**UCD** 616.127-005.8
**DOI** 10.17802/2306-1278-2022-11-1-78-89

# CONTROVERSIAL ISSUES OF TYPE 2 MYOCARDIAL INFARCTION PATIENTS MANAGEMENT

**V.I. Kinash[1], A.S. Vorobiev[1, 2], I.A. Urvantseva[1, 2], L.V. Kovalenko[2], V.V. Kashtalap[3, 4]**

*[1] Budgetary Institution of the Khanty-Mansiysk Autonomous Okrug – Ugra "District Cardiology Dispensary" of the Center for Diagnosis and Cardiovascular Surgery", 69/1, Lenina Ave., Surgut, Khanty-Mansiysk Autonomous Okrug − Ugra, Russian Federation, 628416; [2] Surgut State University, 1, Lenin Ave., Surgut, Khanty-Mansiysk Autonomous Okrug − Ugra, Russian Federation, 628412; [3] Federal State Budgetary Institution "Research Institute for Complex Issues of Cardiovascular Diseases", 6, Sosnoviy blvd., Kemerovo, Russian Federation, 650002; [4] Federal State Budgetary Educational Institution of Higher Education "Kemerovo State Medical University" of the Ministry of Health of the Russian Federation, Voroshilova Street, 22a, Kemerovo, Russian Federation, 650000*

**Highlights**

• The article presents relevant literary data on the epidemiology, main causes, approaches to the diagnostics and treatment of type 2 myocardial infarction patients. The authors emphasize an unfavorable prognosis in these patients due to comorbidity that leads to development of myocardial infarction. They highlight the need to improve and unify approaches to identifying this phenomenon, as well as the necessity to conduct observational and randomized studies to evaluate approaches to the treatment of type 2 myocardial infarction patients.

**Abstract**

The article summarizes the available data from clinical trials and current guidelines, approaches to the definition and type 2 myocardial infarction (MI) differential diagnosis in clinical practice. The attention is focused on the fundamental difference between type 1 and type 2 MI and the need to consider the comorbidities for the identification of etiological factors type 2 MI development. The lack of evidence-based medical data regarding the prognosis and effective treatment of patients with type 2 MI is emphasized. Nevertheless, such patients are characterized with high rates of overall and cardiovascular mortality in hospital and long-term disease course, as well as a high rate of readmission. Thus, there is the need for multicenter observational studies of type 2 MI patients and the development of algorithms for treatment and rehabilitation of this category of patients.

**Keywords** Type 2 myocardial infarction • Myocardial injury • Definition • Differential diagnosis

***Received:*** *15.10.2021;* ***received in revised form:*** *17.11.2021;* ***accepted:*** *02.12.2021*

**Список сокращений**

| | | | |
|---|---|---|---|
| CA | – coronary artery | MI | – myocardial infarction |
| CAG | – coronary angiography | MRI | – magnetic resonance imaging |
| hsTnT | – high sensitivity troponin T | MSCT | – multislice computed tomography |

## Introduction

In recent decades there has been a decrease in the frequency of circulatory system diseases complications in the world and Russian Federation, although acute coronary syndrome and myocardial infarction (MI) still remain the leading causes of cardiovascular mortality in industrialized countries [1, 2]. Thus, in the European Union countries various forms of coronary heart disease lead to 2 million deaths annually [2]. More than 8 million Americans a year visit hospitals with signs of acute coronary syndrome and approximately 700 thousand patients are diagnosed with it [3]. Nevertheless, mortality rates from coronary heart disease among the working population in Russia are several (3−9) times higher than in Europe and the USA [4].

During the process of MI etiopathogenesis data collection its definitions are being developed and improved, which require a revision of views on approaches to the diagnosis, treatment and rehabilitation of patients with MI in real clinical practice [5].

A coronary thrombus on the surface of a ruptured fibrous capsule of an atherosclerotic plaque is considered a distinctive feature and the main therapeutic target of acute MI type 1, however, many other mechanisms

***Corresponding author:*** *Anton S. Vorobiev, a.s.vorobyov@gmail.com; address: 69/1, Lenina Ave., Surgut, Russia, 628412*

that cause or contribute to the development of MI are currently known. The "Fourth Universal Definition of myocardial infarction" identifies five types of MI, as well as ischemic myocardial injury [6].

"Myocardial infarction" is diagnosed in patients with verified myocardial ischemia as the main cause of its damage, regardless of whether this is due to acute atherothrombosis (MI type 1) or a mismatch between delivery and myocardial oxygen demand without acute atherothrombosis (MI type 2). A diagnostically significant increase in necrosis biomarkers (high sensitivity troponin T (hsTnT) or I) of the myocardium in the absence of clinical signs of its ischemia is classified as acute or chronic non-ischemic myocardial damage. However, optimal strategies for the assessment and treatment of these etiologically different pathological conditions have not been determined [7].

**Myocardial injury and its differences from myocardial infarction**

Myocardial injury can be acute and manifest itself by dynamic changes in the concentration of hsTnT with successive measurements: an increase in hsTnT of more than the 99th percentile of the upper reference limit for patients without an initial increase, or an increase of more than 20.0% if the previous level of hsTnT was higher than the 99th percentile of the upper reference limit (while remained stable at a variation of ≤20.0% or decreased altogether). In chronic myocardial injury, the concentrations of hsTnT are stable or change minimally with successive measurements. The causes of chronic myocardial injury can be both structural heart diseases (hypertrophy/dysfunction of the left ventricle) and non-cardiac diseases (diabetes mellitus, chronic kidney disease). Myocardial injury prevelence, according to various data, ranges from 4.0% to 72.0% [8, 9, 5, 10−14].

In contrast to MI its acute ischemic injury is a broader diagnostic category which is subsequently followed by the development of MI. Both conditions combine an increase and subsequent decrease in serum levels of myocardial necrosis markers mainly hsTnT. The main differences between MI and myocardial injury are considered to be clinical (anginal pain, shortness of breath) and electrocardiographic (ST segment deviation, pathological Q wave) signs of myocardial ischemia; violations of local myocardial contractility, confirmed by instrumental methods (echocardiography, myocardial scintigraphy, heart magnetic resonance imaging (MRI)) [15].

