Early Diagnosis of Acute Coronary Syndrome

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Abstract

The diagnostic evaluation of acute chest pain has been augmented in recent years by advances in the sensitivity and precision of cardiac troponin assays, new biomarkers, improvements in imaging modalities, and release of new clinical decision algorithms. This progress has enabled physicians to diagnose or rule-out acute myocardial infarction earlier after the initial patient presentation, usually in emergency department settings, which may facilitate prompt initiation of evidence-based treatments, investigation of alternative diagnoses for chest pain, or discharge, and permit better utilization of healthcare resources. A non-trivial proportion of patients fall in an indeterminate category according to rule-out algorithms, and minimal evidence-based guidance exists for the optimal evaluation, monitoring, and treatment of these patients. The Cardiovascular Round Table of the ESC proposes approaches for the optimal application of early strategies in clinical practice to improve patient care following the review of recent advances in the early diagnosis of acute coronary syndrome. The following specific "indeterminate" patient categories were considered: 1) patients with symptoms and high-sensitivity cardiac troponin <99th percentile; 2) patients with symptoms and high-sensitivity troponin <99th percentile but above the limit of detection; 3) patients with symptoms and high-sensitivity troponin >99th percentile but without dynamic change; and 4) patients with symptoms and high-sensitivity troponin >99th percentile and dynamic change but without coronary plaque rupture/erosion/dissection. Definitive evidence is currently lacking to manage these patients whose early diagnosis is "indeterminate" and these areas of uncertainty should be assigned a high priority for research.

INTRODUCTION

The diagnostic evaluation of acute chest pain has been augmented in recent years by advances in the sensitivity and precision of cardiac troponin (cTn) assays,[1] improvements in imaging modalities, and release of new clinical decision algorithms.[2-7] This progress has enabled physicians to diagnose or rule-out acute myocardial infarction (AMI) earlier after the initial presentation of patients in the emergency department with symptoms related to possible acute ischemia, which may facilitate prompt initiation of evidence-based treatments, investigation of alternative diagnoses for chest pain, or discharge, and permit better utilization of healthcare resources.[5;8] It is also important to note that these protocols have not been evaluated in other hospitalized patient subsets (e.g., possible post-operative myocardial infarction, the critically ill, renal failure); thus, the scope of this manuscript is limited to emergency or acute care settings.

These advances have also introduced some challenges and opportunities.[9] First, in addition to an earlier diagnosis, high sensitivity cardiac troponin (hs-cTn) assays also detect lower levels of circulating cTn, which has generated important discussions about the thresholds that should be implemented to identify myocardial necrosis, injury, or unstable angina, and to inform prognosis and treatment pathways or discharge decisions. Second, several rule-out algorithms have been proposed and validated,[3;10-15] three of which are recommended for use in the European Society of Cardiology (ESC) guideline for non-ST-elevation myocardial infarction (NSTEMI).[4] Uncertainties remain about applying the algorithms to a broader population with possible AMI (e.g., patients with atypical symptoms, or early or late presenters).[2] Applying these algorithms in this population, half of patients (40-60%) fall into the rule-out category, and thus into a group that potentially qualifies for earlier discharge after risk assessment. However, a non-trivial proportion of patients (up to 44%)[2;3;12] fall in an indeterminate category, and minimal

evidence-based guidance exists for the optimal evaluation, monitoring, and treatment of these patients. Third, the advent of hs-cTn assays has shortened the timeline between symptom onset and interpretable biomarker results. Thus, non-cardiologists (e.g., emergency department physicians or general practitioners) are increasingly engaged in making triage decisions based on rapid algorithms, but in general, these clinicians ask for guidance as they have not been involved in data collection or algorithm development. In addition, the recent ESC guidelines on non-ST-elevation acute coronary syndrome (NSTE-ACS) encourage the use of copeptin in combination with cTn specifically when no hs-cTn is available as an alternative strategy for rapid rule out. This recommendation is based on one randomized study and a meta-analysis.[4;16] Finally, cost-effectiveness is an important consideration, and it is necessary to demonstrate that the rapid diagnosis or rule-out of MI improves patient outcome, impacts the appropriate use of non-invasive or invasive testing, and promotes efficient resource utilization in the emergency setting.

