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ORIGINAL PAPER

Variations on classification of main types of myocardial infarction: a systematic review and outcome meta-analysis

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Abstract

Objective Classifying myocardial infarction into type 1 (T1MI) or type 2 (T2MI) remains a challenge in clinical practice. We aimed to identify factors contributing to variation in the classifications of MI into type 1 or type 2. In addition, pooled analyses of long-term mortality and reinfarction outcomes were performed.

Methods We searched Medline, Embase and Web of Science through January 2018 for observational studies or clinical trials classifying patients as either T1MI or T2MI. Studies with baseline characteristics allowing a comparison between both groups were included. Inverse variance random-effects models were used to pool risk ratios (RR).

Results Overall, 93,194 patients from 20 included observational studies were classified as T1MI and 9291 as T2MI; corresponding to 87.9% and 8.8% of all patients diagnosed with MI. Inclusion of ST-elevation MI patients was inconsistent among studies. Coronary angiography was performed in 77.7% and 31.5% of all patients with T1MI and T2MI, respectively. From a subgroup of 11 studies, percutaneous coronary intervention was performed in 79.2% of all patients classified as T1MI (range 44.2–93.0%) and 40.2% of all T2MI patients (range 0–87.5%). A meta-analysis of 6 studies (44,366 in total) on 2-year mortality showed worse outcome among T2MI patients (RR: 1.52, CI 1.07–2.17, $P=0.02$; $I^2=92\%$). Risk of reinfarction at 1.6 years was higher among T2MI patients (RR: 1.68, CI 1.22–2.31, $P=0.001$; $I^2=9\%$).

Conclusions Classification of T1MI and T2MI varies widely among studies. A standardized approach with clear definitions is needed to avoid misclassification and ensure appropriate patient management.

Keywords Type 1 myocardial infarction · Type 2 myocardial infarction · Acute coronary syndrome · Universal definition · Classification

Introduction

The Universal Definition of Myocardial Infarction consensus document recommends classifying myocardial infarction (MI) into five different types [1, 2]. From these, type 1 and type 2 MI (T1MI and T2MI, respectively) are most frequently identified. The differentiation among these subtypes, however, has been the subject of ongoing discussion and controversy [3–6].

The 2012 document version defined T1MI as being spontaneous, in relation to an atherosclerotic plaque event (e.g., rupture or ulceration) with consequent intraluminal thrombus [1]. The newly released 2018 version further emphasizes on the causal relationship of plaque disruption with coronary thrombosis [2]. T2MI, on the other hand, was described as myocardial injury with necrosis when a condition other than coronary artery disease (CAD) contributed to imbalance

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between myocardial oxygen supply and/or demand [1]. The 2018 version highlights the exclusion of coronary thrombus in this definition [2]. T2MI may, however, occur in patients with or without CAD.

In spite of the proposed classification, the proportion of MI subtypes varies widely across different studies [7–9]. These disparities may bring about important implications given that patients are expected to be managed invasive- or conservatively depending on whether they are classified as T1MI or T2MI. We thus aimed to systematically identify all publications providing baseline characteristics of both MI types to determine which factors (clinical criteria and/or use of certain auxiliary tests) may be contributing to variation in their classifications. In addition, we aimed to perform a pooled analysis of long-term mortality and reinfarction risks.

Methods

Data sources and study selection

We performed a comprehensive search on Medline, Embase and Web of Science through January 2018. The following keywords were combined: 'type 1 (or type 2) myocardial infarction', 'acute coronary syndrome', 'universal definition' and 'classification'. The search strategy for Medline is available online. We looked for observational or interventional studies in the English language since 2007 (year when the consensus document was first released) which classified and reported on baseline characteristics and outcomes for both T1MI and T2MI. We excluded reviews, comments, studies reporting on just one of two subgroups, records without baseline information limiting a comparison and reclassification of MI types; and those on MI types 3, 4 or 5 only.

Data extraction and study quality

Data extraction was performed by two independent investigators with disagreements resolved by consensus through a third reviewer. Using a predefined data extraction form, we collected information on author, site, country, publication year, cardiac troponin (cTn) assay used, percentage of patients with angiography results, and specified primary outcomes. We considered the study population as all patients attending a medical facility with suspected acute coronary syndrome (ACS) and in whom cTn was measured. When not reported, the total number of patients diagnosed with MI (irrespective of subclassification type) was calculated and presented as a percentage of its study population. Similarly, after extracting the number of T1MI and T2MI, they were shown as a fraction of all MI patients. Finally, we retrieved the percentage of male participants, risk factors, frequent comorbidities and diagnostic and management approaches for each MI subtype. Also extracted were mortality and adverse cardiovascular events during follow-up. The risk of study bias was assessed as proposed by the NIH Quality Assessment Tool and studies were rated as being of either good, fair or poor quality [10].

Statistical analysis

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and the meta-analysis of observational studies (MOOSE) guideline [11, 12]. Studies are presented by year of publication and data reported as percentages, means ± standard deviations (SD) or medians and interquartile ranges (IQR). Due to expected heterogeneity among studies, analyses on mortality were evaluated with DerSimonian-Laird random-effects models and the inverse variance method. Summary measures were calculated as risk ratios (RR) with 95% confidence intervals (CI). T1MI values were used as control groups. Heterogeneity across studies was examined by the the I^2 statistic (< 25%, low; >75%, high). Because < 10 studies were used in the meta-analyses, funnel plots were not used to evaluate publication bias. P values < 0.05 were considered statistically significant. All analyses were performed using Review Manager 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark 2014).

