Pregledni članak / Review article

Uloga antiaritmika u liječenju fibrilacije atrija

Antiarrhythmic drug therapy to treat atrial fibrillation

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SAŽETAK: Tijekom zadnjih 10 godina uložen je značajan trud u utvrđivanju uloge antaritmičnog liječenja za održavanje sinusnog ritma u bolesnika s fibrilacijom atrija (FA). Podaci randomiziranih kontroliranih studija su pokazali da strategija kontrole ritma, u pogledu smrtnosti ili moždanog udara, nije bolja od strategije kontrole frekvencije, većinom zbog ograničene učinkovitosti i toksičnosti antiaritmika u bolesnika s kontrolom ritma. S obzirom na to, sadašnja antiaritmična terapija za održavanje sinusnog ritma u bolesnika s FA preporuča se na temelju odabira sigurnijeg, iako možda manje učinkovitog lijeka. Razlog zbog kojeg se počinje s antiaritmičnom terapijom jest taj da se ovim pristupom može učinkovito liječiti do 50% bolesnika, i da je uz pravilnu primjenu, rizik za bolesnike malen. Sukladno tome, odabir antiaritmika ovisi o karakteristikama bolesnika i mogućoj toksičnosti lijeka.

U bolesnika s minimalnom srčanom bolešću ili bez srčane bolesti, ili arterijskom hipertenzijom bez značajne hipertrofije lijeve klijetke, mogu se kao prvi lijekovi izbora za održavanje sinusnog ritma koristiti flekainid, propafenon i sotalol. Za bolesnike s koronarnom bolešću srca bez znakova zatajivanja srca, preporuča se kao prvi lijek izbora sotalol i dronedaron kao opravdana alternativa. Amiodaron je rezerviran za one bolesnike u kojih je terapija drugim antiaritmičnim lijekovima bila bezuspješna, ili za one koji imaju značajnu strukturalnu bolest srca, tj. zatajivanje srca ili značajnu hipertrofiju lijeve klijetke.

KLJUČNE RIJEČI: fibrilacija atrija, antiaritmici, dronedaron.

SUMMARY: Over the past 10 years a considerable effort has been made in establishing the role of antiarrhythmic drug therapy for maintenance of sinus rhythm in patients with atrial fibrillation (AF). Data from randomized controlled studies have demonstrated that rhythm control strategy is not superior to the rate control strategy in terms of mortality or stroke, mostly due to limited efficacy and toxicity of antiarrhyhtmic drugs in the rhythm control patients. Regarding to these data, current antiarrhythmic therapy to maintain sinus rhythm in patients with AF is recommended on the basis of choosing safer, although possibly less efficacious drug. The rationale for starting with a trial of antiarrhythmic therapy is that up to 50% of patients may be effectively treated with this approach, and when properly administered, there is little risk to the patient. Accordingly, the choice of antiarrhyhtmic drugs depends on patient characteristics and potential drug toxicity.

In patients with a minimal or no heart disease, or hypertension without left ventricular hypertrophy, dronedarone, flecainide, propafenone, and sotalol may be used for maintaining of sinus rhythm as the first-line drugs. For patients with coronary artery disease without overt heart failure, sotalol is recommended as first-line treatment option, and dronedarone as reasonable alternative. Amiodarone is reserved for those who have failed treatment with other antiarrhythmic drugs or have significant structural heart disease, i.e. heart failure or significant left ventricular hypertrophy.

KEYWORDS: atrial fibrillation, antiarrhyhtmic drugs, dronedarone.

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Uvod

Farmakološko liječenje bolesnika s fibrilacijom atrija (FA) se tijekom proteklih 10 godina iscrpno proučavalo u nizu randomiziranih kontroliranih studija, koje su uspoređivale strategije kontrole ritma i frekvencije. Rezultati ovih studija nisu uspjeli dokazati da je strategija kontrole ritma, u pogledu mortaliteta ili moždanog udara, bolja od strategije kontrole frekvencije, čak i u bolesnika s istovremenim zatajivanjem srca.[1,2] Glavni razlog za to bili su nedostaci antiaritmika i prekid antikoagulantne terapije u bolesnika s kontrolom ritma nakon konverzije u sinusni ritam.[2,3] Unatoč tomu, uporaba antiaritmika za kontrolu ritma ostaje prvi izbor liječenja u

Introduction

The pharmacological treatement of patients with atrial fibrillation (AF) has been extensively studied over the past 10 years by number of randomized controlled studies, which compared the rhythm and rate control strategies. The results of these studies have failed to demonstrate that the rhythm control strategy is superior to the rate control strategy in terms of mortality or stroke, even among those with concomitant heart failure.[1,2] The main reason for that were the shortcomings of antiarrhythmic drugs and discontinuation of the anticoagulant therapy after sinus rhythm restoration in the rhythm control patients.[2,3] Nevertheless, a trial of antiarrhyht-

mnogih bolesnika s FA. Nedavno odobrenje dronedarona za prevenciju kardiovaskularnih hospitalizacija u bolesnika s nepermanentnom FA ili undulacijom atrija (UA), pruža mogućnost da se smanji rizik nekih kliničkih ishoda.[4] Cilj ovog pregleda je prikazati domete i ograničenja sadašnjih antiaritmika u održavanju sinusnog ritma u bolesnika s FA.

