Int J Cardiovasc Sci. 2023;36:e20220046

ORIGINAL ARTICLE

General Approach to Acute Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA): A Systematic Review

Marcos Aurélio Barboza de Oliveira,[1] Alan Vinicius Gamero Ósti,[2] Bruno Vargas Teixeira Cavalheiro,[1] Déborah Barbosa Naves,[1] Emanuelle Ribeiro de Oliveira,[1] Gabriel Freitas de Campos,[1] Gabriel Mael Sussuarana Silva Lobo,[1] Gabriely de Oliveira,[1] Marcela Paula Mainardi,[1] Marília Cardoso Guimarães,[1] Robert Filipe Barbosa,[1] Vilian Veloso de Moura Fé[1]

Universidade Federal de Mato Grosso,[1] Cuiabá, MT – Brazil
Faculdade de Medicina de São José do Rio Preto,[2] São José do Rio Preto, SP – Brazil

Abstract

Background: Acute myocardial infarction (AMI) without obstructive coronary arteries (MINOCA) is a medical condition of great relevance, with clinical characteristics of AMI, but without evidence of coronary artery obstruction. The mechanism involved in the pathophysiology of the disease and its possible etiologies are important objects of study due to their impact on the morbidity and mortality of affected patients.

Objectives: The aim of this study was to systematically review MINOCA and its characteristics, with emphasis on the clinical profile of patients, etiology, pathophysiology, diagnosis, and treatment of the syndrome.

Methods: Relevant articles related to MINOCA were analyzed in the PubMed and LILACS databases. In the initial search stage, 619 eligible articles were obtained, with final inclusion criteria being: original systematic reviews with clinical, epidemiological, diagnostic, or treatment data on MINOCA, published in Portuguese or English, with an abstract, and a publication date limit of September 2020.

Results: A total of 10 articles classified as systematic reviews that considered clinical data on MINOCA were included in this review.

Conclusion: After analyzing various literature, the present study provided a tool to better understand MINOCA, not only regarding its casuistry but also in grouping parameters and information that contribute to a healthy approach to this clinical situation. It was possible to identify and better outline the clinical profile of patients who presented this condition and the use of appropriate tools for correct diagnosis and ideal treatment.

Keywords: Myocardial infarction; myocardial ischemia; angiography; systematic review.

Introduction

MINOCA, a priori, generates reflections and concerns for the healthcare team. Thus, it is necessary to investigate the probable causes that lead to this condition and to understand the appropriate management that avoids greater harm to the patient. The increased use of early diagnostic and therapeutic tools that assist in the management of acute myocardial infarction (AMI), such as coronary angiography, has led to the identification of enigmatic findings as the absence of coronary artery obstruction, even in the presence of signs and symptoms of AMI, with elevated biomarkers, and changes in electrocardiogram (ECG).[1] It is estimated that 10–25% of patients who undergo angiography do not have coronary artery disease (CAD).[1-3] Furthermore, MINOCA has been shown to be more prevalent in young people, women, and individuals with fewer comorbidities than those with AMI resulting from CAD.[4-7] Although some studies reveal a plural prognosis for this condition, there is evidence of increased risk of cardiovascular and extracardiac events in patients with MINOCA.[1,4] Thus, this is not a benign

Mailing Address: Marcos Aurélio Barboza de Oliveira
Universidade Federal de Mato Grosso, Campus Sinop, Instituto de Ciências da Saúde. Rua Alexandre Ferronato, 1200. Postal code: 78557-267. Sinop, MT – Brazil
E-mail: maboliveira@gmail.com

DOI: https://doi.org/10.36660/ijcs.20220046

Manuscript received March 21, 2022; revised manuscript April 13, 2022; accepted November 27, 2022.

situation and is characterized by several long-term harms, even greater than those of patients diagnosed with AMI and CAD. Its management and follow-up should be done properly, aiming at the search for underlying causes.[1,6,8,9] What makes the recognition of this condition difficult is that the mechanisms that lead to AMI are not immediately identified.[3] Despite the uncertainty of its etiology, there are more frequent conditions that establish certain patterns, such as the identification of coronary artery spasms, plaque rupture, microvascular dysfunction, coronary dissection, and thrombophilia.[1,5,8] Thus, in addition to cardiac magnetic resonance imaging (MRI), the physician should also request some tests such as provocative spasm tests, polymerase chain reaction (PCR), coronary angiography, which can both confirm MINOCA and exclude and differentiate it from other causes, such as previous infections or Takotsubo Syndrome.[1,7,9,10] Pelliccia et al.6 revealed that the knowledge about its outcome remains obscure. The objective of this review was to group several systematic studies that aid in the better approach to MINOCA.

