Optimalna medikamentna terapija stabilne angine pektoris

Optimal Medical Therapy for Stable Angina Pectoris

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SAŽETAK: Patomorfološki supstrat stabilne angine pektoris uvelike se razlikuje od nestabilne angine pektoris. Akutni koronarni sindrom prezentira se slikom nestabilne angine pektoris, infarkta miokarda s elevacijom ili bez elevacije ST segmenta, a indicirani su invazivni pristup perkutanom koronarnom intevencijom ili kirurškom revaskularizacijom miokarda uz optimalnu medikamentnu terapiju. Za razliku od toga stabilna angina pektoris razvija se postupno i brojna su ispitivanja dokazala da se dugoročni rezultati (smrtni ishodi) ne razlikuju s obzirom na invazivni pristup. Osnovni je preduvjet primjena optimalne medikamentne terapije. U osnovi je čini trijas lijekova: nitrata produženog učinka, beta-blokatora i antagonista kalcija, uz drugu terapiju.

SUMMARY: The pathomorphological substrate of stable angina pectoris differs significantly from that of unstable angina pectoris. Acute coronary syndrome presents with the clinical picture of unstable angina pectoris and myocardial infarction with or without ST-segment elevation, and the invasive approach through percutaneous coronary intervention or surgical myocardial revascularization with optimal medical therapy is indicated. In contrast, stable angina pectoris develops gradually, and many studies have demonstrated that the long-term results (fatal outcomes) do not differ in comparison with the invasive approach. The main prerequisite is the application of optimal medical therapy. It is based on three medications: extended-release nitrates, beta blockers, and calcium antagonists, in addition to other treatment.

KLJUČNE RIJEČI: stabilna angina pektoris, klinička procjena bolesti, perkutana koronarna intervencija, kirurška revaskularizacija miokarda.

KEYWORDS: stable coronary heart disease, clinical assessment of disease, percutaneous coronary intervention, coronary artery bypass surgery.

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Razlikujemo nestabilnu i stabilnu anginu pektoris. Nestabilna angina pektoris sastavnica je akutnoga koronarnog sindroma uz infarkt miokarda s elevacijom ili bez elevacije ST segmenta. Najvećim dijelom nastaje na bazi rupture ili fisure aterosklerotskoga plaka i akutno je, za život opasno zbivanje. Zahtijeva više-manje hitnu intervenciju kao što je perkutana koronarna intervencija (PCI) ili kardiokirurško liječenje (CABG)[1]. Postupak kod stabilne angine pektoris trebao bi biti bitno drukčiji jer je riječ o stanju koje se, u pravilu, razvija postupno.

Podsjetimo se da je učestalost stabilne angine pektoris u porastu i prisutna je u 3 % populacije, a posebice u zemljama u kojima se ne pridaje dovoljno pozornosti prevenciji kardiovaskularnih čimbenika rizika, uključujući nikotinizam, neadekvatno liječenu ili neliječenu arterijsku hipertenziju, hiperlipoproteinemiju, šećernu bolest,

We distinguish between unstable and stable angina pectoris. Unstable angina pectoris is a constitutive part of an acute coronary syndrome with myocardial infarction with or without ST segment elevation. It is most commonly based on the rupture or fissure in atherosclerotic plaque and represents an acute, life-threatening event. It requires relatively rapid emergency intervention in the form of percutaneous coronary intervention (PCI) or cardiac surgery (coronary artery bypass grafting, CABG)[1]. In stable angina pectoris, the procedure should be significantly different, since it is a state that usually develops only gradually.

It bears reminding that the prevalence of stable angina pectoris is on the rise and is present in 3% of the population, especially in countries that do not give enough attention to the prevention of risk factors for cardiovascular diseases,

prekomjernu tjelesnu težinu, a dijelom zbog produženja životnog vijeka i konačno zbog moguće obiteljske sklonosti.

Stabilna angina pektoris najvećim je dijelom posljedica znatnoga aterosklerotskog suženja koronarnih arterija, ≥ 50 % suženja stabla lijeve koronarne arterije ili ≥ 70 % suženja jedne ili više epikardijalnih koronarnih arterija. Smjernice Europskoga kardiološkog društva za liječenje stabilne angine pektoris iz 2013. godine[2], osim aterosklerotskog suženja, uvode i novi pojam, mikrovaskularne bolesti i koronarnog spazma bez znatnijih (≥ 50 %) promjena na velikim koronarnim arterijama. Bolest se u muškaraca može pojaviti već u četvrtom desetljeću života, u žena nastupa kasnije, dok u dobi nakon šestog desetljeća učestalost bolesti ne ovisi o spolu.

