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STATE OF THE ART REVIEW
Ischaemic heart disease

Myocardial ischaemic 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 ischaemia, various classifications have emerged over time, often with conflicting terminology—e.g. 'stable coronary artery disease' (CAD), 'stable ischaemic 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 ischaemia that fosters conceptual clarity and unifies dyssynchronous nomenclatures across guidelines. We, therefore, propose a new binary classification of 'acute myocardial ischaemic syndromes' and 'non-acute myocardial ischaemic 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 ischaemia and MI with non-obstructive coronary arteries. Overall, such a more encompassing nomenclature better aligns, unifies, and harmonizes different pathophysiologic causes of myocardial ischaemia and should result in more refined diagnostic and therapeutic approaches targeted to the multiple pathobiological precipitants of angina pectoris, ischaemia and infarction.

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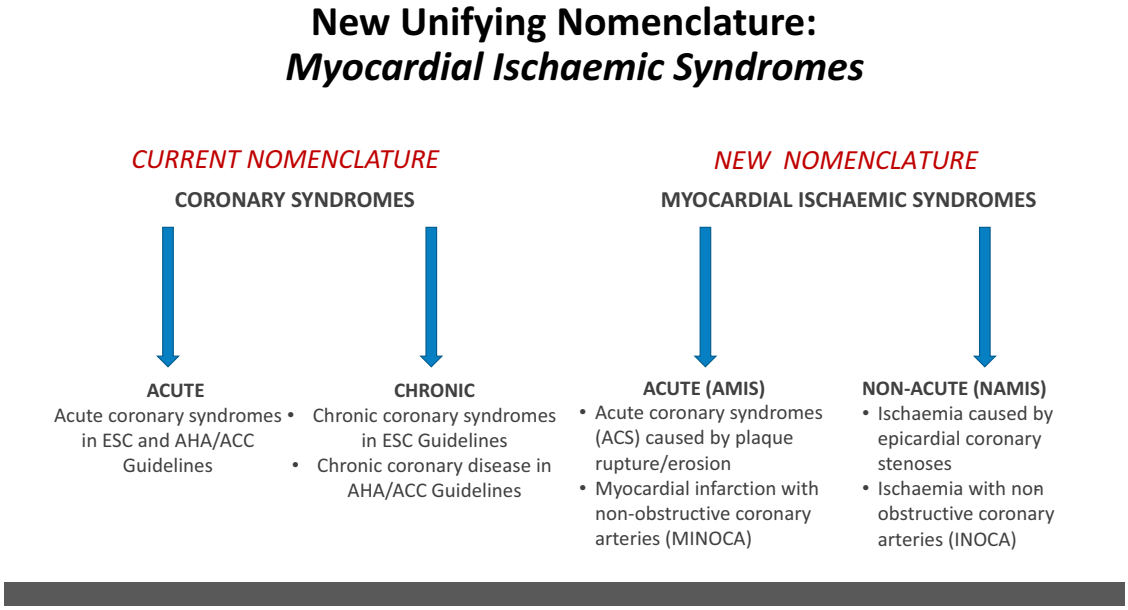
Graphical Abstract



Myocardial ischaemic syndromes—rationale for a new unifying nomenclature

Keywords Acute myocardial ischaemic syndromes • Non-acute myocardial ischaemic syndromes • AMIS • NAMIS • Coronary artery disease • Ischaemic heart disease

'*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 favourably impacted patient management over the past 20 years.[1–6] Yet, the current ACS nomenclature neglects many important non-obstructive coronary causes of both myocardial ischaemia and MI.

Moreover, among patients with chronic stable manifestations of myocardial ischaemia, various classifications have emerged over time but often with conflicting terminology and implications—e.g. 'stable coronary artery disease' (CAD), 'stable ischaemic 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 ischaemia 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 ischaemia, 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 (e.g. 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 vs 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 ischaemia and, conversely, both myocardial ischaemia 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 ischaemia 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 ischaemia 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 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 ischaemia 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 ischaemia demands a more comprehensive and inclusive taxonomy

