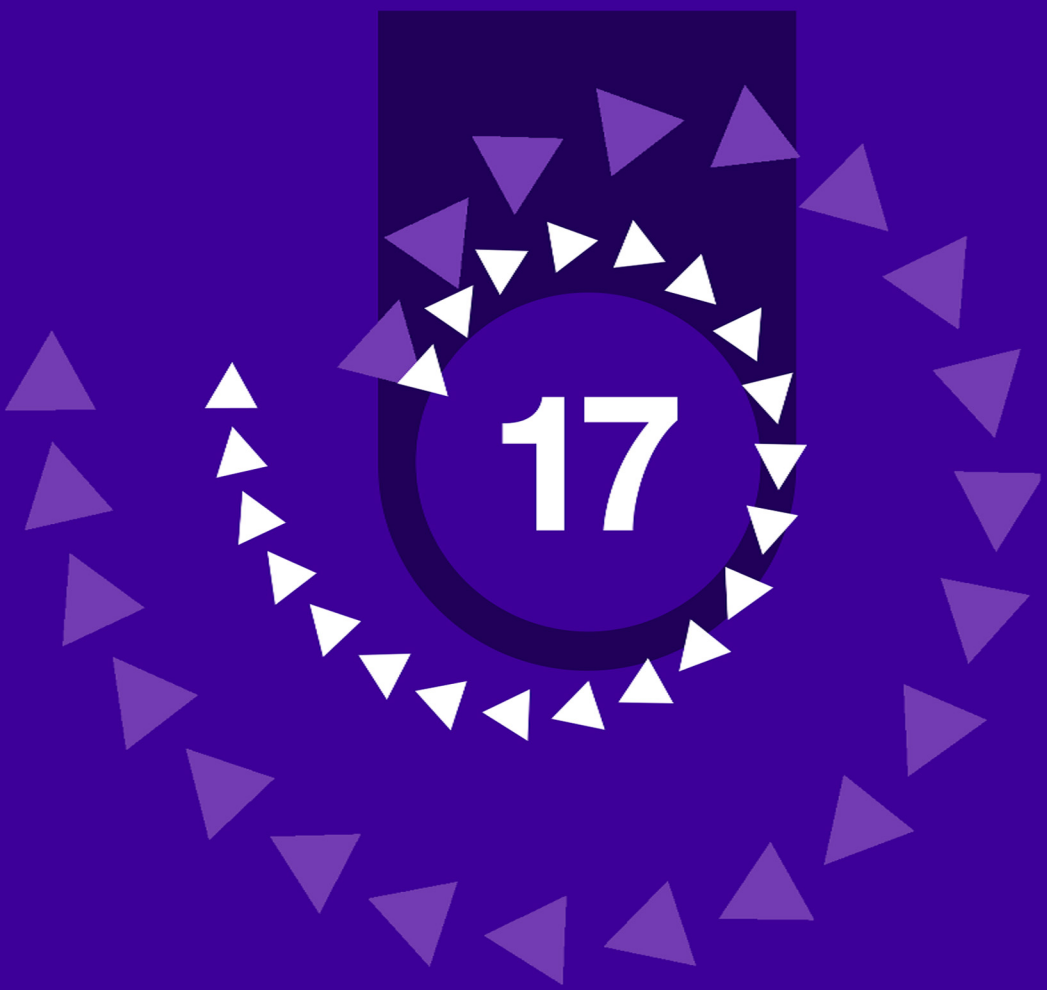
Recent Advances in Cardiology



Edited by
Derek Rowlands • Bernard Clarke

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Chapter 4

Cardiac biomarkers and risk stratification

Richard Body

INTRODUCTION AND SCOPE

Biomarkers play an essential role in the diagnosis and risk stratification of patients with suspected and confirmed acute coronary syndromes. Biomarkers may have additional applications outside of the acute coronary syndromes, for example in patients with heart failure, transient loss of consciousness or for predicting risk in apparently healthy individuals. There may be clinical applications for biomarkers in congenital heart disease, valvular heart disease, atrial fibrillation and stable angina. This chapter will address the role of biomarkers in the risk stratification and diagnosis of acute coronary syndromes.

