Journal of the American Heart Association

ORIGINAL RESEARCH

Treatment With Cardiovascular Medications: Prognosis in Patients With Myocardial Injury

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BACKGROUND: There is no clinical guidance on treatment in patients with non-ischemic myocardial injury and type 2 myocardial infarction (T2MI).

METHODS AND RESULTS: In a cohort of 22 589 patients in the emergency department at Karolinska University Hospital in Sweden during 2011 to 2014 we identified 3853 patients who were categorized into either type 1 myocardial infarction, T2MI, non-ischemic acute and chronic myocardial injury. Data from all dispensed prescriptions within 180 days of the visit to the emergency department were obtained concerning β-blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, statins, and platelet inhibitors. We estimated adjusted hazard ratios (HR) with 95% CI for all-cause mortality in relationship to the number of medications (categorized into 0–1 [referent], 2–3 and 4 medications) in the groups of myocardial injury. In patients with T2MI, treatment with 2 to 3 and 4 medications was associated with a 50% and 56% lower mortality, respectively (adjusted HR [95% CI], 0.50 [0.25–1.01], and 0.43 [0.19–0.96]), while corresponding associations in patients with acute myocardial injury were 24% and 29%, respectively (adjusted HR [95% CI], 0.76 [0.59–0.99] and 0.71 [0.5–1.02]), and in patients with chronic myocardial injury 27% and 37%, respectively (adjusted HR [95% CI], 0.73 [0.58–0.92] and 0.63 [0.46–0.87]).

CONCLUSIONS: Patients with T2MI and non-ischemic acute or chronic myocardial injury are infrequently prescribed common cardiovascular medications compared with patients with type 1 myocardial infarction. However, treatment with guideline recommended drugs in patients with T2MI and acute or chronic myocardial injury is associated with a lower risk of death after adjustment for confounders.

Key Words: cardiac biomarker ■ medical treatment ■ mortality ■ prognosis ■ troponin

See Editorial by White

Myocardial injury is caused by either ischemic or non-ischemic events and is defined by any cardiac troponin (cTn) concentration above the upper reference limit, ie, the 99th percentile value. The diagnosis of myocardial infarction (MI) relies on the presence of acute myocardial injury (ie, myocardial injury with a dynamic change of cTn levels) together with evidence of myocardial ischemia. Patients with MI have signs and symptoms of myocardial ischemia either as a consequence of a coronary plaque rupture (type 1 MI), or a condition of inadequate supply or demand of oxygen to the heart (type 2 MI).[1]

The prognosis in patients with type 1 MI (T1MI) is better than in patients with type 2 MI (T2MI).[2–5] Non-ischemic myocardial injury, ie, myocardial injury without signs of myocardial ischemia, is also associated with a high risk of death and poor outcome.[3,6,7] Patients with T2MI and non-ischemic injury die more

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.017239

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Patients with acute and chronic myocardial injury have been associated with poor outcomes, but there are no recommended therapies for these patients.
- There is a gap of knowledge on whether cardiovascular medications are associated with a risk-reduction in patients with non-ischemic injury.
- In this study, we show that patients with type 2 myocardial infarction, acute and chronic myocardial injury are infrequently prescribed β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins, and platelet inhibitors. Patients with type 2 myocardial infarction, acute and chronic non-ischemic myocardial injury have a lower risks of adverse outcomes if they are treated with higher numbers of cardiovascular medications.

What Are the Clinical Implications?

- Our study shows that patients with type 2 myocardial infarction, acute and chronic non-ischemic myocardial injury may benefit from guideline-recommended cardiovascular treatments.

Nonstandard Abbreviations and Acronyms

T1MI	Type 1 myocardial infarction
T2MI	Type 2 myocardial infarction

often from cardiovascular causes than the general emergency department patient population.[8] However, it is difficult to distinguish different myocardial injury from each other, and not rarely a T1MI may be misjudged as a T2MI.[9] Currently, there is no consensus or clinical guidelines on how to treat patients with T2MI or non-ischemic myocardial injury. However, it is likely important to acknowledge and appreciate the opportunity to investigate these patients to exclude underlying cardiac disease. The evidence about treatment effects in patients with myocardial injury other than T1MI are scarce. Whether recommended cardiovascular drugs for T1MI reduce risks in patients with other types of myocardial injury is unknown. We hypothesized that groups of treatment with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), β-blockers, statins, and platelet inhibitors would reduce mortality and cardiovascular events in patients with T2MI, and non-ischemic (acute or chronic) myocardial injury. In addition, we hypothesized that the reduced mortality would be dependent on the number of drugs used.

METHODS

Patient and Public Involvement Statement

We report no direct patient or public involvement in this study.

Study Cohort

All patients who visited the emergency department at the Karolinska University Hospital in Stockholm, Sweden between January 1, 2011, and October 20, 2014, and presented with at least one visit for chest pain and were aged >25 years (n=22 589) were eligible for inclusion. Information about every visit with complaints other than chest pain was also available. The selection process has been described in detail elsewhere.[3] In brief, to identify all patients with any acute myocardial injury and categorize these into groups of T1MI, T2MI, and non-ischemic acute myocardial injury; all patients with a discharge diagnosis of MI in the Swedish National Patient Register were identified and all eligible patients with any visit with both of the following fulfilled criteria were identified: (1) a delta-troponin of ± ≥3 ng/L measured with a high-sensitivity cardiac troponin T (hs-cTnT) assay within 24 hours, and (2) at least one of these hs-cTnT levels being >14 ng/L. All the identified patients' medical records were then reviewed for adjudication using the Fourth Universal Definition of Myocardial Injury document[1] as a guidance for the categorization (Figure S1). Patients with chronic myocardial injury (ie, stable and elevated hs-cTnT levels in the absence of any acute medical condition) were identified previously.[6] Briefly, all patients with at least 1 hs-cTnT level of >14 ng/L, or <12 ng/L and a delta-troponin of ± ≥3 ng/L proposed by the European Society of Cardiology guidelines to identify patients at high risk for MI,[10] during the index visit were identified and adjudicated to exclude patients with any concurrent acute medical conditions that could have resulted in elevated hs-cTnT levels. Only patients with at least 2 hs-cTnT measurements recorded during index visit were considered as having chronic myocardial injury, and no specific absolute or relative delta criteria were applied to define stable hs-cTnT levels.

