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Defining Myocardial Infarction in trials of people receiving hemodialysis: consensus report from the SONG-HD MI Expert Working group

Brief title: Defining MI in patients on hemodialysis.

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Abstract:

Cardiovascular disease is the leading cause of death in patients receiving hemodialysis. Currently there is no standardized definition of myocardial infarction (MI) for patients receiving hemodialysis. Through an international consensus process MI was established as the core CVD measure for this population in clinical trials. The Standardised Outcomes in Nephrology Group – Hemodialysis (SONG-HD) initiative convened a multidisciplinary, international working group to address the definition of MI in this population. Based on current evidence, the working group recommends using the 4th Universal Definition of MI with specific caveats with regard to the interpretation of "ischemic symptoms" and performing a baseline 12-lead electrocardiogram to facilitate interpretation of acute changes on subsequent tracings. The working group does not recommend obtaining baseline cardiac troponin values, though does recommend obtaining serial cardiac biomarkers in settings where ischemia is suspected. Application of an evidence-based uniform definition should increase the reliability and accuracy of trial results.

Keywords: hemodialysis, myocardial infarction, outcome, definition, trials, recommendations

One sentence summary. An international expert working group support the use of the 4th Universal definition of myocardial infarction for use in trials in people requiring hemodialysis.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in patients with kidney failure requiring replacement therapy [1]. The incidence of myocardial infarction (MI) in patients receiving hemodialysis is at least 4-times higher than in the general population and is associated with substantially poorer outcomes [1-3]. One-year mortality after a MI in patients receiving hemodialysis is also 60% compared to less than 10% in the general population [4-7].

The higher prevalence of MI in the hemodialysis population is multifactorial. Traditional cardiovascular (CV) risk factors, including hypertension and diabetes, are more common. In addition, there are risk factors that are unique to patients receiving hemodialysis, including dysregulation of bone and mineral metabolism leading to increased vascular calcification and uremic toxins. Dialysis also results in rapid hemodynamic changes, heightened inflammation, endothelial and immune dysfunction [8-11].

Patients receiving hemodialysis are usually excluded from large-scale CV interventional trials[12] but when included the most frequently measured and reported CV outcomes are surrogate endpoints such as serum biomarkers which may be of uncertain clinical significance and of little relevance to patients [13, 14]. Composite CV outcomes in this population are frequently used to achieve adequate statistical power however, across different trials use different components (e.g. stroke, MI, heart failure) to form each composite outcome[13]. MI, which in a recent international survey including patients and clinicians has been shown to be of the highest importance to patients receiving hemodialysis [15], is frequently a component of a CV composite endpoint but is defined inconsistently [13, 16]. A review of five large CV trials in patients receiving hemodialysis demonstrated four different definitions of MI (Table 1) and different adjudication processes.

Applying an alternative definition or adjudication process to each trial potentially lead a to clinically significant difference in number of reported events. Although not specific to trials in this population, the lack of a standardized and validated definition for MI in patients receiving hemodialysis and the heterogenous measurement and reporting of MI limit the comparison of interventions across trials.

The Standardised Outcomes in Nephrology (SONG) Initiative, a National Health and Medical Research Council (NHMRC) funded project, has established core outcome sets across the spectrum of kidney disease since 2014. A core outcome set is an agreed standardized set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health [17]. The core outcomes are based on priorities defined by patients, caregivers, and health professionals. Through the SONG-HD (hemodialysis) consensus process involving over 1500 patients, caregivers, and health professionals from more than 70 countries, CVD was identified as a core outcome, with MI established as the core outcome measure [15, 18]. To use MI as a core outcome measure in trials involving patients receiving hemodialysis, consensus on a uniform definition for MI in this population is needed.

