Review

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Cardiac troponins and mortality in type 1 and 2 myocardial infarction

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Abstract

Background: The pathogenesis of different types of myocardial infarction (MI) differs widely, so that accurate and timely differential diagnosis is essential for tailoring treatments according to the underlying causal mechanisms. As the measurement of cardiac troponins is a mainstay for diagnosis and management of MI, we performed a systematic literature analysis of published works which concomitantly measured cardiac troponins in type 1 and 2 MI.
Methods: The electronic search was conducted in Medline, Scopus and Web of Science using the keywords "myocardial infarction" AND "type(-)2" OR "type II" AND "troponin" in "Title/Abstract/Keywords", with no language restriction and date limited from 2007 to the present.
Results: Overall, 103 documents were identified, but 95 were excluded as precise comparison of troponin values in patients with type 1 and 2 MI was unavailable. Therefore, eight studies were finally selected for our analysis. Two studies used high-sensitivity (HS) immunoassays for measuring cardiac troponin T (HS-TnT), one used a HS immunoassay for measuring cardiac troponin I (HS-TnI), whereas the remaining used conventional methods for measuring TnI. In all studies, regardless of type and assay sensitivity, troponin values were higher in type 1 than in type 2 MI. The weighted percentage difference between type 1 and 2 MI was 32% for TnT and 91% for TnI, respectively. Post-discharge mortality obtained from pooling individual data was instead three times higher in type 2 than in type 1 MI.
Conclusions: The results of our analysis suggest that the value of cardiac troponins is consistently higher in type 1 than in type 2 MI.

Keywords: mortality; myocardial infarction; troponin; type 2.

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Introduction

Despite that the frequency curve has slightly and progressively bent in the past decade, cardiovascular disorders remain the leading cause of death and disability around the globe. According to the 2016 Update of Heart Disease and Stroke Statistics [1], approximately 660,000 persons have a new event of myocardial infarction (MI) each year in the US, whereas the annual recurrence of MI is as high as 300,000. In addition to this already concerning picture, it is estimated that an additional 160,000 silent cases of MI may occur, thus raising the overall frequency of MI up to approximately 1.15 million cases per year in the US (i.e. 0.36% of the overall resident population). Even more importantly, nearly one-third of patients who experience a coronary event in a given year will ultimately die of it, which makes MI an underlying cause of death in nearly one of every seven deaths. As concerns the economic perspective, the estimated direct and indirect cost of heart disease approximates to $207.3 billion per year in the US, exhibiting a trend that is projected to increase further by ~100% between 2013 and 2030, mainly attributable to disability and long-term management of patients [1].

Although MI has for a long time been considered a single pathological entity [2], the increasing knowledge about its pathogenesis, the development of more precise and sensitive serological biomarkers, combined with the introduction of more accurate imaging techniques have allowed us to revolutionize our understanding of the underlying mechanisms ultimately leading to cardiac ischemia and to the following irreversible myocardiocyte injury [3]. More specifically, in the 2007 an official document entitled "Third Universal Definition of Myocardial Infarction" has been released by a Joint ESC/ACCF/AHA/

WHF (European Society of Cardiology; the American College of Cardiology; the American Heart Association; the World Heart Federation) Task Force for the Redefinition of MI [4], which officially introduced for the very first time the concept that MI should be classified by as many as five different types according to the pathogenetic mechanisms causing myocardial ischemia and injury. Accordingly, type I MI is defined as myocyte necrosis secondary to reduced myocardial blood and intraluminal thrombosis due to rupture, ulceration, fissuring, erosion or dissection of atherosclerotic plaque(s), type 2 MI is defined as irreversible myocardial injury secondary to an imbalance between myocardial oxygen supply and/or demand due to conditions other than coronary atherosclerosis (e.g. acute and severe anemia, coronary vasospasm, endothelial dysfunction, toxic effects of endogenous or exogenous catecholamine, shock, respiratory failure, heart failure, tachyarrhythmias including atrial fibrillation, hypertension or hypotension, coronary embolism and cardiotoxic substances). Overall, the primary clinical conditions and the underlying mechanisms leading to the occurrence of type 2 MI seem thereby more important, wherein the term MI type 2 is more related to secondary myocardial injury, in which the primary cause of troponin elevation and clinical symptoms plays a major role. The remaining three types of MI are reportedly less frequent than the previous (i.e. <5% altogether) and encompass cardiac death due to MI (type 3 MI) or MI secondary and/or associated with revascularization procedures (types 4 and 5 MI) [4]. Notably, the diagnosis of type 2 MI remains challenging, wherein the definitive demonstration of supply/demand imbalance which has triggered myocardial ischemia is not reliably identifiable on the basis of clinical symptoms alone, but would require the objective demonstration that ischemia has not been triggered by preexisting coronary abnormalities (i.e. culprit lesions), thus entailing the use of accurate imaging techniques (prevalently angiography) [5].

