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Defining Myocardial Infarction in trials of patients receiving hemodialysis: recommendations from the SONG-HD MI Expert Working group

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INTRODUCTION

Cardiovascular disease is the leading cause of death in people with kidney disease requiring hemodialysis, with myocardial infarction (MI) being one of the predominant clinical manifestations (1). The incidence of MI in patients receiving hemodialysis is about 4-times higher than in the general population and is associated with poorer outcomes (2-4). The one-year mortality rate after a MI in patients receiving hemodialysis is 60% compared to less than 10% in the general population (5-8).

The higher prevalence of MI in the hemodialysis population is thought to be multifactorial. Traditional cardiovascular risk factors including hypertension and diabetes are more common in patients receiving hemodialysis. In addition, there are a number of risk factors that are unique to patients receiving hemodialysis including dysregulation of bone and mineral metabolism leading to increased vascular calcification, as well as uremic toxins and the dialysis therapy itself resulting in rapid hemodynamic changes, heightened inflammation, endothelial and immune dysfunction (9-12).

Patients on hemodialysis are usually excluded from large-scale cardiovascular interventional trials (13). When trials do include people on hemodialysis, the most frequently measured and reported cardiovascular outcomes are surrogate markers which may be of uncertain clinical significance and are often of little relevance to patients (14, 15). When composite cardiovascular outcomes were used, the components of each composite were very heterogenous across the trials (14). MI, which has been shown to be of the highest importance to patients (survey ref when published) is frequently a component of a cardiovascular composite endpoint in hemodialysis trials and yet is defined inconsistently (14, 16). A review of four recent large cardiovascular trials in patients receiving hemodialysis revealed four different definitions of MI (Figure 1) as well as different adjudication processes, which can meaningfully alter reported treatment effects. The lack of a standardized and validated definition for MI in patients receiving hemodialysis and the inconsistent and heterogenous measurement and reporting of MI limits the ability to compare the effects of interventions across trials.

The Standardised Outcomes in Nephrology (SONG) initiative 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 or health care(17). The core outcomes are based on priorities of 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, cardiovascular disease was identified as a core outcome, with MI established as the cardiovascular disease core outcome measure (to add references when workshop and survey are published). To use MI as a core outcome measure in trials involving patients receiving hemodialysis, consensus on a standardized definition for MI in this population is needed.

We convened an international expert working group meeting, which included patients with personal experience of hemodialysis, cardiologists, nephrologists, a clinical biochemist and representatives from regulatory bodies, registries and clinical trialists. The aim of the expert working group was to recommend an appropriate definition of MI for use in trials in people receiving hemodialysis. We began the discussion based on the definition of MI formulated for the general population; the 4th Universal Definition of MI(18). This definition has not been validated in people receiving hemodialysis and has a number of limitations in this population; however, there is currently no other reference standard. Specific considerations raised in the SONG-HD CVD consensus workshop regarding criteria required for an appropriate definition of MI (workshop reference) informed the direction of discussion. These considerations included consistency, applicability and specificity of the definition to people receiving hemodialysis, the importance of the type of MI, the recognition of the variability of symptoms of MI in people receiving hemodialysis and the uncertainty in the clinical utility of biomarkers specific to haemodialysis. This report summarizes the discussions and resulting recommendations.

THE 4TH UNIVERSAL DEFINITION OF MI

In 2018 the European Society of Cardiology(ESC)/the American College of Cardiology (ACC)/the American Heart Association (AHA)/The World Heart Federation (WHF) published an expert consensus document on the Fourth Universal Definition of Myocardial Infarction(18). The document sought to clarify the clinical definition of MI, identifying the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia. This definition of MI was based on data determined from trials in the general population. There was a caveat within this document for myocardial injury/infarction in people with chronic kidney disease but not specifically for those on hemodialysis. A summary of the limitations of the 4th Universal Definition with regards to the diagnosis of a Type 1 MI in ESKD are shown in Box 1

TYPES OF MI

The Fourth Universal definition of myocardial infarction classifies MI into five types. The main discrepancies in the diagnosis of MI in the hemodialysis population relate to Type 1 and 2. Type 3 relates to 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 can be obtained, or before increases in cardiac biomarkers can be identified, or in whom MI is detected by autopsy examination. Types 4 and 5 relate to peri-procedural myocardial ischemia. Types 3 to 5 are relevant to people requiring kidney replacement therapy and should be diagnosed as per the general population referring to the 4th Universal Definition.

