A new clinical classification of acute myocardial infarction

PERSPECTIVE

A new clinical classification of acute myocardial infarction

Bertil Lindahl, MD [1,2] and Nicholas L Mills, MBChB[2,3†]

Running title – classification of myocardial infarction

[1] *Department of Medical Sciences, University of Uppsala, Uppsala, Sweden*
[2] *BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom*
[3] *Usher Institute, University of Edinburgh, Edinburgh, United Kingdom*

†Corresponding author: nick.mills@ed.ac.uk

Abstract

The existence of a universal definition of myocardial infarction – which involves classification into multiple subtypes – has promoted the use of standard diagnostic criteria across the world. However, this classification has not been applied consistently in practice and is perceived by some as too complicated. Where there is diagnostic uncertainty, patients have worse outcomes. This uncertainty has also impacted on the validity of the diagnosis of myocardial infarction in clinical trials. To address these issues and to encourage clinicians to recognise that different mechanisms of myocardial infarction have differing treatment implications, we propose an alternative clinical classification for consideration; one that recognises that myocardial infarction can arise spontaneously, secondary to another condition, or as a complication of a cardiac procedure. This classification is aligned with clinical practice and proposes more objective and specific diagnostic criteria that, if agreed by international consensus, could reduce diagnostic uncertainty in practice and research.

The accurate diagnosis of acute myocardial infarction is essential to ensure timely treatment to limit the extent of myocardial injury and prevent complications, such as heart failure or sudden cardiac death. To standardise the diagnostic criteria for myocardial infarction and encourage the application of these standards worldwide, the Universal Definition of Myocardial Infarction was proposed and endorsed by the World Health Organisation and major national and international cardiac societies (1-3). This has been an important global effort, but like all scientific and medical standards, it requires regular review and revision as new evidence emerges.

The current definition states that the term 'acute myocardial infarction' should be used when there is acute myocardial injury with clinical evidence of myocardial ischaemia. Several criteria must be met for a diagnosis of myocardial infarction – including a rise and/or fall in circulating cardiac troponin with at least one value above the 99th percentile upper reference limit – and the 2007 iteration introduced five subtypes of myocardial infarction (2) (**Box 1**). Finally, the term myocardial injury was introduced to describe any elevation in cardiac troponin above the 99th percentile (4), irrespective of whether this is due to ischemic or non-ischemic mechanisms.

Despite the logic of the latest definition of myocardial infarction, this classification has been perceived by some as too complicated and adoption in clinical practice and in research has been inconsistent. In this Perspective, we first outline the controversies and challenges that have arisen in applying the current classification. We then propose an alternative clinical classification with more objective diagnostic criteria, for consideration by the scientific community. Lastly, we describe the steps required to achieve a new consensus.

Controversies and challenges with the current classification

Some recommendations from the current classification are considered controversial. Type 2 myocardial infarction (**Box 1**) currently encompasses both coronary mechanisms (such as spontaneous dissection, embolism or vasospasm) and non-coronary mechanisms (resulting from tachycardia, hypotension, hypoxia or anaemia), the latter of which can occur in patients with or without underlying coronary artery disease. Different treatments are needed for each of these scenarios, which has limited the utility of this diagnosis in practice. Furthermore, there is often uncertainty in how to distinguish type 1 from type 2 myocardial infarction, and type 2 myocardial infarction from non-ischemic myocardial injury in practice (5). Type 4 and type 5 myocardial infarction are rarely applied to describe periprocedural complications in practice and the diagnostic criteria are debated by cardiologists and cardiac surgeons alike — with disagreement regarding the cut-off values for cardiac troponin elevation and whether additional evidence of a complication is required (6). The following paragraphs expand on key factors that have limited adoption and generated uncertainty.

First, the classical description of ischemic symptoms was derived from studies dominated by patients with type 1 myocardial infarction. Studies have shown that classical symptoms (chest pain radiating to the jaw, neck, back, arm or shoulder) are less common in patients with type 2 than in those with type 1 myocardial infarction (7). Dyspnoea is a particularly challenging symptom in this context as it is common and has both ischemic and non-ischemic causes. Furthermore, patients with type 2 myocardial infarction usually have other symptoms due the condition triggering oxygen supply-demand imbalance, making it even more difficult to determine whether symptoms are caused by myocardial ischemia.

Second, while electrocardiographic findings of ST-segment elevation or depression strongly indicate an acute coronary event (such as type 1 or type 2 myocardial infarction due to coronary causes), other less-specific changes on the electrocardiogram (or no changes at all) are also common in both myocardial infarction and acute myocardial injury (8).

