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Pregledni članak | Review article

# Ranolazin: nova mogućnost i novi mehanizam u liječenju kronične angine pektoris

# Ranolazine: a new possibility and a new mechanism in the treatment of chronic angina pectoris

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***SAŽETAK:*** *U liječenju kronične angine pektoris u zadnjih nekoliko godina, pored lijekova s antianginalnim učinkom (blokatori beta adrenergičkih receptora, kalcijski antagonisti i nitrati) moguće je primjeniti i ranolazin. Ovaj inovativni lijek, djelujući na patološki proces koji se zbiva u vrlo ranom stadiju ishemije, može blokirati štetne posljedice koje nastaju kaskadnim procesom. Ranolazin je prvi antianginalni metabolički modulator koji se pojavio u posljednjih 25 godina liječenja angine pektoris, koji djeluje inhibicijski na sarkoplazmatske kasne natrijske kanale bez znakovitog učinka na srčanu frekvenciju i arterijski tlak te dišne puteve. Pored dokazanog antianginalnog učinka, ranolazin može predstavljati novu mogućnost liječenja za bolesti srca udružene s narušenom homeostazom iona miokarda i to poglavito kod bolesnika s poremećenom homeostazom iona natrija kao što se zbiva u zatajivanju srca. Inhibicija kasnih natrijskih kanala može predstavljati i novi antiaritmijski pristup navlastito supraventrikulskim i ventrikulskim poremetnjama ritma (tahikardijama), a potencijalne studije zatajivanja srca sa sistoličkom i/ili dijastoličkom disfunkcijom te atrijskom fibrilacijom predstavljaju budućnost istraživanja moguće dobrobiti primjene ranolazina.*

***KLJUČNE RIJEČI:*** *angina pektoris, ranolazin, aritmije, zatajivanje srca.*

***SUMMARY:*** *In treatment of chronic angina pectoris in the last few years, besides the medicines with antianginal effect (adrenergic receptor beta blockers, calcium antagonists and nitrates) even ranolazine may be applied. This innovative drug having effect on pathological process that occurs at a very early stage of ischemia, may block harmful effects that occur in cascade process. Ranolazine is the first antianginal metabolic modulator that has appeared in the last 25 years of treatment of angina pectoris, having inhibition effect on sarkoplasmatic late Na channels with no significant effect on heart rate and blood pressure as well as respiratory tract. Apart from proved antianginal effect, ranolazine represents a new possibility of treatment of heart diseases associated with impaired homeostasis of myocardial ions, especially in patients with impaired homeostasis of Na ions as it occurs in heart failure. The inhibition of late Na channels may be a new antiarrhythmic approach to supraventricular and ventricular arrhythmias (tachycardias), while potential studies of heart failure with systolic and/or diastolic dysfunction and atrial fibrillation represent the future of research of potential benefit of application of ranolazine.*

***KEYWORDS:*** *angina pectoris, ranolazine, arrhythmia, heart failure.*

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U Republici Hrvatskoj, kao i diljem suvremenog svijeta, skupina srčanožilnih bolesti predstavlja vodeći uzrok mortaliteta i morbiditeta te stoga i vodeći javnozdravstveni problem[1]. Angina pektoris susreće se u gotovo polovice bolesnika s koronarnom bolesti srca (KBS). U Hrvatskoj primjerice prevalencija ove bolesti kod muškaraca srednje dobi iznosi oko 2-5%, a u starijih muškaraca 11-20%. Kod osoba ženskog spola do 54 godine života prevalencija je do 1%, ali u dobi od 65 do 74 godine raste na 10-15%. Predmnijeva se da u Hrvatskoj od kronične angine pektoris boluje oko 150.000 osoba. Prema podacima kliničkih ispitivanja učinka antianginozne terapije i revaskularizacije miokarda te podacima iz registra Hrvatskog zavoda za javno zdravstvo, godišnja stopa mortaliteta od stabilne angine pektoris iznosi 0,9-1,4[2].

Ciljevi liječenja kronične angine pektoris su smanjenje učestalosti anginoznih napada, produljenje trajanja života i boljitak kvalitete života. Korekcija čimbenika rizika je bitna sastavnica liječenja, a smanjenje broja i učestalosti anginoznih napada kao i produljenje tolerancije napora utječu na poboljšanje kvalitete življenja. Osnovu farmakološkog liječenja čine antianginozni lijekovi, a u slučaju da se njima ne može postići kontrola bolesti radi se perkutana

In the Republic of Croatia and a part of the contemporary world as well, a group of cardiovascular diseases represents a major cause of mortality and morbidity and is therefore a major public health problem[1]. Angina pectoris is diagnosed in almost a half of the patients with coronary heart diseases (CHD). In Croatia, the prevalence of this disease in middle-age men is 2-5%, and in elderly men it ranges from 11-20%. In women aged up to 54 the prevalence is up to 1%, but at the age between 65 and 74 it rises to 10-15%. It is assumed that around 150 000 persons suffer from chronic angina pectoris in Croatia. According to the data on clinical testing of the effect of the antianginal therapy and myocardial revascularization and data from the Registry of the Croatian National Institute of Public Health, the annual rate of mortality from angina pectoris ranges from 0.9 to 1,4[2].