The study protocol was approved by The Regional Ethical Review Board in Stockholm and the study complies with the guidelines of 1975 Declaration of Helsinki. Since the review of the medical records was done retrospectively the need for patient consent was waived. The final data set was anonymized to eliminate the risk of identification. The authors

declare that all supporting data are available within the article and supplementary material.

Definitions

The first event of myocardial injury in the emergency department was defined as the index date. Medication at discharge was defined as at least one dispensed prescription 0 to 180 days from the index date to capture patients who waited with starting their medical therapy. Prescriptions in Sweden normally last for 3 months. Information about medication use was retrieved from the National Prescribed Drug Register. The number of medications was defined as number of dispensed prescriptions of different types of classes of cardiovascular medication; β-blockers (ATC C07A), ACE-i/ARB (ATC C09A and C09C), statins (ATC C10AA), and platelet inhibitors (ACT B01AC). For example, if a patient had a dispensed prescription of different classes of cardiovascular drugs, every represented class would be counted, but, if a patient had several dispensed prescriptions of the same class of drugs, it would only be counted as one. Platelet inhibitors (acetyl salicylic acid and P2Y12 inhibitors) was defined as one group because P2Y12 are seldom used in patients with T2MI and only in patient with non-ischemic myocardial injury with e.g., prior revascularization, stroke or T1MI. The number of medications were categorized into the following 3 groups; 0 to 1, 2 to 3, or 4 medications. All comorbidities were defined as discharge diagnosis in the primary position coded according to the *International Classification of Diseases, Tenth Revision (ICD-10)* in the National Patient Register. Estimated glomerular filtration rates were estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Outcomes

The primary outcome was all-cause mortality. The secondary outcome was a composite of all-cause mortality, MI, heart failure, and stroke. Information about dates and causes of death was collected from the National Cause of Death Register. This register has virtually complete nationwide coverage of all deaths.[11] Follow-up started after 180 days from index visit and ended on December 31, 2016.

Statistical Analysis

Baseline characteristics are presented as mean and SD for continuous variables and for categorial variables as frequencies and percentages. Unadjusted and multivariable-adjusted Cox regression models were used to estimate hazard ratios (HR) for all-cause mortality and the composite outcome with 95% CI for the association between number of medications, using 0 to 1 medication as the referent, and stratified according to type of myocardial injury. The following covariates were included in the adjusted analysis: age, sex, estimated glomerular filtration rates, prior MI, revascularization, stroke, cancer, diabetes mellitus, hypertension, atrial fibrillation, heart failure, and chronic obstructive pulmonary disease. There was complete information about deaths and complete information on all medications dispensed in Sweden. Data management and statistical analyses were performed using Stata (v. 16.0; Stata Corp, College Station, TX, USA) and R software (v. 3.6.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population

In 3853 patients with myocardial injury with a mean age of 73±13 years, 25% (n=947) had 0 to 1 medications, 45% (n=1734) had 2 to 3 medications, and 30% (n=1172) had 4 medications of either ACEi/ARB, β-blockers, platelet inhibitors, or statins (Table 1). In patients with 4 medications, 5% had T2MI, 17% had non-ischemic acute myocardial injury, 20% had chronic myocardial injury, and 59% had T1MI. Patients with 0 to 1 or 2 to 3 medications had a higher prevalence of non-cardiovascular diseases than patients with 4 medications. The proportion of patients with T1MI compared with the other categories of myocardial injury gradually increased with the increasing number of medications. Proportions of patients with non-ischemic myocardial injury gradually decreased with the increasing number of medications, from 86% to 36% in patients treated with 0 to 1 and 4 medications, respectively (Table 1). Baseline characteristics in relationship to myocardial injury are depicted in Table S1. Baseline characteristics in relationship to number of medications are depicted in Table S2.

Medical Treatment

Less than half of all patients with T2MI, or non-ischemic acute or chronic myocardial injury were treated with statins, 43%, 40%, and 40%, respectively, and half of the equivalent patient groups were treated with a platelet inhibitor, 50%, 47%, and 52%, respectively. Corresponding proportions for treatment with statins and platelet inhibitors in patients with T1MI were 87% and 93%, respectively (Figure 1). In patients with non-ischemic acute or chronic myocardial injury, 66% and 62% were treated with β-blockers, respectively. The proportions treated with β-blockers in patients with T1MI and T2MI were 91% and 75%, respectively. Proportions of patients

