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Effect of Definition on Incidence and Prognosis of Type 2 Myocardial Infarction

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ABSTRACT

BACKGROUND Uncertainties regarding the most appropriate definition and treatment of type 2 myocardial infarction (T2MI) due to supply-demand mismatch have contributed to inconsistent adoption in clinical practice.

OBJECTIVES This study sought a better understanding of the effect of the definition of T2MI on its incidence, treatment, and event-related mortality, thereby addressing an important unmet clinical need.

METHODS The final diagnosis was adjudicated in patients presenting with symptoms suggestive of myocardial infarction by 2 independent cardiologists by 2 methods: 1 method required the presence of coronary artery disease, a common interpretation of the 2007 universal definition ($T2MI_{2007}$); and 1 method did not require coronary artery disease, the 2012 universal definition ($T2MI_{2012}$).

RESULTS Overall, 4,015 consecutive patients were adjudicated. The incidence of T2MI based on the $T2MI_{2007}$ definition was 2.8% ($n = 112$). The application of the more liberal $T2MI_{2012}$ definition resulted in an increase of T2MI incidence of 6% ($n = 240$), a relative increase of 114% (128 reclassified patients, defined as $T2MI_{2012reclassified}$). Among $T2MI_{2007}$, 6.3% of patients received coronary revascularization, 22% dual-antiplatelet therapy, and 71% high-dose statin therapy versus 0.8%, 1.6%, and 31% among $T2MI_{2012reclassified}$ patients, respectively (all $p < 0.01$). Cardiovascular mortality at 90 days was 0% among $T2MI_{2012reclassified}$, which was similar to patients with noncardiac causes of chest discomfort (0.2%), and lower than $T2MI_{2007}$ (3.6%) and type 1 myocardial infarction (T1MI) (4.8%) ($T2MI_{2012reclassified}$ vs. $T2MI_{2007}$ and T1MI: $p = 0.03$ and 0.01, respectively).

CONCLUSIONS $T2MI_{2012reclassified}$ has a substantially lower event-related mortality rate compared with $T2MI_{2007}$ and T1MI. (Advantageous Predictors of Acute Coronary Syndromes Evaluation [APACE] Study; NCT00470587) (J Am Coll Cardiol 2017;70:1558–68) © 2017 by the American College of Cardiology Foundation.

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Myocardial infarction (MI) is an acute ischemic event associated with cardiomyocyte injury and associated with substantial mortality (1,2). The early detection and treatment of MI is essential; immediate rhythm monitoring, early revascularization, dual-antiplatelet therapy (DAPT), and high-dose statins have all been shown to improve patient outcomes and therefore are uniformly recommended in current clinical practice guidelines (1,3). The introduction of the universal definition of MI 17 years ago has contributed to standardization and harmonization of treatments of MI worldwide.

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Recently, it was recognized that beyond MI secondary to plaque rupture or fissure, other pathophysiological processes may lead to ischemic cardiomyocyte injury, including oxygen supply demand mismatch (e.g., due to anemia or tachyarrhythmias). Since 2007, such MIs are called type 2 myocardial infarction (T2MI) (4). Uncertainties regarding the most appropriate definition and therapeutic consequences of T2MI have contributed to inconsistent and only limited adoption in clinical practice (5–8). Perhaps the most important controversy relates to the question of whether T2MI should require the presence of coronary artery disease (CAD) or not (9,10). Although this was a possible interpretation of the 2007 universal definition, the third universal definition published in 2012 highlighted that patients without CAD may also have cardiomyocyte injury from supply-demand mismatch, and suggested that these events should also be labeled T2MI (then reclassified patients, defined as $T2MI_{2012reclassified}$). Unfortunately, the characteristics of these reclassified patients, the therapeutic consequences, and most importantly, the mortality possibly directly related to $T2MI_{2012reclassified}$ are poorly understood.

We therefore performed a large multicenter diagnostic study with central adjudication to address this major gap in knowledge and to contribute to a better understanding of $T2MI_{2012reclassified}$.

METHODS

PATIENT POPULATION. APACE (Advantageous Predictors of Acute Coronary Syndrome Evaluation) is an ongoing prospective international multicenter study with 12 centers in 5 European countries designed to contribute to improving the management of patients with MI (NCT00470587) (11–15). Adult patients presenting to the emergency department (ED) with symptoms suggestive of MI (such as acute chest discomfort and angina pectoris) with an onset or peak within the previous 12 h were recruited. Enrollment was independent from renal function at presentation, although patients with terminal renal failure on chronic dialysis were excluded. For this analysis, patients were also excluded if the final diagnosis remained unclear after adjudication. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients.

The authors designed the study, and gathered and analyzed the data according to the STARD guidelines (16) for studies of diagnostic accuracy (Online Table 1).

CLINICAL ASSESSMENT. All patients underwent a clinical assessment with a standardized and detailed medical history including 34 pre-defined chest pain characteristics, vital signs, physical examination, 12-lead electrocardiography (ECG), continuous ECG rhythm monitoring, pulse oximetry, standard blood test, and chest radiography if indicated. Levels of cardiac troponin (cTn), including high-sensitivity (hs) cTn in some centers, were measured at presentation and serially thereafter as long as clinically indicated. Treatment of patients was left to the discretion of the attending physician.

ADJUDICATED FINAL DIAGNOSIS. Two independent cardiologists reviewed all available medical records—patient history, physical examination, results of laboratory testing, radiological testing, ECG, echocardiography, cardiac exercise stress test, lesion

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

ECG = electrocardiography

ED = emergency department

hs-cTn = high-sensitivity cardiac troponin

PCI = percutaneous coronary intervention

T1MI = type 1 myocardial infarction

$T2MI_{2007}$ = type 2 myocardial infarction 2007 definition

$T2MI_{2012}$ = type 2 myocardial infarction 2012 definition

$T2MI_{2012reclassified}$ = type 2 myocardial infarction reclassified per 2012 definition

Vaduz, University of Basel, and the Department of Internal Medicine, University Hospital Basel; and has received speaker honoraria from Brahms and Roche. Dr. Mueller has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, the KTI, the Stiftung für kardiovaskuläre Forschung Basel, Abbott, Alere, AstraZeneca, Beckman Coulter, Biomerieux, Brahms, Roche, Siemens, Singulex, Sphingotec, and the Department of Internal Medicine, University Hospital Basel; and has received speaker/consulting honoraria from Abbott, Alere, AstraZeneca, Biomerieux, Boehringer Ingelheim, Bristol-Myers Squibb, Brahms, Cardiorentis, Novartis, Roche, Siemens, and Singulex. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Nestelberger and Boeddinghaus contributed equally to this work.

