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Impact of clinical diagnosis of myocardial infarction in patients with elevated cardiac troponin

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ABSTRACT

Objective Type 2 myocardial infarction (MI) and myocardial injury are common conditions associated with an adverse prognosis. Physicians experience uncertainty how to distinguish these conditions, as well as how to manage and treat them. Therefore, the objective of this study was to compare treatment and prognosis in patients with an adjudicated diagnosis of type 2 MI and myocardial injury, who were discharged with and without a clinical diagnosis of MI.

Design The study consisted of two cohorts, 964 and 281 consecutive patients with elevated cardiac troponin, discharged with and without a clinical diagnosis of MI, respectively. All cases were adjudicated into MI type 1–5 or myocardial injury and followed regarding all-cause death.

Results The adjudication identified 138 and 37 cases of type 2 MI, and 86 and 185 of myocardial injury, with and without a clinical MI diagnosis, respectively. In patients with type 2 MI, a clinical MI diagnosis was associated with more coronary angiography investigations (39.1% vs 5.4%, p<0.001) and an increased use of secondary prevention medications (all p<0.001). However, no difference was observed in adjusted 5-year mortality between patients with and without a clinical MI diagnosis (HR: 0.77 with 95% CI 0.43 to 1.38). The results were similar for adjudicated myocardial injury.

Conclusion In both type 2 MI and myocardial injury, a clinical diagnosis of MI at discharge was associated with more investigations and treatments. However, no prognostic effect of receiving a clinical MI diagnosis was observed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Type 2 myocardial infarction (MI) and myocardial injury are heterogeneous conditions that are difficult to distinguish in clinical practice. The therapeutic and prognostic effects of assessing either of these serious conditions as MI or not are unknown.

WHAT THIS STUDY ADDS

⇒ Receiving a clinical diagnosis of MI was associated with more cardiology care including an increased use of coronary assessments and secondary preventive therapies both in patients adjudicated as having type 2 MI and myocardial injury, respectively. However, no long-term prognostic effect of receiving a clinical diagnosis of MI was observed for either of these conditions.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The use of the term MI among patients currently defined as type 2 MI and myocardial injury, as well as the current distinction between these conditions, may not be clinically relevant. Further studies are needed to identify patients for whom specific and prognostically relevant recommendations could be applied.

INTRODUCTION

Measurement of cardiac troponin (cTn) levels in blood is recommended in patients presenting with a suspected acute coronary syndrome and levels above the 99th percentile with a significant rising and/or falling pattern is an obligatory criterion for a diagnosis of myocardial infarction (MI).[1] However, elevated levels of cTn are a common finding also in the absence of the coronary atherothrombotic event that currently defines type 1 MI. Among patients with elevated cTn at emergency departments, 19%–35% have been reported to have type 2 MI and 35%–56% to have non-ischaemic myocardial injury (later referred to as myocardial injury).[2–4] These are two different conditions according to the current classification of MI, where type 2 MI is caused by ischaemia due to myocardial oxygen supply/demand mismatch, while myocardial injury is thought to be caused by non-ischaemic mechanisms and therefore not classified as MI.[1] However, type 2 MI and myocardial injury are resembling each other in many aspects. They are both provoked by or associated with other underlying disease, often occur in older, multimorbid individuals and are both associated with a poor short-term and long-term prognosis.[5] Due to the difficulty to distinguish type 2 MI from myocardial injury, misclassification is common and there is a large variation in the use of an MI diagnosis in both these conditions in clinical practice.[6 7] However, the effects on therapeutic strategies and prognosis of receiving a clinical diagnosis of MI in these conditions are unknown. In the light of this, the aims of this study were (1) to describe patients with elevated cTn that were not clinically diagnosed as having MI, and (2) to compare treatment strategies and prognosis among patients with an adjudicated diagnosis of type 2 MI and myocardial injury with and without a clinical diagnosis of MI at discharge.

METHODS

Clinical diagnosis of MI

During the study period, clinicians recorded diagnoses according to the 10th revision of International Statistical Classification of Diseases and Related

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Health Problems (ICD-10). The ICD-10 code I.21 was used to identify patients with a clinical diagnosis of MI regardless of ST-elevation myocardial infarction or non-ST elevation myocardial infarction. ICD-10 does not include specific codes for MI subtypes.

Study population

Two patient cohorts were used in this observational study, one which included patients with elevated cTn but without a clinical MI diagnosis (no ICD-10 code: I.21) and one which included patients with a clinical MI diagnosis (with ICD-10 code: I.21).

All 17 122 patients with a cTn measurement at Uppsala University Hospital in 2011 were identified using the local laboratory records. After exclusion of patients without elevated cTn values and patients with a clinical MI diagnosis, 3218 with at least one cTn measurement above the 99th percentile upper reference limit remained. From these, the first 300 patients with at least one additional cTn measurement within 24 hours were selected for inclusion.

The second cohort consisted of 964 consecutive patients with a clinical MI diagnosis at discharge from eight Swedish hospitals of different size and geographical location in 2011 (figure 1 and online supplemental figure S1).

Data collection

Data were collected from the local electronic patient records in a similar way for the two patient cohorts, using a pre-specified case report form (including dates, demographical information, clinical parameters, laboratory results, results from invasive and non-invasive investigations and treatment). Copies of ECGs and relevant medical notes were also collected from the electronic patient records.

Date of death was provided by the Swedish Tax Agency.

Diagnosis adjudication

Based on the collected information, all patients in both cohorts were adjudicated and classified into MI subtypes 1–5 or myocardial injury by two independent reviewers (online supplemental table S1 and S2). In case of disagreement, a third independent reviewer decided the final diagnosis. The classification was done using a pre-specified form based on the Third Universal Definition of MI and the reviewers were physicians (cardiologists or cardiology residents) or physicians in training, specially trained in the MI classification presented in the Third Universal Definition of MI (online supplemental file—definition of MI and myocardial injury subtypes).[8] In addition to the diagnosis adjudication, reviewers also assessed the underlying condition

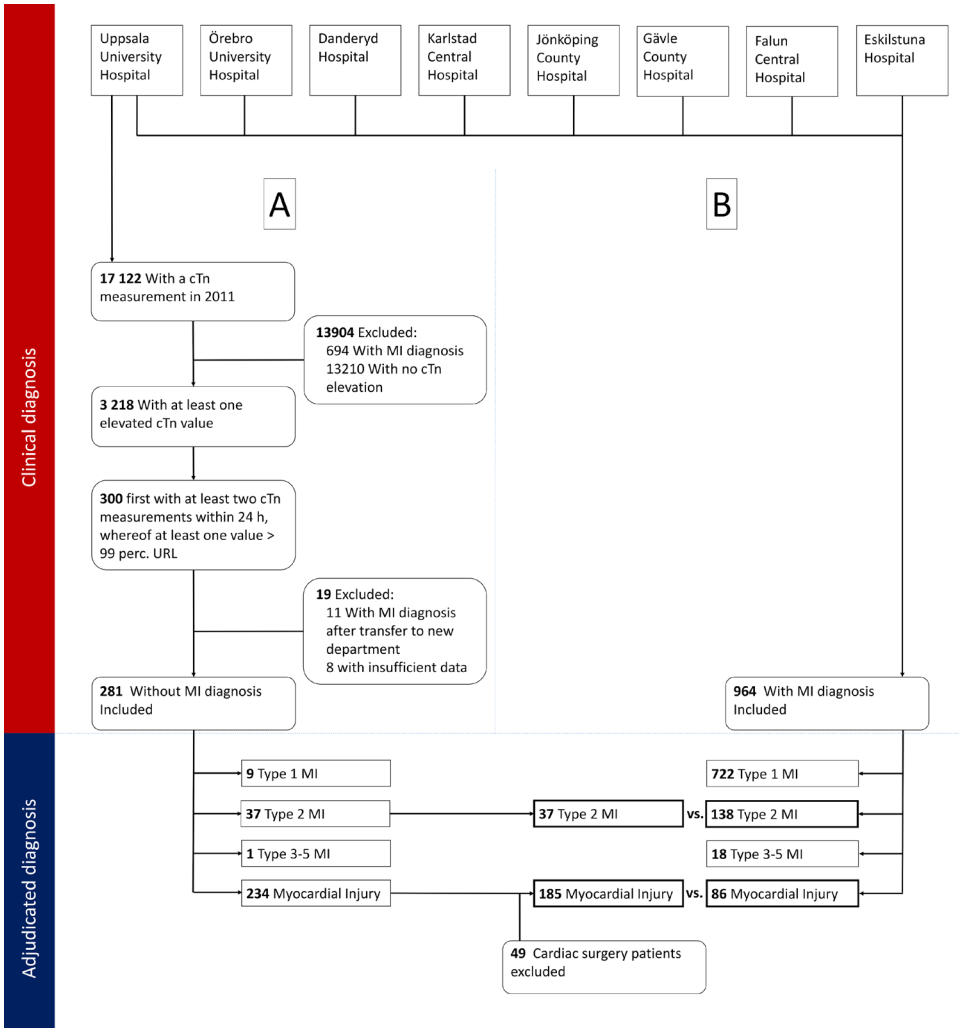

Figure 1 Patient selection and diagnosis adjudication for(A) patients with elevated troponins without a clinical MI diagnosis and for (B) patients with a clinical MI diagnosis. cTn, cardiac troponin; MI, myocardial infarction; URL, upper reference limit.

