europsko porijeklo čimbenik rizika za nastanak FA.[54]

Kateterska ablacija fibrilacije atrija

U velikoj prospektivnoj, multicentričnoj studiji (19 centara), uspoređena je kateterska ablacija s liječenjem antiaritmicima.[55] Ukupno 167 pacijenata s paroksimalnom FA kod koje bar jedan antiaritmik nije bio uspješan i koji su doživjeli bar tri epizode FA tijekom prethodnih šest mjeseci bilo je randomizirano (2:1) na katetersku ablaciju ili farmakološko liječenje. Nakon devetmjesečnog razdoblja praćenja, istraživači su ustanovili da je kateterska ablacija omogućila dulje vrijeme do neučinkovitosti terapije i značajno poboljšala kvalitetu života. Veći neželjeni događaji tijekom 30 dana povezani s terapijom nastupili su kod pet od 103 pacijenta (4,9%) liječenih kateterskom ablacijom te kod pet od 57 pacijenata (8,8%) liječenih antiaritmicima. U prospektivnoj studiji s uključenih 502 simptomatskih ispitanika koji su bili podvrgnuti ablaciji FA također je registrirano poboljšanje kvalitete života. Poboljšanje kvalitete života bilo je održano nakon dvije godine kod pacijenata sa ili bez recidiva FA, iako je promjena bila najveća kod pacijenata kod kojih nije bilo recidiva FA i kod onih koji nisu bili liječeni antiaritmicima.

Nekoliko uglednih visokovolumnih centara je nedavno objavilo rezultate dugoročnih ishoda nakon kateterske ablacije FA. Skupina iz Bordeauxa je objavila podatke petogodišnjeg praćenja 100 pacijenata (86% muškarci, dob 55,7±9,6 godina; 63% paroksimalna FA, 36% sa strukturalnom bolesti srca).[57] Udjeli preživljavanja bez aritmije nakon jedne kateterske ablacije su iznosili 40%, 37% i 29% nakon jedne, dvije i pet godina (većina recidiva aritmije je nastupila unutar prvih šest mjeseci). Ukupno 175 postupaka je obavljeno uz prosjek od dva po svakom pacijentu (51 pacijent je podvrgnut drugom postupku, a njih 17 trećem). Nije bilo periproceduralnih smrti, iako su značajne komplikacije (tamponada srca koja je zahtjevala dre-

scent that two sequence variations on chromosome 4q25 are associated with an increased risk of developing AF.[47] two new AF susceptibility signals have been identified on the same chromosome.[48] A meta-analysis of four independent cohorts of European descent (the Framingham Heart Study, Rotterdam Study, Vanderbilt AF Registry and German AF Network) confirmed a significant relationship between AF and intergenic regions on chromosome 4.[49] Interestingly, genetic variants in the chromosome 4q25 region also appear to modulate the risk of AF recurrence after catheter ablation[50] and are associated with the development of AF after cardiac surgery.[51,52] Whether genetic sequencing of chromosome 4q25 will prove useful in risk stratification for the development of AF after catheter ablation or cardiac surgery remains to be determined-at present, this remains a distinct and promising possibility. In line with the newly emerging genetic data on AF, studies on population-based cohorts have also provided evidence for a heredity component. Using data from the Framingham Heart Study, investigators found that familial AF occurred in 1,185 (26.8%) and premature familial AF occurred among 351 (7.9%) participants out of 4,421 participants (11.971 examinations) during the period 1968-2007.[53] The association was not attenuated by adjustment for AF risk factors or reported AF-related genetic variants. Racial factors and ancestry also appear to be related to the risk of AF. Data from white and African-American subjects enrolled in the CHS and Atherosclerosis Risk in Communities (ARIC) study suggest that European ancestry is a risk factor for incident AF.[54]

Catheter ablation of AF

In a large prospective, multicentre trial involving 19 centres, the use of catheter ablation was compared with antiarrhythmic drug treatment.[55] A total of 167 patients with paroxysmal AF for whom at least one antiarrhythmic drug had failed and who had experienced at least three AF episodes in the preceding 6 months were randomised (2:1) to undergo catheter ablation or medical treatment. After a 9 month follow-up period, the investigators found that catheter ablation resulted in a longer time to treatment failure and significantly improved quality-of-life scores. Major 30-day treatment-related adverse events occurred in five of 103 patients (4.9%) treated with catheter ablation and five of 57 patients (8.8%) treated with antiarrhythmic drugs. An improvement in the quality of life was also demonstrated in a prospective follow-up study of 502 symptomatic subjects who underwent AF ablation.[56] The improvement in quality of life was sustained at 2 years in patients with and without recurrence of AF, although the change was greatest in patients who remained free from AF and without antiarrhythmic drug treatment.

Several well-respected, high-volume centres have recently published their long-term outcomes following catheter ablation for AF. The Bordeaux group reported their 5 year follow-up data on 100 patients (86% male; age 55.7±9.6 years; 63% paroxysmal AF; 36% with structural heart disease).[57] Arrhythmia-free survival rates after a single catheter ablation procedure were 40%, 37% and 29% at 1, 2 and 5 years, respectively (most recurrences occurred over the first 6 months). A total of 175 procedures were perfor-

nažu) nastupile kod tri pacijenta (3%), a manje komplikacije (arteriovenska fistula, femoralna pseudoaneurizma i asimptomatska stenoza pulmonarne vene) su nastupile kod još tri pacijenta. Važna činjenica iz ove studije je da čak i u iskusnim rukama s odabranom populacijom pacijenata s FA (u prosjeku mlađi i s manje komorbiditeta), postoji stalno smanjenje razdoblja preživljavanja bez aritmije te se recidivi FA dešavaju unutar 5 godina od ablacije, iako većina njih nastupa unutar prvih 6-12 mjeseci.

Iskusan njemački centar je također nedavno izvijestio o svojim dugoročnim podacima praćenja kateterske ablacije kod 161 pacijenta (75% muškarci; dob 59,8±9,7 godina) sa simptomatskom paroksimalnom FA i normalnom funkcijom lijeve klijetke.[58] Ustanovili su da je 75 pacijenata (46,6%) bilo u sinusnom ritmu nakon inicijalnog postupka tijekom srednjeg razdoblja praćenja od 4,8 godine (0,33 do 5,5 godina). Drugi postupak je obavljen kod 66, a treći kod 12 pacijenata. Jedan pacijent je imao aspiracijsku pneumoniju koja je uspješno liječena, a dvoje je razvilo sterilni perikardijalni izljev koji nije zahtijevao drenažu (nisu zabilježene nikakve druge proceduralne komplikacije). Došlo je do manjeg udjela progresije u kroničnu FA tijekom razdoblja praćenja, što je zabilježeno kod samo četiri pacijenta (2,5%).

Skupina iz Londona je izvijestila o sličnim dugoročnim rezultatima nakon kateterske ablacije kod 285 pacijenata s FA (75% muškaraca; srednja dob 57±11 godina; 53% paroksimalna FA; 20% sa strukturalnom bolesti srca) koji su podvrgnuti ukupno 530 postupaka.[59] Tijekom srednjeg vremena praćenja od 2,7 godine (0,2 do 7,4 godine), 86% pacijenata s paroksimalnom FA i 68% onih s perzistentnom FA je bilo bez FA/atrijske tahiaritmije. Komplikacije su uključivale tri moždana udara/TIA. Kasni povrat je bio tri na 100 godina praćenja nakon >3 godine. Istraživači su također ustanovili da je ciljanje kompleksnih frakcioniranih atrijskih elektrograma (CFAE) tijekom postupka ablacije poboljšalo ishode kod pacijenata s perzistentnom FA. Međutim, ovo nije zabilježeno u randomiziranoj studiji od druge skupine istraživača u kojoj je 119 pacijenata s perzistentnom FA randomizirano na dodatnu CFAE ablaciju nakon izolacije pulmonalnih vena ili bez dodatne ablacije.[60]

U sažetku, izvješća o dugoročnom uspjehu nakon kateterske ablacije zbog FA pokazuju da je postupak učinkovit za odabranu skupinu simptomatskih pacijenata s FA, iako značajni udio zahtjeva više od jednog postupka ablacije, postoje rizici od periproceduralnih komplikacija i mogući problem ostaje recidiv FA, čak i nakon petogodišnjeg razdoblja praćenja. Trebalo bi napomenuti da se ishodi iz različitih centara ne mogu izravno uspoređivati jer postoje razlike u izboru pacijenata (npr. udio pacijenata s paroksimalnom i permanentnom FA, pacijenti sa strukturalnom bolesti srca), korištenim tehnikama (segmentna izolacija pulmonalne vene naspram sveobuhvatnoj ablaciji širokog područja), duljini trajanja praćenja i metodama koje su se koristile za detektiranje recidiva FA.