The Cardiovascular Round Table (CRT) of the ESC convened a dedicated two-day workshop (16-17 June 2016) to discuss advances in the early diagnosis of acute coronary syndrome (ACS) and the optimal application of early strategies in clinical practice to improve patient care. This paper summarizes the key outputs from the workshop and provides an overview on current diagnostic strategies in early ACS, indicates the challenges in acute care that have arisen from the application of these highly sensitive tools, and identifies opportunities to enhance precision in acute care.

HIGH SENSITIVITY CARDIAC TROPONIN IN THE EARLY DIAGNOSIS OF ACUTE CORONARY SYNDROME

High sensitivity cTn assays are capable of measuring cTn above the level of detection and below the 99th percentile upper reference limit (URL) in at least 50% of a reference population, with low imprecision (i.e., coefficient of variation [CV] ≤10% at the 99th percentile URL).[1;17] The introduction of hs-cTn assays has enabled the rapid diagnosis (dynamic elevation above the 99th percentile URL[4]) or rule-out of MI, typically in emergency department or other acute care settings, and it minimizes the need for prolonged (i.e., over 9 hours) repeat cTn measurements for many patients. High-sensitive assays have better precision at the 99th percentile URL than earlier generation assays, which facilitates earlier detection of myocardial injury and permits reliable evaluation of cTn kinetics.

However, several clinical controversies have followed the introduction of hs-cTn assays, which have been reviewed in depth elsewhere.[1;5;17;18] It is outside the scope of this manuscript to comprehensively revisit these issues, but the primary concerns involve the clinical translation of hs-cTn results in the context of assay characteristics. The interpretation of mildly elevated hs-cTn can be challenging, especially for hs-cTn I, since the 99th percentile varies depending on the specific assay used.[3;19] Additionally, manufacturer reported characteristics (i.e., the 99th percentile and the associated CV) have not been consistently replicated in clinical studies.[7] The composition of the reference population is also of key importance, including the impact of different gender reference ranges, but the process for defining "normal" has been inconsistent across manufacturers.[1] The selected "normal" population influences the 99th percentile reference value;[20] thus, it is recommended that studies aiming to identify the 99th percentile value should use specific criteria to define the population (e.g., age, estimated glomerular filtration rate [eGFR], natriuretic peptide [BNP or NT-proBNP] cut-off values, and health questionnaires).[20] Only two of the rapid rule-out algorithms include hs-cTn change criteria,[3] but a dynamic rise and

fall pattern is an important factor for differentiating between acute and chronic myocardial injury.[6;17;21]

APPLICATION OF EARLY DIAGNOSTIC STRATEGIES IN ACUTE MYOCARDIAL INFARCTION

Physicians caring for patients with acute chest pain are tasked with making a diagnosis, evaluating a patient's risk level, and selecting the correct treatment or assessing a patient's readiness for discharge. It is important to recognize that non-cardiologists in emergency departments are often responsible for this triage. In patients with suspected myocardial ischemia, very high baseline hs-cTn concentrations or large concentration changes (i.e. ≥5 ng/L at 1 hour for hs-cTnT) in conjunction with clinical evidence as required by the universal definition[4] qualify for ruling in an MI. It should be noted that in the TRAPID-AMI (High Sensitivity Cardiac Troponin T Assay for Rapid Rule-out of Acute Myocardial Infarction) study, the positive predictive value of the hs-cTnT 0-hour/1-hour algorithm for rule-in MI was 77.2%;[22] other common diagnoses meeting rule-in criteria were myocarditis, unstable angina, takotsubo cardiomyopathy, heart failure, arrhythmia, and symptoms of unknown origin.[22] Aortic dissection or pulmonary embolism are other potential differential diagnoses. Patients who meet rule-in criteria should undergo invasive coronary angiography according to the ESC NSTEMI guideline.[4] While some patients who rule-in will not have MI but other diagnoses as above, coronary angiography is usually still needed for accurate diagnosis of these conditions.[4] In specific cases, clinicians may use their clinical judgment not to proceed with angiography if the potential risks of the procedure outweigh the diagnostic benefits or if alternative diagnoses can be made with certainty by other means. When angiography reveals non-obstructive

