Interferencija fibrilacije atrija s terapijom implantabilnog kardioverterskog defibrilatora u bolesnika sa zatajivanjem srca i smanjenom ejekcijskom frakcijom

Interference of Atrial Fibrillation with Implantable Cardioverter Defibrillator Therapy in Patients with Heart Failure and Reduced Ejection Fraction

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SAŽETAK: Implantabilni kardioverterski defibrilatori (ICD) važna su terapijska opcija u smanjenju smrtnosti zbog ventrikularnih aritmija u bolesnika sa zatajivanjem srca i smanjenom ejekcijskom frakcijom. Fibrilacija atrija (FA) često je prisutna u ovih bolesnika i može interferirati s ICD terapijom izazivanjem neprikladnih i prikladnih šokova. Ovo je važno pitanje jer oba tipa šoka povećavaju smrtnost u bolesnika s ICD-om. Strategije za smanjenje učestalosti ICD šokova izazvanih FA-om uključuju optimizaciju programiranja ICD-a, farmakološku terapiju za kontrolu frekvencije ili kontrolu ritma, te ablaciju FA-a ili atrioventrikularnoga spoja. U ovome preglednom radu istražujemo interferenciju FA-a s terapijom ICD-a, analiziramo utjecaj te interferencije na preživljenje i raspravljamo o strategijama za njezino smanjivanje.

SUMMARY: Implantable cardioverter defibrillators (ICD) are an important therapeutic option in reducing mortality due to ventricular arrhythmias in patients with heart failure with reduced ejection fraction. Atrial fibrillation (AF) is often present in these patients and may interfere with ICD therapy by inducing inappropriate and appropriate shocks. This issue is important because both types of shock increase mortality in patients with ICD. The strategies to minimize the rate of ICD shocks induced by AF include the optimization of ICD programming, pharmacological therapy for rate or rhythm control, and ablation of AF or atrioventricular junction ablation. In this review, we describe the interference of AF with ICD therapy, examine the impact of this interference on survival, and discuss the strategies for its reduction.

KLJUČNE RIJEČI: interferencija, fibrilacija atrija, implantabilni kardioverterski defibrilator.

KEYWORDS: interference, atrial fibrillation, implantable cardioverter defibrillator.

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Uvod

Implantabilni kardioverterski defibrilatori (ICD) dobro su uspostavljena i učinkovita terapija za bolesnike s zatajivanjem srca i smanjenom ejekcijskom frakcijom (HFrEF), koji su preživjeli postojanu ventrikularnu tahikardiju (VT) ili ventrikularnu fibrilaciju (VF), ili oni koji su izloženi povećanom riziku od tih aritmija.[1] S obzirom na lošu sistoličku funkciju lijeve klijetke, FA je često prisutna u bolesnika s ICD-om, s prevalencijom od 17 do 36 % u vrijeme implantacije.[2,3] Osim negativnog učinka na preživljenje,[4,5] FA može interferirati s terapijom ICD-a i ograničiti njegovu

Introduction

Implantable cardioverter defibrillators (ICD) are a well-established and effective therapy for patients with heart failure with reduced ejection fraction (HFrEF) who survived sustained ventricular tachycardia (VT) or ventricular fibrillation (VF), or those who are exposed to an increased risk of these arrhythmias.[1] With regard to poor left ventricular systolic function, AF is often present in patients with ICD, with a prevalence from 17% to 36% at time of implantation in clinical practice.[2,3] Except for the negative effect on survival,[4,5] AF may interfere with ICD therapy

kliničku korisnost izazivanjem neprikladnih i prikladnih šokova. Ovo je pitanje važno jer su šokovi ICD-a bolni, uzrokuju psihološke smetnje, mogu izazvati ventrikularnu proaritmiju, pa čak i smrt.[6-9] Svrha je ovoga preglednog rada istražiti mehanizme interferencije FA-a s terapijom ICD-a, ispitati utjecaj te interferencije na preživljavanje i raspraviti o dostupnim opcijama liječenja za njezino smanjenje.

Mehanizmi interferencije fibrilacije atrija s terapijom implantabilnoga kardioverterskog defibrilatora

Implantabilni kardioverterski defibrilatori su važna terapijska opcija za smanjenje smrtnosti zbog ventrikularnih aritmija u bolesnika s HFrEF-om.[10] Primarni cilj terapije ICD-a jest otkrivanje i zaustavljanje za život opasnih ventrikularnih aritmija isporukom električnog šoka i na taj način spriječiti iznenadnu srčanu smrt. S tog aspekta, šokovi ICD-a isporučeni za VT/VF smatraju se prikladnima jer spašavaju život.[11] Suprotno tomu, šokovi ICD-a isporučeni za neventrikularne aritmije, poput FA-a, undulacija atrija (AFL), supraventrikularne tahikardije (SVT), atrijalne tahikardije (AT), sinusne tahikardije (ST) ili nearitmijske događaje, poput elektromagnetske interferencije, mioelektričnih potencijala, kvarova uređaja ili oversensinga nepotrebni su i smatraju se neprikladnima.[12]

