Godina 2022. u kardiovaskularnoj medicini: 10 najznačajnijih radova iz područja aritmologije

The year in cardiovascular medicine 2022: the top 10 papers in arrhythmias

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Najbolji radovi o aritmijama u 2022. – smjernice o ventrikulskim tahikardijama

Među 10 najboljih radova u 2022. godini Smjernice su Europskoga kardiološkog društva (ESC) za zbrinjavanje bolesnika s ventrikulskim aritmijama (VA) i prevenciju iznenadne srčane smrti (SCD).[1] Sažeta slika u smjernicama pruža sveobuhvatan klinički, elektrokardiografski i genetski pregled različitih bolesti povezanih s VA-om ili SCD-om (**grafički sažetak A u originalnom članku**). One promiču javni pristup defibrilaciji uz podršku mobilnih zdravstvenih jedinica i mnogo veću ulogu kateterske ablacije (**grafički sažetak B u originalnom članku**). Usto, postoje mnogobrojne preporuke o uporabi magnetne

Top arrhythmia papers — the 2022 ventricular arrhythmia guidelines

Among the top 10 arrhythmia papers is the 2022 ESC guidelines for the management of patients with ventricular arrhythmias (VAs) and the prevention of sudden cardiac death (SCD).[1] The Guidelines summarizing figure provides a comprehensive clinical, electrocardiographic, and genetic overview of the various diseases associated with VA or SCD (**Graphical Abstract, A in the original article**). They promote public access to defibrillation supported by mobile health and a much larger role in catheter ablation (**Graphical Abstract, B in the original article**). Also, multiple recommendations are provided on the use

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rezonancije (MR) srca i genskog testiranja radi poboljšanja dijagnostike i primjene terapije za više kardiomiopatija, posebice ako su prisutni specifični čimbenici rizika. Kako bi se poboljšala učinkovitost terapije kardioverterskim defibrilatorom (ICD) u kardiomiopatijama, dane su nove preporuke koje se temelje na čimbenicima rizika[1].

Prelazak granica – slikovne pretrage i aritmije

Sve veća uloga MR-a srca u VA-u u suprotnosti je s negativnim rezultatima randomiziranog istraživanja *DECAAF* u perzistentnoj fibrilaciji atrija (AF) koja je pokazala da ablacija vođena MR-om srca, usmjerena na gadolinijem pojačane kasne potencijale u atrijskim aritmogenim regijama, ne utječe na recidiv aritmije u usporedbi sa standardnom izolacijom plućnih vena i da prošireni pristup može biti povezan s moždanim udarom[2]. Trenutačno, MR srca nije dovoljno snažan da identificira bitne ablacijske ciljeve u atriju. Očito su potrebna istraživanja koje povezuju nalaze MR-a srca s elektroanatomskim i funkcijskim aritmogenim regijama, uključujući i istraživanja elektrofiziološkog i patološkog učinka ablacije u regijama ožiljnoga tkiva.

Translacijski radovi – aritmogena kardiomiopatija desne klijetke

Na koji način vježbanje pogoršava aritmogenu kardiomiopatiju desne klijetke (ARVC), nije dokraja jasno. Cerrone *i sur*[3] pretpostavljaju da vježbanje oštećuje dezmosomske pričuve u kardiomiocitima, što ubrzava progresiju kardiomiopatije u slučaju genskog oštećenja kao što je gubitak plakofilina (PKP2) (**grafički sažetak C u originalnom članku**). Dezmosomi ne reguliraju samo stanično-stanični mehanički spoj nego imaju također značajnu ulogu u staničnoj signalizaciji regulirajući staničnu proliferaciju, apoptozu i elektrolitsku signalizaciju te mitohondrijsko i metaboličko funkcioniranje. Kada su rezerve dezmosoma u miocitima smanjene, oni nisu dovoljno dobro zaštićeni od učinka vježbanja, što dovodi do njihove smrti i aritmija[3].