Third, elevation in circulating cardiac troponin is a prerequisite for the diagnosis of myocardial infarction. However, recent research has not only challenged the concept that elevation of cardiac troponin always represents cardiomyocyte death (9), but also that cardiac troponin elevation in the context of myocardial ischemia always represents necrosis (10). The introduction of high-sensitivity cardiac troponin assays has enabled earlier diagnosis (11), but has decreased the specificity of cardiac troponin for myocardial infarction (8). Furthermore, elevation in cardiac troponin is an inevitable consequence of cardiac surgery (12,13) and is common and often asymptomatic following coronary intervention (14). As such, the diagnostic threshold for myocardial infarction following coronary intervention and cardiac surgery is arbitrarily set at greater than 5- and 10-times the 99th percentile upper reference limit, respectively (4).

Fourth, it is not possible to distinguish type 1 from type 2 myocardial infarction due to dissection, spasm or embolism without performing coronary angiography. If angiography is not performed, patients with coronary causes of type 2 will almost certainly be classified incorrectly as type 1 myocardial infarction. Similarly, since coronary angiography is seldom performed in patients thought to have type 2 myocardial infarction (8, 15-17), an unknown proportion will actually have had a type 1 myocardial infarction.

Finally, in the current classification, evidence of imbalance between myocardial oxygen supply or demand is a prerequisite for a diagnosis of type 2 myocardial infarction, which means that an underlying trigger must be identified. Sometimes the trigger is obvious, but often the mechanism is unclear. The ischemic threshold will vary in relation to the duration and magnitude of supply-demand imbalance, and the extent and severity of underlying coronary artery disease (18). The current classification even allows for the diagnosis of type 2 myocardial infarction to be made in patients without coronary artery disease, despite this being the hallmark of acute myocardial infarction for more than a century (19) and one of the main determinants of long-term prognosis (20).

These uncertainties arise every day in clinical practice and have important consequences for patient care. Where there is diagnostic uncertainty, patients have worse outcomes (21). Many patients fulfilling the criteria for type 2 myocardial infarction are not classified as such in practice as the diagnosis is not considered important by some clinicians (22). Whilst there is a wealth of evidence to guide how patients with type 1 myocardial infarction should be managed, there is no evidence or agreement on how patients with type 2 myocardial infarction or acute myocardial injury should be managed and no studies demonstrating that recognition of these conditions has improved outcomes (23). The current classification is perceived by some as too complicated and has resulted in a lack of agreement even among experts. As such, the classification has been used and interpreted in different ways in the development of early diagnostic pathways (24-27) and in clinical trials of coronary revascularisation (28), making it difficult to compare findings between studies.

A new clinical classification of myocardial infarction

To address these uncertainties and encourage clinicians to recognise that there are different mechanisms of myocardial infarction with differing treatment implications, we propose a simplified clinical classification that recognises myocardial infarction can arise in three clinical settings: spontaneously, secondary to another acute condition, or as a procedural complication following percutaneous intervention or cardiac surgery (**Figure 1**). To increase adoption in practice we propose diagnostic criteria that are more specific, less reliant on symptoms and electrocardiographic changes, and more aligned with clinical practice (**Table 1**).

For the diagnosis of spontaneous myocardial infarction, the definition needs to be as sensitive as possible, as failure to recognise an acute coronary syndrome may delay the initiation of treatment resulting in a more substantial myocardial infarction with ventricular impairment or cardiac death in the community. In contrast, for secondary or procedural myocardial infarction, the diagnostic criteria should be more specific to minimise uncertainty, as cardiac troponin elevation is common in these settings. Here, the diagnosis of myocardial infarction should identify patients in whom there are clear treatment implications. The classification of type 3 myocardial infarction (per the current definition) would become obsolete. If a patient died suddenly from what was thought to be myocardial infarction prior to undergoing testing, this would be classified as spontaneous, secondary, or procedural myocardial infarction depending on the setting.

Spontaneous myocardial infarction

In patients with the spontaneous onset of symptoms or signs suspicious of myocardial ischemia, treatment is initiated on the assumption that atherothrombosis is the underlying mechanism — and in the majority, this assumption is correct. However, there are other

causes of spontaneous presentation with myocardial infarction, including coronary dissection, embolism, and vasospasm; or late stent thrombosis, restenosis and late graft failure in those with prior revascularisation (29). In practice, clinicians should be encouraged to identify the underlying coronary mechanism through angiography with or without adjunctive intravascular imaging, and to tailor subsequent treatment accordingly.

