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Universal Definition of Myocardial Infarction: Clinical Insights

Luis Paiva[a, b] Rui Providência[a, b] Sérgio Barra[a, b] Paulo Dinis[a, b]
Ana C. Faustino[a, b] Lino Gonçalves[a, b]

[a]Coimbra's Hospital and University Centre, and [b]Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Key Words
Myocardial infarction · Definition of myocardial infarction · Types of myocardial infarction

Abstract
Aims: The universal definition of myocardial infarction (MI) classifies acute ischaemia into different classes according to lesion mechanism. Our aim was to perform a detailed comparison between these different types of MI in terms of baseline characteristics, management and prognosis. ***Methods and Results:*** An observational retrospective single-centre cohort study was performed, including 1,000 consecutive patients admitted for type 1 (76.4%) or type 2 MI (23.6%). Type 2 MI patients were older, had a higher prevalence of comorbidities and worse medical status at admission. In-hospital mortality did not differ significantly between the MI groups (8.8 vs. 9.7%, $p = 0.602$). However, mortality during follow-up was almost 3 times higher in type 2 MIs (HR 2.75, $p < 0.001$). Type 2 MI was an independent all-cause mortality risk marker, adding discriminatory power to the GRACE model. Finally, important differences in traditional risk score performances (GRACE, CRUSADE) were found between both MI types. ***Conclusions:*** Several important baseline differences were found between these MI types. Regarding prognosis, long-term survival is significantly compromised in type 2 MIs, potentially translating patients' higher medical complexity and frailty. Distinction between type 1 and type 2 MI seems to have important implications in clinical practice and likely also in the results of clinical trials.

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Introduction

Myocardial infarction (MI) is one of the main causes of mortality and morbidity worldwide [1]. Its definition has been subject of constant discussions and evolving characterisation. The latest MI consensus – the third universal definition of MI [2] – defines it according to standardized criteria and emphasizes diagnosis of MI on the basis of cardiac troponin (cTn) values [3].

This MI classification uses 5 categories according to the myocardial lesion mechanism [2], which importantly acknowledges the heterogeneity of MI pathophysiology and triggers. Type 1 MI relates to atherosclerotic plaque instability and type 2 MI occurs due to an imbalance between myocardial oxygen supply and demand. Type 2 is usually secondary to other illnesses and its definition is strongly dependent on clinical judgment, to distinguish it from type 1 MI or small myocardial injuries without cardiac ischaemia involved (i.e. renal failure, critically ill) [3–5]. Type 3 MI includes cardiac death suggestive of ischaemia, occurring before cardiac bio-

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Luis Paiva, MD
Avenida Bissaya Barreto
Praceta Prof. Mota Pinto
PT–3000 Coimbra (Portugal)
E-Mail luisvpaiva@gmail.com

markers could be obtained. Finally, type 4 and 5 are categories of MI associated with revascularisation procedures: percutaneous coronary intervention (PCI) and coronary artery bypass grafting, respectively. These are not perceived as spontaneous MI, instead they are mostly related to procedure technique and complications, and are arbitrarily defined according to cardiac biomarker values [2].

Previous studies have already shown the implications of the new definition of MI in prognosis, mainly owing to the extraordinary sensitivity and specificity of troponin to myocardial injury [6, 7]. Although interesting from a theoretical point of view, evidence that MI differentiation into classes has significant practical usefulness is lacking, namely for type 1 and 2 MI, which represent the vast majority of spontaneous MI cases in clinical practice.

Risk assessment is fundamental in ischaemic disease management for the estimation of a patient's prognosis. Current MI recommendations advise on assessing ischaemic and bleeding risk on an individual basis, using quantitative risk scoring systems (such as GRACE [8] and CRUSADE scores [9]) to allow a more rational therapeutic decision-making.

We aimed to compare type 1 and type 2 MI and assess differences concerning baseline characteristics, the performance of risk stratification models, short- and long-term prognosis, and the impact of invasive versus conservative therapeutic strategies.

Methods

Patient Selection

An observational retrospective single-centre cohort study was conducted, including all patients consecutively admitted to our University Hospital's Acute Cardiac Care Unit (ACCU) with a final diagnosis of MI between December 1, 2008, and May 31, 2012. MI was defined according to the recently updated definition of MI [2], which excluded patients with unstable angina and with myocardial injury (elevated cardiac biomarkers) without evidence of ischaemia.

