Srp Arh Celok Lek. 2016 Nov-Dec;144(11-12):590-596
ОРИГИНАЛНИ РАД / ORIGINAL ARTICLE
DOI: 10.2298/SARH161259OI
UDC: 616.12-085

The effects of implementation of guideline-directed medical therapy on relief of angina in patients with stable coronary artery disease in Serbia

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SUMMARY

Introduction Adherence to proposed lifestyle changes and prescribed medication in patients with stable coronary artery disease (SCAD) is poor.

Objective We sought to investigate the influence of adjusting guideline proposed medications on relief of angina in a large group of patients with SCAD in Serbia.

Methods The study included a total of 3,490 patients from 15 cardiology clinics with symptoms of stable angina and at least one of the following criteria: abnormal electrocardiogram (ECG), history of myocardial infarction (MI), positive stress test, significant coronary artery disease on coronary angiogram or previous revascularization. All the patients underwent comprehensive evaluation at initial visit and after two months. The relief of angina was study end-point defined as any reduction in Canadian Cardiology Society (CCS) class, number of angina attacks per week and/or number of tablets of short-acting nitrates per week.

Results Most patients were included based on abnormal ECG (48.4%). At Visit 1, the average number of prescribed classes of medications to a single patient increased from 4.16 ± 1.29 to 4.63 ± 1.57 ($p < 0.001$). At the follow-up, the patients had significantly lower blood pressure (141 ± 19 / 85 ± 11 vs. 130 ± 12 / 80 ± 8 mmHg; $p < 0.001$) and most of them reported CCS class I (63.3%). The average weekly number of angina attacks was reduced from 2.82 ± 2.50 at Visit 1 to 1.72 0 ± 1.66 at Visit 2, as well as average weekly use of short-acting nitrates to treat these attacks (2.69 ± 2.53 to 1.74 ± 1.47 tablets; $p < 0.001$ for all).

Conclusion Adjustment of prescribed medications to guideline recommendations in a large Serbian patient population with prevalent risk factors led to significant relief of angina.

Keywords: stable coronary artery disease; guidelines; medical therapy; trimetazidine

INTRODUCTION

As a consequence of high prevalence of risk factors for atherosclerosis, low income, and insufficient level of health education, ischemic heart disease is the leading cause of death in Serbian population [1]. The latest guidelines on stable coronary artery disease (SCAD) have been implemented for several years, but patients' adherence to proposed lifestyle changes, prescribed medication, and cardiovascular rehabilitation remains poor [2, 3]. Although improvement in medical treatment has been noted in large registries of patients with SCAD, there is room for further step-up [4].

Traditionally, the treatment of SCAD is based on hemodynamic agents that reduce the energy requirements of myocardial cells by lowering blood pressure and heart rate (beta blockers, calcium antagonists) or through vasodilation enhance coronary blood flow by systemic and coronary arteriolar and venous vasodilatation with consequent preload reduction (nitrates), leading to symptom relief. On the other hand, lately, along with these well established drugs, new classes of treatments with entirely (trimetazidine, ivabradine) or partly (nicorandil) different mechanisms of action have been introduced in the treatment of SCAD and supported by current guidelines

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[2]. Metabolic agents, like trimetazidine (TMZ), act as anti-ischemic medications by metabolic modulation. Angina patients accumulate free fatty acids (FFAs), which the cardiac muscle oxidizes for its energy requirements. FFAs oxidation demands more ATP to breakdown FFAs than glucose oxidation, requiring more oxygen to be supplied to the ischemic myocardium. Trimetazidine inhibits the use of FFAs as an energy source, shifting the myocardial metabolism to glucose utilization (glycolysis), which requires less oxygen than FFAs.

The effect of TMZ has been extensively studied in patients with SCAD. It has been shown that adding TMZ to standard therapy in patients with CAD, especially beta-blocking agents, confers clinical benefit of reduction of number of angina attacks, increasing exercise capacity, and prolonging exercise period before occurrence of ischemia (time to 1 mm ST segment depression). These benefits have been proven in different subsets of patients with coronary artery disease such as diabetics, patients with previous myocardial infarction or acute myocardial infarction undergoing primary percutaneous coronary intervention (PCI) or thrombolysis, undergoing coronary artery bypass grafting (CABG), as well as those not suitable for any kind of revascularization [4–10].