Obavljen je niz studija kako bi se istražile nove neinvazivne varijable koje bi mogli pomoći pri predviđanju recidiva FA nakon kateterske ablacije. Ovi čimbenici uključuju oštećenje bubrega,[61] nove ehokardiografske varijable poput atrijsog elektromehaničkog intervala,[62] atrijske fi-

med with a median of two for each patient (51 patients underwent a second procedure and 17 a third). There were no periprocedural deaths, although major complications (cardiac tamponade requiring drainage) occurred in three patients (3%), and minor complications (arteriovenous (AV) fistula, femoral pseudoaneurysm and asymptomatic pulmonary vein stenosis) occurred in another three patients. The important point to note from this study is that even in experienced hands with a selected AF population (patients who are referred for AF ablation tend to be younger and have fewer comorbidities), there is a steady decline in arrhythmia-free survival with recurrences seen up to 5 years after ablation, although the majority occur within the first 6-12 months.

An experienced German centre also recently reported their long-term follow-up data of catheter ablation in 161 patients (75% male; age 59.8±9.7 years) with symptomatic paroxysmal AF and normal left ventricular function.[58] They found that 75 patients (46.6%) were in sinus rhythm after the initial procedure during a median follow-up period of 4.8 years (0.33 to 5.5 years). A second procedure was performed in 66 and a third procedure in 12 patients. One patient had an aspiration pneumonia that was successfully treated and two developed a sterile pericardial effusion that did not require drainage (no other procedural complications were noted). There was a low rate of progression to chronic AF during the follow-up period, which was seen in only four patients (2.5%).

A group from London, UK, similarly reported their long-term results following catheter ablation for AF in 285 patients (75% male; mean age 57 (SD 11) years; 53% paroxysmal AF; 20% with structural heart disease) undergoing a total of 530 procedures.[59] During a mean follow-up of 2.7 years (0.2 to 7.4 years), freedom from AF/atrial tachyarrhythmia was 86% for patients with paroxysmal AF and 68% for those with persistent AF. Complications included three strokes/TIAs. Late recurrence was three per 100 years of follow-up after >3 years. The investigators also found that targeting complex fractionated atrial electrograms (CFAEs) during the ablation procedure improved outcome in patients with persistent AF. However, this was not seen in a randomised study performed by another group in which 119 patients with persistent AF were randomised to additional CFAE ablation following pulmonary vein isolation or no additional ablation.[60]

In summary, the reports on long-term success rates following catheter ablation for AF demonstrate that the procedure is effective in a selected group of symptomatic patients with AF, although a significant proportion require more than one ablation procedure, there are risks of periprocedural complications and AF recurrence remains a possible problem, even after follow-up periods as long as 5 years. It should be noted that reported outcomes from the different centres cannot be directly compared, since there are differences in patient population (eg, percentage of patients with paroxysmal and permanent AF, patients with structural heart disease), techniques used (segmental pulmonary vein isolation vs wide area circumferential ablation), length of follow-up and methods used to detect AF recurrence.

A number of studies have been performed to search for new non-invasive parameters which may help to predict AF recurrence following catheter ablation. These factors

broze procijenjena ehokardiografijom[63] ili magnetnom rezonancom[64] i vrijednostima BNP.[65]

Ventrikulske aritmije i iznenadna srčana smrt

Ventrikulske aritmije nakon infarkta miokarda

Kako bi shvatili značaj pojavnosti ventrikulskih aritmija u okružju primarne perkutane koronarne intervencije (PCI) učinjena je sekundarna analiza studije APEX AMI.[66] Od 5.745 pacijenata s akutnim infarktom miokarda s elevacijom ST-segmenta koji su bili podvrgnuti primarnoj PCI (u 296 bolnica u 17 zemalja), ventrikulska tahikardija/fibrilacija (VT/VF) je nastupila kod njih 329 (5,7%). Ustanovljeno je da su klinički ishodi i 90-dnevna smrtnost bili su lošiji kod onih pacijenta s VT/VF nego u skupini bez VT/VF. Štoviše, ishodi su bili lošiji ako je VT/VF nastupila kasnije (nakon završetka kateterizacije), a ne ranije (prije završetka kateterizacije srca). Pojava ventrikulskih aritmija ostaje povezana sa značajnim povećanjem smrtnosti nakon prilagodbe za potencijalne dodatne varijable, iako nije jasno jesu li bile uzročno povezane s lošijom prognozom ili su jednostavno bile odraz teže bolesti srca.

U studiji OAT-EP otvaranje trajno okludirane arterije povezane s infarktom primjenom PCI nakon razdoblja akutnog infarkta miokarda (AIM) bio je uspoređen s optimalnom farmakološkom terapijom, kako bi se odredilo koja strategija smanjuje markere vulnerabilnosti od ventrikularskih aritmija.[67] Nije bilo značajnijih razlika u varijabilnosti srčane frekvencije, signalom usrednjenog EKG prema vremenskoj domeni ili varijablama promjenjivosti T-valova (surogati ventrikulske nestabilnosti) između obje skupine nakon 30 dana i 1 godinu po AIM, što je dosljedno s nedostatkom kliničke dobrobiti od PCI kod stabilnih pacijenata nakon AIM s trajno okludiranom arterijom koja je povezana s infarktom u glavnoj OAT studiji.

Studija CARISMA je bila dizajnirana da bi istražila učestalost i prognostičku važnost aritmija detektiranih implatibilnim srčanim monitorima kod pacijenata nakon AIM s oštećenjem funkcije lijeve klijetke (LV).[68] Ukupno 297 (od početnih 5.969) koji su nedavno preboljeli AIM sa sniženom ejekcijskom frakcijom LV (LVEF; ≤40%) je zaprimilo implatibilni uređaj za snimanje srčane frekvencije unutar 11±5 dana od AIM te su praćeni svaka 3 mjeseca u prosječnom trajanju od 1,9±0,5 godina. Istraživači su otkrili klinički značajan broj bradiaritmija i tahiaritmija kod ovih pacijenata (28% novonastalih FA, 13% nepostojana VT, 10% AV blokovi visokog stupnja, 7% značajne sinusne bradikardije, 3% sinusni arest, 3% postojana VT i 3% VF). Intermitentni AV blok visokog stupnja posebno je povezan s veoma visokim rizikom od srčane smrti. Aritmogeni substrat za ventrikulske aritmije nakon reperfuzijske terapije kod AIM je istraživan u studiji kod 36 pacijenata koji su preživjeli AMI te su upućeni na katatersku ablaciju ablaciju VT (13±9 godina nakon AMI).[69] Od njih, 14 pacijenata je imalo ranu reperfuziju tijekom AIM, dok kod 22 nije bilo reperfuzije. Istraživači su, korištenjem detaljnog elektroanatomskog mapiranja, ustanovili da su veličina i uzorak ožiljka bili različiti između VT pacijenata sa i bez reperfuzije tijekom AIM te da su rana reperfuzija i manje zarasli elektroanatomski ožiljci povezani s brzom VT.