The SONG-HD initiative convened an international working group of experts at a roundtable meeting in Washington, D.C. on November 8, 2019. The expert working group was formed using purposive sampling to represent a broad range of countries and experience. It included cardiologists, nephrologists, clinical trialists, a clinical chemist, representatives from regulatory bodies and registries, and patients with experience of hemodialysis, to recommend a uniform definition of MI for use in clinical trials evaluating patients receiving hemodialysis as well as potential for use in clinical practice. We began by considering whether the 4th Universal Definition of Myocardial Infarction (UDMI) [19], a standard definition formulated for the general population, was applicable to patients receiving hemodialysis. This definition has not been specifically validated in the dialysis population although it is felt to be applicable to all patients with the caveat that there may be a greater percentage with chronic myocardial injury. There remain several limitations to the definition in people receiving hemodialysis. Specific considerations raised in the SONG-HD CVD consensus workshop regarding criteria required for an appropriate definition of MI informed the deliberations [18]. These considerations included consistency, applicability and specificity of the definition to patients receiving hemodialysis, the importance of the type of MI, variability in MI symptoms in patients receiving hemodialysis, and the uncertainty in the clinical utility of biomarkers specific to hemodialysis. This report summarizes the meeting discussion and the resulting recommendations.

THE 4TH UNIVERSAL DEFINITION OF MYOCARDIAL INFARCTION

In 2018 the European Society of Cardiology (ESC)/ American College of Cardiology (ACC)/the American Heart Association (AHA)and the World Heart Federation (WHF) jointly published an expert consensus document designated the Fourth UDMI[19] (Box 1). This definition was based on studies of MI in the general population. Although the document briefly discusses myocardial injury/infarction in patients with chronic kidney disease (CKD), including those with kidney failure, the publication does not address patients receiving hemodialysis specifically. Box 2 summarizes the limitations of the 4th UDMI and its applicability to Type 1 MI in people with kidney failure receiving hemodialysis.

TYPES OF MI

The Fourth UDMI classifies MI into five types. Criteria for the types of MI as laid out by the 4th UDMI are summarised in Box 1. The criteria required for diagnosing type 1 and 2 MIs in people requiring hemodialysis are outlined below. In brief, MI is defined as follows: (1) a rise and/or fall in cTn with at least 1 value >99th percentile URL in patients with an initial cTn ≤99th percentile URL; and (2) a >20% rise and/or fall in cTn in patients with an initial cTn >99th percentile URL.

Patients receiving hemodialysis have both a high prevalence of acute myocardial injury and are predisposed to acute MI, due to underlying pathophysiological features. Diagnosis of a type 2 MI requires consideration of both the context and mechanism leading to the imbalance of oxygen supply and demand. This is of particular importance to patients receiving hemodialysis, a process which has been shown to have significant hemodynamic effects which increase myocardial oxygen demand [20]. Hemodialysis also induces significant global and segmental reductions in myocardial blood flow [21]. Underlying pathophysiological changes related to kidney failure, including left ventricular hypertrophy and associated capillary/myocyte mismatch, reduced peripheral arterial compliance, endothelial dysfunction, anemia, and reduced coronary flow reserve, predispose patients requiring hemodialysis to demand ischemia. The prevalence of type 2 MIs is high in the hemodialysis population [22]. Estimating prevalence is difficult because differentiation between MI types 1 and 2 often requires expert adjudication in large clinical cohorts and ideally includes coronary angiography to definitively exclude coronary thrombosis [22].

To establish appropriate treatment according to current guidelines [23, 24], it is important to classify MI into ST-elevation MI (STEMI) or non-ST-elevation MI (NSTEMI). In the setting of a STEMI, primary percutaneous coronary intervention or thrombolytic therapy may be required and in the setting of a NSTEMI, coronary angiography may be indicated. Further classification into a Type 1 or 2 MI is not as well defined and there are limited quantitative data on the efficacy of coronary angiography in differentiating a type 1 from type 2 MI. Short and long-term mortality rates for type 2 MI are higher than for type 1 MI, although it is unclear whether there are differences in attributable cause-specific mortality [25-28]. Treatment of type 2 MI largely consists of addressing the underlying supply and demand imbalance noninvasively. In the case of hemodialysis, reducing "demand" may be possible through reducing ultrafiltration rates but there are often patient or centre based limitations to moving away from standard short intermittent dialysis sessions. Even in the general population long-term treatment strategies for type 2 MI in the absence of coronary artery disease lack trial data or guidelines [29]. Differentiating type 1 from type 2 MIs is challenging for adjudication experts as well as clinicians. Recent published guidelines advocate that in the absence of a clear alternative cause, the initial working diagnosis for most patients with evidence of acute myocardial injury and signs and symptoms consistent with ischemia should prompt classification and management according to established guidelines for type 1 MI [29]. Although treatment based on the type of MI may differ, the working group considered MI, regardless of type, to be the most important outcome captured in clinical trials. Evidence-based protocols for the management of type 2 MI remain limited.