Temeljni razlozi održavanja sinusnog ritma

Kad bi mogli birati između FA i sinusnog ritma, odabrali bi sinusni ritam kako bi izbjegli negativne posljedice FA. Međutim, unatoč prednosti koja se daje sinusnom ritmu, sadašnji antiaritmici za prevenciju FA nisu dovoljno učinkoviti i sigurni. Sveukupno, samo 40-60% bolesnika, koji su liječeni antiaritmicima ostaje u sinusnom ritmu na kraju praćenja, dok su ostali u FA.[1,2,5]

Unatoč ovim podacima, čini se logičnim da bi održavanje sinusnog ritma trebalo biti povezano sa smanjenim mortalitetom. U Framinghamskoj studiji bolesnici s fibrilacijom atrija imali su veći rizik od smrti i moždanog udara nego bolesnici u sinusnom ritmu.[6,7] Nekoliko drugih studija, uključujući odabrane skupine s različitom patologijom (**Slika 1**), također je pokazalo da je fibrilacija atrija povezana s povećanim rizikom od smrti.[8,9]

mic medications for rhyhtm control remains the first-line therapy for many patients with AF. The recent approval of dronedarone for the prevention of cardiovascular hospitalization in patients with nonpermanent AF or atrial flutter (AFL), offers the possibility to lower the risk of some clinical outcomes.[4] This review will focus on the role of current antiarrhythmic drugs to maintain sinus rhythm in patients with AF.

Rationale for maintenance of sinus rhythm

If we could choose between AF and sinus rhythm, we would chose the sinus rhythm to avoid the negative consequences of AF. However, despite the preference for sinus rhythm, current antiarrhythmic drugs for preventing AF were not as effective and safe as we would like. Overall, only 40-60% of the patients treated with antiarrhyhtmic drugs are in sinus rhythm at the end of follow-up, while the reminder are in AF.[1,2,5]

In spite of these data, it seems logical that the maintenance of sinus rhythm should be associated with reduced mortality. The Framingham study has found a higher risk of death and stroke in patients with AF when compared with those in sinus rhythm.[6,7] Several others studies, including selected populations with a different pathology (**Figure 1**), have also demonstrated an increased risk associated with AF.[8,9]

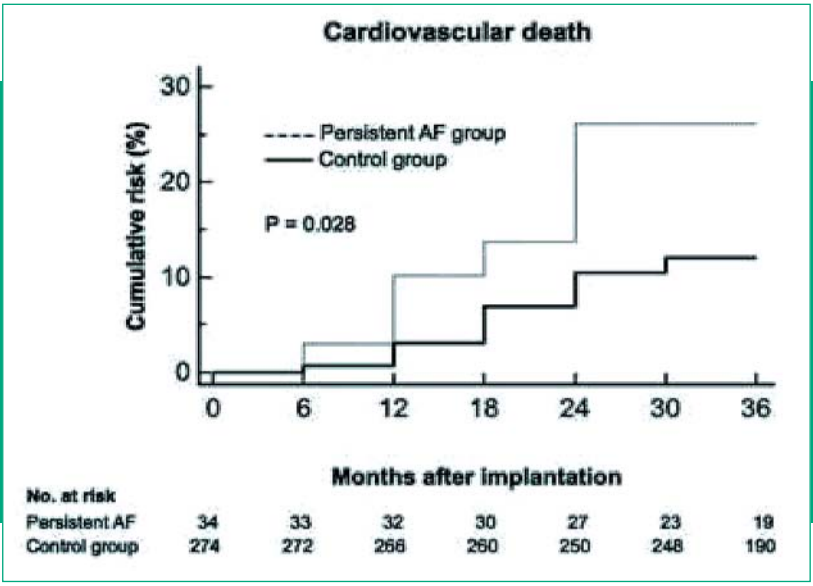

Figure 1. *Cumulative risk of cardiovascular death in patients with second- or third-degree AV block and DDD pacemaker according to the development (persistent AF group) or nondevelopment (control group) of persistent atrial fibrillation (adapted with permission from Petrač D, et al[9]).*

Neke nerandomizirane studije smatraju da su uspostava i održavanje sinusnog ritma znak veće vjerojatnosti preživljenja.[10,11] Kada je studija AFFIRM bila analizirana na temelju stvarnog ritma pri praćenju bolesnika, prisutnost sinusnog ritma bila je čvrsto povezana sa smanjenim rizikom od smrti (omjer rizika = 0.53).[12] Prisutnost sinusnog ritma je u ovoj analizi bila važnija odrednica ishoda od uporabe antiaritmika. Stoga se čini da čak i u odabranoj populaciji bolesnika uključenih u ovu studiju postoji dobrobit sinusnog ritma. Ograničavajući faktor nije nužno bio strategija kontrole ritma, već neadekvatna sredstva koja imamo na raspolaganju za uspostavu i održavanje sinusnog ritma. Naglašavamo da je u ovoj studiji bila testirana strategija, a ne postignuti ritam. Sve studije s ovom tematikom pokazale su bolje ishode u bolesnika sa sinusnim ritmom. Problem je, stoga, kako ga ostvariti. U nerandomiziranoj studiji, Pappone *i sur.* su pokazali da radiofrekventna ablacija kod liječenja FA poboljšava smrtnost, pobol i kvalitetu života u usporedbi s medikament-

