

National epidemiological study of recently diagnosed patients with stable angina pectoris

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Abstract

Background. Coronary artery disease (CAD) is a condition marked by the build-up of fatty deposits known as atherosclerotic plaque within the coronary arteries, which may or may not completely block these arteries. Stable angina refers to consistent episodes of angina over a period of 3 to 6 months.

Methods. The main aim of our study was to collect epidemiological data concerning newly diagnosed patients with stable angina pectoris, including details about their treatments, acquire up-to-date information regarding the extent of control achieved in managing stable angina pectoris, and gather insights into patient adherence to prescribed treatments and therapies for stable angina pectoris. This national observational study was conducted in February and March 2023 in Serbia.

Results. Out of 810 patients, a total number of 796 patients fulfilled the inclusion criteria for the study. The mean age was 67.3 ± 9.8 years and 52.9% were women. At the time of screening 89.2% of patients had angina or angina equivalent symptoms. A total of 476 (59.9%) patients had a family history of coronary artery disease (CAD), 720 (90.6%) had hypertension (HTA), 305 (38.9%) had diabetes mellitus type 2 (DMT2), and 595 (77.5%) had dyslipidemia. Among patients, 32.2% were in Canadian Cardiovascular Society (CCS) Class I, nearly half of them (47.3%) were in class II and 19.3% were in Class III. Most of the patients with high levels of total cholesterol, HDL, LDL and triglycerides (high-risk groups) were in CCS class III. The most frequently used combination of anti-anginal drugs in patients (26.7%) was beta-blockers (BB), trimetazidine and calcium channel blockers (CCA) (90.5%, 85.4%, 53.4% respectively). Patients with CCS class III had the highest frequency of usage of long-acting nitrates, oral anticoagulants, diuretics, digoxin, and its derivatives. There was a significantly higher percentage of patients without any physical activity in Class III compared with class I and II (26% vs 7.7% and 19.3%, $p < 0.001$). Furthermore, patients with any level of physical activity (mild, moderate or intensive) were mostly classified as CCS class I.

Conclusion. In summary, our results correlated with findings from similar studies and registries. These findings could serve as a basis for the further improvement of the treatment of these patients in Serbia.

Key words

coronary artery disease, stable angina pectoris, epidemiology data

Introduction

Coronary artery disease (CAD) is a condition marked by the build-up of fatty deposits known as atherosclerotic plaque within the coronary arteries, which may or may not completely block these arteries. The evolving nature of coronary artery disease (CAD) can manifest clinically in different ways. It is typically grouped into two main categories: acute coronary syndromes and chronic coronary syndromes¹. Angina pectoris as a clinical entity was described as a sensation of pressure or tightness felt across the chest that could extend to the left arm, both arms, jaw, or back. It is typically triggered by physical exertion or emotional stress, it could also worsen after eating a heavy meal. The discomfort usually fades away when exercise

stops or with the use of sublingual nitroglycerin². Stable angina refers to consistent episodes of angina over a period of 3 to 6 months^{3,4}. However, there are atypical symptoms such as breathlessness during exercise without any lung issues or extreme fatigue during exertion, which are considered as equivalents to angina⁵. These unusual presentations, lacking the typical chest pain, are frequently observed in women, older individuals, and people diagnosed with diabetes. The Canadian Cardiovascular Society (CCS) grading system (Class I-IV) is a widely used method to categorize and assess the severity of stable angina symptoms. This grading system serves as a valuable tool for healthcare providers to evaluate the severity of stable angina symptoms, aiding in the selection of appropriate treatment strategies and interventions for effective management of the condition⁶.

Main aim of our study was to collect epidemiological data concerning newly diagnosed patients with stable angina pectoris, including details about their treatments, acquire up-to-date information regarding the extent of control achieved in managing stable angina pectoris, and gather insights into patient adherence to prescribed treatments and therapies for stable angina pectoris.

