

JACC REVIEW TOPIC OF THE WEEK

# Type 2 Myocardial Infarction

## JACC Review Topic of the Week



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### ABSTRACT

Acute myocardial infarction (MI) can occur from increased myocardial oxygen demand and/or reduced supply in the absence of acute atherothrombotic plaque disruption; a condition called type 2 myocardial infarction (T2MI). As with any MI subtype, there must be clinical evidence of myocardial ischemia to make the diagnosis. This condition is increasingly diagnosed due to the increasing sensitivity of cardiac troponin assays and is associated with adverse short-term and long-term prognoses. Limited data exist defining optimal management strategies because T2MI is a heterogeneous entity with varying etiologies and triggers. Thus, these patients require individualized care. A major barrier is the absence of a uniform definition that can be operationalized with high reproducibility. This document provides a synthesis of the data about T2MI to assist clinicians' understanding of its pathobiology, when to deploy the diagnosis, and its associated treatments. It also clarifies prognosis, identifies gaps in knowledge, and provides recommendations for moving forward. (J Am Coll Cardiol 2019;73:1846-60) © 2019 by the American College of Cardiology Foundation.

Myocardial infarction (MI) is a syndrome where myocardial cells die due to imbalances between myocardial oxygen supply and demand (1). It can be secondary to acute atherosclerotic plaque disruption (type 1 myocardial infarction [T1MI]), or alterations in myocardial oxygen supply and/or demand in the absence of acute atherothrombosis (type 2 myocardial infarction [T2MI]) (1).

Based on a comprehensive review of the peer-reviewed published data (Online Appendix), this report synthesizes the information on T2MI. It identifies gaps and makes recommendations for moving forward, including a phenotype-specific approach. Recognizing the heterogeneity of the mechanisms, it emphasizes individualized care.

### CLINICAL PRESENTATION

Patients' presentations depend on the pathobiology and clinical context (Figure 1) (2). Data suggest that women present more often with T2MIs (~46%), whereas men present mostly with T1MIs (~71%) (Online Figure 1) (3). Most patients with T2MI present with ischemia driven by another illness (Online Table 1). Some present due to coronary etiologies.

Diagnosing ischemia is the critical step. Patients with T2MI have less chest pain and more often have dyspnea or other atypical presentations (Online Table 2) (4). The clinical distinction is challenging. Certain patient subsets, such as women, the elderly, and those with diabetes, can



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Manuscript received August 21, 2018; revised manuscript received January 29, 2019, accepted February 4, 2019.

## HIGHLIGHTS

- T2MI occurs due to myocardial oxygen supply/demand mismatch without acute atherothrombotic plaque disruption and is associated with adverse short- and long-term prognoses.
- T2MI is a heterogeneous entity usually caused by a noncoronary trigger. Individualized care is needed.
- Consensus is needed about diagnosis. Imaging may help characterize processes leading to myocardial injury, facilitate the identification of acute myocardial ischemia, and help distinguish MI from injury.

acute MI is possible if ischemia is present (1). In the absence of ischemia, the diagnosis of acute myocardial injury is favored. Because T2MIs are often smaller events, there may not be ischemic electrocardiographic (ECG) findings or imaging abnormalities (5,6). Diagnostic evaluations such as advanced imaging may be precluded by comorbidities such as impaired renal function or critical illness.

## PATHOPHYSIOLOGY

There are multiple mechanisms for supply-demand imbalance (Figure 2). Some directly affect coronary blood flow (Figure 3); however, most T2MIs are triggered by noncoronary etiologies that reduce oxygen delivery and/or increase oxygen demand (Online Table 1). In most cases *both* supply and demand are likely altered either directly or indirectly. The presence and severity of concomitant coronary artery disease (CAD) likely defines the extent of supply-demand imbalance necessary to evoke ischemia.

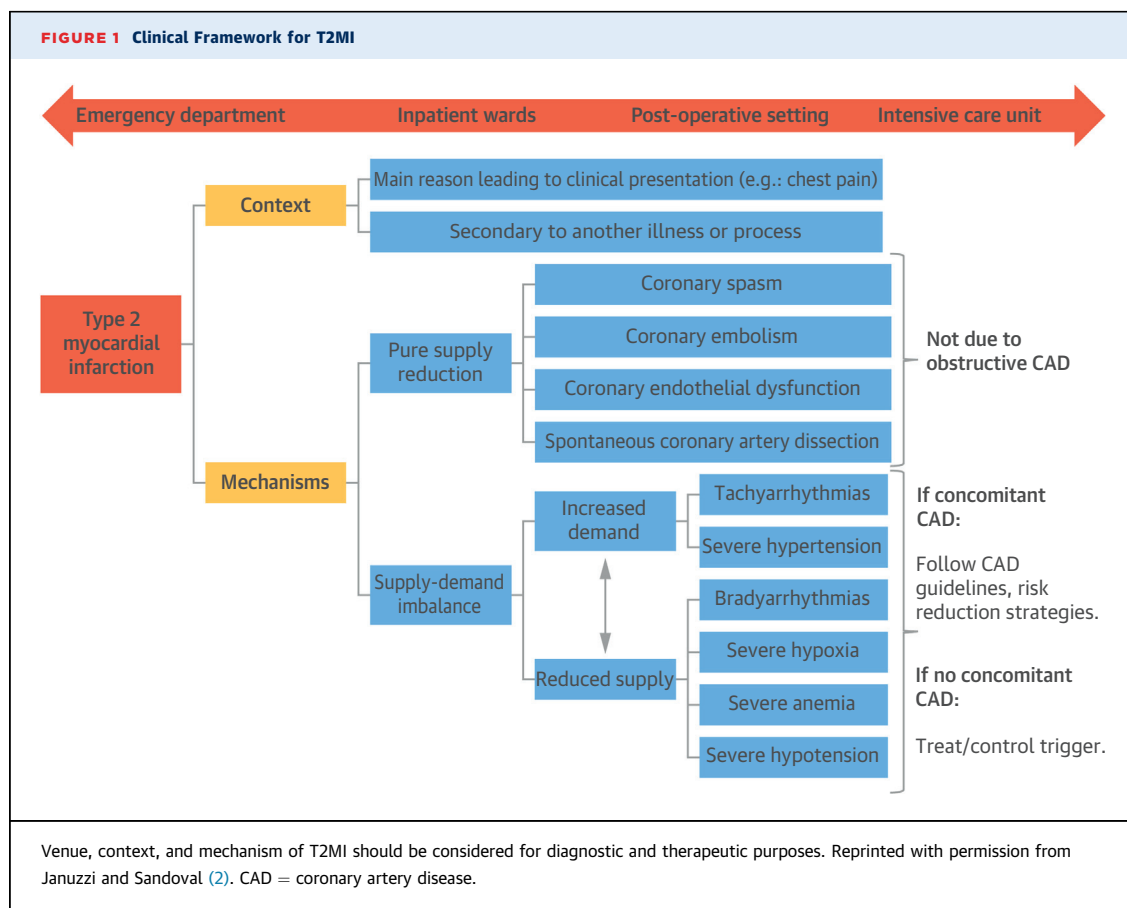
## ABBREVIATIONS AND ACRONYMS

**CAD** = coronary artery disease  
**cTn** = cardiac troponin  
**ECG** = electrocardiogram  
**MI** = myocardial infarction  
**OCT** = optical coherence tomography  
**STEMI** = ST-segment elevation myocardial infarction  
**T1MI** = type 1 myocardial infarction  
**T2MI** = type 2 myocardial infarction

