

Fibrilacija atrijska u bolesnika s resinkronizacijskom terapijom srca: terapijske mogućnosti

Atrial Fibrillation in Patients with Cardiac Resynchronization Therapy: Therapeutic Options

Dubravko Petrač¹*

Kardiološka poliklinika
«Bogdan», Zagreb, Hrvatska
«Bogdan» Outpatient
Cardiology Clinic, Zagreb,
Croatia

SAŽETAK: Fibrilacija atrijska (FA) često je prisutna u bolesnika s resinkronizacijskom terapijom srca (CRT) i može imati znatan negativan utjecaj na prognozu i odgovor na CRT. Liječenje FA-a u bolesnika s CRT-om uključuje optimalnu medikamentu terapiju za zatajivanje srca, antikoagulantnu terapiju i terapiju za kontrolu frekvencije ili kontrolu ritma sa specifičnim ciljem da se osigura visoki postotak ($\geq 98\%$) biventrikularne (BiV) stimulacije. U bolesnika sa zatajivanjem srca i FA-om, kontrola ritma antiaritmikima nije uspjela pokazati nikakvu dobit u preživljenju u usporedbi s lijekovima za kontrolu frekvencije. U tom kontekstu kontrola frekvencije lijekovima preferira se kao prvi izbor liječenja u bolesnika s CRT-om i perzistentnom ili trajnom FA. Međutim, opservacijske prospektivne studije i metaanalize pokazuju da je ablacija AV spoja bolja od lijekova za kontrolu frekvencije u postizanju visokog postotka BiV stimulacije i smanjenju smrtnosti. Zbog toga ablacija AV spoja može biti prvi izbor liječenja u bolesnika s CRT-om i trajnom FA. Amiodaron i dofetilid jedini su antiaritmici pogodni za kontrolu ritma u bolesnika s CRT-om, ali uz umjerenu učinkovitost i znatne nuspojave. Kateterska ablacija FA-a drugi je mogući izbor za kontrolu ritma u bolesnika sa CRT-om, jer poboljšava odgovor na CRT pospešujući atrioventrikularnu i interventrikularnu sinkroniju. Prema rezultatima randomiziranih kontroliranih studija u bolesnika sa zatajivanjem srca, ablacija FA može se uzeti u obzir u bolesnika s CRT-om i paroksizmalnom FA, koji ne reagiraju na antiaritmikne lijekove, kao i u odabраних bolesnika s perzistentnom FA prije nego što se prihvati terapija za kontrolu frekvencije.

SUMMARY: Atrial fibrillation (AF) is often present in patients with cardiac resynchronization therapy (CRT), and may have a significant negative impact on the prognosis and CRT response. Management of AF in CRT patients includes the optimal pharmacological heart failure therapy, anticoagulation therapy, and rate or rhythm control therapy with specific goal to ensure a high percentage ($\geq 98\%$) of biventricular (BiV) pacing. In heart failure patients with AF, a rhythm control with antiarrhythmic drugs has failed to show any survival benefit compared with a rate control drugs. In this context, a rate control with drugs is preferred as first-line therapy in CRT patients with persistent or permanent AF. However, the observational prospective studies and meta-analyses indicate that AV junction ablation is superior to rate control drugs in achieving adequate BiV pacing and reducing mortality. Therefore, an ablation of AV junction should be considered as the first therapeutic choice in CRT patients with permanent AF. Amiodarone and dofetilide are the lone antiarrhythmic drugs suitable for the rhythm control in CRT patients, but with a moderate efficacy and significant side effects. Catheter ablation of AF is another option for the rhythm control, which can improve CRT response by promoting adequate atrioventricular and interventricular synchrony. According to randomized controlled studies in heart failure patients, AF ablation should be considered in CRT patients with paroxysmal AF, who are non-responders to antiarrhythmic drugs, or in selected patients with persistent AF before accepting a rate control therapy.

KLJUČNE RIJEČI: fibrilacija atrijska, resinkronizacijska terapija srca, terapijske mogućnosti.

KEYWORDS: atrial fibrillation, cardiac resynchronization therapy, therapeutic options.

CITATION: *Cardiol Croat.* 2017;12(5-6):254-263. | <https://doi.org/10.15836/ccar2017.254>

***ADDRESS FOR CORRESPONDENCE:** Dubravko Petrač, Kardiološka poliklinika «Bogdan», Bužanova 4, HR-10000 Zagreb, Croatia. / Phone: +385-1-4821-934 / E-mail: d.petrac@inet.hr

ORCID: Dubravko Petrač, <http://orcid.org/0000-0003-2623-1475>

RECEIVED:
April 4, 2017

UPDATED:
April 26, 2017

ACCEPTED:
May 10, 2017



Uvod

Resinkronizacijska terapija srca (CRT) učinkovit je način liječenja za bolesnike s umjerenim do teškim zatajivanjem srca, sinusnim ritmom, di-

Introduction

Cardiac resynchronization therapy (CRT) is an efficient way of treatment for patients with mild to severe heart failure, sinus rhythm, left ventric-

sinkronijom lijevoga ventrikula (LV) i oštećenom sistoličkom funkcijom LV-a.¹ S obzirom na klinički profil, fibrilacija atriya (FA) često je prisutna u tih bolesnika, a njezina zastupljenost raste povećanjem težine zatajavanja srca. Sposobnost uređaja za CRT da otkrije i pohrane epizode FA daje mogućnost da se dobije realniji uvid u ukupno opterećenje FA u ovoj skupini bolesnika. Procijenjena na ovaj način, kumulativna učestalost novonastale FA u bolesnika liječenih CRT-om kreće se u rasponu od 21 do 42%.² Razvoj FA-a u bolesnika s CRT-om pogoršava simptome, pogoduje novim epizodama zatajavanja srca, povećava rizik od tromboembolijskih događaja, smanjuje postotak biventrikularne (BiV) stimulacije i povećava rizik od terapije elektroškom u bolesnika s ugrađenim CRT defibrilatorom.²⁻⁵

Cilj je ovoga preglednog rada: 1. ukratko prikazati glavne negativne učinke FA-a u bolesnika s CRT-om i 2. predložiti sadašnje terapijske opcije za liječenje FA-a u ovoj populaciji bolesnika.

Povećava li fibrilacija atriya smrtnost u bolesnika s resinkronizacijskom terapijom srca?

Podatci o prognostičkim implikacijama FA nakon CRT-a prilično su rijetki. Prema izvješću *European CRT Survey*⁶, bolesnici s FA-om imaju lošije jednogodišnje preživljenje od onih u sinusnom ritmu (86 % prema 91 %, $p = 0,0038$). *Wilton i sur.*⁷ proveli su metaanalizu 23 studije koje su uspoređivale ishode bolesnika s CRT-om koji su imali ($n = 1912$) i onih koji nisu imali FA ($n = 5583$). Nakon praćenja od prosječno 33 mjeseca, FA je bila povezana s povećanim rizikom od ukupne smrtnosti (10,8 % prema 7,1 % godišnje, $p = 0,015$). *Ousdigian i sur.*⁴ istraživali su učinak FA-a na preživljenje u više od 50 000 bolesnika s CRT-om kroz razdoblje praćenja od 2,3 godine. U usporedbi s bolesnicima bez FA ili s malo FA, bolesnici s paroksizmalnom, perzistentnom ili permanentnom FA imali su povećanje smrtnosti od 32 %, 51 %, odnosno 28 % ($p < 0,001$ za sve tri skupine s FA-om).

U nedavnoj analizi 63 866 bolesnika s CRT defibrilatorima koji su bili telemedicinski kontrolirani, bilo koje opterećenje s FA $> 0,01$ % bilo je povezano sa smanjenim preživljenjem u usporedbi s onima bez FA ($p < 0,001$).⁸ Skupine s najvećim rizikom od povećane smrtnosti bile su one u kojima je FA značilo opterećenje od 10 do 90 %. Bolesnici s epizodama FA-a u trajanju 1 – 7 dana imali su slično preživljenje kao oni s trajanjem FA-a dužim od 7 dana. Ovi podatci ukazuju da postoji znatan rizik od smrtnosti koji je povezan sa širokim rasponom opterećenja i trajanja FA-a.

