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EXPERT CONSENSUS DOCUMENT

Fourth universal definition of myocardial infarction (2018)

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Table of contents

Abbreviations and acronyms

ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACS	acute coronary syndrome
AHA	American Heart Association
ARC-2	Academic Research Consortium-2
AUC	area under the curve
CAD	coronary artery disease
CABG	coronary artery bypass grafting
CKD	chronic kidney disease
CK-MB	creatine kinase MB isoform
CMR	cardiac magnetic resonance
CTCA	computed tomographic coronary angiography
cTn	cardiac troponin
cTnI	cardiac troponin I
cTnT	cardiac troponin T
CT	computed tomography
CV	coefficient of variation
EF	ejection fraction
ECG	electrocardiogram or electrocardiographic
ESC	European Society of Cardiology
g	gram(s)
h	hour(s)
HF	heart failure
hs-cTn	high-sensitivity cardiac troponin
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
ISFC	International Society and Federation of Cardiology
LAD	left anterior descending artery
LBBB	left bundle branch block
LoD	limit of detection
LGE	late gadolinium enhancement
LGE-CMR	late gadolinium enhancement cardiac magnetic resonance
LV	left ventricular
LVH	left ventricular hypertrophy
MI	myocardial infarction
min	minute(s)
MINOCA	myocardial infarction with non-obstructive coronary arteries
mm	millimetre
MONICA	MONItoring of trends and determinants in CArdiovascular disease
MPS	myocardial perfusion scintigraphy
ms	millisecond
mV	millivolt
ng/L	nanograms per litre

NHLBI	National Heart, Lung, and Blood Institute
NSTEMI	non-ST-elevation myocardial infarction
PET	positron emission tomography
PCI	percutaneous coronary intervention
POC	point of care
RBBB	right bundle branch block
s	second(s)
SPECT	single photon emission computed tomography
STEMI	ST-elevation myocardial infarction
ST-T	ST-segment–T wave
TIMI	Thrombolysis in Myocardial Infarction
TTS	takotsubo syndrome
UDMI	Universal Definition of Myocardial Infarction
URL	upper reference limit
WHF	World Heart Federation
WHO	World Health Organization

What's new in the universal definition of myocardial infarction?

New concepts

- Differentiation of myocardial infarction from myocardial injury.
- Highlighting peri-procedural myocardial injury after cardiac and non- cardiac procedures as discrete from myocardial infarction.
- Consideration of electrical remodelling (cardiac memory) in assessing repolarization abnormalities with tachyarrhythmia, pacing, and rate-related conduction disturbances.
- Use of cardiovascular magnetic resonance to define aetiology of myocardial injury.
- Use of computed tomographic coronary angiography in suspected myocardial infarction.

Updated concepts

- Type 1 myocardial infarction: Emphasis on the causal relationship of plaque disruption with coronary athero-thrombosis; *new Figure 3*.
- Type 2 myocardial infarction: Settings with oxygen demand and supply imbalance unrelated to acute coronary athero-thrombosis; *new Figures 4 and 5*.
- Type 2 myocardial infarction: Relevance of presence or absence of coronary artery disease to prognosis and therapy.
- Differentiation of myocardial injury from type 2 myocardial infarction; *new Figure 6*.
- Type 3 myocardial infarction: Clarify why type 3 myocardial infarction is a useful category to differentiate from sudden cardiac death.
- Types 4-5 myocardial infarction: Emphasis on distinction between procedure-related myocardial injury and procedure-related myocardial infarction.
- Cardiac troponin: Analytical issues for cardiac troponins; *new Figure 7*.
- Emphasis on the benefits of high-sensitivity cardiac troponin assays.
- Considerations relevant to the use of rapid rule-out and rule-in protocols for myocardial injury and myocardial infarction.
- Issues related to specific diagnostic change ('delta') criteria for the use of cardiac troponins to detect or exclude acute myocardial injury.
- Consideration of new non-rate-related right bundle branch block with specific repolarization patterns.
- ST-segment elevation in lead aVR with specific repolarization patterns, as a STEMI equivalent.
- ECG detection of myocardial ischaemia in patients with an implantable cardiac defibrillator or a pacemaker.
- Enhanced role of imaging including cardiac magnetic resonance imaging for the diagnosis of myocardial infarction; *new Figure 8*.

New sections

- Takotsubo syndrome.
- MINOCA.
- Chronic kidney disease.
- Atrial fibrillation.
- Regulatory perspective on myocardial infarction.
- Silent or unrecognized myocardial infarction.

ECG = electrocardiogram; MINOCA = myocardial infarction with non-obstructive coronary arteries; STEMI = ST-elevation myocardial infarction.

Universal definitions of myocardial injury and myocardial infarction

Criteria for myocardial injury

The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

Criteria for acute myocardial infarction (types 1, 2 and 3 MI)

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:

- Symptoms of myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography or autopsy.

Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*.
Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for *type 2 MI*.
Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for *type 3 MI*.

Criteria for coronary procedure-related myocardial infarction (types 4 and 5 MI)

Percutaneous coronary intervention (PCI) related MI is termed *type 4a MI*.
Coronary artery bypass grafting (CABG) related MI is termed *type 5 MI*.
Coronary procedure-related MI ≤48 hours after the index procedure is arbitrarily defined by an elevation of cTn values >5 times for *type 4a MI* and >10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable (≤20% variation) or falling, must meet the criteria for a 5 or 10 fold increase and manifest a change from the baseline value of >20%. In addition with at least one of the following:

- New ischaemic ECG changes (this criterion is related to *type 4a MI* only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.

Isolated development of new pathological Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.
Other types 4 MI include *type 4b MI* stent thrombosis and *type 4c MI* restenosis that both meet *type 1 MI* criteria.
Post-mortem demonstration of a procedure-related thrombus meets the *type 4b MI* criteria.

Criteria for prior or silent/unrecognized myocardial infarction

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

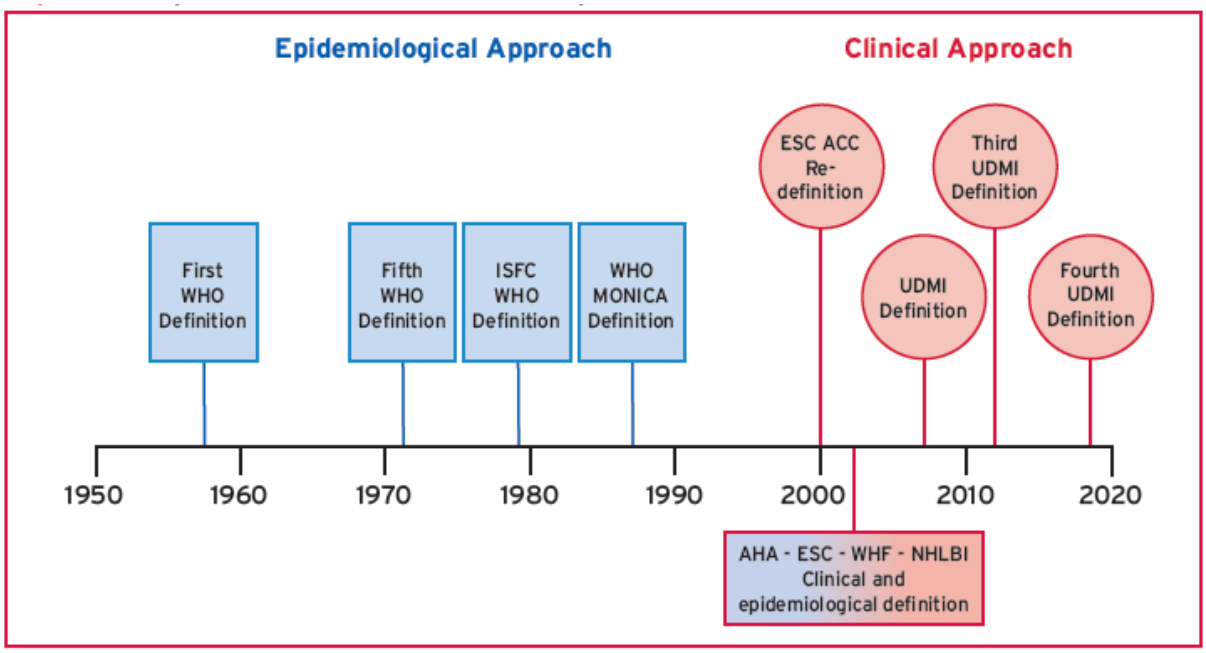
- Abnormal Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology.
- Patho-anatomical findings of a prior MI.

CABG = coronary artery bypass grafting; cTn = cardiac troponin; ECG = electrocardiogram; MI = myocardial infarction; PCI = percutaneous coronary intervention; URL = upper reference limit.

Introduction

In the late 19th century, post-mortem examinations demonstrated a possible relationship between thrombotic occlusion of a coronary artery and myocardial infarction (MI).[1] However, it was not until the beginning of the 20th century that the first clinical descriptions appeared describing a connection between the formation of a thrombus in a coronary artery and its associated clinical features.[2,3] Despite these landmark observations, considerable time elapsed before general clinical acceptance of this entity was achieved, in part due to one autopsy study showing no thrombi in the coronary arteries of 31% of deceased patients with an MI.[4] The clinical entity was referred to as coronary thrombosis, although ultimately, the term 'myocardial infarction' prevailed. Over the years, several different definitions of MI were used, leading to controversy and confusion. Hence, a general and worldwide definition for MI was needed. This occurred for the first time in the 1950–70s, when working groups from the World Health Organization (WHO) established a primarily electrocardiographic (ECG)-based definition of MI intended for epidemiological use.[5] The original description, with minor modifications, is still used in epidemiological surveys.[6–8] (**Figure 1**)

Figure 1 History of documents on the definition of myocardial infarction



ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; ISFC = International Society and Federation of Cardiology; MONICA = MONItoring of trends and determinants in CArdiovascular disease; NHLBI = National Heart, Lung, and Blood Institute; UDMI = Universal Definition of Myocardial Infarction; WHF = World Heart Federation; WHO = World Health Organization.

With the introduction of more sensitive cardiac biomarkers, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) collaborated *to redefine*

MI using a biochemical and clinical approach, and reported that myocardial injury detected by abnormal biomarkers in the setting of acute myocardial ischaemia should be labelled as MI.[9] The principle was further refined by the Global MI Task Force, leading to the Universal Definition of Myocardial Infarction Consensus Document in 2007, introducing a novel MI classification system with five subcategories.[10] This document, endorsed by the ESC, the American College of Cardiology (ACC), the American Heart Association (AHA), and the World Heart Federation (WHF), was adopted by the WHO.[11] The development of even more sensitive assays for markers of myocardial injury made further revision of the document necessary, particularly for patients who undergo coronary procedures or cardiac surgery. As a result, the Joint ESC/ACC/AHA/WHF Task Force produced the Third Universal Definition of Myocardial Infarction Consensus Document in 2012.[12]

Studies have shown that myocardial injury, defined by an elevated cardiac troponin (cTn) value, is frequently encountered clinically and is associated with an adverse prognosis.[13,14] Although myocardial injury is a prerequisite for the diagnosis of MI it is also an entity in itself. To establish a diagnosis of MI, criteria in addition to abnormal biomarkers are required. Non-ischaemic myocardial injury may arise secondary to many cardiac conditions such as myocarditis, or may be associated with non-cardiac conditions such as renal failure.[15] Therefore, for patients with increased cTn values, clinicians must distinguish whether patients have suffered a non-ischaemic myocardial injury or one of the MI subtypes. If there is no evidence to support the presence of myocardial ischaemia, a diagnosis of myocardial injury should be made. This diagnosis can be changed if subsequent evaluation indicates criteria for MI. The current Fourth Universal Definition of Myocardial Infarction Consensus Document reflects these considerations through adhering to the clinical approach of the definition of myocardial infarction.

Clinical criteria for myocardial infarction

Clinical definition of MI denotes presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischaemia.

Pathological characteristics of myocardial ischaemia and infarction

MI is defined *pathologically* as myocardial cell death due to prolonged ischaemia. Diminished cellular glycogen and relaxed myofibrils and sarcolemmal disruption are the first ultrastructural changes and are seen as early as at 10–15 minutes (min) after the onset of ischaemia.[16] Mitochondrial abnormalities are observed as early as 10 min after coronary occlusion by electron microscopy and are progressive.[17] It can take hours before myocyte necrosis can be identified by post-mortem examination in humans; this is in contrast to animal models, in which biochemical evidence of myocardial cell death due

to apoptosis can be detected within 10 min of induced myocardial ischaemia in association with myocyte death.[15] Experimentally, necrosis progresses from the subendocardium to the subepicardium over several hours. The time course may be prolonged by increased collateral flow, reduced determinants of myocardial oxygen consumption and intermittent occlusion/reperfusion which can precondition the heart.[18] Timely implementation of reperfusion therapy, when appropriate, reduces ischaemic injury of the myocardium.[19,20]

Biomarker detection of myocardial injury and infarction

Cardiac troponin I (cTnI) and T (cTnT) are components of the contractile apparatus of myocardial cells and are expressed almost exclusively in the heart.[21,22] Increases in cTnI values have not been reported to occur following injury to non-cardiac tissues. The situation is more complex for cTnT. Biochemical data indicate that injured skeletal muscle expresses proteins that are detected by the cTnT assay, leading to some situations where elevations of cTnT could emanate from skeletal muscle.[23–27] Recent data suggest that the frequency of such elevations in the absence of ischaemic heart disease may be higher than originally thought.[28,29] cTnI and cTnT are the preferred biomarkers for the evaluation of myocardial injury,[12,21,22,30] and high-sensitivity (hs)-cTn assays are recommended for routine clinical use.[22] Other biomarkers e.g. creatine kinase MB isoform (CK-MB) are less sensitive and less specific.[31] Myocardial injury is defined to be present when blood levels of cTn are increased above the 99th percentile upper reference limit (URL).[12,21,22,30] The injury may be acute, as evidenced by a newly detected dynamic rising and/or falling pattern of cTn values above the 99th percentile URL, or chronic, in the setting of persistently elevated cTn levels.

Criteria for myocardial injury

Detection of an elevated cTn value above the 99th percentile URL is defined as myocardial injury. The injury is considered acute if there is a rise and/or fall of cTn values.

Although elevated cTn values reflect injury to myocardial cells, they do not indicate the underlying pathophysiologic mechanisms, and can arise following preload-induced mechanical stretch or physiological stresses in otherwise normal hearts.[32–34] Various causes have been suggested for the release of structural proteins from the myocardium, including normal turnover of myocardial cells, apoptosis, cellular release of cTn degradation products, increased cellular wall permeability, formation and release of membranous blebs, and myocyte necrosis.[27,35] Yet, it is not possible clinically to distinguish which increases of cTn levels are due to which mechanisms.[36] However, regardless of the mechanism, acute myocardial injury when associated with a rising

and/or falling pattern of cTn values with at least one value above the 99th percentile URL and caused by myocardial ischaemia is designated as an acute MI.[12,21,22,30] Histological evidence of myocardial injury with myocyte death can be detected in clinical conditions associated with non-ischaemic mechanisms of myocardial injury as well.[37,38] **(Figure 2)**

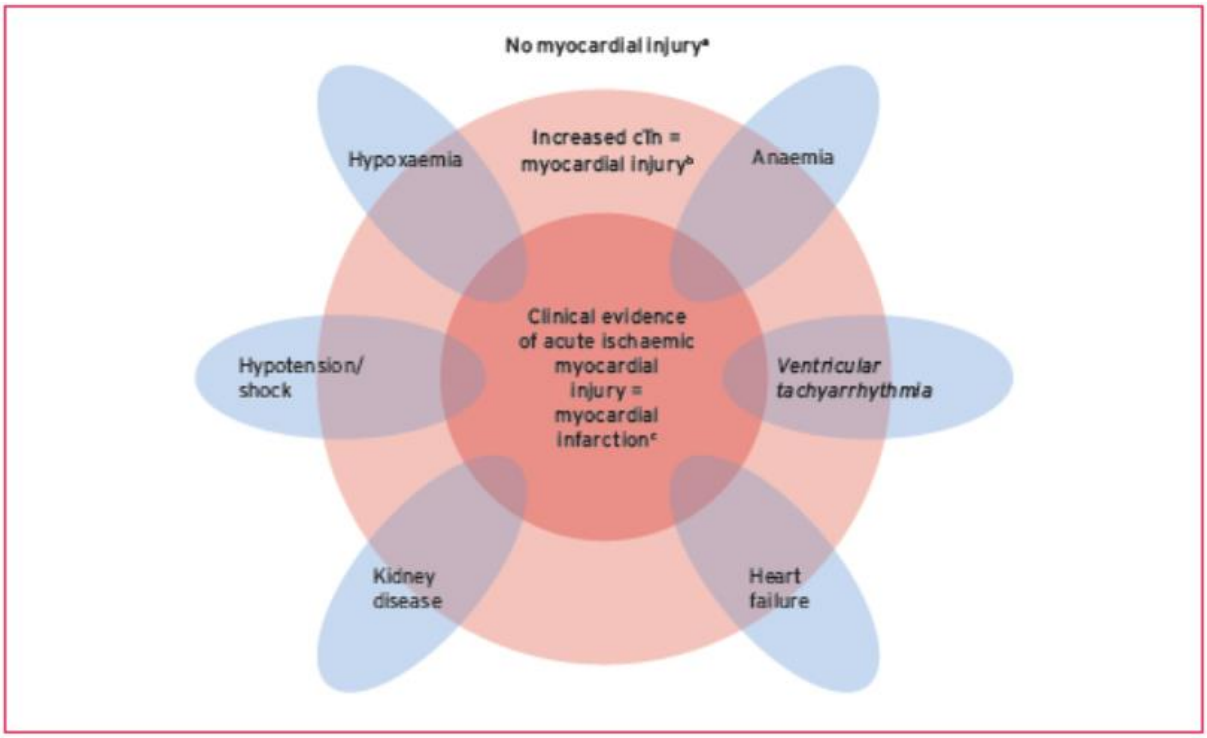


Figure 2 Spectrum of myocardial injury, ranging from no injury to myocardial infarction
cTn = cardiac troponin; URL = upper reference limit.
[a]No myocardial injury = cTn values ≤99th percentile URL or not detectable.
[b]Myocardial injury = cTn values >99th percentile URL.
[c]Myocardial infarction = clinical evidence of myocardial ischaemia and a rise and/or fall of cTn values >99th percentile URL.
Various clinical entities may involve these myocardial categories for example, ventricular tachyarrhythmia, heart failure, kidney disease, hypotension/shock, hypoxaemia and anaemia.

Myocardial ischaemic or non-ischaemic conditions associated with increased cTn values are presented in **Table 1**. The complexity of clinical circumstances may sometimes make it difficult to discriminate specific individual mechanism(s) of myocardial injury. In this situation, the multifactorial contributions resulting in myocardial injury should be described in the patient record.

Table 1 **Reasons for elevation of cardiac troponin values because of myocardial injury**

Myocardial injury related to acute myocardial ischaemia
Atherosclerotic plaque disruption with thrombosis.
Myocardial injury related to acute myocardial ischaemia because of oxygen supply/demand imbalance
Reduced myocardial perfusion, e.g. • Coronary artery spasm, microvascular dysfunction • Coronary embolism • Coronary artery dissection • Sustained bradyarrhythmia • Hypotension or shock • Respiratory failure • Severe anaemia
Increased myocardial oxygen demand, e.g. • Sustained tachyarrhythmia • Severe hypertension with or without left ventricular hypertrophy
Other causes of myocardial injury
Cardiac conditions, e.g. • Heart failure • Myocarditis • Cardiomyopathy (any type) • Takotsubo syndrome • Coronary revascularization procedure • Cardiac procedure other than revascularization • Catheter ablation • Defibrillator shocks • Cardiac contusion
Systemic conditions, e.g. • Sepsis, infectious disease • Chronic kidney disease • Stroke, subarachnoid haemorrhage • Pulmonary embolism, pulmonary hypertension • Infiltrative diseases, e.g. amyloidosis, sarcoidosis • Chemotherapeutic agents • Critically ill patients • Strenuous exercise

For a more comprehensive listing, see[39–41]

Clinical presentations of myocardial infarction

Onset of myocardial ischaemia is the initial step in the development of MI and results from an imbalance between oxygen supply and demand. Myocardial ischaemia in a clinical setting can most often be identified from the patient's history and from the ECG. Possible ischaemic symptoms include various combinations of chest, upper extremity, mandibular or epigastric discomfort during exertion or at rest or an ischaemic equivalent such as dyspnoea or fatigue. Often, the discomfort is diffuse, not localized, nor positional, nor affected by movement of the region. However, these symptoms are not specific for myocardial ischaemia and can be observed in other conditions such as gastrointestinal, neurological, pulmonary or musculoskeletal complaints. MI may occur with atypical symptoms such as palpitations or cardiac arrest, or even without symptoms.[12] Very brief episodes of ischaemia too short to cause necrosis can also cause cTn release and elevations. The involved myocytes can subsequently die due to apoptosis.[42]

If myocardial ischaemia is present clinically or detected by ECG changes together with myocardial injury, manifested by a rising and/or falling pattern of cTn values, a diagnosis of acute MI is appropriate. If myocardial ischaemia is not present clinically, then elevated cTn levels may be indicative of acute myocardial injury if the pattern of values is rising and/or falling, or related to more chronic ongoing injury if the pattern is unchanging.[14] Similar considerations are relevant when evaluating events potentially related to procedures that may cause myocardial injury and/or MI. Additional evaluations may lead to the need for the initial diagnosis to be revised.