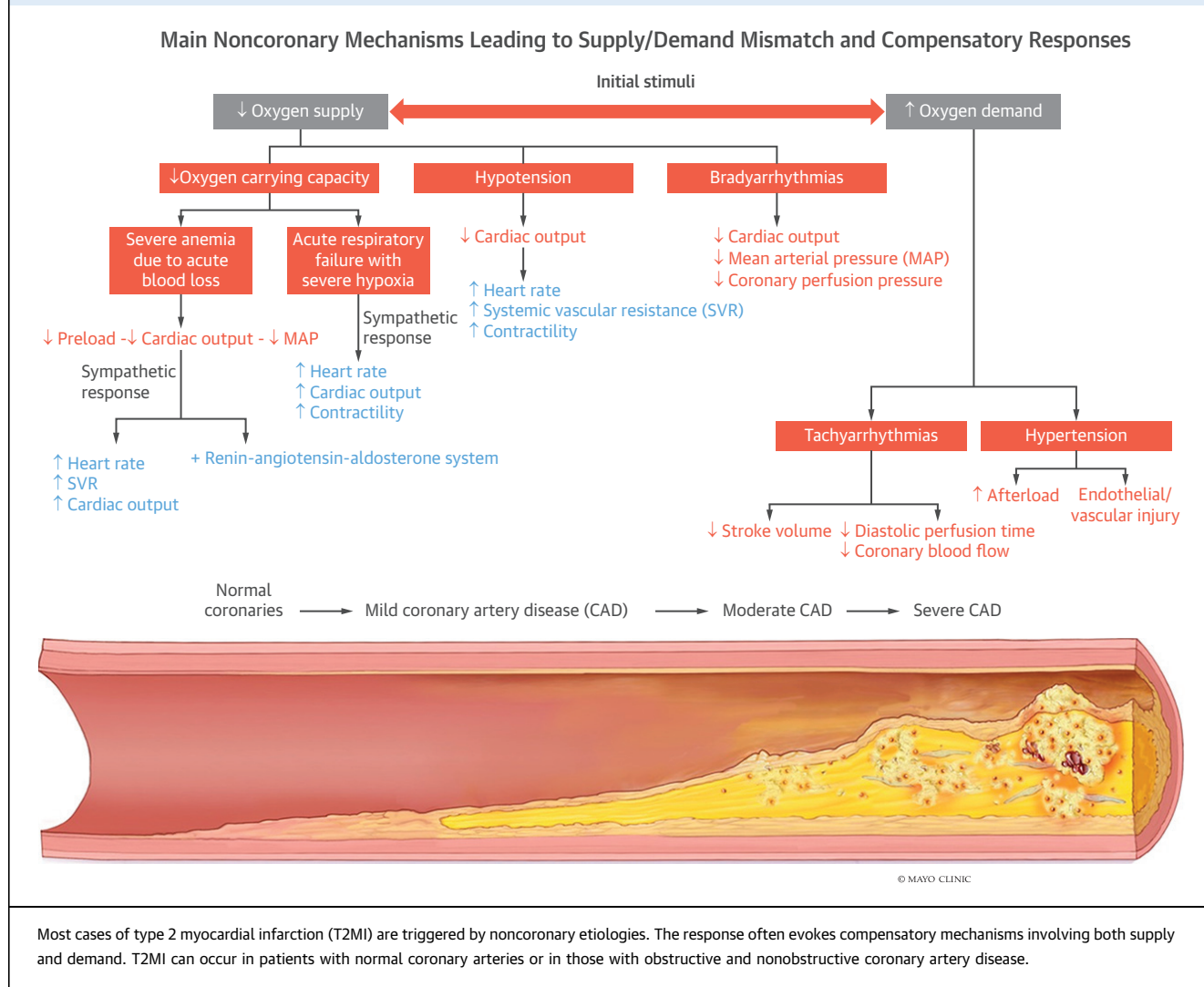
have either T2MI or T1MI with subtle atypical presentations (1).

For patients with cardiac troponin (cTn) increases with a rising and/or falling pattern, a diagnosis of

**FIGURE 1 Clinical Framework for T2MI**



**FIGURE 2** Main Noncoronary Mechanisms Leading to T2MI



Distinguishing mechanisms is difficult. For example, in sepsis, despite marked increases in coronary flow, patients can have sufficient alterations in myocardial oxygen demand that ischemia can occur, especially if coronary abnormalities are present. The toxic effects of tumor necrosis factor (TNF), heat shock proteins, and catecholamines can also cause cTn release.

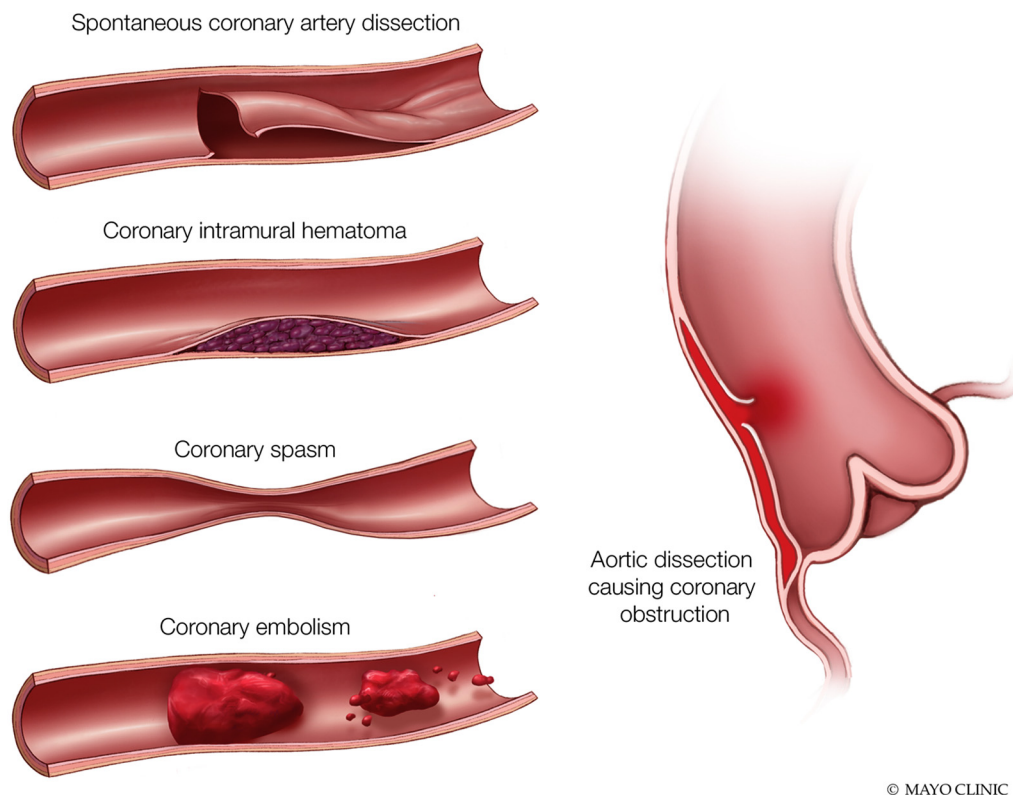
Thus, elevated cTn values alone, even if rising, do not make a diagnosis of T2MI. At times, both T2MI and myocardial injury are present. If clinicians focus only on supply-demand issues, opportunities to discover novel insights into pathobiology and treatments may be missed. The critical principle is that

there must be evidence of myocardial ischemia to diagnose T2MI.