The reports dealing with management of SCAD in Serbia are scarce. Furthermore, there are no data regarding the current use of these "new treatments" in Serbian population of patients with SCAD.

OBJECTIVE

We sought to investigate the influence of strict implementation of current guideline-proposed medications on relief of angina assessed by the reduction of the functional class of angina pectoris, weekly occurrence of the angina, and the weekly use of short acting nitrates in a large cohort of Serbian patients with SCAD.

METHODS

In this multicenter, longitudinal study, we prospectively enrolled 3,490 consecutive patients from 15 outpatient cardiology clinics with symptoms of stable angina in an open design with repeated measurements of the patients' characteristics at two office visits. Patients were enrolled during February and March of 2014. Fifty cardiologists in those clinics evaluated the patients and included them in the study.

Before inclusion in the study, the patients were fully informed about the aims of the study and accepted correction of their prescribed therapy to meet the guideline-proposed goals. The patients were asked to consent to collecting data from their medical records on their condition, and were explained that their treatment will be corrected based on their clinical status and following the current recommendations for the condition. They had an opportunity to refuse institution of new medicines and use of their medical records for study purposes. The participating physicians were asked to act based on their own clinical judgment and to follow the recommendations given by the current guidelines. This means they had an opportunity to implement second-line drugs for treatment of SCAD if they considered that first-line drugs were not sufficient or if patients experienced any of the undesirable effects of the first-line treatment. Also, physicians had an opportunity not to change treatment of patients for whom they thought were in stable condition with well controlled risk factors for atherosclerosis. The study protocol was approved by the ethics committee of each participating institution. Patients were included in the study if they were older than 18 years of age and had SCAD defined according to clinical symptoms (typical or atypical chest pain, or angina equivalent, related to physical activity, lasting several minutes and ceases after stopping exertion or taking short-acting nitrates) and at least one of the following:

- ECG abnormality (presence of abnormal Q waves in any lead, ST segment depression or elevation equal to or greater than 0.5 mm in any two consecutive leads, negative T waves in any two consecutive leads);
- History of documented myocardial infarction (MI) more than three months previously;
- Positive stress test (exercise stress test, echocardiography stress test or myocardial perfusion scintigraphy);
- Performed coronary angiography with at least one diameter stenosis of epicardial coronary artery of more than 70%;
- History of revascularization either by PCI or CABG.

The patients were seen at the office visit on the day of inclusion in the study. The symptoms of angina were assessed and classified using Canadian Cardiology Society (CCS) classification [11]. The frequency of angina attacks and use of short-acting nitrates were also assessed. A 12-channel ECG was recorded in all the patients. Physical examination of the patients included height, weight and blood pressure measurement, the presence of known risk factors for atherosclerosis (diabetes, smoking, hypertension, heredity), and manifestations of atherosclerotic disease (peripheral arterial disease, cerebrovascular disease, heart failure, erectile dysfunction, renal failure) were also examined.

The patients' prescribed medications were thoroughly assessed including type of agent, daily dose and total duration of therapy. These include antiplatelet agents, beta blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), long-acting nitrates, lipid lowering agents and metabolic agents to treat the angina (TMZ, ranolazine and nicorandil). According to the current European Society of Cardiology guidelines on stable coronary artery disease, new medications were added or previously prescribed ones were stopped, or their dose was adjusted to meet the guideline-proposed recommendations [2].

After two months, the patients were seen again and underwent physical examination and blood pressure measurement. Weekly number of angina attacks, angina class using CCS classification, and use of antianginal medica-

tions were assessed, as well as the tolerance and adherence to medications prescribed on the previous visit. The prescribed medications and their dosage remained unchanged throughout the follow-up period.

The primary end-point of the study was relief from angina consisting of any reduction in CCS class, any reduction in number of angina attacks per week and any reduction in number of tablets of short-acting nitrates taken per week.

