Circulation

FRONTIERS

Myocardial Ischemic Syndromes: A New Nomenclature to Harmonize Evolving International Clinical Practice Guidelines

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ABSTRACT: Since the 1960s, cardiologists have adopted several binary classification systems for acute myocardial infarction (MI) that facilitated improved patient management. Conversely, for chronic stable manifestations of myocardial ischemia, various classifications have emerged over time, often with conflicting terminology—eg, "stable coronary artery disease" (CAD), "stable ischemic heart disease," and "chronic coronary syndromes" (CCS). While the 2019 European guidelines introduced CCS to impart symmetry with "acute coronary syndromes" (ACS), the 2023 American guidelines endorsed the alternative term "chronic coronary disease." An unintended consequence of these competing classifications is perpetuation of the restrictive terms "coronary" and 'disease', often connoting only a singular obstructive CAD mechanism. It is now important to advance a more broadly inclusive terminology for both obstructive and non-obstructive causes of angina and myocardial ischemia that fosters conceptual clarity and unifies dyssynchronous nomenclatures across guidelines. We, therefore, propose a new binary classification of "acute myocardial ischemic syndromes" and "non-acute myocardial ischemic syndromes," which comprises both obstructive epicardial and non-obstructive pathogenetic mechanisms, including microvascular dysfunction, vasospastic disorders, and non-coronary causes. We herein retain accepted categories of ACS, ST-segment elevation MI, and non-ST-segment elevation MI, as important subsets for which revascularization is of proven clinical benefit, as well as new terms like ischemia and MI with non-obstructive coronary arteries. Overall, such a more encompassing nomenclature better aligns, unifies, and harmonizes different pathophysiologic causes of myocardial ischemia and should result in more refined diagnostic and therapeutic approaches targeted to the multiple pathobiological precipitants of angina pectoris, ischemia, and infarction.

Key Words: acute myocardial ischemic syndromes ■ AMIS ■ coronary artery disease ■ ischemic heart disease ■ NAMIS ■ non-acute myocardial ischemic syndromes

Nomina sunt consequentia rerum (Names are the consequences of facts).

—Emperor Justinian, *Institutiones*, vol. II, 7, 3, 533 A.D.

INTRODUCTION

As our understanding of pathophysiologic mechanisms, clinical manifestations, diagnosis, and management of angina pectoris and myocardial infarction (MI) has matured and evolved over decades, so too has our nomenclature for classifying these conditions. There has been a remarkable partnership of joint collaboration across major international cardiovascular societies in the classification of acute coronary syndromes (ACS), including both diagnosis and treatment, which has been well-received by clinicians and has favorably impacted patient management over the past 20 years[1–6] Yet, the current ACS

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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This article has been copublished in *European Heart Journal*.

For Sources of Funding and Disclosures, see page XXX.

Circulation is available at www.ahajournals.org/journal/circ

nomenclature neglects many important non-obstructive coronary causes of both myocardial ischemia and MI.

Moreover, among patients with chronic stable manifestations of myocardial ischemia, various classifications have emerged over time but often with conflicting terminology and implications—eg, "stable coronary artery disease" (CAD), "stable ischemic heart disease" (SIHD), "chronic coronary syndromes" (CCS), and, most recently, "chronic coronary disease" (CCD). This lack of unanimity in accurately clarifying the many chronic manifestations of angina pectoris and myocardial ischemia has resulted in competing classification systems and dyssynchronous nomenclatures across clinical practice guidelines and among various professional societies, most notably those endorsed by the American College of Cardiology (ACC)/American Heart Association (AHA) and the European Society of Cardiology (ESC).[7] While the 2019 European guidelines[8] introduced CCS to provide symmetry with ACS, the most recent 2023 American guidelines[6] endorsed the alternative (and competing) term CCD. Though such changes may be viewed as subtle and perhaps nuanced distinctions, the lack of harmonious classification across major professional societies highlights an unmet need, as well as an important opportunity to achieve improvements in better aligning our overall descriptive nomenclature of important and common cardiovascular disorders.

