Interferencija fibrilacije atrija s resinkronizacijskom terapijom srca

Interference of Atrial Fibrillation with Cardiac Resynchronization Therapy

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SAŽETAK: Resinkronizacijska terapija srca (CRT) postala je važna opcija liječenja za bolesnike sa zatajivanjem srca (HF) koji imaju oslabljenu funkciju lijevog ventrikula (LV) i kašnjenje ventrikularnog provođenja. Fibrilacija atrija (FA) najčešća je aritmija u ovakvih bolesnika, a njezina prisutnost može interferirati s CRT-om zbog gubitka atrioventrikularne sinkronije i kompeticije između biventrikularne (BIV) stimulacije i normalno provedenih otkucaja. Ovo je pitanje važno jer je gubitak djelotvorne BIV stimulacije povezan s lošijim ishodima. Terapijske opcije za FA u bolesnika s CRT-om odnose se na kontrolu frekvencije lijekovima ili ablacijom atrioventrikularnoga spoja ili pak na kontrolu ritma amiodaronom ili ablacijom FA-a, sa svrhom da se osigura visok postotak BIV stimulacije. U ovome preglednom članku objašnjavamo kako FA može interferirati s CRT-om, prikazujemo negativne učinke FA-a u takvim okolnostima i raspravljamo o terapijskim opcijama za FA u ovoj specifičnoj populaciji s HF-om.

SUMMARY: Cardiac resynchronization therapy (CRT) has become an important treatment option for patients with heart failure (HF) with impaired left ventricular function and ventricular conduction delay. Atrial fibrillation (AF) is the most common arrhythmia in these patients, and its presence may interfere with CRT due to a loss of atrioventricular synchrony and competition between biventricular (BIV) capture and normally conducted beats. This issue is important because the loss of effective BIV pacing is associated with poorer outcomes. Therapeutic options for AF in patients receiving CRT include rate control, with drugs or atrioventricular junction ablation, or rhythm control, with amiodarone or AF ablation, with the main goal of ensuring a high percentage of BIV pacing. In this review, we explain how AF may interfere with CRT, present negative effects of AF in these circumstances, and discuss the therapeutic options for AF in this specific population with HF.

KLJUČNE RIJEČI: interferencija, fibrilacija atrija, resinkronizacijska terapija srca.

KEYWORDS: interference, atrial fibrillation, cardiac resynchronization therapy.

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Uvod

Resinkronizacijska terapija srca (CRT) postala je važna opcija liječenja za bolesnike sa zatajivanjem srca (HF) i oslabljenom funkcijom lijevog ventrikula (LV) i kašnjenjem ventrikularnoga provođenja, koji su simptomatski unatoč optimalnoj terapiji lijekovima.[1] U takvih bolesnika CRT smanjuje intraventrikularno i interventrikularno kašnjenje provođenja, može usporiti napredovanje bolesti induciranjem obrnutog remodeliranja i poboljšava kliničke ishode, uključujući mortalitet.[2-5] Sadašnje indikacije za implantaciju CRT-a u bolesnika sa sinusnim ritmom[1] prikazane su u **tablici 1.**

Fibrilacija atrija (FA) najčešća je aritmija u bolesnika s CRT-om. Prema posljednjem izvješću *European CRT Survey,* 41 % bolesnika s CRT-om

Introduction

Cardiac resynchronization therapy (CRT) has become an important treatment option for patients with heart failure (HF) with impaired left ventricular (LV) function and ventricular conduction delay, who are symptomatic despite optimal medical therapy.[1] In such patients, CRT reduces intra- and interventricular conduction delay, can slow disease progression by inducing cardiac reverse remodeling, and improves clinical outcomes, including mortality.[2-5] The current indications for CRT implantation in patients in sinus rhythm[1] are presented in **Table 1**.

Atrial fibrillation (AF) is the most common arrhythmia in patients receiving CRT. According to the report of the last European CRT Survey, 41% of patients receiving CRT had a history of prior AF

TABLE 1. Recommendations for CRT in patients in sinus rhythm.

LBBB QRS morphology
CRT is recommended for symptomatic patients with HF in SR with LVEF ≤35%, QRS duration ≥150 ms, and LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity and mortality (Class I).
CRT should be considered for symptomatic patients with HF in SR with LVEF ≤35%, QRS duration 130-149 ms, and LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity and mortality (Class IIa).
Non-LBBB QRS morphology
CRT should be considered for symptomatic patients with HF in SR with LVEF ≤35%, QRS duration ≥150 ms, and non-LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity (Class IIa).
CRT may be considered for symptomatic patients with HF in SR with LVEF ≤35%, QRS duration 130-149 ms, and non-LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity (Class IIb).

CRT = cardiac resynchronization therapy, LBBB = left bundle branch block, HF = heart failure, SR = sinus rhythm, LVEF = left ventricular ejection fraction, OPT = optimal medical therapy

imalo je anamnestički podatak o prethodnoj FA, a 26 % od njih imalo je FA u vrijeme implantacije.[6] Evaluacijom preko CRT uređaja novonastala FA pronađena je u 20 do 27 % bolesnika bez prethodnih anamnestičkih podataka o FA-u.[7-9] Osim toga što općenito pogoršava prognozu HF-a,[10,11] FA može interferirati s CRT-om zbog gubitka atrioventrikularne (AV) sinkronije i kompeticije između BIV stimulacije i provedenih otkucaja preko FA-a. Ovo je pitanje klinički relevantno jer je gubitak djelotvorne BIV stimulacije povezan s pogoršanjem HF-a i većim mortalitetom.[12-15] Cilj je ovoga preglednog članka objasniti na koji način FA može interferirati s CRT-om, prikazati negativne učinke FA-a na preživljenje i isporuku CRT-a, te raspraviti o terapijskim opcijama za FA u ovoj specifičnoj skupini bolesnika s HF-om.

Mehanizmi kojima resinkronizacijska terapija interferira s fibrilacijom atrija

Osnovni je cilj CRT-a obnavljanje intraventrikularne i interventrikularne sinkronije, kada su ventrikularne kontrakcije nesinkronizirane zbog intrinzičnog kašnjenja provođenja, posebno u bolesnika s blokom lijeve grane. FA interferira s CRT-om na dva načina: 1) uzrokujući gubitak AV-sinkronije, što se događa u svakoj epizodi FA-a, i 2) uzrokujući kompeticiju između BIV stimulacije i provedenih otkucaja, što ovisi o brzini i nepravilnosti ventrikularnog ritma FA-a.