Differentiating types 1 and 2 MI can be challenging. Improving our ability to recognize and treat MIs is a priority for future research.

MI should be a core outcome reported in clinical trials involving people with kidney failure receiving hemodialysis and a uniform definition should be used.

CRITERIA USED TO DEFINE TYPES 1, 2 AND 3 MI

1. Ischemic symptoms

Studies indicate that patients with CKD, and particularly those receiving hemodialysis, often do not describe typical symptoms of MI. The classic triad of chest discomfort, arm/jaw pain and sweating is experienced by less than 50% of patients with CKD [30]. In patients receiving hemodialysis, the most common “ischemic symptom” is shortness of breath, experienced by nearly 50% of patients receiving dialysis [30, 31]. Chest pain or discomfort associated with MI is experienced by less than 20% of patients receiving dialysis compared to over 35% of patients with normal kidney function [31]. Patient receiving dialysis described a background level of pain and discomfort and felt that non-specific symptoms or a change in sensation or degree of unwellness should also raise suspicion as an “ischemic symptom.” It is important to note that highlighting more non-specific ischemic symptoms may result in increased diagnosis of myocardial injury as well as MI [32].

In a patient receiving hemodialysis, atypical symptoms or any changes in symptoms should raise a high index of suspicion for a potential MI and prompt further investigation and treatment.

2. ELECTROCARDIOGRAM

Fluid and electrolyte changes during hemodialysis affect ECG waveforms. The removal of fluid over the course of a dialysis session has been shown to augment the P wave as well as the QRS amplitude and duration [33]. Similarly, electrolyte shifts during dialysis have been shown to affect the P wave, QRS, and QTc [33, 34]. Whether an ECG is acquired during, before or after dialysis should be considered in its interpretation; persistent changes such as left bundle-branch-block (BBB) are unlikely to be influenced by variations in dialysis.

Patients receiving hemodialysis often have abnormal baseline ECGs making it difficult to determine acute change. In one series approximately 30% of such patients were found to have electrical conduction abnormalities including left and right BBB on a baseline ECG. ST elevation occurs in less than 20% of patients with an MI on dialysis compared to over 35% of patients who are not on dialysis [35]. A non-specific ECG change is the most common finding in patients presenting with MI on hemodialysis [35.] Patients with CKD are significantly less likely to develop a pathological Q wave than patients without CKD (19% compared to 34%) [30]. It is important that non-specific ECG findings are taken in the context of the clinical presentation and in combination with troponin findings to help rule-in an MI though may not help ruling out MI.

Although patients with CKD, and particularly patients receiving hemodialysis, have a higher prevalence of silent MI compared to the general population [36, 37], there is no consensus regarding whether routine (annual or more frequent) collection of ECGs in this population confer incremental value in the absence of other clinical or biochemical abnormalities. Hence, for the purposes of clinical trials, the working group recommends obtaining ECGs in association with acute events but recommends where relevant discussing with regulators prior to study conduct, to consider whether baseline ECG and any subsequent changes consistent with silent MI events should be considered as an MI in a trial.

Patients indicated that an additional ECG at baseline "would not be a burden because it is non-invasive" and clinicians thought a baseline ECG would better inform trial endpoint definitions and patient care.

A baseline ECG in all patients receiving hemodialysis when stable and asymptomatic may aid in the interpretation of acute ECG changes on subsequent tracings in the setting of acute clinical symptoms or biomarker changes suggestive of MI. On trial entry, we suggest performing a single baseline ECG on each patient. We also recommend obtaining serial ECGs during an acute event followed by another ECG when the patient is clinically stable.