atherosclerosis or angiographically normal coronary arteries, further evaluation of MI with non-obstructive coronary arteries (MINOCA) is indicated and may include additional invasive investigation, laboratory assays to identify potential causes of type-2 MI, echocardiography, cardiac magnetic resonance imaging, transesophageal echocardiography, or consideration of other diagnoses (e.g., dissection, Takotsubo cardiomyopathy, coronary vasospasm, myocarditis, cardioembolism).[23]

Importantly, a second blood draw is not always required in a patient with clearly elevated hs-cTn (>5 times the 99th percentile of the upper reference limit)[4] and typical clinical and electrocardiogram changes, as serial concentration changes do not improve the already high pre-test probability for an MI;[24] therefore, patients should be referred for acute management according to ESC guidelines.[4;25] For other patient presentations, the diagnosis may be less clear. The ESC-CRT workshop participants proposed approaches that could be considered for the clinical evaluation of these patients, most of whom will present to the emergency department (Table 1, Figure 1). The participants acknowledge that definitive evidence is currently lacking and emphasize the need to set a high priority for research in these areas.

Patients with Symptoms and High Sensitivity Cardiac Troponin <99th Percentile and Below the Limit of Detection

Patients falling within this category are generally considered to be low risk,[2] and they have been proposed as candidates for early discharge from the emergency department.[2] However, such decisions can be premature leading to the fact that many such patients might not get the needed clinical care and medical treatment. Patients with unstable angina can fall into this category (i.e., symptoms and hs-cTn <99th percentile), since the diagnosis of unstable angina

generally requires anginal symptoms without evidence of cardiomyocyte necrosis.[6] Thus, decisions to proceed with early discharge should include consideration of hs-cTn levels in conjunction with other clinical parameters (e.g., electrocardiogram, symptoms, risk factors, non-cardiac etiology for symptoms). Risk scores may also be helpful to assess prognosis and to guide clinical and therapeutic decision making[26] (e.g., Thrombolysis in Myocardial Infarction [TIMI],[27] Global Registry of Acute Coronary Events [GRACE],[28-31] or History, Electrocardiogram, Age, Risk Factors, Troponin [HEART][32-34]). The HEART score was developed in patients presenting to the emergency department with chest pain.[32-34] Use of the HEART score in conjunction with cTn reduced cardiac testing within 30 days, shortened length of hospital stays, and increased early discharge compared to guideline-directed usual care in patients presenting to the emergency department with ACS symptoms.[35] Patients with negative serial hs-cTn below the limit of detection and a low-risk HEART score (or GRACE score) may be considered for discharge, whereas patients with negative serial hs-cTn below the limit of detection and a high-risk HEART score may be considered for admission to an observational unit, cardiac imaging, or stress testing. However, it is acknowledged that a prospective, randomized trial is needed to test a specific strategy. Such evidence coming from the randomized interventional Biomarkers in Cardiology (BIC)-8 trial is currently only available for an instant rule-out strategy in the presence of normal cTn concentration using a contemporary sensitive or hs-cTn assay in combination with a normal copeptin (CT-pro-vasopressin) value.[16] A cluster randomized trial using the GRACE score is underway in Australia (AGRIS)[36] and in the United Kingdom (UKGRIS, ISRCTN registry number 29731761)[37].