Patients with suspected acute coronary syndrome (ACS) that rule-out for MI with normal cardiac biomarker values (≤99th percentile URL) may have unstable angina or an alternative diagnosis. These patients should be evaluated and treated accordingly.[11,43]

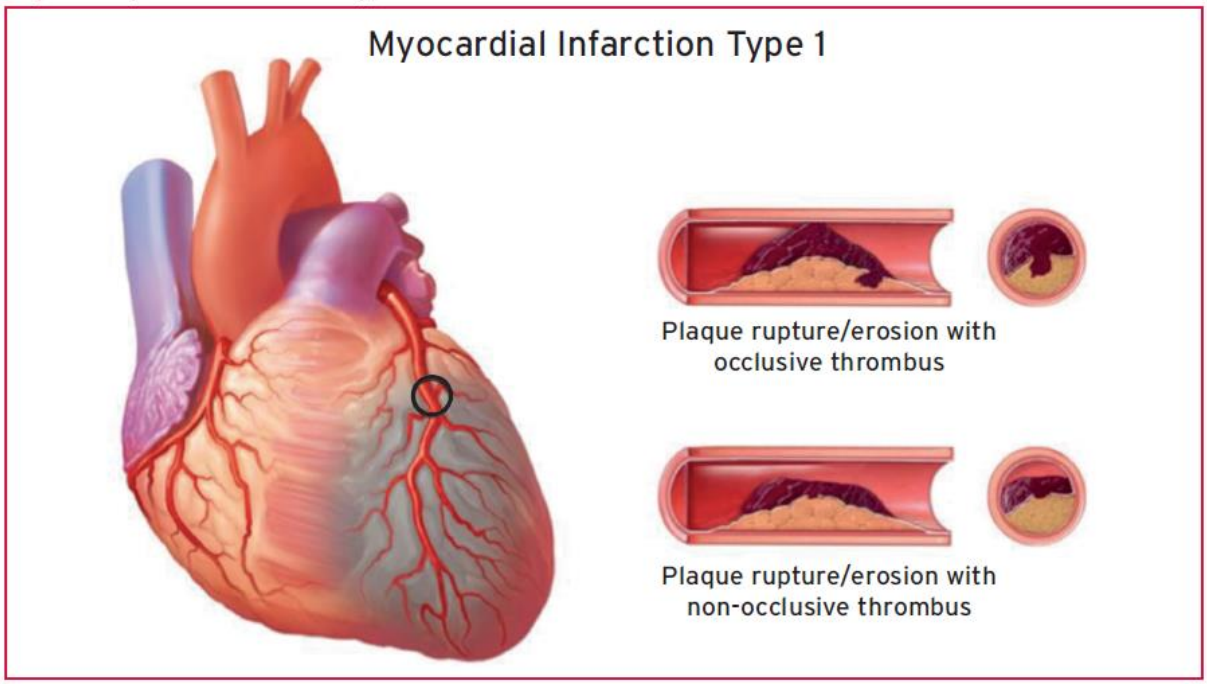
Clinical classification of myocardial infarction

For the sake of immediate treatment strategies such as reperfusion therapy, it is usual practice to designate MI in patients with chest discomfort or other ischaemic symptoms, who develop new ST-segment elevations in two contiguous leads, or new bundle branch blocks with ischaemic repolarization patterns as an ST-elevation MI (STEMI) (see ECG section). In contrast, patients without ST-segment elevation at presentation are usually designated non-ST-elevation MI (NSTEMI). The categories of patients with STEMI, NSTEMI or unstable angina are customarily included in the concept of ACS. In addition to these categories, MI may be classified into various types based on pathological, clinical, and prognostic differences along with different treatment strategies.

Myocardial infarction type 1

MI caused by athero-thrombotic coronary artery disease (CAD) and usually precipitated by atherosclerotic plaque disruption (rupture or erosion) is designated as a type 1 MI. The relative burden of atherosclerosis and thrombosis in the culprit lesion varies greatly, and the dynamic thrombotic component may lead to distal coronary embolization resulting in myocyte necrosis.[44,45] Plaque rupture may not only be complicated by intraluminal thrombosis but also by haemorrhage into the plaque through the disrupted surface.[44,45] (**Figure 3**).

Figure 3 Myocardial infarction type 1



Criteria for type 1 MI

Detection of a rise and/or fall of cTn with at least one value above the 99th percentile URL and with at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.[a]

cTn = cardiac troponin; ECG = electrocardiogram; URL = upper reference limit.

[a]Post-mortem demonstration of an athero-thrombus in the artery supplying the infarcted myocardium or macroscopically a large circumscribed area of necrosis with or without intramyocardial haemorrhage meets the type 1 MI criteria regardless of cTn values.

It is essential to integrate the ECG findings with the aim of classifying type 1 MI into STEMI or NSTEMI in order to establish the appropriate treatment according to current guidelines.[46,47]

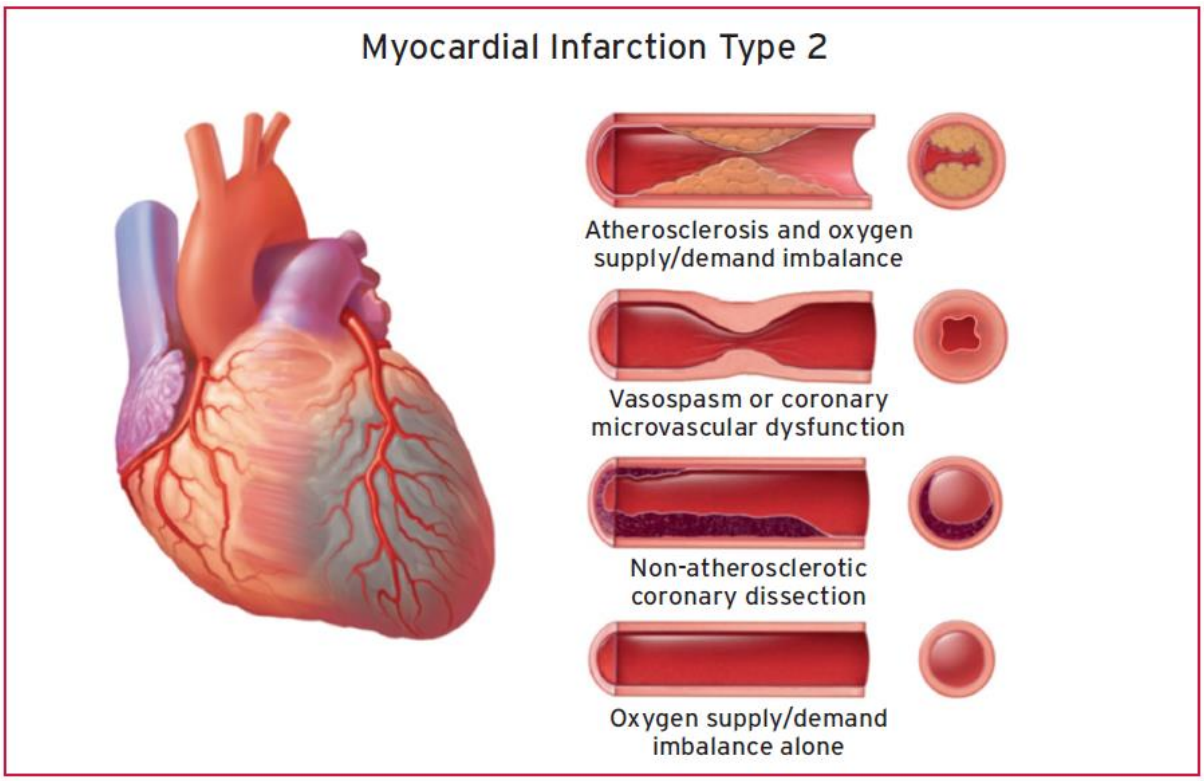
Myocardial infarction type 2

The pathophysiological mechanism leading to ischaemic myocardial injury in the context of a mismatch between oxygen supply and demand has been classified as type 2 MI.[!0,12] By definition, acute athero-thrombotic plaque disruption is not a feature of type 2 MI. In patients with stable known or presumed CAD, an acute stressor such as an acute gastrointestinal bleed with a precipitous drop in haemoglobin, or a sustained tachyarrhythmia with clinical manifestations of myocardial ischaemia, may result in myocardial injury and a type 2 MI. These effects are due to insufficient blood flow to the ischaemic myocardium to meet the increased myocardial oxygen demand of the stressor. Ischaemic thresholds may vary substantially in individual patients depending on the magnitude of the stressor, the presence of non-cardiac comorbidities and the extent of underlying CAD and cardiac structural abnormalities.

Studies have shown variable occurrences of type 2 MI depending on criteria used for diagnosis. Some reports rely on specific predetermined oxygen mismatch criteria,[48,49] whereas others apply more liberal criteria. Most studies show a higher frequency of type 2 MI in women. The short- and long-term mortality rates for patients with type 2 MI are generally higher than for type 1 MI patients in most but not all studies due to an increased prevalence of comorbid conditions,[49–57] Coronary atherosclerosis is a common finding in type 2 MI patients selected for coronary angiography. In general these patients have a worse prognosis than those without CAD.[54–57] Prospective evaluations of the importance of CAD with type 2 MI using consistent definitions and approaches are needed.

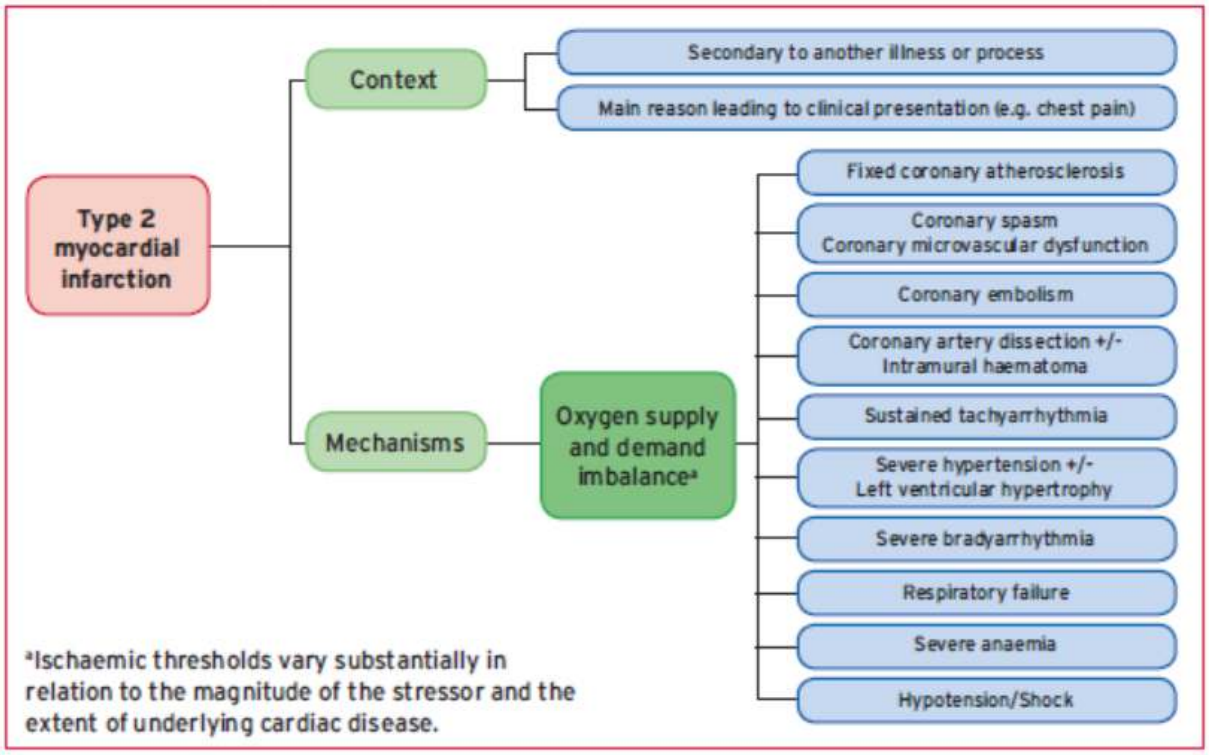
It has been shown that the frequency of ST-segment elevation in type 2 MI varies from 3–24%.[53] In some cases, coronary embolism caused by thrombi, calcium or vegetation from the atria or ventricles or acute aortic dissection may result in a type 2 MI. Spontaneous coronary artery dissection with or without intramural haematoma is another non-atherosclerotic condition that may occur, especially in young women. It is defined as spontaneous dissection of the coronary artery wall with accumulation of blood within the false lumen, which can compress the true lumen to varying degrees.[58] **(Figure 4)**

Figure 4 Myocardial infarction type 2



All of the clinical information available should be considered in distinguishing type 1 MI from type 2 MI. The context and mechanisms of type 2 MI should be considered when establishing this diagnosis (**Figure 5).** The myocardial oxygen supply/demand imbalance attributable to acute myocardial ischaemia may be *multifactorial*, related either to: reduced myocardial perfusion due to fixed coronary atherosclerosis without plaque rupture, coronary artery spasm, coronary microvascular dysfunction (which includes endothelial dysfunction, smooth muscle cell dysfunction and dysregulation of sympathetic innervation), coronary embolism, coronary artery dissection with or without intramural haematoma, or other mechanisms that reduce oxygen supply such as severe bradyarrhythmia, respiratory failure with severe hypoxaemia, severe anaemia, and hypotension/shock; or to increased myocardial oxygen demand due to sustained tachyarrhythmia or severe hypertension with or without left ventricular hypertrophy. In patients who undergo timely coronary angiography, description of a ruptured plaque with thrombus in the infarct-related artery may be helpful in making the distinction between type 2 MI vs. type 1 MI, but angiography is not always definitive, clinically indicated, or required to establish the diagnosis of type 2 MI.

Figure 5 Framework for type 2 MI considering the clinical context and pathophysiological mechanisms attributable to acute myocardial ischaemia. The illustration is modified from[59]



Criteria for type 2 MI

Detection of a rise and/or fall of cTn with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.

cTn = cardiac troponin; ECG = electrocardiogram; URL = upper reference limit.

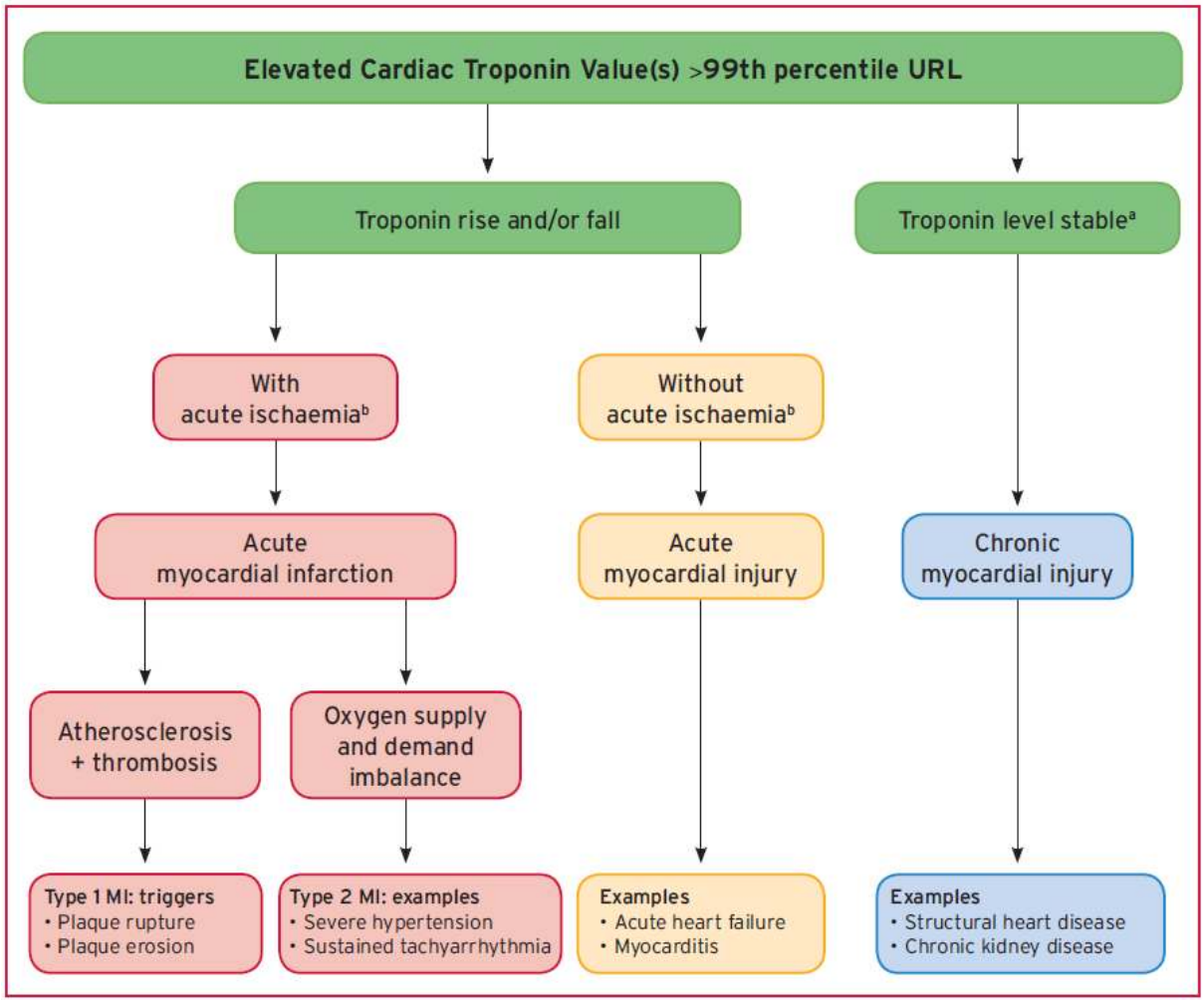
It appears advisable in the acute setting to treat the underlying ischaemic imbalance of oxygen supply and demand. This treatment may include volume adjustment, blood pressure management, administration of blood products, heart rate control, and respiratory support.[47,48] Depending on the clinical situation, coronary evaluations may be indicated to assess the likelihood of CAD. If that is present, the MI guidelines may be applied in accordance with the ECG findings of STEMI or NSTEMI.[46,47] However, if CAD is

absent, the benefit of cardiovascular risk reduction strategies with type 2 MI remains uncertain.

Myocardial infarction type 2 and myocardial injury

Type 2 MI and myocardial injury are frequently encountered in clinical practice and both are related to a poor outcome.[13,14,49,51,56] A conceptual model to facilitate the clinical distinction between acute ischaemic myocardial injury with or without an acute athero-thrombotic event (type 1 or type 2 MI) vs. conditions without acute ischaemic myocardial injury is displayed in **Figure 6**. Acute MI requires a rising and/or falling pattern of cTn values. Acute myocardial injury may also manifest such a pattern but if the injury is related to structural heart disease, the cTn values may be stable and unchanging. Type 2 MI and non-ischaemic myocardial injury may coexist. It should be recognized that some disease entities could be on both sides of the diagram, e. g. acute heart failure that may occur in the context of acute myocardial ischaemia. Nevertheless, abnormal cTn values in the setting of acute and/or chronic heart failure are often better categorized as a myocardial injury condition. Few studies have compared the incidence and clinical features of type 2 MI vs. myocardial injury without acute myocardial ischaemia.

Figure 6 A model for interpreting myocardial injury



URL = upper reference limit.
[a] Stable denotes ≤20% variation of troponin values in the appropriate clinical context.
[b] Ischaemia denotes signs and/or symptoms of clinical myocardial ischaemia.
Ischaemic thresholds vary substantially in relation to the magnitude of the stressor and the extent of underlying cardiac disease.

Myocardial infarction type 3

The detection of cardiac biomarkers in blood is fundamental for establishing the diagnosis of MI.[10,12] However, patients can manifest a typical presentation of myocardial ischaemia/infarction including presumed new ischaemic ECG changes or ventricular fibrillation and die before it is possible to obtain blood for cardiac biomarker determination; or the patient may succumb soon after the onset of symptoms before elevation of biomarker values has occurred. Such patients are designated as having a type 3 MI, when suspicion for an acute myocardial ischaemic event is high, even when cardiac biomarker evidence of MI is lacking.[10,12] This category allows the separation of fatal MI events from the much larger group of sudden death episodes that may be cardiac (non-ischaemic) or non-cardiac in origin. When a type 3 MI is diagnosed, and a subsequent autopsy reveals recent evidence of an MI, with a fresh or recent thrombus in the infarct-related artery, the type 3 MI should be reclassified to a type 1 MI. Original

investigations addressing the incidence of type 3 MI are sparse but a study showed an annual incidence below 10/100 000 person-years and a frequency of 3–4% among all types of MI.[60]

Criteria for type 3 MI

Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified or MI detected by autopsy examination.