## EPIDEMIOLOGY

The heterogeneous epidemiology of T2MI is shown in **Figure 4** (Online Table 3) (6-45). The frequency of T2MI is dependent on the population, comorbidities, disease definitions, adjudication processes, and the cTn assay and concentration thresholds used to detect myocardial injury (46). In the absence of uniform definitions, rates vary. Further, as difficult as it is to distinguish T1MI and T2MI, it is also difficult to distinguish T2MI from myocardial injury (3), with

**FIGURE 3** Coronary Etiologies of T2MI



Prevalence relates to how often these etiologies are considered. T2MI = type 2 myocardial infarction.

trained adjudicators having agreement rates of 64% (47).

Most studies use *broad criteria* evaluating all clinical information (3). Others use *specific criteria* (32) with strict thresholds (e.g., supraventricular tachyarrhythmia lasting  $\geq 20$  min with a ventricular rate  $>150$  beats/min, and so on) to define a mismatch. These latter criteria do not take into account that the threshold for myocardial ischemia varies based on the coronary anatomy. Finally, because hemodynamic abnormalities are easy to observe, it is seductive to think that all cTn elevations are secondary to them, potentially underappreciating other mechanisms.

Several investigations suggest T2MI is more frequent than T1MI in all-comers studies compared with chest pain populations. Such findings are common in U.S. studies where 57% to 75% of MIs are T2MI

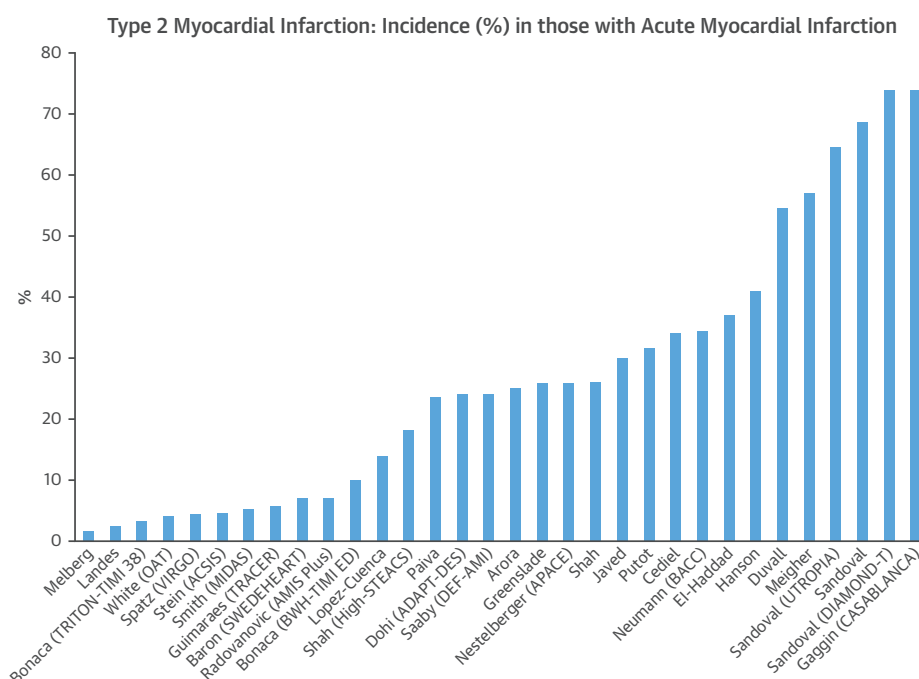
(18,25,36,38), potentially reflecting that cTn is used more broadly in the United States (48).

## 12-LEAD ECG AND ECHOCARDIOGRAPHY

The ECG classification of ST-segment elevation myocardial infarction (STEMI) and non-STEMI applies to T2MI as it does for T1MI. ST-segment elevation occurs in 1% to 24% of patients with T2MI (3). The frequency depends on the given population involved and how closely those entities are looked for, for example, using intracoronary imaging.

Patients with T2MI are less likely to have ischemic ECG changes and regional wall motion abnormalities (5,6,19,28). We support the concept that the more severe the ST-segment changes, the worse the outcomes (49).

**FIGURE 4** Epidemiology of T2MI



Marked variability in the proportion of T2MI diagnoses among patients with acute MI. ACSIS = Acute Coronary Syndrome Israeli Survey; ADAPT-DES = Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents; AMIS Plus = Acute Myocardial Infarction in Switzerland registry; APACE = Advantageous Predictors of Acute Coronary Syndromes Evaluation; BACC = Biomarkers in Acute Cardiac Care; BWH-TIMI ED = Brigham and Women's Hospital-Thrombolysis In Myocardial Infarction Emergency Department Chest Pain Study; CASABLANCA = Catheter Sampled Blood Archive in Cardiovascular Diseases; DEF-AMI = Consequences of the universal 2007 DEFINITION of Acute Myocardial Infarction studied in a Danish consecutive hospital population; DIAMOND-T = Diagnostic Improved Accuracy for Myocardial infarction with Delta Troponin; High-STEACS = High-Sensitivity Troponin in the Evaluation of patients with suspected Acute Coronary Syndrome; MIDAS = Myeloperoxidase in the Diagnosis of Acute Coronary Syndromes; OAT = Occluded Artery Trial; SWEDEHEART = Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies registry; TRACER = Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome; TRITON-TIMI 38 = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38; UTROPIA = Use of TROPonin I in Acute coronary syndromes; VIRGO = Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients.

## ADVANCED IMAGING AND CORONARY ANGIOGRAPHY

Coronary angiography is routinely used to evaluate patients with T1MI. For patients with T2MI, there is greater variability (range 5% to 60%), often reflecting the population involved ([Online Table 4](#)).

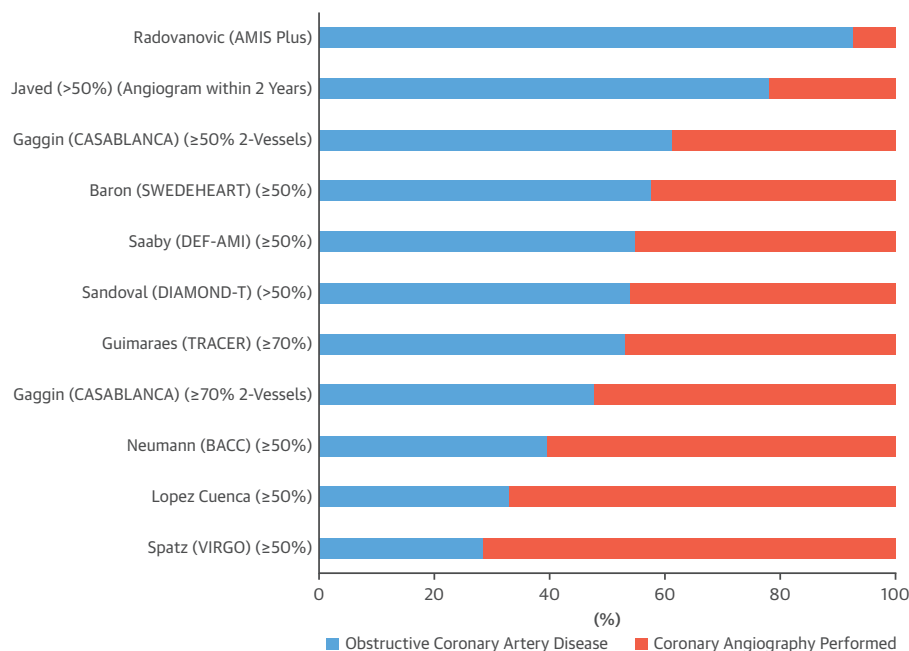
Coronary angiography is not 100% sensitive for plaque disruption. If the information will influence care, intracoronary imaging with optical coherence tomography (OCT) or intravascular ultrasound can be helpful ([50–53](#)). Ruptured plaques, however, are not exclusive to MI and are seen in patients with stable

angina and those who are asymptomatic ([52](#)). The timing of coronary angiography is also important, as following treatment, findings may change.