A clinical review of each case was performed by 2 co-investigators, blind to the final purpose of the study, classifying the cohort as either type 1 or type 2 MI according to clinical, electrocardiographic, analytical, angiographic and/or echocardiographic features. Therefore, patients with MI related to coronary artery bypass grafting or PCI, namely stent thrombosis, were not included. The latter subcategory of PCI-related MI was considered present in the case of angiographic documentation of thrombus in relation to previous stenting (as per the definite criteria of the Academic Research Consortium) [10], occurring within or after 30 days of PCI. A third co-investigator was assigned to reviewing the MI classification and served as a referee on ambiguous MI cases. The final study cohort included a total of 1,000 MI patients.

The study complied with the principles of the Declaration of Helsinki, and the local (university hospital) ethics committee approved the implemented research protocol. Moreover, informed consent was obtained from the subjects to be included in the study.

Data Collection and Patient Follow-Up

Demographic and clinical features were collected at admission and during hospitalisation. The electrocardiogram and analytical assessment (including a complete blood count, and biochemical and clotting tests) were performed according to ACCU standards at admission and followed by at least a daily frequency, according to each patient's clinical evaluation. The cTn I measurements were done at admission, between 12 and 24 h of admission, and daily thereafter. The measurement of cTn I was performed with the chemiluminescent technique (OrtoCLinical diagnostic Vitrus® Troponin I ES Assay, Johnson & Johnson©, High Wycombe, UK). The lower detection limit for this trial is 0.012 ng/ml. The 99th percentile upper reference limit is 0.034 ng/ml, with a reported imprecision of 10% of the coefficient of variation. Results greater than 0.034 ng/ml were considered positive. The creatinine clearance was estimated using the Modification of Diet in Renal Disease (MDRD) equation [11]. The reference for coronary angiography and potential percutaneous myocardial revascularisation was an individual-tailored decision, concerning ACCU and interventional cardiologists' clinical judgment, and according to European Society of Cardiology (ESC) guidelines for MI management [12, 13]. Finally, systolic global function from a pre-discharge transthoracic echocardiogram was obtained in accordance with European Association of Cardiovascular Imaging standards [14].

We tested and compared the prognostic performance of traditional risk stratification models – GRACE [8] and CRUSADE [9] – in both types of MI. Those risk models were evaluated for their overall discriminative performance and calibration in the prediction of in-hospital/follow-up all-cause mortality and in-hospital bleeding, respectively.

Patients were followed for 21.1 ± 7.5 months after their discharge by means of their clinical records, routine visits and phone calls after a 2-year period following discharge and whenever the clinical files were considered insufficient. A total of 67 patients were lost to follow-up and, to complete the data, the 2-year period vital status was derived from consultation of the National Health System User Card database.

Criteria for MI Types

MI characterisation as type 1 or type 2 followed the 2012 consensus document [2], as outlined below.

Type 1

An event related to atherosclerotic plaque instability with resulting intraluminal thrombus, and followed by a decreased myocardial blood flow. The patient usually presents with severe CAD, although no CAD was not considered an excluding finding.

Type 2

MI where a condition other than CAD contributed to an imbalance between oxygen demand and/or supply. The coronary artery system may be normal or present lesions; however, it must be considered a stable CAD (angiography). Other findings related to type 2 MI were coronary artery spasm and coronary embolism on angiography. As per the ESC guidelines, MI may be considered type 2

Table 1. Type 2 MI-triggering mechanisms

MI mechanism	Overall (n = 236)
Severe anaemia	16 (6.8%)
Shock (cardiogenic, hypovolemic, septic)	27 (11.4%)
Severe respiratory failure	22 (9.3%)
Brady-/tachyarrhythmia	41 (17.4%)
Pulmonary oedema	20 (8.5%)
Severe aortic stenosis	15 (6.4%)
Coronary emboli	12 (5.1%)
Coronary spasm/endothelial dysfunction	11 (4.7%)
Hypertension	38 (16.1%)
Mixed/unresolved	34 (14.4%)

in the presence of severe anaemia, brady-/tachyarrhythmias, shock, severe respiratory failure, hypertension, severe aortic valve disease and other causes. Since the MI consensus document does not establish any specific cut-off points for the aforementioned myocardial lesion triggers (i.e. anaemia, respiratory failure), the study investigators used all available data and relied on clinical judgement to establish type 2 MI, whenever type 1 MI was carefully excluded. The presumed mechanisms leading to type 2 MI were classified into pre-defined categories (table 1) [2]. In some type 2 MI cases admitted with typical MI symptoms and 12-lead electrocardiogram the trigger could not be recognised, yet those patients also presented features of heart failure (i.e. pre-/pulmonary oedema) and were ultimately categorised by their clinical presentation.