3. Cardiac Troponin

Troponin is a complex of three regulatory proteins (troponin I, C and T). During myocardial injury cTnI and cTnT are released as individual subunits as well as non-covalent ternary and binary complexes [38, 39]. cTnT and cTnI are now the preferred biomarkers of myocardial injury. Troponin is a biomarker for myocardial injury; the 4th UDMI includes clinical evidence of acute myocardial ischemia with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile upper reference limit (URL) plus additional criteria as summarized in Box 1.

Assay variability

High sensitivity cardiac troponin (hs-cTn) assays need to meet two criteria: a coefficient of variation (total imprecision) of $\leq$ 10% at the 99th percentile URL for both men and women and measurable concentrations below the 99th percentile URL need to be detectable above the assay's limit of detection for $\geq$ 50% of healthy individuals in the population of interest [40-42]. Sex-specific 99th percentile URLs for hs-cTn assays have been derived and validated in the general population based on healthy individuals[42]. It is not possible to achieve disease specific thresholds due to the heterogeneity within each specific disease population.

hs-Tn assays are now in widespread use and accurately and precisely measure five to 100-fold lower concentrations of cTn in blood than older, contemporary assays [43, 44]. The various hs-Tn assays use monoclonal antibodies to a number of different epitopes along the cTnT or cTnI protein [45]. On account of the large variations in epitopes targeted by the different antibodies used in each assay, it is not possible to standardize URLs across assays.

Biological variability

Biological variability describes the fluctuation of biomarker levels around a homeostatic set-point in healthy individuals or those with stable disease and which is of no clinical significance. Biological variability is low, with intra-patient coefficients of variation quoted as 7.9% for weekly measurements and 12.6% for monthly measurements. Although, there may be increased biological variability when using hs-cTn[46.] , over the course of a year this biological variability is minimal and if an acute event occurs, cTn subsequently returns to the individual patient's baseline [47,48]. Inter-patient variability is high in patients on hemodialysis [46,47].

Effect of dialysis on cardiac troponin:

To date only relatively small studies have been conducted to evaluate the effect of dialysis on cTn. The troponin complex (52 kDa), as well as the subunits (cTnI is 24 kDa and cTnT is 37 kDa) are classified as middle molecules by size. Older dialyzer membranes predominantly filtered out small, water-soluble molecules and not the “middle molecules”, now thought to be the cause of much of the historical morbidity and mortality. New synthetic membranes and the increase in convective therapies have improved the clearance of a number of these molecules. There remains a lack of consensus regarding the effect of dialysis on cTnI and cTnT levels however there is some evidence that cTnI is adsorbed onto the surface of the dialyzer membrane [49-51]. High flux dialyzers may increase cTn clearance more than low flux dialyzers [52, 53] and clearance is potentially increased further still with hemodiafiltration [53]. The increasing use of nocturnal dialysis and prolonged hours dialysis may have significant effect on both the production and handling of troponin. To date, changes in levels of both cTnT and cTnI are relatively small and there is insufficient evidence at this time to suggest that the effect of standard dialysis on troponin is significant enough to alter the diagnosis of MI in patients receiving hemodialysis.

Elevated baseline troponin

Levels of cTnT and cTnI over the sex specific 99th percentile URL have been demonstrated in up to 80% for cTnT but < 20% for cTnI of patients requiring hemodialysis [47, 54, 55]. Reduced kidney clearance is not the main driver of an elevated cTn in this population [56]. The exact etiology/mechanism of elevated baseline cTn, or why cTnT remains increased longer than cTnI, is not entirely clear but is likely to be multifactorial including increased instability of the cardiac myocyte membrane, microinfarctions, and myocardial necrosis as well as increased left ventricular hypertrophy and heart failure causing myocyte strain and apoptotic cell death [57-61].

In the absence of an acute event, elevated baseline cTn in patients receiving hemodialysis is a strong predictor of adverse outcomes. It has been shown that increased cTnT and cTnI are both predictive of CV and all-cause mortality in ESKD [47, 62-65]. Identifying risk has an effect on the individual patient and the cost to healthcare. There is currently insufficient evidence to suggest a pathway in response to the identified increased risk.

