Srce i krvni sudovi 2023; 42(3): 74-77

Review article

Treatment approach for patients with MINOCA: What we know today and what to expect tomorrow?

Ivan Bešenji, Milenko Čanković

Institute of Cardiovascular Diseases, Sremska Kamenica, Medical Faculty, University of Novi Sad

Abstract Myocardial infarction with non-obstructive coronary arteries (MINOCA) is a clinical entity characterized by the presence of symptoms of myocardial infarction (MI) and evidence of myocardial ischemia, despite coronary angiography revealing insignificant coronary artery disease. Therefore, this condition presents significant diagnostic and therapeutic challenge. This paper provides a concise overview of therapeutic strategies for MINOCA patients, highlighting the complexities and approaches to managing this unique patient population. The multifactorial etiology of MINOCA requires an adapted approach, so the therapeutic approach to patients with MINOCA is primarily focused on addressing the underlying causes and minimizing the risk of future cardiac events.

Key words MINOCA, therapy, adverse events

Introduction

When we talk about myocardial infarction with non-obstructive coronary arteries (MINOCA), it is important to note that many healthcare institutions still do not have a well-organized diagnostic process in their clinical practice, either due to lack of knowledge or lack of clear recommendations from clinical guidelines. Therefore, there is a need for an appropriate and valid diagnostic protocol to be applied in clinical practice when treating these patients in order to avoid relying solely on cardiologists for making the diagnosis.[1] So far, only the American Heart Association (AHA) has attempted to summarize and align the diagnostic path and treatment of MINOCA in its scientific statement, where a diagnostic algorithm was proposed, but clear guidelines regarding the use of additional diagnostic methods alongside coronary angiography were not provided, most likely due to limited evidence-based data.[2] Understanding the fundamental etiological factors is crucial for selecting the most effective therapeutic approach in MINOCA. Treating all cases in the same way does not yield consistent results. For example, what may benefit a specific subgroup of patients may be ineffective or even harmful to others. For instance, the use of Dual Antiplatelet Therapy (DAPT) may increase the risk of bleeding, and the use of beta-blockers may cause constriction of coronary arteries in patients with epicardial artery spasm by unmasking α-adrenoreceptors.[3] Because of these considerations, the term MINOCA should not be used as a specific diagnosis but rather as a "working diagnosis." Through an appropriate diagnostic process, which includes both invasive and non-invasive tests, we can gradually uncover the underlying mechanisms and apply the appropriate treatment approach.

Medical therapy – available data

The diagnostic criteria for MINOCA are proposed as follows: 1) meeting the universal definition criteria for acute myocardial infarction (AMI), 2) angiographically verified coronary arteries without obstruction (with stenosis less than 50%), 3) no obvious specific clinical cause for acute presentation (elevated troponin levels). The etiology of MINOCA is diverse and can be categorized into coronary, cardiac, and extracardiac factors. Coronary factors include rupture or erosion of an occult plaque, coronary spasm, spontaneous coronary artery dissection, coronary embolism, and coronary microvascular disorders. Cardiac factors encompass myocarditis, Takotsubo syndrome, cardiomyopathies, cardiac trauma, and tachyarrhythmias. Extracardiac factors include stroke, pulmonary embolism, sepsis, kidney failure, and hypoxemia. Consequently, MINOCA should be viewed as a working diagnosis that requires further investigation into its underlying cause.[2,4,5]

Although identifying the underlying etiology of MINOCA can guide appropriate and personalized long-term treatment, there is limited data on the optimal pharmacotherapeutic approach. In a large study involving 9,136 patients, registered in the SWEDEHEART registry, diagnosed with MINOCA, the use of statins and renin-angiotensin system inhibitors significantly reduced the rate of major cardiovascular events (MACE, defined as mortality from any cause, as well as hospitalization due to myocardial infarction, ischemic stroke, or heart failure) during an average follow-up of 4.1 years. There was a trend towards reducing events with the use of beta-blockers, while the use of DAPT as the primary therapy for atherosclerotic obstructive coronary disease did not significantly affect the clinical outcomes of patients. However, it is important to note that the study group was highly heterogeneous, as the specific pathogenetic

Corresponding author: Ivan Bešenji, Branka Bajića 70A, Novi Sad, Mobile phone: 0606866361, E-mail: besenjiivan@gmail.com

mechanism leading to MINOCA had not been identified, and medical therapy was not tailored accordingly.[6]