Jedno je kliničko istraživanje o ARVC-u prvi put istaknulo da status dezmosomske mutacije ima ključnu ulogu u riziku od pojave VA-a. Prethodni modeli rizika su stavljali naglasak na funkciju ventrikula, opterećenje ventrikulskim ekstrasistolama i biomarkera u EKG-u[4]. Bolesnici s postavljenom dijagnozom ARVC-a i bez anamnestičkih podataka o postojanim VA praćeni su u prosjeku 6 godina. Klasična procjena rizika za od VA-a s pomoću modela rizika od ARVC-a iz 2019. pokazala je dobru diskriminatornu sposobnost, no uz precijenjen rizik od VA-a. Proučavane su četiri skupine: plakofilin-2 (PKP2), dezmoplakin (DSP), drugi dezmosomski geni i bolesnici s nedefiniranim genotipom. Diskriminatorna moć i kalibracija rizika bile su najveće u skupini PKP2, a najmanje u onih s nedefiniranim genotipom. Zanimljivo, klinički markeri imali su različitu važnost ovisno o genskoj skupini, npr. dimenzije desne klijetke i sistolička funkcija bile su važni čimbenici rizika u skupini PKP2, no ne i u skupini DSP, dok je obrnuto vrijedilo za sistoličku funkciju lijeve klijetke. Ukupno gledajući, model rizika od ARVC-a iz 2019. godine imao je prilično dobre rezultate kod genski pozitivnog ARVC-a (posebno za PKP2), a ograničenije u bolesnika s nedefiniranim genotipom. Ovo istraživanje naglašava potrebu uključivanja genetskog

of CMR and genetic testing to improve diagnosis and steer therapy for several cardiomyopathies in particular if specific risk features are present. To enhance efficient ICD therapy in cardiomyopathies, novel risk factor-based recommendations are provided.[1]

Crossing borders—imaging and arrhythmias

The increasing role of CMR in VAs contrasts with the negative randomized DECAAF trial in persistent atrial fibrillation (AF) indicating that CMR-steered ablation targeting gadolinium late-enhanced potentially arrhythmogenic atrial areas does not impact recurrences compared with standard pulmonary vein isolation, and the extended approach may even be associated with stroke.[2] At present, atrial CMR is not robust enough in identifying relevant ablation targets. Studies linking CMR findings with electro-anatomic and functional arrhythmogenesis are clearly needed including studies into electrophysiologic and pathological effects of ablation in so-called fibrotic tissue.

Translational papers — arrhythmogenic right ventricular cardiomyopathy

How exercise aggravates arrhythmogenic right ventricular cardiomyopathy (ARVC) is not well known. In their translational study, Cerrone et al.[3] speculate that exercise challenges a cardiomyocyte's desmosomal reserve which, if impaired genetically [e.g. plakophilin (PKP2) loss], accelerates the progression of cardiomyopathy (**Graphical Abstract, C in the original article**). Desmosomes not only regulate cell–cell mechanical coupling but also play a significant role in cell signalling regulating cell proliferation, apoptosis, electrolyte signalling, and mitochondrial and metabolic functioning. When desmosomal reserve is reduced, myocytes are not well protected by their desmosomes against the effects of exercise leading to cell death and arrhythmias.[3]

One clinical study in ARVC highlighted for the first time that desmosomal mutation status plays a key role in the risk of VA events, whilst previous risk models have focused on ventricular function, PVC burden, and ECG biomarkers.[4] Patients with a definite diagnosis of ARVC and no history of sustained VAs were followed for a mean of 6 years. Classical risk estimates for VA using the 2019 ARVC risk model showed reasonable discriminative ability but overestimated VA risk. Four gene groups were studied: plakophilin-2 (PKP2), desmoplakin (DSP), other desmosomal, and gene-elusive patients. PKP2 had the highest discrimination and calibration of risk while these were lowest in gene-elusive patients. Interestingly, clinical markers performed differently in the specific gene groups e.g. right ventricular dimensions and systolic function are significant risk markers in PKP2 but not in DSP patients and the opposite was true for left ventricular systolic function. Overall, the 2019 ARVC risk model performed reasonably well in gene-positive ARVC (particularly for PKP2) but is more limited in gene-elusive patients. This study highlights that gene status should be included in future risk models for ARVC. Furthermore, there still needs to be independent cohort comparisons of risk models in ARVC, a major challenge for all rare diseases.