**Type 2 MI: the main causes and prevalence**

According to the "Fourth Universal Definition of myocardial infarction" [6], type 2 MI is developed due to a mismatch between delivery and myocardial oxygen demand. A decrease in myocardial perfusion, as a cause of infarction, is produced by spasm, embolism or dissection of the coronary artery (CA), dysfunction of the microcirculatory bed, systemic hypotension or shock, respiratory failure, severe anemia. Persistent tachyarrhythmias, high systemic arterial hypertension, severe myocardial hypertrophy of any genesis (including hypertrophic cardiomyopathy or severe aortic stenosis) cause an increase in myocardial oxygen demand. The authors proposed the so-called geriatric concept of type 2 MI on this basis. It included three components:

1) age-related physiological decrease in adaptive mechanisms of the cardiovascular system ("aging");

2) chronic comorbidity (aortic stenosis, hypertrophic cardiomyopathy, thyrotoxicosis, chronic anemia);

3) acute stress triggers (acute bleeding, acute respiratory failure, severe acute cardiovascular insufficiency, pronounced bradyarrhythmias, conditions after non-cardiosurgical operations, coronary spasm, coronary embolism, acute infection, supraventricular arrhythmias, ventricular tachycardia, seizures).

F. Szymański and colleagues in 39.6% of cases call coronarospasm, in 19.0% – severe anemia, in 15.5% – hypertensive crisis, in 25.9% of cases – tachyarrhythmias and bradiarrhythmias among the causes leading to the development of type 2 MI [17]. F. Borges and co-authors indicated that supraventricular tachycardia might be the cause of type 2 MI in 19.4% of cases, ventricular tachycardia − in 9.0%. The authors identified anemia as a factor in the development of type 2 MI in 19.0%−34.0% of cases. Sepsis, as an acute trigger of type 2 MI, was detected in 17.5%−39.0% of cases [18].

According to A. Putot and colleagues, acute infections, mainly of the respiratory tract, caused type 2 MI in 39.0% of cases, tachyarrhythmias − in 13.0%, acute heart failure − in 10.0% of cases [19]. A combination of several factors provoking the development of type 2 MI was noted in 14.0% of patients. Nevertheless, the data about the frequency of type 2 MI among all patients with MI are very variable − from 2.0% to 58.0% [20].

According to the results of the Danish study in which 4,500 clinical cases with elevated levels of troponin I were analyzed, only 553 met the criteria of MI and type 2 MI was diagnosed in 144 cases (26.0%) [21]. According to the Wake Forest Medical School (USA), out of 807 examined patients, the frequency of type 2 MI was 36.6% (295cases) [22].

Statistics from the Swedish registry SWEDEHEART indicates that out of 20,138 cases type 2 MI was diagnosed in 1,429 (7.1%) patients [3]. According to a retrospective cohort study conducted in Norway [23] out of 1,102 cases of MI, the second type was only 17 (1.6%) cases.

According to the database of clinics in Israel, out of 2,818 cases of MI, the second type was determined in 127 (4.5%) patients [24]. Out of 2,882 patients examined in the cardiology department of the Medical University of Warsaw, only 57 (2.0%) patients were diagnosed with type 2 MI [17]. According to the study by T. Melberg and co-authors [25], out of 1,093 patients with MI the second type was established in 21 (2.0%) cases. The group of researchers led by Y. Sandoval examined 1,640 patients with MI and revealed the second type of MI in 951 (58.0%) patients [7]. S. Meigher and co-authors diagnosed type 2 MI in 705 (57.0%) patients out of 1,283 the examined ones; L. Sarkisian and colleagues detected type 2 MI in 26.0% of patients [9, 10]. According to Russian researchers led by H.C. Hoang, in a retrospective analysis of 450 patients with MI, the second type was found in 175 (38.9%) patients [26].

In our opinion, a significant role in such variations of type 2 MI detection frequency can be played by the initial differences in the clinical and epidemiological cohorts of patients selected for observation, the accuracy (sensitivity and specificity) of laboratory test systems for troponins, as well as differences in the interpretation of the provisions of the "Fourth Universal Definition of Myocardial infarction" in the context of this type MI diagnosis [27].

**Clinical Characteristics of Patients with type 2 MI**

According to observational studies, the clinical characteristics of patients with type 2 MI, are quite diverse. As a rule, patients with this type of MI are significantly older (by 10 years or more) and are mostly females compared with the group of type 1 MI patients [5, 9, 16]. Although Y. Seo and colleagues found no statistically significant age difference between patients with MI of the first and second types [28]. People with MI 2 are also significantly more likely than those with MI 1 to have a history of comorbid diseases such as chronic heart failure (20.5 vs. 10.6%), a stroke (13.9 vs. 9.2%) that preceded them (40.1 vs. 30.4%), diabetes mellitus (26.8 vs. 22.2%) [29].

When comparing clinical symptoms in the acute phase of MI, pain syndrome was established in 84.8% of cases with type 1 MI and only in 62.0% of patients with type 2 MI, dyspnea − in 7.0% and 19.2% of cases. [30]. Type 2 MI causes hospitalization for 38%–45% of patients in real clinical practice [31]. Changes in the electrocardiogram recorded at the admission of patients with a later diagnosis of type 2 MI also have their own characteristics. In particular, ST-segment depression (31.8% vs. 22.7%), atrial fibrillation (28.1% vs. 8.4%), left bundle branch block (11.6 vs. 6.3%), as well as the absence of ischemic changes according to ECG data (25.9% vs. 22.2%).

It has been proved that patients with type 2 MI demonstrate lower levels of troponins and naturally less pronounced atherosclerotic changes during coronary angiography (CAG). Thus, according to the Swedish registry SWEDEHEART, the absence of atherosclerotic changes of CA was registered in 42.4% of patients with type 2 MI versus 7.4% in people with type 1 MI [33]. This angiographic phenomenon has been commonly referred to as MINOCA (Myocardial Infarction with Non-obstructive Coronary Arteries) in the international medical literature since 2017 [34]. Similar results were obtained when analyzing the Danish registry, where the absence of significant stenoses in MI of the second and first types was 45.0 and 12.0% respectively if to consider the total number of MI patients [21, 35].