Methodology

Search strategy

This study is a systematic review conducted based on PRISMA guidelines. Two databases, PubMed and LILACS, were used for the initial search of articles containing relevant data related to MINOCA. The searches consisted of text terms and controlled vocabulary such as MeSH, as shown in Table 1. Terms related to the type of article or study design were not included in the search. At this stage, 619 eligible articles were obtained.

Eligibility criteria

The searches with the generated algorithms were performed by two independent researchers on a predefined date and then compared. The articles obtained at this stage were analyzed with the support of the Mendeley Reference Manager in order to remove duplicate manuscripts. The final inclusion criteria were: original systematic reviews that provided relevant clinical, epidemiological, diagnostic, or treatment data related to MINOCA, published up to September 2020. Restrictions were applied to articles that were not in English or Portuguese and those that did not contain an abstract.

Thus, in the initial stage, 615 titles were analyzed by independent reviewers. For articles in which there was disagreement, a third evaluator was requested to reevaluate. Of the titles analyzed, 299 studies were included in the abstract evaluation. Of these, 229 were considered relevant, with 10 of them being systematic reviews used in this work (Figure 1).

Results

Pathophysiology

MINOCA is a syndrome with different causes, characterized by clinical features of myocardial infarction (AMI), but with normal or near-normal coronary arteries on angiography.[9,11,12] Regarding its pathophysiology, Scalone et al. review proposed two main patterns, based in angiography: 1) Epicardial pattern: Regional wall motion abnormality limited to a single territory of the epicardial coronary artery; 2) Microvascular pattern: Regional wall motion abnormality extending beyond a single territory of the epicardial coronary artery.[9,13]

Epicardial pattern

Coronary plaque disease

Based on the classification of AMI , plaque rupture and plaque erosion are understood in type 1, even when no

Table 1 – Keywords used for the initial search of articles

Pubmed	(MINOCA OR ((Myocardial infarction OR myocardial infarct* OR cardiac infarct* OR heart attack* OR myocardium infarct* OR subendocardial infarct* OR transmural infarct* OR ventricle infarct* OR ventricular infarct*) AND (“Non obstructive” OR nonobstructive OR unobstruct * OR “un obstructed” OR “un obstructive”)))
LILACS	(tw:(((Myocardial infarction OR myocardial infarct* OR cardiac infarct* OR heart attack* OR myocardium infarct* OR subendocardial infarct* OR transmural infarct* OR ventricle infarct* OR ventricular infarct*) AND (“Non obstructive” OR nonobstructive OR unobstruct* OR “un obstructed” OR “un obstructive”))))

Source: prepared by the authors, 2021

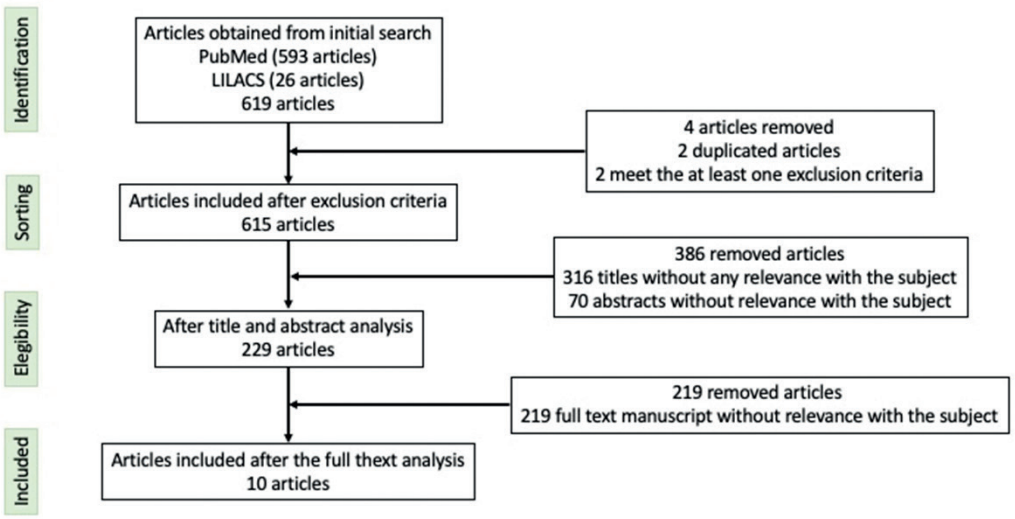

Figure 1 – Patients' Flow-chart.