A BRIEF HISTORY OF CARDIAC BIOMARKERS

Cardiac biomarkers have been used for the diagnosis of acute myocardial infarction (AMI) since the 1950s. Before the advent of cardiac troponin, AMI could be diagnosed on the basis of a characteristic release pattern of three cardiac enzymes: creatine kinase (CK), lactate dehydrogenase (LDH) and alanine aminotransferase (ALT). The observation of an early rise and fall of CK levels with later rises in serum levels of ALT and LDH was consistent with the diagnosis of AMI. Unfortunately, the biomarkers in use at that time were neither sensitive nor specific for AMI. CK levels will rise following skeletal muscle injury, whereas ALT and LDH levels will rise following liver injury and ALT is also found in bone. A further, significant limitation of this biomarker combination is that it took 72 hours before the diagnosis of AMI could be excluded or 'ruled out', which required a prolonged hospital admission for patients.

The development of assays for the more cardiac-specific MB fraction of CK (CK-MB) promised to improve matters further, although, when used alone, CK-MB still has imperfect sensitivity and specificity for the diagnosis of AMI. The advent of assays for cardiac troponin, however, made it possible to 'rule out' the possibility of AMI as early as 12 hours after a patient's symptoms developed and enabled the detection of myocardial injury with unprecedented sensitivity and specificity. This led to its incorporation into the World Health Organization definition of AMI by the year 2000, which stipulated that a rise and fall of either troponin or CK-MB was required to make the diagnosis except when pathologic findings were available [1].

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Since then, assays for cardiac troponin have improved progressively such that the more recent universal definition of myocardial infarction gives cardiac troponin the central role in the diagnosis of AMI. In summary, the universal definition of myocardial infarction from 2012 requires the following: detection of a rise and/or fall of cardiac troponin with at least one level above the 99th percentile upper reference limit, together with at least one of the following:

a. Symptoms and/or signs compatible with myocardial ischaemia
b. ECG changes compatible with myocardial ischaemia including new or presumed new ST-segment changes, T wave changes or left bundle branch block
c. The development of pathological Q waves on the ECG
d. Imaging evidence of new loss of viable myocardium
e. Identification of an intracoronary thrombus by angiography or postmortem [2]

WHAT IS TROPONIN?

Troponin is a subunit of the troponin–tropomyosin complex, part of the myofibrillar contractile apparatus. There are three forms of troponin: I, T and C. Troponin itself is not cardiac specific and is present within the contractile apparatus of both skeletal and cardiac muscle. The development of immunoassays for the cardiac isoform of troponins I and T has, however, yielded a highly cardiac-specific biomarker with very little skeletal muscle crossover.

There are many commercially available automated immunoassays for cardiac troponins I and T. An exhaustive list of currently available assays is available from the International Federation of Clinical Chemistry [3]. For diagnostic purposes, cardiac troponins I and T are essentially considered equivalent. There is some evidence that troponin I assays may yield fewer positive results outside of the context of AMI than troponin T [4]. However, the analytical characteristics of the cardiac troponin assay itself are far more important determinants of diagnostic accuracy than whether the assay targets troponin T or troponin I.

WHY IS THE DIAGNOSTIC CUT-OFF FOR AMI SET SO LOW?

Since 2000, international guidance has stipulated that AMI can be diagnosed when troponin levels rise above the 99th percentile of levels observed in apparently healthy individuals [1]. For many years, however, higher diagnostic cut-offs have been used in clinical practice. There were two reasons for setting the cut-off above the 99th percentile: firstly, a higher cut-off will yield higher diagnostic specificity and fewer 'false positive' results in patients who do not have AMI; and secondly, there were concerns about the precision of troponin assays at low levels. As troponin assays have improved, the issue of precision has largely been resolved. Some people have, however, remained concerned about the clinical significance of marginal troponin elevations.

