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КОНСЕНСУС ЕВРОПЕЙСКИХ ЭКСПЕРТОВ ПО ВЕДЕНИЮ ПАЦИЕНТОВ С ИШЕМИЕЙ С НЕОБСТРУКТИВНЫМ ПОРАЖЕНИЕМ КОРОНАРНЫХ АРТЕРИЙ ПРИ ХРОНИЧЕСКОМ КОРОНАРНОМ СИНДРОМЕ: ВОЗМОЖНОСТИ ПРИМЕНЕНИЯ В АМБУЛАТОРНОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ В РОССИИ

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Consensus of European Experts on the Management of Patients with Ischemia with Non-Obstructive Coronary Arteries with Chronic Coronary Syndrome: Possibilities for Use in Outpatient Clinical Practice in Russia

Резюме

В 2020 г вышел консенсусный документ Европейского общество кардиологов по ведению пациентов с ишемией миокарда, связанной с необструктивным поражением коронарных артерий. Основные положения нового документа ориентированы на выделение особой группы пациентов с хроническим коронарным синдромом и подозрением на вазоспастическую или микрососудистую стенокардию с целью рационализации и персонификации подхода к их ведению. Большая часть пациентов с установленной ишемией, при прохождении коронарной ангиографии не имеет гемодинамически значимой обструкции коронарных артерий. Коронарная микрососудистая дисфункция и эпикардиальный вазоспазм, отдельно или в сочетании с атеросклеротическим поражением коронарных артерий сердца, являются причинами ише-

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мии миокарда. При этом микроваскулярная дисфункция рассматривается в качестве значимого провоцирующего фактора развития рефрактерной стенокардии. Диагностика подобных состояний нередко затруднена, и поэтому для таких пациентов не назначается оптимальная терапия. Как следствие, эти пациенты имеют низкое качество жизни, что приводит к повторным госпитализациям, неблагоприятным сердечно-сосудистым исходам в краткосрочной и долгосрочной перспективе и значительной нагрузке на ресурсы здравоохранения. В статье рассматриваются возможности применения новых рекомендаций и консенсуса в диагностике и ведении таких пациентов в условиях амбулаторной клинической практики в России. На начальных этапах диагностики приоритет отдается неинвазивным методам исследования, для детального обследования проводится инвазивное обследование с фармакологической нагрузкой. При ведении пациентов используется пошаговая стратегия в зависимости от конкретной клинической ситуации. Препаратами первой линии антиишемической терапии остаются блокаторы кальциевых каналов или бета-блокаторы.

Ключевые слова: *хронический коронарный синдром, вазоспастическая стенокардия, ишемия, микрососудистая дисфункция, рефрактерная стенокардия*

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Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

In 2020, a consensus document of the European Society of Cardiology on the management of patients with myocardial ischemia with non-obstructive coronary arteries was released. The main provisions of the new document are aimed at identifying a special group of patients with chronic coronary syndrome and suspected vasospastic or microvascular angina in order to rationalize and personalize the approach to their management. Most patients with established myocardial ischemia do not have obstructive coronary arteries when undergoing coronary angiography. Coronary microvascular dysfunction and epicardial vasospasm, alone or in combination with obstructive coronary artery atherosclerosis, are the causes of myocardial ischemia. In this case, microvascular dysfunction is considered as a significant provoking factor in the pathogenesis of refractory angina pectoris. Diagnosis of such conditions is often difficult, and therefore the correct therapy is not prescribed for such patients. As a consequence, these patients have a poor quality of life, which leads to hospital readmissions, poor cardiovascular outcomes in the short and long term, and a significant burden on health care resources. The article discusses the possibilities of applying new recommendations and consensus in the diagnosis and management of such patients in outpatient clinical practice in Russia. At the initial stages of diagnosis, priority is given to non-invasive research methods; in-depth examination, carried out using invasive methods with a pharmacological testing. Patient management uses a stepwise strategy depending on the specific clinical situation. Calcium channel blockers or beta blockers remain the first line anti-ischemic therapy.

Key words: *chronic coronary syndrome, vasospastic angina, ischemia, microvascular dysfunction, refractory angina*

Conflict of interests

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ACEI — angiotensin-converting enzyme inhibitors, ACS — acute coronary syndrome, ARB — angiotensin II receptor blockers, CA — coronary arteries, CABG — coronary artery bypass grafting, CAD — coronary artery disease, CCBs — calcium channel blockers, CCS — chronic coronary syndromes, CFR –coronary flow reserve, CMD — coronary microvascular dysfunction, CVC — cardiovascular complications, ECG — electrocardiogram, ECHO-CG — echocardiography, ED — endothelial dysfunction, ESC — European Society of Cardiology, FFR — fractional flow reserve, ICAG — invasive coronary angiography, IHD — ischaemic heart disease, INOCA — ischaemia with non-obstructive coronary arteries, IOCA — ischaemia with obstructive coronary arteries, LV — left ventricle, MRI — magnetic resonance imaging, MSCT — multispiral computed tomography, PCI — percutaneous coronary intervention, PET — positron emission tomography, VSA — vasospastic angina

