ANTIISHEMIJSKA TERAPIJA U LEČENJU HRONIČNOG KORONARNOG SINDROMA

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REVIEW ARTICLE

ANTIISCHEMIC THERAPY IN TREATING CHRONIC CORONARY SYNDROME

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SAŽETAK

Ishemija srčanog mišića ima, kao patofiziološku osnovu, neadekvatan odnos između snabdevenosti i potreba miokarda za oksigenisanom krvlju. Klinički se manifestuje kao anginozni bol sa tipičnom lokalizacijom, karakterom, intenzitetom i pratećim tegobama, pre svega netolerancijom napora. Dijagnostički algoritam obuhvata klinički pregled, neinvanzivne i invazivne dijagnostičke procedure, uključujući koronarografiju kao zlatni standard. Konzervativno lečenje stabilne angine pektoris, sem modifikacije načina života i eliminisanja tradicionalnih faktora rizika, podrazumeva primenu savremenih lekova, među kojima je i ranolazin, koji se izdvojio svojim jedinstvenim mehanizmom dejstva, efikasnošću i bezbednošću. Ranolazin je efikasan u redukciji manifestacija ishemije i angine sa potencijalnim efektom na disfunkciju leve komore – pre svega dijastolnu i električnu nestabilnost.

Ključne reči: ishemija miokarda, konzervativno lečenje angine pektoris, ranolazin

ABSTRACT

Myocardial ischemia is pathophysiologically based on the inadequate balance between the supply of oxygenated blood and the myocardial oxygen demand. Clinically, it presents as anginal pain with a typical localization, nature, intensity, and accompanying symptoms, primarily exercise intolerance. The diagnostic algorithm includes clinical examination, non-invasive and invasive diagnostic procedures, with coronary angiography as the gold standard. Conservative treatment of stable angina pectoris, in addition to lifestyle modification and elimination of traditional risk factors, involves the use of novel medications, including ranolazine, which stands out for its unique mechanism of action, effectiveness, and safety. Ranolazine is effective in reducing manifestations of ischemia and angina, with a potential effect on left ventricular dysfunction-primarily diastolic and electrical instability.

Keywords: myocardial ischemia, conservative treatment of angina pectoris, ranolazine

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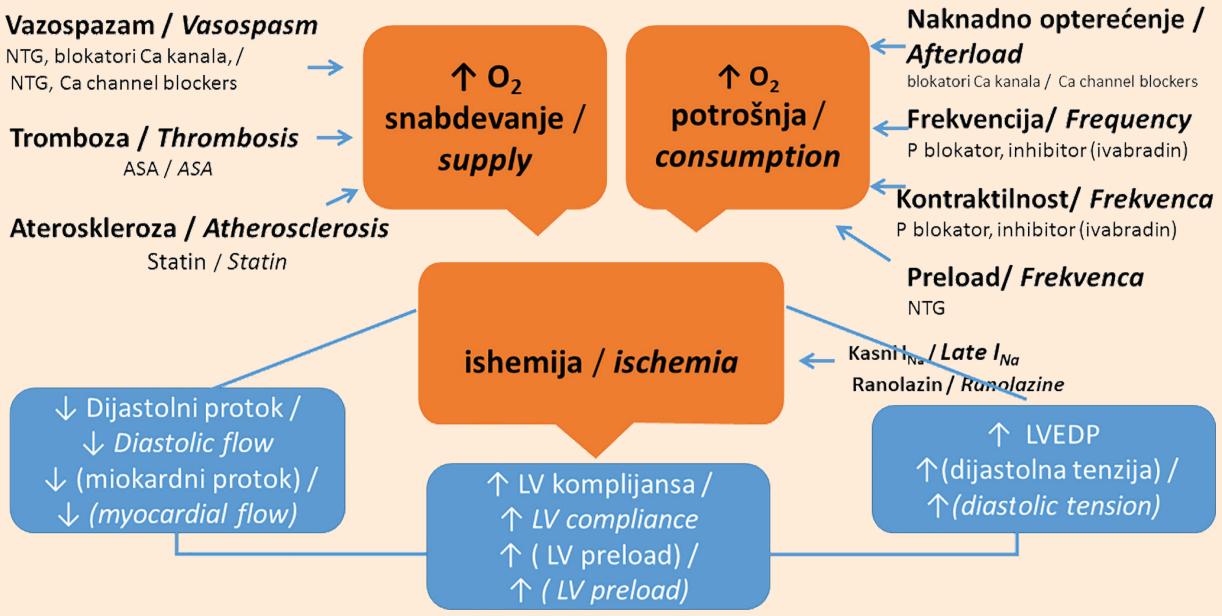
STABILNA ANGINA PEKTORIS

Ishemija srčanog mišića ima, kao patofiziološku osnovu, neadekvatan odnos između snabdevenosti i potreba miokarda za oksigenisanom krvlju (Slika 1) [1].

STABLE ANGINA PECTORIS

The pathophysiological basis of myocardial ischemia lies in the inadequate balance between the supply of oxygenated blood to the myocardium and its demand for oxygen (Figure 1) [1].



Slika 1. Patofiziološka osnova ishemije i mesta dejstva antianginoznih lekova
(Adapted from: Morrow DA, Boden WE. Chapter 57: Stable Ischemic Heart Disease. In: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th ed. (2012). Saunders; pp 1210-1269)

Figure 1. Pathophysiological basis of ischemia and the sites of the action of antianginal drugs
(Adapted from: Morrow DA, Boden WE. Chapter 57: Stable Ischemic Heart Disease. In: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th ed. (2012). Saunders; pp 1210-1269)

Ishemija srčanog mišića se klinički manifestuje kao anginozni bol sa tipičnom lokalizacijom, karakterom, intenzitetom i pratećim tegobama, pre svega netolerancijom napora [1]. Dvogodišnja studija praćenja, koju su sproveli Mozafarian i saradnici na skoro 9.000 pacijenata sa koronarnom arterijskom bolešću, potvrdila je da su simptomi angine pektoris nezavistan prediktor kardiovaskularnog mortaliteta, potencirajući fizičko ograničenje kao prediktor lošeg preživljavanja [2]. Dominantno, morfološki suspstrat stabilne angine pektoris je stabilan, nekomplikovani aterosklerotski plak, koji sužava koronarnu arteriju.

Dijagnostički algoritam obuhvata klinički pregled, neinvanzivne i invazivne dijagnostičke procedure, uključujući koronarografiju kao zlatni standard. Konzervativno lečenje stabilne angine pektoris, osim modifikacije načina života i eliminisanja tradicionalnih faktora rizika, podrazumeva primenu savremenih lekova, među kojima je i ranolazin, koji se izdvojio svojim jedinstvenim mehanizmom dejstva, efikasnošću i bezbednošću. Ranolazin je efikasan u redukciji manifestacija ishemije i angine, sa potencijalnim efektom na disfunkciju leve komore, pre svega dijastolnu i električnu nestabilnost [1-5].

Myocardial ischemia clinically presents as anginal pain with a typical localization, nature, intensity, and accompanying symptoms, primarily exercise intolerance [1]. A two-year follow-up study conducted by Mozaffarian et al. on nearly 9,000 patients with coronary artery disease confirmed that angina pectoris symptoms were an independent predictor of cardiovascular mortality, emphasizing physical limitation as a predictor of poor survival [2]. The predominant morphological substrate of stable angina pectoris is a stable, uncomplicated atherosclerotic plaque that narrows the coronary artery.

The diagnostic algorithm includes clinical examination, non-invasive and invasive diagnostic procedures, with coronary angiography as the gold standard. Conservative treatment of stable angina pectoris, in addition to lifestyle modification and elimination of traditional risk factors, involves the use of modern medications, among which ranolazine stands out due to its unique mechanism of action, efficacy, and safety. Ranolazine is effective in reducing manifestations of ischemia and angina, with a potential effect on left ventricular dysfunction, particularly diastolic dysfunction and electrical instability [1-5].