Coronary procedure-related myocardial injury Cardiac procedural myocardial injury related to coronary revascularization procedures, whether percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), may be temporally related to the procedure itself, reflecting periprocedural issues, or may occur later reflecting complications of a device, such as early or late stent thrombosis or in-stent restenosis for PCI, or graft occlusion or stenosis with CABG. Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) allows assessment of procedural myocardial injury.[61–63] When quantifying procedural injury using LGE-CMR before and shortly after PCI or CABG it was found that 32% of patients had evidence of procedural myocardial injury.[63] Furthermore, it has been shown that patients with elevation of cTnI values after PCI or after CABG have evidence of procedural myocardial injury on CMR imaging.[61,62] For that reason, increased cTn values detected following a coronary revascularization procedure may reflect procedural myocardial injury. Of importance, if the baseline value before the procedure is above the 99th percentile URL, it is essential that cTn levels are stable prior to the evaluation in order to reliably establish the presence of acute procedural myocardial injury. It is not possible to determine, when intervening in a patient with an acute MI event resulting in an increased cTn level, how much of any given increase is related to the MI and how much is due to the procedure.

Criteria for cardiac procedural myocardial injury

Cardiac procedural myocardial injury is arbitrarily defined by increases of cTn values (>99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% of the baseline value when it is above the 99th percentile URL but it is stable or falling.

cTn = cardiac troponin; URL = upper reference limit.

A large proportion of patients have abnormal values of cTn after PCI, ranging from ~20–40% in stable CAD to 40–50% in MI.[64] The occurrence of procedural myocardial injury can be detected by measurement of cTn before the procedure and repeated 3–6

hours (h) later. Where the second value is rising, further sampling should be performed to document the peak cTn value. Increasing levels after the procedure can only be attributed with certainty to procedural myocardial injury when the pre-procedural cTn values are normal (≤99th percentile URL) or if they are stable or falling. For patients that present with an ACS and undergo a prompt coronary revascularization procedure resulting in only a single pre-procedural baseline value that is normal or mildly elevated, followed by subsequent post-procedural values that continue to increase, the post-procedural increase should be attributed to the index event. Recent data corroborate the importance of elevated pre-procedure cTn values as a prognostic marker in patients that have values that rise after the procedure.[65] To diagnose procedural myocardial injury in the clinical setting of only a single pre-procedural cTn value, the cardiac Tn values would need to be stable or falling post-procedure, followed by a subsequent increase that exceeds the 99th percentile URL, and if the value has not returned to baseline, the increase should be >20% with an absolute value > the 99th percentile URL.

Myocardial infarction associated with PCI (type 4a MI)

Stand-alone post-procedural increases of cTn values are sufficient to establish a diagnosis of procedural myocardial injury but not for the diagnosis of type 4a MI. Type 4a MI requires an elevation of cTn values >5 times the 99th percentile URL in patients with normal baseline values or in patients with elevated pre-procedure cTn in whom the cTn levels are stable (≤20% variation) or falling, the post-procedure cTn must rise >20% to an absolute value >5 times the 99th percentile URL. In addition, there should be evidence of new myocardial ischaemia, either from ECG changes, or from imaging evidence, or from procedure-related complications associated with reduced coronary blood flow such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, slow flow or no-reflow, or distal embolization. The use of hs-cTn assays to diagnose type 4a MI (and type 5 MI) is an area of active research. Many hs-cTn assays are available, which have wide dynamic ranges. Different criteria may be required for different assays. However, it has recently been shown that the optimal hs-cTnT threshold to predict cardiovascular events at 30 days and one year was very close to the five-fold increase suggested by the Third Universal Definition of MI.[12,66,67] These criteria are therefore retained because of a lack of new scientific evidence that identifies superior criteria for defining this MI subtype. Other criteria that meet the definition of type 4a MI regardless of hs-cTn or cTn values are the development of new pathological Q waves or autopsy evidence of recent procedure-related thrombus in the culprit artery.

Criteria for PCI-related MI ≤48 h after the index procedure (type 4a MI)

Coronary intervention-related MI is arbitrarily defined by elevation of cTn values >5 times the 99th percentile URL in patients with normal baseline values. In patients with elevated pre-procedure cTn in whom the cTn level are stable (≤20% variation) or falling, the post-procedure cTn must rise by >20%. However, the absolute post-procedural value must still be at least five times the 99th percentile URL. In addition, one of the following elements is required:

- New ischaemic ECG changes;
- Development of new pathological Q waves;[a]
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/ thrombus, disruption of collateral flow or distal embolization.[b]

cTn = cardiac troponin; ECG = electrocardiographic; h = hours; MI = myocardial infarction; PCI = percutaneous coronary intervention; URL = upper reference limit.

• [a]Isolated development of new pathological Q waves meets the type 4a MI criteria if cTn values are elevated and rising but <5 times the 99th percentile URL.

• [b]Post-mortem demonstration of a procedure-related thrombus in the culprit artery or macroscopically a large circumscribed area of necrosis with or without intra-myocardial haemorrhage meets the type 4a MI criteria.

Stent/scaffold thrombosis associated with PCI (type 4b MI)

A subcategory of PCI-related MI is stent/scaffold thrombosis, type 4b MI, as documented by angiography or autopsy using the same criteria utilized for type 1 MI. It is important to indicate the time of the occurrence of the stent/scaffold thrombosis in relation to the timing of the PCI procedure. The following temporal categories are suggested: *acute* 0–24 h, *subacute* >24 h to 30 days, *late* >30 days to 1 year, and *very late* >1 year after stent/scaffold implantation.[68]

Restenosis associated with PCI (type 4c MI)

Occasionally MI occurs and, at angiography, in-stent restenosis, or restenosis following balloon angioplasty in the infarct territory, is the only angiographic explanation since no other culprit lesion or thrombus can be identified. This PCI-related MI type is designated as type 4c MI, defined as focal or diffuse restenosis or a complex lesion associated with a

rise and/or fall of cTn values above the 99th percentile URL applying the same criteria utilized for type 1 MI.

Myocardial infarction associated with CABG (type 5 MI)

Numerous factors can lead to procedural myocardial injury during a CABG procedure. Many of them are related to the details of the cardiac preservation, the extent of the direct traumatic injury to the myocardium as well as any potential ischaemic injury. For that reason, increases in cTn values should be expected after all CABG procedures,[69,70] which need to be taken into account when comparing the extent of procedural myocardial injury after cardiac surgery to that associated with less invasive approaches. Depending on whether it is off-pump or on-pump surgery, procedural myocardial injury is observed among 32−44% of CABG patients when quantified by LGE-CMR.[61,63] The area under the curve (AUC) and routine cTn sampling has demonstrated an excellent linear relationship with the mass of the new injury as defined by LGE-CMR. AUC for CK-MB is also good although clearly inferior to cTnI.[69] However, these relationships vary depending on the nature of the procedure, the nature of the cardioplegia and the specific assay used to measure cTn. Very high cTn values are most often associated with coronary artery-related events.[61,63,69] Thus, although cardiac biomarkers and especially cTn appear robust for the detection of procedural myocardial injury and also, in the presence of new myocardial ischaemia, for the detection of type 5 MI, a specific cut-off value for all procedures and all cTn assays is difficult to define. However, in order to ensure consistency with the analogous standards of the preceding definition of type 5 MI[12] and because of the lack of new scientific evidence that identifies superior criteria for defining this MI subtype, it is suggested to apply a cTn value >10 times the 99th percentile URL as the cut-point during the first 48 h following CABG, occurring from a normal baseline cTn value (≤99th percentile URL), for diagnosing type 5 MI. It is important that the post-procedural elevation of cTn values is accompanied by ECG, angiographic or imaging evidence of new myocardial ischaemia/new loss of myocardial viability.[71] The higher cut-off of MI after CABG than after PCI (10 times vs. 5 times 99th percentile URL) has been arbitrarily selected due to the occurrence of more unavoidable myocardial injury during surgery than during PCI.

It should be recognized that ST-segment deviation and T wave changes are common after CABG due to epicardial injury and are not reliable indicators of myocardial ischaemia in this setting. However, ST-segment elevation with reciprocal ST-segment depression or other specific ECG patterns may be a more reliable finding of a potential ischaemic event.

Criteria for CABG-related MI ≤48 h after the index procedure (type 5 MI)

CABG-related MI is arbitrarily defined as elevation of cTn values >10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom cTn levels are stable (≤20% variation) or falling, the post-procedure cTn must rise by >20%. However, the absolute post-procedural value still must be >10 times the 99th percentile URL. In addition, one of the following elements is required:

- Development of new pathological Q waves;[a]
- Angiographic documented new graft occlusion or new native coronary artery occlusion;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.

CABG = coronary artery bypass grafting; cTn = cardiac troponin; h = hours; MI = myocardial infarction; URL = upper reference limit.

[a]Isolated development of new pathological Q waves meets the type 5 MI criteria if cTn values are elevated and rising but <10 times the 99th percentile URL.

Marked isolated elevation of cTn values within the 48 h post-operative period even in the absence of ECG/angiographic or other imaging evidence of MI indicates prognostically significant cardiac procedural myocardial injury.[72] The presence of significant procedural myocardial injury in patients with operative problems (e.g. difficulty coming off bypass, technically difficult anastomoses in a heavily calcified aorta, perioperative evidence of myocardial ischaemia, etc.) should prompt clinical review of the procedure and/or consideration of additional diagnostic testing for possible type 5 MI.

Other definitions of myocardial infarction related to PCI or CABG

There is no universal consensus on the cTn or hs-cTn cut-points that clearly distinguishe cardiac procedural myocardial injury from MI. The distinction is made on the basis of an injury created by a flow-limiting complication during the procedure that results in sufficient myocardial ischaemia to generate a procedure-related MI. The size of the insult will determine the magnitude of cTn release. Various groups have used multiples of the 99th percentile URL and set thresholds to diagnose peri-procedural MIs for clinical trials.[68,73] Unless a standard assay is used for all analyses, given the heterogeneity of cTn assays, this approach could lead to very different values depending on the assay used locally. The Academic Research Consortium-2 (ARC-2) suggests a post-procedural cTn value ≥35 times the 99th percentile URL for both PCI and CABG in patients that have a

normal baseline cTn value or in patients with elevated pre-procedure cTn values in whom the cTn levels are stable or falling. ARC-2 proposes that one ancillary criterion be required in addition to the ≥35 cTn rise to fulfill the definition of peri-procedural MI. The ancillary criteria are one or more of the following: new significant Q waves (or equivalent), flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch, or a substantial new loss of viable myocardium on echocardiography related to the procedure.[68] Furthermore, ARC-2 has defined stand-alone criteria for significant procedural myocardial injury if the rise in cTn is ≥70 times the 99th percentile URL (where the baseline is <URL or elevated and stable or falling).[68]

Recurrent myocardial infarction

Incident MI is defined as the individual's first MI. When features of MI occur in the first 28 days after an incident event, the second event is not counted as a new MI for epidemiological purposes. If characteristics of MI occur after 28 days following an incident MI, it is considered to be a recurrent MI.[11]

Reinfarction

The term reinfarction is used clinically for an acute MI that occurs within 28 days of an incident or recurrent MI.[11] The ECG diagnosis of suspected reinfarction following the initial MI may be confounded by the initial evolutionary ECG changes. Reinfarction should be considered when ST-elevation ≥1 mm recurs or new pathognomonic Q waves appear in at least two contiguous leads, particularly when associated with ischaemic symptoms. Re-elevation of the ST-segment can, however, also be seen in threatened myocardial rupture or in cases of pericarditis and should lead to additional diagnostic evaluation.

In patients where reinfarction is suspected from clinical signs or symptoms following the initial MI, an immediate measurement of cTn is recommended. A second sample should be obtained 3–6 h later or earlier with more sensitive cTn assays. If the cTn concentration is elevated, but stable or decreasing at the time of suspected reinfarction, the diagnosis of reinfarction requires a >20% increase of the cTn value in the second sample.[74] If the initial cTn concentration is normal, the criteria for new acute MI apply.[12]

Myocardial injury and infarction associated with cardiac procedures other than revascularization

Cardiac procedures such as transcatheter valve interventions may cause myocardial injury, both by direct trauma to the myocardium and by creating regional ischaemia secondary to coronary obstruction or embolization. Ablation of arrhythmias involves controlled procedural myocardial injury by application of warming or cooling of the tissue.

The extent of procedural myocardial injury can be assessed by serial cTn measurements. Increases of cTn values in this context should be considered procedural myocardial injury and not labelled as MI unless the biomarker criteria and one of the ancillary criteria for acute myocardial ischaemia listed for type 5 MI are present.[75,76]

Myocardial injury and infarction associated with non-cardiac procedures

Perioperative MI is one of the most important complications in major non-cardiac surgery, and it is associated with a poor prognosis.[77,78] Most patients who have a perioperative MI will not experience ischaemic symptoms due to anaesthesia, sedation, or pain relieving medications. Nevertheless, asymptomatic perioperative MI is as strongly associated with 30-day mortality as symptomatic MI.[77,78] Knowledge about hs-cTn values at baseline can help to identify patients having chronic cTn elevation before surgery as well as those at increased risk during and after the procedure.[79,80] Measurement of hs-cTn in post-operative samples reveals that as many as 35% of patients have levels above the 99th percentile URL and 17% have an elevation and a rising pattern of values indicative of evolving myocardial injury.[81] Those with a rising pattern of elevated hs-cTn values are at particular risk – the greater the rise, the greater the risk.[82,83]

The pathophysiologic mechanism of perioperative MI is subject to debate. It is recognized that the perioperative period is characterized by increased cardiac metabolic demand that may lead to MI in patients with otherwise stable CAD.[84,85] Thus, an angiographic investigation has identified demand myocardial ischaemia as the predominant aetiology of perioperative MI,[84,85] which together with a rise and/or fall of cTn values indicates type 2 MI. However, other angiographic studies have detected coronary plaque rupture in ~50–60% of patients with perioperative MI, [86,87] which qualifies as type 1 MI. On the other hand, perioperative myocardial injury without ancillary ischaemic evidence indicative for MI is a common complication after non-cardiac surgery that is associated with substantial short- and long-term mortality on a level with perioperative MI.[83]

Post-operative cTn surveillance is recommended for high-risk individuals. In order to properly interpret the aetiology of elevated post-operative values, a baseline pre-operative value is necessary to determine whether the increase is acute or more chronic. A diagnosis of MI, however, still requires, in addition to an increase of cTn values, evidence of myocardial ischaemia that may be evident from the peri- and post-operative period e.g. ST-segment changes on telemetry/ECG, repeated episodes of hypoxia, hypotension, tachycardia, etc. or imaging evidence of MI. In the absence of evidence for acute myocardial ischaemia, a diagnosis of acute myocardial injury is more appropriate. Ongoing research suggests the possibility that interventions may be helpful in this clinical situation.

Myocardial injury or infarction associated with heart failure

Depending on the assay used, detectable to clearly elevated cTn values being indicative of myocardial injury may be seen in patients with heart failure (HF), both with reduced ejection fraction (EF) and with preserved EF.[88] Using hs-cTn assays, measurable hs-cTn concentrations may be present in nearly all patients with HF, with a significant percentage exceeding the 99th percentile URL, particularly in those patients with more severe HF syndromes, such as in acutely decompensated HF.[87]

Beyond type 1 MI, multiple mechanisms have been proposed to explain measurable to pathologically elevated cTn concentrations in patients with HF.[88,89] For example, type 2 MI may result from increased transmural pressure, small-vessel coronary obstruction, endothelial dysfunction, anaemia or hypotension. Besides type 1 MI or type 2 MI, cardiomyocyte apoptosis and autophagy due to wall stretch have been experimentally demonstrated. Direct cellular toxicity related to inflammation, circulating neurohormones and infiltrative processes may present with HF and abnormal cTn measurements indicating myocardial injury. Finally, exocytosis of the early releasable cytosolic troponin pool into the blood stream from stressed cardiomyocytes has also been suggested as a cause of elevated cTn values.[89]

In the context of an acutely decompensated HF presentation, cTn should always be promptly measured and the ECG recorded, with the goal of identifying or excluding myocardial ischaemia as the precipitant. In this setting, elevated cTn values should be interpreted with a high level of suspicion for type 1 MI if a significant rise and/or fall of the marker is seen, especially if it is accompanied by chest discomfort or other symptoms suggestive of myocardial ischaemia, and/or if new ischaemic ECG changes or loss of myocardial function on non-invasive testing are found. Shortness of breath, the cardinal symptom of acutely decompensated HF, may be an ischaemic equivalent, but in the absence of corroborating evidence for a coronary mechanism, caution is advised in its interpretation. Coronary artery anatomy may be known and this knowledge may be used to interpret abnormal cTn results. However, further information, such as renal function, myocardial perfusion studies, coronary angiography, or CMR is often required to better understand the cause of deviant cTn values.

Takotsubo syndrome

Takotsubo syndrome (TTS) can mimic MI and is found in ~1−2% of patients presenting with suspected STEMI.[90] The onset of TTS is often triggered by intense emotional or

physical stresses such as bereavement. Over 90% of patients are post-menopausal women. Cardiovascular complications occur in ~50% of patients presenting with TTS, and the inpatient mortality is similar to STEMI (4−5%) due to cardiogenic shock, ventricular rupture or malignant arrhythmias.[90] TTS usually presents similar to ACS. ST-segment elevation is frequent (44%) but the extent of the ST-segment elevation is usually widespread across the lateral and precordial leads, beyond that of a single coronary artery distribution. ST-segment depression occurs in <10% of patients and after 12−24 h, deep, symmetric T wave inversion and QTc prolongation are typically observed.[91,92]

There are usually transient elevations in cTn levels (>95% cases), but the peak cTn values observed are modest and in contrast with the large territory of ECG changes or left ventricular (LV) dysfunction. The rise and fall in cTn levels support an acute myocardial injury, secondary to the high catecholamine surges which are known to trigger cTn release from cardiomyocytes. Coronary vasospasm or high myocardial strain hypercontractility or high ventricular afterload may also contribute to myocardial ischaemia. The diagnosis of TTS should be suspected when the clinical manifestations and ECG abnormalities are out of proportion to the degree of elevation of cTn values and when the distribution of the LV wall motion abnormalities does not correlate with a single coronary artery distribution. However, coronary angiography and ventriculography are often needed to secure the diagnosis.

In most cases the coronary arteries are angiographically normal and where CAD is present (~15% cases) it is not sufficient to explain the observed pattern of regional wall motion abnormalities. Left ventriculography during catheterization and/or echocardiography may show a variety of LV regional wall motion abnormalities including apical (82% of patients), mid-ventricular (14.6%), basal (2.2%) or focal (1.5%) akinesis or hypokinesis in a circumferential pattern involving >1 coronary artery territory. Evidence of myocardial oedema is often seen on CMR imaging during the acute phase but LGE is usually absent. The recovery time for LV function varies from hours to several weeks.[93] Cardiac function may not return to normal, with persisting abnormalities of diastolic function, myocardial reserve during exercise, or rhythm disturbances at long term follow up in 10−15% of patients. In the absence of recovery of regional wall motion abnormalities, LGE-CMR is recommended to exclude MI with spontaneous recanalization.

The distinction between MI and TTS can be challenging, particularly when concurrent CAD is present (15% in the International Takotsubo Registry).[91] Two additional features that are helpful in distinguishing TTS from acute MI are QTc prolongation >500 ms during the acute phase, and recovery of LV function over 2−4 weeks. There are rare

cases described where MI and TTS co-exist, e.g. MI-induced TTS or TTS with secondary plaque rupture, but this occurs where the acute regional wall motion abnormalities are more extensive than the culprit coronary artery territory and fulfil the pattern and definition of TTS.[94]

Myocardial infarction with non-obstructive coronary arteries (MINOCA)

It is increasingly recognized that there is a group of MI patients with no angiographic obstructive CAD (≥50% diameter stenosis in a major epicardial vessel) and the term myocardial infarction with non-obstructive coronary arteries (MINOCA) has been coined for this entity.[95,96] The diagnosis of MINOCA, like the diagnosis of MI, indicates that there is an ischaemic mechanism responsible for the myocyte injury, (i.e. non-ischaemic causes such as myocarditis have been excluded). Furthermore, the diagnosis of MINOCA necessitates that obstructive CAD has not been inadvertently overlooked (e.g. spontaneous coronary artery dissection). The prevalence of MINOCA is estimated to be 6−8% among patients diagnosed with MI and more common in women than men as well as in patients presenting with NSTEMI than STEMI.[96–98] Atherosclerotic plaque disruption and coronary thrombosis may be a cause of MINOCA, i.e. type 1 MI. However, coronary spasm and spontaneous coronary dissection may be involved as well, i.e. type 2 MI, along with other possible causes. Additional coronary imaging and functional testing methods may be useful to elucidate the mechanisms of ischaemia in MINOCA.[46]

Myocardial injury and/or infarction associated with kidney disease

Many patients with chronic kidney disease (CKD) have elevation of cTn values.[99,100] With hs-cTn assays, the majority of patients with end-stage renal disease will have elevation of hs-cTn values above the 99th percentile URL.[99,101] This is particularly the case for hs-cTnT which is more often elevated compared to hs-cTnI.[99,102] It has been shown using hs-cTn assays that renal dysfunction is commonly associated with cardiovascular abnormalities.[102–104] In autopsy studies, elevation of cTn values was invariably associated with evidence of myocardial injury.[15] Recently, a minor effect on renal clearance of cTn has been shown when levels are low but not in response to acute episodes of myocardial injury.[105] The mechanisms include increased ventricular pressure, small-vessel coronary obstruction, anaemia, hypotension, and possibly direct toxic effects on the myocardium associated with the uraemic state.[89] Cardiomyocyte apoptosis and autophagy due to acute wall stretch have been demonstrated experimentally.[18] Thus, baseline elevation of cTn values is common, and because they reflect myocardial injury, such elevation is highly prognostic over time.[99]

Diagnosing MI in patients with CKD and elevated cTn levels may be difficult if symptoms or ECG changes indicating myocardial ischaemia are absent. However, studies suggest that serial changes in cTn levels are equally effective in diagnosing MI in patients with CKD and in those with normal renal function.[106] If the level of elevated cTn values is unchanging, and the timing of the event makes a rising and/or falling pattern unlikely, the elevated level, even if substantial, is likely a reflection of chronic myocardial injury. This does not imply that these patients are free of CAD since renal dysfunction and CAD are correlated. However, if a rising and/or falling pattern is present then the aetiology of the abnormal cTn values could be acute volume overload, congestive HF, or MI. If a rising and falling pattern is seen, and it is accompanied by ischaemic symptoms, new ischaemic ECG changes, or loss of viable myocardium on imaging, a diagnosis of acute MI is likely. There are no data to suggest that different criteria for the cTn decision levels are needed for these patients. At times, additional imaging studies may be necessary to determine the appropriate diagnosis. It should be noted that if CKD patients present late after the onset of chest pain, it may be difficult to observe a rise and/or fall of cTn values in the short term, particularly when the baseline value is elevated. Such a situation should not obviate the diagnosis of MI when the clinical evidence is strong.