T2MI can occur with or without obstructive CAD and in patients with angiographically normal coronary arteries, such as due to spasm, embolism, SCAD, endothelial dysfunction, or with aortic dissection ([54–58](#)) ([Figure 3](#)). Intracoronary thrombus is not exclusive of T1MI and can result from obstruction, as in coronary spasm ([59](#)).

MI with nonobstructive coronary arteries ([60](#)) does not refer to MI subtypes. In SWEDEHEART (Swedish Web-system for Enhancement and

**FIGURE 5** Prevalence of CAD Among Patients With T2MI Undergoing Coronary Angiography



Note variability. Abbreviations as in Figure 4.

Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies registry), MI with nonobstructive coronary arteries occurred in 8% of MIs undergoing coronary angiography (61), of which 18% were T2MIs and 82% T1MIs.

Among patients with T2MI who undergo coronary angiography, CAD is common (Figure 5). In CASABLANCA (Catheter Sampled Blood Archive in Cardiovascular Diseases) (18), where all patients with subsequent T2MI had angiography, nearly 60% had  $\geq 50\%$  obstruction in 2 vessels. In other studies, a bimodal distribution is observed with either no disease or severe CAD (32).

Cardiac magnetic resonance imaging (CMR) is helpful in discerning alternative etiologies for myocardial injury. In some cases, CMR confirms acute MI despite the absence of an angiographic culprit (62). Similarly, coronary computed tomography angiography (CTA) can help assess for underlying CAD. DEMAND-MI (Determining the Mechanism of Myocardial Injury and Role of Coronary Disease in Type 2 Myocardial Infarction) (NCT03338504), where patients undergo CMR, and either: 1) coronary CTA, computed tomographic calcium scoring, and

computed tomography-derived fractional flow reserve fractional flow reserve; or 2) invasive coronary angiography with OCT and invasive fractional flow reserve, should provide novel insights.

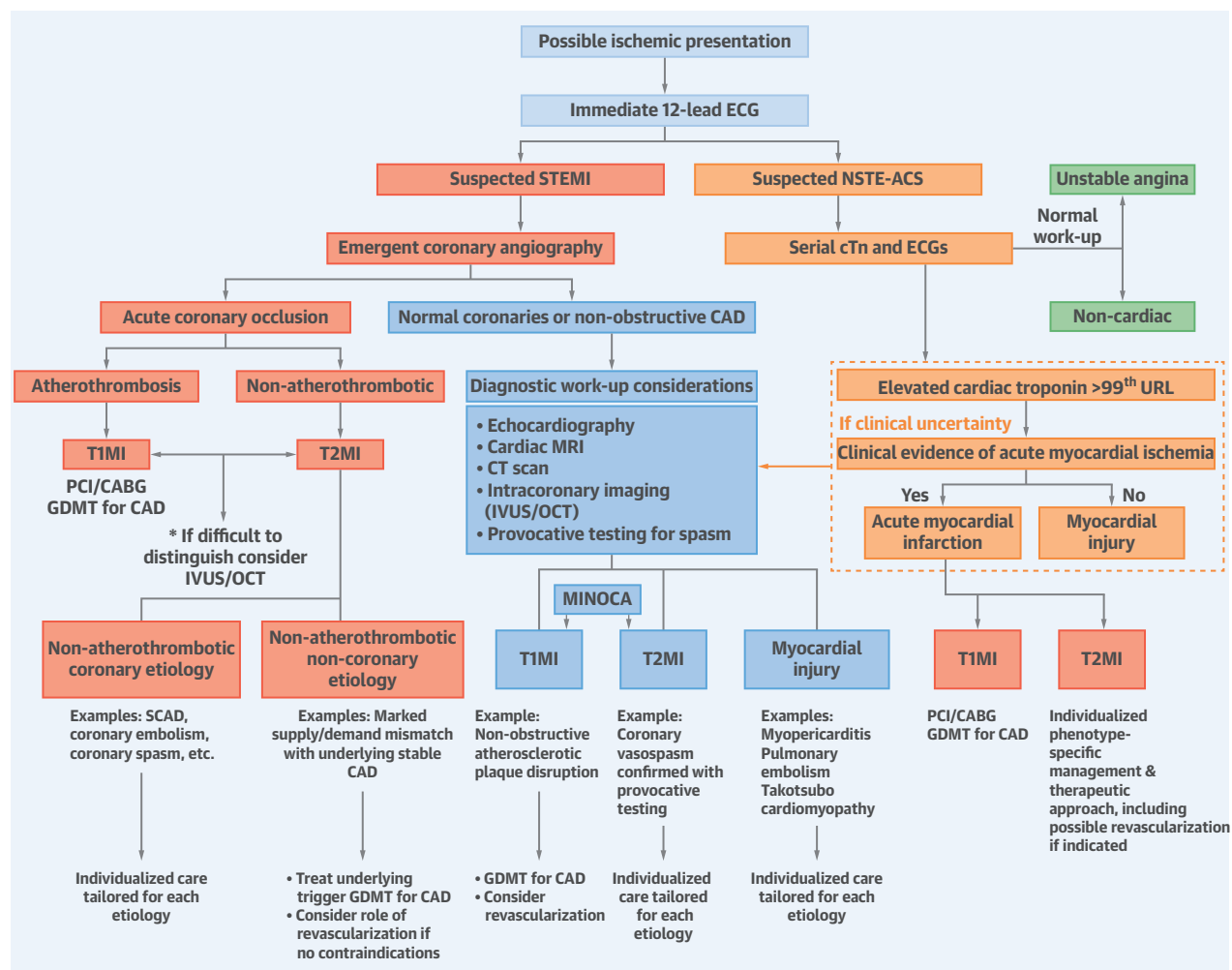
## CARDIAC TROPONIN

T2MI is increasingly recognized because of more sensitive cTn assays (63). Nearly all investigations indicate that patients with T2MI manifest lower cTn values (Online Table 5). Absolute concentrations and changes across serial measurements are greater with T1MI than T2MI (19,27). Sufficient overlap exists, however, that neither absolute values nor serial cTn changes (delta) distinguish T1MI from T2MI or myocardial injury (38).

An added challenge is that patients who present late after onset of symptoms may not manifest a rise and/or fall in cTn over short intervals because of the slower downslope of the time-concentration curve. In some series,  $\leq 26\%$  of MIs present this way (64).

Implementation of high-sensitivity (hs) cTn assays may translate into more acute MI diagnoses, particularly if transitioning from less sensitive assays (65).

## CENTRAL ILLUSTRATION Diagnostic Approach for Patients With Suspected Acute Myocardial Ischemia



Sandoval, Y. et al. J Am Coll Cardiol. 2019;73(14):1846–60.

In the absence of myocardial ischemia, the diagnosis of myocardial injury is favored, whereas in the presence of ischemia, T1MI or T2MI are possible. CABG = coronary artery bypass graft; CAD = coronary artery disease; CT = computed tomography; cTn = cardiac troponin; ECG = electrocardiogram; GDMT = guideline-directed medical therapy; IVUS = intravascular ultrasound; MINOCA = myocardial infarction with nonobstructive coronary arteries; MRI = magnetic resonance imaging; NSTEMI-ACS = non-ST-segment elevation acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction; OCT = optical coherence tomography; PCI = percutaneous coronary intervention; SCAD = spontaneous coronary artery dissection; STEMI = ST-segment elevation myocardial infarction; T1MI = type 1 myocardial infarction; T2MI = type 2 myocardial infarction; URL = upper-reference limit.