Medikamentozna terapija stabilne angine pektoris – osnovni principi

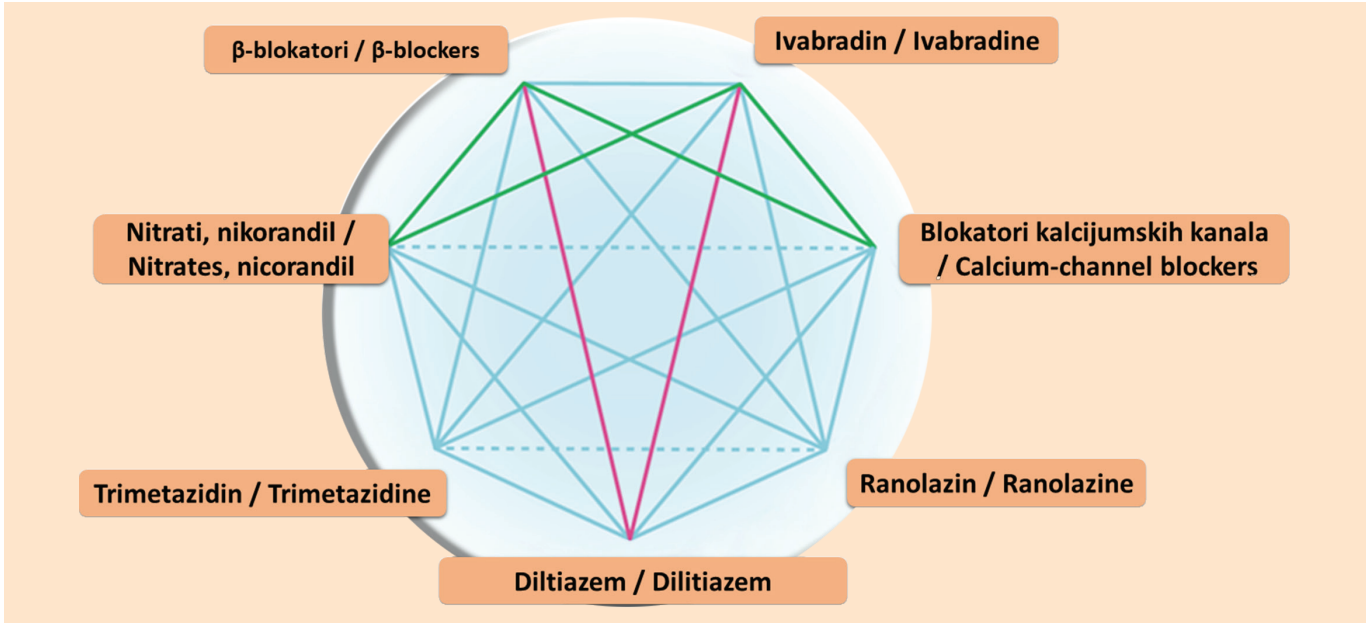
Konvencionalni antiishemijski lekovi smanjuju razvoj ishemije, primarno smanjujući determinante miokardnih zahteva za kiseonikom: broj srčanih otkucaja, krvni pritisak, predopterećenje, kontraktilnost. Veoma je bitna činjenica da ne postoji preklapanje između lekova koji poboljšavaju prognozu i lekova koji olakšavaju simptome, izuzev beta blokatora nakon infarkta miokarda. Prethodno rečeno govori u prilog hipotezi da simptomatska ishemija miokarda ne mora da bude bazičan mehanizam relevantan za prognozu, već da specifični mehanizmi koji utiču na funkciju trombocita i antiinflamatornu ili citokinima posredovanu neurohumoralnu aktivnost mogu da poboljšaju preživljavanje.

Aktuelne strategije lečenja su bazirane na ublažavanju simptoma pomoću lekova kroz uspostavljanje ravnoteže između snabdevanja miokarda kiseonikom i njegove potrošnje, što je relevantno za ishemiju miokarda i anginu pektoris. Svi agensi u ovoj kategoriji: beta blokatori, antagonisti kalcijumskih kanala, nitrati, aktivatori kalijumovih kanala, i blokatori sinusnog čvora, smanjuju zahteve miokarda za kiseonikom. Ovo se postiže kroz direktne efekte na srčani mišić ili indirektno, kroz kompleksne efekte na hemodinamske determinante. Antagonisti kalcijumskih kanala, nitrati i aktivatori kalijumovih kanala mogu dodatno da poboljšaju protok krvi i snabdevanje kiseonikom (Slika 2) [1-6].

Pharmacological treatment of stable angina pectoris – fundamental principles

Conventional anti-ischemic drugs reduce the development of ischemia, primarily by decreasing the determinants of myocardial oxygen demand: heart rate, blood pressure, preload, and contractility. It is important to note that there is no overlap between drugs that improve prognosis and those that alleviate symptoms, except for beta-blockers following myocardial infarction. The above supports the hypothesis that symptomatic myocardial ischemia is not necessarily the fundamental mechanism relevant to prognosis, but rather that specific mechanisms affecting platelet function and anti-inflammatory or cytokine-mediated neurohumoral activity may contribute to improved survival.

Current treatment strategies are based on symptom relief through pharmacological agents by restoring the balance between myocardial oxygen supply and demand, which is crucial for myocardial ischemia and angina pectoris. All pharmacological agents in this category – beta-blockers, calcium channel blockers, nitrates, potassium channel activators, and sinus node inhibitors – reduce myocardial oxygen demand. This is achieved either through direct effects on the myocardium or indirectly via complex effects on hemodynamic determinants. Calcium channel blockers, nitrates, and potassium channel activators can additionally improve blood flow and oxygen delivery (Figure 2) [1-6].



Slika 2. Individualizacija lečenja angine pektoris, tzv. diamond approach sa mogućim kombinacijama različitih klasa antianginoznih lekova (preporučene kombinacije – zelene linije; kombinacije koje se ne preporučuju – crvene linije; moguće kombinacije – plave pune linije; lekovi sa sličnom aktivnošću – plave isprekidane linije)
(Preuzeto iz: Ferrari R, Camici PG, Crea F, Danchin N, Fox K, Maggioni AP, et al. Expert consensus document: A 'diamond' approach to personalized treatment of angina. Nat Rev Cardiol. 2018 ;15(2):120-132.)

Figure 2. Individualization of angina pectoris treatment, the so-called diamond approach, with possible combinations of different classes of antianginal drugs (recommended combinations – green lines; combinations that are not recommended – red lines; possible combinations – blue solid lines; drugs with similar actions – blue dashed lines)
(From: Ferrari R, Camici PG, Crea F, Danchin N, Fox K, Maggioni AP, et al. Expert consensus document: A 'diamond' approach to personalized treatment of angina. Nat Rev Cardiol. 2018 ;15(2):120-132.)

U patofiziološkom smislu, u toku miokardne ishemije, razvija se intracelularno opterećenje kalcijumom sa konsekutivnim razvojem ishemije, uključujući i sistolnu i dijastolnu disfunkciju miokarda i električnu nestabilnost [1-6]. Ranolazin nema klinički značajan uticaj na varijable miokardne potrebe za kiseonikom ali potencira njihov antiishemijski efekat prevenirajući intracelularno opterećenje kalcijumom, smanjujući na taj način rigidnost srčanog mišića koja dovodi do redukcije miokardne perfuzije [7-10].

Nedavna studija ističe da se dozno-zavisno poboljšanje miokardne ishemije pri submaksimalnom i maksimalnom opterećenju, postignuto ranolazinom kod pacijenata sa stabilnom koronarnom bolešću, pripisuje poboljšanju miokardnog protoka bez merljivog uticaja na srčane otkucaje i krvni pritisak [9]. Iz navedenog proizilazi da ranolazin može biti idealna komplementarna dopuna standardnoj antianginoznoj terapiji.

Medikamentozna terapija ishemije

Antianginozni efekat lekova se ostvaruje na različitim nivoima, delujući komplementarno – sa jedne strane na povećano snabdevanje miokarda kiseonikom (smanjenjem vazospazma, progresije ateroskleroze i tromboze), a sa druge strane na smanjenu potrošnji kiseonika (smanjenjem predopterećenja i naknadnog opterećenja, srčane frekvencije i kontraktilnosti) (Slike 1 i 2) [7-10].

Ishemija na ćelijskom nivou remeti funkciju Na kanala kardiomiocita, koja je odgovorna za prolongirano povećanje kasne Na struje i konsekutivno prekomerno povećanje intracelularne koncentracije Na i Ca. Prekomerna intracelularna koncentracija Ca remeti dijastolnu relaksaciju i dovodi do povećanja dijastolnog opterećenja i potrošnje kiseonika, te do redukcije miokardnog protoka i snabdevanja kiseonikom. Na ovaj način nastala miokardna hipoperfuzija doprinosi pogoršanju ishemije i angine (Slika 3) [1-2].