As the pathogenesis of the different types of MI differs widely, recent focus has been placed on the fact that an accurate diagnosis is essential for tailoring the treatment according to the underlying causal mechanism(s). As a rule of thumb, patients with type 1 MI should be managed with timely reperfusion of the occluded coronary vessel(s), promptly establishment of anticoagulant and/or antiaggregant therapy, combined with management of heart rhythm (e.g. administration of beta blockers) and underlying risk factors (e.g. cholesterol-lowering drugs). Most of these mechanical or medical treatments may be useless (i.e. revascularization procedures, cholesterol-lowering drugs) or even inappropriate (i.e. beta blockers) in patients with type 2 MI [5]. It has also been reported that the overall and cardiac mortality of patients with type 2 MI may be substantially higher than that of patients with type 1 MI, wherein patients with type 2 MI display higher mortality rates after hospital discharge, as well as a larger number of in-hospital complications and prolonged hospitalization compared to patients with type 2 MI [5, 6]. Therefore, the evidence accumulated so far suggests that an accurate and timely differential diagnosis between type 1 and 2 MI is advisable, if not indispensable, to achieve the best possible outcome for the patients.

Recent evidence suggests that the clinical presentation may considerably differ between type 1 and 2 MI. Patients with type 2 MI more frequently present with "atypical" symptoms (e.g. dyspnea and symptoms other than chest pain), whereas the frequency of "typical" symptoms (namely chest pain) is over three times more likely in patients with type 1 than in those with type 2 MI [7]. As for other conditions, clinical judgment is an active part of patient evaluation, and the clinical heterogeneity between type 1 and 2 MI may, going forward, be helpful to preliminarily guide the diagnostic process [8]. However, the individual expertise may vary widely among physicians, so that the predictive value of the clinics remains overall limited to discriminate between type 1 and 2 MI.

The introduction of cardiac troponins testing at the beginning of this century has virtually revolutionized the diagnosis and management of MI [9]. The ensuing development and introduction into clinical practice of high-sensitivity (HS) cardiac troponin immunoassays has represented another breakthrough for the diagnosis of MI, especially of non-ST elevation MI (NSTEMI) [9–13]. Since the measurement of these biomarkers has become a mainstay of current MI management, it is worthwhile exploring whether cardiac troponin values may help improving the differential diagnosis between type 1 and 2 MI. Therefore, we carried out a systematic literature analysis of all published studies which have concomitantly analyzed the values of cardiac troponins in patients with type 1 and 2 MI, to investigate whether a different range of cardiac troponin concentrations may characterize patients with one MI type or another.

Materials and methods

We conducted an electronic search in Medline (using the PubMed interface), Scopus and Web of Science with the keywords "myocardial infarction" AND "Type(-)2" OR "Type II" AND "troponin" in "Title/Abstract/Keywords", with no language restriction and date limited from year

2007 (i.e. after the publication of the official definition of type 2 MI) to the present. Exclusion criteria were (i) lack of comparison of troponin values between patients with type 1 and 2 MI, (ii) no definition of the cardiac troponin isoform that was measured, and (iii) lack of the measure unit for expressing cardiac troponin concentration. All articles identified according to the search criteria were systematically reviewed by two authors (GL and GC). The references of selected articles were also hand-searched to identify other pertinent items. The effect size (ES) was calculated as weighted difference and 95% confidence interval (95% CI) and expressed as both absolute (i.e. mean) percent (%) values using effect size calculator for Microsoft Excel 5/95 (Center for Evaluation and Monitoring, Durham, UK). To convert interquartile range into min–max range, the following equations were used: A=median+2×(Q_3–median) and B=median–2×(median–Q_1), where A, B, Q_1 and Q_3 are upper and lower ends of the range, and upper and lower ends of the interquartile range, respectively. When only the standard error of the mean (SEM) was available, the standard deviation (SD) was estimated with the formula: SD=SEM×sqrt (*n*), where *n* is the number of subjects. When no SD was provided for troponin concentrations, the pooled SD of other studies was used as the substitute.