Results

The initial search identified a total of 852 records, including 4 through citation tracking. Following screening based on titles and abstracts, 41 articles were considered for full-text evaluation. Twenty studies met our inclusion criteria and were entered into the qualitative synthesis of this review; from these, 8 studies were used in the quantitative analysis. The selection process according to PRISMA is shown in Fig. 1.

General characteristics of included studies

Table 1 summarizes key characteristics of the included studies; all observational in design. Eleven were conducted in Europe, 7 in North America, 1 in Australia and 1 in the Middle East. Fifteen were single-center studies, 1 a multicenter and 4 were part of a nationwide survey/registry. Nine of the 20 studies stated the emergency department (ED) as their patient source; while most others recruited patients from more specialized departments such as cardiac and/or intensive care units. The study population ranged from 310 to 59,394 individuals [8, 13]. In aggregate, 93,194 patients

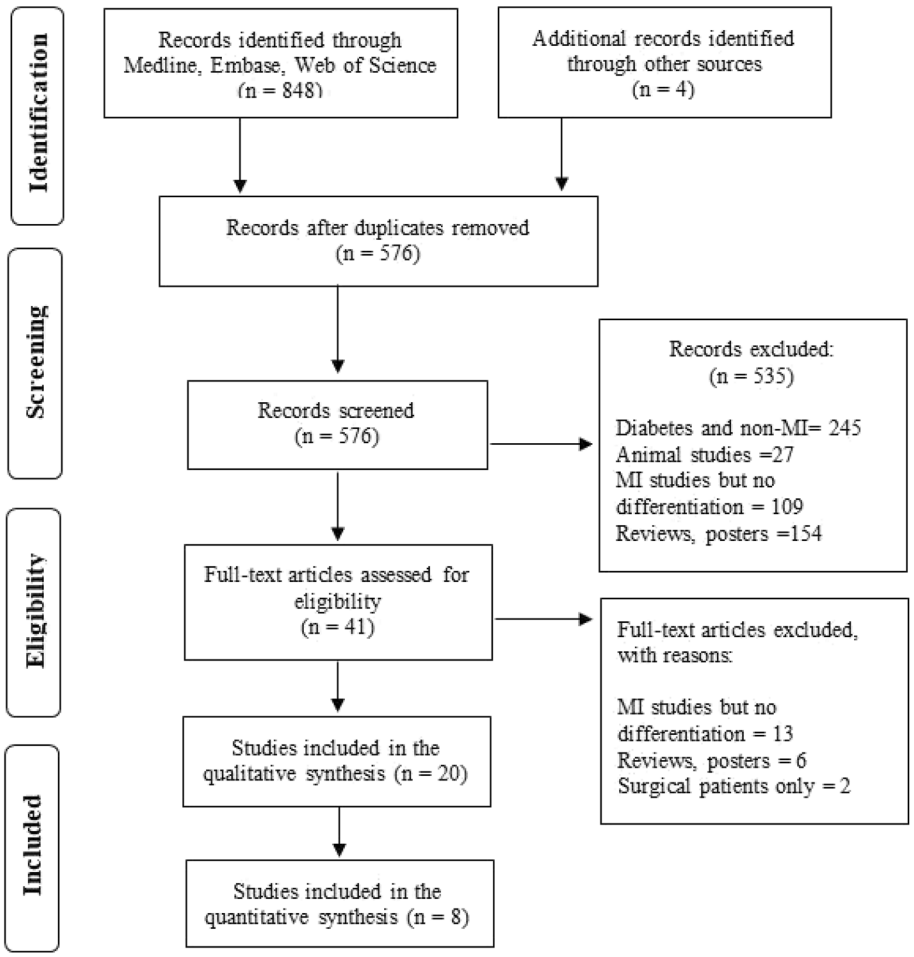


Fig. 1 PRISMA flow diagram of systematic review

were classified as T1MI and 9291 as T2MI; corresponding, respectively, to 87.9% and 8.8% of all patients diagnosed with MI (Fig. 2a).

Using the NIH Quality Assessment Tool, 10 studies were judged to be of good quality, 8 of fair quality and 2 of poor quality (Suppl. Table 6).

Diagnosis and classification of MI

As shown on Table 1, sixteen of the 20 studies included patients with ST-elevation myocardial infarction (STEMI); 2 excluded STEMI patients from their final analyses [19, 25], while 2 others did not report whether patients with ST-elevation on the electrocardiogram (ECG) were considered at all [17, 22]. The biomarker of preference was cTn; with 11 studies using conventional cTnI, 6 using high-sensitivity cTn, and 3 not reporting on troponin assay type used (Table 2).

The use of coronary angiography (CAG) was reported as an aid to diagnosis of MI in all but 3 studies [15, 19, 22]. Similarly, the process of classification of MI types was performed retrospectively in all but 3 studies [7, 8, 18]. Only when available, angiography results were considered in this classification procedure; however, description of angiographic findings themselves were largely unreported in the published studies. Overall, CAG was performed in 77.7% and 31.5% of all patients classified as having T1MI and T2MI, respectively (Fig. 2B).

