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ORIGINAL RESEARCH

The Intersection of Type 2 Myocardial Infarction and Heart Failure

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BACKGROUND: Type 2 myocardial infarction (T2MI) is common and associated with high cardiovascular event rates. However, the relationship between T2MI and heart failure (HF) is uncertain.

METHODS AND RESULTS: We identified patients with T2MI at a large tertiary hospital between October 2017 and May 2018. Patient characteristics, causes of T2MI, and subsequent HF hospitalizations were determined by physician chart review. We identified 359 patients with T2MI over the study period; 184 patients had a history of HF. Among patients with ejection fraction (EF) assessment (N=180), the majority had preserved EF (N=107; 59.4%), followed by reduced EF (N=54; 30.0%), and mid-range EF (N=19; 10.6%). Acute HF was the most common cause of T2MI (20.9%). Of those whose T2MI was precipitated by HF (N=75), the mean EF was 53.0±16.8% and 16 (21.3%) were de novo diagnoses of HF. Among patients with T2MI who were discharged alive with available follow-up (N=289), 5.5% were hospitalized with acute HF within 30 days, 17.3% within 180 days, and 22.1% within 1 year. In subgroup analyses, among patients with T2MI with prevalent or new HF (N=161), the rate of HF hospitalization at 1 year was 34.2%, considerably higher than those with T2MI and no HF diagnosis at discharge (7.0%; N=9/128).

CONCLUSIONS: Index presentations of HF or worsening chronic HF represent the most common causes of T2MI. ≈1 in 5 patients with T2MI will be readmitted for HF within 1 year of their event. Strategies to prevent HF events after a T2MI are needed.

Key Words: heart failure ∎ outcomes ∎ type 2 myocardial infarction

Describing the varying presentation patterns and pathophysiology of acute myocardial infarction (MI), in 2007 the Universal Definition of MI introduced 5 distinct subtypes of MI.[1] Type 2 MI (T2MI) is defined as myocardial injury resulting from a mismatch in myocardial oxygen supply-demand and occurring in the absence of acute atherothrombosis.[1]

As recognition of T2MI has increased, emerging data have demonstrated that this form of MI is common and may even be more prevalent than type 1 MI.[2] Moreover, as hospitals transition to high-sensitivity cardiac troponin assays, the incidence of T2MI is anticipated to further increase.[3] Patients with T2MI have

a concerning prognosis; the 5-year mortality rate is approximately 60%.[4,5] Although most patients die from non-cardiovascular causes following T2MI, it is increasingly recognized that patients with T2MI are also at high-risk for subsequent cardiovascular events.[4,5] Almost one-third of patients with T2MI will experience a recurrent MI or die from a cardiovascular event within 5 years.[4] In this setting, efforts to improve risk stratification and identify therapeutic strategies for patients with T2MI are essential.[6]

The relationship between T2MI and heart failure (HF) is underexplored. The 2 conditions are closely intertwined: HF can be both a precipitant of T2MI but

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CLINICAL PERSPECTIVE

What Is New?

- In this retrospective single center study of 359 patients with type 2 myocardial infarction (T2MI), acute heart failure (HF) was a common precipitant of T2MI (21.9%).
- Subsequent HF hospitalizations were common, occurring in 22.1% of patients at 1 year; the event rate was 34.2% among those with known HF and 7% among those with no history of HF upon discharge from their index T2MI admission.
- The risk of subsequent HF hospitalization was similar among patients with T2MI and those with myocardial injury without infarction.

What Are the Clinical Implications?

- Patients with T2MI and myocardial injury are at high-risk for subsequent HF hospitalizations.
- Strategies to prevent HF events after a T2MI are needed including optimization of guideline-directed medical therapies.

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Nonstandard Abbreviations and Acronyms

HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
SGLT2i	sodium glucose co-transporter-2 inhibitor

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also be an adverse outcome of the infarction. Given the morbidity and mortality associated with HF, identification of at-risk patients is critical to facilitate primary and secondary preventive interventions. In the setting of this pressing need, we examined the risk of HF events following T2MI.

METHODS

The data, analytic methods, and study materials may be available from the corresponding author upon reasonable request.