statusa u buduće modele rizika od ARVC-a. Nadalje, još je uvijek potrebna neovisna usporedba različitih modela rizika za ARVC, što je velik izazov za sve rijetke bolesti.

Novo, pročitajte sve o tome! – randomizirana istraživanja o ablacijama ventrikulske tahikardije

Ove su godine objavljena tri randomizirana istraživanja iz područja ablacije ventrikulske tahikardije (VT) s naglaskom na optimalno vrijeme kada učiniti VT ablaciju, treba li je primijeniti preventivno i istodobno s implantacijom ICD-a[5] ili nakon prve epizode terapije ICD-om[6,7] (**grafički sažetak B u originalnom članku**). U istraživanju *PARTITA* u 56 bolesnika s ishemijskom i neishemijskom kardiomiopatijom randomizirano je nakon prvoga prikladnog ICD šoka na ablaciju, odnosno medikamentnu terapiju. Zanimljivo, amiodaron nije bio dopušten.[6] U ablacijskoj skupini nije bilo nijednoga smrtnog slučaja nasuprot njih 8 (33 %) u kontrolnoj skupini (P = 0,004); kod 1 (4 %), odnosno 4 (17 %) bolesnika registrirano je pogoršanje zatajivanja srca (HF) koje je zahtijevalo hospitalizaciju (P = 0,159). Šokovi ICD-a bili su rjeđi u ablacijskoj skupini (9 %) nego u kontrolnoj skupini (42 %; P = 0,039). U ablacijskoj strategiji primjenjivan je pristup opsežne modifikacije supstrata s višestrukim indukcijama VT-a radi osiguranja neinducibilnosti, što je, sigurno, pridonijelo pozitivnom ishodu u centrima izvrsnosti za VT ablacije. Ključno je zapažanje činjenica da je smrtnost smanjena ranom VT ablacijom, ali to nije dokazano u prethodnim randomiziranim ispitivanjima. U istraživanju *SURVIVE-VT* u 144 bolesnika s ishemijskom kardiomiopatijom koji su doživjeli ICD šok, imali sinkopu zbog VT-a ili monomorfnu VT zbog koje je indiciran ICD, randomizirani su u skupine kateterske endokardne supstratom vođene ablacije ili antiaritmičke terapije (amiodaron, sotalol, beta-blokatori). Primarni je ishod bio složen i uključio je kardiovaskularnu (KV) smrt, prikladni/terapijski ICD šok, neplaniranu hospitalizaciju zbog pogoršanja HF-a ili liječenje značajnih komplikacija postupka. Nakon 24 mjeseca primarni se ishod dogodio u 28,2 % bolesnika u ablacijskoj skupini i 46,6 % bolesnika u AAD skupini[7]. Ta razlika proizlazi iz znatne redukcije teških komplikacija povezanih s antiaritmijskom terapijom, posebice kod sporih ili kontinuiranih VT-ova. U istraživanju *PAUSE-SCD* bio je uključen 121 bolesnik (35 % s ishemijskom, 30 % neishemijskom i 35 % s ARVC-om) i randomiziran (1 : 1) za ablaciju odnosu prema konvencionalnom medicinskom terapijom u vrijeme implantacije ICD-a[5]. Zajednički primarni ishod uključio je recidiv VT-a, KV hospitalizaciju ili smrt. U 31. mjesecu primarni ishod dogodio se u 49,3 % bolesnika u ablacijskoj i 65,5 % bolesnika u kontrolnoj skupini (P = 0,04). Uočena je razlika bila potaknuta smanjenjem recidiva VT-a u ablacijskoj skupini (P = 0,02). Slični su rezultati uočeni u registru bez ICD-a u skupini koja je liječena ablacijom. Nisu postojale razlike u hospitalizaciji zbog KV komplikacija ili smrtnosti, a 8,3 % bolesnika imalo je komplikacije povezane s ablacijom[5]. Iako su sva ta istraživanja bile mala[5-7] te su imala vrlo dugo razdoblje uključivanja[6,7], njihovi zaključci govore u prilog ranoj ablaciji VT-a u nositelja ICD-a s rizikom od recidiva, pri čemu istraživanja *PARTITA* i *PAUSE-SCD* podupiru proširenje indikacija na ranu ablaciju VT-a kod strukturnih bolesti srca, osim ishemijske kardiomiopatije[5,6]. Činjenica je da postoji veliko opterećenje komplikacijama koje treba smanjiti, posebice ako se ablacija kao prva linija liječenja želi više