The terms ST-segment elevation and non-ST-segment elevation for spontaneous myocardial infarction will remain useful to stratify patients at presentation and to indicate the timing of coronary angiography. However, they are less useful to guide subsequent management than a classification identifying the underlying coronary mechanism, as proposed here. In some settings where the patient does not have ongoing symptoms or ST-segment elevation it may be reasonable to treat for atherothrombosis without performing coronary angiography, particularly if the risks of an invasive procedure are prohibitive or in healthcare settings where access is limited, and especially if there is a high clinical likelihood this is the underlying mechanism. In younger patients without traditional cardiovascular risk factors or in those with prior revascularisation, alternative coronary mechanisms of spontaneous myocardial infarction may be more likely and coronary angiography should be encouraged. Irrespective of the coronary mechanism, the definition of spontaneous myocardial infarction should prioritise sensitivity; therefore, clear symptoms or signs of myocardial ischemia with a rise and/or fall in cardiac troponin above the 99th percentile upper reference limit may be sufficient to make the diagnosis, and further imaging evidence of infarction may not be required. However, if no coronary mechanism is evident following coronary angiography, echocardiography or cardiac magnetic resonance imaging should be considered to clarify the diagnosis or identify alternative causes of the presentation and acute myocardial injury, such as takotsubo cardiomyopathy or myocarditis.

Secondary myocardial infarction

In patients with symptoms or signs that are suspicious of myocardial ischemia secondary to another acute illness resulting in myocardial oxygen supply-demand imbalance, the initial priority is to manage the acute illness. Cardiac troponin testing in acute illness identifies a substantial proportion of patients with myocardial injury of uncertain cause or significance (30). In this setting, specificity rather than sensitivity is important, and the diagnosis of secondary myocardial infarction is likely to be better accepted by clinicians and patients if injury was associated with functional consequences. The diagnosis of secondary myocardial infarction should require the identification of new loss of viable myocardium or a regional wall motion abnormality on echocardiography or cardiac magnetic resonance imaging. This is one of several possible criteria for a diagnosis of myocardial infarction in the existing universal definition (4), but it should be essential for the diagnosis of secondary myocardial infarction. The only exception would be where myocardial ischemia or myocardial injury in the context of another acute illness unmasks the presence of obstructive coronary artery disease on invasive or computed tomography coronary angiography (18, 31). In both these circumstances, the diagnosis of secondary myocardial infarction would have treatment implications as secondary prevention, medical therapy or coronary revascularisation may prevent recurrent symptoms and future cardiovascular events. However, most patients with supply-demand imbalance will have neither new loss of viable myocardium nor obstructive coronary artery disease. Here the term acute myocardial injury is a good description – similar to acute kidney or liver injury – with prognostic implications, which should stimulate further investigation but not be considered a definitive diagnosis.

Procedural myocardial infarction

Commented [KO1]: We reserve 'significant' for the statistical context; if this is not the case here, please rephrase (eg to 'substantial')

Commented [BL2R1]: ok

The use of more sensitive diagnostic criteria for procedural myocardial infarction proposed in the universal definition, has not been embraced by practitioners or applied in clinical trials of coronary revascularisation (6). In defining a procedural complication, specificity is more important than sensitivity. The diagnosis of myocardial infarction is appropriate in patients with an overt complication of coronary intervention or cardiac surgery, or in those where the complication is less obvious but new left ventricular impairment or loss of viable myocardium with a regional wall motion abnormality is identified. Coronary complications following percutaneous coronary intervention are usually self-evident, but following cardiac surgery, echocardiography to identify unrecognized procedural myocardial infarction should be systematically performed in the post-operative period. Procedural myocardial infarction defined in this way is important as it gives direct insight into the effectiveness of revascularisation and may have treatment implications. Acute or subacute stent thrombosis and early graft failure within 30 days are recognised complications of revascularization and should be classified as procedural myocardial infarction (32). In contrast, late stent or graft failure is often a consequence of *de novo* disease or non-compliance with anti-platelet therapy and therefore should be classified as spontaneous myocardial infarction rather than a procedural complication. Myocardial injury following a cardiac procedure has been associated with poor prognosis in some studies (12), and could be used to support the evaluation of quality of care, but alone it should not be considered a complication unless a coronary mechanism or new regional wall motion abnormality or ventricular impairment is identified on cardiac imaging.