Methods

This was a national observational study conducted in February and March 2023 in Serbia. Patients were enrolled by investigators employed in various healthcare institutions throughout the territory of Serbia (hospitals, clinical centers, private practices, etc.). The total number of 810 patients were screened for eligibility and 796 among them fulfilled the inclusion criteria. Inclusion criteria were that the patient is male or female, older or equal 18 years (or legal age), patient presenting for a routine visit and confirming recently diagnosed stable angina pectoris according to the European Society of cardiology guidelines for chronic coronary syndrome¹. Exclusion criteria were patients less than 18 years old (or legal age) and if the patient is unwilling or unable to give his consent. Also, patients that refused personal data collection weren't included in this study. All the patients signed informed consent for participation in the study. We used CCS angina score⁶. Data on risk factors, medical therapy and the previous treatment were obtained during a routine patient visit and review of medical records. Physical activity was defined as follows: without physical activity, most weeks only light physical activity, intense physical activity for at least 20 minutes once or twice a week, intense physical activity for at least 20 minutes three or more times per week. Limitations of daily activities were rated on a visual analog scale by patients from 0 to 10 grades. Adherence was assessed with a compliance evaluation test and it was defined as "good adherence", "moderate adherence" or

"nonadherence" depending on the patient's responses⁷. Body mass index (BMI) was calculated as body weight divided by body height squared. BMI was categorized as "underweight" ($<18.5\text{kg/m}^2$), "healthy weight" ($18.5\text{--}24.9\text{kg/m}^2$), "overweight" ($25.0\text{--}29.9\text{kg/m}^2$) and "obesity" (30+ kg/m^2). Blood pressure was measured in every patient with a sphygmomanometer.

Data processing was done in the statistical package SPSS version 24. Qualitative variables are represented through frequencies and percentages. Numeric data were presented using the mean with standard deviation, median and range (minimum-maximum). Differences between categorical variables were tested with the Chi square test (χ^2). Statistical significance is defined at the level of the probability of the null hypothesis $p \leq 0.05$. For a better and more accurate assessment of the severity of anginal complaints, we tested the ratio of CCS class and other research variables. In addition to statistical significance, the proportion of each category by CCS classes is also presented. There were only 10 patients classified as CCS class IV, hence, due to the small proportion in the sample, this group was excluded from further analysis.

Results

Demographics, personal medical history and socio-epidemiological data

The mean age was 67.3 ± 9.8 years (68.0, 40-92 years), 52.9% were women. At the time of screening, 89.2% of patients had angina or angina equivalent symptoms. The average number of angina attacks per week was 2.4 ± 2.2 . The total of 476 (59.9%) patients had family history of coronary artery disease (CAD), 720 (90.6%) had a hypertension (HTA), 305 (38.9%) had diabetes mellitus type 2 (DMT2), and 595 (77.5%) had a dyslipidemia. More than half of patients were active or former smokers, and the majority of them had only light physical activity most weeks (Table 1).

Table 1. Demographic characteristics, risk factors and medical history

Baseline characteristics of the patients	f	%
Male	368	47.1%
Female	413	52.9%
	M ± SD	
Age – yr	67.3 ± 9.8	
Risk factors:	f	%
Hypertension (HTA)	720	90.6%
Diabetes mellitus (DM)	305	38.9%
Dyslipidemia	595	77.5%
Family history of coronary artery disease (CAD)	476	59.9%
Active smoker	232	29.7%
Former smoker	249	31.8%
Medical history:	f	%
Myocardial infarction (MI)	217	27.3%
Percutaneous Coronary Intervention (PCI)	252	31.7%
Coronary artery bypass grafting (CABG)	58	7.3%
Peripheral arterial disease (PAD)	120	15.1%
Pacemaker (PM)	40	5.0%
Atrial fibrillation (AF)	113	14.2%

Table 2. Physical activity, systolic and diastolic blood pressure according to CCS class