FA može interferirati s terapijom ICD-a na dva načina. Prvi je način češći i pojavljuje se kada brzi ventrikularni ritam FA-a s relativno pravilnim R-R intervalima dosegne programiranu zonu detekcije za VT/VF-a, pogrešno se klasificira kao ventrikularna aritmija i izazove isporuku neprikladnog šoka (**slika 1**). Prema podatcima iz randomiziranih kliničkih istraživanja, anamnestički podatci o FA-u pronađeni su u 9 do 24 % bolesnika s ICD-om (**tablica 1**), češće u bolesnika s neishemičnom nego u onih s ishemičnom kardiomiopatijom.[13-19]

and limits its clinical usefulness by inducing inappropriate and appropriate shocks. This issue is important because ICD shocks are painful, cause psychological disturbances, and may induce ventricular pro-arrhythmia and even death.[6-9] The aim of this review was to explore the possible interference mechanisms of AF with ICD therapy, examine the impact of this interference on survival, and discuss the treatment options available for its reduction.

Mechanisms of atrial fibrillation interference with implantable cardioverter-defibrillator therapy

ICDs are an important therapeutic option in reducing mortality due to ventricular arrhythmias in patients with HFrEF.[10] The primary goal of ICD therapy is to detect and stop the life-threatening ventricular arrhythmia by delivering electrical shock and thus prevent a sudden cardiac death. In that context, ICD shocks delivered for VT/VF are considered appropriate because they save lives.[11] In contrast, ICD shocks delivered for the non-ventricular arrhythmias, like AF, atrial flutter (AFL), supraventricular tachycardia (SVT), atrial tachycardia (AT), sinus tachycardia (ST), or non-arrhythmic events, like electromagnetic interference, myopotentials, and device malfunction or oversensing, are unnecessary and are considered inappropriate.[12]

AF may interfere with ICD therapy in two ways. The first way is more common, and occurs when the fast ventricular rate of AF with relatively regular R-R intervals reaches a device's programmed detection zone for VT/VF, is misclassified as ventricular arrhythmia, and induces the delivery of inappropriate shock (**Figure 1**). According to data from randomized clinical trials, a history of AF was found in 9% to 24% of patients with ICD (**Table 1**), more often in patients with non-ischemic than in those with ischemic cardiomyopathy.[13-19] On

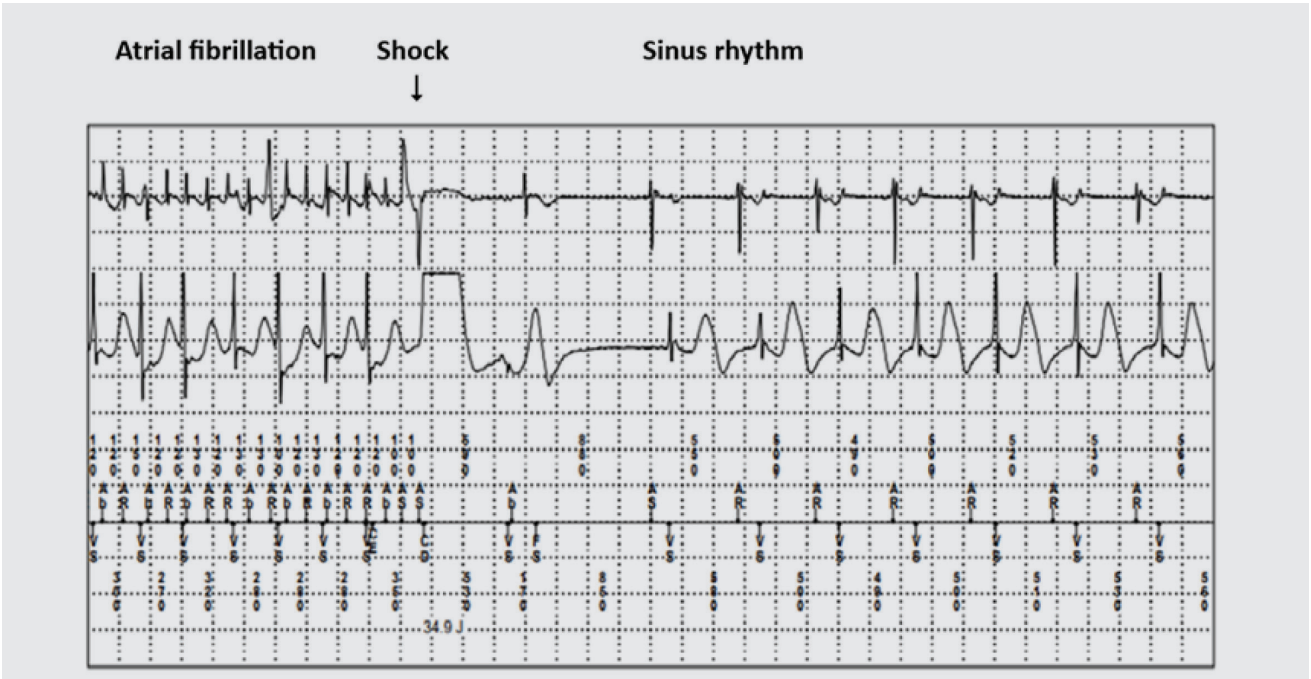

FIGURE 1. Inappropriate shock induced by atrial fibrillation in a patient with a double-chamber implantable cardioverter defibrillator.
AS = atrial sensing, VS = ventricular sensing, CD = cardioversion.