Therefore, although a determinant of risk, an historical baseline troponin should not contribute to the diagnosis of acute MI and we do not support the concept of acquiring a cTnI or cTnT on entry into a trial in HD dialysis patients. We acknowledge that a baseline level of cTnI or cTnT in an individual patient is a useful tool in identifying chronic myocardial injury and that the collection of a baseline troponin may offer future opportunities for further biomarker investigation and clarification of the role of troponin. However, in the assessment of a symptomatic patient presenting to the hospital, serial troponin monitoring should be used for ruling in or ruling out an MI.

Currently we do not suggest collecting a baseline (trial entry) cTn in a trial setting. Performing baseline cTn in stable, asymptomatic patients receiving hemodialysis may identify patients at increased risk for adverse outcome but with no currently proven treatment to reduce risk, resulting in unwanted concerns for patients without contributing to the diagnosis of acute MI.

Delta Troponin

The US National Academy of Clinical Biochemistry (NACB) (redesignated as, Academy of the American Association of Clinical Chemistry [AACC]) recommended a δ in standard assays for cTn of > 50% if cTn is less than the 99th percentile URL and ≥ 20% once values are elevated above the 99th percentile URL. These values are calculated to distinguish a true change from one that could be attributed to biological variability alone and yet maintain sensitivity [44].

The clinical sensitivity of hs-cTn assays to detect myocardial injury remain high in patients on hemodialysis, reported as 100% [31] however high prevalence of elevated baseline cTn can reduce specificity to as low as 40%. Hence, in a hemodialysis patient with an initial cTn value greater than the 99th percentile URL, a rise and/or fall of more than 20% is suggestive of an acute MI and should be included in the endpoint definitions in a trial setting. Short-term intra-patient biological and analytical variability is minimal in the absence of an acute event, however, a one to two hour follow up sample after initial testing may not be sufficient to rule out MI. Patients presenting early after an MI are unlikely to be missed using a two-hour sample but for patients who present with atypical symptoms, it may be harder to know where on the cTn kinetic curve (Figure 1) they are at a given time point. Any dynamic change in cTn or strong clinical suspicion should prompt further cTn samples so as not to miss a significant delta. This may require samples to be taken after up to 6 hours to ensure an MI is not missed.

Current evidence suggests that, in the context of an initial cTn above the sex specific 99th percentile URL, a δ cTn > 20% in cTn in addition to the clinical criteria should be an accepted rise

and/or fall to diagnose acute MI in the patients requiring hemodialysis. An early rule-out sample may not be sufficient to exclude MI in patients requiring hemodialysis.

SUMMARY

The (SONG-HD) Initiative convened an expert working group to discuss MI definitions most appropriate for use in clinical trials enrolling patients requiring hemodialysis. Although all definitions have limitations, the working group recommends using the 4th UDMI and suggests that trialists and clinicians maintain a broad interpretation of “ischemic symptoms” in this population. The working group also recommends obtaining a baseline ECG to aid in the interpretation of acute changes noted on subsequent tracings. Serial cardiac biomarkers, optimally measured by hs-cTn assays, are needed to evaluate potential events of myocardial ischemia and myocardial injury. In addition, a greater than 20% delta in cTn is required to define an acute MI event in patients on hemodialysis with a baseline (at time of presentation) cTn that exceeds 99th percentile URL. Our future work will include validation of the use of the 4th UDMI in patients receiving hemodialysis. Box 3 summarizes the recommendations for clinical end point committee adjudication criteria for diagnosis of myocardial infarction in trials including people receiving hemodialysis. Supplementary material 1 outlines the recommended elements to incorporate into a Case Report Form for suspected or confirmed acute myocardial infarction events in trials including people receiving hemodialysis.

The working group has identified a number of directions for future research. At this time there are limited data in the hemodialysis population to create evidence-based guidelines. We recommend evaluating diagnostic methods for MI and MI type in patients receiving hemodialysis as well as improving the prevention and treatment of type 2 MI. We recommend investigating the reported lower percentage of STEMIs in this population and whether this is due to fewer acute coronary occlusions noted on angiography or confounders related to baseline ECG abnormalities. We recommend determining whether these findings impact reperfusion therapy in this

population. Consistent definitions and standardized reporting should improve trial quality, reproducibility, and comparability which will assist in endeavours to improve outcomes for this high-risk population.

Disclosures:

EO, JC, DF, KH, KS, NS, AT, AV, DW, WW have no disclosures.