In 2019, the European Society of Cardiology (ESC) [1] published guidelines on the diagnosis and management of patients with "chronic coronary syndromes" (CCS), with a proposal to use this term instead of the previously used one — "stable coronary artery disease (CAD)". The discussion paper on these guidelines [2] brings up the issues that required extensive medical discussion and consensus, as well as the problems that prevented the implementation of these guidelines in Russian clinical practice. In 2020, a consensus document "An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with the European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group" [3] was published. The document is a summarized point of view of the experts of the European Association of Percutaneous Cardiovascular Interventions, the Working Group on Coronary Pathophysiology and Microcirculation supported by Coronary Vasomotor Disorders International Study Group on the importance of ischaemia with non-obstructive coronary arteries (INOCA). The document specifies that among the patients who underwent invasive coronary angiography (ICAG) for angina (or painless ischaemia), ischaemia with non-obstructive coronary arteries developed in about 70 % of patients; more often in women (50–70 %) than in men (30–50 %). INOCA (according to experts) is not a benign condition and is associated with a high incidence of adverse events and impaired quality of life. Timely diagnosis of INOCA is often complicated and is associated with an delayed choice of appropriate specific treatment.

The terms used in the consensus documents do not refer to the "secondary" ischaemia/angina caused by the following diseases: cardiomyopathy (hypertrophic, dilated), myocarditis, aortic stenosis, infiltrative cardiomyopathies, systemic inflammatory or autoimmune diseases, i.e. systemic lupus erythematosus, rheumatoid arthritis, dysfunction of platelets/impaired coagulation; management of these diseases (in the absence of concomitant atherosclerotic lesions of coronary arteries (CA)) differs from the strategy of treatment for patients with impaired blood flow in coronary arteries.

Moreover, in both consensus documents there is no clear definition of ischaemic heart disease (IHD); the term is replaced by INOCA or ischaemia with obstructive coronary arteries (IOCA) with the description of the clinical features of their course that, however, are not diagnostic criteria and allow only suggesting damage to coronary arteries and/or microvasculature.

Despite the fact that at present the functions and capabilities of a general practitioner do not allow using of the proposed provisions of two consensus documents, the objective of this article is to briefly present the main points of these ~~two~~ documents and the possibility of their implementation in outpatient clinical practice in Russia. The paper will discuss the strategy of managing patients with ischaemia with non-obstructive and obstructive atherosclerotic CAD.

The main provisions of the new document are aimed at identifying a special group of patients with chronic coronary syndrome and suspected vasospastic or microvascular angina in order to rationalize and personalize the approach to their management.

- First of all, the authors define the very concept of INOCA, as well as the examination methods that allow to diagnose it, i.e. to exclude CA obstruction and at the same time to confirm myocardial ischaemia. To that end, non-invasive examination methods are preferred.
- Secondly, the consensus document highlights INOCA "endotypes" depending on the level and nature of CAD, providing their diagnostic criteria using interventional research methods.
- Finally, based on the data on the presence of risk factors, type of coronary artery disease, comorbidities and patient characteristics, it is proposed to choose the optimal treatment strategy.

As new possibilities and instrumental methods are implemented into outpatient practice, such a scenario for identifying and managing patients with INOCA can improve patients' life quality, and slow down the further continuous progression of ischaemic heart disease (coronary artery disease). It is the primary care physician who initially faces the task of suspecting non-obstructive CAD and carrying out the correct routing of this patient for a more detailed diagnosis. Besides, the objective of a physician is to further control the symptoms and the course of the disease based on the principles of evidence-based medicine.

Myocardial ischaemia is a multifactorial process and can be either of structural or of functional nature. At the level of epicardial CA, the structural causes include atherosclerotic vascular lesions (local or diffuse) and myocardial muscle bridge; the functional ones include epicardial vasospasm. In individuals with local and/or diffuse (obstructive or non-obstructive) CAD, coronary microvascular dysfunction (CMD) and vascular epicardial dysfunction (spasm) can be independent or ancillary pathophysiological mechanism of ischaemia.

There are two "endotypes" at the microvascular level: structural remodeling of microvasculature and functional dysregulation of arterioles. Endothelial dysfunction (ED) and local inflammation of vascular wall with increased level of proinflammatory cytokines (tumor necrosis factor-alpha, interleukin-6) and overproduction of endothelin-1 are the key factors in the CMD

pathogenesis [4]. In other words, microvascular dysfunction can result either from structural or functional changes, or from both.