U sinusnom ritmu CRT resinkronizira kontrakcije srca optimiranjem AV vremena i BIV stimulacijom. S kliničkoga gledišta, optimalno AV vrijeme trebalo bi biti AV-interval koji promovira maksimalan doprinos kontrakcije lijevog atrija punjenju LV-a, produljuje vrijeme punjenja, povećava minutni volumen srca i minimizira mitralnu regurgitaciju.[16] Bolesnici s CRT-om nemaju AV-sinkroniju, a stoga ni mogućnosti za AV optimizaciju s prikladno tempiranim AV-intervalom. Stoga oni dobivaju kliničku korist od CRT-a samo uz BIV stimulaciju. U tom kontekstu FA može interferirati s isporukom CRT-a jer provedeni otkucaji aktivirani FA-om konkuriraju s BIV stimulacijom. To se događa kada ventrikularna frekvencija FA-a nadmašuje, prekida ili remeti BIV stimulaciju, rezultirajući spontanim, fuzijskim i pseudofuzijskim otkucajima.[17,18] To se dodatno pogoršava u situacijama povećane potrebe

and 26% of them had AF at the time of implantation.[6] Evaluated by device diagnostics, new-onset AF was found in 20% to 27% of patients with no previous history of AF.[7-9] Apart from worsening the prognosis of HF in general,[10,11] AF may interfere with CRT delivery due to loss of atrioventricular (AV) synchrony and competition between biventricular (BIV) capture and conducted beats due to AF. This issue is clinically relevant because the loss of effective BIV pacing is associated with a worsening of HF and higher mortality.[12-15] The aim of this review was to explain how AF may interfere with CRT, present the negative effects of AF on survival and CRT delivery, and discuss therapeutic options for AF in this specific group of patients with HF.

The mechanisms by which atrial fibrillation interferes with cardiac resynchronization therapy

The basic goal of CRT is to restore intra- and interventricular synchrony when ventricular contractions are dyssynchronous due to intrinsic conduction delay, especially in patients with left bundle branch block. AF interferes with CRT in two ways: 1) by causing the loss of AV synchrony, which happens in every episode of AF, and 2) by causing the competition between BIV capture and conducted beats due to AF, which depends on the speed and irregularity of AF ventricular rate. In sinus rhythm, CRT resynchronizes cardiac contractions by optimizing of AV timing and by BIV pacing. From a clinical point of view, the optimal AV timing should be the AV interval that promotes a maximum contribution of the left atrial contraction to left ventricular (LV) filling, lengthens the filling time, increases the cardiac output, and minimizes mitral regurgitation.[16] Patients with AF do not have AV synchrony and thus no possibility of AV optimization with an appropriately timed AV interval. Therefore, they gain clinical benefit from the CRT only with BIV pacing. In this context, AF may interfere with CRT delivery because conducted beats caused by AF compete with BIV pacing. That happens when the ventricular rate of AF exceeds, interrupts, or disrupts the BIV capture, resulting in spontaneous, fusion, and pseudo-fusion beats.[17,18] This is further exacerbated in situations of increased myocar-

miokarda, kao što se događa kod povećanoga adrenergičkog tonusa tijekom stresa ili napora.[19] Fuzijski i pseudofuzijski otkucaji rezultat su interakcije između provedenih otkucaja FA i BIV stimuliranih otkucaja (**slika 1**). Fuzijski otkucaji nastaju kada se ventrikuli aktiviraju istodobno i preko BIV impulsa i normalno provedenog impulsa, stvarajući varijabilni oblik QRS-kompleksa koji ovisi o relativnom doprinosu BIV-om stimulirane i intrinzične aktivacije ventrikula. Pseudofuzijski otkucaji nastaju kada se BIV impuls isporuči nakon što su ventrikuli već depolarizirani normalno provedenim impulsom i imaju oblik QRS-kompleksa intrinzičnog otkucaja, ali sa superponiranim BIV stimulusom. Svi spontani, fuzijski i pseudofuzijski otkucaji terapeijski su nepoželjni jer je za osiguranje optimalnog odgovora CRT-a potrebno gotovo maksimalno djelotvorno i potpuno BIV „hvatanje".[19]

dial demand, as occurs from increased adrenergic tone during stress or exertion.[19] Fusion and pseudo-fusion beats result from an interaction between AF-conducted and BIV-paced beats (**Figure 1**). Fusion beats occur when the ventricles are activated at the same time by both the BIV impulse and the normal conducted impulse, producing a variable shape of the QRS complex, which depends on the relative contribution of BIV-paced and intrinsic ventricular activation. Pseudo-fusion beats occur when the BIV impulse is delivered after the ventricles have already been depolarized by normal conducted impulse, and have a QRS shape of the intrinsic beat but with a superimposed BIV spike. All spontaneous, fusion, and pseudo-fusion beats are therapeutically undesirable, because near maximally effective and complete BIV capture is necessary to assure optimal CRT response.[19]