include renal impairment,[61] novel echo parameters such as the atrial electromechanical interval,[62] atrial fibrosis assessed with echo[63] or MRI64 and B-type natriuretic levels.[65]

Ventricular arrhythmias and sudden cardiac death

Ventricular arrhythmias after myocardial infarction

To further understand the significance of the occurrence and timing of ventricular arrhythmias in the context of primary percutaneous coronary intervention (PCI), a secondary analysis of the APEX AMI (Assessment of PEXelizumab in Acute Myocardial Infarction) trial was undertaken.[66] Of the 5745 patients with ST-elevation myocardial infarction presenting for primary PCI (across 296 hospitals in 17 countries), ventricular tachycardia/ventricular fibrillation (VT/VF) occurred in 329 (5.7%). Clinical outcomes and 90-day mortality were found to be worse in those with VT/VF than in those without. Furthermore, outcomes were worse if the VT/VF occurred late (after the end of cardiac catheterisation) rather than early (before the end of cardiac catheterisation). The occurrence of ventricular arrhythmias remained associated with a significantly increased mortality after adjustment for potential confounders, although whether they were causally related to a poorer prognosis or simply a reflection of more severe heart disease is not yet clear.

In the Occluded Artery Trial-Electrophysiological Mechanisms (OAT-EP) study, PCI to open a persistently occluded infarct-related artery after an acute myocardial infarction (AMI) phase was compared with optimal medical treatment alone to determine which strategy reduced markers of vulnerability to ventricular arrhythmias.[67] There were no significant differences in HR variability, time-domain signal-averaged ECG, or T-wave variability parameters (all surrogate markers of ventricular instability) between either group at 30 days and 1 year after the AMI, which is consistent with the lack of clinical benefit from PCI in stable patients after AMI with persistently occluded infarct-related arteries in the main OAT study.

The Cardiac Arrhythmias and Risk Stratification After Myocardial Infarction (CARISMA) trial was designed to investigate the incidence and prognostic significance of arrhythmias detected by an implantable cardiac monitor among patients after AMI with impaired left ventricular (LV) function.[68] A total of 297 patients (out of 5,969 initially screened) who had had a recent AMI and had reduced LV ejection fraction (LVEF; ≤40%) received an implantable loop recorder within 11±5 days of the AMI and were followed up every 3 months for an average of 1.9±0.5 years. The investigators detected a clinically significant number of bradyarrhythmias and tachyarrhythmias in these patients (28% new-onset AF, 13% non-sustained VT, 10% high-degree AV block, 7% significant sinus bradycardia, 3% sinus arrest, 3% sustained VT and 3% VF). In particular, intermittent high-degree AV block was associated with a very high risk of cardiac death. The arrhythmogenic substrate for ventricular arrhythmias following reperfusion therapy for AMI was investigated in a study of 36 AMI survivors referred for catheter ablation of VT (13±9 years after the AMI).[69] Of these, 14 patients had early reperfusion during AMI, while 22 were non-reperfused. The investigators found, using detailed electroanatomical mapping, that scar size and pattern

Stratifikacija rizika za iznenadnu srčanu smrt i implatibilni kardioverter defibrilatori

Područje trajnog istraživanja ventrikulskih aritmija i iznenadne srčane smrti (SCD) poboljšava metode stratifikacije rizika i odabira odgovarajućih kandidata za implatibilni kardioverter defibrilator (ICD).[70] Brojni neinvazivni kardiološki testovi su nedavno procijenjeni kod pacijenata s povećanim rizikom od SCD (npr. pacijenti koji su preživjeli AIM i pacijenti s koronarnom bolesti srca i kardiomiopatijom), a rezultati su obećavajući. Ovi testovi uključuju alternans T-valova,[71,72] oslikavanje perfuzije primjenom SPECT,[73] oslikavanje simpatičkih živaca primjenom 123-jod metajodobenzilguanidin scintigrafije[74] i oslikavanje magnetnom rezonancom srca uz primjenu tehnike LGE (late-gadolinium enhancement).[75] Također, plazmatski biomarkeri, poput razine kolagena u serumu, koji odražava promjene vanstaničnog matriksa koje mogu imati ulogu u stvaranju aritmogenog substrata,[76] mogu imati dodatnu ulogu u stratifikaciji rizika. Genski markeri bi također mogli biti značajni, kao što to ukazuju zapažanja iz kombinirane populacije od 19.295 crnaca i bijelaca iz ARIC studije i CHS studije da su sekvencijske varijacije u adaptor proteinu sintaze 1 nitričnog oksida (NOS1AP) povezane s bazalnim QT intervalom i rizikom od SCD kod odraslih američkih bijelaca (no ne i kod crnaca).[77,78]

Još jedno važno područje koje traži dodatno razjašnjavanje je optimalno vrijeme implantacije ICD kod pacijenata koji su preživjeli AIM te za koje se smatra da imaju najveći rizik od SCD. Ključna studija DINAMIT nije pokazala nikakvu dobrobit od profilaktičke implantacije ICD pacijentima koji su preživjeli AIM mjerenu smanjenjem smrtnosti ukoliko je ICD implantiran unutar 40 dana od AIM, što je implementirano u smjernice. Nedavna sekundarna analiza ove studije je potvrdila originalne rezultate da je smanjenje učestalosti iznenadne smrti kod pacijenata s ICD kompenzirana povišenom učestalosti nearitmijskih smrti,najčešće kod onih pacijenata koji su primili šokove sa ICD.[80]

Postmortem studija koja je proučavala 105 zapisa autopsija pacijenata iz studije VALIANT koji su umrli iznenada je pokazala da su rekurentni infarkt miokarda ili ruptura srca bili odgovorni za veći udio iznenadnih smrti u ranom razdoblju nakon AIM te je tako objasnila nedostatak dobrobiti od rane implantacije ICD mjeren ukupnom smrtnosti.[81] Bila je veća vjerojatnost da će aritmijska smrt nastupiti kasnije (nakon tri mjeseca), što je u skladu s rezultatima poboljšanog preživljavanja među primateljima ICD u drugim važnim studijama u kojima je ICD implantiran u kasnijem stadiju. Međutim, treba napomenuti da se za 20% iznenadnih smrti u prvom mjesecu nakon AIM pretpostavilo da su aritmijske budući nije bilo specifičnih postmortalnih dokaza bilo kakve dodatne abnormalnosti koje bi mogle uzrokovati iznenadnu smrt. Stoga se čini da značajan dio pacijenata koji imaju AIM u ranom postinfarktnom razdoblju i dalje iznenadno umire od srčanih aritmija. Ovi pacijenti nisu uključeni u trenutne međunarodne smjernice za implantaciju ICD te ostaju skupina za koju su potrebne dodatne studije. Još jedna skupina pacijenata koji nisu pokriveni trenutnim ICD smjernicama za primarnu prevenciju su oni s relativno očuvanom LVEF nakon AIM. Iako ovi pacijenti imaju niži rizik od SCD od onih s lošom

were different between VT patients with and without reperfusion during AMI, with early reperfusion and less confluent electroanatomical scar being associated with faster VTs.