Knowledge gaps and potential limitations

We acknowledge that further research is needed to evaluate the potential impact of this proposed new definition of myocardial infarction on patient care and healthcare utilisation.

This could take advantage of existing clinical datasets from well characterised patient populations to retrospectively compare the current classification with the proposed clinical classification. However, prospective studies will also be needed, in which cardiac imaging is performed systematically. Also, there are potential limitations of the proposed classification that merit consideration.

First, although the proposal aims to simplify the classification of myocardial infarction and remove the need for an alpha numeric subclassification that clinicians will not remember or apply, we recognise the importance of identifying the different coronary mechanisms of spontaneous myocardial infarction. The majority of patients with spontaneous myocardial infarction will have atherothrombosis and will receive a diagnosis of 'myocardial infarction due to atherothrombosis' or simply 'myocardial infarction' in practice. However, where spontaneous myocardial infarction is a consequence of an alternative coronary mechanism, the final diagnosis would identify this, for example 'myocardial infarction due to coronary embolism' or 'myocardial infarction due to late stent thrombosis'.

Second, we recognise that for a diagnosis of secondary myocardial infarction, it may be challenging to determine whether a regional wall motion abnormality on imaging is old or new. Where a patient is known to have coronary artery disease or previous myocardial infarction, then comparison with previous imaging may be helpful. Where there is no prior history, then the identification of any regional wall motion abnormality is important and would have therapeutic implications. Whilst often it is possible to differentiate an acute from chronic infarct pattern on echocardiography or magnetic resonance imaging (based on thinning of the myocardium or the presence of oedema), some clinical judgement will be required.

Third, by defining more specific and objective criteria for the diagnosis for secondary myocardial infarction, we do not wish to undermine the importance of recognising those with acute myocardial injury. We hope that our proposal will encourage the use of cardiac imaging in this setting and improve the care and outcomes of patients with and without secondary myocardial infarction. Whilst imaging may rule out secondary myocardial infarction, it could identify other important clinical diagnoses, such as heart failure or pulmonary embolism, or it could identify patients with unobstructive coronary artery disease in whom the use of secondary prevention may be beneficial.

Future directions

This proposal is based on new research and our clinical observations; however, we acknowledge that any change in practice will require a new international consensus as changes to the current universal definition would have important implications for clinicians, coders, researchers and clinical trialists. A new global task force will need to be convened with input from a broad range of stakeholders including both patients and practicing clinicians across a range of specialties, in addition to expertise in cardiac biomarkers, coronary intervention, cardiac surgery, clinical trials, and international registries. Greater diversity and wider representation are needed if we are to achieve consensus on the need for a more applied classification.

Once international consensus has been reached, it would be important to propose additional supplementary codes beyond the primary classification within the eleventh revision of the International Classification of Diseases (ICD-11). These supplementary codes would enable standard hospital coding for the different mechanisms of spontaneous myocardial infarction

(e.g., BA82 for coronary artery dissection, BA85 for coronary vasospasm and others), secondary myocardial infarction, and procedural myocardial infarction following percutaneous intervention and cardiac surgery. These should be published in parallel to the consensus statement and combined with educational initiatives, as well as a systematic evaluation of the impact of implementation of a new classification of myocardial infarction on patients and healthcare systems.

Conclusion

The classification of myocardial infarction is important for patients, practice, and research. We propose a new approach that prioritises sensitivity for patients with spontaneous coronary events, and specificity for those with oxygen supply-demand imbalance secondary to other conditions, or complications from coronary intervention or cardiac surgery. We argue that such an approach may encourage adoption in practice and improve patient care, and we encourage research and debate with the goal of a new international consensus.

Contributors

BL and NLM drafted and revised the manuscript critically for important intellectual content, provided approval of the final version to be published and are accountable for the work.

Acknowledgments

BL was a member of the Task Force for the Universal Definition of Myocardial Infarction. NLM is supported by a Chair Award (CH/F/21/90010), Programme Grant (RG/20/10/34966) and a Research Excellent Award (RE/18/5/34216) from the British Heart Foundation.

Declaration of interests

BL has no conflicts of interest to report. NLM reports research grants awarded to the University of Edinburgh from Abbott Diagnostics and Siemens Healthineers, and honoraria from Abbott Diagnostics, Siemens Healthineers, Roche Diagnostics and LumiraDx.