S druge strane, učestalost novonastale FA koji traje najmanje 24 sata na dan bila je 6,3 %, odnosno 7,1 % u bolesnika s jednokomornim i dvokomornim ICD-om.[20] Stoga ne iznenađuje da je FA/AFL bio najčešći uzrok neprikladnog ICD-šoka, a slijedile su ga ST/SVT i nearitmijski događaji.[21,22] U ranijim randomiziranim kliničkim ispitivanjima[15,21,23,24] učestalost neprikladnih šokova ICD-a kretala se od 15 do 21 % tijekom praćenja od 20 do 45,5 mjeseci (**tablica 1**). Kasnije, zahvaljujući prilagodbi programiranja uređaja i poboljšanim algoritmima za diskriminaciju aritmija učestalost neprikladnih šokova se smanjila,[18,19,25] ali čak i uz ova poboljšanja, oni se pojavljuju u 1,9 do 3,7 % bolesnika s ICD-om tijekom dvije godine.[26,27]

Drugi način na koji FA može interferirati s terapijom ICD-a jest izravno djelovanje FA-a u izazivanju epizode VT/VF-a s posljedičnom terapijom prikladnog šoka. Ranija analiza pohranjenih elektrograma ICD-a otkrila je da FA , obično s brzim ventrikularnim odgovorom, prethodi VT-u u otprilike 10 % epizoda.[28] Poslije su Gronefeld *i sur.*[29] izvijestili o tome da su bolesnici s FA-om češće doživjeli prikladnu terapiju ICD-om za ponavljajuće ventrikularne aritmije nego oni u sinusnom ritmu (63 % prema 38 %, p = 0,01) zbog veće učestalosti kratko-dugo-kratkih ciklusa koji su prethodili ventrikularnim aritmijama u FA-u (50% naspram 16%, p = 0,002). U studiji Stein *i sur.*,[30] koja je uključila 537 bolesnika s dvokomornim ICD-om, 233 (8,6%) od 2602 epizode VT/VF-a bile su prethođene napadajima AT-a ili FA-a. Srednje trajanje tih aritmija prije pojave VT/VF-a iznosilo je otprilike jedan sat. Ventrikularne terapije bile su isporučene za liječenje 205 od spomenutih VT/VF-epizoda, dok se preostalih 28 epizoda završilo spontano prije nego što je mogla biti isporučena terapija ICD-a. S druge strane, Borleffs *i sur.* izvijestili su da bolesnici s trajnom FA-om imaju veći rizik od aktivacije ICD-a izazvane ventrikularnim aritmijama u usporedbi s onima bez FA-a i onima s paroksizmalnom ili perzistentnom FA (49 % prema 29 %, 26 % i 26 %, redom; p <0,001).[4]

the other hand, the incidence of new-onset AF lasting at least 24 hours per day was 6.3% and 7.1% in single chamber and doubled chamber patients with ICD, respectively.[20] Therefore, it is not surprising that AF/AFL was the most common reason for an inappropriate ICD shock, followed by ST/SVT and non-arrhythmic events.[21,22] In earlier randomized clinical trials,[15,21,23,24] the rate of inappropriate ICD shocks ranged from 15% to 21% over 20 to 45.5 months of follow-up (**Table 1**). Later, thanks to device programming adjustment and enhanced algorithm discrimination of arrhythmias, the rate of inappropriate shocks decreased,[18,19,25] but even with these improvements, they occur in 1.9% to 3.7% of patients with ICD over a period of two years.[26,27]

The second way in which AF may interfere with ICD therapy is direct action of AF in causing an episode of VT/VF, with consequent appropriate shock therapy. An earlier analysis of stored ICD electrograms revealed that approximately 10% of VT episodes were preceded by atrial fibrillation typically associated with a rapid ventricular response.[28] Subsequently, Gronefeld *et al.*[29] reported that patients in AF experienced appropriate ICD therapy for recurrent ventricular arrhythmias more frequently than those in sinus rhythm (63% vs. 38%, p=0.01) because of a higher incidence of short-long-short cycles preceding ventricular arrhythmias in AF (50% vs. 16%, p=0.002). In the study by Stein *et al.*[30] which included 537 patients with dual-chamber ICD, 233 (8.6%) of 2602 VT/VF episodes were preceded by a paroxysm of AT or AF. The median duration of these arrhythmias preceding VT/VF was approximately one hour. Ventricular therapies were delivered to treat 205 of these VT/VF episodes, while the remaining 28 episodes terminated spontaneously before an ICD therapy could be delivered. On the other hand, Borleffs *et al.* reported that patients with permanent AF had higher risk of ventricular arrhythmias triggering ICD discharge compared with those without AF and those with paroxysmal or persistent AF (49% vs. 29%, 26%, and 26%, respectively; p<0.001).[4]

TABLE 1. Summary of atrial fibrillation history and implantable cardioverter-defibrillator shocks in randomized controlled trials.