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severity, and morphology in coronary angiography—from the time of ED presentation to 90-day follow-up. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist. Adjudication of the final diagnosis was performed centrally in the core laboratory (University Hospital, Basel) and included 2 sets of serial cTn measurements: serial cTn measurements obtained as part of routine clinical care locally (different hs-cTn assays), and serial measurements of high-sensitivity cardiac troponin T (hs-cTnT) from study blood draws performed centrally in the core laboratory to take advantage of the higher sensitivity and higher overall diagnostic accuracy offered by hs-cTnT (17).

MI was defined and hs-cTn levels were interpreted as recommended in current guidelines (4). In brief, MI was diagnosed when there was evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Myocardial necrosis was diagnosed by at least 1 hs-cTnT value above the 99th percentile, together with a significant rise and/or fall. Absolute changes in hs-cTnT were used to determine significant changes based on the diagnostic superiority of absolute over relative changes (18,19). Based on studies of the biological variation of cTnT (20,21), as well as on data from previous chest pain cohort studies (22–24), a significant absolute change was defined as a rise or fall of at least 10 ng/l within 6 h, or 6 ng/l within 3 h.

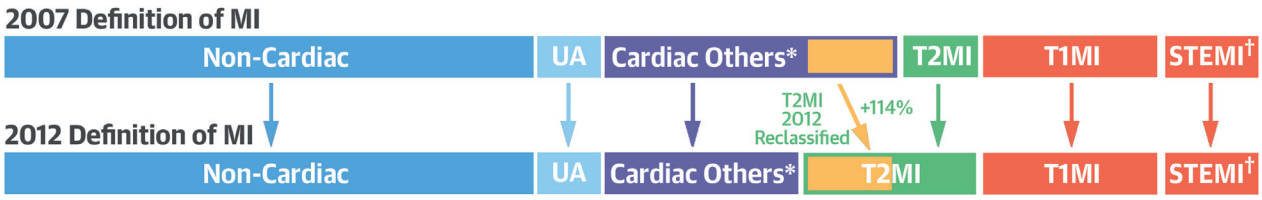
STUDY DEFINITIONS. In addition to the evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia, T1MI was defined as spontaneous MI related to ischemia due to a primary coronary event such as a plaque erosion or rupture, intraluminal coronary thrombus, distal microembolization, or coronary artery dissection (1). $T2MI_{2007}$ was defined, according to the second universal definition of MI (4), as MI secondary to ischemia with known or newly diagnosed CAD. Presence of CAD was adjudicated based on history of T1MI, history of coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention [PCI]), coronary angiography or coronary computed tomography showing a coronary artery diameter stenosis of at least 50%, cardiac imaging showing a myocardial scar, or cardiac imaging documenting exercise-inducible myocardial ischemia. Information obtained from a detailed predefined case report form in the ED in all patients, obtained during the inpatient and outpatient work-up related to the current event, and that became available during follow-up has been used for adjudication (25,26). Conditions reflecting an imbalance between myocardial oxygen supply and demand in the presence of CAD included but were not limited to coronary artery spasm, coronary embolism or vasculitis, bradyarrhythmias or tachyarrhythmias, severe respiratory failure, hypertension with or without left ventricular hypertrophy, and severe anemia. $T2MI_{2012}$ required the same criteria as $T2MI_{2007}$, but not the presence of CAD. Patients fulfilling only the $T2MI_{2012}$ but not the $T2MI_{2007}$ definition, and therefore considered reclassified patients, were analyzed as a separate group ($T2MI_{2012reclassified}$; $T2M1_{2012} = T2MI_{2007} + T2MI_{2012reclassified}$). To qualify for T2MI, the same dynamic changes in cTn were required as for T1MI (1,4).

In contrast, adjudication to "myocardial injury" was possible for both acute and chronic myocardial injury diagnosed when cTn blood concentrations were elevated above the 99th percentile, with or without dynamic changes, respectively, in the absence of overt myocardial ischemia (9,10). Myocardial injury included patients with myocarditis, Takotsubo cardiomyopathy, acute or chronic heart failure, valvular heart disease, cardiomyopathy, pulmonary embolism, pulmonary hypertension, septic shock, critical illness, ablation, cardioversion, cardiotoxic drugs, cardiac contusion, and rhabdomyolysis. The final adjudicated diagnosis, "cardiac others," included all "myocardial injury" patients and patients with the same underlying conditions as T2MI or myocardial injury patients, but without cTn elevation.

BLOOD SAMPLING AND LABORATORY METHODS. The limit of blank and limit of detection of the hs-cTnT assay (Elecsys 2010, Roche Diagnostics, Mannheim, Germany) were determined to be 3 and 5 ng/l, respectively. The 99th percentile of a healthy reference population was reported at 14 ng/l, with an imprecision corresponding to 10% coefficient of variation at 13 ng/l (27). Calculation of the estimated glomerular filtration rate was performed using the abbreviated Modification of Diet in Renal disease formula (28).

FOLLOW-UP AND CLINICAL ENDPOINTS. After hospital discharge, patients were followed up by telephone or in written form after 3, 12, and 24 months. Major adverse cardiovascular events were recorded by establishing contact with the patient and the family physician. Information regarding death was also obtained from the national mortality registry. To evaluate mortality possibly directly related to the index event, cardiovascular mortality at 90 days was assessed as the primary prognostic endpoint and was compared among the different diagnostic groups. To evaluate the use of therapies that have been

CENTRAL ILLUSTRATION **Definition of Type 2 Myocardial Infarction: Adjudicated Diagnoses**



Nestelberger, T. et al. J Am Coll Cardiol. 2017;70(13):1558–68.