References

1. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. *Eur Heart J.* 2000; 21:1502–1513.
2. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller GA, Bonow R, Van der Wall EE, Bassand JP, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox KA, Hamm CW, Ohman EM, Simoons ML, Poole-Wilson PA, Gurfinkel EP, Lopez-Sendon JL, Pais P, Mendis S, Zhu JR, Wallentin LC, Fernández-Avilés F, Fox KM, Parkhomenko AN, Priori SG, Tendera M, Voipio-Pulkki LM, Vahanian A, Camm AJ, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Morais J, Brener S, Harrington R, Morrow D, Lim M, Martinez-Rios MA, Steinhubl S, Levine GN, Gibler WB, Goff D, Tubaro M, Dudek D, Al-Attar N. Universal definition of myocardial infarction. *Circulation*. 2007;116(22):2634-53.
3. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP,

Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Circulation*. 2012;126(16):2020-35.

4. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction. *Circulation.* 2018;138(20):e618-e651.
5. Gard A, Lindahl B, Batra G, Hjort M, Szummer K, Baron T. Diagnosing type 2 myocardial infarction in clinical routine. A validation study. *Scand Cardiovasc J.* 2019;53(5):259-265.
6. Gregson J, Stone GW, Ben-Yehuda O, Redfors B, Kandzari DE, Morice MC, Leon MB, Kosmidou I, Lembo NJ, Brown WM 3rd, Karmpaliotis D, Banning AP, Pomar J, Sabaté M, Simonton CA, Dressler O, Kappetein AP, Sabik JF 3rd, Serruys PW, Pocock SJ. Implications of Alternative Definitions of Peri-Procedural Myocardial Infarction After Coronary Revascularization. *J Am Coll Cardiol.* 2020;76(14):1609-1621.
7. Neumann JT, Sörensen NA, Rübsamen N, Ojeda F, Renné T, Qaderi V, Teltrop E, Kramer S, Quantius L, Zeller T, Karakas M, Blankenberg S, Westermann D. Discrimination of patients with type 2 myocardial infarction. *Eur Heart J.* 2017;38(47):3514-3520.
8. Chapman AR, Adamson PD, Shah ASV, Anand A, Strachan FE, Ferry AV, Lee KK, Berry C, Findlay I, Cruikshank A, Reid A, Gray A, Collinson PO, Apple F,

McAllister DA, Maguire D, Fox KAA, Vallejos CA, Keerie C, Weir CJ, Newby DE, Mills NL; High-STEACS Investigators. High-Sensitivity Cardiac Troponin and the Universal Definition of Myocardial Infarction. *Circulation.* 2020;141(3):161-171.

9. Hammarsten O, Mair J, Möckel M, Lindahl B, Jaffe AS. Possible mechanisms behind cardiac troponin elevations. *Biomarkers.* 2018;23(8):725-734.
10. Árnadóttir A, Pedersen S, Hasselbalch RB, Goetze JP, Friis-Hansen LJ, Bloch-Münster A, Jensen JS, Bundgaard H, Iversen K. Temporal release of high-sensitivity cardiac troponin T and I and copeptin after brief induced coronary artery balloon occlusion in humans. *Circulation*. 2021;143(11):1095-1104.
11. Shah AS, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD, Chapman AR, Langdon T, Sandeman D, Vaswani A, Strachan FE, Ferry A, Stirzaker AG, Reid A, Gray AJ, Collinson PO, McAllister DA, Apple FS, Newby DE, Mills NL; High-STEACS investigators. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. *Lancet.* 2015;386(10012):2481-8.
12. Devereaux PJ, Lamy A, Chan MTV, Allard RV, Lomivorotov VV, Landoni G, Zheng H, Paparella D, McGillion MH, Belley-Côté EP, Parlow JL, Underwood MJ, Wang CY, Dvirnik N, Abubakirov M, Fominskiy E, Choi S, Fremes S, Monaco F, Urrútia G, Maestre M, Hajjar LA, Hillis GS, Mills NL, Margari V, Mills JD, Billing JS, Methangkool E, Polanczyk CA, Sant'Anna R, Shukevich D, Conen D, Kavsak PA, McQueen MJ, Brady K, Spence J, Le Manach Y, Mian R, Lee SF, Bangdiwala SI, Hussain S, Borges FK, Pettit S, Vincent J, Guyatt GH, Yusuf S, Alpert JS, White HD, Whitlock RP; VISION Cardiac Surgery Investigators. High-Sensitivity Troponin I after Cardiac Surgery and 30-Day Mortality. *N Engl J Med.* 2022;386(9):827-836.