RCT	No of ICD patients	Heart disease (%)	History of AF (%)	EF (median)	FU (m) (mean)	ICD shocks (%) Approp	ICD shocks (%) Inapprop
AVID[13,23]	507	ICM 81 DICM 19	21	32%	18	39	20
MADIT II[14,21]	719	ICM 100	9	23%	20	18	15
DEFINITE[15]	229	DICM 100	23	29%	29	18	21
SCD-HeFT[16,24]	811	ICM 53 DICM 47	17	25%	45	22	17
MADIT-CRT[17,25]	1790	ICM 55 DICM 45	11	28%	39	13	7
MADIT-RIT[18]	1500	ICM 53 DICM 47	13	26%	17	13	4
DANISH[19]	556	DICM 100	24	25%	67	12	6

RCT = randomized controlled trial, No = number, AF = atrial fibrillation, EF = ejection fraction, FU = follow-up, m = months, ICD = implantable cardioverter-defibrillator, approp = appropriate, inapprop = inappropriate, ISM = ischemic cardiomyopathy, NICM = non-ischemic cardiomyopathy.

Postoji nekoliko mehanizama koji mogu objasniti povezanost između FA-a i prikladne terapije ICD-om. Prvo, moguće je da FA i ventrikularne aritmije dijele čimbenike rizika kao što su ishemija, zatajenje bubrega, povećani simpatički tonus ili povećan tlak punjenja lijeve klijetke, što olakšava inicijaciju obiju aritmija.[31,32] Drugo, u strukturnim bolestima srca sa smanjenom ejekcijskom frakcijom, brzi ventrikularni odgovor izazvan FA-om može izravno utjecati na ventrikularnu refraktarnost i na taj način izazvati ventrikularne aritmije (**slika 2**). Treće, nepravilan ritam FA-a rezultira nepravilnim aktiviranjem ventrikula stvarajući kratko-dugo-kratke sekvence, što dovodi do nehomogene depolarizacije, a time i veće osjetljivosti miokarda za ventrikularne aritmije.[29]

There are several mechanisms that can explain the association between AF and appropriate ICD shocks. First, it is possible that AF and ventricular arrhythmias share risk factors such as ischemia, renal failure, increased sympathetic tone, or increased left ventricular filling pressure,[31,32] which facilitate the initiation of both arrhythmias. Second, in structural heart disease with reduced EF, the rapid ventricular response caused by AF may directly affect ventricular refractoriness and therefore induce ventricular arrhythmia (**Figure 2**).[30,33] Third, the irregular rhythm of AF results in irregular ventricular activation, creating the short-long-short sequences, which lead to inhomogeneous depolarization and thus to a higher myocardium susceptibility for ventricular arrhythmias.[29]

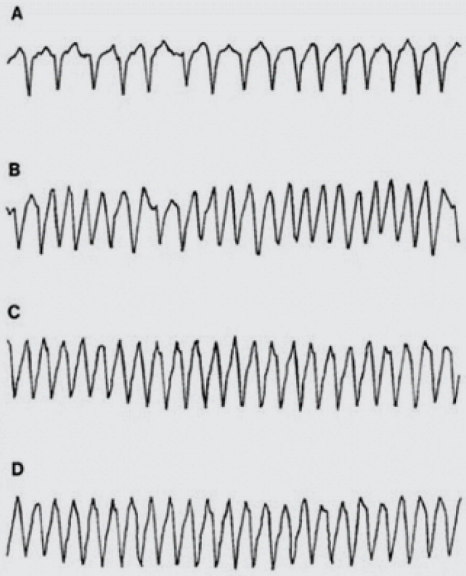

FIGURE 2. Ventricular tachycardia (VT) induced by rapid ventricular response in patient with permanent atrial fibrillation (AF). Trace A: an acceleration of the ventricular rate in permanent AF. Trace B: the onset of VT with a progressive acceleration of ventricular rate. Traces C and D: established VT with very fast rate (R-R interval of 270 ms). (Adapted from reference[33]).

