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Predictors of Coronary Plaque Vulnerability in Patients with Stable Coronary Artery Disease

Aim	To identify new predictors for vulnerability of atherosclerotic coronary plaques in patients with stable ischemic heart disease (sIHD).
Material and methods	This prospective, single-center study included 58 patients with sIHD. Unstable plaques were detected with virtual histology intravascular ultrasound of proximal and medium segments of a coronary artery without significant lesions according to coronarography data. Indexes of inflammation, dyslipidemia and carbohydrate metabolism were considered as candidate predictors for coronary plaque vulnerability.
Results	In 56 coronary arteries, 58 plaques were detected, 12 of which (20.7%) were unstable. Vulnerable plaques differed morphologically from stable ones by a greater size of the necrotic core (35.1±8.5% vs. 24.0±13.2%; p=0.008), calcified nodules (2.0 [1.0; 5.0] % vs. 1.0 [0; 2.0] %; p=0.006), and a lower content of fibrous components (54.9±10.2% vs. 66.4±15.8%; p=0.02). In addition, vulnerable plaques more frequently narrowed the arterial lumen by >70% of the lumen area (33.3% vs. 2.2%; p=0.0006). Correlation analysis showed a negative correlation between the level of high-density lipoproteins (HDL) and calcium volume (r= –0.4104; p=0.023); a positive correlation between the blood glucose level as determined by the oral glucose tolerance test and the lipid component (r=0.48198; p=0.033); and a negative correlation between the apolipoprotein A level and the calcium volume (r= –0.4297; p=0.008).
Conclusion	The study demonstrated a high prevalence of vulnerable plaques in nontarget coronary arteries in patients with sIHD. In this process, dyslipidemia indexes (LDL, apolipoproteins A) correlate with the calcium volume whereas blood glucose, as measured in the oral glucose tolerance test, correlates with the lipid component of coronary plaque.

Keywords	Unstable plaque; virtual histology intravascular ultrasound; thin-cap fibroatheroma; acute coronary syndrome
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The main cause of acute coronary syndrome (ACS) is most commonly the rupture of an unstable atherosclerotic plaque (AP) in a diseased coronary artery [1]. A plaque is unstable, i.e., vulnerable, if it is prone to splitting its fibrous cap and leaving a necrotic nucleus exposed. This event activates inflammation and thrombogenesis [2]. The structure of an AP and its stability depend on various factors [3, 4]. Among these factors, the influence of carbohydrate exchange on coronary AP morphology is currently of particular interest.

Standard coronary angiography cannot detect unstable atherosclerotic coronary lesions. Intravascular imaging techniques, which allow for histology-like morphological analysis of APs, have recently become more widespread [2]. The use of virtual histology intravascular ultrasound (IVUS) has contributed to the identification and better understanding of the predictors of acute coronary events. APs with a stenosis area of >70% and a minimum lumen of <4 mm^2 have the highest predictive potency for risk of adverse events [5].

The best possible drug therapy is essential for primary and secondary prevention of acute coronary events. Myocardial revascularization reduces ischemia symptoms and improves the quality of life, and yet it does not always prevent development of ACS [6, 7]. There is still a risk of adverse outcomes despite treatment. Assessing the risk of adverse outcomes, identifying predictors of ACS, developing preventive measures, and justifying the best possible therapy is among the key tasks of real-world cardiology.

Objective

The objective of this study was to identify new predictors of coronary AP vulnerability in patients with stable coronary artery disease.