FA is on the Board of Directors for HyTest Ltd, is the Associate Editor of Clinical Chemistry. He is also on Advisory Boards at: Instrumentation Laboratory, Siemens Healthcare, and Qurvo. He has received Honorariums for Speaking at Industry Sponsored Conferences for Siemens Healthcare and Abbott Diagnostics. He is the PI on Industry Funded Grants (non-salaried) on cardiac biomarkers through hospital research institute (HHRI) with Abbott Diagnostics, Abbott POC, BD, Beckman Coulter, Ortho-Clinical Diagnostics, Roche Diagnostics, Siemens Healthcare, ET Healthcare and Quidel.

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Boxes, Tables, and Figures

Box 1. 4th Universal Definition of Myocardial Infarction, Type 1 MI. Adapted with permission. Circulation.2018;138:e618-e651, ©2018 American Heart Association, Inc.

Box 2. Summary of the Limitations of the 4th Universal Definition in diagnosing Type 1 MI in patients receiving hemodialysis therapy. Adapted with permission. Circulation.2018;138:e618-e651, ©2018 American Heart Association, Inc.

Box 3. Recommendations for clinical end point committee adjudication criteria for diagnosis of myocardial infarction in trials including people receiving hemodialysis. Adapted with permission. Circulation.2018;138:e618-e651, ©2018 American Heart Association, Inc.

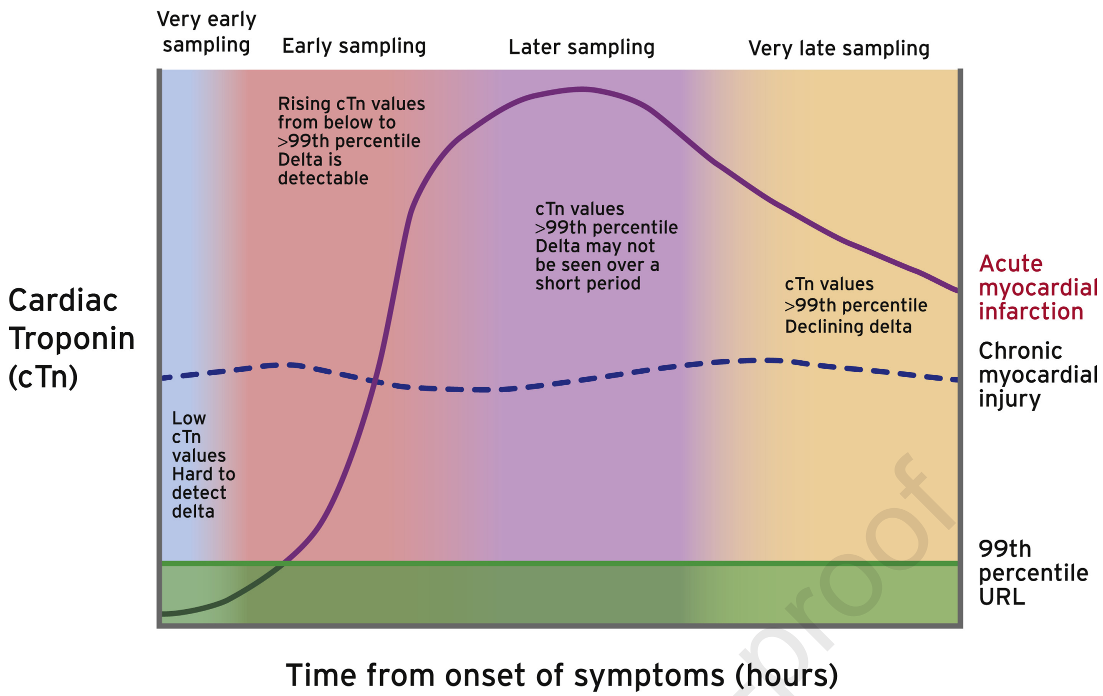
Table 1. Comparison of definitions for myocardial infarction used in large cardiovascular trials in patients receiving hemodialysis

Figure 1. Early cardiac troponin kinetics in patients after acute myocardial injury including acute myocardial infarction. Reprinted from Circulation, Volume 138, Issue 20, November 2018, Kristian Thygesen et al, The Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction, Fourth Universal Definition of Myocardial Infarction (2018), Pages e618-e651, with permission from Elsevier.