Study Endpoints

The primary outcome measures were: (i) in-hospital all-cause mortality, and (ii) all-cause mortality during follow-up. The secondary endpoints of this study were: (i) in-hospital significant bleeding (defined as per the CRUSADE investigators [9]); (ii) follow-up re-infarction; (iii) heart failure (HF) hospitalisation, and (iv) stroke during follow-up. The latter was defined as the occurrence of an International Classification of Diseases diagnosis of embolic stroke [15], confirmed through cerebral computed tomography. A composite endpoint, consisting of all-cause mortality during follow-up, in-hospital bleeding, follow-up re-infarction, HF hospitalisation and stroke, was also defined as an overall measure of morbimortality.

Statistical Analysis

Statistical analysis was done using SPSS®, v.17.0. When needed, baseline characteristics were described with the mean ± standard deviation for continuous variables, and counts and proportions for categorical data. The Kolmogorov-Smirnov test was used to test the normal distribution of continuous variables. The χ^2 test, Student t test and non-parametric equivalent tests were used when appropriate. Regression estimation techniques were applied to replace missing values whenever the number of missing values was negligible, otherwise cases with missing values were omitted. p values <0.05 (two-sided) were considered statistically significant.

Univariate analysis was performed to evaluate a potential association between the types of MI and the study endpoints. Discrimination usually measured in terms of the area under (AUC) each receiver operating characteristic (ROC) curve was performed to assess the predictive power of the in-hospital version of the GRACE score ($GRACE_{IH}$) and the 6-month post-discharge score ($GRACE_{6M}$) for in-hospital and follow-up mortality, respectively, and of the CRUSADE model for in-hospital significant bleeding. Calibration of each score was also assessed through the Hosmer-Lemeshow test. Moreover, Kaplan-Meier curves were constructed to evaluate survival during follow-up according to MI types and performance of myocardial revascularisation. In order to evaluate the independent value of variables associated with the study endpoints, we used a time-to-event model (Cox regression or proportional hazards regression), a multivariate analysis method that analyses outcomes over time.

Results

Cohort Characteristics

The cohort included a total of 1,000 patients, with a mean age of 68.7 ± 13.4 years (range 29–99); 60.2% were male, 45.2% had a diagnosis of ST-segment elevation MI (STEMI) and 76.4% (764/1,000) had type 1 MI. Table 1 presents the presumed triggering mechanism of the type 2 MIs.

The patient baseline clinical, analytic and imaging characteristics and subanalysis according to type 1 and type 2 MI are shown in table 2. Type 2 patients were older and more frequently male, had longer hospital stays and a higher prevalence of comorbidities (i.e. cardiovascular risk factors, stroke, atrial fibrillation). Moreover, they presented with worse clinical signs and several worse analytical parameters at admission, as well as higher GRACE and CRUSADE risk scores. In contrast, the type 1 MI group had a higher prevalence of STEMI diagnosis, underwent coronary angiography and percutaneous/surgical revascularisation more frequently, and had higher mean peak cTn I levels.

Mortality Analysis

In the population sample, the in-hospital mortality rate was 8.9% (n = 89), and 16.9% (n = 154) of patients died during follow-up. Patients who reached the primary endpoints were older, had several worse clinical and analytical findings, and higher GRACE and CRUSADE scores (table 3). The predictors of death on univariate analysis are shown in table 4, featuring myocardial revascularisation (either percutaneous or surgical), which was associated with a lower risk of in-hospital (HR 0.29, 95% CI 0.17–0.48, p < 0.001) and follow-up mortality (HR 0.26, 95% CI 0.18–0.38, p < 0.001). Moreover, in-hospital mortality did not differ significantly between type 1 and type 2 MI [n = 66 (8.8%) vs. 23 (9.7%), p = 0.602], despite

Table 2. Sample characteristics and subanalysis according to type 1 and type 2 MI

