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Original Scientific Paper

THE ASSOCIATION OF SYNTAX SCORE II WITH LIPID PROFILE, SERUM URIC ACID LEVELS AND DIABETES MELLITUS IN PATIENTS WITH MULTIVESSEL CORONARY DISEASE

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SUMMARY – The SYNTAX Score II (SS II) is a clinical tool that allows individualized prediction of mortality in patients with multivessel coronary artery disease (CAD) treated with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The aim was to examine whether lipid profile, uric acid and diabetes had a positive correlation with higher values of SS II. The study included 72 CAD patients. An online calculator was used to calculate SS II. Statistical tests (Mann Whitney U test and Shapiro-Wilk test) were used to assess correlations and differences in lipid profile, uric acid and diabetes status according to SS II values. There was a significant positive correlation between the proportion of patients with HDL levels above the reference values and SS II PCI. Patients with lower LDL values had significantly increased values of SS II CABG, but not SS II PCI. There was no significant correlation of total cholesterol and triglycerides with SS II PCI or SS II CABG. Patients with hyperuricemia had significantly higher SS II PCI but not SS II CABG. People with diabetes had significantly increased SS II PCI but not SS II CABG compared to non-diabetic patients. In conclusion, SS II is associated with some of the classic risk factors for atherosclerosis (uric acid, diabetes), whereas in our patient cohort there was a surprising correlation of SS II with high HDL levels and low LDL levels.

Key words: *Diabetes mellitus; Hyperuricemia; Lipid profile; Multivessel coronary disease; SYNTAX Score II*

Introduction

Atherosclerosis is a multifactorial, diffuse, progressive, chronic, multisystemic and inflammatory disease characterized by long-term high blood cholesterol levels[1]. The most common causes of atherosclerosis include excess caloric intake, too much fat and saccharides, hypertension, smoking, lack of physical activity, chronic stress, genetically determined problems with lipid metabolism, and many others[2]. Risk factors can

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significantly structurally and functionally alter coronary arteries accelerating the development of atherosclerosis, leading to earlier endothelial dysfunction and disorders of endothelial cell metabolism regulation[3]. The most important risk factors for the development of multicore coronary artery disease (CAD) are hyperlipidemia, hypertension, obesity, diabetes mellitus (DM), smoking, and old age[4].

Hyperlipidemia is the main risk factor for CAD, which is manifested by elevated laboratory values of lipids and/or lipoproteins in the blood (lipid profile)[5,6]. The most problematic form of lipid is low-density lipoprotein (LDL), for which there is a direct relationship between high LDL levels and recurrent coronary events in patients with established CAD[7]. Modification of LDL by oxidation by oxygen radicals or enzymatically leads to the release of cholesterol, which, by activating the endothelium, triggers the inflammatory response of endothelial cells. Inflammatory cells are the main initiators of the atherosclerotic process, when monocytes turn into foam cells that phagocytose cholesterol[8]. The resulting atherosclerotic plaque causes local narrowing of the lumen of the coronary artery and, together with arterial spasm, leads to myocardial ischemia, but the plaque can calcify or ulcerate, where thrombi accumulate that can narrow the artery and cause complete blockage of the coronary artery[2].

Diabetes mellitus is a chronic metabolic disease which significantly increases mortality from coronary heart disease by almost 2 to 4 times as compared with people without DM, and over 70% of people over 65 years of age with DM die from some form of heart disease[9,10]. It has been proven that the incidence and intensity of atherosclerosis is more pronounced in people with DM, and special emphasis is placed on vascular dysfunction, especially coronary microcirculation characterized by endothelial dysfunction, autonomic regulation, and impaired vasodilation response to hypoxia[3]. Patients with DM have a more complex form of coronary lesions and diffusely diseased blood vessels[11]. The protein adropin participates in the maintenance of endothelial energy homeostasis and thus has a protective effect on endothelial dysfunction in case of insulin resistance[12]. A study showed that serum adropin levels were lower in patients with type 2 DM, suggesting that it is a new marker for the development of coronary atherosclerosis[13]. There is increasing evidence that DM is a major risk factor for restenosis after percutaneous coronary intervention (PCI)[14,15]. Very low-density lipoprotein (VLDL) may be the most important lipid profile in promoting this phenomenon, as demonstrated by the research conducted by Wang *et al.*[14].

Hyperuricemia is elevated level of uric acid (urate) in serum (at the laboratory of the Osijek University Hospital Center, the reference value is 134-403 μmol/L), and is caused by breakdown of nucleic acids (purine bases). Uric acid in physiological concentrations makes up more than half of blood serum antioxidants, improves endothelial function by reducing oxygen radical synthesis, and thus restores the ability to synthesize and regenerate nitric oxide (NO) which reduces vascular tone and increases myocardial blood flow[16]. Hyperuricemia is most commonly associated with urinary arthritis (gout), but also with DM and metabolic syndrome, as an important risk factor for the development of insulin resistance[17]. Several studies also suggest an association between increased uric acid levels and increased mortality from heart failure, coronary heart disease, hypertension, chronic obstructive pulmonary disease (COPD), and chronic kidney disease[18,19]. Studies have shown that people with hyperuricemia have more inflammation and injury caused by oxidative stress, which can further increase the severity and progression of atherosclerosis and thus multicore coronary disease[20,21]. Hyperuricemia stimulates oxidative stress and stimulates the secretion of C-reactive protein (CRP), which together strongly trigger inflammatory mechanisms leading to endothelial dysfunction and proliferation of smooth muscle cells in blood vessels, resulting in reduced NO biosynthesis and increased stimulation of the renin-angiotensin system[22-24]. Elevated blood urate levels play an important role in the formation of inflammatory coronary artery plaques and may serve as an important marker in patients undergoing PCI, especially in diabetics, as an important risk factor for coronary artery restenosis[25].