Results

A total number of 103 documents were identified after excluding replicates, but 95 of these were omitted after accurate reading of the title, abstract or full text (when available). More specifically, 38 studies were excluded because "type 2" referred to diabetic subjects, 28 articles did not report a direct comparison of cardiac troponin values between patients with type 1 and 2 MI, nine were review articles, six were case reports, 10 were editorials (n=5) or letters (n=5), two studies replicated data using the same study population, one article did not provide indications regarding the cardiac troponin isoform and the relative measure unit, and another one did not describe the cardiac troponin isoform that was measured (Figure 1).

Therefore, eight studies were finally selected for our analysis (Table 1) [14–21]. Inter-rater agreement was perfect (kappa statistics, 1.00). Two of these studies used HS immunoassays for measuring cardiac troponin T (HS-TnT), one study used a HS immunoassay for measuring cardiac troponin I (HS-TnI), whereas the remaining five studies used conventional methods for measuring TnI.

López-Cuenca et al. [14] studied 824 consecutive patients with MI, 117 of whom (14%) had type 2 MI. The presence of obstructive coronary artery disease was much more common in patients with type 2 MI than in those with type 1 MI (9% vs. 67%; p<0.001). Reperfusion strategy (i.e. percutaneous coronary intervention, PCI) was also used less frequently in patients with type 2 MI than those with type 1 MI (9% vs. 69%; p<0.001). Similar data were reported for the use of β blockers (78% in type 2 MI vs. 93% in type 1 MI; p<0.001). The median concentration (and interquartile range, IQR) of HS-TnT was found to be significantly higher in patients with type 1 MI (70 ng/L; IQR, 26–283 ng/L) than in those with type 2 MI (36 ng/L; IQR, 22–131 ng/L; mean difference, 49%; p<0.001). Interestingly, Cox regression analysis showed that patients with type 2 MI had a nearly double mortality risk than those with type 1 MI (hazard ratio, 1.75; 95% CI, 1.14–2.68; p=0.001).

Baron et al. [15] studied 19,763 patients with MI, 17,488 of whom had type 1 MI (88%), 1403 had type 2 MI (7%), and the remaining had other types of MI. As in the previous study, PCI (12% vs. 61%; p<0.001) and administration of β blockers (82% vs. 88%, p<0.001) were less frequent in patients with type 2 MI than in those with type 1 MI. The median concentration of HS-TnT was found to be significantly higher in patients with type 1 MI (352 ng/L; IQR, 84–1432 ng/L) than in those with type 2 MI (247 ng/L; IQR, 89–721 ng/L; mean difference, 30%; p<0.001). The crude 1-year mortality was instead nearly double in patients with type 2 MI than in those with type 1 MI (24.7% vs. 13.5%; p<0.001).

In a small study, Sandoval et al. [16] studied 32 patients with MI, 22 of whom (69%) with type 2 MI. The mean concentration of HS-TnI on admission was significantly higher in patients with type 1 MI (913 ng/L; 95% CI, 30–2347 ng/L) than in those with type 2 MI (259 ng/L; 95% CI, 30–638 ng/L; mean difference, 72%; p<0.001). The difference between type 1 and 2 MI was amplified using peak HS-TnI (7767 ng/L and 95% CI, 30–17,338 ng/L vs. 615 ng/L and 95% CI, 89–1140 ng/L; mean difference, 92%; p<0.001). The overall mortality at 150 days after discharge was 10% in patients with type 2 MI compared to 0% (i.e. 0/10) in those with type 1 MI (p=0.150).

Shah et al. [17] studied 1600 patients with MI, 429 of whom (27%) had type 2 MI. The use of PCI (0% vs. 49%; p<0.001) and the administration of β blockers (36% vs. 63%, p<0.001) were less frequent in patients with type 2 MI than in those with type 1 MI. The median concentration of TnI was consistently higher in patients with type 1 MI (2420 ng/L, IQR, 270–15,230 ng/L) than in those with type 2 MI (140 ng/L; IQR, 70–660 ng/L; mean difference, 94%; p<0.01). The median hospital length of stay (7 vs. 4 days; p<0.001) and death rate (31% vs. 16%; p<0.01) were instead higher in patients with type 2 MI than in those with type 1 MI.