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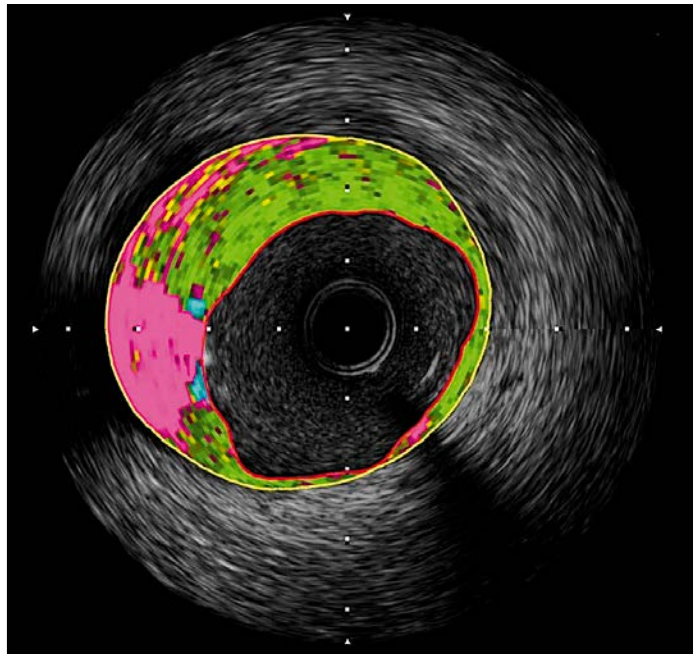
Material and Methods

This prospective, single-center trial included patients with stable coronary artery disease (CAD) who needed stenting of a single coronary vessel. The study excluded patients with ACS. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee. All patients gave informed consent. The day before the index intervention, all patients underwent a complex clinical and laboratory examination that included 1) anthropometry (body mass index, waist and hip circumferences); 2) inflammation factors (C-reactive protein, erythrocyte sedimentation rate); 3) blood lipid composition analysis (total cholesterol, low-density (LDL) and high-density lipoprotein (HDL), triglycerides, apolipoproteins A and B). Particular attention was paid to carbohydrate metabolism regardless of the presence of diabetes mellitus (DM), as reflected by fasting blood glucose, oral glucose challenge test (OGCT), glycated hemoglobin, and fructosamine. All of the above indicators were considered as potential factors associated with the vulnerability of atherosclerotic coronary lesions.

To identify vulnerable plaques after stenting of a hemodynamically significant lesion of the target vessel, all patients underwent virtual histology IVUS of the proximal and middle segments (6–8 cm) of a non-target coronary artery without hemodynamically significant lesions according to coronary angiography. If that artery had no stenosis changes according to IVUS, an intravascular examination was performed in another non-target vessel. IVUS data of lesions with lumen stenosis of 40% or more in three consecutive frames were analyzed. The minimum lumen area, i.e., the AP area with respect to the vessel lumen were estimated. Plaque morphology was assessed using virtual histology IVUS. In the AP structure, four components were estimated (Figure 1): fibrous (green), lipid (yellow), necrotic nucleus (pink), and calcium inclusions (blue). The percentages of all AP components were calculated. An AP with a large necrotic nucleus (>10%) adjacent to the coronary lumen was considered unstable (thin-cap fibroatheroma; Figure 1). All intravascular ultrasound examinations were performed using an iLab imaging system and the iMap virtual histology software. The catheter was threaded automatically at a rate of 0.5 mm/sec.

Statistical analysis. The data are expressed as a percentage, or as the mean and standard deviation (M±SD) if normally distributed, otherwise as the median and interquartile range (Me [Lq; Uq]). The Shapiro-Wilk test was applied to determine data normality. Qualitative and quantitative indicators were compared using Fisher's exact test and the Student's t-test,

Figures 1. Thin-cap fibroatheroma



respectively. Simple linear correlations were calculated as Pearson's correlation coefficients. Statistical analyses were performed using Statistica 10.0. The type I error probability (p) was set at 0.05.

Results

Baseline patient characteristics

The study included 58 patients with mean age of 60.4 yrs. Male patients (65.5%) predominated. 60.3% of patients were hospitalized with diagnosed stable angina functional class II. All patients had arterial hypertension, 53 (91.4%) had excess body weight or obesity, 16 (27.6%) had type 2 DM, 11 (18.9%) were active smokers at the time of inclusion, 34 (58.6%) had hypercholesterolemia while taking statins (Table 1). Index interventions on the target vessels were described earlier [8].

