

VIEWPOINT

Type 2 Myocardial Infarction— Diagnosis, Prognosis, and Treatment

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Over the past 3 decades, mortality rates for acute myocardial infarction (MI) have declined significantly in large part due to improved evidence-based revascularization techniques, medical therapies, and systems of care. Yet, patients with acute MI represent a diverse group with varying causes for their infarction. Recognizing this, in 2007, the Task Force for the Redefinition of MI created the **Universal Definition of MI** consensus document, which introduced **5 subtypes** of MI (Table).¹ One common subtype, **type 2 MI**, is defined as an MI **driven** by a **myocardial oxygen supply and demand mismatch** in the **absence** of coronary **thrombosis**.

Despite the introduction of type 2 MI over a decade ago, **no guidelines** or consensus documents are available to aid physicians in clinical management, and **limited** prospective, high-quality **evidence** has been generated thus far in this cohort. To date, limited nationally representative data are available estimating the relative incidence of type 2 MI in the United States. Currently, only 1 study listed on ClinicalTrials.gov is actively enrolling patients with type 2 MI (NCT03338504).

Why Is Action Needed?

Patients with type 2 MI are frequently encountered in clinical practice. **Diagnostic criteria** for **type 2 MI** include the following: (1) detection of markers of cardiac myonecrosis (ie, elevated **troponin** concentrations); (2) clinical context **lacking** signs or symptoms **suggestive** of **acute coronary syndrome** or **nonischemic contributors** to myocardial injury (such as **myocarditis**); and (3) identification of **physiological stressors** resulting in myocardial supply and demand imbalance.

Depending on the **source** of information, **type 2 MI** may be **more common** than **type 1 MI**.² For example, of the 249 MIs in the observational **UTROPIA** (Use of Troponin In Acute Coronary Syndromes) registry of patients with available troponin I levels measured for clinical indications in the emergency department, **64%** were ultimately adjudicated as **type 2 MI**.² Furthermore, the reported incidence of type 2 MI is expected to increase: in October 2017, an *International Classification of Diseases* code for type 2 MI was introduced; prior to this change, administrative coding of type 2 MI was infrequent.² In addition, given the widespread introduction and use of high-sensitivity troponin assays in the United States, the detection of myocardial injury due to MI (including type 2 MI) is anticipated to increase.

The diagnosis of **type 2 MI** is associated with a **poor prognosis**: **less than 40%** of patients will **live 5 years** past their diagnosis.³ In contrast, patients with **type 1 MI** (**60%-65%**), **heart failure** (**50%-60%**), and **common cancers** (breast, prostate, and colorectal; **45%-80%**) have **higher 5-year survival rates**.^{3,4} This poor prognosis is not en-

tirely surprising because **type 2 MI** typically occurs among **older** patients with **greater comorbidities**³ and is identified in the context of **hemodynamic instability**, including **shock**, **tachycardia**, **respiratory failure**, **gastrointestinal bleeding**, **decompensated heart failure**, or **recent surgery**. Moreover, in **contrast** with **type 1 MI** that has a clear set of guideline-based recommendations for treatment, **management of type 2 MI remains uncertain**.

Efforts to improve outcomes of type 2 MI are relevant to patients, health care professionals, hospital systems, payors, and regulatory bodies across medicine and surgery. **Most deaths** among patients with **type 2 MI** are **due to non-cardiovascular causes**.³ Yet, major adverse cardiovascular event rates are also high in this cohort; approximately **30%** of patients will have a cardiovascular event over 5 years.³ The rates of recurrent cardiovascular events are similar, if not higher, than for patients with type 1 MI.⁵

A diagnosis of type 2 MI also has potential financial implications for institutions. Patients with type 2 MI are included in the Hospital Readmission Reduction Program (HRRP), and hospitals are subject to financial penalties if their 30-day readmission rates exceed risk-standardized readmission rates, with penalties of up to 3% of total Medicare reimbursement. Data are limited to date, but an estimated 10% of all readmitted patients who contribute to the HRRP penalty have type 2 MI.⁶

Future Directions

Studies to identify optimal management strategies for patients with type 2 MI are needed; several **areas for further investigation** include the following.

1. Improved Definition and More Precise Profiling

Although subtypes of MI developed in the Universal Definition of MI have been useful, the increased recognition of the breadth of type 2 MI and detection of myocardial injury in other clinical states call for further attempts to differentiate these clinical entities. Given the **heterogeneity of type 2 MI**, **more precise definitions** grounded in the pathophysiologic basis of its occurrence may facilitate development of targeted interventions.