Coronary artery disease and SYNTAX Score

Coronary artery disease is the leading cause of death in the world and is a local manifestation of atherosclerosis that can be clinically manifested in several entities[26] (Fig. 1). The term multivessel coronary disease refers to the involvement of at least two coronary arteries and/or involvement of the main trunk of the left

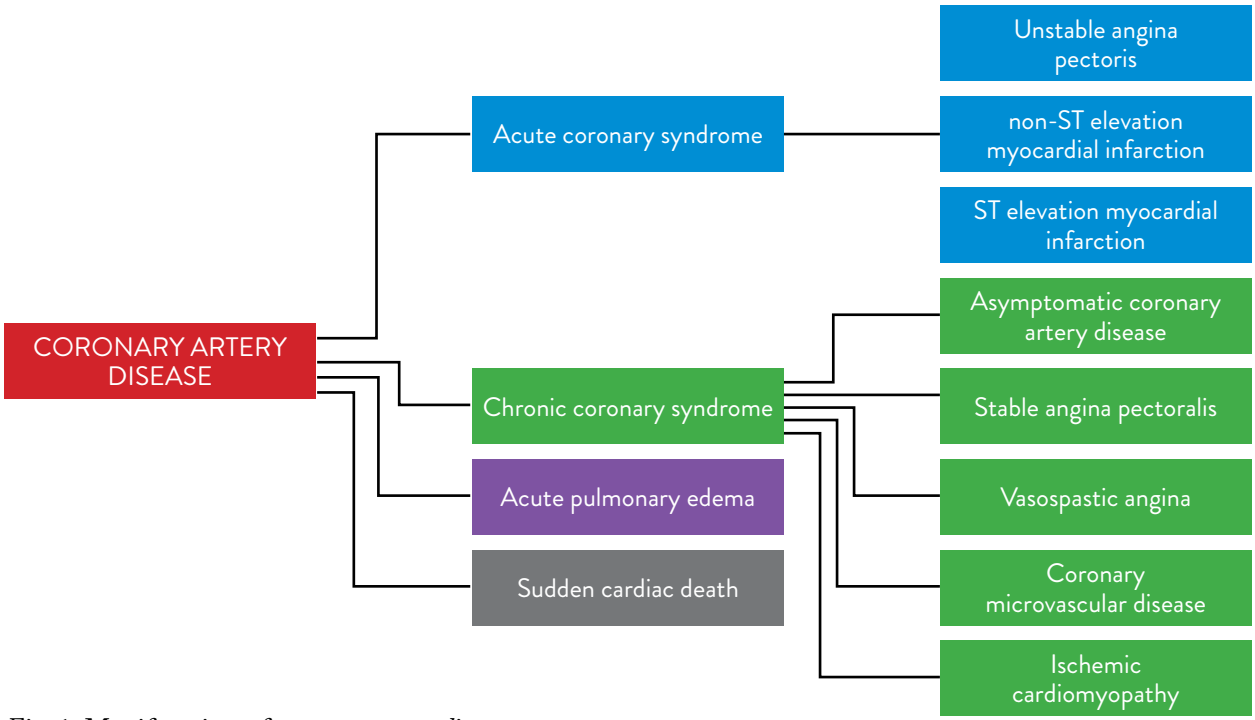

Fig. 1. Manifestations of coronary artery disease.

coronary artery[27]. The epicardial coronary arteries are most commonly affected, whereas the intramyocardial branches are mostly spared major changes[28]. Milder CAD is treated with drug therapy, and studies have shown that at least 30% of such patients undergo one of two invasive forms of myocardial revascularization[27]. With the development of PCI and surgical revascularization techniques (coronary artery bypass grafting, CABG), medical therapy has advanced to treat acute coronary syndrome (ACS) and manage stable CAD to improve angina, symptoms of heart failure, and quality of life[26,27,29].

The severity of CAD can be quantified/scored by the SYNTAX Score I (acronym from SYNergy between Percutaneous Coronary Intervention with TAXus and Cardiac Surgery, SS I)[4]. SS I was introduced as an angiographic tool that allows objective individualization of mortality prediction in patients with CAD and has become an important, even decisive factor in patients with multivessel CAD[30,31]. Given the absence of clinical factors in its computation, SYNTAX Score II (SS II) has been developed and showed better discriminant ability than SS I[32]. According to the latest American and European guidelines for myocardial revascularization, the decision whether to recommend CABG or PCI may be based on the SS II value obtained[30]. SS II is a scoring system for the integration of the interpreted coronary angiography findings (included in the SS I) and clinical variables[31,33]. SS II contains six clinical variables (age, sex, creatinine clearance, peripheral vascular disease, COPD and ejection fraction (LVEF)), and two anatomical variables of SS I and left main coronary artery involvement (LMCA)[34]. Some variables included in SS II remain the same after revascularization (age, sex, presence of peripheral artery disease and COPD), whereas some may change after PCI (creatinine clearance, LVEF) as in SS I[31]. The SS II value is based on the anatomy of coronary arteries and types of lesions, as well as by including crucial clinical characteristics, with a resulting score that predicts the probable percentage of morbidity in case a PCI is performed, or in case a CABG is performed, which may be useful before preparing for elective treatments in patients with multivessel coronary disease. Thus, there are two subgroups of SS numerical values for predicting mortality after CABG (SS II CABG) and PCI (SS II PCI) in patients with complex CAD. In patients with an SS II value greater than 33, CABG offers significan-