Prognostička važnost prikladnih i neprikladnih šokova implantabilnoga kardioverterskog defibrilatora

Dva poznata istraživanja o primarnoj prevenciji ICD-a, *MADIT-II* (*Multicenter Automatic Defibrillation Trial*) i *SCD-HeFT* (*Sudden Cardiac Death in Heart Failure Trial*), utvrdila su da su prikladni i neprikladni šokovi ICD-a značajni prediktori smrtnosti, povećavajući rizik od smrti za prikladne šokove za 3, odnosno 5 puta, a za neprikladne šokove za 2 puta.[21,24,34] U obama istraživanja progresivno je zatajivanje srca bilo vodeći uzrok smrti među bolesnicima koji su primili barem jedan ICD šok.[24,34] Metaanaliza Proietti *i sur.*[35] sažela je postojeće dokaze o prognostičkoj važnosti ICD šokova u bolesnika s HFrEF-om. U skupnoj analizi gotovo 200 000 bolesnika s ICD-om pronađena je znatna povezanost između šokova ICD-a i smrtnosti, koja je izrazitija za prikladne (HR 2,95, p <0,001) nego za neprikladne šokove (HR 1,71, p <0,001), dok je

Prognostic significance of appropriate and inappropriate implantable cardioverter defibrillator shocks

Two landmark primary prevention ICD studies, MADIT-II (Multicenter Automatic Defibrillation Trial) and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), have found that both appropriate and inappropriate ICD shocks were significant predictors of death, increasing risk of death for appropriate shocks by 3 and 5 times, respectively, and with a 2-fold increase for inappropriate shocks.[21,24,34] In both studies, progressive HF was the leading cause of death among the patients who received at least one ICD shock.[24,34] A meta-analysis by Proietti *et al.*[35] summarized the existing evidence on the prognostic significance of ICD shocks in patients with HFrEF. In a pooled analysis of almost 200 000 patients with ICD, a significant association was found between ICD shocks and mortality, stronger for appropriate (HR 2.95, p<0.001) than inappropriate shocks (HR 1.71, p<0.001), while the combination of both

kombinacija obaju tipova šokova bila povezana s većim rizikom od smrti (HR 4,18, p <0,001) nego svaki tip šoka zasebno.

Kako možemo objasniti povezanost između ICD šokova i povećane smrtnosti? Postoji nekoliko potencijalnih mehanizama preko kojih šokovi mogu izravno povećati rizik od smrti, kao što su izazvana ventrikularna proaritmija, privremena disfunkcija miokarda, postšokni vazospazam, omamljenost miokarda ili postšokna električna aktivnost bez pulsa, ali ovi mehanizmi potencijalno mogu biti odgovorni za smrt unutar prva 24 sata od šoka.[7, 24,36-38] Drugo objašnjenje proizlazi iz činjenice da bolesnici s HFrEF i ozbiljnijim oblikom bolesti srca imaju povećanu sklonost razvoju ventrikularnih aritmija i FA-a i, posljedično, veću učestalost neprikladnih i prikladnih šokova, što upućuje na mogućnost da su šokovi ICD-a pokazatelj bolesnika s većim rizikom. Ovo je objašnjenje ilustrirano u istraživanju Powel *i sur.*[22] koji su analizirali ritmove pri isporučenju prvog šoka u 7439 randomiziranih bolesnika s ICD-om ili defibrilatorom s resinkronizirajućom terapijom srca (CRT-D) da bi odredili njihov odnos s preživljenjem. Od prvih šoknih epizoda, 58,7 % bilo je prikladnih šokova za postojane ventrikularne aritmije, a 41,3 % neprikladnih šokova za neventrikularne aritmije ili nearitmijske događaje. U usporedbi s bolesnicima bez šoka, oni koji su primili svoj prvi šok za VT/VF ili FA/AFL imali su povećan rizik od smrti (**tablica 2**). Nasuprot tomu, bolesnici koji su primili neprikladan šok za ST/SVT ili nearitmijske događaje imali su preživljenje slično onima bez šoka. Dvije važne poruke proizlaze iz tog ispitivanja: 1) rizik povezan s neprikladnim šokovima ograničen je na bolesnike s FA/AFL i 2) dugoročna smrtnost nakon šoka više je povezana s predležećim aritmijskim supstratom nego štetnim djelovanjima samih šokova. Uzevši sve zajedno, može se prihvatiti objašnjenje da je povezanost između ICD šokova i povećane smrtnosti multifaktorska, uključujući uznapredovalu bolest srca, progresiju predležećega aritmijskog supstrata, komorbiditet, a u manjoj mjeri štetne učinke samoga šoka.[22,24,25,41]

appropriate and inappropriate shocks was associated with a higher risk of death (HR 4.18, p<0.001) than either type of shock alone.