DAPT. Two secondary analyses of randomized controlled trials (RCTs) have assessed the effect of antiplatelet therapy in patients diagnosed with MINOCA. In the CURRENT-OASIS7 trial, a total of 23,783 patients with myocardial infarction, of whom 1,599 (6.7%) had MINOCA, were included. In this study, compared to DAPT based on clopidogrel, intensive therapy does not seem to provide additional benefit, but there is an indication of potential harm. There was no difference in bleeding events among patients with MINOCA.[7] In the PURSUIT trial, which included a total of 5,767 patients with non-ST segment elevation myocardial infarction (NSTEMI), of whom 366 (6%) had MINOCA, it was found that these patients did not benefit from eptifibatide therapy, whereas patients with obstructive coronary disease did. There was no increased frequency of bleeding events in MINOCA patients in this study either.[8]

Several retrospective studies have assessed the effect of secondary prevention on clinical outcomes in patients with MINOCA.[9,10,11] In none of these studies was DAPT associated with a reduction in the frequency of MACE. Overall, current evidence on the role of antiplatelet therapy in patients with MINOCA comes from registries or secondary analyses of RCTs and is therefore of low quality.[7-13] However, available evidence suggests that antiplatelet therapy is not associated with an improvement in clinical outcomes.

A study that assessed the role of DAPT therapy without stent implantation in patients with plaque erosion-induced myocardial infarction, documented using optical coherence tomography (OCT) was called the EROSION study.[14] During a 30-day follow-up, the use of DAPT with aspirin and ticagrelor was associated with a significant reduction in thrombus volume and a low rate of adverse events. Furthermore, during one-year follow-up, 92.5% of patients with plaque erosion-induced myocardial infarction treated with DAPT without stent implantation were free from MACE. One patient had to discontinue DAPT due to gastrointestinal bleeding.[15] In the final report after four years, 21% of patients underwent revascularization of the target vessel.[16] This study provides compelling data supporting the effectiveness of DAPT involving aspirin and ticagrelor in plaque erosion-induced myocardial infarction. However, this was a pilot study without randomization and an open-label design with a surrogate primary outcome. Therefore, this hypothesis should be adequately confirmed through RCTs with an adequate number of patients and clinical outcomes as endpoints.

The role of DAPT in patients with Spontaneous Coronary Artery Dissection (SCAD) is a subject of debate. SCAD is a condition that typically results in acute coronary syndrome (ACS). In most cases, SCAD leads to simultaneous and significant coronary artery narrowing (>50% stenosis), making it a rare cause of MINOCA.(5) Some experts argue that DAPT may increase the risk of bleeding and the expansion of the hematoma/dissection, while others contend that the rupture of the vessel's intima may be prothrombotic, and the additional use of clopidogrel alongside aspirin may be justified.[17] Data from the DISCO registry suggest that in patients managed conservatively, DAPT may be associated with worse clinical outcomes compared to therapy with a single antiplatelet agent (SAPT).[18] The authors assessed MACE, defined as death from any cause, non-fatal myocardial infarction, and any unplanned percutaneous coronary intervention (PCI) after 12 months. DAPT, mainly with aspirin and clopidogrel (63%), was associated with an increase in MACE compared to aspirin SAPT therapy (93%). This difference was due to recurrent infarction and urgent revascularization shortly after the initial presentation of SCAD. Currently, there are no randomized clinical trials on this topic, and available evidence suffers from limitations of retrospective registries.

While vasospastic angina has been the subject of continuous research, specific data on MINOCA resulting from coronary vasospasm are limited. Lin et al.(19*)* conducted a systematic review and meta-analysis evaluating the role of low-dose aspirin in patients with vasospastic angina without significant coronary lesions. The authors included six studies encompassing a total of 3,661 patients. The primary outcome was MACE, defined as cardiac death, ACS, hospitalization for unstable angina, PCI, symptomatic arrhythmia, appropriate implantable cardioverter-defibrillator use, and cardiogenic shock. Aspirin was not associated with a reduction in MACE. However, this analysis did not include any RCTs, and there was very high heterogeneity in the results within the included studies.

The role of DAPT in coronary vasospasm was prospectively assessed in the multicenter VA-Korean registry.[20] Researchers compared the effect of DAPT with aspirin and clopidogrel versus aspirin alone on MACE. The primary outcome was time to composite events, including death from any cause, acute coronary events, and symptomatic arrhythmia after 3 years of follow-up. Patients treated with DAPT had worse clinical outcomes compared to those treated with aspirin alone. Patients presenting as ACS and smokers had a higher risk of cardiovascular events. However, RCTs did not include this analysis.

There have been differing results regarding the role of antiplatelet therapy in Takotsubo syndrome (TTS) to date. In a single-center retrospective registry of TTS patients assessing clinical outcomes during hospitalization, authors found that the use of DAPT with aspirin and clopidogrel was associated with a lower incidence of MACE.[21] MACE was defined as heart failure during hospitalization, in-hospital death, stroke, or respiratory failure requiring mechanical ventilation. However, it's important to note that a small sample size and retrospective methodology are significant limitations to consider. On the other hand, in a systematic review and meta-analysis involving nearly two thousand patients, DAPT was associated with an increase in cardiovascular events and mortality.[22] Bleeding rates were not reported.