There is now convincing evidence for the use of a cut-off set at the 99th percentile in apparently healthy individuals as recommended in international guidance. In an observational study, Body et al showed that minimal troponin rises above the 99th percentile upper reference limit independently and predicted major adverse cardiac events within 6 months [5].

More recently, Mills et al provided the first evidence that changing clinical protocols to diagnose AMI at lower cut-offs leads to improved outcomes for patients. They reported that

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an outdated troponin cut-off had been in clinical use to diagnose AMI at the Edinburgh Royal Infirmary (0.2 ng/mL, whereas the 99th percentile of the assay was 0.04 ng/mL). In an initial retrospective 'validation study' of 1038 patients, this group studied the prognosis of patients with minimal troponin elevations that were above the 99th percentile cut-off but below the diagnostic cut-off for AMI that was being used at that institution. They found that this group had a disproportionately high incidence of death or AMI at 1 year. The incidence was 39% among patients with troponin levels between 0.05 and 0.19 ng/mL, compared with 24% among patients whose troponin levels were ≥0.20 ng/mL [6].

Subsequently, they lowered the diagnostic cut-off that was used in practice such that patients with troponin levels above 0.05 ng/mL would be diagnosed with AMI and would receive the relevant treatment. After implementing this change, Mills' group re-evaluated clinical outcomes. They found that clinical outcomes remained unchanged for patients with troponin levels below the new diagnostic cut-off or above the previous cut-off. However, the patients with minimal troponin elevations – who had disproportionately bad outcomes in the validation phase and who were now being diagnosed with and treated for AMI – had significantly better outcomes such that the incidence of death or AMI had been reduced to 21% [6]. This provides the strongest evidence to date that accepting a lower diagnostic cut-off for cardiac troponin leads to better clinical outcomes for patients. Of course, it remains important to remember that the diagnosis of AMI requires not just a single troponin elevation but a rise and/or fall of cardiac troponin on serial sampling in conjunction with the appropriate clinical context.

HIGH-SENSITIVITY TROPONIN

Cardiac troponin has revolutionised the diagnosis of AMI, enabling detection of microscopic amounts of myocardial necrosis that had previously been impossible. However, the available tests are imperfect tools to enable its detection and quantification. Until recently, commercially available troponin assays have been subject to two important analytical limitations. Firstly, the precision of a biomarker assay determines the reliability of the results reported. With increasing precision, the results reported when re-testing the same sample for a number of times will be closer together. Precision is measured by the coefficient of variation (CV), which is equal to the mean value returned when testing a sample several times divided by its standard deviation. The CV tends to be higher (indicating lower precision) at lower troponin concentrations. For an assay to be acceptable according to contemporary international guidance, the CV should be <10% when the troponin concentration in the sample is equal to the 99th percentile in an apparently healthy population [2]. Historically, troponin assays have failed to achieve this standard.

Secondly, until recently it has not been possible to detect troponin levels in apparently healthy individuals. As such, the 99th percentile upper reference limit has been equal to the detection limit of the test. It has, therefore, been impossible to know whether detection of lesser troponin rises could lead to benefits for patients.

High-sensitivity troponin assays overcome both of these analytical limitations. In order for a troponin assay to be labelled as 'high sensitivity' it must, therefore, meet two criteria:

1. The CV must be <10% at the 99th percentile upper reference limit, i.e. the assays have improved precision
2. It must be possible to detect troponin levels in at least half of apparently healthy individuals, i.e. the assays have improved analytical sensitivity [7]

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IMPORTANT TERMINOLOGY

In order to understand how high-sensitivity troponins can be optimally used in clinical practice, it is important to be aware of the definition of several important terms, discussed below [8]:

The limit of blank

This is essentially the highest level of troponin that we might reasonably expect to see reported if a sample containing no troponin is tested. It is calculated as the mean +1.645 standard deviations of the results obtained after repeated testing of a sample containing no troponin.