Structural remodeling of coronary microvasculature is associated with decreased microcirculation and impaired oxygen delivery. It is normally caused by internal remodeling of coronary arterioles with the subsequently increased ratio of vessel wall thickness to its lumen, or reduced myocardial capillary density (capillary rarefaction), or both.

Functional dysregulation of arterioles usually develops in medium to large arterioles, with the prevalence of subsequent vasodilation mediated by blood flow.

Epicardial vasospasm usually develops as a result of hyperreactivity of epicardial vascular segment, especially associated with vasoconstrictive stimuli, including smoking, medications, increased blood pressure, exposure to cold, emotional stress, and hyperventilation. Severe coronary spasm can also be associated with allergic reactions (for example, Kounis syndrome) [5, 6].

Primary and nonspecific hyperreactivity of coronary smooth muscles is usually observed in patients with variant angina and is apparently a key element of epicardial vasospasm. The available data indicate that endothelial dysfunction contributes to the triggering of spasm in predisposed segments of coronary vessels [7].

Clinical variants of CCS and INOCA

According to ESC experts, chronic coronary syndromes are represented by the following clinical variants ("scenarios", settings): 1) patients with suspected CAD, symptoms of stable angina and/or dyspnea; 2) patients with the development of heart failure or left ventricular (LV) dysfunction and suspected CAD; 3) patients in stable condition (with or without symptoms) less than 1 year after acute coronary syndrome (ACS) or recent revascularization; 4) patients 1 year after the initial diagnosis or revascularization (with or without symptoms); 5) patients with angina and suspected vasospasm or microvascular lesions; 6) individuals diagnosed with asymptomatic CAD during screening. Drapkina O.M. et al. [2] emphasize that there are much more such scenarios in clinical practice, and the suggested variants cannot help to appropriately consider the cases of disease, conduct registered observations and choose optimal management strategy. At the same time, one should totally agree that these "scenarios" can overlap, moving from one clinical variant into another.

In 2019 Guidelines under consideration, ESC experts associate one of CCS types with the spasm of coronary arteries and/or dysfunction of small vessels; it is likely that this particular type of CCS that is often observed in outpatient practice is highlighted in the new consensus document on INOCA.

Similar to the clinical guidelines on the management of patients with CCS as of 2019, the experts who presented INOCA consensus document also proposed to consider some its clinical variants:

- Epicardial vasospastic angina (VA, Prinzmetal angina) is a clinical sign of myocardial ischaemia that is characterized by dynamic obstruction of epicardial coronary arteries caused by vasomotor disorder;
- Microvascular angina (MVA) is a clinical sign of myocardial ischaemia caused by CMD as a result of structural remodeling of microvasculature or vasomotor disorders of arterioles;
- Microvascular and epicardial vasospastic angina.

Clinical manifestations of CCS and INOCA are nonspecific: from typical angina pain to an isolated feeling of lack of air and other symptoms (anxiety, pain between shoulder blades, gastrointestinal disorder, nausea, fatigue, weakness, vomiting, sleep disturbances) which certainly complicate timely diagnosis of these conditions. However, the INOCA document indicates that the following signs are more common in this type of ischaemia:

- chest discomfort (both at rest and after exercise; lasts more than 1 minute and is poorly controlled with nitroglycerin);
- severity of pain syndrome can vary during days or weeks: increase, then decrease ("Crescendo-decrescendo");
- stress-related symptoms;

Besides, the experts mention higher incidence of INOCA signs in women than in men.

Thus, ***vasospastic angina*** can be suspected in the presence of symptoms that appear mainly at rest, with preserved exercise tolerance. As a rule, patients with vasospastic angina, in contrast to patients with stable angina, are younger, have fewer cardiovascular risk factors than patients with stable angina, and the possibility of vasospastic angina increases when attacks are circadian and predominate at night or in early morning.

The specific feature of anginal pain in ***microvascular angina*** is its development sometime after physical activity, as well as after emotional stress; it is poorly controlled by short-acting nitrates. Pain episodes associated with exposure to cold, may occur at rest. Angina in such patients is usually of mixed nature.

Despite the widespread use of antianginal agents and/or percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG), the percentage of patients with CHD with daily or weekly angina episodes ranges from 2 % to 24 % [8].

In this aspect, it is important to consider the ***refractory angina*** presented in the 2019 ESC Guidelines on the

diagnosis and management of patients with "chronic coronary syndromes". Refractory angina is considered in the case when the symptoms of angina last more than three months, the presence of reversible myocardial ischaemia is confirmed, there are pronounced coronary bed lesions, and these symptoms cannot be controlled by intensification of drug treatment, adding second and third line antianginal agents, CABG or stenting, including PCI for chronic coronary total occlusion [1]. This definition is also specified in the current Guidelines of the Russian Society of Cardiology [9].