thrombus can be identified.[9,14] MINOCA encompasses 5–20% of all type 1 AMI cases.[9,15] Plaque rupture and erosion can occur in areas where the vessel appears normal on conventional angiography or even when it minimally presents some degree of atherosclerosis.[9]

It is proposed that there is spontaneous thrombolysis or autolysis of coronary thrombosis.[9] These are considered endogenous protective mechanisms against thrombus formation, even in the presence of plaque rupture.[9,15] Cardiac MRI was able to demonstrate large areas of myocardial edema among patients with MINOCA and plaque rupture, suggesting transient impairment of flow in a larger vessel. However, this theory cannot be confirmed, as vasospasm would also lead to this appearance, and both could play a role. Late gadolinium enhancement MRI can demonstrate a smaller, well-defined area, a smaller vessel, suggesting that embolization of atherothrombotic debris from the site of rupture is the most likely mechanism of myocardial necrosis.[9,16]

Coronary dissection

Spontaneous coronary artery dissection usually causes AMI due to luminal obstruction, which is not always apparent on coronary angiography.[9,17] This condition is more common in women.[9,18] Despite the reasons for the occurrence of coronary dissection are not clear to date, in most of the cases tracked, fibromuscular dysplasia is present in other vascular beds.[9,19] Due to hormonal alterations during pregnancy and childbirth, there are changes in the composition of the intima-media, implicating involvement in this etiology.[9,20]

Coronary artery spasm

The prevalence of coronary artery spasm varies between 3–9% of patients with MINOCA[21] due to hyper-reactivity of vascular smooth muscle to endogenous and exogenous vasospastic substances.[9,22] Patients with vasospastic angina or a provisional event in those with established chronic form are prone to have a new presentation of MINOCA.[9,21] A study by Montone et al., which performed provocative tests in patients with MINOCA, obtained 46% positive tests.[9,23]

Microvascular pattern

Coronary microvascular spasm

Coronary microvascular spasm is characterized by transient myocardial ischemia, identified by changes in the ST-segment and angina, and with non-obstructive coronary arteries.[9,24] Approximately 25% of patients with MINOCA have evidence of coronary microvascular spasm.[9,25]

Takotsubo cardiomyopathy

Takotsubo cardiomyopathy is transient in nature[9,26] and usually presents as an acute coronary syndrome

(ACS) with ST-segment changes.[9,27,28] The mechanisms responsible for this cardiomyopathy are complex and may vary according to the patient. Regardless of its etiology, reversible coronary microvascular dysfunction is considered a pathophysiological determinant.[9,29]

Myocarditis

Myocarditis is responsible for approximately one-third of the clinical diagnosis of MINOCA.[1,9,10] Viral infection is the most frequent cause of myocarditis, with the most common being adenovirus, parvovirus B19, human herpesvirus 6, and Coxsackie virus.[9,30]

Coronary thromboembolism

Coronary thromboembolism can arise from hereditary thrombotic disorders such as factor V Leiden thrombophilia, protein S and C deficiencies, or acquired disorders such as antiphospholipid syndrome and myeloproliferative disorders; and coronary emboli can occur from coronary or systemic arterial thrombi as well as from predisposing hypercoagulable states, such as atrial fibrillation, and can also arise from non-thrombotic sources, such as valvular vegetations.[9]

Miscellany

Type 2 AMI should also be considered when there is profound supply-demand mismatch.[9] In addition, MINOCA may present with uncertain etiology, with no specific changes identifiable in cardiac MRI.[9,16,30]

Clinical features

- **Sex**

Pasupathy et al. analyzed 15 publications (n = 11,334) and found that 40% of patients who presented MINOCA were female.[1] However, an analysis of 10 publications, comparing MINOCA patients (n = 5,322) with AMI patients with obstructive CAD (MI-CAD) (n = 70,253), revealed a higher percentage of women with MINOCA (43%) compared to the MI-CAD group (24%).[1]

- **Age**

From the analysis of 13 studies (n=9,986), Pasupathy et al. calculated the average age of MINOCA patients in approximately 55 years.[1] In another evaluation of 6 publications, it was found that MINOCA patients (n = 3,927) were younger compared to those with MI-CAD (n = 48,082), with respective mean ages of 58.8 years and 61.2 years.[1]