Myocardial injury and/or infarction in critically ill patients

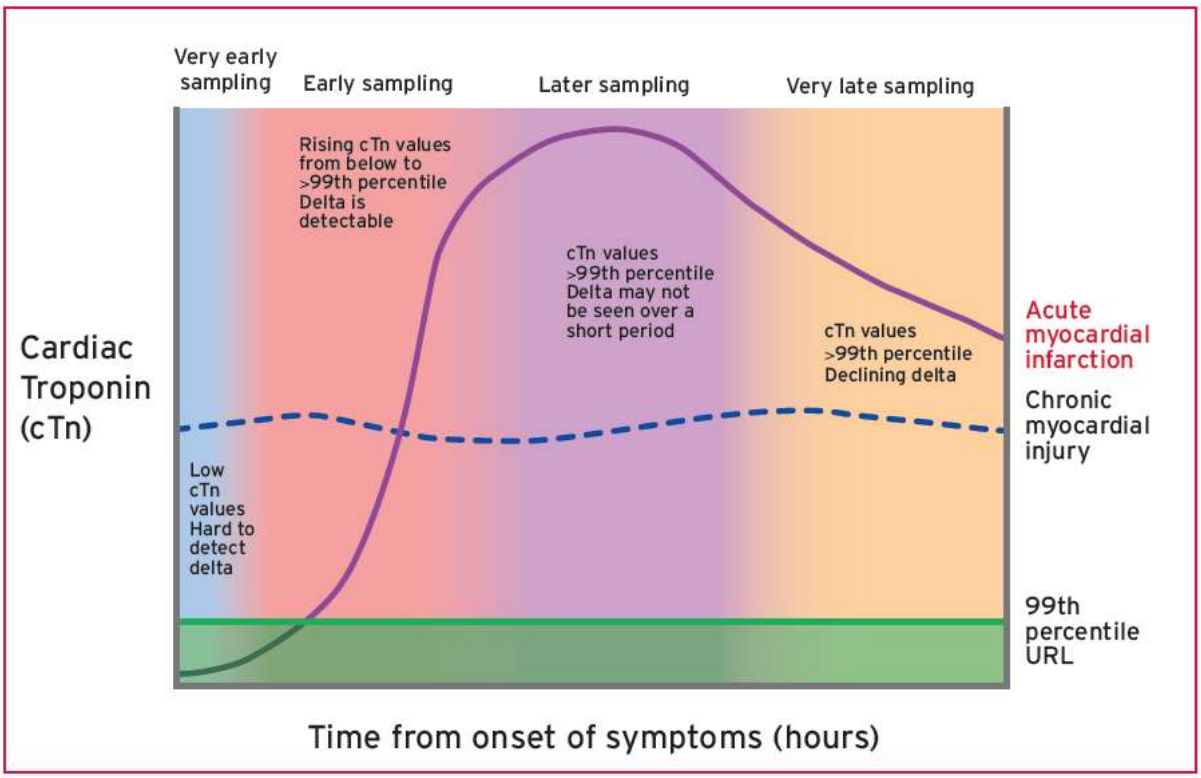
Elevations of cTn values are common in patients in the intensive care unit and are associated with adverse prognosis regardless of the underlying disease state.[107,108] Some elevation of cTn values may reflect type 2 MI due to underlying CAD and increased myocardial oxygen demand,[109] whereas in other patients, type 1 MI may occur because of plaque disruption leading to thrombosis in a coronary artery. However, other patients may have elevated cTn values and marked decreases in EF due to sepsis caused by endotoxin, with myocardial function recovering completely with normal EF once the sepsis is treated. It is frequently challenging for the clinician caring for a critically ill patient with a severe single organ or multi-organ pathological condition to decide on a plan of action when the patient has elevated cTn values. If and when the patient recovers from the critical illness, clinical judgement should be employed to decide whether, and to what extent, further evaluation for CAD or structural heart disease is indicated.[110]

Biochemical approach for diagnosing myocardial injury and infarction

cTnI and cTnT are the preferred biomarkers recommended to both rule in and rule out myocardial injury and thus to define MI and each specific subtype of MI.[12,22,23,31] Detection of a rise and/or fall of cTn values is essential and a key early component along with other elements of the clinical evaluation to establish the diagnosis of acute MI. Criteria for determining a pathological rise between two serial cTn values are assay-

dependent and continue to evolve. An idealized view of troponin kinetics in patients with acute MI is shown in **Figure 7**.

Figure 7 Conceptual illustration of early cardiac troponin kinetics in patients after acute myocardial injury including acute myocardial infarction



cTn = cardiac troponin; URL = upper reference limit.

The timing of biomarker release into the circulation is dependent on blood flow and how soon after the onset of symptoms samples are obtained. Thus, the ability to consider small changes as diagnostic can be problematic. In addition, many comorbidities increase cTn values, and in particular hs-cTn values, so that elevations can be present at baseline even in those with myocardial infarction who present early after the onset of symptoms. Changes in cTn values or deltas can be used to define acute compared to chronic events and the ability to detect these is indicated in the figure. Increased cTn values can often be detected for days after an acute event.

It should be appreciated that because biomarker release is substantially dependent on blood flow,[111,112] there is significant variability in the time to peak value (velocity), the time when a normal value may become greater than the 99th percentile URL or when a changing pattern of values can be observed. The ability to define a changing pattern will also depend on timing. For example, around peak values, it may be difficult to observe a changing pattern of values. Similarly, the downslope of the time-concentration curve is much slower than the upslope. These issues need to be taken into account when defining whether or not a changing pattern is present. In addition, it is important to make sure that a given change is greater than can be anticipated by variability alone. This is defined for conventional cTn assays as a change ≥3 times the standard deviation around the measurement of the individual assay at relevant values.[12,22] For hs-cTn assays, biological

variation also needs to be considered. In most studies, conjoint analytical and biological variation is in the range of 50−60%.

For that reason, this percentage has been suggested for use when initial baseline values are ≤99th percentile URL.[23,31,113] However, for individuals with an initial value >99th percentile URL, a lesser degree of change during serial measurements is necessary to achieve improved clinical sensitivity (as compared to individuals with initial values ≤99th percentile URL). Thus, an expert consensus group has recommended serial changes ≥20% be used in this situation.[23] Absolute changes are assay dependent but appear superior to relative percent changes with hs-cTn assays,[114] and in some studies this is especially the case when the initial value is increased.[115] The use of a fixed absolute value change criteria translates into a smaller percentage or relative change as absolute values rise and therefore provides greater sensitivity. The use of a changing pattern is important in allowing clinicians to differentiate an acute from a chronic cTn increase above the 99th percentile URL.[113-115] Using criteria less than conjoint analytical and biological variation will reduce the clinical specificity of hs-cTn assays.[113,116] An imprecision of ≤10% coefficient of variation (CV) at the 99th percentile URL is also mandatory for hs-cTn assays.[31] The use of non-hs-cTn assays that do not have imprecision (≤10% CV at the 99th percentile URL) makes determination of a significant serial change more difficult but does not cause false positive results. Assays with CVs between 10−20% are acceptable for clinical use. However, assays with CVs >20% at the 99th percentile URL should not be used.[117]

If a cTn assay is not available, the best alternative is CK-MB measured by a mass assay. As with cTn, an increased CK-MB value is defined as a measurement above the 99th percentile URL, which is designated as the decision level for the diagnosis of MI. Sex-specific CK-MB values should be employed.[118]

Analytical issues of cardiac troponins

The analytical sensitivity (limit of detection [LoD]) of cTnI and cTnT assays varies 10-fold.[31,119] Because assays are not standardized, values from one assay cannot be directly compared with those from another assay. Furthermore, values may be different between assay generations[120] and changes can even occur when the same assay reagents are measured on different instruments.[121] Thus, clinicians must learn about their local assay and should look for reliable information, e.g. available on the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) website (http://www.ifcc.org/executive-board-and-council/eb-task-forces/task-force-on-clinical-applications-of-cardiac-bio-markers-tf-cb/), when they have questions concerning analytical issues. The current guidelines accommodate all assays, whether hs-cTn,

contemporary (conventional) cTn or point of care (POC) cTn. While hs-cTn assays are able to measure relatively low values and document small increases above the 99th percentile URL, many contemporary and POC cTn assays may not detect small increasing values within the reference interval or slightly above the 99th percentile URL, leading to substantial differences in the frequency of events based solely on the cTn assay used. These differences are amplified when multiples of the 99th percentile URL are used. At present, IFCC guidelines support the concept that hs-cTn assays are differentiated from contemporary or POC cTn assays by their ability to measure cTn values above the assay's LoD in ≥50% of healthy individuals.[31,118,119,122] This provides a rough estimate of assay sensitivity. It is recommended that values for cTn assays be reported as whole numbers in nanograms per litre (ng/L) to avoid interpretation problems associated with multiple zeroes and decimal points that can often result in confusion.[31] Clinicians should avoid mixing the units from contemporary assays with those from hs-cTn assays. All assays, including cTn assays, have some analytic problems resulting in false positive and false negative results but these are uncommon (<0.5%).[22] These problems are less common with hs-cTn assays.[23]

Conjoint biologic and analytic variation of hs-cTn assays is in the range of 50–60%.[123] When values are elevated, analytic variation is less and a value of 20% can be used to determine that values are stable in the proper clinical context. For example, changes may be difficult to observe over short periods of time in those who present early after the onset of symptoms of acute MI, those who present late and are on the downslope of the time-concentration curve, and those who have values near peak where they may be transitioning from a rising to a falling pattern.[113,123]

The 99th percentile upper reference limit

The 99th percentile URL is designated as the decision level for the presence of myocardial injury and must be determined for each specific assay with quality control materials used at the URL to validate appropriate assay imprecision. The cTn assay 99th percentile URL values used in clinical practice and research can be found both in manufacturers' package inserts or in peer-reviewed publications and on the IFCC website.[118–120] Clinicians should be aware that for all cTn assays, including hs-cTn assays, there is still no expert opinion or consensus about specific criteria for how the 99th percentile URL should be defined.[124] We endorse IFCC guidelines on the technical issues related to hs-cTn assays including how studies should be configured to determine 99th percentile URLs.[120] The guidelines include the clinical or surrogate biomarker screening that may be needed to better define the 99th percentile URL and the statistical methods that can be applied, but do not include a requirement for cardiac imaging.[120] Screening of apparently healthy subjects with imaging has been shown to lower the observed 99th

938 percentile URL value, but is not a practical standard for the *in vitro* diagnostic industry to
939 use.[124,125] Thus, there is the possibility of false negative values using the manufacturer's
940 reported 99th percentile URL values. hs-cTn assays demonstrate shifts to higher values
941 for the 99th percentile URL in association with comorbidities and age over >60
942 years.[101,125–127] However, at present, age-dependent cut-points are not recommended for
943 clinical use. Clinicians should rely instead on changing values during serial measurements
944 of cTn for the diagnosis of acute myocardial injury, including MI. Significantly lower
945 values are observed among women compared to men, and therefore sex-specific 99th
946 percentile URLs are recommended for hs-cTn assays.[31,118–120] For some hs-cTn assays,
947 sex-specific cut-off values have been reported to improve diagnostic and prognostic
948 information in patients with possible acute MI.[128,129] However, there is controversy as to
949 whether this approach provides valuable additional information for all hs-cTn assays.[130]
950
951 **Operationalizing criteria for myocardial injury and infarction**
952 Blood samples for the measurement of cTn should be drawn on first assessment
953 (designated as 0 h) and repeated 3–6 h later, or earlier with hs-cTn assays. The
954 sampling interval will impact the clinical cut-off at baseline and what is determined to be
955 a pathological rise and/or fall of the biomarker. Sampling beyond 6 h may be required if
956 further ischaemic episodes occur, or in high-risk patients. To establish the diagnosis of an
957 acute MI, a rise and/or fall in cTn values with at least one value above the 99th
958 percentile URL is required, coupled with a high clinical and/or ECG likelihood of
959 myocardial ischaemia. hs-cTn assays shorten the time to diagnosis in many patients to
960 within 3 h of onset of symptoms, but there are still some patients who may rule in late
961 (at 6 h).[131] Furthermore, some patients with acute myocardial injury presenting late after
962 the onset of acute MI (>12–18 h) and who are on the downslope of the time-
963 concentration curve may require longer periods of time for a changing pattern to be
964 detected.[131] In addition, it should be noted that with the implementation of cTn and hs-
965 cTn assays, the frequency of unstable angina will decrease and the diagnosis of NSTEMI
966 will increase.[132,133] The magnitude of these changes using hs-cTn assays have been
967 reported in the range of 18–30%.[134] Assuming proper timing of symptoms, acute
968 ischaemia should result in a change in hs-cTn; however, there may be patients in whom
969 it is difficult to ascertain the timing of symptom onset. Thus, despite typical chest
970 discomfort, these patients may have hs-cTn values that are not elevated. Other patients
971 with symptoms suggestive of unstable angina may have increased hs-cTn values as a
972 result of structural heart disease with or without acute myocardial ischaemia. This latter
973 group may be particularly difficult to distinguish from patients presenting with late
974 NSTEMI with a slow decline in troponin values that can be observed in late presenters.[131]
975 Finally, some patients may manifest a changing pattern of troponin values with a
976 magnitude that does not exceed the delta suggested for diagnosis or who fail to manifest

a value >99th percentile URL. This is a group of patients that deserves close scrutiny because they may be at high risk. The triage of these patients can only be accomplished based on clinical evaluation.

Strategies employing either very low levels of hs-cTn on presentation or the lack of any change and persistently normal hs-cTn values over a 1–2 h period after presentation have been advocated to exclude acute myocardial injury and MI as well. A single sample rule out strategy using a very low value (in many cases the LoD of the assay) has high sensitivity for myocardial injury and therefore high negative predictive value to exclude MI.[135] This strategy should not be used in those who present early, i.e. <2 h after the onset of chest discomfort. Some studies indicate that the single sample approach provides optimal sensitivity and negative predictive accuracy in patients otherwise at low risk and those with a normal ECG.[136-138] However, one concern about very short rule out periods is that the precision of the assays may not permit small differences to be distinguished.[139–142] These criteria have not, and should not, be applied to patients with hs-cTn elevations.

The clinical specificity and positive predictive value of such 1–2 h sampling approaches for ruling in MI are limited by the substantial proportion of individuals who meet the proposed biomarker criteria with diagnoses other than MI.[136,141] Thus, the use of a rapid rule in/out MI protocol does not absolve the clinician from considering other causes for acute myocardial injury.[142] In addition, considering a broader population of patients, inclusive of those who present atypically, those with end-stage renal disease and the critically ill, the cut-points to be used will likely need to be altered.[139] Such patients were excluded from the majority of emergency department evaluation studies.[108,136,142]

The demonstration of a rising and/or falling pattern is needed to distinguish acute injury from chronic conditions associated with structural heart disease that can have chronic increases of cTn values. For example, patients with renal failure[99,143,144] or LV hypertrophy[145] can have significant chronic increases in cTn values. These increases can be marked but do not change acutely during serial sampling. However, a falling pattern may take longer to be observed in patients with a high pre-test risk of MI who present late after symptom onset.[146] These patients who have cTn values on the downslope of the time-concentration curve have a slow decline in values (**Figure 7**). Thus, detecting a changing pattern over short periods of time may be difficult.[117] Depending on the extent of myocardial injury, cTn values may remain above the 99th percentile URL for a longer period of time.[22,23] An increased cTn value above the 99th percentile URL, with or without a dynamic change of values or in the absence of clinical evidence of ischaemia, should prompt a search for other diagnoses associated with myocardial injury, as shown in **Table 1**.

Electrocardiographic detection of myocardial infarction

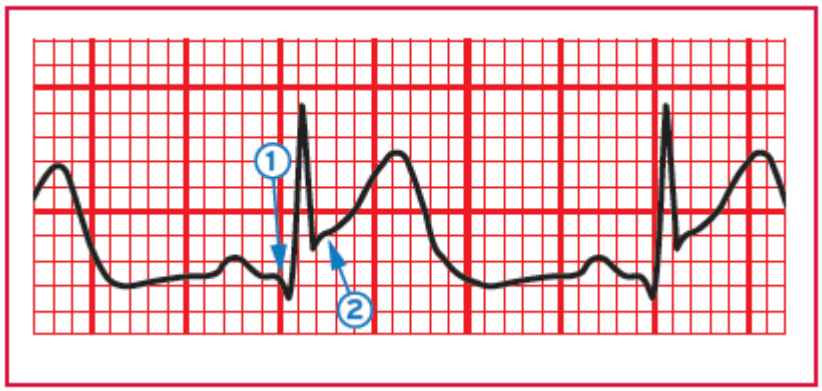
The ECG is an integral part of the diagnostic work-up of patients with suspected MI and should be acquired and interpreted promptly (i.e. target within 10 min) after first medical contact.[47,147] Pre-hospital ECGs reduce the time to diagnosis and treatment, and can facilitate triage of STEMI patients to hospitals with PCI capability if within the recommended time interval (120 min from STEMI diagnosis).[148] Acute myocardial ischaemia is often associated with dynamic changes in ECG waveform and serial ECG acquisition can provide critical information, particularly if the ECG at initial presentation is non-diagnostic. Recording several standard ECGs with fixed electrode positions at 15−30 min intervals for the initial 1−2 h, or the use of continuous computer-assisted 12-lead ECG recording, if available, to detect dynamic ECG changes, is reasonable for patients with persistent or recurrent symptoms or an initial non-diagnostic ECG.[149] Serial or continuous ECG recordings may be helpful in determining reperfusion or reocclusion status. Reperfusion is usually associated with a large and prompt reduction in ST-segment elevation.

More profound ST-segment shift or T wave inversion involving multiple leads/territories are associated with a greater degree of myocardial ischaemia, and a worse prognosis. For example, ST-segment depression ≥1 mm in six leads that may be associated with ST-segment elevation in leads aVR or lead V_1 and haemodynamic compromise is suggestive evidence of multivessel disease or left main disease. Pathologic Q waves increase the prognostic risk. Other ECG signs associated with acute myocardial ischaemia include cardiac arrhythmias, intraventricular bundle branch blocks, atrioventricular conduction delays, and loss of precordial R wave amplitude, a less specific finding. The ECG by itself is often insufficient to diagnose acute myocardial ischaemia or infarction, since ST deviation may be observed in other conditions, such as acute pericarditis, LV hypertrophy (LVH), left bundle branch block (LBBB), Brugada syndrome, TTS, and early repolarization patterns.[150] A prior ECG is often helpful in distinguishing a new from a chronic finding but should not delay the decision for treatment.