According to the domestic data, type 2 MI was more common in women (44.6% vs. 32.7%) and elderly patients (the average age of type 2 MI patient is 3.2 years higher than that of type 1 MI patient and it is 66.9 vs. 63.7 years old respectively); electrocardiogram shows ST segment elevation less often with type 2 MI than in the first type of MI (24.6 vs. 72.0%) [26]. 114 patients (65.1%) with type 2 MI also had triggers for the development of an imbalance between the need and oxygen delivery to myocardial cells: arterial hypertension or hypotension (blood pressure >160 or <90 mmHg) − in 21 (12.2%) participants, severe anemia − in 67 (38.3%) patients, atrial fibrillation − in 24 (13.7%), bronchopulmonary infection – in 10 (5.7%) people. In the past history of patients with type 2 MI cardiovascular diseases were significantly more common than in the first type: preceding MI (46.9% vs. 18.9%), symptomatic coronary heart disease (66.9% vs. 53.5%), myocardial revascularization (19.4% vs. 9.0%; p = 0.002). It is worth mentioning that in type 2 MI low (52.1% vs. 54.7%) and moderate (29.0% vs. 33.9%) degrees of valvular heart defects were detected less often than in the first type, but severe valve defects were diagnosed more often (16.5% vs. 7.5%) [26].

According to C. McCarthy and other authors the following diseases were identified as comorbid in 359 patients diagnosed with type 2 MI: chronic heart failure − in 21.7% of cases, respiratory failure − in 19.2%, acute and chronic sepsis − in 14.2%, life-threatening arrhythmias − in 14.5%, hypertensive crisis − in 10.6%, acute bleeding − in 5.3%, chronic anemia − in 3.9%, severe hypotension − in 3.9%, non-cardiac surgical interventions − in 2.8%, acute dissection of CA − in 0.3% of cases [14, 21, 36].

Thus, type 2 MI is characterized by a high frequency of concomitant or background diseases, often life-threatening to patients and may also represent a direct mechanism of thanatogenesis.

**Specific Features of Type 2 MI Diagnosis**

Taking into account the polymorphism of etiological and pathogenetic factors contributing to the development of type 2 MI, the diagnostic process can be complex, lengthy and require individual diagnostic algorithms. According to some studies, up to 45%

of all cases of acute coronary syndrome are asymptomatic which further complicates the differential diagnosis of type 2 MI [15, 18, 32].

According to the results of the OPTIMUS study, the practitioners' accuracy in identifying type 2 MI was 56% after non-cardiosurgical interventions and 63% for cases of primary type 2 MI, which confirms the relevance of a more detailed study of this MI type [18].

Both invasive and non-invasive research methods are currently used in the diagnosis of MI. T. Baron and colleagues report that CAG was performed in 36% of cases with type 2 MI and in 77% of cases with type 1 MI. CAG with intravascular ultrasound or optical coherence tomography is the "gold standard" in the study of the anatomy and virtual histology of CA and is widely used to identify local signs of rupture of atherosclerotic plaques and coronary thrombosis, which allows the most reliable diagnosis of the first type of MI. In patients with MI the presence of atherosclerotic plaque damage is detected only in 73% of cases with optical coherence tomography, in 47% of cases with contrast video angioscopy and in 40% of cases with intravascular ultrasound [37].

Other studies have shown that up to 79% of atherosclerotic plaques with signs of damage detected by intravascular ultrasound "heal" without obstructive coronary atherothrombosis and the development of MI. Consequently, the violation of the integrity of plaques by itself does not always end with atherothrombosis and the formation of type 1 MI [38].

Noninvasive imaging methods, such as multislice computed tomography (MSCT), MRI can be useful for distinguishing type 1 MI from other causes of myocardial damage based on the assessment of the coronary bed for the presence of atherosclerotic plaques and blood clots, the presence and nature of myocardial edema, myocardial inflammation or scarring zones [38, 6].

MSCT is suitable for non-invasive assessment of the coronary bed due to its high resolution. Coronary MSCT can detect small atherosclerotic plaques, which clearly correlates with intravascular ultrasound data. Nevertheless, it is often difficult to distinguish an intracoronary thrombus from an uncalcified atherosclerotic plaque with the help of MSCT. Ruptures of atherosclerotic plaques can be visualized using tomography but the sensitivity of this method is significantly lower if compared with intravascular ultrasound. The value of MSCT-coronary angiography for the detection of thrombotic lesions may increase with the further improvement of technology, for example, with the improvement of spatial resolution [6].

Since atherosclerosis is a necessary condition for type 1 MI development, its absence according to MSCT-coronary angiography largely excludes this possibility and suggests the presence of type 2 MI or ischemic myocardial damage. Spontaneous dissection of the CA intima is a recognized etiological cause of MI development in more than a third of women under the age of 50, which is why MSCT-coronary angiography can be useful for identifying patients with spontaneous dissection of CA and type 2 MI [39].

Echocardiography can be used to diagnose myocardial damage non-coronary causes, such as severe aortic stenosis, mitral and tricuspid valve defects, septum integrity disorders, cardiomyopathy [40]. It is possible to assess the degree of violation of myocardial perfusion in the differential diagnosis of MI with myocarditis with the help of contrast echocardiography.

Visualization of myocardial perfusion can also be performed if to use single-photon emission computed tomography, positron emission tomography, MRI. Nuclear magnetic resonance is a non-invasive instrumental method, and in combination with delayed contrast enhancement can detect myocardial damage by the presence of edema of its tissues. Ischemic myocardial damage usually spreads from the endocardium to the epicardium, whereas ischemic damage can be visualized in the epicardium and intramural regions of the myocardium. MRI has limitations in assessing coronary anatomy due to insufficient spatial resolution. The advantage of MRI is the ability to diagnose myocardial damage that is not associated with ischemia. MRI can detect signs of acute myocarditis in 15-75% of cases in patients without coronary obstruction, [41].