Adjudicated final diagnoses in the whole cohort using the 2007 definition of MI **(top)** and the 2012 definition of MI **(bottom)**. $T2MI_{2012} = T2MI_{2007} + T2MI_{2012reclassified}$. These reclassifications led to a relative increase of 114% of T2MI patients at the expense of a decrease in patients classified as "myocardial injury" or "cardiac others." The proportion of the final diagnoses is visualized by the size of the respective boxes. "Cardiac others" include, among others, myocarditis, Takotsubo cardiomyopathy, or tachyarrhythmias. "Noncardiac" refers to thoracic diseases such as pneumonia or pneumothorax. *The term "myocardial injury" is used in "cardiac others" patients if troponin elevation is present. †Only 1 patient with STEMI had T2MI. MI = myocardial infarction; STEMI = ST-segment elevation myocardial infarction; T1MI = type 1 myocardial infarction; T2MI = type 2 myocardial infarction; $T2MI_{2012reclassified}$ = type 2 myocardial infarction reclassified by 2012 definition; UA = unstable angina.

shown to improve outcomes in MI patients among the different T2MI definitions, the use of coronary revascularization, DAPT, and high-dose statins was assessed at hospital discharge.

STATISTICAL ANALYSIS. Data were expressed as median ± interquartile range for continuous variables, and as numbers and percentages for categorical variables. Baseline characteristics and outcomes between T1MI, $T2MI_{2007}$, $T2MI_{2012reclassified}$, and myocardial injury were compared by the Mann-Whitney *U* test for continuous variables and Pearson chi-square test for categorical variables. We did not adjust for multiple testing. Cardiovascular and all-cause mortality at 60, 90, and 120 days according to the adjudicated diagnosis were plotted in Kaplan-Meier curves, and the log-rank test was used for comparison of survival between groups.

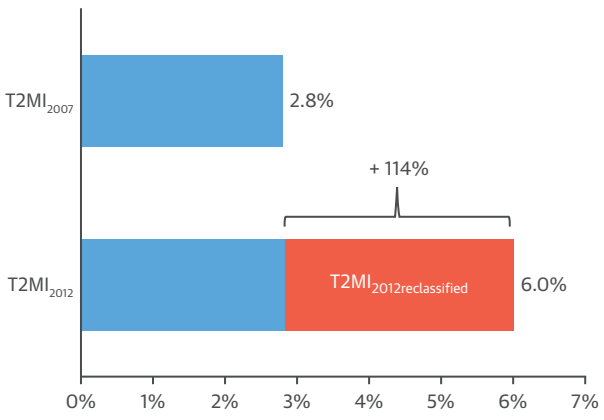
All hypothesis testing was 2-tailed, and p values <0.05 were considered to indicate statistical significance. All statistical analyses were performed with the use of IBM SPSS Statistics for Windows, version 24.0 (SPSS Inc., Chicago, Illinois).

RESULTS

PATIENT CHARACTERISTICS. From April 2006 to August 2015, a total of 4,015 patients were eligible for analysis (Online Figure 1). T1MI was the adjudicated final diagnosis in 684 (17%) patients. ST-segment elevation MI was present in 141 (21%) T1MI patients. The application of the more liberal $T2MI_{2012}$ definition resulted in an increase of T2MI incidence from 112 patients (2.8%, $T2MI_{2007}$) to 240 patients (6%), a relative increase of 114% (128 reclassified patients defined as $T2MI_{2012reclassified}$) (**Central Illustration, Figure 1**). The underlying pathophysiological mechanism in these reclassified patients with $T2MI_{2012reclassified}$ were: bradyarrhythmias (n = 10, relative change +167%), tachyarrhythmias (n = 73, +146%), hypertensive crisis (n = 38, +146%), 2 or more contributed equally (n = 2, +100%), severe respiratory failure (n = 1, +50%), others (n = 3, +38%), and severe anemia (n = 1, +17%) (**Figure 2**). The CAD work-up in the 128 $T2MI_{2012reclassified}$ patients is described in the Online Appendix.

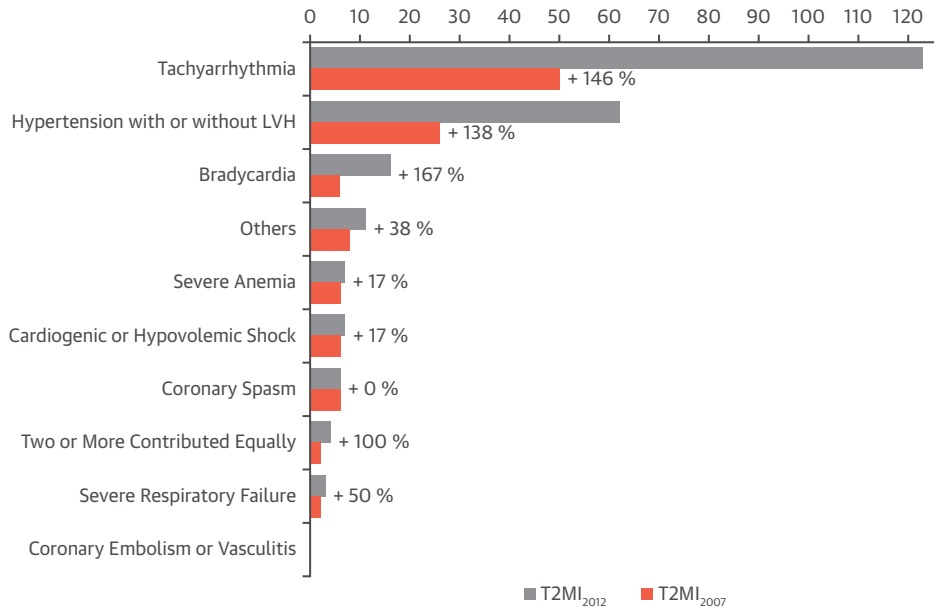
Using the $T2MI_{2007}$ definition, patients were older, and more often had pre-existing CAD, a lower

FIGURE 1 **Incidence of Type 2 Myocardial Infarction**



Bars representing the percentage of patients for each adjudicated final diagnosis for $T2MI_{2007}$ and $T2MI_{2012}$ ($T2MI_{2012} = T2MI_{2007} + T2MI_{2012reclassified}$). Using the 2012 definition led to a relative increase of 114% of T2MI patients. $T2MI_{2007}$ = type 2 myocardial infarction 2007 definition; $T2MI_{2012}$ = type 2 myocardial infarction 2012 definition.