Učinak fibrilacije atriya na biventrikularnu stimulaciju

Osnovni je cilj CRT-a ponovna uspostava sinkronije LV-a u bolesnika sa zatajivanjem srca i disinkronijom LV-a. U bolesnika sa sinusnim ritmom, CRT resinkronizira kontrakcije srca optimiranjem atrioventrikularnog (AV) vremena i s pomoću BiV stimulacije. U bolesnika s FA-om AV sinkronija ne postoji, zbog čega klinička korist CRT-a proizlazi samo iz BiV sinkronizacije. Međutim, FA uzrokuje nepravilan ritam ventrikula koji je često brži nego stimulirani ritam, što uzrokuje spontane, fuzijske ili pseudofuzijske kontrakcije te može smanjiti učinkovitu stimulaciju CRT-a. To se dodatno pogoršava kad bolesnici s FA-om imaju povremeno ili stalno ubranu frekvenciju ventrikula.

ular (LV) dyssynchrony, and impaired LV systolic function.¹ With regard to clinical profile, atrial fibrillation (AF) is often present in these patients and its prevalence rises as the severity of heart failure increases. The ability of CRT devices to detect and store AF episodes offers the opportunity to have a more realistic insight in overall AF burden in this group of patients. Evaluated in this fashion, the cumulative incidence of new onset AF in patients treated with CRT ranges from 21% to 42%.² Development of AF in patients with CRT leads to symptomatic deterioration, predisposes to episodes of worsening heart failure, increases the risk of thromboembolic incidents, reduces the percent of biventricular (BiV) pacing and increases the risk of shock therapy in patients with an implanted CRT-defibrillator.^{2,3,4,5}

The aim of this review is to: 1) summarize the main negative effects of AF in patients with CRT, and 2) present the current therapeutic options for the treatment of AF in this patient population.

Does AF increase mortality in patients with CRT?

Data on prognostic implications of AF following CRT are scarce. In a current report of the *European CRT Survey*,⁶ patients with AF have a poorer 1-year survival than those with sinus rhythm (86% vs. 91%, $p = 0.0038$). *Wilton et al.*⁷ performed a meta-analysis of 23 studies, which have compared the outcomes of CRT patients with ($n = 1912$) and patients without ($n = 5583$) AF. After a mean follow-up of 33 months, AF was associated with an increased risk of all-cause mortality (10.8% vs 7.1% per year, $p = 0.015$). *Ousdigian et al.*⁴ investigated the impact of AF on survival in $> 50,000$ patients with CRT-defibrillators during a follow-up period 2.3 years. In comparison to patients with no/little AF, patients with paroxysmal AF, persistent AF or permanent AF had an increase in mortality of 32%, 51% and 28% respectively ($p < 0.001$ for all 3 AF groups).

In a recent analysis of 63,866 patients with CRT-defibrillators followed on a remote monitoring network, any AF burden > 0.01 % was associated with decreased survival compared with no AF ($p < 0.001$).⁸ The highest risk groups for increased mortality were those with AF that represented a burden of 10% to 90%. Patients with duration of AF episodes of 1-7 days had similar survival to those with the longer duration of AF lasting > 7 days. These data suggest that there is significant mortality risk associated with a broad range of AF burden and duration.

Impact of AF on biventricular pacing

The basic goal of CRT is to restore left ventricular synchrony in patients with heart failure and LV dyssynchrony. In sinus rhythm patients, CRT resynchronizes cardiac contractions by optimizing of atrioventricular (AV) timing and by BiV pacing. In patients with AF, AV synchrony does not exist, and therefore, clinical benefit of CRT is predicated only on BiV synchronization. However, AF causes irregular ventricular rate which is often faster than paced rate resulting in spontaneous, fusion or pseudo-fusion beats, and may reduce effective CRT delivery. This is further exacerbated when patients with AF have intermittent or consistently accelerated ventricular rates.

Recently, *Hayes et al.*⁹ examined the association between the percentage of BiV pacing and survival in a large cohort

Hayes i sur.⁹ nedavno su istraživali povezanost između postotka BiV stimulacije i preživljenja u velikoj kohorti od >30 000 bolesnika s CRT-om koje se pratilo putem telemedicinskog nadzora. Smrtnost je bila obrnuto proporcionalna s postotkom BiV stimulacije u prisutnosti normalnoga sinusnog ritma i stimuliranoga atrijskog ritma, kao i kad je atrijski ritam bila FA. BiV stimulacija >98,5% bila je prijelomna vrijednosna točka za znatnu korist u preživljenju. Bolesnici s BiV stimulacijom >99,6% imali su smanjenje smrtnosti od 24% (p <0,001), dok su oni s BiV stimulacijom <94,8% imali porast smrtnosti od 19%. Pri istom postotku BiV stimulacije bolesnici s FA-om imali su nižu učestalost preživljenja od onih bez FA-a.

U retrospektivnoj studiji Ousdigiane i sur.⁴ visoki postotak BiV stimulacije (>98%) nije postignut u dvije trećine od 8686 bolesnika s perzistentnom ili trajnom FA i ti su bolesnici imali povećani rizik od smrti. U multivarijantnoj analizi smanjeni postotak BiV stimulacije (≤98%) bio je neovisni čimbenik veće smrtnosti. S obzirom na bolesnike s visokom BiV stimulacijom (≥98%), bolesnici s umjerenom BiV stimulacijom (90–98%) imali su povećanje smrtnosti od 20% (p <0,001), a bolesnici s niskom BiV stimulacijom (<90%) imali su povećanje smrtnosti od 32% (p <0,001). Zbog toga je u bolesnika s CRT-om i FA-om potreban najveći mogući postotak BiV stimulacije (≥98%) da bi se dobila maksimalna korist od CRT-a.¹⁰

Opća načela liječenja fibrilacija atrijske

Najnovije smjernice Europskoga kardiološkog društva za liječenje FA-a i smjernice za dijagnosticiranje i liječenje akutnog i kroničnog zatajavanja srca, objavljene u 2016. godini, opširni su dokumenti o liječenju FA-a,^{11,12} koji se odnose i na bolesnike s CRT-om (Slika 1).^{11,12}

Optimalna medikamentna terapija za zatajavanje srca čini osnovu liječenja za sve bolesnike sa zatajivanjem srca i FA-om i jedan je od uvjeta za implantaciju CRT uređaja.¹ Takva terapija uključuje inhibitore angiotenzina konvertirajućeg enzima (ACE) ili blokatore angiotenzinskih receptora (ARBs) i maksimalno podnošljive doze beta-blokatora. Primjenu kombinirane inhibicije receptora angiotenzina II i neprilizina treba razmotriti u bolesnika koji mogu podnositi ACE inhibitor ili ARB uz simptome.¹¹ Digoksin, antagonisti aldosterona i diuretici mogu se rabiti ovisno o potrebi. Valja napomenuti da ovakva optimalna farmakološka terapija također ima koristan učinak u liječenju FA-a.

Antikoagulantna terapija obvezna je u svih bolesnika s FA-om i CRT-om jer ovakvi bolesnici imaju povećani rizik od tromboembolije i najmanje dva boda CHA₂DS₂-VASc sustava. Ipak, omjer između koristi od antikoagulantne terapije i rizika od krvarenja treba procijeniti u svakog bolesnika. Novi oralni antikoagulansi (NOAC-i) preferiraju se u bolesnika s CRT-om i nevalvularnom FA, jer su NOAC-i u usporedbi s antagonistima vitamina K najmanje jednako djelotvorni i čak sigurniji, osobito u smanjenju intrakranijalnoga krvarenja (Tablica 1).^{12,13} U bolesnika s CRT-om koji imaju mehaničke srčane zastojke ili barem umjerenu mitralnu stenozu samo se oralni antagonisti vitamina K trebaju koristiti za prevenciju tromboembolijskoga moždanog udara.¹⁴ Važno je napomenuti da se doza NOAC-a treba smanjiti u starijih bolesnika (više od 80 godina) te u onih s lošom bubrežnom funkcijom.

Management of AF in CRT Patients

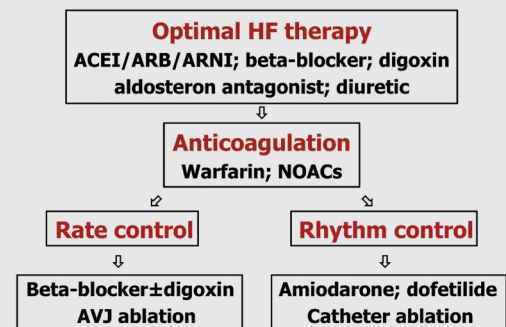


FIGURE 1. Overview of the management considerations for patients with atrial fibrillation (AF) and cardiac resynchronization therapy (CRT).