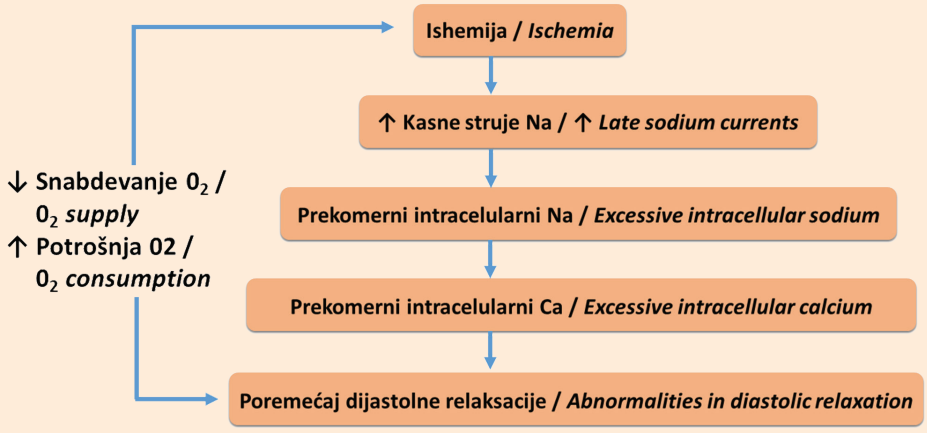
From a pathophysiological perspective, during myocardial ischemia, intracellular calcium overload develops, leading to the progression of ischemia, including both systolic and diastolic myocardial dysfunction, as well as electrical instability [1-6]. Ranolazine does not have a clinically significant impact on variables related to myocardial oxygen demand, however, it does enhance their anti-ischemic effect by preventing intracellular calcium overload. In doing so, it reduces myocardial stiffness that contributes to decreased myocardial perfusion [7-10].

A recent study emphasizes that the dose-dependent improvement in myocardial ischemia during submaximal and maximal exertion achieved with ranolazine in patients with stable coronary artery disease is attributed to enhanced myocardial perfusion, without a measurable effect on heart rate or blood pressure [9]. This suggests that ranolazine may serve as an ideal complementary addition to standard antianginal therapy.

Pharmacological treatment of ischemia

The antianginal effect of medications is achieved at different levels, acting in a complementary manner – on one hand, by increasing myocardial oxygen supply (by reducing vasospasm, atherosclerosis progression, and thrombosis), and on the other, by decreasing oxygen demand (by reducing preload and afterload, heart rate, and contractility) (Figures 1 and 2) [7-10].

At the cellular level, ischemia disrupts the function of sodium channels in cardiomyocytes, leading to a prolonged increase in late sodium current and consequently excessive intracellular accumulation of sodium and calcium. The elevated intracellular calcium concentration impairs diastolic relaxation, resulting in increased diastolic wall stress and oxygen consumption, as well as reduced myocardial perfusion and oxygen supply. The resulting myocardial hypoperfusion further contributes to the worsening of ischemia and angina (Figure 3) [1-2].

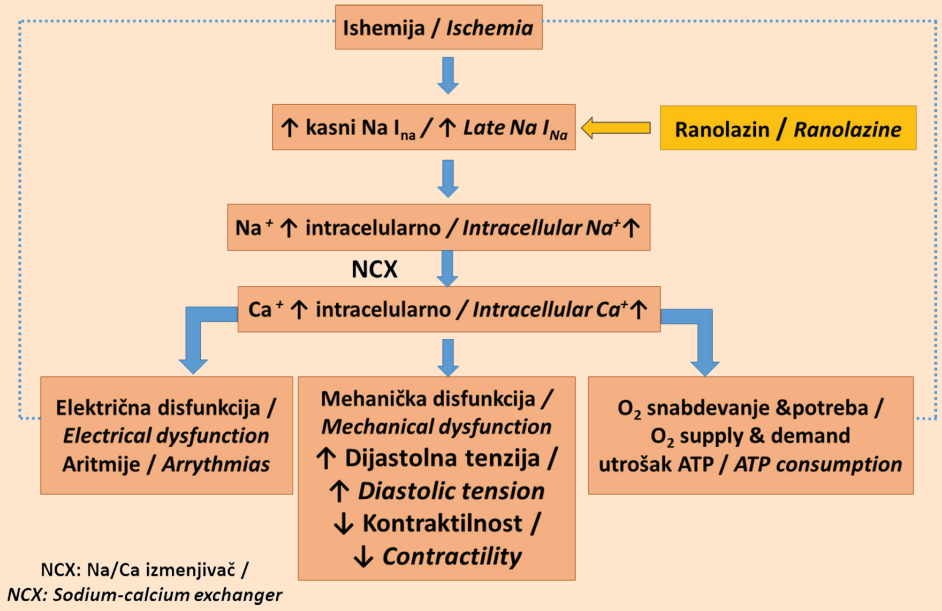


Slika 3. Patofiziologija miokardne hipoperfuzije

Figure 3. Pathophysiology of myocardial hypoperfusion

U ishemijom pogođenom miocitu, intracelularna koncentracija Na je povećana, što dovodi do povećanja intracelularnog nivoa Ca i posledične kontraktilne disfunkcije. Štaviše, povećano dijastolno opterećenje povećava mikrovaskularnu rezistenciju i potencira oštećenje energetske ravnoteže u ishemijom pogođenom miokardu. Formira se jedan začaran krug u kome dijastolna disfunkcija, koja se javlja kao posledica ishemije miokarda, povećava potrošnju energije i potencira energetski disbalans. Patološko pojačanje kasne Na struje doprinosi Na zavisnom opterećenju kalcijumom. Smanjenjem magnitude patološkog pojačanja kasne Na struje, ranolazin prevenira ili dovodi do smanjenja intracelularne koncentracije Ca i na taj način prekida značajan mehanizam u patofiziološkoj osnovi miokardne ishemije (Slika 4) [8].

In an ischemia-affected cardiomyocyte, intracellular sodium concentration increases, leading to elevated intracellular calcium levels and resulting in contractile dysfunction. Moreover, increased diastolic wall stress increases microvascular resistance and exacerbates the disturbance of the energy balance in the ischemic myocardium. This creates a vicious cycle wherein diastolic dysfunction – arising as a consequence of myocardial ischemia – increases energy consumption and further aggravates the energy imbalance. Pathological increase of the late sodium current contributes to sodium-dependent calcium overload. By reducing the magnitude of this pathological late sodium current increase, ranolazine prevents or decreases the intracellular calcium concentration, thereby interrupting a key mechanism in the pathophysiology of myocardial ischemia (Figure 4) [8].



Slika 4. Mehanizam antiishemijskog delovanja ranolazina
(Preuzeto iz: Hasenfuss G, Maier LS. Mechanism of action of the new anti-ischemia drug ranolazine. Clin Res Cardiol. 2008;97(4):222-6.)

Figure 4. Mechanism of the anti-ischemic action of ranolazine
(From: Hasenfuss G, Maier LS. Mechanism of action of the new anti-ischemia drug ranolazine. Clin Res Cardiol. 2008;97(4):222-6.)

Antiishemijski mehanizam, farmakokinetika i farmakodinamika ranolazina

Osnovu delovanja ranolazina predstavlja poboljšanje regionalnog koronarnog protoka u zoni ishemije. Antianginalno delovanje ranolazina se ostvaruje bez značajnijeg uticaja na frekvenciju i visinu arterijskog pritiska. U kliničkim studijama je registrovano zanemarljivo smanjenje srednje frekvencije (< 2 /min) i sistolnog pritiska (< 3 mmHg) [9-10]. Antianginalna efikasnost ne zavisi od pola i životnog doba, kao ni od komorbiditeta (pridruženog dijabetesa melitusa), ali je povezana za povoljnim metaboličkim profilom kod pacijenata sa šećernom bolešću (redukcija HbA1c) [9, 11-12]. Osnov-

Anti-ischemic mechanism, pharmacokinetics, and pharmacodynamics of ranolazine

The primary mechanism of ranolazine action is the improvement of regional coronary blood flow in the ischemic zone. Its antianginal effect is achieved without a significant impact on heart rate or arterial blood pressure. Clinical studies have reported only negligible reductions in average heart rate (< 2 bpm) and systolic blood pressure (< 3 mmHg) [9-10]. The antianginal efficacy of ranolazine is not dependent on gender, age, or comorbidities (such as diabetes mellitus), but it is associated with a favorable metabolic profile in diabetic patients (reduction in HbA1c levels) [9, 11-12]. The key