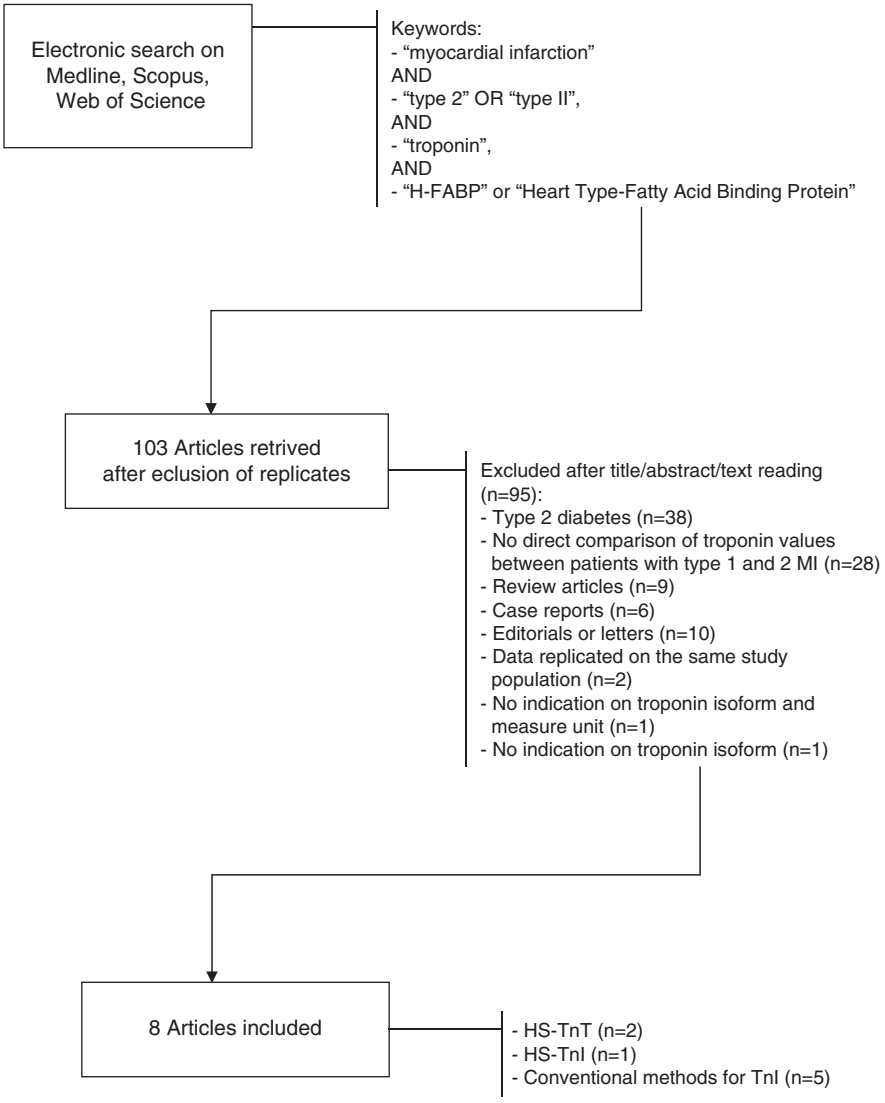

Figure 1: Illustration of the search strategy.

In another study, Sandoval et al. [18] investigated 256 patients with MI, 190 of whom (74%) had type 2 MI. The median concentration of TnI on admission was consistently higher in patients with type 1 MI (450 ng/L; IQR, 34–2600 ng/L) than in those with type 2 MI (150 ng/L; IQR, 34–490 ng/L; mean difference, 67%; p=0.007). The 180-day mortality was instead higher in patients with type 2 MI than in those with type 1 MI (35% vs. 26%; p<0.01).