The aims of treatment of chronic angina pectoris are to reduce the frequency of chest pain attacks, extension of life and better quality of life. The correction of risk factors is an important component of treatment, while reduction of a number and frequency of anginal attacks and the extension of tolerance of efforts affect the betterment of quality of life. The basis of pharmacological treatment is the antianginal drugs, and in case that they may not put the disease under control, percutaneous coronary intervention (PCI) with or

koronarna intervencija (PCI) sa ili bez postavljanja stenta ili pak kirurška revaskularizacija miokarda.

U konzervativnom liječenju koriste se tri osnovne vrste antianginalnih lijekova: blokatori beta adrenergičkih receptora (beta-blokatori), kalcijski antagonisti i nitrati. Lijek izbora za većinu bolesnika predstavljaju beta-blokatori jer smanjuju simptome, ali i mortalitet. Oni smanjuju potrošnju kisika u miokardu zbog usporavanja frekvencije srca i smanjenja kontraktilnosti te boljitka dijastoličke perfuzije. Beta-blokatori se ne bi trebali koristiti kod bolesnika sa značajnom bradikardijom, atrioventrikularnim blokom višeg stupnja i težim respiracijskim smetnjama. U racionalnoj primjeni slijede blokatori kalcijevih kanala, najčešće iz dihidropiridinske skupine te verapamil, poglavito kada postoji kontraindikacija za uporabu beta-blokatora ili njima nije moguća učinkovita kontrola anginoznih smetnji. Nitrati, koji su isključivo simptomatski lijekovi, uglavnom se koriste kao dodatni lijek ako se drugim lijekom ne postiže učinak. Oni smanjuju anginalne epizode i poboljšavaju toleranciju napora zahvaljujući smanjenju potrošnje kisika. U meta-analizi 90 kliničkih ispitivanja stabilne angine pektoris, kao i u studijama IMAGE, TIBBS i TIBET nije dokazana bitna razlika u smanjenju učestalosti anginoznih napada, uporabom nitroglicerina ili poboljšanju tolerancije napora u bolesnika koji su upotrebljavali beta-blokatore, antagoniste kalcija ili dugodjelujuće nitrate[3,4]. Premda je monoterapija učinkovita, većini bolesnika najčešće treba dva ili više antianginoznih lijekova za kontrolu simptoma bolesti. Kako je većina bolesnika s anginom pektoris u starijoj životnoj dobi te mogu imati i pridružene bolesti (npr. kroničnu opstruktivnu bolest pluća, perifernu arterijsku bolest, dijabetes, zatajivanje srca), uzimanje nekih od antianginoznih lijekova može biti kontraindicirano. Planiranje i probir antianginozne farmakoterapije zahtjeva pozornu procjenu učinkovitosti, suradljivosti bolesnika te mogućih interakcija i nuspojava primjenjenih lijekova[3]. Sastavnice preporučenog liječenja stabilne KBS su i acetilsalicilna kiselina, statini, ACE inhibitori ili sartani, navlastito kod bolesnika sa sistoličkom i/ili dijastoličkom disfunkcijom lijeve klijetke, arterijskom hipertenzijom, dijabetesom i kroničnom bolesti bubrega[5].

Revaskularizacija se primjenjuje ako se anginozni simptomi ne mogu kontrolirati farmakoterapijom. Ipak i nakon uspješne revaskularizacije veći dio bolesnika nastavlja uzimati antianginozne lijekove. Tako nakon kiruške revaskularizacije miokarda ili PCI čak 10-34% bolesnika ima ponovne anginozne tegobe nakon godine dana po učinjenom zahvatu gotovo 80% i dalje uzima medikamentoznu antianginoznu terapiju[3,5].

Glede ograničenosti postojeće standardne terapije može se učiniti i transmiokardijalna revaskularizacija, no iskustva nisu posebito pozitivna. Eksterna kontrapulzacija i genska terapija su metode još uvijek u fazi kliničkih ispitivanja, a poglavito su predviđene za bolesnike s refraktornom anginom kojima se standardnom farmakološkom terapijom, nakon učinjene revaskularizacije, ne mogu kontrolirati simptomi bolesti[6,7].

Zadnjih godina imamo na raspolaganju terapiju koja ne spada u standardnu, ali u kliničkim je ispitivanjima pokazala učinkovitost u smanjenju anginoznih tegoba i to modificiranjem metabolizma miokarda. KBS je također i metabolička bolest. Čuvanjem energetskog metabolizma

without implantation of stent or surgical myocardial revascularization is done.