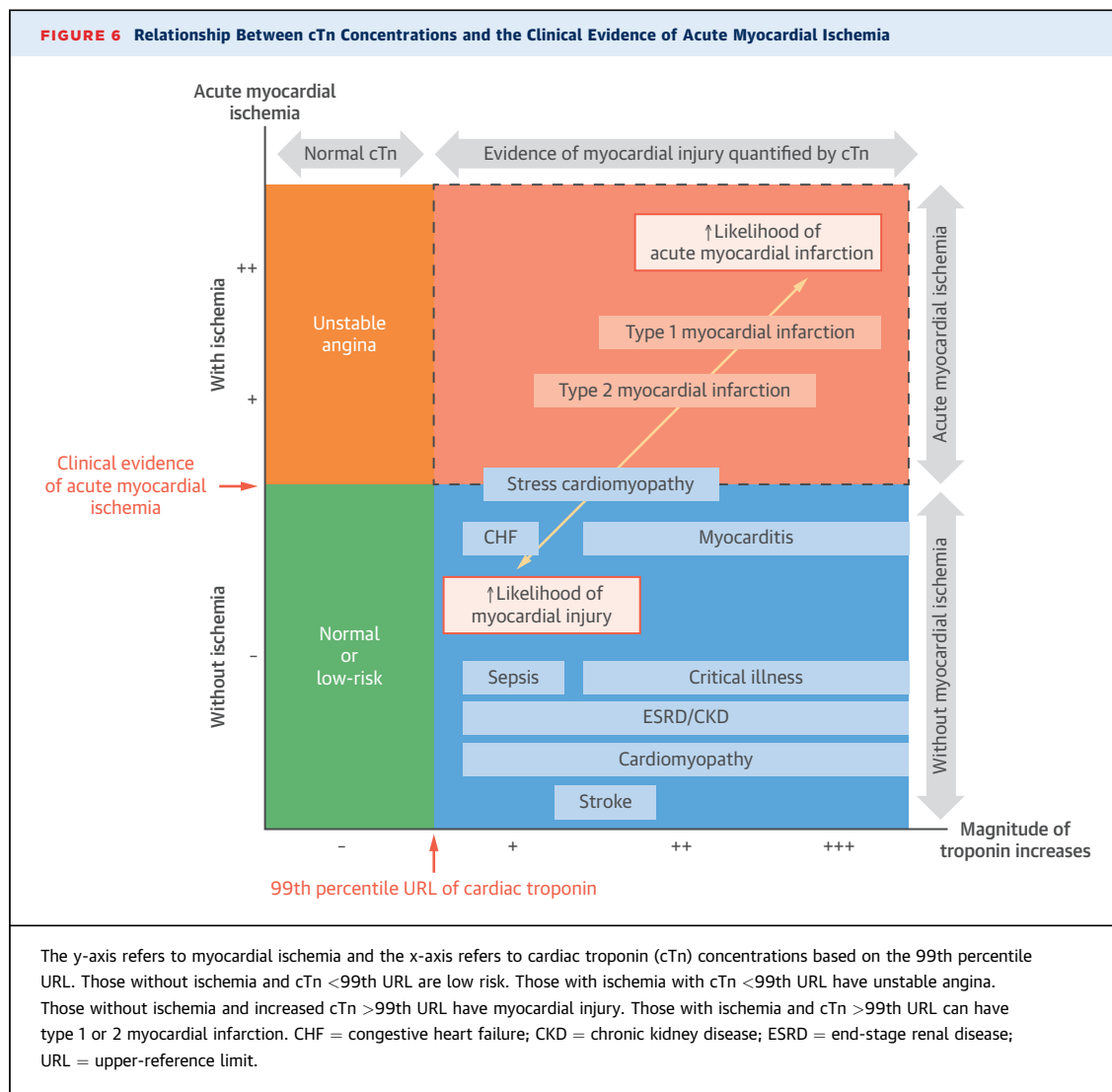
The magnitude of the effect on diagnostic rates is influenced by the assay and/or threshold used before and after hs-implementation (66). In some studies, there is no increase in T2MI diagnoses (36). Given T2MI is associated with lower cTn values, it is conceivable that the relative number of T2MIs will increase more than T1MI. In contrast, data from the Advantageous Predictors of Acute Coronary

Syndromes (APACE) study suggests that compared to cTnT, most new MIs identified using hs-cTn are T1MIs (65).

## APPROACH TO ASSESSMENT AND DIAGNOSIS

An algorithmic approach to T2MI is shown in the Central Illustration. The diagnosis requires: 1) a rising





and/or falling cTn with  $\geq$  value >99th percentile; and 2) clinical evidence of myocardial ischemia (1). When symptoms and signs are unclear, emphasis should be placed on finding objective evidence of myocardial ischemia (5), for example with cardiac imaging.

The first steps include a careful history and physical examination, cTn measurements, and 12-lead ECGs. Imaging studies should be used selectively. If clear evidence of acute myocardial ischemia cannot be identified, the term *myocardial injury* is favored (Figure 6). If myocardial ischemia is present, distinguishing T2MI from T1MI is clinically based.

Most cases of T2MI are non-STEMIs secondary to another illness. Therefore, except for cases where

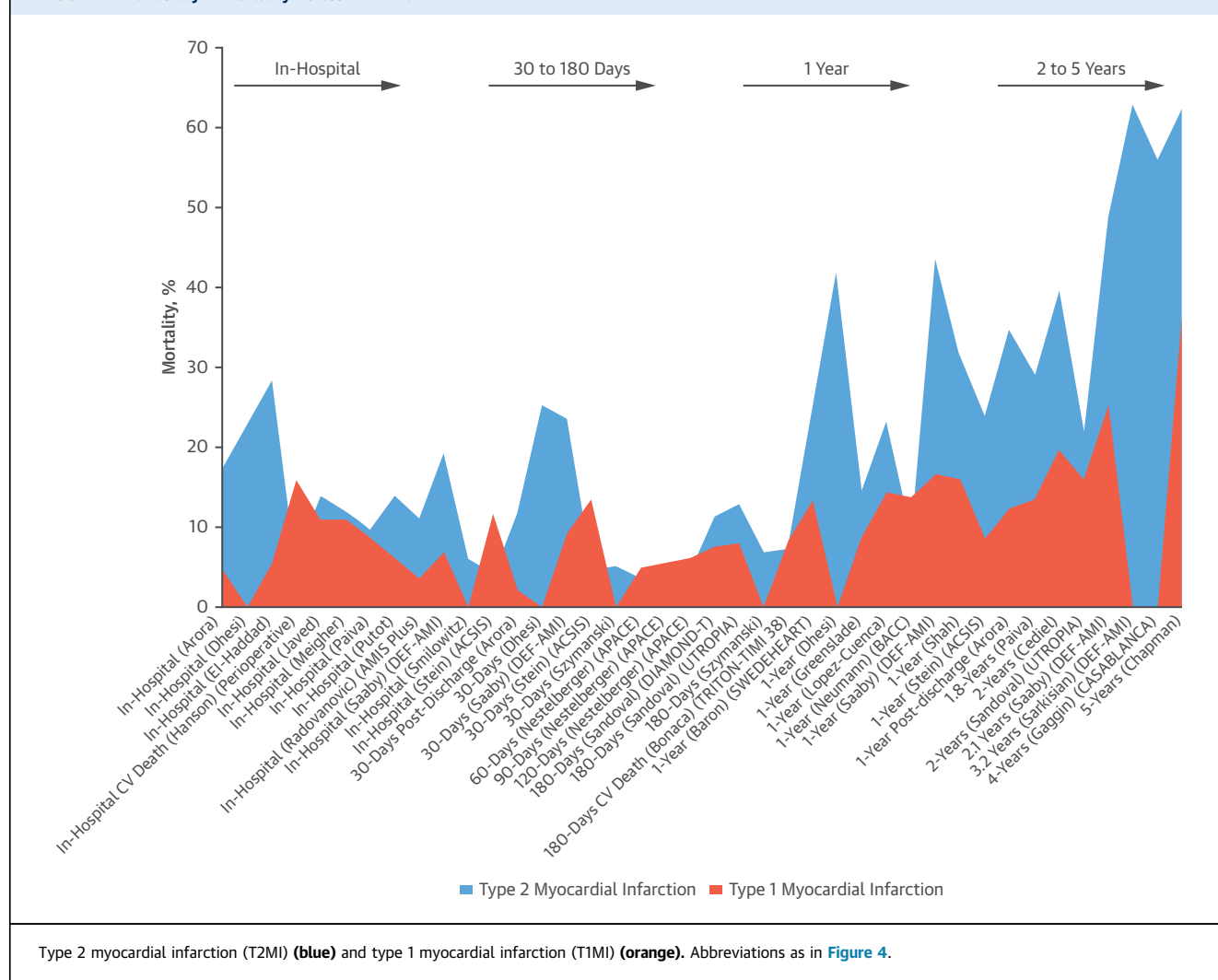
prompt cardiovascular diagnosis and/or therapy are indicated, evaluations can wait until underlying problems are stabilized.