Saaby et al. [19] studied 479 patients with MI, 119 of whom (25%) with type 2 MI. The use of PCI (3% vs. 54%; p<0.001) and the administration of β blockers (46% vs. 62%; p=0.004) were less frequent in patients with type 2 MI than in those with type 1 MI. The median concentration of TnI on admission was consistently higher in patients with type 1 MI (3820 ng/L; IQR, 530–19,030 ng/L) than in those with type 2 MI (850 ng/L; IQR, 309–3270; mean difference, 78%; p<0.001). The median hospital length of stay (7 vs. 3 days; p<0.001) and 1-year death rate (44% vs. 17%; p<0.01) were instead higher in patients with type 2 MI than in those with type 1 MI.

Hanson et al. [20] studied 54 patients with MI, 22 of whom (41%) with type 2 MI. The use of PCI was similar among the two groups of patients (100% in type 1 vs. 97% in type 2; p=1.00). The median concentration of TnI was significantly higher in patients with type 1 MI (15,300 ng/L; IQR, 410–50,000 ng/L) than in those with type 2 MI (5300 ng/L; IQR, 1000–10,100 ng/L; mean difference, 65%; p=0.035). The post-discharge mortality was not investigated in this study.

Javed et al. [21] studied 207 patients with MI, 64 of whom (31%) had type 2 MI. The mean concentration of TnI was significantly higher in patients with type 1 MI than

Table 1: Summary of the studies included in our analysis.

Authors	Study cohort (% type 2 MI)	Troponin immunoassay	Diagnostic procedure for defining type II MI	Difference of troponin values between type 1 and 2 MI	Statistical significance (p)
López-Cuenca et al. [14]	824 (14%)	HS-TnT (Roche)	Angiography	49%	<0.001
Baron et al. [15]	18,891 (7%)	HS-TnT (Roche)	Universal definition of MI	30%	<0.001
Sandoval et al. [16]	32 (69%)	HS-TnI (Abbott)	Local protocol derived from the third universal definition of MI	72%	<0.001
Shah et al. [17]	1600 (27%)	TnI (Abbott)	Universal definition of MI	94%	<0.01
Sandoval et al. [18]	256 (74%)	TnI (Ortho-Clinical Diagnostics)	Universal definition of MI	67%	0.007
Saaby et al. [19]	479 (25%)	TnI (Abbott)	Local protocol derived from the Third Universal Definition of MI	78%	<0.001
Hanson et al. [20]	54 (41%)	TnI (unspecified assay)	Angiography	65%	0.035
Javed et al. [21]	207 (31%)	TnI (Siemens Healthcare Diagnostics)	Angiography	94%	<0.001

MI, myocardial infarction.

in those with type 2 MI (29,950±5290 vs. 1680±0.40 ng/L; mean difference, 94%; p<0.001). The post-discharge death rate was not investigated in this study.

One of the studies originally identified by our search criteria was excluded from pooled analysis because no indication was provided about the type of cardiac troponin that was measured [22]. However, the results deserve a brief mention. Gonzalez et al. followed up 330 consecutive patients diagnosed with MI (54 with type 2 MI; 16%) for up of 30.6 months. The peak concentration of cardiac troponin was found to be higher in patients with type 1 MI than in those with type 2 MI (74,200±122,000 vs. 38,200± 72,000 ng/L; p<0.01). Interestingly, a significant association was found between quartiles of cardiac troponin in patients with type 1 MI (odds ratio of 1st vs. 4th quartile of cardiac troponin, 2.94; 95% CI, 1.31–6.62; p=0.001), whereas a similar association could not be observed in patients with type 2 MI (p=0.294).

Overall, when the variation of troponin values observed in the individual eight studies included in our analysis were pooled, the weighted mean difference of TnI values was 4596 ng/L (95% CI, 4054–5078 ng/L; p<0.001), which translates into a weighted percentage difference of 91% (95% CI, 80–100). The ES was medium (0.73; 95% CI, 0.65–0.81; p<0.001), corresponding to a non-overlap rate of 44% (95% CI, 41–48). The weighted mean difference of HS-TnT values was instead 110 ng/L (95% CI, 107–113 ng/L; p<0.001), which translates into a weighted percentage difference of 32% (95% CI, 31–33). The ES was large (2.03; 95% CI, 1.97–2.09; p<0.001), corresponding to a non-overlap rate of 82% (95% CI, 81–83). Interestingly, the overall post-discharge mortality (i.e. 150–365 days) obtained by pooling data from the six studies in which it was reported was found to be nearly three times higher in patients with type 2 MI compared to those with type 1 MI (30% vs. 13%; odds ratio, 2.71 and 95% CI, 2.46–3.00; p<0.001) (Table 2).