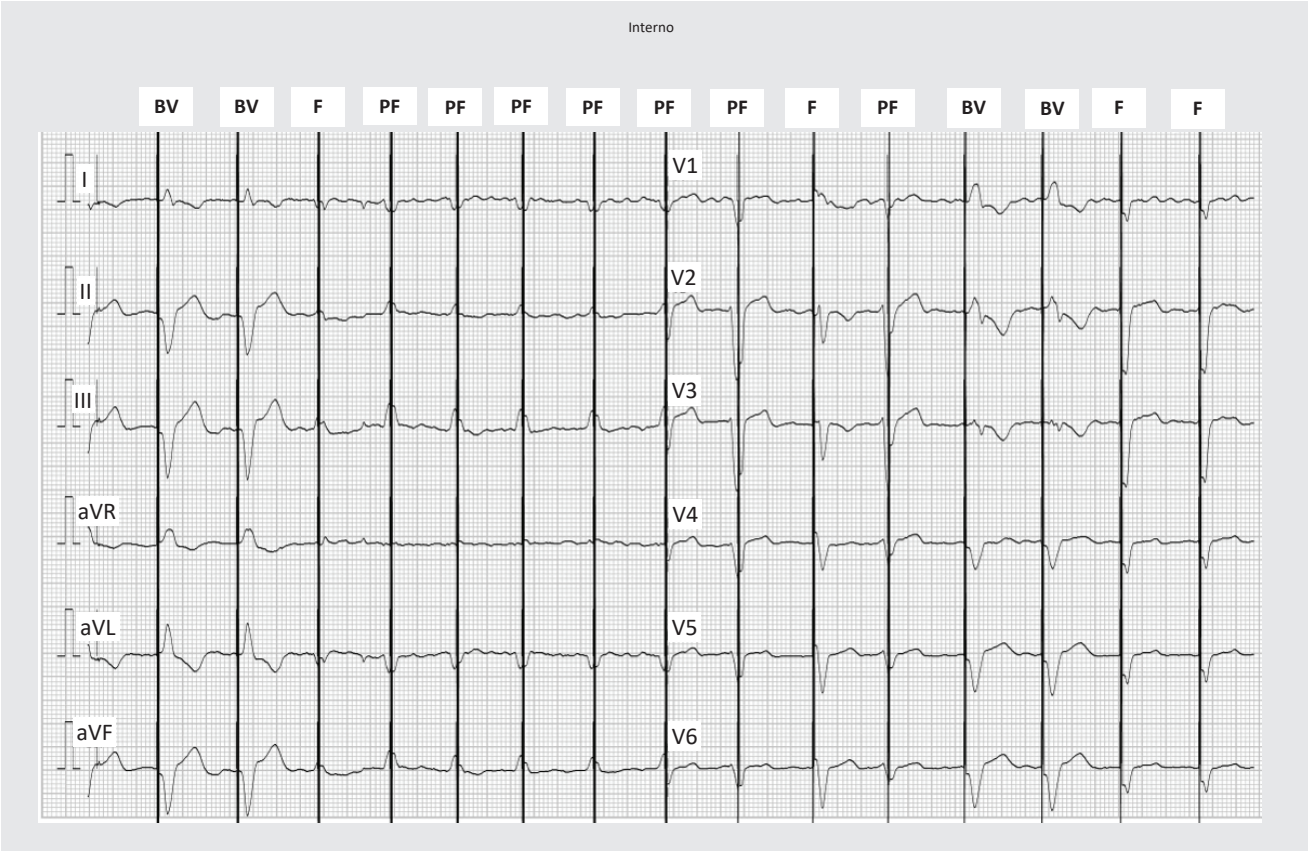

FIGURE 1. Electrocardiogram in patient with cardiac resynchronization therapy (CRT) and atrial fibrillation. Out of 15 recorded cardiac beats, only four were paced appropriately by biventricular pacing (BV). The other beats were pseudofusion (PF) or fusion (F) beats, which markedly reduced effective CRT.

Negativni učinci fibrilacije atrija u bolesnika s resinkronizacijskom terapijom

Postoje važni dokazi da FA negativno utječe na preživljavanje i djelotvornu BIV stimulaciju u bolesnika s CRT-om.[12-15,20,21] Wilton *i sur.* proveli su metaanalizu 23 opservacijskih istraživanja[12] koja su uspoređivala ishode u bolesnika s CRT-om s FA-om (n = 1912) i bez njega (n = 5583). Nakon prosječnoga praćenja od 33 mjeseca FA je bio povezan s većim rizikom od svih uzroka smrtnosti (10,8 % prema 7,1 %, p = 0,015) i većim rizikom od

Negative effects of atrial fibrillation in patients with cardiac resynchronization therapy

There is substantial evidence that AF has a negative impact on survival and effective BIV pacing in patients receiving CRT.[12-15,20,21] Wilton *et al.* performed a meta-analysis of 23 observational studies,[12] which compared the outcomes of patients receiving CRT with (n=1912) and those without (n=5583) AF. After a mean follow-up of 33 months, AF was associated

neodgovora na CRT (35 % prema 27 %, p = 0,001). Prvo izvješće Europskog CRT Registra potvrdilo je ove rezultate.[20] Među 2438 uključenih bolesnika s CRT-om, oni s FA-om imali su lošije jednogodišnje preživljavanje od onih sa sinusnim ritmom (86 % prema 91 %, p = 0,0038). Cesario *i sur.*[15] ispitali su utjecaj FA-a na preživljavanje u više od 60 000 bolesnika s implantiranim CRT defibrilatorom praćenih preko mreže za daljinsko praćenje. Otkrili su da bolesnici s opterećenjem FA-a >0,01% i epizodom FA-a koja traje >1 min imaju smanjeno preživljavanje u usporedbi s bolesnicima bez FA-a ili trajanjem FA-a <1 min (p <0,001). Bolesnici s opterećenjem FA-a >10 % i njegovim trajanjem od jednog dana imali su najniže dugoročne stope preživljenja. Nedavna metaanaliza 31 istraživanja koja su obuhvatila više od 80 000 bolesnika jednoznačno je pokazala da bolesnici s CRT-om u FA-u imaju mnogo veću ukupnu i kardiovaskularnu smrtnost u usporedbi s onima u sinusnom ritmu (oba p = 0,000). [21]

Koplan *i sur.*[22] bili su prvi koji su istraživali odgovarajući cilj BIV stimulacije u bolesnika s HF-om koji su dobili CRT. U njihovoj *post hoc* analizi dvaju ispitivanja s CRT-om (n = 1812), najveći stupanj smanjenja hospitalizacije zbog HF-a i ukupne smrtnosti zabilježen je s pragom BIV stimulacije od 92 %. Bolesnici stimulirani 93 do 100 % imali su manji rizik od smrti ili hospitalizacije zbog HF-a u usporedbi s bolesnicima stimuliranim od 0 do 92 % (p <0,00001). Među bolesnicima s BIV stimulacijom <93 %, rizik od kliničkih događaja bio je veći kod onih u kojih su se razvile FA / atrijska tahikardija (AT) tijekom praćenja nego u onih bez FA-a/AT-a (p = 0,.018).

U istraživanju Boriani *i sur.*[8] suboptimalan CRT, definiran kao postotak BIV stimulacije <95 %, bio je znatno povezan s pojavom perzistentne ili trajne FA (p <0,001) i nekontroliranom ventrikularnom frekvencijom (p = 0,002). Kada su bolesnici s FA-om bili u sinusnom ritmu, postotak BIV stimulacije bio je 98 % u usporedbi sa 71 % za vrijeme FA-a (p <0,01).

Važnost visokog postotka BIV stimulacije pokazana je u istraživanju Hayes *i sur.*[13], koje je uključilo >30 000 bolesnika praćenih u mreži za daljinsko praćenje. Smrtnost je bila obrnuto proporcionalna s postotkom BIV stimulacije u prisutnosti sinusnog ritma, stimuliranoga atrijskog ritma, kao i kad je atrijski ritam bio FA. BIV stimulacija >98,5 % bila je nađena kao prijelomna vrijednosna točka za znatnu korist u preživljenju. Bolesnici s BIV stimulacijom >99,6% imali su smanjenje smrtnosti za 24 % (p <0,001), dok su oni s BIV% stimulacijom <94,8 % imali povećanje smrtnosti za 19 %. Važno je napomenuti da su pri istom postotku BIV stimulacije, uključujući i BIV stimulaciju >98,5 %, bolesnici s FA-om imali manje preživljenje nego oni bez FA-a.

U istraživanju Ousdigian *i sur.*[14] znatan postotak bolesnika s perzistentnim (69 %) i trajnim (62 %) oblikom FA-a nije postigao visoku BIV stimulaciju (>98 %) i takvi su bolesnici imali povećan rizik od smrti. U multivarijabilnoj analizi smanjen postotak BIV stimulacije (≤ 98%) bio je neovisan čimbenik većeg rizika od smrtnosti. U usporedbi s bolesnicim s visokom BIV stimulacijom (>98 %), bolesnici s umjerenom (90 – 98 %) i niskom (<90 %) BIV stimulacijom imali su povećanje smrtnosti od 20 %, odnosno 32 % (p <0,001 za obje skupine). U svakoj od triju BIV stimulacijskih skupina, sve skupine s FA-om imale su povećanu smrtnost u usporedbi s grupom bez FA-a ili s malo FA-a (p <0,001). Stoga je u bolesnika s CRT-om i FA-om potreban najveći mogući postotak BIV stimulacije da bi se postignula maksimalna korist od CRT-a i ostvario terapijski učinak.