Prolonged new convex ST-segment elevation, particularly when associated with reciprocal ST-segment depression, usually reflects acute coronary occlusion and results in myocardial injury with necrosis. Reciprocal changes can help to differentiate STEMI from pericarditis or early repolarization changes. As in cardiomyopathy, Q waves may also occur due to myocardial fibrosis in the absence of CAD. One of the earlier manifestations of myocardial ischaemia is typical T wave and ST-segment changes. Increased hyperacute T wave amplitude, with prominent symmetrical T waves in at least two contiguous leads, is an early sign that may precede the elevation of the ST-segment. In

general, the development of new Q waves indicates myocardial necrosis, which starts in minutes/hours after the myocardial insult. Transient Q waves may be observed during an episode of acute ischaemia or (rarely) during acute MI with successful reperfusion. **Table 2** lists ST-segment–T wave (ST-T) criteria suggestive of acute myocardial ischaemia that may or may not lead to MI. The J-point (junction between QRS termination and ST-segment onset) is used to determine the magnitude of the ST-segment shift with the onset of the QRS serving as the reference point. In patients with a stable baseline, the TP segment (isoelectric interval) is a more accurate method to assess the magnitude of ST-segment shift, and in distinguishing pericarditis (PTa depression) from acute myocardial ischaemia. Tachycardia and baseline shift are common in the acute setting and can make this determination difficult. Therefore, QRS onset is recommended as the reference point for J-point determination. **(Figure 8)**

Figure 8 ECG example of ST-segment elevation



ECG = electrocardiogram.
The initial onset of the Q wave shown by arrow 1 serves as the reference point and arrow 2 shows the onset of the ST-segment or J-point. The difference between the two identifies the magnitude of displacement. Measurements of both arrows should be made from the top of the ECG line tracing.

New, or presumed new, J-point elevation ≥1 mm (1 mm = 0.1 millivolt [mV]) is required in all leads other than V_2 and V_3 as an ischaemic response. In healthy men under age 40, J-point elevation can be as much as 2.5 mm in leads V_2 or V_3, but it decreases with increasing age. Sex differences require different cut-points for women, since J-point elevation in healthy women in leads V_2 and V_3 is less than in men.[5] The criteria in **Table 2** require that the ST shift be present in two or more contiguous leads. For example, ≥2 mm of ST-elevation in lead V_2 and ≥1 mm in lead V_1 would meet the criteria of two abnormal contiguous leads in a man ≥40 years old. However, ≥1 mm and <2 mm of ST-elevation, seen only in leads V_2–V_3 in men (or <1.5 mm in women), may represent a normal finding.

Table 2 Electrocardiographic manifestations suggestive of acute myocardial ischaemia (in the absence of left ventricular hypertrophy and bundle branch block)

ST-elevation
New ST-elevation at the J-point in two contiguous leads with the cut-point: ≥1 mm in all leads other than leads V_2-V_3 where the following cut-points apply: ≥2mm in men ≥40 years; ≥2.5 mm in men <40 years, or ≥1.5 mm in women regardless of age.[a]
ST-depression and T wave changes
New horizontal or downsloping ST-depression ≥0.5 mm in two contiguous leads and/or T inversion >1 mm in two contiguous leads with prominent R wave or R/S ratio >1.

[a]When the magnitudes of J-point elevation in leads V2 and V3 are registered from a prior ECG, new J-point elevation ≥1 mm (as compared to the earlier ECG) should be considered an ischaemic response. For bundle branch block, see section below.

It should be noted that lesser degrees of ST displacement or T wave inversion than those described in **Table 2** can also represent an acute myocardial ischaemic response. In patients with known or high likelihood of CAD, the clinical presentation is critical to enhance the specificity of these findings.

Absence of ST-elevation in the precordial leads, tall, prominent, symmetrical T waves in the precordial leads, upsloping ST-segment depression >1 mm at the J-point in the precordial leads, and in most cases ST-segment elevation (>1 mm) in lead aVR or the symmetrical, often deep (>2 mm), T wave inversions in the anterior precordial leads are associated with significant left anterior descending artery (LAD) occlusion.[151–153] ST-elevation in lead aVR >1 mm may accompany anterior or inferior STEMI and is associated with increased 30 day mortality in patients with acute MI.[154] Pulmonary embolism, intracranial processes, electrolyte abnormalities, hypothermia, or perimyocarditis may also result in ST-T abnormalities and should be considered in the differential diagnosis.

The ECG diagnosis of atrial infarction should be suspected in the context of ventricular infarction (particularly when the right ventricle is involved) if small, transient elevations and reciprocal depressions of the PR (PTa) segment are noted associated with changes in configuration of the P wave.

Application of supplemental ECG leads

Supplemental leads as well as serial ECG recordings should be deployed with a very low threshold in patients who present with ischaemic chest pain and a non-diagnostic initial ECG.[155,156] ECG evidence of myocardial ischaemia in the distribution of a left circumflex artery is often overlooked. Isolated ST-segment depression ≥0.5 mm in leads V_1–V_3 may indicate left circumflex occlusion and can best be captured using posterior leads at the fifth intercostal space (V_7 at the left posterior axillary line, V_8 at the left mid-scapular line, and V_9 at the left paraspinal border). Recording of these leads is strongly recommended in patients with high clinical suspicion for acute circumflex occlusion (e.g. initial ECG non-diagnostic, or ST-segment depression in leads V_1-V_3).[156] A cut-point of 0.5 mm ST-elevation is recommended in leads V_7–V_9; specificity is increased at a cut-point ≥1 mm ST-elevation and this cut-point should be used in men <40 years old. ST-segment depression in leads V_1–V_3 may be suggestive of inferobasal myocardial ischaemia (previously termed posterior infarction), especially when the terminal T wave is positive (ST-elevation equivalent); however, this is non-specific.

In patients with inferior and suspected right ventricular infarction, leads aVR or V_1 may exhibit ST-segment elevation ≥1 mm. The early recording of right precordial leads V_3R and V_4R should be performed, since ST-elevation ≥0.5 mm (≥1 mm in men <30 years old) provides supportive criteria for the diagnosis.[157] Changes in right precordial leads may be transient, and absence of ECG changes in leads V_3R and V_4R does not exclude right ventricular infarction. Myocardial imaging can be helpful in this clinical setting.

Electrocardiographic detection of myocardial injury

It is not possible to initially distinguish ECG manifestations of acute or chronic myocardial injury from acute myocardial ischaemia. Rapidly developing dynamic ECG changes that temporally match the clinical presentation may be helpful in diagnosing a symptomatic patient with elevated cTn values as having acute myocardial ischaemia resulting in MI. However, ECG abnormalities are also common in patients who have myocardial injury, e.g. myocarditis or TTS.[158–160]

Prior or silent/unrecognized myocardial infarction

Q wave criteria associated with MI and increased relative risk of death are illustrated in **Table 3** and are contained in Q wave coding algorithms such as the Minnesota Code and the WHO MONItoring of trends and determinants in CArdiovascular disease (MONICA) code.[11,161,162]

Table 3 Electrocardiographic changes associated with prior myocardial infarction (in the absence of left ventricular hypertrophy and left bundle branch block)

Any Q wave in leads V_2-V_3 >0.02 s or QS complex in leads V_2-V_3.
Q wave ≥0.03 s and ≥1 mm deep or QS complex in leads I, II, aVL, aVF or V_4-V_6 in any two leads of a contiguous lead grouping (I, aVL; V_1-V_6; II, III, aVF).[a]
R wave >0.04 s in V_1-V_2 and R/S >1 with a concordant positive T wave in absence of conduction defect.

s = seconds.

[a]The same criteria are used for supplemental leads V_7–V_9.

The specificity of the ECG diagnosis for MI is greatest when Q waves occur in several leads or lead groupings or are >0.04 seconds (s). When the Q waves are associated with ST deviations or T wave changes in the same leads, the likelihood of MI is increased; for example, minor Q waves ≥0.02 s and <0.03 s that are ≥1 mm deep are suggestive of prior MI if accompanied by inverted T waves in the same lead group. Non-invasive imaging techniques also provide important supportive evidence of prior MI. In the absence of non-ischaemic causes, regional myocardial thinning, scar or reduced wall motion shown by echocardiography, myocardial perfusion scintigraphy (MPS) with single photon emission computed tomography (SPECT) or positron emission tomography (PET), or magnetic resonance imaging provide strong evidence for prior MI, particularly when ECG criteria are equivocal.

Asymptomatic patients who develop new Q wave criteria for MI detected during routine ECG follow-up, or reveal evidence of MI by cardiac imaging that cannot be directly attributed to an interim coronary revascularization procedure or an ACS admission, should be termed 'silent or unrecognized MI'. In studies where serial ECG analysis was applied, silent or unrecognized Q wave MI accounted for 9–37% of all non-fatal MI events and was associated with a significantly increased mortality risk.[163,164] Improper lead placement, QRS abnormalities, or technical error (e.g. lead reversal) may result in the appearance of new Q waves or QS complexes, as compared to a prior tracing. Thus, the diagnosis of a new silent Q wave MI should be confirmed by a repeat ECG recording with correct lead placement, focused questioning about potential interim ischaemic symptoms, or by an imaging study. Imaging techniques are useful if there is abnormal myocardial motion or thickening or thinning in the region of interest but absence of these does not exclude MI.[165]

Criteria for prior or silent/unrecognized myocardial infarction

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Pathological Q waves as described in table 3, with or without symptoms, in the absence of non-ischaemic causes.
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology.
- Pathological findings of a prior MI.

MI = myocardial infarction.

Conditions that confound the ECG diagnosis of myocardial infarction

A QS complex in lead V_1 is normal. A Q wave <0.03 s and <0.25 of the R wave amplitude in lead III is normal if the frontal QRS axis is between −30° and 0°. A Q wave may also be normal in aVL if the frontal QRS axis is between 60–90°. Septal Q waves are small, non-pathological Q waves <0.03 s and <0.25 of the R-wave amplitude in leads I, aVL, aVF, and V_4–V_6. Pre-excitation, cardiomyopathy, TTS, cardiac amyloidosis, LBBB, left anterior hemiblock, LVH, right ventricular hypertrophy, myocarditis, acute cor pulmonale, or hyperkalaemia may be associated with Q waves or QS complexes in the absence of MI. Clinicians should be aware of confounders to the ECG diagnosis of myocardial ischaemia since ST-T wave abnormalities are commonly observed with different pathological cardiac conditions, such as pre-excitation, pericarditis, cardiomyopathy, etc.

Conduction disturbances, pacemakers

The diagnosis of MI is more difficult in the presence of conduction disturbances, related in part to ST-T wave changes caused by the conduction disturbance and the fact that the conduction disturbance itself may be heart rate dependent.[166,167] Comparison to a pre-admission ECG may be helpful in determining if the conduction defect or ST-T wave changes are new, as long as it does not delay time to treatment. Ischaemic symptoms and presumed new LBBB or right bundle branch block (RBBB) that is not rate-related are associated with an adverse prognosis. In patients with LBBB, ST-segment elevation ≥1 mm concordant with the QRS complex in any lead may be an indicator of acute myocardial ischaemia. Similar findings can be useful in detecting ECG evidence for acute myocardial ischaemia in patients with right ventricular paced rhythms.[167] Recording an ECG tracing with the pacemaker temporarily switched off may also be useful in patients who are not pacemaker dependent, but careful interpretation of repolarization is needed due to the possible presence of stimulation-induced changes (electrical memory). The ECG diagnosis of acute myocardial ischaemia in patients with biventricular pacing is more difficult. In patients with RBBB, new or presumed new ST-segment elevation ≥1 mm or

ST-segment or T wave abnormalities (excluding leads V_1–V_4) (**Table 2**) may indicate acute myocardial ischaemia. New, or presumed new, RBBB without associated ST-segment or T wave changes is associated with Thrombolysis in Myocardial Infarction (TIMI) 0–2 flow in as many as 66% of patients (compared to >90% in those with ST-segment or T wave changes).[168]

Atrial fibrillation

In patients with atrial fibrillation and rapid ventricular rate or paroxysmal supraventricular tachycardia, ST-segment depression or T wave inversion may occur in the absence of CAD.[169,170] The causes are not completely understood. Cardiac memory, an electrical remodelling phenomenon characterized by marked diffuse T wave inversions following periods of abnormal ventricular activation, that may also be caused by transient rate-related conduction disturbances or pacing, may explain these findings. In some patients, the tachycardia may result in insufficient increase in coronary flow to match myocardial oxygen demand, resulting in cellular hypoxia and abnormal repolarization.[171,172] For these reasons, a patient with new onset atrial fibrillation, elevated baseline cTn concentration, and new ST-segment depression should not automatically be classified as type 2 MI without additional information. In this clinical setting, signs of overt ischaemic symptoms, the timing of symptoms relative to atrial fibrillation onset, a changing pattern of cTn, and imaging and/or angiographic findings may be helpful in establishing the diagnosis. However, in the absence of evidence for myocardial ischaemia the aetiology of the elevated cTn values should be attributed to myocardial injury.

Imaging techniques

Non-invasive imaging plays many roles in patients with known or suspected MI, but this section concerns only its role in the diagnosis and characterization of myocardial injury and MI. The underlying rationale is that regional myocardial hypoperfusion and ischaemia lead to a cascade of events including myocardial dysfunction, cell death and healing by fibrosis. Important imaging parameters are therefore myocardial perfusion, myocyte viability, myocardial thickness, thickening and motion, and the effects of myocyte loss on the kinetics of paramagnetic or radio-opaque contrast agents indicating myocardial fibrosis or scar.

Commonly used imaging techniques in acute and prior MI are echocardiography, MPS using SPECT or PET, CMR, and possibly computed tomography (CT).[173] There is considerable overlap in their capabilities and each of the techniques can assess myocardial viability, perfusion and function to a greater or lesser extent. Only the radionuclide techniques provide a direct assessment of myocyte viability because of the

inherent properties of the tracers used. Other techniques provide indirect assessments of myocardial viability such as contractile response to dobutamine by echocardiography or increased extracellular space secondary to myocyte loss by CMR or CT.

Echocardiography

The strength of echocardiography is the combined assessment of cardiac structure and function, in particular myocardial thickness, thickening/thinning and motion. Regional wall motion abnormalities induced by ischaemia can be detected by echocardiography almost immediately after onset when >20% transmural myocardial thickness is affected.[174–176] These abnormalities, when new and without alternative aetiology, support the diagnosis of MI when cTn values show a rising and/or falling pattern. Echocardiography also allows detection of non-coronary cardiac pathologies known to cause chest pain, e.g. acute pericarditis, severe aortic stenosis, and hypertrophic cardiomyopathy among others. The technique is useful in diagnosing mechanical complications in patients with MI and haemodynamic compromise (shock) or other potentially fatal entities such as acute aortic dissection or massive pulmonary embolism where the clinical presentation might be similar to that seen with acute MI.

Intravenous echocardiographic contrast agents can improve visualization of the endocardial border and can be used to assess myocardial perfusion and microvascular obstruction. Tissue Doppler and strain imaging permit quantification of global and regional function.[177,178] Intravascular echocardiographic contrast agents that are targeted at specific molecular processes have been developed, but these techniques have not yet been applied in the setting of MI.[179]

Radionuclide imaging

Several radionuclide tracers allow viable myocytes to be imaged directly, including the SPECT tracers ^{201}TI chloride, ^{99m}Tc sestamibi and tetrofosmin; and the PET tracers ^{18}F 2-fluorodeoxyglucose and ^{82}Rb.[173] A strength of the radionuclide techniques is that they are the only commonly available methods for assessing viability directly, although the relatively low resolution of the images limits them for detecting the smallest areas of MI. Phantom studies suggest that myocyte loss as little as 4% of the myocardium can be detected, corresponding to 5−10 grams (g) of muscle.[180] ECG-gated imaging provides a reliable assessment of myocardial motion, thickening and global function. Evolving radionuclide techniques relevant to the assessment of MI include imaging of sympathetic innervation using ^{123}I labelled meta-iodobenzylguanidine,[181] imaging of matrix metalloproteinase activation in ventricular remodelling,[182,183] and assessment of myocardial metabolism.[184]

Cardiac magnetic resonance imaging

The high tissue contrast and resolution of CMR provides an accurate assessment of myocardial structure and function. Although less commonly used in the acute setting, it has similar capability to echocardiography in suspected MI. Paramagnetic contrast agents can be used to assess myocardial perfusion and the increase in extracellular space that is associated with the fibrosis of prior MI (detected by LGE-CMR). These techniques have been used in the setting of acute MI[185,186] and localized delay in contrast enhancement is able to detect even small areas of subendocardial MI, thought to be as little as 1 g.[187] CMR also has the ability to identify the presence and extent of myocardial oedema/inflammation, allowing the distinction of acute vs. chronic myocardial injury. The patterns of LGE when reflecting ischaemic and non-ischaemic myocardial injury are shown in **Figure 9.**

Figure 9. Post-contrast cardiac magnetic resonance images: the gadolinium-based contrasts wash out slowly from myocardium with increased extracellular space such as fibrosis, thus enhancing areas of scar (white arrows). The different patterns of scar are divided into ischaemic and non-ischaemic. Typically, ischaemic scar/fibrosis (upper panel) extends from the subendocardium to the epicardium (subendocardial, non-transmural scar vs. transmural scar). Conversely non-ischaemic fibrosis/scar can be encountered at the epicardium, in the mid-wall, or at the insertion points of the right ventricle (lower panel).

Computed tomographic coronary angiography

Infarcted myocardium is initially visible as a focal area of decreased LV myocardial enhancement but later imaging shows hyper-enhancement as with LGE-CMR.[188] This finding is clinically relevant because contrast-enhanced CT may be performed for suspected pulmonary embolism and aortic dissection, conditions with clinical features that overlap with those of acute MI, but the technique is not used routinely. Similarly, CT assessment of myocardial perfusion is technically feasible but not widely applied.[189] CT coronary angiography (CTCA) may be used to diagnose CAD in patients with an ACS in the emergency department or chest pain unit, particularly in low- to intermediate-risk patients with normal cTn at presentation.[189–193] The only randomized trial in these patients that included both hs-cTn and CTCA found that imaging did not reduce the length of stay in hospital but it did decrease subsequent outpatient testing and costs.[189] A diagnosis of MI cannot be established based on a CTCA scan alone.

Applying imaging in acute myocardial infarction

Imaging techniques can be useful in the diagnosis of acute MI because of the ability to detect wall motion abnormalities or loss of viable myocardium in the presence of elevated cardiac biomarker values. Demonstration of new loss of myocardial viability in the absence of non-ischaemic causes supports the diagnosis of MI. Normal function practically excludes significant MI but a small MI cannot be ruled out.[194] Thus, imaging techniques are useful for early triage and discharge of patients with suspected MI. However, if biomarkers have been measured at appropriate times and are normal, this excludes acute MI and takes precedence over the imaging criteria.

Abnormal regional myocardial motion and thickening may be caused by acute MI or by one or more of several other conditions including prior infarction, acute ischaemia, stunning, or hibernation. Non-ischaemic conditions such as cardiomyopathy and inflammatory or infiltrative diseases can also lead to regional loss of viable myocardium or functional abnormality. Therefore, the positive predictive value of imaging for acute MI

is not high unless these conditions can be excluded and unless a new abnormality is detected or can be presumed to have arisen in the setting of other features of acute MI.

In the setting of acute MI, CMR can also be used to assess the presence and extent of myocardium at risk (myocardial oedema), myocardial salvage, microvascular obstruction, intramyocardial haemorrhage and infarct size – all markers of myocardial injury that have prognostic value.[190] In patients with possible acute MI but unobstructed coronary arteries, CMR can help to diagnose alternative conditions such as myocarditis, TTS, embolic infarction, or MI with spontaneous recanalization.[189]

Applying imaging in late presentation of myocardial infarction

In the case of late presentation after suspected MI, the presence of a regional abnormality of myocardial motion, thickening, thinning, or scar in the absence of a non-ischaemic cause provides supportive evidence of past MI. The resolution and specificity of CMR for the detection of myocardial scar has made this a valuable technique. In particular, the ability to distinguish between subendocardial and other patterns of scar helps to differentiate between ischaemic heart disease and other myocardial pathology. Imaging techniques are also useful for risk stratification after a definitive diagnosis of MI.

Regulatory perspective on myocardial infarction in clinical trials

In drug and device development programmes, MI may be an entry criterion or be used as an efficacy endpoint, commonly as a component of the primary endpoint, as well as a safety endpoint of interest in drug development programmes.[195,196] A universal definition of MI is of great benefit for clinical studies, since it will allow a standardized approach for meaningful interpretation and comparison across different trials, or the pooling of results for the detection of safety signals. For the harmonization of the MI definition it is important to standardize the reporting of MI events by clinical events committees. This would allow a more optimal comparison of MI rates among drug and device trials.

One cannot presume that values from one cTn assay are equivalent to those of another. These differences are amplified when multiples of the values are used. This could affect results, especially in trials which compare strategies such as PCI and CABG. The use of one single assay and/or a central core laboratory within a trial could help to decrease this variability and might be particularly relevant to decrease variability in trials of a drug or intervention in which cTn concentration is a principal safety endpoint. However, the uniform use of a single assay is generally not feasible in trials with follow-up post-discharge since recurrent ischaemic events may occur in different hospitals using different cTn assays. In clinical trials, a standardized approach to establish the 99th percentile URL for a particular assay should be established. One approach in large

multicentre trials is to use the manufacturer's recommended 99th percentile URL for a particular assay to reduce site-to-site variability in selection of the MI decision cut-point.

Multiples for hs-cTn vs. conventional cTn could have markedly different prognostic implications. The assay types should be reported when possible. Multiples of the 99th percentile URL should be indicated and reported both for those with cardiac procedural myocardial injury and those diagnosed with types 4a and 5 MI. Cumulative frequency distribution of peak cTn measurements for MI endpoint assessments by treatment group should also be provided. This will facilitate comparison of trials and meta-analyses.