Statistical analysis

Continuous variables are presented as mean values ± standard deviation (SD). Categorical variables are presented as percentages. Depending on the distribution of the data, t-test or Mann-Whitney test were used to compare continuous variables, whereas χ^2 and Fisher's test were used for categorical variables. P-value of <0.05 was considered significant. Statistical analysis was performed using commercially available software (PASW Statistics, version 18, SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 3,490 patients, mean age 67 ± 10 years (53.2% males) were enrolled in the study. Most patients fulfilled only the ECG criterion for inclusion in the study (Table 1). Significant proportion of enrolled patients were hypertensive, while other atherosclerotic risk factors were present in expected proportions. The patients' clinical characteristics are given in Table 2. For every class of medications (antiplatelets, long-acting nitrates, beta-blocking agents, Ca-antagonists, ACE-inhibitors, ARBs or statins) there was significant change in number of patients taking them, when their therapy was corrected according to guidelines at Visit 1. Of note, this difference was the greatest regarding trimetazidine and it was instituted for the first time in 3,064 out of 3,490 (87.8%) patients, while use of nicorandil

Table 1. Enrolment of patients in the study based on inclusion criteria (n = 3,490)

Inclusion criterion		Number of patients (%)
Abnormal ECG at Visit 1		1,689 (48.4)
History of myocardial infarction		1,270 (36.4)
Positive stress test	Exercise stress test	997 (28.6)
	Echocardiography stress test	121 (3.5)
	Positive coronary angiography	567 (16.2)
History of revascularization	Previous PCI	833 (23.9)
	Previous CABG	475 (13.6)

CABG – coronary artery bypass grafting; PCI – percutaneous coronary intervention

Table 2. Clinical characteristics of the patients at Visit 1 (n = 3,490)

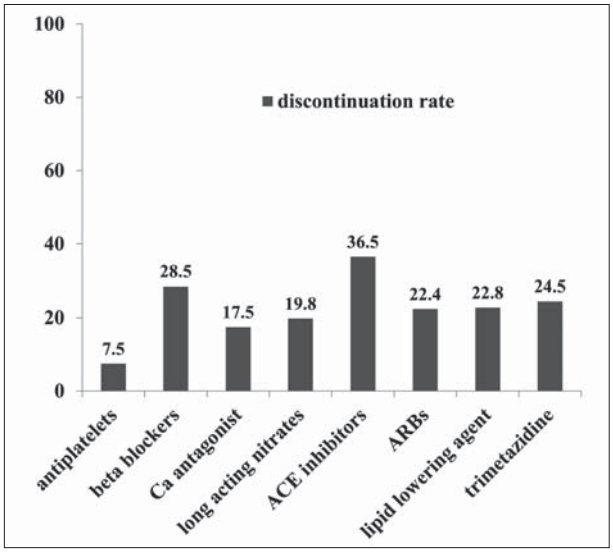
Clinical characteristics	Values*
Age (years)	66.71 ± 9.75
Male gender (%)	1,857/3,490 (53.2%)
Smoking (%)	1,361/3,294 (39.0%)
Hypertension (%)	3,162/3,490 (90.6%)
DM on OAD (%)	973/3,490 (27.9%)
DM on insulin (%)	300/3,190 (8.6%)
PAD (%)	475/3,490 (13.6%)
Previous CVA (%)	395/3,490 (11.3%)
Chronic renal failure (%)	211/3,490 (6.0%)
BMI (kg/m2)	27.01 ± 3.58
Systolic BP (mmHg)	141 ± 19
Diastolic BP (mmHg)	84 ± 11
Heart failure	592/3,490 (17.0%)
Erectile dysfunction	126/3,490 (3.6%)

* The values are presented as mean ± standard deviation and as the number of patients with percentage.
DM – diabetes mellitus; OAD – oral antidiabetics; PAD – peripheral arteria disease; CVA – cerebrovascular accident; BMI – body mass index; BP – blood pressure

Table 3. Change in prescribed medication to patients in the study at Visit 1 (n = 3,490)