Risk stratification for sudden cardiac death and implantable cardioverter defibrillators

A continuing area of active research in ventricular arrhythmias and sudden cardiac death (SCD) is in improved methods of risk stratification and selection of appropriate implantable cardioverter defibrillator (ICD) recipients.[70] A number of non-invasive cardiovascular tests have recently been evaluated among patients with an increased risk of SCD (eg, AMI survivors and patients with coronary artery disease and cardiomyopathies) with promising results. These include T-wave alternans,[71,72] single-photon emission CT myocardial perfusion imaging,[73] sympathetic nerve imaging with 123-iodine metaiodobenzylguanidine[74] and late-gadolinium enhancement on cardiac MRI.[75] In addition, plasma biomarkers, such as serum collagen levels, which reflect extracellular matrix alterations that may play a part in the generation of the arrhythmogenic substrate,[76] may have a future role in risk stratification. Genetic markers may also be relevant, as suggested by the observation from a combined population of 19,295 black and white adults from the Atherosclerosis Risk In Communities Study and the Cardiovascular Health Study that sequence variations in the nitric oxide synthase 1 adaptor protein (NOS1AP) were associated with baseline QT interval and the risk of SCD in white (but not black) US adults.[77,78]

Another important area requiring further clarification is the optimal timing of ICD insertion among AMI survivors who are deemed to be at greatest risk of SCD. The landmark DINAMIT study (Defibrillation IN Acute Myocardial Infarction Trial), which did not show any mortality benefit from prophylactic ICD insertion in patients after AMI if the device was inserted within 40 days of the index event,[79] has been used to guide current recommendations on ICD insertion among AMI survivors. A recent secondary analysis of this trial confirmed the original findings that the reduction in sudden death in ICD patients was offset by an increase in non-arrhythmic deaths, which was greatest in those who received ICD shocks.[80]

A postmortem study looking at 105 autopsy records of patients from the VALIANT (VALsartan In Acute myocardial infarctioN Trial) study who had died suddenly showed that recurrent myocardial infarction or cardiac rupture accounted for a high proportion of sudden death in the early period after an AMI, thereby partly explaining the lack of benefit of early ICD insertion on overall mortality.[81] Arrhythmic death was more likely to occur later on (after 3 months), which is consistent with the findings of improved survival among ICD recipients from other major ICD trials in which the devices were inserted at a later stage. It should be noted, however, that 20% of sudden deaths in the first month after AMI were presumed arrhythmic as there was no specific postmortem evidence of any additional abnormality that might have caused the sudden death. A significant proportion of patients who have an AMI therefore appear to continue to die suddenly in the early postinfarction period from cardiac arrhythmias. These patients are not included in current international guidelines for ICD insertion and remain a group for which more research is re-

LVEF predstavljaju veći dio pacijenata koji su preživjeli AIM.

Podaci iz multicentrične japanske studije ukazuju da u okružju primarne PCI postoji niža učestalost SCD među pacijentima koji su preživjeli AMI (ukupna smrtnosti je iznosila 13,1%, a SCD tijekom prosječnog razdoblja praćenja od 4,2 godine kod 4.122 pacijenta je iznosila 1,2%).[82] Rizik je bio najviši za one s lošom LVEF (<30%), iako je apsolutni broj za najveći rizik bio kod onih koji su imali relativno očuvanu LVEF (>40%).

Studija IRIS objavljena 2009. godine testirala je hipotezu da rana implantacija ICD odmah nakon AIM može poboljšati preživljavanje u usporedbi s optimalnom farmakološkom terapijom.[83] Ovo je bila randomizirana, prospektivna, multicentrična studija s uključenih 898 pacijenata, od 5. do 31. dana nakon AIM, koji su zadovoljili sljedeće kliničke kriterije: LVEF ≤40% i srčana frekvencija ≥90/min na prvom dostupnom EKG ili nepostojana VT (≥150/min) za vrijeme registracije 24-satnog EKG. Glavna razlika između spomenute i studije DINAMIT je bila moderna populacija pacijenata (70% je liječeno primjenom PCI i većina je primala optimalno dugoročnu terapiju) te dodatnim neinvazivni kriteriji za identifikaciju populacije s potencijalno višim rizikom. Međutim, istraživači nisu ustanovili da primjena ICD smanjuje ukupnu smrtnost nakon srednjeg praćenja od 37 mjeseci. Dosljedno nalazima studije DINAMIT, smanjena učestalost SCD kod pacijenata s implantiranim ICD u studiji IRIS je poništena povećanom učestalosti smrtnih ishoda koji nisu nastupili naglo.

Kateterska ablacija ventrikulskih aritmija

Studija VTACH uključila je 16 centara u četiri europske zemlje, a procjenjivala je potencijalnu dobrobit od kateterske ablacije VT prije implantacije ICD kod pacijenata s anamnezom VT, infarkta miokarda i LVEF ≤50%.[84] Pacijenti (n=110) su bili randomizirani na katetersku ablaciju i ICD ili samo ICD te su bili praćeni u srednjem trajanju od 22,5±9,0 mjeseci. Istraživači su ustanovili da profilaktička ablacija VT prije implantacije ICD produljuje vrijeme do povrata VT s 5,9 mjeseci (IQR 0,8-26,7) u skupini koja je liječena samo implantacijom ICD na 18,6 mjeseci (donja kvartila 2,4 mj.; gornja kvartila se nije mogla odrediti) u ablacijskoj i ICD skupini. Komplikacije vezane za postupak ablacije su nastupile kod dva pacijenta. Rezultati ove studije su u skladu s ranijom prospektivnom randomiziranom studijom s uključenih 128 pacijenata koja je dokazala da profilaktička kateterska ablacija ventrikulskog aritmogenog supstrata smanjuje učestalost liječenja primjenom ICD kod pacijenata s anamnezom infarkta miokarda i ranijim ventrikulskim aritmijama.[85] Treba napomenuti da je u obje ove studije ablacija VT bila obavljena u iskusnim centrima te da nije bilo značajnijeg utjecaja kateterske ablacije na ukupnu smrtnost. Da li bi se ablacija VT trebala rutinski učiniti prije implantacije ICD u svrhu sekundarne prevencije SCD kod stabilnih pacijenata s prethodnim infarktom miokarda tek treba utvrditi.

Postoji porast broja publikacija o epikardijalnoj ablaciji VT tijekom posljednjih nekoliko godina obzirom da se sve VT ne mogu uspješno eliminirati isključivo endokardijalnim pristupom.[86,87] U retrospektivnoj studiji 156 epikardijalnih ablacija radi VT (od ukupno 913 ablacija VT) u tri

quired. Another group of patients who are not covered by current primary prevention ICD guidelines are those with relatively preserved LVEF after an AMI. Although these patients are at lower risk of SCD than those with poor LVEF, they represent a larger proportion of AMI survivors.

Data from a multicentre Japanese study suggest that in the era of primary PCI there is a low incidence of SCD among AMI survivors (overall mortality was 13.1% and SCD 1.2% over an average follow-up period of 4.2 years among 4,122 patients).82 The risk was highest for those with poor LVEF (<30%), although the absolute number at risk was greatest in those with relatively preserved LVEF (>40%).

The Intermediate Risk Stratification Improves Survival (IRIS) trial published in 2009 further tested the hypothesis that early implantation of an ICD soon after an AMI could improve survival compared with optimal medical treatment.[83] This was a randomised, prospective, multicentre trial which enrolled 898 patients, 5-31 days after their AMI, who met the following clinical criteria: LVEF ≤40% and a HR ≥90 bpm on the first available ECG or non-sustained VT (≥150 bpm) during Holter monitoring. The main difference between this study and DINAMIT was a contemporary patient population (70% had undergone PCI and the majority were receiving optimal long-term medication) and additional non-invasive criteria to identify a population at potentially higher risk. However, the investigators did not find that ICD therapy reduced overall mortality after a mean follow-up of 37 months. Consistent with the findings from DINAMIT, the reduced incidence of SCD among ICD recipients in the IRIS study was offset by an increased incidence of non-SCD.