FIGURE 2 Adjudicated Diagnoses in T2MI



Bars represent the number of patients for each adjudicated final diagnosis for T2MI ($T2MI_{2007}$ and $T2MI_{2012}$). Percentages represent the relative increase of patients using the 2012 definition. LVH = left ventricular hypertension; T2MI = type 2 myocardial infarction; other abbreviations as in Figure 1.

creatinine clearance, and a left bundle branch block in the presenting ECG compared with T1MI patients (Table 1). $T2MI_{2012reclassified}$ patients were slightly younger, were more often female, and had a lower rate of cardiovascular risk factors and previous cardiac diseases compared with $T2MI_{2007}$ and T1MI patients. Although $T2MI_{2007}$ accounted only for a small proportion of all T2MI patients in young patients, $T2MI_{2007}$ represented more than one-half of T2MI patients in the elderly (Figure 3).

IN-HOSPITAL PROCEDURES. A total of 76% of patients with T1MI underwent coronary revascularization (PCI or coronary artery bypass grafting) versus 6.3% and 0.8% of patients with $T2MI_{2007}$ and $T2MI_{2012reclassified}$, respectively. $T2MI_{2007}$ patients were more often on antihypertensive agents, beta-blockers, or statins at presentation compared with T1MI patients, although this relationship reversed after discharge. Among patients with $T2MI_{2007}$, 22% were discharged on DAPT compared with 1.6% in patients with $T2MI_{2012reclassified}$ ($p < 0.001$). $T2MI_{2012reclassified}$ patients had a lower rate of former cardiovascular medication as well as after discharge compared with T1MI and $T2MI_{2007}$ patients, respectively (Table 2).

INCIDENCE OF MYOCARDIAL INJURY. Myocardial injury occurred in 172 (4.3%) of all patients. The main adjudicated final diagnoses were acute or chronic heart failure (n = 82, 47%), myocarditis (n = 33, 19%), pulmonary embolism (n = 24, 14%), Takotsubo cardiomyopathy (n = 8, 5%), aortic dissection (n = 4, 2%), and others (n = 2, 1%) (Online Tables 2 and 3).

hS-cTnT PLASMA CONCENTRATION. Boxplots of hs-cTnT plasma concentrations quantifying the extent of cardiomyocyte injury at presentation and absolute changes within 1 h are depicted in Figure 4 for T1MI, $T2MI_{2007}$, $T2MI_{2012reclassified}$, myocardial injury, and noncardiac causes of chest pain. Overall, hs-cTnT plasma concentrations were highest in patients with T1MI and lowest in patients with $T2MI_{2012reclassified}$ or noncardiac causes of acute chest discomfort. The median baseline values were 63 ng/l in T1MI, 28 ng/l in $T2MI_{2007}$, 22 ng/l in $T2MI_{2012reclassified}$, 33 ng/l in patients diagnosed with myocardial injury, and 5 ng/l in patients with noncardiac causes of chest pain ($p = 0.005$ between $T2MI_{2012reclassified}$ and $T2MI_{2007}$; and $p < 0.001$ between $T2MI_{2012reclassified}$ and myocardial injury). Absolute changes within 1 h was highest in T1MI (10 ng/l) and significantly higher compared with $T2MI_{2007}$ (3 ng/l), $T2MI_{2012reclassified}$ (2 ng/l), myocardial injury (1.7 ng/l), and noncardiac causes

TABLE 1 Baseline Characteristics for Differentiation Between T1MI, $T2MI_{2007}$, and $T2MI_{2012reclassified}$