Novel, read all about it! — randomized VT ablation studies

In the field of VT ablation, three randomized controlled trials were published this year focusing on the timing of VT ablation, either first-line pre-emptive ablation at the time of ICD implantation[5] or after the first ICD therapy[6,7] (**Graphical Abstract, B in the original article**). PARTITA randomized 56 patients with ischaemic and non-ischaemic cardiomyopathy to ablation vs. medical therapy after their first appropriate ICD shock. Interestingly, amiodarone was not allowed.[6] No deaths occurred in the ablation group vs. eight deaths (33%) in the control group (P=0.004); there were one (4%) and four (17%) worsening heart failure hospitalizations, respectively; P=0.159. ICD shocks were less frequent in the ablation group (9%) than in the control group (42%; P=0.039). The ablation strategy employed an extensive substrate-modification approach with multiple inductions of VT to ensure non-inducibility which almost certainly contributed to the positive outcome in highly experienced centres of excellence for VT ablation. The fact that mortality was reduced by early VT ablation is a key observation but not proven in previous randomized trials. In SURVIVE-VT, 144 patients with ischaemic cardiomyopathy who suffered ICD shock, had syncopal VT or monomorphic VT needing ICD, were randomized to complete endocardial substrate-based catheter ablation or antiarrhythmic therapy (amiodarone, sotalol, beta-blockers). The primary outcome was a composite of cardiovascular death, appropriate ICD shock, unplanned hospitalization for worsening heart failure, or severe treatment-related complications. After 24 months, the primary outcome occurred in 28.2% of patients in the ablation group and 46.6% of those in the AAD group.[7] This difference was driven by a significant reduction in severe antiarrhythmic treatment-related complications, in particular slow or incessant VT. In the PAUSE-SCD trial, 121 patients comprising 35% ischaemic, 30% non-ischaemic, and 35% ARVC, were randomly assigned (1:1) to ablation vs. conventional medical therapy at the time of ICD implantation.5 The primary outcome was a composite endpoint of VT recurrence, cardiovascular hospitalization, or death. At 31 months, the primary outcome occurred in 49.3% of the ablation group and 65.5% in the control group (P=0.04). The observed difference was driven by a reduction in VT recurrence in the ablation arm (P= 0.02). Similar results were seen in a non-ICD registry arm receiving ablation. No differences in cardiovascular hospitalization or mortality occurred and 8.3% of patients had ablation-related complications.[5] Although all these studies were relatively small[5–7] and had very long inclusion periods[6,7] their findings promote early ablation of VT in ICD carriers at risk of recurrences, with PARTITA and PAUSE-SCD helping to expand early VT ablation to structural heart disease other than ischaemic cardiomyopathy.[5,6] The fact there was a significant complication burden needs to be minimized especially if first-line ablation is to develop traction more widely. Since AAD complications drove the outcomes in SURVIVE-VT, this indicates that these drugs especially amiodarone are not an optimal alternative in a high proportion of patients. The challenge is to achieve successful ablation with minimal complications in these often fragile patients as it is clear that ablation is certainly effective in reducing VA events. However, newer heart failure medications including SGLT2 inhibitors and sacubitril-valsartan mean the background risk is changing.