Table 1. Baseline Characteristics

	All Patients	No. of Medications			*P* Value
		0–1	2–3	4	
No.	3853	947	1734	1172	
Age, y, mean (SD)	73.4 (13.5)	73.4 (16.3)	76.0 (12.3)	69.6 (11.7)	<0.001
Women	1537 (40)	426 (45)	776 (45)	335 (29)	<0.001
eGFR, mL/min per 1.73 m^2					<0.001
>60	2216 (58)	515 (54)	917 (53)	784 (70)	
45–60	729 (19)	191 (20)	341 (20)	197 (17)	
30–45	564 (15)	149 (16)	296 (17)	119 (10)	
<30	344 (9)	92 (10)	180 (10)	72 (6)	
CAD	1311 (34)	195 (21)	612 (35)	504 (43)	<0.001
Hypertension	1738 (45)	311 (33)	871 (50)	556 (47)	<0.001
Diabetes mellitus	833 (22)	127 (13)	359 (21)	347 (30)	<0.001
AMI	730 (19)	111 (12)	301 (17)	318 (27)	<0.001
Heart failure	741 (19)	146 (15)	416 (24)	179 (15)	<0.001
Revascularization	772 (20)	95 (10)	326 (19)	351 (30)	<0.001
Atrial fibrillation	1037 (27)	257 (27)	605 (35)	175 (15)	<0.001
COPD	325 (8)	108 (11)	142 (8)	75 (6)	<0.001
Stroke	369 (10)	77 (8)	204 (12)	88 (8)	<0.001
Cancer	521 (14)	180 (19)	232 (13)	109 (9)	<0.001
Beta-blocker	2792 (73)	193 (20)	1427 (82)	1172 (100)	<0.001
ACEi/ARB	2367 (61)	126 (13)	1069 (62)	1172 (100)	<0.001
Platelet inhibitor	2391 (62)	126 (13)	1093 (63)	1172 (100)	<0.001
Statin	2069 (53)	31 (3)	866 (50)	1172 (100)	<0.001
No. of medications					<0.001
0	471 (12)	471 (50)	n/a	n/a	
1	476 (12)	476 (50)	n/a	n/a	
2	747 (19)	n/a	747 (43)	n/a	
3	987 (26)	n/a	987 (57)	n/a	
4	1172 (30)	n/a	n/a	1172 (100)	
Group					<0.001
Type 1 MI	1111 (29)	58 (6)	363 (21)	690 (59)	
Type 2 MI	251 (7)	79 (8)	114 (7)	58 (5)	
Acute myocardial injury	1144 (30)	387 (41)	561 (32)	196 (17)	
Chronic myocardial injury	1347 (35)	423 (45)	696 (40)	228 (20)	

Numbers are n (%) unless otherwise stated. ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; AMI, prior acute myocardial infarction; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; and eGFR, estimated glomerular filtration rate.

with T1MI were gradually higher in increasing number of medications and a larger proportion of patients with T2MI and non-ischemic acute and chronic myocardial injury had 2 or 3 medications (Figure 2). Proportions of different anti-platelet medication are depicted in Table S3.

Revascularization

Within 30 days from the index date 51% of patients with T1MI underwent revascularization. The corresponding figures among patients with T2MI, and non-ischemic acute or chronic myocardial injury were 2.9%, 1.2%, and 1.3%, respectively. From day 31 to day 365, 3.4%, 1.9%, 2.2%, and 1.3% of patients with T1MI, T2MI, and acute or chronic myocardial injury, respectively, underwent revascularization.

Mortality

During a mean follow-up of 3.1±1.5 years, 1059 (27%) patients died. Yearly mortality rates decreased with increasing numbers of medications in all groups of myocardial injury; from 17% to 4% in patients with T1MI; 12% to 9% in patients with T2MI, 12% to 11% among patients with non-ischemic acute myocardial injury;

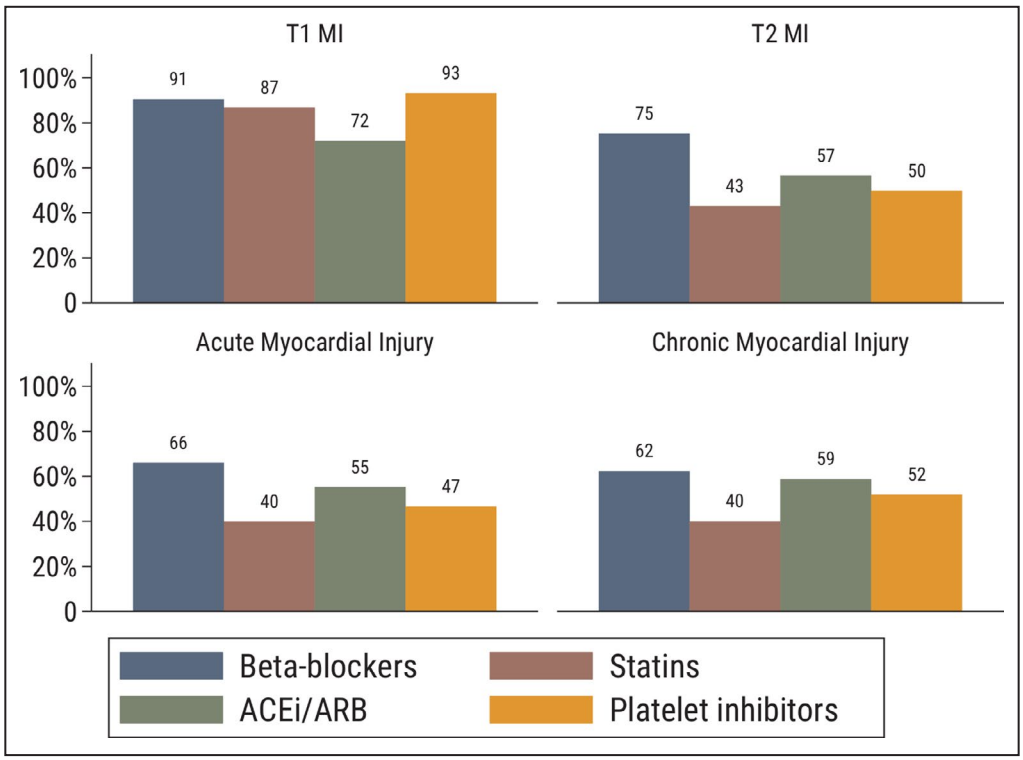

Figure 1. Proportions of treatments in patients with different myocardial injury.
T1MI indicates type 1 myocardial infarction; and T2MI, type 2 myocardial infarction.