ACEI/ARB/ARNI = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibition, NOACs = non-vitamin K antagonist oral anticoagulants, AVJ=atrioventricular junction.

of >30,000 CRT patients who were followed up in the remote monitoring network. Mortality was inversely correlated with the percentage of BiV pacing in the presence of both normal sinus rhythm and paced atrial rhythm, and when the atrial rhythm was AF. The BiV pacing >98.5% was found as a cut-point value for the 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. At the same percentage of BiV pacing, patients with AF had a lower survival than those without AF.

In a retrospective study by Ousdigian *et al.*⁴ high percent of BiV pacing (>98%) was not achieved in two thirds of 8686 patients with persistent or permanent AF, 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%) BiV pacing had a 20% increase in mortality (p<0.001), and the patients who received low BiV pacing (<90%) had a 32% increase in mortality (p<0.001). Therefore, in CRT patients with AF, the highest possible percentage of BiV pacing (≥98%) is necessary to extract maximum benefit from CRT.¹⁰

General principles of the atrial fibrillation management

The most recent European Society of Cardiology guidelines for the management of AF and the guidelines for the diagnosis and treatment of acute and chronic HF, both published in 2016, provide an extensive referenced documents for the management of AF,^{11,12} that are also relative to CRT patients (Figure 1).

Optimal pharmacological therapy for heart failure forms the basis of treatment in all heart failure patients with AF and represents one of conditions for CRT device implantation.¹ This therapy includes angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) for all patients with maximum tolerated doses of beta-blockers. Combined angiotensin receptor neprilysin inhibition should be

TABLE 1. The hazard ratio (HR) and 95% confidence interval of the efficacy and safety outcomes of the non-vitamin K antagonist oral anticoagulants (NOACs) versus warfarin in patients with atrial fibrillation and heart failure.

| NOAC | Risk of stroke/embolism | Risk of major bleeding | Risk of intracranial hemorrhage |
|-----------------------|-------------------------|------------------------|---------------------------------|
| Dabigatran 150 mg bid | HR 0.75 (0.51-1.10) | HR 0.79 (0.60-1.03) | HR 0.39 (0.17-0.89) |
| Dabigatran 110 mg bid | HR 0.99 (0.69-1.42) | HR 0.83 (0.64-1.09) | HR 0.34 (0.14-0.80) |
| Rivaroxaban 20 mg od | HR 0.91 (0.74-1.13) | NA | HR 0.63 (0.40-1.02) |
| Apixaban 5 mg bid | HR 0.55 (0.34-0.91) | HR 0.81 (0.58-1.14) | HR 0.25 (0.08-0.73) |

bid = twice daily, od = once daily, NA = not available.

Kontrola ritma ili kontrola frekvencije za fibrilaciju atrijsku?

Brojne su studije pokazale da kontrola ritma i kontrola frekvencije antiaritmičnim lijekovima imaju usporedivu učinkovitost u liječenju FA-a s obzirom na kardiovaskularnu smrtnost i moždani udar.¹⁵ U studiji AF-CHF (*Atrial Fibrillation and Congestive Heart Failure*)¹⁶ više od 1300 bolesnika s ežekcijskom frakcijom lijevoga ventrikula (LVEF) $\leq 35\%$, NYHA II. do IV. stupnjem zatajivanja srca i paroksizmalnom ili perzistentnom FA, bilo je randomizirano na kontrolu ritma (82 % amiodaronom) ili kontrolu frekvencije (88 % beta-blokatorima). Nakon praćenja od prosječno 37 mjeseci nije bilo značajne razlike u primarnim ishodu, smrti zbog kardiovaskularnih uzroka, između skupine s kontrolom ritma i skupine s kontrolom frekvencije (27 % prema 25 %, $p = 0.59$). Isto tako nije bilo prednosti s obzirom na prevenciju moždanog udara, hospitalizacije zbog zatajivanja srca i ukupnu smrtnost u skupini s kontrolom ritma. U dodatnoj analizi o djelotvornosti liječenja u AF-CHF studiji,¹⁷ prisutnost sinusnog ritma ili strategija kontrole ritma nije bila povezana s boljim kliničkim ishodom. Bolesnici s visokom zastupljenošću sinusnog ritma imali su sličnu učestalost kardiovaskularne smrti, ukupne smrtnosti i pogoršanja zatajivanja srca kao i bolesnici s niskom zastupljenošću sinusnog ritma. Glavni razlozi koji su doveli do ovakvih rezultata bili su ograničena djelotvornost i štetni učinci antiaritmikih lijekova ili zakašnjele terapijske intervencije koje nisu uspjele obrnuti kumulativne učinke FA na atrijsku.¹⁸ Prema tome, ograničavajući čimbenik nije nužno bio strategija kontrole ritma, već neadekvatna sredstva koja su na raspolaganju za održavanje sinusnog ritma.¹⁹ Hoće li moderno liječenje kontrolom ritma koje uključuje katetersku ablaciju kombinacijsku terapiju i ranu terapiju dovesti do smanjenja u velikim kardiovaskularnim događajima jest pitanje koje se sada istražuje.^{11,20}

Kontrola frekvencije

Kontrola frekvencije obuhvaća terapijske opcije koje uspješno smanjuju i reguliraju frekvenciju srca u bolesnika s CRT-om, koji imaju permanentnu ili perzistentnu FA koja se ne može lako konvertirati u sinusni ritam. Farmakološka kontrola frekvencije ventrikula početni je izbor liječenja u tih bolesnika, ali su lijekovi koji se rabe u tu svrhu rijetko dovoljni da osiguraju visoki postotak stimulacije bez fuzijskih kontrakcija.²¹ Beta-blokatori se preporučuju kao terapija prve linije za kontrolu frekvencije ventrikula zbog njihove učinkovitosti pri visokom tonusu simpatikusa.¹² Digoksin treba razmotriti kada frekvencija ventrikula ostaje visoka usprkos terapiji beta-blokatorima, kada se oni ne podnose ili kada su kontraindicirani. Beta-blokatori bolje smanjuju frekvenciju ventrikula tijekom razdoblja aktivnosti, dok digoksin ima veći učinak noću zbog toga što usporava frekvenciju

considered in patients able to tolerate an ACE inhibitor or ARB with ongoing symptoms.¹¹ Digoxin, aldosterone antagonists, and diuretics should be used as appropriate. It is noteworthy that this optimal pharmacological therapy has also beneficial effect in the treatment of AF.

Anticoagulant therapy is mandatory for all patients with AF and CRT because these patients have an increased risk of thromboembolism and CHA₂DS₂-VASc score at least 2. However, the balance between benefit of anticoagulants and the risk of bleeding should be evaluated in every patient. Non-vitamin K antagonist oral anticoagulants (NOACs) are preferred for CRT patients with nonvalvular AF, as NOACs compared with vitamin K antagonists seem to be at least similarly effective and even safer, especially in reducing intracranial hemorrhage (**Table 1**).^{12,13} In CRT patients who have mechanical heart valves or at least moderate mitral stenosis, only oral vitamin K antagonists should be used for prevention of thromboembolic stroke.¹⁴ It is important to note that the doses of NOACs should be reduced in older patients (age ≥ 80 years) and those with a poor renal function.

Rhythm control or rate control for atrial fibrillation?