**Approaches to type 2 MI patients treatment**

Timely diagnosis of MI type 1 is necessary for the immediate initiation of a complex active treatment, including statins, antithrombotics, anticoagulants and percutaneous coronary intervention. In the absence of an aggravating comorbid background (severe anemia, acute bleeding, sepsis, arrhythmogenic shock, acute respiratory failure) the preliminary diagnosis for most patients with signs of acute myocardial injury and symptoms of its ischemia before CAG or other imaging methods of the coronary bed should be type 1, which requires initiation of recommended therapy before clarifying the diagnosis. If a subsequent diagnosis does not confirm the presence of coronary atherothrombosis, it is necessary to search for the etiological causes of type 2 MI (coronary embolism, spasm, CA dissection) or myocardial damage (pulmonary embolism, myocarditis). It is important to note that many patients with MI of the first type may have tachycardia, hypertensive crisis and even chronic anemia, which must be taken into account to prevent overdiagnosis of MI of the second type before CAG [42].

However, in cases where the first type MI is not the most likely cause of myocardial damage, the use of diagnostic and therapeutic strategies that can potentially cause iatrogenic harm should be cautious. When acute myocardial injury occurs in the context of another

acute disease or surgical intervention, type 2 MI or myocardial injury is more likely than type 1 MI. Nevertheless, in a number of clinical situations, plaque rupture can be triggered by acute infectious diseases (including COVID-19) or perioperative stress [43].

The treatment of patients with type 2 MI is a complex task and should be based on an individual approach and a thorough assessment of clinical data in each case. The evidence base for the management of patients with this type of MI is currently significantly limited; however, it is possible to identify the most important areas of treatment. The first thing is emergency care, which consists of symptomatic and supportive therapy in cases with the threat of complications development (life–threatening arrhythmias, cardiogenic shock, hypotension,etc.). The second direction includes a timely diagnostic search for the cause of type 2 MI and subsequent treatment aimed at eliminating the etiological cause, including compensation for comorbid diseases. The third direction is the therapy aimed at improving the prognosis. Emergency myocardial revascularization in uncomplicated type 2 MI is not the method to be chosen [44].

Thrombolytic therapy does not seem appropriate for type 2 MI, except for obvious signs of embologized MI. The absence of atherothrombosis and the low frequency of CA stenting in these patients make it unreasonable to conduct dual antiplatelet, anticoagulant therapy and aggressive statin therapy regimens. Thus, according to T. Barron and co-authors, stenting for type 2 MI is performed only in 13% of cases in Swedish clinics [33]. According to Israeli authors, the frequency of coronary stenting was 50% in patients with such type of MI [3, 37, 44].

If coronary spasm is the cause of type 2 MI, it is advisable to use calcium channel blockers due to their proven effectiveness in patients with vasospastic angina [46, 30, 47]. In cases of coronary embolism or thrombosis (without damage to the atherosclerotic plaque), the question of the expediency of anticoagulant and long-term antiplatelet therapy is debatable and there are currently no unambiguous positions in these clinical situations [48].

If the cause of the development of type 2 MI was spontaneous dissection of the CA, then the experience of clinical practice demonstrates the inexpediency of percutaneous coronary intervention, except for the cases of clinical instability and the development of MI with ST segment elevation as a result of coronary occlusion. In most cases, coronary dissection resolves spontaneously, and stenting of this CA section is associated with certain risks [9, 48].

In practice the treatment of patients with both types of MI differs only in the frequency of antiplatelet agents, anticoagulants and statins subscription [3, 39, 48]. Thus, aspirin is used in patients with type 2 MI in 74.2% vs. 92.6% of cases with type 1 MI, two-component antiplatelet therapy is applied to in 40.2% vs. 75.9% of cases, statins are used in 66.0% and 86.0% of cases, respectively.

According to the SWEDEHEART registry, anticoagulants were prescribed with relatively the same frequency for both types of MI: in 65% and 67% of cases, respectively [37]. Statins and beta-blockers were prescribed somewhat less frequently for type 2 MI, but still more than 60% of patients in both groups took these drugs. Some publications revising pharmacotherapeutic strategies for managing the patients with type 2 MI and myocardial injury have recently appeared in the scientific literature. Such drugs as colchicine, eplerenone and ticagrelor can form the basis of pharmacotherapy in this group of patients [49].

Thus, there are no generally accepted positions regarding the treatment of type 2 MI patients due to the lack of evidence, the extreme heterogeneity of the reasons how this type of MI is developed, and certain difficulties in diagnosing a specific type of MI in real clinical practice, which in most cases leads to an undifferentiated approach to therapy prescriptions.

**Type 2 MI patients' prognosis**

According to a number of foreign studies, the immediate and long-term prognoses in patients with different types of MI may vary significantly towards more negative outcomes in type 2 MI. Some researchers report that only 30% of patients with the second type of MI survive for 5 years [10–13, 19, 44, 45].

A. Singh and the colleagues analyzed the outcomes of 3,829 young patients with primary suspicion about acute coronary syndrome with increased troponins, among whom 55% of individuals were with type 1 MI, 32% with type 2 MI, in 13% of cases myocardial damage was detected. During 10.2 years of the follow up period the highest mortality from all causes was recorded among patients with myocardial injury and it was 45.6% of cases, in patients with type 2 MI the mortality rate was 34.2%, in patients with type 1 MI it equaled 12%. Patients with type 2 MI have higher mortality rates from all causes and the cardiovascular ones compared with patients with type 1 MI [36, 39, 50].

According to Y. Sandoval and the colleagues, the mortality rate of patients with type 2 MI within 180 days was 13%, within 2 years it came up to 22%; in patients with type 1 MI the 180-day mortality rate was 8%, within 2 years it equaled 16%. Other authors point to a higher frequency of repeated hospitalizations with MI of the second type if to compare with the first [6–8, 29, 50].

According to C.E. Raphael and co-authors, ACT-2 (Appropriateness of Coronary Investigation in Myocardial Injury and Type 2 Myocardial Infarction) study is currently underway and it will assess the role of early coronary angiography in reducing cardiovascular mortality in patients with type 2 MI and myocardial injury in comparison with conservative therapy.

The detection and treatment of coronary heart disease obstructive forms can increase the threshold for the occurrence of ischemia and reduce the frequency of relapses of acute coronary syndrome and cardiovascular mortality in patients with an established diagnosis of type 2 MI. According to the results of this study, screening and careful correction of cardiovascular risk factors, as well as the treatment of the underlying disease and comorbid background are recommended to improve the prognosis in people with type 2 MI [30, 42, 50].