and 13% to 10% among patients with chronic myocardial injury (Table 2). In addition, the survival curves for all groups of myocardial injury indicated higher proportions of survival in patients with 2 to 3 or 4 numbers of treatment over time. High proportions of patients die over time with T2MI, non-ischemic acute or

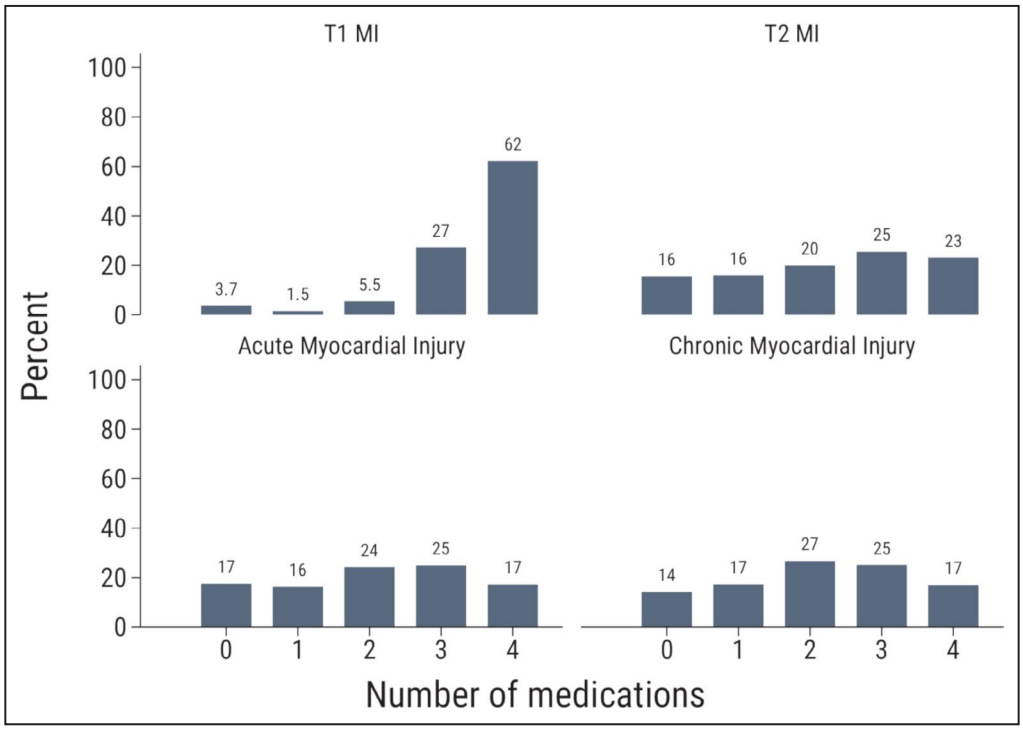

Figure 2. Proportions of different numbers of medications in patients with myocardial injury.
T1MI indicates type 1 myocardial infarction; and T2MI, type 2 myocardial infarction.

Table 2. Incidence Rate in Mortality Among Patients With Type 1 and Type 2 Myocardial Infarction, and Acute and Chronic Myocardial Injury in Relation to the Number of Cardiovascular Drugs Dispensed at Discharge

	No. of Medications		
	0–1	2–3	4
Incidence rate all-cause mortality			
Type 1 MI			
Event/person-years	8/48	78/1045	91/2413
Incidence rate (95 % CI)*	17 (8.3–33)	7.5 (6.0–9.3)	3.8 (3.1–4.6)
Type 2 MI			
Event/person-years	16/138	39/315	16/176
Incidence rate (95 % CI)*	12 (7.1–19)	12 (9.0–17)	9.1 (9.0–17)
Acute myocardial injury			
Event/person-years	99/835	189/1503	63/568
Incidence rate (95 % CI)*	12 (9.7–14)	13 (11–15)	11 (8.7–14)
Chronic myocardial injury			
Event/person-years	133/1013	254/1925	73/699
Incidence rate (95% CI)*	13 (11–16)	13 (12–15)	10 (8–13)

HR indicates hazard ratio; MI, myocardial infarction.
*Incidence rate per 100 person-years.

chronic myocardial injury in all numbers of treatment (Figure 3). In the unadjusted model, 2 to 3 or 4 medications compared with 0 to 1 drugs were associated with a lower mortality risk in patients with T1MI, while an unadjusted mortality risk reduction was found in patients with T2MI treated with 4 medications. Treatment with 4 drugs was associated with lower adjusted risk of death in patients with T2MI (HR, 0.43; CI, 0.19–0.96), and chronic myocardial injury (HR, 0.63; CI, 0.46–0.87). A lower adjusted mortality risk was also found among patients with non-ischemic acute and chronic myocardial injury treated with 2 to 3 medications, compared with the reference group (Table 3).

Secondary Outcomes

For the combined outcome of death, MI, heart failure, and stroke, patients with T2MI who were treated with 4 drugs had a 55% (HR, 0.45; CI, 0.21–0.95) lower risk, and patients with chronic myocardial injury had a 27% (HR, 0.73; CI 0.54–1.00) lower risk compared with the reference group. Patients with T1MI who were treated with 4 drugs had a 67% (HR, 0.33; CI, 0.15–0.71) lower risk for the combined outcome compared with patients treated with 0 to 1 drugs (Table 3).