Results of virtual histology IVUS

IVUS was performed in 64 coronary arteries of 58 patients, and 58 APs in 56 coronary arteries were identified. Two patients had no lesions in non-target coronary arteries, according to IVUS. Two APs were detected in two patients in one non-target coronary artery.

According to virtual histology IVUS, 12 (20.7%) lesions had large thin-cap necrotic nuclei, 5 (8.6%) narrowed the artery lumen area by more than 70% (including 4 cases of stenosis area >70% combined with lumen area <4 mm^2), 10 (17.2%) had minimum lumen area <4 mm^2 (Table 1). Of 12 thin-cap fibroatheromas, 2 (3.4%) lesions narrowed artery lumen by >70%, 2 leasons (3.4%) were combined with the minimum

Table 1. Characteristics of the study patients

Variable	All patients (n=58)	Patients with unstable plaques (n=12)	Patients with stable plaques (n=46)	p
Age, yrs	60.4±6.6	59.6±6.5	60.9±6.7	0.55
Male	65.5 (38)	66.6 (8)	65.2 (30)	0.93
Body mass index, kg/m²	31.3±5.3	31.9±5.8	31.2±5.2	0.69
Smoking	18.9 (11)	16.6 (2)	19.5 (9)	0.82
Hypertensive heart disease	100 (58)	100 (12)	100 (46)	1.0
History of stroke	5.2 (3)	16.6 (2)	2.2 (1)	0.045
LVEF, %	61.4±11.5	63.8±7.4	60.8±12.4	0.43
Coronary lesions, % (n):				
• Single-vessel CAD	25.8 (15)	25.0 (3)	26.1 (12)	0.94
• двухсосудистое	74.1 (43)	75.0 (9)	73.9 (34)	0.94
C-reactive protein, mg/ml	3.0 [3.0; 4.0]	3.0 [3.0; 4.5]	3.1 [3.0; 4.0]	0.26
Hypercholesterolemia	58.6 (34)	58.3 (7)	58.7 (27)	0.98
Lipidogram, M±SD:				
• Total cholesterol, mmol/l	4.6±1.4	4.8±1.2	4.6±1.4	0.65
• LDL, mmol/l	2.8±1.2	2.8±1.1	2.9±1.3	0.80
• HDV, mmol/l	1.1±0.3	1.25±0.4	1.1±0.3	0.16
• Triglycerides, mmol/l	1.8±1.3	1.8±1.2	1.8±1.1	0.78
• Apolipoprotein A, mmol/l	1.8±0.3	1.8±0.3	1.8±0.3	1.0
• Apolipoprotein B, mmol/l	1.0±0.4	1.0±0.4	1.1±0.5	0.52
• Atherogenicity index	3.3±1.6	3.2±1.8	3.3±1.6	0.85
Type 2 diabetes mellitus	27.6 (16)	25.0 (3)	28.3 (13)	0.28
Carbohydrate metabolism, Me [Lq; Uq]:				
• Blood glucose, fasting, mmol/l	6.1 [5.4; 7.0]	5.9 [5.3; 6.4]	6.3 [5.4; 7.1]	0.89
• Blood glucose, OGCT, mmol/l	5.6 [4.9; 7.4]	5.6 [4.9; 6.2]	6.1 [5.0; 7.8]	0.31
• Glycated hemoglobin, %	5.7 [5.0; 6.3]	5.2 [4.9; 5.7]	5.8 [5.1; 6.5]	0.21
• Fructosamine, mmol/l	297.0 [274.0; 345.0]	290.0 [277.5; 307.5]	305.0 [270.0; 360.0]	0.45
Results of virtual histology IVUS				
Minimum lumen area, mm²	6.6±2.6	5.7±2.6	6.8±2.6	0.19
Plaque area, %	56.5±10.7	60.7±11.9	55.2±10.2	0.11
Fibrous component, %	64.3±15.5	54.9±10.2	66.4±15.8	0.02
Lipid component, %	7.5±3.5	6.4±1.9	7.8±3.8	0.22
Necrotic core, %	26.0±13.1	35.1±8.5	24.0±13.2	0.008
Calcification, %	1.0 [0; 3.0]	2.0 [1.0; 5.0]	1.0 [0; 2.0]	0.006
Thin-cap fibroatheroma	20.7 (12)	100 (12)	0	–
Stenosis area >70%	8.6 (5)	33.3 (4)	2.2 (1)	0.0006
Minimum lumen area <4 mm²	17.2 (10)	33.3 (4)	13.0 (6)	0.09