Multiple studies have demonstrated that rhythm control and rate control with antiarrhythmic drugs have comparable efficacy in the treatment of AF with regard to cardiovascular mortality and stroke.¹⁵ In the AF-CHF (*Atrial Fibrillation and Congestive Heart Failure*) study,¹⁶ >1300 patients with a left ventricular ejection fraction (LVEF) $\leq 35\%$, NYHA class II-IV, and a paroxysmal or persistent AF were randomized to rhythm control (82% with amiodarone) or rate control (88% with beta-blockers). At a mean follow-up of 37 months, there was no significant difference in the primary outcome of death from cardiovascular causes between the rhythm and rate control groups (27% vs. 25%, $p = 0.59$). There was also no advantage with regard to stroke prevention, heart failure hospitalization and all-cause mortality in the rhythm control group. In a subsequent on-treatment-efficacy analysis of the AF-CHF study,¹⁷ the presence of sinus rhythm or rhythm control strategy was not associated with better clinical outcome. Patients with high prevalence of sinus rhythm had similar rates of cardiovascular death, total mortality, and worsening heart failure as the patients with low prevalence of sinus rhythm. The main reasons for these results were limited efficacy and adverse effects of the antiarrhythmic drugs, or delayed therapeutic intervention that was unable to reverse cumulative effects of AF on atria.¹⁸ Thus, the limiting factor was not necessarily the rhythm-control strategy, but the inadequate tools available to maintain the sinus rhythm.¹⁹ Whether modern rhythm control management involving catheter ablation, combination therapy,

ventrikula tako što povećava djelovanje parasimpatikusa na AV čvor.²² Prema rezultatima nedavnih metaanaliza, oba lijeka imaju neutralni učinak na smrtnost u bolesnika s FA i popratnim zatajivanjem srca.^{18,23} Nedihidropiridinski blokatori kalcijevih kanala, verapamil i diltiazem, ne smiju se davati za kontrolu frekvenciju ventrikula u bolesnika s CRT-om zbog njihova negativnoga inotropijskoga djelovanja.^{11,12}

Kateterska ablacija AV spoja (AVS) pojavila se kao atraktivna dodatna terapija za bolesnike s CRT-om i permanentnom ili perzistentnom FA čiji je cilj osigurati visoki postotak BiV stimulacije. Moguće koristi i negativni učinci ablacije AVS-a prikazani su u **Tablici 2**. Nekoliko je opservacijskih studija pokazalo da bolesnici s CRT-om i permanentnom FA, koji su podvrgnuti ablaciji AVS-a, pokazuju poboljšanje u LVEF-u, obrnuti učinak remodeliranja, poboljšanje u podnošenju napora i moguće poboljšanje u preživljenju, dok oni koji su liječeni lijekovima za kontrolu frekvencije to ne pokazuju.²⁴⁻²⁶ U analizi 768 bolesnika s CRT-om i FA-om Ganesan i sur.²⁷ pronašli su da bolesnici s dodatnom ablacijom AVS-a imaju znatno smanjenje ukupne smrtnosti (omjer rizika: 0,42, p <0,001) i kardiovaskularne smrtnosti (omjer rizika: 0,44, p <0,003) u usporedbi s onima koji su liječeni lijekovima za kontrolu frekvencije ventrikula.

Studija CERTIFY (*Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry*)²⁸ multicentrično je, opservacijsko i prospektivno istraživanje koje je bilo osmišljeno s nakanom da se utvrdi imaju li bolesnici s permanentnom FA i ugrađenim CRT-om bolje ishode s ablacijom AVS-a ili s lijekovima koji kontroliraju frekvenciju ventrikula. U studiju su uključene tri skupine bolesnika s CRT-om: bolesnici sa sinusnim ritmom (n = 6046), bolesnici s FA-om i ablacijom AVS-a (n = 443) i bolesnici s FA i lijekovima za kontrolu frekvencije ventrikula (n = 895). Nakon praćenja od prosječno 37 mjeseci, bolesnici s FA i ablacijom AVS-a imali su 52 % nižu ukupnu smrtnost i 57 % nižu kardijalnu smrtnost nego bolesnici s FA-om i lijekovima za kontrolu frekvencije (**Slika 2**). Nije uočena razlika u smrtnosti između bolesnika s FA-om i ablacijom AVS-a i bolesnika sa sinusnim ritmom. Osim toga, poboljšanje u LVEF-u i smanjenje u volumenu LV-a na kraju sistole u bolesnika s FA i ablacijom AVS-a bili su usporedivi s onim koje je bilo zapaženo u bolesnika sa sinusnim ritmom i mnogo bolje od onoga zapaženog u bolesnika s FA i lijekovima za kontrolu frekvencije ventrikula (p <0,001 za oba rezultata). Rezultati studije CERTIFY snažno podupiru preporuku da se ablacija AVS-a treba provesti u većine, ako ne i u svih, bolesnika s CRT-om i trajnom FA, kao i u onih s dugim epizodama paroksizmalne FA.

Kontrola ritma

Sadašnje smjernice namjenjuju farmakološku kontrolu ritma bolesnicima sa zatajenjem srca čiji simptomi ili pogoršanje za-

and early therapy leads to a reduction in major cardiovascular events is currently under investigation.^{11,20}

Rate control

Rate control includes treatment options which effectively reduce and regularize heart rate in CRT patients, who have permanent or persistent AF which cannot be readily converted to sinus rhythm. Pharmacological rate control is an initial treatment option in these patients, but the drugs for rate control are rarely adequate to ensure that a high percentage of beats are paced without fusion.²¹ Beta-blockers are recommended as first-line therapy to control ventricular rate because of their effectiveness at high sympathetic tone.¹² Digoxin should be considered when ventricular rate remains high despite beta-blockers or when beta-blockers are not tolerated or contraindicated. Beta-blockers reduce better ventricular rate during periods of activity, while digoxin exerts a greater effect at night because it slows ventricular rate by increasing parasympathetic tone on the AV node.²² Regarding to results from the recent meta-analyses, both drugs have a neutral effect on mortality in patients with AF and concomitant heart failure.^{18,23} Non-dihydropyridine calcium channel blockers, verapamil and diltiazem, should not be given for ventricular rate control in patients with CRT because of their negative inotropic effects.

Catheter ablation of the AV junction (AVJ) has emerged as an attractive adjunctive therapy for CRT patients with permanent or persistent AF to ensure a high percentage of BiV pacing. The potential benefits and negative effects of AVJ ablation are presented in **Table 2**. Several observational studies have shown that in CRT patients with permanent AF, those who underwent AVJ ablation showed an improvement in LVEF, reverse remodeling effect, improved exercise tolerance and might lead to improved survival, while those treated with drugs for rate control did not.^{24,25,26} In a systematic review of 768 CRT patients with AF, Ganesan *et al.*²⁷ found that patients with additional AVJ ablation had a substantial reduction of all-cause mortality (risk ratio: 0.42, p<0.001) and cardiovascular mortality (risk ratio: 0.44, p<0.003), compared with those, who were treated with rate-controlling drugs.

The CERTIFY (*Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry*) study²⁸ is multicenter, observational, prospective study, which was designed to determine whether patients with permanent AF undergoing CRT have better outcome with AVJ ablation or rate-slowng drugs. Three groups of CRT patients were included in the study: patients in sinus rhythm (n=6046), patients with AF plus AVJ ablation (n=443) and patients with AF plus rate controlling drugs (n=895). At a mean follow-up of 37 months, patients with

TABLE 2. Benefits and negative effects of atrioventricular junction ablation in patients with cardiac resynchronization therapy and atrial fibrillation.

| Benefits | Negative effects |
|--|--|
| Cardiac rate regularization | Procedure is irreversible |
| Elimination of rapid ventricular rates | Patient is rendered pacemaker-independent |
| Discontinuation of rate control drugs | Possible SR restoration after CRT implantation |
| Nearly 100% of biventricular pacing | |

SR = sinus rhythm, CRT = cardiac resynchronization therapy.

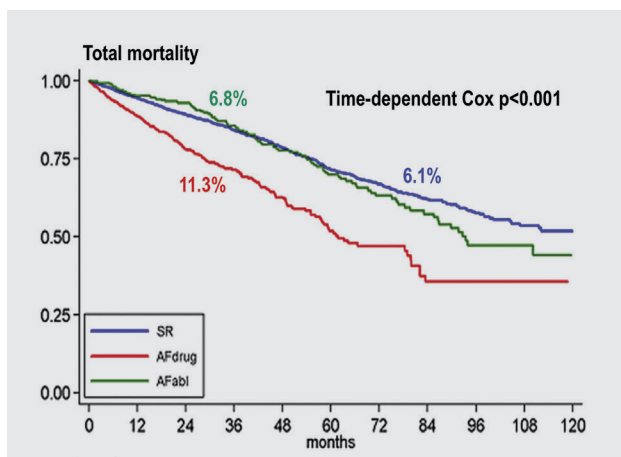


FIGURE 2. Kaplan-Meier survival after cardiac resynchronization therapy from total mortality for the three patient groups: sinus rhythm (SR, blue color), atrial fibrillation plus drugs (AFdrug, red color), and atrial fibrillation plus AVJ ablation (AFabl, green color) (Adapted from reference ³⁰).