The concept of "***refractory angina***" was first proposed by ESC experts in 2002: a chronic condition (lasts more than three months) that is characterized by angina caused by the failure of coronary circulation (associated with the coronary artery disease); it is accompanied by pronounced clinical symptoms uncontrolled by combined drug treatment in maximum tolerable doses when myocardial revascularization (percutaneous coronary angioplasty, or CABG) is impossible [10].

In other words, any stable angina associated with adequate drug treatment can be considered refractory if myocardial revascularization is impossible. Due to the lack of clear criteria for assessing patient's clinical condition (in particular, severity — the incidence of anginal pain episodes over a certain period of time), this definition is a debatable reference. It should be mentioned that refractory angina can be diagnosed only after confirmation of the ineffectiveness of combined antianginal treatment in maximum tolerated dose [8].

Although the presence of IHD, suggested as an epicardial coronary arteries obstruction, is usually considered to be a basis for the development of refractory angina, in fact, refractory angina can also develop in microvasculare damage (microvascular dysfunction is considered as a significant precipitating factor in the development of refractory angina), hypertrophic cardiomyopathy, and diastolic dysfunction of left ventricle (LV) [3]. As a rule, the patients with refractory angina have poor life quality suffer with psychological stress, which caused significant burden on healthcare resources [11].

According to epidemiological studies, 5 to 10 % (7.7 % women, 7.3 % men) of patients with stable coronary heart disease who underwent cardiac catheterization had refractory angina; the annual incidence of refractory angina in Europe reaches 30- 50 thousand, in the USA — 75 thousand cases [12].

Thus, clinical variants of CCS and INOCA have no specific clinical manifestations that distinguish them from those in impaired blood flow in coronary arteries; they suggest higher or lower probability of structural or functional coronary artery disease, and need further clarification of diagnosis using instrumental methods, depending on individual characteristics of a patient.

It should be mentioned that the category of "patients with angina and suspected vasospasm or microvascular disease" that was identified in CCS includes the groups of patients, heterogeneous in terms of age, sex, and comorbidities, as well as in terms of degree of cardiovascular complications (CVC) risk. Such patients are quite common in outpatient practice, and only computed tomography and angiography or ICAG with additional functional tests (what is recommended by the experts) can help to finally confirm or exclude the suspected diagnosis.

Ischaemia diagnosing methods

Functional and structural disorders of coronary microcirculation can result in decreased myocardial perfusion and ischaemia, even in the absence of large coronary artery stenosis. The role of a primary care physician (in particular, general practitioner) in diagnosing these conditions is to suspect the disease and carry out examinations adequate for this stage (complete blood count and blood biochemistry, electrocardiographic and echocardiographic examinations, 24h Holter monitoring of electrocardiogram (ECG) (24h ECG). If the symptoms persist and there are no ECG changes, the patient should be referred to a cardiologist to verify the diagnosis and undergo specific examinations.

According to the 2019 ESC Guidelines for CCS, 2020 Guidelines for INOCA, and 2020 Guidelines for stable IHD of the Russian Society of Cardiology, diagnostic examination should start with non-invasive methods: stress echocardiography (ECHO CG), stress cardiac magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), positron emission tomography (PET), or multispiral computed tomography (MSCT angiography). The choice of particular diagnostic method depends on the clinical presentation, however, taking into consideration the individual characteristics and preferences of a patient, as well as local resources. The clinical probability of obstructive CAD is assessed using such determinants as family history, dyslipidemia, diabetes mellitus, arterial hypertension, smoking, and other modifiable risk factors and changes on ECG.

ESC Guidelines for CCS describe a structured approach to the differential diagnosis of BCA that includes:

1. initial physical examination, diagnosis, risk assessment that should include 6 steps of diagnosis;
2. measures aimed at changing lifestyle;
3. prescription of drug products — antianginal drugs and the agents that affect on the prognosis.

Unlike the procedure for CCS diagnosing, non-invasive INOCA diagnostics includes 2 stages (steps) with the

mandatory assessment of patient's complaints, history, description of clinical symptoms, ECG, and referral to a cardiologist at the first stage of diagnosis. At the second stage of diagnosis, non-invasive examinations are recommended. Invasive examinations are carried out, first of all, in high clinical probability of CAD and if revascularization is required. At the same stage, functional tests with physical exertion, transthoracic echocardiogram, contrast stress echocardiogram, PET, imaging studies, MRI are performed.

Since non-invasive methods do not provide direct visualization of blood flow in coronary arteries and coronary microcirculation, invasive examinations are required to confirm INOCA, including CAG at the first stage, adenosine test at the second stage, and vasoreactivity test at the third stage.