Some nonrandomized studies suggested that restoration and maintenance of sinus is a marker of a greater likelihood of survival.[10,11] When the AFFIRM study was analyzed on the basis of actual rhythm at follow-up, the presence of sinus rhythm was strongly associated with a decreased risk of death (hazard ratio = 0.53).[12] The presence of sinus rhythm was a more important determinant of outcome than the use of antiarrhythmic medications in this analysis. Therefore, even in the selected population of patients enrolled in this trial, there appears to be a benefit to sinus rhythm. The limiting factor was not necessarily the rhythm-control strategy, but the inadequate tools available to restore and maintain the sinus rhythm. We emphasize that it was the strategy, not the achieved rhythm, that was being tested in this trial. All studies of this issue have demonstrated superior outcomes in patients with sinus rhythm. The problem, therefore, is how to achieve it. In a nonrandomized study, Pappone et al showed that radiofrequency ablation to cure AF improves mortality, morbidity and quality of life compared with medical therapy.[13]

nom terapijom.[13] Održavanje sinusnog ritma bilo je povezano sa značajno manjom smrtnošću i manjom učestalošću neželjenih događaja, bilo da se radi o svim bolesnicim, ili o dvije liječene skupine. Rezultati ove studije su u skladu s konceptom da je sinusni ritam bolji od FA, ako imamo sigurne načine da ga postignemo i održimo.

Indikacije i principi farmakološke terapije antiaritmicima

Farmakološka terapija antiaritmicima u bolesnika s paroksimalnom ili perzistentnom FA usmjerena je na održavanje sinusnog ritma, prevenciju električnog remodeliranja i na fibrozu atrija. Postoje tri klinička okvira u kojih bi trebalo razmotriti strategiju za održavanje sinusnog ritma:[14] **1**) neprestani simptomi unatoč adekvatnoj kontroli frekvencije, **2**) nemogućnost održavanja adekvatne kontrole frekvencije (kako bi se spriječio nastanak kardiomiopatije posredovane tahikardijom) i **3**) odluka bolesnika, jer neki bolesnici ne žele prihvatiti nitijedan oblik FA. Nove europske smjernice za zbrinjavanje FA sugeriraju sljedeće principe farmakološke terapije antiaritmicima za održavanje sinusnog ritma u FA[15]:

1. Liječenje je motivirano pokušajima da se ublaže simptomi vezani za FA.

2. Učinkovitost antiaritmika za održavanje sinusnog ritma je skromno.

3. Klinički uspješna terapija antiaritmicima može prije smanjiti nego eliminirati povratak FA.

4. Ako jedan antiaritmični lijek bude neuspješan, klinička dobrobit se može postići drugim lijekom.

5. Česte su lijekovima izazvane proaritmije ili nekardijalne nuspojave.

6. Sigurnost, a ne učinkovitost bi trebala biti primarna vodilja pri odabiru antiaritmičnog lijeka.

Djelotvornost i sigurnost starih antiaritmijskih lijekova

Farmakološko liječenje FA antiaritmicima ima za cilj održavanje sinusnog ritma i prevenciju električnog remodeliranja i fibroze atrija.[16] Sada dostupni antiaritmici imaju ograničenu djelotvornost i značajnu toksičnost (**Tablica 1**), što ograničava njihovu uporabu.

Maintenance of sinus rhythm was associated with significantly lower mortality and advers event rates, either considering all patients, or the two treatment groups. This finding is consistent with the concept that the sinus rhythm is better than AF if we have safe means to achieve and maintain it.

Indications and principles for antiarrhythmic drug therapy

Antiarrhythmic drug treatment in patients with paroxysmal or persistent AF is directed at both maintenance of sinus rhythm and prevention of electrical remodeling and fibrosis of the atria. There are three settings in which a rhythm control strategy for the maintanance of sinus rhythm should be considered:[14] **1**) persistent symptoms despite adequate rate control, **2**) an inability to attain adequate rate control (to prevent tachycardia-mediated cardimyopatha), and **3**) patient preference, because some patients will strongly prefer to avoid either paroxysmal or persistent AF. Recent European guidelines for the management of AF suggest the following principles of antiarrhythmic drug therapy to maintain sinus rhythm in AF[15]:

1. Treatment is motivated by attempts to reduce AF-related symptoms.

2. Efficacy of antarrhythmic drugs to maintain sinus rhythm is modest.

3. Clinically successful antiarrhythmic drug therapy may reduce rahter than eliminate recurrence of AF.

4. If one antiarrhythmic drug "fails", a clinically acceptable response may be achieved with another agent.

5. Drug-induced proarrhythmia or extra-cardiac side effects are frequent.

6. Safety rather than efficacy considerations should primarly guide the choice of antiarrhythmic agent.

Efficacy and safety of old antiarrhythmic drugs

Antiarrhyhtmic drug treatment of AF is directed at both maintenance of sinus rhythm and prevention of electrical remodeling and fibrosis of the atria.[16] However, currently available antiarrhythmic medications have limited efficacy and significant toxicities (**Table 1**) that limited their use.

Table 1.

Potential adverse effects of antiarrhythmic drugs.