	Overall (n = 1,000)	Type 1 MI (n = 764)	Type 2 MI (n = 236)	p value
Demographics				
Age, years	68.7±13.4	67.4±13.6	72.8±12.1	<0.001
Male gender	638 (63.8%)	510 (66.8%)	128 (54.2%)	<0.001
Clinical				
Hospital stay, days	5.9±4.4	5.6±4.3	6.7±4.9	0.001
Arterial hypertension	774 (77.4%)	580 (75.9%)	192 (82.2%)	0.044
Diabetes mellitus	357 (35.7%)	249 (32.6%)	108 (45.8%)	<0.001
Dyslipidaemia	567 (56.7%)	442 (57.9%)	125 (53.0%)	0.185
Atrial fibrillation	189 (18.9%)	117 (15.3%)	72 (30.5%)	<0.001
Previous stroke	88 (8.8%)	59 (7.7%)	29 (12.3%)	0.030
ST-elevation MI	452 (45.2%)	417 (54.6%)	35 (14.8%)	<0.001
Systolic arterial pressure, mm Hg	131.3±26.4	130.5±35.6	134.0±25.6	0.075
Heart rate, bpm	77.4±18.1	76.2±17.4	81.4±19.9	0.003
Killip-Kimball class (admission)	1.4±0.7	1.3±0.8	1.5±0.7	<0.001
GRACE score				
In-hospital	158.5±42.8	156.4±42.5	165.1±43.7	<0.001
Follow-up	129.2±35.2	126.6±35.0	137.4±34.7	<0.001
CRUSADE score	34.8±16.1	32.8±15.4	41.3±17.0	<0.001
In-hospital mortality	89 (8.9%)	66 (8.8%)	23 (9.7%)	0.602
Follow-up mortality	154 (16.9%)	92 (13.4%)	62 (29.1%)	<0.001
Ancillary tests				
Haemoglobin, g/dl	13.4±1.9	13.7±1.9	12.7±2.0	<0.001
Glycaemia, mmol/l	8.8±4.8	8.7±4.8	9.0±4.7	<0.001
Haemoglobin A1c, %	6.5±1.6	6.4±1.6	6.6±1.6	0.005
Serum creatinine, µmol/l	118.3±100.8	110.2±84.7	144.7±137.7	<0.001
Creatinine clearance[1], ml/min	68.2±29.3	70.9±27.9	59.5±31.9	<0.001
Maximum troponin I, ng/ml	47.8±87.7	57.9±96.6	15.2±32.9	<0.001
NT-proBNP, pg/ml	7,167.9±16,775.9	5,614.5±14,409.0	12,145.9±22,086.5	<0.001
Coronary angiography	740 (74.0%)	619 (81.0%)	121 (51.2%)	<0.001
Coronary revascularization	534 (53.4%)	507 (66.3%)	27 (11.4%)	<0.001
Left ventricle ejection fraction <40%[2]	137 (13.7%)	104 (13.6%)	33 (14.0%)	0.289

[1] Clearance of creatinine as per MDRD. [2] Pre-discharge transthoracic echocardiogram.

Table 3. Sample mortality analysis

	In-hospital survival (n = 911; 91.1%)	In-hospital mortality (n = 89; 8.9%)	p value	Follow-up survival (n = 757; 83.1%)	Follow-up mortality (n = 154; 16.9%)	p value
Age, years	68.0±13.4	76.1±10.9	<0.001	65.9±13.3	77.4±9.8	<0.001
Systolic arterial pressure, mm Hg	132.5±26.0	119.2±27.5	<0.001	132.9±26.4	131.9±25.1	0.642
Heart rate, bpm	76.9±17.7	83.2±21.4	0.001	76.1±17.6	80.9±18.9	0.003
Killip-Kimball class (admission)	1.3±0.7	2.2±1.1	<0.001	1.2±0.6	1.6±0.8	<0.001
Haemoglobin, g/dl	13.5±2.0	12.8±2.2	0.008	13.8±1.9	12.2±2.0	<0.001
Glycaemia, mmol/l	8.5±4.6	11.7±5.9	<0.001	8.3±4.7	9.4±4.4	<0.001
Haemoglobin A1c, %	6.5±1.5	8.0±2.8	0.001	6.4±1.5	6.6±1.4	0.005
Serum creatinine, µmol/l	115.4±101.1	149.4±92.1	<0.001	102.1±75.0	176.1±173.5	<0.001
Creatinine clearance[1], ml/min	70.0±28.9	49.5±26.7	<0.001	75.3±27.1	48.3±27.5	<0.001
Maximum troponin I, ng/ml	44.4±81.6	86.7±135.0	<0.001	43.0±80.0	47.4±93.8	0.590
NT-proBNP, pg/ml	6,279.1±15,805.5	18,459.1±23,564.7	<0.001	3,238.1±8,124.4	17,561.4±27,288.1	<0.001
$GRACE_{IH/6M}$ score	153.7±39.8	207.6±42.6	<0.001	119.8±31.8	151.2±29.5	<0.001
CRUSADE score	33.5±15.7	48.3±15.0	<0.001	30.6±14.7	45.9±14.4	<0.001
Coronary lesions, n	1.5±1.0	2.1±0.9	0.001	1.5±0.9	1.8±1.3	0.017

[1] Clearance of creatinine as per MDRD.