Obstructive CAD has been viewed widely as the prevalent pathogenetic mechanism across the clinical spectrum of angina pectoris, transient myocardial ischemia, and MI in the great majority of patients. However, a growing body of scientific evidence has highlighted that distinct alternative pathogenetic mechanisms are at play, which can act either in isolation (eg, in the absence of flow-limiting CAD) or in combination with epicardial CAD, which itself may or may not be flow-limiting. It is now increasingly clear[9] that there are many important non-obstructive causes that are not comprehensively captured in the current ACS versus CCS/CCD nomenclatures with the terms "coronary" or "disease" and which are equally applicable to both acute and non-acute clinical presentations. Because obstructive CAD does not inevitably lead to symptomatic ischemia and, conversely, both myocardial ischemia and MI can occur in the absence of obstructive CAD,[10–12] a practical, accurate nomenclature should fully reflect the totality of potential obstructive and non-obstructive causes of ischemia occurring in both the acute and the non-acute clinical settings.

This holds true also for MI. It is worth noting that in the Fourth Universal Definition of MI (UDMI-4),[2] the diagnosis of MI is based on a functional rather than anatomical criterion (troponin rise and fall) and that a sizeable percentage of patients with type 2 MI develops MI with non-obstructive coronary arteries (MINOCA).[13] Thus, the current nomenclatures do not fully reflect the totality and distribution of all MIs.

For all these reasons, we believe that a contemporary classification system across the spectrum of myocardial ischemia and MI should be accurate, comprehensive and inclusive, and convey clear actionable information to both guide and optimize patient management. Accordingly, the objective of this *Frontiers* publication is to advance a more consistent, unifying nomenclature that better aligns with—and is inclusive of—the many underlying mechanisms and precipitants of myocardial ischemia and MI observed in contemporary clinical practice while also serving to harmonize both coronary and non-coronary aetiologies.

Notably, we wish to underscore at the outset that the views and opinions expressed in this article are those of the authors and do not reflect the views or official positions of the ACC, AHA, or ESC.

The Pathobiology of Myocardial Ischemia Demands a More Comprehensive and Inclusive Taxonomy

Myocardial ischemia results when coronary flow is inadequate to permit or sustain cardiac performance at a level sufficient to support the body over its full physiological range of activity.[14] It represents the final common pathway by which coronary atherosclerosis, with or without superimposed thrombosis, or other non-obstructive pathogenetic mechanisms lead to symptoms, impaired quality of life, myocardial damage, and major adverse cardiovascular events (MACE). When myocardial ischemia occurs, it often produces angina and triggers a cascade of pathophysiologic changes that may include left ventricular relaxation abnormalities, regional contractile impairment, MI, and arrhythmias—including sudden cardiac death. While obstructive CAD is obviously a very important cause of myocardial ischemia, a sole focus on epicardial CAD that neglects other notable non-obstructive pathophysiological mechanisms represents a limitation, because the principal target structure that bears the brunt of ischemia (regardless of pathogenetic mechanisms) is the myocardium and, ultimately, the cardiac myocyte. And since myocardial ischemia can be provoked by multiple causes and precipitants other than obstructive CAD (Figure 1), which is now fully recognized in most recent guidelines[6,15] and consensus documents, including UDMI-4,[2] it is essential that our nomenclature and classification system accurately reflect these new perspectives and current thinking.