	SHARP	4D	Aurora	EVOLVE	PIVOTAL
Criteria required/ reported	**Reported as: Definite/ Possible/ Probable**	**Requires 2 out of 3 criteria**	**Reported as: Definite/ Suspected**	**Requires: Biomarker changes plus one further criterion**	**Requires: Biomarker changes AND supporting information**
Chest pain	Typical ischaemic CP, APO syncope or shock	Typical symptoms lasting ≥ 30 mins		Symptoms of pain, dyspnoea, pressure at rest or accelerated ischemic symptoms (lasts ≥ 10 mins)	The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction.
ECG changes	Q-waves and/or localised ST↑ followed by T-wave inversion in ≥2 of 12 standard ECG leads	Diagnostic ECG	ECG findings*	New Q waves (or R waves in V1-V2) in 2 continuous leads with no previous LVH or conduction probs; Evolving ST/T wave changes in ≥2 contiguous leads; New LBBB/ST ↑ requiring thrombolytics or PCI	New, or presumed new, significant ST-T wave changes or LBBB or development of pathological Q waves on the ECG
Biomarker	Rise and fall of CK >2x ULN, elevated CK-MB, elevated cardiac troponin (cTn)	Elevated cardiac biomarkers	Elevated cardiac biomarkers	Any combination of biomarkers where cTn result is ≥ 2x ULN or CKMB ≥ 2x ULN. If CK only, serial changes of ≥ 2x ULN must be shown.	Detection of a rise and/or fall of cardiac biomarkers [preferably cTn] with at least one value above the 99th percentile of the upper reference limit

CP = Chest pain, APO = acute pulmonary oedema, ECG = 12-lead electrocardiogram, LVH = left ventricular hypertrophy, LBBB = Left bundle branch block

ULN = Upper limit of normal, PCI = percutaneous coronary intervention, CK = creatinine kinase


Very early sampling
Early sampling
Later sampling
Very late sampling
Rising cTn values from below to >99th percentile Delta is detectable
cTn values >99th percentile Delta may not be seen over a short period
cTn values >99th percentile Declining delta
Low cTn values Hard to detect delta
Cardiac Troponin (cTn)
Acute myocardial infarction
Chronic myocardial injury
99th percentile URL
Time from onset of symptoms (hours)

Box 1. 4th Universal Definition of Myocardial Infarction, Type 1 MI.

Type 1	Detection of a rise and/or fall of cTn values with at least one value above the sex-specific 99th percentile URL, and at least one of the following: • Symptoms of acute myocardial ischemia • New ischemic 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 ischemic etiology • Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy
Type 2	Detection of a rise and/or fall of cardiac cTn values with at least one value above the sex-specific 99th percentile URL and evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis in addition to the symptoms, ECG findings, and imaging criteria discussed above for a type 1 MI
Type 3	Patients who suffer a cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers (preferably cTn) can be obtained, or before increases in cardiac biomarkers can be identified, or in whom MI is detected by autopsy examination
Type 4	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. Type 4a is ≤48 hours PCI, type 4b PCI-related MI is stent/scaffold thrombosis, type 4c is restenosis post balloon angioplasty.
Type 5	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 preprocedure cTn in whom cTn levels are stable (≤20% variation) or falling, the postprocedure cTn must rise by >20%. However, the absolute postprocedural value still must be >10 times the 99th percentile URL. In addition, 1 of the following elements is required: • Development of new pathological Q waves* • 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 ischemic etiology *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

cTn – cardiac troponin, URL – upper reference limit, ECG – electrocardiogram, MI – myocardial infarction, PCI – percutaneous coronary intervention

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Circulation.2018;138:e618-e651