How we can explain the association between ICD shocks and increased mortality? There are a number of potential mechanisms by which shocks may directly increase the risk of death, such as induced ventricular proarrhythmia, transient myocardial dysfunction, post-shock vasospasm, myocardial stunning, or post-shock pulseless electrical activity,[7,24,36-38] but these mechanisms can potentially be the cause of death within the first 24 hours of a shock. Another explanation arises from the fact that patients with HFrEF and more severe forms of heart disease have an increased tendency to develop ventricular arrhythmias and AF[34,39,40] and consequently a tendency towards a higher incidence of appropriate and inappropriate shocks,[4] which suggests the possibility that ICD shocks are indicator of a higher-risk patient. This explanation is illustrated in the study by Powel *et al.*[22] who analyzed the rhythms of the first shock delivery in 7 439 randomly-selected patients with an ICD or cardiac resynchronization therapy defibrillator (CRT-D) to determine their relationship with survival. Of the first shock episodes, 58.7% were appropriate shocks for sustained ventricular arrhythmias, and 41.3% were inappropriate shocks for non-ventricular arrhythmias or non-arrhythmic events. Compared with no-shock patients, those who received their first shock for VT/VF or AF/AFL had an increased risk of death (**Table 2**). In contrast, patients who received an inappropriate shock for ST/SVT or non-arrhythmic events (noise, artifact, and oversensing) had similar survival to those who did not receive a shock. Two important messages emerge from this study: 1) the risk associated with inappropriate shocks is limited to patients receiving shocks for AF/AFL, and 2) increased long-term mortality after shock is more related to the underlying arrhythmia substrate than to an adverse effect from the shock itself. Taking all this together, it is a plausible explanation that the association between ICD shocks and increased mortality is multifactorial, including more advanced heart disease, progression of the underlying arrhythmia substrate, co-morbid conditions, and, to a lesser extent, detrimental effects from the ICD shocks themselves.[22,24,25,41]

TABLE 2. Mortality risk after the first shock in comparison with no shock patients in the ALTITUDE study[22].

Shocked rhythm	Hazard ratio (95% CL)	p value
Ventricular		
Monomorphic VT	1.65 (1.36-2.01)	<0.0001
VF/Polymorphic VT	2.10 (1.54-2.86)	<0.0001
Non-ventricular		
AF/AFL	1.61 (1.17-2.21)	0.003
ST/SVT	0.97 (0.68-1.37)	0.86
Noise/artefact/oversensing	0.91 (0.50-1.67)	0.76

VT = ventricular tachycardia, VF = ventricular fibrillation, AF= atrial fibrillation, AFL = atrial flutter, ST = sinus tachycardia

Strategije za smanjenje interferencije fibrilacije atrija s terapijom implantabilnog kardioverterakog defibrilatora

Prema nedavnim smjernicama, optimizacija programiranja ICD-a početna je opcija za smanjenje učestalosti ICD šokova

Strategies to minimize the interference of atrial fibrillation with implantable cardioverter therapy

According to recent guidelines, the optimization of ICD programming is the initial option to minimize the rate of ICD

izazvanih FA-om i poboljšanje bolesnikova ishoda. Ova se preporuka temelji na rezultatima dviju metaanaliza,[42,43] koje su istraživale učinak programiranja za smanjenje terapije ICD-a na nekoliko kliničkih ishoda, uključujući smrtnost (**tablica 3**). U objema metaanalizama programiranje smanjenja terapije bilo je povezano s 50 %-tnim smanjenjem neprikladnih šokova i smanjenjem smrtnosti za 30 %, odnosno 23 %, u usporedbi s konvencionalnim programiranjem. Nije zabilježen porast rizika od prikladnih šokova ili sinkope u programiranju smanjenja terapije. Programiranje ICD-a trebalo bi uključivati: 1) prilagođen način bradikardne stimulacije kako bi se spriječila nepotrebna stimulacija desne klijetke u bolesnika bez indikacija za trajnu stimulaciju[44,45], 2) programiranje više zona za detekciju tahikardije s inkorporiranim postavkama produljenog vremena detekcije i visokih frekvencija kako bi se izbjegli neprikladni šokovi zbog nepostojanih VT-a ili klinički stabilnih VT-a[46-48], 3) dosljednu uporabu algoritama za razlikovanje supraventrikularnih od ventrikularnih aritmija, čak i za tahikardije s frekvencijama do 230/min[17,26,48], 4) pravilan atrijski sensing za aktivaciju dvokomornog diskriminatora[48], 5) sistematsku primjenu antitahikardne stimulacije prije terapije šokom, čak i za vrlo brzu VT[46,49,50] i 6) specifične algoritme za diskriminaciju T-vala i buke desnoga komorskog vodiča.[48]

shocks induced by AF and to improve patient outcomes.[1] This recommendation is based on the results of two meta-analyses,[42,43] which examined the overall effect of ICD therapy reduction programming on several clinical outcomes, including mortality (**Table 3**). In both meta-analyses, therapy reduction programming was associated with a 50% reduction in inappropriate shocks and with a 30% and 23% reduction in mortality, respectively, compared with the conventional programming. No increase was seen in risk of appropriate shocks or syncope in therapy reduction programming. In line with this recommendation, ICD programming should include: 1) customized bradycardia pacing mode to prevent unnecessary right ventricular pacing in patients without an indication for permanent pacing,[44,45] 2) multi-zone tachycardia detection programming with incorporated prolonged detection time settings and high rate thresholds to avoid unnecessary shocks due to non-sustained VT or clinically stable VT,[46-48] 3) consistent use of algorithms for supraventricular versus ventricular arrhythmias discrimination even for tachycardias with rates up to 230 bpm,[17,26,48] 4) proper atrial sensing for activation of dual-chamber discriminators,[48] 5) systematic use of ATP before shock therapy, also for very fast VT,[46,49,50] and 6) specific algorithms for T-wave discrimination and right ventricular lead noise.[48]

TABLE 3. The effect of therapy reduction versus conventional implantable cardioverter defibrillator programming on clinical outcomes[42].