U postavljanju dijagnoze angine pektoris ključno mjesto zauzimaju podatci dobiveni od bolesnika. Bolesnici se žale na bol u prsištu, a osjećaj je bola individualan, od pritiska pa sve do razdirućeg bola. Osim opisa bola, vrijedno je dobiti podatak o tome pojavljuje li se bol pri naporu. Posebno treba naglasiti da opseg napora odgovoran za pojavu bola nije stalan, a to znači da bolesnik jednog dana može podnijeti određeni napor, npr. penjanje stubama na treći kat, a sljedećeg dana bol se pojavljuje već pri penjanju na prvi kat. Zašto je to tako? Ako se bolesnik fizički opterećuje npr. neposredno nakon obilnijeg obroka, bol će se pojaviti ranije, a bol može izazvati i uzbuđenje. Tegobe su mnogo učestalije u zimskim mjesecima, a posebice izlaskom iz tople prostorije na hladnoću. Napadaji angine pektoris mogu se pojavljivati vrlo rijetko, primarno potaknuti tek težim opterećenjima, ali mogu postati svakodnevni, uzrokovani blažim opterećenjem i u mirovanju i tada se pristup bolesti mijenja i indicira invazivnu dijagnostiku. Stabilna angina pektoris, kako joj samo ime kaže, ne mijenja se tijekom dužega vremena, a barem ne u posljednja dva mjeseca. Dijagnoza se potvrđuje popuštanjem bola mirovanjem ili na nitroglicerol, unutar samo nekoliko minuta, ili tipičnim promjenama na elektrokardiogramu koje se potpuno povlače prestankom bola.[2,3]

Studija *COURAGE*[4], čiji su rezultati su objavljeni 2007. godine, uključila je 2287 bolesnika u 50 američkih i kanadskih centara s dokazanom simptomatskom stabilnom koronarnom bolesti srca (KBS). Kriteriji uključenja bili su dokazana, najmanje 70 %-tna stenoza u proksimalnom segmentu barem jedne epikardijalne koronarne arterije, kao i bolesnici kojima je ishemija objektivizirana neinvazivnim tehnikama: elektrokardiogramom, ergometrijskim testiranjem i slično. Bolesnici su potom randomizirani u dvije grupe. Prva skupina bolesnika (1149) obuhvaćala je bolesnike s optimalnom medikamentnom terapijom kojima je učinjena PCI, dok je druga skupina (1138) uključila bolesnike koji su bili samo optimalno medikamentno liječeni. Zanimljivo je da je upravo zahvaljujući toj studiji u liječenje stabilne angine pektoris uveden pojam optimalne medikamentne terapije. Praćenje bolesnika u prosjeku je trajalo 4,6 godina. Kumulativna stopa neželjenih kardiovaskularnih ishoda (smrt, infarkt i moždani udar) iznosila je 19,0 % u bolesnika liječenih primjenom PCI-ja, dok je u onih liječenih samo optimalnom medikamentnom terapijom bila 18,5 %. Razloga za ovakve rezultate ima više, ali, kako navode vodeći stručnjaci na ovom području, glavni je razlog u tome da koronarna arterija, koja je kronično aterosklerotski sužena, najčešće nije uzrok akutnih koronarnih zbivanja. U novije se doba susrećemo s rezultatima studija koje upućuju na to da otklanjanje „kritične" aterosklerotske stenoze primjenom PCI-

including nicotine abuse, untreated or inadequately treated arterial hypertension, hyperlipoproteinemia, diabetes, obesity, and partly also due to lifespan extension and possible family predisposition.

Stable angina pectoris is mostly the consequence of significant atherosclerotic stenosis of coronary arteries, ≥50% constriction of the left main coronary artery or ≥70% stenosis of one or more epicardial coronary arteries. The guidelines of the European Society of Cardiology for the treatment of stable angina pectoris from 2013 [2] introduced a new term in addition to atherosclerotic constriction: microvascular disease and coronary spasm with no significant (≥50%) changes on the great coronary arteries. In men, the disease can manifest as early as the fourth decade of life, whereas it appears later in women; after the age of 60 the incidence of the disease is not associated with the sex.