primjenjivati. Činjenica da su na ishode u istraživanju *SURVIVE-VT* utjecale komplikacije vezane uz AAD upućuje na to da lijekovi ispitivani u istraživanju, posebice amiodaron, nisu optimalna mogućnost za velik broj bolesnika. Izazov je postizanje uspješne ablacije s minimalnim komplikacijama u tih, često fragilnih, bolesnika s jasnom porukom da je ablacija svakako učinkovita u redukciji VA događaja. Međutim, novi lijekovi za HF, uključujući SGLT2 inhibitore i sakubitril-valsartan, mijenjaju rizik.

Još vijesti – prevencija moždanog udara kod fibrilacije atrija

U 2022. godini tri rada koja su inovativna i važna za uključenje u smjernice o aritmijama, analizirala su prevenciju moždanog udara kod AF-a. Bolesnici s nasljednim nedostatkom faktora XI ne pate od spontanoga krvarenja i mogu imati nižu učestalost KV događaja, uključujući embolijski moždani udar. Ovaj prividni paradoks možda je povezan s aktiviranim faktorom XI (FXIa) koji pridonosi progresiji ugruška, ali bez njegove konsolidacije. U istraživanju *PACIFIC-AF* utvrđeno je da 20 i 50 mg asundexiana u jednoj dnevnoj dozi pouzdano suprimiraju FXIa, pritom uz mnogo manju učestalost krvarenja u usporedbi s apiksabanom[8]. Stoga FXIa može biti nova terapijska opcija za prevenciju ugrušaka u različitim tromboembolijskim bolestima uz znatnu redukciju krvarenja, što treba ispitati kroz ishode većih kliničkih istraživanja. Randomizirano istraživanje *INVICTUS* popunjava prazninu u dokazima kod primjene novih oralnih antikoagulancija (NOAC) kod AF te daje bitne podatke za zemlje s velikom prevalencijom reumatskih bolesti srca povezanih s AF-om[9]. Bolesnici s AF-om i ehokardiografski dokumentiranom reumatskom bolesti srca (uključujući umjerenu i značajnu mitralnu stenozu u više od 80 % bolesnika) bili su randomizirani da primaju dnevnu terapiju antagonistom vitamina K (VKA) ili 20 mg rivaroksabana. Primjena VKA-a imala je nižu učestalost zajedničkih KV događaja ili smrti (osobito iznenadne srčane smrti i smrti zbog HF) u usporedbi s na rivaroksabanom, bez veće učestalosti krvarenja. U bolesnika na VKA-u redovito se pratio INR i zbog toga su vjerojatno dobili bolju sveukupnu skrb dok su u bolesnika na randomiziranoj terapiji (bilo kojom antikoagulancijom) češće bili zaustavljani ogranci istraživanja s NOAC-om. Sveukupno, rezultati ispitivanja pokazuju da bi VKA trebali biti antikoagulancije izbora s obzirom na NOAC[9]. Treće istraživanje iz ovog područja bilo je *RAFAS*, otvoreno randomizirano kliničko ispitivanje koje uspoređuje ranu kontrolu ritma s uobičajenim liječenjem AF-a u 273 bolesnika s novodijagnosticiranim AF-om i akutnim ishemijskim moždanim udarom[10]. Stopa ponovnog moždanog udara unutar 12 mjeseci bila je niža u skupini s ranom kontrolom ritma – 3 (1,7 %) nasuprot 6 bolesnika (6,3 %), dok se nisu razlikovale sveukupna smrtnost i hospitalizacija zbog bilo kojeg razloga ni uz aritmije povezani događaji. Postojana AF unutar 12 mjeseci u skupini s kontrolom ritma bila je manje učestala (34 %) s obzirom na uobičajenu skrb (63 %). Iako je bilo malo i otvorenog tipa, ovo istraživanje upućuje na važan klinički problem, a to je da je stopa ponovnoga moždanog udara velika u akutnih ishemijskih moždanih udara, posebice ako su komplicirani novonastalom AF. Kod te skupine bolesnika obično se ne uzima u obzir kontrola ritma, a rezultati istraživanja *RAFAS* upućuju na to da bi rana ablacija mogla biti korisna[10]. Definitivno su potrebna veća, dobro kontrolirana klinička ispitivanja