Thus, in patients with type 2 MI, both the early and long-term prognosis is less favorable than in patients with type 1 MI. It happens not only due to overall mortality rates but also due to cardiovascular causes, which indicates the need for the patients focus monitoring of patients with such a diagnosis.

## Conclusion

The true prevalence and prognosis of the disease are unknown and it requires regional and international observational clinical studies with a thorough assessment of the effectiveness and safety of therapeutic and diagnostic strategies and risk stratification in this type of MI. It seems impractical to mechanically transfer evidence-based (based on the results of randomized clinical trials) positions of clinical recommendations related to risk management in patients with type 1 MI, in relation to type 2 MI patients.

Currently, it is generally accepted that the management of patients with type 2 MI in each case is the subject of multidisciplinary team of doctors interaction and presents a complex clinical task, taking into account the underlying disease, comorbid background and pathogenetic processes underlying acute coronary syndrome.

## Conflict of Interest

V.I. Kinash declares no conflict of interest. A.S. Vorobiev declares no conflict of interest. I.A. Urvantseva declares no conflict of interest. L.V. Kovalenko declares no conflict of interest. V.V. Kashtalap is a member of the editorial board of the journal "Complex Issues of Cardiovascular Diseases".

## Financing

The scientific article was carried out within the framework of the state task (2021–2023) "DNA methylation profile in the indigenous and alien population of Yugra as an epigenetic biomarker of age-associated cardiovascular pathology and the possibility of its personalized early diagnosis" (scientific and educational center of the Medical Institute of the Khanty-Mansiysk Autonomous Okrug - Yugra "Surgut State University", Surgut, Russia) and with the information support of the world-class Scientific and Educational Center "Kuzbass" (Kemerovo, Russia).



**Author Information Form**

*Kinash Vladimir I.,* X-ray Endovascular Surgeon, Budgetary Institution of Khanty-Mansiysk Autonomous Okrug – Ugra "District Cardiology Hospital" of the Diagnostic and Cardiovascular Surgery Center", Khanty-Mansiysk Autonomous Okrug – Ugra, Surgut, Russian Federation; graduate student at the Department of Cardiology, Budgetary Institution of Higher Education, Khanty-Mansiysk Autonomous Okrug – Ugra, "Surgut State University", Khanty-Mansiysk Autonomous Okrug − Ugra, Surgut, Russian Federation; **ORCID** 0000-0002-0209-4878

*Vorobiev Anton S.,* PhD, Associate Professor Cardiologist, Budgetary Institution of Khanty-Mansiysk Autonomous Okrug – Ugra "District Cardiology Hospital" of the Diagnostic and Cardiovascular Surgery Center", Khanty-Mansiysk Autonomous Okrug − Ugra, Surgut, Russian Federation; Associate Professor at the Cardiology Department, Senior Research Assistant at the Scientific Educational Center, Surgut State Medical Institute of Higher Education, Khanty-Mansiysk Autonomous Okrug − Ugra, "Surgut State University", Khanty-Mansiysk Autonomous Okrug − Ugra, Surgut, Russian Federation; **ORCID** 0000-0001-7014-2096

*Urvantseva Irina A.,* PhD, Associate Professor, Head Doctor, Budgetary Institution of Khanty-Mansiysk Autonomous Okrug – Ugra "District Cardiology Hospital" of the Diagnostic and Cardiovascular Surgery Center", Khanty-Mansiysk Autonomous Okrug − Ugra, Surgut, Russian Federation; Head of the Cardiology Department, Surgut State University, Khanty-Mansiysk Autonomous Okrug − Ugra, Surgut, Russian Federation; **ORCID** 0000-0002-5545-9826

*Kovalenko Lyudmila V.,* PhD, Professor, Head of the Medical Institute, Head of the Department of Pathophysiology and General Pathology, Budgetary Institution of Khanty-Mansiysk Autonomous Okrug – Ugra "Surgut State University", Khanty-Mansiysk Autonomous Okrug − Ugra, Surgut, Russian Federation; **ORCID** 0000-0001-5708-7328

*Kashtalap Vasily V.,* PhD, Associate Professor, Head of Clinical Cardiology Department, Federal State Budgetary Institution "Research Institute for Complex Issues of Cardiovascular Diseases", Kemerovo, Russian Federation; Professor at the Department of Cardiology and Cardiovascular Surgery of Federal State Budgetary Educational Institution of Higher Education "Kemerovo State Medical University" the Ministry of Health of the Russian Federation, Kemerovo, Russian Federation; **ORCID** 0000-0003-3729-616X

**Author Contribution Statement**

*KVI* – data analysis, manuscript writing, approval of the final version, fully responsible for the content

*VAS* – data collection, manuscript writing, editing, approval of the final version, fully responsible for the content

*UIA* – contribution to the concept of the study, editing, approval of the final version, fully responsible for the content

*KLV* – data interpretation, manuscript writing, approval of the final version, fully responsible for the content

*KVV* – data interpretation, manuscript writing, editing, approval of the final version, fully responsible for the content

## REFERENCES


1. Ministry of health Russian Federation. The incidence rate of adult population of Russia – 2018: Statistical materials (Zabolevaemost vzroslogo naseleniya Rossii- 2018: Statisticheskii sbornik (in Russian) Available at: https://minzdrav.gov.ru/ministry/61/22/stranitsa-979/statisticheskie-i-informatsionnye-materialy/statisticheskiy-sbornik-2018-god. (accessed 19.01.2022)

2. Townsend N., Wilson L., Bhatnagar P., Wickramasinghe K., Rayner M., Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. Eur Heart J. 2016;37(42):3232-3245. doi: 10.1093/eurheartj/ehw334..

3. DeFilippis A.P., Chapman A.R., Mills N.L., de Lemos J.A., Arbab-Zadeh A., Newby L.K., Morrow D.A. Assessment and Treatment of Patients With Type 2 Myocardial Infarction and Acute Nonischemic Myocardial Injury. Circulation. 2019; 140 (20): 1661-1678. doi: 10.1161/CIRCULATIONAHA.119.040631.