The limit of detection

This level is higher than the limit of blank (LoB). It is the lowest level of troponin that could be reliably distinguished from a sample containing no troponin. It is calculated as the mean +1.645 standard deviations of the results obtained after repeated testing of a sample containing a very low concentration of troponin.

The limit of quantification

This is defined at the lowest concentration at which certain precision criteria can be fulfilled. For a troponin assay, this is usually considered to be the lowest troponin concentration at which the CV is <10%.

Familiarity with these terms will be required in order to understand some of the novel clinical applications of high-sensitivity troponin assays, as described below.

CLINICAL IMPLICATIONS OF HIGH-SENSITIVITY TROPONIN ASSAYS

In addition to the analytical imperfections of commercially available assays, cardiac troponin has some important clinical limitations as a biomarker for the diagnosis of acute coronary syndromes that directly affect clinical care.

1. It takes several hours for troponin levels to rise in the bloodstream after the onset of myocardial injury. This necessitates serial sampling of a number of hours and means that the diagnosis of AMI cannot usually be 'ruled out' when patients first present to the hospital: a phenomenon known as 'troponin blindness'
2. Patients with unstable angina, who have symptomatic coronary plaque rupture or erosion, will have no detectable troponin rise even with serial sampling, which is a problem of 'troponin invisibility'

'Troponin blindness' and early 'rule out' strategies

The first of these issues (troponin blindness) means that many patients must be admitted to hospital for serial troponin testing before acute coronary syndromes can safely be 'ruled out.' This has substantial resource implications for health services. Chest pain is the most common reason for emergency hospital admission in England and Wales, accounting for over a quarter of acute medical admissions [9,10]. Of those who are initially suspected to have the diagnosis

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of an acute coronary syndrome, only a minority actually has that diagnosis. A strategy that could 'rule out' acute coronary syndromes without the requirement for serial sampling over a number of hours could enable patients to receive earlier reassurance about the nature of their symptoms, unburdening overcrowded emergency departments and substantially reducing resource utilisation for hospitals.

In 2009, the first reports of the diagnostic accuracy of high-sensitivity troponin tests when used to 'rule out' AMI at the time of first presentation to the hospital were published. In a landmark study of 786 patients with chest pain presenting to the emergency department, Reichlin et al showed that, using the high-sensitivity troponin T assay (Roche diagnostics), 95% of patients with AMI had positive results (above the 99th percentile upper reference limit) at the time of arrival in the emergency department. In comparison, only 83% of patients with AMI had a positive result using the previous generation of troponin T assay [11]. Such evidence shows how the use of high-sensitivity troponin assays will ameliorate the problem of 'troponin blindness' by reducing the proportion of patients with AMI whose troponin levels are normal at the time of presentation. However, because the strategy would miss 5% of AMIs this evidence also shows that serial sampling remains necessary before we can consider the diagnosis of AMI to be 'ruled out'.

However, with high-sensitivity troponin assays it may be possible to reduce the period of 'troponin blindness' by bringing forward the timing of serial samples. With the previous generations of troponin assay, it was necessary to undertake serial sampling 6–9 hours after arrival in the hospital or 12 hours after symptom onset before the diagnosis of AMI could be 'ruled out' [12,13]. The advent of high-sensitivity troponins has led to hope that AMI may be excluded by serial sampling within 2–3 hours of presentation.