- **Comorbidities and Risk Factors**

Studies comparing MINOCA with MI-CAD patients revealed that the former have a lower propensity for hyperlipidemia, 21% versus 32%, respectively.[1] However, when analyzing risk factors such as hypertension, diabetes mellitus, smoking, and family history of premature CAD, similarities were found between the two groups.1 In evaluating the overall MINOCA cohort, these risk factors presented the following percentages: hypertension 44%, diabetes mellitus 13%, smoking 42%, and family history 28%.[1]

- **ECG Presentation**

Through the evaluation of ten studies (n = 1,998), the prevalence of ST-segment elevation myocardial infarction (STEMI) among MINOCA patients was calculated. The pooled analysis revealed that 33% presented STEMI.[1] Therefore, approximately two-thirds of patients presented non-ST-segment elevation myocardial infarction (NSTEMI).[1]

- **Prevalence of Malignancy in MINOCA Patients**

Kobo et al. showed that malignancy in MINOCA patients is common.[31] In a systematic review of 9 studies, a diagnosis of malignancy was found in 2.5% of MINOCA patients.[6] From the analysis of 6 studies that compared the prevalence of malignancy between MINOCA and MI-CAD patients, a higher number of cases were observed in MINOCA patients (2.3% versus 1.9%).[6] However, since the included meta-analyses did not describe the types of cancer in detail, it was not possible to evaluate if they had different associations with the occurrence of MINOCA.[6]

Diagnosis and differential diagnosis

In summary, the diagnosis of MINOCA occurs in patients who present with typical features of an AMI, but angiography does not show CAD and there is no other cause that explains this condition.[3]

Regarding the diagnosis of AMI, it is based on the Fourth Universal Definition of Myocardial Infarction.[14]

Angiography can be performed invasively, such as with cineangiocardiography, or non-invasively, such as with computed tomography. In both situations, in order

to diagnose MINOCA, there can be no significant CAD with arteries obstructed in 50% or more.[3]

The diagnosis of MINOCA should not be considered as the final cause of the patient's illness, but rather as a factor that prompts the physician to seek its underlying cause. Thus, many complementary exams may be necessary to uncover the root cause of this condition.[3]

The clinical history, ECG, cardiac enzymes, echocardiography, coronary angiography, and left ventriculography represent the initial investigation exams to identify the underlying causes of MINOCA.[9]

In this regard, various pathologies can be suspected to have caused MINOCA, including non-cardiac conditions such as kidney injury or pulmonary embolism, which may be investigated with serum creatinine and angiotomography exams. Hyperlipoproteinemia and thrombotic disorders may also be related to the condition, particularly factor V Leiden and protein C and S deficiencies. In addition, dilated, hypertrophic or Takotsubo cardiomyopathy, myocarditis, spontaneous coronary artery dissection, and coronary spasm are also identified as potential causes of MINOCA. Knowing and establishing the diagnosis of MINOCA is critical for improving patient care. However, there is still no consensus on the investigative pathway for these patients in attempting to elucidate the underlying cause.

Imaging tests

As previously described, patients with MINOCA are those with clinical characteristics similar to AMI, but coronary angiography does not reveal coronary obstruction (<50% diameter stenosis) and there is no apparent cause for the presentation.[3]

After confirming the absence of obstruction in angiography, an investigation of the underlying cause of the clinical presentation of AMI should be initiated since different mechanisms require different treatments.[3]

Increased attention during coronary angiography can provide insights into the mechanism, such as spontaneous episodes of coronary artery spasm, evidence of slow flow, coronary emboli or thrombi, or even spontaneous coronary artery dissection.[3]

In MINOCA patients whose clinical evaluation does not lead to the cause, cardiac MRI is an initial non-invasive method of great utility for the investigation.[10] This exam makes it possible to differentiate myocarditis (subepicardial) and "true" AMI (subendocardial), based mainly on the myocardial distribution of gadolinium contrast.[10] This analysis has been shown to be more accurate than myocardial biopsy in cases of suspected myocarditis.[10]

Regarding structural myocardial dysfunction on MRI, myocarditis was the most common finding, occurring in 33% of patients while subendocardial infarction was found in 24%.[1] Other abnormalities reported on MRI included Takotsubo cardiomyopathy in 18% of patients, hypertrophic cardiomyopathy in 3%, dilated cardiomyopathy in 2%, and other causes in 7% of patients, such as pericarditis and amyloidosis.[1] Approximately 26% of MINOCA patients undergoing contrast-enhanced MRI had no myocardial abnormalities.[1]