	All Patients (N = 4,015)	T1MI (n = 684)	$T2MI_{2007}$ (n = 112)	$T2MI_{2012reclassified}$ (n = 128)	p Values		
					T1MI/$T2MI_{2007}$	T1MI/$T2MI_{2012reclassified}$	$T2MI_{2007/2012reclassified}$
Age, yrs	61 (49-74)	70 (58-79)	76 (66-81)	72 (58-81)	0.001	0.642	0.030
Male	2,708 (67.0)	498 (73.0)	80 (71.0)	68 (53.0)	0.762	<0.001	0.004
BMI, kg/m^2	26 (24-30)	27 (24-30)	26 (24-28)	26 (24-30)	0.027	0.754	0.149
Risk factors							
Hypertension	2,463 (61.0)	521 (76.0)	90 (80.0)	92 (72.0)	0.331	0.300	0.126
Hypercholesterolemia	1,958 (49.0)	440 (64.0)	78 (70.0)	46 (36.0)	0.274	<0.001	<0.001
Diabetes	697 (17.0)	180 (26.0)	29 (26.0)	26 (20.0)	0.925	0.152	0.305
Current smoking	1,032 (26.0)	181 (27.0)	21 (19.0)	21 (16.0)	0.082	0.016	0.634
History of smoking	1,471 (37.0)	277 (41.0)	51 (46.0)	41 (32.0)	0.315	0.072	0.032
Medical history							
Coronary artery disease	1,319 (33.0)	283 (41.0)	86 (77.0)	0 (0.0)	<0.001	<0.001	<0.001
Previous myocardial infarction	933 (23.0)	215 (31.0)	58 (52.0)	0 (0.0)	<0.001	<0.001	<0.001
Previous revascularization	1,077 (27.0)	219 (32.0)	64 (57.0)	0 (0.0)	<0.001	<0.001	<0.001
Peripheral artery disease	219 (5.5)	72 (11.0)	20 (18.0)	2 (1.6)	0.024	0.001	<0.001
Previous stroke	215 (5.4)	52 (7.6)	13 (12.0)	5 (3.9)	0.151	0.133	0.024
Positive cardiovascular family history	639 (17.0)	133 (22.0)	14 (14.0)	15 (13.0)	0.066	0.027	0.828
Biochemistry							
Hemoglobin, g/l	143 (132-153)	143 (131-154)	135 (118-146)	143 (125-155)	<0.001	0.997	0.002
BNP, pg/ml	82 (29-221)	168 (72-429)	322 (104-630)	162 (50-312)	0.120	0.090	0.006
Creatinine clearance (MDRD), $ml/min/m^2$	85 (69-101)	76 (60-96)	66 (49-84)	71 (58-91)	<0.001	0.101	0.063
ECG findings							
Left bundle branch block	140 (3.5)	34 (5.1)	12 (11.0)	9 (7.0)	0.016	0.367	0.293
ST-segment elevation	184 (4.7)	115 (17.0)	2 (1.8)	4 (3.1)	<0.001	<0.001	0.514
ST-segment depression	476 (12.0)	234 (35.0)	28 (25.0)	33 (26.0)	0.044	0.043	0.922
T-wave inversion	482 (12.0)	167 (24.0)	23 (21.0)	17 (13.0)	0.372	0.006	0.132
No significant ECG abnormalities	2,928 (73.0)	284 (42.0)	61 (55.0)	74 (58.0)	0.010	0.001	0.602
In-hospital procedures							
Coronary angiography	1,047 (26.0)	582 (85.0)	35 (31.0)	23 (18.0)	<0.001	<0.001	0.016
Percutaneous coronary intervention	636 (16.0)	457 (67.0)	6 (5.4)	1 (0.8)	<0.001	<0.001	0.019
CABG	86 (2.1)	59 (8.6)	1 (0.9)	0 (0.0)	0.004	0.001	0.284
Ergometry	928 (23.0)	127 (19.0)	25 (22.0)	25 (20)	0.349	0.797	0.595
Myocardial perfusion scanning	397 (9.9)	44 (6.4)	18 (16.0)	12 (9.4)	<0.001	0.228	0.118
Procedure performed after discharge until 90 days of follow-up							
Revascularization	448 (11.0)	244 (36.0)	9 (8.0)	0 (0.0)	<0.001	<0.001	0.001
Functional stress testing	463 (12.0)	50 (7.3)	7 (6.0)	14 (11.0)	0.687	0.162	0.200

Values are median (interquartile range) or n (%), unless otherwise indicated.

BMI = body mass index; BNP = B-type natriuretic peptide; CABG = coronary artery bypass graft; ECG = electrocardiography; MDRD = abbreviated Modification of Diet in Renal Disease; T1MI = type 1 myocardial infarction; T2MI = type 2 myocardial infarction; $T2MI_{2007}$ = type 2 myocardial infarction 2007 definition; $T2MI_{2012reclassified}$ = type 2 myocardial infarction reclassified per 2012 definition.

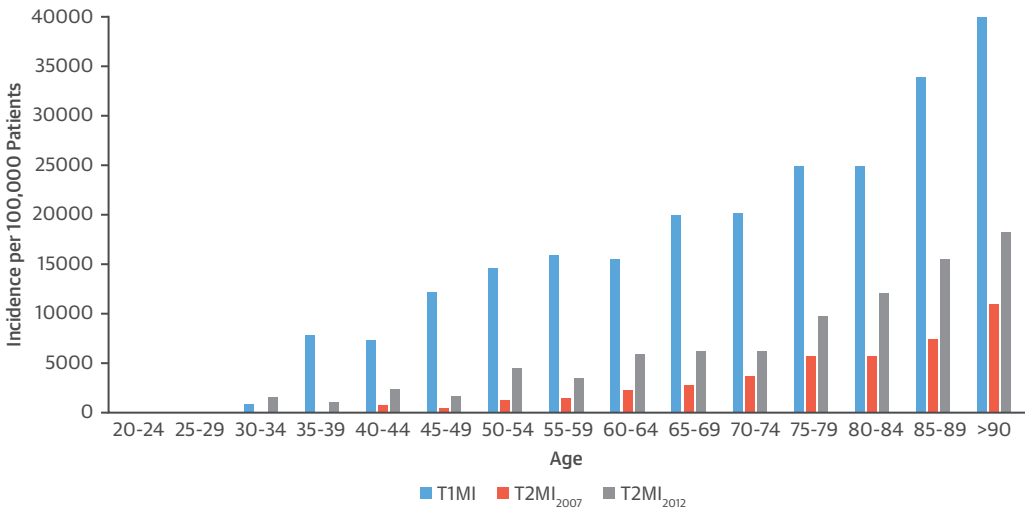
(0.2 ng/l; $p < 0.001$ for comparison between T1MI and all other groups).

MORTALITY. There were 33 cardiovascular deaths (4.8%) within 90 days among 684 T1MI patients, 4 deaths (3.7%) among 112 patients with $T2MI_{2007}$, no deaths (0%) among 128 patients with $T2MI_{2012reclassified}$, 4 deaths (1.7%) among 240 patients with $T2MI_{2012}$ ($T2MI_{2007}$ and $T2MI_{2012reclassified}$ patients together), 2 deaths (1.2%) among 172 patients with myocardial injury, and 4 deaths (0.2%) among patients with noncardiac causes of chest pain (Table 3). The 90-day mortality was significantly lower in $T2MI_{2012reclassified}$ compared with $T2MI_{2007}$ and T1MI (p by log rank test = 0.03 and 0.01, respectively) (Figure 5). Sensitivity analysis showed similar findings in cardiovascular and all-cause mortality at 60 and 120 days (Table 3).