tly better treatment outcomes and a reduced mortality rate[35]. CABG, regardless of SS value, is considered to be a better therapeutic option in patients with complex coronary anatomy, diffuse coronary disease, severe left atrial dysfunction, DM present, or high procedural risk in performing PCI[36]. Numerous large studies (ARTS I, MASS II, ERACI-II, AWESOME) showed that PCI had similar survival rates compared to CABG, but higher revascularization rates were among patients undergoing PCI[37]. Nevertheless, in patients with multivessel coronary disease, revascularization *via* either PCI or CABG has been shown to prolong survival, and synergy between PCI and CABG has been enhanced by the introduction of SS II into clinical practice[26]. In this study, we wanted to investigate whether dyslipidemia, hyperuricemia and presence of DM as traditional risk factors for atherosclerosis, had a positive correlation with higher SS II values, i.e., whether the presence of the mentioned risk factors increased the mortality rate (SS numerical value) in patients if they were exposed to treatment with PCI (SS II PCI) or CABG (SS II CABG).

Patients and Methods

Study population

The study population consisted of patients with multivessel CAD who were hospitalized *via* emergency hospital admissions at the Department of Cardiovascular Diseases, Osijek University Hospital Center, and who had coronary angiography performed within a two-year period from October 1, 2015 until October 1, 2017. We retrospectively analyzed the available documentation only on patients for whom complete data required were available. Patients whose documentation was incomplete or did not contain the data necessary for analysis were excluded from the study.

Source of data

All necessary data were collected from the hospital information system and hospital archives. Baseline data (age and sex) and data required to calculate SS II (coronary angiogram findings) were collected on each patient. A review of medical records also collected data on lipid profile values (high-density lipoprotein (HDL), LDL, triglycerides, total serum cholesterol) and serum uric acid, as well as the presence or absence of DM in the subjects' medical history.

Measurement of lipid and uric acid serum levels

Data on lipid profiles and uric acid values were obtained from the findings recorded at the Department of Clinical Laboratory Diagnostics, Osijek University Hospital Center. Total cholesterol was calculated by a photometric method with cholesterol-oxidase (CHOD-PAP) and reference serum value defined by the laboratory was <5 mmol/L; HDL levels were determined with a homogeneous enzyme immuno-inhibitory method with a reference serum value of >1.2 mol/L; LDL levels were determined by a direct homogeneous method with a reference value of <3 mmol/L; and triglyceride levels were determined by an enzymatic glycerol phosphate oxidase (GPO) method with a reference value of <1.7 mmol/L. The uric acid values were calculated using a photometric ultraviolet-visible (UV) method with uricase, reference range 134-403 μmol/L, while CRP value was calculated by the immunoturbidimetric latex method with a reference value of <5 mg/L. All these measurements were performed on a Beckman Coulter AU680 biochemical analyzer with reagents from the same manufacturer, Beckman Coulter Diagnostics (Brea, CA, USA).

The process of calculating the SS II value

First, *via* an online calculator (www.syntaxscore.com) SS I was calculated, which requires a detailed coronary angiography analysis and answers to the specific questions regarding involvement of specific coronary arteries within multiple CAD. After obtaining the SS I value, which showed patient mortality on the basis of a detailed coronary angiogram analysis, SS II was calculated, which required the following data: endogenous creatinine clearance (which was calculated *via* the Modification of Diet in Renal Disease (MDRD) glomerular filtration rate (GFR) equation that included 4 variables, i.e., serum creatinine in μmol/L, age, sex, and ethnicity); the endogenous creatinine clearance value was expressed in mL/min/1.73 m^2. The findings of coronary angiogram revealed whether there was involvement of the left coronary artery; the ejection fraction value was needed, as well as data on the presence or absence of peripheral vascular disease and COPD in the subject's medical history. After obtaining the SS II

value, the correlations and differences in lipid profile, uric acid and DM according to SS II values were examined using appropriate statistical methods.

Statistical analysis

Categorical data were presented as absolute and relative frequencies. Numerical data were described by median and interquartile range limits. The normality of distribution of numerical variables was tested by use of Shapiro-Wilk test. Differences in numerical variables between the groups were tested by Mann Whitney U test. Association between variables was expressed with Spearman's correlation coefficient[38]. The level of significance was set at alpha=0.05. MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org, 2018) was used on statistical analysis.

Results

The study included data on 72 patients, 46 (64%) men and 26 (36%) women. The average age of the subjects was 67 (interquartile range, 60-73) years ranging from 41 to 84 years. DM as comorbidity was present in 32 (44%) patients (Table 1).