Patients with Symptoms and High Sensitivity Troponin <99th Percentile but Above the Limit of Detection

Patients with hs-cTn results in this category may be considered higher risk than patients with hs-cTn below the 99th percentile and below the limit of detection, since any elevation in cTn yields prognostic information.[38] Patients with elevated hs-cTnI above a cut-off value (≥6 ng/L) (ARCHITECT i2000SR, Abbott Diagnostics, 99th percentile 27 ng/L) in the Biomarkers in Acute Cardiac Care (BACC) study but without dynamic change had a higher 12-month mortality (8.2%) than patients who ruled-out (1%) or ruled-in (6.7%) for NSTEMI.[12] Similar findings were observed for a cut-off value of 5 ng/L in a large prospective cohort in Scotland, strengthening the generalizability of this approach to risk stratification.[39;40]

Consensus has not yet been achieved with regard to whether the limit of detection or the limit of blank should be used for interpretation of hs-cTn results. The limit of blank is the highest cTn concentration that is measured when a sample containing no cTn is tested, whereas the limit of detection is the lowest detectable cTn concentration that can be measured in a sample containing a low amount of cTn and can be distinguished from the limit of blank.[5] hs-cTnT levels between the limit of blank and limit of detection are associated with a higher prevalence of cardiovascular risk factors, cardiac pathology, and worse prognosis.[41] However, the imprecision of measurements at low levels (i.e., the limit of blank) is too great for clinical application. Reporting both limit of blank and limit of detection concentrations for hs-cTn and determining which limits are most informative for risk stratification, determining prognosis, and guiding treatment decisions should be research priorities. Determining the correlation between risk scores and hs-cTn concentrations at the limit of blank or limit of detection may also help clarify the relevance of using these low levels of hs-cTn.

The presence or absence of some patient characteristics should be taken into account in the interpretation of hs-cTn (e.g., renal impairment, atrial fibrillation, cardiac decompensation, advanced age, female gender, comorbidities, early and late presentation). It is therefore critical to assess the clinical presentation, history, and electrocardiogram, as well as serial hs-cTn measurements to evaluate cTn kinetics. Although thresholds of hs-cTn change to rule-in have been proposed,[13;42] they are assay specific[2] and the optimal threshold changes have not been determined.[43] Additionally, application of change values may be limited in patients with low baseline hs-cTn values because of greater imprecision at low levels.[44] Risk scores as described above should also be applied in this clinical scenario. Other biomarkers may provide additional information about a patient's potential risk, particularly natriuretic peptides (e.g., N-terminal pro-B-type natriuretic peptide [NT-proBNP]) and to some extent also copeptin and growth differentiation factor-15 (GDF-15), as recommended in the ESC guidelines.[3;4]

Patients in this category may be appropriate candidates for early implementation of imaging strategies.[45] Non-invasive imaging modalities (e.g., transthoracic, contrast, and/or stress echocardiography, cardiac magnetic resonance, nuclear myocardial perfusion, multi-detector computed tomography) to evaluate cardiac function, perfusion, and anatomy are recommended by current guidelines.[4] Echocardiography is the most commonly used imaging modality, and although it cannot rule-out ACS, it can be helpful to exclude other disease and support the ACS diagnosis. Coronary computed tomography angiography (coronary CTA) provides high and isotropic spatial resolution, and robust visualization of the coronary arteries. It has a high sensitivity to detect stenosis; thus, a normal scan is extremely reliable to exclude stenosis, with a negative likelihood ratio of 0.022 in a meta-analysis of 30 studies representing 3422 patients.[46] As reviewed in the ESC guideline, outcomes are comparable for patients assessed with coronary