Drug	Adverse effects
Disopyramide	Torsades de pointes, heart failure, glaucoma, urinary retention, dry mouth
Flecainide	Ventricular tachycardia, heart failure, conversion to atrial flutter with rapid conduction through atrioventricular node
Propafenone	Ventricular tachycardia, heart failure, conversion to atrial flutter with rapid conduction through atrioventricular nod
Sotalol	Torsades de pointes, heart failure, bradycardia, exacerbation of chronic obstructive or bronchospastic lung disease
Dronedarone	Gastrointestinal events, hepatic toxicity, heart failure, bradycardia, skin-related events
Amiodarone	Photosensitivity, pulmonary toxicity, thyroid dysfunction, polyneurophaty, hepatic toxicity, bradycardia, gastrointestinal upset, eye complications

Djelotvornost i sigurnost cijelog niza antiaritmika analizirana je u meta-analizi[17] koja je uključila 44 studije s ukupno 11.322 bolesnika u kojih je antiaritmik za liječenje FA uspoređivan s placebom, drugim antiaritmikom ili neliječenom kontrolnom skupinom, uz praćenje u trajanju od najmanje šest mjeseci. U usporedbi s placebom, lijekovi skupine IA (dizopiramid, kinidin), skupine IC (flekainid, propafenon) i skupine III (amiodaron, sotalol) značajno smanjuju ponovnu pojavu FA, s omjerom vjerojatnosti od 0.51, 0.36 i 0.37. Amiodaron je bio najučinkovitiji antiaritmik u usporedbi s neliječenom kontrolnom skupinom (omjer vjerojatnosti 0,19, P<0,001) te bolji od lijekova skupine I (omjer vjerojatnosti 0.31, P<0.001) i sotalola (omjer vjerojatnosti 0.43, P<0.001). Odgovarajući broj bolesnika koje je potrebno liječiti da bi se spriječio jedan povrat FA kroz godinu dana bio je 3 s amiodaronom, 4 s flekainidom, 5 s propafenonom i 8 s kinidinom i sotalolom. Prestanak uzimanja lijeka zbog nuspojava bio je veći sa svim antiaritmicima u usporedbi s placebom.

Svi antiaritmici, osim amiodarona i propafenona, imali su proaritmični učinak. U usporedbi s kontrolnom skupinom, samo su lijekovi skupine IA (kinidin i dizopiramid zajedno) bili povezani s povećanom smrtnošću (omjer vjerojatnosti 2.39, p = 0.04), dok su drugi antiaritmici imali neutralan učinak na smrtnost.

Djelotvornost i sigurnost dronedarona

Dronedaron je derivativ benzofurana koji ima elektrofiziološki učinak sličan amiodaronu, no bez jodovog supstituenta. Antiaritmična djelotvornost i sigurnost dronedarona bila je procijenjena u 4 placebom-kontrolirane, randomizirane studije.[4] Podaci prikupljeni u ovim studijama su pokazali da su bolesnici liječeni dronedaronom imali manju učestalost prvog povrata FA/UA u usporedbi s bolesnicima liječenim placebom (43% prema 54%, P<0.001) (**Tablica 2**). Nije bilo

The efficacy and safety of a number of antiarrhythmic drugs were assessed in a meta-analysis,[17] which included 44 trials with a total of 11.322 patients, in which an antiarrhythmic drug for the treatment of AF was compared against placebo, another antiarrhythmic, or untreated controls, with at least six months' follow-up. Compared to placebo, class IA (disopyramide, quinidine), class IC (flecainide, propafenone), and class III (amiodarone, sotalol) drugs significantly reduced recurrence of AF, with odds ratios of 0.51, 0.36, and 0.37, respectively. Amiodarone was the most effective antarrhythmic compared to untreated controls (odds ratio 0.19, P<0.001), and superior to class I agents (odds ratio 0.31, P<0.001), and sotalol (odds ratio 0.43, P<0.001). Corresponding numbers of patients needed to be treated to prevent one AF recurrence for 1 year were 3 with amiodarone, 4 with flecainide, 5 with propafenone and 8 with quinidine and sotalol. Withdrawals due to adverse effects were higher with all antiarrhythmic drugs compared to placebo. All antiarrhythmic drugs except for amiodarone and propafenone had proarrhythmic effect. Compared with controls, only class IA drugs (quinidine and disopyramide togheter) were associated with increased mortality (odds ratio 2.39, p = 0.04), while other antiarrhythmic drugs had neutral effect on mortality.

Efficacy and safety of dronedarone

Dronedarone is a benzofuran derivative that has electrophysiologic effects similar to amiodarone, but without iodine substituens. The antiarrhythmic efficacy and saffety of dronedarone has been evaluated in 4 placebo-controlled, randomized trials.[4] Pooled data from these studies demonstrate that dronedarone-treated patients have experienced a lower rate of first AF/AFL recurrence when compared with placebo-treated patients (43% vs 54%, P<0.001) (**Table 2**). There was no increased risk of serious arrhythmia, and the num-

Table 2.
Relative risk of atrial fibrillation recurrence with dronedarone versus placebo.

Study	Dronedarone	Placebo	Relative risk (95% CI)	P value
DAFNE[18] Recurrence rate	35/ 54	43/48	0.72 (0.58 - 0.90)	**0.004**
EURIDIS[19] Recurrence rate	159/411	95/201	0.77 (0.64 - 0.94)	**0.009**
ADONIS[19] Recurrence rate	154/417	89/208	0.86 (0.71 - 0.80)	**0.51**
ATHENA[20] Recurrence rate	779/1732	950/1741	0.82 (0.77 - 0.86)	**< 0.001**
Pooled fixed effect	1118/2614 (43%)	1177/2196 (54%)	0.82 (0.77 - 0.87)	**< 0.0001**

DAFNE = Dronedarone Atrial Fibrillation Study After Electrical Cardioversion, EURIDIS = European Trial in Atrial Fibrillation or Flutter Pateints Receiving Dronedarone for the Maintenance of Sinus Rhythm, ADONIS = American-Australian Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm, ATHENA = A Placebo-Controlled, Double Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients with Atrial Fibrillation/Atrial Flutter

povećanog rizika od ozbiljne aritmije, a broj bolesnika koji je trebao liječiti FA u jednoj godini bio je 9. U kratkoročnoj studiji u trajanju od najmanje 7 mjeseci,[21] djelotvornost dronedarona u održavanju sinusnog ritma bila je manja od djelotvornosti amiodarona, dok su raniji prekid uzimanja lijeka i nekardijalne nuspojave bile manje s dronedaronom. Moguće je da bi s duljim razdobljima praćenja razlike u nekardiološkim nuspojavama bile veće, jer se toksičnost amiodarona povećava nakon nekoliko mjeseci ili godina uporabe.