DISCUSSION

The clinical implementation of hs-cTn has increased the number of patients detected to have other causes of cardiomyocyte injury than T1M1, including T2MI. This large, multicenter diagnostic study using central adjudication aimed to address an important unmet clinical need: to better understand of the effect of the definition of T2MI on its incidence, treatment

FIGURE 3 Incidence Per 100,000 Patients



Bars represent incidence per 100,000 patients for T1MI and T2MI ($T2MI_{2007}$ and $T2MI_{2012}$) for each age group. T1MI = type 1 myocardial infarction; other abbreviations as in Figure 1.

pattern, and event-related mortality. We reported 6 major findings.

First, applying the more liberal 2012 universal definition of T2MI more than doubled the incidence of T2MI compared with the interpretation of the 2007 universal definition requiring the presence of CAD. This occurred by reclassifying patients from myocardial injury due to primarily non-CAD causes, including tachyarrhythmias to T2MI. Second, in the ED setting of patients presenting with chest pain, the vast majority of MI patients was still found to have T1MI, independent of the definition used for T2MI

TABLE 2 Medication at Admission and at Discharge

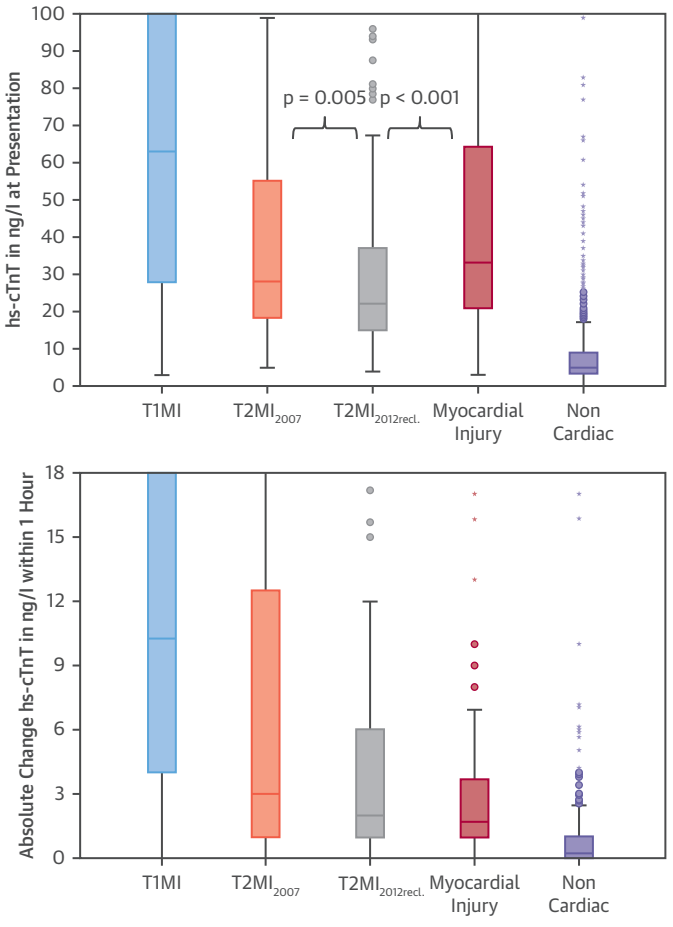
	All Patients (N = 4,015)	T1MI (n = 684)	$T2MI_{2007}$ (n = 112)	$T2MI_{2012reclassified}$ (n = 128)	p Values		
					$T1MI/T2MI_{2007}$	$T1MI/T2MI_{2012reclassified}$	$T2MI_{2007/2012reclassified}$
Medication at admission							
Aspirin	1,434 (36.0)	319 (47.0)	59 (53.0)	30 (23.0)	0.235	<0.001	<0.001
$P2Y_{12}$ inhibitors	441 (11.0)	85 (12.0)	21 (19.0)	2 (1.6)	0.068	<0.001	<0.001
Aspirin and $P2Y_{12}$ inhibitors	329 (8.2)	68 (9.9)	12 (11.0)	1 (0.8)	0.801	<0.001	0.001
Marcoumar/warfarin	389 (10.0)	53 (7.7)	27 (24.0)	17 (13.0)	<0.001	0.041	0.031
ACE/AT2 inhibitors	1,561 (39.0)	334 (49.0)	69 (62.0)	59 (46.0)	0.012	0.570	0.016
Beta-blockers	1,365 (34.0)	261 (38.0)	66 (59.0)	45 (35.0)	<0.001	0.520	<0.001
Ca-antagonists	589 (15.0)	127 (19.0)	16 (14.0)	21 (16.0)	0.274	0.561	0.650
Nitrates	413 (10.0)	106 (16.0)	20 (18.0)	7 (5.5)	0.526	0.003	0.002
Statins	1,399 (35.0)	278 (41.0)	68 (61.0)	29 (23.0)	<0.001	<0.001	<0.001
Medication at discharge							
Aspirin	1,922 (48.0)	619 (91.0)	66 (59.0)	36 (28.0)	<0.001	<0.001	<0.001
$P2Y_{12}$ inhibitors	1,011 (25.0)	523 (77.0)	35 (31.0)	4 (3.1)	<0.001	<0.001	<0.001
Aspirin and $P2Y_{12}$ inhibitors	910 (23.0)	509 (74.0)	25 (22.0)	2 (1.6)	<0.001	<0.001	<0.001
Marcoumar/warfarin	542 (14.0)	81 (12.0)	41 (37.0)	37 (29.0)	<0.001	<0.001	0.204
ACE/AT2 inhibitors	1,910 (48.0)	546 (80.0)	77 (69.0)	70 (55.0)	0.008	<0.001	0.026
Beta-blockers	1,836 (46.0)	548 (80.0)	83 (74.0)	72 (56.0)	0.146	<0.001	0.004
Ca-antagonists	674 (17.0)	124 (18.0)	24 (21.0)	29 (23.0)	0.405	0.229	0.819
Nitrates	556 (14.0)	168 (29.0)	24 (21.0)	13 (10.0)	0.473	<0.001	0.016
Statins	1,923 (48.0)	606 (89.0)	80 (71.0)	39 (31.0)	<0.001	<0.001	<0.001

Values are n (%) unless otherwise indicated.
ACE/AT2 = angiotensin-converting enzyme/angiotensin 2; Ca = calcium; other abbreviations as in Table 1.