Tabela 1. Osnovne farmakokinetske i farmakodinamske karakteristike ranolazina

Ranolazin	Farmakokinetika i farmakodinamika
Bioraspoloživost	35% – 50%
Maksimalna koncentracija	2–6 časova
Poluvreme eliminacije	7 časova
Stabilno delovanje	3 dana
Vezivanje za proteine plazme	62%
Ekskrecija	73% putem urina, 25% putem fecesa
Interakcije sa lekovima (Oprez potreban kod korišćenja drugih inhibitora CYP3A4 i lekova koji utiču na produženje QT intervala)	Moguća INTERAKCIJA sa digoksinom, simvastatinom, ciklosporinom, diltiazemom, verapamilom, ketokonazolom, makrolidima
Interakcije sa hranom	Ne preporučuje se unos grejpfruta.
Ekstenzivan hepatični metabolizam	5% doze se izlučuje nepromenjeno putem urina i fecesa
Primarni metabolizam	Preko CYP3A4
Minorni metabolizam	Preko CYP2D6
Maksimalna preporučena dnevna doza	2 x 750 mg

(Preuzeto i modifikovano iz: Hasenfuss G, Maier LS. Mechanism of action of the new anti-ischemia drug ranolazine. Clin Res Cardiol. 2008;97(4):222-6; Sažetak karakteristika leka Ranexa, februar 2021)

Table 1. Key pharmacokinetic and pharmacodynamic properties of ranolazine

Ranolazine	*Pharmacokinetics and pharmacodynamics*
Bioavailability	35% – 50%
Maximum concentration	2–6 hours
Elimination half-life	7 hours
Stable action	3 days
Plasma protein binding	62%
Route of elimination	73% renally; 25% in the feces
Drug interactions (Caution is necessary when using other CYP3A4 inhibitors and drugs that affect QT interval prolongation)	Possible INTERACTION with digoxin, simvastatin, cyclosporine, diltiazem, verapamil, ketoconazole, macrolides
Food interactions	Grapefruit consumption is not recommended.
Extensive hepatic metabolism	An estimated 5% of the dose is eliminated as unchanged drug, renally and in the feces.
Primary metabolism	Through CYP3A4
Minor metabolism	Through CYP2D6
Maximum recommended daily dose	2 x 750 mg

(Adapted and modified from: Hasenfuss G, Maier LS. Mechanism of action of the new anti-ischemia drug ranolazine. Clin Res Cardiol. 2008;97(4):222-6; Summary of drug characteristics for Ranexa, February 2021)

ne farmakokinetske i farmakodinamske karakteristike ranolazina su date u Tabeli 1.

Antianginalna terapija u svakodnevnoj kliničkoj praksi

Cilj antianginalnih lekova je da obezbede adekvatno olakšanje simptoma angine kod pacijenata sa hroničnim koronarnim sindromom (engl. *chronic coronary syndrome - CCS*), delimično nezavisno od njihovog efekta ili nedostatka efekta na *MACE* (engl. *major adverse cardiac events*). Početna monoterapija, sa naknadnom eskalacijom na kombinaciju antianginalnih lekova u slučaju neadekvatnih ublažavanja simptoma, predstavlja racionalan pristup [13].

Prema aktuelnim evropskim vodičima, terapijski ciljevi u medikamentoznom lečenju stabilne angine pektoris mogu se podeliti u tri grupe:

1. neposredno kratkoročno olakšanje tegoba
2. simptomatska terapija
3. etiološko lečenje sa poboljšanjem prognoze [1-2,14].

U tom smislu, optimizacijom terapije se postiže poboljšanje kvaliteta života (ublažavanje simptoma), smanjenje mortaliteta i morbiditeta, redukcija progresije bolesti i indukcija regresije [1-2,14].

U ovom kontekstu, empirijski pristup započinjanja sa beta-blokatorom može se preporučiti kod mnogih pacijenata sa hroničnim koronarnim sindromom, osim ako ne postoje kontraindikacije ili ako su drugi lekovi

pharmacokinetic and pharmacodynamic properties of ranolazine are presented in Table 1.

Antianginal therapy in everyday clinical practice

The goal of antianginal drugs is to provide adequate relief of angina symptoms in patients with chronic coronary syndrome (CCS), somewhat independently of their effect or lack thereof on major adverse cardiac events (MACE). Initial monotherapy, followed by escalation to combination antianginal therapy in cases of inadequate symptom relief, represents a reasonable approach [13].

According to current European guidelines, therapeutic goals in the pharmacological treatment of stable angina pectoris can be categorized into three groups:

1. immediate short-term relief of symptoms
2. symptomatic therapy
3. etiological treatment with improved prognosis [1-2,14].

Therapy optimization leads to improved quality of life (symptom relief), reduced mortality and morbidity, slowed disease progression, and induction of regression [1-2,14].

In this context, an empirical approach of starting with a beta-blocker may be recommended for many patients with chronic coronary syndrome, unless there are contraindications or unless other drugs are more

prikladniji od beta-blokatora (npr. pacijenti sa niskim brojem otkucaja srca i/ili krvnim pritiskom) [15].

Preporučuje se da izbor antianginalnih lekova bude individualizovan i prilagođen karakteristikama pacijenta, uzimajući u obzir hemodinamski profil, prisustvo komorbiditeta, postojeću terapiju (komedikaciju), podnošljivost lekova, kao i osnovnu patofiziologiju angine. Takođe, važno je razmotriti lokalnu dostupnost i cenu terapije (razred preporuke: Ic).

U skladu sa aktuelnim preporukama, treba razmotriti dugodelujuće nitrate ili ranolazin kao dodatnu terapiju kod pacijenata kod kojih beta-blokatori i/ili antagonisti kalcijumskih kanala ne omogućavaju zadovoljavajuću kontrolu simptoma, ili kao deo inicijalne terapije kod pažljivo odabranih pacijenata (razred preporuke: IIa) [13-15].

Trenutna empirijska paradigma za izbor antianginalne terapije podrazumeva hijerarhijski, postupni pristup koji uključuje lekove prve linije (beta-blokatori, antagonisti kalcijumskih receptora) i lekove druge linije (nitrati dugog dejstva, nikorandil, ranolazin, ivabradin, trimetazidin). Ovaj pristup potencira koncept da medicinska terapija za kontrolu simptoma kod hroničnog koronarnog sindroma (*CSS*) treba da bude prilagođena hemodinamskom profilu svakog pacijenta (krvni pritisak, srčana frekvencija), komorbiditetima (naročito kod prisustva srčane slabosti), istovremenom uzimanju lekova koji imaju potencijalne interakcije sa antianginalnim lekovima, istovremeno uzimajući u obzir patofiziološku osnovu ishemije miokarda kod svakog pacijenta, kao i lokalnu dostupnost različitih lekova.

Za mnoge pacijente sa hroničnim koronarnim sindromom, početna terapija lekovima treba da uključuje beta blokator i/ili blokator kalcijumskih kanala (engl. *calcium channel blockers – CCB*). Ako se simptomi angine ne mogu uspešno kontrolisati početnom monoterapijom beta-blokatorom ili blokatorom kalcijumskih kanala, treba razmotriti kombinaciju beta-blokatora i dihidropiridina-blokatora kalcijumskih kanala (*DHP-CCB*), osim ako nije kontraindikovana (razred preporuke: IIa).

Drugi antianginalni lekovi (nitrati dugog dejstva, ranolazin, nikorandil, trimetazidin, ili ivabradin kod pacijenata sa sistolnom disfunkcijom leve komore) mogu se dodati uz beta-blokator i/ili *CCB*, ili kao deo početne kombinovane terapije kod adekvatno odabranih pacijenata kada je lečenje beta-blokatorom i/ili blokatorom kalcijumskih kanala kontraindikovano ili se slabo toleriše, ili kada su simptomi angine neadekvatno kontrolisani (Slika 5) (razred preporuke: IIa).

Kada je u pitanju izbor antianginalnih lekova, kratkodelujući nitrati se preporučuju za trenutno ublažavanje angine (razred preporuke: Ib). Kada su propisani nitrati dugog dejstva, treba razmotriti interval bez nitrata

suitable than beta-blockers (e.g., patients with a low heart rate and/or low blood pressure) [15].

It is recommended that the choice of antianginal drugs be individualized and tailored to the patient's characteristics, taking into account the hemodynamic profile, presence of comorbidities, current therapy (comedication), drug tolerability, as well as the underlying pathophysiology of angina. Additionally, local availability and cost of medications should also be considered (recommendation grade: Ic).