with a higher risk of all-cause mortality (10.8% vs 7.1 %, p=0.015) and higher risk of nonresponse to CRT (35% vs 27%, p=0.001). The first report of the European CRT Survey has confirmed these results.[20] Among 2438 enrolled patients receiving CRT, those with AF had a poorer 1-year survival than those with sinus rhythm (86% vs 91%, p=0.0038). Cesario *et al.*[15] examined the impact of AF on survival in >60 000 patients with an implanted CRT-defibrillator followed using a remote monitoring network. They found that patients with an AF burden >0.01% with an AF episode lasting >1 min had decreased survival compared with patients with no AF or AF duration <1 min (p<0.001). The patients with an AF burden >10% and AF lasting 1 day had the lowest long-term survival rates. A recent meta-analysis of 31 studies with over 80 000 patients has unequivocally demonstrated that patients with AF receiving CRT had significantly higher all-cause and cardiovascular mortality than those with sinus rhythm (both p=0.001).[21]

Koplan *et al.* were the first[22] who investigated appropriate BIV pacing targets in patients with HF receiving CRT. In their post-hoc analysis of two CRT trials (n=1812), the greatest magnitude of reduction in HF hospitalization and all-cause mortality was observed with a biventricular pacing cutoff of 92%. The patients paced 93% to 100% had a lower risk of death or HF hospitalization compared with patients paced 0% to 92% (p<0.00001). Among patients with BIV pacing <93%, the risk of clinical events was higher in those who developed AF/atrial tachycardia (AT) during follow-up than in those who were without AF/AT (p=0.018).

In a study by Boriani *et al.*,[8] sub-optimal CRT, defined as a percentage of BIV pacing <95%, was significantly associated with the occurrence of persistent or permanent AF (p<0.001) and uncontrolled ventricular rate (p=0.002). When the patients with AF were in sinus rhythm, the percentage of BIV pacing was 98% versus 71% during AF (p<0.01).

The importance of a high percentage of BIV pacing has been demonstrated in a study by Hayes *et al.*[13], which included >30 000 patients followed in a remote-monitoring network. The mortality was inversely correlated with the percentage of BIV pacing in the presence of sinus rhythm, paced atrial rhythm, and when the atrial rhythm was AF. BIV pacing >98.5% was found to be a cutoff value for significant benefit in survival. Patients with BIV pacing >99.6% experienced a 24% reduction in mortality (p<0.001), while those with BIV% pacing <94.8% had a 19% increase in mortality. Importantly, at the same percentage of BIV pacing, including BIV pacing >98.5%, patients with AF had a lower survival than those without AF.

In a study by Ousdigian *et al.*[14] a significant percentage of patients with permanent (69%) and persistent (62%) AF did not achieve high BIV pacing (>98%), and these patients had an increased risk of death. In a multivariable analysis, reduced percentage of BIV pacing (≤98%) was an independent risk factor of higher mortality. Relative to patients with high BIV pacing (>98%), patients with moderate (90-98%) and low (<90%) BIV pacing had an increase in mortality of 20% and 32%, respectively (p<0.001 for both pacing groups). In each of the three BIV pacing groups, all AF groups had increased mortality in comparison with the group with no/little AF (p<0.001). Therefore, in patients with AF receiving CRT, the highest possible percentage of BIV pacing is necessary to achieve maximum benefit from CRT and achieve the therapeutic effect.

Terapijske opcije za fibrilaciju atrija u bolesnika s resinkronizacijskom terapijom

Kao i za druge bolesnike s FA-om, terapijske opcije za bolesnike s CRT-om uključuju kontrolu frekvencije ili kontrolu ritma. Izbor tih opcija ovisi o vrsti AF-a, a njihov je glavni cilj osigurati visok postotak BIV stimulacije (**slika 2**).[23]

Therapeutic options for atrial fibrillation in patients receiving cardiac resynchronization therapy

As for other patients with AF, therapeutic options for patients receiving CRT include rate or rhythm control. The choice of these options depends on the type of AF (**Figure 2**), and their main goal is to ensure a high percentage of BIV pacing (>98%).[23]

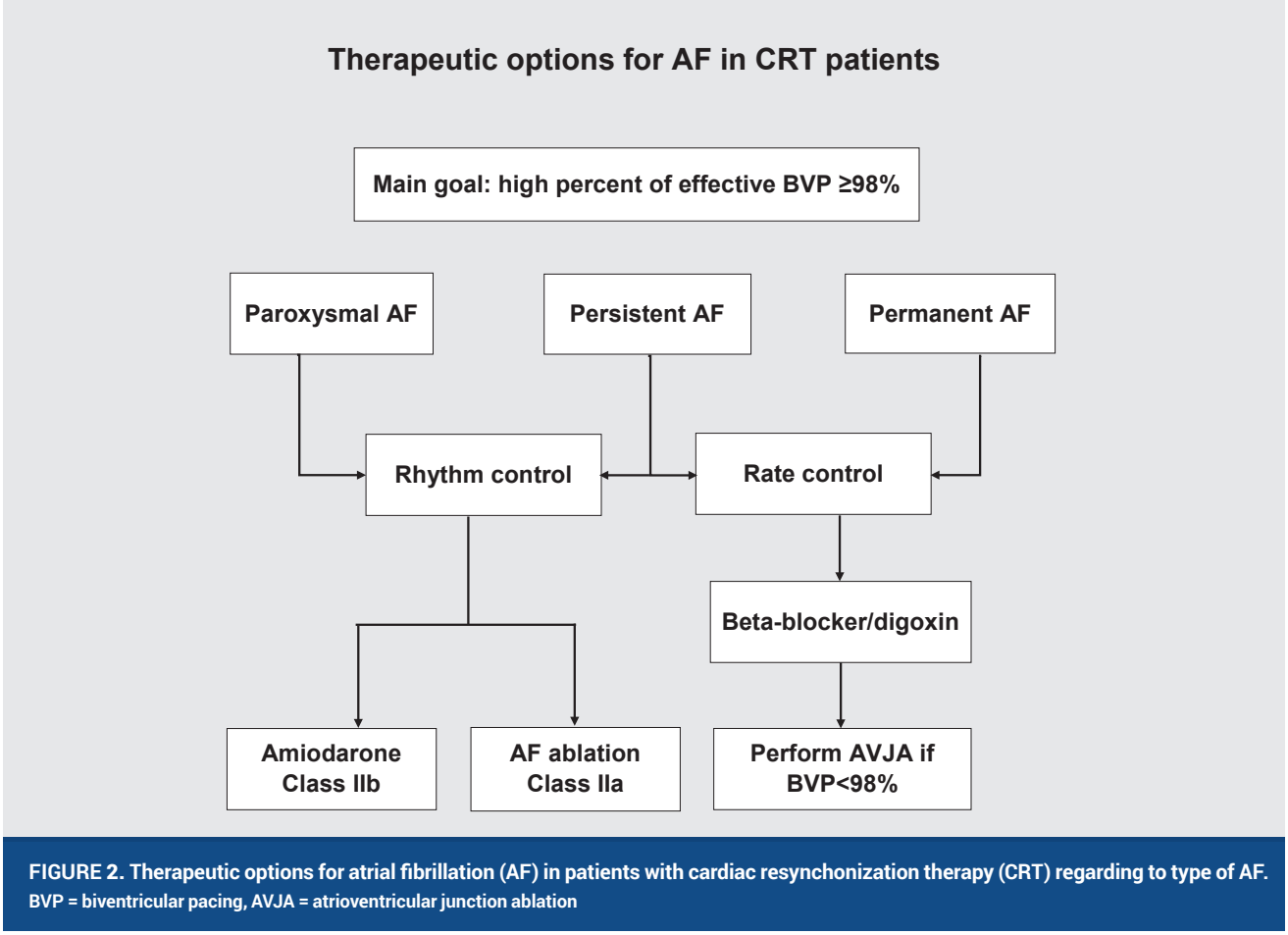

FIGURE 2. Therapeutic options for atrial fibrillation (AF) in patients with cardiac resynchonization therapy (CRT) regarding to type of AF.
BVP = biventricular pacing, AVJA = atrioventricular junction ablation