CTA versus standard care, but coronary CTA is associated with lower costs and shorter length of stay.[4] Thus, coronary CTA "should be considered as an alternative to invasive angiography to exclude ACS when there is a low to intermediate likelihood of coronary artery disease and when cTn and/or electrocardiograms are inconclusive" (Class IIa, Level of Evidence A).[4] However, the guideline acknowledges that none of the studies supporting the recommendation used hs-cTn assays. In the open-label, randomized Better Evaluation of Acute Chest Pain with Coronary Computed Tomography Angiography (BEACON) trial, coronary CTA performed early (after the initial work-up) had similar rates of 30-day coronary revascularization and discharge from the emergency department, as well as length of stay compared to standard of care that included hs-cTn testing.[47] Direct medical costs and the proportion of patients with outpatient testing were lower in the coronary CTA group compared to standard of care.[47] In a retrospective analysis of data from the ROMICAT II (Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography) trial, coronary CTA had a negative predictive value of 100% for ACS in patients with measurable but not elevated hs-cTnI and no evidence of significant stenosis or high risk plaque on coronary CTA.[45] The rate of ACS was 69% in those patients with measurable but not elevated hs-cTnI and significant stenosis or high risk plaque on coronary CTA.[45] The application of both hs-cTnI and coronary CTA in this retrospective analysis could have resulted in discharge for 60% of patients (i.e., with hs-cTnI below the limit of detection and negative coronary CTA) and triage of 16% of patients to receive early appropriate therapies (i.e., hs-cTnI >99th percentile or positive coronary CTA).[45] Whether coronary CTA can be useful in the early evaluation of ACS depends on its timely availability, both of equipment and appropriate technical expertise to obtain quality images. Cardiac magnetic resonance (CMR) imaging is a guideline recommended strategy to assess perfusion and wall motion abnormalities, as well as

the presence of myocardial edema in acute myocardial infarction as well as necrotic and scarred myocardium.[48] CMR can well distinguish chest pain due to ACS from that of other causes.[4] While the clinical utility in emergency settings may be hampered by a limited local access to an MRI scanner and trained personnel, it can reliably diagnosis acute coronary syndrome[49] and can even reduce the cost of the diagnostic workup.[50] CMR is especially useful in patients with suspected acute myocardial injury due to myocarditis[51] or stress-induced cardiomyopathies,[52] and in patients with MINOCA.[23;53;54]

Patients with Symptoms and High Sensitivity Troponin >99th Percentile Without Dynamic Change

The clinical history should be carefully reviewed for patients presenting with hs-cTn above the 99th percentile but without dynamic changes to estimate the onset of symptoms and to allow for assessment of whether the patient may be an early or late presenter, since early presenters may have had insufficient time to exhibit change and 10% to 26% of patients with MI may not demonstrate delta cTn criteria possibly because they present late during the cTn plateau phase.[55;56] Risk scores may also be helpful in the evaluation of these patients.[26] Repeat hs-cTn testing should be performed in early presenters according to guideline recommended algorithms.[4] Late presenters with high-risk scores may warrant more aggressive evaluation, either with imaging or angiography, depending on the clinical assessment and risk level. In high-risk patients, there is no reasonable alternative to angiography.

Patients in whom an early or late presentation has been excluded should be evaluated for other causes of cTn release (e.g., heart failure, renal impairment, pulmonary embolism, arrhythmia, valvular disease, shock, anemia, hypertension, defibrillator shocks, contusion,

myocarditis, cardiotoxic agents[57;58]). Recent publications suggest that these presentations do not necessarily represent MI, but rather, stable myocardial injury.[6] Specific diagnostic criteria and evidence based treatment guidelines are absent for this group of patients. Thus, until evidence specific for this presentation are available, these patients should undergo further testing and treatment appropriate for the underlying cause, recognizing that cTn release, even if not diagnostic for ACS, is associated with greater risk for poor outcomes.[4;59;60] Crude mortality in these patients is high,[12] but mortality seems to be related to comorbidities rather than ACS events. Unstable angina could also be a factor in these patients who have chronically elevated cTn for other reasons (i.e., chronic heart failure, renal impairment) if they have symptoms consistent with unstable angina and no dynamic change patterns. Imaging strategies as described above may be particularly relevant in patients with hs-cTn values above the 99th percentile that are indeterminate for a NSTEMI diagnosis.