Silent/unrecognized myocardial infarction in epidemiological studies and quality programmes

ECG monitoring for unrecognized or silent Q wave MI is usually acquired annually in epidemiological studies and clinical trials that assess cardiovascular endpoints. These events are associated with adverse outcomes.[197] There is no firm consensus on how frequently to monitor for ECG evidence of silent Q wave MI or whether surveillance for silent MI events should be routinely implemented. Serial monitoring of patients who have had a symptomatic Q wave MI event revealed Q wave regression in a substantial number of patients.[198] An annual ECG is reasonable in clinical trials to monitor for silent Q wave MI events if the study population is expected to have an accelerated rate of atherosclerotic events. The review should consider the baseline tracing, interim event ECG tracings, and protocol mandated annual tracings along with review of imaging studies if available.

Individual and public implications of the myocardial infarction definition

Revision of the definition of MI has a number of implications for individuals, health professionals, and society at large. A tentative or final diagnosis is the basis for advice about further diagnostic testing, lifestyle changes, treatment and prognosis for the patient. The aggregate of patients with a particular diagnosis is the basis for healthcare planning and policy and resource allocation.

One of the goals of good clinical practice is to reach a definitive and specific diagnosis, which is supported by current scientific knowledge. The approach to the definition of myocardial injury and MI outlined in this document meets this goal. In general, the conceptual meaning of the term myocardial infarction has not changed, although new sensitive methods have been developed to diagnose this entity. Thus, the diagnosis of an acute MI is a clinical diagnosis based on patient symptoms, ECG changes, and highly sensitive biochemical markers, as well as information gleaned from various imaging techniques.

It should be appreciated that the universal definition of MI may be associated with consequences for patients and their families with respect to psychological status, life and health insurance, and professional career, as well as driving and pilot licences. The diagnosis is also associated with societal implications with regards to diagnosis-related coding, hospital reimbursement, public health statistics, sick leave, and disability attestation. In order to meet these challenges, physicians must be adequately informed of the diagnostic criteria. Hence, educational materials will need to be created and treatment guidelines must be appropriately adapted.

Global perspectives of the definition of myocardial infarction

Cardiovascular disease is a global health problem and prevalence is increasing in the developing world. Understanding the burden and effects of CAD in populations is of critical importance. Changing clinical definitions, criteria and biomarkers add challenges to our understanding and ability to improve the health of the public. For clinicians, the definition of MI has important and immediate therapeutic implications. For epidemiologists, the data are often retrospective, so consistent case definitions are critical for comparisons and trend analysis. The standards described in this report are suitable for epidemiology studies and for international classification of diseases.[199] However, to analyze trends over time, it is important to have consistent definitions and to quantify adjustments when biomarkers or other diagnostic methods change,[200] considering that the advent of cTn has dramatically increased the number of diagnosable MIs for epidemiologists.[11,201]

In countries with limited economic resources, cardiac biomarkers and imaging techniques may not be available except in a few centres, and even the option of ECG recordings may be lacking. The WHO recommends the use of the ESC/ACC/AHA/WHF Universal Definition of MI in countries without resource constraints, but recommends more flexible standards in resource-constrained locations. Thus, when the only information available is the clinical history and ECG, and when data on cardiac biomarkers are not available or incomplete, the diagnosis of MI can be confirmed by the development of pathological Q waves.[11]

Using the Universal Definition of Myocardial Infarction in the healthcare system

Arriving at a diagnosis of MI using the criteria set forth in this document requires integration of clinical findings, patterns on the ECG, laboratory data, observations from imaging procedures, and on occasion pathological findings, all viewed in the context of the time horizon over which the suspected event unfolds. Contemporary healthcare

systems are increasingly using electronic medical records where medical information is entered, curated, and available for retrieval at a later date. This evolution offers the advantages of a modern electronic database that is useful for a variety of purposes, including scientific discovery and quality improvement in clinical care, but carries with it the challenges of sifting through variable locations and formats where key data elements for confirming a diagnosis of MI are located. Also, use of the electronic medical record as an epidemiological and research tool of the future is likely to require efforts to verify the accuracy of an acute MI diagnosis rather than accepting the coded diagnoses used for administrative and billing purposes. Such an effort to create a computable phenotype of MI (further categorized as types 1−5 MI) will require input from informaticians and experts in implementation science to translate the recommendations from this Universal Definition of MI into the routine practice of healthcare delivery and documentation.

Given the evolution of biomarker assays used to support the diagnosis of MI, it is important that a consistent approach be used in the construction of the computable phenotype of MI so as to reliably make comparisons across institutions and track epidemiological trends. Ideally, the information provided should include the assay used to make the diagnosis of MI, the 99th percentile of the URL, and the full sequence of values obtained to discern a rise and fall in biomarker levels.[196]

Appendix

Approved by the **ESC Committee for Practice Guidelines (CPG)** on behalf of the ESC Board 2016-2018.

ESC National Cardiac Societies actively involved in the review process of the **Fourth universal definition of myocardial infarction:**
Algeria: Algerian Society of Cardiology**,** Mohamed Chettibi**; Armenia:** Armenian Cardiologists Association**,** Hamlet Hayrapetyan**; Austria:** Austrian Society of Cardiology, Franz Xaver Roithinger; **Azerbaijan:** Azerbaijan Society of Cardiology, Farid Aliyev; **Belarus:** Belorussian Scientific Society of Cardiologists, Volha Sujayeva; **Belgium:** Belgian Society of Cardiology, Marc J. Claeys; **Bosnia and Herzegovina:** Association of Cardiologists of Bosnia and Herzegovina, Elnur Smajić; **Czech Republic:** Czech Society of Cardiology, Petr Kala; **Denmark:** Danish Society of Cardiology, Kasper Karmak Iversen; **Egypt:** Egyptian Society of Cardiology, Ehab El Hefny; **Estonia:** Estonian Society of Cardiology, Toomas Marandi; **Finland:** Finnish Cardiac Society, Pekka Porela; **The Former Yugoslav Republic of Macedonia**: Macedonian FYR Society of Cardiology, Slobodan Antov; **France:** French Society of Cardiology, Martine Gilard; **Germany:** German Cardiac Society, Stefan Blankenberg; **Greece:** Hellenic Society of Cardiology, Periklis Davlouros; **Iceland:** Icelandic Society of Cardiology, Thorarinn Gudnason; **Israel:** Israel Heart Society, Ronny Alcalai; **Italy:** Italian Federation of Cardiology, Furio Colivicchi; **Kosovo:** Kosovo Society of Cardiology, Shpend Elezi; **Kyrgyzstan:** Kyrgyz Society of Cardiology, Gulmira Baitova, **Latvia:** Latvian Society of Cardiology, Ilja Zakke; **Lithuania:** Lithuanian Society of Cardiology, Olivija Gustiene; **Luxembourg:** Luxembourg Society of Cardiology, Jean Beissel; **Malta:** Maltese Cardiac Society, Philip Dingli; **Moldova:** Moldavian Society of Cardiology, Aurel Grosu; **The Netherlands**: Netherlands Society of Cardiology, Peter Damman; **Norway:** Norwegian Society of Cardiology, Vibeke Juliebø; **Poland:** Polish Cardiac Society, Jacek Legutko; **Portugal:** Portuguese Society of Cardiology, João Morais; **Romania:** Romanian Society of Cardiology, Gabriel Tatu-Chitoiu; **Russian Federation:** Russian Society of Cardiology, Alexey Yakovlev; **San Marino:** San Marino Society of Cardiology, Marco Zavatta; **Serbia:** Cardiology Society of Serbia, Milan Nedeljkovic; **Slovenia:** Slovenian Society of Cardiology, Peter Radsel; **Spain:** Spanish Society of Cardiology, Alessandro Sionis; **Sweden:** Swedish Society of Cardiology, Tomas Jemberg; **Switzerland:** Swiss Society of Cardiology**,** Christian Müller; **Tunisia:** Tunisian Society of Cardiology and Cardio-Vascular Surgery, Leila Abid; **Turkey:** Turkish Society of Cardiology, Adnan Abaci; **Ukraine:** Ukrainian Association of Cardiology, Alexandr Parkhomenko; **United Kingdom:** British Cardiovascular Society, Simon Corbett.

Approved by the **ACC Clinical Policy Approval Committee**.

Approved by the **AHA Science Advisory and Coordinating Committee**.

Approved by the **WHF Board.**

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References

1. Hammer A. Ein Fall von thrombotischem Verschlusse einer der Kranzarterien des Herzens. *Wien Med Wschr* 1878;**28**:97–102.
2. Obraztzow VP, Straschesko ND. Zur Kenntnis der Thrombose der Koronararterien des Herzens. *Z Klin Med* 1910;**71**:116–132.
3. Herrick JB. Clinical features of sudden obstruction of the coronary arteries. *JAMA* 1912;**59**:2015–2022.
4. Friedberg CK, Horn H. Acute myocardial infarction not due to coronary artery occlusion. *JAMA* 1939;**112**:1675–1679.

5. World Health Organization. Working Group on the Establishment of Ischemic Heart Disease Registers. Report of the Fifth Working Group, Copenhagen. In: *Report No. Eur 8201 (5)*. Geneva: World Health Organization; 1971.
6. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. Nomenclature and criteria for diagnosis of ischemic heart disease. *Circulation* 1979;**59**:607–609.
7. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994;**90**:583–612.
8. Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, Goldberg RJ, Hand MM, Jaffe AS, Julian DG, Levy D, Manolio T, Mendis S, Mensah G, Pajak A, Prineas RJ, Reddy KS, Roger VL, Rosamond WD, Shahar E, Sharrett AR, Sorlie P, Tunstall-Pedoe H. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. *Circulation* 2003;**108**:2543–2549.
9. 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; *J Am Coll Cardiol* 2000;**36**:959–969.
10. Thygesen K, Alpert JS, White HD; Joint ESC/ACC/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Eur Heart J* 2007;**28**:2525–2538; *Circulation* 2007;**116**:2634–2653; *J Am Coll Cardiol* 2007;**50**:2173–2195.
11. Mendis S, Thygesen K, Kuulasmaa K, Giampaoli S, Mähönen M, Ngu Blackett K, Lisheng L; Writing group on behalf of the participating experts of the WHO consultation for revision of WHO definition of myocardial infarction. World Health Organization definition of myocardial infarction: 2008-09 revision. *Int J Epidemiol* 2011;**40**:139–146.
12. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Writing Group on the Joint ESC/ACC/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Eur*

Heart J 2012;**33**:2551–2567; *Circulation* 2012;**126**:2020–2035; *J Am Coll Cardiol* 2012;**60**:1581–1598.

13. Sarkisian L, Saaby L, Poulsen TS, Gerke O, Jangaard N, Hosbond S, Diederichsen ACP, Thygesen K, Mickley H. Clinical characteristics and outcomes of patients with myocardial infarction, myocardial injury, and nonelevated troponins. *Am J Med* 2016;**129**:446e.5–446e.21.
14. Sarkisian L, Saaby L, Poulsen TS, Gerke O, Hosbond S, Jangaard N, Diederichsen ACP, Thygesen K, Mickley H. Prognostic impact of myocardial injury related to various cardiac and noncardiac conditions. *Am J Med* 2016;**129**:506–514.
15. Ooi DS, Isotalo PA, Veinot JP. Correlation of antemortem serum creatine kinase, creatine kinase-MB, troponin I, and troponin T with cardiac pathology. *Clin Chem* 2000;**46**:338–344.
16. Jennings RB, Ganote CE. Structural changes in myocardium during acute ischemia. Circ Res 1974;**35**(Suppl. 3):156–172.
17. Virmani R, Forman MB, Kolodgie FD. Myocardial reperfusion injury. Histopathological effects of perfluorochemical. *Circulation* 1990;**81**:IV57–IV68.
18. Reimer KA, Jennings RB, Tatum AH. Pathobiology of acute myocardial ischemia: metabolic, functional and ultrastructural studies. *Am J Cardiol* 1983;**52**:72A–81A.
19. Ibáñez B, Heusch G, Ovize M, Van de Werf F. Evolving therapies for myocardial ischemia/reperfusion injury. *J Am Coll Cardiol* 2015;**65**:1454–1471.
20. Montecucco F, Carbone F, Schindler TH. Pathophysiology of ST-segment elevation myocardial infarction: novel mechanisms and treatments. *Eur Heart J* 2016;**37**:1268–1283.
21. Thygesen K, Mair J, Katus H, Plebani M, Venge P, Collinson P, Lindahl B, Giannitsis E, Hasin Y, Galvani M, Tubaro M, Alpert JS, Biasucci LM, Koenig W, Mueller CH, Huber K, Hamm C, Jaffe AS; The Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. Recommendations for the use of cardiac troponin measurement in acute cardiac care. *Eur Heart J* 2010;**31**:2197–2204.
22. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, Huber K, Plebani M, Biasucci LM. Tubaro M, Collinson P, Venge P, Hasin Y, Galvani M, Koenig W, Hamm C, Alpert JS, Katus H, Jaffe AS; Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J* 2012;**33**:2252–2257.

23. Rittoo D, Jones A, Lecky B, Neithercut D. Elevation of cardiac troponin T, but not cardiac troponin I, in patients with neuromuscular diseases: implications for the diagnosis of myocardial infarction. *J Am Coll Cardiol* 2014;**63**:2411–2420.
24. Jaffe AS, Vasile VC, Milone M, Saenger AK, Olson KN, Apple FS. Diseased skeletal muscle: a noncardiac source of increased circulating concentrations of cardiac troponin T. *J Am Coll Cardiol* 2011;**58**:1819–1824.
25. Wens SCA, Schaaf GJ, Michels M, Kruijshaar ME, van Gestel TJM, in 't Groen S, Pijnenburg J, Dekkers DHW, Demmers JAA, Verdijk LB, Brusse E, van Schaik RHN, van der Ploeg AT, van Doorn PA, Pijnappel WWMP. Elevated plasma cardiac troponin T levels caused by skeletal muscle damage in Pompe disease. *Circ Cardiovasc Genet* 2016;**9**:6–13.
26. Mair J, Lindahl B, Müller C, Giannitsis E, Huber K, Möckel M, Plebani M, Thygesen K, Jaffe AS. What to do when you question cardiac troponin values. *Eur Heart J Acute Cardiovasc Care* 2017 May 1. [Epub ahead of print]
27. Mair J, Lindahl B, Hammarsten O, Müller C, Giannitsis E, Huber K, Möckel M, Plebani M, Thygesen K, Jaffe AS; European Society of Cardiology (ESC) Study Group on Biomarkers in Cardiology of the Acute Cardiovascular Care Association (ACCA). How is cardiac troponin released from injured myocardium? *Eur Heart J Acute Cardiovasc Care* 2017 Dec 1. [Epub ahead of print]
28. Vestergaard KR, Jespersen CB, Arnadottir A, Soletormos G, Schou M, Steffensen R, Goetze JP, Kjoller E, Iversen KK. Prevalence and significance of troponin elevations in patients without acute coronary disease. *Int J Cardiol* 2016;**222**:819–825.
29. Schmid J, Liesinger L, Birner-Gruenberger R, Stojakovic T, Scharnagl H, Dieplinger B, Asslaber M, Radl R, Beer M, Polacin M, Mair J, Szolar D, Berghold A, Quasthoff S, Binder JS. Rainer PP. Elevated cardiac troponin T in skeletal myopathies. *J Am Cardiol Coll* 2018;**71**:1540-1549.
30. Apple FS, Jaffe AS, Collinson P, Mockel M, Ordonez-Llanos J, Lindahl B, Hollander J, Plebani M, Than M, Chan MH; on behalf of the International Federation of Clinical Chemistry (IFCC) Task Force on Clinical Applications of Cardiac Bio-Markers. IFCC educational materials on selected analytical and clinical applications of high sensitivity cardiac troponin assays. *Clin Biochem* 2015;**48**:201–203.
31. Goodman SG, Steg PG, Eagle KA, Fox KA, López-Sendón J, Montalescot G, Budaj A, Kennelly BM, Gore JM, Allegrone J, Granger CB, Gurfinkel EP; GRACE Investigators. The diagnostic and prognostic impact of the redefinition of acute myocardial infarction: lessons from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J* 2006;**151**:654–660.

32. Weil BR, Suzuki G, Young RF, Iyer V, Canty JM Jr. Cardiac troponin I release and reversible left ventricular dysfunction following transient pressure overload: stress-induced myocardial stunning. *J Am Cardiol Coll* 2018 (in press).
33. Turer AT, Addo TA, Martin JL, Sabatine MS, Lewis GD, Gerszten RE, Keeley EC, Cigarroa JE, Lange RA, Hillis LD, de Lemos JA. Myocardial ischemia induced by rapid atrial pacing causes troponin T release detectable by a highly sensitive assay: insights from a coronary sinus sampling study. *J Am Coll Cardiol* 2011;**57**:2398–2405.
34. Siriwardena M, Campbell V, Richards AM, Pemberton CJ. Cardiac biomarker responses to dobutamine stress echocardiography in healthy volunteers and patients with coronary artery disease. *Clin Chem* 2012;**58**:1492–1494.
35. White HD. Pathobiology of troponin elevations: do elevations occur with myocardial ischemia as well as necrosis? *J Am Coll Cardiol* 2011;**57**:2406–2408.
36. Jaffe AS, Wu AH. Troponin release—reversible or irreversible injury? Should we care? *Clin Chem* 2012;**58**:148–150.
37. Eggers KM, Lindahl B. Application of cardiac troponin in cardiovascular diseases other than acute coronary syndrome. *Clin Chem* 2017;**63**:223–235.
38. Giannitsis E, Katus HA. Cardiac troponin level elevations not related to acute coronary syndromes. *Nat Rev Cardiol* 2013;**10**:623–634.
39. Agewall S, Giannitsis E, Jernberg T, Katus H. Troponin elevation in coronary vs. non-coronary disease. *Eur Heart J* 2011;**32**:404–411.
40. Kelley WE, Januzzi JL, Christenson RH. Increases of cardiac troponin in conditions other than acute coronary syndrome and heart failure. *Clin Chem* 2009;**55**:2098–2112.
41. Jeremias A, Gibson CM. Alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. *Ann Intern Med* 2005;**142**:786–791.

42. Weil BR, Young RF, Shen X, Suzuki G, Qu J, Malhotra S, Canty JM Jr. Brief myocardial ischemia produces cardiac troponin I release and focal myocyte apoptosis in the absence of pathological infarction in swine. *JACC Basic Transl Sci* 2017;**2**:105–114.
43. Braunwald E, Morrow DA. Unstable angina: is it time for a requiem? *Circulation* 2013;**127**:2452–2457.
44. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res* 2014;**114**:1852–1866.
45. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. *Eur Heart J* 2013;**34**:719–728.

46. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2018;**39**:119–177.
47. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, da Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2016;**37**:267–315.
48. 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**:789–797.
49. Cediel G, Gonzalez-del-Hoyo M, Carrasquer A, Sanchez R, Boqué C, Bardají A. Outcomes with type 2 myocardial infarction compared with non-ischemic myocardial injury. *Heart* 2017;**103**:616–622.
50. Baron T, Hambraeus K, Sundström J, Erlinge D, Jernberg T, Lindahl B; TOTAL-AMI study group. Type 2 myocardial infarction in clinical practice. *Heart* 2015;**101**:101–106.
51. Shah AS, McAllister DA, Mills R, Lee KK, Churchhouse AM, Fleming KM, Layden E, Anand A, Fersia O, Joshi NV, Walker S, Jaffe AS, Fox KA, Newby DE, Mills NL. Sensitive troponin assay and the classification of myocardial infarction. *Am J Med* 2015;**128**:493–501.
52. Gupta S, Vaidya SR, Arora S, Bahekar A, Devarapally SR. Type 2 versus type 1 myocardial infarction: a comparison of clinical characteristics and outcomes with a meta-analysis of observational studies. *Cardiovasc Diagn Ther* 2017;**7**:348–358.
53. Sandoval Y, Thygesen K. Myocardial infarction type 2 and myocardial injury. *Clin Chem* 2017;**63**:101–107.
54. Saaby L, Poulsen TS, Diederichsen ACP, Hosbond S, Larsen TB, Schmidt H, Gerke O, Hallas J, Thygesen K, Mickley H. Mortality rate in type 2 myocardial infarction: observations from an unselected hospital cohort. *Am J Med* 2014;**127**:295–302.
55. Lambrecht S, Sarkisian L, Saaby L, Poulsen TS, Gerke O, Hosbond S, Diederichsen ACP, Thygesen K, Mickley H. Different causes of death in patients with myocardial infarction type 1, type 2 and myocardial injury. *Am J Med* 2018;**131**:548–554.