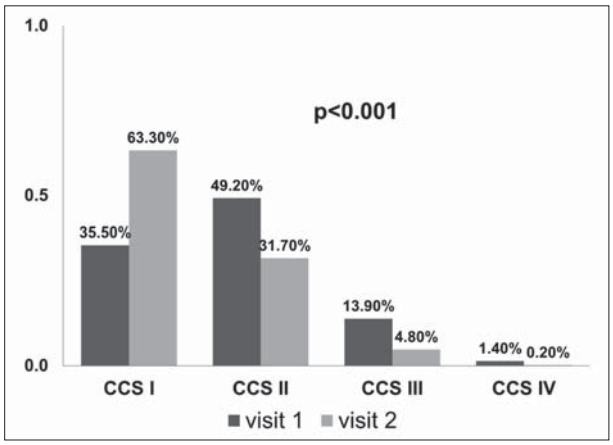
Drug class		Number of patients (%)		p	Duration of therapy before V1 (months)
		Prescribed	Not prescribed		
Antiplatelets	Taken before	2,777 (79.6)	224 (6.4)	<0.001	9.6 ± 6.6
	Not taken before	239 (6.8)	250 (7.2)		
Long-acting nitrates	Taken before	1,070 (30.6)	264 (7.6)	<0.001	36.5 ± 28.6
	Not taken before	221 (6.4)	1,935 (55.4)		
Beta-blocking agent	Taken before	1,890 (54.2)	753 (21.6)	<0.001	52.0 ± 25.7
	Not taken before	297 (8.5)	550 (15.7)		
Calcium antagonist	Taken before	1,200 (34.4)	254 (7.3)	<0.001	48.3 ± 28.2
	Not taken before	326 (9.3)	1,710 (49.0)		
ACE inhibitor	Taken before	1,901 (54.7)	416 (11.8)	<0.001	42.0 ± 30.5
	Not taken before	316 (9.0)	857 (24.5)		
Angiotensin receptor blocker	Taken before	249 (7.1)	72 (2.1)	<0.001	12.8 ± 8.4
	Not taken before	101 (2.9)	3,068 (87.9)		
Lipid lowering agent	Taken before	1,706 (48.9)	504 (14.4)	<0.001	28.4 ± 22.8
	Not taken before	365 (10.5)	915 (26.2)		
Trimetazidine	Taken before	182 (5.2)	59 (1.7)	<0.001	6.2 ± 3.4
	Not taken before	3,064 (87.8)	185 (5.3)		

ACE – angiotensin-converting enzyme; V1 – Visit 1



Graph 1. The rate of discontinuation of prescribed medications at Visit 1; the graph displays high rate of discontinuation of several classes of medications at Visit 1

ACE – angiotensin-converting enzyme; ARB – angiotensin II receptor antagonist



Graph 2. Canadian Cardiovascular Society (CCS) angina class in patients at Visit 1 and 2; the graph displays significant reduction in angina severity, expressed as CCS class, in study population at Visit 2, after institution of adjusted medical therapy according to current guidelines

and ranolazine was negligible (0.05% and 0.00%, respectively) (Table 3). There was a high rate of discontinuation of previously prescribed medications, classified in groups, at Visit 1, initiated by treating physician (Graph 1). At Visit 1, number of prescribed medications from previously defined groups of medication increased from 4.16 ± 1.29 to 4.63 ± 1.57 ($p < 0.001$). The median number of prescribed drugs rose from four at Visit 1 (1–8) to five (0–7) at Visit 2.

There were 3,425 patients (98.14%) that were seen at Visit 2 and the data on study end-points were collected for them. At Visit 2, the patients had significantly lower blood pressure (141 ± 19 / 85 ± 11 vs. 130 ± 12 / 80 ± 8 mmHg; $p < 0.001$). The patients' functional class data were available for 3,425 patients (98.14%) and it improved significantly, with most patients reporting CCS class I (Graph 2). While most patients improved their CCS class, several patients deteriorated and some remained in the CCS class III and IV, warranting further investigation and possible need for invasive coronary angiography (Table 4). The average weekly number of angina attacks was reduced from 2.82 ± 2.50 at Visit 1 to 1.72 ± 1.66 at Visit 2, as well as the average weekly use of short-acting nitrates to treat these attacks (2.69 ± 2.53 to 1.74 ± 1.47 tablets; $p < 0.001$ for all).