The criteria required for diagnosing Type 1 and 2 MI in the hemodialysis population are discussed below. *Post mortem* demonstration of acute atherothrombosis 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 atherothrombosis meets criteria for type 2 MI. Cardiac death in patients with symptoms

suggestive of myocardial ischemia and presumed new ischemic ECG changes before cardiac Troponin (cTn) values become available or abnormal meets criteria for type 3 MI.

According to the 4th Universal Definition, Type 2 MI is diagnosed using the following criteria: detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile upper reference limit (URL), and evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis, in addition to symptom, ECG and imaging criteria defined in the Type 1. Diagnosis of a Type 2 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 who undergo dialysis sessions 2-3 times a week. Hemodialysis has been shown to have significant hemodynamic effects and increase myocardial oxygen demand (19). Hemodialysis may induce significant global and segmental reductions in myocardial blood flow (20). Furthermore, underlying pathophysiological changes related to ESKD including left ventricular hypertrophy, reduced peripheral arterial compliance, endothelial dysfunction, anemia, microvascular disease, and reduced coronary flow reserve predispose hemodialysis patients to demand ischemia. It is assumed that the prevalence of Type 2 MI is high in the hemodialysis population; however, determining accurate prevalence data is very hard as differentiation between Types 1 and 2 requires expert adjudication in large clinical cohorts, ideally including coronary angiography to definitively exclude coronary thrombosis(21).

Short and long-term mortality rates for Type 2 are higher than for Type 1 (22-24). However, there are currently no treatment guidelines other than to address the underlying supply and demand imbalance. In the case of hemodialysis, there are currently few alternatives to standard short intermittent dialysis sessions which reduces the ability to alter the “demand” end of the equation. Patients present at the meeting did not feel that knowledge of the type of MI was essential, particularly if it had no impact on their management at the time of presentation.

Due to the difficulties in diagnosis and the current lack of differentiated therapeutic algorithms linked to type of MI, the requirement to determine the Type of MI in hemodialysis patients as a trial outcome is considered unnecessary at this stage.

CRITERIA USED TO DEFINE TYPE 1, 2 AND 3 MI

1. Ischemic symptoms

Multiple studies have shown that patients with chronic kidney disease and particularly those receiving hemodialysis often do not describe classical symptoms of MI. The classic triad of chest discomfort, arm/jaw pain and sweating is experienced by less than 50% of patients with chronic kidney disease(25). In patients requiring kidney replacement therapy the most common "ischemic symptom" is shortness of breath, experienced by nearly 50% of patients receiving dialysis (25, 26). Chest pain or discomfort is experienced by less than 20% of patients receiving dialysis compared to over 35% of patients with normal renal function(26). Patients 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 of being an "ischemic symptom".

Any non-specific symptom or change in symptom in a patient receiving dialysis should raise a high index of suspicion for investigation of MI.

2. ECG

Fluid and electrolyte changes during hemodialysis have long been known to 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(27). Similarly electrolyte shifts during dialysis have been shown to affect the P wave, QRS and the QTc (27). Timing of dialysis should be considered in the interpretation of an ECG;

however, persistent changes such as left bundle branch block are unlikely to be influenced by variations in dialysis.

Patients receiving hemodialysis often have abnormal baseline ECGs, making it difficult to determine if there has been an acute change and thus always require comparison with previous baseline ECGs. In one series about 30% of patients receiving hemodialysis were found to have electrical conduction abnormalities including left and right bundle branch block on a baseline ECG (28). A diagnosed MI presented with ST elevation in less than 20% of patients on dialysis compared to over 35% of patients with normal kidney function(29). A non-specific ECG change was the most prevalent finding in patients presenting with MI on hemodialysis (29). Patients with chronic kidney disease are significantly less likely to develop a pathological Q wave than patients with no chronic kidney disease (19% compared to 34%) (25).

Patients with chronic kidney disease, and particularly patients receiving hemodialysis, have a higher prevalence of silent MI compared to the general population (30, 31) and a baseline ECG may change over time. However, in a trial setting repeated baseline ECGs may be problematic; there is no guideline for investigation of baseline ECG changes which are not in association with an acute event and they do not help to predict acute events in the absence of other symptoms, clinical or biochemical abnormalities.

Patients indicated that an additional, baseline ECG would not be a burden as it is non-invasive and clinicians felt it would facilitate interpretation of new ECG changes and diagnosis of MI when it develops and better inform patient care then.

A baseline ECG in all patients receiving hemodialysis when stable and asymptomatic, may aid in the interpretation of acute ECG changes in the setting of MI. We recommend a single baseline ECG should be performed on entry into a trial and again following an acute event.