Three basic types of antianginal drugs are used in conservative treatment: adrenergic receptor beta blockers (beta-blockers), calcium antagonists and nitrates. The drug of choice must for most of the patient be beta-blockers since they reduce the symptoms and mortality as well. They reduce the consumption of oxygen in myocardium as a consequence of slowdown of heart rate and reduction of contractility and improvement of diastolic perfusion. Beta-blockers should not be applied in patients with significant bradycardia, higher grade of atrioventricular block and more serious respiratory disorders. Calcium chanel blockers are rationally applied, most frequently from the dihydropyridine group and verapamil, especially when there is a side-effect for the use of beta-blocker and they may not efficiently control anginal attacks. Nitrates that are only symptomatic drugs are mainly used as additional drug if some other drugs have no effect. They reduce anginal episodes and improve effort tolerance owing to reduced consumption of oxygen. In meta-analysis of 90 clinical tests of stable angina pectoris and in the studies IMAGE, TIBBS and TIBET we proved no significant difference in reduction of anginous attacks by using nitroglycerine or improvement of effort tolerance in patients who used beta-blockers, calcium antagonists or long-acting nitrates[3,4]. Although the monotherapy is efficient, the most patients usually need two or several antianginal drugs to control the symptoms of the disease. Since the most of the patients suffering from angina pectoris are elderly patients and may have some related diseases (such as chronic obstructive pulmonary disease, peripheral arterial disease, diabetes, heart failure) taking some of antianginal drugs may have side-effects. Planning and selection of antianginal pharmacotherapy requires due evaluation of efficacy, patient's cooperation and potential interactions and side-effects of applied drugs[3]. The components of the recommended treatment of stable CHD also include aspirin, statins, ACE inhibitors or sartans, especially in patients with systolic and/or diastolic dysfunction of the left ventricle, hypertension, diabetes and chronic renal disease[5].

Revascularization is used if anginal symptoms may not be controlled by pharmacotherapy. Anyway, following the successful revascularization, the major number of patients continues to take antianginal drugs. So, following the surgical myocardial revascularization or PCI even 10-34% patients again have anginal problems following one year after the operation has been performed and almost 80% continue to take medicamentous antianginal therapy[3,5].

Regarding the limitation of the existing standard therapy, transmyocardial revascularization may be done, but experience is not very positive in connection with that. External counterpulsation and gene therapy are the methods that are still at the stage of clinical testing and are especially envisaged for the patients with refractory angina in whom the standard pharmalogical therapy after the performed revascularization cannot control the symptoms of the disease[6,7].

During the last few years, we have a therapy available that is included in the standard therapy, but in clinical tests it has showed efficacy in reduction of anginal problems by modifying the myocardial metabolism. CHD is also a metabolic disease. Keeping energetic metabolism within cells

unutar stanica izloženih hipoksiji ili ishemiji, sprječava se smanjenje unutarstanične koncentracije ATP-a. Na taj način osigurava se pravilno funkcioniranje ionskih crpki i transmembranski protok natrija i kalija, održavajući staničnu homeostazu. Primjerice, kočenje oksidacije masnih kiselina putem inhibicije dugolančane 3-ketoacil-CoA tiolaze (3-KAT) uzrokuje povećanje oksidacije glukoze i tako štiti srce izloženo ishemiji.

Predstavnik skupine tzv. djelomičnih inhibitora oksidacije masnih kiselina je trimetazidin, koji je godinama registriran u Hrvatskoj. On je u kontroliranim kliničkim ispitivanjima dokazao (kao monoterapija ili u kombinaciji sa standardnim antianginoznim lijekovima) učinkovitost u povećanju tolerancije napora, smanjenju elektrokardiografskih znakova ishemije, anginoznih bolova i potrebe za kratkodjelujućim nitratima[8]. Za razliku od klasičnih antianginoznih lijekova ne djeluje na frekvenciju srca, arterijski tlak (AT) ili koronarni protok tako da je učinak izravna posljedica modifikacije metabolizma stanica miokarda[9-11].

U liječenju kronične angine može se primijeniti i jedan inovativni antianginalni lijek koji djelujuje na patološki proces koji se zbiva u vrlo ranom stadiju ishemije i koji može blokirati kaskadni proces štetnih posljedica. Ranolazin predstavlja prvi antianginalni metabolički modulator koji se pojavio u posljednjih 25 godina liječenja angine pektoris i djeluje inhibicijski na sarkoplazmatske kasne natrijske struje bez znakovitog učinka na srčanu frekvenciju i AT. U početku ispitivanja ranolazina predmnijevalo se da je mehanizam djelovanja također parcijalna inhibicija beta oksidacije masnih kiselina poput trimetazidina. No, brzo je postalo razvidno da bi koncentracija ranolazina potrebita za tu inhibiciju trebala biti neusporedivo veća nego što su preporučene terapijske koncentracije, primjerice za 12% inhibicije treba koncentracija od 100 μmol/L ranolazina, dok se boljitak srčane funkcije bilježi već pri koncentraciji od 20 μmol/L. Daljnim ispitivanjem ranolazina zabilježeno je značajno poboljšanje srčane funkcije kod ishemije i reperfuzije *in vivo* i *in vitro*, kod izlaganja vodik peroksidu, palmitol-l-karnitinu, ali i zatajivanju srca kada u perfuzijskim srčanim otopinama nije bilo masnih kiselina. To je potvrdilo da je mehanizam djelovanja ranolazina sasvim drugačiji[12]. Vremenom se potvrdilo da je ranolazin potentni blokator (inhibitor) kasnih natrijskih kanala već pri koncentraciji od 10 μmol/L i da smanjuje električnu i mehaničku disfunkciju koja nastaje gomilanjem iona kalcija u kardiomiocitima na osnovi suviška iona natrija. Poznato je da se poremećaj otvaranja kasnih natrijskih kanala poglavito zbiva kod različitih srčanih bolesti. Ta abnormalnost uzrokuje povišenje koncentracije natrija intracelularno, poremećaj izmjene iona natrija i kalcija, nagomilavanje kalcija intracelularno, poremećaj repolarizacije i kontrakcija miokarda, električnu nestabilnost i mehaničku disfunkciju. Ranolazin koji ima terapijski učinak samo u patološkim stanjima, omogućava prekid patofiziološkog slijeda ishemije miokarda i disregulacije intracelularne homeostaze iona[12-14]. Kao vrlo pozitivnu posljedicu mehanizma svog djelovanja može imati i antiaritmijski učinak, koji se tumači malim, i o dozi, ovisnim porastom akcijskog potencijala u stanicama miokarda. Eksperimenti i klinički rezultati pokazuju da ova inhibicija u najranijoj fazi ishemije rezultira i boljitkom dijastoličkog tonusa, poglavito u težoj dijastoličkoj disfunkciji[15,16].