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Table 1 Characteristics of patients with elevated cardiac troponins

	Without clinical MI diagnosis	With clinical MI diagnosis
Total number of patients	281	964
cTn dynamics >20%, n (%)	233 (82.9)	796 (92.8)*
Cardiovascular risk factors		
Age, mean (SD)	73.3 (14.2)	72.8 (12.5)
Male sex	159 (56.6)	605 (62.8)
Active smoking†	34 (12.1)	181 (18.8)
Hypertension	166 (59.1)	523 (54.2)
Hyperlipidaemia	36 (12.8)	254 (26.3)
Diabetes mellitus	60 (21.3)	218 (22.6)
Medical history		
MI	77 (27.4)	297 (30.8)
Heart failure	69 (24.6)	139 (14.4)
COPD	22 (7.8)	68 (7.0)
Dementia	19 (6.8)	42 (4.4)
Investigations in hospital		
Coronary angiography	12 (4.3)	680 (70.5)
Echocardiography	83 (29.5)	612 (63.5)
Alive at discharge	257 (91.5)	875 (90.8)
Treatment at discharge, % of alive		
Aspirin	120 (46.7)	826 (94.4)
Statin	74 (28.4)	714 (81.6)
Beta-blocker	155 (60.3)	761 (87.0)
Death during follow-up (mean 6.0 years)	160 (56.9)	397 (41.2)

Values are number (%).
*11% of patients with a clinical diagnosis of MI had less than two recorded troponin values.
†16.4% missing data for patients without a clinical MI diagnosis and 17.0% for patients with a clinical MI diagnosis.
COPD, chronic obstructive pulmonary disease; cTn, cardiac troponin; MI, myocardial infarction.

triggering the ischaemic (in case of type 2 MI) or non-ischaemic myocardial injury.

Troponin assay

Several different cTn assays, conventional and high-sensitive, were used in the participating hospitals. Therefore, all cTn values presented on a group level were standardised by division with the 99th percentile upper reference limit of the assay used.[8]

Uppsala University Hospital mainly used Abbott Architect STAT troponin I during the study period.

Outcomes and follow-up

The analysed outcome was all-cause mortality. Follow-up started from hospital arrival and continued until the 1 February 2017.

Statistics

For all statistical analyses, a p value <0.05 was considered to indicate statistical significance. Groups were compared using Mann-Whitney U test for non-normally distributed continuous variables, Student's t-test for normally distributed continuous variables and Pearson's χ^2 test for categorical variables. Related samples were compared with McNemar's test.

Agreement between the reviewers in the MI classification was analysed with Cohen's kappa.

To compare time to all-cause mortality in patients with and without a clinical MI diagnosis at 1 year and 5 years of follow-up, Kaplan-Meier survival estimates and multivariable Cox regression models were created. The proportional hazards assumption was tested by analysing the correlation between Schoenfeld residuals and survival time and was met in survival analyses starting at 30 days after hospital admission.[9] In addition to crude analysis, the following models were used:

Model 1: Adjustment for age, sex, active smoking and modified Charlson comorbidity index (1 p for MI, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease and history of bleeding; 1.5 p for diabetes mellitus; 2 p for kidney disease and liver disease; 6 p for metastatic tumour).

Model 2: As per model 1 plus heart rate at admission, systolic blood pressure at admission, reaction level scale (RLS) >1 at admission (yes or no), creatinine level at admission, maximal troponin level, maximal C reactive protein (CRP) level and invasive or non-invasive ventilation during hospital stay (yes or no).

In addition, frailty models with random effect were used to account for the clustering by hospital.[10]

Multiple imputation of missing values of current smoking, heart rate, blood pressure, RLS level, troponin level (one patient with type 2 MI and two with myocardial injury) CRP level and creatinine level was performed (using the SAS function PROC MI and arbitrary missing pattern) with all variables in the covariate section used to produce the values for imputation. Fifty imputed datasets were used to ensure that the effect estimates were not overly inaccurate due to Monte Carlo variability. The results for each imputation were combined (using SAS function PROC MIANALYZE). In total, the proportion of missing data was 17.0% and 16.4% for current smoking and 12.8% and 0.4% for RLS level among patients with and without a clinical MI diagnosis, respectively. For the other covariates, less than 5% of the data were missing in both groups.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this study.

RESULTS

Description of patients without a clinical MI diagnosis

During the data collection process, 19 patients were excluded due to receiving an ICD-10 code I.21 after transfer to a new department or due to insufficient data. Consequently, 281 patients with elevated cTn between 1 January and 5 February 2011 but without a clinical MI diagnosis was included in further analyses (figure 1).

Clinical features among the 281 patients with elevated cTn but without a clinical MI diagnosis are presented in table 1 as well as in online supplemental table S3 and online supplemental figure S2. In 49 cases, the main reason for hospital admission was elective or subacute cardiac surgery. These patients are described in detail in online supplemental tables S4 and S5 and since they had a very distinctive clinical and prognostic profile, they were not included in the comparative analyses below.

Adjudicated diagnoses

Among the 281 patients with elevated cTn but without a clinical MI diagnosis, 47 (16.7%) met the MI criteria with 9 (3.2%) adjudicated as type 1 MI, 37 (13.2%) as type 2 MI and 1 (0.4%) as type 4a MI. The remaining 234 patients (83.3%), including all patients admitted for cardiac surgery, were adjudicated as myocardial injury (figure 1).

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Table 2 Characteristics and in-hospital treatment

Adjudicated diagnosis	Type 2 MI		P value	Myocardial injury		P value
Clinical MI diagnosis	Yes	No		Yes	No	
Total number of patients	138	37		86	185	
Age, mean (SD)	77.8 (10.7)	70.2 (13.6)	<0.01	78.5 (11.7)	76.0 (14.1)	0.15
Male sex, n (%)	69 (50.0)	17 (45.9)	0.66	53 (61.6)	98 (53.0)	0.18
Active smoking, n (%)*	14 (10.1)	9 (24.3)	0.11	8 (9.3)	20 (10.8)	0.54
Medical history, n (%)						
Hypertension	79 (57.2)	24 (64.9)	0.40	49 (57.0)	109 (58.9)	0.76
Hyperlipidaemia	25 (18.1)	1 (2.7)	0.02	21 (24.4)	21 (11.4)	<0.01
Diabetes mellitus	36 (26.1)	7 (18.9)	0.37	19 (22.1)	43 (23.2)	0.83
Myocardial infarction	57 (41.3)	13 (35.1)	0.50	36 (41.9)	48 (25.9)	<0.01
Heart failure	33 (23.9)	7 (18.9)	0.52	27 (31.4)	49 (26.5)	0.42
COPD	22 (15.9)	2 (5.4)	0.10	10 (11.6)	17 (9.2)	0.53
Clinical findings, median (IQR)						
Chest pain, n (%)	85 (61.6)	6 (16.2)	<0.01	36 (41.9)	24 (13.0)	<0.01
Oxygen saturation*	95 (6)	94.5 (6)	0.52	95 (5)	96 (4)	0.02
Systolic blood pressure	147 (60)	135 (68)	0.09	145 (39)	140 (40)	0.34
Heart rate	94 (41)	80 (33)	0.01	86 (35)	80 (30)	0.81
Reaction Level Scale >1, n (%)†	4 (3.3)	2 (5.4)	0.56	7 (8.1)	18 (9.7)	0.99
Laboratory results, median (IQR)						
cTn max value, std	25.0 (106.0)	9.6 (47.2)	<0.01	8.0 (39.7)	4.5 (12.8)	<0.01
cTn dynamic >20%, n (%)	127 (95.5)	35 (94.6)	0.82	55 (71.4)	143 (77.3)	0.31
CRP max value	16 (60)	101 (214)	<0.01	36 (110)	55 (148)	0.21
Haemoglobin at admission	126 (32)	138 (28)	<0.01	131 (21)	132 (27)	0.93
Creatinine at admission	92 (47)	89 (49)	0.24	102 (65)	93 (54)	0.20
In hospital care, n (%)						
Echocardiography	66 (47.8)	12 (32.4)	0.09	38 (44.2)	33 (17.8)	<0.01
Coronary angiography	54 (39.1)	2 (5.4)	<0.01	24 (27.9)	3 (1.6)	<0.01
Significant stenosis >50%	36 (66.7)	1 (50.0)		9 (37.5)	1 (33.0)	
PCI	19 (13.8)	1 (0.3)	0.06	10 (11.6)	0 (0.0)	<0.01
Fondaparinux SC	62 (44.9)	1 (2.7)	<0.01	32 (37.2)	5 (2.7)	<0.01
Antibiotics IV or PO	47 (34.1)	25 (67.6)	<0.01	32 (37.2)	94 (50.8)	0.04
Invasive/non-invasive ventilation	13 (9.4)	10 (27.0)	<0.01	9 (10.5)	22 (11.9)	0.73

P values for adjudicated type 2 MI and myocardial injury patients with vs without a clinical MI diagnosis.
*18% missing data
†7% missing data
COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; cTn, cardiac troponin; MI, myocardial infarction; n, number; PCI, percutaneous coronary intervention; PO, per oral; SC, subcutaneous; std, standardised value (multiplies of the 99th percentile URL regardless of assay).