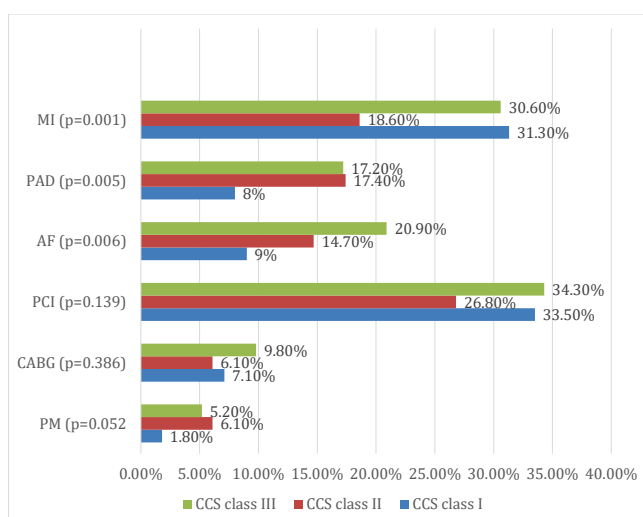
Physical activity (p<0.001)	CCS class I	CCS class II	CCS class III
No physical activity	17 (7.7%)	63 (19.3%)	34 (26.0%)
Most weeks mild physical activity	148 (66.7%)	210 (64.2%)	70 (53.4%)
Intensive physical activity at least 20 minutes, once or twice a week	44 (19.8%)	44 (13.5%)	22 (16.8%)
Intensive physical activity at least 20 minutes, three or more per week	13 (5.9%)	10 (3.1%)	5 (3.8%)
All (Σ)	222 (100%)	327 (100%)	131 (100%)
Systolic pressure (p=0.231)	CCS class I	CCS class II	CCS class III
<120 mmHg	28 (12.5%)	45 (13.9%)	17 (12.8%)
120-139 mmHg	107 (47.8%)	151 (46.6%)	51 (38.3%)
140-159 mmHg	75 (33.5%)	96 (29.6%)	47 (35.3%)
≥ 160 mmHg	14 (6.3%)	32 (9.9%)	18 (13.5%)
All (Σ)	224 (100%)	324 (100%)	133 (100%)
Diastolic pressure (p=0.032)	CCS class I	CCS class II	CCS class III
<80 mmHg	79 (35.3%)	95 (29.1%)	33 (24.8%)
80-89 mmHg	85 (37.9%)	151 (46.3%)	57 (42.9%)
90-99 mmHg	47 (21.0%)	65 (19.9%)	27 (20.3%)
≥ 100 mmHg	13 (5.8%)	15 (4.6%)	16 (12.0%)
All (Σ)	224 (100%)	326 (100%)	133 (100%)

CCS class and physical activity

Among included patients 32.2% were CCS Class I, nearly half of them (47.3%) were class II and 19.3% were Class III. There was a significantly higher percentage of patients without any physical activity in Class III compared with class I and II (26% vs 7.7% and 19.3%, p<0.001). Furthermore, patients with any level of physical activity (mild, moderate or intensive) were mostly classified as CCS class I. The average rate of limitations of every day activity was 3.6 ± 2.1 (Table 2).

CCS class and blood pressure

Only 9.2 % patients had a high systolic pressure at the time of physical examination, and most of them had a pulse in normal range. The lowest values of diastolic pressure (<80 mmHg) were associated with CCS class I, while the highest values of diastolic pressure (>100 mmHg) were associated with CCS class III (Table 2).

**Figure 1.** CCS class and medical history

CAD, PAD and CCS class

Approximately one third of patients had a history of myocardial infarction (MI) and percutaneous coronary intervention (PCI). The majority of patients with history of MI were in class I and III. Patients that had peripheral arterial disease (PAD) were in the larger percent in class II, and the largest part of patients with atrial fibrillation had class III (Figure 1).