## PROGNOSIS

Patients with T2MI have similar or higher all-cause mortality than patients with T1MI (Figure 7, Online Table 3), in part because many studies include critically ill patients with comorbidities. They are at high risk for cardiovascular mortality and major adverse cardiovascular events. In the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) trial, patients with T2MI had a nearly 3-fold



**FIGURE 7** Variability in Mortality Across T1MI and T2MI



increased risk for cardiovascular death (10). In CASABLANCA, incident T2MI predicted all-cause and cardiovascular death, as well as the composite of all-cause death, nonfatal MI, heart failure (HF), stroke, transient ischemic attack, peripheral arterial complication, and cardiac arrhythmia (18).

Studies focused only on patients with chest pain often exclude high-risk or critically ill patients, such as those with advanced renal disease, and suggest a more benign prognosis (27,28). In APACE, patients with T2MI had 120-day rates of cardiovascular and all-cause death rate of 1.7% and 4.6%, respectively (27).

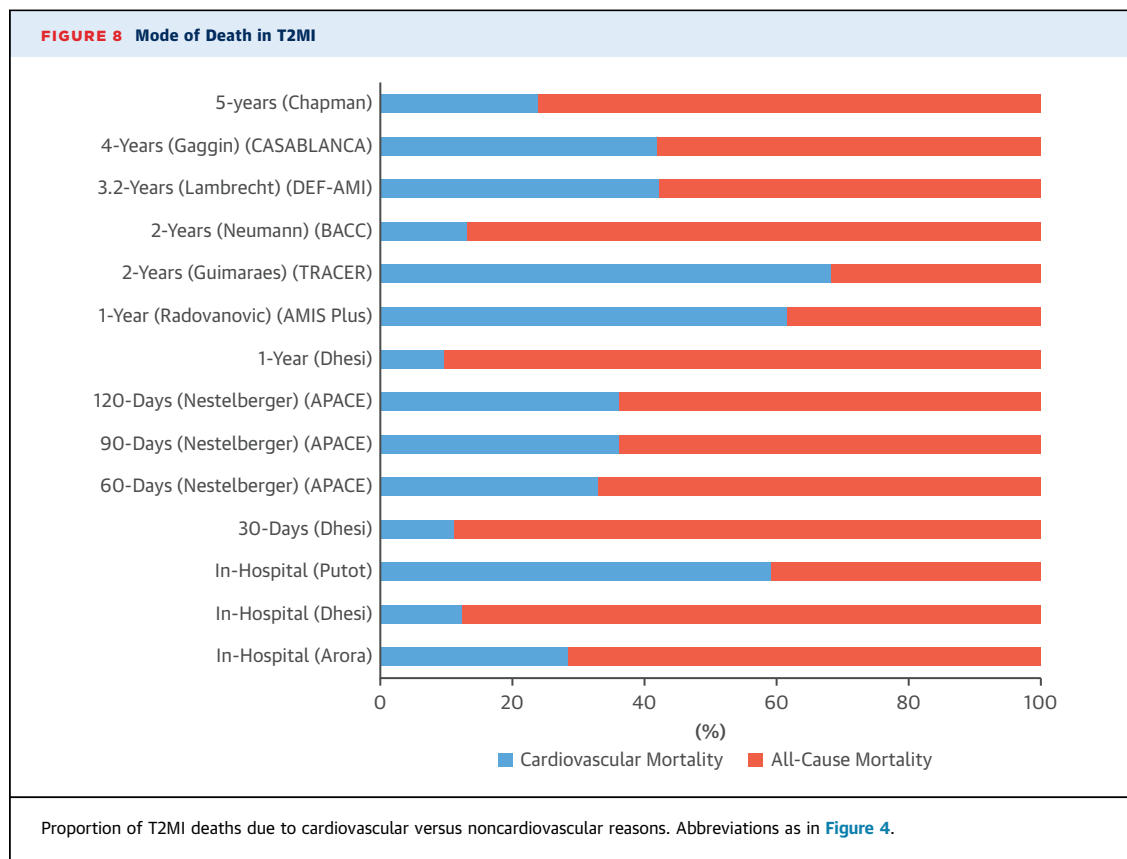
Most patients with T2MI die from non-cardiovascular causes (Figure 8), as in studies of the critically ill where conjoint cardiovascular disease

and critical illness increase death rates (67). Nonetheless, studies with long-term follow-up indicate that cardiovascular mortality is common and explains 24% to 43% of deaths (13,18,35). Thus, opportunities exist to identify high-risk patients and improve their outcomes.

Among patients with T2MI or myocardial injury, CAD is an independent predictor of cardiovascular death or recurrent MI (13). In these studies, however, only small numbers of patients underwent coronary angiography (39,61).

## TREATMENT

Recognizing the heterogeneous mechanisms leading to T2MI, we endorse a phenotype-specific



approach (2). A conceptual model is proposed in Table 1, which can be refined using phenomapping and machine learning, as with HF with preserved ejection fraction (68).

For those who present with a primary coronary problem, the appropriate treatment is dictated by that process (54-58). For those with T2MI caused by supply-demand mismatch, individualized therapies should be tailored to the specific conditions (1,3).

Observational studies suggest that T2MI patients with CAD have adverse outcomes (13,61). Thus, those with known or suspected CAD, more marked ST-segment depression, and/or higher cTn concentrations may require evaluation for CAD. ACT-2 (Appropriateness of Coronary investigation in myocardial injury and Type 2 myocardial infarction) is a randomized trial comparing invasive coronary angiography (or coronary CTA) versus conservative management on 2-year all-cause mortality that should provide insights into management (69).

For patients with T2MI and CAD, guideline-directed therapies are appropriate. The role of

revascularization remains uncertain. At present, careful decisions should be made following clinical-practice guidelines, while balancing the risk/benefit of dual-antiplatelet therapy. Studies indicate wide variations in revascularization (PCI or CABG) (Online Table 4), with a recent meta-analysis showing a PCI use rate of 40% (range 0% to 87.5%) (70).