Catheter ablation of ventricular arrhythmias

The VTACH (Ventricular Tachycardia Ablation in Coronary Heart disease) study, involving 16 centres in four European countries, assessed the potential benefit of catheter ablation of VT before ICD implantation in patients with a history of VT, myocardial infarction and LVEF ≤50%.[84] Patients (n=110) were randomly allocated to receive catheter ablation and an ICD or an ICD alone and followed-up for a mean period of 22.5 months (SD 9.0). The investigators found that prophylactic VT ablation before ICD implantation prolonged the time to VT recurrence from 5.9 months (IQR 0.8-26.7) in the ICD only group to 18.6 months (lower quartile 2.4 months; upper quartile could not be determined) in the ablation and ICD group. Complications related to the ablation procedure occurred in two patients. This study is in accordance with an earlier prospective randomised study of 128 patients, which demonstrated that prophylactic catheter ablation of the ventricular arrhythmogenic substrate reduced the incidence of ICD therapy in patients with a history of myocardial infarction and previous ventricular arrhythmias.[85] It should be noted that VT ablation was performed in experienced centres in both these trials and that there was no significant effect of catheter ablation on overall mortality. Whether VT ablation should routinely be performed before ICD insertion for secondary prevention of SCD in stable patients with previous myocardial infarction remains to be determined.

There has been an increase in the number of publications on epicardial ablation for VT over the past few years

tercijarna centra evaluacija sigurnosti i srednjoročnih komplikacija eprikardijalne ablacije VT, ustanovljeno je da je rizik od značajnih akutnih (epikardijalno krvarenje, koronarna stenoza) i odgođenih (perikardijalna upalna reakcija, odgođena tamponada, koronarna okluzija) komplikacija povezanih s epikardijalnim pristupom 5%, odnosno 2%. Stoga, iako ova tehnika može biti učinkovita u nekim slučajevima, naročito tamo gdje endokardijalna ablacija nije uspjela, povezana je sa značajnim morbiditetom te bi se trebala obavljati isključivo u centrima koji su iskusni u ovoj tehnici.

Prognostički značaj učestalih ventrikulskih ekstrasistola (VES) i učinak kateterske ablacije ovih ektopija su nedavno izazvale dodatnu pozornost. U studiji s uključenih 239 asimptomatskih pacijenata s urednom srčanom strukturom i učestalim VES (>1000/dnevno) iz desnog ili lijevog ventrikularnog izlaznog trakta, tijekom razdoblja od 5,6±1,7 godina zapažena je značajna negativna povezanost između učestalosti VES i promjene LVEF te pozitivna povezanost s promjenom dijastoličkog promjera LV.[89] Uz opterećenje zbog VES, ostali čimbenici poput duljeg trajanja VES, prisutnost nepostojane VT, polimorfnih VES i VES iz desne klijetke mogu biti povezani sa sniženjem funkcije LV.[90,91] Iako je dobro poznato da kateterska ablacija učestalih VES može poboljšati i obnoviti funkciju LV kod nekih pacijenata, potencijalna dobrobit od ablacije kod pacijenata s normalnom funkcijom LV je mnogo manje proučavana. Prospektivna studija kod 49 pacijenata s učestalim VES i normalnom bazalnom LVEF je primjenom analize speckle tracking oslikavanja pokazala da kateterska ablacija može poboljšati jedva zamjetnu disfunkciju LV utvrđenu prije ablacije.[92] Ostaju neodgovorena pitanja poput onog o dobrobiti od kateterske ablacije na krajnje ishode (naročito smrtnost) te kada bi trebalo učiniti ablaciju (stupanj opterećenja zbog VES, funkcija LV, nakon pokušaja s antiaritmicima?).

Srčana resinkronizacijska terapija i elektrostimulacija

U posljednje dvije godine su objavljene dvije ključne kliničke studije srčane resinkronizacijske terapije (CRT) koje potencijalno proširuju indikacije za CRT kod pacijenata sa ZS na one sa simptomima NYHA I. i II. stupnja. Studija MADIT-CRT je usporedila uporabu ICD s CRT-D (CRT s komponentom defibrilatora) kod pacijenata s asimptomatskim ili blago simptomatskim simptomima ZS (NYHA I. ili II. stupnja), LVEF ≤30% i trajanjem QRS ≥130 ms.[93] Tijekom prosječnog vremena praćenja od 2,4 godine, manje pacijenata u skupini s CRT-D je doživjelo primarne zajedničke ishode (smrtnost od svih uzroka i ZS) u usporedbi sa skupinom s ICD (17,2% naspram 25,3%, p=0,001). Iako se na prvi pogled ovi rezultati čine impresivni, podrobnija analiza podataka otkriva da je glavna prednost CRT-D bila u snižavanju učestalosti hospitalizacije zbog ZS te nije bilo registrirane značajne razlike u smrtnosti između obje skupine (koji je iznosio 3% godišnje). Nadalje, studija nije dokazala da pacijenti u I. stupnju prema NYHA ljestvici ispunjavaju kriterije za dobrobit primjene CRT-D.

U studiji RFAT primjena CRT-D je uspoređena s ICD kod pacijenata sa ZS u II. ili III. stupnju prema NYHA, LVEF

in view of the realisation that not all VTs can be successfully eliminated by an endocardial-only approach.86,87 In a retrospective study of 156 epicardial ablations for VT (out of a total of 913 VT ablations) in three tertiary centres evaluating the safety and mid-term complications of epicardial VT ablation, the risk of major acute (epicardial bleeding, coronary stenosis) and delayed (pericardial inflammatory reaction, delayed tamponade, coronary occlusion) complications related to epicardial access was found to be 5% and 2%, respectively.[88] Therefore, although this technique can be effective in some cases, especially where endocardial ablation has failed, it is associated with significant morbidity and should only be performed in centres experienced with this technique.

The prognostic significance of frequent premature ventricular contractions (PVCs) and the effect of catheter ablation of these ectopics has received further attention recently. In a study of 239 asymptomatic patients with structurally normal hearts and frequent PVCs (>1000/day) from the right or left ventricular outflow tract, a significant negative correlation between PVC prevalence and δLVEF and positive correlation with δLV diastolic diameter was observed over a 5.6 (SD 1.7)-year period.[89] In addition to PVC burden, other factors such as longer PVC duration, presence of non-sustained VT, multiform PVCs and right ventricular PVCs may be associated with a decline in LV function.[90,91] Although it is well known that catheter ablation of frequent PVCs can improve and restore LV function in some patients, the potential benefits of ablation in patients with normal LV function have been less well studied. A prospective study of 49 patients with frequent PVCs and normal baseline LVEF demonstrated that catheter ablation can improve the subtle LV dysfunction-detected pre-ablation using speckle tracking imaging analysis.[92] However, unanswered questions remain, including benefits of catheter ablation on hard end points (especially mortality) and when ablation should be performed (degree of PVC burden, LV function, after a trial of antiarrhythmic medication?).

Cardiac resynchronisation therapy and pacing

Two pivotal cardiac resynchronisation therapy (CRT) clinical trials have been published in the past 2 years that potentially expand the indications for CRT in patients with HF to those in NYHA class I and II symptoms. MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-CRT) compared the use of ICD alone with CRT-D (CRT with a defibrillator component) in patients with asymptomatic or mildly symptomatic HF symptoms (NYHA class I or II), LVEF≤30% and QRS duration of ≥130 ms.[93] During an average follow-up of 2.4 years, fewer patients in the CRT-D group experienced the primary composite end point (all-cause mortality and HF) compared with the ICD group (17.2% compared with 25.3%, respectively, p=0.001). Although these results appear impressive at first glance, closer examination of the data reveals that the main superiority of CRT-D was in reducing the rate of hospitalisation for HF and that there was no significant difference in mortality between the two groups (which was 3% annually). Furthermore, the study failed to show that NYHA class I patients fulfilling the enrolment criteria benefited from CRT-D.