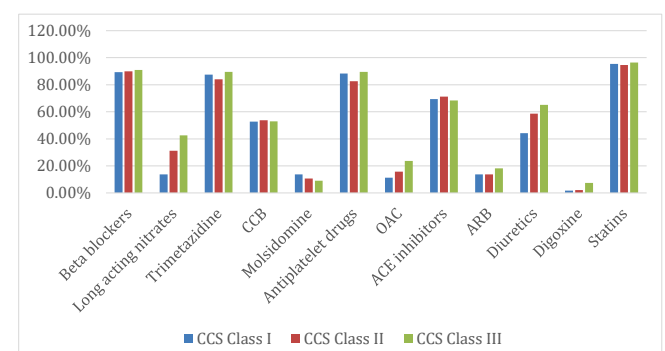
CCS class and medical therapy

The most used combination of anti-anginal drugs in patients (26.7%) was beta blockers (BB), trimetazidine and calcium channel blockers (CCA) (90.5%, 85.4%, 53.4% respectively). Among CCS classes in class III was the highest frequency of usage of long-acting nitrates, oral anti-coagulants, diuretics, digoxin and its derivatives (Figure 2).

CCS class and adherence

Half of patients had a moderate adherence to the therapy. The highest percentage of patients with a good adherence level were classified in CCS class I, with moderate adherence in CCS class II, and without adherence in CCS class III (Figure 3).

The mean body mass index (BMI) was 27.4 ± 5.9 kg/m², and the most of them were in the overweight category

**Figure 2.** CCS class and medical therapy

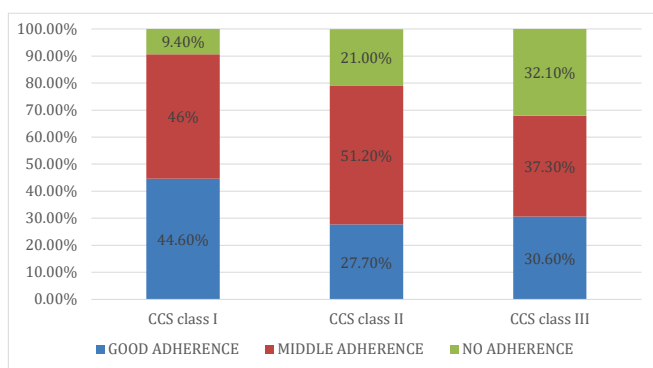


Figure 3. CCS class and adherence ($p < 0.001$)

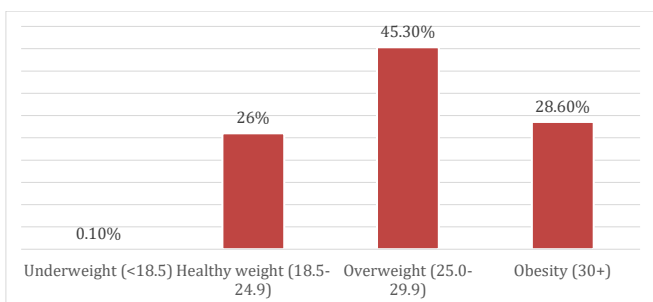


Figure 4. Body mass index

(Figure 4). The mean ejection fraction of the left ventricle was $55.0 \pm 8.9\%$.

CCS class and lipid profile

According to laboratory findings, 21.3% of patients had a high-risk range of LDL levels (21.3%) and 25% of patients had a high-risk range of triglyceride levels. Most of the patients with high levels of total cholesterol, HDL, LDL and triglycerides (high-risk groups) were in CCS class III. On the other hand, most of the patients with preferably lipid levels were in CCS class I (Figure 5).

Most of the patients (64.2%) had normal creatinine values and there was no statistically significant difference in CCS class in relation to creatinine levels (Figure 5).

There was no statistically significant difference among CCS classes in relation to gender, age, family history of CAD, HTA, DMT2, dyslipidemia, smoking status, BMI and systolic blood pressure.

Discussion

Angina pectoris is a clinical syndrome characterized by discomfort in the chest, but it can also be felt in the epigastrium, lower jaw, between the shoulder blades, or in the arms. The discomfort is most commonly described as pressure, tightness, fatigue, burning, a sense of shortness of breath, etc. Factors that can lead to an increase in the intensity of symptoms include increased physical activity and cold air. The pain typically lasts up to 10 minutes and decreases after rest or the use of medication^{1,8}.