Table 4. Predictors of in-hospital and follow-up mortality in univariate analysis (categorical variables)

	In-hospital mortality		Follow-up mortality	
	HR; 95% CI	p value	HR; 95% CI	p value
Male gender	1.42; 0.91–2.21	0.117	1.49; 1.05–2.12	0.027
Age ≥75 years	2.37; 1.52–3.69	<0.001	4.72; 3.25–6.87	<0.001
Arterial hypertension	1.37; 0.78–2.40	0.275	1.65; 1.04–2.62	0.033
Diabetes mellitus	1.52; 0.98–2.37	0.059	1.74; 1.22–2.48	0.002
Atrial fibrillation	2.23; 1.38–3.62	0.001	2.78; 1.87–4.14	<0.001
Stroke	1.73; 0.90–3.32	0.096	3.00; 1.78–5.05	<0.001
Type 2 MI	1.14; 0.69–1.88	0.602	2.75; 1.89–3.99	<0.001
Myocardial revascularisation	0.29; 0.17–0.48	<0.001	0.26; 0.18–0.38	<0.001
Left ventricle ejection fraction <40%[1]	15.10; 6.33–36.05	<0.001	4.71; 2.94–7.55	<0.001

[1] Pre-discharge transthoracic echocardiogram.

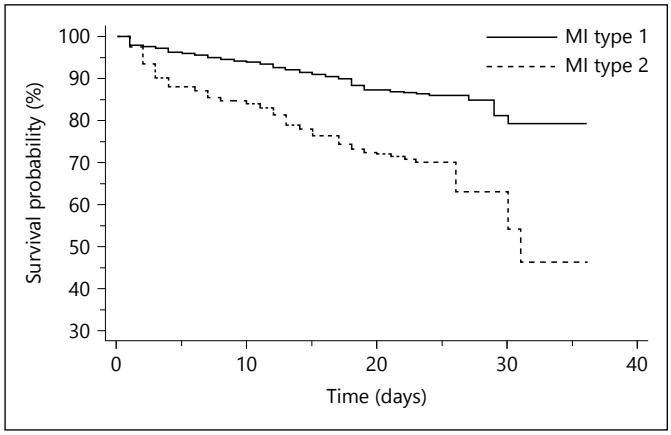

Fig. 1. Cumulative incidence of mortality during follow-up for patients with type 1 and type 2 MI.

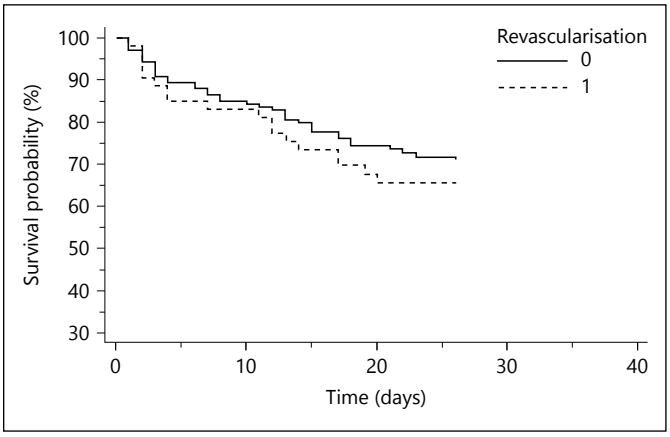

Fig. 2. Type 2 MI cumulative incidence of mortality during follow-up, according to myocardial revascularisation.

the higher mean GRACE risk score found in type 2 MI patients. Mortality during follow-up was higher in the type 2 MI group [n = 92 (12.0%) vs. 62 (26.3%), HR 2.75, 95% CI 1.89–3.99, p < 0.001), and the cumulative incidence of death during follow-up is shown in figure 1. The time-to-event model (Cox regression) revealed that the prognostic value of type 2 MI (HR 1.89, 95% CI 1.36–2.62, p < 0.001) was independent and additive to that of the $GRACE_{6M}$ score (HR 1.03, 95% CI 1.02–1.03, p < 0.001) for mortality during follow-up.