Sigurnost dronedarona je procijenjena u dvije randomizirane kontrolirane studije. Studija ATHENA (placebom kontrolirana, dvostruko slijepa studija s paralelnim skupinama sa svrhom procjene djelotvornosti 400 mg dronedarona u prevenciji kardiovaskularne hospitalizacije ili smrti od bilo kojeg uzroka u bolesnika s fibrilacijom/undulacijom atrija) je randomizirana studija koja je procjenjivala dugoročni utjecaj dronedarona u usporedbi s placebom na kombinirani rizik od kardiovaskularne hospitalizacije ili ukupne smrtnosti u 4.628 pacijenata s FA ili UA i dodatnim čimbenicima rizika za smrt.[20] Bolesnici s NYHA II. ili III. stupnjem zatajivanja srca činili su 21% ispitanika, dok su oni s NYHA IV. stupnjem zatajivanja srca bili isključeni. Nakon srednjeg razdoblja praćenja od 21-nog mjeseca, dronedaron je značajno smanjio primarni ishod smrti ili prve kardiovaskularne hospitalizacije (31.9% prema 39.4% za placebo, omjer vjerojatnosti 0.76, P <0.0001) i sekundarni ishod kardiovaskularne smrti (2.7% prema 3.9% za placebo, omjer rizika 0.71, P <0.03). Druge analize su pokazale značajno smanjenje smrtnosti zbog aritmije (RR 0.55; 0.34—0.88; P <0.01) i moždanog udara (RR 0.66; 0.46—0.96, P <0,03).[22] Skupina na dronedaronu imala je veću učestalost bradikardije, produljenja QT intervala, proljeva, mučnine, osipa i povišene serumske vrijednosti kreatinina nego skupina na placebu. U međuvremenu je, nakon puštanja dronedarona na tržište, objavljeno i akutno oštećenje jetre izazvano ovim lijekom.[23]

Studija ANDROMEDA (Antiaritmična studija uporabe dronedarona kod umjerenog do teškog kongestivnog zatajivanja srca s procjenom smanjenja morbiditeta),[24] koja je uključivala bolesnike s uznapredovalim zatajivanjem srca zbog disfunkcije lijeve klijetke (NYHA II. do IV. stupnja), prekinuta je ranije jer je u bolesnika liječenih dronedaronom registrirana veća smrtnost od onih liječenih placebom (8.1% prema 3.8%, P = 0.03). Kao rezultat toga, dronedaron ne bi trebalo koristiti u bolesnika s anamnestičkim podacima o zatajivanju srca ili ejekcijskom frakcijom lijevog ventrikula (LVEF) <40%.

Skupna analiza 5 studija dronedarona koja je uključila ukupno 6.597 pacijenata nije otkrila značajnije razlike u riziku od ukupne smrtnosti u usporedbi s placebom (**Tablica 3**). Sukladno tome, u analizi osjetljivosti koja je isključila rezultate studije ANDROMEDA, uporaba dronedarona bila je povezana s 15% nižim rizikom od smrti. Ovi podaci sugeriraju da je uporaba dronedarona vjerojatno sigurna u stabilnih bolesnika s niskim, odnosno srednjim rizikom, tj. u onih bez nedavnog zatajivanja srca ili disfunkcije lijeve klijetke.

Kliničke implikacije

Prvi korak u liječenju bolesnika s FA je utvrditi rizik od moždanog udara i potrebu za primjenom antikoagulantnog liječenja sukladno objavljenim smjernicama. Sljedeći korak je odrediti da li bolesnici imaju simptome koji opravdavaju strategiju koja je usmjerena na uspostavu i održavanje sinusnog ritma. Na temelju sadašnjeg kliničkog stava, liječenje antiariticima treba razmotriti samo kada simptomi perzistiraju,

ber of patients needed to treat AF at 1 year was 9. In a short-term study for at least 7 months,[21] the efficacy of dronedarone to maintain sinus rhyhtm was lower than that of amiodarone, while the premature drug discontinuation and the main saffety end points of extra-cardiac toxicity tended to be less with dronedarone. It is possible that with longer follow-up periods there would have been greater difference in noncardiac side-effects, since the toxicity with amiodarone increases after several months to years of use.