Myocarditis and MINOCA

Myocarditis is an important cause of MINOCA and is ideally diagnosed by MRI.[1] The chances of this underlying cause increase when associated with angiographically normal coronary artery profile, male sex, and younger age.[1]

A patient without a clinically apparent cause for acute presentation as a previous viral illness or fever – which could indicate viral myocarditis –, and who presents nonspecific signs such as chest pain, ECG changes, and elevated troponin in the context of non-obstructive CAD should be diagnosed as MINOCA at the time of angiography; however, MRI may later reveal myocarditis.[3]

Other tests

In some institutions, additional delineation of the cause of MINOCA may be considered, such as intravascular ultrasound imaging, provocative spasm testing, and screening for thrombophilic disorders.[3] Furthermore, left ventriculography can also reveal myocardial causes of MINOCA, such as Takotsubo or other cardiomyopathies.[3]

Although echocardiography is generally more widely available than MRI and can provide useful information on myocardial function, it is not as specific as MRI in detecting myocarditis.[3] Besides, the low image quality of echocardiography can limit its usefulness in diagnosing some disorders, such as Takotsubo.[3] This is demonstrated, for example, in the study by Laraudogoitia Zaldumbide et al., in which the clinical diagnosis was uncertain between at least two possible underlying causes, and MRI provided a formal diagnosis in 69.3% of cases.[3] Therefore, although echocardiography

and ECG are commonly performed in clinical practice before MRI, the additive value of MRI for these other tests is of paramount importance.[3]

Treatment

It is essential to understand MINOCA as a clinically distinguishable entity with diverse pathophysiology, as this can expand and direct treatment approaches, improving patient care quality.

Studies suggest that patients who suffer from coronary plaque rupture may require antiplatelet therapy and statin use if they have atherosclerosis.[9] In patients with MINOCA resulting from coronary dissection, interventional procedures such as stent implantation could worsen the patient's condition,[7] so studies suggest more conservative measures, such as the use of β-blockers and antiplatelet therapy.[9] Coronary artery spasm is also featured as an etiology for MINOCA, and the use of calcium channel blockers and vasodilators such as nitrates have been shown to be the best strategy for these patients' profile.[9] Other causes that deserve attention are Takotsubo cardiomyopathy and myocarditis, which may require medications used in heart failure, such as β-blockers and angiotensin-converting enzyme inhibitors (along with antithrombotic therapies for Takotsubo).[7] In addition, MINOCA resulting from coronary thromboembolism and type 2 AMI are managed, respectively, with anticoagulant therapy, and aspirin and β-blockers.[9]

Finally, it is observed that the implementation of a single protocol that analyzes MINOCA as a single etiology may not be the best strategy for combating and controlling the disease, given that the underlying pathophysiology shows a high variability.[7]

Prognosis

Unlike patients with obstructive CAD, many individuals with non-obstructive CAD are discharged without further evaluation if they present angina associated with normal or near-normal coronary arteries in angiography.[2] Pasupathy et al. sugges/t that patients with MINOCA form a heterogeneous group within the population.[1] However, even though this phenomenon makes it difficult to compare prognoses among these patients, Pelliccia et al. presented significantly lower annual mortality rates in individuals with MINOCA compared to patients with obstructive CAD (2.2% vs. 5.0%).[6] It was also indicated that normal coronary arteries were associated with a better prognosis, whereas the use of β-blockers in the presence of poor left ventricular function was significantly associated with a worse outcome.[6]

On the other hand, although the prognosis of patients with non-obstructive CAD may be more favorable, these individuals obtained absolute annual rates of up to 9.2% for major cardiac events and 4.0% for all-cause mortality including AMI when compared to patients with obstruction.[32] A meta-analysis suggested that this unfavorable outcome could be partially explained by the lower prescription rate of β-blockers, angiotensin-converting enzyme inhibitors, statins, and antiplatelet drugs.[33]

Patients with MINOCA have a lower mortality rate for all causes than those with obstructive CAD. Pasupathy et al. reported 63% lower in-hospital mortality and 41% lower one-year mortality.[1] De Ferrari et al. reinforced this by bringing that patients with non-obstructive CAD were significantly less likely to experience death or AMI within 30 days when compared with patients with obstructive CAD, with 2.2% and 13.3% deaths, respectively.[4]

Therefore, even though patients with MINOCA have significantly lower rates of cardiac events compared to patients with obstructive CAD,[4] it should not be neglected, and the isolated presence of MINOCA does not justify the reduction of secondary prevention.