We found that 11.9% (3381/28,497) of all patients with suspected ACS attended by emergency had MI as the underlying disease. However, 5 of the 9 studies conducted in the ED reported higher T1MI and consequently lower T2MI values [14, 23, 25, 26, 29]; while the remaining 4 reported an opposite proportion with lower T1MI and thus higher T2MI [13, 19, 22, 27]. The T1MI frequency was found to be lower in the ED than in the non-ED (60.1 vs. 88.8%); whereas T2MI was higher in the ED than in the non-ED (39.7 vs. 7.7%). This may demonstrate that selection bias by recruitment site exaggerates or underestimates the frequency of MI types (Table 1). In general, studies without an all-comer patient population as well as different recruitment settings most likely account for contrasting MI subtype values.

Table 1 Studies reporting on type 1 and type 2 myocardial infarction

Lead author and year of publication	Study site; Country	Patient source	Study population	Total MI (% of population)	T1MI (% of total MI)	T2MI (% of total MI)	STEMI in study population	Primary outcome
Javed (2009) [14]	Single-center, USA	ED, inpatient service, transferals	2979	216 (7.2)	143 (66.2)	64 (29.6)	STEMI ($n=41$) classified as T1MI	Identification and classification of MI based on the UD
Gonzalez (2011) [15]	Single-center, USA	ND	348	348 (100)	278 (79,9)	55 (15.8)	STEMI ($n=168$) and NSTEMI classified separately from that of the UD	Long-term major adverse cardiovascular events on MI patients classified according to the UD
Saaby (2013) [16]	Single-center; Denmark	Hospital admissions	4499	553 (12.3)	397 (71.8)	144 (26)	STEMI: ($n=130$) classified as T1MI and $n=5$ as T2MI	Frequency and characteristics of T2MI patients
Saaby (2014) [17]	Single-center; Denmark	27 clinical departments within the hospital	3762	488 (13)	360 (73.7)	119 (24.4)	ND	Mortality of T2MI patients
Stein (2014) [18]	Two nationwide ACS surveys; Israel	26 intensive cardiac care units and cardiology wards	2818	2818 (100)	2691 (95.5)	127 (4.5)	STEMI, NSTEMI and undetermined; each classified as T1MI and T2MI	Comparison of T1MI and T2MI patients, including mortality at 30 days and 1 year
Sandoval (2014) [19]	Single-center; USA	ED	1144	256 (22.4)	66 (25.8)	190 (74.2)	Excluded STEMI ($n=32$) from final analyses	Delta cTnI to distinguish T1MI and T2MI; and 180-day mortality
Sandoval (2015) [13]	Single-center; USA	ED	310	32 (10.3)	10 (31.3)	22 (68.7)	Included STEMI ($n=1$) and classified as T1MI	Frequency, characteristics and up to 150 days mortality using sex-specific cutoff values
Paiva (2015) [20]	Single-center; Portugal	Acute cardiac care unit	1000	1000 (100)	764 (76.4)	236 (23.6)	STEMI: $n=417$ classified as T1MI and $n=35$ as T2MI	Comparison of T1MI and T2MI patients in terms of baseline characteristics, management and prognosis
Shah (2015) [21]	Single-center; UK	Cardiac center	2165	1643 (75.9)	1,171 (71.3)	429 (26.1)	STEMI: $n=427$ classified as T1MI and $n=40$ as T2MI	Incidence, management and clinical outcomes of patients with T2MI and myocardial injury
Baron (2015) [7]	Nationwide registry during 2011, Sweden	73 hospital cardiac or intensive care unit	19,763	19,763 (100)	17,488 (88.5)	1403 (7.1)	STEMI: 31.7% of all T1MI and 9.7% of all T2MI	Comparison of T1MI and T2MI incidence, management, complications and 1-year mortality
Baron (2016) [8]	Nationwide registry from 2011 to 2013, Sweden	73 hospital cardiac or intensive care unit	59,394	59,394 (100)	53,342 (89.8)	4083 (6.9)	STEMI: reported for T1MI and T2MI, with and without coronary artery disease, each	Comparison of T1MI and T2MI incidence, management, and 3-year mortality

Table 1 (continued)