Clinical outcome	Therapy RP (n=4089)	Conventional P (n = 3598)	Hazard ratio (95% CI)	p value
All-cause mortality	207 (5.0%)	162 (7.3%)	0.70 (0.59-0.84)	<0.001
Syncope	105 (3.1%)	74 (2.5%)	1.09 (0.83-1.44)	0.5
Appropriate shocks	153 (5.2%)	137 (5.6%)	1.06 (0.75-1.16)	0.5
Inappropriate shocks	99 (3.4%)	168 (6.9%)	0.50 (0.39-0.63)	<0.001

RP = reduction programming

Farmakološka je terapija sljedeća opcija za smanjenje šokova ICD-a izazvanih FA-om, ali su podatci o tome ograničeni. Cilj je farmakološke terapije usporiti frekvenciju srca da ne dosegne zonu detekcije za VT/VF ili smanjiti povrate FA-a. U sekundarnoj analizi *MADIT II* studije,[51] terapija beta-blokatorima (metoprolol 44 %, karvedilol 42 %, atenolol 13 %) smanjila je terapiju ICD-a za VT ili VF, ali nije uspjela u sprječavanju neprikladnih šokova izazvanih FA-om ili SVT-om. S druge strane, retrospektivna analiza istraživanja *MADIT-CRT* (*Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy*) utvrdila je da je rizik od neprikladne terapije ICD-a zbog FA-a znatno smanjen u bolesnika koji su primali karvedilol u usporedbi s onima koji su primali metoprolol (HR: 0,50, p = 0,004).[52] Bolji klinički učinak karvedilola s obzirom na metoprolol vjerojatno je rezultat njegova šireg elektrofiziološkog i farmakološkog profila.[53] U randomiziranom kontroliranom ispitivanju na 412 bolesnika s ugrađenim ICD-om za sekundarnu prevenciju,[54] kombinacija amiodarona i beta-blokatora bila je djelotovornija u sprječavanju neprikladnih šokova (većinom za supraventrikularne

Pharmacological therapy is the next option for the reduction of ICD shocks caused by AF,[1] but data on this issue are limited. The goal of pharmacological therapy is to slow down the heart rate so that it does not reach the detection zone for VT/VF, or to reduce AF recurrences. In a secondary analysis of the MADIT II study,[51] beta-blocker therapy (metoprolol 44%, carvedilol 42%, atenolol 13%) reduced ICD therapy for VT or VF, but failed to prevent inappropriate shocks induced by AF or SVT. On the other hand, a retrospective analysis of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy) study found that the risk of inappropriate therapy due to AF was significantly reduced in patients receiving carvedilol compared with those who received metoprolol (HR: 0.50, p=0.004).[52] The superior clinical effect of carvedilol versus metoprolol was probably the result of its a larger electrophysiological and pharmacological profile.[53] In a randomized controlled trial on 412 patients with implanted ICD for secondary prevention,[54] a combination of amiodarone and beta-blocker was more effective in the prevention of inappropriate shocks (mostly for

tahiaritmije) od samog beta-blokatora (3,3 % prema 15,4 %, p = 0,006), ali uz veći rizik od štetnih učinaka na štitnjaču i pluća te simptomatske bradikardije. S druge strane, sotalol nije bio djelotvorniji u smanjenju rizika od neprikladnih šokova od beta-blokatora. Amiodaron se može primjenjivati za održavanje sinusnog ritma nakon kardioverzije, ali njegova uspješnost u sprječavanju povrata FA-a u bolesnika s ICD-om ili CRT-D-om, te HFrEF-om i perzistentnim FA-om nije bila veća od 34 % nakon dvije godine praćenja.[55]

Kateterska ablacija FA-a ili AV-spoja preporučuje se u bolesnika s FA-om povezanim s neprikladnim šokovima, koji ne reagiraju na farmakološku terapiju.[1] Više je istraživanja potvrdilo izvedivost i korisnost od ovih terapijskih opcija.[55-58] Godine 2014. Kosiak *i sur.*[56] objavili su rezultate ablacije FA-a u 73 bolesnika s implantiranim ICD-om zbog ishemijske ili neishemijske kardiomiopatije. Potpuna izolacija plućnih vena (PVI) kao proceduralni cilj postignuta je u svih bolesnika, a ponovna je ablacija bila potrebna u njih 20. U usporedbi s razdobljem prije ablacije, nakon ablacije došlo je do znatnog smanjenja prikladnih i neprikladnih šokova (p = 0,03 i p = 0,001, redom). U istraživanju Miyazaki *i sur.*[57] 14 od 106 bolesnika s ICD-om doživjelo je neprikladne šokove ICD-a zbog FA-a. PVI je izvedena u 13 bolesnika, jedan je bolesnik podvrgnut ablaciji AV-spoja zbog odsutnosti donje šuplje vene, a 4 su bolesnika ponovno podvrgnuta ablaciji zbog povrata FA-a. Nakon posljednje ablacije nijedan bolesnik nije doživio neprikladan šok tijekom prosječnoga praćenja od 19 mjeseci. U skupnoj analizi 664 bolesnika s CRT-D-om i trajnim FA-om[58] bolesnici s ablacijom AV-spoja imali su mnogo manju učestalost neprikladnih i prikladnih šokova izazvanih FA-om u usporedbi s bolesnicima koji su bili liječeni lijekovima (oba p <0,001). Ti su podatci važni za liječenje bolesnika s CRT-D-om, jer otprilike 26 % te populacije ima FA.[59]