Among the 964 patients with a clinical MI diagnosis, 878 (91.1%) met the MI criteria with 722 (74.9%) adjudicated as type 1 MI, 138 (14.3%) as type 2 MI and 18 (1.9%) as type 3 or 4 MI. In 86 (8.9%) patients, the MI diagnosis was considered as incorrect, and hence adjudicated as having myocardial injury.

Comparison of adjudicated type 2 MI and myocardial injury patients with and without a clinical MI diagnosis

Comparisons of clinical characteristics between patients with and without a clinical MI diagnosis, among adjudicated type 2 MI and myocardial injury respectively, are presented in table 2. In adjudicated type 2 MI with a clinical MI diagnosis, a majority had been treated at a cardiology department (68.1%). On the contrary, treatment at a cardiology department was rare among those without a clinical MI diagnosis (10.8%, p<0.01 for treatment at a cardiology department vs any other department) (online supplemental figure S3). In adjudicated myocardial injury, care was given at a cardiology department in 48.8% and 13.5% of those with and without a clinical MI diagnosis, respectively (p<0.01) (online supplemental figure S4).

Triggering mechanisms

In adjudicated type 2 MI, tachycardia, anaemia and respiratory failure were common triggering mechanisms regardless of the clinical diagnosis (figure 2). However, shock was less often the triggering cause among patients with a clinical MI diagnosis when compared with patients without a clinical MI diagnosis (7% vs 30%, p<0.01). In adjudicated myocardial injury, heart failure and infections were the most common underlying conditions contributing to the myocardial injury in both groups.

Investigations and treatment

Regardless of the adjudicated diagnosis, the frequency of coronary angiography investigations as well as treatment with Fondaparinux were higher in patients with a clinical MI diagnosis (table 2). As regards both adjudicated type 2 MI and myocardial injury patients, a clinical MI diagnosis was associated with an increased use of Aspirin, P2Y12 inhibitors, statins, renin-angiotensin-aldosterone system blockers and beta-blockers. On the contrary, the use of secondary preventive pharmacological treatments remained essentially unchanged in patients without a

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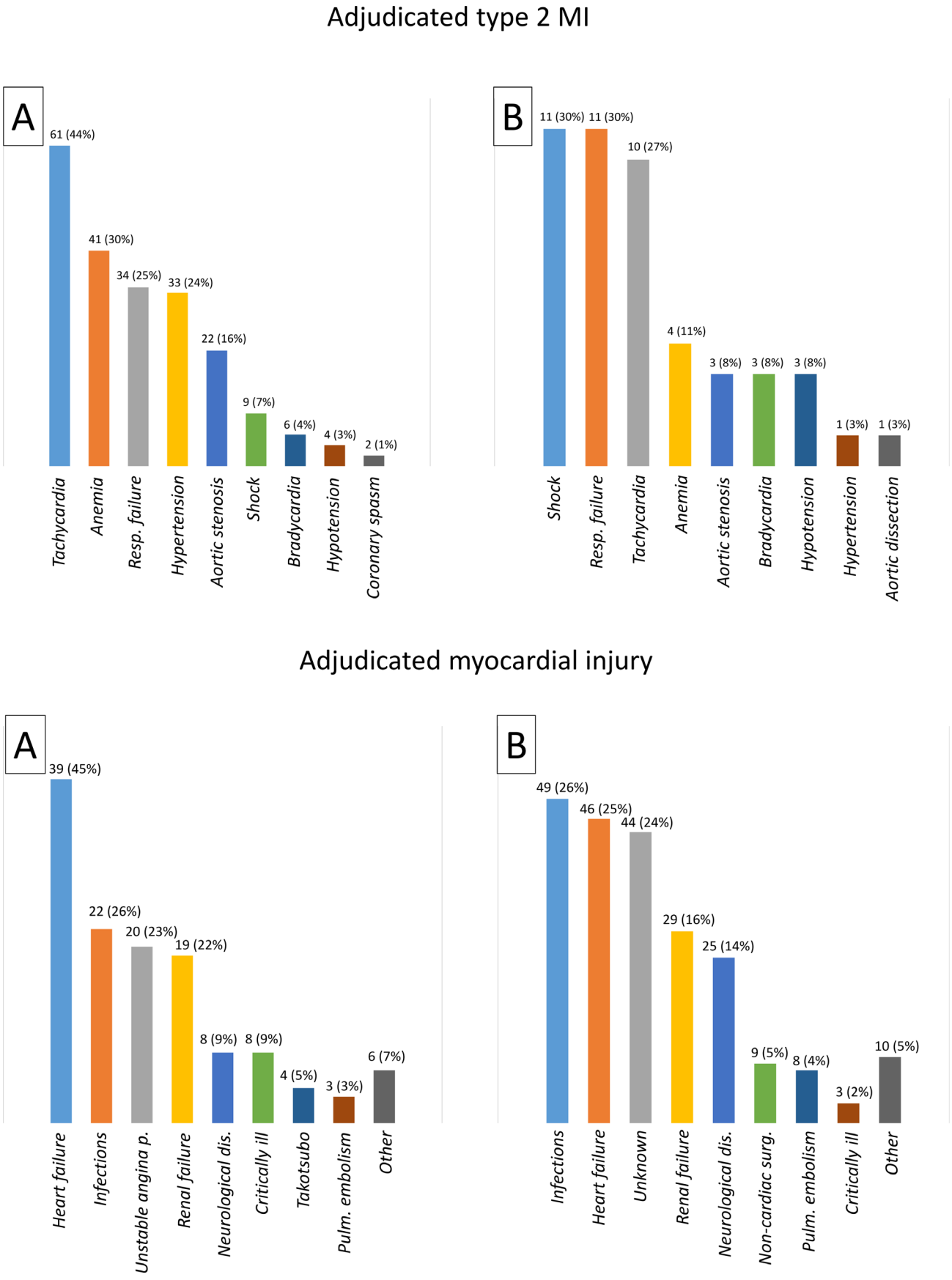

Figure 2 Adjudicated triggering mechanisms of type 2 MI and conditions contributing to a myocardial injury among (A) patients with a clinical MI diagnosis and among (B) patients without a clinical MI diagnosis. Several were possible in each case. In patients with a clinical MI diagnosis, 'Other' include rhabdomyolysis, non-cardiac surgery, dehydration or other unknown causes. In patients without a clinical MI diagnosis, 'Other' include cardiac ablation, unstable angina pectoris, pancreatitis, rhabdomyolysis, ileus and hypertrophic cardiomyopathy. MI, myocardial infarction.