To detect atherosclerosis, MSCT coronary angiography is performed; it is the preferable method in the patients with a low clinical probability of obstructive CAD. According to the 2019 Guidelines for CCS, obstructive CAD is the 50 % or higher stenosis, based on the results of MSCT coronary angiography or ICAG. In high clinical probability of coronary artery obstruction, typical and atypical angina at low level of physical activity, refractoriness to drug treatment, as well as the presence of high risk of cardiovascular events, the readiness of the patient for revascularization and the absence of somatic contraindications, if there are appropriate indications for coronary artery bypass grafting or stenting, ICAG is recommended (with supplementary functional tests).

Invasive examinations make it possible to determine the presence and degree of CAD and the nature of dysfunction (whether there is a functional impairment — vasodilation (or vasospasm) and/or impaired microcirculatory conduction with increased minimum microcirculatory resistance).

INOCA diagnosis is based on the measurement of myocardial functional state parameters, namely, myocardial blood flow and coronary reserve flow (CRF). CRF is the ratio of coronary blood flow during the maximal coronary vasodilation to the blood flow at rest.

CRF is an integrated measure of blood flow in large epicardial coronary arteries, therefore, the decreased CRF with excluded severe obstructive lesions of epicardial coronary arteries serves as a CMD marker. CRF index <2.0 or microcirculatory resistance ≥25 U are the indicators of impaired microcircular function.

CRF can be measured non-invasively: using transthoracic Doppler echocardiography of left coronary artery with the measurement of diastolic coronary blood flow after IV administration of adenosine, or magnetic resonance imaging with determination of myocardial perfusion index, or positron emission tomography.

Microcirculatory resistance can be measured using coronary artery catheterization (calculation of microcirculatory resistance index) or Doppler flow velocity (calculation of hyperemic microvascular resistance).

To exclude hemodynamically relevant CA stenosis, fractional flow reserve (FFR) is measured. FFR is an indicator of the functional relevance of stenosis; it is defined as the ratio of the pressure measured more distally from the stenosis to the pressure more proximally to stenosis (in aorta) measured at maximum vasodilation. At FFR <0.8, CA stenosis is hemodynamically insignificant.

According to ESC criteria, a combination of ICAG, pressure and flow measurements, as well as pharmacological tests should be used to determine the INOCA endotype. Following the criteria, first, it is necessary to exclude CA obstruction using one of the methods, second, mind the possible endotype with MVA+VSA combination. There is the opinion of ESC experts that requires further discussion; according to it, identification of transient ischaemia using 24h ECG is indicative of VSA (ESC I A (GR C, LE 5)[1], however, in such cases, the ESC also recommends to exclude possible CA stenosis and to perform angiographic imaging of the spasm using pharmacological loading (ESC I A (GR C, LE 4)[1] which is currently quite difficult to implement in primary health care facilities.

Diagnostic criteria for microvascular angina, vasospastic angina, their combination, and atherosclerotic lesions of CA with no blood flow restriction are presented in Table 1.

Thus, at the outpatient level, it is difficult to make differential diagnosis of primary (IOCA and INOCA) and secondary (CMP, defects, CTD) ischemia due to the lack of adequate instrumental examination. General practitioner at a local clinic can assume myocardial ischemia of a particular nature and refer the patient to a cardiologist based on the presence of risk factors, specific complaints and symptoms, comorbidities, angina, and the presence/absence of ECG changes, and in case of vasospastic angina, judging from transient episodes of ischemia at rest identified using 24h Holter ECG. The next stage is the referral of a patient to a cardiologist to make decision on the issue of further examination, possibly — in hospital conditions. Considering new guidelines and extended indications for non-invasive studies, the issue of expanding the functions of physicians and general practitioners of the outpatient stage needs further discussion. From our point of view, this approach should be brought into accordance, since it will definitely entail: a) further increase in the incidence of ischaemic heart

[1] GR — grades of recommendations; LE — levels of evidence

Table 1. *Diagnostic criteria for microvascular, vasospatic angina, their combination and atherosclerotic CAD that does not restrict blood flow*