Discussion

Despite MI remains the leading cause of death around the globe, a deepening understanding of the underlying pathophysiological mechanisms combined with the development of more sensitive cardiac troponin immunoassays have substantially contributed to improve the diagnosis and ameliorate the outcomes [1]. Nearly a decade ago the clear definition of the pathological characteristics of myocardial ischemia and infarction led the way to a revised classification of MI into five different types, which are characterized by a distinctive clinical presentation and also necessitate specific treatments [4]. Type 1 MI is now regarded as an event mainly occurring after complication of an existing coronary atherosclerotic disease, whereas type 2 MI is thought to be secondary to ischemia which develops in the setting of a supply-and-demand imbalance. A number of clinical reasons makes it necessary to accurately distinguish between these two types of

Table 2: Comparison of post-discharge mortality (150–365 days) in patients with type 1 and type 2 myocardial infarction (MI).

Authors	All cases (type 1/2 MI)	Deaths (type 1/2 MI)	Death rate (type 1/2 MI)	Odds ratio and 95% CI (type 2 vs. 1 MI)
López-Cuenca et al. [14]	707/117	102/27	14.4/23.0%	–
Baron et al. [15]	17,488/1403	2361/347	13.5/24.7%	–
Sandoval et al. [16]	10/20	0/2	0/10.0%	–
Shah et al. [17]	1171/429	134/187	11.4/43.6%	–
Sandoval et al. [18]	57/147	15/51	26.3/34.7%	–
Saaby et al. [19]	360/119	60/52	16.7/43.7%	–
Pooled analysis	19,763/2235	2672/665	13.5/29.8%	2.71 (2.46–3.00)

MI, which include the nearly three-fold higher mortality of type 2 MI (Table 2) and the need to tailor mechanical of medical treatments according to the different pathogenetic mechanisms (e.g. the optimal therapy depends on the underlying cause of the supply-demand mismatch). Indeed, coronary angiography is now regarded as the mainstay for the differential diagnosis, wherein patients with type 2 MI do not usually present with plaque rupture and/or culprit lesions with thrombosis [23–25]. Recent evidence also attests that the clinical presentation may be partially distinctive between these two types of MI, but signs and symptoms do not allow to reach a definitive diagnosis [7]. Accordingly, additional tools may be used beside coronary angiography, which is an invasive and expensive means, for a timely and accurate classification.

The results of our analysis of published studies which have concomitantly assessed both cardiac troponins in type 1 and 2 MI, suggest that the value of either of these biomarkers is consistently higher in the former type of MI (Figure 2), thus confirming previous evidence that the measurement of both troponins may be used for diagnosis and prognostication of MI patients [26, 27]. Notably, cardiac troponin values were from 30% to 94% higher in patients with type 1 MI in all studies included in our analysis (Table 1), yielding to a weighted percent difference of 32% for TnT and 91% for TnI, respectively. The non-overlap between type 1 and 2 MI was 82% for TnT and 44% for TnI, and this latter figure can be explained by the much larger pooled standard deviation of TnI values compared to TnT. On the other hand, we could confirm previous data that the mortality of patients with type 2 MI was always higher than that of type 1 MI (Table 2). Interestingly, the lower use of invasive procedures (i.e. PCI) and β blockers consistently observed across all studies further confirms that the mechanisms responsible for myocardial ischemia are rather different between type 1 and 2 MI, and that the treatment should be tailored accordingly.

Therefore, an apparent paradox emerges, wherein the repeated observation that cardiac troponin values are higher in type 1 MI than in type 2 MI does not translate into higher mortality. How can this be explained? Is seems now undeniable that type 2 MI occurs at a later age compared to type 1 MI, the pathophysiology of myocardial necrosis in type 2 MI is multifactorial and the presence of illnesses or multiple underlying disorders (e.g. diabetes, heart failure and stroke) is commonplace in patients with this type of MI [7]. Thus, it is reasonable that the lower increase of both cardiac troponins after a type 2 MI would not translate into a higher mortality rate,