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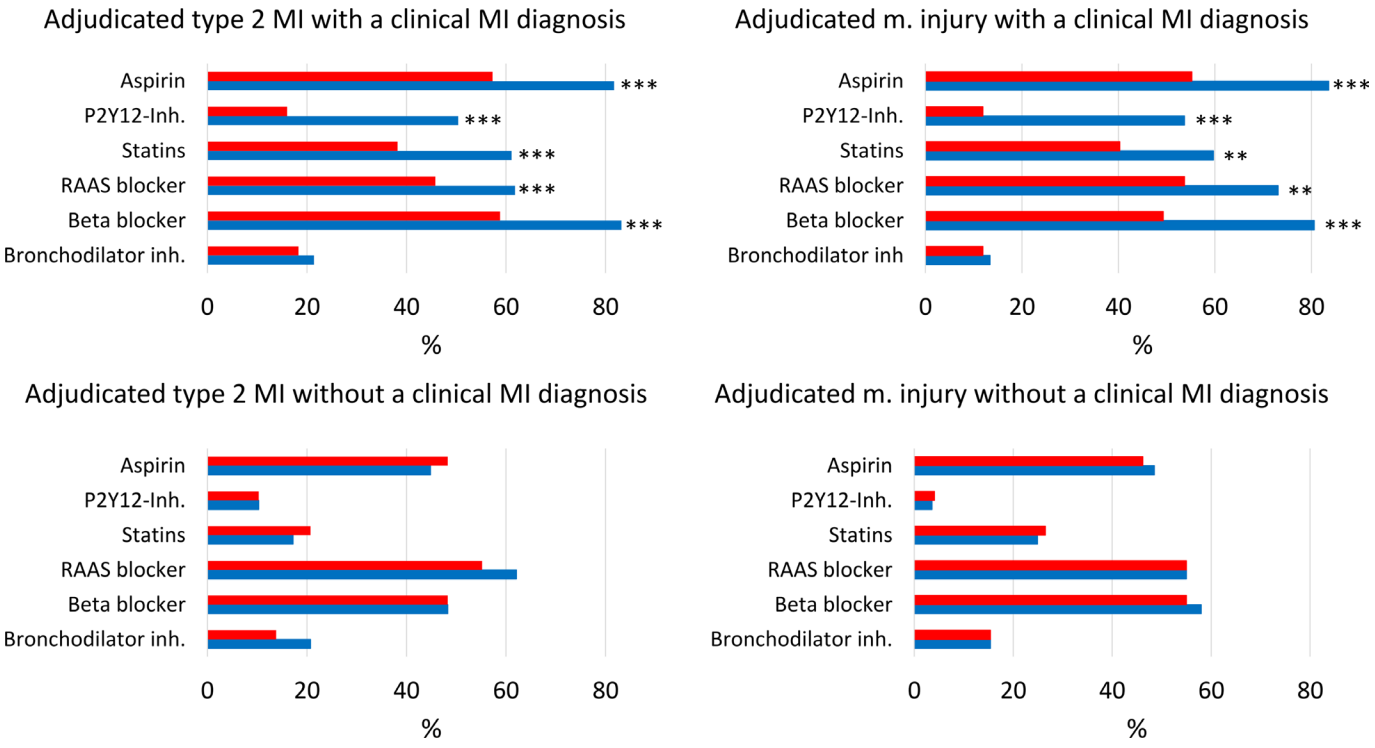
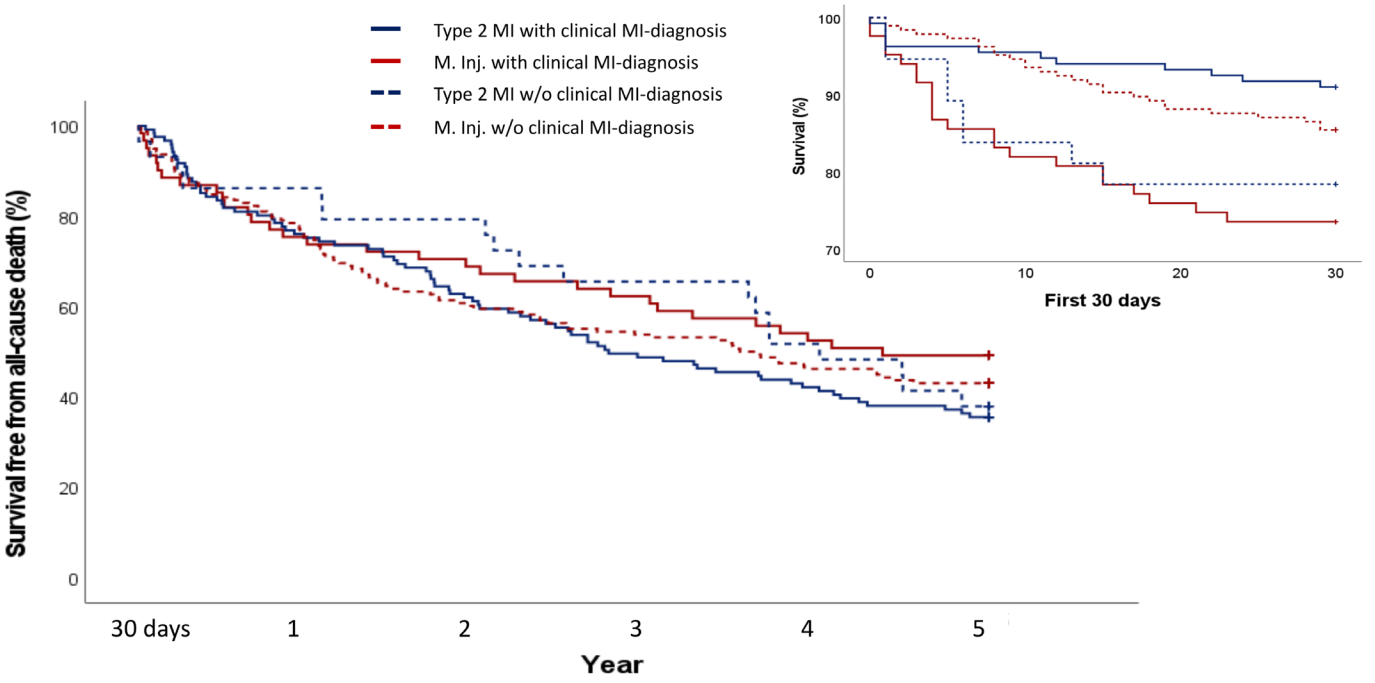


Figure 3 Pharmacological treatment at admission (red) and at discharge (blue) among patients alive at discharge. MI, myocardial infarction; M. injury, myocardial injury. *p<0.05; **p<0.01; ***p<0.001.



Number at risk	Time 0	10 days	20 days	30 days	1 year	2 years	3 years	4 years	5 years	
	133	127	124	121	92	75	59	51	43	Type 2 MI with I.21
	83	68	63	61	46	42	38	32	30	M. inj. With I.21
	37	31	29	29	25	23	19	15	11	Type 2 MI w/o I.21
	185	175	163	158	123	96	85	73	68	M. inj. w/o I.21

Figure 4 Crude zero days to 30 days and 30 days to 5 years survival curves for adjudicated type 2 MI and myocardial injury patients with and without a clinical myocardial infarction diagnosis (ICD-10 code I.21). MI, myocardial infarction.

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Table 3 All-cause mortality with time zero at 30 days after hospital admission

Adjudicated type 2 MI with vs without a clinical MI diagnosis			Adjudicated myocardial injury with vs without a clinical MI diagnosis		
Model	**Valid cases (events)**	**HR (95% CI)**	**Model**	**Valid cases (events)**	**HR (95% CI)**
1 year			1 year		
Crude	152 (34)	1.73 (0.61 to 4.91)	Crude	219 (50)	1.41 (0.38 to 5.22)
Model 1	152 (34)	1.03 (0.35 to 3.01)	Model 1	219 (50)	1.21 (0.65 to 2.25)
5 years			5 years		
Crude	152 (97)	1.17 (0.70 to 1.96)	Crude	219 (121)	1.09 (0.41 to 2.91)
Model 1	152 (97)	0.83 (0.49 to 1.40)	Model 1	219 (121)	0.80 (0.51 to 1.24)
Model 2	152 (97)	0.77 (0.43 to 1.38)	Model 2	219 (121)	0.89 (0.58 to 1.38)

Cox regression models for all-cause mortality with time zero at 30 days after hospital admission in adjudicated type 2 MI (left) and myocardial injury patients with a clinical MI diagnosis compared with patients without a clinical MI diagnosis.
Model 1: Adjusted for age, sex, active smoking and modified Charlson comorbidity index.
Model 2: As per model 1 with adjustment for clinical parameters at admission (systolic blood pressure, heart rate and reaction level scale >1 y/n), laboratory results (troponin max level, CRP max level and creatinine at admission) and invasive/non-invasive ventilation y/n.
MI, myocardial infarction.

clinical MI diagnosis (figure 3). In adjudicated cases of myocardial injury, this difference in treatment was most prominent among cases with a <20% rise or fall in troponin levels (online supplemental table S6).

Survival

The mean follow-up was 6.0 years. Information on date of death could not be retrieved from the Swedish Tax Agency in seven patients with a clinical MI diagnosis (four adjudicated type 2 MI and three adjudicated myocardial injury). In adjudicated type 2 MI, 95 (68.8%) patients with and 29 (78.4%) without a clinical MI diagnosis died during follow-up. In adjudicated myocardial injury, the corresponding numbers of deceased patients were 54 (62.8%) and 123 (66.5%).

As presented in figure 4, a high rate of early deaths was observed among adjudicated type 2 MI patients without a clinical MI diagnosis and among adjudicated myocardial injury patients with a clinical MI diagnosis. However, regardless of the adjudicated diagnosis, no clear difference in survival could be observed between patients with and without a clinical MI diagnosis after the first 30 days of follow-up.

As regards both adjudicated type 2 MI and adjudicated myocardial injury, no significant difference in all-cause mortality was observed between patients with and without a clinical MI diagnosis between 30 days and 1 year or 5 years of follow-up, neither in crude nor in adjusted models (table 3). Online supplemental table S7 presents the proportion of patients discharged with each secondary preventive treatment among patients alive and diseased after 5 years of follow-up.

With follow-up starting at hospital admission, no significant difference in all-cause mortality was observed between patients with and without a clinical MI diagnosis, regardless of an adjudicated type 2 MI (fully adjusted 5-year HR: 0.70 with 95% CI 0.42 to 1.17) or myocardial injury (fully adjusted 5-year HR: 1.38 with 95% CI 0.56 to 3.39) diagnosis (online supplemental figure S5 and table S8).

After merging adjudicated type 2 MI and myocardial injury patients into one group, no significant difference in all-cause mortality was observed between patients with and without a clinical MI diagnosis, neither with follow-up starting at 30 days after hospital admission (fully adjusted 5-year HR: 0.97 with 95% CI 0.54 to 1.75) nor with follow-up starting at hospital admission (fully adjusted 5-year HR: 1.03 with 95% CI 0.59 to 1.80) (online supplemental table S9).

DISCUSSION

In this study, comparing consecutive patients with cTn elevation, discharged with and without a clinical MI diagnosis, type 2 MI was observed to be a commonly unrecognised condition. A clinical MI diagnosis was associated with more cardiac care, including more coronary investigations and an increased use of secondary preventive treatment in both adjudicated type 2 MI and myocardial injury patients. However, no difference in long-term prognosis between patients with and without a clinical MI diagnosis could be observed in either of these conditions.

A clear majority (82.3%) of the patients with elevated cTn at Uppsala University Hospital in 2011 did not receive a clinical MI diagnosis. After adjudication, this was judged to be incorrect in 16.7% of the cases with predominantly missed cases of type 2 MI, which suggests that a high number of patients with type 2 MI are not being diagnosed and treated as MI in clinical routine.