In 2009, Keller et al evaluated a contemporary, sensitive assay (troponin I, Siemens Ultra, which has since failed to meet the criteria for being labelled as 'high sensitivity'). The sensitivity of this troponin I test when used at the time of arrival and 3 hours later was shown to be 100.0% [14]. A secondary analysis from the same study evaluating another troponin assay (Abbott ARCHITECT high-sensitivity troponin I), which does fulfil the criteria for being a 'high-sensitivity' assay, showed that testing 3 hours after admission and using the 99th percentile upper reference limit as a cut-off, the sensitivity was 98.2% [15]. This evidence led to a change in the wording of the universal definition of myocardial infarction in 2012, to state [2] the following.

'Blood samples should be for the measurement of cardiac troponin should be drawn on first assessment and repeated 3–6 hours later'.

The European Society of Cardiology and the National Institute for Health and Care Excellence in the United Kingdom have also recommended that an early rule out protocol incorporating testing on arrival and 3 hours later can be used when a high-sensitivity troponin assay is available [16,17].

Early rule out strategies using extremely low troponin cut-offs

The 3-hour rule out strategy will reduce the period of 'troponin blindness' but it still requires patients to stay in the hospital for at least 4 hours, allowing for the turnaround time of the tests. A strategy that would enable the diagnosis of AMI to be rapidly excluded using a single blood test would have great advantages. Using the conventional 99th percentile upper reference limit as a cut-off it is not possible to do this, even with a high-sensitivity assay. However, high-sensitivity troponin allows the detection of much smaller levels of troponin. If the cut-off was lowered such that patients with extremely low levels of troponin

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on arrival were considered to have AMI 'ruled out', we could avoid the need for serial sampling in a proportion of patients.

With the Roche high-sensitivity troponin T assay, setting the cut-off at the LoB of the assay (such that patients with completely undetectable levels of troponin would have AMI 'ruled out') has been shown to have 100% sensitivity for AMI using a single blood test at the time of arrival in the emergency department, regardless of the time from symptom onset [18]. By excluding AMI in patients with troponin levels below the LoB, further investigation could be avoided in a quarter of all patients. Using a slightly higher cut-off set at the limit of detection (5 ng/L), a Swedish group showed that 'ruling out' AMI in patients with an initial troponin level <5 ng/L and no evidence of ECG ischaemia would give a negative predictive value of 99.8% for AMI occurring within the next 30 days [19]. These strategies therefore have great promise as means of immediately excluding the diagnosis of AMI without the need for any serial sampling. However, there have been concerns about the precision of the assays at such low troponin concentrations [20]. To date, these concerns have precluded clinical implementation and mean that further evidence is likely to be required before these strategies are incorporated into international guidance.

Biomarkers as part of clinical decision rules

Clinical decision rules are tools designed to aid decision-making processes in clinical medicine. Usually, they are derived through original research using multivariate analysis. An advantage of clinical decision rules is that they can optimise the combination of biomarker levels with other clinical information, e.g. ECG findings or details of a patient's symptoms. There are several examples of clinical decision rules that could be used in patients presenting to the emergency department with symptoms that are compatible with an acute coronary syndrome.

The Thrombolysis in Myocardial Infarction (TIMI) risk score was originally derived to risk stratify patients who have a confirmed diagnosis of an acute coronary syndrome (see **Table 4.1**) [21]. It has since been shown to effectively risk stratify patients with suspected acute coronary syndromes in the emergency department [22]. Patients with a TIMI risk score of 0 who have normal troponin levels (below the 99th percentile upper reference limit) on arrival and 2 hours later could potentially have the diagnosis of acute coronary syndrome excluded. In the ADAPT trial, which included 1975 patients, this strategy could have enabled the early discharge of 20% of patients with suspected cardiac chest pain

Table 4.1 The Thrombolysis in Myocardial Infarction (TIMI) risk score*

Age >65 years
Current use of aspirin
At least three risk factors for coronary artery disease (hypertension, hyperlipidaemia, family history, tobacco smoking, diabetes mellitus)
Known coronary stenosis
Severe symptoms (at least two episodes in the preceding 24 hours)
ECG ischaemia
Troponin level >99th percentile

*1 point for each parameter. definitions may vary between studies.