In our study the mean age of patients with angina was 67.3 ± 9.8 years in a slightly higher percentage in women (52.9%). According to data from ESC-EORP CICC-LT registry which analyzed 6655 patients in 1-year follow-up, the median age was 67 years and, in contrast to our

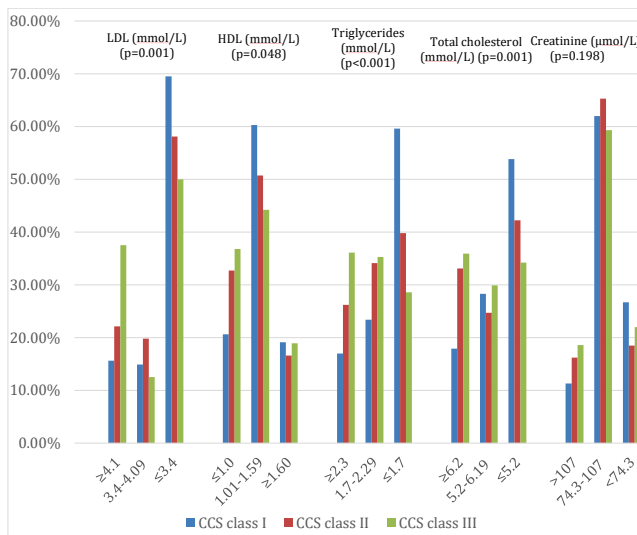


Figure 5. CCS class and laboratory findings

results, 73% were men⁹. In the Hemmingway et al. trial, the prevalence of angina varied from 0.73% to 14.4% in women and from 0.76% to 15.1% in men, with similar or slightly higher prevalence in women¹⁰.

Apart from the prevalent risk factors associated with CAD, physical inactivity has been recognized as a distinct predictor for the onset of CAD¹¹. In contrast, consistent engagement in physical activity seems to be efficacious in preventing CAD by influencing traditional risk factors and preserving endothelial function¹². Routine physical activity proves advantageous not only in preventing and treating CAD but also in modifying risk factors associated with coronary heart disease (CHD), including diabetes, HTA and hyperlipidemia¹³⁻¹⁵. In a meta-analysis conducted by Sattelmair et al, a notable association was discovered between engaging in physical activity and the primary prevention of CAD. The study revealed a 20% risk reduction for men and women participating in mild or moderate physical activity per week¹². In our study, we found a meaningful connection between the severity of angina symptoms and physical activity. This suggests that engaging in any level of physical activity is more beneficial than having no physical activity at all according to CCS classifications.

Data from literature suggests that occurrence of refractory angina in post – MI patients is common, with a frequency of 25% during 1- year follow up period, regardless of the presence of non-obstructive or obstructive coronary artery disease. Fanaroff et al. reported that post MI angina was present in nearly 30% of post PCI treated MI patients during 6 weeks follow-up period, without statistically significant difference between patients who presented with STEMI and NSTEMI. In addition, complete revascularization did not significantly reduce the angina when compared to incompletely revascularized patients. These results emphasize the importance of optimal medical management and other non-invasive strategies in treatment of these patients^{16, 17}.

Results of our study showed that there was a significantly lower percentage of patients with concomitant peripheral arterial disease (PAD) among patients who were classified as CCS Class I when compared to those

in CCS classes II and III. These results were in accordance with other large studies and registries, in which was shown that there is a large number of patients with overlap of CAD and PAD and that multiple atherosclerotic disease location was associated with significantly higher 1-year mortality when compared to patients with single-vessel disease¹⁸⁻²⁰. In addition, it is well-known that CAD and PAD share mutual risk factors and pathogenesis and that the prognosis and disease outcomes of these patients can be significantly improved through implementation of secondary prevention measures¹⁸. Many studies show that atrial fibrillation AF is an independent risk factor for the onset of CAD and the occurrence of acute coronary syndromes²¹⁻²³. The connection between AF and CAD is intricate, with a complex interplay at the pathophysiological level. These two conditions not only share common risk factors and disease development mechanisms but also tend to exacerbate each other in a harmful cycle. Consequently, addressing these ailments in isolation is impractical. The deterioration of one condition inevitably leads to the accelerated advancement of the other, emphasizing the need for a holistic and integrated approach to their management²⁴. The findings from our research indicate that individuals with both atrial fibrillation and stable coronary artery disease are predominantly categorized under CCS class III.