2. A Multidisciplinary Approach

Given medical complexity and high rates of noncardiovascular mortality in patients with type 2 MI, a multidisciplinary approach could be beneficial. This may represent involvement from cardiologists, other medical subspecialists, **surgeons**, and other health care professionals, depending on the clinical scenario. Participation in cardiac rehabilitation has demonstrated reductions in morbidity, mortality, and readmissions in a cost-effective manner for patients with type 1 MI. Whether similar benefits may occur among patients with type 2 MI warrants investigation.

Table. Universal Definition of MI

Type	Classification	Clinical and Diagnostic Criteria
1	Spontaneous MI	Plaque rupture, ulceration, fissuring, erosion, or dissection resulting in coronary thrombosis
2	Supply/demand mismatch	Mismatch between myocardial oxygen supply and demand driven by a secondary process other than coronary artery disease
3	Suspected MI-related death	Cardiac death in a setting suggestive of ischemic process without definitive cardiac biomarker evidence of MI
4a	PCI-related MI	Rise in cardiac biomarkers accompanied by symptoms, electrocardiographic, angiographic, or imaging evidence of ischemia after PCI
4b	Stent thrombosis	Confirmed stent thrombosis in context of ischemia and dynamic cardiac biomarker changes
5	CABG-related MI	Rise in cardiac biomarkers accompanied by electrocardiographic, angiographic, or imaging evidence of ischemia after CABG

Abbreviations: CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention.

3. Traditional Medical Therapies That Reduce Cardiovascular Risk in Type 1 MI Need Validation in Type 2 MI

Although the benefits of antiplatelet agents, β -blockers, and statins have been demonstrated among patients with type 1 MI, the utility of these medications among patients with type 2 MI remains uncertain. Currently, patients with type 2 MI are less likely to be discharged while taking these cardioprotective agents.³ While it would be reasonable to assume that these medications are beneficial in patients with type 2 MI, this may not necessarily be the case. In the prospective CASABLANCA (Catheter Sampled Blood Archive in Cardiovascular Diseases) study, approximately 80% of patients received aspirin, statin, and β -blocker therapies prior to their type 2 MI diagnosis.⁵ Further, with a 1-year mortality rate of approximately 22%, it is also possible that patients with type 2 MI may not benefit from these cardioprotective therapies during this timeline. Thus, randomized clinical trials investigating the utility of traditional MI therapies in this cohort are needed.

4. Non-Vitamin K Antagonist Oral Anticoagulants

Recently, the MANAGE (Management of Myocardial Injury After Non-cardiac Surgery) trial randomized 1754 patients with myocardial injury after noncardiac surgery to dabigatran, 110 mg twice daily, vs

placebo.⁷ Most patients had myocardial injury absent a diagnosis of MI, although approximately 19% had an MI (most likely type 2 MI).⁷ In this trial, dabigatran was associated with lower major vascular event rates compared with placebo (11% vs 15%; $P = .01$), with similar bleeding complications (3% vs 4%; $P = .76$), suggesting a potential benefit of oral anticoagulation in patients with type 2 MI. Nevertheless, these results should be interpreted with caution because the trial was terminated early, the primary outcome definition was changed midway through the trial, and rates of therapy discontinuation were also high (>40%). Additional trials investigating the utility of these agents in patients with type 2 MI may be informative.

5. Coronary Artery Revascularization

Reported prevalence of coronary artery disease among patients with type 2 MI varies with study design, with estimates of coronary disease ranging from 36% to 78%.³ With an estimated 30% of patients with type 2 MI experiencing major adverse cardiovascular events at 5 years, it is plausible that coronary revascularization could be beneficial in those with obstructive coronary disease. This is an untested theory that requires investigation.

6. Health Policy Initiatives

Currently, patients with type 2 MI are included in the HRRP. It is possible that inclusion of this cohort in the program may improve post-discharge quality of care. Yet to date, this has not been studied, and the inclusion of type 2 MI in the HRRP could be harmful if rehospitalization of complex medical patients is inappropriately circumvented to avoid financial penalties.

Conclusions

Type 2 MI is prevalent and its detection is expected to increase with the recent introduction of high-sensitivity troponin assays and specific administrative coding. This clinical entity appears to be associated with excess financial expenditures and important health implications. Broad-scale efforts are needed to improve its definition, better understand its biological underpinnings, and ultimately identify effective management approaches. Without such focus, this increasingly common diagnosis will continue to be beset by a lack of effective strategies to lower the considerable associated risk for mortality.

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