(86% vs. 70% using the 2007 or the 2012 definition, respectively). This observation extends and corroborates findings from previous pilot studies (5). The observed variations in the relative frequency of T1MI versus T2MI most probably reflect methodological differences, including patient population and the heterogeneity in the diagnostic criteria applied (29,30). Third, reclassified patients ($T2MI_{2012reclassified}$) differed in several characteristics from patients with T1MI or $T2MI_{2007}$, including a lower prevalence of pre-existing cardiovascular diseases and cardiovascular risk factors. Fourth, in-hospital management of reclassified patients with $T2MI_{2012reclassified}$ focused on the correction of the trigger of supply-demand mismatch, such as hypotension, hypertension, tachycardia, or anemia, and only included coronary revascularization in <1%. This supports the concept that the optimal treatment for T2MI will depend on the underlying cause of the supply-demand mismatch and is fundamentally different from T1MI (5,6). Fifth, the extent of cardiomyocyte injury as quantified by plasma concentrations of hs-cTnT was substantially lower in reclassified patients with $T2MI_{2012reclassified}$ compared with patients with $T2MI_{2007}$, and even more so in comparison to patients with T1MI. This finding extends previous studies documenting the important role of CAD as a modifier of the individual patient response to myocardial supply-demand mismatch (31). Sixth, and likely of most clinical importance, cardiovascular mortality at 90 days as a proxy of event-related mortality was very low (0%) among $T2MI_{2012reclassified}$ patients; this value was similar to patients with noncardiac causes of chest discomfort (0.2%) and was much lower than patients with $T2MI_{2007}$ (3.6%) and T1MI (4.8%). Of note, our adjudication underlying this analysis strictly adhered to the line of thought provided by the universal definition of MI, emphasizing that the mechanisms of cardiomyocyte injury in patients with heart failure are usually multifactorial and that patients with acute heart failure represent a specific patient phenotype that should not be included in the T2MI category (1,4,32). Some of the previous studies, which had found a higher long-term mortality in T2MI compared with T1MI patients, had included additional patients, for example, those with acute heart failure, in the T2MI category (6,7,30,31,33–36).

These findings corroborate and extend previous studies documenting that patients with T2MI represent a heterogeneous group of patients with substantial diversity in both baseline characteristics and the triggering condition (3,29,36,37). Our findings are well in line with previous studies, and strengthen the concept that T2MI patients, when classified according to the common interpretation of the more restrictive second universal definition of MI ($T2MI_{2007}$) requiring the presence of CAD, are older, have a greater number of comorbidities, and have high cardiovascular mortality (36,38). Bonaca et al. (38) reported that among 1,118 patients with an acute coronary syndrome treated with PCI, 42 patients (3.7%) developed T2MI and had a cardiovascular death rate at 180 days of 7.3%, which was similar to patients who developed recurrent T1MI (8.3%) during follow-up. Gaggin et al. (36) followed 1,251 patients who had undergone invasive procedures for a median of 3.4 years. During

FIGURE 4 Plasma Concentrations of hs-cTnT



Boxplots of high-sensitivity cardiac troponin T (hs-cTnT) in ng/l at presentation and absolute (unsigned) changes within 1 h for T1MI, $T2MI_{2007}$, $T2MI_{2012reclassified}$, myocardial injury, and noncardiac causes of chest pain. **Boxes** represent medians and interquartile ranges (IQRs), **whiskers** display the smallest and the largest nonoutlier, **circles** indicate outliers further than 1.5 IQRs, and **asterisks** indicate outliers further than 3 IQRs from the respective end of the box. $T2MI_{2012recla.}$ = type 2 myocardial infarction reclassified per 2012 definition; other abbreviations as in Figures 1 and 3.

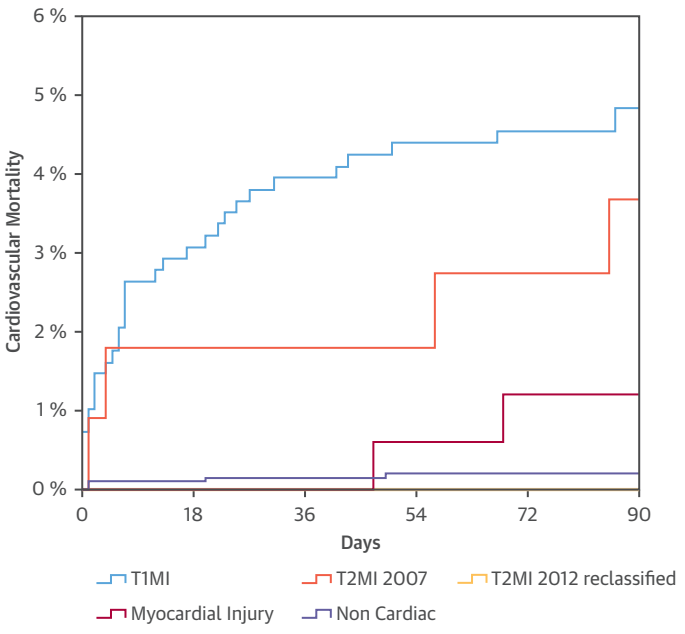
TABLE 3 Number of Deaths and Mortality Within 60, 90, and 120 Days of Follow-Up

	60 Days		90 Days		120 Days	
	Deaths (n)	Mortality (%)	Deaths (n)	Mortality (%)	Deaths (n)	Mortality (%)
Cardiovascular causes of death						
T1MI	30	4.4	33	4.8	36	5.3
$T2MI_{2007}$	3	2.7	4	3.7	4	3.7
$T2MI_{2012reclassified}$	0	0.0	0	0.0	0	0.0
$T2MI_{2012}$	3	1.3	4	1.7	4	1.7
Myocardial injury	1	0.6	2	1.2	3	1.8
Noncardiac causes	4	0.2	4	0.2	4	0.2
All-cause death						
T1MI	34	5.0	38	5.6	42	6.2
$T2MI_{2007}$	8	7.2	10	9.0	10	9.0
$T2MI_{2012reclassified}$	1	0.8	1	0.8	1	0.8
$T2MI_{2012}$	9	3.8	11	4.6	11	4.6
Myocardial injury	5	2.9	9	5.3	10	5.9
Noncardiac causes	10	0.5	14	0.7	17	0.8

$T2MI_{2012}$ = type 2 myocardial infarction 2012 definition; other abbreviations as in Table 1.

follow-up, 16.5% of patients had at least 1 MI, and of these patients, 73.8% had at least 1 incident T2MI. T2MI was frequently recurrent (36.8% had more than 1 T2MI) and was associated with a substantial increase in cardiovascular mortality. In these studies, all patients (as in Bonaca et al. [38]) or nearly all patients (as in Gaggin et al. [36]) had known or newly diagnosed CAD.