Box 2

<table>
<tr><th colspan="2">4^{th} Universal Definition:
Criteria for Type 1 Myocardial Infarction</th><th>Limitation in patients receiving hemodialysis</th></tr>
<tr><td colspan="2">cTn >99^{th} percentile URL</td><td>In a stable population of patients receiving hemodialysis, 50% to 90% of hs-cTnT concentrations are above the 99th percentile URL compared to 5-25% for hs-cTnI assays (46,54,55)</td></tr>
<tr><td rowspan="5">Plus one of these criteria</td><td>Symptoms of acute myocardial ischemia</td><td>Typical ischemic symptoms are >50% less likely in patients receiving dialysis; <20% of these patients present with chest discomfort (30, 31)</td></tr>
<tr><td>New ischemic ECG changes</td><td>About 30% of patients receiving hemodialysis have conduction abnormalities at baseline (35).
>40% of patients receiving kidney replacement therapy present with non-specific changes and <20% present with typical ST elevation. (35)</td></tr>
<tr><td>Development of pathological Q waves</td><td>>5% of patients receiving hemodialysis already have Q waves on baseline ECG and are less likely to develop a Q wave MI (30, 35)</td></tr>
<tr><td>Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology</td><td></td></tr>
<tr><td>Identification of a coronary thrombus by angiography including intracoronary imaging or by post mortem examination</td><td><10% of patients receiving hemodialysis with MI undergo reperfusion/angiography</td></tr>
</table>

Hs-cTnT – high sensitivity cardiac troponin T, URL – Upper reference limit, ECG - electrocardiogram, cTn – cardiac troponin

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Box 3. Recommendations for clinical end point committee adjudication criteria for diagnosis of myocardial infarction in trials including people receiving hemodialysis

Acute myocardial infarction in people receiving haemodialysis is a syndrome defined as acute myocardial injury plus clinical evidence of acute myocardial ischemia (MI). An acute myocardial infarction may or may not result in death (fatal or non-fatal MI). Acute MI may be further sub classified by type as defined by the Fourth Universal Definition of Myocardial Infarction (2018)(4th UDMI).

Acute non-fatal myocardial infarction criteria Types 1 and 2 (adapted from 4th UDMI):

	Criteria	Notes
Required	Cardiac enzyme	• If index cTn is <99th percentile URL: Detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL • If index cTn is >99th percentile URL: Detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL AND a rise or fall of >20% cTn
Plus one or more of these additional criteria	1. Clinical presentation	Symptoms suspicious of acute myocardial ischemia including: • Chest pain/discomfort • Sweating • Arm/throat/neck/jaw pain or discomfort • Shortness of breath • Non-specific pain, discomfort or nausea, over and above or different to, usual background pain, discomfort or nausea

	2. ECG
	
	Comparison should be made to trial entry ECG or ECG performed prior to event when patient was stable and asymptomatic
		New ischemic ECG changes or new development of pathological Q waves:
		• New ST-elevation at the J-point in 2 contiguous leads with the cutpoint: =1 mm in all leads other than leads V2-V3 where the following cutpoints apply: =2 mm in men =40 years; =2.5 mm in <40 years, or =1.5 mm in women regardless of age
		• New horizontal or downsloping ST-depression =0.5 mm in 2 contiguous leads and/or T inversion >1 mm in 2 contiguous leads with prominent R wave or R/S ratio >1
		• In patients with pre-existing LBBB, ST-segment elevation =1 mm concordant with the QRS complex in any lead may be an indicator of acute myocardial ischemia
		• Presumed new LBBB or RBBB that is not rate-related may be an indicator or acute myocardial ischemia
		• New Q wave development:
		    o ECG Changes Associated With Prior Myocardial Infarction (In the Absence of Left Ventricular Hypertrophy and LBBB)
		    o Any Q wave in leads V2-V3 >0.02 s or QS complex in leads V2-V3

		○ Q wave ?0.03 s and ?1 mm deep or QS complex in leads I, II, aVL, aVF or V4-V6 in any 2 leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, aVF).* ○ R wave >0.04 s in V1-V2 and R/S >1 with a concordant positive T wave in absence of conduction defect *The same criteria are used for supplemental leads V7-V9. s indicates seconds
	3. Imaging	Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
	4. Acute thrombus	Identification of a coronary thrombus by angiography including intracoronary imaging or by post mortem examination

URL – upper reference limit, ECG – electrocardiogram, LBBB – left bundle branch block, RBBB – right bundle branch block

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