Condition	Pathophysiology	Diagnostic criteria
Microvascular angina*	CMD	Evidence of CMD: Impaired coronary flow reserve (<2,0) Abnormal coronary microvascular resistance indices (IMR≥25)
		Adenosine test: FFR >0,8 CFR <2,0 IMR ≥25 HMR ≥1,9
		Acetylcholine test: no or <90 % diameter reduction + angina + ischemic ECG changes
Vasospastic angina	Epicardial spasm	Adenosine test: FFR >0,8; CFR ≥2,0; IMR <25; HMR <1,9
		Acetylcholine test: ≥90 % diameter reduction + angina + ischemic ECG changes
Both microvascular and vasospastic angina	CMD + epicardial spasm	Adenosine test: FFR>0,8 CFR<2,0 IMR ≥25 HMR≥1,9
		Acetylcholine test: no or <90 % or ≥90 % diameter reduction + angina + ischemic ECG changes
Atherosclerotic CAD without blood flow-liming***	Diffuse coronary artery atherosclerosis	Adenosine test: FFR>0,8 CFR≥2,0 IMR <25 HMR<1,9
		Acetylcholine test: no or <90 % diameter reduction + no angina + no ischemic ECG changes
Common criteria	Symptoms of myocardial ischaemia: effort or rest angina or exertional dyspnoea**** Myocardial ischaemia: functional imaging test (reversible defect, abnormality or flow reserve) — is not necessary. Coronary CTA, ICA: Absence of coronary obstruction (<50 % or FFR >0,80)	

Note: CFR, coronary flow reserve; FFR, fractional flow reserve; HMR, hyperaemic myocardial velocity resistance; IMR, index of microvascular resistance; CMD — coronary microvascular dysfunction; CAD — coronary artery disease; ECG — electrocardiography; ICA — Invasive coronary angiography; Coronary CTA — coronary computed tomography angiography.
* Non endothelial dependent microvascular angina may be diagnosed non-invasively by the methods described
** as alternative measures of microcirculatory resistance, based on thermodilution or Doppler, respectively
*** <50 % stenosis severity by visual assessment
**** Many patients with HF with preserved LVEF have dyspnoea, absence of obstructive CAD and impaired CFR. Measurement of LV end-diastolic pressure (normal ≤10 mmHg) and NT-proBNP normal <125 pg/mL is recommended

disease (coronary artery disease) due to diagnosing of all patients with risk factors of cardiovascular complications who seek medical help; b) prescription of unreasonable treatment [2]. In future, non-invasive assessment of the signs of endothelial dysfunction based on photoplethysmography and video capillaroscopy can provide a certain prognostic value in case of suspected INOCA at the stage of outpatient treatment [4].

Management strategy for patients with ischaemia with non-obstructive and obstructive atherosclerotic lesions of coronary arteries

It is quite possible to agree with the principle proposed in the 2019 ESC Guidelines on CCS that the patients with different risk levels of developing CVD, with different levels and grades of coronary artery disease, with or without ischemia based on the results of functional tests require different approaches to management and treatment. However, according to the conventional clinical approach, the same approach to the management of patients with suspected chronic IHD and patients with chronic IHD is justified only in certain situations, which should be clearly defined in the Russian guidelines.

General rules for the treatment of patients with CCS, INOCA and IOCA include identification and management of diseases or conditions that contribute to the development of angina or myocardial ischaemia (anemia, overweight, fever, thyroid hyperfunction, infection, rhythm disorders, etc.); change of lifestyle regardless of disease severity and drug treatment; addressing risk factors for cardiovascular complications, drug treatment and interventions.

The choice of treatment methods (including the choice of a particular drug) is based on evidence, improving quality of life and/or reducing the risk of cardiovascular complications, increasing life expectancy, considering the somatic and mental characteristics of a patient.

Risk factors such as arterial hypertension, diabetes mellitus, smoking, and dyslipidemia contribute to the progression of coronary macro-, microvascular and vasospastic dysfunction and structural remodeling of

microcirculation. The optimal choice of antianginal agents depends on the predominant mechanism of anginal symptoms (vasospastic and/or microcirculatory). Angiotensin-converting enzyme inhibitors (ACEI)/ angiotensin II receptor blockers (ARBs) are able to improve CFR indicators in coronary microvascular dysfunction; they can be easily combined with both calcium channel blockers and beta blockers and slow down the remodeling of small vessels. ESC experts emphasize that, due to their anti-inflammatory properties, statins can also be used in patients with INOCA with reduced CFR and vascular spasm.

The management of patients with INOCA is complicated by the fact that they are a very heterogeneous population, and no randomized studies on their treatment has been performed as of now, therefore, it is recommended to adhere to the principles of stepwise antianginal therapy presented in the 2019 ESC Guidelines for CCS. The list of antianginal agents discussed in these Guidelines is presented in Table 2.

The standard antianginal drug treatment is not always effective. Short-acting nitrates have variable effectiveness and require frequent administration. Long-acting nitrates are ~~often~~, as a rule, ineffective, and can provoke an increase in symptoms in patients with MVA due to subclavian steal syndrome.

The patients with epicardial or microvascular spasm based on the results of acetylcholine test are recommended to use calcium channel blockers (CCB). In cases of MVA when calcium antagonists are ineffective, ESC experts suggest adding ranolazine to therapy. In cases of persistent anginal symptoms ivabradine should be considered, however, its effectiveness in MVA has not been adequately studied.