It has previously been reported that approximately half of the patients with type 2 MI are found outside cardiology departments.[11] In the present study, receiving care at cardiology departments was rare among both type 2 MI and myocardial injury patients, who were not diagnosed clinically with MI. Treatment of MI outside cardiology departments has been reported to be associated with an adverse prognosis.[12]

Elevated cTn in patients without a type 1 MI has been observed to increase cardiology care and coronary angiography investigations, without altering the use of MI therapies or the prognosis.[13] A clinical MI diagnosis was associated with an increased use of MI-specific therapies in the present study. Still, no significant difference in 5-year all-cause mortality could be observed, neither in type 2 MI nor in myocardial injury. This questions the clinical relevance of an MI diagnosis in either of these conditions. Further, the clinical importance of distinguishing type 2 MI from myocardial injury is yet to be demonstrated. Given the ischaemic aetiology of a type 2 MI, it is theoretically appealing to expect a high proportion of patients with underlying CAD which would benefit from pharmacological and possibly also invasive MI treatment. In a recently published study, the prevalence of non-obstructive and obstructive CAD was 38% and 30%, respectively, among patients with type 2 MI.[14] Further, it has been observed that CAD is an important risk factor for future cardiovascular events in type 2 MI.[15 16] These findings suggest that there is an important subgroup of patients with type 2 MI with CAD in which the MI diagnosis would be clinically relevant. Therefore, it is important to note that the present study only

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attempts to evaluate the use of an MI diagnosis and associated treatment in the whole population of what is currently defined as patients with type 2 MI. Unfortunately, corresponding studies of CAD and its importance in myocardial injury are lacking.

Limitations

During the study period, the laboratory in Uppsala recommended a decision limit for MI (0.3 µg/L) with Abbott Architect troponin I, which was higher than the 99th percentile (0.022 µg/L) (personal communication). This may have contributed to the large number of clinically unrecognised type 2 MI cases. Another possible cause is that adjudicators classified patients according to the 2012 universal definition of myocardial infarction which was released after the study period.[17] However, the reported prevalence of type 2 MI in the national SWEDEHEART registry has been stable since the study period, arguing against any significant changes in the tendency to diagnose type 2 MI.[18 19]

It is important to note that, among patients with a clinical MI diagnosis, the clinical assessment of MI type may have been different from the adjudicated MI type. Hence, some patients adjudicated as either type 2 MI or myocardial injury may have been assessed as type 1 MI by the attending physician. This could for example explain the increased use of Fondaparinux and P2Y12 inhibitors for which the rationale is doubtful in MI in the absence of an atherothrombotic event. Consequently, some patients may have received MI treatment that would be considered, by most, to be unreasonably aggressive in these conditions. Further, it may be suspected that patients with a clinical profile indicative of an underlying coronary artery disease were more likely to receive a clinical MI diagnosis and that these patients therefore had a higher rate of cardiovascular death compared with patients not receiving a clinical MI diagnosis. Unfortunately, however, this study lacks data on causes of death.

There was a relatively small number of patients in the assigned groups, especially among type 2 MI without a clinical MI diagnosis. This gives an increased risk of type 2 errors. However, when merging type 2 MI and myocardial injury patients into one group as a sub analysis, still, the results were essentially neutral, suggesting that a possible effect of a clinical MI diagnosis on survival would be small.

Potential residual confounding in the survival analyses most probably include unrecognised factors, for example, frailty, negatively associated with both a clinical MI diagnosis and survival. In accordance with prior studies, tachycardia and respiratory failure were common adjudicated triggering mechanisms of a type 2 MI[3 4 11] regardless of the clinical diagnosis. However, the much higher prevalence of shock as an underlying trigger among adjudicated type 2 MI patients without a clinical MI diagnosis may be important since shock has been reported as the only triggering mechanism independently predicting all-cause mortality.[20] The multivariable survival analyses in the present study included systolic blood pressure as an attempt to adjust for this difference.

Finally, a minor selection bias may be present since a higher proportion of patients without a clinical MI diagnosis declined participation and since only patients alive were asked for informed consent (in accordance with the decision from the ethical committee). The best approximation of the magnitude of this bias is that the informed consent inquiry may have led to a 1 and 2.3 percentage points higher mortality among patients with and without a clinical MI diagnosis at 2 and 4.6 years of follow-up, respectively. Hence, the observed HRs in the present study may be slightly underestimated.

CONCLUSION

This study demonstrates that the currently defined type 2 MI often is not recognised as MI in clinical practice. In both adjudicated type 2 MI and myocardial injury, a clinical diagnosis of MI at discharge was associated with increased cardiology care, including a greater use of coronary angiography and secondary preventive therapies. However, no prognostic effect of receiving a clinical diagnosis of MI could be observed for either of these conditions. This questions the clinical relevance of the term MI outside type 1 MI and highlights the need for further studies in both these heterogeneous conditions.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Regional Ethical Review Board Uppsala, reference number 2012/208. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Due to Swedish laws on personal integrity and health data, as well as the Ethics Committee, we are not allowed to make any data including health variables open to the public even if made anonymous. The data could be shared with other researchers after a request to the head of our department (es.uu.icsdem@grebdnil.ave).

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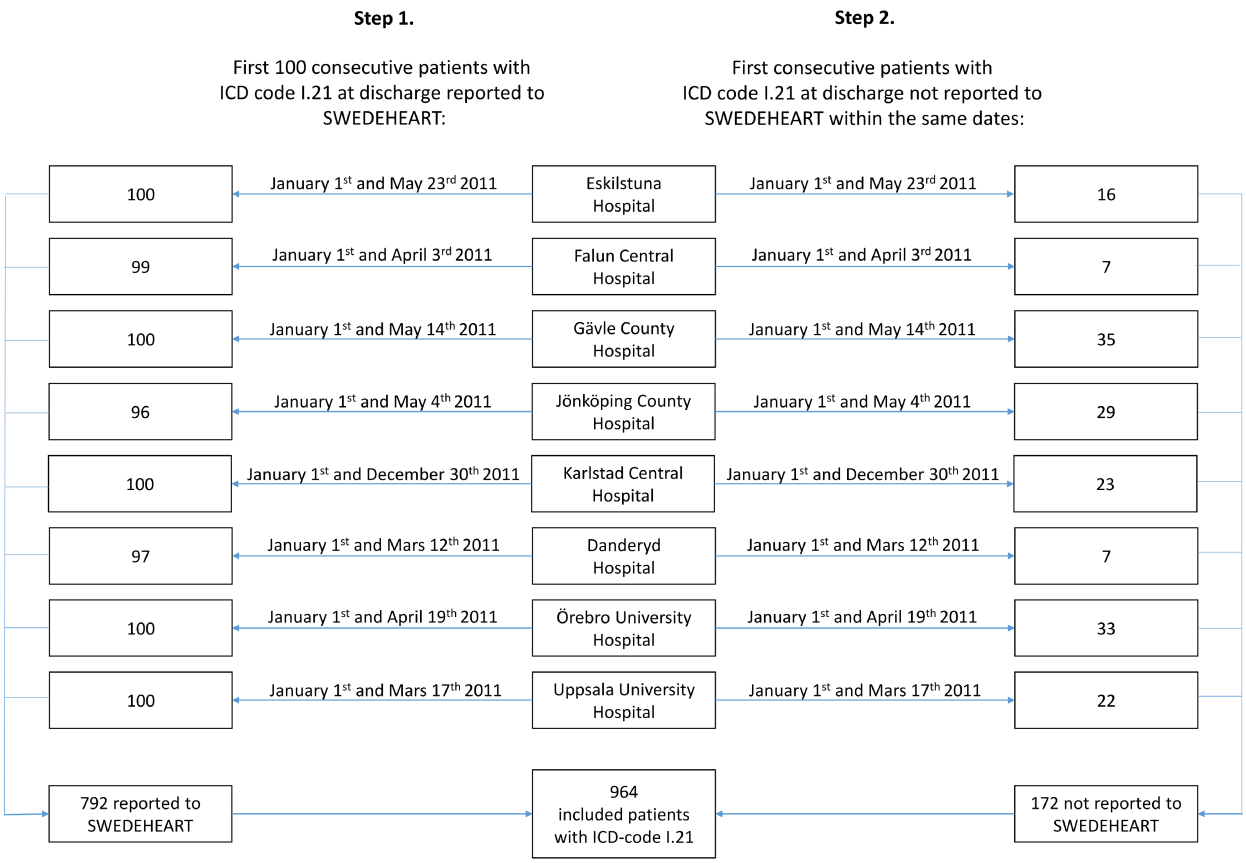
Figure S1.pdf