tajivanja srca traju usprkos lijekovima za kontrolu frekvencije ventrikula ili bolesnicima u kojih se frekvencija ventrikula ne može kontrolirati.^{11,12} Kao i u drugih bolesnika sa zatajivanjem srca, amiodaron i dofetilid jedini su prikladni lijekovi za bolesnike s CRT-om. Amiodaron je najučinkovitiji antiaritmijski lijek s obzirom na uspostavu i održavanje sinusnog ritma^{29,30} i može se bez opasnosti početi primjenjivati u ambulantnim uvjetima. Amiodaron ima neutralni učinak na smrtnost i niski proaritmijski rizik, no njegova je dugoročna primjena povezana sa znatnim oštećenjima pluća, jetre i štitnjače. Usprkos njegovoj jakosti, učestalost povrata FA-a u bolesnika sa zatajivanjem srca i ugrađenim defibrilatorom može biti i do 64 % tijekom dvogodišnjega praćenja.³¹ Dofetilid je učinkovitiji od placeba u postizanju i održavanju sinusnog ritma u bolesnika s FA-om i zatajivanjem srca (omjer rizika za povrat FA 0,35, $p < 0,001$).³² Dofetilid nema negativno inotropno djelovanje i ne utječe na smrtnost.^{33,34} Zbog rizika od razvoja torsades de pointes unutar prva tri dana, liječenje dofetilidom mora se započeti u bolnici uz pažljivo praćenje QT intervala i prilagođenja doze u bolesnika s oštećenom bubrežnom funkcijom.^{32,34}

S obzirom na ograničenja sadašnje farmakološke terapija za kontrolu ritma i superiornosti kateterske ablacije FA u odnosu prema antiaritmijskim lijekovima u bolesnika bez zatajivanja srca i normalnom funkcijom LV-a,³⁵ uporaba ablacije FA proširena je na bolesnike sa zatajivanjem srca i smanjenom funkcijom LV-a. Uloga kateterske ablacije u liječenju FA-a u bolesnika sa zatajivanjem srca bila je nedavno ispitivana u sustavnom pregledu koji je obuhvatio 16 opservacijskih studija s 1253 bolesnika.³⁶ Svi su bolesnici bili podvrgnuti izolaciji plućnih vena (IPV), a 55 % ih je dobilo dodatnu leziju u lijevom atriju. Učinkovitost ablacije FA-a u održavanju sinusnog ritma bila je 75 %, uključujući ponovljene postupke i antiaritmijske lijekove. Osim toga, poboljšanje LVEF-a nakon ablacije zapaženo je u svim studijama s prosječnim povećanjem od 13 %, dok je učestalost ozbiljnih komplikacija bila 4,5 %.

Do danas su provedene četiri randomizirane kontrolirane studije čiji je cilj bio utvrditi je li kontrola ritma s ablacijom FA-a uspješnija od kontrole frekvencije ventrikula u bolesnika sa zatajivanjem srca i FA-om (Tablica 3). Studija PABA-CHF (*Pulmonary-vein isolation for atrial fibrillation in patients with heart*

AF plus AVJ ablation had 52% lower total mortality and 57% lower cardiac mortality than patients with AF plus rate-controlling drugs (Figure 2). No difference in mortality was observed between the patients with AF plus AVJ ablation and the patients in sinus rhythm. Moreover, the improvement in LVEF and reduction in LV end systolic volume in patients with AF plus AVJ ablation were comparable to that observed in sinus rhythm patients, and significantly better than that observed in patients with AF plus rate-controlling drugs (both $p < 0.001$). The results of CERTIFY study strongly support recommendation that AVJ ablation should be performed in most, if not all, patients with CRT and permanent AF as well as those with frequent and prolonged episodes of paroxysmal AF.

Rhythm control

Current guidelines reserve pharmacological rhythm control for patients with heart failure whose symptoms or worsening heart failure persist despite rate control therapy, or for patients in whom the heart rate cannot be controlled.^{11,12} As in other heart failure patients, amiodarone and dofetilide are the lone drugs suitable for patients with AF and CRT. Amiodarone is the most effective antiarrhythmic drug with regard to restoring and maintaining sinus rhythm,^{29,30} and it can safely be initiated in an outpatient setting. Amiodarone has neutral impact on mortality and low proarrhythmia risk, but its long-term use is associated with significant pulmonary, hepatic, and thyroid toxicity. Despite its potency, the recurrence rate of AF in heart failure patients with implanted defibrillators can be such great as 64% over the 2-year follow-up.³¹ Dofetilide is more effective than placebo in converting to and maintaining sinus rhythm in patients with AF and heart failure (hazard ratio for the recurrence of AF 0.35, $p < 0.001$).³² Dofetilide has no negative inotropic effects and does not affect mortality.^{33,34} Because of the risk of torsade de pointes within first three days, therapy with dofetilide requires in-hospital initiation with close monitoring of the QT interval and dosage adjustments in patients with impaired renal function.^{32,34}

Regarding to limitations of current pharmacological therapy for rhythm control and superiority of AF catheter ablation to antiarrhythmic drugs in patients with no heart failure and normal LV function,³⁵ the use of AF ablation is extended to patients with heart failure and reduced LV function. The role of catheter ablation in the treatment of AF in heart failure patients was examined in recent systematic review, that included 16 observational studies with 1253 patient.³⁶ All patients underwent pulmonary vein isolation (PVI), and 55% received an additional left atrial lesions. The efficacy of AF ablation in maintaining sinus rhythm was 75%, including redo procedures and antiarrhythmic drugs. Moreover, the improvement in LVEF following ablation was observed in all studies with a mean increase of 13%, while the rate of serious complications was 4.5%.

To date, four randomized controlled studies were conducted to determine if the rhythm control with AF ablation is superior to the rate control therapy in heart failure patients with AF (Table 3). The PABA-CHF (Pulmonary-vein isolation for atrial fibrillation in patients with heart failure) study³⁷ compared AF ablation with the combination of AVJ ablation and CRT in 81 patients, who were in NYHA class II-III heart failure. After 6 months, 71% of patients who underwent AF ablation were free from AF of antiarrhythmic drugs and 88% were free from AF with antiarrhythmic drugs. The patients randomized to AF

TABLE 3. Randomized clinical studies on catheter ablation versus a rate control therapy in patients with atrial fibrillation and heart failure.

| Study | N | Age (yrs) | Complications | Change in LVEF (%) | Outcomes |
|--|-------------------|-----------|---------------|--------------------|--|
| Khan, 2008 ³⁴ catheter ablation | 41 | 60 | 12% | 27 35* | 88% AF freedom with ablation at 6 mo; improvement in QoL and 6-MWT with ablation |
| | AVJA+CRT | 40 | 61 | 15% | |
| MacDonald, 2011 ³⁵ catheter ablation | 22 | 62 | 15% | 36 41 | 50% AF freedom with ablation at 6 mo; no difference in QoL and 6-MWT between groups |
| | rate control drug | 10 | 64 | NA | |
| Jones, 2013 ³⁶ catheter ablation | 26 | 64 | 8% | 22 33 | 88% AF freedom with ablation at 12 mo; improvement in QoL and peak VO ₂ with ablation |
| | rate control drug | 26 | 62 | NA | |
| Hunter, 2014 ³⁷ catheter ablation | 26 | 55 | 8% | 32 40* | 81% AF freedom with ablation at 12 mo; improvement in QoL and peak VO ₂ with ablation |
| | rate control drug | 24 | 60 | 8% | |

N = number of patients, yrs = years, LVEF = left ventricular ejection fraction, AF = atrial fibrillation, m = months, QoL = quality of life, 6-MWT = six minute walk test, AVJA = atrioventricular junction ablation, CRT = cardiac resynchronization therapy, NA = not available, VO₂ = peak oxygen consumption.