There is also large individual variability as to how ischemia is perceived and a sizeable proportion of ischemic episodes are not associated with angina;[8,16] thus, ischemia may be "silent" in a certain proportion of individuals, possibly depending on alterations in neural pain processing mechanisms.[16] "Silent myocardial ischemia" is thought to occur more commonly in patients with diabetes who have autonomic neuropathy and altered pain

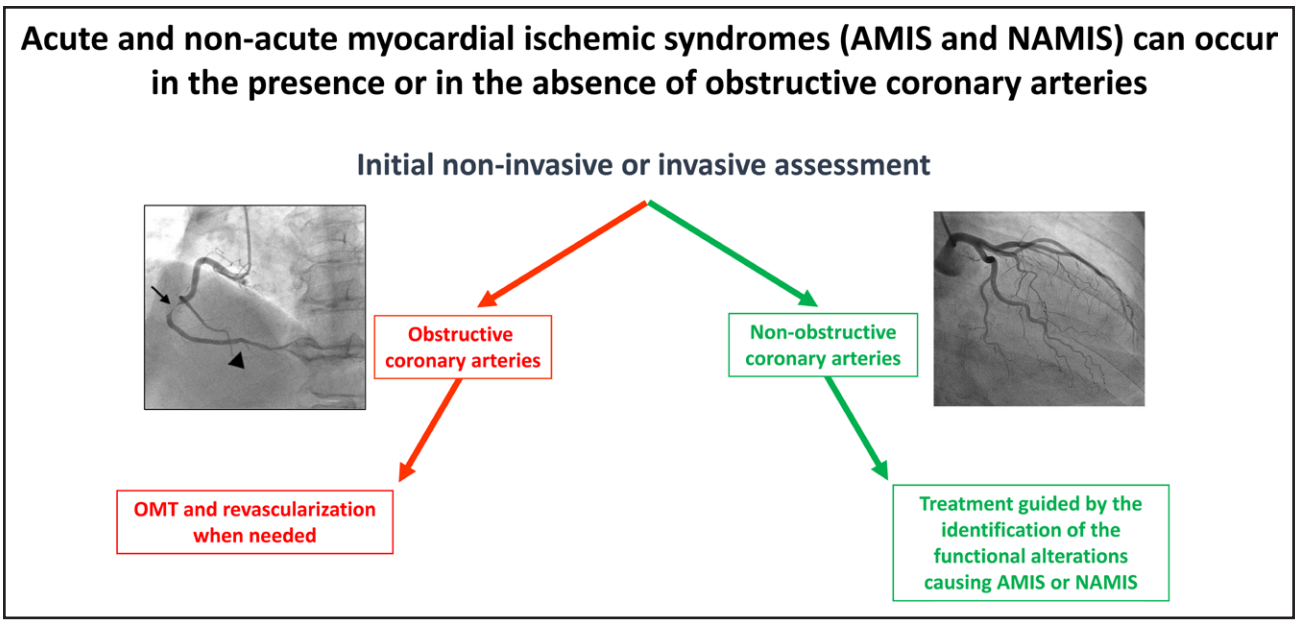

Figure 1. Clinical assessment of myocardial ischemia and coronary artery disease in a population of patients with chest pain. AMIS indicates acute myocardial ischemic syndromes; NAMIS, non-acute myocardial ischemic syndromes; and OMT, optimal medical therapy. Redrawn and modified from Boden et al,[9] with permission.

perception.[6,8] Whereas silent or asymptomatic myocardial ischemia may occur in 10%–20% of stable CAD patients, the absence of anginal symptoms should not be considered synonymous with low cardiovascular risk.[9] Thus, myocardial ischemia and angina do not necessarily coexist in all patients, but ischemia is the fundamental underlying pathophysiologic mechanism.

Finally, the continued schism in terminology is exemplified by the different nomenclatures that have evolved internationally. While the older ACC/AHA guidelines referred to chronic manifestations of angina as "SIHD,"[17] the new ACC/AHA guidelines now classify these as "CCD."[6] The migration away from the 2013 ESC designation of "stable CAD"[18] to CCS in the 2019 ESC guidelines[8] was a notable step forward by creating descriptive symmetry with the universally accepted classification of ACS. However, the recent shift from SIHD[17] to CCD[6] in American guidelines continues to bolster an overly restrictive concept that epicardial coronary stenosis or obstruction is the predominant (if not the sole) cause of angina and ischemia. This is perhaps further amplified by the frequent use of related terms such as "disease" or 'lesion' in our daily cardiology lexicon that unwittingly draws attention towards the sole objective of epicardial stenosis identification and intervention. Because the immediate and long-term manifestations of myocardial ischemia are dictated by the severity, location, extent, and duration of the cardiomyocyte insult, there is a strong rationale to address both coronary and non-coronary aetiologies of myocardial insults more broadly with a contemporary terminology that also includes ischemia with non-obstructive coronary arteries (INOCA)[10] and MINOCA.[13]