Per current recommendations, long-acting nitrates or ranolazine should be considered as add-on therapy in patients whose symptoms are not adequately controlled by beta-blockers and/or calcium channel blockers, or as part of initial therapy in carefully selected patients (recommendation grade: IIa) [13-15].

The current empirical paradigm for selecting antianginal therapy involves a hierarchical, stepwise approach that includes first-line drugs (beta-blockers, calcium channel blockers) and second-line drugs (long-acting nitrates, nicorandil, ranolazine, ivabradine, trimetazidine). This approach emphasizes the concept that medical therapy for symptom control in chronic coronary syndrome (CCS) should be tailored to the hemodynamic profile of each patient (blood pressure, heart rate), comorbidities (especially in the presence of heart failure), concurrent use of medications with potential interactions with antianginal drugs, while also considering the pathophysiological basis of myocardial ischemia in each patient, as well as the local availability of different drugs.

For many patients with chronic coronary syndrome, initial drug therapy should include a beta-blocker and/or a calcium channel blocker (CCB). If angina symptoms cannot be adequately controlled with initial monotherapy with a beta-blocker or calcium channel blocker, a combination of a beta-blocker and a dihydropyridine calcium channel blocker (DHP-CCB) should be considered, unless contraindicated (recommendation grade: IIa).

Other antianginal drugs (long-acting nitrates, ranolazine, nicorandil, trimetazidine, or ivabradine in patients with left ventricular systolic dysfunction) can be added to beta-blockers and/or CCBs, or applied as part of initial combination therapy in appropriately selected patients when treatment with beta-blockers and/or calcium channel blockers is contraindicated or poorly tolerated, or when angina symptoms are inadequately controlled (Figure 5) (recommendation grade: IIa).

As to the choice of antianginal drugs, short-acting nitrates are recommended for immediate relief of angina (recommendation grade: Ib). When long-acting nitrates are prescribed, a nitrate-free or low-nitrate in-

ili sa niskim sadržajem nitrata da bi se smanjila tolerancija (razred preporuke: IIa). Nikorandil ili trimetazidin se mogu smatrati dodatnom terapijom kod pacijenata sa neadekvatnom kontrolom simptoma dok su na terapiji beta-blokatorima i/ili blokatorima kalcijumskih kanala, ili delom početnog lečenja kod pravilno odabranih pacijenata (razred preporuke: IIb).

Ivabradin treba smatrati dodatnom antianginalnom terapijom kod pacijenata sa sistolnom disfunkcijom leve komore (*LVEF* < 40%) i neadekvatnom kontrolom simptoma, ili delom početnog lečenja kod pravilno odabranih pacijenata (razred preporuke: IIa). Ivabradin se ne preporučuje kao dodatna terapija kod pacijenata sa *CCS, LVEF* > 40% i bez kliničke srčane insuficijencije (razred preporuke: IIIb). Ne preporučuje se kombinacija ivabradina sa ne-*DHP-CCB* (verapamil ili diltiazem) ili drugim jakim inhibitorima CYP3A4 (razred preporuke: IIIb) [13-15].

Nitrati se ne preporučuju kod pacijenata sa hipertrofičnom kardiomiopatijom ili u kombinaciji sa inhibitorima fosfodiesteraze (razred preporuke: IIIb). Ovi lekovi mogu zahtevati oprez ili mogu biti kontraindikovani kod određenih pacijenata sa niskim krvnim pritiskom, (beta-blokatori i *DHP-CCB*), dijabetes melitusom (beta-blokatori), poremećajima atrioventrikularne provodljivosti (beta-blokatori i ne-*DHP-CCB*), hroničnom opstruktivnom bolešću pluća (neselektivni beta-blokatori) [13-15].

Za inicijalnu terapiju treba razmotriti ivabradin, nikorandil, dugodelujuće nitrate, ranolazin ili trimetazidin kod pacijenata sa netolerancijom ili kontraindikacijama na beta-blokatore i/ili blokatore kalcijumskih kanala; ranolazin i trimetazidin kod pacijenata sa mikrovaskularnom anginom; nikorandil ili nitrati kod pacijenata sa spazmom koronarnih arterija (razred preporuke: IIb) [13-15].

Ovi lekovi mogu da izazovu poremećaj atrioventrikularne provodljivosti i treba da se primenjuju oprezno kod pacijenata sa perifernom arterijskom bolešću (engl. *peripheral arterial disease – PAD*) i hroničnom opstruktivnom bolešću pluća (HOBP). Blokatori kalcijumskih kanala zahtevaju oprez kod pacijenata sa srčanom insuficijencijom sa redukovanom ejekcionom frakcijom (engl. *heart failure with reduced ejection fraction – HFrEF*). Ranolazin i trimetazidin su racionalne alternative kao deo antianginalne kombinovane terapije kod pacijenata sa niskim otkucajima srca [13-15].

Kod pacijenata sa srčanom insuficijencijom sa očuvanom ejekcionom frakcijom (engl. *heart failure with preserved ejection fraction – HFpEF*), pored diuretika za lečenje kongestije, preporučuju se SGLT2 inhibitori za poboljšanje ishoda (razred preporuke: I). Pored toga, beta-blokatori, dugodelujući nitrati, *CCB*, ivabradin, ranolazin, trimetazidin, nikorandil i njihove kombinacije treba da se razmotre kod pacijenata sa *HFpEF* i koronarterval should be considered to reduce tolerance (recommendation grade: IIa). Nicorandil or trimetazidine may be considered as add-on therapy in patients with inadequate symptom control while on beta-blockers and/or calcium channel blockers, or as part of initial therapy in appropriately selected patients (recommendation grade: IIb).

Ivabradine should be considered as additional antianginal therapy in patients with left ventricular systolic dysfunction (LVEF < 40%) and inadequate symptom control, or as part of initial treatment in appropriately selected patients (recommendation grade: IIa). Ivabradine is not recommended as add-on therapy in patients with CCS, LVEF > 40%, and no clinical heart failure (recommendation grade: IIIb). The combination of ivabradine with non-DHP CCBs (verapamil or diltiazem) or other strong CYP3A4 inhibitors is not recommended (recommendation grade: IIIb) [13-15].

Nitrates are not recommended in patients with hypertrophic cardiomyopathy or combined with phosphodiesterase inhibitors (recommendation grade: IIIb). These drugs may require caution or may be contraindicated in certain patients, such as those with low blood pressure (beta-blockers and DHP-CCBs), diabetes mellitus (beta-blockers), atrioventricular conduction disorders (beta-blockers and non-DHP-CCBs), or chronic obstructive pulmonary disease (non-selective beta-blockers) [13-15].

For initial therapy, ivabradine, nicorandil, long-acting nitrates, ranolazine, or trimetazidine should be considered in patients with intolerance or contraindications to beta-blockers and/or calcium channel blockers. Ranolazine and trimetazidine may be considered in patients with microvascular angina, while nicorandil or nitrates may be considered in patients with coronary artery spasm (recommendation grade: IIb) [13-15].

These drugs may cause atrioventricular conduction disturbances and should be used with caution in patients with peripheral arterial disease (PAD) and chronic obstructive pulmonary disease (COPD). Calcium channel blockers require caution in patients with heart failure with reduced ejection fraction (HFrEF). Ranolazine and trimetazidine are reasonable alternatives as part of combination antianginal therapy in patients with a low heart rate [13-15].

In patients with heart failure with preserved ejection fraction (HFpEF), in addition to diuretics for treating congestion, SGLT2 inhibitors are recommended to improve outcomes (recommendation grade: I). Additionally, beta-blockers, long-acting nitrates, calcium channel blockers (CCBs), ivabradine, ranolazine, trimetazidine, nicorandil, and their combinations should be considered in patients with HFpEF and coronary artery disease (CAD) for angina relief, though

nom arterijskom bolešću (KAB) za ublažavanje angine, ali bez efekta na srčanu slabost i krajnje ishode u koronarnom sindromu [13-15].

Redukovane doze rivaroksabana mogu se razmotriti kod pacijenata sa KAB i srčanom insuficijencijom, *LVEF* > 40% i sinusnim ritmom kada su pod visokim rizikom od moždanog udara, i sa malim rizikom od hemoragije [15].

Lečenje simptoma angine kod pacijenata sa neokludiranom anginom koronarne arterije/neokludiranom ishemijom koronarne arterije (engl. *angina with nonobstructive coronary arteries/ischemia with nonobstructive coronary arteries - ANOCA/INOCA*) predstavlja izazov jer pacijenti čine heterogenu grupu i nedostaju randomizovana ispitivanja. Jedna mala studija je pokazala da je stratifikovani algoritam antianginalne terapije zasnovan na koronarnom funkcionalnom testiranju doveo do ublažavanja simptoma angine i poboljšanja kvaliteta života u poređenju sa kontrolnom grupom lečenom standardnom terapijom.