Study Population

We identified patients coded as T2MI (*International Classification of Diseases, Tenth Revision [ICD-10]* code I21.A1) between October 2017 and May 2018 at Massachusetts General Hospital. Strict adjudication with physician chart reviewers using the fourth Universal Definition of MI was then applied to confirm or refute the diagnosis.[7] To ensure consistency with the diagnoses, uncertain cases were reviewed by C.M.C. A cardiac troponin T concentration ≥0.03 ng/mL (10% coefficient of variation) or a fifth generation high sensitivity cardiac troponin T concentration of ≥10 ng/L for women or ≥15 ng/L for men were diagnostic of myocardial injury. An MI was defined as a rising and/ or falling elevation in cardiac troponin (conventional or high sensitivity) >99th percentile and at least one of the following: (1) symptoms of ischemia, (2) new electrocardiographic evidence of ischemia, (3) new pathological Q waves, (4) new regional wall motions on imaging in an ischemic territory, or (5) coronary thrombus on angiography. Symptoms suggestive of ischemia included chest pain consistent with angina or shortness of breath not otherwise attributed to a respiratory condition (Table S1). Electrocardiographic evidence of ischemia included new dynamic ST segment depressions or ST segment elevations or new T wave flattening or inversions (excluding leads III, aVR and V1 which may represent a normal variant). T2MI was defined as an MI with an identifiable preceding imbalance between myocardial oxygen supply and demand. Acute HF was considered a precipitant of T2MI when physiologic changes that could lead to an imbalance between myocardial oxygen supply and demand were present, including hypoxia, tachycardia, hypotension, or hypertension.

Patient Characteristics, Testing, and Treatments

Baseline characteristics, precipitating etiology, diagnostic testing, and in-hospital treatments for patients with T2MI were recorded. For those who underwent a transthoracic echocardiogram during admission, the left ventricular ejection fraction (EF) was recorded. Among patients with T2MI and a history of HF, the classification of HF (ie, preserved [HFpEF], mid-range [HFmrEF], or reduced EF [HFrEF]) was recorded. Among T2MI patients with a history of HFrEF or newly diagnosed HFrEF, admission and discharge guideline directed medications and dosages were recorded (ie, angiotensin-converting-enzyme inhibitors [ACEI], angiotensin II receptor blockers [ARB], beta blockers, aldosterone antagonists, and sacubitril/valsartan).

Outcomes

Among patients with T2MI with available follow-up data, the occurrence and number of hospitalizations for HF was determined at 30 days, 180 days, and 1 year post discharge. Hospitalizations for HF were identified at our institution or outside institutions when data were

available (identified by chart review of available records from outside institutions and data linked to our medical record system). Patients who were discharged to hospice or who did not have clear follow-up data beyond their index T2MI hospitalization in the electronic medical record were excluded from the event analyses. The median number of HF hospitalizations were determined. Among patients who experienced a HF hospitalization during the follow-up period, the classification of HF was determined (HFpEF, HFmrEF, and HFrEF) based on available echocardiography data at that time. In subgroup analyses, the incidence of HF hospitalization among T2MI with prevalent or newly diagnosed HF during their index T2MI event was determined. The incidence of HF among patients with T2MI with no history of HF (either prior to or during their index T2MI admission) was also recorded. Lastly, we compared outcomes among patients with myocardial injury who were miscoded as a T2MI and patients adjudicated to have T2MI.

Secondary outcomes recorded included cardiovascular death at 30 days, 180 days, and 1 year post discharge and a composite end point of cardiovascular death or hospitalization for HF at each timepoint. Cardiovascular death includes death from acute MI, HF, ventricular tachycardia or ventricular fibrillation, or sudden cardiac death.

Statistical Analysis

Baseline characteristics among patients with T2MI with or without a history of HF were compared using Chi-square tests for dichotomous variables and Welch's 2 sample t tests for continuous variables. Similarly, patients with T2MI were compared to those with myocardial injury using Chi-square tests for dichotomous variables and Welch's 2 sample t test for continuous variables.

Time-to-first HF hospitalization event and first HF hospitalization or cardiovascular death were displayed as Kaplan-Meier survival curves for all patients with T2MI, those with prevalent or newly diagnosed HF, those without prevalent or newly diagnosed HF, and among patients with T2MI compared to myocardial injury. Log-rank tests were used to compare groups in Kaplan-Meier analyses. Median NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentrations among patients with T2MI who did or did not have a subsequent HF hospitalization were compared with Wilcoxon rank-sum test. Additionally, we performed multivariable logistic regression analyses to compare HF hospitalization and a composite end point of HF hospitalization or cardiovascular death at 1 year among patients with T2MI versus those with myocardial injury. Age, sex, known coronary artery disease, history of HF, chronic kidney disease, diabetes mellitus, and atrial fibrillation were included as covariates in the model. Covariates were selected a priori based on known or hypothesized risk factors for the outcomes.