Revascularisation and MI Types

The rate of revascularised (surgical and/or percutaneous) type 2 MI patients was small compared to type 1 MI (table 2). Myocardial revascularisation in type 1 MI had a beneficial impact on both in-hospital [n = 28 (42.9%) vs. 38 (57.1%), HR 0.23, 95% CI 0.13–0.41, p < 0.001] and follow-up mortality [n = 43 (46.5%) vs. 49 (53.5%), HR 0.29, 95% CI 0.18–0.47, p < 0.001]. In the case of type 2 MI, the performance of myocardial revascularisation was associated with a trend for lower in-hospital mortality [n = 5 (21.7%) vs. 18 (78.3%), p = 0.080], and a significant lower follow-up mortality [n = 5 (7.5%) vs. 57 (92.5%), HR 0.33, 95% CI 0.11–0.98, p = 0.041; fig. 2].

Risk Score Performance

The $GRACE_{IH}$ (for in-hospital mortality) and $GRACE_{6M}$ (for follow-up mortality), and CRUSADE (for in-hospital bleeding) were tested in our cohort, and their discrimination performances are displayed in table 5. In the type 1 MI group, $GRACE_{IH}$ and $GRACE_{6M}$ showed higher areas under the ROC curves for the

Table 5. Cohort risk model performance and subgroup analysis, according to MI type

	Overall		Type 1 MI		Type 2 MI	
	AUC; 95% CI	p value	AUC; 95% CI	p value	AUC; 95% CI	p value
$GRACE_{IH}$	0.82; 0.78–0.86	<0.001	0.82; 0.78–0.88	<0.001	0.79; 0.71–0.87	<0.001
$GRACE_{6M}$	0.78; 0.74–0.82	<0.001	0.80; 0.74–0.84	<0.001	0.74; 0.66–0.81	<0.001
CRUSADE	0.70; 0.64–0.76	<0.001	0.64; 0.55–0.73	0.001	0.74; 0.66–0.82	<0.001

prediction of the respective endpoints. In contrast, the CRUSADE model showed a superior discrimination performance in type 2 MIs. All scores showed good calibration in both MI types, as demonstrated by Hosmer-Lemeshow test p values >0.05.

Secondary Endpoints

In the type 2 MI group, we found a higher bleeding rate [n = 31 (13.1%) vs. 48 (6.4%), HR 2.26, 95% CI 1.40–3.63, p = 0.001], and a trend concerning stroke during follow-up [n = 18 (8.5%) vs. 30 (4.4%), HR 1.73, 95% CI 0.92–3.25, p = 0.084]. Concerning bleeding complications, the multivariate model included the variables, 'haemoglobin levels' (p = 0.001) and 'creatinine clearance' (p = 0.007).

No significant differences between both groups were found regarding reinfarction [n = 33 (15.5%) vs. 85 (12.3%), p = 0.239] and HF hospitalisation [n = 51 (22.1%) vs. 138 (18.5%), p = 0.230]. The composite endpoint, an overall measure of morbimortality, was higher in type 2 MIs [n = 99 (41.9%) vs. 212 (28.1%), HR 2.02, 95% CI 1.45–2.82, p < 0.001].

Discussion

Although MI types have been defined since 2007 [16], research conducted to characterise MI classes and their implications on clinical practice and trials is very limited. Our study demonstrated important differences between these two common MI types, concerning baseline characteristics, prognosis, risk stratification performance and myocardial revascularisation.

The distinction of type 1 and type 2 MIs may not always be clear in daily practice and the latter is a particularly heterogeneous group, involving many underlying injury mechanisms, such as arrhythmias, shock, respiratory failure or severe aortic valve stenosis in patients with or without CAD. Certainly, in some cases different and simultaneous kinds of lesion concur (i.e. coronary spasm and thrombosis) and, in others, the true cause of injury may be impossible to ascertain [17]. Moreover, the latest definition of MI [2] does not establish what should be considered severe anaemia or respiratory failure, hyper- or hypotension, or what ought to be a significant arrhythmia. Some patients might tolerate a noteworthy variation in their vital signs and others may suffer a type 2 MI with only small increases in the heart's workload. It is noteworthy that type 2 MI diagnosis and identification of its trigger mechanism largely relies on clinical judgment, and warrants careful exclusion of type 1 MI and myocardial cell death (i.e. troponin rise) without ischaemia involvement. Our study's method aimed at ameliorating potential selection bias by assigning two co-investigators to separately classify the cohort, followed by a third party that revised unsettled MI cases.