## SPECIAL SCENARIOS

**PERIOPERATIVE MYOCARDIAL INJURY AND INFARCTION.** The perioperative setting is unique and T2MI is common (71). Pre-operative cTn measurements and surveillance sampling are recommended for those at risk (1). Because of analgesics, few patients have symptoms (71). Although ischemic changes are rarely detected on routine ECGs, studies using continuous 12-lead Holter monitoring show that transient tachycardia and ST-segment changes are common and correlate with cTn (72). Using OCT, most perioperative MIs are T2MI (53). However, autopsy data suggest that fatal events are evenly distributed between plaque rupture and nonplaque rupture

**TABLE 1** Phenotype-Specific Approach to T2MI: A Conceptual Model

| Type 2 Myocardial Infarction Phenotypes                                                                                                                                                                                                                                                                                                   | Examples                                                                                                                                                                                                                             | Suggested Approach                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Noncoronary Phenotypes</b>                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Older patients with many comorbid conditions (++++) including CAD or suspected CAD who are critically ill:</b> Poor prognosis, often burdened with many comorbidities such as CAD, chronic kidney disease, and congestive heart failure in addition to the primary illness/condition/trigger leading to secondary myocardial ischemia. | Example: Older patient with chronic kidney disease, COPD, stable CAD, HFpEF admitted with acute gastrointestinal hemorrhage found to have critical anemia and identified to have ST-T-wave changes and increased cTn.                | Stabilize first; in most cases, management should focus on correction/control of the trigger/condition/illness leading to secondary myocardial ischemia, with more aggressive management (e.g.: angiography) reserved for those with high-risk features of objective myocardial ischemia once the acute issues have been resolved and in whom further action is reasonable after careful risk/benefit assessment (e.g., profound ST-T-wave changes, marked cTn increases, large new regional wall motion abnormalities). |
| <b>Older patients with some comorbid conditions (+) including CAD or suspected CAD:</b> Fair prognosis in the absence of critical illness, particularly when trigger/illness leading to T2MI can be easily corrected.                                                                                                                     | Examples: Middle-age or elderly patient without overt critical illness or extensive comorbidities; e.g., patients with atrial fibrillation with rapid ventricular rate and underlying stable CAD with increased cTn and ECG changes. | Requires correction/control of the trigger/condition/illness leading to secondary myocardial ischemia. If no history of CAD, may require risk stratification for such. If CAD present, follow CAD guidelines (i.e., aspirin, statin). Definite role of revascularization uncertain; at present, follow revascularization guidelines (symptoms, ischemia, physiology-guided revascularization) and balance risk/benefit of DAPT in such population.                                                                       |
| <b>Older patients with T2MI with no evidence of obstructive CAD.</b>                                                                                                                                                                                                                                                                      | Example: Patient with chest discomfort in the context of hypertensive emergency requiring intravenous antihypertensive therapy in whom there is increase in cTn.                                                                     | Requires correction/control of the trigger/condition/illness leading to secondary myocardial ischemia. Consider primary prevention for CAD as indicated.                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Younger patients with minimal to no comorbidities:</b> Prognosis good, particularly when in the absence of known or suspected coronary artery disease and other major underlying comorbidities.                                                                                                                                        | Examples: Young patient with chest pressure found to have prolonged supraventricular tachycardia and ECG changes with increased cTn.                                                                                                 | Most often requires only correction of the trigger/condition/illness leading to secondary myocardial ischemia. If no history of CAD, may require risk stratification for such.                                                                                                                                                                                                                                                                                                                                           |
| <b>Coronary Phenotypes</b>                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Often have clear definite evidence of acute myocardial ischemia; many manifest as STEMI. Likely a diagnosis of exclusion once atherosclerotic plaque disruption (T1MI) has been excluded.                                                                                                                                                 | SCAD, coronary embolism, coronary spasm, endothelial dysfunction                                                                                                                                                                     | Most often will require invasive angiography to confirm the diagnosis. May require use of intracoronary imaging (IVUS/OCT) and/or coronary physiology to confirm or exclude diagnoses. Individualized care tailored for each etiology.                                                                                                                                                                                                                                                                                   |

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; cTn = cardiac troponin; DAPT = dual antiplatelet therapy; ECG = electrocardiogram; HFpEF = heart failure with preserved ejection fraction; IVUS = intravascular ultrasound; OCT = optical coherence tomography; SCAD = spontaneous coronary artery dissection; T1MI = type 1 myocardial infarction; T2MI = type 2 myocardial infarction.

events (73). Thus, while most events are T2MI, the fatal ones may be T1MI.

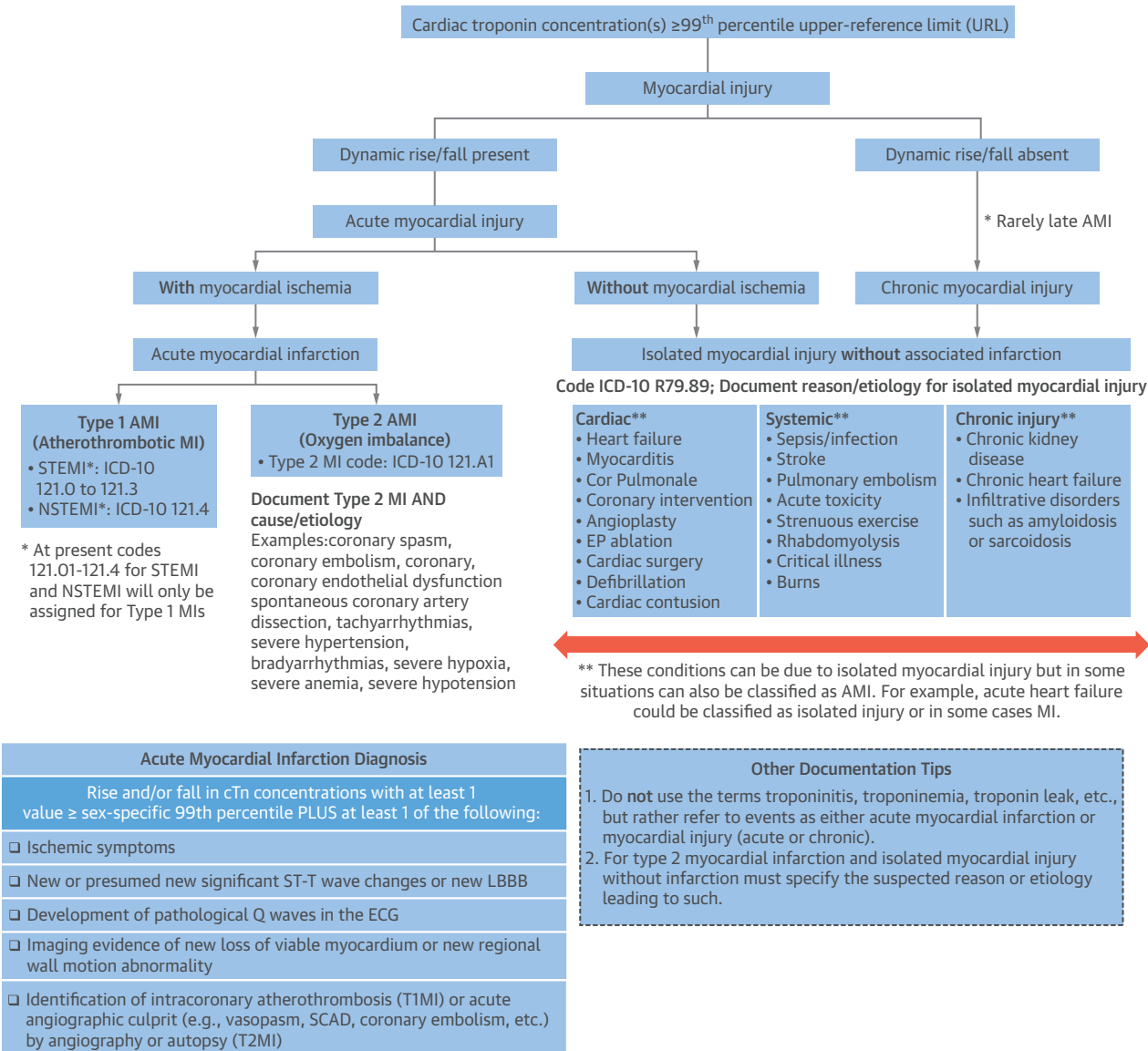
Defining therapies is challenging because of the risk for bleeding. A randomized trial suggested that dabigatran may be effective (74); however, uncertainty persists. For now, treatment should be individualized and include correction of supply-demand imbalance.