All statistical tests were 2-sided, with $P<0.05$ considered statistically significant; no adjustments were made for multiplicity. All analyses were performed using R software (version 3.6.2). This study was approved by the Partners Healthcare Mass General Brigham Institutional Review Board and no informed consent was required.

RESULTS

Patient Characteristics

We identified 633 patients who were coded as having a T2MI over the study period; 359 patients were adjudicated to have T2MI, 265 patients had myocardial injury, 6 had type 1 MI, and 3 had unstable angina.[8] The most common causes of T2MI were HF (N=75; 20.9%), respiratory failure (N=69; 19.2%), arrhythmias (N=52; 14.5%), sepsis (N=46; 12.8%), hypertensive urgency (N=36; 10.0%), and bleeding (N=20; 5.6%). Of those whose T2MI was precipitated by HF (N=75), 16 cases (21.3%) represented new diagnoses of HF.

Of those admitted with a T2MI, 184 patients (51.3%) had a prevalent history of HF. Among those with available subtype data (N=180), the majority had HFpEF (N=107; 59.4%), followed by HFrEF (N=54; 30.0%) and HFmrEF (N=19; 10.6%). Among patients with T2MI with a history of HFrEF, prescriptions of guideline-directed medical therapy were low prior to admission (Figure 1). Patients with T2MI with a history of HF were more likely to be older and have prevalent risk factors for and prior diagnoses of coronary and peripheral artery disease, prior revascularization, and atrial fibrillation (Table 1). Additionally, patients with T2MI and HF were more likely to have advanced kidney disease (Table 1). Compared with patients with myocardial injury, patients with T2MI more commonly had a prior history of MI (21.7% versus 14.3%, $P=0.03$), prior percutaneous coronary evaluation (17% versus 9.1%, $P=0.006$), known coronary artery disease (50.4% versus 33.2%, $P<0.001$), heart failure (51.3% versus 37.4%, $P<0.001$) and peripheral artery disease (22.8% versus 12.1%, $P=0.001$; Table 2).

NT-proBNP was measured in 290 patients with T2MI; 1 patient had a NT-proBNP level of >70 000 pg/mL, the remainder had measurable values (N=289; Table S2). Most patients (N=243; 67.7%) underwent a transthoracic echocardiogram during their admission; the mean EF was 53±16.8%. Coronary angiography was performed in 44 patients with T2MI (12.3%), of whom 22 had obstructive CAD (50%). Only 7 patients (2.6%) of patients with myocardial injury underwent coronary angiography of whom 2 had obstructive CAD (28.6%).
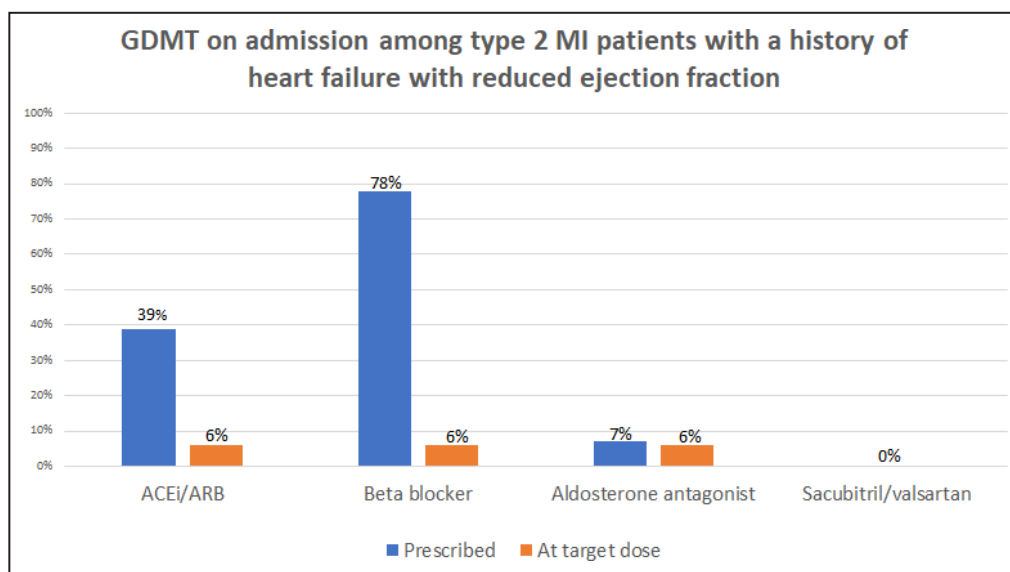
Figure 1. Guideline-directed medical therapy on admission among patients with type 2 MI with a history of heart failure with reduced ejection fraction (N=54).
ACEi indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; GDMT, guideline directed medical therapy; and MI, myocardial infarction.