Data collected from the patient have a key role in establishing the diagnosis of angina pectoris. Patients complain of chest pains, and the feeling of pain can vary individually from pressure to severe pain. In addition to a description of the pain, it is valuable to know whether the pain manifests during exertion. It should be stressed that the extent of the exertion responsible for the appearance of the pain is not constant, which means that the patient can withstand a certain level of exertion on a given day, for instance climbing three flights of stairs, whereas the next day the pain appears already while climbing to the first floor. Why is this the case? If the patient undertakes physical exertion e.g. immediately after a large meal, the pain will manifest earlier, and it can be caused by excitement as well. Symptoms are much more common in winter months, especially when moving to the outside cold from a warm room. Angina pectoris episodes can be very rare, primarily incited only by more severe exertion, but can become a daily occurrence, caused by mild exertion and even happen at rest, which is when the approach to treatment changes and invasive diagnostics are indicated. Stable angina pectoris, as the term itself indicates, has not changed over a longer period, at least for the previous two months. Diagnosis is established by the pain lessening at rest or with nitroglycerin within as little as a few minutes or by typical changes on the electrocardiogram that disappear completely once the pain stops.[2,3]

The COURAGE[4] study, published in 2007, included 2287 patients in 50 American and Canadian centers with established symptomatic stable coronary heart disease (CHD). Inclusion criteria were proven, at least 70% stenosis in the proximal segment of at least one epicardial coronary artery and patients whose ischemia was objectivized using non-invasive techniques: electrocardiograms, ergometry, etc. Patients were then randomized into two groups. The first group of patients (1149) consisted of patients with optimal medical therapy who underwent PCI, whereas the second group (1138) consisted of patients who were only treated with optimal medical therapy. It is interesting to note that it was this study that introduced the concept of optimal medical therapy to the treatment of stable angina pectoris. Patient follow-up lasted an average of 4.6 years. The cumulative rate of adverse cardiovascular outcomes (death, infarction, and stroke) was 19.0% in patients treated with PCI application and 18.5% in those treated only with optimal medical therapy. There are multiple reasons for this result, but according to the leading experts in

ja ili kardiokirurškim zahvatom ne dovodi uvijek do nestanka simptoma. Usprkos uspješnoj revaskularizaciji 25 – 35 % bolesnika i dalje navode više ili manje izražene simptome angine pektoris uz pozitivan nalaz testa opterećenja. Ovaj podatak pridonosi novim spoznajama u patogenezi angine pektoris i uključuje mnoge mehanizme s aterosklerotskom opstrukcijom ili bez nje, koji mogu izazvati ishemiju miokarda, a time i anginu pektoris. Spominje se fokalni ili difuzni spazam koronarne arterije s aterosklerotskim plakovima ili pak bez njih, kao i promjene na razini mikrocirkulacije.[5]

Perkutana koronarna intervencija, bez ikakvih dvojbi, superioran je i nezamjenjiv oblik liječenja akutnoga koronarnog sindroma. Akutni koronarni sindrom razlog je najmanje 50 % PCI-ja u Sjedinjenim Američkim Državama i u svijetu. U takvim slučajevima uloga PCI-ja ostaje neprijeporna. Istraživači studije *COURAGE*, a posljednjih godina i drugi autori poručuju da se u stabilnoj KBS ne treba žuriti s liječenjem primjenom PCI-ja jer se istovjetni rezultati postižu i optimalnom medikamentnom terapijom.[6-8]

Vrlo je dobro poznato da neliječena KBS rezultira progresivnom slikom angine pektoris, infarktom miokarda, kongestivnim popuštanjem lijevoga srca i, konačno, smrtnim ishodom. Iako neki bolesnici, ako su neliječeni, ostaju asimptomatski ili imaju simptomatologiju kronične stabilne angine pektoris, vrlo su izgledni kandidati za iznenadnu srčanu smrt.[9]

Osnovna svrha terapije u bolesnika sa stabilnom anginom pektoris jest podići kvalitetu života, to jest ublažiti simptome, smanjiti učestalost anginoznih napadaja, usporiti, odnosno otkloniti progresiju bolesti i spriječiti neželjene događaje poput infarkta miokarda ili smrti. Ono što je danas nedvojbeno i poznato, intervencijska terapija ublažuje, odnosno većim dijelom uklanja simptome, ali u usporedbi s medikamentnom terapijom ne produžuje životni vijek.