Lead author and year of publication	Study site; Country	Patient source	Study population	Total MI (% of population)	T1MI (% of total MI)	T2MI (% of total MI)	STEMI in study population	Primary outcome
López-Cuenca (2016) [9]	Single-center; Spain	Cardiology department	824	824 (100)	707 (85.8)	117 (14.2)	STEMI: $n=225$ classified as T1MI and $n=1$ as T2MI	Comparison of T1MI and T2MI patients: all-cause mortality, non-fatal MI, stroke, major bleeding
Meigher (2016) [22]	Single-center; USA	ED	13,502	792 (5.9)	340 (42.9)	452 (57.1)	ND	Etiology of cTn elevations and comparison of characteristics and outcomes of T1MI and non-T1MI
Cediel (2017) [23]	Single-center; Spain	ED	1010	570 (56.4)	376 (66)	194 (34)	STEMI: $n=92$ classified as T1MI and $n=5$ as T2MI	2-year all-cause mortality in T2MI and non-ischemic myoardial injury and comparison to that of T1MI
Radovanovic (2017) [24]	Nationwide cohort of ACS patients, Switzerland	83 medical institutions ranging from community to tertiary facilities	15,505	15,505 (100)	13,828 (89.2)	1091 (7.0)	STEMI: n = 7436 classified as T1MI and n = 213 as T2MI	In-hospital mortality and differences in presentation and treatment of T1MI and T2MI
Neumann (2017) [25]	Single-center; Germany	ED	1548	287 (18.5)	188 (65.5)	99 (34.5)	Excluded from the analyses: STEMI ($n=75$) and "NSTEMI type 4" ($n=2$)	Differentiation of T1MI and T2MI. Clinical characteristics and cardiovascular outcomes
Greenslade (2017) [26]	Single-center; Australia	ED	2349	199 (8.5)	147 (73.9)	52 (26.1)	T1MI was made up by 35 STEMI and 112 NSTEMI patients	Prevalence, characteristics and outcomes of T2MI. Comparison to T1MI
Sandoval (2017) [27]	Single-center; USA	ED	1640	217 (13.2)	77 (35.5)	140 (64.5)	STEMI: $n=6$ classified as T1MI and $n=1$ as T2MI	Differentiation of T1MI, T2MI and myocardial injury. Mortality of T2MI and incidences using hs-cTnI
Smilowitz (2017) [28]	Single-center; USA	Hospital admissions	710	290 (40.8)	137 (47.2)	146 (50.3)	T1MI was made up by 20 STEMI and 117 NSTEMI patients	Intermediate-term all-cause and cardiovascular mortality of T1MI, T2MI and myocardial injury
Nestelberger (2017) [29]	Twelve centers in 5 european countries	ED	4015	812 (20.2)	684 (84.2)	128 (15.8) using the 2012 consensus document	STEMI: $n=115$ classified as T1MI and $n=4$ as T2MI	Effect of the definition of T2MI on its incidence, treatment and event-related mortality

ACS acute coronary syndrome, *cTn* cardiac troponin, *ED* emergency department, *hs-cTn* high sensitivity cardiac troponin, *ND* not defined, *T1MI* type 1 myocardial infarction, *T2MI* type 2 myocardial infarction, *STEMI* ST-elevation myocardial infarction, *UD* universal definition

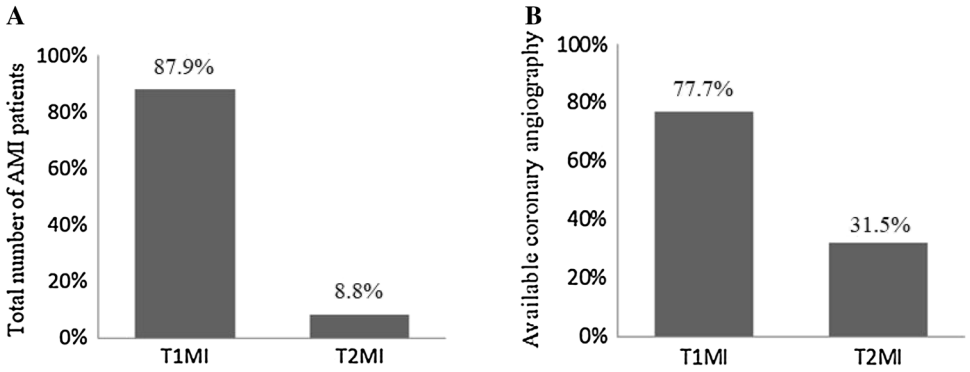


Fig. 2 Proportion of patients by MI type and availability of coronary angiography. **a** From the overall number of patients diagnosed with AMI (10,6007), 87.9% were classified as T1MI and 8.8% as T2MI. **b** From all patients classified as T1MI, coronary angiography was available in 77.7% of them (72,412 / 93,194). Similary from those classified as T2MI, coronary angiography was available in 31.5% (2927/9291). *AMI* acute myocardial infarction, *T1MI* type 1 myocardial infarction, *T2MI* type 2 myocardial infarction

Management by type of MI

Description of the management procedure was absent from 6 of the 20 studies [13, 19, 22, 23, 25, 26], while 3 others stated in general whether or not patients received revascularization or were admitted to a coronary or intensive care unit [14, 16, 20]. The remaining 11 studies described whether percutaneous coronary intervention (PCI) or coronary artery bypass grafting was performed, in addition to medication given on discharge (Table 2). Considering this subgroup of 11 studies, PCI was performed in 79.2% of all T1MI patients (range 38.7–93%) [18, 28] and 40.2% of all T2MI patients (range 0–87.5%) [18, 21] (Table 2). Medical treatment included aspirin, clopidogrel, angiotensin-converting enzyme inhibitors, statins, beta blockers, oral anticoagulants and dual antiplatelet therapy. Medications on discharge were more frequently administered to T1MI patients (Suppl. Table 2).

Male patients made up the greatest proportion of those classified as either T1MI and T2MI; with predominantly older patients described in the T2MI group (Suppl. Table 1). The most commonly reported cardiovascular risk factors/comorbidities were hypertension and diabetes mellitus (all studies); followed by hyperlipidemia and/or hypercholesterolemia (19 studies). Other risk factors such as smoking, obesity, previous MI or stroke were reported by fewer studies.