Myocardial ischaemia 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 ischaemia 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 ischaemia, 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 ischaemia (regardless of pathogenetic mechanisms) is the myocardium and, ultimately, the cardiac myocyte. And since myocardial ischaemia 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 ischaemia is perceived and a sizeable proportion of ischaemic episodes are not associated with angina;[8,16] thus, ischaemia may be 'silent' in a certain proportion of individuals, possibly depending on alterations in neural pain processing mechanisms.[16] 'Silent myocardial ischaemia' is thought to occur more commonly in patients with diabetes who have autonomic neuropathy and altered pain perception.[6,8] Whereas silent or asymptomatic myocardial ischaemia 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 ischaemia and angina do not necessarily coexist in all patients, but ischaemia 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 ischaemia. 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 ischaemia 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 ischaemia with non-obstructive coronary arteries (INOCA)[10] and MINOCA.[13]

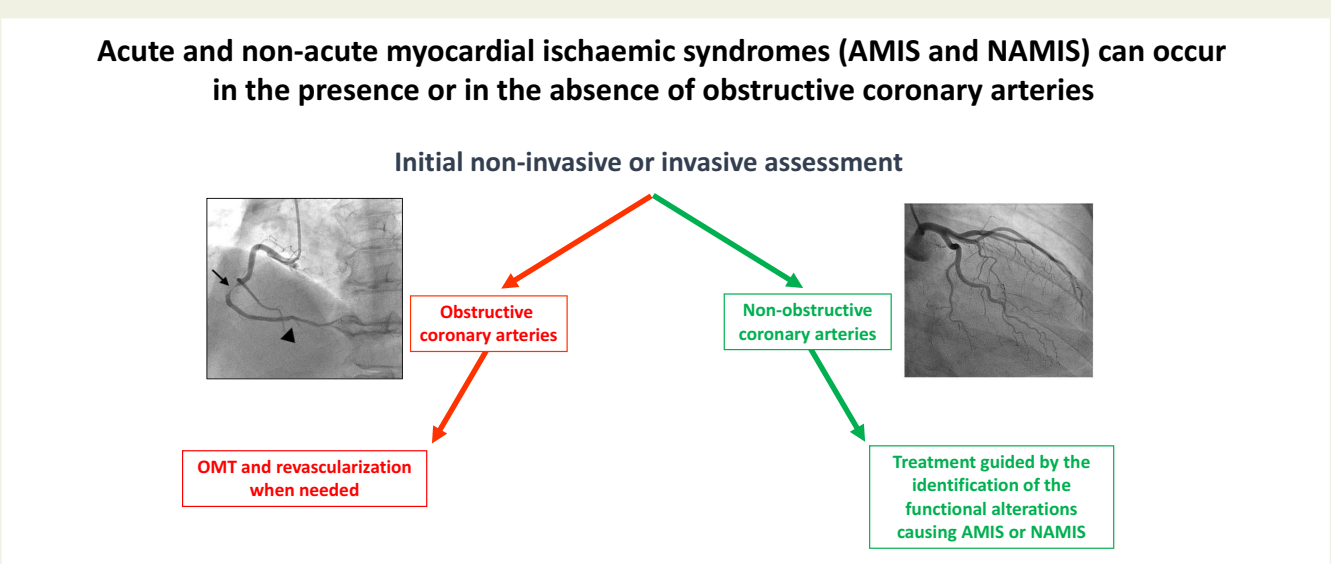


Figure 1 Clinical assessment of myocardial ischaemia and coronary artery disease in a population of patients with chest pain. OMT, optimal medical therapy; AMIS, acute myocardial ischaemic syndromes; NAMIS, non-acute myocardial ischaemic syndromes. Redrawn and modified from Boden *et al.*[9], with permission

Pivoting away from the terms 'coronary' and from 'disease' to 'syndrome'

The term 'ischaemic syndrome' better characterizes and captures the many pathogenetic causes of angina and ischaemia 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 ischaemia, 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 ischaemia 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 ischaemia 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 ischaemia.[19] Because treatment differs according to the different aetiologies, a more comprehensive classification system should promote a more diversified and personalized approach to therapy. We acknowledge that myocardial injury (e.g. with traumas, hypoxaemia, anaemia, or some poisonings) may also occur because of *non-cardiac* causes and mimic myocardial *ischaemic* syndromes, but these are out of the scope of the present report.