Data are M±SD, Me [Lq; Uq], or percentage (n). LVIF, left ventricular ejection fraction; CAD, coronary artery disease; IVUS, intravascular ultrasound; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OGCT, oral glucose challenge test.

lumen area <4 mm², and 2 lesions (3.4%) had all three risk criteria (thin-cap fibroatheroma, stenosis area >70%, minimum lumen area <4 mm²).

Predictors of coronary plaque vulnerability

Patients were divided into two groups depending on the presence of APs as detected by virtual histology IVUS. A stroke history was more common in patients with APs than in patients without vulnerable lesions (16.6% vs. 2.2%, respectively, p=0.045). The morphology of thin-cap fibroteromes differed from stable plaques by larger necrotic nucleus (35.1±8.5% vs. 24.0±13.2%, respectively; p=0.008), calcium volume (2.0 [1.0; 5.0] % vs. 1.0 [0; 2.0] %, respectively; p=0.006), and smaller fibrous component content (54.9±10.2% vs. 66.4±15.8%, respectively; p=0.02). Moreover, vulnerable plaques more often narrowed the artery lumen area >70% (33.3% vs. 2.2%, respectively; p=0.0006). As for other indicators, there were no statistically significant differences between the groups (Table 1).

Correlation analysis found a negative correlation between HDL and calcium (r=–0.4104; p=0.023), a positive correlation between OGCT blood glucose concentrations and lipid component (r=0.48198; p=0.033), and a negative correlation between apolipoproteins A and calcium volume (r= –0.4297; p=0.008) (Figure 2). Other potential factors were not significantly correlated with coronary AP morphology.

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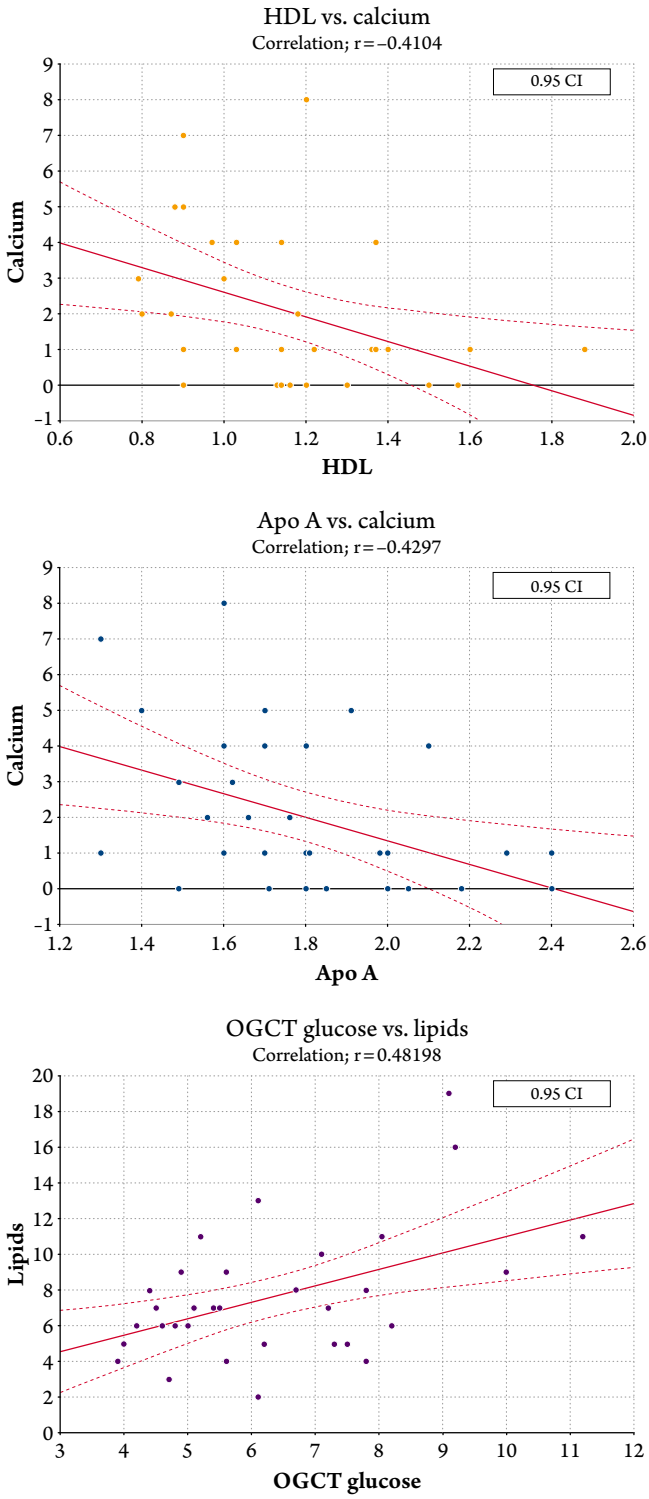
Discussion