We found that type 1 MI (76.4%) was much more prevalent than type 2 MI (23.6%), as has been previously reported [18–21]. The most frequent triggers for type 2 MI in our cohort were brady-/tachyarrhythmias (17.4%) and hypertensive crisis (16.1%). However, in many cases the MI mechanism was not clearly established (14.4%), despite all the available patient clinical data. Only a few studies in the literature have identified type 2 MI triggers using a suitable approach and adjudicating the final diagnosis through independent reviewers. Saaby et al. [18] specifically evaluated type 2 MI and showed that anaemia, tachyarrhythmias and respiratory failure were the most prevalent conditions underlying type 2 MI.

In our cohort, regardless of the underlying illness, type 2 MI patients were older, had prolonged hospital stays, a higher prevalence of comorbidities and worse medical status depicted by admission clinical (arterial pressure, heart rate, Killip class) and analytical findings (haemoglobin, creatinine clearance, NTproBNP) as well as through traditional risk stratification schemes (GRACE, CRUSADE). Consequently, this set of patients may have a major impact on medical resources and costs (i.e. complex medical conditions, specialist referral, coronary angiography, hospital stay) [22]. Although type 2 MI patients had worse illness indicators, namely GRACE score

values, in-hospital mortality did not differ significantly within the two MI groups. This finding may suggest the following: first, the severe medical condition causing MI does not confer a poorer in-hospital prognosis, second, the traditional illness markers may be less accurate when applied to a type 2 MI setting and, finally, type 2 MI patients seemed to at least benefit as much from the standard management of acute ischaemia as the type 1 MI group. Nonetheless, mortality during follow-up was 3 times higher in type 2 MIs (HR 2.75, $p < 0.001$), with an increasing cumulative incidence of death throughout follow-up. Moreover, the occurrence of type 2 MI was an independent mid-term mortality marker, adding prognostic power to $GRACE_{6M}$. The lower follow-up survival may presumably be the reflection of differences in baseline characteristics between MI types. Furthermore, we should keep in mind the heterogeneity of the type 2 MI group, and question if standard secondary MI prevention is a truly valuable and/or safe option for these patients, since CAD was often unchanged (stable) from previous remote evaluations or no coronary culprit lesion was found on angiography. Further research is needed to clarify the causes of increased long-term mortality, assess the prognostic impact of the triggering mechanisms, and maybe rethink management strategies (thromboembolism and atherothrombosis prevention, heart remodelling, sudden cardiac death) to improve outcomes for these challenging patients.

A key section of our research was to evaluate the differences in traditional risk score performances. We found that $GRACE_{IH}$ (for in-hospital mortality) and $GRACE_{6M}$ (for follow-up mortality) presented lower discriminatory power when applied to type 2 MIs (smaller AUCs). Those patients had a significantly higher $GRACE_{IH}$, yet this was not translated into a higher in-hospital mortality rate. The less accurate risk stratification should be carefully considered in these cases, since it may have important clinical implications, including failure to capture the true mortality risk or misclassification of patients as high-risk, subjecting them to more aggressive management with its potential complications. Interestingly, the CRUSADE model showed superior discriminative performance in the type 2 MI group, which was composed of older patients and with a higher prevalence of comorbidities (diabetes, renal dysfunction, anaemia). In this case, risk stratification was better accomplished in the high-risk bleeding group (type 2 MIs). Recommendations on MI management [8] advise on the use of the GRACE and CRUSADE risk stratification scores to allow the quantification of the ischaemic and bleeding burden. Our results showed that identifying the MI type is also an important issue to be taken into consideration in the initial patient approach and, mainly, in the long-term to allow a more rational therapeutic decision making.

Regarding secondary endpoints, we found that in-hospital bleeding was twice more frequent in type 2 MIs (HR 2.26, $p = 0.001$). This finding raises concerns about certain drugs used in standard MI treatment which target platelet activity and coagulation cascade, and may imply that we should eventually consider a more conservative management in high-bleeding risk settings. However, type 2 MI patients also appeared to represent a high-risk population for stroke, which in theory would benefit from antiplatelet therapy or anticoagulation. Additionally, re-infarction and HF hospitalisation rates did not significantly differ between the groups. Therefore, such events did not seem to explain the higher follow-up mortality rate found in type 2 MIs. Finally, the overall measure of morbimortality (composite endpoint) was significantly higher within the type 2 MI group (HR 2.02, $p < 0.001$), reflecting the patients' medical complexity and frailty. Although the cause of death was not presented in this study, our results showed a higher prevalence of non-cardiac endpoints (bleeding complications and a trend in stroke) in type 2 MIs, and no differences between other cardiac endpoints (re-infarction, heart failure), possibly implying that type 2 MI patients may be at higher risk for non-cardiac death.

The reference for myocardial revascularisation should derive from an individual patient discussion of potential procedure benefits and complications. In our cohort, the vast majority of cases submitted to revascularisation were type 1 MI patients (95% of all procedures), which had an expected strong impact on both in-hospital (HR 0.23, $p < 0.001$) and follow-up mortalities (HR 0.29, $p < 0.001$). Although more than half of type 2 MI cases underwent coronary angiography, only a small number of patients were actually submitted to a revascularisation procedure ($n = 27$). This finding seems to be in accordance with the type 2 MI definition, which states that the coronary system is not unstable in this subgroup and a condition other than CAD leads to an ischaemic myocardial injury. The latter impression was further reinforced as we did not find a significant association between myocardial revascularisation and in-hospital mortality ($p = 0.080$). However, our results showed that revascularised type 2 MI patients had a lower follow-up mortality (HR 0.33, $p = 0.041$). Although it may simply represent an ill-defined MI type, it may also imply that a minority of type 2 MIs benefit from myocardial revascularisation, since type 2 MI patients are known to be at a higher risk of recurring MI. However, as

these patients are discharged in a stable condition on medical treatment, myocardial revascularisation should only be recommended if myocardial ischaemia is documented on further testing or symptom recurrence [22].

The worldwide adoption of the universal definition of MI by clinical trials will certainly have a huge impact on result reliability, since many clinical trials to date have not used a consistent MI definition [23]. For instance, in the CHAMPION study [24], the implementation of the new definition changed the results of that trial. In the first study, the reversible P2Y12 inhibitor cangrelor was not found to be superior to clopidogrel in reducing the primary endpoint. However, when the studies were re-analysed applying a universal definition of MI, cangrelor was associated with a significant benefit compared with clopidogrel in patients undergoing PCI [25]. The same phenomenon may continue to occur if trial protocols start to demand differentiating of the type of MI, setting apart type 1 from type 2 MI patients.

In our view this study provided support to a common thinking that type 1 and type 2 MI patients are truly different from each other. The distinction of these MI types, given by the universal definition of MI, may have a strong impact in daily clinical practice and trial protocol design. It is our belief that by acknowledging MI heterogeneity, we will better tailor MI management and improve outcomes.

Limitations

This was a single-centre case-control study that included MI patients admitted to the ACCU, disregarding those who may have had a proper MI diagnosis in other hospital wards (medical or surgical). The main limitation of this study was the potential inaccurate definition of the MI mechanism and, subsequently, type 1 and type 2 MI categorisation that strongly relies on clinical judgment. Additionally, the distinction of myocardial injury (without findings of ischaemia) from a correct MI diagnosis may also be challenging in some cases. However, the chosen study's method intended to reduce interobserver variability, and conflicting results were decided by an independent referee. There is no test confirming/excluding the presence of ischaemia, hence, the investigators could only assemble all available information (patient history, symptoms and signs, analytical parameters, electrocardiographic and imaging findings, clinical evolution) and make a judgement according to MI consensus criteria. The relatively small number of patients with type 2 MI (n = 236) and an even smaller subgroup of revascularised type 2 MI cases represent further significant limitations, which should be considered by the reader. Although this study provides an honest attempt at evaluating MI classes, our results still warrant further validation in larger and independent cohorts before drawing any clinical applicability from this data.

Conclusions

Type 1 MI was much more frequent than type 2 MI, and several important baseline differences were found between the groups. We found no difference regarding in-hospital mortality, though long-term survival was significantly compromised in type 2 MI patients. These patients had a higher rate of in-hospital bleeding and higher overall morbimortality. Moreover, discrepancies were identified in the performance of traditional risk scores between MI classes. The distinction of MI into several types respects the heterogeneity found in an MI population, and may have a strong impact on daily clinical practice and trial results.

Disclosure Statement

The authors have no financial or non-financial competing interests to disclose.

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