Pivoting Away From the Terms "Coronary" and From "Disease" to "Syndrome"

The term "ischemic syndrome" better characterizes and captures the many pathogenetic causes of angina and ischemia more inclusively and accurately than the narrower terms "coronary" and "disease." We certainly recognize that coronary obstruction or epicardial coronary stenosis remains an important mechanistic cause of ACS and accounts also for many clinical presentations of CCS or CCD. However, the very same term 'coronary' fails to encompass the many non-coronary processes that may also cause myocardial ischemia, such as microvascular dysfunction, extramural microcirculatory compression, microvascular embolization and rarefaction, and myocardial bridges (Figure 2). Thus, an unforeseen consequence of disproportionately focusing on epicardial coronary obstruction is that other pathogenetically important causes of angina and ischemia too often fail to be considered. A purely anatomical diagnostic approach using invasive coronary angiography or coronary computed tomography angiography (CCTA) may likewise fail to diagnose microvascular and/or vasospastic angina as treatable causes of angina—a situation in which many patients in whom no obstructive coronary lesions are identified may be falsely reassured that ischemia is not present. Often such patients are discharged from cardiology settings, at which point a myriad of potential (and costly) non-cardiac causes are probed rather than pursuing a more diligent evaluation of non-coronary causes of angina and ischemia.[19] Because treatment differs according to the different aetiologies, a more comprehensive

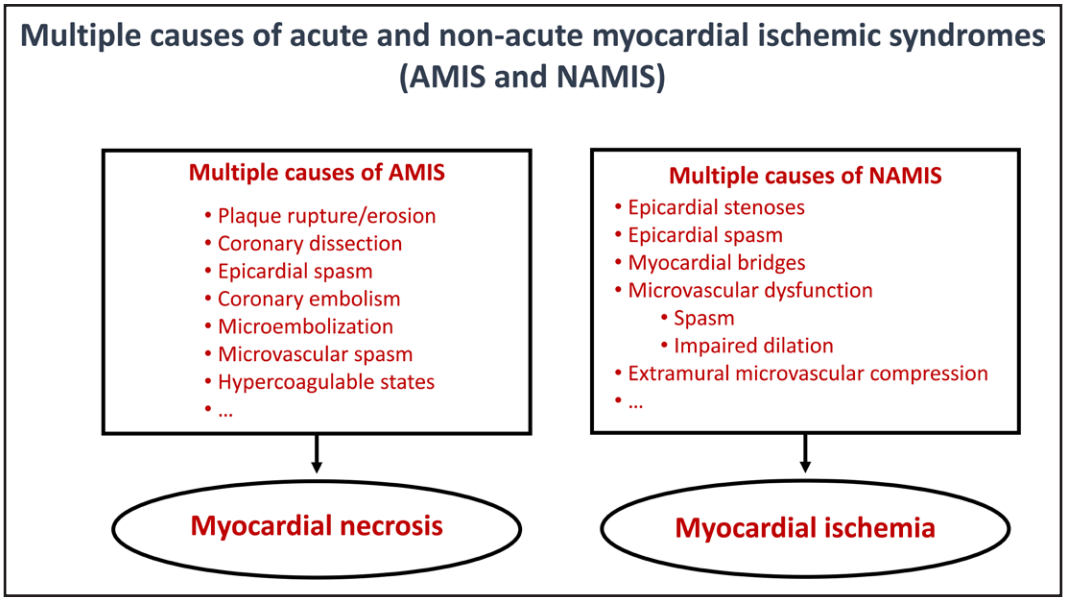

Figure 2. Multiple causes of acute and non-acute myocardial ischemic syndromes (AMIS and NAMIS): a non-exhaustive list.
AMIS indicates acute myocardial ischemic syndromes; and NAMIS, non-acute myocardial ischemic syndromes.