Intervencijsko je liječenje (PCI ili CABG) u stabilnoj angini pektoris opravdano u slučaju terapijski refraktorne angine pektoris, višežilne koronarne bolesti, stenoze (> 50 %) debla lijeve koronarne arterije, znatnih stenoza i reducirane istisne frakcije (EF < 30%).[10]

U konačnici treba postaviti pitanje što je to optimalna medikamentna terapija stabilne angine pektoris. U osnovi je čini trijas: nitrata produženog učinka, beta-blokatora i antagonista kalcija. Naravno, uz ovo slijedi acetilsalicilatna kiselina, ACE inhibitor ili sartan, a u slučaju komorbiditeta (arterijska hipertenzija, dijabetes, hiperliproteinemija, hiperurikemija) i druga odgovarajuća terapija. Usprkos ovim recentnim preporukama kombinacije učinkovitih lijekova, njihova šira primjena nije zadovoljavajuća i mnogi bolesnici sa stabilnom anginom pektoris ostaju i dalje suboptimalno liječeni, pri čemu se u njih indikacija za PCI nerijetko prelako postavlja.[6] O nitratima ne treba mnogo govoriti. Njihova su vazodilatacijska svojstva poznata, a poznata je i mogućnost zasićenja njihovih receptora ako se preučestalo ordiniraju. Antagonisti kalcija dihidropridinskog reda treće generacije, a ovo se primarno odnosi na amlodipin i njemu srodne lijekove, selektivno blokiraju ulazak kalcija u mišićje vaskularne stijenke, uključujući i koronarne arterije, te uzrokuju vazodilataciju i sniženje arterijskoga tlaka, olakšani rad srca i smanjene potrebe za oksigenacijom miokarda.[11] Riječ je o lijeku koji za razliku od verapamila i diltiazema ne uzrokuje produženje atrioventrikularnog provođenja i može se kombinirati s beta-blokatorom. Kardioselektivni beta-blokatori blokiraju noradrenalinske beta-1-adrenergijske

this field, the main reason lies in the fact that the coronary artery with its chronic atherosclerotic constriction is usually not the cause of acute coronary events. Lately, we have seen study results which indicate that removing the "critical" atherosclerotic stenosis through PCI application or through cardiac surgery does not always lead to the disappearance of the symptoms. Despite successful revascularization, 25-35% of patients still report pronounced angina pectoris symptoms with positive cardiac stress test. This contributes to new insight in the pathogenesis of angina pectoris and includes many mechanisms with or without atherosclerotic obstruction which can cause myocardial ischemia, and thus angina pectoris as well. The focal or diffuse spasm of the coronary artery with or without atherosclerotic plaques has been mentioned, as well as changes at the level of microcirculation.[5]

There is no doubt that percutaneous coronary intervention represents a superior and irreplaceable form of treatment for acute coronary syndrome. Acute coronary syndrome is the reason for at least 50% of PCI interventions in the United States of America and the world. In these cases, the rule of PCI remains uncontroversial. The researchers in the COURAGE study, as well as other authors over the last few years, report that applying PCI in stable CHD should not be rushed, since identical results can be achieved with optimal medical therapy as well.[6-8]

It is very well known that untreated CHD results in the progression of diseases – angina pectoris, myocardial infarction, congestive left heart failure, and finally death. Although some untreated patients remain asymptomatic or have the symptomatology of chronic stable angina pectoris, they are very likely candidates for sudden cardiac death.[9]

The main treatment goal in patients with stable angina pectoris is to improve quality of life, i.e. ameliorate symptoms, reduce the frequency of angina attacks, slow or stop progression of the disease, and prevent adverse events such as heart attack or death. It has now become known and indubitable that interventional therapy reduces or mostly removes the symptoms, but does not prolong life in comparison with medical therapy.