We likewise believe that referring to acute ischaemic manifestations (i.e. ACS or unstable angina) as a 'syndrome' while depicting the chronic manifestations of exertional angina and ischaemia as a 'disease' is dyssynchronous. The ultimate mechanism by which MACE—unstable angina, MI, and death, including sudden cardiac (arrhythmic) death—occur is myocardial ischaemia, 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 Coronary Microvascular Angina (CorMicA) trial revealed that ~45% of patients presenting with angina or ischaemia 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 ischaemia 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 centres on the ischaemic 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 ischaemia in the *non-acute* clinical setting might also

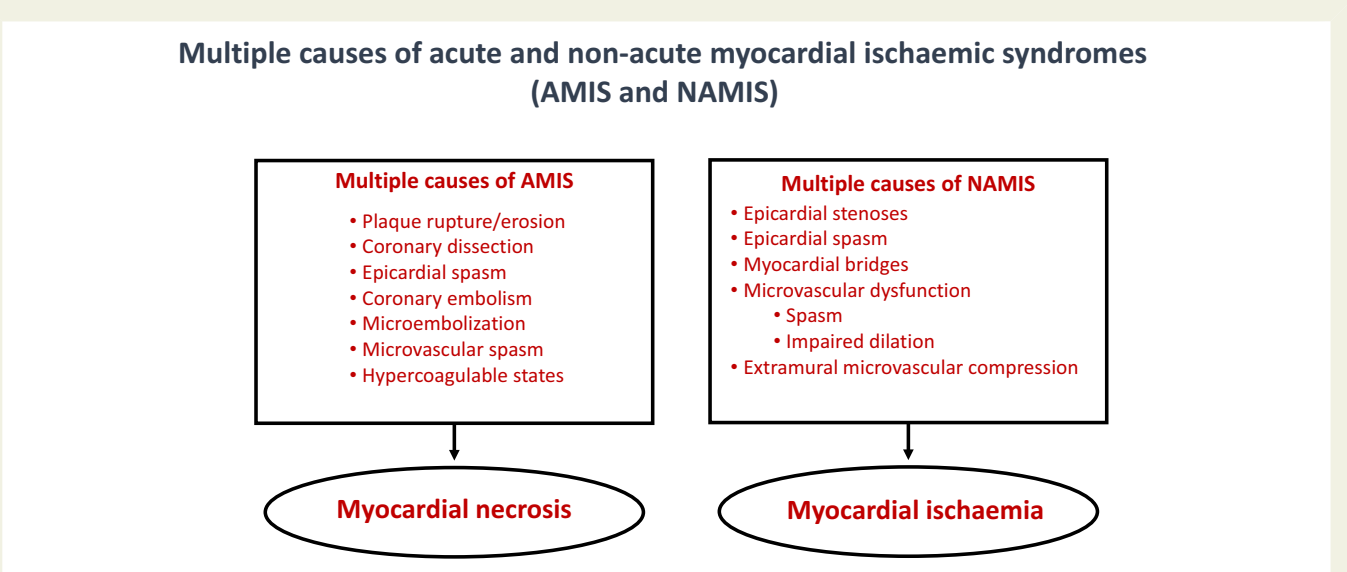


Figure 2 Multiple causes of acute and non-acute myocardial ischaemic syndromes (AMIS and NAMIS): a non-exhaustive list

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 'ischaemic myocardium', not solely on 'coronary disease'

We, therefore, propose the adoption of *myocardial ischaemic syndromes* as a more accurately descriptive nomenclature that encompasses the many clinical presentations and pathogenetic 'phenotypes' of angina and myocardial ischaemia that may occur beyond epicardial coronary obstruction alone. Because non-obstructive functional mechanisms may co-exist with anatomic obstructive CAD, these ischaemia 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 ischaemia occurs both in the presence and absence of obstructive CAD. With all the limitations of clinically available methods for ischaemia testing and their lack of precision in detecting non-obstructive mechanisms, we now know that the prevalence of ischaemia 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 ischaemia 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 ischaemia without CAD, including identification of more specific tailored treatments and understanding reasons for the often-found disconnection between ischaemia and angina, which is well-illustrated by the recent CIAO-ISCHEMIA trial findings.[35]

The proposed new binary classification system of 'myocardial ischaemic syndromes' is shown in *Graphical Abstract*, with the overall subcategories of 'acute myocardial ischaemic syndromes' (AMIS) and 'non-acute myocardial ischaemic syndromes' (NAMIS) to depict both the more acute and 'chronic' manifestations of angina and myocardial ischaemia, 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]

Conversely, patients with chronic angina and myocardial ischaemia 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 ischaemia are due to *non-epicardial* coronary obstruction responsible for INOCA, as noted and depicted in *Graphical Abstract*.