3. Troponin

Troponin is a complex of three regulatory proteins (troponin C, troponin I, and troponin T). There is little or no difference in troponin C (TnC) between skeletal and cardiac muscle, but troponin I (TnI) and troponin T (TnT) have different isoforms in cardiac (cTnT and cTnI) and skeletal muscle. During myocardial injury cTnI and cTnT are released both as individual subunits as well as non-covalent ternary and binary complexes (32, 33). cTnT and cTnI are now the preferred biomarkers of myocardial injury. The 4th Universal Definition of Myocardial Infarction includes clinical evidence of acute myocardial ischemia with detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL plus additional criteria as above (Box 1).

Assay variability

Assays are required to meet two criteria: a coefficient of variation (CV) of <10% at the 99th percentile value and measureable concentrations below the 99th percentile should be detectable above the assay's limit of detection for >50% of healthy individuals in the population of interest (34, 35). High sensitivity troponin (hs-Tn) assays more often fulfil these criteria and are now in widespread use, they are able to accurately measure five to 100-fold lower concentrations of cardiac troponin in blood than older assays(36, 37). The various hs-Tn assays use monoclonal antibodies to a number of different binding sites along the cTnT or cTnI protein (38). Due to the different target binding sites for each assay it is not possible to standardize a threshold across assays.

Biological variability

Biological variability describes the random fluctuation of biomarker levels around a homeostatic set-point in healthy individuals or those with stable disease and which is of no clinical significance. Small studies have been conducted looking at cTnT and cTnI at daily, weekly, monthly and yearly intervals in patients on hemodialysis(26, 39, 40). Biological variability is low, with intra-patient coefficients of variation quoted as

7.9% for weekly measurements and 12.6% for monthly measurements. Over the course of a year biological variability is minimal and if an acute event occurs, troponin returns to the individual patient's baseline(40). Inter-patient variability is very high in patients on hemodialysis(39).

Effect of dialysis on troponin:

To date only relatively small studies have been conducted looking at the effect of dialysis on troponin. The European Uremic Toxin Work Group has defined the term middle molecule to be between 500 Daltons – 60 kD(41). The troponin complex (52KDa), as well as the subunits (cTnI is 24 kDa and cTnT is 37 kDa) are classified as middle molecules. Older dialyzer membranes of the 1970s predominantly filtered out only small, water-soluble molecules such as potassium and much of the morbidity and mortality associated with older dialysis regimes were felt to be due to poor clearance of "middle molecules". New synthetic membranes and the increase in convective therapies have improved the clearance of a number of these molecules. There is a lack of consensus regarding the effect of dialysis on troponin levels. A number of trials have found small decreases in concentration in cTnI during dialysis. The process by which these levels decrease is not entirely clear but there is some evidence that cTnI is adsorbed onto the surface of the dialyzer membrane (42-44). There is also evidence to suggest that high flux dialyzers affect troponin clearance more than low flux dialyzers (45, 46) and clearance is potentially increased further with hemodiafiltration(46). To date, the evidence suggests that the changes in levels of both cTnT and cTnI are relatively small and there is insufficient evidence at present to suggest that the effect of dialysis on troponin is significant enough to alter the diagnosis of MI in patients receiving hemodialysis including those who develop MI during hemodialysis procedure or peri-hemodialysis.

Elevated baseline troponin

Levels of cTnT and cTnI over the 99th percentile URL have been demonstrated in up to 80% of patients requiring dialysis (39, 47, 48). Hs-cTnT is elevated more frequently that hs-cTnI (49). Poor kidney clearance

is not the main driver of an elevated troponin in this population (50). The exact etiology of elevated baseline troponins is not entirely clear but is likely to be multifactorial including increased instability of the cardiac myocyte membrane, microinfarctions and necrosis of myocardium as well as increased left ventricular hypertrophy and heart failure causing myocyte strain and death (51-55). Even in the absence of an acute event, elevated baseline troponin in patients receiving hemodialysis is a poor prognostic marker. It has been shown that raised cTnT and cTnI are both predictive of cardiovascular and all-cause mortality in ESKD (40, 56-59). The predictive value of elevated cTn is true for both, people on hemodialysis and the general population (60). Screening troponins will lower the level of detection and increase the false positive rate for MI. This has an effect on the individual patient, the cost to healthcare and also lowers the test performance and specificity of cTn for MI. There is currently insufficient evidence to suggest a pathway in response to the identified increased risk and therefore no indication for baseline troponin screening in either the hemodialysis population or the general population. In a trial setting the addition of a baseline troponin would also be a significant expense.