In RAFT (Resynchronisation-Defibrillation for Ambulatory Heart Failure Trial), CRT-D was compared with ICD

≤30%, stvarnim trajanjem QRS ≥120 ms ili trajenjem QRS uz elektrostimulaciju ≥200 ms.[94] Istraživači su ustanovili da je tijekom srednjeg razdoblja od 40 mjeseci, primarni ishod (smrtnost od svih uzroka ili hospitalizacija zbog ZS) nastupio kod manje pacijenata u skupini na CRT-D (33,2% naspram 40,3% u skupini ICD, p<0,001). Za razliku od studije MADIT-CRT, studija RFAT je dokazala da CRT-D značajno smanjuje ukupnu i kardiovaskularnu smrtnost u usporedbi s ICD, iako je u skupini CRT-D uočeno više neželjenih događaja koji su bili povezani s uređajem. Mogući razlozi dobrobiti na smrtnost koji je registriran u studiji RFAT, no ne i u MADIT-CRT studiji, su da je studija RFAT uključivala pacijente sa značajno uznapredovalom bolesti (i većim udjelom ishemijske bolesti srca) te je praćenje bilo dulje i potpunije.

Od tada je provedeno niz podanaliza studije MADIT-CRT kako bi se dobilo više informacija. Jedna podanaliza je dokazala da je kod žena registrirano znatno veće sniženje smrtnosti od svih uzroka i ZS nego kod muškaraca, što je bilo popraćeno većim ehokardiografskim dokazima o reverznom modeliranju srca.[95] Druga podanaliza koja je bila specifično usmjerena na ehokardiografske varijable i učinkovitost između obje skupine je ustanovila da je u skupini na CRT značajno poboljšana veličina i učinkovitost srca u usporedbi sa skupinom na ICD, što je vjerojatno rezultiralo boljim ishodima u skupini CRT-D.[96] Druge studije su također donijele ehokardiografske dokaze da CRT kod blagog stupnja ZS (I./II. stupanj prema NYHA) donosi veće strukturalno i funkcijsko reverzno remodeliranje koji može spriječiti progresiju bolesti.[97,98] Studija PACE je istraživala da li je biventrikulska elektrostimulacija bila bolja od apikalne elektrostimulacije desne klijetke za prevenciju neželjenog srčanog remodeliranja kod pacijenata s bradikardijom i normalnom početnom funkcijom klijetki.[99] U ovoj manjoj randomiziranoj studiji sa 177 pacijenata koji su praćeni u razdoblju od 12 mjeseci istraživači su ustanovili da je srednja LVEF bila značajno niža u skupini s desnostranom nego u skupini s biventrikulskom elektrostimulacijom (54,8±9,1% naspram 62,2±7,0%, p<0,001), uz apsolutnu razliku od 7,4%. Međutim, korisni učinci biventrikulske elektrostimulacije na ehokardiografske varijable u ovoj skupini pacijenata nisu bili popraćeni kliničkom dobrobiti.

Druga važna i kontinuirana područja istraživanja na području CRT uključuju kako najbolje odabrati kandidate koji će najbolje odgovoriti na primjenu CRT i kako optimizirati odgovor. Varijable za poboljšanje odabira pacijenata koji su nedavno proučavani uključuju morfologiju QRS iz studije MADIT-CRT (čini se da je uzorak bloka lijeve grane predominantna morfologija povezana s odzivom više nego drugi oblici),[100] početna radijalna disinkronija LV, položaj elektrode u LV i oživljak miokarda u području elektrode za elektrostimulaciju u LV,[101] i sistolička disinkronija mjerena tkivnim Dopplerom prije elektrostimulacije.[102] U skladu s postojećim znanjem, potvrđeno je da je pozicioniranje elektrode LV bilo važno za pacijente u studiji MADIT-CRT[103] i u pacijenata s neishemijskom dilatativnom kardiomiopatijom.[104] Prospektivna, randomizirana studija SMART-AV je usporedila tri različite metode AV optimizacije (fiksna empirijska AV odgoda od 120 ms, ehokardiografski optimizirana AV odgoda ili AV optimizacija temeljena na EKG algoritmu) kod 980 pacijenata s

alone in patients with NYHA class II or III HF, LVEF≤30%, intrinsic QRS duration ≥120 ms or a paced QRS duration of ≥200 ms.[94] The investigators found that over a mean period of 40 months, the primary outcome (all-cause mortality or HF hospitalisation) occurred in fewer patients in the CRT-D group (33.2% compared with 40.3% in the ICD group, p<0.001). Unlike MADIT-CRT, RAFT demonstrated that CRT-D significantly reduced overall mortality and cardiovascular mortality compared with ICD alone, although more adverse device-related events were also seen in the CRT-D group. Possible reasons for mortality benefit seen in RAFT, but not MADIT-CRT, are that RAFT included patients with more advanced disease (and a higher proportion with ischaemic heart disease) and follow-up was longer and more complete.

A number of subanalyses of MADIT-CRT have since been conducted to provide further information on the findings. One subanalysis demonstrated that women experienced significantly greater reductions in all-cause mortality and HF than men, which was accompanied by greater echo evidence of reverse cardiac remodelling.[95] Another subanalysis looking specifically at the echo parameters and performance between the two groups found that CRT significantly improved cardiac size and performance compared with the ICD-only strategy, which probably accounted for the outcomes benefit in the CRT-D group.[96] Other studies have also provided additional echo evidence that CRT in mild HF (NYHA class I/II) results in major structural and functional reverse remodelling which may prevent disease progression.[97,98] The PACE (Pacing to Avoid Cardiac Enlargement) study explored whether biventricular pacing was better than right ventricular (RV) apical pacing in preventing adverse cardiac remodelling in patients with bradycardia and normal ventricular function at baseline.[99] In this small randomised study of 177 patients followed up over a 12-month period, the investigators found that the mean LVEF was significantly lower in the RV-pacing group than in the biventricular-pacing group (54.8±9.1% vs 62.2±7.0%, p<0.001), with an absolute difference of 7.4% points. However, the beneficial effects of biventricular pacing on echo parameters in this group of patients were not accompanied by any clinical benefit.

Other important and continuing areas of investigation in the field of CRT include how best to select candidates who are most likely to respond to CRT and how to optimise response. Parameters that have recently been studied to improve patient selection include QRS morphology in MADIT-CRT (left bundle branch block (LBBB), rather than non-LBBB, patterns appears to be the predominant morphology-that is, related to response),[100] baseline LV radial dyssynchrony, discordant LV lead position, and myocardial scar in the region of the LV pacing lead,[101] and pre-pacing systolic dyssynchrony measured by tissue Doppler imaging velocity.[102] Consistent with existing knowledge, LV lead positioning has been reconfirmed to be important in MADIT-CRT patients[103] and patients with non-ischaemic dilated cardiomyopathy.[104] The prospective, randomised SMART-AV (SmartDelay determined AV optimisation: a comparison with other AV delay methods used in CRT) study compared three different methods of AV optimisation (fixed empirical AV delay of 120 ms, echo-optimised AV delay, or AV optimisation with an ECG-based algorithm) in 980 patients with a CRT device to determine if any method

CRT uređajem kako bi se utvrdilo koja je metoda najbolja.[105] Studija je ustanovila da niti jedna optimizacija nije bolja od fiksne AV odgode od 120 ms te je stoga zaključila da se ne preporuča rutinsko korištenje tehnika AV optimizacije. Međutim, podaci nisu isključili mogućnost da AV optimizacija može imati ulogu kod odabranih pacijenata koji ne odgovaraju na empirijske postavke CRT.