The safety of dronedarone has been evaluated in 2 randomized controlled studies. The ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients with Atrial Fibrillation/Atrial Flutter) was a randomized trial to evaluate the long-term effect of dronedarone versus palacebo on the combined risk of cardiovascular hospitalization or all cause mortality in 4,628 patients with AF or AFL and additional risk factors for death.[20] Patients with NYHA class II or III heart failure comprised 21% of the study population, but patients with NYHA class IV heart failure were excluded. After a mean follow-up period of 21 months, dronedarone significantly reduced the primary outcome of death or first cardiovascular hospitalization (31.9% vs 39.4% for placebo, hazard ratio 0.76, P <0.0001) and the secondary outcome of cardiovascular death (2.7% vs 3.9% for placebo, hazard ratio 0.71, P <0.03). Other analyses demonstrated a significant reduction in arrhythmic mortality (RR 0.55; 0.34-0.88; P <0.01), and stroke (RR 0.66; 0.46-0.96, P <0.03).[22] Dronedarone group had higher rates of bradycardia, QT-prolongation, diarrhea, nausea, rash, and an increased serum creatinin level than the placebo group. In the meantime, acute liver injury has also been reported in the postmarket release experience with the drug.[23]

The ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate-to-Sever Congestive Heart Failure Evaluating Morbidity Decrease) trial,[24] which included patients with advanced heart failure from left ventricular dysfunction (NYHA class II to IV), was terminated earlier because patients treated with dronedarone had higher mortality rate than patients treated with placebo (8.1% vs 3.8%, P = 0.03). As a result, dronedarone should not be used in patients with a history of heart failure or a left ventricular ejection fraction (LVEF) <40%.

Pooled analysis of 5 dronedarone trials involving a total of 6,597 patients revealed no significant difference in the risk of all-cause mortality compared with placebo (**Table 3**). Accordingly, in a sensitivity analysis that exclude ANDROMEDA results, use of dronedarone was associated with 15% lower risk of death. These data suggest that dronedarone use is likely to be safe for low-intermediate risk stable patients, namely those without recently decompensated heart failure or left ventricular dysfunction.

Clinical implications

The first step in the management of patients with AF is to determine their stroke risk and need for anticoagulation according to published guidelines. The next step is to determine whether they have symptoms that warrant a strategy directed at restoration and maintenance of sinus rhythm. In general, based on available evidence, treatment with antiarrhythmic drugs should be considered only when symptoms persist despite adequate rate control. In this case, the choice of aniarrhythmic drug for long-term therapy must be indi-

Table 3.
Relative risk of all-cause mortality alone dronedarone versus placebo.

Study	Dronedarone	Placebo	Relative risk	P value
DAFNE Mortality rate	0/76	0/66	0.87 (0.02 – 43.21)	**Not significant**
EURIDIS Mortality rate	2/411	0/201	1.96 (0.09 – 43.29)	**Not significant**
ADONIS Mortality rate	9/417	5/208	0.90 (0.30 – 2.65)	**Not significant**
ANDROMEDA Mortality rate	25/310	12/317	2.13 (1.09 – 4.16)	**0.03**
ATHENA Mortality rate	116/2327	139/3201	0.84 (0.66 – 1.07)	**0.18**
Pooled fixed effect	152/3615 (4.2%)	156/3114 (5%)	0.95 (0.76 – 1.19)	**Not significant**

ANDROMEDA = Antiarrhythmic Trial with Dronedarone in Moderate-to-Sever Congestive Heart Failure Evaluating Morbidity Decrease. Other abbrevations as in Table 2.

unatoč adekvatnoj kontroli frekvencije. U tom slučaju, odabir antiaritmika za dugoročnu terapiju mora biti individualan, a korist od održavanja sinusnog ritma treba biti u ravnoteži s nuspojavama lijeka. Sukladno novim europskim smjernicama za zbrinjavanje FA, liječenje antiaritmicima se preporuča na temelju odabira sigurnijeg, iako možda manje učinkovitog lijeka prije nego pribjegnemo učinkovitijoj ali manje sigurnoj terapiji.[15] Odabir antiaritmika ovisi o patološkoj podlozi i funkcionalnom stanju srca (**Tablica 4**).[16,25]

Lijekovi skupine IC, flekainid i propafenon, općenito se dobro podnose i pokazuju sličnu učinkovitost (dvostruka veća mogućnost održavanja sinusnog ritma u odnosu na placebo), no oba lijeka su manje učinkovita od amiodarona (60% prema 34% za flekainid i 65% prema 37% za propafenon).[26,27] Mogu se sigurno davati bolesnicima bez ili s minimalnom bolešću srca, uključujući bolesnike s arterijskom hipertenzijom, ali bez značajne hipertrofije lijeve klijetke. Zbog potencijala flekainida i propafenona da konvertiraju FA u UA, koja se tada može brzo prenijeti na klijetke, preporuča se istodobna blokada atrioventrikularnog čvora beta-blokatorima ili blokatorima kalcijevih kanala. Treba poštivati mjere opreza pri uporabi flekainida ili propafenona u prisutnosti intraventrikularnog bloka, a posebice kod bloka lijeve grane.

vidualized, and the benefit of maintaining sinus rhythm should be balanced against the side-effect profile of antiarrhythmic drug. According to new European guidelines for the management of AF, antiarrhythmic drug therapy is recommended on the basis of choosing a safer, although possibly less efficacious medication before resorting to more effective but less safe therapy.[15] The choice of antiarrhythmic drug depends on underlying pathology and functional status of the heart (**Table 4**).[16,25]

Class IC drugs flecainide and propafenone are generally well tolerated and show similar effectiveness, (double the likelihood of maintaing sinus rhythm), but the both drugs are less effective than amiodarone (60% vs. 34% for flecainide, and 65% vs. 37% for propafenone).[26,27] They can be safely administrated in patients with no or minimal heart disease, including patients with hypertension but without substantional left ventricular hypertrophy. Concomitant atrioventricular node blockade with a beta-blocker or calcium channel blocker is recommended because of the potential of flecainide and propafenone to convert AF to atrial flutter (AFL), which then may be conducted rapidly to the ventricles. Precautions should be observed when using flecainide or propafenone in the presence of intraventricular conduction delay,

Table 4.
Choice of antiarrhyhtmic drug according to underlying pathology.