If microvascular angina is first diagnosed based on abnormal CFR and/or high microcirculatory resistance (suggesting microvascular remodeling), it is recommended to prescribe beta blockers as an initial therapy, followed by the addition of CCB; with persisting symptoms — nicorandil and ranolazine.

The further discussion and consensus decisions are required on several treatment-related issues. In severe forms of VSA, ESC specialists consider the use of calcium antagonists in higher doses (up to 200 mg diltiazem twice daily) and the combination of dihydropyridine calcium antagonists (amlodipine) with nondihydropyridine antagonists (diltiazem); this therapy cannot be applied to a wide population of patients, the decision should be made on an individual basis and is controversial from our point of view. If the symptoms of vasospastic angina do not resolve during treatment with calcium channel blockers followed by nitrate therapy, the use of nicorandil should be considered.

Besides, ESC experts are discussing the use of low doses of tricyclic antidepressants (imipramine and xanthine derivatives) to reduce the incidence and intensity of symptoms, considering them as second-line agents in patients with poorly controlled symptoms or with poor tolerance to antianginal drugs. Trimetazidine is also suggested to use in such cases.

Table 2. *Medical therapy of INOCA*

Diagnosis	Treatment
Microvascular angina	Beta-blockers (Nebivolol 2.5–10 mg daily)
	Calcium channel blockers (Amlodipine 10 mg daily)
	Ranolazine (375–750 mg twice daily)
	Trimetazidine (35 mg twice daily)
	ACE inhibitors (Ramipril 2,5 — 10mg), ARBs
Vasospastic angina	Calcium channel blockers (Amlodipine 10 mg or Verapamil 240 mg SR or Diltiazem 90 mg twice daily or 120–360 mg single or divided doses)
	Nitrates (Isosorbide mononitrate XL 30 mg)
	Nicorandil (10-20 mg twice daily)
Both microvascular and vasospastic angina	Calcium channel blockers (Amlodipine 10 mg or Verapamil 240 mg SR or Diltiazem 90 mg twice daily or 120–360 mg single or divided doses)
	Nicorandil (10-20 mg twice daily)
	Trimetazidine (35 mg twice daily)
	ACE inhibitors (Ramipril 2.5 -10mg), ARBs
	Statins (Rosuvastatin 10–20 mg)

Note: ACE — angiotensin-converting enzyme inhibitor; ARBs angiotensin receptor blocker

The enhanced external counterpulsation can be used as an additional treatment for INOCA patients, in case of ineffectiveness of drug therapy.

Currently, the studies of the effect of Rho-kinase inhibitors (Rho-associated protein kinase (ROCK)) on the reduction of coronary vasoreactivity and contractility of vascular wall are ongoing. The results of a multicenter, randomized, double-blind, placebo-controlled trial Women's Ischemia Trial to Reduce Events in Non-Obstructive CAD (WARRIOR NCT03417388) that investigates the effects of statins (rosuvastatin or atorvastatin)/ACEI (lisinopril) or ARBs (losartan)/acetylsalicylic acid (aspirin) in high doses in 4,422 women aged 18 to 100 years with the symptoms of INOCA, CA stenosis <50 % and FFR >0.80 are highly expected. The hypothesis of this trial is that intensive drug treatment will reduce the risk of major cardiovascular events by 20 % compared to the conventional management strategy for this category of patients. Follow-up period will be 3 years. The expected trial completion date is December 30, 2023.

Myocardial revascularization (percutaneous coronary intervention (stenting of coronary arteries), or CABG) is used as an additional treatment method for stable angina that is refractory to drug therapy and/or hemodynamically significant atherosclerotic lesions of the left coronary artery trunk , large epicardial branches and large painless ischemia. The decision on the choice of surgical treatment is made by an X-ray endovascular surgeon, a cardiovascular surgeon and a cardiologist based on the results of CAG, non-invasive and invasive studies, and patient's clinical condition. Revascularization can contribute to reducing the amount and dose of antianginal drugs, increasing exercise tolerance and improving the life quality compared to only drug treatment. Myocardial revascularization is not performed in vasospastic angina with no hemodynamically significant atherosclerotic CAD [9].

More than half of patients (55 %) with microvascular angina are refractory to drug therapy. This situation is complicated by the fact that the choice of effective treatment for refractory angina is in fact, currently limited. Moreover, since microvascular angina is not routinely diagnosed using invasive methods (coronary angiography), it often remains undetected. Therefore, the management of refractory angina should focus not only on macro- but also on microvascular dysfunction.

Despite the growing number of patients with coronary heart disease with limitations for revascularization or "no choice", the options for refractory angina management are currently limited. Ranolazine was approved for the management of refractory angina on the basis of studies with the participation of patients with IHD, and the use of enhanced external counterpulsation demonstrated an improvement in the time before ST segment depression on the ECG, however, not the general tolerance to physical exertion in patients with refractory angina. However, the effectiveness of ranolazine with refractory angina has recently become an issue for discussion.