Performing baseline troponins in stable asymptomatic patients receiving hemodialysis may result in unwanted concerns for patients; informing them of a higher risk of death but without any pathway by which to minimize this risk. Currently we also do not recommend a baseline troponin as a requirement in a trial setting.

Delta Troponin

The rise and/or fall in cTn referred to in the 4th Universal Definition is a ≥20% change (δ). The US National Academy of Clinical Biochemistry (NACB) recommended a δ change 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 (37). This is calculated to distinguish a true change from one that could be attributed to variability alone and yet maintain sensitivity (37).

The sensitivity of hs-cTn assays remain high in patients on hemodialysis, reported as 100% (26). As such in a population with a high prevalence of elevated baseline cTn, the specificity of the hs-cTn assay is as low as 40% (26). Within-person weekly reference change values for hemodialysis patients have been calculated at ≤ 20% and reference change values in diagnosing AMI have been calculated at 20% (39, 48).

These data suggest that within-person biological variability is relatively low and analytical variation of hs-cTn assays play a minimal role. A dynamic change with a rise or fall of more than 20% in people on hemodialysis with symptoms or new ECG changes is still suggestive of MI. In a trial setting, this finding should trigger referral to a clinical endpoint committee for adjudication. Short term intra-patient biological and analytical variability is minimal if there is no acute event but a one hour sample may not be sufficient to rule out MI. Patients who present with atypical symptoms make it harder to know where on the troponin kinetic curve (Figure 2) they are at a given time point. The recommendation is that any dynamic change in troponin should prompt further samples to identify the maximum delta. This may require samples to be taken after 6 to 12 hours to ensure an MI is not missed.

Current evidence suggests a δ of 20% in cTn in addition to the clinical criteria should be an accepted rise and/or fall to diagnose MI in the hemodialysis population. Sensitivity of diagnosis may be further improved by end point adjudication. An accelerated, early rule-out sample is insufficient in patients requiring hemodialysis to exclude an MI.

SUMMARY

Participants in the expert working group determined that there is currently no compelling evidence to move away from the 4th Universal Definition of Myocardial Infarction in trials in people receiving hemodialysis. We suggest that trialists and clinicians should keep a very broad interpretation of “ischemic symptoms”, a baseline ECG should be performed to aid interpretation of acute changes and repeat

troponin samples are more likely to be required to ascertain a 20% delta change in troponin. The recommendations are also summarized in Box 2.

The review of evidence and expert opinion has highlighted a number of directions for future research as insufficient evidence exists in the hemodialysis population to create purely evidence-based guidelines. We recommend further research into diagnostic methods for MI in people receiving hemodialysis as well as improved prevention and treatment of Type 2 MI. Consistent definitions and standardized reporting should improve trial quality, reproducibility and comparability which will assist in endeavours to improve outcomes for this very high-risk population.

BOX 1 SUMMARY OF THE LIMITATIONS OF THE 4TH UNIVERSAL DEFINITION IN DIAGNOSING TYPE 1 MI IN PATIENTS RECEIVING KIDNEY REPLACEMENT THERAPY

4th Universal definition: Criteria for Type 1 Myocardial Infarction		Limitation in patients requiring kidney replacement therapy
cTn >99th percentile URL		In a stable population of patients requiring dialysis, 50% to 90% of hs-cTnT concentrations are above the 99th percentile URL compared to <25% for hs-cTnI assays(26)
Plus one of these criteria	Symptoms of acute myocardial ischemia	Typical ischemic symptoms are >50% less likely in patients with ESKD, <20% of ESKD patients present with chest discomfort(25, 26)
	New ischemic ECG changes	About 30% of patients requiring dialysis have conduction abnormalities at baseline (28). >40% of patients requiring kidney replacement therapy present with non-specific changes and <20% present with ST changes(29)
	Development of pathological Q waves	>5% of patients requiring kidney replacement therapy already have Q waves in baseline ECG and are less likely to develop a Q wave MI (25, 29)
	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 post mortem autopsy	<10% of patients requiring kidney replacement therapy are felt eligible for reperfusion/angiography (61)

URL – Upper reference limit, ESKD – end stage kidney disease, cTn – cardiac troponin