exposed to hypoxia or ischemia leads to prevention of reduction of intracellular ATP concentration. This is how proper functioning of ion pumps and transmembrane flow of sodium and potassium is ensured, maintaining cellular homeostasis. For example, halting the fatty acid oxidation by inhibiting the long-chain 3-ketoacyl-CoA thiolase (3-KAT) causes an increase in oxidation of glucose and thus prevents the heart exposed to ischemia.

The representative of the group of so-called partial fatty acid oxidation inhibitors is trimetazidine that has been registered in Croatia for years. It has in controlled clinical tests proved (as monotherapy or in combination with standard antianginal drugs) efficacy in increasing effort tolerance, by reducing electrocardiographic signs of ischemia, anginal pains and need for short-acting nitrates[8]. Unlike the traditional antianginal drugs, it has no effect on the heart rate, blood pressure (BP) or coronary flow, so that the effect is the direct consequence of modification of metabolism of myocardial cells[9-11].

In treatment of chronic angina, one innovative antianginal drug having effect on pathological process that occurs in a very early stage of ischemia and that may block cascade process of harmful effects may be used as well. Ranolazine is the first antianginal metabolic modulator that has appeared in the last 25 years of treatment of angina pectoris, having inhibition effect on sarkoplasmatic late Na currents with no significant effect on heart rate and BP. At the beginning of testing ranolazine, it was assumed that the mechanism of action is also a partial inhibition of beta oxidation of fatty acids such as trimetazidine. However, it soon became obvious that the concentration of ranolazine necessary for that inhibition should be much greater than what are the recommended therapeutical concentrations, for instance for 12% inhibition, the concentration of 100 μmol/L ranolazine is required, while the improvement of cardiac function is recorded in concentration of 20 μmol/L. Further testing of ranolazine recorded a significant improvement of cardiac function in case of ischemia and reperfusion *in vivo* and *in vitro*, in case of hydrogen-peroxide exposure, palmitoyl-l-carnitine, but even the heart failure when in perfusion heart solutions there were no fatty acids. This confirmed that the mechanism of ranolazine action is completely different[12]. With time, it was confirmed that ranolazine is a potent blocker (inhibitor) of late Na channels already in concentration of 10 μmol/L and that it reduces electrical and mechanical dysfunction that is caused by accumulation of calcium ions in cardiomyocytes based on the surplus of sodium ions. It is well-known that the disorder of opening of late Na channels mainly occurs in different heart diseases. This abnormality causes higher intracellular concentration of sodium, disorder of sodium - calcium ion exchange, intracellular accumulation of calcium, disorder of repolarization and myocardial contraction, electrical instability and mechanical dysfunction. Ranolazine that has therapeutic effect only in pathological conditions enables an interruption of pathophysiologic sequence of myocardial ischemia and deregulation of intracellular ion homeostasis[12-14]. The antiarrhythmic effect may have a very positive consequence of mechanism of its action that is interpreted by small and dose-dependant rise in action potential in the myocardial cells. Experiments and clinical results show that this inhibition at the earliest stage of ischemia results in the improvement of diastolic tonus, mainly in a serious diastolic dysfunction[15,16].

Učinkovitost ranolazina je ispitivana u nekoliko randomiziranih multicentričnih kliničkih studija. U istraživanju MARISA, dvostruko slijepoj studiji, primjenjen je ranolazin kao monoterapija u tri dugootpuštajuće doze (500, 1.000 i 1.500 mg dva puta dnevno) naspram placeba kod 175 bolesnika sa kroničnom anginom pektoris koji imaju anginozne smetnje i značajnu depresiju ST-segmenta u elektrokardiogramu. Rezultati nakon tri mjeseca su pokazali da sve tri doze statistički značajno poboljšavaju primarni cilj studije — toleranciju napora (produljenje tolerancije napora na dozi od 750 mg 23,7s, na 1.000 mg 33,7s i 45,9s na dozi od 1.500 mg). Rezultati sekundarnog ishodišta također su pokazali statističku značajnost i to u odlaganju vremena do pojave anginoznih napada (27s vs. 45,9s vs. 59,6s na dozama od 500 vs. 1.000 mg vs. 1.500 mg 2 x dnevno), kao i produljenje vremena do pojavnosti depresije ST-segmenta od 1mm (27,6s vs. 44,5s vs. 64,6s). Ukupno 168 bolesnika su prošli sva 4 razdoblja praćenja (od placeba do maksimalne doze ranolazina), a praćenje ispitanika na 1.500mg ranolazina 2x dnevno nakon 1 godine je pokazalo preživljenje od 96,3%, a nakon 2 godine 93,6%. Nije bilo nikakovog značajnijeg učinka na srčanu frekvenciju i AT. Ranolazin se dobro podnosio, a 8 % bolesnika iz studije je prekinulo terapiju radi nuspojava i to navlastito vrtoglavice, mučnine i astenije, od toga 3/4 ispitanika koji su primali najveću dozu lijeka. Ukupno, tri ispitanika su prekinuli studiju radi sinkope. Treba napomenuti da ranolazin kao monoterapija nije odobren u Europi[17].

