

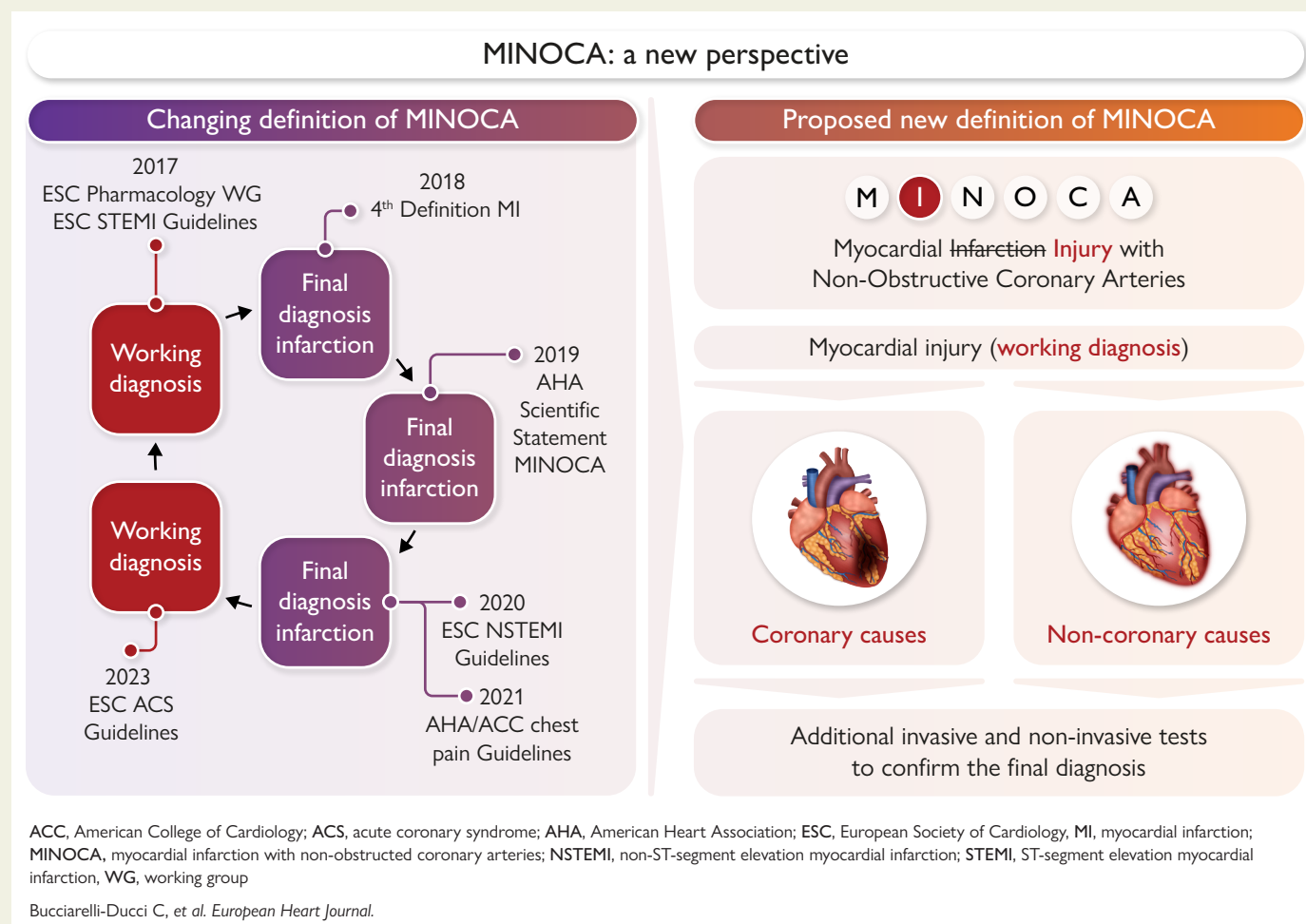
A new definition of MINOCA: from infarction to injury

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Graphical abstract



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Introduction

Myocardial infarction (MI) in the absence of obstructive coronary artery disease was first documented almost 100 years ago in patients whose autopsies demonstrated myocardial necrosis in the absence of significant atherosclerosis of epicardial coronary arteries.^{1,2} More contemporary data suggest that up to 7–15% of patients presenting with acute coronary syndromes (ACSs) have non-obstructed coronary arteries, thus posing a diagnostic dilemma and clinical challenges.³ In addition, while it was initially considered a benign condition given the absence of obstructed epicardial coronary arteries, it was later shown to be associated with a non-negligible all-cause mortality of 4.7% at 12 months.⁴