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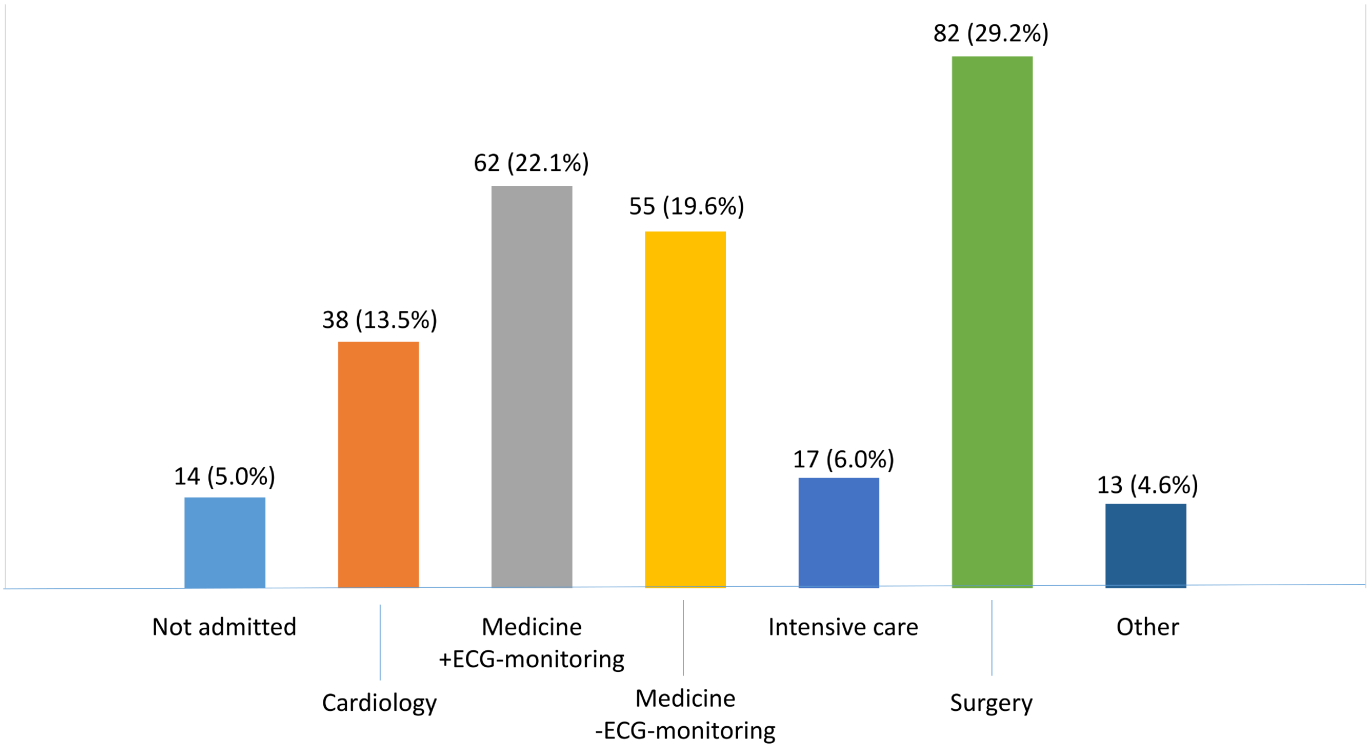

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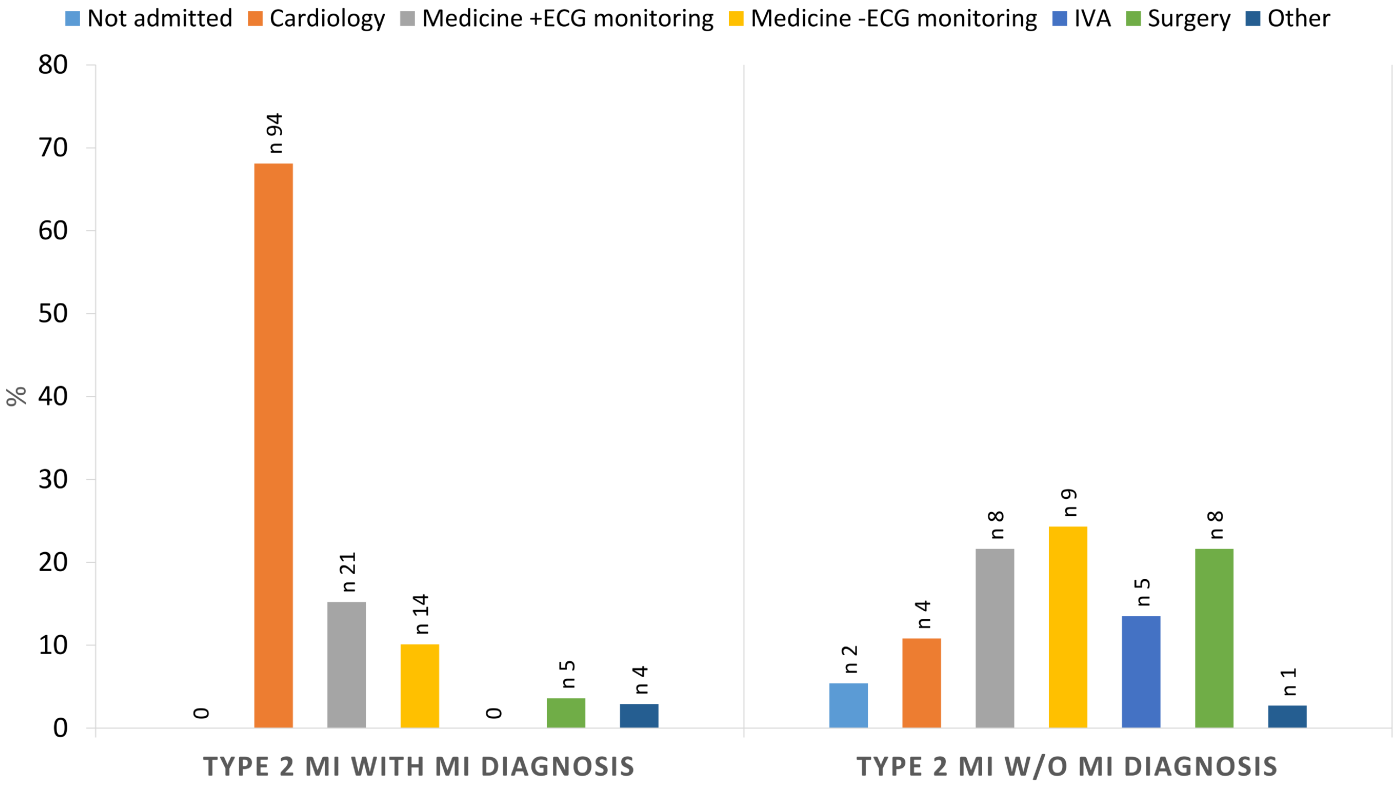

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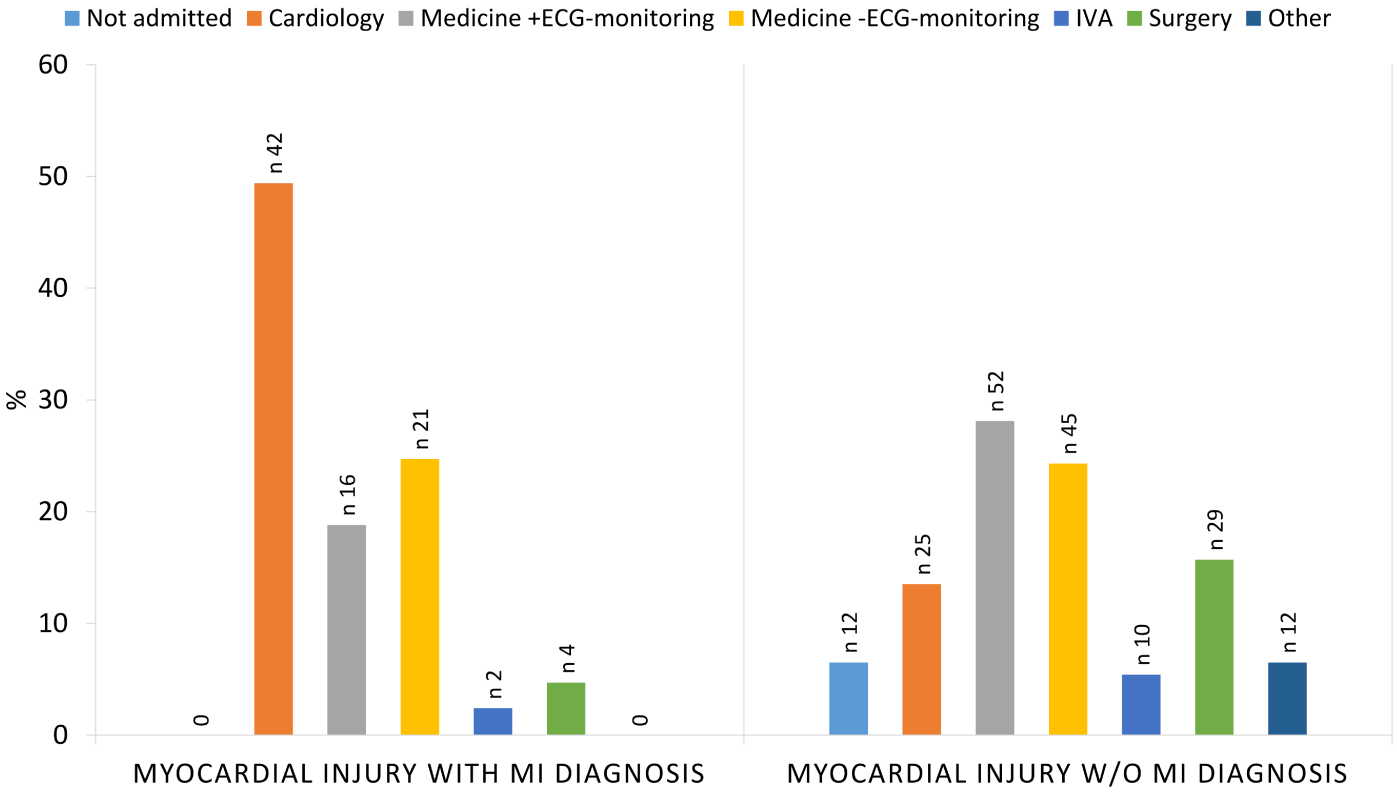