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 ischaemic attack' (TIA), which has been in use since 1975, towards the revised term 'acute ischaemic cerebrovascular syndromes', which was first introduced in 2003[36] and more recently advocated as an analogous concept to 'myocardial ischaemic syndromes'[37]. Such a proposed conceptual shift in terminology would thus also impart nomenclature symmetry across different but related clinical disciplines and ischaemic 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 ischaemia 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 ischaemia, and MI and should result in more refined diagnostic and therapeutic approaches targeted to the multiple underlying pathobiological precipitants.

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Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

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References

1. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M *et al.* Universal definition of myocardial infarction. *Circulation* 2007;**116**:2634–2653. https://doi.org/10.1161/CIRCULATIONAHA.107.187397
2. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA *et al.* , for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol* 2018;**72**:2231–2264. https://doi.org/10.1016/j.jacc.2018.08.1038
3. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK *et al.* 2021 aha/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;**144**:e368–e454. https://doi.org/10.1161/cir.0000000000001029
4. Sabik JF III, Bakaeen FG, Ruel M, Moon MR, Malaisrie SC, Calhoon JH *et al.* The American Association for Thoracic Surgery and the Society of Thoracic Surgeons reasoning for not endorsing the 2021 ACC/AHA/SCAI coronary revascularization guidelines. *Ann Thorac Surg* 2022;**113**:1065–1068. https://doi.org/10.1016/j.athoracsur.2021.12.003
5. Yadava OP, Narayan P, Padmanabhan C, Sajja LR, Sarkar K, Varma PK *et al.* IACTS position statement on "2021 ACC/AHA/SCAI guideline for coronary artery revascularization": section 7.1-a consensus document. *Indian J Thorac Cardiovasc Surg* 2022;**38**:126–133. https://doi.org/10.1007/s12055-022-01329-y
6. Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH *et al.* 2023 aha/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation* 2023;**148**:e9–e119. https://doi.org/10.1161/cir.0000000000001168
7. De Caterina R, Boden WE. The nomenclature vagaries for the clinical manifestations of myocardial ischemic syndromes - a call to action. *Int J Cardiol* 2020;**304**:5–7. https://doi.org/10.1016/j.ijcard.2019.12.049
8. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, *et al.* ESC guidelines for the diagnosis and management of chronic coronary syndromes: the task force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J* 2020;**41**:407–477. https://doi.org/10.1093/eurheartj/ehz425
9. Boden WE, Marzilli M, Crea F, Mancini GBJ, Weintraub WS, Taqueti VR *et al.* Evolving management paradigm for stable ischemic heart disease patients: JACC review topic of the week. *J Am Coll Cardiol* 2023;**81**:505–514. https://doi.org/10.1016/j.jacc.2022.08.814
10. Marzilli M, Merz CN, Boden WE, Bonow RO, Capozza PG, Chilian WM *et al.* Obstructive coronary atherosclerosis and ischemic heart disease: an elusive link!. *J Am Coll Cardiol* 2012;**60**:951–956. https://doi.org/10.1016/j.jacc.2012.02.082
11. Niccoli G, Montone RA, Lanza GA, Crea F. Angina after percutaneous coronary intervention: the need for precision medicine. *Int J Cardiol* 2017;**248**:14–19. https://doi.org/10.1016/j.ijcard.2017.07.105
12. Kwok CS, Rao SV, Potts JE, Kontopantelis E, Rashid M, Kinnaird T *et al.* Burden of 30-day readmissions after percutaneous coronary intervention in 833,344 patients in the United States: predictors, causes, and cost: insights from the Nationwide Readmission Database. *JACC Cardiovasc Interv* 2018;**11**:665–674. https://doi.org/10.1016/j.jcin.2018.01.248
13. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation* 2015;**131**:861–870. https://doi.org/10.1161/circulationaha.114.011201
14. Hearse DJ. Myocardial ischaemia: can we agree on a definition for the 21st century? *Cardiovasc Res* 1994;**28**:1737–1744. discussion 1745-1736. https://doi.org/10.1093/cvr/28.12.1737
15. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A *et al.* 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023;**44**:3720–3826. https://doi.org/10.1093/eurheartj/ehad191
16. Boden WE, Kaski JC, Berry C. Reprising Heberden's description of angina pectoris after 250 years. *Eur Heart J* 2023;**44**:1684–1686. https://doi.org/10.1093/eurheartj/ehac643
17. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ *et al.* 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Thorac Cardiovasc Surg* 2015;**149**:e5–23. https://doi.org/10.1016/j.jtcvs.2014.11.002
18. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A *et al.* 2013 ESC guidelines on the management of stable coronary artery disease: the task force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949–3003. https://doi.org/10.1093/eurheartj/eht296
19. Pepine CJ. Multiple causes for ischemia without obstructive coronary artery disease: not a short list. *Circulation* 2015;**131**:1044–1046. https://doi.org/10.1161/circulationaha.115.015553
20. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B *et al.* Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med* 2015;**372**:1291–1300. https://doi.org/10.1056/NEJMoa1415516
21. Newby DE, Adamson PD, Berry C, Boon NA, Dweck MR, Flather M *et al.* Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med* 2018;**379**:924–933. https://doi.org/10.1056/NEJMoa1805971
22. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE *et al.* Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med* 2007;**356**:2388–2398. https://doi.org/10.1056/NEJMsa053935
23. The SCOT-HEART Investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet* 2015;**385**:2383–2391. https://doi.org/10.1016/s0140-6736(15)60291-4
24. Ford TJ, Stanley B, Good R, Rocchiccioli P, McEntegart M, Watkins S *et al.* Stratified medical therapy using invasive coronary function testing in angina: the CorMicA trial. *J Am Coll Cardiol* 2018;**72**:2841–2855. https://doi.org/10.1016/j.jacc.2018.09.006
25. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV *et al.* Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010;**362**:886–895. https://doi.org/10.1056/NEJMoa0907272
26. Ong P, Camici PG, Beltrame JF, Crea F, Shimokawa H, Sechtem U *et al.* International standardization of diagnostic criteria for microvascular angina. *Int J Cardiol* 2018;**250**:16–20. https://doi.org/10.1016/j.ijcard.2017.08.068
27. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ *et al.* Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;**356**:1503–1516. https://doi.org/10.1056/NEJMoa070829
28. Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM *et al.* A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;**360**:2503–2515. https://doi.org/10.1056/NEJMoa0805796
29. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O *et al.* Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;**377**:1319–1330. https://doi.org/10.1056/NEJMoa1709118
30. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE *et al.* Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 2020;**382**:1395–1407. https://doi.org/10.1056/NEJMoa1915922
31. Sabatine MS, Morrow DA, de Lemos JA, Jarolim P, Braunwald E. Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: results from TIMI 35. *Eur Heart J* 2009;**30**:162–169. https://doi.org/10.1093/eurheartj/ehn504
32. Buchthal SD, den Hollander JA, Merz CN, Rogers WJ, Pepine CJ, Reichek N *et al.* Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. *N Engl J Med* 2000;**342**:829–835. https://doi.org/10.1056/nejm200003233421201
33. Chung JH, Lee KE, Lee JM, Her AY, Kim CH, Choi KH *et al.* Effect of sex difference of coronary microvascular dysfunction on long-term outcomes in deferred lesions. *JACC Cardiovasc Interv* 2020;**13**:1669–1679. https://doi.org/10.1016/j.jcin.2020.04.002
34. Kelshiker MA, Seligman H, Howard JP, Rahman H, Foley M, Nowbar AN *et al.* Coronary flow reserve and cardiovascular outcomes: a systematic review and meta-analysis. *Eur Heart J* 2022;**43**:1582–1593. https://doi.org/10.1093/eurheartj/ehab775
35. Reynolds HR, Picard MH, Spertus JA, Peteiro J, Lopez Sendon JL, Senior R *et al.* Natural history of patients with ischemia and no obstructive coronary artery disease: the CIAO-ISCHEMIA study. *Circulation* 2021;**144**:1008–1023. https://doi.org/10.1161/circulationaha.120.046791
36. Kidwell CS, Warach S. Acute ischemic cerebrovascular syndrome: diagnostic criteria. *Stroke* 2003;**34**:2995–2998. https://doi.org/10.1161/01.Str.0000098902.69855.A9
37. Easton JD, Johnston SC. Time to retire the concept of transient ischemic attack. *JAMA* 2022;**327**:813–814. https://doi.org/10.1001/jama.2022.0300