* = p < 0.001

failure)³⁷ uspoređivala je ablaciju FA-a s kombinacijom ablacije AVS-a i CRT-a u 81 bolesnika, koji su bili u II. do III. stupnju zatajivanja srca prema NYHA klasifikaciji. Nakon 6 mjeseci 71 % bolesnika podvrgnutih ablaciji FA bilo je slobodno od FA-a bez antiaritmjskih lijekova, a 88 % ih je bilo slobodno od FA-a uz antiaritmjske lijekove. Bolesnici koji su bili određeni za ablaciju FA imali su veće poboljšanje LVEF-a, dužu šestominutnu hodnu prugu i bolju kvalitetu života vezanu uz zatajivanje srca od onih koji su bili određeni za ablaciju AVS-a i CRT. U ostale tri studije bolesnici s perzistentnom FA i zatajivanjem srca bili su nasumce podijeljeni za ablaciju FA ili farmakološku kontrolu frekvencije. Od bolesnika s farmakološkom kontrolom frekvencije (beta-blokatori i/ili digoksin) tražilo se da postignu prosječnu frekvenciju ventrikula od ≤80/min u mirovanju do ≥110/min pri umjerenom opterećenju. MacDonald i sur.³⁸ izvijestili su o manjem uspjehu ablacije FA i nisu ustanovili poboljšanje u LVEF-u ili podnošenju napora s ablacijom. Ipak, treba primijetiti da su bolesnici uključeni u ovu studiju imali uznapredovalo zatajivanje srca, duže trajanje FA-a i lošiji funkcionalni razred prema NYHA u usporedbi s bolesnicima u ostalim trima studijama. Nasuprot tomu, dvije kasnije studije^{39,40} zabilježile su 88 %-tni i 81 %-tni uspjeh ablacije FA-a i znatno poboljšanje u podnošenju napora i kvaliteta života u bolesnika koji su bili podvrgnuti ablaciji FA-a u usporedbi s onima koji su dobivali lijekove za kontrolu frekvencije. Rezultati tih studija ukazuju da je ablacija FA-a bolja od lijekova za kontrolu frekvencije srca u bolesnika sa zatajivanjem srca koji imaju perzistentnu FA ili FA otpornu na lijekove, u poboljšanju LVEF-a, kvalitete života i funkcionalne sposobnosti. Zbog tih razloga, ablaciju FA-a treba razmotriti u takvih bolesnika prije nego što se prihvati terapija za kontrolu frekvencije.

Studija AATAC (*Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device*) bila je osmišljena s nakanom da se utvrdi je li kateterska ablacija bolja od amiodarona za kontrolu ritma u bolesnika sa zatajivanjem srca, perzistentnom FA i ugrađenim dvokomornim ili CRT defi-

brillation had a greater improvement in LVEF, longer six-minute walk test, and better heart failure-related quality of life than those randomized to AVJ ablation and CRT. In the other three studies, the patients with persistent AF and heart failure were randomized to AF ablation or pharmacological rate control. Patients with a pharmacological rate control (beta-blockers and/or digoxin) were targeted to achieve a mean heart rate ≤80 beats/min at rest and ≤110 beats/min on moderate exertion. MacDonald *et al.*³⁸ reported lower success rates of AF ablation, and no improvement in LVEF or exercise tolerance in patients with ablation. However, it should be noted that patients included in this study had advanced heart failure, longer AF duration, and a worse NYHA class compared with patients in the other three studies. In contrast, two subsequent studies^{39,40} reported 88% and 81% freedom from AF with ablation, and a significant improvement in exercise capacity and quality of life in patients who underwent AF ablation compared with those who received pharmacological rate control. The results of these studies suggest that AF ablation is superior to rate control therapy in heart failure patients with persistent or drug refractory AF in improving LVEF, quality of life and functional capacity. For these reasons, AF ablation should be considered in these patients before accepting a rate control strategy.

The AATAC (*Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device*) study³¹ was designed to investigate whether catheter ablation is superior to amiodarone for the rhythm control in heart failure patients with persistent AF and implanted a dual chamber implantable defibrillator or CRT-defibrillator. The study included 203 patients, who were randomly assigned to AF ablation or amiodarone. Amiodarone was orally loaded and then dosed at 200 mg daily. AF ablation included pulmonary vein antrum isolation, and in the vast majority, isolation of the posterior wall of the left atrium. Freedom from AF or atrial tachycardia (AT) off antiarrhythmic drugs at 24 months was the primary

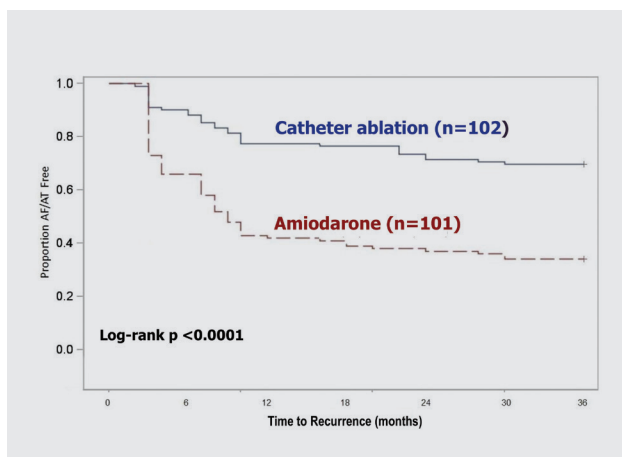


FIGURE 3. Kaplan-Meier curves comparing freedom from the recurrences of atrial fibrillation/atrial tachycardia in patients undergoing catheter ablation and those receiving amiodarone (Adapted from reference¹¹).

brilatorom. Studija je uključila 203 bolesnika koji su nasumično dodijeljeni za ablaciju FA-a ili amiodaron. Amiodaron je primijenjen oralno u dozi od 200 mg na dan. Ablacija FA uključivala je izolaciju ulaza plućnih vena, a u velikoj većini i izolaciju stražnje stijenke lijevog atrija. Primarna točka ispitivanja bila je zaštita od FA-a ili atrijske tahikardije (AT) bez primjene antiaritmjskih lijekova tijekom 24 mjeseca. Na kraju studije 70 % bolesnika u skupini s ablacijom bilo je bez povrata FA/AT-a u usporedbi s 34 % bolesnika u skupini s amiodaronom ($p < 0,001$) (Slika 3). Učestalost proceduralnih komplikacija u skupini s ablacijom bila je mala (2 %), dok je 10 % bolesnika u skupini s amiodaronom moralo prekinuti liječenje zbog nuspojava. Nakon razdoblja od dvije godine praćenja, učestalosti neplanirane hospitalizacije i smrtnosti bile su mnogo niže u skupini s ablacijom (31 % prema 38 %, $p < 0,001$, i 8 % prema 18 %, $p = 0,037$). Ovo je prva randomizirana studija koja pokazuje da je kateterska ablacija perzistentne FA bolja od amiodarona u postizanju zaštite od povrata FA i u smanjenju hospitalizacije i smrtnosti u bolesnika sa zatajivanjem srca, i da kateterska ablacija može imati koristan učinak u bolesnika s CRT-om i FA-om.

Kliničke implikacije

Liječenje FA-a u bolesnika s CRT-om ovisi o tipu FA-a, težini simptoma, veličini lijevog atrija, osnovnoj srčanoj bolesti i o sklonosti bolesnika. Ključni je cilj takvoga liječenja osigurati visoki postotak BiV stimulacije (≥ 98 %). Terapijske opcije za liječenje FA-a u bolesnika s CRT-om, ovisno o tipu FA-a, prikazane su na Slici 4.

Prema smjernicama Europskoga kardiološkog društva^{12,13}, farmakološka kontrola frekvencije prva je linija liječenja za perzistentnu ili permanentnu FA u bolesnika sa zatajivanjem srca liječenih CRT-om, iako su lijekovi koji su na raspolaganju za kontrolu frekvencije malokad dovoljni da osiguraju zadovoljavajuću BiV stimulaciju.²¹ S druge strane, studija CERTIFY²⁸ nepobitno je pokazala superiornost ablacije AVS-a u usporedbi s lijekovima za kontrolu frekvencije u postizanju visoke BiV stimulacije i smanjenju smrtnosti. U tom je smislu čvrsta preporuka da se ablacija AVS-a provede u gotovo svih bolesnika s CRT-om i trajnom FA, kao i u onih, u kojih nije uspjelo liječenje kontrolom ritma.

Therapeutic Options for AF in CRT Patients

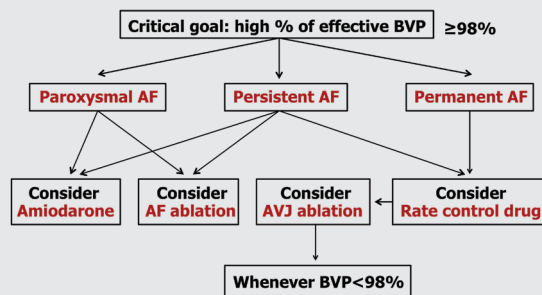


FIGURE 4. Therapeutic options for atrial fibrillation (AF) in patients with cardiac resynchronization therapy (CRT) regarding to type of AF.