Kod pacijenata sa mikrovaskularnom anginom i smanjenom rezervom koronarnog protoka (engl. *coronary flow reserve – CFR*) i/ili povećanim indeksom otpora mikrocirkulacije (engl. *index of microcirculatory resistance – IMR*), što može odražavati remodeliranje arteriola, koriste se beta-blokatori, *CCB*, ranolazin i inhibitori angiotenzin konvertujućeg enzima (engl. *angiotensin-converting enzyme inhibitors – ACE-I*). Kod ovih pacijenata, antiishemična terapija sa amlodipinom je dovela do značajnog poboljšanja.

U lečenju pacijenata sa epikardijalnim ili mikrovaskularnim spazmom nakon acetilholinskog testa (engl. *acetylcholine testing – ACH testing*), antagoniste kalcijuma treba smatrati terapijom prve linije. Kod pacijenata sa teškom vazospastičnom anginom, može biti neophodna primena neuobičajeno visokih doza antagonista kalcijuma (npr. diltiazem u dozi od 2 × 200 mg dnevno ili čak do 960 mg dnevno), a u određenim slučajevima i kombinacija nedihidropiridina (kao što je diltiazem) i dihidropiridinskih blokatora kalcijumskih kanala (kao što je amlodipin).

Važno je napomenuti da, u maloj studiji tokom koje se u periodu od šest nedelja primenjivala oralna terapija diltiazemom u dozi do 360 mg dnevno ili placebo, kod pacijenata sa koronarnom mikrovaskularnom disfunkcijom (engl. *coronary microvascular dysfunction – CMD*), nije utvrđeno značajno poboljšanje simptoma ili kvaliteta života. Ipak, terapija diltiazemom je dovela do smanjenja prevalencije epikardijalnog spazma. Nikorandil, kombinovani vazodilatator koji deluje putem nitratno i kalijum zavisnih kanala, može predstavljati efikasnu alternativu, iako su neželjeni efekti česti (razred preporuke: IIb) [15].

without effect on heart failure progression or end outcomes in coronary syndrome [13-15].

Reduced doses of rivaroxaban may be considered in patients with coronary artery disease (CAD) and heart failure, LVEF > 40%, and sinus rhythm, who are at high risk of stroke and have a low risk of hemorrhage [15].

Managing angina symptoms in patients with angina with nonobstructive coronary arteries/ischemia with nonobstructive coronary arteries (ANOCA/INOCA) is challenging, as these patients represent a heterogeneous group and randomized trials are lacking. A small study showed that a stratified algorithm for antianginal therapy based on coronary functional testing led to symptom relief and improved quality of life compared to the control group treated with standard therapy.

In patients with microvascular angina and reduced coronary flow reserve (CFR) and/or increased index of microcirculatory resistance (IMR), which may reflect arteriolar remodeling, beta-blockers, CCB, ranolazine, and angiotensin-converting enzyme inhibitors (ACE-I) are administered. In these patients, anti-ischemic therapy with amlodipine has led to significant improvement.

In the treatment of patients with epicardial or microvascular spasm after acetylcholine testing (ACH testing), calcium antagonists should be considered as first-line therapy. In patients with severe vasospastic angina, the use of unusually high doses of calcium antagonists (e.g., diltiazem at a dose of 2 × 200 mg daily or even up to 960 mg daily) and in certain cases a combination of nondihydropyridines (such as diltiazem) and dihydropyridine calcium channel blockers (such as amlodipine) may be necessary.

It is important to note that, in a small study wherein oral therapy with diltiazem at a dose of up to 360 mg per day or a placebo was administered for six weeks, in patients with coronary microvascular dysfunction (CMD), no significant improvement in symptoms or quality of life was found. However, diltiazem therapy reduced the prevalence of epicardial spasm. Nicorandil, a combined vasodilator that acts via nitrate- and potassium-dependent channels, may represent an effective alternative, although side effects are common (recommendation grade: IIb) [15].

Combination treatment with ranolazine, an antianginal agent that improves myocyte relaxation and ventricular compliance by reducing sodium and calcium overload, has shown significant results. In patients with INOCA, spinal cord stimulation is an option for those with refractory complaints after drug therapy [15].

Due to inconsistencies in data collection over time, there is no clear and well-founded evidence to support the existence of clearly defined first- and second-line

Lečenje kombinacijom sa ranolazinom, antianginalnim agensom koji poboljšava relaksaciju miocita i ventrikularnu komplijansu smanjenjem preopterećenja natrijumom i kalcijumom, pokazalo je zapažene rezultate. Kod pacijenata sa neokludiranom ishemijom koronarne arterije, stimulacija kičmene moždine je opcija za one sa refraktornim tegobama nakon medikamentozne terapije [15].

Zbog nedoslednosti u prikupljanju podataka tokom vremena, ne postoje jasni i utemeljeni dokazi koji bi potkrepili postojanje jasno definisane antianginalne terapije prve i druge linije. I dalje nije dovoljno razjašnjeno da li dugodelujući nitrati, ranolazin, nikorandil, ivabradin, trimetazidin ili njihove kombinacije pružaju veće olakšanje simptoma angine u poređenju sa beta-blokatorima ili blokatorima kalcijumskih kanala [15].

Ranolazin u pivotalnim studijama i svakodnevnoj kliničkoj praksi

Do sada nisu sprovedena velika randomizovana ispitivanja koja bi direktno uporedila klasične, istorijski prve odobrene antianginalne lekove (beta-blokatore i blokatore kalcijumskih kanala – *CCB*) sa novijim antiishemijskim agensima kao što su ivabradin, nikorandil, ranolazin i trimetazidin. Noviji lekovi su uglavnom ispitivani u manjim studijama koje su procenjivale njihovu neinferiornost u poređenju sa beta-blokatorima ili blokatorima kalcijumskih kanala, ili u većim ispitivanjima, gde su posmatrani kao dodatak standardnoj terapiji zasnovanoj na beta-blokatorima i/ili blokatorima kalcijumskih kanala. U prilog tezi da ranolazin treba dati pre beta blokatora kod hronične angine govori i nedavna studija sprovedena na 158 pacijenata sa anginoznim simptomima. U toj studiji, ranolazin je poboljšao toleranciju na fizički napor, smanjio naporom indukovanu ishemiju i anginu, pokazujući efikasnost najmanje jednaku atenololu, pri čemu nije imao uticaj na arterijski pritisak ni puls [16].

Jedna od pivotalnih studija koja je etablirala mesto ranolazina u lečenju pacijenata sa stabilnom anginom pektoris bila je dvostruko slepa, placebom kontrolisana studija sa ukrštanjem modaliteta lečenja u četiri perioda *MARISA* (*Monotherapy Assessment of Ranolazine in Stable Angina*) koja je uključila 175 pacijenata lečenih ranolazinom u dve dnevne doze kao monoterapijom angine. U poređenju sa placebom, ranolazin je pokazao održiv dozno zavisni efekat, povećao toleranciju na napor i smanjio naporom indukovanu ishemiju bez klinički merljivih hemodinamskih efekata, a da pri tom kratkoročno preživljavanje nije bilo kraće od očekivanog [17].

U skladu sa prethodno citiranom studijom su i rezultati *CARISA* studije (*Combination Assessment of Ranolazine in Stable Angina*) sprovedene na 450 pacijenata kod kojih je konvencionalnoj antiishemijskoj terapiji

antianginal therapy. Whether long-acting nitrates, ranolazine, nicorandil, ivabradine, trimetazidine, or their combinations provide greater relief of angina symptoms compared to beta-blockers or calcium channel blockers remains unclear [15].

Ranolazine in pivotal studies and daily clinical practice

To date, no large, randomized trials have directly compared the classic, historically first-approved antianginal agents (beta-blockers and calcium channel blockers - CCBs) with newer anti-ischemic drugs such as ivabradine, nicorandil, ranolazine, and trimetazidine. Newer drugs have mostly been investigated in smaller studies evaluating their non-inferiority compared to beta-blockers or calcium channel blockers, or in larger trials, where they have been examined as an addition to standard therapy founded on beta-blockers and/or calcium channel blockers. A recent study conducted on 158 patients with angina symptoms also supports the thesis that ranolazine should be given rather than beta-blockers in chronic angina. In this study, ranolazine improved exercise tolerance, reduced exercise-induced ischemia and angina, showing efficacy at least equal to atenolol, with no effect on arterial pressure or heart rate [16].