DISCUSSION

In a cohort study that included 3893 patients with myocardial injury, we investigated the association between number of cardiovascular drugs used and mortality and cardiovascular outcomes. We found that patients with non-ischemic acute or chronic myocardial injury and T2MI were less frequently prescribed ACEi/ARB, β-blockers, platelet inhibitors, or statins compared with patients with T1MI. There was a lower mortality in patients with T2MI and chronic myocardial injury who were treated with 4 medications compared with 0 to 1 medications. Both patients with non-ischemic acute and chronic myocardial injury who were treated with 2 to 3 medications had lower mortality than patients treated with 0 to 1 drugs. In patients with T1MI, there was no association between number of drugs used and mortality. However, the CIs were wide and non-significant because there were only 8 deaths in the reference group, although the point estimates indicated a lower mortality in those who were treated with cardiovascular drugs.

Several studies have shown higher risks of death in patients with non-ischemic myocardial injury or T2MI compared with patients with T1MI,[2,3,5,12] but there are no studies that we know of that have explored the combined effects of cardiovascular drugs on outcomes in patients with non-ischemic myocardial injury, or T2MI. One study shows indications that Alirocumab may lower risk for T2MI compared with placebo.[13] Furthermore, data suggest that statin therapy may lower cTn concentrations and the associated mortality risk was independent of cholesterol levels among healthy middle-aged men.[14] Intensified rate control in chronic atrial fibrillation control has shown to lower cTnT levels in patients with non-ischemic myocardial injury,[15] and T2MI, which further underline the importance of treating underlying cardiovascular diseases in patients with non-ischemic myocardial injury, and T2MI.

The reason for the mortality reductions found in our study is most likely because of a combination of the cardiovascular drugs given. All of the drugs given are well-documented as preventive medication.[16,17] The evidence of positive cardiovascular effects of aspirin is vast,[18] in addition it is beneficial to add platelet inhibitor to aspirin (P2Y12 inhibition) after MI, so-called dual platelet inhibition.[19–21] Treatment with β-blockers has been found to be associated with beneficial outcomes in patients with heart failure with reduced ejection fraction[22,23] and also in patients with heart failure with reduced ejection fraction after MI.[24] Although the same risk reduction is present in low-risk as well as high-risk populations, ACEi or ARB are mainly recommended for patients with reduced LVEF[25] or risk factors such as diabetes mellitus,[26] hypertension[27] and/or chronic kidney disease.[28] Statins are used as secondary prevention of cardiovascular disease.[29] Thus, we believe that it is beneficial for patients with non-ischemic myocardial