The study focused on identifying predictors of coronary plaque vulnerability in patients with stable CAD. Great efforts are currently made to develop ways of stratifying the risk of an adverse course of CAD. Detecting coronary plaques with signs of vulnerability and subsequent monitoring of these patients, registering cardiovascular complications (CVCs), and assessing independent contributions of various clinical and laboratory factors in their development seem to be promising methods. In the study cohort, 20.7% of patients had unstable APs in non-target coronary arteries. Moreover, half of the identified vulnerable plaques had additional risk criteria for coronary complications, i.e., stenosis area >70% and/or minimum lumen area <4 mm^2.

Figures 2. Correlations identified



Apo A, apolipoproteins A; HDL, high density lipoprotein; OGCT, oral glucose challenge test.

Inflammation has been shown to have a major role in the progression of atherosclerosis, and inflammation factors increase plaque thrombogenicity [9]. Several clinical trials demonstrated a positive correlation between increased blood C-reactive protein and the progression of coronary atherosclerosis and the risk of developing CVCs [10, 11]. However, in our study, inflammatory factors were not correlated with coronary plaque morphology as assessed by IVUS.

Dyslipidemia is the most well-studied clinical factor that has a proven negative predictive value. Several studies have confirmed that correction of dyslipidemia contributes to the stabilization of APs and reduces the risk of developing CVCs [12, 13]. Unlike LDL, HDL has an antiatherogenic effect, since its content is inversely proportional to the incidence of CAD [14]. In this study, the concentrations of HDL and apolipoprotein A were inversely correlated with the calcium volume in APs. Coronary plaques with calcium inclusions are known to be more prone to rupture as they are found more commonly in the symptom-related lesions in patients with myocardial infarction [15].

Recently, there has been increasing interest in the correlation between disorders of carbohydrate metabolism and progression of coronary atherosclerosis. In patients with DM, several trials have shown that the proportion of the necrotic nucleus in the plaque structure is large, which increases the risk of developing ACS [16]. It has also been demonstrated that severe hyperglycemia, as assessed by OGCT, was associated with an increased risk of death that was independent of fasting blood glucose [17]. Moreover, prominent daily fluctuations in blood glucose concentrations affect the vulnerability of coronary plaques in patients with CAD [18].

This study was the first to demonstrate a correlation between blood glucose concentrations as assessed by OGCT and coronary plaque morphology (lipid component) regardless of DM. This can, additionally, increase the risk of adverse outcomes. Thus, it is necessary to pay more attention not only to patients with DM, but also to those with prediabetes.