Patients with Symptoms and High Sensitivity Troponin >99th Percentile and Dynamic Change but without Coronary Plaque Rupture/Erosion/Dissection

These patients with type 2 MI fulfill the diagnostic criteria of MI but share a different pathophysiologic mechanism than type 1 MI, which is characterized by plaque rupture, erosion or dissection.[57] Type 2 MI is thought to result from an imbalance between oxygen supply and demand, regardless of the presence or absence of an obstructive coronary lesion.[57] Differentiation of patients with plaque erosion, thrombus development, and micro-embolisation may be difficult or impossible without invasive advanced imaging (for example OCT) and such patients may have apparently trivial or no coronary obstructive disease, yet they could have suffered a type 1 MI. The prevalence of type 2 MI varies widely across studies according to the

heterogeneity of definitions.[61] Although there are several differences regarding baseline characteristics of patients and troponin kinetics, prospective differentiation of type 2 from type 1 MI is almost impossible without knowledge of coronary anatomy.[62] However, differentiation is important as type 2 MI is associated with mortality rates at least as high as encountered with type 1 MI.[63;64] In addition, sparse data are available on the appropriate pharmacological treatment, particularly the balance between bleeding risk and benefits.

CONCLUSION

The availability of highly sensitive and precise tools for the diagnosis of AMI has the potential to improve patient care by facilitating faster diagnosis and implementation of evidence-based therapies or interventions. It may also benefit non-ACS patients by quickly ruling out MI, allowing physicians to confidently discharge patients from the emergency department, pursue other diagnoses for chest pain, or appropriately redirect limited resources in the emergency setting. However, careful inspection of cTn based rapid algorithms brings attention to the evidence gaps, where the diagnosis remains inconclusive for a substantial proportion (up to 44%) of patients; additional strategies are needed for this group. The only strategy tested in a randomized, prospective study is the combination of cTn and copeptin with limited evidence for the use of hsTn assays. These areas of uncertainty should be assigned a high priority for research. As the field advances, evidence on cost-effectiveness must also be generated to inform optimal implementation of early detection strategies. Use of early diagnostic tools that lead to uncertainty, and therefore use of unnecessary tests, will not be supported by payers. In contrast, tools that effectively identify high-risk patients, leading to appropriate interventional or prevention strategies that impact outcomes, will be clinically valuable.

Figure 1. Proposed Risk Based Assessment of Patients Indeterminate for Acute Myocardial Infarction

This figure presents a risk-based flow for evaluation of patients who fall in the "indeterminate" category for acute myocardial infarction. Patients considered low-risk by hs-cTn evaluation can be further risk stratified using risk scores, then subsequent decisions (e.g., discharge, observation, further evaluation) made based on this risk assessment. A variety of laboratory and imaging tests, as well as risk scores can be implemented to further delineate the risk of patients initially at intermediate risk. The highest risk patients should generally be considered for coronary angiography or advanced imaging, with other evaluations as appropriate to determine the type of MI or other cardiac etiology.

*According to the Biomarker Study Group of the ESC Acute Cardiovascular Care Association, "This combination provides incremental diagnostic value as compared to the use of a single conventional cTn concentration, but provides no or only minor incremental value when using hs-cTn assays. The limitations of this strategy include the complexity of an additional biomarker, low positive predictive value for the combination of an elevated copeptin with a negative cTn, and the need for an additional analyser."[3]

AF, atrial fibrillation; CKD, chronic kidney disease; CTA, computed tomography angiography; GDF-15, growth differentiation factor-15; GRACE, Global Registry of Acute Coronary Events score; HEART, History, Electrocardiogram, Age, Risk Factors, Troponin score; HF, heart failure; hs-cTn, high-sensitivity cardiac troponin; LOD, limit of detection; MINOCA, MI with non-obstructive coronary arteries NT-proBNP, N-terminal pro-B-type natriuretic peptide; TIMI, Thrombolysis in Myocardial Infarction score