Table 1. Values of SS II PCI and CABG, lipid profile, uric acid and CRP

Parameter	Median (interquartile range)	Minimum--maximum
SS II PCI	41 (31.46-49.93)	19.1-71.1
SS II CABG	34.95 (26.18-40.28)	5.4-55.6
Total cholesterol (mmol/L)	5.45 (4.01-8.46)	2.32-8.76
HDL (mmol/L)	1.08 (0.87-1.34)	0.6-2.68
LDL (mmol/L)	3.52 (2.39-4.22)	0.69-5.62
Triglycerides (mmol/L)	1.56 (1.06-2.12)	0.74-7.49
Uric acid (μmol/L)	389.5 (313-513.5)	129-981
CRP mg/L (n=63)	6.45 (2.1-55.38)	0.20-166.9

SS II = SYNTAX Score II; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; HDL = high-density lipoprotein; LDL = low-density lipoprotein; CRP = C-reactive protein

There was a significant positive correlation between SS II PCI and HDL (Spearman's correlation coefficient ρ=0.299, p=0.01), i.e., if the values of HDL were higher, the values of SS II PCI were higher and *vice versa*, whereas other variables showed no significant association with SS II PCI. In case of SS II CABG, there was no significant association with lipid profile, uric acid and CRP (Table 2).

Table 2. Relationship of SYNTAX Score II PCI and CABG with lipid profile, uric acid and CRP

Parameter	Spearman correlation coefficient Rho (p value)	
	SS II PCI	SS II CABG
Total cholesterol (mmol/L)	-0.097 (0.42)	-0.208 (0.08)
HDL (mmol/L)	**0.299 (0.01)**	0.081 (0.50)
LDL (mmol/L)	-0.205 (0.08)	-0.234 (0.05)
Triglycerides (mmol/L)	-0.112 (0.35)	-0.188 (0.11)
Uric acid (μmol/L)	0.207 (0.08)	0.093 (0.44)
CRP (mg/L) (n=63)	0.124 (0.34)	0.115 (0.37)

SS II = SYNTAX Score II; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; HDL = high-density lipoprotein; LDL = low-density lipoprotein; CRP = C-reactive protein

Patients with HDL values greater than 1.2 mmol/L had significantly higher values of SS II PCI, median 46.3 (interquartile range, 36.2-54.5; Mann Whitney U test, p=0.03) compared to patients with HDL within the reference values. Furthermore, patients with elevated uric acid levels (greater than 403 μmol/L) had significantly higher values of SS II PCI, with a SS II median of 43.7 (interquartile range, 36.1-58.4; Mann Whitney U test, p=0.03) compared to patients with normal uric acid values (134-403 μmol/L) (Table 3).

Patients with LDL levels less than 3.0 mmol/L had significantly higher values of SS II CABG, median 35.50 (interquartile range, 31-43.9, Mann Whitney U test, p=0.04) compared to patients with LDL levels above 3 mmol/L (Table 4).

Patients with DM had significantly higher values of SS IIPCI, median 43.4 (interquartile range, 37.9-51.8) compared to non-diabetic patients (Mann Whitney U

Table 3. Values of SYNTAX Score II PCI relative to reference values of lipid profile, uric acid and CRP

Parameter		**Median (interquartile range) SS II PCI**	**p***
Total cholesterol	<5 mmol/L (n=31)	43.1 (34.8-54.8)	
	≥5 mmol/L (n=41)	40.2 (33.35-49.75)	0.26
High-density lipoprotein	<1.2 mmol/L (n=43)	39.5 (31.6-45.6)	
	>1.2 mmol/L (n=29)	46.3 (36.2-54.5)	0.04
Low-density lipoprotein	<3.0 mmol/L (n=29)	43.2 (35.35-55.45)	
	>3.0 mmol/L (n=43)	39.5 (32.8-49.4)	0.13
Triglycerides	<1.7 mmol/L (n=45)	42.6 (35.35-51.2)	
	>1.7 mmol/L (n=27)	39.5 (32.9-49.4)	0.38
Uric acid	134 – 403 μmol/L (n=39)	40.3 (32.8-46.3)	
	>403 μmol/L (n=33)	43.7 (36.1-58.4)	0.04
C-reactive protein	≤5 (n=26)	40.65 (32.15-45.2)	
	>5 (n=37)	41.95 (34.27-53.13)	0.24

*p<0.05, Mann Whitney U test; SS II = SYNTAX Score II; PCI = percutaneous coronary intervention

Table 4. SYNTAX Score II CABG values relative to reference values of lipid profile, uric acid and CRP

Parameter		**Median (interquartile range) SS II CABG**	**p***
Total cholesterol	<5 mmol/L (n=31)	35.3 (27.3-43.3)	
	≥5 mmol/L (n=41)	33.6 (24.2-38.8)	0.22
High-density lipoprotein	<1.2 mmol/L (n=43)	34.7 (24.9-38.9)	
	>1.2 mmol/L (n=29)	35.1 (27.35-43.9)	0.34
Low-density lipoprotein	<3.0 mmol/L (n=29)	35.5 (31-43.9)	
	>3 mmol/L (n=43)	32.6 (23.9-38.7)	0.04
Triglycerides	<1.7 mmol/L (n=45)	35.3 (26.6-41.6)	
	>1.7 mmol/L (n=27)	32.8 (21.2-38.9)	0.24
Uric acid	134-403 μmol/L (n=39)	33.6 (24.5-39.7)	
	>403 μmol/L (n=33)	35.5 (27.35-43.15)	0.35
C-reactive protein	≤5 (n=26)	33.4 (26.67-40.03)	
	>5 (n=37)	35.25 (26.18-39.87)	0.79