Conclusion

In recent years, the diagnosis of this pathology has become more prevalent due to easier access to coronary angiography,[4] and much knowledge has been gained regarding this intriguing condition. The present review contributes to this repository by consolidating available data in the literature. Thus, based on the findings of this study, it is known that women and young people are most affected by MINOCA compared to the MI-CAD group.[1] Additionally, hyperlipidemia was less prevalent, but other risk factors for AMI were similar between patients with or without coronary obstruction.[1] It is also known that two-thirds of patients presented with NSTEMI in the initial approach,[1] and malignancy is common in patients with MINOCA.[31] The diagnosis of this disease is made from a typical case of AMI, in which coronary disease is not observed in angiography (arteries <50% obstructed), without any other cause explaining this situation.[1] Several pathologies may culminate in MINOCA, whether

cardiac or not.[1] Therefore, it is essential to note that the diagnosis of MINOCA should serve as an alert for additional investigations, with specific tests requested to identify the underlying cause.[9] However, this review has shown that there is still no consensus on the best way to initially investigate patients diagnosed with MINOCA. Nonetheless, it is known that MRI is a useful method to be used for better cardiac analysis of these patients.[10] This exam mainly diagnoses cases of myocarditis, which is the most common abnormality (33%) in patients with MINOCA,[1] even surpassing myocardial biopsy.[10] Other tests such as intravascular ultrasound, provocative spasm testing, and screening for thrombophilia disorders can be used for initial investigation of MINOCA.[3] Regarding echocardiography, which is less specific than MRI, it may hinder diagnoses such as Takotsubo cardiomyopathy in MINOCA.[3]

To begin the treatment for these patients, it is necessary to elucidate the underlying cause.[3] Thus, the treatment of patients with coronary spasm will be different from those with plaque rupture, coronary dissection, or myocarditis.[3] This review also analyzed that patients with MINOCA have lower mortality for all causes than those with obstructive CAD.[6] However, there is still a risk for these patients, and thus, secondary prevention should not be neglected,[6] as there is evidence of an increased risk of cardiovascular and non-cardiac events in patients with MINOCA.[4] Finally, we suggest further studies on this topic, aiming to develop guidelines for more reliable guidance regarding initial investigation and treatment of patients affected by this condition.

Author Contributions

Conception and design of the research, Analysis and interpretation of the data and critical revision of the manuscript for intellectual content: de Oliveira MAB, Osti AVG; acquisition of data and witing of the manuscript: liveira MAB, Osti AVG, Cavalheiro BVT, Naves DB, de Oliveira ER, de Campos GF, Lobo GMSS, de Oliveira G, Mainardi MP, Guimarães MC, Barbosa RF, Fé VVM