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with a sensitivity of 99.7% and a negative predictive value of 99.7% for major adverse cardiac events occurring within 30 days [23]. In a subsequent randomised controlled trial comparing the use of this strategy to routine care (including delayed troponin testing), the TIMI-based protocol allowed 19.3% of patients to be safely discharged within 6 hours, compared to 11.0% of patients who received standard care [24]. Having been subjected to a randomised controlled trial, therefore, this strategy could be used immediately in the clinical environment to facilitate early discharge, although the proportion of patients discharged early may be relatively modest.

The HEART score is an alternative clinical decision rule, which relies on information available at the time of arrival in the hospital (**Table 4.2**). This score was derived using the intuition of a cardiologist (Jacob Six) rather than through statistical analysis. However, its performance has been validated in several large cohort studies. In general, these studies support clinical use of the HEART score, reporting that the incidence of major adverse cardiac events within 30 days is below 2% for patients with a low HEART score (0–3 points) [25–27], although there have been reports that the HEART score has lower accuracy [28]. The results of an interventional trial that is currently recruiting will help to inform the field whether the HEART score is a safe and efficient tool to reduce unnecessary hospital admissions [29].

Another clinical decision rule that has recently been described is the Manchester Acute Coronary Syndromes (MACS) rule. This decision rule was derived by multivariate analysis in a cohort of 698 patients and subsequently validated in 463 patients at a separate centre [30]. The MACS rule incorporates eight variables including two biomarker levels (**Table 4.3**). The rule requires calibration for each troponin assay in order to optimise the diagnostic performance and considers each biomarker level to be a continuous variable.

Table 4.2 The HEART score*

Category	Score
H: history	Highly suspicious: 2 points
	Moderately suspicious: 1 point
	Slightly or nonsuspicious: 0 point
E: ECG	Significant standard deviation: 2 points
	Nonspecific repolarisation abnormality: 1 point
	Normal: 0 point
A: age	≥65 years: 2 points
	46–64 years: 1 point
	≤45 years: 0 point
R: risk factors	≥3 risk factors or known atherosclerotic disease: 2 points
	1–2 risk factors: 1 point
	0 risk factor: 0 point
T: troponin	≥3 times upper reference limit: 2 points
	1–3 times upper reference limit: 1 point
	≤ upper reference limit: 0 point

*Patients with a score of 0–3 points are considered to be at 'low risk' and suitable for early discharge from the emergency department [29].

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Thus, there is no single diagnostic cut-off but the MACS rule recognises that, with rising levels of each biomarker, there is a continuum of risk. Similar to the Global Registry of Acute Cardiac Events score, which is used to risk stratify patients with confirmed acute coronary syndromes, the MACS rule requires a computerised calculation. Patients are stratified into four risk groups based on this calculation. The 'very low risk' group includes 27% of all patients. In the validation study, none of these patients had an AMI and 1.6% developed a major adverse cardiac event within 30 days. As well as facilitating early discharge of patients from the emergency department and thus reduction of the need for unnecessary hospital admission, the MACS rule enables overall risk stratification. In the 'high risk' group (9.9% of all patients), over 95% of patients developed a major adverse cardiac event within 30 days. However, prior to widespread clinical implementation it will be important to gather further data on the likely impact of the rule when used in clinical practice, e.g. from interventional trials.