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Table 1. Clinical Scenarios, Potential Approaches, and Need for Research

Clinical Scenario	Potential Approaches	Areas of Uncertainty	Future Research
Chest pain or symptoms suggestive of myocardial ischaemia with hs-cTn <99th percentile and below the limit of detection[2]	• Review clinical parameters (ECG, symptoms, risk factors) • Use risk scores[26;32-35] (e.g., HEART, GRACE, TIMI) • Low risk patients: discharge or further investigate non-cardiac causes • High-risk patients: chest pain observation unit, repeat hs-cTn (early rule-out protocols), obtain cardiac imaging or stress	• Which score is optimal to aid in risk assessment in this specific patient population • Do established thresholds that define low and high risk translate to this patient population • Does a risk score approach combined with hs-cTn improve the specificity and sensitivity of detecting ACS and improve patient outcome?	AGRIS[36] and UK Grace Risk Score Intervention Study[37]

Table 1. Clinical Scenarios, Potential Approaches, and Need for Research (continued)

Clinical Scenario	Potential Approaches	Areas of Uncertainty	Future Research
	test	• Definition of unstable angina in the era of hs-cTn	
Chest pain or symptoms suggestive of myocardial ischaemia with hs-cTn <99th percentile but above the limit of detection[2;12]	• Repeat hs-cTn (early rule-out protocols), chest pain observation unit, obtain cardiac imaging (coronary CTA) or stress test, risk assessment (e.g., risk scores, NT-proBNP, co-peptin, GDF-15)[3;4;45] • Evaluate for comorbidities (e.g., atrial fibrillation, heart failure, chronic kidney disease) • Assess symptom onset and	• hs-cTn kinetics and potential influence of presentation time • Thresholds of hs-cTn change that signify myocardial necrosis at low baseline hs-cTn levels	• Prospective analysis of utility of cardiac imaging strategies on top of hs-cTn in this population • ROC analyses to find optimal thresholds for hs-cTn change criteria • hs-cTn kinetics especially in patients with comorbidities commonly encountered in practice

Table 1. Clinical Scenarios, Potential Approaches, and Need for Research (continued)

Clinical Scenario	Potential Approaches	Areas of Uncertainty	Future Research
	time of presentation		
Chest pain or symptoms suggestive of myocardial ischaemia with hs-cTn >99th percentile without dynamic change[2]	• Serial hs-cTn (1, 2, or 3 hour protocols) in early presenters[4] • Chest pain observation unit, obtain cardiac imaging (coronary CTA) or stress test, risk assessment (e.g., risk scores, NT-proBNP, co-peptin, GDF-15) • Late presenters with high-risk scores should undergo angiography or imaging (as appropriate for risk level)[55;56]	• Diagnosis and treatment guidelines for non-ACS myocardial injury	• Better characterize stable myocardial injury • Determine treatment approaches to reduce myocardial injury and improve outcomes in these patients

Table 1. Clinical Scenarios, Potential Approaches, and Need for Research (continued)

Clinical Scenario	Potential Approaches	Areas of Uncertainty	Future Research
	• Evaluate for comorbidities (e.g., arrhythmia, heart failure, chronic kidney disease, and others)[23;57;58]		
Chest pain or symptoms suggestive of myocardial ischaemia with hs-cTn >99th percentile and dynamic change but without coronary plaque rupture, erosion, or dissection[2]	• Invasive advanced imaging or coronary angiography to differentiate type 2 from type 1 MI[57]	• Treatment strategies • Net benefit from antiplatelet or anticoagulant therapy (potential for benefit vs. bleeding risk)	• Determine treatment approaches to improve outcomes in these patients

CTA, computed tomography angiography; GDF-15, growth differentiation factor-15; hs-cTn, high-sensitivity cardiac troponin; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide