The Canadian Cardiovascular Society Classification of Acute Atherothrombotic Myocardial Infarction Based on Stages of Tissue Injury Severity: An Expert Consensus Statement

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ABSTRACT
Myocardial infarction (MI) remains a leading cause of morbidity and mortality. In atherothrombotic MI (ST-elevation MI and type 1 non-ST-elevation MI), coronary artery occlusion leads to ischemia. Subsequent cardiomyocyte necrosis evolves over time as a wavefront within the territory at risk. The spectrum of ischemia and reperfusion injury is wide: it can be minimal in aborted MI or myocardial necrosis can be large and complicated by microvascular obstruction and reperfusion hemorrhage. Established risk scores and infarct classifications help with patient management but do not consider tissue injury characteristics. This document outlines the Canadian Cardiovascular Society classification of acute MI. It is an expert consensus formed on the basis of decades of data on atherothrombotic MI with reperfusion therapy. Four stages of progressively worsening myocardial tissue injury are identified: (1) aborted MI (no/minimal myocardial necrosis); (2) MI with significant cardiomyocyte necrosis, but without microvascular injury; (3) cardiomyocyte necrosis and microvascular dysfunction leading to microvascular obstruction (ie, "no-reflow"); and (4) cardiomyocyte and microvascular necrosis leading to reperfusion hemorrhage. Each stage reflects progression of tissue pathology of myocardial ischemia and reperfusion injury from the previous stage. Clinical studies have shown worse remodeling and increase in adverse clinical outcomes with progressive injury. Notably, microvascular injury is of particular importance, with the most severe form (hemorrhagic MI) leading to infarct expansion and risk of mechanical complications. This classification has the potential to stratify risk in MI patients and lay the groundwork for development of new, injury stage-specific and tissue pathology-based therapies for MI.

Despite enormous progress in diagnostics and therapy, myocardial infarction (MI) remains one of the leading causes of death in Canada and worldwide. The past 50 years have seen improvement in survival of patients with ST-elevation MI (STEMI). However, at the same time, heart failure from ischemic cardiomyopathy in MI survivors has become an important problem affecting a large proportion of MI patients. Multiple scores and classifications have evolved for acute MI to help with patient care and research. The existing tools play a fundamental role in clinical care, informing the health care team about the potential risk of adverse events, and help determine the intensity of care and surveillance and specifics for medical and interventional therapy. They frequently have a direct effect on medical management and allow for research to be refined. The “universal definition of MI” categorizes MI according to its etiology: the dichotomization of STEMI vs non-STEMI (NSTEMI), on the basis of electrocardiogram (ECG) changes, helps with risk stratification and management. Other helpful tools include, among others, the Thrombolysis in Myocardial Infarction (TIMI) risk score, the History, ECG, Age, Risk factors, Troponin (HEART) score and the Killip classification. These well-established classifications and scores rely on clinical parameters. However, they do not take into account underlying myocardial tissue pathology. The degree and type of tissue injury in MI is predictive of ventricular remodeling, and adverse events such as heart failure, arrhythmia, hospitalization, and death. A new classification that incorporates tissue-level changes is much needed, to exploit the predictive power of tissue damage for improving clinical care and research, beyond clinical parameters alone.

In acute atherothrombotic MI (type 1 MI), cardiomyocyte necrosis evolves as a wavefront within an area at risk, the latter being defined as myocardial tissue subtended by the occluded epicardial coronary artery. Early reperfusion treatments emerged as life-saving therapy, halting the wavefront of...
necrosis and saving salvageable myocardium, thereby reducing final infarct size, and diminishing risk of heart failure, arrhythmia, and death.4,6

Myocardial necrosis is not the only form of tissue damage that contributes to acute MI. In the 1970s, autopsy studies revealed that myocardial edema occurs concomitantly and can precede myocardial necrosis; microvascular compromise is also observed leading to microvascular obstruction (MVO) and myocardial hemorrhage.7,11 In recent years, advanced imaging technologies have allowed tissue changes to be studied in vivo, in patients as well as in animal models. Substantial insight has been gained into the pathophysiology of MI.12 A new picture of MI has now emerged: at the tissue level, not all MIs are the same. Tissue changes in reperfused atherothrombotic MI evolve in 4 sequential, progressive stages. These stages reflect a fundamental biological cascade of ischemia/reperfusion injury, and yield a new classification of MI, reflecting the degree of severity of tissue injury. The new classification is based on the ground truth of pathophysiology and might help with refined patient risk assessment and documentation. It might lay the groundwork for development of future tissue-directed therapies.

Process
This new classification was initially developed by 2 of the authors (A.K., R.D.). The Canadian Cardiovascular Society (CCS) endorsed the development of this expert consensus as a starting point for a proposed novel definition of MI and requested the formation of a writing group under the oversight of the president. It is hoped that this document will serve as a starting point for continued clinical and scientific refinement to help define our present understanding of acute atherothrombotic MI.

Expert Consensus Classification: Underlying Principles
The CCS classification of acute MI from epicardial coronary atherothrombosis is an expert consensus formed on the basis of cumulative research on acute MI with reperfusion therapy over the past 5 decades. It extends the wavefront paradigm and formulates a new categorization of myocardial ischemia and reperfusion injury into 4 sequential and progressive stages: myocardial edema occurs first, followed by cardiomyocyte necrosis, then MVO, and last, myocardial hemorrhage. (Figs. 1-4) The injury at each stage adds to and builds on the injury of the previous stage, following a sequence of escalating severity. This translates into worsening patient prognosis with each stage (Fig. 5).

The staging is on the basis of the near universal observation that edema occurs first, cardiomyocyte necrosis follows, and never exists without myocardial edema. MVO is a possible further progression, never observed without cardiomyocyte necrosis, and therefore represents the next stage of severity. The final stage is severely damaged capillaries that disrupt with reperfusion, leading to myocardial hemorrhage. Hemorrhage is always associated with MVO and never occurs alone; it is a more severe form of microvascular injury, and the most severe form of ischemia-reperfusion injury. Mechanical complications have been strongly associated with hemorrhagic infarction,13 supporting the notion that hemorrhagic MI is the most serious form of MI. Clinical studies over the past several decades have shown that patient prognosis deteriorates with each progressive stage (Fig. 5).

Early initiation of reperfusion therapy along with a short duration of ischemia can significantly reduce the likelihood of injury progressing to the next stage with the best case scenario of near perfect prevention of cardiomyocyte necrosis (aborted MI; Fig. 6).

A detailed description of the 4 stages of tissue injury is outlined in the following section (Figs. 1-4).

The 4 CCS Stages of Acute MI Secondary to Coronary Atherothrombosis

CCS stage 1 MI: Aborted MI
Aborted MI traditionally has been defined as MI with less than twofold increase in creatine kinase level in blood, as well as > 50% ST-segment elevation resolution within 90 minutes post thrombolysis or 30 minutes post primary coronary angioplasty with the absence of residual new pathologic Q waves.14,15 Alternatively, some have suggested a cutoff of < 0.5 ng/mL of troponin I,16 albeit others have suggested that a troponin level above the 99th percentile of normal is too sensitive for detection of aborted MI.17 A troponin I/T cutoff of ≤ 5 times the upper limit of normal has been used in more recent clinical trials.15,18 Aborted MI is observed more frequently with timely reperfusion therapy (typically < 4 hours of ischemic symptoms, but most notably within 1-2 hours after onset of ischemia), which led to the term “golden hour” of reperfusion.19-22 It is observed more frequently with prehospital fibrinolysis compared with primary percutaneous intervention.15 The incidence of aborted MI is reported to be approximately 5%-15%,4,2,24 but can be as high as 30% in patients treated within the first hour of myocardial ischemia (Fig. 5).21,25,26

By definition, the myocardial damage in aborted MI is minimal, and in the best case the entire area of myocardium at risk can be salvaged.24 In aborted MI, the evolving wavefront of ischemic injury is halted very early, and further damage to the cardiomyocytes or the associated vascular bed is prevented (Figs. 1-4). Cardiac magnetic resonance imaging (CMR) studies in this population have shown the absence of myocardial necrosis in approximately half of these patients, and only minor myocardial necrosis in the remaining patients.26,27 Increased salvage has also been shown with technetium 99m sestamibi single photon emission computed tomography imaging.28 Aborted MIs are smaller and less transmural compared with further evolved MIs.28 Myocardial edema is observed to occur early, before cardiomyocyte necrosis and reflects reversible myocardial injury (Figs. 2 and 3). It can be assessed using T2-weighted CMR.27,29,30 Using quantitative CMR, subendocardial injury, mostly less than 5% of left ventricular (LV) myocardial mass is observed.28,31 Angiographically, aborted MIs have normal coronary flow (ie, TIMI 3 flow).32

Absence of cardiomyocyte necrosis or minimal cardiomyocyte necrosis, and near complete salvage of myocardium at risk in CCS stage 1 MI translate into markedly reduced event rates and favourable patient outcome. The
long-term event rate is multifold lower compared with nonaborted MI, with absolute event rates often < 5% (Figs. 2, 5).

CCS stage 2 MI: Cardiomyocyte necrosis without microvascular injury

Stage 2 MI is defined by significant myocardial necrosis that exceeds the level of necrosis observed in the stage of aborted MI (CCS stage 1). However, this stage of injury does not extend to microvascular injury (CCS stages 3 and 4). At CCS stage 2, the window of near complete salvage of aborted MI is surpassed and significant myocardial necrosis has occurred. At this stage, ischemic damage remains mostly restricted to cardiomyocyte necrosis; the vascular bed is intact and microvascular flow and tissue perfusion are mostly preserved after the reestablishment of epicardial blood flow. Cardiomyocyte necrosis occurs in the subendocardium first and subsequently progresses transmurally with its final extent being determined by the duration and severity of ischemia. This concept is substantiated clinically, with longer time to reperfusion leading to a higher cardiomyocyte necrosis-related enzyme level increase, reflecting larger MI size. MI might present with or without ST-elevation on the ECG; ST-elevation is a well-established marker of very high risk, with an indication for immediate reperfusion therapy.

CMR with late gadolinium enhancement is a highly accurate method to quantify ischemic myocardial necrosis and infarct size in vivo in patients and has validated early pathology findings; MIs always involve the subendocardium, and evolve toward the epicardium within an area at risk with increasing duration of ischemia. The longer ischemia persists, the greater the loss of salvageable myocardium; the size of MI and transmurality are larger. Progressive loss of salvageable myocardium is associated with reduced functional recovery, worse LV systolic function, and progressive increase in mortality and adverse events including ventricular arrhythmia, heart failure, and hospitalization. Infarct size is a strong predictor of adverse outcome, independent of and stronger than LV dysfunction alone (Fig. 5). The tissue damage at this stage will frequently lead to regional wall motion abnormality detectable on echocardiography. Revascularization therapy will result in restoration of normal coronary flow (TIMI 3 flow).

The incidence of CCS stage 2 MI is yet to be assessed in contrast to CCS stages 1, 3, and 4. Because CCS stage 1 (aborted MI) occurs at a rate of approximately 10% and MI with reperfusion injury (stages 3 and 4) occurs at a rate of approximately 40%-60%, then CCS stage 2 will likely represent 30%-50% of patients with acute MI (Fig. 5).

CCS stage 3 MI: Cardiomyocyte necrosis combined with MVO

At CCS stage 3, the ischemic injury extends beyond cardiomyocyte injury to now involve the myocardial microvasculature resulting in MVO. MVO was first described in the heart by Kloner et al., followed by others. Ischemic
microvascular injury leads to endothelial swelling, compression of capillaries by tissue edema, and upregulation of endothelial cell adhesion molecules and subsequent luminal obstruction with erythrocytes, white blood cells, and activated platelets, driven by inflammatory mediators. Distal coronary artery blood flow is obstructed, leading to the clinical observation of "no reflow" on coronary angiography when the affected area is large enough. Epicardial coronary thrombus embolization can also contribute to MVO (Figs. 1-3). Only rarely can isolated erythrocytes be observed with MVO in the extravascular space on histology, if any at all. This is distinct from hemorrhagic MI (stage 4), where hemorrhage becomes the predominant tissue component.

The clinical importance of MVO was first established when semiquantitative epicardial coronary flow assessment studies showed a marked increase in adverse outcome events in patients with reduced flow in acute reperfused MI. When TIMI flow or TIMI frame count remained reduced, despite successful treatment of the culprit lesion, an increase in mortality was observed, with mortality increase correlating with decreasing TIMI frame count. Subsequently, studies using myocardial contrast echocardiography and CMR confirmed MVO as an independent predictor of adverse ventricular remodeling and a key independent predictor of major adverse cardiovascular events beyond infarct size alone.

Myocardial contrast echocardiography and CMR are used to assess perfusion at the tissue level (as opposed to coronary angiography methods, which rely on epicardial coronary artery flow), and have been shown to be more sensitive than coronary angiography in detecting reduced tissue perfusion. They might identify patients with reduced tissue perfusion despite normal epicardial coronary flow. Contrast echocardiography perfusion studies have also shown
predictive power for adverse ventricular remodeling, reduced functional recovery, and adverse cardiovascular events.\textsuperscript{45,47,49-52}

On CMR, MVO is detected with contrast enhanced techniques, using gadolinium enhancement-based approaches.\textsuperscript{53} MVO detected using CMR has been shown to predict mortality, adverse cardiac events, and adverse ventricular remodeling. The major cardiac event rate is increased two- to sixfold at long-term follow-up and is independent of infarct size and ventricular systolic function when MVO is present (Fig. 5).\textsuperscript{40} As a limitation, in many studies on MVO myocardial hemorrhage was not concomitantly assessed, which might be confounding in the assessment of patient prognosis.

CCS stage 4 acute MI: Cardiomyocyte necrosis, MVO, and reperfusion hemorrhage

CCS stage 4 MI is the most severe form of ischemic and reperfusion injury across the 4 stages. Very severe, sustained

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**Figure 3.** The Canadian Cardiovascular Society (CCS) classification of acute atherothrombotic myocardial infarction: representation of defining pathological tissue changes that occur in the 4 progressive stages of ischemia and reperfusion injury in acute myocardial infarction.
ischemia affects the cardiac microvasculature well beyond MVO (CCS stage 3): histological studies have revealed anatomical capillary integrity is compromised at this stage, and reperfusion will lead to capillary rupture and intramyocardial hemorrhage. The presence of intramyocardial hemorrhage is the hallmark injury of CCS stage 4 MI (Figs. 1-4). Hemorrhagic MI has been strongly associated with mechanical complications including myocardial rupture.13 Since the first observations of myocardial hemorrhage in experimental models and patient autopsy studies,9-11 CMR techniques have been validated and established as an accurate method for diagnosing and quantifying hemorrhage in living patients.60,61

Hemorrhage leads to an additional injury by blood extravasation into the necrotic tissue (Fig. 3).62 In patients and in experimental animal models, hemorrhage-driven infarct expansion has been observed, leading up to a doubling of infarct size after reperfusion.9,63 Hemorrhage culminates in the deposition of ferric iron crystals within MI tissue, triggering a sustained pro-inflammatory response not observed in nonhemorrhagic infarction,64 contributing to adverse remodeling and a unique inflammatory pathway toward heart failure.65,66 Hemorrhage has been proposed as a mechanism for generation of ventricular arrhythmia.67,68 Hemorrhagic infarction leads to fatty degeneration of cardiac tissue driven by macrophage activation, lipid peroxidation, foam cell formation, and ceroid production, which is not observed in nonhemorrhagic MIs.69 Fatty metaplasia of infarct scar has been identified as a driver of increased ventricular arrhythmia risk.70

Although higher troponin levels and incomplete resolution of ST elevation have been reported in hemorrhagic MI, T2* CMR is the standard diagnostic strategy for accurately detecting myocardial hemorrhage patients with acute MI. Currently, there are no biochemical-, echocardiographic-, or coronary angiography-based methods that exist to detect...
hemorrhage in the clinical setting. Most CMR patient studies showed an incidence of hemorrhage between 25% and 40%; a large meta-analysis reported an incidence of 39% (Fig. 5). Hemorrhagic MI is associated with marked infarct expansion resulting in additional loss of salvageable myocardium. Larger infarct size relative to the myocardium at risk is associated with impaired LV systolic function after reperfusion therapy. Hemorrhagic MI has been identified as a key predictor of adverse cardiovascular events, with some studies reporting more than a doubling of cardiovascular event rates with hemorrhagic MI compared with nonhemorrhagic MI (Figs. 4 and 5).

In autopsy studies of patients with fatal mechanical complications such as myocardial rupture, hemorrhage has been observed in as many as 80% of cases. Hemorrhagic MI is thus considered a predisposing factor for mechanical complications and might also result in intramural dissecting hematoma.

**Discussion**

**Wavefronts of ischemia and reperfusion injury**

The expert consensus leading to the CCS classification of acute atherothrombotic myocardial infarction presented...
herein is the first to define stages of MI on the basis of underlying tissue pathology (Figs. 1-5). These 4 stages of tissue injury are not independent; they build on each other and reflect the progressive and sequential damage that occurs within the myocardium in acute ischemia and reperfusion injury due to epicardial coronary atherothrombosis (Fig. 6).

Advanced imaging techniques that have evolved over the past few decades have repeatedly shown the validity of the wavefront hypothesis of ischemic cardiomyocyte death of Reimer and Jennings, which can now be considered an evidence-based paradigm. The occurrence of reperfusion injury in the subendocardium first, then extending toward the epicardium with progressive injury severity, allows for MVO and hemorrhage to be regarded as additional wavefronts of reperfusion injury. The classification presented herein captures fundamental pathophysiology in an easily applicable schematic for clinical care and research. Timely reperfusion therapy can halt injury at an early stage and prevent progression to the next worse stage.

Implications for clinical care and research

We envision this classification to be an important framework for the advancement of clinical care and research. An overview of how the classification can be used for clinical translation is provided in Table 1. This classification scheme allows for a simplified understanding of pathophysiology. Clinical translation could help with risk stratification of patients; the risk of cardiovascular complications increases with each stage, from comparatively low risk at CCS stage 1 (aborted MI) to highest risk of adverse events at stage 4, including risk for infarct expansion and mechanical complications (Figs. 5 and 6). Applying the classification we have put forth herein can improve clinical care by differentiating high-risk and lower-risk patients. Advancing our understanding of injury stage progression could lay the groundwork for development of much needed cardioprotective therapies.

There is an enormous body of research on ventricular remodeling, heart failure, and arrhythmia after acute MI. Most studies take into account underlying clinical patient characteristics (such as STEMI vs NSTEMI, LV ejection fraction), but fail to take into account the underlying tissue changes associated with MI. Compelling data support that ventricular remodeling and risk of arrhythmia strongly depend on the underlying tissue composition. The CCS classification presented herein has the potential to enable the assessment of heart failure and arrhythmia risk in context of stages of severity of tissue injury. This could lead to a more refined understanding of pathophysiology, arrhythmia, and heart failure risk after MI and might profoundly affect patient management in the future.

The new classification might enable research and development of more differentiated, tissue injury stage-specific therapies; it seems plausible to assume that optimal medical therapies for acute MI will evolve to be different for each stage, because the underlying tissue injury is very different with each stage.
Table 1. Clinical application of the CCS classification of acute atherothrombotic MI

<table>
<thead>
<tr>
<th>Infarction stage</th>
<th>Clinical diagnostic criteria</th>
</tr>
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<tbody>
<tr>
<td>CCS stage 1</td>
<td>Aborted MI: ≥ 50% ST-segment resolution of the initial ST-segment elevation on the presenting ECG at either 90 minutes post fibrinolysis or 30 minutes post PCI in pharmacoinvasive and primary PCI patients, respectively. In addition, a lack of enzyme biomarker increase of cardiac troponin I/T levels ≤ 5 times the upper limit of normal on at least 2 measurements within 24 hours of reperfusion. Reperfusion ECGs should show no evidence of significant new Q-wave development. Normal reperfusion flow on angiogram. No microvascular obstruction on contrast perfusion echocardiogram and CMR.</td>
</tr>
<tr>
<td>CCS stage 1(+)</td>
<td>Apparent aborted MI according to all clinically available diagnostic tests, but complete assessment with all diagnostic methods not performed, therefore worse stage cannot be excluded</td>
</tr>
<tr>
<td>CCS stage 2</td>
<td>“Classic” MI. Infarction progressed with significant cardiomyocyte necrosis, exceeding criteria for aborted MI. No evidence for no-reflow on angiogram, no microvascular obstruction on contrast echocardiogram or CMR</td>
</tr>
<tr>
<td>CCS stage 2(+)</td>
<td>Apparent stage 2 MI according to all clinically available diagnostic tests, but complete assessment for reperfusion injury was not performed and thus injury more severe than stage 2 cannot be excluded</td>
</tr>
<tr>
<td>CCS stage 3</td>
<td>MI with microvascular obstruction ascertained according to no-reflow on angiogram or perfusion deficit on contrast perfusion echocardiogram or microvascular obstruction on CMR. No hemorrhage detected on CMR</td>
</tr>
<tr>
<td>CCS stage 3(+)</td>
<td>Apparent stage 3 MI according to all clinically available diagnostic tests, but hemorrhagic infarction cannot be excluded (CMR assessment for hemorrhage nondiagnostic or not performed)</td>
</tr>
<tr>
<td>CCS stage 4</td>
<td>Hemorrhagic MI, ascertained according to CMR (presently there are no other diagnostic tests for hemorrhagic MI)</td>
</tr>
<tr>
<td>MC</td>
<td>“MC” to be added for presence of mechanical complication (ventricular septal defect, free wall rupture, papillary muscle rupture); for example, “CCS stage 4 MC”</td>
</tr>
</tbody>
</table>

The table shows the diagnostic criteria to facilitate clinical application of the CCS infarction stages.

CCS, Canadian Cardiovascular Society; CMR, cardiac magnetic resonance imaging; ECG, electrocardiogram; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Future clinical trials might therefore benefit from applying the CCS classification of acute MI for subgroup analyses.

Myocardial ischemia and reperfusion injury are progressive; cardioprotective therapeutic interventions might target halting tissue injury progression to the next worse stage. The classification presented herein provides a metric to capture and document the extent of tissue injury in clinical trials. The CCS stages of acute MI could be applied as outcome measures and end points for research in patients with acute MI. Incorporating tissue injury end points into clinical research might help identify therapeutic opportunities that might otherwise go undiscovered, if only traditional clinical end points and outcome measures are used. The CCS stages of acute MI might serve as therapeutic targets in this context.

The classification stages could also be applied as quality outcome measures to assess the effectiveness of health care systems, beyond traditional measures like door-to-balloon time.

In a patient who presents with acute MI, the ultimate goal would be to limit tissue injury to stage 1, where the patient remains at low risk and the injury is minimal and mostly or completely reversible.

In brief, future personalized therapies and research in acute MI should take the type and severity of tissue injury into account; the CCS classification of acute MI presented herein is a tool to facilitate that (Table 2).

Although this new classification is formed on the basis of a strong body of evidence, challenges remain for its clinical translation. The classification relies on the comprehensive use of extensive patient data, including ECG, blood work, angiography, and advanced imaging data (Fig. 4, Table 1). Not all patients, however, will receive this complete and comprehensive workup. For example, currently, most patients with acute MI will not undergo a CMR study. For those patients, the writing group suggests determining the infarction stage using the best available information (Fig. 4, Table 1). If MVO

Table 2. Potential implications of CCS classification of acute atherothrombotic myocardial infarction

<table>
<thead>
<tr>
<th>Areas of focus</th>
<th>Potential implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical care</td>
<td>CCS stages of acute MI as a risk stratification tool on the basis of tissue injury in acute MI patients</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>CCS stages of acute MI as endpoints/outcome measures, refined assessment of MI beyond commonly used traditional clinical markers</td>
</tr>
<tr>
<td>Basic and translational research</td>
<td>CCS stages of acute MI to be used as tissue-specific therapeutic targets for cardioprotective therapy</td>
</tr>
<tr>
<td>Health systems research</td>
<td>CCS stage of acute MI could be used as metric to monitor effectiveness of care delivery at a health systems level</td>
</tr>
</tbody>
</table>

CCS, Canadian Cardiovascular Society; MI, myocardial infarction.
and hemorrhage cannot be excluded (for example because a contrast echocardiogram or CMR were not performed), then we suggest that the best evidenced stage be quoted for patient care, with addition of “(+)” indicating that a worse degree of injury might be possible but was not ascertained; such a patient could be labelled for example as “CCS stage 2(+).” We also recommend for documentation that “MC” be added to the stage when a mechanical complication occurs. Not all diagnostic tests will concur on a given stage, hence the infarct stage should be defined according to the worst documented injury marker. For example, if coronary artery flow is normal post angioplasty in an acute MI patient (TIMI 3 flow), but CMR shows MVO and absence of hemorrhage, then the patient should be labelled “CCS stage 3,” accounting for MVO. In principle, the available evidence of worst tissue injury should determine the stage of MI. The clinical application of the MI stages is presented in Table 2.

Reperfusion injury in patients with acute MI is progressive in the first hours and few days post reperfusion. The infarct size at the moment of presentation will almost universally be smaller than what will be observed later at the moment of reperfusion, because ischemic injury will have progressed following the wavefront phenomenon; an additional injury caused by hemorrhagic conversion might lead to a further increase in infarct size post reperfusion within 24-72 hours.63

Infarct size is thus dynamic in the acute phase. For clinical and research purposes, the best time to determine infarct stage might be in the subacute phase, 3-7 days post presentation.67

The boundaries between CCS infarct stages as defined are not sharp and will require further clarification through future research and expert consensus. For example, the troponin cutoff between CCS stages 1 and 2 needs to be better defined and might depend on the troponin assay used. ECG changes for stage 3 vs stage 4 are also ill defined and need further investigation. Future research might lead to further refinements of the classification to empower patient care and research.

The classification encompasses MI from epicardial coronary disease (atherothrombosis), which includes STEMI and type 1 NSTEMI according to the universal definition of MI.1

It remains to be determined, to what extent the principles of pathophysiology captured in this classification might apply to other types of MI, such as those due to spontaneous coronary artery dissection, coronary embolism, and supply/demand mismatch (for example noncardiogenic shock).1 The CCS classification is mostly on the basis of data derived from MI treated with reperfusion therapy, and its application to primarily nonreperfused MI remains to be investigated. The current classification has been developed using data at discrete time points. The evolution of post MI remodeling remains a continuous process. Further research, with more intensive clinical characterization along with imaging or biomarker-based assessments might yield greater insight into the evolution of acute and subacute phases of tissue injury and facilitate further refinements of the proposed classification.

Although it is premature to apply the classification immediately to guide clinical treatment at this time, this proposed classification might help to incorporate stages of tissue injury into clinical care for future patient risk assessment, management, and documentation.

The classification provides outcome measures and end points for MI research at the clinical and health systems level. It provides the fundamental framework for the development of future therapies.

Not all MIs are the same, and the best possible treatment might not be “one size fits all.” The best possible individualized treatment needs to take into account the underlying tissue pathology. The CCS classification of acute MI as outlined could be instrumental in facilitating the development of such treatments and ultimately help with the delivery of personalized, differentiated, tissue injury-directed care in the future. It can facilitate research in acute MI by providing the stages of MI as useful outcome measures, clinical study end points, and therapeutic targets.

**Ethics Statement**

This is an expert consensus document, not an original research report. Ethics guidelines of the authors’ affiliated institutions were respected.

**Patient Consent**

The authors confirm that patient consent is not applicable to this article; patient data are not presented in this report.

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**Disclosures**

Dr Kumar is the President of the Canadian Society of Cardiovascular Magnetic Resonance Imaging. Dr Dharmakumar has an ownership interest in Cardio-Theranostics, LLC. Dr Leipsic is a consultant and has stock options in Heartflow and Circle CVI, and is a consultant to Arineta. The remaining authors have no conflicts of interest to disclose.

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