Meta-analyses on mortality and reinfarction

Data on mortality are provided by most studies; though at various time points ranging from in-hospital up to 24-month follow-up (Suppl. Table 3). In-hospital mortality was reported by 6 studies (1 ED and 5 non-ED) including 5120 MI patients, with no difference found between both MI type groups (for T2MI, RR: 1.32, CI: 0.80–2.20, $P=0.28$; $I^2=78\%$) (Suppl. Figure 1). One-year mortality was reported by 8 studies (2 ED and 6 non-ED) with a total of 69,730 MI patients. From these, meta-analysis results suggest an increased risk of death in patients with T2MI (RR: 1.41, CI 1.02–1.94, P = 0.04; $I^2=91\%$); though at high heterogeneity among studies (Fig. 3, upper panel). Similarly, from the 6 studies (2 ED and 4 non-ED; 44,366 MI in total) reporting on 2-year mortality, our analysis showed a worse outcome among T2MI patients (RR: 1.52, CI 1.07–2.17, $P=0.02$; $I^2=92\%$) (Fig. 3, lower panel). A pooled analysis of 4 studies reporting on reinfarction with a mean follow-up time of 1.6 years revealed a statistically significant higher risk for this event among T2MI patients (RR: 1.68, CI 1.22–2.31, $P=0.001$; $I^2=9\%$) (Fig. 4).

Discussion

The Universal Definition consensus document aims to provide a standardized approach for the diagnosis of MI and for its classification into several MI types which should facilitate the interpretation and comparison across different trials [2, 30, 31]. This systematic review, however, shows that the objectives put forth by the consensus document may not have been reached, as reflected in published observational studies. We found no randomized trial reporting baseline characteristics for patients classified as T1MI and T2MI. Though a few potential interventional studies (e.g., TRITON-TIMI 38 study and the Occluded Artery Trial) were identified at the screening phase, they were later excluded due to lack of comprehensive data to assign MI into a particular type; a limitation likely due to the use of the Universal Definition classification not being prespecified in the study protocols [32–34]. A former meta-analysis identified a similar percentage of T2MI; with higher mortality (as compared to T1MI) at 1-year follow-up. However, the study aimed to compare prevalences of coronary risk factors among MI

Table 2 Diagnostic and in-hospital procedures

Lead author, year	Troponin assay	Troponin peak values		Angiography	In-hospital procedures	
		T1MI	T2MI		T1MI	T2MI
Javed (2009) [14]	cTnI, Siemens Healthcare; 99th percentile > 0.04 ng/mL	29.95 ± 5.29	1.68 ± 0.4	Available in 87%, 50% and 33% of all T1MI, T2MI and non-MI patients, respectively	ICU admission 11%	ICU admission 13%
Gonzalez (2011) [15]	ND	Peak cTn, mean ± SD 74.2 ± 122.5	Peak cTn, mean ± SD 38.3 ± 72.3	ND	Urgent PCI 52.5% Nonurgent PCI 20.5%*	Urgent PCI 30.9% Nonurgent PCI 25.5%
Saaby (2013) [16]	cTnI, Abbott Diagnostics; 99th percentile 0.028 µg/L	Median (IQR) 2.96 (0.44–15.85)	Median (IQR) 1.09 (0.43–3.24)	Available in 70.8% and 21.5% of all T1MI and T2MI patients, respectively	Coronary care unit admission: 82.6%	Coronary care unit admission: 54.9%
Saaby (2014) [17]	cTnI, Abbott Diagnostics; 99th percentile 0.028 µg/L	Median (IQR) 3.82 (0.53–17.03)	Median (IQR) 0.85 (0.39–3.27)	Available in 74.4% and 25.5% of all T1MI and T2MI patients, respectively	PCI 53.8%* CABG 2.5%	PCI 3.4% CABG 0%
Stein (2014) [18]	ND	ND	ND	Available in 88.7% and 36.2% of all T1MI and T2MI patients, respectively	PCI 93% Thrombolysis 6.4% CABG 0.6%	PCI 87.5% Thrombolysis 12.5% CABG 0%
Sandoval (2014) [19]	cTnI, Ortho-Clinical Diagnostics; 99th percentile 34 ng/L	Median (IQR) at 6 h 450 (2600)	Median (IQR) at 6 h 150 (490)	ND	ND	ND
Sandoval (2015) [13]	hs-cTn, Abbott; 99th percentile 16 ng/L and 34 ng/L (males and females, respectively)	Mean (95% CI) 7767 (0-17338)	Mean (95% CI) 615 (89-1140)	Performed in 3 (10%) and 1 (4.5%) of all T1MI and T2MI patients, respectively	ND	ND
Paiva (2015) [20]	cTnI, OrtoClinical diagnostic Vitrus; 99th percentile (0.034 ng/L)	57.9 ± 96.6	15.2 ± 32.9	Available in 619 (81%) and 121 (51.2%) of all T1MI and T2MI patients, respectively	Coronary revascularization 66.3%	Coronary revascularization 11.4%
Shah (2015) [21]	cTnI Abbott ARCHITECT; 99th percentile: 200 ng/L in validation phase; and 50 ng/L in implementation phase	Median (IQR) 2420 (270–15,230)	Median (IQR) 140 (70–660)	Available in 744 (65%) and 31 (7%) of all T1MI and T2MI patients, respectively	PCI 49%* CABG 5%*	PCI 0% CABG 1%
Baron (2015) [7]	Diverse assays; mostly hs-cTnT	Median (IQR) hs-cTnT 351.5 ng/L (84–1432) cTnI 3.1 µg/L (0.59–16.0)	Median (IQR) hs-cTnT 247.0 ng/L (89.4–721.3) cTnI 1.5 µg/L (0.41–6.3)	Available in 77.3% and 35.9% of all T1MI and T2MI patients, respectively	PCI 60.6%* CABG 5.2%	PCI 12.5% CABG 1.1%

