Myocardial Ischaemic Syndromes: Shifting from a Coronary-centric to a Substrate-based Nomenclature is More Accurate and Inclusive

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Abstract

This article highlights the rationale for a more accurate and inclusive classification that does not focus solely on epicardial coronary lesions as the *causa sine qua non* for angina and myocardial ischaemia in all patients but rather represents a more comprehensive classification encompassing both obstructive and non-obstructive causes. Ischaemia may be 'silent' clinically or electrocardiographically and is observed in both acute and non-acute settings, as seen in patients with diabetes and other conditions associated with microvascular dysfunction. By pivoting away from the more restrictive and overly simplistic 'vessel-based' classification that disproportionately focuses on obstructed epicardial arteries to a 'substrate-based' nomenclature inclusive of both obstructive and non-obstructive causes, 'myocardial ischaemic syndromes' will better align and unify a patient-centric approach by harmonising the full spectrum of pathophysiologic causes.

Keywords

Chronic coronary syndromes, chronic coronary disease, epicardial coronary obstruction, acute and non-acute myocardial ischaemic syndromes, nomenclature

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Our recent simultaneous publication in *European Heart Journal* and *Circulation* of a new binary nomenclature to better characterise acute and chronic myocardial ischaemic syndromes triggered a comment in *Nature Reviews Cardiology* by Byrne and Kastrati titled 'Trade-offs between vessel-based and substrate-based nomenclatures for coronary heart diseases'.[1–3] Their commentary raises important points regarding the proposed new terms acute myocardial ischaemic syndromes (AMIS) and non-acute myocardial ischaemic syndromes (NAMIS).[1]

The primary impetus for this new classification was to emphasise that the current terminology of acute coronary syndromes (ACS) and chronic coronary syndromes (CCS), as well as chronic coronary disease (CCD), are commonly understood to depict only epicardial *obstructive* pathogenetic aetiologies and are not assumed to be inclusive of the common *non-obstructive* mechanisms that underly angina pectoris and ischaemia in many patients.[4–6]

Byrne and Kastrati acknowledge that the term AMIS "seems to characterize the qualifying clinical situations better than the term acute coronary syndromes (ACS)… because the unplanned presentation to the clinic of the patient is directly related to myocardial ischaemic events". They further emphasise that "even patients without myocardial infarction (MI) according to cardiac biomarker elevation, but classified into the category of unstable angina, have symptoms (such as angina) and/or signs of cardiac disease (electrocardiographic [ECG] changes or regional wall motion abnormalities on non-invasive imaging) that have a myocardial ischaemic origin". They agree that the AMIS and NAMIS classification comports well with "nomenclature used for acute events in other atherosclerotic vascular diseases, such as acute ischaemic cerebrovascular syndrome or acute limb ischaemic syndrome".[7,8]

However, Byrne and Kastrati challenge the utility of the NAMIS nomenclature over the current CCS/CCD designations, citing that:

- Outside the setting of hibernating myocardium underlying left ventricular dysfunction, be it either episodic (i.e. acute and transient,

spontaneous, or provoked by diagnostic tests) or non-resolving and thus leading to ACS or AMIS… "the description of non-acute ischaemia makes less clinical sense," although the explicit reasons for this are not well-elucidated.
- "The newly proposed definition is not sufficiently comprehensive," in that "certain patients, such as those with chronic total coronary occlusions, have definite coronary artery disease but have no symptoms and no signs of myocardial ischaemia (such as perfusion defects or regional wall motion abnormalities), and that patients can have non-obstructive vulnerable atherosclerotic plaques in the coronary arteries that are not associated with overt symptoms or signs of myocardial ischaemia but are clearly an important part of the disease spectrum".
- "In CCS, the prognostic role of ischaemia burden has been called into question by the results of clinical trials such as the ISCHAEMIA trial".

In turn, we dispute this logic based on the following four considerations:

- The terms AMIS and NAMIS do not constitute a binary condition that is either episodic (acute/transient) or non-resolving (resulting in AMIS); many patients with NAMIS have episodic presentations that may initially stabilise and become clinically quiescent over time only to recur and destabilise, and that then may become recurrent and persistent; thus, there is not a one-size-fits-all description for NAMIS.
- Our proposed classification does not address acute ischaemia or non-acute ischaemia per se, as the authors allege, but rather addresses the need for a phenotypic clinical classification encompassing both obstructive and non-obstructive causes, be it episodic, recurrent, or persistent; hence we propose the terms acute or non-acute *myocardial ischaemic syndromes*, denoting the principal acute or non-acute clinical presentations.
- Contrary to their assertion that chronic total occlusions without symptoms or signs of myocardial ischaemia (such as perfusion defects or regional wall motion abnormalities) would "render the term NAMIS imprecise or inaccurate", it must be emphasised that the absence of angina and ischaemia indicates only that the myocardium (substrate) remains viable because of intact collateral blood flow, not that NAMIS is an inaccurate classification. Additionally, the authors cite "hibernating myocardium underlying left ventricular dysfunction" as a singular exception to their dislike of the term NAMIS, yet they neglect to cite stunned myocardium (ischaemia too brief in duration to cause myocardial necrosis) as a potential clinical condition that can result in either AMIS or NAMIS.[9] Moreover, 30 years ago, one of us (WEB) advanced a 'third altered myocardial state' (incomplete, delayed functional recovery that occurs with chronically ischaemic, or partially infarcted myocardium) as an additional myocardial substrate – a concept that was termed 'maimed myocardium'.[10] Thus, we must recognise that ischaemia may be both silent clinically or electrocardiographically – and is often observed in both acute and non-acute settings.[11,12]
- The absence of angina does not negate the presence of ischaemia in many patients, such as those with diabetes, where the absence of angina may signify a faulty early warning mechanism because of disrupted neural pathways in both the recognition and description of angina.[13,14]

For these reasons, we believe a substrate-based nomenclature is both pathobiologically sound and evidence-based.

Byrne and Kastrati also cite the results of the recent PREVENT trial as an example of atherosclerotic burden and the potential that prophylactic stenting of high-risk, non-flow-limiting vulnerable plaques may represent a new and innovative therapeutic approach to prevent new plaque ruptures leading to AMIS. While Park et al. showed that there were significantly fewer cardiovascular events in patients whose non-flow-limiting plaques were treated with percutaneous coronary interventions (PCI), this was largely driven by a reduction in ischaemia-driven target-vessel MI, target-vessel revascularisations, and hospitalisations for unstable or progressive angina, with no effect on cardiovascular mortality.[15]

Open-label randomisation and prior knowledge of treatment arm assignment may create ascertainment bias, and a significant imbalance, e.g. in dual platelet therapy favouring PCI-treated patients, representing unavoidable treatment confounders that seriously limit the attribution of benefit to PCI. Because of the very low, non-significant differences in cardiovascular death and MI between groups, wherein placebo effects and play of chance may thus lead to spurious findings, it remains unclear whether preventive PCI of vulnerable plaques is a justification for more expanded use of such interventions. Importantly, to confirm that a pre-emptive PCI approach to stenting vulnerable, non-flow-limiting plaques is causally associated with subsequent MI reduction, it will be necessary to confirm that the site of the 'prevented MI' is in the same epicardial coronary segment harbouring the vulnerable plaque that was stented prophylactically. Without such correlative anatomic, electrocardiographic, or myocardial imaging confirmation, it may be difficult to establish causality of presumed treatment benefit.

The related issue of ischaemic burden has been questioned in the context of recent negative randomised trials, most notably the ISCHEMIA trial, which failed to demonstrate a direct relationship between the extent and severity of inducible ischaemia with worse clinical outcomes or improvement with revascularisation.[16] Much like the issue of asymptomatic (silent) ischaemia discussed above, the absence of revascularisation benefit should not be construed as an argument against a substrate-based nomenclature. We further emphasise that a vessel-based nomenclature may lead to an overly simplistic approach that disproportionately focuses on epicardial conduit arteries.

Much of the cardiology verbiage we use routinely in clinical discussions with both colleagues and patients embodies the pervasively restrictive terms 'coronary' and 'disease' when we assert the 'need to fix the lesion' or 'treat the stenosis' in a manner that imparts a virtual singularity of purpose in diagnosing and treating patients based on the presumption that epicardial obstruction/stenosis is the dominant, proximate cause of angina and ischaemia. A predominantly vessel-based model of epicardial coronary obstruction favoured by the authors may engender an agnostic view of other important non-obstructive pathogenetic triggers that may be at play, but are often ignored, particularly if patients are found either at invasive angiography or computed tomographic angiography to not have obstructive coronary artery disease (CAD); all too often, the diagnosis and management quickly pivot away from *cardiac* to *non-cardiac* aetiologies, rather than seeking to explore and treat *non-obstructive coronary* causes.

We agree with the authors that no nomenclature can perfectly describe all possible pathologies to which it is directed. We acknowledge that the expeditious diagnosis and management of AMIS patients who present with acute plaque rupture must proceed to urgent revascularisation to reduce cardiac events, and therefore advocate retaining the well-established subclassifications of ST-elevation MI

(STEMI), non-ST elevation MI (NSTEMI), and ACS as important subsets for which revascularisation is of proven benefit for event reduction within our AMIS/NAMIS classification. But, contrary to the view espoused by Byrne and Kastrati stating that our AMIS and NAMIS classification is intended to replace ACS and CCS terminology, we respectfully underscore that our substrate-based nomenclature *explicitly retains* the well-established terms ACS, STEMI, and NSTEMI as important anatomic subsets of AMIS.[1,2]

In summary, we need to embrace a contemporary classification for angina and myocardial ischaemia that is more broadly inclusive of both *obstructive* epicardial coronary and *non-obstructive* causes and the underlying mechanisms of acute and non-acute myocardial ischaemia. Moving away from the terms 'coronary' and 'disease' will facilitate, in our opinion, a more accurate, inclusive, and comprehensive approach that enlightens and refines patient-centred management by better aligning, unifying, and harmonising the spectrum of pathophysiological causes. ❑

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