One of the pivotal studies that established the role of ranolazine in the treatment of patients with stable angina pectoris was the double-blind, placebo-controlled, four-period crossover study MARISA (Monotherapy Assessment of Ranolazine in Stable Angina), which included 175 patients treated with ranolazine in two daily doses as monotherapy for angina. Compared to placebo, ranolazine demonstrated a sustained, dose-dependent effect, increased exercise tolerance, and reduced exercise-induced ischemia without clinically significant hemodynamic effects, and without any reduction in short-term survival compared to expectations [17].

Consistent with the previously cited study are the results of the CARISA study (Combination Assessment of Ranolazine in Stable Angina), conducted on 450 patients in whom ranolazine was added to conventional anti-ischemic therapy at standard doses, and in whom long-term survival was not shorter than expected. The same applies to the post-hoc CARISA analysis, which recorded improved exercise tolerance and symptom relief, along with a reduction in exercise-induced ischemia and hemodynamic neutrality in patients with more severe forms of angina who received ranolazine in addition to standard antianginal therapy, with maximum doses of beta-blockers and calcium channel antagonists [18].

u standardnim dozama dodat ranolazin i kod kojih dugoročno preživljavanje nije bilo kraće od očekivanog. Isto važi i za *post-hoc CARISA* analizu gde je zabeleženo poboljšanje tolerancije na napor i ublažavanje simptoma, uz smanjenje naporom indukovane ishemije i hemodinamsku inerciju kod pacijenata sa težom formom angine kojima je na standardnu antianginoznu terapiju maksimalnim dozama beta blokatora i kalcijumskih antagonista dodat ranolazin [18].

Značajno smanjenje učestalosti anginoznih napada, a samim tim i upotrebe nitroglicerina, zabeleženo je i u velikoj studiji Stouna i saradnika, gde je pacijentima na monoterapiji amlodipinom u maksimalnoj dnevnoj dozi dodat ranolazin. Interesantno je da su pacijenti sa težom formom angine imali značajniji efekat terapije bez hemodinamskih promena [19].

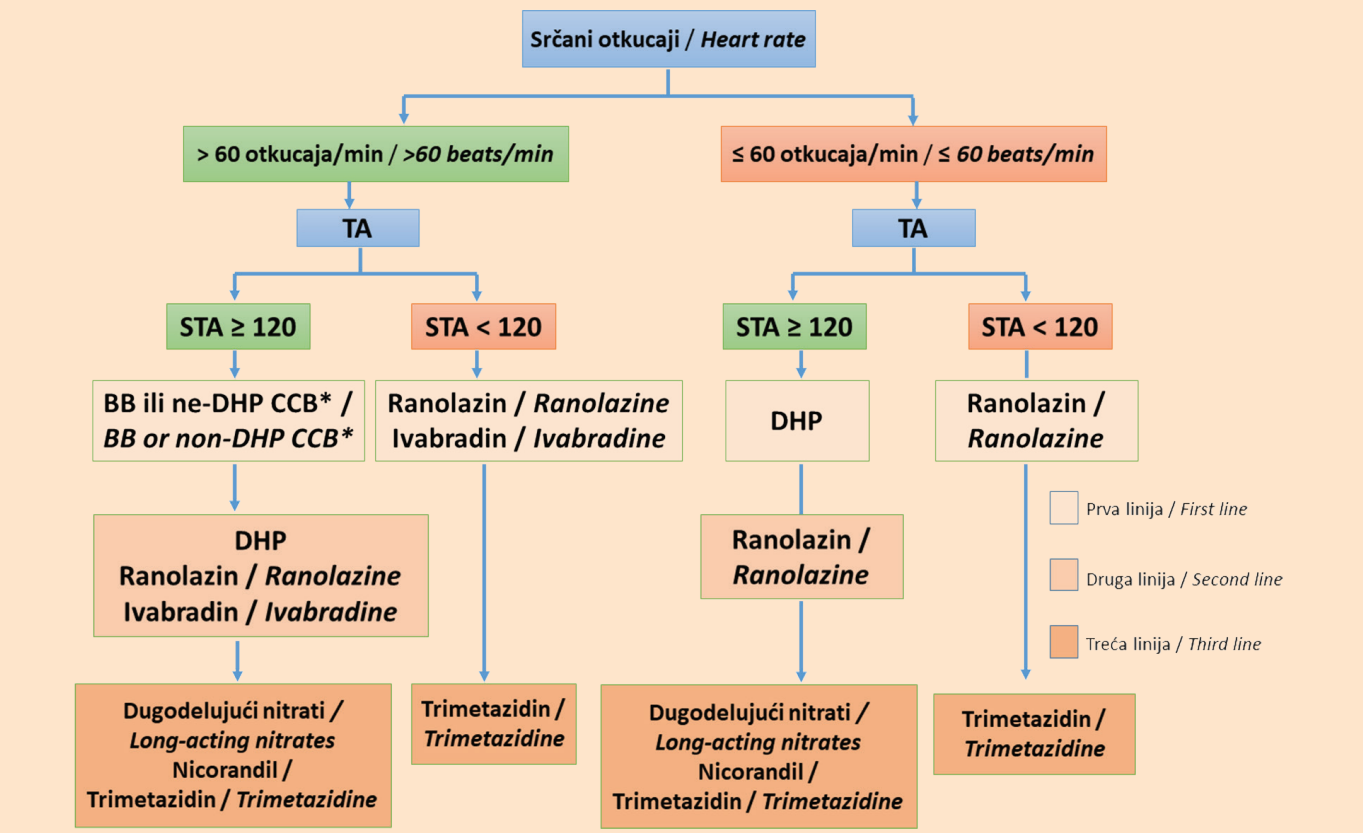
Antiishemijski efekat je konzistentan kroz sve podgrupe pacijenata sa hroničnom anginom, uključujući i pacijente sa dijabetesom, kod kojih je, osim održivog antianginoznog efekta u smislu smanjenja učestalosti ataka angine i korišćenja nitroglicerina tokom lečenja, zabeležen povoljniji metabolički profil i redukcija HbA1c, nezavisno od inicijalnih vrednosti (Slika 5) [12,20-21].

A significant reduction in the frequency of anginal attacks – and consequently, in the use of nitroglycerin – was also recorded in a large study by Stone et al., wherein ranolazine was added to the therapy of patients already receiving amlodipine monotherapy at the maximum daily dose. Interestingly, patients with more severe forms of angina experienced a more pronounced therapeutic effect without hemodynamic changes [19].

The anti-ischemic effect is consistent across all subgroups of patients with chronic angina, including patients with diabetes, in whom – besides the sustained antianginal effect in terms of reduced frequency of angina attacks and nitroglycerin use during treatment – a more favorable metabolic profile and a reduction in HbA1c were observed, regardless of baseline values (Figure 5) [12,20-21].

The results of the ROLE (Ranolazine Open Label Experience) study, which included 746 patients with chronic angina, confirmed the long-term safety of ranolazine use in this population. Treatment was associated with symptomatic improvement and good tolerance of therapy, with no observed increase in mortality [21].

In addition to patients with chronic angina, pa-



Slika 5. Preporuke za lečenje hroničnog koronarnog sindroma

*Normalna ejekciona frakcija; **Srčani otkucaji >70/min

TA = arterial blood pressure (Lat. tensio arterialis); BB = beta bloker; CCB = kalcijumski antagonista; DHP = dihidropiridin; STA = sistolni arterijski krvni pritisak

Figure 5. Treatment recommendations for chronic coronary syndrome

*Normal ejection fraction; **Heart rate >70 bpm

TA = arterial blood pressure (Lat. tensio arterialis); BB = beta-blocker; CCB = calcium channel blocker; DHP = dihydropyridine; STA = systolic arterial blood pressure

Rezultati ROLE (*Ranolazine Open Label Experience*) studije, koja je obuhvatila 746 pacijenata sa hroničnom anginom, potvrdili su dugoročnu bezbednost primene ranolazina u ovoj populaciji. Lečenje je bilo praćeno simptomatskim poboljšanjem i dobrom tolerancijom terapije bez zabeleženog povećanja mortaliteta [21].