Istraživanje CARISA uključila je 823 bolesnika s kroničnom anginom pektoris koji već primaju standardnu antianginalnu terapiju (atenolol 50 mg, diltiazem 180 mg ili amlodipin 5 mg dnevno). Bolesnici su bili randomizirani u tri paralelne dvostruko slijepe, placebo kontrolirane skupine. Prva skupina ispitanika dobivala je 750 mg ranolazina 2x dnevno, druga 1.000 mg 2x dnevno, a treća placebo. Test opterećenja proveden je po istom protokolu kao u studiji MARISA, četiri i 12 sati nakon uzimanja terapije na početku studije i nakon tri mjeseca. Primarni cilj, duljina podnošenja tjelesnog napora je bila signifikantno veća u obje skupine ispitanika koji su dobivali ranolazin, jednako kao i sekundarni cilj, tj. duljina vremena do pojavnosti anginoznog napada odnosno vrijeme do objektivizacije elektrokardiografske depresije ST-segmenta od 1mm. Učinak ranolazina je bio postojan tijekom cijele studije što ukazuje da se ne razvija tolerancija na lijek. Rezultati CARISA studije su pokazali da ranolazin pruža dodatni antiishemijski i antianginalni učinak kod bolesnika sa značajnom kroničnom anginom koji imaju simptome unatoč standardnoj antianginalnoj terapiji. Najčešće nuspojave (ranolazin vs. placebo) su bile opstipacija (7,3% vs. 0,7%), vrtoglavica (6,9% vs. 1,9%) i astenija (4,7% vs. 2,2%)[16]. Iako naknadna analiza studije CARISA nije pokazala razlike u toleranciji napora i kontroli angine između dijabetičara i nedijabetičara, zabilježeni su vrlo zanimljivi glukometabolički nalazi. Naime, ranolazin u dozi od 750 mg i 1.000 mg statistički je značajno snižavao HbA1C nasuprot placebu. Mehanizam ovog učinka ranolazina nije poznat i predmetom je daljnjih istraživanja[18].

Istraživanje ERICA dalo je odgovor na upit da li ranolazin može poboljšati kontrolu anginoznih napada kod bolesnika koji su simptomatski, unatoč maksimalnoj standard-

The efficiency of ranolazine has been tested in several randomized multicentric clinical studies. The MARISA research, double-blind study, has applied ranolazine as a monotherapy in three long-release doses (500, 1000 and 1500 mg twice a day) compared to placebo in 175 patients with chronic angina pectoris who have anginous attacks and significant ST-segment depression in electrocardiogram. The results after the three months have shown that all three doses statistically greatly improve the primary goal of the study — effort tolerance (extended effort tolerance on dose of 750 mg 23.7s, on 1000 mg 33.7s and 45.9s on dose of 1500 mg). The results of the secondary starting point have also showed statistical importance in delaying time till occurrence of anginal attacks (27s vs. 45.9s vs. 59.6s on doses of 500 vs. 1000 mg vs. 1500 mg 2 x a day), as well as extension of time till occurrence of 1 mm ST-segment depression (27.6s vs. 44.5s vs. 64.6s). Totally 168 patients have undergone all 4 periods of follow-up (from placebo to maximum dose of ranolazine), while the follow-up of patients on 1500 mg ranolazine 2X a day following 1 year has showed the survival of 96.3% and following the period of 2 years it was 93.6%. There was no significant effect on heart rate and BP. Ranolazine was well tolerated, and 8% of patients involved in the study interrupted the therapy especially as a consequence of side-effects, especially dizziness, nausea and asthenia, of whom 3/4 of patients who received the largest drug dose. Totally, three patients interrupted the study as a consequence of syncope. It should be mentioned that ranolazine as a monotherapy is not approved in Europe[17].