classification system should promote a more diversified and personalized approach to therapy. We acknowledge that myocardial injury (eg, with traumas, hypoxaemia, anaemia, or some poisonings) may also occur because of non-cardiac causes and mimic myocardial ischemic syndromes, but these are out of the scope of the present *Frontiers* report.

We likewise believe that referring to acute ischemic manifestations (ie, ACS or unstable angina) as a "syndrome" while depicting the chronic manifestations of exertional angina and ischemia as a "disease" is dyssynchronous. The ultimate mechanism by which MACE—unstable angina, MI, and death, including sudden cardiac (arrhythmic) death—occur is myocardial ischemia, whether this is due to epicardial coronary plaque rupture, erosion, or to a host of other alternative or complementary non-obstructive mechanisms occurring in up to 12% of patients.[13] Similarly, among "stable angina" patients, recent trials[20,21] have compared non-invasive functional versus anatomic testing in patients with suspected CAD, confirming low-to-modest rates of epicardial coronary obstruction, ranging from 20% to 45%.[22] In the CCTA arm of SCOT-HEART (n=2073), 1239 patients (60%) had anginal symptoms by the National Institute for Health and Care Excellence criteria, including 737 (36%) with typical angina and 502 (24%) with atypical angina, while only 452 patients (25%) among 1778 patients with an available CCTA result had obstructive CAD.[23]

The 2019 CCS ESC guidelines also acknowledged that among patients with typical angina in the most common age range for detecting stable CAD (age 50–59 years), 68% of men and 87% of women did not have obstructive coronary stenoses,[8] while the CorMicA trial (Coronary Microvascular Angina) revealed that ~45% of patients presenting with angina or ischemia did not have CAD at angiography.[24] Finally, in a large US registry of almost 400 000 patients with suspected CAD referred to coronary angiography for documented myocardial ischemia on stress testing, coronary obstruction >70% was found in only 38% of patients, while in a similar percentage of patients (37%) with atypical symptoms, obstructive CAD was found in only 25%. Overall, non-obstructive CAD (<20% stenosis in all vessels) was found in almost 40% of subjects.[25] Such findings underscore that a high proportion of such INOCA patients display objective evidence of coronary vasomotor dysfunction or abnormalities of myocardial microcirculation,[26] which reinforces the need for adopting a comprehensive, unifying nomenclature that centers on the ischemic myocardium rather than on obstructed coronary arteries alone.

Transitioning From "Chronic" to "Non-Acute" Terminology

Importantly, a binary classification system that uses "chronic" or "stable" as the contrasting description of "acute" does not accurately depict the full measure of subsequent cardiovascular risk and likewise may perhaps convey an inadvertent misperception of a clinically benign condition. Such descriptive terminology using "chronic" or 'stable' when referring to myocardial ischemia in the non-acute clinical setting might also mistakenly imply low risk for subsequent cardiac events. Several trials[27–30] in such a setting show intermediate-to-high cardiac event rates during long-term follow-ups. Accordingly, the term non-acute better conveys the important message of persistent and, often substantial, residual prognostic risk of cardiac events that occurs (or recurs) over time in such patients.