Interventional treatment (PCI or CABG) for stable angina pectoris is justified in cases of therapeutic refractory angina pectoris, multivessel coronary disease, stenosis (>50%) of the left main coronary artery, significant stenoses and reduced ejection fraction (EF <30%).[10]

Ultimately, the question that needs to be asked is what optimal medical therapy for stable angina pectoris really is? Its basis is the triad of nitrates, beta blockers, and calcium antagonists. This is of course followed by aspirin, ACE inhibitors, or sartans, and other appropriate treatment in cases of comorbidity (arterial hypertension, diabetes, hyperlipoproteinemia, hyperuricemia). Despite these recent recommendations for effective medication combinations, the prevalence of their use is not satisfactory, and many patients with stable angina pectoris remain sub-optimally treated, with the indication for PCI often too easily set.[6] Nitrates need no special mention. Their vasodilatory effects are well known, as is the possibility of the oversaturation of their receptors if they are prescribed too often. Third-generation calcium antagonists based on dihydropyridine, primarily amlodipine and related drugs, selectively block calcium entry into the musculature of the vascular wall, including the coronary arteries, causing

receptore, usporuju rad srca, produžuju dijastolu, a također smanjuju vrijednosti arterijskoga tlaka i potrebu miokarda za kisikom. Iz ovoga slijedi da je kombinacija antagonista kalcija i beta-blokatora učinkovitija nego primjena samo jednog od navedenih lijekova zasebno.[12]

Ivabradin, osim bazične, trojne terapije stabilne angine pektoris, nalazi svoje mjesto u bolesnika u kojih sinusna aktivnost prelazi 60/min usprkos terapiji beta-blokatorom, ili pak u onih koji ne podnose beta-blokator zbog hipotenzivnih vrijednosti arterijskoga tlaka ili nekih drugih razloga. Preporučuje se pokušati kombinirati beta-blokator s ivabradinom.

Već je 1999. godine prof. Lionel Opie u časopisu „Lancet" napisao: „Ishemijsku bolest uglavnom smatramo posljedicom hemodinamskih promjena. Međutim, posljednjih smo godina shvatili da ishemijska bolest srca ima važnu metaboličku komponentu u svojoj patogenezi i danas prepoznajemo važnost liječenja i te komponente."[13] Lijekovi koji djeluju na metabolička svojstva miokarda jesu trimetazidin i ranolazin. To su lijekovi koji su, prema smjernicama liječenja stabilne angine pektoris[2], svrstani u lijekove druge linije: trimetazidin razreda II. b, a ranolazin u II. a.

Zaključak

Brojne studije, počevši od studije *COURAGE* pa dalje, pokazale su opravdanost primjene optimalne medikamentne terapije, tj. kombinacije nitrata, beta-blokatora i antagonista kalcija u liječenju stabilne angine pektoris. Dugoročno je dokazano da ovakav oblik liječenja nije inferioran s obzirom na primjenu invazivnih postupaka s pomoću PCI-ja i CABG-a. Postavlja se pitanje koliko su bolesnici informirani o rizicima i dobrobitima od invazivnog liječenja. Učestalost PCI-ja u SAD-u se od objave studije *COURAGE* ne smanjuje, a većina se oboljelih ne liječi primjenom optimalnoga medikamentnog liječenja.[14] U Europi situacija nije bitno bolja, a omjer intervencija u stabilnih i nestabilnih bolesnika iznosi 50 : 50 %.[15]

vasodilation and a drop in arterial pressure, better cardiac work, and reduced need for myocardial reoxygenation.[11] This is a drug that, unlike verapamil and diltiazem, does not result in the prolongation of atrioventricular conduction and can be combined with beta blockers. Cardioselective beta blockers block the noradrenaline beta-1 adrenergic receptors, reduce heart rate, prolong the diastole, and also reduce arterial pressure values and myocardial oxygen requirements. It follows that the combination of calcium antagonists and beta blockers is more effective than separate application of only one of these drugs.[12]

Aside from the basic triple therapy for stable angina pectoris, ivabradine has its use in patients where sinus activity is above 60/min despite beta blocker treatment, or in those who do not tolerate beta blockers due to hypotensive arterial pressure values or for some other reason. It is recommended to try to combine beta blockers with ivabradine.