Kontrola frekvencije odnosi se na terapijske opcije koje djelotvorno smanjuju i reguliraju frekvenciju srca u bolesnika s CRT-om i perzistentnom ili trajnom FA, koji se ne može lako kardiovertirati u sinusni ritam.[23] Farmakološka kontrola frekvencije početna je terapijska opcija,[24,25] ali lijekovi malokad mogu osigurati visok postotak BIV stimulacije bez fuzijskih otkucaja.[18,26] U jednom prospektivnom istraživanju čak 71 % bolesnika s trajnom FA nije moglo postići zadovoljavajuću kontrolu frekvencije lijekovima.[27] Beta-blokatori se obično primjenjuju kao prva terapija za kontrolu frekvencije klijetki zbog njihove dokazane sigurnosti i djelotvornosti pri tjelesnom naporu i visokom tonusu simpatikusa.[24,28] Digoksin ili digitoksin uporabljuju se kada frekvencija klijetki ostaje visoka unatoč beta-blokatorima ili kada se ta skupina lijekova ne podnosi ili je kontraindicirana.[24,29]

Za razliku od terapije lijekovima, ablacija atrioventrikularnoga spoja (AVJ) potpuno eliminira AV provođenje i osigurava

Rate control refers to therapeutic options which effectively reduce and regularize heart rate in patients receiving CRT who have permanent or persistent AF that cannot be readily cardioverted to sinus rhythm.[23] Pharmacological rate control is an initial therapeutic option,[24,25] but the drugs are rarely adequate in ensuring a high percentage of BIV pacing without fusion beats.[18,26] In one prospective study, as many as 71% of patients with permanent AF could not achieve satisfactory rate control with drugs.[27] Beta-blockers are usually used as first-line therapy to control ventricular rate because of their established safety and effectiveness during physical exertion and high sympathetic tone.[24,28] Digoxin or digitoxin come into play when ventricular rate remains high despite beta-blockers or when beta-blockers are not tolerated or contraindicated.[24,29]

In contrast to drug therapy, atrioventricular junction (AVJ) ablation completely eliminates AV conduction and ensures almost 100% BIV pacing,[30] but with consequent perma-

gotovo 100 % BIV stimulaciju[30], ali s posljedicom trajne ovisnosti o elektrostimulatoru srca. Nekoliko je opservacijskih istraživanja pokazalo znatnu korist ablacije AVJ-a u usporedbi s lijekovima za kontrolu frekvencije u bolesnika s CRT-om i trajnim ili dugotrajnim perizistentnim FA-om u poboljšanju ejekcijske frakcije lijevog ventrikula (LVEF), obrnutom remodeliranju, podnošenju napora i preživljavanju.[27,31,32] U sustavnom pregledu 768 bolesnika s CRT-om i FA-om,[33] bolesnici s dodatnom ablacijom AVJ-a imali su znatno smanjenje ukupne i kardiovaskularne smrtnosti u usporedbi s onima liječenima lijekovima za kontrolu frekvencije. Ovi su rezultati potvrđeni u istraživanju *CERTIFY* (*Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry*),[34] koja je usporedila kliničke ishode u trima skupinama bolesnika s CRT-om: u onih u sinusnom ritmu (n = 6046), u onih s trajnom FA i ablacijom AVJ-a (n = 895) te u onih s trajnom FA i lijekovima za kontrolu frekvencije (n = 895). Tijekom prosječnoga praćenja od 37 mjeseci ukupna smrtnost (6,8 % prema 6,1 %) i kardiovaskularna smrtnost (4,2 % prema 4,0 %) bile su slične za bolesnike s FA-om i ablacijom AVJ-a i za bolesnike u sinusnom ritmu. Nasuprot tomu, bolesnici s FA-om koji su se koristili lijekovima za kontrolu frekvencije imali su mnogo višu ukupnu i kardiovaskularnu smrtnost nego oni sa sinusnim ritmom ili oni s FA-om i ablacijom AVJ-a (oba p <0,001). Nadalje, poboljšanje LVEF-a i volumena LV-a na kraju sistole u bolesnika s FA-om i ablacijom AVJ-a bilo je usporedivo s onim u bolesnika sa sinusnim ritmom, a mnogo veće nego u bolesnika s FA-om koji su se koristili lijekovima za kontrolu frekvencije (oba p <0,001).

Prvo randomizirano istraživanje[35] koje je usporedilo ablaciju AVJ-a s optimalnom medicinskom terapijom u bolesnika s CRT-om i trajnom FA, nije utvrdilo da ablacija poboljšava ehokardiografske ili kliničke ishode. Međutim, to je istraživanje uključilo premali broj bolesnika (12 u svakoj randomiziranoj skupini) za relevantnu kliničku preporuku ili zaključak.

U zaključku, prospektivna opservacijska istraživanja dosljedno su pokazala da je ablacija AVJ-a bila bolja od lijekova za kontrolu frekvencije u postizanju adekvatne BIV stimulacije i u smanjenju dugoročne smrtnosti, kao i u poboljšanju LVEF-a, funkcionalnog kapaciteta i obrnutog remodeliranja ventrikula. Zbog tih razloga ablaciju AVJ-a trebalo bi izvesti u većine, ako ne i u svih bolesnika s CRT-om i trajnom FA, te u onih s učestalim i dugotrajnim epizodama perzistentnog FA-a, koji ne reagiraju ili ne podnose terapiju lijekovima.[23]

Kontrola ritma odnosi se na terapijske opcije koje mogu vratiti i održati sinusni ritam. U bolesnika s CRT-om i FA-om vraćanje sinusnog ritma može se postići električnom ili farmakološkom kardioverzijom. Kada se preferira farmakološka kardioverzija, amiodaron je lijek izbora[36,37] jer su drugi antiaritmici povezani s negativnim utjecajem na preživljenje.[38-40] Amiodaron je jedini lijek pogodan za kontrolu ritma u bolesnika s CRT-om,[41,42] ali je njegova uspješnost u održavanju sinusnog ritma skromna i ne prelazi 34 % nakon 24 mjeseca praćenja.[42]

U nedostatku randomiziranih istraživanja o ablaciji FA-a u bolesnika s CRT-om, njezina se korist može pretpostaviti iz randomiziranih istraživanja o ablaciji FA-a u bolesnika s HF-om i LVEF-om manjim od 40 % (**tablica 2**). Istraživanje *PABA-CHF* (engl. *Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure*)[43] usporedilo je ablaciju FA-a s kombinacijom ablacije AVJ-a i BIV stimulacije.