	Minimal or no HD, or HHD with no LVH	HHD with LVH	CAD	Heart failure
First-line	dronedarone, flecainide, propafenone, sotalol	dronedarone	sotalol, dronedarone	**amiodarone**
Second-line	**amiodarone**	**amiodarone**	**amiodarone**	

HD = heart disease, HHD = hypertensive heart disease, LVH = left ventricular hypertrophy, CAD = coronary artery disease

Zbog negativnog inotropnog učinka i proaritmičkog potencijala flekainida i propafenona, trebalo bi ih izbjegavati u bolesnika koji imaju zatajivanje srca, koronarnu bolest srca ili hipertrofiju lijeve klijetke. Drugi lijekovi skupine I, kao što su kinidin i dizopiramid imaju sličnu učinkovitost ali manje pogodne nuspojave i profile toksičnosti.[15] Zbog toga je danas kinidin uglavnom napušten, a dizopiramid se koristi isključivo za FA izazvanu vagusom.

Kako beta-blokatori nemaju izravan učinak na atrijsko tkivo, oni su tek umjereno učinkoviti u prevenciji FA, a njihova uporaba je ograničena na bolesnike s tireotoksikozom i bolesnike u kojih je FA izazvana stresom ili fizičkim opterećenjem.[15,16]

Sotalol se može koristiti u širjem spektru bolesnika s FA, ali je za početak terapije potrebna hospitalizacija i brižan nadzor zbog potencijalno fatalnog produljenja QT intervala i razvoja *torsades de pointes*. Sotalol sprječava povrat FA jednako učinkovito kao i propafenon, ali manje učinkovito od amiodarona.[27-29] Za bolesnike s koronarnom bolešću srca i očuvanom ejekcijskom frakcijom lijeve klijetke, sotalol se preporuča kao prvi lijek izbora. U bolesnika s QT intervalom >500 ms, sotalol bi trebalo obustaviti ili smanjiti njegovu dozu. Žene i bolesnici s bradikardijom, hipertrofijom lijeve klijetke, renalnom disfunkcijom, hipokalijemijom ili hipomagnezemijom imaju povećani rizik od nastanka proaritmija. Sotalol ne bi trebalo koristiti u bolesnika koji imaju značajnu hipertrofiju lijeve klijetke, zatajivanje srca ili LVEF ≤35%.

Dronedaron je multikanalni blokator koji inhibira natrijeve, kalijeve i kalcijeve kanale i ima nekompetitivnu antiadrenergičku aktivnost. Slično sotalolu, propafenonu i flekainidu, njegova učinkovitost u održavanju sinusnog ritma je manja nego kod amiodarona (36,5% prema 58% za amiodaron).[21] Dronedaron se može koristiti sigurno u bolesnika s minimalnom bolešću ili bez bolesti srca i s koronarnom bolešću srca bez vidljivog zatajivanja srca. Kako je studija ATHENA pokazala da je dornedaron siguran i dobro podnošljiv lijek za bolesnike s FA, uključujući i one s arterijskom hipertenzijom i mogućom hipertrofijom lijeve klijetke,[20] on bi se mogao koristiti kao alternativa amiodaronu za ovu populaciju, iako o tome još nema konačnih podataka. U ažuriranim ESC smjernicama za zbrinjavanje FA iz 2012. god.[25], dronedaron je kontraindiciran u bolesnika s nestabilnim hemodinamskim stanjima, s anamnezom (ili sadašnjeg) zatajivanja srca ili disfunkcijom lijeve klijetke (LVEF<40%). Osim toga, dronedaron je u nekoliko slučajeva bio povezan s teškim oštećenjem jetre.[22] Stoga se u bolesnika koji su na dugoročnoj terapiji dronedaronom preporuča kontrola jetrenih transferaza.

Dokazano je da je amiodaron najučinkovitiji lijek za održavanje sinusnog ritma u svim kliničkim okruženjima, uključujući bolesnike sa značajnom strukturalnom bolesti srca, sa 60% do 70% bolesnika koji održavaju sinusni ritam nakon 1 godine.[21,26-29] Unatoč njegovoj učinkovitosti u usporedbi s drugim lijekovima, potencijalne nuspojave tijekom dugotrajne primjene čine ga lijekom drugog izbora u bolesnika koji nemaju kontraindikacije na ostale antiaritmike. Uzevši u obzir kumulativnu toksičnost amiodarona, često ga se ne smatra primjerenim odabirom terapije za mlađe bolesnike s očekivanim duljim životnim vijekom. Među bolesnicima sa zatajivanjem srca, amiodaron se preporuča kao prvi lijek izbora, jer nema negativan učinak na preživljenje ovih bolesnika.

Kada zataje lijekovi iz prve antiaritmičke linije, preporuča se kateterska ablacija FA. Ova preporuka je potkrijepljena multicentričnim prospektivnim studijama koje su uspoređivale

particularly left bundle branch block. Because of negative inotropic effect and proarrhythmic potential of flecainide and propafenone, they should be avoided in patients who have heart failure, coronary artery disease or left ventricular hypertrophy. Other class I agents such as quinidine and disopyramide have similar efficacy but less favorable side-effect and toxicity profiles.[15] Because of that quinidin is now largely abandoned, and dysopiramide is used only for vagally induced AF.