It has previously been confirmed that metabolic syndrome is more common among patients with ACS. Of the components of metabolic syndrome, abdominal obesity and dyslipidemia are major predictor of ACS [19]. However, body mass index and obesity were not correlated with the coronary AP structure in this study.

In summary, this study revealed several factors that are associated with coronary AP morphology. Confirmed predictors of plaque vulnerability can be targeted as factors to be modified during interventions to prevent coronary complications.

Limitations

The major limitation of the study was its single-center nature and a relatively small number of patients. Moreover, patients with ACS were excluded from the study, as this pathology is known to destabilize symptom-unrelated lesions [5]. ACS is accompanied by stress disorders of carbohydrate and lipid metabolism, which could have distorted the study results.

Virtual histology IVUS was performed mainly in one, non-target vessel. However, the ATHEROREMO-IVUS study demonstrated that virtual histology of only one symptom-unrelated, coronary artery predicts the risk of cardiovascular complication within 12 mos [20].

Conclusion

Thus, our findings demonstrate a high prevalence of vulnerable plaques in non-targeted coronary arteries of patients with stable CAD. Indicators of dyslipidemia, e.g., high-density lipoproteins, apolipoproteins A, are correlated with calcium volume, and blood glucose concentrations, as assessed by an oral glucose challenge test, are correlated with the lipid component of coronary plaques.

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No conflict of interest is reported.

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REFERENCES

1. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. Journal of the American College of Cardiology. 2017;70(1):1—25. DOI: 10.1016/j.jacc.2017.04.052
2. Yonetsu T, Jang I-K. Advances in Intravascular Imaging: New Insights into the Vulnerable Plaque from Imaging Studies. Korean Circulation Journal. 2018;48(1):1–15. DOI: 10.4070/kcj.2017.0182
3. Costopoulos C, Huang Y, Brown AJ, Calvert PA, Hoole SP, West NEJ et al. Plaque Rupture in Coronary Atherosclerosis Is Associated With Increased Plaque Structural Stress. JACC: Cardiovascular Imaging. 2017;10(12):1472–83. DOI: 10.1016/j.jcmg.2017.04.017
4. Tagieva N.R., Shakhnovich R.M., Mironov V.M., Ezhov M.V., Matchin Yu.G., Mitroshkin M.G. et al. Comparison of Atherosclerotic Lesions in Patients With Acute Myocardial Infarction and Stable Angina Pectoris Using Intravascular Ultrasound. Kardiologiia. 2015;55(7):5–13. [Russian: Тагиева Н.Р., Шахнович Р.М., Миронов В.М., Ежов М.В., Матчин Ю.Г., Митрошкин М.Г. и др. Сравнение атеросклеротических поражений коронарных артерий у больных острым инфарктом миокарда и стабильной стенокардией по данным внутрисосудистого ультразвукового исследования. Кардиология. 2015;55(7):5-13]
5. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS et al. A Prospective Natural-History Study of Coronary Atherosclerosis. New England Journal of Medicine. 2011;364(3):226–35. DOI: 10.1056/NEJMoa1002358
6. Laimoud M, Faris F, Elghawaby H. Coronary Atherosclerotic Plaque Vulnerability Rather than Stenosis Predisposes to Non-ST Elevation Acute Coronary Syndromes. Cardiology Research and Practice. 2019;2019:1–7. DOI: 10.1155/2019/2642740
7. Theodorou K, Boon RA. Endothelial Cell Metabolism in Atherosclerosis. Frontiers in Cell and Developmental Biology. 2018;6:82. DOI: 10.3389/fcell.2018.00082
8. Kochergin N.A., Kochergina A.M., Ganjukov V.I., Barbarash O.L. Vulnerable atherosclerotic plaques of coronary arteries in patients with stable coronary artery disease. Complex Issues of Cardiovascular Diseases. 2018;7(3):65–71. [Russian: Кочергин Н.А., Кочергина А.М., Ганюков В.И., Барбараш О.Л. Нестабильные атеросклеротические бляшки коронарных артерий у пациентов со стабильной ишемической болезнью сердца. Комплексные проблемы сердечно-сосудистых заболеваний. 2018;7(3):65-71]. DOI: 10.17802/2306-1278-2018-7-3-65-71
9. Stefanadis C, Antoniou C, Tsiachris D, Pietri P. Coronary Atherosclerotic Vulnerable Plaque: Current Perspectives. Journal of the American Heart Association. 2017;6(3):e005543. DOI: 10.1161/JAHA.117.005543
10. Tong DC, Whitbourn R, MacIsaac A, Wilson A, Burns A, Palmer S et al. High-Sensitivity C-Reactive Protein Is a Predictor of Coronary Microvascular Dysfunction in Patients with Ischemic Heart Disease. Frontiers in Cardiovascular Medicine. 2018;4:81. DOI: 10.3389/fcvm.2017.00081
11. Liu H-H, Cao Y-X, Sun D, Jin J-L, Zhang H-W, Guo Y-L et al. High-sensitivity C-reactive protein and hypertension: combined effects on coronary severity and cardiovascular outcomes. Hypertension Research. 2019;42(11):1783–93. DOI: 10.1038/s41440-019-0293-8
12. Tsujita K, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K et al. Impact of Dual Lipid-Lowering Strategy with Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention: The Multicenter Randomized Controlled PRECISE-IVUS Trial. Journal of the American College of Cardiology. 2015;66(5):495–507. DOI: 10.1016/j.jacc.2015.05.065
13. Cheng JM, Oemrawsingh RM, Garcia-Garcia HM, Boersma E, van Geuns R-J, Serruys PW et al. PCSK9 in relation to coronary plaque inflammation: Results of the ATHEROREMO-IVUS study. Atherosclerosis. 2016;248:117–22. DOI: 10.1016/j.atherosclerosis.2016.03.010