13. Hinton J, Augustine M, Gabara L, Mariathas M, Allan R, Borca F, Nicholas Z, Ikwuobe J, Gillett N, Kwok CS, Cook P, Grocott MPW, Mamas M, Curzen N. Incidence and 1-year outcome of periprocedural myocardial infarction following cardiac surgery: are the Universal Definition and Society for Cardiovascular Angiography and Intervention criteria fit for purpose? *Eur J Cardiothorac Surg.* 2022;62(2):ezac019
14. Zeitouni M, Silvain J, Guedeney P, Kerneis M, Yan Y, Overtchouk P, Barthelemy O, Hauguel-Moreau M, Choussat R, Helft G, Le Feuvre C, Collet JP, Montalescot G; ACTION Study Group. Periprocedural myocardial infarction and injury in elective coronary stenting. *Eur Heart J.* 2018;39(13):1100-1109.
15. Saaby L, Poulsen TS, Hosbond S, Larsen TB, Pyndt Diederichsen AC, Hallas J, Thygesen K, Mickley H. Classification of myocardial infarction: frequency and features of type 2 myocardial infarction. *Am J Med.* 2013;126(9):789-97.
16. McCarthy CP, Kolte D, Kennedy KF, Vaduganathan M, Wasfy JH, Januzzi JL Jr. Patient Characteristics and Clinical Outcomes of Type 1 Versus Type 2 Myocardial Infarction. *J Am Coll Cardiol.* 2021;77(7):848-857.
17. Eggers KM, Baron T, Chapman AR, Gard A, Lindahl B. Management and outcome trends in type 2 myocardial infarction: an investigation from the SWEDEHEART registry. *Sci Rep.* 2023;13(1):7194.
18. Bularga A, Hung J, Daghem M, Stewart S, Taggart C, Wereski R, Singh T, Meah MN, Fujisawa T, Ferry AV, Chiong J, Jenkins WS, Strachan FE, Semple S, van Beek EJR, Williams M, Dey D, Tuck C, Baker AH, Newby DE, Dweck MR, Mills NL, Chapman AR. Coronary Artery and Cardiac Disease in Patients with Type 2 Myocardial Infarction: A Prospective Cohort Study. *Circulation.* 2022;145(16):1188-1200.

19. Herrick, JB. Certain clinical features of sudden obstruction of the coronary arteries. *JAMA*. 1912; 59:2015-2020.
20. Chapman AR, Shah ASV, Lee KK, Anand A, Francis O, Adamson P, McAllister DA, Strachan FE, Newby DE, Mills NL. Long-term outcomes in patients with type 2 myocardial infarction and myocardial injury. *Circulation.* 2018;137(12):1236-1245.
21. Sepehrvand N, Zheng Y, Armstrong PW, Welsh R, Goodman SG, Tymchak W, Khadour F, Chan M, Weiss D, Ezekowitz JA. Alignment of site versus adjudication committee-based diagnosis with patient outcomes: Insights from the Providing Rapid Out of Hospital Acute Cardiovascular Treatment 3 trial. *Clin Trials.* 2016;13(2):140-8.
22. Gard A, Lindahl B, Baron T. Impact of clinical diagnosis of myocardial infarction in patients with elevated cardiac troponin. *Heart.* 2023 May 22: heartjnl-2022-322298.
23. DeFilippis AP, Chapman AR, Mills NL, de Lemos JA, Arbab-Zadeh A, Newby LK, Morrow DA. Assessment and Treatment of Patients with Type 2 Myocardial Infarction and Acute Nonischemic Myocardial Injury. *Circulation.* 2019;140(20):1661-1678.
24. Mueller C, Giannitsis E, Christ M, Ordóñez-Llanos J, deFilippi C, McCord J, Body R, Panteghini M, Jernberg T, Plebani M, Verschuren F, French J, Christenson R, Weiser S, Bendig G, Dilba P, Lindahl B; TRAPID-AMI Investigators. Multicenter Evaluation of a 0-Hour/1-Hour Algorithm in the Diagnosis of Myocardial Infarction With High-Sensitivity Cardiac Troponin T. *Ann Emerg Med.* 2016;68(1):76-87.e4
25. Ljung L, Lindahl B, Eggers KM, Frick M, Linder R, Löfmark HB, Martinsson A, Melki D, Sarkar N, Svensson P, Jernberg T. A Rule-Out Strategy Based on High-Sensitivity Troponin and HEART Score Reduces Hospital Admissions. *Ann Emerg Med.* 2019;73(5):491-499.