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Pasupathy S, Tavella R, Beltrame JF. The What, When, Who, Why, How and Where of Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA). Circ J. 2016;80(1):11-6. doi: 10.1253/circj.CJ-15-1096. doi: 10.1253/circj.CJ-15-1096.
2. Huang FY, Huang BT, Lv WY, Liu W, Peng Y, Xia TL, et al. The Prognosis of Patients with Nonobstructive Coronary Artery Disease Versus Normal Arteries Determined by Invasive Coronary Angiography or Computed Tomography Coronary Angiography: A Systematic Review. Medicine. 2016 Mar;95(11):e3117. doi: 10.1097/MD.0000000000003117.
3. Pasupathy S, Tavella R, Beltrame JF. Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA): The Past, Present, and Future Management. Circulation. 2017;135(16):1490-3. doi: 10.1161/CIRCULATIONAHA.117.027666.
4. De Ferrari GM, Fox KA, White JA, Giugliano RP, Tricoci P, Reynolds HR, et al. Outcomes Among Non-ST-Segment Elevation Acute Coronary Syndromes Patients with no Angiographically Obstructive Coronary Artery Disease: Observations from 37,101 Patients. Eur Heart J Acute Cardiovasc Care. 2014;3(1):37-45. doi: 10.1177/2048872613489315.
5. Hausvater A, Smilowitz NR, Li B, Redel-Traub G, Quien M, Qian Y, et al. Myocarditis in Relation to Angiographic Findings in Patients with Provisional Diagnoses of MINOCA. JACC Cardiovasc Imaging. 2020;13(9):1906-13. doi: 10.1016/j.jcmg.2020.02.037.
6. Pelliccia F, Pasceri V, Niccoli G, Tanzilli G, Speciale G, Gaudio C, et al. Predictors of Mortality in Myocardial Infarction and Nonobstructed Coronary Arteries: A Systematic Review and Meta-Regression. Am J Med. 2020;133(1):73-83.e4. doi: 10.1016/j.amjmed.2019.05.048.
7. Sluchinski SL, Pituskin E, Bainey KR, Norris CM. A Review of the Evidence for Treatment of Myocardial Infarction with Nonobstructive Coronary Arteries. CJC Open. 2020;2(5):395-401. doi: 10.1016/j.cjco.2020.03.016.
8. Pelliccia F, Pasceri V, Tanzilli G, Speciale G, Camici PG, Gaudio C. Malignancy in Patients with Myocardial Infarction and Non-Obstructive Coronary Arteries: A Systematic Review and Meta-Regression. Eur J Intern Med. 2020;81:38-43. doi: 10.1016/j.ejim.2020.06.018.
9. Scalone G, Niccoli G, Crea F. Editor's Choice- Pathophysiology, Diagnosis and Management of MINOCA: An Update. Eur Heart J Acute Cardiovasc Care. 2019;8(1):54-62. doi: 10.1177/2048872618782414.
10. Tornvall P, Gerbaud E, Behaghel A, Chopard R, Collste O, Laraudogoitia E, et al. Myocarditis or "true" Infarction by Cardiac Magnetic Resonance in Patients with a Clinical Diagnosis of Myocardial Infarction without Obstructive Coronary Disease: A Meta-Analysis of Individual Patient Data. Atherosclerosis. 2015;241(1):87-91. doi: 10.1016/j.atherosclerosis.2015.04.816..
11. Niccoli G, Scalone G, Crea F. Acute Myocardial Infarction with no Obstructive Coronary Atherosclerosis: Mechanisms and Management. Eur Heart J. 2015;36(8):475-81. doi: 10.1093/eurheartj/ehu469.

12. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the Management of Acute Myocardial Infarction in patients presenting with ST-Segment Elevation: The Task Force for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119-177. doi: 10.1093/eurheartj/ehx393.

13. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, et al. ESC Working Group Position Paper on Myocardial Infarction with Non-Obstructive Coronary Arteries. Eur Heart J. 2017;38(3):143-53. doi: 10.1093/eurheartj/ehw149.

14. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018;72(18):2231-64. doi: 10.1016/j.jacc.2018.08.1038.

15. Iqbal SN, Feit F, Mancini GB, Wood D, Patel R, Pena-Sing I, et al. Characteristics of Plaque Disruption by Intravascular Ultrasound in Women Presenting with Myocardial Infarction without Obstructive Coronary Artery Disease. Am Heart J. 2014;167(5):715-22. doi: 10.1016/j.ahj.2014.01.011.

16. Reynolds HR, Srichai MB, Iqbal SN, Slater JN, Mancini GB, Feit F, et al. Mechanisms of Myocardial Infarction in Women without Angiographically Obstructive Coronary Artery Disease. Circulation. 2011;124(13):1414-25. doi: 10.1161/CIRCULATIONAHA.111.026542.

17. Alfonso F, Paulo M, Dutary J. Endovascular Imaging of Angiographically Invisible Spontaneous Coronary Artery Dissection. JACC Cardiovasc Interv. 2012;5(4):452-3. doi: 10.1016/j.jcin.2012.01.016.

18. Saw J, Aymong E, Mancini GB, Sedlak T, Starovoytov A, Ricci D. Nonatherosclerotic Coronary Artery Disease in Young Women. Can J Cardiol. 2014;30(7):814-9. doi: 10.1016/j.cjca.2014.01.011.

19. Saw J, Aymong E, Sedlak T, Buller CE, Starovoytov A, Ricci D, et al. Spontaneous Coronary Artery Dissection: Association with Predisposing Arteriopathies and Precipitating Stressors and Cardiovascular Outcomes. Circ Cardiovasc Interv. 2014;7(5):645-55. doi: 10.1161/CIRCINTERVENTIONS.114.001760.

20. Tweet MS, Hayes SN, Pitta SR, Simari RD, Lerman A, Lennon RJ, et al. Clinical Features, Management, and Prognosis of Spontaneous Coronary Artery Dissection. Circulation. 2012;126(5):579-88. doi: 10.1161/CIRCULATIONAHA.112.105718.