Potencijalno štetni učinci kroničnog elektrostimulacije desne klijetke na srčanu funkciju su preispitani kod 103 pacijenta s izoliranim kongenitalnim AV blokom. Nije utvrđeno da je dugoročna elektrostimulacija bila povezana s razvojem ZS ili pogoršanjem ventrikulske funkcije kod pacijenata koji su bili negativni na antinuklearna protutijela, iako su pacijenti koji su bili pozitivni na protutijela imali veću šansu razvoja ZS.[106] Elektrostimulacija kod hipertrofijske kardiomiopatije je bila također nedavno istraživana u studiji provedenoj u jednom centru, koja je, nakon razdoblja praćenja od 10 godina, pronašla određene dokaze dobrobiti od elektrostimulacije obje klijetke kod pacijenata s hipertrofijskom kardiomiopatijom sa simptomima III./IV. stupnja prema NYHA, gradijentu u mirovanju od >50 mmHg te koji su bili refraktorni na druge lijekove.[107] Druga skupina pacijenata kod kojih je uloga elektrostimulacije ostala kontroverzna su oni s hipersenzitivnim karotidnim sinusom (CHS) i sinkopom. U dvostruko slijepoj, placebom kontroliranoj, unakrsnoj studiji, 34 pacijenta (dob >55 godina) s CSH i više od tri neobjašnjena pada tijekom prethodnih 6 mjeseci bilo je randomizirano na dvokomorni elektrostimulator s programiranjem odziva na pad frekvencije koje je bilo uključeno ili isključeno.[108] Istraživači su ustanovili da intervencija elektrostimulatorom nema učinak na broj padova i zaključili da uloga elektrostimulacije u ovoj skupini pacijenata ostala kontroverzna. Sličan zaključak je bio i u multicentričnoj studiji s 141 pacijentom (srednja dob 78 godina) s kardioinhibitornim CHS.[109]

Nasljedne aritmogene bolesti

Tijekom posljednje dvije godine registriran je značajan napredak u razumijevanju osnovnih mehanizama, genetike i kliničkih značajki nasljednih aritmogenih bolesti (IAD). Kako nije moguće sve obraditi u ovom kratkom pregledu, spomenut ćemo samo neke od glavnih studija s važnim implikacijama za opće kardiologe. Brzo širenje znanja o genskoj pozadini IAD i porast komercijalno dostupnih kliničkih genskih usluga je sa sobom donijelo dodatnu dimenziju upravljanja ovim stanjima. Čitatelje upućujemo na niz korisnih nedavno objavljenih preglednih članaka.[110-112]

Iznenadna srčana smrt bez morfološke bolesti srca registrirana je u 23% slučajeva u nedavnoj patološkoj studiji sa sportašima iz Ujedinjenog Kraljevstva.[113] Mogući uzroci neobjašnjenog srčanog zastoja bili su sistematski evaluirani u prospektivnoj studiji koja je uključivala 63 pacijenta u devet centara diljem Kanade.[114] Testovi, koji su uključivali srčanu MRI, na signalu usrednjenog EKG, ergometrijsko testiranje, ispitivanje na droge i selektivno elektrofiziološko ispitivanje (EP) rezultirali su specifičnom dijagnozom (IAD, rana repolarizacija, koronarni spazam i miokarditis) kod 35 pacijenata (56%). Smatralo se da preostalih 28 pacijenata ima idiopatsku VF. Dodatna genska testiranja obavljena na 19 pacijenata su našla dokaze

was superior.[105] The study found that neither echo- or ECG-based AV optimisation was better than a fixed AV delay of 120 ms and therefore concluded that the routine use of AV optimisation techniques was not indicated. However, the data did not exclude the possibility that AV optimisation might have a role in selected patients who do not respond to CRT with empirical settings.

The potentially deleterious effects of chronic RV pacing on cardiac function were re-examined in 103 patients with isolated congenital AV block. Long-term pacing was not found to be associated with the development of HF or deterioration of ventricular function in patients who were negative for antinuclear antibody, although patients who tested positive for the antibody were more likely to develop HF.[106] Pacing in hypertrophic cardiomyopathy was also recently re-examined in a single-centre study, which found some evidence of benefit from dual chamber pacing in patients with hypertrophic cardiomyopathy with NYHA III-IV symptoms, rest gradients of >50 mm Hg and who were refractory to other drugs, after follow-up periods of up to 10 years.[107] Another group of patients in whom the role of pacing has remained controversial are those with carotid sinus hypersensitivity (CSH) with syncope. In a double-blind, placebo-controlled, crossover study, 34 patients (aged >55 years) with CSH and more than three unexplained falls in the preceding 6 months were randomised to receive a dual-chamber pacemaker with rate-drop response programming which was switched on or off.[108] The investigators found that the pacing intervention had no effect on the number of falls and concluded that the role of pacing for this group of patients remains controversial. A similar conclusion was reached in a multicentre study of 141 patients (mean age 78 years) with cardioinhibitory CSH.[109]

Inherited arrhythmogenic diseases

Major advances have been made in our understanding of the basic mechanisms, genetics and clinical features of the inherited arrhythmogenic diseases (IADs) over the past two years. Since these cannot all be covered in this short overview, only some of the major studies with important implications for general cardiologists will be mentioned. The rapid expansion in our knowledge of the genetic basis of the IADs and rise in commercially available clinical genetic services has brought with it an additional dimension to how we manage these conditions. The reader is referred to a number of useful recently published reviews that examine these issues in more detail.[110-112]

SCD without morphological evidence of heart disease accounted for 23% of cases in a recent pathological study of UK athletes.[113] Potential causes of unexplained cardiac arrest were systematically evaluated in a prospective study involving 63 patients in nine centres across Canada.[114] The tests, which included cardiac MRI, signal-averaged ECG, exercise testing, drug challenge and selective electrophysiology (EP) testing, resulted in a specific diagnosis (IAD, early repolarisation, coronary spasm and myocarditis) in 35 patients (56%). The remaining 28 patients were considered to have idiopathic VF. Subsequent genetic testing performed in 19 patients found evidence of causative mutations in nine (47%) of these. Family screening of 64 family members of the nine patients with causative mutations led

uzročnih mutacija kod njih devet (47%). Obiteljski probir 64 člana obitelji od devet pacijenata s uzročnim mutacijama je dovelo do otkrića mutacija kod 15 pojedinaca (23%) koji su nakon toga liječeni. Ove studije daju dokaze da ciljna genska testiranja mogu odigrati ulogu pri dijagnosticiranju genski posredovanih aritmijskih sindroma, koji mogu rezultirati uspješnim obiteljskim probirom.

Važna studija koja je istraživala prisutnost genskih čimbenika ili modifikatora koji bi djelomično mogli objasniti fenomen nepotpune penetracije registrirane u kongenitalnom long QT sindromu (LQTS) je utvrdila NOS1AP kao jedan od kandidata.[115] Ovaj protein je odabran temeljem prethodnih studija koje su pokazale vezu između genskih varijacija NOS1AP i malih kvantitativnih povećanja QT intervala s povećanim rizikom od smrti u općoj populaciji.[77,116] U studiji koja je uključivala južnoafričku populaciju s LQTS (500 ispitanika, 205 nositelja mutacija), ustanovljeno je da su NOS1AP varijacije značajno povezane s pojavom simptoma, kliničkom težinom (uključujući srčani zastoj i SCD) i većom vjerojatnosti postojanja QT intervala u gornjih 40% vrijednosti među svim nositeljima mutacija. U drugoj studiji kod 901 pacijenata uključenih u prospektivni registar LQTS, tri NOS1AP markera pojedinačnih polimorfiznih nukleotida (SNPs rs4657139, rs16847548 i rs10494366) su genotipizirana kako bi procijenili učinke varijantnih alela na QTc i na učestalost kardioloških događaja.[117] Istraživači su ustanovili da su varijantne alele označene sa SNPs rs4657139 i rs16847548 povezane s prosječnim QTc produljenjem od 7 i 8 ms, dok su rs4657139 i rs10494366 povezani s povećanom učestalosti kardioloških događaja. Nadalje, manja alela rs10494366 je bila neovisni prognostički marker među pacijentima s QTc <500 ms, no ne i u cijeloj kohorti. Ove dvije studije ukazuju da gensko testiranje na varijante u NOS1AP i obilježenim SNP mogu biti klinički korisni za stratifikaciju rizika kod pacijenata s kongenitalnim LQTS i potencijalno voditi izbor terapijskih strategija.