26. Anand A, Lee KK, Chapman AR, Ferry AV, Adamson PD, Strachan FE, Berry C, Findlay I, Cruikshank A, Reid A, Collinson PO, Apple FS, McAllister DA, Maguire D, Fox KAA, Newby DE, Tuck C, Harkess R, Keerie C, Weir CJ, Parker RA, Gray A, Shah ASV, Mills NL; HiSTORIC Investigators. High-Sensitivity Cardiac Troponin on Presentation to Rule Out Myocardial Infarction: A Stepped-Wedge Cluster Randomized Controlled Trial. *Circulation.* 2021;143(23):2214-2224.
27. Doudesis D, Lee KK, Boeddinghaus J, Bularga A, Ferry AV, Tuck C, Lowry MTH, Lopez-Ayala P, Nestelberger T, Koechlin L, Bernabeu MO, Neubeck L, Anand A, Schulz K, Apple FS, Parsonage W, Greenslade JH, Cullen L, Pickering JW, Than MP, Gray A, Mueller C, Mills NL; CoDE-ACS Investigators. Machine learning for diagnosis of myocardial infarction using cardiac troponin concentrations. *Nat Med.* 2023;29(5):1201-1210.
28. Spitzer E, McFadden E, Vranckx P, Garcia-Garcia HM, Seltzer JH, Held C, de Vries T, Menon V, Brown KJ, Soliman OII, Onuma Y, Lopes RD, Stone GW, Cutlip DE, Serruys PW. Critical Appraisal of Contemporary Clinical Endpoint Definitions in Coronary Intervention Trials: A Guidance Document. *JACC Cardiovasc Interv.* 2019;12(9):805-819.
29. de Lemos JA, Newby LK, Mills NL. A Proposal for Modest Revision of the Definition of Type 1 and Type 2 Myocardial Infarction. *Circulation.* 2019;140(22):1773-1775.
30. Lee KK, Noaman A, Vaswani A, Gibbins M, Griffiths M, Chapman AR, Strachan F, Anand A, McAllister DA, Newby DE, Gray AJ, Mills NL, Shah ASV. Prevalence, Determinants, and Clinical Associations of High-Sensitivity Cardiac Troponin in Patients Attending Emergency Departments. *Am J Med.* 2019;132(1): 110.e8-110.e21.

31. Baron T, Hambraeus K, Sundström J, Erlinge D, Jernberg T, Lindahl B; TOTAL-AMI study group. Impact on Long-Term Mortality of Presence of Obstructive Coronary Artery Disease and Classification of Myocardial Infarction. *Am J Med.* 2016;129(4):398-406.

32. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel MA, van Es GA, Zuckerman B, Fearon WF, Taggart D, Kappetein AP, Krucoff MW, Vranckx P, Windecker S, Cutlip D, Serruys PW; Academic Research Consortium. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. *Circulation.* 2018;137(24):2635-2650.

Box 1. The current standard: Universal definition of myocardial infarction.

The diagnosis requires a rise and/or fall in cardiac troponin with at least one value above the 99th percentile upper reference limit and any one of the following: symptoms of myocardial ischemia, new ischemic changes on the electrocardiogram, imaging evidence of new loss of viable myocardium or the identification of thrombosis on coronary angiography.

Type 1 myocardial infarction is limited to patients with coronary atherothrombosis and is specified when plaque rupture or erosion results in partial or complete coronary occlusion, myocardial ischemia and necrosis. Type 2 myocardial infarction identifies patients where myocardial ischemia and necrosis occur as a consequence of an imbalance between myocardial oxygen supply or demand unrelated to coronary atherothrombosis. Type 3 myocardial infarction is defined as cardiac death where myocardial infarction is the likely cause, but the death occurred before diagnostic testing could be performed. The classification was further updated in the third and fourth iterations (3-4), introducing additional subgroups following percutaneous coronary intervention (type 4 a), stent or scaffold thrombosis (type 4b) or in-stent restenosis (type 4c), and to refine the criteria for myocardial infarction following cardiac surgery (type 5).