A strong association between HTA and coronary heart disease has been reported in PROCAM study²⁵. Increased systolic blood pressure has a greater effect on angina while diastolic blood pressure has a weaker influence on it²⁶. In opposite, our study results showed statistically significant correlation between raised diastolic blood pressure (>100mmHg) and CCS class III of angina and no difference in CCS class in correlation to personal history of HTA or raised systolic pressure.

Hyperlipidaemia is one of the main risk factors for cardiovascular disease. In PROCAM study hyperlipidaemia has been shown as a more significant risk factor for coronary heart disease in comparison with HTA and DM²⁵. Blood lipid levels are one of the essential components in many cardiovascular disease risk assessment systems. The Systematic Coronary Risk Estimation (SCORE 2 and SCORE 2 – OP) system is recommended as the risk assessment system of choice in European Guidelines on CVD prevention in clinical practice^{27,28}. The results in our study showed that the higher the levels of cholesterol are, the higher is the CCS class indicating the importance of lipids in the pathogenesis of angina. Patti G. et al metanalysis of 13 studies showed that lipid lowering therapy (high doses of statins) as a PCI pre-treatment leads to a significant reduction in periprocedural myocardial infarction and 30-day MACE (death, MI, or target vessel revascularization)²⁹. According to all of the above, the importance of adequate treatment of hyperlipidaemia in the field of cardiovascular diseases has been demonstrated once again.

Exogenous nitrates are the source of nitric oxide (NO), which is well known as a potent vasodilator. Nitrates provide their effect through venodilation and coronary and arteriolar dilation by increasing the level of cyclic guanosine monophosphate (cGMP) and lowering the level of free intracellular calcium³⁰. This consequently

results in reduction of the preload and myocardial oxygen consumption and in increase of subendocardial blood flow. Moreover, in higher doses, nitrates can act as arterial vasodilators, which results in reduction of afterload³⁰. Finally, nitrates cause platelet disaggregation by inhibiting fibrinogen binding to Gp IIB/IIIa receptors through increasing levels of platelet cGMP³¹. These data give the explanation of the fact that in our study nitrates were among the most used medications and they were most often used in CCS Class III patients.

The use of oral anticoagulant therapy in the context of stable angina is not a standard or typical treatment. While it is not yet used in routine practice for patients with stable coronary artery disease, oral anticoagulation might have a role in selected patients with a high risk of ischemic events but a low bleeding risk, as suggested by studies like the COMPASS trial³². Our study highlights a significant correlation between the majority of patients on oral anticoagulant medications and their classification into Class III of CCS classification. This association indicates a heightened risk of ischemic events among these patients, gesturing to a potentially more severe underlying coronary artery disease.

Diuretics are marked as first-line treatment of hypertension, according to European Society of cardiology guidelines for arterial hypertension³³. Results of the ALLHAT study shown superiority of thiazide and thiazide-like diuretics in reduction of adverse cardiovascular events³⁴. In addition, loop diuretics remain the cornerstone of acute heart failure treatment in terms of decongestion, symptom alleviation and reduction of HF rehospitalization rates³⁵, while potassium-sparing diuretics had a role in reduction of death and rehospitalization rates in patients with systolic HF³⁶. These data show that diuretics are effective in both hypertensive and volume overloaded patients and, as a result of existence of one of these, or even co-existence of both conditions, these patients are more often placed in higher CCS class and are more often treated with diuretics, which was also shown in the results of our study.