Table 4. Change in CCS class at Visit 2 after adjustment of medical therapy

CCS class Visit 1 (No. of patients)	CCS class Visit 2 No. of patients (%)			
	1	2	3	4
1 (1,217)	1,199 (98.5)	18 (1.5)	0 (0.0)	0 (0.0)
2 (1,684)	923 (54.8)	749 (44.5)	12 (0.7)	0 (0.0)
3 (475)	46 (9.7)	295 (62.1)	134 (28.2)	0 (0.0)
4 (49)	6 (12.2)	21 (42.9)	15 (30.6)	7 (14.3)

CCS – Canadian Cardiovascular Society

DISCUSSION

To the best of our knowledge, this is the first study evaluating implementation of guideline directed treatment of stable coronary artery disease in Serbian population which is characterized by prevalent atherosclerotic risk factors and low socioeconomic level. Our study demonstrated that strict implementation of guideline-directed medical therapy in patients with SCAD led to significant improvement in patients' status, as indicated by the reduction of number of angina attacks, use of short-acting nitrates, and lower CCS class, but at a cost of increased number of prescribed classes of medications patients are taking. As expected and documented in previous publications, the use of beta-blocking agents and long acting nitrates was independently associated with relief of angina [12, 13, 14]. The use of trimetazidine at the initial study visit was low and substantially increased during the follow-up period. Of note, the existing use of nicorandil and ranolazine in Serbian population with SCAD was negligible.

We also observed a high rate of discontinuation of previously prescribed medication at Visit 1 (Graph 1). It was especially high for ACE inhibitors, but it was also worth of notice for beta blocking agents, ARBs, lipid lowering agents, and trimetazidine. The reason for this could be the presence of adverse events of the drugs, decreased patient compliance, and inefficient treatment for hypertension, which lead to switch from one drug class to another. Unfortunately, adverse events of the medicines and the patients' compliance were not systematically evaluated in the study.

The patients included in the study had a very high prevalence of hypertension, although significant proportion of them had been treated with antihypertensive medications. At Visit 1, besides adding trimetazidine to most patients' treatment, new medications were added and dosage of already instituted antihypertensive medication was corrected to meet the guideline- defined goals. At Visit 2, the patients had significantly lower blood pressure, within treatment goals proposed by guidelines. This might have caused an improvement in angina status and influence the primary end-point of the study *per se* [15]. Also, the increased compliance with already prescribed medication

could cause this effect on blood pressure regulation. Although adjustment of medical therapy has led to improvement in clinical status and CCS class in most of the patients, some still remained in CCS classes III and IV (Table 4). This demonstrates limitations of medical therapy alone in treatment of patients with SCAD, because the patients that haven't improved after correction of therapy may be candidates for invasive coronary angiography and interventional treatment. The important issue is an increase in already high number of classes of medications prescribed to patients at Visit 1. This may be caused by already inefficient treatment for angina, hypertension or dyslipidemia. The patients' blood pressure at Visit 1 was not in the range recommended by the current guidelines [15]. Also, many patients had an already proven CAD, so their treatment must have consisted of antiplatelet agent(s), a lipid lowering drug, and potentially a beta blocker [16], besides treatment for hypertension. It can be argued that already instituted medications were not prescribed in optimal doses, so that participating physicians might have increased the dose of already prescribed medication instead of implementing new ones. Noteworthy, potential interaction between the drugs prescribed affecting their efficacy can also be the issue.

Antiplatelet agents were frequently prescribed to our patients (Table 3), given as secondary prevention, because most patients had a previously proven CAD (history of MI, PCI or CABG) (Table 1) [16]. The same applies for beta-blocking and lipid lowering agents. Increased use of trimetazidine is in line with current guidelines that recommend its use as a second line treatment for patients who are still symptomatic despite use of the first line medications (beta-blocking agents, calcium antagonists and, nitrates) or who cannot tolerate them [2]. However, it should be underlined that indication for its use bears IIB class indication, level of evidence B [2]. The reason to prescribe a second line agent, like TMZ, as a monotherapy should be guided by intolerance of the first line treatment, notably bradycardia induced by beta-blocking agents, headache and hypotension caused by long acting nitrates or bradycardia, hypotension and peripheral edema caused by Ca antagonists. This finding corroborates a large meta-analysis by Peng et al. [17] of randomized trials comparing efficacy of TMZ added to conventional therapy vs. conventional therapy only in patients with stable angina. On the other hand, another meta-analysis, done by Belsey et al. [18], has demonstrated beneficial effects of adding TMZ to beta-blocking agents or Ca antagonists on exercise tolerance and weekly angina frequency, but it was not associated with the decrease in use of short-acting nitrates. The evidence for TMZ as mono-therapy is not so robust and large meta-analysis did not demonstrate clear benefits from TMZ compared to alternative regimen with nitrates. However, relatively few side effects is one of the most important advantages of TMZ that supports its use in stable coronary artery disease [19]. Since the effects of TMZ are related to metabolism of FFA, it also benefited patients with heart failure, improving echocardiographic indices of systolic and diastolic function [20]. It can be argued that the period of two months between the study visits may not be sufficient for instituted therapies to reveal their full effect. However, the studies on effects of TMZ in patients with SCAD evaluated its effects after four to eight weeks of therapy, which makes our study design appropriate [7, 21, 22].