The use of the acronym MINOCA (i.e. MI with non-obstructed coronary arteries) to label this condition has changed over the years and across consensus documents and guidelines from a working diagnosis^{5,6} to a final diagnosis of MI with non-obstructive coronary arteries^{7–9} and eventually again a working diagnosis.³ Using a single terminology to identify a group of patients with similar clinical presentation, but very diverse underlying aetiologies and final diagnoses, presents challenges. In this document, we propose a novel connotation for the acronym MINOCA that would reconcile the condition as a working diagnosis encompassing a few diverse aetiologies.

Evolution of the terminology MINOCA

The terminology to describe this entity has evolved over the years, initially called 'Myocardial Infarction and Normal Coronaries' (MINC), becoming 'Myocardial Infarction and Normal Coronaries Arteries' (MINCA), then settling with the acronym MINOCA (Myocardial Infarction with Non-Obstructed Coronary Arteries), first coined by John Beltrame in 2013. It was then accepted in 2017 by the European Society of Cardiology (ESC) Working on Cardiovascular Pharmacotherapy,⁵ which defined MINOCA by the presence of four criteria: (1) symptoms or signs indicative of MI (e.g. typical chest pain, ischaemic ECG changes, new regional wall motion abnormalities); (2) biochemical evidence of MI (elevated cardiac troponin >99th percentile with a rise or fall on serial assessment); (3) non-obstructive coronary artery disease (CAD), with no stenosis $\geq 50\%$ in any major epicardial vessel by either invasive or computed tomography coronary angiography; and (4) exclusion of non-ischaemic causes of troponin elevation (e.g. myocarditis).^{5,8} The 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation embraced this definition and diagnostic criteria, calling it 'suspected diagnosis' where additional testing is required.⁶ The non-invasive testing recommended was an echocardiogram or cardiovascular magnetic resonance (CMR) to identify coronary and non-coronary causes, such as Takotsubo syndrome (TTS), acute myocarditis, or cardiomyopathies, respectively. Invasive testing was recommended to identify coronary (using intravascular ultrasound; IVUS or optical coherence tomography; OCT or functional testing) and myocardial causes (by endomyocardial biopsy; EMB).

In 2018, the 4th Definition of Myocardial Infarction (UDMI) restricted the terminology of MINOCA to myocardial injury with evidence of ischaemia (type 1 or type 2 MI), thus excluding

from this terminology other working diagnoses such as myocarditis, TTS, and cardiomyopathies.⁷ Subsequently, both a 2019 Scientific Statement of the American Heart Association (AHA) on *Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease* and the 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation recommended the terminology MINOCA to be used just to identify the **final diagnosis** of infarction with unobstructed coronary arteries.^{8,9} Similarly, the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain uses the terminology MINOCA to indicate a final diagnosis of MI.¹⁰ More recently, the 2023 ESC Guidelines for the management of acute coronary syndromes returned to the original definition of MINOCA as a **working diagnosis**, thus using it as an umbrella term that encompasses both coronary and non-coronary aetiologies, with the latter including both cardiovascular and systemic disorders.³ The changing definition of MINOCA over the years has created inconsistency in the use of this terminology, both in clinical practice (used both as a working diagnosis or as a final diagnosis in discharge summaries) and in published original research.

Over the years, the oscillating definition of MINOCA between a working diagnosis and a final diagnosis of MI has created challenges. This uncertainty has been settled in the 2023 ESC Guidelines for the management of acute coronary syndrome³ proposing MINOCA as a working diagnosis. However, the 'I for infarction' in the word MINOCA does not reflect the working diagnosis nature of this terminology, as it already prematurely assigns the diagnosis of infarction before subsequent invasive and non-invasive tests required to identify the final diagnosis are performed, as indicated in the ESC and AHA/ACC Guidelines.^{2,11} Patients presenting with MINOCA (working diagnosis) have in common symptoms or signs suggestive of ischaemic origin (acute chest pain presentation and/or abnormal ECG), transient troponin rise, and non-obstructive epicardial coronary arteries, but they can have very different final diagnoses. Thus, it might be inappropriate and potentially misleading for physicians and patients alike to assume in all MINOCA patients a diagnosis of MI. In fact, a small study on patients presenting with MINOCA (working diagnosis) and subsequently diagnosed with Takotsubo syndrome, reported that the change of diagnosis from MI (diagnosis at admission using MINOCA as infarction) to a non-myocardial infarction diagnosis (TTS) at discharge created a certain degree of confusion and uncertainty.¹²