*p<0.05, Mann Whitney U test; SS II = SYNTAX Score II; CABG = coronary artery bypass grafting

Table 5. SYNTAX Score II PCI and CABG relative to the presence of diabetes mellitus

SYNTAX Score	Median (interquartile range)		p*
	Without DM	With DM	
SYNTAX Score II PCI	38.9 (29.5-9.0)	43.4 (37.9-51.8)	0.03
SYNTAX Score II CABG	34.15 (24.5-40.1)	35.35 (28.6-42.3)	0.27

*p<0.05, Mann Whitney U test; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; DM = diabetes mellitus

test, p=0.03). There was no significant difference in SS II CABG according to the presence or absence of DM (Table 5).

Discussion

SYNTAX Score is one of the newly developed scoring tools in cardiology that serves to objectively determine the state of CAD (SS I) and to help make a decision on the choice of invasive cardiac treatment or cardiac surgery based on the values obtained for SS II CABG and SS II PCI[34]. Numerous studies have confirmed clinical validity of this tool for identifying and evaluating complex CAD patients and for contributing to the appropriate choice of treatment in a wide range of different types of patients with CAD[39-42]. One study demonstrated the relevance of SS II by comparing the SS II in patients with DM and non-diabetic patients with multivessel coronary disease. The results showed that the SS II value obtained was almost equal regardless of diabetic status[43]. Therefore, it can be assumed that other clinical variables included in SS II, such as endogenous creatinine clearance or renal disease, are of greater importance than DM for assessing the risk of adverse outcomes in patients with CAD[43,44]. Brener *et al.* conducted a study in which they calculated SS I and SS II in 834 patients, where 42 patients died after four years (Kaplan-Meier rate, 4.3%) who had significantly higher SS II PCI than surviving patients (p<0.001)[45]. The SS II represents the complexity and degree of CAD as a representation of coronary atherosclerosis, so it should be assumed that it is also a reflection of systemic atherosclerosis. A study conducted by Yammine *et al.* showed that patients with a SS II value greater than 33 had severe atherosclerosis of the ascending aorta, which is the most important surgical site during CABG[30]. Thus, the SS II value must not only serve as a prognostic parameter and aid in the selection of invasive cardiac treatment for CAD, but may help modify surgical approach. Given that the SS II value obtained is a reflection of the complexity and degree of CAD, and risk factors for the development of CAD are known, this study investigated the possible link of several known risk factors for CAD, i.e., dyslipidemia, hyperuricemia and type 2 DM, with the SS II.

The study included 73 patients who underwent coronary angiography and demonstrated the presence of multivessel coronary disease, regardless of the type of coronary syndrome, 46 (64%) men and 26 (36%) women, median age 67 years. A total of 32 (44%) patients had DM as a comorbidity. The results showed a significant positive correlation between the proportion of patients with HDL levels above the reference value (1.2 mmol/L) with SS II PCI (ρ=0.299, p=0.01) and significant positive correlation between serum HDL concentration and SS II PCI (p=0.04). Patients with decreased LDL values had significantly elevated SS II CABG (p=0.04) but not SS II PCI values. Total cholesterol and triglyceride levels had no significant association with SSI II PCI or SS II CABG. Patients with elevated urate had significantly elevated SS II PCI (p=0.04) but not SS II CABG. Patients with DM had significantly higher SS II PCI values compared to those without DM (p=0.03), whereas there was no significant association between SS II CABG values and presence of DM. An observational study involving 1113 subjects, mean age 31.8, showed that traditional risk factors including cigarette smoking, body mass index (BMI), family history of CAD, hypertriglyceridemia, low HDL, metabolic syndrome, and DM were

significantly associated with the presence of CAD ($p<0.05$), whereas hypertension and hypercholesterolemia were not significantly associated with CAD[46]. Numerous epidemiological studies have, however, confirmed hyperlipidemia as an important risk factor for the development of atherosclerosis, which is the main cause of CAD, so through this study we expected confirmation of a positive association of total cholesterol, triglycerides and LDL with SS II. The results obtained were somewhat unexpected, i.e., a positive correlation between HDL and higher values of SS II PCI and negative correlation between LDL and higher values of SS II CABG. Large prospective studies show that decreased plasma HDL-cholesterol levels are associated with an increased risk of CAD[47,48]. In patients with hypobetalipoproteinemia, serum LDL is low throughout the patient life, which is associated with a reduced cardiovascular risk even in the presence of other important risk factors (smoking, hypertension)[49]. Several studies have shown that, despite the use of dalcetrapib and the consequent increase in HDL, the risk of recurrent cardiovascular events was not reduced[50-52]. HDL has distinctly heterogeneous effects on vascular endothelium due to changes in the proteins and lipids found in HDL. HDL can directly stimulate NO production in endothelial cells, in addition it has anti-inflammatory, anti-atherosclerotic and antiapoptotic effect. Interestingly, HDL may lose its vasoprotective effects and become dysfunctional in patients with chronic inflammatory disorders such as CAD, chronic renal dysfunction, DM, metabolic syndrome, rheumatoid arthritis, etc.[53-55] (Fig. 2). Dysfunctional HDL can