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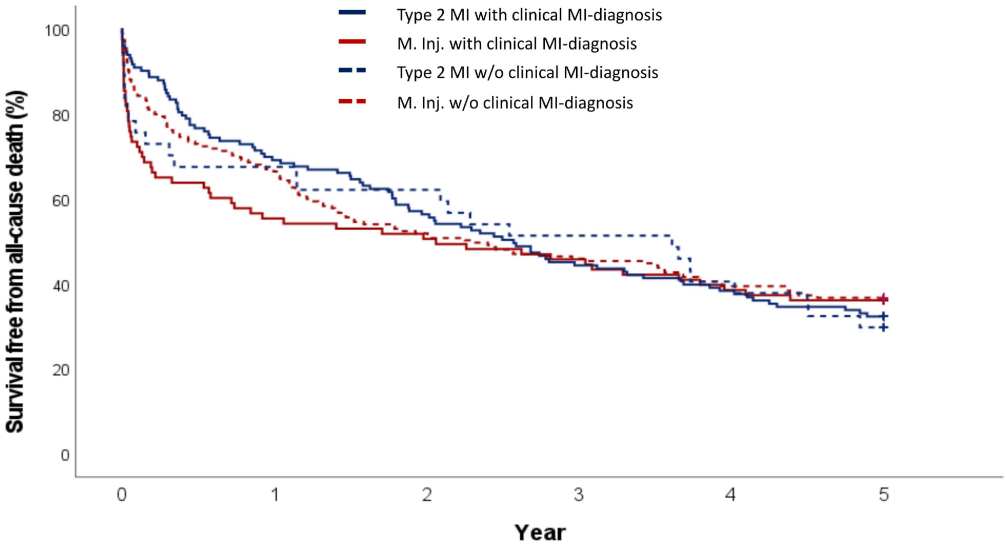

Number at risk	Time 0	10 days	20 days	30 days	1 year	2 years	3 years	4 years	5 years	
	133	127	124	121	92	75	59	51	43	Type 2 MI with I.21
	83	68	63	61	46	42	38	32	30	M. inj. With I.21
	37	31	29	29	25	23	19	15	11	Type 2 MI w/o I.21
	185	175	163	158	123	96	85	73	68	M. inj. w/o I.21

Supplemental material

Tables

Table S1. Reviewer classification

Reviewer 1	Reviewer 2				
	Type 1	Type 2	Type 3-5	M. Injury	Total
Type 1	644	52	9	40	745
Type 2	30	102	1	48	181
Type 3-5	11	1	7	2	21
M. Injury	22	24	0	203	249
Total	707	179	17	293	1196

Overall Inter-reviewer agreement in classifying patients according to the Third Universal Definition of Myocardial Infarction. There was agreement in 79.9 % of the cases, with a kappa value of 0.64 (95% confidence interval 0.60-0.68) and AC_1 of 0.75 (95% confidence interval 0.72-0.78). MI – myocardial infarction. M. injury – myocardial injury.

Table S2. Agreement in distinguishing type 1 MI, type 2 MI and myocardial injury.

1st Adjudicator	2nd Adjudicator		
	Type 1 MI	Other	Total
Type 1 MI	644	101	745
Other	63	388	451
Total	707	489	1196
	Type 2 MI	Other	Total
Type 2 MI	102	79	181
Other	77	938	1015
Total	179	1017	1196
	Myocardial injury	Other	Total
Myocardial injury	203	46	249
Other	90	857	947
Total	293	903	1196

Cohen's κ for agreement between the initial two adjudicators were 0.71, 0.49 and 0.68 for type 1 MI, type 2 MI and myocardial injury respectively.

Table S3. Cause of hospital admission and first diagnosis among patients without a clinical myocardial infarction diagnosis.

Cause of hospital admission	n (%)	First diagnosis at discharge (ICD-10 code)	n (%)
Dyspnoea	61 (21.7)	Valvular heart disease (I33-I39)	35 (12.5)
Cardiac surgery	49 (17.4)	Heart failure (I50)	25 (8.9)
Chest pain	45 (16.0)	Arrhythmia (I47-I49)	21 (7.5)
Other pain	40 (14.2)	Circulatory or respiratory symptoms (R00-R09)	19 (6.8)
General condition	31 (11.0)	Cerebrovascular diseases (I60–I69)	17 (6.0)
Fall	31 (11.0)	Influenza and pneumonia (J09–J18)	15 (5.3)
Nausea/vomiting	25 (8.9)	Ischaemic heart diseases (I20–I25)	13 (4.6)
Fever	21 (7.5)	Arterial diseases (I70–I79)	11 (3.9)
Syncope	18 (6.4)	General symptoms and signs (R50–R69)	10 (3.6)
Non-cardiac surgery	18 (6.4)	Pulmonary heart/circulation disease (I26-I28)	7 (2.5)
None of the above	49 (17.4)	None of the above	108 (38.4)

Several causes of hospital admission were possible in each case.

Table S4. First diagnoses, stratified by cardiac surgery as the reason for hospital admission

First diagnosis at discharge (ICD-10 code)	Patients without clinical MI diagnosis (cardiac surgery excluded)	Patients without clinical MI diagnosis admitted for cardiac surgery
Total number of patients	232	49
Valvular heart disease (I33-I39)	2 (0.9)	31 (63.3)
Heart failure (I50)	22 (9.5)	3 (6.1)
Arrhythmia (I47-I49)	18 (7.6)	3 (6.1)
Circulatory or respiratory symptoms (R00-R09)	19 (8.2)	0
Cerebrovascular diseases (I60–I69)	17 (7.3)	0
Influenza and pneumonia (J09–J18)	15 (6.5)	0
Ischaemic heart diseases (I20–I25)	5 (2.2)	8 (16.3)
Arterial diseases (I70–I79)	9 (3.9)	2 (4.1)
General symptoms and signs (R50–R69)	10 (4.3)	0
Pulmonary heart/circulation disease (I26-I28)	7 (3.0)	0
None of the above	106 (45.7)	2 (4.1)

First diagnoses among patients without a clinical myocardial infarction diagnosis, stratified by cardiac surgery as the cause of hospital admission or not. Among patients admitted for cardiac surgery, “none of the above” include benign neoplasm of the heart (D15) in one case and complication of valve graft (T82) in one case. MI – myocardial infarction

Table S5. Patient characteristics, stratified by cardiac surgery as the reason for hospital admission

	Patients without clinical MI diagnosis (cardiac surgery excluded)	Patients without clinical MI diagnosis admitted for cardiac surgery
Total number of patients	232	49
cTn dynamics >20%	186 (80.2)	47 (95.9)
MI type		
Type 1	9 (3.2)	0
Type 2	37 (13.2)	0
Type 3-5	1 (0.4)	0
Myocardial injury	185 (83.3)	49 (100.0)
Department of care		
Not admitted	14 (6.0)	0
Cardiology	34 (14.7)	4 (8.2)
Medicine with ECG-monitoring	62 (26.7)	0
Medicine without ECG-monitoring	55 (23.7)	0
Intensive care unit	17 (7.3)	0
Surgery	37 (15.9)	45 (91.8)
Other	13 (5.6)	0
Cardiovascular risk factors		
Age, mean (SD)	74.8 (14.4)	66.0 (10.6)
Male Sex	122 (52.6)	37 (75.5)
Active smoking	29 (12.5)*	5 (10.2)
Hypertension	139 (59.9)	27 (55.1)
Hyperlipidemia	23 (9.9)	13 (26.5)
Diabetes mellitus	54 (23.3)	6 (12.2)
Medical history		
Myocardial infarction	65 (28.0)	12 (24.5)
Heart failure	20 (26.0)	9 (18.4)
COPD	19 (8.2)	3 (6.1)
Dementia	19 (8.2)	0
Investigations in hospital		
Coronary angiography	11 (4.8)	1 (2.0)
Echocardiography	48 (20.7)	35 (71.4)
Alive at discharge	208 (89.7)	49 (100.0)
Treatment at discharge		
Aspirin	103 (49.5)	17 (34.7)
Statin	50 (24.0)	24 (49.0)
Beta blocker	119 (57.2)	36 (73.5)
Death during Follow up (median 6.0 years)	157 (67.7)	3 (6.1)

Characteristics of patients without a clinical myocardial infarction diagnosis, stratified by cardiac surgery as the cause of hospital admission or not. Values are numbers (%). cTn – cardiac troponin, MI – myocardial infarction, COPD – chronic obstructive pulmonary disease.

* 16.4% missing data

Table S6. Adjudicated cases of myocardial injury stratified by troponin dynamics.