New Unifying Nomenclature Focusing on the "Ischemic Myocardium," Not Solely on "Coronary Disease"

We, therefore, propose the adoption of myocardial ischemic syndromes as a more accurately descriptive nomenclature that encompasses the many clinical presentations and pathogenetic "phenotypes" of angina and myocardial ischemia that may occur beyond epicardial coronary obstruction alone. Because non-obstructive functional mechanisms may co-exist with anatomic obstructive CAD, these ischemia precipitants should not be viewed as mutually exclusive and may often occur contemporaneously—even in the same patient. Such a nomenclature would thus represent an overall more accurate, inclusive, and comprehensive classification system with distinct relevance both prognostically and therapeutically. Invasive biomarker[31] and non-invasive cardiac magnetic resonance spectroscopy[32] studies now rigorously confirm that myocardial ischemia occurs both in the presence and absence of obstructive CAD. With all the limitations of clinically available methods for ischemia testing and their lack of precision in detecting non-obstructive mechanisms, we now know that the prevalence of ischemia and MI in the absence of obstructive CAD is more common than previously thought[25] and that coronary microvascular dysfunction documented by a reduction of coronary flow reserve (CFR) is associated with a worse outcome both among patients without and those with obstructive CAD.[33,34] A nomenclature that highlights the broad array of mechanisms that may precipitate ischemia would be an important reminder to practising physicians that only a comprehensive assessment can identify a large patient population at increased risk of MACE despite the absence of CAD. Certainly, more research is needed to better understand the mechanisms of myocardial ischemia without CAD, including identification of more specific tailored treatments and understanding reasons for the often-found disconnection between ischemia and angina, which is well-illustrated by the recent CIAO-ISCHEMIA trial findings.[35]

The proposed new binary classification system of 'myocardial ischemic syndromes' is shown in Figure 3, with the overall subcategories of "acute myocardial ischemic syndromes" (AMIS) and "non-acute myocardial ischemic syndromes" (NAMIS) to depict both the more acute and 'chronic' manifestations of angina and myocardial ischemia, respectively. As noted above, among patients with ST-elevation MI (STEMI), non-ST-elevation MI (NSTEMI), or unstable angina who most often present with presumed epicardial coronary artery plaque rupture or erosion, we herein retain "ACS" as a critically important subcategory of AMIS, for which revascularization is of proven benefit, and to distinguish this from other causes of AMIS that are not of obstructive epicardial coronary origin. Additionally, within each broad category of AMIS and NAMIS, we likewise distinguish the respective phenotypes of epicardial coronary causes and non-coronary causes responsible for MINOCA, as acknowledged and reported in the latest 2023 ESC Guidelines on ACS.[15]