The positive inotropic effect of digitalis elevates myocardium's contractile state leading to increased myocardial oxygen consumption. Consequently, this has the potential to exacerbate angina pectoris³⁷, as the results of our study also show.

The CCS class of angina was proportional to the level of patients adherence to therapy – the better the adherence, the lower was the CCS class of angina. Hence, if there is adequate physicians adherence to the guidelines and good patients adherence to therapy, it could be translated into a better results in terms of patients' quality of life, cardiovascular mortality, etc. It is certainly necessary to apply all possible strategies in order to influence patient adherence as much as possible^{38, 39}.

Study limitations

National observational study designed to gather information on the characteristics of patients with angina pectoris, their comorbidities and therapy, with no intention of evolving into a longitudinal study.

Conclusion

In summary, the gathered information regarding the characteristics of patients with angina pectoris, their adherence, and angina control in Serbia generally correlated with findings from other studies and registries. These findings could serve as a basis for advancing the treatment of these patients.

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Sažetak

Nacionalna epidemiološka studija skoro dijagnostikovanih pacijenata sa stabilnom anginom pektoris

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Uvod. Bolest koronarnih arterija (CAD) je stanje obeleženo nagomilavanjem masnih naslaga poznatih kao aterosklerotski plak unutar koronarnih arterija, koje mogu ili ne moraju u potpunosti da blokiraju ove arterije. Stabilna angina se odnosi na stalne epizode angine tokom perioda od 3 do 6 meseci.

Metode. Glavni cilj naše studije bio je da prikupimo epidemiološke podatke o novodijagnostikovanim pacijentima sa stabilnom anginom pektoris, uključujući detalje o njihovim tretmanima, dobijemo najnovije informacije o stepenu kontrole postignute u lečenju stabilne angine pektoris i prikupimo uvid u pacijente što se tiče propisanih tretmana i terapija za stabilnu anginu pektoris. Ova nacionalna opservaciona studija sprovedena je u februaru i martu 2023. godine u Srbiji.

Rezultati. Od 810 pacijenata, ukupan broj od 796 pacijenata je ispunio kriterijume za uključivanje u studiju. Prosečna starost bila je 67,3±9,8 godina, a 52,9% su bile žene. U vreme skrininga 89,2% pacijenata imalo je anginu ili simptome ekvivalentne angini. Ukupno 476 (59,9%) pacijenata je imalo porodičnu istoriju bolesti koronarnih arterija (CAD), 720 (90,6%) je imalo hipertenziju (HTA), 305 (38,9%) je imalo dijabetes melitus tip 2 (DMT2), a 595 (77,5%) su imali dislipidemiju. Među pacijentima, 32,2% je imalo prema Kanadskom kardiovaskularnom društvu (CCS) klasu I, skoro polovina (47,3%) je bilo u klasi II i 19,3% u klasi III. Većina pacijenata sa visokim nivoom ukupnog holesterola, HDL, LDL i triglicerida (grupe visokog rizika) bila je u CCS klasi III. Najčešće korišćena kombinacija antianginalnih lekova kod pacijenata (26,7%) su beta-blokatori (BB), trimetazidin i blokatori kalcijumskih kanala (CCA) (90,5%, 85,4%, 53,4%). Najveću učestalost upotrebe dugodelujućih nitrata, oralnih antikoagulansa, diuretika, digoksina i njegovih derivata imali su pacijenti sa CCS klase III. Bio je značajno veći procenat pacijenata bez fizičke aktivnosti u klasi III u poređenju sa klasom I i II (26% prema 7,7% i 19,3%, $p < 0,001$). Štaviše, pacijenti sa bilo kojim nivoom fizičke aktivnosti (blage, umerene ili intenzivne) su uglavnom klasifikovani kao CCS klasa I.

Zaključak. Ukratko, naši rezultati su u korelaciji sa nalazima sličnih studija i registara. Ovi nalazi mogli bi poslužiti kao osnova za dalje unapređenje lečenja ovih pacijenata u Srbiji.

Ključne reči: koronarna bolest, stabina angina pektoris, epidemiološki podaci