4. Andreenko E.Yu., Yavelov I.S., Loukianov M.M., Vernohaeva A.N., Drapkina O.M., Boytsov S.A. Ischemic Heart Disease in Subjects of Young Age: Current State of the Problem. Prevalence and Cardio-Vascular Risk Factors. Kardiologiia. 2018;58(10):53-58. (In Russ.) https://doi.org/10.18087/cardio.2018.10.10184

5. Nestelberger T., Boeddinghaus J., Badertscher P., Twerenbold R., Wildi K., Breitenbücher D., Sabti Z., Puelacher C., Rubini Giménez M., Kozhuharov N., Strebel I., Sazgary L., Schneider D., Jann J., du Fay de Lavallaz J., Miró Ò., Martin-Sanchez F.J., Morawiec B., Kawecki D., Muzyk P., Keller D.I., Geigy N., Osswald S., Reichlin T., Mueller C.; APACE Investigators. Effect of Definition on Incidence and Prognosis of Type 2 Myocardial Infarction. Journal of American College of Cardiology. 2017; 70 (13): 1558-1568. doi: 10.1016/j.jacc.2017.07.774.

6. Thygesen K., Alpert J.S., Jaffe A.S., Chaitman B.R., Bax J.J., Morrow D.A., White H.D.; Executive Group on behalf of the Joint European Society of Cardiology (ESC) / American College of Cardiology (ACC) / American Heart Association (AHA) /World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018; 138 (20): e618-e651. doi: 10.1161/CIR.0000000000000617.

7. Sandoval Y., Smith S.W., Sexter A., Schulz K., Apple F.S. Use of objective evidence of myocardial ischemia to facilitate the diagnostic and prognostic distinction between type 2 myocardial infarction and myocardial injury. European Heart Journal: Acute Cardiovascular Care. 2020; 9 (1): 62-69. doi: 10.1177/2048872618787796.

8. Smilowitz N.R., Subramanyam P., Gianos E., Reynolds H.R., Shah B., Sedlis S.P. Treatment and outcomes of type 2 myocardial infarction and myocardial injury compared with type 1 myocardial infarction. Coronary Artery Diseases. 2018; 29 (1): 46-52. doi:10.1097/MCA.0000000000000545.

9. Meigher S., Thode H.C., Peacock W.F., Bock J.L., Gruberg L., Singer A.J. Causes of Elevated Cardiac Troponins in the Emergency Department and Their Associated Mortality. Academic Emergency Medicine. 2016; 23 (11): 1267-1273. doi: 10.1111/acem.13033.

10. Sarkisian L., Saaby L., Poulsen T.S., Gerke O., Jangaard N., Hosbond S., Diederichsen A.C., Thygesen K., Mickley H. Clinical Characteristics and Outcomes of Patients with Myocardial Infarction, Myocardial Injury, and Non-elevated Troponins. American Journal of Medicine. 2016; 129 (4): 446.e5-446.e21. doi: 10.1016/j.amjmed.2015.11.006.

11. Javed U., Aftab W., Ambrose J.A., Wessel R.J., Mouanoutoua M., Huang G., Barua R.S., Weilert M., Sy F., Thatai D. Frequency of elevated troponin I and diagnosis of acute myocardial infarction. American Journal of Cardiology. 2009; 104 (1): 9-13. doi: 10.1016/j.amjcard.2009.03.003.

12. Chapman A.R., Shah A.S., Lee K.K., Anand A., Francis O., Adamson P., McAllister D.A., Strachan F.E., Newby D.E., Mills N.L. Long-Term Outcomes in Patients With Type 2 Myocardial Infarction and Myocardial Injury. Circulation. 2018; 137 (12): 1236-1245. doi: 10.1161/CIRCULATIONAHA.117.031806.

13. Smilowitz N.R., Gupta N., Guo Y., Berger J.S., Bangalore S. Perioperative acute myocardial infarction associated with non-cardiac surgery. European Heart Journal. 2017; 38 (31): 2409-2417. DOI: 10.1093/eurheartj/ehx313.

14. Lambrecht S., Sarkisian L., Saaby L., Poulsen T.S., Gerke O., Hosbond S., Diederichsen A.C., Thygesen K., Mickley H. Different Causes of Death in Patients with Myocardial Infarction Type 1, Type 2, and Myocardial Injury. American Journal of Medicine. 2018; 131 (5): 548-554. doi: 10.1016/j.amjmed.2017.11.043.

15. Dahhan A. Type 2 myocardial infarction: a grim diagnosis with different shades of gray. Journal of Cardiovascular Medicine (Hagerstown). 2019; 20 (8): 510-517. doi: 10.2459/JCM.0000000000000813.

16. Putot A., Jeanmichel M., Chague F., Manckoundia P., Cottin Y., Zeller M. Type 2 Myocardial Infarction: A Geriatric Population-based Model of Pathogenesis. Aging Diseases. 2020; 11 (1): 108-117. doi:10.14336/AD.2019.0405.

17. Szymański F.M., Karpiński G., Płatek A.E., Majstrak F., Hrynkiewicz-Szymańska A., Kotkowski M., Puchalski B., Filipiak K.J., Opolski G. Clinical characteristics, etiology and occurrence of type 2 acute myocardial infarction. Kardiologia Polska. 2014; 72 (4): 339-44. doi: 10.5603/KP.a2013.0284.

18. Borges F.K., Sheth T., Patel A., Marcucci M., Yung T., Langer T., Alboim C., Polanczyk C.A., Germini F., Azeredo-da-Silva A.F., Sloan E., Kaila K., Ree R., Bertoletti A., Vedovati M.C., Galzerano A., Spence J., Devereaux P.J. Accuracy of Physicians in Differentiating Type 1 and Type 2 Myocardial Infarction Based on Clinical Information. Canadian Journal of Cardiology. 2020; 2 (6): 577-584. doi: 10.1016/j.cjco.2020.07.009.

19. Putot A., Chagué F., Manckoundia P., Brunel P., Beer J.C., Cottin, Y., Zeller M. Post-Infectious Myocardial Infarction: Does Percutaneous Coronary Intervention Improve Outcomes? A Propensity Score-Matched Analysis. Journal of Clinical Medicine. 2020; 9 (6), 1608. https://doi.org/10.3390/jcm9061608.

20. Januzzi J.L., Sandoval Y. The Many Faces of Type 2 Myocardial Infarction. Journal of American College of Cardiology. 2017; 70 (13): 1569-1572. doi: 10.1016/j.jacc.2017.07.784.