Study limitations

The study was not randomized and the effects of such design have to be acknowledged. The time interval during which stable angina was present was not assessed at the inclusion in the study, so that complaints may be caused by in-stent restenosis after PCI, especially within six months after intervention, or graft failure after CABG. The effects of prescribed treatment were measured by subjective patient's evaluation of their condition. The design of the study did not allow for a washout period between the discontinuation of the old and the introduction of any new medication. Also, for medical reasons of continuing treatment of angina, the study design did not include a crossover between prescribed medications groups. The patients were interviewed about their compliance and possible undesirable effects of the prescribed treatment both at Visit 1 and Visit 2, but this was not recorded in the study database, which may lead to erroneous conclusions regarding their effectiveness. All this limits the power of the study to assess the effects of individual medication groups on relief of angina as a study end-point.

CONCLUSION

Adjustment of prescribed medications to meet guideline-proposed goals in a large population of Serbian patients with stable coronary artery disease, characterized by high prevalence of risk factors, led to significant relief of angina, supporting the concept of guideline-directed medical therapy

NOTE

Epidemiology study database was provided by the Les Laboratoires Servier. Data analysis was performed solely by the authors and the scientific content of the manuscript was not influenced in any way by the Les Laboratoires Servier.

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Утицај медикаментне терапије усклађене према актуелним терапијским водичима на тежину стабилне коронарне болести код болесника у Србији

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КРАТАК САДРЖАЈ

Увод Особе које болују од стабилне коронарне болести недовољно се придржавају препорука о промени животних навика и редовном узимању терапије.

Циљ рада Циљ студије је испитати утицај медикаментне терапије усклађене према актуелним препорукама на тежину ангине пекторис код пацијената са стабилном коронарном болешћу у Србији.

Методе рада У студију је укључено 3.490 пацијената у 15 кардиолошких клиника са симптомима стабилне ангине и/или променама на електрокардиограму (ЕКГ), прележаним инфарктом миокарда (ИМ), позитивним тестом физичког оптерећења, ангиографски доказаном значајном коронарном болешћу или претходном реваскуларизацијом миокарда. Сви болесници су свеобухватно прегледани на првој посети и након два месеца. Циљ истраживања је смањење ангинозних тегоба, дефинисано као било какво смањење класе дефинисане Канадским кардиолошким друштвом (*CCS*), броја ангинозних напада недељно и/или смањење броја узетих таблета краткоделујућих нитрата.

Резултати Већина болесника је укључена на основу промена на ЕКГ-у (48,4%). На првом прегледу просечан број класа лекова прописаних пацијенту порастао је са 4,16 ± 1,29 на 4,63 ± 1,57 ($p < 0,001$). На контролном прегледу болесници су имали значајно мање вредности крвног притиска (141 ± 19 / 85 ± 11 вс. 130 ± 12 / 80 ± 8 *mmHg*; $p < 0,001$) и већина је припадала *CCS* класи I (63,3%). Просечан број ангинозних напада недељно смањен је са 2,82 ± 2,50 на првој посети на 1,72 ± 1,66 на другој посети. Такође је смањена недељна употреба краткоделујућих нитрата ради купирања ангинозних напада, са 2,69 ± 2,53 на 1,74 ± 1,47 таблете ($p < 0,001$ за све).

Закључак Усклађивање медикаментне терапије према актуелним препорукама доводи до значајног смањења ангинозних тегоба код болесника са присутним факторима ризика у Србији.

Кључне речи: стабилна коронарна болест; препоруке; медикаментна терапија; триметазидин

Примљен • Received: 10/09/2015 **Ревизија • Revision:** 07/03/2016 **Прихваћен • Accepted:** 01/04/2016