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артериальная гипертензия, стабильная хроническая сердечная недостаточность легкой и средней степени тяжести (в составе комбинированной терапии) у пациентов старше 70 лет

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Показания к применению: артериальная гипертензия; стабильная хроническая сердечная недостаточность легкой и средней степени тяжести (в составе комбинированной терапии) у пациентов старше 70 лет. **Способ применения и дозы:** внутрь, один раз в сутки, желательно в одно и то же время, независимо от времени приема пищи, запивая достаточным количеством жидкости. Средняя суточная доза для лечения артериальной гипертензии составляет 5 мг небиволола. Препарат Небилет® можно применять как в монотерапии, так и в комбинации с другими гипотензивными средствами. Лечение стабильной ХСН должно начинаться с постепенной титрации дозы небиволола до достижения индивидуальной оптимальной поддерживающей дозы. Начальная доза при этом – 1,25 мг/сут. Далее осуществляется титрование доз до 2,5 – 5 мг/сут, а затем до 10 мг/сут (максимальная суточная доза). **Противопоказания:** повышенная чувствительность к небивололу или к любому из компонентов препарата; печёночная недостаточность (класс В и С по классификации Чайлд-Пью) или нарушения функции печени; острая сердечная недостаточность; кардиогенный шок; хроническая сердечная недостаточность в стадии декомпенсации (требующая внутривенного введения препаратов, обладающих положительным инотропным действием); тяжелая артериальная гипотензия (систолическое АД менее 90 мм рт. ст.); синдром слабости синусового узла, включая синоаурикулярную блокаду; атриовентрикулярная (АВ) блокада **II** и **III** степени (без электрокардиостимулятора); брадикардия (ЧСС менее 60 уд/мин до начала терапии); нелеченная феохромоцитома (без одновременного применения альфа-адреноблокаторов); метаболический ацидоз; бронхоспазм и бронхиальная астма в анамнезе; тяжелые нарушения периферического кровообращения; непереносимость лактозы, дефицит лактазы и синдром глюкозо-галактозной мальабсорбции; возраст до 18 лет (эффективность и безопасность в этой возрастной группе не изучены); период грудного вскармливания; одновременное применение с флоктафенином, сультопридом (см. раздел «Взаимодействие с другими лекарственными средствами»). **С осторожностью:** почечная недостаточность тяжелой степени (скорость клубочковой фильтрации (СКФ) < 30 мл/мин/1,73 м2 площади поверхности тела); сахарный диабет; гиперфункция щитовидной железы; аллергические заболевания в анамнезе, псориаз; хроническая обструктивная болезнь легких; облитерирующие заболевания периферических сосудов (перемежающаяся хромота, синдром Рейно); атриовентрикулярная блокада **I** степени; стенокардия Принцметала; возраст старше 75 лет; артериальная гипотензия; феохромоцитома (при одновременном применении альфа-адреноблокаторов); хирургические вмешательства и общая анестезия; проведение десенсибилизирующей терапии; беременность. **Побочное действие** (ниже приведены часто встречающиеся нежелательные реакции). Нарушения со стороны нервной системы: головокружение, головная боль, парестезия. Нарушения со стороны дыхательной системы, органов грудной клетки и средостения: одышка. Нарушения со стороны желудочно-кишечного тракта: тошнота, диарея, запор. Общие расстройства и нарушения в месте введения: отеки, повышенная утомляемость. **Более подробную информацию см. в инструкции по медицинскому применению лекарственного препарата Небилет® от 05.02.2020.**