Since beta-blockers have not direct effect on atrial tissue they are only modestly effective in the preventing AF, and thier use is limited to patients with thyrotoxycosis and patients with stress or exercise-induced AF.[15,16]

Sotalol can be used in a broader spectrum of patients with AF, but require hospitalization for initiation of therapy and careful monitoring due to potentially fatal QT prolongation and torsade de pointes. It prevents recurrent AF as effectively as propafeonone, but less effectively than amiodarone.[27-29] For patients with coronary artery disease and preserved left ventricular ejection fraction, sotalol is recommended as first-line treatement option. In patients reaching a QT interval >500 ms, sotalol should be stopped or the dose reduced. Women, and patients with bradycardia, left ventricular hypertrophy, renal dyfunction, hypokalaemia or hypomagnesaemia are at increased risk of proarrhythmia. Sotalol should not be used in patients who have significant left ventricular hypertrophy, heart failure or LVEF ≤35%.

Dronedarone is a multichannel blocker that inhibits the sodium, potassium, and calcium channels, and has non-competitive antiadrenergic activity. Similarly to sotalol, propafenone, and flecainide, its efficacy to maintain sinus rhythm is lower than that of amiodarone (36.5% vs 58% for amiodarone).[21] Dronedarone can be used safely in patients with minimal or no heart disease and coronary artery disease without overt heart failure. Since dronedarone was demonstrated to be safe and well tolerated in a large study,[20] including patients with hypertension and possible left ventricular hypertrophy, it might be used as an alternative to amiodarone for this population, although definitive data do not exist. In 2012 focused update of ESC guidelines for AF management,[25] dronedarone is contraindicated in patients with unstable haemodynamic conditions, with a history of (or current) heart failure or left ventricular dysfunction (LVEF <40%). In addition, dronedarone has been associated with severe hepatotoxicity in a few instances.[22] Hence, monitoring of liver function tests is advisable in patients on long-term dronedarone treatment.

Amiodarone has been proven to be the most effective drug for maintenance of sinus rhythm in all clinical settings, including patients with significant structural heart disease, with 60% to 70% of patients maintaining sinus rhythm after 1 year.[21,26-29] Despite its effectiveness over other agents, the potential adverse effects with a long-term amiodarone use makes it a second-line agent in patients who do not have contraindications to other antiarrhythmic drugs. Given the cumulative toxicity of amiodarone, it is often not considered an appropriate choice of therapy for younger patients with a longer life expectancy. Among patients with heart failure, amiodarone is recommended as a first-line agent based on its neutral effects on survival in these patients.

When first-line antiarrhythmic drugs fail, curative catheter ablation is recommended. This practice is supported by multicentre prospectives studies comparing antiarrhythmic drug treatment with catheter ablation, showing a significantly better rhythm outcome after ablation (**Table 5**)[13,30-32]. The ongo-

Table 5. *Radiofrequency catheter ablation versus antiarrhythmic drug therapy in patients with paroxysmal atrial fibrillation.*

Study	Pts (n)	Mean age	F/U (months)	Free of AF	Adverse effects
Vazni (2005)[30]					
RF ablation	32	53	12	87%*	pv stenosis 2
AA drugs	35	54	12	37%	0
Papone (2006)[13]					
RF ablation	99	55	12	86%*	TIA 1, pericardial effusion 1
AA drugs	99	57	12	22%	23% drug withdrawal
Jaix (2008)[31]					
RF ablation	53	50	12	89%*	tamponade 2, pv stenosis 1
AA drugs	59	52	12	23%	hypothyreoidism 1
Wilber (2010)[32]					
RF ablation	106	56	9	66%*	5% (within 30 days)
AA drugs	61	56	9	16%	8% drug withdrawal

n = number, F/U = follow-up, RF = radiofrequency, AA = antiarrhythmic, pv = pulmonary vein, TIA = transitory ischemic attack; * P < 0.001 compared with AA drugs

liječenje antiaritmicima s kateterskom ablacijom i pokazale značajno bolji ishod kontrole ritma nakon ablacije (**Tablica 5**).[13,30-32] Nadolazeća CABANA (Kateterska Ablacija naspram Antiaritmičnoj Terapiji Lijekovima za Fibrilaciju Atrija) studija, koja uključuje bolesnike s paroksimalnom ili perzistentnom FA, trebala bi odgovoriti na pitanje da li je ablacija FA bolja od sadašnjih lijekova za kontrolu ritma u smanjenju smrtnosti i kardiovaskularnog pobola. Postoje neki bolesnici u kojih se postupak ablacije FA može smatrati prvim terapijskim izborom. To uključuje bolesnike koji nisu u mogućnosti ili ne žele uzimati antiaritmične lijekove ili bolesnike kojima je amiodaron jedina održiva opcija za medicinsku terapiju. Unatoč impresivnoj uspješnosti koja se ostvaruje ablacijom FA, potrebno je razmotriti rizike koji su povezani s ovim invazivnim postupkom i raspraviti ih s bolesnicima.

ing Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial, which is enrolling patients with paroxysmal or persistent AF, should give the answer if the ablation of AF is superior to the current rhythm control drugs in reducing mortality and cardiovascular morbidity. There are some patients in whom an AF ablation procedure can be considered the first-line therapy. These include patients unable or unwilling to take an antiarrhythmic medication or patients in whom the only viable option for medical therapy is amiodarone. Despite the impressive success rates achieved with AF ablation, the risks associated with this invasive procedure must be considered and discussed with patients.

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