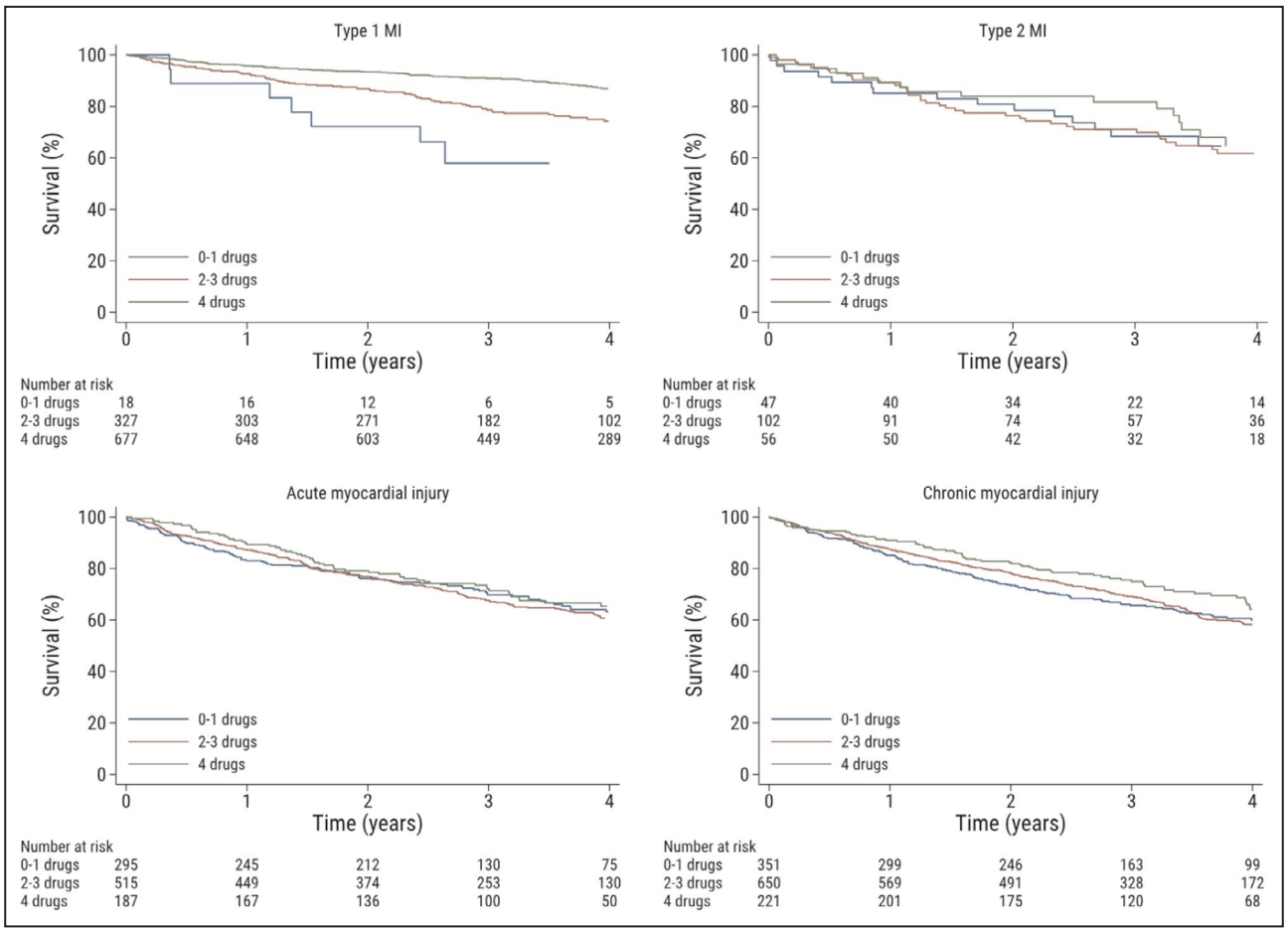

Figure 3. Kaplan–Meier curves for all-cause mortality in patients with myocardial injury separated by 0 to 1, 2 to 3, and 4 medications.
MI indicates myocardial infarction.

injury and T2MI to be treated with cardiovascular medication to a larger degree than what is done today. Our results suggest that this may prevent deaths.

In our study ≈15% of patients with chronic myocardial injury and T2MI were not treated with any type of studied medicine. Although mortality risk in T2MI is high[2,3,5,16] studies show that these patients are infrequently treated over time with platelet inhibitors, statins, ACEi/ARB, and β-blockers.[2,11,30] Similarly, patients with non-ischemic myocardial injury are also not treated regularly with cardiovascular medication.[2,16,30] The need for clinical guidelines in patients with T2MI and non-ischemic acute or chronic myocardial injury is urgent. Furthermore, only 40% of patients with non-ischemic acute or chronic myocardial injury and T2MI were treated with a statin in the present study despite studies having shown that statin therapy is effective,[31–34] and it appears that as low-density lipoprotein cholesterol levels decrease, the prognosis in high-risk patients with previous cardiovascular events improves.[35,36] Most likely, patients with non-ischemic myocardial injury, and T2MI would benefit from intensive statin therapy considering the massive evidence there is for the preventive effects of statins in various patient groups.

A substantial proportion of patients from our cohort that were recognized with acute or chronic myocardial injury were not admitted to a hospital but discharged home directly from the emergency department.[3] A more generous referral strategy with recommended medical treatment to primary care may create an opportunity for better treatment because patients benefit from closer and more continuous attention from 1 doctor,[37] and normally prevention of cardiovascular disease is dealt with by the general practitioner. In patients with T2MI, 75% were treated with β-blockers. This could be because of the frequent etiology of tachycardia and underlying medical conditions such as atrial fibrillation, heart failure, or supraventricular tachycardia, which may have been the cause of T2MI in some instances.[3] However, the high prescription rate of β-blockers may also be simply “a force of habit” because β-blockers

Table 3. Outcomes Among Patients With Type 1 and Type 2 Myocardial Infarction, and Acute and Chronic Myocardial Injury in Relation to the Number of Cardiovascular Drugs Dispensed at Discharge. Follow-Up Started at 180 Days After Index Date

	No. of Medications		
	0–1	2–3	4
All-cause mortality			
Type 1 MI			
No. of events (%)	8 (44%)	78 (24%)	91 (13%)
Unadjusted HR (95% CI)	Ref	0.45 (0.22–0.92)	0.22 (0.11–0.46)
Adjusted HR (95% CI)*	Ref	0.82 (0.38–1.79)	0.54 (0.25–1.17)
Type 2 MI			
No. of events (%)	16 (34%)	39 (38%)	16 (29%)
Unadjusted HR (95% CI)	Ref	1.06 (0.59–1.91)	0.78 (0.39–1.56)
Adjusted HR (95% CI)*	Ref	0.50 (0.25–1.01)	0.43 (0.19–0.96)
Acute myocardial injury			
No of events (%)	99 (34%)	189 (37%)	63 (34%)
Unadjusted HR (95% CI)	Ref	1.06 (0.83–1.36)	0.94 (0.68–1.29)
Adjusted HR (95% CI)*	Ref	0.76 (0.59–0.99)	0.71 (0.50–1.02)
Chronic myocardial injury			
No. of events (%)	133 (38%)	254 (39%)	73 (33%)
Unadjusted HR (95% CI)	Ref	1.01 (0.82–1.25)	0.80 (0.60–1.06)
Adjusted HR (95% CI)*	Ref	0.73 (0.58–0.92)	0.63 (0.46–0.87)
Combined outcome (death, myocardial infarction, stroke, heart failure)†			
Type 1 MI			
No. of events (%)	8 (67%)	82 (30%)	137 (24%)
Unadjusted HR (95% CI)	Ref	0.40 (0.19–0.82)	0.30 (0.15–0.61)
Adjusted HR (95% CI)*	Ref	0.45 (0.21–0.98)	0.33 (0.15–0.71)
Type 2 MI			
No. of events (%)	17 (38%)	47 (52%)	16 (36%)
Unadjusted HR (95% CI)	Ref	1.46 (0.84–2.55)	0.89 (0.45–1.76)
Adjusted HR (95% CI)*	Ref	0.74 (0.39–1.39)	0.45 (0.21–0.95)
Acute myocardial injury			
No. of events (%)	107 (38%)	214 (48%)	61 (45%)
Unadjusted HR (95% CI)	Ref	1.34 (1.06–1.69)	1.15 (0.84–1.58)
Adjusted HR (95% CI)*	Ref	0.99 (0.77–1.27)	0.88 (0.62–1.26)
Chronic myocardial injury			
No. of events (%)	149 (45%)	291 (51%)	87 (47%)
Unadjusted HR (95% CI)	Ref	1.18 (0.97–1.44)	1.04 (0.80–1.35)
Adjusted HR (95% CI)*	Ref	0.81 (0.66–1.01)	0.73 (0.54–1.00)

HR indicates hazard ratio.