56. Chapman AR, Shah ASV, Lee KK, Anand A, Francis O, Adamson P, McAllister DA, Strachan F, Newby DE, Mills NL. Long term outcomes in patients with type 2 myocardial infarction and myocardial injury. *Circulation* 2018;**137**:1236–1245.
57. Neumann JT, Sörensen NA, Rübsamen N, Ojeda F, Renne 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**:3514–3520.
58. Saw J, Mancini GB, Humphries KH. Contemporary review on spontaneous coronary artery dissection. *J Am Coll Cardiol* 2016;**68**:297–312.
59. Januzzi JL, Sandoval Y. The many faces of type 2 myocardial infarction. *J Am Cardiol Coll* 2017;**70**:1569–1572.
60. Jangaard N, Sarkisian L, Saaby L, Mikkelsen S, Lassen AM, Marcussen N, Thomsen JL, Diederichsen A, Thygesen K, Mickley H. Incidence, frequency and clinical characteristics of type 3 myocardial infarction in clinical practice. *Am J Med* 2017;**130**:862.e9–862.e14.
61. Selvanayagam JB, Petersen SE, Francis JM, Robson MD, Kardos A, Neubauer S, Taggart DP. Effects of off-pump versus on-pump coronary surgery on reversible and irreversible myocardial injury: a randomized trial using cardiovascular magnetic resonance imaging and biochemical markers. *Circulation* 2004;**109**:345–350.
62. Selvanayagam JB, Porto I, Channon K, Petersen SE, Francis JM, Neubauer S, Banning AP. Troponin elevation after percutaneous coronary intervention directly represents the extent of irreversible myocardial injury: insights from cardiovascular magnetic resonance imaging. *Circulation* 2005;**111**:1027–1032.
63. Rahimi K, Banning AP, Cheng AS, Pegg TJ, Karamitsos TD, Channon KM, Darby S, Taggart DP, Neubauer S, Selvanayagam JB. Prognostic value of coronary revascularisation-related myocardial injury: a cardiac magnetic resonance imaging study. *Heart* 2009;**95**:1937–1943.
64. Tricoci P. Consensus or controversy?: Evolution of criteria for myocardial infarction after percutaneous coronary intervention. *Clin Chem* 2017;**63**:82–90.
65. Ndrepepa G, Colleran R, Braun S, Cassese S, Hieber J, Fusaro M, Kufner S, Ott I, Byrne RA, Husser O, Hengstenberg C, Laugwitz KL, Schunkert H, Kastrati A. High-sensitivity troponin T and mortality after elective percutaneous coronary intervention. *J Am Coll Cardiol* 2016;**68**:2259–2268.
66. 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**:1100–1109.

67. Thygesen K, Jaffe AS. The prognostic impact of periprocedural myocardial infarction and injury. *Eur Heart J* 2018;**39**:1110–1112.
68. 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. Standardized endpoint definitions for coronary intervention trials: The Academic Research Consortium-2 Consensus Document. *Eur Heart J, Circulation* 2018 (in press).
69. Pegg TJ, Maunsell Z, Karamitsos TD, Taylor RP, James T, Francis JM, Taggart DP, White H, Neubauer S, Selvanayagam JB. Utility of cardiac biomarkers for the diagnosis of type V myocardial infarction after coronary artery bypass grafting: insights from serial cardiac MRI. *Heart* 2011;**97**:810–816.
70. Jørgensen PH, Nybo M, Jensen MK, Mortensen PE, Poulsen TS, Diederichsen ACP, Mickley H. Optimal cut-off value for cardiac troponin I in ruling out type 5 myocardial infarction. *Interact Cardiovasc Thorac Surg* 2014;**18**:544–550.
71. Wang TK, Stewart RA, Ramanathan T, Kang N, Gamble G, White HD. Diagnosis of MI after CABG with high-sensitivity troponin T and new ECG or echocardiogram changes: Relationship with mortality and validation of the universal definition of MI. *Eur Heart J Acute Cardiovasc Care* 2013;**2**:323–333.
72. Thielmann M, Sharma V, Al-Attar N, Bulluck H, Bisleri G, Bunge JJH, Czerny M, Ferdinandy P, Frey UH, Heusch G, Holfeld J, Kleinbongard P, Kunst G, Lang I, Lentini S, Madonna R, Meybohm P, Muneretto C, Obadia JF, Perrino C, Prunier F, Sluijter JPG, Van Laake LW, Sousa-Uva M, Hausenloy DJ. ESC Joint Working Groups on Cardiovascular Surgery and the Cellular Biology of the Heart Position Paper: Peri-operative myocardial injury and infarction in patients undergoing coronary artery bypass graft surgery. *Eur Heart J* 2017;**38**:2392–2411.
73. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol* 2013;**62**:1563–1570.
74. Apple FS, Murakami MM. Cardiac troponin and creatine kinase MB monitoring during in-hospital myocardial reinfarction. *Clin Chem* 2005;**51**:460–463.
75. Sinning JM, Hammerstingl C, Schueler R, Neugebauer A, Keul S, Ghanem A, Mellert F, Schiller W, Müller C, Vasa-Nicotera M, Zur B, Welz A, Grube E, Nickenig G, Werner N. The prognostic value of acute and chronic troponin elevation after transcatheter aortic valve implantation. *EuroIntervention* 2016;**11**:1522–1529.

76. Wang TKM, Stewart RAH, Ramanathan T, Choi D, Gamble G, Ruygrok PN, White HD. Diagnosis of myocardial infarction and prognostic utility of high-sensitivity troponin T after isolated aortic valve replacement. *Clin Trials Regul Sci Cardiol* 2016;**16**:1–5.

77. Devereaux PJ, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Rao-Melacini P, Chrolavicius S, Yang H, Macdonald C, Avezum A, Lanthier L, Hu W, Yusuf S; POISE (PeriOperative ISchemic Evaluation) Investigators. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med* 2011;**154**:523–528.

78. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012;**307**:2295–2304.

79. Nagele P, Brown F, Gage BF, Gibson DW, Miller JP, Jaffe AS, Apple FS, Scott MG. High-sensitivity cardiac troponin T in prediction and diagnosis of myocardial infarction and long-term mortality after noncardiac surgery. *Am Heart J* 2013;**166**:325–332.

80. Weber M, Luchner A, Manfred S, Mueller C, Liebetrau C, Schlitt A, Apostolovic S, Jankovic R, Bankovic D, Jovic M, Mitrovic V, Nef H, Mollmann H, Hamm CW. Incremental value of high-sensitive troponin T in addition to the revised cardiac index for perioperative risk stratification in non-cardiac surgery. *Eur Heart J* 2013;**34**:853–862.

81. Kavsak PA, Walsh M, Srinathan S, Thorlacius L, Buse GL, Botto F, Pettit S, McQueen MJ, Hill SA, Thomas S, Mrkobrada M, Alonso-Coello P, Berwanger O, Biccard BM, Cembrowski G, Chan MT, Chow CK, de Miguel A, Garcia M, Graham MM, Jacka MJ, Kueh JH, Li SC, Lit LC, Martínez-Brú C, Naidoo P, Nagele P, Pearse RM, Rodseth RN, Sessler DI, Sigamani A, Szczeklik W, Tiboni M, Villar JC, Wang CY, Xavier D, Devereaux PJ. High sensitivity troponin T concentrations in patients undergoing noncardiac surgery: a prospective cohort study. *Clin Biochem* 2011;**44**:1021–1024.

82. Devereaux PJ, Biccard BM, Sigamani A, Xavier D, Chan MTV, Srinathan SK, Walsh M, Abraham V, Pearse R, Wang CY, Sessler DI, Kurz A, Szczeklik W, Berwanger O, Villar JC, Malaga G, Garg AX, Chow CK, Ackland G, Patel A, Borges FK, Belley-Cote EP, Duceppe E, Spence J, Tandon V, Williams C, Sapsford RJ, Polanczyk CA, Tiboni M, Alonso-Coello P, Faruqui A, Heels-Ansdell D, Lamy A, Whitlock R, LeManach Y, Roshanov PS, McGillion M, Kavsak P, McQueen MJ, Thabane L, Rodseth RN, Buse GAL, Bhandari M, Garutti I, Jacka MJ, Schünemann HJ, Cortes OL, Coriat P, Dvirnik N, Botto F, Pettit S, Jaffe AS,

Guyatt GH. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2017;**317**:1642–1651.

83. Puelacher C, Lurati Buse G, Seeberger D, Sazgary L, Marbot S, Lampart A, Espinola J, Kindler C, Hammerer A, Seeberger E, Strebel I, Wildi K, Twerenbold R, du Fay de Lavallaz J, Steiner L, Gurke L, Breidthardt T, Rentsch K, Buser A, Gualandro DM, Osswald S, Mueller C. Perioperative myocardial injury after noncardiac surgery: Incidence, mortality, and characterization. *Circulation* 2018;**137**:1221–1232.
84. Duvall WL, Sealove B, Pungoti C, Katz D, Moreno P, Kim M. Angiographic investigation of the pathophysiology of perioperative myocardial infarction. *Catheter Cardiovasc Interv* 2012;**80**:768–776.
85. Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS. *Circulation* 2009;**119**:2936–2944.
86. Hanson I, Kahn J, Dixon S, Goldstein J. Angiographic and clinical characteristics of type 1 versus type 2 perioperative myocardial infarction. *Catheter Cardiovasc Interv* 2013;**82**:622–628.
87. Gualandro DM, Campos CA, Calderaro D, Yu PC, Marques AC, Pastana AF, Lemos PA, Caramelli B. Coronary plaque rupture in patients with myocardial infarction after noncardiac surgery: frequent and dangerous. *Atherosclerosis* 2012;**222**:191–195.

88. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker GM. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. *J Am Coll Cardiol* 2010;**56**:1071–1078.
89. Januzzi JL Jr, Filippatos G, Nieminen M, Gheorghiade M. Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: *Heart Failure Section*. *Eur Heart J* 2012;**33**:2265–2271.
90. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, Sheppard MN, Figtree GA, Parodi G, Akashi YJ, Ruschitzka F, Filippatos G, Mebazaa A, Omerovic E. Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2016;**18**:8–27.
91. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tschöpe C, Schultheiss

HP, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Böhm M, Erbel R, Cuneo A, Kuck KH, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KE, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairez O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Lüscher TF. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. *N Engl J Med* 2015;**373**:929–938.

92. Medeiros K, O'Connor MJ, Baicu CF, Fitzgibbons TP, Shaw P, Tighe DA, Zile MR, Aurigemma GP. Systolic and diastolic mechanics in stress cardiomyopathy. *Circulation* 2014;**129**:1659–1667.

93. Sharkey SW, Lesser JR, Zenovich AG, Maron MS, Lindberg J, Longe TF, Maron BJ. Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation* 2005;**111**:472–479.

94. Redfors B, Råmunddal T, Shao Y, Omerovic E. Takotsubo triggered by acute myocardial infarction: a common but overlooked syndrome? *J Geriatr Cardiol* 2014;**11**:171–173.

95. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, De Caterina R, Zimarino M, Roffi M, Kjeldsen K, Atar D, Kaski JC, Sechtem U, Tornvall P; Working Group on Cardiovascular Pharmacotherapy. ESC Working Group position paper on myocardial infarction with non-obstructive coronary arteries. *Eur Heart J* 2017;**38**:143–153.

96. Lindahl B, Baron T, Erlinge D, Hadziosmanovic N, Nordenskjöld AM, Gard A, Jernberg T. Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with nonobstructive coronary artery disease. *Circulation* 2017;**135**:1481–1489.

97. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation* 2015;**131**:861–870.

98. Smilowitz NR, Mahajan AM, Roe MT, Hellkamp AS, Chiswell K, Gulati M, Reynolds HR. Mortality of Myocardial Infarction by Sex, Age, and Obstructive Coronary Artery Disease Status in the ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines). *Circ Cardiovasc Qual Outcomes* 2017 Dec;10:e003443.

99. Jacobs LH, van de Kerkhof J, Mingels AM, Kleijnen VW, van der Sande FM, Wodzig WK, Kooman JP, van Dieijen-Visser MP. Haemodialysis patients longitudinally assessed by highly sensitive cardiac troponin T and commercial cardiac troponin T and cardiac troponin I assays. *Ann Clin Biochem* 2009;**46**:283–290.

100. Unger ED, Dubin RF, Deo R, Daruwalla V, Friedman JL, Medina C, Beussink L, Freed BH, Shah SJ. Association of chronic kidney disease with abnormal cardiac mechanics and adverse outcomes in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail* 2016;**18**:103–112.

101. Twerenbold R, Wildi K, Jaeger C, Gimenez MR, Reiter M, Reichlin T, Walukiewicz A, Gugala M, Krivoshei L, Marti N, Moreno Weidmann Z, Hillinger P, Puelacher C, Rentsch K, Honegger U, Schumacher C, Zurbriggen F, Freese M, Stelzig C, Campodarve I, Bassetti S, Osswald S, Mueller C. Optimal cutoff levels of more sensitive cardiac troponin assays for the early diagnosis of myocardial infarction in patients with renal dysfunction. *Circulation* 2015;**131**:2041–2050.

102. deFilippi C, Seliger SL, Kelley W, Duh SH, Hise M, Christenson RH, Wolf M, Gaggin H, Januzzi J. Interpreting cardiac troponin results from high-sensitivity assays in chronic kidney disease without acute coronary syndrome. *Clin Chem* 2012;**58**:1342–1351.

103. Michos ED, Wilson LM, Yeh HC, Berger Z, Suarez-Cuervo C, Stacy SR, Bass EB. Prognostic value of cardiac troponin in patients with chronic kidney disease without suspected acute coronary syndrome: a systematic review and meta-analysis. *Ann Intern Med* 2014;**161**:491–501.

104. Parikh RH, Seliger SL, deFilippi CR. Use and interpretation of high sensitivity cardiac troponins in patients with chronic kidney disease with and without acute myocardial infarction. *Clin Biochem* 2015;**48**:247–253.

105. Friden V, Starnberg K, Muslimovic A, Ricksten SE, Bjurman C, Forsgard N, Wickman A, Hammarsten O. Clearance of cardiac troponin T with and without kidney function. *Clin Biochem* 2017;**50**:468–474.

106. Stacy SR, Suarez-Cuervo C, Berger Z, Wilson LM, Yeh HC, Bass EB, Michos ED. Role of troponin in patients with chronic kidney disease and suspected acute coronary syndrome: a systematic review. *Ann Intern Med* 2014;**161**:502–512.

107. Guest TM, Ramanathan AV, Tuteur PG, Schechtman KB, Ladenson JH, Jaffe AS. Myocardial injury in critically ill medical patients: a surprisingly frequent complication. *JAMA* 1995;**273**:1945–1949.

108. Babuin L, Vasile VC, Rio Perez JA, Alegria JR, Chai HS, Afessa B, Jaffe AS. Elevated cardiac troponin is an independent risk factor for short- and long-term mortality in medical intensive care unit patients. *Crit Care Med* 2008;**36**:759–765.

109. Landesberg G, Vesselov Y, Einav S, Goodman S, Sprung CL, Weissman C. Myocardial ischemia, cardiac troponin, and long-term survival of high-cardiac risk critically ill intensive care unit patients. *Crit Care Med* 2005;**33**:1281–1287.

110. Thygesen K, Alpert JS, Jaffe AS, White HD. Diagnostic application of the universal definition of myocardial infarction in the intensive care unit. *Curr Opin Crit Care* 2008;**14**:543–548.

111. Vatner SF, Baig H, Manders WT, Maroko PR. The effects of coronary artery reperfusion on myocardial infarct size calculated from creatine kinase. *J Clin Invest* 1978;**61**:1048–1056.

112. Starnberg K, Jeppsson A, Lindahl B, Hammarsten O. Revision of the troponin T release mechanism from damaged human myocardium. *Clin Chem* 2014;**60**:1098–1104.

113. Jaffe AS, Moeckel M, Giannitsis E, Huber K, Mair J, Mueller C, Plebani M, Thygesen K, Lindahl B. In search for the Holy Grail: Suggestions for studies to define delta changes to diagnose or exclude acute myocardial infarction: a position paper from the study group on biomarkers of the Acute Cardiovascular Care Association. *Eur Heart J Acute Cardiovasc Care* 2014;**3**:313–316.

114. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, Bassetti S, Steuer S, Winkler K, Peter F, Meissner J, Haaf P, Potocki M, Drexler B, Osswald S, Mueller C. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. *Circulation* 2011;**124**:136–145.

115. Mueller M, Biener M, Vafaie M, Doerr S, Keller T, Blankenberg S, Katus HA, Giannitsis E. Absolute and relative kinetic changes of high-sensitivity cardiac troponin T in acute coronary syndrome and in patients with increased troponin in the absence of acute coronary syndrome. *Clin Chem* 2012;**58**:209–218.

116. Keller T, Zeller T, Ojeda F, Tzikas S, Lillpopp L, Sinning C, Wild P, Genth-Zotz S, Warnholtz A, Giannitsis E, Mockel M, Bickel C, Peetz D, Lackner K, Baldus S, Munzel T, Blankenberg S. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. *JAMA* 2011;**306**:2684–2693.

117. Jaffe AS, Apple FS, Morrow DA, Lindahl B, Katus HA. Being rational about (im)precision: a statement from the Biochemistry Subcommittee of the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task force for the definition of myocardial infarction. *Clin Chem* 2010;**56**:941–943.

118. Sandoval Y, Apple FS. The global need to define normality: the 99th percentile value of cardiac troponin. *Clin Chem* 2013;**60**:455–462.

119. Apple FS, Sandoval Y, Jaffe AS, Ordonez-Llanos J, for the IFCC Task Force on Clinical Applications of Cardiac Bio-Markers. Cardiac troponin assays: guide

to understanding analytical characteristics and their impact on clinical care. *Clin Chem* 2017;**63**:73–81.

120. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem* 2010;**56**:254–261.

121. Frankenstein L, Wu AHB, Hallermayer K, Wians FH, Giannitsis E, Katus HA. Biological variation and reference change value of high-sensitivity troponin T in healthy individuals during short and intermediate follow-up periods. *Clin Chem* 2011;**57**:1068–1071.

122. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. *Clin Chem* 2012;**58**:1574–1581.

123. Wu AHB, Christenson RH, Greene DN, Jaffe AS, Kavsak PA, Ordonez-Llanos J, Apple FS. Clinical laboratory practice recommendations for the use of cardiac troponin in acute coronary syndrome: Expert opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. *Clin Chem* 2018;**64**:645–655.

124. Collinson PO, Heung YM, Gaze D, Boa F, Senior R, Christenson R, Apple FS. Influence of population selection on the 99th percentile reference value for cardiac troponin assays. *Clin Chem* 2012;**58**:219–225.

125. McKie PM, Heublein DM, Scott CG, Gantzer ML, Mehta RA, Rodeheffer RJ, Redfield MM, Burnett JC Jr, Jaffe AS. Defining high-sensitivity cardiac troponin concentrations in the community. *Clin Chem* 2013;**59**:1099–1107.

126. Olivieri F, Galeazzi R, Giavarina D, Testa R, Abbatecola AM, Ceka A, Tamburrini P, Busco F, Lazzarini R, Monti D, Franceschi C, Procopio AD, Antonicelli R. Aged-related increase of high sensitive troponin T and its implication in acute myocardial infarction diagnosis of elderly patients. *Mech Ageing Dev* 2012;**133**:300–305.

127. Reiter M, Twerenbold R, Reichlin T, Haaf P, Peter F, Meissner J, Hochholzer W, Stelzig C, Freese M, Heinisch C, Breidthardt T, Freidank H, Winkler K, Campodarve I, Gea J, Mueller C. Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. *Eur Heart J* 2011;**32**:1379–1389.

128. Shah AS, Griffiths M, Lee KK, McAllister DA, Hunter AL, Ferry AV, Cruikshank A, Reid A, Stoddart M, Strachan F, Walker S, Collinson PO, Apple FS, Gray AJ, Fox KA, Newby DE, Mills NL. High sensitivity cardiac troponin and

the under-diagnosis of myocardial infarction in women: prospective cohort study. *BMJ* 2015;**350**:g7873.

129. Eggers KM, Johnston N, James S, Lindahl B, Venge P. Cardiac troponin I levels in patients with non-ST-elevation acute coronary syndrome-the importance of gender. *Am Heart J* 2014;**168**:317–324.

130. Balmelli C, Meune C, Twerenbold R, Reichlin T, Rieder S, Drexler B, Rubini MG, Mosimann T, Reiter M, Haaf P, Mueller M, Ernst S, Ballarino P, Alafify AA, Zellweger C, Wildi K, Moehring B, Vilaplana C, Bernhard D, Merk S, Ebmeyer S, Freidank H, Osswald S, Mueller C. Comparison of the performances of cardiac troponins, including sensitive assays, and copeptin in the diagnostic of acute myocardial infarction and long-term prognosis between women and men. *Am Heart J* 2013;**166**:30–37.

131. Bjurman C, Larsson M, Johanson P, Petzold M, Lindahl B, Fu ML, Hammarsten O. Small changes in troponin T levels are common in patients with non-ST segment elevation myocardial infarction and are linked to higher mortality. *J Am Coll Cardiol* 2013;**62**:1231–1238.

132. D'Souza M, Sarkisian L, Saaby L, Poulsen TS, Gerke O, Larsen TB, Diederichsen ACP, Jangaard N, Diederichsen SZ, Hosbond S, Hove J, Thygesen K, Mickley H. Diagnosis of unstable angina pectoris has declined markedly with the advent of more sensitive troponin assays. *Am J Med* 2015;**128**:852–860.