Box 2 Recommendations for defining MI in patients on hemodialysis

4th Universal definition: Criteria for Type 1, 2,3 Myocardial Infarction		Additional recommendation in the hemodialysis population
The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with:		
Detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and at least 1 of the following: cTn >99th percentile URL		A significant rise/fall of 20% is appropriate. Any elevation in cTn should prompt serial testing
Plus one of these criteria	Symptoms of acute myocardial ischemia	Patients on hemodialysis often present atypically, non-specific or change in symptoms should raise a high index of suspicion
	New ischemic ECG changes or development of pathological Q waves	To aid in identification of acute ECG changes patients should have a baseline ECG performed
	Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology	As per general population
	Identification of a coronary thrombus by angiography including intracoronary imaging or by post mortem autopsy	As per general population

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FIGURE 1 COMPARISON OF DEFINITIONS FOR MYOCARDIAL INFARCTION USED IN LARGE CARDIOVASCULAR TRIALS IN PEOPLE RECEIVING HEMODIALYSIS

	SHARP	4D	Aurora	EVOLVE
Criteria required/reported	Definite/ possible/ Probable*	Requires 2 out of 3	Definite/ Suspected*	
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)
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
Biomarker	Rise and fall of CK >2 x ULN, elevated CK-MB, elevated troponin*	Elevated cardiac biomarkers	Elevated cardiac biomarkers*	Any combination of markers where Troponin result is ≥ 2x ULN or CKMB ≥ 2x ULN If CK only, serial changes of ≥ 2x ULN must be shown

FIGURE 2 EARLY CARDIAC TROPONIN KINETICS IN PATIENTS AFTER ACUTE MYOCARDIAL INJURY INCLUDING ACUTE MYOCARDIAL INFARCTION

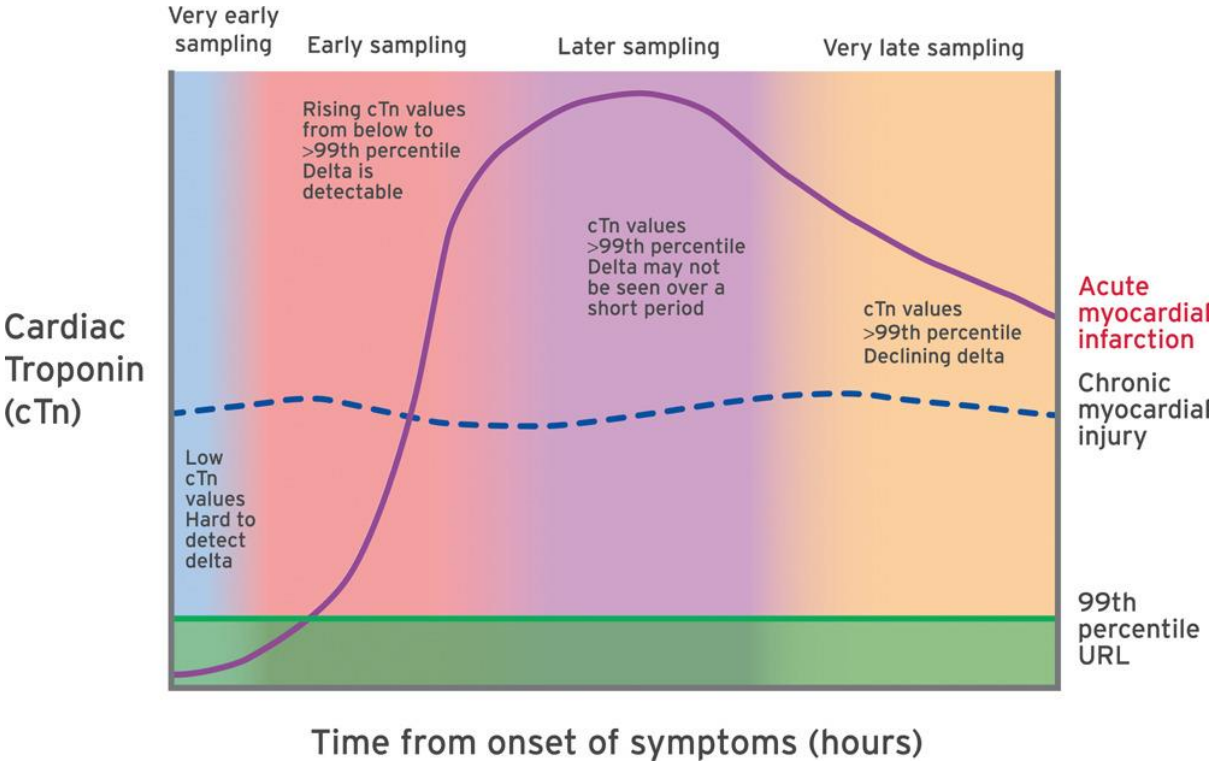

Figure taken from Thygessen et al JACC 2018;72(18):2231-64 with permission.