In RIVER-PCI trial (Ranolazine in Patients With Incomplete Revascularization After Percutaneous Coronary Intervention), 2,604 patients (average age 63.4 years) after incomplete revascularization (one or more coronary artery lesions with a stenosis diameter of 50 % or higher with a reference value of ≥2.0 mm in diameter by visual assessment) using PCI with stenting were randomized in groups to receive ranolazine 1,000 mg twice daily (n = 1,317) and placebo (n = 1,287). The results of 1.8 year median follow-up demonstrated that 26.2 % of patients in ranolazine group and 28.3 % of patients in placebo group (p = 0.48) developed the events of primary combined endpoint (revascularization as a result of myocardial ischaemia or hospitalization with no revascularization). There was a high incidence of cardiovascular events in patients with incomplete revascularization (15.3 % in ranolazine group and 15.5 % in placebo group, p = 0.14). The results of this study revealed the ineffectiveness of ranolazine in improving the prognosis in patients with IHD and incomplete revascularization [13].

In a single-center, prospective, open-label study by S. Calcagno et al., the effectiveness of treatment with ranolazine (375 mg twice daily) in addition to conventional anti-ischaemic therapy in 49 patients (age 62.6 ± 11.3 years)who underwent CAG for persistent/recurrent angina after PCI and residual ischemia of the small branches of coronary arteries that were not subject to further revascularization. In the course of the treatment with ranolazine, in 30 days, the extended duration of stress test compared with the baseline value (9'1" ± 2' vs 8'10" ± 2', p = 0.01) was observed, as well as the decreased frequency of exertional angina attacks (4.1 % vs 16.3 %, p = 0.04). Thus, the addition of low-dose ranolazine to standard anti-ischaemic drug therapy resulted in improved results of stress test and decreased frequency of angina attacks in patients with persistent/recurrent angina and residual myocardial ischaemia when revascularization is impossible. In view of the small sample of patients and short follow-up period, these results require further investigation and confirmation [14].

The 2020 Russian Guidelines for stable coronary artery disease largely coincide with European ones both at the diagnostic stage and at the stage of treatment selection. Invasive CAG is no longer the "gold standard" in the diagnosis of ischaemic lesions. The drug therapy selection is considers the mechanism and nature of CA lesions. CCB are the agents of choice for hyperreactivity of smooth muscle cells, epicardial or microcirculatory

vessels (positive acetylcholine test). Beta blockers, nitrates, CCB, and ACEI or ARBs are recommended for endothelial dysfunction (positive adenosine test).

However, the opinions of the professional communities of cardiologists in the USA, Canada, Great Britain, European countries, and Australia regarding the guidelines on separate methods of managing IHD are quite different. There is a number of drugs, "food supplements", surgical and other methods that are mentioned in some guidelines on the management of patients with chronic ischaemia caused by atherosclerotic lesions of coronary arteries, as appropriate/ with possible positive effect on the course of IHD, however, are absent in other guidelines or are indicated as "unproven" and not recommended for use [15].

Thus, the management of patients with suspected myocardial ischaemia with any pathogenetic mechanism (CMD or spasm) should be carried out with the participation of general practitioners, cardiologists, specialists in the field of interventional cardiology (if necessary, consultations with other specialists are also indicated). When symptoms of ischaemia or asymptomatic ischaemia are detected, beta blockers and/or calcium channel blockers are the first choice drugs for all patients; these agents depending on the clinical situation may be recommend by a general practitioner/general practitioner of the outpatient stage. If adjustment of treatment or additional examination is required, the patient is referred for a cardiologist' consultation.

Conclusion

The accumulation of new knowledge and performing new studies necessitate a continuous analysis of existing solutions, implementation of new terms more precisely describing the pathological processes associated with myocardial ischaemia, for establishment of new and revision of old IHD criteria and the parameters for assessing patient's condition.

With the development of new technologies, the non-invasive examination methods that reveal certain specific features of blood flow functional state, perfusion and myocardial contractility are prioritized at the initial stage of diagnostics. The choice of methods depends on resources available, staff experience, preferences of physicians and patients. Diagnostic methods listed in the ESC Guidelines for general clinic networks can hardly be generally available in our country. This issue, of course, requires clarification and further discussion.

In view of the lack of evidence (including the management of patients with INOCA), there is no single approach to the choice of anti-ischaemic drugs and agents that affect life quality, atherosclerosis progression and the incidence of cardiovascular events. The step-by-step strategy depending on the clinical course of disease and risk factors for cardiovascular events associated with atherosclerosis remains the reference. Calcium channel blockers or beta blockers are still the first-line anti-ischaemic agents.

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