The CARISA study involved 823 patients with chronic angina pectoris who are already receiving standard antianginal therapy (atenolol 50mg, diltiazem 180 mg or amlopine 5 mg a day). The patients were randomized in three parallel double-blind, placebo controlled groups. The first group of examinees received 750 mg ranolazine 2x a day, another received 1000 mg 2x a day, while the third received placebo. The stress test has been conducted according to the same protocol as in the MARISA study, four and 12 hours after taking the therapy at the beginning of the study and following three months' period. The primary goal, the length of tolerance of exercise was significantly greater in the both groups of examinees who were receiving ranolazine, the same as the secondary goal, that is, the length of time till occurrence of anginal seizure or time till objectivization of electrocardiographic depression of ST-segment of 1mm. The effect of ranolazine was very stable throughout the entire study which shows that no tolerance to the drug is developed. The results of the CARISA study has showed that ranolazine provides additional antiischemic and antianginal effect in patients with a significant chronic angina who have symptoms despite the standard antianginal therapy. The most frequent side-effects (ranolazine vs placebo) were constipation (7.3% vs. 0.7%), dizziness (6.9% vs. 1.9%) and asthenia (4.7% vs. 2.2%)[16]. Although the subsequent analysis of the CARISA study showed no difference in tolerance of exercise and control of angina between the diabetics and non-diabetics, some very interesting glucometabolic results were recorded. Ranolazine in dose of 750 mg and 1000 mg statistically greatly reduced HbA1C compared to placebo. The mechanism of this effect of ranalozine is unknown and is subject to further researches[18].

The ERICA study has given an answer to the question whether ranolazine may improve the control of anginal attacks in patients which are symptomatical, despite maximum standard antianginal therapy. Totally 565 patients

noj antianginalnoj terapiji. Ukupno 565 bolesnika sa stabilnom koronarnom bolesti i 3 anginozna napada tjedno unatoč maksimalnoj dnevnoj dozi od 10 mg amlodipina su bili randomizirani na dvije skupine (1.000 mg ranolazina 2x dnevno i druga na placebu) tijekom 6 tjedana. Ranolazin je značajno smanjio broj anginoznih napada usporedivo s placebom (p = 0.028), kao i potrebu za uzimanjem nitroglicerina (p = 0.014). Analiza podskupina je pokazala još veću korist kod bolesnika koji su imali >4,5 anginoznih napada tjedno. Zasnovano na rezultatima studije ERICA, FDA (Food and Drug Administration) i AHA (American Heart Association) su u kolovozu 2007. godine preporučili promjenu smjernica i upotrebu ranolazina u liječenju kronične stabilne angine pektoris[19]. Podanaliza istraživanja ERICA je pokazala i druge korisne učinke ranolazina. Učestalost infarkta miokarda (5,7% vs. 7,8%) i kongestivnog zatajivanja srca (0,7% vs. 0,45%) je bila manja u skupini sa ranolazinom naspram placebu. Nuspojave u studiji su bile opstipacija, periferni edemi i vrtoglavica.

Istraživanje MERLIN-TIMI 36 je bila dvostruko slijepa, placebo kontrolirana studija i tražila je odgovor glede učinkovitosti i sigurnosti ranolazina kod visoko rizičnih bolesnika sa KBS. Ukupno 6.560 ispitanika s nestabilnom anginom ili akutnim infarktom miokarda bez elevacije ST-segmenta (NSTEMI) su bili randomizirani na skupinu koja je dobivala ranolazin, prvo intravenozno, nakon čega je slijedila oralna doza od 1.000 mg 2x dnevno nasuprot placebu tijekom 48 sati od pojave akutnog koronarnog sindroma i koja je nastavljena sljedećih 348 dana. Iako rezultati nisu pokazali statističku značajnost u kombiniranom primarnom cilju studije, analiza pojedinačnih elemenata pokazala je značajno statističko sniženje rekurentne ishemije u skupini s ranolazinom (13,9% vs. 16,1%, p = 0.03). Sukladno rezultatima istraživanja CARISA i ERICA i studija MERLIN je pokazala da i dugotrajno liječenje ranolazinom kod simptomatskih bolesnika također znakovito poboljšava anginoznu kontrolu. Nije bilo statističke razike u smrtnosti između skupina, dok je u skupini ispitanika s ranolazinom bilo više sinkopa nego u placebo skupini, kao i produljenja QT-intervala. Bilo je više vrtoglavice, mučnine i opstipacije u skupini s ranolazinom[20,21]. Naknadne analize MERLIN studije ukazale su na niz vrlo povoljnih učinaka ranolazina. Kao i u studiji CARISA, ranolazin je usporedivo sa placebom također statistički značajno snizio vrijednost HbA1C nakon 4 mjeseca terapije[22-24]. Značajno je bilo i smanjenje atrijskih i ventrikulskih ekstrasistola. Antianginozni učinak ranolazina bio je bolji kod bolesnika s povišenim vrijednostima BNP. Učinak ranolazina bio je bolji kod žena, koje su primjerice u primarnom ishodištu studije imale relativno smanjenje ishemije za čak 29%. Rezultati MERLIN studije potvrđuju učinkovitost i sigurnost ranolazina kao antianginalne terapije podjednako u skupinama stabilne angine i visoko rizičnih koronarnih bolesnika, ali ne donosi sniženje velikih kardiovaskularnih događaja i ukupne smrtnosti u skupini ispitanika sa NSTEMI, unatoč pozitivnim antiaritmijskim svojstvima[20].