nent pacemaker dependency. Several observational studies showed a significant benefit of AVJ ablation versus rate control drugs in patients receiving CRT with permanent or longstanding persistent AF in improving LVEF, reversing the remodeling effect, and improving exercise tolerance and survival.[27,31,32] In systematic review of 768 patients receiving CRT with AF,[33] patients with additional AVJ ablation had a substantial reduction of all-cause mortality and cardiovascular mortality compared with those treated with rate control drugs. These results have been confirmed in the CERTIFY (Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry) study,[34] which compared the clinical outcomes in three groups of patients receiving CRT: those with sinus rhythm (n=6046), those with permanent AF and AVJ ablation (n=895), and those with permanent AF and rate control drugs (n=895). At a mean follow-up of 37 months, total mortality (6.8% vs 6.1%) and cardiac mortality (4.2 % vs 4.0%) were similar for patients with AF with AVJ ablation and patients in sinus rhythm. In contrast, patients with AF receiving rate control drugs had a significantly higher total and cardiac mortality than both the patients sinus with and the patients with AF with AVJ ablation (both p<0.001). Furthermore, the improvement in left ventricular ejection fraction (LVEF) and LV end-systolic volume in patients with AF with AVJ ablation was comparable to that observed in patients with sinus rhythm, and significantly higher than that observed in patients with AF receiving rate control drugs (both p<0.001).

The first randomized study[35] that compared AVJ ablation with optimal medical therapy in patients with permanent AF receiving CRT did not find that AVJ ablation improved echocardiographic or clinical outcomes. However, the study included too small a number of patients (12 in each randomized group) to allow relevant clinical suggestions or conclusions.

In conclusion, prospective observational studies have consistently shown that AVJ ablation was superior to rate control drugs in achieving adequate BIV pacing and reducing long-term mortality, as well as in improving LVEF, functional capacity, and reversing ventricular remodeling. For these reasons, AVJ ablation should be performed in most, if not all, patients with permanent AF receiving CRT, and in those with frequent and prolonged episodes of persistent AF that are unresponsive or intolerant to drug therapy.[23]

Rhythm control refers to therapeutic options that can restore and maintain sinus rhythm. In patients with AF receiving CRT, the restoration of sinus rhythm can be achieved with electrical or pharmacological cardioversion. When pharmacological cardioversion is preferred, amiodarone is the drug of choice[36,37] because other antiarrhythmic drugs are associated with a negative impact on survival.[38-40] Amiodarone is the only drug suitable for rhythm control in patients receiving CRT,[41,42] but its success rate in the maintenance of sinus rhythm is modest and no higher than 34% after 24 months of follow-up.[42]

In the absence of randomized studies on AF ablation in patients receiving CRT, its benefit in these patients can be assumed based on randomized studies on AF ablation in patients with HF with LVEF less than 40% (**Table 2**). The PABA-CHF (Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure) study[43] compared AF ablation with a combination of AVJ ablation and

mulacije u 81 bolesnika s LVEF-om ≤40 %, NYHA II. ili III. stupnjem HF-a i paroksizmalnim ili trajnim FA-om. Nakon šest mjeseci praćenja bolesnici randomizirani na ablaciju FA-a imali su veće poboljšanje u primarnom cilju ispitivanja sastavljenog od LVEF-a, 6-minutne hodne udaljenosti (*6-MWD*) i rezultata na *Minnesota Living with Heart Failure* (*MLWHF*) ljestvici nego oni randomizirani na kombinaciju ablacije AVJ-a i BIV stimulacije (35 % prema 28 %, p <0,001), a 71 % bolesnika u ablacijskoj grupi nije imalo FA niti antiaritmik. U dvama kasnijim istraživanjima,[44,45] bolesnici sa simptomatskim HF-om, LVEF-om <40 % i trajnom FA-om bili su randomizirani na ablaciju FA-a ili lijekove za kontrolu frekvencije. U istraživanju MacDonalda *i sur.*[44] ablacija FA-a nije poboljšala LVEF-a, razinu NT-proBNP-a, 6-MWD i kvalitetu života (QoL) u usporedbi s lijekovima za kontrolu frekvencije, a samo 50 % bolesnika koji su podvrgnuti ablaciji FA-a bilo je u sinusom ritmu nakon 6 mjeseci. Nasuprot tomu, Jones *i sur.*[45] izvijestili su o znatnoj koristi ablacije FA-a s obzirom na lijekove za kontrolu frekvencije u poboljšanju vršne potrošnje kisika (PVO_2), razine BNP-a i vrijednosti na MLWHF ljestvici, a 88 % bolesnika u ablacijskoj grupi uspjelo je održati sinusni ritam nakon 12 mjeseci.

Istraživanje *AATAC* (*Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted Device*)[42] uključilo je 203 bolesnika s HF-om, LVEF-om <40 %, perzistentnim FA-om i ugrađenim dvokomornim kardioverterskim defibrilatorom

BIV pacing in 81 patients with LVEF <40%, NYHA class II or III HF, and paroxysmal or persistent AF. At six-month follow-up, the patients randomized to AF ablation had a greater improvement in primary end points comprising LVEF, 6-minute walk distance (6-MWD), and Minnesota Living with Heart Failure (MLWHF) score than those randomized to a combination of AVJ ablation and BIV pacing (35% vs 28%, p<0.001), and 71% of patients in the ablation group were AF-free with no antiarrhythmic medication. In two subsequent studies,[44,45] patients with symptomatic HF, LVEF<40%, and persistent AF were randomized to AF ablation or rate control drugs. In the study by MacDonald *et al.*,[44] AF ablation did not improve LVEF, level of N-terminal pro brain natriuretic peptide (BNP), 6-MWD, and quality of life (QoL) compared with rate-control drugs, and only 50% of patients who underwent AF ablation were in sinus rhythm at 6 months. In contrast, Jones *et al.*[45] reported a significant benefit of AF ablation versus rate control drugs in improving peak oxygen consumption, BNP level, and MLWHF score, and 88% of patients in the ablation group were able to maintain sinus rhythm at 12 months.

The AATAC (Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted Device) study[42] enrolled 203 patients with HF and LVEF <40%, persistent AF, and an implanted dual chamber cardioverter-defibrillator or CRT-defibrillator, who were randomly assigned to AF ablation or amiodarone. Over

TABLE 2. Randomized clinical studies on ablation in patients with atrial fibrillation, heart failure, and left ventricular ejection fraction <40%.