ACEi and ARB. Earlier in the text, it was mentioned that the SWEDEHEART study[4] demonstrated a significant reduction in the rate of MACE with the use of renin-angio-

tensin system inhibitors, but it did not compare angiotensin II receptor type I blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEi). In a retrospective study by Ahn JH et al. aimed at comparing the impact of ACEi and ARB, it was shown that the frequency and risk of MACE were similar in both groups of patients[23]. Regarding cardiovascular event-related mortality, it was similar in both treatment groups, consistent with previous RCTs comparing ACEi and ARB.[24,25] However, the results indicate that ACEi reduce the risk of recurrent myocardial infarction more significantly compared to ARB. These results can be interpreted as a specific effect of ACEi through the suppression of angiotensin II and preservation of bradykinin, ultimately leading to the prevention of endothelial dysfunction.[26,27]

STATINS. Masson W et al. conducted a meta-analysis[28] whose results suggest that statin therapy has a positive impact on clinical outcomes in MINOCA patients. The use of statins has proven beneficial in reducing the risk of MACE and mortality in this group of patients. The results imply that statin therapy has prognostic value in improving outcomes in these patients.

What to expect?

Available research has mainly focused on assessing the role of traditional cardiovascular drugs (such as ACE inhibitors, ARBs, statins, beta-blockers, and DAPT) in the treatment of MINOCA, with only a few currently active RCTs exploring the best approach and pharmacological treatment. It's worth mentioning a few upcoming prospective studies. One of these currently active clinical trials is the *MINOCA-BAT* study, which aims to determine whether therapy with oral beta-blockers or ACEi/ARBs can reduce the incidence of all-cause mortality, recurrent hospitalizations for myocardial infarction, ischemic stroke, or heart failure in patients discharged after MINOCA with left ventricular ejection fraction ≥40%.[29,30]

StratMed-MINOCA[15] is an ongoing clinical trial that will analyze whether early risk stratification through coronary microcirculation dysfunction (defined by a microvascular resistance index ≥25), combined with therapy using the cardioprotective mineralocorticoid antagonist eplerenone, can reduce changes in N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels as a marker of myocardial damage in MINOCA patients.[31]

The currently active clinical trial *PROMISE17* aims to evaluate whether a "personalized medicine approach," which involves comprehensive diagnostic analysis followed by tailored pharmacological treatment targeting the underlying cause, is more effective than "standard therapy", which includes coronary angiography with conventional treatment for myocardial infarction, including DAPT for all patients, beta-blockers, statins, and ACEi/ARBs. The goal is to determine whether this personalized medicine approach can improve the prognosis and quality of life for MINOCA patients.[32,33]

One of the most interesting upcoming trials is a randomized trial *of beta-blockers and antiplatelet drugs in SCAD patients*, where 600 patients will be randomized in a 2x2 factorial design to assess the safety and efficacy of beta-blockers and DAPT in SCAD patients.[34]

Conclusions

The role of pharmacological therapy in patients diagnosed with MINOCA remains poorly defined. Currently, most scientific evidence and guidelines are supported by low-quality studies. It's important to note that there are no RCTs evaluating the role of medication therapy in the entire cohort of these patients or for any of its specific etiologies. In clinical practice, the management of most MINOCA cases is based on studies of patients with obstructive coronary artery disease. RCTs are essential to determine the role of medication therapy and given the complex etiology and limited amount of evidence, medical treatment remains uncertain.

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Sažetak

Pristup lečenju pacijentiama sa MINOCA-om: Šta znamo i šta očekivati sutra?

Ivan Bešenji, Milenko Čanković

Institut za kardiovaskularne bolesti Vojvodina, Sremska Kamenica, Medicinski fakultet, Univerzitet u Novom Sadu

Infarkt miokarda bez opstrukcije koronarnih arterija (engl. Myocardial infarction with non-obstructive coronary arteries - MINOCA) je klinički entitet koji karakteriše prisustvo simptoma infarkta miokarda (IM) i dokaz o ishemiji miokarda, uprkos koronarnoj angiografiji koja otkriva nesignifikantnu koronarnu bolest. Stoga, ovo stanje predstavlja značajni dijagnostički i terapijski izazov. Ovaj rad pruža sažet pregled terapijskih strategija za pacijente kojima je dijagnostikovan MINOCA, naglašavajući složenost pristupa ovoj jedinstvenoj populaciji pacijenata. Multifaktorska etiologija MINOCA-e zahteva prilagođen terapijski pristup ovim bolesnicima te je fokus na rešavanju osnovnih uzroka i na minimiziranju rizika od budućih srčanih događaja.

Ključne reči: *MINOCA, terapija, MACE*