Of note, a recent meta-analysis indicates that among patients presenting with MINOCA (working diagnosis), only a minority of 22% has an epicardial coronary cause of MI, while about two-thirds having a non-epicardial coronary, microvascular (e.g. Takotsubo syndrome), or myocardial cause of MINOCA (e.g. acute myocarditis, and other cardiomyopathies).¹³ These findings are also confirmed by a large single centre MINOCA registry study in which MI was observed only in 27% of patients, with a non-MI diagnosis present in 73% of patients.¹⁴ Cardiovascular magnetic resonance (CMR) was used to obtain a myocardial tissue diagnosis of the underlying myocardial injury, thus establishing the final diagnosis and reclassifying patients with the correct diagnosis requiring specific management strategies. Thus, based on the available literature, only <30% of patients with MINOCA (working diagnosis) have a final diagnosis

of MI. This underscores the importance of not using the term MINOCA as the final diagnosis of MI, which in fact occurs in a minority of patients.

Accordingly, in this Viewpoint, we propose to redefine the acronym **MINOCA with the 'I' for 'injury'** (Myocardial Injury with Non-Obstructive Coronary Arteries), which would more adequately reflect a **working diagnosis** that can be due to cardiac vasculature (both epicardial and/microvascular), or non-vascular, such as myocardial or systemic causes. In fact, myocardial 'injury' indicates a transient troponin rise with at least one value above the 99th percentile, and signs and symptoms suggestive of ischaemic origin—all common signs and symptoms present in patients with MINOCA (working diagnosis)—whilst also reconciling the working diagnosis nature of the terminology that would include both ischaemic and non-ischaemic mechanisms (*Graphical Abstract*). This represents a subtle deviation from the 4th UDMI in which 'myocardial injury' is defined only as an elevation of cardiac troponin above the 99th percentile with or without evidence of ischaemia, whereas 'myocardial infarction' requires additional proof of (1) symptoms of myocardial ischaemia, (2) new ischaemic ECG changes, (3) development of pathological Q waves, (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology, (5) Identification of a coronary thrombus by angiography or autopsy'. However, in the clinical realm some of the above signs or symptoms, such as 'symptoms of myocardial ischemia' (i.e. chest pain) and 'new ischaemic ECG changes' (i.e. ST elevation, ST depression, T-wave changes) can often overlap in ischemia and acute myocarditis. Therefore, it appears pertinent that acute myocardial injury, in addition to troponin rise, can be accompanied by chest pain and ECG changes either ischaemic or non-ischaemic. Further assessment is warranted to identify the aetiology and indeed the differential diagnosis, thus making the terminology of myocardial injury a working diagnosis.

Indeed, myocardial injury associated to hsTn raise can be caused by (1) insufficient oxygen supply due to obstructed arteries (i.e. infarction); (2) insufficient oxygen in the blood (i.e. hypoxia); (3) myocardial infections, severe stress, toxins, inflammation, severe illnesses, trauma, etc (i.e. non-ischaemic necrosis). Thus, myocardial injury can be related to MI, yet not all myocardial injuries lead to an MI. As indicated by the current guidelines, only the implementation of subsequent invasive and non-invasive testing can identify the cause of MINOCA. When an MI is confirmed in a patient with MINOCA (i.e. myocardial injury), then it should be simply referred to as 'myocardial infarction'. As myocardial injury is a descriptive term that underpins ischaemic, hypoxic, and tissue damage-related mechanisms, it provides an opportunity to propose a new classification of MINOCA (working diagnosis) which encompasses all the underlying pathophysiological processes that present with pain, ECG changes, and transient troponin rise, thus leading to a final diagnosis and thus optimal stratified therapeutic strategies.

Conclusion

This new definition of MINOCA, replacing the 'I' for infarction with the 'I' for injury, better reflects the working diagnosis nature of this terminology, whilst also emphasizing the need for

further invasive and non-invasive testing to identify the final diagnosis, which can be epicardial, microvascular, myocardial, and non-cardiac.

Declarations

Disclosure of Interest

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