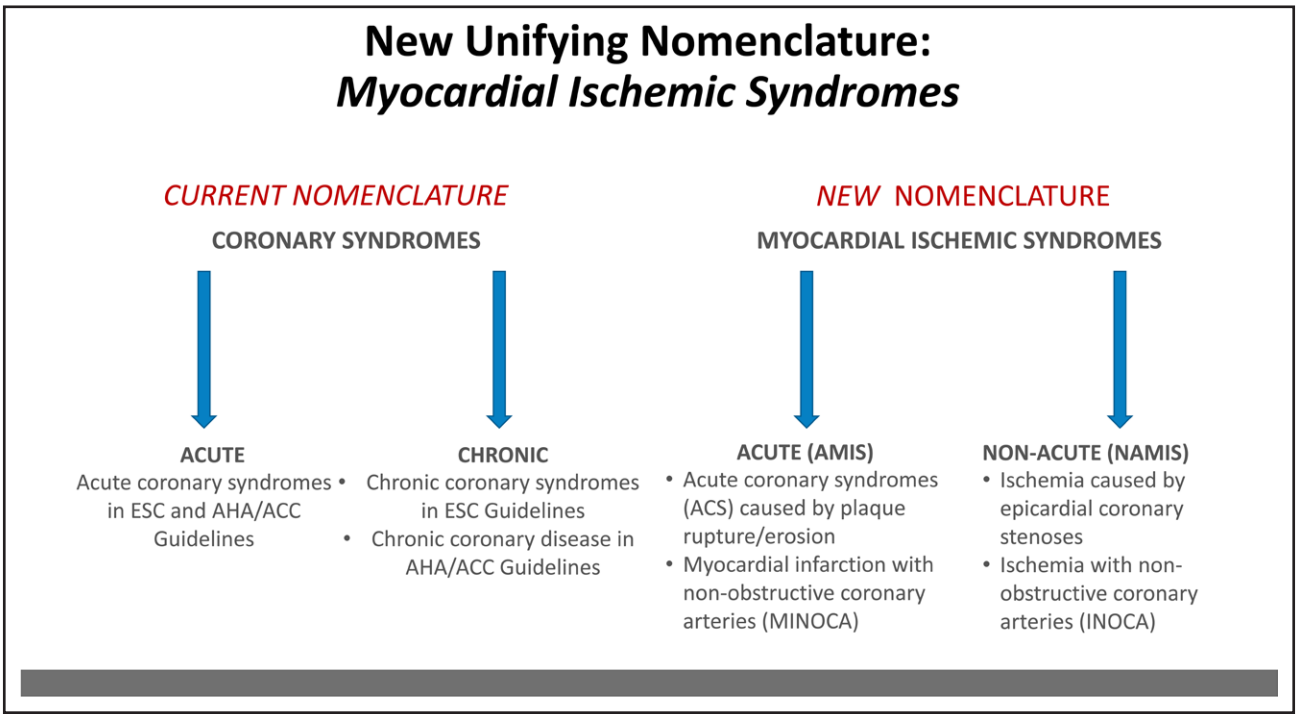

Figure 3. Myocardial ischemic syndromes–rationale for a new unifying nomenclature.
ACC indicates American College of Cardiology; AHA, American Heart Association; AMIS, acute myocardial ischemic syndromes; ESC, European Society of Cardiology; and NAMIS, non-acute myocardial ischemic syndromes.

Conversely, patients with chronic angina and myocardial ischemia who at coronary angiography are found to have one or more obstructive, flow-limiting epicardial coronary stenoses would be classified as having a NAMIS and best subclassified as 'non-acute obstructive coronary disease', for whom additional functional or anatomic testing would be appropriate to identify which subsets of patients would be candidates for coronary intervention. Such subcategorization will permit distinguishing this clinical presentation from other causes of NAMIS, in which chronic angina and/or myocardial ischemia are due to non-epicardial coronary obstruction responsible for INOCA, as noted and depicted in Figure 3.

As a final consideration, it is noteworthy that a similar movement is underway in neurology to pivot the nomenclature away from the long-used term "transient ischemic attack" (TIA), which has been in use since 1975, towards the revised term "acute ischemic cerebrovascular syndromes," which was first introduced in 2003[36] and more recently advocated as an analogous concept to "myocardial ischemic syndromes."[37] Such a proposed conceptual shift in terminology would thus also impart nomenclature symmetry across different but related clinical disciplines and ischemic disease states.

CONCLUSIONS

The time has come to consider a new, unifying nomenclature that more broadly and accurately classifies both the acute and non-acute expressions of myocardial ischemia and infarction, inclusive of both epicardial obstructive coronary and non-obstructive causes. It is our collective view that a new binary classification of "AMIS" and "NAMIS" should likewise foster improved conceptual clarity and unify dyssynchronous—and competing—nomenclatures across international guidelines. Within this construct, we likewise strongly advocate retaining the well-established subclassifications of STEMI, NSTEMI, unstable angina, and ACS as critically important subsets for which revascularization is of proven benefit for cardiovascular event reduction, as well as the most recent subclassifications of INOCA and MINOCA. Such a nomenclature better aligns, unifies, and harmonizes different pathophysiologic causes of angina, myocardial ischemia, and MI and should result in more refined diagnostic and therapeutic approaches targeted to the multiple underlying pathobiological precipitants.

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Received May 19, 2023; accepted March 14, 2024.

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Acknowledgments

We thank the *Circulation* Editors and Reviewers for the opportunity to publish this *Frontiers* article. We also iterate that the views and opinions expressed in this publication are those of the authors, and do not reflect the views or official positions of the ACC, AHA, or ESC.

Sources of Funding

None.

Disclosures

None.

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