Study (year)	Inclusion criteria	Randomized treatment groups	F/U (months)	Outcomes regarding the primary end point	AF ablation procedural success
PABA-CHF[42] (2008)	Paroxysmal or persistent AF NYHA II-III HF LVEF <40%	AF ablation (n=41) AVJA + CRT (n=40)	6	Significant improvement in LVEF, 6-MWD, and MLWHF in the ablation group	88.0%
MacDonald *et al.*[43] (2011)	Persistent AF NYHA II-IV HF LVEF ≤35%	AF ablation (n=22) Rate control drugs (n=10)	6	No difference in LVEF between the groups	50.0%
Jones *et al.*[44] (2013)	Persistent AF NYHA II-III HF LVEF ≤35%	AF ablation (n=25) Rate control drugs (n=26)	12	Significant improvement in PO2 in the ablation group	88.0%
AATAC[41] (2017)	Persistent AF NYHA II-III HF LVEF <40%	AF ablation (n=102) Amiodarone (n=101)	36	Significant improvement in freedom from AF in the ablation group	70.0%
CASTLE-AF[45] (2018)	Paroxysmal or persistent AF NYHA II-IV HF LVEF ≤35%	AF ablation (n=179) Rate/rhythm control drugs (n=184)	60	Significant improvement in mortality or HFH in the ablation group	63.1%
AMICA[46] (2019)	Persistent AF NYHA II-IV HF LVEF ≤35%	AF ablation (n=68) Best medical therapy (n=72)	12	No difference in LVEF between the groups	73.5%

F/U = follow up, AF = atrial fibrillation, NYHA = New York Heart Association, LVEF = left ventricular ejection fraction, AVJA = atrioventricular junction ablation, 6-MWD = six-minute walking distance, MLWHF = Minessota Living with Heart Failure, PVO2 = peak oxygen consumption, HFH = hospitalization for heart failure

ili CRT defibrilatorom, koji su bili randomizirani na ablaciju FA-a ili amiodaron. Tijekom dvogodišnjega praćenja ablacija FA-a bila je superiornija od amiodarona u postizanju zaštite od FA-a (70 % prema 34 %, p <0,001), smanjenju neplanirane hospitalizacije zbog HF-a (31 % prema 38 %, p <0,001), smrtnosti (8 % prema 18 %, p = 0,037), kao i u poboljšanju LVEF-a (p=0.02), 6-MWD-a (p=0.02) i rezultata MLWHF skora (p=0.04).

Istraživanje *CASTLE-AF* (*Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation*)[46] uključilo je 363 bolesnika sa simptomatskom paroksizmalnom ili perzistentnom FA, NYHA stupnjem II. – IV. HF-a, LVEF-om ≤35 % i ugrađenim kardioverterskim defibrilatorom (n = 263) ili CRT defibrilatorom (n = 100), koji su bili randomizirani na ablaciju FA-a ili terapiju lijekovima (kontrolu frekvencije ili ritma). Nakon prosječnoga praćenja od 37,8 mjeseci, uporaba ablacije FA-a bila je povezana s mnogo nižom stopom zajedničkog ishoda od ukupne smrtnosti ili hospitalizacije zbog HF-a nego terapija lijekovima (51 prema 82, p = 0.007). Također je bilo znatne koristi u ukupnoj smrtnosti, koja je bila vođena mnogo nižom stopom kardiovaskularne smrti u ablacijskoj grupi (**tablica 3**). Važno je napomenuti da korist od ablacije u smanjenju smrtnosti nije postala vidljiva do nakon 3 godine. Nadalje, ablacija FA-a poboljšala je LVEF (p = 0,005 s obzirom na grupu s lijekovima), povećala 6-MWD, a 63 % bolesnika liječenih ablacijom bili su bez FA-a nakon 60 mjeseci praćenja. Ograničenja istraživanja *CASTLE-AF* uključuju produljeni period upisivanja visokoselektiranih ispitanika (samo 12% od 3013 regrutiranih bolesnika tijekom 8 godina) i nedostacima u pogledu randomizacije i liječenja.

Istraživanje *AMICA* uključilo je 140 bolesnika s perzistentnim ili dugotrajnim perzistentnim FA-om i LVEF-om ≤35 %, koji su bili nasumično raspoređeni na ablaciju FA-a ili najbolju medicinsku terapiju.[47] Prekinuto ranije zbog beskorisnosti, istraživanje nije našlo statistički značajne razlike između grupa u liječenju LVEF-u, 6-MWD-u, MLWHF ljestvici, razini BNP-a i vraćanju sinusnog ritma. Različiti rezultati u istraživanjima *AMICA* i *CASTLE-AF* mogu se objasniti činjenicom da je *AMICA* uključila bolesničku populaciju s uznapredovalim HF-om i FA-om koja je bila manje pogodni za ablaciju. Doista, izravna usporedba bolesnika koji su prošli ablaciju u ovim

the 2-year follow-up, AF ablation was superior to amiodarone in achieving freedom from AF (70% vs 34%, p<0.001) and reducing unplanned HF hospitalization (31% vs 38%, p<0.001) and mortality (8% vs 18%, p=0.037), as well as in improving LVEF (p=0.02), 6-MWD (p=0.02), and MLFHQ scores (p=0.04).

The CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) study[46] included 363 patients with symptomatic paroxysmal or persistent AF, NYHA class II-IV HF, LVEF ≤35%, and an implanted cardioverter-defibrillator (n=263) or CRT-defibrillator (n=100), who were randomized to either AF ablation or medical therapy (rate or rhythm control). After a median follow-up of 37.8 months, the use of AF ablation was associated with a significantly lower rate of a composite end point of death from any cause or HF hospitalization than medical therapy (51 vs 82, p=0.007). There was also significant benefit in all-cause mortality alone, which was driven by a significantly lower rate of cardiovascular death in the ablation group (**Table 3**). Importantly, the mortality benefit of ablation did not emerge until after 3 years. Furthermore, AF ablation improved LVEF (p=0.005 vs the medical group), increased 6-MWD, and 63% of patients treated with ablation were free of AF after 60 months of follow-up. The limitations of the CASTLE-AF study were extended enrollment period of highly-selected population (only 12% of 3013 recruited patients during 8 years) and lack of blinding with respect to randomization and treatment.

The AMICA study included 140 patients with persistent or longstanding persistent AF and LVEF ≤35%, who were randomly allocated to AF ablation or best medical therapy.[47] Terminated earlier due to futility, the study did not find statistically significant differences between treatment groups in LVEF, 6-MWD, MLWHF score, BNP level, and restoration of sinus rhythm. The different results in the AMICA and CASTLE-AF studies might be explained by the fact that AMICA enrolled a patient population with more advanced HF and AF, who were less suitable for ablation. Indeed, a direct comparison of patients receiving ablation in these two studies shows that patients in the AMICA study had a lower mean LVEF (27.6% vs 32.5%), higher prevalence of persistent AF (100% vs 70%), and more prevalent NYHA class III or IV (60% vs 31%) at baseline evaluation.[47]

TABLE 3. Secondary end points in the Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation Study.