21. Saaby L., Poulsen T.S., Diederichsen A.C., Hosbond S., Larsen T.B., Schmidt H., Gerke O., Hallas J., Thygesen K., Mickley H. Mortality rate in type 2 myocardial infarction: observations from an unselected hospital cohort. American Journal of Medicine. 2014; 127 (4): 295-302. doi: 10.1016/j.amjmed.2013.12.020.

22. Jogu H.R., Arora S., Vaduganathan M., Qamar A., Pandey A., Chevli P.A., Pansuriya T.H., Ahmad M.I., Dutta A., Sunkara P.R., Qureshi W., Vasu S., Upadhya B., Bhatt D.L., Januzzi J.L., Herrington D. Wake Forest University long-term follow-up of type 2 myocardial infarction: The Wake-Up T2MI Registry. Clinical Cardiology. 2019; 42 (6): 592-604. doi: 10.1002/clc.23182.

23. Sulo G., Igland J., Vollset S.E., Ebbing M., Egeland G.M., Ariansen I., Tell G.S. Trends in incident acute myocardial infarction in Norway: An updated analysis to 2014 using national data from the CVDNOR project. European Journal of Preventive Cardiology. 2018; 25 (10): 1031-1039. doi: 10.1177/2047487318780033.

24. Furie N., Israel A., Gilad L., Neuman G., Assad F., Ben-Zvi I., Grossman C. Type 2 myocardial infarction in general medical wards: Clinical features, treatment, and prognosis in comparison with type 1 myocardial infarction. Medicine (Baltimore). 2019; 98 (41): e17404. doi: 10.1097/MD.0000000000017404.

25. Melberg T., Burman R., Dickstein K. The impact of the 2007 ESC-ACC-AHA-WHF Universal definition on the incidence and classification of acute myocardial infarction: a retrospective cohort study. International Journal of Cardiology. 2010; 139 (3): 228-33. doi: 10.1016/j.ijcard.2008.10.021.

26. Hoang H.T., Kitbalyan A.A., Lazarev P.V., Maiskov V.V., Shkolinikova E.E., Meray I.A. Type 2 myocardial infarction: clinical and demographic features, laboratory and instrumental associations. RUDN Journal of Medicine. 2018; 22 (2), 148-158. (In Russian) doi: 10.22363/2313-0245-2018-22-2-148-158

27. Urvantseva I.A., Vorobiev A.S., Suleymanov R.R., Kovalenko L.V. “Should practicing cardiologists know about type 2 myocardial infarction?” (Opinion statement of the Ugra cardiologists). Complex Issues of Cardiovascular Diseases. 2019; 8 (4): 13-15. (In Russian). https://doi.org/10.17802/2306-1278-2019-8-4-13-15.

28. Seo Y., Paik J., Shin S., Kim A., Kang S. Differential diagnostic factors of type 1 and type 2 myocardial infarction in patients with elevated cardiac troponin levels. Clin. Exp. Emerg. Med. 2020;7(3):213-219 https://doi.org/10.15441/ceem.19.049.

29. Greenslade J.H., Adikari T., Mueller C., Sandoval Y., Nestelberger T., Parsonage W., Hawkins T., Cullen L. Characteristics and occurrence of type 2 myocardial infarction in emergency department patients: a prospective study. Emergency Medicine Journal. 2018; 35 (3): 169-175. doi: 10.1136/emermed-2017-206869.

30. Averkov O.V., Barbarash O.L., Boytsov S.A., Vasilieva E.Yu., Drapkina O.M., Galyavich A.S., Gilyarov M.Yu., Zayratiants O.V., Kakturskiy L.V., Karpov Yu.A., Mishnev O.D., Nikulina N.N., Orekhov O.O., Samorodskaya I.V., Soboleva G.N., Cherkasov S.N., Shakhnovich R.M., Shilova A.S., Shlyakhto E.V., Shpektor A.V., Yavelov I.S., Yakushin S.S. Differentiated approach in diagnostics, diagnosis formulation, case management and statistical accounting of type 2 myocardial infarction (Position Paper). Russian Journal of Cardiology. 2019; (6): 7-21. (In Russian) https://doi.org/10.15829/1560-4071-2019-6-7-21

31. Stein G.Y., Herscovici G., Korenfeld R., Matetzky S., Gottlieb S., Alon D., Gevrielov-Yusim N., Iakobishvili Z., Fuchs S. Type-II myocardial infarction--patient characteristics, management and outcomes. PLoS One. 2014 Jan 2;9(1):e84285. doi: 10.1371/journal.pone.0084285..

32. Oblavatckii D.V., Boldueva S.A., Soloveva M.V., Vinnichuk S.A., Mikhailov R.R. The Frequency of Type 2 Myocardial Infarction in the Structure of Hospital Mortality According to 7-Years Data of a State University Clinic. Kardiologiia. 2020; 60 (6): 76–83. (In Russian) https://doi.org/10.18087/cardio.2020.6.n896.

33. Baron T., Hambraeus K., Sundström J., Erlinge D., Jernberg T., Lindahl B.; TOTAL-AMI study group. Type 2 myocardial infarction in clinical practice. Heart. 2015;101(2):101-6. doi: 10.1136/heartjnl-2014-306093.

34. Agewall S., Beltrame J.F, Reynolds H.R, Niessner A., Rosano G., Caforio A.L., De Caterina R., Zimarino M., Roffi M., Kjeldsen K., Atar D., Kaski J.C, Sechtem U., Tornvall P; Working Group on Cardiovascular Pharmacotherapy. ESC Working Group position paper on myocardial infarction with non-obstructive coronary arteries. Eur. Heart J. 2017;38:143–153.

35. Goyal A., Gluckman T.J., Tcheng J.E. What's in a Name? The New ICD-10 (10th Revision of the International Statistical Classification of Diseases and Related Health Problems) Codes and Type 2 Myocardial Infarction. Circulation. 2017; 136 (13): 1180-1182. doi: 10.1161/CIRCULATIONAHA.117.030347.

36. McCarthy C.P., Murphy S., Rehman S., Jones-O'Connor M., Olshan D.S., Cohen J.A., Cui J., Singh A., Vaduganathan M., Januzzi J.L., Wasfy J.H. Home-Time After Discharge Among Patients With Type 2 Myocardial Infarction. Journal of American Heart Association. 2020; 9 (10): e015978. doi: 10.1161/JAHA.119.015978.