Table 2 (continued)

Lead author, year	Troponin assay	Troponin peak values		Angiography	In-hospital procedures	
		T1MI	T2MI		T1MI	T2MI
Baron (2016) [8]	Diverse assays; mostly hs-cTnT	Values for obstructive CAD / non-obstructive CAD Median (IQR) for hs-cTnT 492 ng/L (121–2000) / 163.5 (63–447)	Values for obstructive CAD / non-obstructive CAD Median (IQR) for hs-cTnT 322.5 ng/L (97.5–850.5) / 209 (83–460)	Available in 40,501 (75.9%) and 1316 (32.2%) of all T1MI and T2MI patients, respectively	Values for obstructive CAD / non-obstructive CAD PCI 84.6%*/ 0% CABG 6.6% / 0%	Values for obstructive CAD / non-obstructive CAD PCI 55.1% / 0% CABG 5.2% / 0%
López-Cuenca (2016) [9]	hs-cTnT, no 99th percentile given	Median (IQR) 70 (26–283)	Median (IQR): 36 (22–131)	Available in 622 (88%) and 46 (39%) of all T1MI and T2MI patients, respectively	PCI 69%* Thrombolysis 4% CABG 4%	PCI 9% Thrombolysis 0% CABG 0%
Meigher (2016) [22]	Point of care i-STAT troponin I, Abbott; 99th percentile 0.04 ng/mL	Median (IQR); 3rd troponin 3.04 (0.43–19.68)	Median (IQR); 3rd troponin 0.17 (0.09–0.56)	ND	ND	ND
Cediel (2017) [23]	cTnI-Ultra, Siemens Advia Centaur. 99th percentile 0.039 µg/mL	Median (IQR) 6.05 (0.61–31.84)	Median (IQR) 0.15 (0.08–0.56)	Available in 278 (73.9%) and 11 (5.7%) of all T1MI and T2MI patients, respectively	ND	ND
Radovanovic (2017) [24]	ND	ND	ND	Available in 12,067 (87.3%) and 660 (60.5%) of all T1MI and T2MI patients, respectively	PCI 84.5%*	PCI 51.1%
Neumann (2017) [25]	hs-cTnI, Abbott ARCHITECT; 99th percentile 27 ng/L	At 3 h, 505.3 (97.8–2008.4)	At 3 h, 108.4 (30.3–602.2)	Available in 163 (86.7%) and 38 (38.4%) of all T1MI and T2MI patients, respectively	ND	ND
Greenslade (2017) [26]	cTnI Beckman Coulter 2nd generation; 99th percentile 0.04 µg/L	ND	ND	Available in 128 (87.1%) and 8 (15.4%) of all T1MI and T2MI patients, respectively	ND	ND
Sandoval 2017 [27]	cTnI Abbott ARCHITECT; 99th percentile 0.03 µg/L	Maximum cTnI (µg/L), mean (SD) 9.9 (18)	Maximum cTnI (µg/L), mean (SD) 0.6 (2.0)	Available in 46 (60%) and 13 (9%) of all T1MI and T2MI patients, respectively	PCI 34/46 (73.9%)* CABG 3 (4%)	PCI 1/13 (8%) CABG 0 (0%)
Smilowitz (2017) [28]	cTnI Ultra assay, Siemens Healthcare; reference range 0.006–0.06 ng/mL	Median (IQR) 3.79 ng/mL (0.54–11.60)	Median (IQR) 0.34 ng/mL (0.14–1.72)	Available in 114 (83.2%) and 19 (13%) of all T1MI and T2MI patients, respectively	PCI 38.69%*	PCI 5.48%

Table 2 (continued)

Lead author, year	Troponin assay	Troponin peak values		Angiography	In-hospital procedures	
		T1MI	T2MI		T1MI	T2MI
Nestelberger (2017) [29]	hs-cTnT (Elecsus 2010, Roche Diagnostics); 99th percentile 14 ng/L	ND	ND	Available in 582 (85%) and 23 (18%) of all T1MI and T2MI patients, respectively	PCI 67%* CABG 8.6%*	PCI 0.8%* CABG 0%*

CABG coronary artery bypass grafting, *CAD* coronary artery disease, *ED* emergency department, *hs-cTn* high sensitivity cardiac troponin, *ICU* intensive care unit, *IQR* interquartile range, *ND* not defined, *PCI* percutaneous coronary intervention, *T1MI* type 1 myocardial infarction, *T2MI* type 2 myocardial infarction, *STEMI* ST-elevation myocardial infarction, *UD* universal definition

*Reported as statistically significant difference ($P < 0.05$) between T1MI and T2MI

types, excluded patients outside of coronary care units, and identified a fewer number of studies likely due to a missing database search strategy [35].

Our study has identified factors likely contributing to variation in the classification of MI types: selection of patients according to certain electrocardiographic findings, variations in the use of angiography, as well as the adoption of novel classification criteria by some research groups.