FIGURE 5 Kaplan-Meier Curves for the Cumulative Survival According to T1MI and T2MI



Kaplan-Meier curves displaying cardiovascular survival during 90 days of follow-up in the cohort according to the classification into T1MI, $T2MI_{2007}$, $T2MI_{2012reclassified}$, myocardial injury, and noncardiac causes of chest pain. Differences in survival were assessed using the log-rank test ($T2MI_{2012reclassified}$ compared with $T2MI_{2007}$ [p = 0.03] and T1MI [p = 0.01], respectively). Abbreviations as in Figures 1, 3, and 4.

T2MI is triggered by many heterogeneous conditions. To increase the likelihood that a specific therapeutic strategy may still be found beneficial in patients with T2MI, the present study supports the use of the more restrictive $T2MI_{2007}$ definition that requires the presence of CAD. These patients may benefit from intensification of secondary prevention measures and possibly coronary revascularization.

In addition to biomarkers, the universal definition of MI requires specific symptoms, ECG changes, or imaging evidence of myocardial loss for all subtypes of MI. The adjudication of causes for T2MI is particularly challenging, because ischemic-related injury cannot easily be distinguished from nonischemic cardiac injury. Therefore, the clear delineation of a trigger including hypotension, hypertension, tachycardia, and anemia is key.

This study also highlights the uncertainty regarding the optimal treatment of T2MI, including the possible use of DAPT. A total of 22% of patients with $T2MI_{2007}$ were discharged on DAPT. Due to previous T1MI or PCI with a drug-eluting stent, about one-half of these patients were already on DAPT prior to the current event, whereas DAPT was initiated following $T2MI_{2007}$ in the remaining patients. Although DAPT would be contraindicated if bleeding has caused the supply-demand mismatch leading to T2MI, it is occasionally used by clinicians in the setting of other triggers and whenever diagnostic uncertainty remains between T2MI and T1MI.

Obviously, further studies are essential to finally develop evidence-based treatment strategies for T2MI, particularly as recent evidence suggested that T2MI often reoccurs (36). Further highlighting the difference between patients with $T2MI_{2007}$ and patients with $T2MI_{2012reclassified}$, DAPT was initiated in only 1.6% of the latter ($p < 0.001$ compared with $T2MI_{2007}$).

STUDY LIMITATIONS. First, our study was conducted in ED patients with symptoms suggestive of MI. Further studies are required to assess the incidence and prognosis of T2MI occurring in the perioperative setting or in critically ill patients. Second, this was a secondary analysis from a large ongoing multicenter study designed to improve the early diagnosis of MI. As such, no specific sample size calculation was performed. Although this secondary analysis from an ongoing multicenter study is 1 of the largest ever performed, it still may have been underpowered for some comparisons among the different groups. Third, although we used the most stringent methodology to adjudicate T2MI, including central adjudication by experienced cardiologists and serial measurements of hs-cTn, we still may have misclassified a small number of patients (1,18). Patients adjudicated to have T2MI might have actually had a T1MI. Such misclassification is inevitable in a small number of patients in the absence of imaging techniques available for routine clinical practice documenting plaque rupture and distal thromboembolism from the culprit coronary lesion. Furthermore, the misclassification of acute cardiac injury as T2MI might also have occurred; such acute cardiac injury is a poorly understood phenomenon, thought to occur via a noncoronary mechanism in many cases, but is similarly associated with poor prognosis (36). Fourth, in a small number of patients with $T2MI_{2012reclassified}$, the presence of underlying CAD may have been missed, as not all patients underwent coronary angiography and/or functional cardiac imaging. However, it is unlikely that these rare cases would have affected the findings of the present analysis. Fifth, this study required informed consent, which inevitably introduces a selection bias. By recruiting all consecutive patients presenting with any kind of chest discomfort as their main symptom to the ED irrespective of the pre-test probability of MI, we tried to ensure that this selection bias is minimal. Sixth, cardiovascular mortality was assessed at 90 days, as this was the pre-defined time point for the assessment of outcomes in APACE and as it seemed to appropriately balance the need for proximity to the event to support a causal relationship, as well as the need for a certain length of follow-up to allow enough events to occur. Although the selection of the 90-day interval at large was arbitrary, sensitivity analysis using 2 alternative intervals (60 and 120 days) revealed consistent findings. Seventh, we cannot generalize these findings to patients with terminal kidney failure requiring dialysis because they were excluded from this study.

CONCLUSIONS

Patients who are reclassified with acute cardiomyocyte injury due to supply-demand mismatch and who do not have underlying CAD ($T2MI_{2012reclassified}$), have substantially lower event-related mortality as compared with those with CAD ($T2MI_{2007}$). Their classification as "MI" may be misleading and should be reconsidered.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: The availability of hs-cTn assays has increased the frequency of diagnosis of T2MI among patients with substantial heterogeneity in baseline characteristics and provocative circumstances.

TRANSLATIONAL OUTLOOK: A more restrictive definition of T2MI that requires CAD could facilitate development of better management strategies and clarify the benefit of secondary prevention measures and coronary revascularization for patients who experience these events.

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KEY WORDS diagnosis, high-sensitivity cardiac troponin, type 2 myocardial infarction

APPENDIX For an expanded Results section, a list of additional APACE investigators and contributors, as well as supplemental tables and a figure, please see the online version of this article.