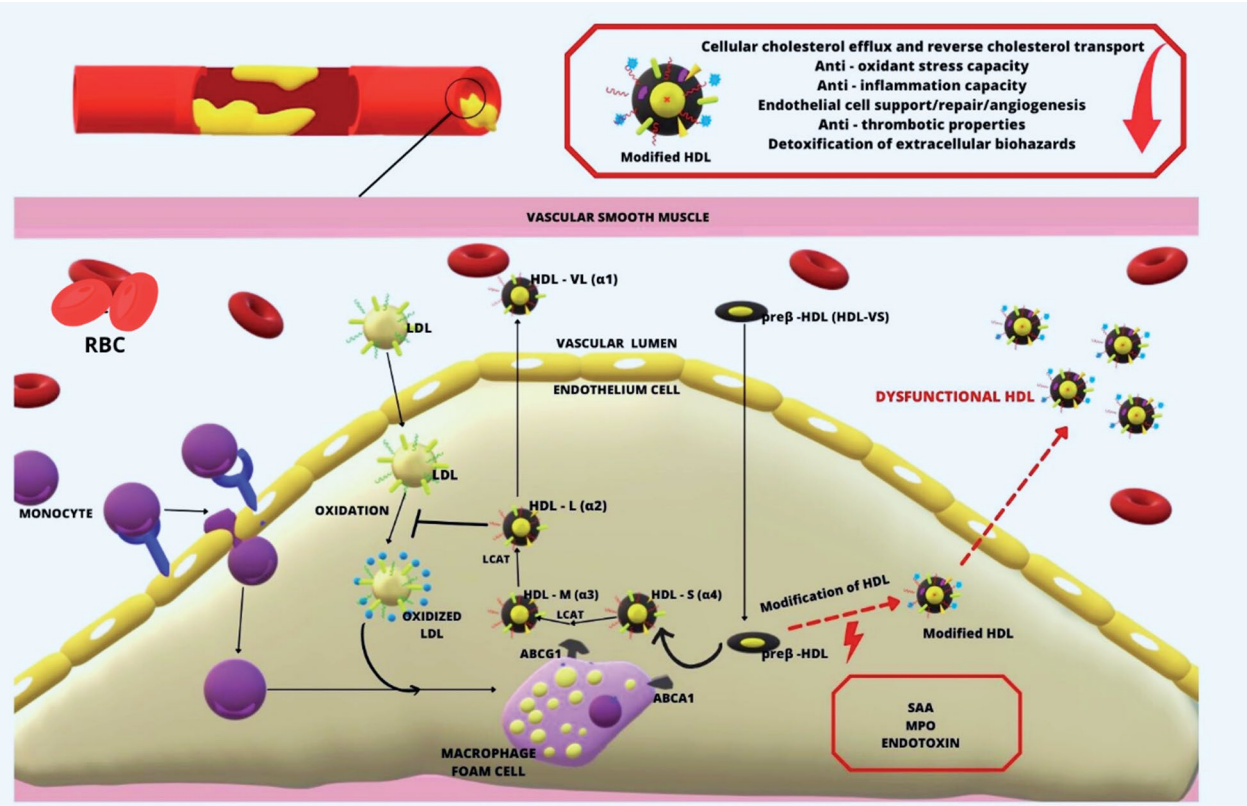

Fig. 2. HDL can lose its atheroprotective effects in chronic and inflammatory diseases, through modification, and become dysfunctional. Loss or modification of protein bonds for HDL or addition of proinflammatory or prothrombotic proteins contributes to HDL modification.

RBC = red blood cell; HDL = high-density lipoprotein; ABCA1 = ATP-binding cassette transporter; ABCG1 = ATP-binding cassette sub-family G member 1; LCAT = lecithin-cholesterol acyltransferase; MPO = myeloperoxidase; SAA = serum amyloid A

occur due to changes in the amount and type of proteins and lipids in the composition of HDL, or be the result of posttranslational modification when exposed to oxidants, as shown by *in vitro* studies, such as metal ions, peroxyl and hydroxyl radicals, aldehydes, various oxidants of myeloperoxidase (MPO), lipoxygenase, phospholipase A2, elastase, non-enzymatic glycation, and homocysteine[56].