**CRITICAL ILLNESS.** It is challenging to distinguish acute and chronic myocardial injury from T1MI and T2MI in this context. Absent evidence of myocardial ischemia, most cTn rises, especially those with sepsis, are likely due to myocardial

injury. These patients are often intubated and/or sedated, which limits the ability to assess symptoms and signs, and ECGs are often not helpful. Upon recovery, if appropriate, these patients may require further evaluation to clarify the etiology of their cardiac injury to improve their adverse long-term prognosis (75).

**HEART FAILURE.** Patients with acute or chronic HF frequently manifest increased cTn (76). Myocardial ischemia can be a trigger for HF. For patients with acute HF, there often is a rise and/or fall in cTn. One mechanism for this is acute left ventricular stretch with proteolysis and release of cTn with cell death

**FIGURE 9** Coding Algorithm for Patients With cTn Increases



Tool for clinicians/coders to categorize patients with increased cTn. \*At present, these codes are being applied only to TIMI for coding purposes. AMI = acute myocardial infarction; ECG = electrocardiogram; ICD = International Classification of Diseases; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TIMI = type 1 myocardial infarction; other abbreviations as in [Figures 2 and 6](#).

due to apoptosis via a calpain mediated mechanism (77). Chronically, cTn values track reasonably with left ventricular end-diastolic pressure, suggesting subendocardial hypoperfusion. In some patients, coronary endothelial dysfunction may also exist. Unless there is evidence of acute myocardial ischemia, cTn increases should be considered myocardial injury.

## CHALLENGES AND FUTURE DIRECTIONS

We have identified gaps where more data are needed. There are disease coding issues, including the proper use of the new International Classification of Disease (ICD)-10 code for T2MI (code I2A1) (Figure 9), hospital reimbursement, mortality statistics, performance and quality measures, health

**TABLE 2 Present Challenges and Future Directions**

| Clinical Controversies                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. <b>Who should undergo cTn testing?</b>                                                                                                                                                                                                            | <ul style="list-style-type: none"> <li>The incidence rate largely relates to the tested population (i.e., if only patients with chest discomfort are tested with cTn, then T1MI may be more common, whereas if all-comers with various symptoms are tested, then T2MI becomes more common). More clarity is needed as to whom should be tested with cTn measurements.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                        |
| 2. <b>Noninvasive advanced cardiac imaging</b>                                                                                                                                                                                                       | <ul style="list-style-type: none"> <li>Making the distinction between T1MI, T2MI, and myocardial injury is challenging and often subjective. More studies, for example using advanced cardiac imaging (CMR or coronary CTA), are needed to better inform diagnostic pathways. If diagnostic uncertainty prevails, cardiac imaging should be used more often to determine whether findings supportive of overt acute myocardial ischemia are present to diagnose acute MI or to help assess for other potential etiologies of myocardial injury. It is acknowledged that some patients may have small MIs that are not large enough to cause regional wall motion abnormalities.</li> </ul>                                                              |
| 3. <b>Intracoronary imaging</b>                                                                                                                                                                                                                      | <ul style="list-style-type: none"> <li>Coronary angiography is often seen as the gold standard; however, it is neither 100% sensitive nor specific for plaque-rupture events. More data is needed with intracoronary imaging (OCT/IVUS).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 4. <b>Should the criteria used to diagnose T2MI be made more specific?</b>                                                                                                                                                                           | <ul style="list-style-type: none"> <li>The absence of established diagnostic criteria allows for the term T2MI to be loosely used in conditions in which supply-demand mismatch is suspected, when clear evidence of myocardial ischemia is lacking. However, atypical ischemic presentations in the elderly, diabetic patients, and women could be inadvertently disadvantaged. Additional evidence is needed to answer this question.</li> </ul>                                                                                                                                                                                                                                                                                                      |
| 5. <b>Personalized care</b>                                                                                                                                                                                                                          | <ul style="list-style-type: none"> <li>Recognizing the distinct heterogeneous mechanisms leading to T2MI, it should be understood that care needs to be individualized and that a phenotype-based approach may be best suited to inform how to best treat these patients.</li> <li>For patients with T2MI with concomitant CAD, further research is required to understand the value of both medical intensification and/or revascularization in the absence of atherothrombosis.</li> </ul>                                                                                                                                                                                                                                                            |
| Disease Coding                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 1. ICD-10 code (I12AI)                                                                                                                                                                                                                               | <ul style="list-style-type: none"> <li>The adoption of a code specific for T2MI should facilitate both epidemiologic and outcomes assessments.</li> <li>Inappropriate use of the T2MI code should be avoided; that is, there should be clear evidence of acute myocardial ischemia before the diagnosis/code is deployed.</li> <li>At present, coders may opt to reserve the STEMI and NSTEMI codes to T1MI (Figure 9). Unless coding is done more consistently, the ability to look across various venues to compare data will be impossible.</li> <li>For patients with T2MI, clinicians should specify the trigger(s); for example, T2MI secondary to atrial fibrillation with rapid ventricular rate, or T2MI due to coronary vasospasm.</li> </ul> |
| Performance and Quality Measures                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 1. The 2017 AHA/ACC Performance and Quality Measures (e.g., aspirin at discharge, beta-blocker at discharge, and so on) pertain only to T1MI.                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 2. Hospital Readmission Reduction Program (HRRP): patients with T2MI are included in the HRRP and hospitals are subject to financial penalties if their 30-day readmission rates exceed risk-standardized readmission rates (78).                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Research                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 1. The absence of operational diagnostic criteria as to what constitutes T2MI has created inconsistencies across the peer-reviewed published data, with clinicians and researchers having distinct perspectives in how the diagnosis is established. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 2. Defining and then insisting on objective evidence of myocardial ischemia would likely facilitate disease coding and adjudication.                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 3. Recognizing the heterogeneous mechanisms/conditions leading to T2MI, the development of evidence-based therapies will benefit from phenotype specific-approach study/trial designs.                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 4. Outcomes may differ across T2MI phenotypes. For example, young patients without comorbidities with arrhythmias may have different outcomes than older sicker patients.                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| CMR = cardiac magnetic resonance; CTA = computed tomographic angiography; MI = myocardial infarction; other abbreviations as in Table 1.                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

policy, societal implications, and research, among others (78). Selected issues are described in Table 2.

## CONCLUSIONS

T2MI is frequent and explains a significant proportion of cTn increases in clinical practice. The mechanisms are heterogeneous, for which reason, individualized approaches to diagnosis, management, and risk stratification are needed. A consensus is needed

about how the diagnosis is established, to facilitate evidence-based therapies geared toward improving outcomes.

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**KEY WORDS** acute myocardial infarction, cardiac troponin, myocardial injury, type 2 myocardial infarction, Universal Definition of Myocardial Infarction

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**APPENDIX** For supplemental tables and a figure, please see the online version of this paper.