Список литературы:

1. Инструкция по медицинскому применению препарата Небилет®
П N011417/01-050220
2. Van Bortel L. M. et al.; Am J Cardiovasc Drugs 2008; 8 (1): 35-44
3. Schmidt A. C. et al.; Clin Drug Invest 2007; 27 (12):841-849

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14. Androulakis E, Zacharia E, Papageorgiou N, Lioudaki E, Bertsias D, Charakida M et al. High-density Lipoprotein and Low-density Lipoprotein Therapeutic Approaches in Acute Coronary Syndromes. Current Cardiology Reviews. 2017;13(3):168–82. DOI: 10.2174/1573403X13666170209145622
15. Zimetti F, Freitas WM, Campos AM, Daher M, Adorni MP, Bernini F et al. Cholesterol efflux capacity does not associate with coronary calcium, plaque vulnerability, and telomere length in healthy octogenarians. Journal of Lipid Research. 2018;59(4):714–21. DOI: 10.1194/jlr.P079525
16. Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, Diabetes, and Cardiovascular Events. Diabetes Care. 2010;33(6):1389–94. DOI: 10.2337/dc09-2082
17. Su G, Mi S, Tao H, Li Z, Yang H, Zheng H et al. Association of glycemic variability and the presence and severity of coronary artery disease in patients with type 2 diabetes. Cardiovascular Diabetology. 2011;10(1):19. DOI: 10.1186/1475-2840-10-19
18. Kuroda M, Shinke T, Sakaguchi K, Otake H, Takaya T, Hirota Y et al. Effect of Daily Glucose Fluctuation on Coronary Plaque Vulnerability in Patients Pre-Treated With Lipid-Lowering Therapy. JACC: Cardiovascular Interventions. 2015;8(6):800–11. DOI: 10.1016/j.jcin.2014.11.025
19. Kato M, Dote K, Naganuma T, Sasaki S, Ueda K, Okita M et al. Clinical Predictors of Culprit Plaque Rupture Assessed on Intravascular Ultrasound in Acute Coronary Syndrome. Circulation Journal. 2010;74(9):1936–42. DOI: 10.1253/circj.CJ-10-0086
20. Cheng JM, Garcia-Garcia HM, de Boer SPM, Kardys I, Heo JH, Akkerhuis KM et al. In vivo detection of high-risk coronary plaques by radiofrequency intravascular ultrasound and cardiovascular outcome: results of the ATHEROREMO-IVUS study. European Heart Journal. 2014;35(10):639–47. DOI: 10.1093/eurheartj/eht484

ISSN 0022-9040. Kardiologiia. 2020;60(10). DOI: 10.18087/cardio.2020.10.n1188