*Adjusted for age, sex, estimated glomerular filtration rates, prior myocardial infarction, heart failure, stroke, revascularization, atrial fibrillation, chronic obstructive pulmonary disease, diabetes mellitus, coronary artery disease, hypertension, and cancer.

†A composite outcome; all-cause death, myocardial infarction, stroke, and heart failure.

have been the most common drugs to treat hypertension since decades.

Last, our results support a more generous approach for prescribing cardiovascular drugs in patients with T2MI and acute or chronic myocardial injury. However, prospective intervention studies are needed to study the effects of cardiovascular medical treatment on outcome in these patient groups.

Strengths

There are several strengths to this study. Considerable attention was made to categorize patients into the different groups of myocardial injury: T1MI, T2MI, acute, or chronic myocardial injury. This level of care was taken because the overlap and misclassification between the different types is common.[9,30] We believe it is essential to consider historical cTn levels when categorizing

patients in different types of myocardial injury. In addition, chronic myocardial injury should only be considered in patients who have persistently elevated hs-cTnT over time (weeks). We believe that our categorization is robust. All the study data were retrieved from validated national healthcare registers and there was no patient lost to follow-up.

Limitations

A limitation of the study was the lack of information on diagnostic coronary angiographies. Furthermore, medications were categorized into the following 3 groups; ie, 0 to 1 medications, 2 to 3 medications, or 4 medications to avoid unstable estimates since cases were few if categories of medications separated into 0, 1, 2, 3, and 4 groups of medications. Still, in some of the analyses, the number of patients and events were small, leading to imprecise estimates. We estimated the exposure of listed medications (β-blockers, ACEi/ARB, statins, or platelet inhibitors) from dispensed prescriptions from the pharmacy and not actual use. Furthermore, we did not investigate the potential effect of prescribed dosage since the main objective was to study the effect of number of studied medications. In addition, we had no information on stress tests. We did not know the proportion of patients who arrived late with TIMI with stable hs-cTnT >99th percentile value in whom troponin levels plateaued. This may have led to T1MI being misclassified as non-ischemic myocardial injury. This is an observational cohort study that carries natural limitations with residual confounding. Important limitations include the lack of information on smoking habits, physical activity, and other lifestyle and socioeconomic factors that could influence prognosis. Last, the study population consisted of patients visiting the emergency department and we believe the external validity is high in similar settings and healthcare systems, but one should be careful to interpret these results in other settings.

CONCLUSIONS

Patients with T2MI and acute or chronic myocardial injury are infrequently treated with common cardiovascular medications such as β-blockers, ACEi/ARB, statins, or platelet inhibitors. Treatment with guideline-recommended cardiovascular drugs in these patients is associated with reduced risks of death, and a combination of death, heart failure, MI, and stroke. Further intervention studies exploring the effects of cardiovascular treatment in patients with T2MI, acute or chronic myocardial injury are needed.

ARTICLE INFORMATION

Received August 19, 2020; accepted October 13, 2020.

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Sources of Funding

No specific funding was obtained for this study. Dr Kadesjö holds a research position funded by the regional agreement on medical training and clinical research between Stockholm County Council and the Karolinska Institute (Grant number: 20190354). Dr Sartipy is supported by the Swedish Heart-Lung Foundation (Grant numbers: 20160525, 20180400, and 20190533). Dr Holzmann holds research positions funded by the Swedish Heart-Lung Foundation (Grant number: 20170804), and the Stockholm County Council (Grant number: 20170686). The sponsors had no role in the design or conduct of this study.

Disclosures

Dr Holzmann has received consultancy honoraria from Idorsia and Pfizer. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics according to myocardial injury.

		Myocardial injury				
	Overall	T1	T2	AMS	KMS	p
n	3853	1111	251	1144	1347	
Age (mean (SD))	73.42 (13.53)	68.76 (12.93)	72.27 (13.38)	72.93 (14.30)	77.88 (11.86)	<0.001
Women	1537 (39.9)	352 (31.7)	128 (51.0)	488 (42.7)	569 (42.2)	<0.001
eGFR						<0.001
>60	2216 (57.5)	820 (73.8)	145 (57.8)	592 (51.7)	659 (48.9)	
45-60	729 (18.9)	137 (12.3)	54 (21.5)	231 (20.2)	307 (22.8)	
30-45	564 (14.6)	101 (9.1)	23 (9.2)	183 (16.0)	257 (19.1)	
<30	344 (8.9)	53 (4.8)	29 (11.6)	138 (12.1)	124 (9.2)	
CAD	1311 (34.0)	334 (30.1)	84 (33.5)	384 (33.6)	509 (37.8)	0.001
Hypertension	1738 (45.1)	391 (35.2)	112 (44.6)	563 (49.2)	672 (49.9)	<0.001
Diabetes	833 (21.6)	213 (19.2)	56 (22.3)	247 (21.6)	317 (23.5)	0.075
AMI	730 (18.9)	192 (17.3)	48 (19.1)	217 (19.0)	273 (20.3)	0.316
Heart failure	741 (19.2)	91 (8.2)	40 (15.9)	273 (23.9)	337 (25.0)	<0.001
Revascularization	772 (20.0)	215 (19.4)	55 (21.9)	229 (20.0)	273 (20.3)	0.820
Atrial fibrillation	1037 (26.9)	128 (11.5)	77 (30.7)	377 (33.0)	455 (33.8)	<0.001