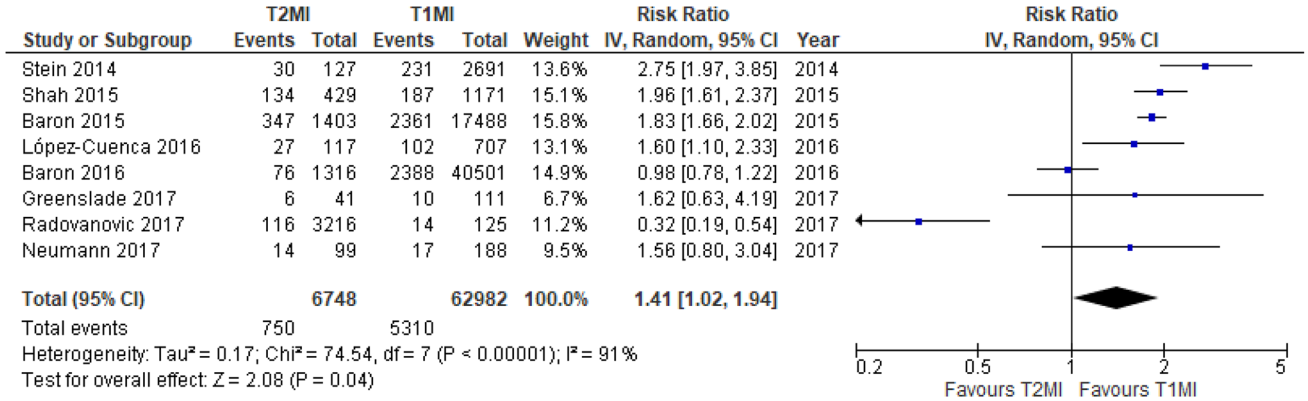
Electrocardiographic findings

The ECG is a fundamental tool for the diagnostic work-up of patients into ST-elevation MI (STEMI) or non-STEMI (NSTEMI) in order to direct patient management. However, applying this practical classification in conjunction with that of the Universal Definition of MI seems to bring about uncertainty among physicians and investigators. We found that most studies reporting on T1MI and T2MI included patients with STEMI, while others plainly excluded or did not specify them in their selection criteria (Table 1). In this regard, Sandoval et al. provided reasonings to exclude STEMI patients in 1 study [19] and yet included them in 2 further ones [13, 27]. These discrepancies may originate from a missing explanation on the consensus document on how to handle the parallel use and reporting of the more practical ECG (STEMI, NSTEMI) with that of the still more "theoretical" Universal Definition classification (T1MI, T2MI). Of note, the consensus document itself highlights the importance of prompt reperfusion therapy following ST-elevation findings [1, 2]. Furthermore, current clinical guidelines from major cardiac societies in Europe and North America base their management recommendations on electrocardiographic findings and just briefly echo the classification of MI by the Universal Definition [36–38].

Role of coronary angiography

We found that most studies (17 of 20) used CAG as an imaging diagnostic aid of MI, with approximately 22% of all patients classified as T1MI (and 68% of T2MI) not undergoing an angiographic procedure (Fig. 2b). This may indicate that a considerable proportion of MI types are being distinguished through clinical assessment and tools other than CAG [3, 39].

Although the consensus document bases the definition of T1MI on events that may solely be detected angiographically (primary coronary event such as plaque erosion/rupture) [1, 2, 31], the majority of current studies using CAG and reporting on the different MI types omit to provide a description of their angiographic findings. In this regard, the number of prospective studies with patients having this imaging test is very limited [40, 41].



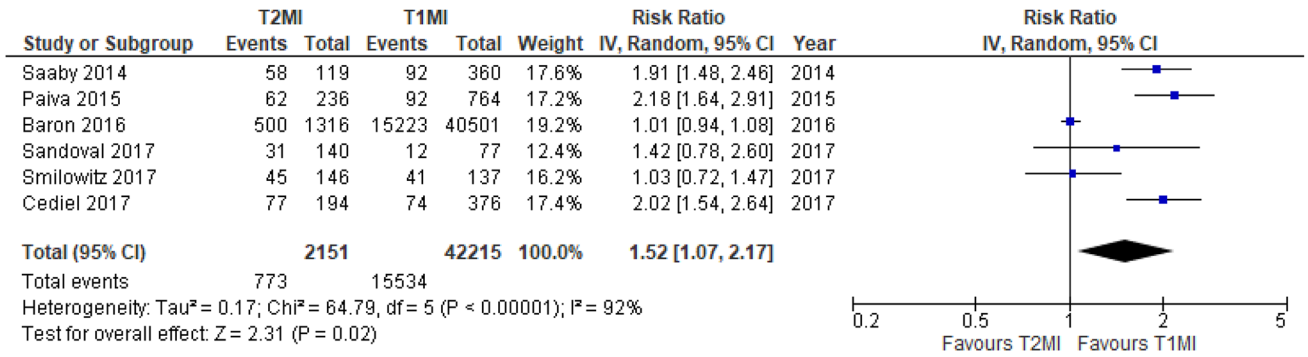


Fig. 3 Forest plots on 1-year mortality (upper panel) and 2-year mortality (lower panel) in T2MI and T1MI patients. Pooled results demonstrate increased mortality risk among type 2 MI patients at both 1-year and 2-year time points. Abbreviations as in Fig. 2