Istraživanje ROLE uključilo je 746 bolesnika sa značajnim funkcijskim poremećajem glede angine pektoris prema Duke Treadmill Score (DTS). Ona je nastavila praćenje bolesnika iz studija MARISA i CARISA potvrdivši sigurnosni profil ranolazina tijekom 2,8 godina praćenja. Najčešće nuspojave su bile vrtoglavica i opstipacija. Nije bilo prekida terapije radi produljenja QTc-intervala niti registriranih

with stable coronary disease and 3 anginal attacs a week despite the maximum daily dose of 10 mg of amlodipine were randomized in two groups (1000 mg of ranolazine 2x a day and the other in placebo) during the period of 6 weeks. Ranolazine greatly reduced the number of anginal attacks comparative to placebo (p = 0.028), and the need for taking nitroglycerin (p = 0.014). The analysis of the subgroups showed even greater benefit in patients who had >4.5 anginal attacs a week. Based on the results of the ERICA study, FDA (Food and Drug Administration) and AHA (American Heart Association) recommended in August 2007 a change to the guidelines and the use of ranolazine in treatment of chronic stable angina pectoris[19]. The subanalysis of the ERICA study also showed some other benefits of ranolazine. The frequency of myocardial infarction (5.7% vs. 7.8%) and congestive heart failure (0.7% vs. 0.45%) was reduced in the group taking ranolazine compared to the group taking placebo. The side-effects in the study were constipation, peripheral edema and dizziness.

The MERLIN-TIMI 36 study was a double-blind, placebo controlled study and required an answer with respect to efficacy and safety of ranolazine in high risk patients with CHD. A total number of 6560 patients with instable angina and non ST-segment elevation myocardial infarction (NSTEMI) were randomized in the group receiving ranolazine, firstly intravenously, followed by oral dose of 1000 mg 2x a day compared to placebo during 48 hours from the occurrence of acute coronary syndrome which was continued in the next 348 days. Although the results showed no statistical significance in combined primary goal of the study, the analysis of specific elements showed significant statistical reduction of recurrent ischemia in the group receiving ranolazine (13.9% vs. 16.1%, p=0.03). According to the CARISA and ERICA research results, the MERLIN study has showed that long-term treatment by ranolazine in symptomatic patients also greatly improves the control of angina. There were no statistical difference in mortality between the groups, while the group of patients taking ranolazine recorded more syncopes and extension of the QT-interval than the group receiving placebo. More dizziness, nausea and constipation were recorded in the group receiving ranolazine[20,21]. Subsequent analyses of the MERLIN study indicated a series of very favorable effects of ranolazine. As in the study CARISA, ranolazine did along with placebo also statistically reduce the value of HbA1C after 4 months of the therapy[22-24]. The reduction of atrial and ventricular premature beats was significant as well. Antianginal effect of ranolazine was better in patients with increased BNP values. The effect of ranolazine was better in women that for example at the primary start of the study had relative reduction of ischemia by even 29%. The MERLIN study results confirm the efficacy and safety of ranolazine as an antianginal therapy both in the groups of stable angina and high risk coronary patients, but it does not lead to reduction of major cardiovascular events and death from all causes in the group of patients with NSTEMI, despite positive antiarrhythmic properties[20].

The ROLE study involved 746 patients with significant functional disorders with regard to angina pectoris according to Duke Treadmill Score (DTS). It continued follow-up of patients from the studies MARISA and CARISA verifying the safety profile of ranolazine during 2.8 years of follow-up. The most frequent side-effects were dizziness and con-

nja aritmije "torsades de pointes". Godišnji mortalitet je iznosio 2,8% usporedivo sa >5% predvidivo prema DTS[21].

Ranolazin može biti koristan u liječenju zatajivanja srca s poremećenom dijastoličkom i/ili sistoličkom funkcijom. On znakovito poboljšava poremećenu homeostazu iona intracelularno i smanjuje porast dijastoličke napetosti. Nekoliko eksperimentalnih modela je demonstriralo poboljšanje end-dijastoličkog tlaka lijeve klijetke (LK), tlaka punjenja LK, dijastoličkog tlaka i dijastoličkog stresa na zid klijetke. Nije bio izražen negativni inotropni učinak.

Potencijalna primjena ranolazina kao antiaritmijskog lijeka je posebito zanimljiva i vrijedna pozornosti. Naime, poradi činjenice da produljuje QTc-interval u početku je postojao prijepor, no nakon objavljivanja rezultata studije MERLIN mišljenje se promijenilo. Naime, unatoč produljenju QTc-intervala rezultati studije su zorno pokazali da ranolazin smanjuje epizode supraventrikulskih i ventrikulskih aritmija kod bolesnika s ishemijom. Recentno, ispitivanja su obavljena kod bolesnika sa tip 3 sindromom dugog QT-intervala koji je udružen s prolongiranim otvorenim natrijskim kanalom za vrijeme depolarizacije membrane što značajno povisuje mogućnost smrtnog ishoda. U toj visoko rizičnoj populaciji, osmosatna infuzija ranolazina signifikantno je skratila QTc-interval za 26,3 ms ($p < 0.0001$) i poboljšala dijastoličku relaksaciju. U objavljenom prikazu slučaja bolesnika s alkoholnom kardiomiopatijom i malignom ventrikulskom tahikardijom refraktornom na agresivnu konvencionalnu terapiju, ranolazin se pokazao vrlo učinkovit u dozi od 1.000.mg 2x dnevno. Ranolazin je bio učinkovit i u prekidanju atrijske fibrilacije i prevenciji njegog ponavljanja na animalnim modelima i kod bolesnika, iako se radio o maloj seriji bolesnika.