% = percentage, BVP = biventricular pacing, AVJ = atrioventricular junction.

endpoint. At the end of the study, 70% of patients in the ablation group were free from AF/AT recurrences in comparison with 34% of patients in the amiodarone group ($p < 0.001$) (Figure 3). The rate of procedural complications in the ablation group was small (2%), while 10% of patients in the amiodarone group had to discontinue a therapy because of side effects. Over two years follow-up, the rates of unplanned hospitalization and mortality were substantially lower in the ablation group (31% vs 38%, $p < 0.001$, and 8% vs 18%, $p = 0.037$, respectively). This is the first randomized study showing that catheter ablation of persistent AF is superior to amiodarone in achieving freedom from AF and reducing hospitalization and mortality in patients with heart failure, and to show that catheter ablation may have a beneficial effect in CRT patients with AF.

Clinical implications

The treatment of AF in CRT patients depends on the type of AF, severity of symptoms, left atrium size, underlying heart disease and patient preference. The critical goal of this treatment is to ensure a high percentage of BiV pacing (≥ 98 %). Therapeutic options for the management of AF in CRT patients regarding to type of AF are presented in Figure 4.

Relative to ESC guidelines,^{12,13} the pharmacological rate control is the first-line therapy for persistent or permanent AF in heart failure patients treated with CRT, although the available drugs for rate control are rarely sufficient to ensure satisfactory BiV pacing.²¹ On the other hand, the CERTIFY study²⁸ undoubtedly demonstrated the superiority of AVJ ablation over the rate control drugs in achieving a high BiV pacing and reducing mortality. Consequently, there is strong recommendation that AVJ ablation should be performed in virtually all patients with CRT and permanent AF, and those who failed the rhythm control therapies.

Current guidelines recommend rhythm control therapy for AF patients with heart failure who remain symptomatic on the rate control therapy.^{11,12} Amiodarone and dofetilide are the lone antiarrhythmic drugs suitable for rhythm control in CRT patients, but its use is limited by moderate efficacy and significant side effects. Catheter ablation of AF is another rhythm control option, which improves CRT response by affecting atri-

Postojeće smjernice preporučuju kontrolu ritma za bolesnike s FA-om i zatajivanjem srca koji imaju simptome usprkos liječenju kontrolom frekvencije.^{11,12} Amiodaron i dofetilid jedini su antiaritmijski lijekovi koji su prikladni za kontrolu ritma u bolesnika s CRT-om, ali je njihova uporaba ograničena umjerenom djelotvornošću i znatnim nuspojavama. Kateterska ablacija FA još je jedna mogućnost za kontrolu ritma koja poboljšava odgovor na CRT djelovanjem na funkciju atrijske i kontrolom frekvencije i/ili regularnosti ventrikula. Prema najnovijim podatcima iz studija o zatajivanju srca³⁶⁻⁴⁰ i AATAC studije,³¹ ablaciju FA treba uzeti u obzir u bolesnika s CRT-om i paroksizmalnom FA koji ne reagiraju na antiaritmijske lijekove i u odabranih bolesnika s perzistentnom FA prije nego što se prihvati terapija kontrole frekvencije. Optimalno liječenje popratnih kardiovaskularnih stanja treba biti sastavan dio terapije kontrole ritma u bolesnika s CRT-om i FA koji se podvrgavaju kateterskoj ablaciji.⁴¹

Zaključak

Fibrilacija atrijske je često prisutna u bolesnika s CRT-om i može imati znatan negativan utjecaj na prognozu i odgovor na CRT. Bolesnici s FA-om i CRT-om trebaju optimalnu terapiju za zatajivanje srca i optimalnu antitrombotičku terapiju, kao i adekvatnu terapiju za kontrolu frekvencije ili kontrolu ritma. Nažalost, antiaritmijski lijekovi za kontrolu frekvencije i kontrolu ritma imaju ograničenu djelotvornost i ne mogu osigurati zadovoljavajuću postotak BiV stimulacije. U tom kontekstu ablaciju AVS-a treba uzeti u obzir kao prvi odabir za kontrolu frekvencije ventrikula u većini bolesnika s trajnom FA. Za sada, kateterska ablacija FA može biti odabir druge linije za kontrolu ritma u bolesnika s CRT-om koji imaju paroksizmalnu ili perzistentnu FA otpornu na lijekove, a treba je provoditi u iskusnom centru. Potrebne su daljnje prospektivne multicentrične studije kako bi se jasno odredila sigurnost i djelotvornost ablacije FA u ovoj skupini bolesnika.

al function and by controlling the ventricular rate and/or regularity. According to the most recent evidence from the heart failure studies³⁶⁻⁴⁰ and AATAC study,³¹ AF ablation should be considered in CRT patients with paroxysmal AF, who are non-responders to antiarrhythmic drugs, and in selected patients with persistent AF before accepting a rate control strategy. Optimal management of concomitant cardiovascular conditions should be an integral part of rhythm control therapy in CRT patients with AF undergoing catheter ablation.⁴¹

Conclusion

AF is often present in patients with CRT and can have a significant negative impact on the prognosis and CRT response. All patients with AF and CRT should receive the optimal heart failure and optimal anti-thrombotic therapy, as well as the adequate rate or rhythm control therapy, whose aim is to achieve a high BiV pacing. Unfortunately, the antiarrhythmic drugs for rate and rhythm control have moderate efficacy and can not ensure a sufficient BiV pacing. In this context, the AVJ ablation can be used as the first option for the rate control in the majority of CRT patients with permanent AF. For now, catheter ablation of AF may be a second-line rhythm control option for CRT patients with paroxysmal or persistent AF refractory to antiarrhythmic drugs, and should be performed in experienced center. Further prospective multicenter studies are needed to clearly define the true safety and efficacy of AF ablation in this group of patients.

LITERATURE

1. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J*. 2013;34:2281-329. <https://doi.org/10.1093/eurheartj/ehf150>
2. Upadhyay GA, Steinberg JS. Managing atrial fibrillation in the CRT patient: controversy or consensus? *Heart Rhythm*. 2012 Aug;9(8 Suppl):S51-9. <https://doi.org/10.1016/j.hrthm.2012.04.030>
3. Witt CT, Kronborg MB, Nohr EA, Mortensen PT, Gerdes C, Nielsen JC. Early detection of atrial high rate episodes predicts atrial fibrillation and thromboembolic events in patients with cardiac resynchronization therapy. *Heart Rhythm*. 2015 Dec;12(12):2368-75. <https://doi.org/10.1016/j.hrthm.2015.07.007>
4. Ousdigian KT, Borek PP, Koehler JL, Heywood JT, Ziegler PD, Wilkoff BL. The epidemic of inadequate biventricular pacing in patients with persistent or permanent atrial fibrillation and its association with mortality. *Circ Arrhythm Electrophysiol*. 2014;7:370-6. <https://doi.org/10.1161/CIRCEP.113.001212>
5. Borleffs CJ, Ypenburg C, Van Bommel RJ, Delgado V, Van Erven L, Schalij MJ, et al. Clinical importance of new onset atrial fibrillation after cardiac resynchronization therapy. *Heart Rhythm*. 2009 Mar;6(3):305-10. <https://doi.org/10.1016/j.hrthm.2008.12.017>
6. Bogale N, Priori S, Cleland JGF, Brugada J, Linde C, Auricchio A, et al.; Scientific Committee, National Coordinators, and Investigators. The European CRT Survey: 1 year (9-15 months) follow-up results. *Eur J Heart Fail*. 2012 Jan;14(1):61-73. <https://doi.org/10.1093/eurjhf/hfr158>
7. Wilton SB, Leung AA, Ghali WA, Faris P, Exner DV. Outcomes of cardiac resynchronization therapy in patients with versus those without atrial fibrillation: a systematic review and meta-analysis. *Heart Rhythm*. 2011 Jul;8(7):1088-94. <https://doi.org/10.1016/j.hrthm.2011.02.014>
8. Cesario D, Powell BD, Gilliam R, Day J, Hayes D, Jones P, et al. The role of atrial fibrillation in CRT-D patients: The ALTITUDE Study Group. *The Journal of Innovations in Cardiac Rhythm Management*. 2015;6:1873-80. <http://www.innovationsincrm.com/images/pdf/crm-06-01-1873.pdf>
9. Hayes DL, Boehmer JP, Day JD, Gilliam FR, Heidenreich PA, Seth M, et al. Cardiac resynchronization therapy and the relationship of percent biventricular pacing to symptoms and survival. *Heart Rhythm*. 2011 Sep;8(9):1469-75. <https://doi.org/10.1016/j.hrthm.2011.04.015>
10. European Heart Rhythm Association; European Society of Cardiology; Heart Rhythm Society; Heart Failure Society of America; American Society of Echocardiography; American Heart Association; European Association of Echocardiography; Heart Failure Association, Daubert JC, Saxon L, Adamson PhB, Auricchio A, Berger RD, Beshai JF, et al. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. *Heart Rhythm*. 2012 Sep;9(9):1524-76. <https://doi.org/10.1016/j.hrthm.2012.07.025>
11. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016 Oct 7;37(38):2893-2962. <https://doi.org/10.1093/eurheartj/ehw210>

12. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al; Authors/Task Force Members. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016 Jul 14;37(27):2129-200. <https://doi.org/10.1093/eurheartj/ehw128>
13. Xiong Q, Lau YC, Senoo K, Lane DA, Hong K, Lip GYH. Non-vitamin K antagonist oral anticoagulants (NOACs) in patients with concomitant atrial fibrillation and heart failure: a systemic review and meta-analysis of randomized trials. *Eur J Heart Fail*. 2015 Nov;17(11):1192-200. <https://doi.org/10.1002/ehf.343>
14. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener H-C, Hacke W, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015;17:1467-507. <https://doi.org/10.1093/europace/euv309>
15. de Denus S, Sanoski CA, Carlsson J, Oplasi G, Spinler SA. Rate vs rhythm control in patients with atrial fibrillation: a meta-analysis. *Arch Intern Med*. 2005;165:258-62. <https://doi.org/10.1001/archinte.165.3.258>
16. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al; for the Atrial Fibrillation and Congestive Heart Failure Investigators. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008; 358:2667-77. <https://doi.org/10.1056/NEJMoa0708789>
17. Talajic M, Khairy P, Levesque S, Connolly SJ, Dorian P, Dubuc M, et al; AF-CHF Investigators. Maintenance of sinus rhythm and survival in patients with heart failure and atrial fibrillation. *J Am Coll Cardiol*. 2010;55:1796-802. <https://doi.org/10.1016/j.jacc.2010.01.023>
18. Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do? *Eur Heart J*. 2015 Dec 7;36(46):3250-7. <https://doi.org/10.1093/eurheartj/ehv513>
19. Petrač D. Antiarrhythmic drug therapy to treat atrial fibrillation. *Cardiol Croat*. 2012;7(11-12):322-30. http://www.kardio.hr/pdf/Cardiologia%20Croatia%202012_7_11-12_322-330.pdf
20. Kirchhof P, Breithardt G, Camm AJ, Crijns HJ, Kuck KH, Vardas P, Wegscheider K. Improving outcomes in patients with atrial fibrillation: rationale and design of the Early treatment of Atrial fibrillation for Stroke prevention Trial. *Am Heart J*. 2013;166:442-48. <https://doi.org/10.1016/j.ahj.2013.05.015>
21. Kamath GS, Cotiga D, Koneru JN, Arshad A, Pierce W, Aziz EF, et al. The utility of 12-lead Holter monitoring in patients with permanent atrial fibrillation for the identification of nonresponders after cardiac resynchronization therapy. *J Am Coll Cardiol*. 2009;53:1050-5. <https://doi.org/10.1016/j.jacc.2008.12.022>
22. Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JGF. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol*. 2003;42:1944-51. <https://doi.org/10.1016/j.jacc.2003.07.020>
23. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, et al; Beta-Blockers in Heart Failure Collaborative Group. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet*. 2014;384:2235-243. [https://doi.org/10.1016/S0140-6736\(14\)61373-8](https://doi.org/10.1016/S0140-6736(14)61373-8)
24. Ferreira AM, Adragao P, Cavaco DM, Candeias R, Morgado FB, Santos KR, et al. Benefit of cardiac resynchronization therapy in atrial fibrillation patients vs. patients in sinus rhythm: the role of atrioventricular junction ablation. *Europace*. 2008;10:809-15. <https://doi.org/10.1093/europace/eun135>
25. Gasparini M, Auricchio A, Metra M, Regoli F, Fantoni C, Lamp B, et al; Multicentre Longitudinal Observational Study (MILOS) Group. Long-term survival in patients undergoing cardiac resynchronization therapy: the importance of performing atrio-ventricular junction ablation in patients with permanent atrial fibrillation. *Eur Heart J*. 2008;29:1644-52. <https://doi.org/10.1093/eurheartj/ehn133>
26. Dong K, Shen WK, Powell BD, Dong YX, Rea RF, Friedman PA, et al. Atrioventricular nodal ablation predicts survival benefit in patients with atrial fibrillation receiving cardiac resynchronization therapy. *Heart Rhythm*. 2010;7:1240-5. <https://doi.org/10.1016/j.hrthm.2010.02.011>
27. Ganesan AN, Brooks AG, Roberts-Thomson KC, Lau DH, Kalman JM, Sanders P. Role of AV nodal ablation in cardiac resynchronization in patients with coexistent atrial fibrillation and heart failure: a systematic review. *J Am Coll Cardiol*. 2012;59:719-26. <https://doi.org/10.1016/j.jacc.2011.10.891>
28. Gasparini M, Leclercq Ch, Lunati M, Landolina M, Auricchio A, Santini M, et al. Cardiac resynchronization therapy in patients with atrial fibrillation. The CERTIFY Study (Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry). *JACC Heart Fail*. 2013 Dec;1(6):500-7. <https://doi.org/10.1016/j.jchf.2013.06.003>
29. Lafuente-Lafuente C, Mouly S, Longas-Tejero MA, Mahe I, Bergmann JF. Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation: a systematic review of randomized trials. *Arch Intern Med*. 2006;166:719-28. <https://doi.org/10.1001/archinte.166.7.719>
30. Doyle JF, Ho MK. Benefits and risks of long-term amiodarone therapy for persistent atrial fibrillation: a meta-analysis. *Mayo Clin Proc*. 2009 Mar;84(3):234-42. <https://doi.org/10.4065/84.3.234>
31. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi Ch, Lakkireddy D, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device. Results from the AATAC multicenter randomized trial. *Circulation*. 2016;133:1637-44. <https://doi.org/10.1161/CIRCULATIONAHA.115.019406>
32. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, Kober L, Sandoe E, Egstrup K, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. *N Engl J Med*. 1999;341:857-65. <https://doi.org/10.1056/NEJM199909163411201>
33. Singh S, Zoble RG, Yellen L, Brodsky MA, Feld GK, Berk M, et al. Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) study. *Circulation*. 2000;102:2385-90. <https://doi.org/10.1161/01.CIR.102.19.2385>
34. Pedersen OD, Bagger H, Keller N, Marchant B, Kober L, Torp-Pedersen C. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) substudy. *Circulation*. 2001;104:292-296. <https://doi.org/10.1161/01.CIR.104.3.292>
35. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol*. 2009 Aug;2(4):349-61. <https://doi.org/10.1161/CIRCEP.108.824789>
36. Anselmino M, Matta M, Castagno D, Giustetto C, Gaita F. Catheter ablation of atrial fibrillation in chronic heart failure: state of the art and future perspectives. *Europace*. 2016;18:638-47. <https://doi.org/10.1093/europace/euv368>
37. Khan MN, Jais P, Cummings J, Di Biase L, Sanders P, Martin DO, et al. for the PABA-CHF Investigators. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med*. 2008 Oct 23;359(17):1778-85. <https://doi.org/10.1056/NEJMoa0708234>
38. MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart*. 2011;97:740-7. <https://doi.org/10.1136/hrt.2010.207340>
39. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol*. 2013;61:1894-903. <https://doi.org/10.1016/j.jacc.2013.01.069>
40. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (The CAMTAF Trial). *Circ Arrhythm Electrophysiol*. 2014 Feb;7(1):31-8. <https://doi.org/10.1161/CIRCEP.113.000806>
41. Kirchhof P, Calkins H. Catheter ablation in patients with persistent atrial fibrillation. *Eur Heart J*. 2017 Jan 1;38(1):20-26. <https://doi.org/10.1093/eurheartj/ehw260>