Zaključak

Fibrilacija atrija može interferirati s terapijom ICD-a na dva načina: 1) izazivanjem neprikladnog šoka kada njezin brz ventrikularni ritam dosegne detekcijsku zonu ICD-a za VT/VF i 2) izravnim izazivanjem epizode VT-a ili /VF-a s posljedičnom terapijom prikladnog šoka. Bolesnici s ICD-om koji primaju prikladne ili neprikladne šokove imaju mnogo veći rizik od smrti od onih koji ih ne primaju. Povezanost je između ICD šokova i povećane smrtnosti multifaktorska, uključujući uznapredovaliju bolest srca, progresiju predležećega aritmijskog supstrata, komorbiditet, a u manjoj mjeri, i štetne učinke samoga ICD šoka.

Optimizacija programiranja ICD-a početna je opcija za smanjenje prikladnih i neprikladnih šokova izazvanih FA-om. Farmakološka terapija beta-blokatorima za kontrolu frekvencije ili amiodaronom za kontrolu ritma sljedeća je opcija u tome smislu. Kateterska ablacija FA-a ili AV spoja preporuča se u bolesnika koji nemaju dobar odgovor na farmakološku terapiju, ovisno o tome da li se radi o paroksizmalnoj i perzistenznoj FA, ili trajnoj FA.

supraventricular tachyarrhythmias) than beta-blocker alone (3.3% vs. 15.4%, p=0.006), but with higher rates of adverse thyroid and pulmonary effects and of symptomatic bradycardia. On the other hand, sotalol was not more effective than beta-blockers in reducing risk of inappropriate shocks. Amiodarone can be used for rhythm control after cardioversion, but its success rate in the prevention of AF recurrences in patients with ICD or CRT-D with HFrEF and persistent AF was not higher than 34% at two-year follow-up.[55]

Catheter ablation of the AF or AV junction is recommended in patients with AF-related inappropriate shocks who are unresponsive to pharmacological therapy.[1] Several studies confirmed the feasibility and usefulness of these therapeutic options.[55-58] In 2014, Kosiak *et al.*[56] published the results of AF catheter ablation in 73 patients with implanted ICD due to ischemic or non-ischemic cardiomyopathy. Complete pulmonary vein isolation (PVI) as the procedural endpoint was achieved in all patients, and re-ablation was necessary in 20 of them. In comparison with the period prior to ablation, there was significant reduction of appropriate and inappropriate shocks after ablation (p=0.03 and p=0.001, respectively). In the study by Miyazaki *et al.*,[57] 14 of 106 ICD patients experienced inappropriate ICD shocks due to AF. PVI was performed in 13 patients, one patient underwent an AVJ ablation because of the absence of an inferior vena, and 4 patients were re-ablated for recurrent AF. After the last ablation procedure, no patients experienced inappropriate shock during the median follow-up of 19 months. In a pooled analysis of 664 patients with CRT-D and permanent AF,[58] patients with AVJ ablation had a significantly lower rate of inappropriate shocks induced by AF and a lower rate of appropriate shocks than those treated with drugs (both p<0.001). These data are important for the treatment of patients with CRT-D, because approximately 26% of this population have AF.[59]

Conclusion

Atrial fibrillation may interfere with ICD therapy in two ways: 1) by inducing inappropriate ICD shock when its rapid ventricular rate reaches a device's programmed detection zone for VT/VF, and 2) by directly inducing a VT or VF episode with consequent appropriate shock therapy. Patients with ICD who receive appropriate or inappropriate shocks related to AF have a substantially higher risk of death than those who do not receive them. The association between ICD shocks and increased mortality is multifactorial, including more advanced heart disease, progression of the underlying arrhythmia substrate, co-morbid conditions, and, to a lesser extent, detrimental effects from ICD shock itself.

The optimization of ICD programming is the initial option for reducing inappropriate and appropriate shocks induced by AF. Pharmacological therapy with beta-blockers for rate or amiodarone for rhythm control is the next option to this effect. The catheter ablation of AF or AV junction is recommended in patients unresponsive to pharmacological therapy depending on whether it is paroxysmal and persistent AF, or permanent AF.

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