Rise or fall in cTn levels	≥20%		<20%	
Clinical MI diagnosis	Yes	No	Yes	No
Total number of patients	55	143	22	42
Age, mean (SD)	79.2 (10.4)	76.0 (14.3)	73.8 (14.2)	76.1 (13.4)
Male sex, n (%)	29 (52.7)	76 (53.1)	18 (81.8)	22 (52.4)
Active smoking, n (%) *	3 (8.6)	16 (11.2)	4 (22.2)	4 (9.5)
Medical history, n (%)				
Hypertension	34 (61.8)	88 (61.5)	9 (40.9)	21 (50.0)
Hyperlipidemia	15 (27.3)	17 (11.9)	6 (27.3)	4 (9.5)
Myocardial infarction	23 (41.8)	40 (28.0)	10 (45.5)	8 (19.0)
Clinical findings, n (%)				
Chest pain, n (%)	18 (32.7)	22 (15.4)	17 (77.3)	10 (23.8)
In hospital treatment, n (%)				
Coronary angiography	10 (18.2)	3 (2.1)	13 (59.9)	0
PCI	4 (7.3)	1 (0.7)	6 (27.3)	0
Fondaparinux s.c.	17 (30.9)	4 (2.8)	14 (63.6)	1 (2.4)
Treatment at discharge, n (%)				
Aspirin	35 (63.6)	67 (50.8)	20 (90.9)	15 (40.5)
P2Y12 inhibitor	22 (40.0)	6 (4.6)	12 (54.5)	0
Statin	24 (43.6)	33 (25.4)	16 (72.2)	9 (24.3)
Beta blocker	36 (65.5)	79 (60.3)	16 (72.2)	19 (51.4)
RAAS blocker	33 (60.0)	71 (54.2)	14 (63.6)	23 (62.2)

Clinical features among patients with myocardial injury with and without a clinical diagnosis of MI, stratified by whether cardiac troponin levels had a ≥20% rise or fall over serial measurements or not. cTn – cardiac troponin, n – number, SD – standard deviation, PCI – percutaneous coronary intervention. S.c. subcutaneous.

Table S7. Secondary preventive therapies at discharge and five year survival.

Adjudicated diagnosis	Type 2 MI		*p*	Myocardial injury		*p*
Dead after five years	Yes	No		Yes	No	
Total number of patients	100	55		136	98	
Aspirin	70 (70.0)	46 (83.6)	0.06	78 (57.4)	59 (60.2)	*0.71*
P2Y12-inhibitors	37 (37.0)	29 (52.7)	0.06	22 (16.2)	19 (19.4)	*0.56*
Statins	45 (45.0)	38 (69.1)	<0.01	40 (29.4)	41 (41.8)	*0.06*
RAAS blocker	56 (56.0)	40 (72.7)	0.03	79 (58.1)	61 (62.2)	0.61
Beta blocker	75 (75.0)	43 (78.2)	0.66	86 (63.2)	64 (65.3)	*0.86*

Secondary preventive therapies at discharge stratified by survival status after five years of follow up. The analysis only includes patients surviving the index care event.

Table S8. All-cause mortality with time zero at hospital admission.

Adjudicated **Type 2 MI** with vs. without a clinical MI diagnosis			Adjudicated **myocardial injury** with vs. without a clinical MI diagnosis		
Model	Valid cases (events)	Hazard ratio (95% CI)	Model	Valid cases (events)	Hazard ratio (95% CI)
1 year			*1 year*		
Crude	171 (53)	0.84 (0.44-1.60)	Crude	268 (99)	1.94 (0.64-5.90)
Model 1	171 (53)	0.54 (0.28-1.05)	Model 1	267 (98)	1.80 (0.65-4.92)
5 year			*5 year*		
Crude	171 (116)	0.94 (0.56-1.55)	Crude	268 (170)	1.53 (0.52-4.52)
Model 1	171 (116)	0.66 (0.42-1.03)	Model 1	267 (169)	1.43 (0.46-4.42)
Model 2	171 (116)	0.70 (0.42-1.17)	Model 2	267 (169)	1.38 (0.56-3.39)

Cox regression models for all-cause mortality with time zero at hospital admission in type 2 MI (left) and myocardial injury patients with a clinical MI diagnosis compared with patients without a clinical MI diagnosis.

Model 1: Adjusted for age, sex, active smoking and modified Charlson comorbidity index.

Model 2: As per model 1 with adjustment for clinical parameters at admission (systolic blood pressure, heart rate and reaction level scale >1 y/n), laboratory results (troponin max level, CRP max level and creatinine at admission) and invasive/non-invasive ventilation y/n.

Table S9. All-cause mortality after merging of adjudicated type 2 MI and myocardial injury

Adjudicated **Type 2 MI** or myocardial injury with vs. without a clinical MI diagnosis with time zero at hospital admission			Adjudicated type 2 MI or **myocardial injury** with vs. without a clinical MI diagnosis with time zero 30 days after hospital admission		
Model	Valid cases (events)	Hazard ratio (95% CI)	Model	Valid cases (events)	Hazard ratio (95% CI)
1 year			*1 year*		
Crude	439 (154)	1.15 (0.61-2.16)	Crude	370 (84)	1.16 (0.75-1.78)
Model 1	438 (153)	1.07 (0.57-2.01)	Model 1	370 (84)	1.09 (0.71-1.68)
5 year			*5 year*		
Crude	439 (288)	1.11 (0.60-2.04)	Crude	370 (218)	1.12 (0.57-2.20)
Model 1	438 (287)	0.97 (0.56-1.69)	Model 1	370 (218)	0.95 (0.56-1.63)
Model 2	438 (287)	1.03 (0.59-1.80)	Model 2	370 (218)	0.97 (0.54-1.75)

Cox regression models for all-cause mortality in patients with a clinical MI diagnosis compared with patients without a clinical MI diagnosis, regardless of a type 2 MI or myocardial injury adjudication. To the left; time zero is set at hospital admission and to the right at 30 days after hospital admission.

Model 1: Adjusted for age, sex, active smoking and modified Charlson comorbidity index.

Model 2: As per model 1 with adjustment for clinical parameters at admission (systolic blood pressure, heart rate and reaction level scale >1 y/n), laboratory results (troponin max level, CRP max level and creatinine at admission) and invasive/non-invasive ventilation y/n.

Figures

Figure S1. Inclusion of patients with a clinical MI diagnosis. The target was to include the first 100 patients with ICD-code I.21 at discharge reported to the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) from each site. However, data had been collected in slightly less than 100 patients with ICD-code I.21 from three of the sites. As a next step, all patients with ICD-code I.21 at discharge not reported to SWEDEHEART, within the same dates as the SWEDEHEART reported patients, were included from each site.

Figure S2. Departments of care after hospital admission among patients without a clinical myocardial infarction diagnosis.

Figure S3. Caring department among adjudicated type 2 MI patients with (left) and without (right) a clinical myocardial infarction diagnosis.

Figure S4. Caring department among adjudicated myocardial injury patients with (left) and without (right) a clinical myocardial infarction diagnosis.

Figure S5. Crude zero days to five years survival curves for adjudicated type 2 MI and myocardial injury patients with and without a clinical myocardial infarction diagnosis (ICD-10 code I.21).

Supplemental file. Definition of myocardial infarction and myocardial injury subtypes.

Myocardial infarction (MI) was defined as myocardial necrosis caused by acute ischemia and diagnosed if there was evidence of myocardial necrosis, in form of elevated cTn with a rising or falling pattern, in a clinical setting of acute myocardial ischemia, such as ischemic symptoms, ischemic ECG findings, imaging evidence of new loss of viable myocardium or identification of an intracoronary thrombus.

Type 1 MI was defined as MI caused by a verified or highly suspected coronary artery plaque rupture, ulceration, fissuring or dissection resulting in an intracoronary thrombus formation.

Type 2 MI was defined as MI without intracoronary thrombus formation where conditions other than atherosclerotic CAD contributed to a cardiac oxygen supply/demand imbalance. The following conditions alone or together were accepted as potential triggering mechanisms (no specified cut off levels other than those presented in *the Third Universal Definition of MI* were used):

- Tachyarrhythmia
- Bradyarrhythmia
- Aortic dissection
- Severe aortic stenosis or insufficiency
- Shock (cardiogenic, hypovolemic or septic)
- Respiratory failure
- Severe anemia
- Hypertension with or without left ventricular hypertrophy
- Coronary spasm, endothelial dysfunction, embolism or vasculitis

Type 3, 4a, 4b and 5 MI were all defined in accordance with the *Third Universal Definition of Myocardial MI* and are not described in detail here.

Myocardial injury was defined as evidence of myocardial necrosis in form of elevated cTn with or without a rising or falling pattern and *without* clear clinical evidence of ischemia (such as ischemic symptoms, ischemic ECG findings or imaging/autopsy findings supporting ischemic necrosis). The following conditions alone or together were accepted as potentially causing a myocardial injury:

- Heart failure
- Takotsubo cardiomyopathy
- Severe pulmonary embolism or pulmonary hypertension
- Sepsis (not septic shock) or critically ill patients
- Renal failure
- Severe acute neurological diseases, e.g. stroke or subarachnoid hemorrhage
- Infiltrative diseases, e.g. amyloidosis or sarcoidosis
- Stenous exersice
- Cardiac contusion, surgery, ablation, pacing or defibrillator shocks
- Rhabdomyolysis with cardiac engagement
- Myocarditis
- Cardiotoxic agents, e.g. anthracyclines or Herceptin

In addition, some patients, presenting with typical ischemic symptoms or ECG-changes, without an underlying provoking condition, and where the cTn concentrations were only slightly elevated without a rising or falling pattern, were classified as unstable angina and categorized as myocardial injury.