37. Gard A., Lindahl B., Hadziosmanovic N., Baron T. Treatment and Prognosis of Myocardial Infarction Outside Cardiology Departments. Journal of Clinical Medicine. 2020; 10 (1): 106. doi:10.3390/jcm10010106.

38. Sheth T., Natarajan M.K., Hsieh V., Valettas N., Rokoss M., Mehta S., Jolly S., Tandon V., Bezerra H., Devereaux P.J. Incidence of thrombosis in perioperative and non-operative myocardial infarction. British Journal of Anaesthesia. 2018; 120 (4): 725-733. doi: 10.1016/j.bja.2017.11.063.

39. Singh A., Gupta A., DeFilippis E.M., Qamar A., Biery D.W., Almarzooq Z., Collins B., Fatima A., Jackson C., Galazka P., Ramsis M., Pipilas D.C., Divakaran S., Cawley M., Hainer J., Klein J., Jarolim P., Nasir K., Januzzi J.L., Di Carli M.F., Bhatt D.L., Blankstein R. Cardiovascular Mortality After Type 1 and Type 2 Myocardial Infarction in Young Adults. Journal of American College Cardiology. 2020; 75 (9): 1003-1013. doi:10.1016/j.jacc.2019.12.052.

40. Lancellotti P., Pellikka P.A., Budts W., Chaudhry F.A., Donal E., Dulgheru R., Edvardsen T., Garbi M., Ha J.W., Kane G.C., Kreeger J., Mertens L., Pibarot P., Picano E., Ryan T., Tsutsui J.M., Varga A. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. European Heart Journal: Cardiovasc Imaging. 2016; 17 (11): 1191-1229. doi: 10.1093/ehjci/jew190.

41. Bulluck H., Dharmakumar R., Arai A.E., Berry C., Hausenloy D.J. Cardiovascular Magnetic Resonance in Acute ST-Segment-Elevation Myocardial Infarction: Recent Advances, Controversies, and Future Directions. Circulation. 2018; 137 (18): 1949-1964. doi:10.1161/CIRCULATIONAHA.117.030693.

42. Lambrakis K., French J.K., Scott I.A., Briffa T., Brieger D., Farkouh M.E., White H., Chuang A.M., Tiver K., Quinn S., Kaambwa B., Horsfall M., Morton E., Chew D.P. The appropriateness of coronary investigation in myocardial injury and type 2 myocardial infarction (ACT-2): A randomized trial design. American Heart Journal. 2019; 208: 11-20. doi: 10.1016/j.ahj.2018.09.016.

43. Giustino G., Pinney S.P., Lala A., Reddy V.Y., Johnston-Cox H.A., Mechanick J.I., Halperin J.L., Fuster V. Coronavirus and Cardiovascular Disease, Myocardial Injury, and Arrhythmia: JACC Focus Seminar. Journal of American College Cardiology. 2020; 76 (17): 2011-2023. doi: 10.1016/j.jacc.2020.08.059.

44. Pillai B., Trikkur S., Farooque U., Ramakrishnan D., Kakkra J.J., Kashyap G., Lalwani C., Mani A.B., Vishwanath J. Type II Myocardial Infarction: Predisposing Factors, Precipitating Elements, and Outcomes. Cureus. 2020; 12 (7): e9254. doi: 10.7759/cureus.9254.

45. Hung J., Roos J., Kadesjö J., McAllister D., Kimenai D., Shah A., Anand A., Strachan F., Fox K., Mills N., Chapman A., Holzmann M. Performance of the GRACE 2.0 score in patients with type 1 and type 2 myocardial infarction. European Heart Journal. 2021; 42 (26): 2552-2561. doi:10.1093/eurheartj/ehaa375.

46. Beltrame J.F., Crea F., Camici P. Advances in coronary microvascular dysfunction. Heart Lung Circ. 2009;18:19-27. doi:10.1016/j.hlc.2008.11.002.

47. Sato R., Sakamoto K., Kaikita K., Tsujita K., Nakao K., Ozaki Y., Kimura Y., Ako J., Noguchi T., Yasuda S., Suwa S., Fujimoto K., Nakama Y., Morita T., Shimizu W., Saito Y., Hirohata Y., Morita Y., Inoue Y., Okamura A., Mano T., Hirata T., Tanabe K., Shibata Y.,Owa M., Funayama H., Kokubu N., Kozuma K., Uemura S., Toubaru T., Saku., Shigeru Ohshima K., Nishimura K., Miyamoto Y., Ogawa H., Ishihara M. Long-Term Prognosis of Patients with Myocardial Infarction Type 1 and Type 2 with and without Involvement of Coronary Vasospasm. J. Clin. Med.2020; 9(6):1686.doi: 10.3390/jcm9061686.

48. Smit M., Coetzee A.R., Lochner A. The Pathophysiology of Myocardial Ischemia and Perioperative Myocardial Infarction. Journal of Cardiothoracic and Vascular Anesthesia. 2020; 34 (9): 2501-2512. doi: 10.1053/j.jvca.2019.10.005.

49. Sykes R., Briscoe M., Krysztofiak T., Peck O., Mangion K., Berry C. Type 2 myocardial infarction and myocardial injury: eligibility for novel medical therapy to derisk clinical trials. Open Heart. 2021 Jun;8(1):e001633. doi: 10.1136/openhrt-2021-001633.

50. Raphael C.E., Roger V.L., Sandoval Y., Singh M., Bell M., Lerman A., Rihal C.S., Gersh B.J., Lewis B., Lennon R.J., Jaffe A.S., Gulati R. Incidence, Trends, and Outcomes of Type 2 Myocardial Infarction in a Community Cohort. Circulation. 2020; 141 (6): 454-463. doi: 10.1161/CIRCULATIONAHA.119.043100.



***To cite:*** *Kinash V.I., Vorobiev A.S., Urvantseva I.A., Kovalenko L.V., Kashtalap V.V. Controversial issues of type 2 myocardial infarction patients management. Complex Issues of Cardiovascular Diseases. 2022;11(1): 78-89. DOI: 10.17802/2306-1278-2022-11-1-78-89*