As early as 1999, Prof. Lionel Opie wrote in the Lancet medical journal that "...Ischemic disease is mostly considered a consequence of hemodynamic changes. However, in recent years we have realized that ischemic heart disease has an important metabolic component in its pathogenesis, and today we recognize the importance of treating that component as well".[13] Drugs that effect the metabolic characteristics of the myocardium are trimetazidine and ranolazine. These are drugs that are considered second line medication according to treatment guidelines for stable angina pectoris[2]: trimetazidine is in class II b and ranolazine in class II a.

Conclusion

Numerous studies starting with the COURAGE study have shown that the application of medical therapy, i.e. the combination of nitrates, beta blockers, and calcium antagonists, is justified in the treatment of stable angina pectoris. There is long-term evidence that this form of treatment is not inferior in comparison with the application of invasive procedures using PCI and CABG. The question of the extent to which patients are informed on the risks and benefits of invasive treatment is yet to be answered. The prevalence of PCI in the US has not gone down since the publication of the COURAGE study, and most patients are not treated using optimal medical treatment.[14] The situation is not significantly better in Europe, where the ratio of interventions in stable and unstable patients is the same at 50%.[15]

LITERATURE

1. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011 Dec;32(23):2999-3054. https://doi.org/10.1093/eurheartj/ehr236
2. Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013 Oct;34(38):2949-3003. https://doi.org/10.1093/eurheartj/eht296
3. Kannel WB, Feinleib M. Natural history of angina pectoris in the Framingham study. Prognosis and survival. Am J Cardiol. 1972 Feb;29(2):154-63. https://doi.org/10.1016/0002-9149(72)90624-8
4. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007 Apr 12;356(15):1503-16. https://doi.org/10.1056/NEJMoa070829
5. Huqi A, Marilli M. Understanding and treating angina occuring after angioplasty. Dialog Cardiovasc Med. 2016;21:177-188.
6. Chan PS, Patel MR, Klein LW, Krone RJ, Dehmer GJ, Kennedy K, et al. Appropriateness of percutaneous coronary intervention. JAMA. 2011 Jul 6;306(1):53-61. https://doi.org/10.1001/jama.2011.916
7. Milo M, Nerla R, Tarzia P, Infusino F, Battipaglia I, Sestito A, et al. Coronary microvascular dysfunction after elective percutaneous coronary intervention: correlation with exercise stress test results. Int J Cardiol. 2013 Sep 20;168(1):121-5. https://doi.org/10.1016/j.ijcard.2012.09.059
8. Yong AS, Ho M, Shah MG, Ng MK, Fearon WF. Coronary microcirculatory resistance is independent of epicardial stenosis. Circ Cardiovasc Interv. 2012 Feb 1;5(1):103-8, S1-2. https://doi.org/10.1161/CIRCINTERVENTIONS.111.966556

9. Deligonul U, Vandormael MG, Shah Y, Galan K, Kern MJ, Chaitman BR. Prognostic value of early exercise stress testing after successful coronary angioplasty: importance of the degree of revascularization. Am Heart J. 1989 Mar;117(3):509-14. https://doi.org/10.1016/0002-8703(89)90722-9
10. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009 Mar 5;360(10):961-72. https://doi.org/10.1056/NEJMoa0804626
11. Kannam JP, Aroesty JM, Gersh BJ. Stable ischemic heart disease: Overview of care. Available at: https://www.uptodate.com/contents/stable-ischemic-heart-disease-overview-of-care#H8 (29.4.2017).
12. Cruickshank JM. The modern role of beta-blockers in cardiovascular medicine. People's Medical Publishing House – USA, 2011.
13. Opie LH. Proof that glucose-insulin-potassium provides metabolic protection of ischaemic myocardium? Lancet. 1999 Mar 6;353(9155):768-9. https://doi.org/10.1016/S0140-6736(98)00385-7
14. Henderson RA, Timmis AD. Almanac 2011: stable coronary artery disease. The national society journals present selected research that has driven recent advances in clinical cardiology. Kardio list. 2011;6(11):271-85. Available at: http://www.kardio.hr/pdf/Kardio%20list_2011_6_11_271-285.pdf (29.4.2017).
15. Strozzi M. Stable angina petoris in Croatia. Kardio list. 2011;6(11):268-70. Available at: http://www.kardio.hr/pdf/Kardio%20list_2011_6_11_268-270.pdf (29.4.2017).

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