'Troponin invisibility' and unstable angina

With high-sensitivity troponin assays a greater proportion of patients will test positive for troponin. This appears to be particularly so for the high-sensitivity troponin T assay (manufactured by Roche). With the previous generation of troponin T assay, the 99th percentile upper reference limit was 0.01 ng/mL or 10 ng/L. If a sample had been shown to contain 10 ng/L of troponin using that assay and was re-tested using the newer, high-sensitivity assay, the equivalent result using the new assay is likely to be approximately 35 ng/L. This means that the apparent troponin concentration is higher using the high-sensitivity assay [31]. As the 99th percentile upper reference limit for the high-sensitivity assay is 14 ng/L, those patients who have troponin levels between 14 and 35 ng/L using the high-sensitivity assay will now test positive, whereas they would previously have had negative (or normal) troponin levels. In patients with acute coronary syndromes, this leads to a greater proportion of patients being diagnosed with non-ST elevation myocardial infarction (NSTEMI), whereas they would previously have been diagnosed with unstable angina [32]. As such, the apparent incidence of NSTEMI will increase and that of unstable angina will decrease. This has led some people to believe that unstable angina will cease to exist as a diagnosis as troponin assays become increasingly sensitive in the future.

Table 4.3 The Manchester Acute Coronary Syndromes (MACS) decision rule for suspected cardiac chest pain*

High-sensitivity troponin T
Heart-type fatty acid binding protein
ECG ischaemia
Pain in association with vomiting
Sweating observed in the emergency department
Hypotension on arrival (systolic blood pressure <100 mmHg)
Worsening angina

*Each variable is entered into a computer. High-sensitivity troponin T is entered in ng/L; heart-type fatty acid binding protein in ng/mL. Categorical variables are considered to be either present (1) or absent (0). The computer then calculates an estimated probability that the patient will develop a major adverse cardiac event within 30 days. Based on this, patients are stratified into four risk groups. The 'very low' risk group can be immediately discharged from hospital.

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Causes of troponin elevation

At the same time, as patients with acute coronary syndromes are more likely to test positive for troponin, when a high-sensitivity assay is used, it is equally true that more patients who do not have an acute coronary syndrome will test positive. It is tempting to label such results as 'false positives' but it is important to remember that troponin is a marker of myocardial injury rather than specifically being a marker of AMI. As such, any cause of myocardial injury will lead to a troponin elevation. Some of these alternative causes of troponin elevation are listed in **Table 4.4**.

On encountering a patient with a troponin elevation, the first priority is to attempt to distinguish those patients who have AMI from those who have another cause for their troponin elevation. In this regard, the clinical context is the most important consideration. Firstly, we need to understand whether the patient is likely to have a chronic troponin elevation. A number of factors are known to influence a patient's baseline troponin level. Advancing age, male gender, renal dysfunction, left ventricular dysfunction and underlying cardiovascular disease are all known to cause chronic troponin elevations. These patients have a worse long-term prognosis but the troponin rise is not caused by an AMI. In a reference ranging study, it has been shown that the 99th percentile upper reference limit for the high-sensitivity troponin T assay is 14 ng/L (as published by the manufacturer) only if the reference population excludes patients with evidence left ventricular dysfunction, cardiovascular disease and renal disease. In the undifferentiated population, the 99th percentile was found to be 29.9 ng/L [33]. This is useful to clinicians as it informs us about the magnitude of troponin elevation we might expect at baseline in patients who have comorbidities such as left ventricular dysfunction. In patients with chronic kidney disease, troponin levels may be even higher at baseline. The 95th percentile in apparently healthy patients with chronic kidney disease from stages 3 to 5 has been shown to be as high as 139 ng/L [34].

Assessing a rise and/or fall of troponin

In a patient who has an elevated troponin level, we must also determine whether the level changes over time. In order to diagnose AMI we must demonstrate that a patient has a rise and/or fall of cardiac troponin [2]. A patient with a troponin elevation that does not change over time is likely to have a chronic troponin elevation but not AMI. This means that serial sampling is necessary to determine the change or 'δ' troponin over time. International guidance now recommends that samples should be drawn 3–6 hours apart but do not precisely define a 'rise and/or fall' of cardiac troponin [2].