And more news — stroke prevention in atrial fibrillation

In 2022, three innovative and guideline-relevant arrhythmia papers dealt with stroke prevention in AF. Patients with inherited factor XI deficiency do not suffer from spontaneous bleeding and may have lower rates of cardiovascular events, including cardioembolic stroke. This seeming paradox may relate to FXIa contributing to clot progression but not to clot consolidation. In the dose-finding PACIFIC-AF trial, 20 and 50 mg of asundexian reliably suppressed activated coagulation factor XI (FXIa) with once-daily dosing and resulted in significantly lower rates of bleeding compared with apixaban.[8] Therefore, FXIa may represent a novel therapeutic target for clot prevention across a variety of thromboembolic diseases significantly avoiding the bleeding side effect which remains to be seen in larger clinical outcome studies. The randomized non-inferiority INVICTUS trial fills an evidence gap in the application of non-vitamin K oral anticoagulants (NOACs) in AF and is very relevant to countries with a high prevalence of rheumatic heart disease-related AF.[9] Patients with AF and echocardiographically documented rheumatic heart disease (including moderate to severe mitral stenosis in over 80%) were randomized to vitamin K antagonist (VKA) therapy or 20 mg rivaroxaban daily. Vitamin K antagonist led to a lower rate of the composite of cardiovascular events or death (in particular sudden death and mechanical or pump failure death) than rivaroxaban, without a higher rate of bleeding. Vitamin K antagonist patients were regularly monitored for INR and for that reason may have received better care overall, whilst randomized therapy (and any anticoagulation) was stopped more often in the NOAC arm. Nevertheless, trial results indicate that VKAs should be the preferred oral anticoagulants over NOACs.[9] The third study in this area was RAFAS, an open-label randomized clinical trial comparing early rhythm control with usual AF care in 273 patients with newly documented AF in the setting of an acute ischaemic stroke.[10] Re-stroke rate at 12 months after index stroke was lower in the early rhythm control group [3 (1.7%) vs. 6 patients (6.3%)] whilst overall mortality, any hospitalization, and arrhythmia-related events did not differ. Sustained AF at 12 months was less frequent under early rhythm control (34%) compared with usual care (63%). Although small-scale and open-label, the study addressed an important clinical problem since the re-stroke rate is high in acute ischaemic stroke particularly when it is complicated by new-onset AF. In these patients, rhythm control is generally not considered whilst RAFAS suggests early ablation may be beneficial.[10] Larger well-controlled clinical trials on catheter ablation in patients with AF detected early after acute ischaemic stroke are definitely needed to settle the issue.

In conclusion, in 2022 several important trials and translational studies have been published in the top cardiovascular journals to push knowledge in the arrhythmia field promisingly forward. They will not only contribute to future cardiovascular guidelines but will also form stepping stones for novel translational research stimulating advances in our field.

kateterske ablacije u bolesnika s akutnim moždanim udarom i rano postavljenom dijagnozom AF-a, radi razrješenja nedoumica.

Zaključno, u 2022. godini u eminentnim KV časopisima objavljeno je nekoliko važnih ispitivanja i translacijskih istraživanja koja obećavaju pomak znanja u aritmologiji. Ona ne daju samo doprinos budućim KV smjernicama nego su odskočna daska za nova translacijska istraživanja koja će potaknuti daljnji napredak u ovom području.

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