A number of mechanisms have been proposed to be responsible for reduction of the anti-inflammatory effects of HDL. One of the mechanisms includes replacement of the ApoA-I particle in HDL cholesterol with serum amyloid A (SAA) particles[57]. Tolle *et al.* isolated HDL from patients with renal disease enriched with SAA, which causes a decrease in the anti-inflammatory response of HDL to inhibition of monocyte chemoattractant production in endothelial cells[58]. An *in vitro* study showed that myeloperoxidase-mediated oxidative modification of HDL or ApoA-I led to the formation of proinflammatory HDL that promotes NF-κB activation and endothelial VCAM-1 expression[59]. Glycation of HDL and ApoA-I in diabetics also leads to the formation of proinflammatory HDL cholesterol[57]. Given that all of these subjects have multivessel coronary disease, it is clear that the question arises whether HDL is vasoprotectively dysfunctional in these subjects, but on the other hand, a very important proinflammatory parameter that contributes to a significant increase in SS II values. Ansell *et al.* conducted a study showing that isolated HDL in patients with CAD failed to prevent LDL oxidation in endothelial cells, nor did it have the ability to inhibit LDL-induced monocyte chemotaxis[60]. In another study, a reduced ability of HDL to prevent LDL oxidation was shown in patients with acute coronary syndrome and ischemic cardiomyopathy, but not in patients with stable coronary artery syndrome[61]. Morgantini *et al.* found an increased number of oxidized fatty acids in HDL in patients with type 2 DM[62], which may be the reason for the reduced antioxidant role of this lipid, given that 44% of our patients had DM, in which CAD and possible renal impairment were certainly present. The initially paradoxical result of the positive correlation between HDL and SS II might now, in this light, be explainable. It is now known with certainty that in patients with severe and long-standing CAD, higher HDL levels are not associated with a reduced risk of cardiovascular events[63]. Does it make sense to apply new therapies aimed at increasing modified HDL in such patients or should a solution be sought in reducing the process of modifying the only protective form of cholesterol, will certainly be the subject of more detailed further research with better HDL particle identification techniques and thus a new era of drug discovery. The reason for the negative correlation between serum LDL and SS II CABG and statistical dissociation of cholesterol and triglycerides with SS II PCI and CABG, which are not pathophysiologically expected, is probably the long-term use of statin therapy that modulates lipid profile component concentrations, but may not necessarily have a marked effect on reducing the progression of atherosclerosis, as it has been shown that fats are not the only factors important for the progression of atherosclerotic disease of the coronary system. It is important to mention that none of the lipid profile parameters showed an association with SS I, which is not shown in the results. This may also be due to the limitations of coronary angiography, which may not provide the most realistic or most detailed picture of the complex coronary artery condition (the issue of microvascular CAD not visible on large epicardial arteries, differences in atherosclerotic plaque structure, etc.) and the possible need of a larger sample to detect discrete connections.

Hyperuricemia is increasingly mentioned as a possible important risk factor for the development of atherosclerosis and thus multivessel CAD, an association about which not enough is known, and hyperuricemia was therefore an interesting parameter to investigate a possible association with SS II. Numerous clinical studies have shown hyperuricemia as an important independent risk factor for cardiovascular mortality in the general population, particularly in hypertensive patients with DM or vascular disease[64-67]. A study conducted by Kim *et al.* showed that the overall risk of CAD death increased by 12% for each 1 mg/dL increase in uric acid and that hyperuricemia significantly increased the risk of death in women (about 70%), which is not the case in men[19]. Elevated uric acid levels were expected to be associated with a higher value of SS II. Increased serum uric acid concentration can lead to decreased lipid metabolism in endothelial

cells, an increase in free radicals that are drivers of endothelial activation and dysfunction leading to the initiation of inflammatory mechanisms that contribute to coronary artery atherogenesis[16]. On the other hand, normal serum uric acid concentration along with other extracellular antioxidants (α-tocopherol, ascorbic acid, carotenoids, and bilirubin) has an antioxidant effect[68]. Recent studies have shown that increased serum uric acid concentrations are present in patients with CAD compared to patients without that disease, but no association has been demonstrated between hyperuricemia and the degree of CAD. A study conducted by Marković Boras *et al*. in 85 patients with acute myocardial infarction (STEMI) who underwent PCI also calculated serum levels of lipids, urate, and CRP. Only six (7%) patients had lipid levels (cholesterol, triglycerides, HDL and LDL) within the reference range, while hypercholesterolemia was present in 70 (82%) patients[16]. A total of 44% of our subjects had DM, and insulin resistance in the proximal renal tubules has been shown to stimulate sodium hydrogen exchange leading to anion retention including uric acid[69,70]. The study showed that hyperuricemia and CRP were elevated in patients with multivessel coronary disease, which confirms that they are relevant markers in the assessment of cardiovascular risk, as both parameters are involved in the atherosclerotic process[19]. In our sample, CRP was not positively associated with higher SS II values. According to some authors, a strict association between hyperuricemia and CAD is not clear[71-75], so this potential link is not fully elucidated because there are studies that show the opposite.

According to the latest data, today about 6.4% of people in the world suffer from DM, and about 4.8% of the population have DM in the Republic of Croatia[76]. The figure of 44% of diabetic individuals, as obtained in our sample, is more significant and in this study, it clearly shows the connection between DM and multivessel CAD. About 80% of people with DM suffer from cardiovascular disease, most commonly CAD[2]. Patients with DM have an increased risk of CAD, chronic kidney disease, and blindness, a poorer prognosis, and higher mortality rates than non-diabetics[47]. SS II does not include DM as a comorbidity because endogenous creatinine clearance is thought to be a sufficient indicator of renal function that is markedly altered in diabetics. The most common signs of impaired renal function in diabetics are decreased GFR, increased blood creatinine concentration, micro- and macro albuminuria[11]. The results of this study showed the expected positive correlation between the presence of DM in patients with multivessel CAD with higher SS II values, and in the Introduction section, the mentioned pathophysiological changes in diabetic blood vessels explain the probable reason for the observed statistical correlation.