End point	AF ablation (n = 179)	Medical therapy (n = 184)	p Value
	Number (%)	Number (%)	Cox regression
Death from any cause	24 (13.4)	46 (25.0)	0.009
HF hospitalization	37 (20.7)	66 (35.9)	0.004
CV death	20 (11.2)	41 (22.3)	0.008
CV hospitalization	64 (35.8)	89 (48.4)	0.04
Hospitalization for any cause	114 (63.7)	122 (66.3)	0.96
Cerebrovascular accident	5 (2.8)	11 (6.0)	0.14

AF = atrial fibrillation, HF = heart failure, CV = cardiovascular

dvama istraživanjima pokazuje da su bolesnici u istraživanju *AMICA* imali nižu prosječnu LVEF (27,6 % prema 32,5 %), višu prevalenciju trajne FA (100 % prema 70 %) i češće NYHA stupanj III. ili IV. (60 % prema 31 %) na početnoj evaluaciji.[47]

Nedavna analiza iz istraživanja *CABANA* odnosi se na 778 bolesnika sa stabilnim HF-om te paroksizmalnom ili trajnom FA, koji su bili raspoređeni na ablaciju AF-a (n = 378) ili terapiju lijekovima (n = 400).[48] Tijekom praćenja od 48,5 mjeseci postojalo je znatno smanjenje u primarnome zajedničkom ishodu sastavljenom od smrti, moždanog udara, ozbiljnog krvarenja ili srčanog zastoja (9 % prema 12,3 %, HR: 0,64) i smrtnosti (6,1 % prema 9,3%, HR: 0,57) u ablacijskoj grupi. Međutim, treba napomenuti da su ti rezultati dobiveni u bolesnika s HF-om od kojih je samo 9,3% imalo LVEF <40 %.

U zaključku, randomizirana istraživanja o ablaciji FA-a u bolesnika s HF-om i smanjenim LVEF-om (<40 %) pokazala su da je ablacija FA-a bila bolja od lijekova za kontrolu frekvencije i kontrolu ritma u poboljšanju, QoL-a, LVEF-a, razine BNP-a, funkcionalnog kapaciteta i zaštite od FA-a na praćenju. Rezultati o hospitalizaciji zbog HF-a i smrtnosti dobiveni su s relativno malim brojem događaja, što ne dopušta donošenje konačnih zaključaka. Sadašnje smjernice preporučuju ablaciju FA-a u bolesnika sa smanjenim LVEF-om, koji ostaju simptomatski na terapiji za kontrolu frekvencije. Sukladno tomu, ablacija FA-a trebala bi se razmotriti u bolesnika s CRT-om i paroksizmalnom ili trajnom FA-om koji imaju simptome i smanjenu isporuku CRT-a (≤98 %) unatoč optimalnoj terapiji lijekovima.

S kliničke točke gledišta, ablacija FA-a može imati prednost nad ablacijom AVJ-a u bolesnika s CRT-om jer istodobno obnavlja AV sinkroniju i osigurava visok postotak isporuke CRT-a. Novi podatci o ovoj temi bit će dostavljeni u prospektivnom istraživanju *RHYTHMIC* (*Rate or Rhythm Control in CRT*)[49] koje će istražiti hoće li obnova AV sinkronije s ablacijom FA-a dovesti do boljega obrnutog remodeliranja LV-a u usporedbi s ablacijom AVJ-a u bolesnika s CRT-om i suboptimalnom (<95 %) BIV stimulacijom uzrokovanom FA-om.

Zaključak

FA interferira s CRT-om zbog gubitka AV sinkronije i kompeticije između BIV „hvatanja" i FA-om vođenih otkucaja, što pak rezultira smanjenjem učinkovite BIV stimulacije i lošijim ishodima. Terapijske opcije za FA u bolesnika s CRT-om odnose se na kontrolu frekvencije i kontrolu ritma s glavnom svrhom da se osigura visoki postotak BIV stimulacije (>98 %) i posljedično bolja prognoza. Farmakološka kontrola frekvencije ili ritma može se primjenjivati u bolesnika s CRT-om, ali je njihova učinkovitost u postizanju dovoljne BIV stimulacije skromna. Ablacija AVJ-a eliminira interferenciju s normalno provedenim srčanim kontrakcijama, osigurava potpuno BIV „hvatanje" i poboljšava ishode, uključujući preživljenje. Zbog tih razloga ablacija AVJ-a trebala bi se primjenjivati kao prva terapijska opcija u većine bolesnika s CRT-om i trajnim FA-om, kao i u onih s perzistentnim FA-om u kojih terapija lijekovima nije uspjela. Ablacija FA-a trebala bi se razmotriti u bolesnika s CRT-om i paroksizmalnim ili perzistentnim FA-om, kada su ove aritmije simptomatske i smanjuju djelotvornu isporuku CRT-a unatoč terapiji lijekovima. Potrebna su randomizirana istraživanja o ablaciji FA-a u bolesnika s CRT-om kako bi se procijenilo može li ona biti prva terapijska opcija za kontrolu ritma u takvih bolesnika.

A recent analysis from the CABANA study examined 778 patients with stable HF and paroxysmal or persistent AF, who were assigned to AF ablation (n=378) or drug therapy (n=400).[48] After 48.5 months of follow-up, there was a significant reduction in a composite end point of death, stroke, serious bleeding, or cardiac arrest (9% versus 12.3%, HR: 0.64) and mortality (6.1 vs 9.3%, HR: 0.57) in the ablation group. However, it should be noted that these results were obtained in patients with HF of whom only 9.3% had LVEF<40%.

In conclusion, randomized studies on AF ablation in patients with HF with reduced LVEF (<40%) have demonstrated that AF ablation was superior to rate and rhythm control drugs in improving QoL, LVEF, BNP levels, functional capacity, and freedom from AF during follow-up. The results on HF hospitalization and mortality were obtained with a relatively small number of events, which does not allow for definitive conclusions. Current guidelines recommend AF ablation in patients with reduced LVEF who remain symptomatic after rate control therapy. Accordingly, AF ablation should be considered in patients receiving CRT with paroxysmal or persistent AF, who are symptomatic and have reduced CRT delivery (≤98) despite optimal medical therapy.

From a clinical point of view, AF ablation may have an advantage over AVJ ablation in patients receiving CRT because simultaneously restores AV synchrony and provides a high percentage of CRT delivery. New data on this topic will be provided by the prospective RHYTHMIC (Rate or Rhythm Control in CRT) study,[49] which will investigate whether the restoration of AV synchrony with AF ablation will lead to better LV reverse remodeling compared to AV node ablation in CRT patients with suboptimal (<95%) BIV pacing caused by AF.

Conclusion

AF interferes with CRT delivery due to the loss of AV synchrony and competition between BIV capture and conducted beats due to AF, which in turn results in a reducing of effective BIV pacing and poorer outcomes. Therapeutic options for patients with AF receiving CRT comprise rate or rhythm control strategies, with the main goal of ensuring a high percentage of BIV pacing (>98%) and thus better prognosis. Pharmacological rate or rhythm control can be used, but their efficacy in achieving sufficient BIV pacing is modest. AVJ ablation eliminates interference with normally conducted beats, provides complete BIV capture, and improves outcomes, including survival. For these reasons, AVJ ablation should be used as the first-line therapeutic option in the majority of CRT patients with permanent AF, and also in patients with persistent AF in whom drug therapy has failed. AF ablation should be considered in CRT patients who have paroxysmal or persistent AF, when these arrhythmias are symptomatic and reduce effective BIV pacing despite medical therapy. Randomized studies on AF ablation in patients receiving CRT are needed in order to assess whether it can be the first-line therapeutic option for rhythm control in these patients.

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