133. Reichlin T, Twerenbold R, Reiter M, Steuer S, Bassetti S, Balmelli C, Winkler K, Kurz S, Stelzig C, Freese M, Drexler B, Haaf P, Zellweger C, Osswald S, Mueller C. Introduction of high-sensitivity troponin assays: impact on myocardial infarction incidence and prognosis. *Am J Med* 2012;**125**:1205–1213.

134. Sandoval Y, Apple FS, Smith SW. High-sensitivity cardiac troponin assays and unstable angina. *Eur Heart J Acute Cardiovasc Care* 2018;**7**:120–128.

135. Morrow DA. Clinician's guide to early rule-out strategies with high-sensitivity cardiac troponin. *Circulation* 2017;**135**:1612–1616.

136. Twerenbold R, Boeddinghaus J, Nestelberger T, Wildi K, Rubini Gimenez M, Badertscher P, Mueller C. Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction. *J Am Coll Cardiol* 2017;**70**:996–1012.

137. Cullen L, Mueller C, Parsonage WA, Wildi K, Greenslade JH, Twerenbold R, Aldous S, Meller B, Tate JR, Reichlin T, Hammett CJ, Zellweger C, Ungerer JPJ, Rubini Gimenez M, Troughton R, Murray K, Brown AFT, Mueller M, George P, Mosimann T, Flaws DF, Reiter M, Lamanna A, Haaf P, Pemberton CJ, Richards AM, Chu K, Reid CM, Peacock WF, Jaffe AS, Florkowski C, Deely JM, Than M. Validation of high-sensitivity troponin I in a 2-hour diagnostic strategy to assess

30-day outcomes in emergency department patients with possible acute coronary syndrome. *J Am Coll Cardiol* 2013;**62**:1242–1249.

138. Pickering JW, Than MP, Cullen L, Aldous S, Ter Avest E, Body R, Carlton EW, Collinson P, Dupuy AM, Ekelund U, Eggers KM, Florkowski CM, Freund Y, George P, Goodacre S, Greenslade JH, Jaffe AS, Lord SJ, Mokhtari A, Mueller C, Munro A, Mustapha S, Parsonage W, Peacock WF, Pemberton C, Richards AM, Sanchis J, Staub LP, Troughton R, Twerenbold R, Wildi K, Young J. Rapid rule-out of acute myocardial infarction with a single high-sensitivity cardiac troponin T measurement below the limit of detection: A collaborative meta-analysis. *Ann Intern Med* 2017;**166**:715–724.

139. Mueller C, Giannitsis E, Möckel M, Huber K, Mair J, Plebani M, Thygesen K, Jaffe AS, Lindahl B; Biomarker Study Group of the ESC Acute Cardiovascular Care Association. Rapid rule out of acute myocardial infarction: novel biomarker-based strategies. *Eur Heart J Acute Cardiovasc Care* 2017;**6**:218–222.

140. Boeddinghaus J, Nestelberger T, Twerenbold R, Wildi K, Badertscher P, Cupa J, Burge T, Machler P, Corbiere S, Grimm K, Rubini Gimenez M, Puelacher C, Shrestha S, Flores Widmer D, Fuhrmann J, Hillinger P, Sabti Z, Honegger U, Schaerli N, Kozhuharov N, Rentsch K, Miro O, Lopez Barbeito B, Martin-Sanchez FJ, Rodriguez-Adrada E, Morawiec B, Kawecki D, Ganovska E, Parenica J, Lohrmann J, Kloos W, Buser A, Geigy N, Keller DI, Osswald S, Reichlin T, Muller C. Direct comparison of 4 very early rule-out strategies for acute myocardial infarction using high-sensitivity cardiac troponin I. *Circulation* 2017;**135**:1597–1611.

141. Möckel M, Giannitsis E, Mueller C, Huber K, Jaffe AS, Mair J, Plebani M, Thygesen K, Lindahl B; Biomarker Study Group of the European Society of Cardiology Acute Cardiovascular Care Association. Rule-in of acute myocardial infarction: focus on troponin. *Eur Heart J Acute Cardiovasc Care* 2017;**6**:212–217.

142. Jaffe AS, White H. Ruling-in myocardial injury and ruling-out myocardial infarction with the European Society of Cardiology (ESC) 1-hour algorithm. *Circulation* 2016;**134**:1542–1545.

143. Sandoval Y, Herzog CA, Love SA, Cao J, Hu Y, Wu AHB, Gilbertson D, Brunelli SM, Young A, Ler R, Apple FS. Prognostic value of serial changes in high-sensitivity cardiac troponin I and T over 3 months using reference change values in hemodialysis patients. *Clin Chem* 2016;**62**:631–638.

144. DeFilippi CF, Herzog CA. Interpreting cardiac biomarkers in the setting of chronic kidney disease. *Clin Chem* 2017;**63**:59–65.

145. Neeland IJ, Drazner MH, Berry JD, Ayers CR, deFilippi C, Seliger SL, Nambi V, McGuire DK, Omland T, de Lemos JA. Biomarkers of chronic cardiac injury and hemodynamic stress identify a malignant phenotype of left ventricular hypertrophy in the general population. *J Am Coll Cardiol* 2013;**61**:187–195.

146. Biner M, Mueller M, Vafaie M, Jaffe AS, Widera C, Katus HA, Giannitsis E. Diagnostic performance of rising, falling, or rising and falling kinetic changes of high-sensitivity cardiac troponin T in an unselected emergency department population. *Eur Heart J Acute Cardiovasc Care* 2013;**2**:314–322.

147. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol* 2014;**64**:e139–e228.

148. Bagai A, Jollis JG, Dauerman HL, Peng SA, Rokos IC, Bates ER, French WJ, Granger CB, Roe MT. Emergency department bypass for ST-segment-elevation myocardial infarction patients identified with a prehospital electrocardiogram. *Circulation* 2013;**128**:352–359.

149. Scirica BM, Morrow DA, Budaj A, Dalby AJ, Mohanavelu S, Qin J, Aroesty J, Hedgepeth CM, Stone PH, Braunwald E. Ischemia detected on continuous electrocardiography after acute coronary syndrome. *J Am Coll Cardiol* 2009;**53**:1411–1421.

150. Wang K, Asinger RW, Marriott HJ. ST-segment elevation in conditions other than acute myocardial infarction. *N Engl J Med* 2003;**349**:2128–2135.

151. de Winter RJ, Verouden NJW, Wellens HJJ, Wilde AAM. A new ECG sign of proximal LAD occlusion. *N Engl J Med* 2008;**359**:2071–2073.

152. de Winter RW, Adams R, Verouden NJW, de Winter RJ. Precordial junctional ST-segment depression with tall symmetric T-waves signifying proximal LAD occlusion, case reports of STEMI equivalence. *J Electrocardiol* 2016;**49**:76–80.

153. de Zwaan C, Bär FWHM, Wellens HJJ. Characteristic electrocardiographic pattern indicating a critical stenosis high in left anterior descending coronary artery in patients admitted because of impending myocardial infarction. *Am Heart J* 1982;**103**:730–736.

154. Wong CK, Gao W, Stewart RA, Benatar J, French JK, Aylward PE, White HD; HERO-2 Investigators. aVR ST elevation: an important but neglected sign in ST elevation acute myocardial infarction. *Eur Heart J* 2010;**31**:1845–1853.

155. Matetzky S, Freimark D, Feinberg MS, Novikov I, Rath S, Rabinowitz B, Kaplinsky E, Hod H. Acute myocardial infarction with isolated ST-segment elevation in posterior chest leads $V_{7\text{-}9}$. *J Am Coll Cardiol* 1999;**34**:748–753.

156. Wong CK, White HD. Patients with circumflex occlusions miss out on reperfusion: how to recognize and manage them. *Curr Opin Cardiol* 2012;**27**:327–330.

157. Lopez-Sendon J, Coma-Canella I, Alcasena S, Seoane J, Gamallo C. Electrocardiographic findings in acute right ventricular infarction: sensitivity and specificity of electrocardiographic alterations in right precordial leads V_4R, V_3R, V_1, V_2 and V_3. *J Am Coll Cardiol* 1985;**6**:1273–1279.

158. Deluigi CC, Ong P, Hill S, Wagner A, Kispert E, Klingel K, Kandolf R, Sechtem U, Mahrholdt H. ECG findings in comparison to cardiovascular MR imaging in viral myocarditis. *Int J Cardiol* 2013;**165**:100–106.

159. Biagini E, Pazzi C, Olivotto I, Musumeci B, Limongelli G, Boriani G, Pacileo G, Mastromarino V, Reggiani MLB, Lorenzini M, Lai F, Berardini A, Mingardi F, Rosmini S, Resciniti E, Borghi C, Autore C, Cecchi F, Rapezzi C. Usefulness of electrocardiographic patterns at presentation to predict long-term risk of cardiac death in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2016;**118**:432–439.

160. Guerra F, Rrapaj E, Pongetti G, Fabbrizioli A, Pelizzoni V, Giannini I, Aschieri D, Costantini C, Capucci A. Differences and similarities of repolarization patterns during hospitalization for takotsubo cardiomyopathy and acute coronary syndrome. *Am J Cardiol* 2013;**112**:1720–1724.

161. Savage RM, Wagner GS, Ideker RE, Podolsky SA, Hackel DB. Correlation of postmortem anatomic findings with electrocardiographic changes in patients with myocardial infarction: retrospective study of patients with typical anterior and posterior infarcts. *Circulation* 1977;**55**:279–285.

162. Horan LG, Flowers NC, Johnson JC. Significance of the diagnostic Q wave of myocardial infarction. *Circulation* 1971;**43**:428–436.

163. Chaitman BR, Hardison RM, Adler D, Gebhart S, Grogan M, Ocampo S, Sopko G, Ramires JA, Schneider D, Frye RL; Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Study Group. The Bypass Angioplasty Revascularization Investigation 2 Diabetes randomized trial of different treatment strategies in type 2 diabetes mellitus with stable ischemic heart disease. *Circulation* 2009;**120**:2529–2540.

164. Burgess DC, Hunt D, Zannino D, Williamson E, Davis TME, Laakso M, Kesaniemi YA, Zhang J, Sy RW, Lehto S, Mann S, Keech AC. Incidence and predictors of silent myocardial infarction in type 2 diabetes and the effect of fenofibrate: an analysis from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Eur Heart J* 2010;**31**:92–99.

165. Kwong RY, Sattar H, Wu H, Vorobiof G, Gandla V, Steel K, Siu S, Brown KA. Incidence and prognostic implication of unrecognized myocardial scar

characterized by cardiac magnetic resonance in diabetic patients without clinical evidence of myocardial infarction. *Circulation* 2008;**118**:1011–1020.

166. Sgarbossa EB, Pinsky SL, Barbagelata A, Underwood DA, Gates KB, Topol EJ, Califf RM, Wagner GS; GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) Investigators. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle branch block. *N Engl J Med* 1996;**334**:481–487.

167. Cai Q, Mehta N, Sgarbossa EB, Pinski SL, Wagner GS, Califf RM, Barbagelata A. The left bundle-branch block puzzle in the 2013 ST-elevation myocardial infarction guideline: from falsely declaring emergency to denying reperfusion in a high-risk population. Are the Sgarbossa Criteria ready for prime time? *Am Heart J* 2013;**166**:409–413.

168. Widimsky P, Rohác F, Stásek J, Kala P, Rokyta R, Kuzmanov B, Jakl M, Poloczek M, Kanovsky J, Bernat I, Hlinomaz O, Belohlávek J, Král A, Mrázek V, Grigorov V, Djambazov S, Petr R, Knot J, Bílková D, Fischerová M, Vondrák K, Maly M, Lorencová A. Primary angioplasty in acute myocardial infarction with right bundle branch block: should new onset right bundle branch block be added to future guidelines as an indication for reperfusion therapy? *Eur Heart J* 2012;**33**:86–95.

169. Brandt RR, Hammill SC, Higano ST. Electrocardiographic diagnosis of acute myocardial infarction during ventricular pacing. *Circulation* 1998;**97**:2274–2275.

170. Pradhan R, Chaudhary A, Donato AA. Predictive accuracy of ST depression during rapid atrial fibrillation on the presence of obstructive coronary artery disease. *Am J Emerg Med* 2012;**30**:1042–1047.

171. Androulakis A, Aznaouridis KA, Aggeli CJ, Roussakis GN, Michaelides AP, Kartalis AN, Stougiannos PN, Dilaveris PE, Misovoulos PI, Stefanadis CI, Kallikazaros IE. Transient ST-segment depression during paroxysms of atrial fibrillation in otherwise normal individuals. *J Am Coll Cardiol* 2007;**50**:1909–1911.

172. Vakil K, Gandhi S, Abidi KS, Tholakanahalli V, Sharma A, Zaharova M, Madlon-Kay R. Deep T-wave inversions: cardiac ischemia or memory? *J Cardiovasc Dis* 2014;**2**:116–119.

173. Stillman AE, Oudkerk M, Bluemke D, Bremerich J, Esteves FP, Garcia EV, Gutberlet M, Hundley WG, Jerosch-Herold M, Kuijpers D, Kwong RK, Nagel E, Lerakis S, Oshinski J, Paul JF, Underwood R, Wintersperger BJ, Rees MR. Assessment of acute myocardial infarction: current status and recommendations from the North American Society for Cardiovascular Imaging and the European Society of Cardiac Radiology. *Int J Cardiovasc Imaging* 2011;**27**:7–24.

174. Scirica BM. Acute coronary syndrome: emerging tools for diagnosis and risk assessment. *J Am Coll Cardiol* 2010;**55**:1403–1415.

175. Kontos MC, Diercks DB, Kirk JD. Emergency department and office-based evaluation of patients with chest pain. *Mayo Clin Proc* 2010;**85**:284–299.

176. Lewis WR. Echocardiography in the evaluation of patients in chest pain units. *Cardiol Clin* 2005;**23**:531–539.

177. Flachskampf FA, Schmid M, Rost C, Achenbach S, de Maria AN, Daniel WG. Cardiac imaging after myocardial infarction. *Eur Heart J* 2011;**32**:272–283.

178. Zamorano J, Wallbridge DR, Ge J, Drozd J, Nesser J, Erbel R. Non-invasive assessment of cardiac physiology by tissue Doppler echocardiography. *Eur Heart J* 1997;**18**:330–339.

179. Kaul S, Miller JG, Grayburn PA, Hashimoto S, Hibberd M, Holland MR, Houle HC, Klein AL, Knoll P, Lang RM, Lindner JR, McCulloch ML, Metz S, Mor-Avi V, Pearlman AS, Pellikka PA, DeMars Plambeck N, Prater D, Porter TR, Sahn DJ, Thomas JD, Thomenius KE, Weissman NJ. A suggested roadmap for cardiovascular ultrasound research for the future. *J Am Soc Echocardiogr* 2011;**24**:455–464.

180. O'Connor MK, Hammell T, Gibbons RJ. In vitro validation of a simple tomographic technique for estimation of percentage myocardium at risk using methoxyisobutyl isonitrile technetium 99m (sestamibi). *Eur J Nucl Med* 1990;**17**:69–76.

181. Carrio I, Cowie MR, Yamazaki J, Udelson J, Camici PG. Cardiac sympathetic imaging with *m*IBG in heart failure. *JACC Cardiovasc Imaging* 2010;**3**:92–100.

182. Nahrendorf M, Sosnovik DE, French BA, Swirski FK, Bengel F, Sadeghi MM, Lindner JR, Wu JC, Kraitchman DL, Fayad ZA, Sinusas AJ. Multimodality cardiovascular molecular imaging, Part II. *Circ Cardiovasc Imaging* 2009;**2**:56–70.

183. Kramer CM, Sinusas AJ, Sosnovik DE, French BA, Bengel FM. Multimodality imaging of myocardial injury and remodelling. *J Nucl Med* 2010;**51**:107S–121S.

184. Taegtmeyer H. Tracing cardiac metabolism in vivo: one substrate at a time. *J Nucl Med* 2010;**51**:80S–87S.

185. Kim HW, Faraneh-Far A, Kim RJ. Cardiovascular magnetic resonance in patients with myocardial infarction. *J Am Coll Cardiol* 2009;**55**:1–16.

186. Beek AM, van Rossum AC. Cardiovascular magnetic resonance imaging in patients with acute myocardial infarction. *Heart* 2010;**96**:237–243.

187. Locca D, Bucciarelli-Ducci C, Ferrante G, La Manna A, Keenan NG, Grasso A, Barlis P, del Furia F, Prasad SK, Kaski JC, Pennell DJ, di Mario C. New universal definition of myocardial infarction applicable after complex

percutaneous coronary interventions? *JACC Cardiovasc Interv* 2010;**3**:950–958.

188. Schuleri KH, George RT, Lardo AC. Assessment of coronary blood flow with computed tomography and magnetic resonance imaging. *J Nucl Cardiol* 2010;**17**:582–590.

189. Dedic A, Lubbers MM, Schaap J, Lammers J, Lamfers EJ, Rensing BJ, Braam RL, Nathoe HM, Post JC, Nielen T, Beelen D, le Cocq d'Armandville MC, Rood PP, Schultz CJ, Moelker A, Ouhlous M, Boersma E, Nieman K. Coronary CT angiography for suspected ACS in the era of high-sensitivity troponins: randomized multicenter study. *J Am Coll Cardiol* 2016;**67**:16–26.

190. Eitel I, de Waha S, Wöhrle J, Fuernau G, Lurz P, Pauschinger M, Desch S, Schuler G, Thiele H. Comprehensive prognosis assessment by CMR imaging after ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2014;**64**:1217–1226.

191. Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodard PK, Nagurney JT, Pope JH, Hauser TH, White CS, Weiner SG, Kalanjian S, Mullins ME, Mikati I, Peacock WF, Zakroysky P, Hayden D, Goehler A, Lee H, Gazelle GS, Wiviott SD, Fleg JL, Udelson JE; ROMICAT-II Investigators. Coronary CT angiography versus standard evaluation in acute chest pain. *N Engl J Med* 2012;**367**:299–308.

192. Puchner SB, Liu T, Mayrhofer T, Truong QA, Lee H, Fleg JL, Nagurney JT, Udelson JE, Hoffmann U, Ferencik M. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. *J Am Coll Cardiol* 2014;**64**:684–692.

193. Ferencik M, Liu T, Mayrhofer T, Puchner SB, Lu MT, Maurovich-Horvat P, Pope JH, Truong QA, Udelson JE, Peacock WF, White CS, Woodard PK, Fleg JL, Nagurney JT, Januzzi JL, Hoffmann U. hs-Troponin I followed by CT angiography improves acute coronary syndrome risk stratification accuracy and work-up in acute chest pain patients: results from ROMICAT II Trial. *JACC Cardiovasc Imaging* 2015;**8**:1272–1281.

194. Amsterdam EA, Kirk JD, Bluemke DA, Diercks D, Farkouh ME, Garvey JL, Kontos MC, McCord J, Miller TD, Morise A, Newby LK, Ruberg FL, Scordo KA, Thompson PD. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. *Circulation* 2010;**122**:1756–1776.

195. European Medicines Agency/Committee for Medicinal Products for Human Use (CHMP). Reflection paper on assessment of cardiovascular safety profile of medical products. EMA/CHMP/50549/2015.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/03/WC500203804.pdf (25 Feb 2016)

196. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, Solomon SD, Marler JR, Teerlink JR, Farb A, Morrow DA, Targum SL, Sila CA, Hai MTT, Jaff MR, Joffe HV, Cutlip DE, Desai AS, Lewis EF, Gibson CM, Landray MJ, Lincoff AM, White CJ, Brooks SS, Rosenfield K, Domanski MJ, Lansky AJ, McMurray JJV, Tcheng JE, Steinhubl SR, Burton P, Mauri L, O'Connor CM, Pfeffer MA, Hung HMJ, Stockbridge NL, Chaitman BR, Temple RJ; Standardized Data Collection for Cardiovascular Trials Initiative (SCTI). 2017 Cardiovascular and stroke endpoint definitions for clinical trials. *Circulation* 2018;**137**:961–972; *J Am Coll Cardiol* 2018;**71**:1021–1034.

197. Leening MJ, Elias-Smale SE, Felix JF, Kors JA, Deckers JW, Hofman A, Stricker BH, Witteman JC. Unrecognised myocardial infarction and long-term risk of heart failure in the elderly: the Rotterdam Study. *Heart* 2010;**96:**1458–1462.

198. Karnegis JN, Matts J, Tuna N. Development and evolution of electrocardiographic Minnesota Q-QS codes in patients with acute myocardial infarction. *Am Heart J* 1985;**110**:452–459.

199. Goyal A, Gluckman TJ, Tcheng JE. What's in a Name? The New ICD-10 (10th Revision of the International Statistical Classification of Diseases and Related Health Problems) Codes and Type 2 Myocardial Infarction. *Circulation* 2017;**136**:1180–1182.

200. Rosamond W, Chambless L, Heiss G, Mosley T, Coresh J, Whitsel E, Wagenknecht L, Ni H, Folsom A. Twenty-two year trends in incidence of myocardial infarction, CHD mortality, and case-fatality in 4 US communities, 1987-2008. *Circulation* 2012;**125**:1848–1857.

201. Luepker R, Duval S, Jacobs D, Smith L, Berger A. The effect of changing diagnostic algorithms on acute myocardial infarction rates. *Ann Epidemiol* 2011;**21**:824–829.