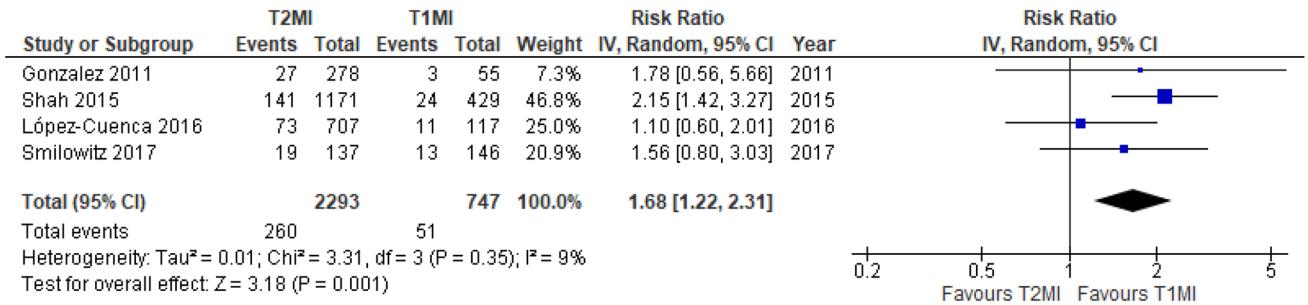


Fig. 4 Forest plot on reinfarction at a mean follow-up of 1.6 years. Type 2 MI patients are clearly disfavoured with higher risk of reinfarction. Abbreviations as in Fig. 2

Clinical criteria

An additional factor influencing the classification of MI involves investigators developing a set of specific clinical criteria to define T2MI. The included study by Saaby et al. used specific cut-off values for conditions decreasing oxygen supply (one example is anemia with hemoglobin < 5.5 mmol/L in men and < 5.0 mmol/L in women) or increasing oxygen need (e.g., hypertension with systolic blood pressure > 160 mmHg and left ventricular hypertrophy) [16, 17]. Using such stringent criteria, they found a higher mortality rate in T2MI (49%; 58/119) as compared to T1MI patients (26%; 92/360). The consensus document recognizes that adaptation of the definition and classification of MI may be appropriate in certain well-founded cases; in consequence, the

proposed clinical criteria have been adopted and replicated by some investigators [23] but also discouraged by others [42] (Suppl. Table 5).

Mortality and reinfarction

The interpretation of our results on mortality is to be taken with caution due to high variability across studies. The higher risk of mortality in T2MI patients at both 1-year and 2-year time points may be related not only to the predominantly increased age and male sex (known risk factors favoring the pathophysiologic oxygen-supply disbalance of T2MI), but also to a higher recurrence of clinical events in the long-term follow-up. In spite of paucity of data on clinical endpoints, we found that T2MI patients experienced a consistently higher risk of reinfarction at a mean time of 1.6 years after the initial event. As noted, in-hospital mortality did not differ between both groups. However, while the treatment of T2MI is directed at removing the triggering condition for myocardial necrosis without clear long-term management guidelines, patients with suspicion of T1MI and a thrombus-occluded artery receive a more thorough examination including coronary angiography, urgent PCI (Table 2 for comparisons) and a close post-discharge follow-up for pharmacologic management; that is, steps which may prevent the ocurrence of future clinical events and death.

Future directions

Guidance is required on how to incorporate electrocardiographic findings, namely STEMI and NSTEMI, into the Universal Definition classification. The extent to which imaging aid such as angiography ought to be used to differentiate T1MI and T2MI should also be further clarified. This should dissipate confusion and overlapping of definitions; especially in those without CAD or coronary obstruction. Whether the incorporation of high-sensitivity cTn improves MI classification, and thus clinical decision-making, remains to be determined. Considerable discussion has taken place on how to best define and classify T2MI in particular [4, 5, 42]. Recent evidence suggests the presence of CAD be included in the definition of T2MI to increase the beneficial effects of secondary prevention measures and potential therapeutic strategies [29]. Our findings show that clarification on the definition of both MI types as well as management recommendations are urgently needed.

Limitations and strengths

First, although no restrictions on type of study design were applied in our search, only observational studies met the selection criteria and were included in this review. This may represent a limitation to the study; however, it also demonstrates the need for prospective trials using the proposed Universal Definition classification system. Potential misclassification of MI types in the individual studies may have also influenced the pooled analyses results. Second, some overlapping in patient recruitment may have occurred between included studies [16, 17]; nevertheless, they followed different study objectives and the exclusion of either one would not affect the overall results of this review. Third, the classification of myocardial injury or perioperative MI was not considered in this work. However, T1MI and T2MI constitute by far the most frequently reported MI types which were prespecified in our study objectives. Fourth, though most of the included studies followed recommendations by the Third Universal Definition, the most recently released consensus document bears no substantial amendments to the previous classification criteria of both T1MI and T2MI and so the results of this work should serve future studies on MI type differentiation.

Conclusions

Although the differentiation of MI has been described to carry implications for patient management, this systematic review did not find the supporting evidence inasmuch as the studies discerning both groups were all observational in design with most classification procedures performed retrospectively. Given that 40.2% of the overall number of patients categorized as T2MI underwent PCI (from the 11 studies reporting on operative intervention), misclassification is highly likely an issue.

Cardiac troponin, ECG and angiography are useful tools in the diagnosis of MI; however, reporting of STEMI or NSTEMI need to be harmonized with the T1MI- and T2MI-classification system. Similarly, the role of angiography needs to be further defined and angiographic findings ought to be better described by investigators. Though less frequent, T2MI carries a higher risk on long-term mortality and reinfarction. Clear definitions for both MI types in prospective trials are required for higher quality evidence.

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Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest in relation to this work.

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