Table 4.4 Causes of troponin elevation

Type 1 myocardial infarction	Type 2 myocardial infarction
Heart failure	Renal failure
Pulmonary embolism	Critical illness
Myocarditis	Aortic dissection
Hypertrophic obstructive cardiomyopathy	Cardiac contusion
Arrhythmias	Subarachnoid haemorrhage
Takotsubo cardiomyopathy	Extreme exertion
Burns	Normal biological variation

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The National Academy of Clinical Biochemistry originally proposed that a 20% change in troponin levels on serial sampling is necessary to make the diagnosis of AMI [35]. However, as there is such heterogeneity between troponin assays, the appropriate δ should be defined for each individual assay. There is evidence that the 20% δ may not be optimal for diagnosis. For example, Mueller et al demonstrated that only 75.2% of patients with NSTEMI will develop a δ >20%, whereas 62.4% of patients who do not have a diagnosis of an acute coronary syndrome will develop a δ of >20% on serial sampling [36]. One of the key limitations of this approach is that the 20% criteria are a 'relative' δ. This means that patients who have a troponin level just above the 99th percentile can develop a 20% δ on serial sampling despite there being only a small absolute change. Conversely, a patient with an extremely high troponin level may not develop a 20% δ despite a very large absolute change on serial sampling, e.g. a patient with a troponin level of 10 ng/L at baseline and 15 ng/L at 6 hours would be diagnosed with AMI using a relative δ (50%), despite having a very small absolute change in troponin (5 ng/L) that could be caused by the imprecision of the assay. A second patient, however, does not meet the 20% criterion despite having an extremely high troponin level (2000 ng/L at baseline; 2200 ng/L at 6 hours) and an absolute change of 200 ng/L on serial sampling (relative δ: 10%).

Thus, using an 'absolute' δ (the absolute difference in troponin levels on serial sampling) may have some advantages. This approach has shown to have higher diagnostic accuracy for AMI than the use of relative ds. For the high-sensitivity troponin T assay, the optimal δ was shown to be an absolute change of ≥9.2 ng/L [36].

Type 2 myocardial infarction

When a patient is shown to have a rise and/or fall of cardiac troponin it is important to again consider the clinical context. We need to differentiate those patients whose AMI has been caused by a primary plaque rupture, erosion or dissection (type 1 AMI) from those in whom a condition other than coronary artery disease has caused an imbalance between myocardial oxygen supply and demand (e.g. AMI caused by severe anaemia, critical illness or haemorrhage). The latter may, e.g. be caused by arrhythmias, critical illness or by coronary artery spasm. Patients with type 2 AMI have a disproportionately high mortality rate [37] but may not benefit from the same antiplatelet and antithrombotic treatment as has been shown to benefit patients with type 1 AMI. Treatment of the underlying condition is likely to have greater importance, particularly in the acute phase.

ALTERNATIVE BIOMARKERS

CK-MB and myoglobin

CK-MB and myoglobin have been proposed as 'early markers' of myocardial injury that could identify patients who present early after symptom onset, during the period of 'troponin blindness'. However, these biomarkers lack specificity. Compared to the use of a contemporary troponin assay alone, they do not increase sensitivity for AMI but they reduce specificity. This means that hospital admission can be avoided for fewer patients [23,38]. In a multi-centre randomised controlled trial, the use of a multimarker panel (CK-MB, myoglobin and troponin) on arrival and 90 minutes later was compared to standard care. In this trial, the proportion of patients that was safely discharged from hospital increased [39]. However, driven by an increase in coronary care utilisation, healthcare

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Recent Advances in Cardiology 17

Recent Advances in Cardiology 17 is the ideal resource for keeping abreast of new developments in this fast-moving field. Written by expert authors and featuring topics such as sudden unexpected cardiac death in young adults and HIV and coronary heart disease, each chapter highlights latest developments of relevance to clinical practice. This book is also an invaluable revision tool for trainees preparing for postgraduate examinations.

- Practical and clinically relevant content, enhanced by *Key Points for Clinical Practice* at the end of each chapter
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