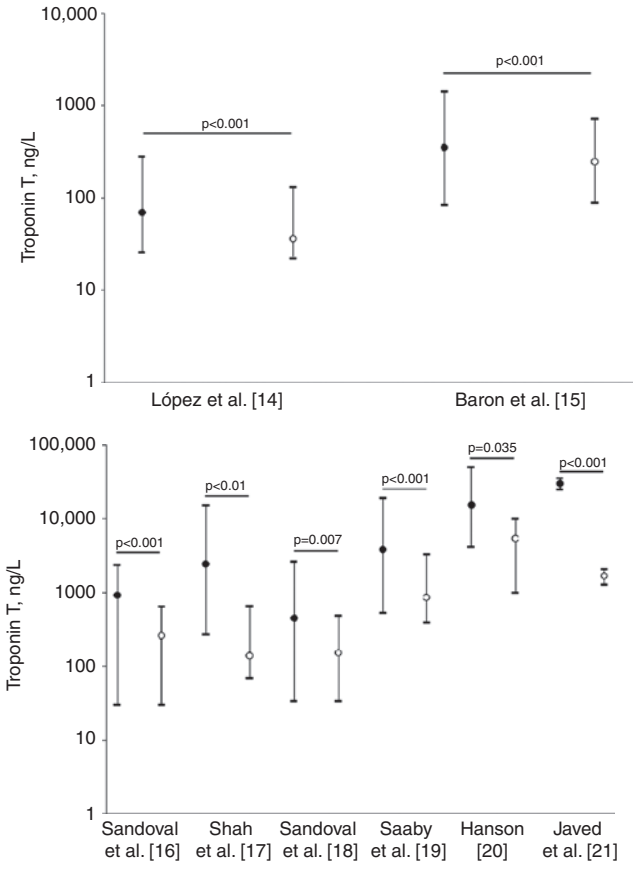

Figure 2: Values of cardiac troponin T and troponin I in patients with type 1 (●) and type 2 (○) myocardial infarction (MI).

in that type 2 MI patients have many other conditions that would ultimately increase the individual risk of morbidity and mortality, perhaps including the so-called Kounis syndrome [28]. This is clearly reflected by the much longer hospital stay that has been recorded throughout the studies reviewed in this literature analysis. The older age of patients with type 2 MI and the higher likelihood of having many different co-morbidities at presentation would also imply that cardiologists and emergency physicians may be persuaded to use less aggressive strategies (e.g. PCI) to manage myocardial ischemia, with a negative impact on reducing the risk of mortality. As such, and in a rather simplistic way, it can be concluded that type 1 MI patients will eventually die due to their MI, whereas patients with type 2 MI seem to die (also) due to their co-morbidity.

Unfortunately, the definition of type 2 MI is subjective so far, which represents an important inconvenience. For instance, in many cases it seems somewhat difficult to detect underlying coronary artery disease in patients with decreased myocardial oxygen supply or increased myocardial oxygen demand (i.e. type 2 MI). Thus, objective diagnostic criteria for type 2 MI have not been clearly specified. Interestingly, the number of cases of type 2 MI varied considerably across the large epidemiological investigations (median frequency, 11%; IQR, 6%–20%) [7], which further emphasizes the current challenge for accurately diagnosing type 2 MI.

Further discussion of the concept of type 2 MI is clearly needed. Distinguishing MI subtypes, especially those of non-coronary etiology, is becoming increasingly relevant as the pathogenesis and the clinical management may vary widely. Cardiac troponin testing, especially combined with clinical presentation, may be regarded as a potential opportunity for preliminary screening of type 1 and 2 MI, as proven by the relatively low overlap of values between the populations, especially using TnT (i.e. 18%). However, if one considers the still broad analytical differences between the different cardiac troponin immunoassays, the diagnostic differentiation between type 1 and 2 MI will not be completely resolved. Moreover, the incidence of type 2 MI may be overestimated in many studies, as many of these failed to provide evidence-based criteria (i.e. angiography) to diagnose type 2 MI (Table 1). The importance of other assessments including clinical symptoms, ECG and cardiac imaging techniques in relation to cardiac troponin concentration therefore remains undeniable.

In conclusion, an urgent need remains for more stringent evidence-based and clinically relevant diagnostic criteria for defining type 2 MI. Further studies should henceforth be planned to accurately assess whether diagnostic algorithms based on clinics and cardiac troponin testing may improve the differential diagnosis between coronary events from non-coronary sources of myocardial injury, as well as between type 1 and 2 MI.

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