Registar FINGER (Francuska, Italija, Nizozemska, Njemačka), jedna od do sada najvećih serija pacijenata s Brugada sindromom (BrS), uključila je 1.029 uzastopnih pojedinaca (745 muškaraca; 72%) s BrS (sa spontanim ili lijekovima potaknutim tipom I prema EKG) koji su praćeni u srednjem razdoblju od 31,9 mjeseci.[118] Učestalost srčanih događaja godišnje je bila 7,7% kod pacijenata s prekinutom SCD, 1,9% kod pacijenata sa sinkopama i 0,5% kod asimptomatskih pacijenata. Ova studija daje važne informacije da je učestalost događaja među asimptomatskim pacijentima s Brugada EKG promjenama (što je činilo 64% pacijenata u registru) niska. Također, simptomi i spontani tip 1 promjena u EKG su predstavljali prediktore aritmijskih događaja, dok spol, obiteljska anamneza SCD, inducibilnost VT tijekom EP i prisutnost SCN5A mutacije nisu bili prediktivni za aritmijske događaje.

U interesantnoj studiji koja je istraživala mehanizam BrS, na desnoj klijetki 18 pacijenata s BrS i kod njih 20 iz kontrolne skupine obavljeno je in vivo mapiranje pomoću nekontaktne maping mreže.[119] Identificiran je značajan regionalni endokardijalni zastoj provođenja i heterogenot kod repolarizacije u pacijenata s BrS te su pretpostavili da zone spore provodnje možda imaju ulogu u nastanku i održavanju ventrikulskih aritmija.

to the discovery of mutations in 15 individuals (23%), who were subsequently treated. This study provides evidence that targeted genetic testing may play a part in helping to diagnose genetically mediated arrhythmia syndromes, which may result in successful family screening.

An important study that investigated the presence of genetic factors or modifiers that could partly explain the phenomenon of incomplete penetrance seen in congenital long QT syndrome (LQTS) identified the nitric oxide synthase 1 adaptor protein (NOS1AP) as one such candidate.[115] This protein was chosen on the basis of previous studies that showed an association between genetic variants of NOS1AP and small quantitative increases in the QT interval and an increased risk of death in a general population.[77,116] In the study involving a South African LQTS population (500 subjects, 205 mutation carriers), NOS1AP variants were found to be significantly associated with the occurrence of symptoms, clinical severity (including cardiac arrest and SCD) and a greater likelihood of having a QT interval in the top 40% of values among all mutation carriers. In another study involving 901 patients enrolled in a prospective LQTS registry, three NOS1AP marker single nucleotide polymorphisms (SNPs rs4657139, rs16847548 and rs10494366) were genotyped to assess the effect of variant alleles on QTc and on the incidence of cardiac events.[117] The investigators found that variant alleles tagged by SNPs rs4657139 and rs16847548 were associated with an average QTc prolongation of 7 and 8 ms, respectively, whereas rs4657139 and rs10494366 were associated with an increased incidence of cardiac events. Furthermore, the rs10494366 minor allele was an independent prognostic marker among patients with QTc <500 ms, but not in the entire cohort. These two studies demonstrate that genetic testing for variants in the NOS1AP and tagged SNPs may be clinically useful for risk stratification of patients with congenital LQTS and potentially guide the choice of therapeutic strategies.

The FINGER (France, Italy, Netherlands, GERmany) registry, one of the largest series on patients with Brugada syndrome (BrS) so far, involved 1,029 consecutive individuals (745 men; 72%) with BrS (with a spontaneous or drug-induced type I ECG) who were followed up for a median period of 31.9 months.[118] The cardiac event rate per year was 7.7% in patients with aborted SCD, 1.9% in patients with syncope and 0.5% in asymptomatic patients. This study provides important information that the event rate among asymptomatic patients with a Brugada ECG (which comprised 64% of subjects in the registry) is low. In addition, symptoms and a spontaneous type 1 ECG were predictors of arrhythmic events, whereas gender, familial history of SCD, inducibility of VTs during an EP study and the presence of an SCN5A mutation were not predictive of arrhythmic events.

In an interesting mechanistic study of BrS, in vivo high-density mapping using non-contact mapping array was performed in the right ventricle of 18 patients with BrS and 20 controls.[119] The investigators identified marked regional endocardial conduction delay and heterogeneities in repolarisation in patients with BrS and proposed that the slow-conduction zones may have a role in the initiation and maintenance of ventricular arrhythmias.

U skladu s ovim nalazima, obavljena je izvrsna studija u kojoj je devet simptomatskih pacijenata s BrS koji su imali ponovljene epizode VF podvrgnuto endokardijalnom i epikardijalnom mapiranju desne klijetke. Ablacija na jedinstvenim lokacijama abnormalno niskog napona (klastering isključivo u prednjem dijelu epikarda izlaznog trakta desne klijetke) je VT/VF učinila neinducibilnim kod sedam od devet pacijenata, bez povrata ventrikulskih aritmija kod svih pacijenata tijekom razdoblja praćenja od 20±6 mjeseci. Interesantno je da je nakon ablacije normalizacija Brugada EKG uzorka ustanovljena kod osam pacijenata. Ova važna studija dokaza koncepta daje daljnju podršku stanovištu da je nasljedni EP mehanizam kod pacijenata s BrS odgođena depolarizacija u izlaznom traktu desne klijetke (specifično iznad prednje epikardijalne regije) te po prvi put pokazuje da promjena supstrata može biti učinkovita strategija kod pacijenata sa simptomatskim BrS i ponovljenim epizodama VF.

Flekainid se nedavno pojavio kao obećavajuća nova terapija za kateholaminergičnu polimorfnu ventrikulsku tahikardiju (CPVT). Na mišjem modelu CPVT ustanovljeno je da flekainid sprječava aritmije tako da inhibira otpuštanje kalcija posredstvom srčanih rianodin receptora.[120] U istoj publikaciji flekainid je također u potpunosti spriječio CPVT kod dva pacijenta koja su ostali izrazito simptomatski usprkos primjene uobičajenih lijekova. U kliničkoj studiji sa 33 pacijenta koji su liječeni flekainidom zbog ventrikulskih aritmija uzrokovanih vježbom usprkos uobičajenoj terapiji, flekainid je djelomično ili potpuno smanjio aritmije kod 76% slučajeva.[121]

In line with these findings, an outstanding study was subsequently performed in which nine symptomatic patients with BrS who had recurrent VF episodes underwent endocardial and epicardial mapping of the right ventricle. Ablation at unique abnormal low voltage sites (clustering exclusively in the anterior aspect of the RVOT epicardium) rendered VT/VF non-inducible in seven of the nine patients, with no recurrence of ventricular arrhythmias in all patients over a follow-up period of 20±6 months. Interestingly, normalisation of the Brugada ECG pattern was seen in eight patients after ablation. This important proof-of-concept study lends further support to the notion that the underlying EP mechanism in patients with BrS is delayed depolarisation in the RV outflow tract (specifically over the anterior epicardial region) and demonstrates for the first time that substrate modification may be an effective strategy in patients with symptomatic BrS with recurrent VF episodes.

Flecainide has recently emerged as a promising new treatment for catecholaminergic polymorphic ventricular tachycardia (CPVT). In a mouse model of CPVT, flecainide was found to prevent arrhythmias by inhibiting cardiac ryanodine receptor-mediated calcium release.[120] In the same publication, flecainide also completely prevented CPVT in two patients who had remained highly symptomatic with conventional drug treatment. In a clinical study of 33 patients who had received flecainide because of exercised-induced ventricular arrhythmias despite conventional treatment, flecainide was found to either partially or completely reduce the arrhythmias in 76% of cases.[121]

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