Pored pacijenata sa hroničnom anginom, i pacijenti sa akutnom koronarnim sindromima bez elevacije ST segmenta imaju merljive dobrobiti kada se ranolazin doda standardnoj antiishemijskoj terapiji. Efekat je održiva redukacija simptoma ishemije, bez uticaja na kardiovaskularni morbiditet i mortalitet kod ovih bolesnika [22]. Zabeležen je pozitivan uticaj ranolazina na miokardnu perfuziju, pa i pacijenti sa endotelnom disfunkcijom ostvaruju jasno subjektivno i objektivno poboljšanje u smislu simptomatskog olakšanja tegoba i popravljanja ishemijskog deficita [23].

O sveukupnoj koristi optimizacije antianginozne terapije ranolazinom svedoči i nedavna ekonomska metaanaliza koja je obuhvatila sedam studija. Ova analiza potvrđuje jasnu finansijsku korist za zdravstveni sistem kroz primenu ranolazina kao dodatka konvencionalnoj antiishemijskoj terapiji, bar u prvoj godini lečenja [24].

Osim kod *HFrEF*, koja najčešće nastaje kao komplikacija koronarne bolesti, merljivi su efekti ranolazina i kod *HFpEF*. Majer i saradnici su, u pilot studiji na 20 pacijenata sa *HFpEF*, lečenih intravenskom infuzijom ranolazina, registrovali akutno poboljšanje hemodinamskih (*LVEDP, PCWP, MPAP*) ali ne i parametara dijastolne funkcije. Sa druge strane, metaanaliza koja je obuhvatila osam randomizovanih studija sa prilično heterogenom populacijom sa *HFpEF* (ishemijska bolest srca, dijabetes, hipertrofična kardiomiopatija), osim poboljšanja hemodinamike kod pacijenata lečenih ranolazinom, ističe i pozitivan uticaj leka na parametre dijastolne funkcije (*LVEDV*, E/e') bez izazivanja hemodinamske i električne nestabilnosti [25-26].

Iako je poznato da ranolazin produžava QT interval u EKG zapisu, kao i da se produžetak korigovanog QT intervala (QTc) kreće od prosečnih 6 ms pa sve do 15 ms u 5 % pacijenata, kliničko iskustvo nije ukazalo na povećanje rizika od proaritmija ili naprasnog umiranja kod pacijenata lečenih ranolazinom [4,17]. Štaviše, rezultati *RAID* studije koja je uključila pacijente sa ugrađenim implantabilnim kardioverter defibrilatorom (engl. *implantable cardioverter defibrillator - ICD*), jasno ističu efekat ranolazina na električnu nestabilnost u smislu smanjenja broja epizoda ventrikularne tahikardije kod visokorizičnih pacijenata, a naročitu korist su imali pacijenti sa nadograđenim biventrikularnim pejsmejkerom, tzv. CRT-om (engl. *cardiac resynchronization therapy*), pacijenti kod kojih nije zabeležena

tients with non–ST-segment elevation acute coronary syndromes also experience measurable benefits when ranolazine is added to standard anti-ischemic therapy. The effect is a sustained reduction of ischemic symptoms, without impact on cardiovascular morbidity and mortality in these patients [22]. A positive effect of ranolazine on myocardial perfusion has been observed, and even patients with endothelial dysfunction have achieved clear subjective and objective benefits in terms of symptom relief and improvement of ischemic deficit [23].

The overall benefit of optimizing antianginal therapy with ranolazine is substantiated by a recent economic meta-analysis that included seven studies. This analysis confirms a clear financial benefit for the health system through the application of ranolazine as an adjunct to conventional anti-ischemic therapy, at least in the first year of treatment [24].

In addition to HFrEF, which most often occurs as a complication of coronary disease, the effects of ranolazine are also measurable in HFpEF. In a pilot study involving 20 patients with HFpEF treated with intravenous ranolazine, Maier et al. registered an acute improvement in hemodynamic (LVEDP, PCWP, MPAP) but not diastolic function parameters. On the other hand, a meta-analysis that included eight randomized studies with a rather heterogeneous population with HFpEF (ischemic heart disease, diabetes, hypertrophic cardiomyopathy), in addition to the improvement of hemodynamics in patients treated with ranolazine, also highlights the positive effect of the drug on diastolic function parameters (LVEDV, E/e'), without causing hemodynamic and electrical instability [25-26].

Although it is known that ranolazine prolongs the QT interval in the ECG recording, and that the prolongation of the corrected QT interval (QTc) ranges from an average of 6 ms up to 15 ms in 5% of patients, clinical experience has not indicated an increase in the risk of proarrhythmias or sudden death in patients treated with ranolazine [4,17]. Moreover, the results of the RAID study, which included patients with an implantable cardioverter defibrillator (ICD), clearly highlight the effect of ranolazine on electrical instability in terms of reducing the number of episodes of ventricular tachycardia in high-risk patients, while particular benefits were observed in patients with an upgraded biventricular pacemaker, the so-called by CRT (cardiac resynchronization therapy), patients in whom atrial fibrillation was not recorded, and in patients without concomitant antiarrhythmic therapy [27].

Precisely because of its mechanism of action, ranolazine has the potential to prevent the occurrence of not only ventricular, but also atrial arrhythmias, such

atrijalna fibrilacija i pacijenti bez konkomitantne antiaritmijske terapije [27].

Upravo zbog svog mehanizma delovanja, ranolazin ima potencijal da prevenira nastanak, ne samo komorskih, već i pretkomorskih aritmija, kakva je atrijalna fibrilacija (AF), i ima naročito značajno mesto u kontroli ritma kod pacijenata sa paroksizmalnom atrijalnom fibrilacijom i različitim kliničkim stanjima.

Rezultati metaanalize Leelapatane i saradnika, koja je uključila pacijente sa AF i sistolnom disfunkcijom, jasno ističu sinergistički efekat ranolazina u kombinaciji sa amiodaronom na Na struje, što rezultira povećanjem učestalosti i brzine konverzije AF u sinusni ritam, uz optimalan bezbedonosni profil [28].

Konzistentan efekat u prevenciji nastanka postoperativne atrijalne fibrilacije komparabilan efektu amiodarona, ranolazin pokazuje i kod hiruški revaskularizovanih pacijenata, bez razlike u učestalosti neželjenih događaja [29].

ZAKLJUČAK

Optimalna terapija angine se ne može zamisliti bez poslednje generacije antiishemsijkih lekova sa ćelijskim mehanizmom delovanja, kojim se postiže smanjenje ishemije na nivou miocita. Ranolazin je prvi inhibitor kasne natrijumske struje, dokazano efikasan i bezbedan, kojim se postiže smanjenje učestalosti stenokardija, bolja tolerancija napora, unapređen kvalitet života i poboljšano preživljavanje uz pozitivan metabolički profil (redukcija HbA1C), a bez uticaja na hemodinamiku, odnosno puls i pritisak.

Ranolazin, dakle, nije „rezervni lek“; optimalan je za pojedine podgrupe pacijenata, kakvi su pacijenti sa dijabetesom, mikrovaskularnom bolešću, hipotenzijom i bradikardijom, gde se pokazao efikasan, kako u monoterapiji, tako i u kombinaciji sa beta blokatorom ili kalcijumskim antagonistom.

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as atrial fibrillation (AF), and has a particularly important place in rhythm control in patients with paroxysmal atrial fibrillation and various clinical conditions.

The results of the meta-analysis by Leelapatana et al., which included patients with AF and systolic dysfunction, clearly highlight the synergistic effect of ranolazine in combination with amiodarone on Na currents, resulting in an increase in the frequency and speed of conversion of AF to sinus rhythm, with an optimal safety profile [28].

Ranolazine has demonstrated a consistent effect in the prevention of postoperative atrial fibrillation comparable to the effect of amiodarone in surgically revascularized patients, without a change in the frequency of adverse events [29].

CONCLUSION

Optimum therapy of angina cannot be conceived without the latest generation of anti-ischemic drugs that have a cellular mechanism of action, which achieves reduction of ischemia at the myocyte level. Ranolazine is the first late sodium current inhibitor, proven effective and safe, which achieves a reduction in the frequency of angina pectoris, better exercise tolerance, improved quality of life, and improved survival, with a positive metabolic profile (reduction of HbA1C), without affecting hemodynamics, i.e. heart rate and blood pressure.

Ranolazine, therefore, is not a “backup drug”; it is optimal for certain patient subgroups, such as those with diabetes, microvascular disease, hypotension, and bradycardia, where it has proven effective both as monotherapy and in combination with a beta-blocker or calcium channel blocker.

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