COPD	325 (8.4)	41 (3.7)	23 (9.2)	150 (13.1)	111 (8.2)	<0.001
Stroke	369 (9.6)	71 (6.4)	19 (7.6)	134 (11.7)	145 (10.8)	<0.001
Cancer	521 (13.5)	109 (9.8)	38 (15.1)	167 (14.6)	207 (15.4)	<0.001
Beta-blocker	2792 (72.5)	1006 (90.5)	189 (75.3)	756 (66.1)	841 (62.4)	<0.001
ACEi/ARB	2367 (61.4)	800 (72.0)	142 (56.6)	632 (55.2)	793 (58.9)	<0.001
Platelet inhibitor	2391 (62.1)	1034 (93.1)	125 (49.8)	532 (46.5)	700 (52.0)	<0.001
Statin	2069 (53.7)	965 (86.9)	108 (43.0)	457 (39.9)	539 (40.0)	<0.001
Number of medications						<0.001
0	471 (12.2)	41 (3.7)	39 (15.5)	200 (17.5)	191 (14.2)	
1	476 (12.4)	17 (1.5)	40 (15.9)	187 (16.3)	232 (17.2)	
2	747 (19.4)	61 (5.5)	50 (19.9)	277 (24.2)	359 (26.7)	
3	987 (25.6)	302 (27.2)	64 (25.5)	284 (24.8)	337 (25.0)	
4	1172 (30.4)	690 (62.1)	58 (23.1)	196 (17.1)	228 (16.9)	

Numbers are n (%) unless otherwise stated

Table S2. Baseline characteristics for separate numbers of medications: 0, 1, 2, 3, and 4 medications.

		Number of medications				
	All patients	**0**	**1**	**2**	**3**	**4**
N	3853	471	476	747	987	1172
Age (mean (SD))	73.42 (13.53)	70.52 (17.93)	76.22 (13.97)	77.98 (11.68)	74.52 (12.62)	69.60 (11.71)
Women	1537 (39.9)	194 (41.2)	232 (48.7)	369 (49.4)	407 (41.2)	335 (28.6)
eGFR						
>60	2216 (57.5)	277 (58.8)	238 (50.0)	362 (48.5)	555 (56.2)	784 (66.9)
45-60	729 (18.9)	93 (19.7)	98 (20.6)	178 (23.8)	163 (16.5)	197 (16.8)
30-45	564 (14.6)	60 (12.7)	89 (18.7)	130 (17.4)	166 (16.8)	119 (10.2)
<30	344 (8.9)	41 (8.7)	51 (10.7)	77 (10.3)	103 (10.4)	72 (6.1)
CAD	1311 (34.0)	92 (19.5)	103 (21.6)	212 (28.4)	400 (40.5)	504 (43.0)
Hypertension	1738 (45.1)	138 (29.3)	173 (36.3)	384 (51.4)	487 (49.3)	556 (47.4)
Diabetes	833 (21.6)	62 (13.2)	65 (13.7)	128 (17.1)	231 (23.4)	347 (29.6)
AMI	730 (18.9)	57 (12.1)	54 (11.3)	104 (13.9)	197 (20.0)	318 (27.1)
Heart failure	741 (19.2)	56 (11.9)	90 (18.9)	202 (27.0)	214 (21.7)	179 (15.3)
Revascularization	772 (20.0)	50 (10.6)	45 (9.5)	98 (13.1)	228 (23.1)	351 (29.9)
Atrial fibrillation	1037 (26.9)	105 (22.3)	152 (31.9)	304 (40.7)	301 (30.5)	175 (14.9)

COPD	325 (8.4)	55 (11.7)	53 (11.1)	77 (10.3)	65 (6.6)	75 (6.4)
Stroke	369 (9.6)	32 (6.8)	45 (9.5)	81 (10.8)	123 (12.5)	88 (7.5)
Cancer	521 (13.5)	100 (21.2)	80 (16.8)	108 (14.5)	124 (12.6)	109 (9.3)
Beta-blocker	2792 (72.5)	0 (0.0)	193 (40.5)	562 (75.2)	865 (87.6)	1172 (100.0)
ACEi/ARB	2367 (61.4)	0 (0.0)	126 (26.5)	431 (57.7)	638 (64.6)	1172 (100.0)
Platelet inhibitor	2391 (62.1)	0 (0.0)	126 (26.5)	327 (43.8)	766 (77.6)	1172 (100.0)
Statin	2069 (53.7)	0 (0.0)	31 (6.5)	174 (23.3)	692 (70.1)	1172 (100.0)
Group						
Type 1 MI	1111 (28.8)	41 (8.7)	17 (3.6)	61 (8.2)	302 (30.6)	690 (58.9)
Type 2 MI	251 (6.5)	39 (8.3)	40 (8.4)	50 (6.7)	64 (6.5)	58 (4.9)
Acute myocardial injury	1144 (29.7)	200 (42.5)	187 (39.3)	277 (37.1)	284 (28.8)	196 (16.7)
Chronic myocardial injury	1347 (35.0)	191 (40.6)	232 (48.7)	359 (48.1)	337 (34.1)	228 (19.5)

Numbers are n (%) unless otherwise stated

Table S3. Antiplatelet agents according to number of cardiovascular drugs dispensed at discharge.

	Number of medications				
	All patients *n=3853*	**0-1** *n=947*	**2-3** *n=1734*	**4** *n=1172*	p-value
Aspirin	2270 (59%)	117 (12%)	1026 (59%)	1127 (96%)	<0.001
Clopidogrel	940 (24%)	6 (1%)	305 (18%)	629 (54%)	<0.001
Ticagrelor	210 (5%)	1 (0%)	53 (3%)	156 (13%)	<0.001
Prasugrel	20 (1%)	0 (0%)	6 (0%)	14 (1%)	<0.001

Numbers are n (%).

Figure S1. Selection of the study population.