Limitations of the study included the fact that the study was retrospective (with all the issues inherent in retrospective research, e.g., the effect of a possible other known and/or unknown confounding factor on the SS II values, etc.), a possibly changed current state of the patient lipid profile resulting from statin intake, dietary changes, or some other internal factor, and inherent limitations for interpreting the angiographic finding that actually constitutes the value of SS I which is relevant to the calculation of SS II, with a consequently unrealistic representation of the modelled state of the coronary system possibly stemming from the attached coronary angiogram. The mere finding of CAD by coronary angiography (which analyzes large epicardial coronary arteries) does not provide data on other aspects of CAD, such as microvascular coronary dysfunction, ultrastructural changes of blood vessel walls and functional changes of coronary arteries and arterioles, consequently endothelial dysfunction and other functional disorders. Selective omission of these additional data, which is an inherent feature of classical coronary angiography (which does not include, for example, intravascular ultrasound or functional measurements) may affect final conclusions in the study of coronary disease, which is much more complex than the morphological substrate detectable on coronary angiograms. Given that SS II takes into account a number of other parameters and comorbidities (in addition to angiographic findings), it can be said that these parameters may have had the greatest impact on the results obtained. Some patients had an SS I value lower than 22 points, but when SS II was calculated, which included the mentioned additional parameters, an extremely higher value of SS II PCI and CABG was obtained. This could be seen as a confirmation of the impact of the additional clinical parameters while opening up new questions about the connection with the lipid profile in general, due to the

additional impact of endogenous creatinine clearance, peripheral vascular disease, COPD, gender and age on the numerical value of SS II.

A study in 543 subjects who underwent coronary angiography and had SS II calculated showed that epicardial adipose tissue thickness (p=0.035), carotid artery intima media thickness (p=0.04), and hypertension (p=0.014) were positively associated with high SS II[32]. Extremely large studies including the Multi-Ethnic Study of Atherosclerosis and Framingham Heart Study have shown that epicardial adipose tissue volume (EMT) is an independent risk factor for cardiovascular disease[77,78] *via* secreting numerous local cytokines such as chimerin, activin A, angiotensin II, IL- 6, macrophage chemoattractant, resistin, tumor necrosis factor, and vascular endothelial proliferation factor, exerting atherogenic potential on coronary blood vessels[79]. Given that these other markers can be determined noninvasively, they might be included in a future version of SS II, which would give the pathological finding of the lipid profile its importance, especially since triglyceride and cholesterol levels have not been shown in this study to have a statistically significant correlation. A retrospective analysis of patients with multivessel CAD who underwent PCI and CABG included 286 patients who had SS I and SS II calculated, with 79 (27.6%) patients dying within five years. This study showed a better estimate of mortality with SS II compared to SS I, and that SS II PCI and CABG predicted mortality well in patients who had low and medium values of SS II, but less well in patients who had extremely high values of SS II (recorded 54.7% compared to the predicted 40.5%)[80]. Thus, it is clear that a number of other parameters inherent in each patient with multivessel coronary disease may affect later or earlier mortality and make the SS II assessment less relevant. In case of hyperuricemia, the presence of diseases in patient history, such as gout or use of a combination of drugs that increase (losartan and hydrochlorothiazide, amiloride and hydrochloride tablets, irbesartan and hydrochlorothiazide[45]) or decrease blood uric acid levels (allopurinol) may have affected the results.

In conclusion, SS II shows an association with some of the classical risk factors for atherosclerosis (urates, DM), while the lipid profile in our group of patients showed surprising association with high HDL and low LDL.

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Sažetak

ODNOS *SYNTAX SCORE 2* S NALAZIMA LIPIDOGRAMA I URATA TE PRISUSTVOM ŠEĆERNE BOLESTI U BOLESNIKA S VIŠEŽILNOM KORONARNOM BOLESTI

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SYNTAX Score II (SS II) je klinički alat koji omogućuje individualizaciju predviđanja smrtnosti u bolesnika s višežilnom koronarnom arterijskom bolešću (*coronary artery disease*, CAD) liječenih putem PCI (*percutaneous coronary intervention*) ili CABG (*coronary artery bypass grafting*). Cilj je bio ispitati imaju li lipidogram, urati i dijabetes pozitivnu korelaciju s višim vrijednostima SS II. Uključena su 72 bolesnika s CAD-om. Internetski kalkulator korišten je za izračun SS II. Statističkim testovima (Mann Whitneyjev U test, Shapiro-Wilkov test) ispitana je korelacija i razlike u statusu lipida, urata i dijabetesa u odnosu na vrijednosti SS II. Utvrđena je značajna pozitivna korelacija između udjela bolesnika s razinama HDL-a iznad referentnih vrijednosti i SS II PCI. Sudionici s nižim vrijednostima LDL imali su značajno povišene vrijednosti SS II CABG, ali ne i SS II PCI. Nije bilo značajne korelacije ukupnog kolesterola i triglicerida s SS II PCI ili SS II CABG. Sudionici s hiperuricemijom imali su značajno višu vrijednost SS II PCI, ali ne i SS II CABG. Osobe s dijabetesom imale su značajno povišen SS II PCI, ali ne i SS II CABG u usporedbi s bolesnicima bez dijabetesa. SS II je povezan s nekima od klasičnih čimbenika rizika za aterosklerozu (mokraćna kiselina, dijabetes), dok je u našoj kohorti bolesnika utvrđena iznenađujuća korelacija SS II s visokim razinama HDL i niskim razinama LDL.

Ključne riječi: *Dijabetes melitus; Hiperuricemija; Lipidogram; Višežilna koronarna bolest; SYNTAX Score II*