Zaključno, inhibicija kasnih natrijskih kanala predstavlja novi oblik liječenja kod bolesnika sa kroničnom anginom pektoris. Pored dokazanog antianginalnog učinka, ranolazin može predstavljati novu mogućnost liječenja za bolesti srca udružene s narušenom homeostazom iona miokarda, poglavito kod bolesnika s poremećenom homeostazom iona natrija, kao što se zbiva u zatajivanju srca. U konačnici, inhibicija kasnih natrijskih struja može predstavljati novi antiaritmijski pristup navlastito atrijskim i ventrikulskim poremetnjama ritma (tahikardijama). Daljnja istraživanja ranolazina kod zatajivanja srca sa sistoličkom i dijastoličkom disfunkcijom i bolesnika s atrijskom fibrilacijom utvrditi će moguće buduće terapijskih indikacije. Budući da nema učinka na srčanu frekvenciju, AT i dišne puteve, ranolazin je primjenljiv kod bolesnika sa anginom sa bradikardijom, AV blokom, hipotenzijom i pobolom dišnih puteva[25].

U Europi preporučena početna doza ranolazina je 375 mg 2x dnevno. Nakon 2-4 tjedna, doza se može titrirati na 500 mg 2x dnevno te ovisno o odgovoru bolesnika do najviše preporučene doze od 750 mg 2x dnevno. Ranolazin je indiciran kao dodatna terapija za simptomatsko liječenje bolesnika sa stabilnom anginom pektoris koji nisu učinkovito kontrolirani ili imaju intoleranciju na lijekove prve linije antianginoznog liječenja. Lijek uskoro možemo očekivati i u Hrvatskoj s indikacijom kao u ostalim zemljama Europe, no vrijedi napomenuti da je FDA ranolazin već odobrila i kao prvu liniju liječenja kronične angine pektoris.

stipation. There was no interruption of the therapy due to extension of the QTc-interval and no recording of arrhythmia "torsades de pointes". Annual mortality was 2.8% compared to >5% according to DTS[21].

Ranolazine may be useful in treatment of heart failure with impaired diastolic and/or systolic function. It greatly improves the impaired intracellular ion homeostasis and reduces the increase in diastolic tension. Several experimental models have demonstrated improvement of left ventricular (LV) end-diastolic pressure, LV filling pressure, diastolic pressure and diastolic stress. No negative inotropic effect was indicated.

The potential application of ranolazine as an antiarhythmic drug is especially interesting and it is worth attention. Namely, due to the fact that it extends the QTc-interval, it was a disputable issue at the beginning, but due to publication of the results of the MERLIN study, the opinion has changed. Despite the extension of the QTc-interval, the study results clearly showed that ranolazine reduces episodes of supraventricular and ventricular arrhythmias in patients with ischemia. Tests have been recently conducted on patients with type 3 syndrome of long QT-interval associated with prolonged open sodium channel during the time of depolarization of the membrane which significantly increases the possibility of deadly outcome. In such risk population, the eight-hour infusion of ranolazine significantly reduced QTc-interval by 26.3 ms ($p < 0.0001$) and improved diastolic relaxation. In conducted presentation of the case of a patient with alcoholic cardiomyopathy and malign ventricular tachycardia refractory to aggressive traditional therapy, ranolazine proved to be very efficient in dose of 1000 mg 2x a day. Ranolazine was efficient both in interruption of atrial fibrillation and prevention of its recurrence on animal models, and in patients although it was registsred in small groups of patients.

To conclude, the inhibition of late sodium channels represents a new form of treatment in patients with chronic angina pectoris. Apart from proved antianginal effect, ranolazine may represent a new possibility of treatment of heart diseases associated with impaired homeostasis of myocardial ions, especially in patients with impaired homeostasis of Na ions as it occurs in case of heart failure. Finally, the inhibition of late sodium currents may represent a new antiarrhythmic approach of especially atrial and ventricular arrhythmias (tachycardias). Further researches of ranolazine in case of heart failure with systolic and diastolic dysfunction and in patients with atrial fibrillation will determine possible future therapeutic indications. Since it has no effect on heart rate, BP and respiratory tract, ranolazine may be used in patients with angina with bradycardia, AV block, hypotension and respiratory tract morbidity[25].

In Europe, a suggested initial dose of ranolazine is 375 mg 2x a day. After 2-4 weeks, the dose may be titrated to 500 mg 2x a day and subject to patient's response, it may be titrated to the highest recommended dose of 750 mg 2x a day. Ranolazine is indicated as an additional therapy for symptomatic treatment of a patient with stable angina pectoris who are not efficiently controlled or show intolerance to antianginal first line drugs. The most common adverse drug reactions with ranolazine are dizziness, headache, and nausea. The drug may be soon expected in Croatia

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with indication as in other European countries, but it is worth mentioning that FDA has already approved ranolazine as the first line drug for chronic angina pectoris.

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