Table. Diagnostic Criteria for the Universal Definition and the Proposed Clinical Classification of Myocardial Infarction

Universal Definition	Proposed Clinical Definition	Rationale for change
Type 1 myocardial infarction Sensitivity prioritised, with the diagnosis based on a rise and or fall in cardiac troponin above the 99th percentile with symptoms or signs of myocardial ischemia. Restricted to coronary atherothrombosis	**Spontaneous myocardial infarction** Sensitivity prioritised, with the diagnosis based on a rise and or fall in cardiac troponin above the 99th percentile with symptoms or signs of myocardial ischemia. Criteria broadened to include all acute coronary events: atherothrombosis, embolism, vasospasm, in-stent restenosis, late stent thrombosis and late graft failure.	Sensitivity is important to minimise the risk of misdiagnosis of all acute coronary mechanisms of myocardial infarction, not just those due to atherothrombosis. Late stent and graft failure are often spontaneous due to *de novo* disease rather than procedural complications.
Type 2 myocardial infarction Sensitivity prioritised, with the diagnosis based on a rise and or fall in cardiac troponin above the 99th percentile with symptoms or signs of myocardial ischemia. Documentation of myocardial oxygen supply or demand imbalance is required, which includes spontaneous coronary dissection, embolism, and vasospasm, and those with other conditions without coronary artery disease.	**Secondary myocardial infarction** Specificity prioritised, with the diagnosis based on loss of viable myocardium or new regional wall motion abnormality, or the presence of obstructive coronary artery disease. Can occur in any acute illness where myocardial oxygen supply or demand imbalance could arise, but must have a functional consequence or unmask obstructive coronary artery disease.	Symptoms and signs of myocardial ischemia are challenging to differentiate from those due to a primary condition. Myocardial injury is common and may be caused by many different mechanisms. Diagnostic criteria should be more specific to minimise uncertainty and identify patients in whom the diagnosis has clear treatment implications.

Type 3 myocardial infarction Cardiac death where myocardial infarction is the likely cause, but death occurs before diagnostic testing is performed.	No longer required.	No utility in clinical practice and death from myocardial infarction can occur due to multiple mechanisms prior to testing.
Type 4 a-c myocardial infarction Type 4a is based on an arbitrary elevation in cardiac troponin greater than 5-times the 99th percentile if there are signs of myocardial ischemia, imaging evidence of new loss of viable myocardium or angiographic evidence of a procedural complication within 48 hours. Type 4b due to stent thrombosis and type 4c due to restenosis can occur any time after the procedure. The same diagnostic criteria are applied as for type 1 myocardial infarction.	**Procedural myocardial infarction** Specificity prioritised, with diagnosis requiring angiographic evidence of a complication of coronary intervention or cardiac surgery and new left ventricular impairment, loss of viable myocardium or a regional wall motion abnormality. Definition broadened to include any stent or graft failure within 30 days of the procedure.	Cardiac troponin thresholds not evidence based and testing not performed in clinical practice following coronary intervention or cardiac surgery. Captures all clinically important failure of coronary revascularisation within 30 days. Late stent or graft failure not considered complications of revascularisation.
Type 5 myocardial infarction Diagnosis based on an arbitrary elevation in cardiac troponin concentration greater than 10-times the 99th percentile if new pathological Q-waves, imaging evidence of new loss of viable myocardium OR angiographic evidence of a graft occlusion within 48 hours.		Addresses inconsistencies between the criteria for diagnosing myocardial infarction following coronary intervention and cardiac surgery, allowing a fairer comparison of outcomes between approaches.

489

Figure legend

Figure 1. Proposal for a clinical classification of acute myocardial infarction

(A) Spontaneous myocardial infarction: whilst the initial impression is often confirmed following coronary angiography or echocardiography, other conditions can present similarly. If no coronary mechanism is evident, echocardiography or cardiac magnetic resonance imaging may be required to identify alternative causes of acute myocardial injury, such as takotsubo cardiomyopathy or myocarditis. (B) Secondary myocardial infarction: the diagnosis of secondary myocardial infarction due to an alternative condition requires evidence of a new regional wall motion abnormality or left ventricular impairment on echocardiography, or evidence of loss of viable myocardium on magnetic resonance imaging, or the presence of obstructive coronary artery disease on invasive or computed tomography coronary angiography. Patients with acute myocardial injury in this setting for whom secondary myocardial infarction is thought unlikely or has been excluded, may benefit from cardiac imaging to identify other non-ischemic structural heart diseases unmasked by acute illness. (C) Procedural myocardial infarction: Coronary complications following percutaneous coronary intervention are usually self-evident, but following cardiac surgery routine echocardiography to recognise asymptomatic procedural myocardial infarction should be performed in the post-operative period.