21. Pristipino C, Beltrame JF, Finocchiaro ML, Hattori R, Fujita M, Mongiardo R, et al. Major Racial Differences in Coronary Constrictor Response between Japanese and Caucasians with Recent Myocardial Infarction. Circulation. 2000;101(10):1102-8. doi: 10.1161/01.cir.101.10.1102.

22. Kaski JC, Crea F, Meran D, Rodriguez L, Araujo L, Chierchia S, et al. Local Coronary Supersensitivity to Diverse Vasoconstrictive Stimuli in Patients with Variant Angina. Circulation. 1986;74(6):1255-65. doi: 10.1161/01.cir.74.6.1255.

23. Montone RA, Niccoli G, Fracassi F, Russo M, Gurgoglione F, Cammà G, et al. Patients with Acute Myocardial Infarction and Non-Obstructive Coronary Arteries: Safety and Prognostic Relevance of Invasive Coronary Provocative Tests. Eur Heart J. 2018;39(2):91-8. doi: 10.1093/eurheartj/ehx667.

24. Lanza GA, Crea F. Primary Coronary Microvascular Dysfunction: Clinical Presentation, Pathophysiology, and Management. Circulation. 2010;121(21):2317-25. doi: 10.1161/CIRCULATIONAHA.109.900191.

25. Mohri M, Koyanagi M, Egashira K, Tagawa H, Ichiki T, Shimokawa H, et al. Angina Pectoris Caused by Coronary Microvascular Spasm. Lancet. 1998;351(9110):1165-9. doi: 10.1016/S0140-6736(97)07329-7.

26. Pelliccia F, Greco C, Vitale C, Rosano G, Gaudio C, Kaski JC. Takotsubo Syndrome (stress Cardiomyopathy): An Intriguing Clinical Condition in Search of Its Identity. Am J Med. 2014;127(8):699-704. doi: 10.1016/j.amjmed.2014.04.004.

27. Bybee KA, Kara T, Prasad A, Lerman A, Barsness GW, Wright RS, et al. Systematic Review: Transient Left Ventricular Apical Ballooning: A Syndrome that Mimics ST-Segment Elevation Myocardial Infarction. Ann Intern Med. 2004;141(11):858-65. doi: 10.7326/0003-4819-141-11-200412070-00010.

28. Prasad A. Apical Ballooning Syndrome: An Important Differential Diagnosis of Acute Myocardial Infarction. Circulation. 2007;115(5):e56-9. doi: 10.1161/CIRCULATIONAHA.106.669341.

29. Galiuto L, Caterina AR, Porfidia A, Paraggio L, Barchetta S, Locorotondo G, et al. Reversible Coronary Microvascular Dysfunction: A Common Pathogenetic Mechanism in Apical Ballooning or Tako-Tsubo Syndrome. Eur Heart J. 2010;31(11):1319-27. doi: 10.1093/eurheartj/ehq039.

30. Collste O, Sörensson P, Frick M, Agewall S, Daniel M, Henareh L, et al. Myocardial Infarction with Normal Coronary Arteries is Common and Associated with Normal Findings on Cardiovascular Magnetic Resonance Imaging: Results from the Stockholm Myocardial Infarction with Normal Coronaries Study. J Intern Med. 2013;273(2):189-96. doi: 10.1111/j.1365-2796.2012.02567.x.

31. Kobo OM, Vainer Evgrafov E, Cohen Y, Lerner Y, Khatib A, Hoffman R, et al. Non-ST-Elevation Myocardial Infarction with Non-significant Coronary Artery Disease as a Symptom of Occult or New Malignancy. Isr Med Assoc J. 2019;21(6):381-385.

32. Rossini R, Capodanno D, Lettieri C, Musumeci G, Limbruno U, Molfese M, et al. Long-Term Outcomes of Patients with Acute Coronary Syndrome and Nonobstructive Coronary Artery Disease. Am J Cardiol. 2013;112(2):150-5. doi: 10.1016/j.amjcard.2013.03.006.

33. Pizzi C, Xhyheri B, Costa GM, Faustino M, Flacco ME, Gualano MR, et al. Nonobstructive Versus Obstructive Coronary Artery Disease in Acute Coronary Syndrome: A Meta-Analysis. J Am Heart Assoc. 2016;5(12):e004185. doi: 10.1161/JAHA.116.004185.