Of the 359 patients with T2MI, 38 died in hospital (10.6%). Among patients with T2MI with a history of or newly diagnosed HFrEF (N=50), prescriptions of guideline-directed medical therapy were low on discharge (Figure 2). Among patients with myocardial injury (N=265), 23 died in hospital (8.7%). Of those

Table 1.   Baseline Characteristics of Patients With Type 2 MI Stratified by Past History of Heart Failure (N=359)

	No History of Heart Failure* (n=175)	History of Heart Failure* (n=184)	*P* Value
Demographics			
Age, mean (SD)	71.7 (13.4)	77.9 (12.8)	<0.001
Men	94 (53.7%)	110 (59.8%)	0.29
Past Medical History			
Diabetes mellitus	70 (40.0%)	79 (42.9%)	0.65
Current or former smoker	24 (13.7%)	14 (7.6%)	0.09
COPD	36 (20.6%)	43 (23.4%)	0.61
Hypertension	138 (78.9%)	153 (83.2%)	0.37
Hyperlipidemia	95 (54.3%)	123 (66.8%)	0.02
Prior MI	23 (13.1%)	55 (29.9%)	<0.001
Prior PCI	26 (14.9%)	35 (19%)	0.36
Prior CABG	16 (9.1%)	38 (20.6%)	0.004
Known CAD	66 (37.7%)	115 (62.5%)	<0.001
Atrial fibrillation	31 (17.7%)	82 (44.6%)	<0.001
Prior stroke or TIA	26 (14.9%)	43 (23.4%)	0.06
PAD	29 (16.6%)	53 (28.8%)	0.008
Cancer	38 (21.7%)	32 (17.4%)	0.37
CKD	54 (30.9%)	115 (62.5%)	<0.001
Dialysis	10 (5.7%)	28 (15.2%)	0.006
Liver cirrhosis	8 (4.6%)	6 (3.3%)	0.71
Prior GI bleed	13 (7.4%)	17 (9.2%)	0.67

CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.
    *Heart failure diagnosis prior to admission.

Table 2. Baseline Characteristics of Patients With Type 2 MI and myocardial injury

	Type 2 MI (n=359)	Myocardial Injury (n=265)	P Value
Demographics			
Age, mean (SD)	74.9 (13.4)	75.8 (15.1)	0.42
Men, n (%)	204 (56.8%)	160 (60.4%)	0.42
Past Medical History			
Diabetes mellitus, n (%)	149 (41.5%)	89 (33.6%)	0.05
Current or former smoker, n (%)	38 (10.6%)	29 (10.9%)	0.99
COPD, n (%)	79 (22%)	66 (24.9%)	0.45
Hypertension, n (%)	291 (81.1%)	215 (81.1%)	1.00
Heart failure, n (%)	184 (51.3%)	99 (37.4%)	<0.001
Hyperlipidemia, n (%)	218 (60.7%)	146 (55.1%)	0.18
Prior MI, n (%)	78 (21.7%)	38 (14.3%)	0.03
Prior PCI, n (%)	61 (17%)	24 (9.1%)	0.006
Prior CABG, n (%)	54 (15%)	25 (9.4%)	0.05
Known CAD, n (%)	181 (50.4%)	88 (33.2%)	<0.001
Atrial fibrillation, n (%)	113 (31.5%)	80 (30.2%)	0.80
Prior stroke or TIA, n (%)	69 (19.2%)	48 (18.1%)	0.81
PAD, n (%)	82 (22.8%)	32 (12.1%)	0.001
Cancer history, n (%)	70 (19.5%)	72 (27.2%)	0.03
CKD, n (%)	169 (47.1%)	116 (43.8%)	0.46
Dialysis, n (%)	38 (10.6%)	13 (4.9%)	0.02
Liver cirrhosis, n (%)	14 (3.9%)	17 (6.4%)	0.21
Prior GI bleed, n (%)	30 (8.4%)	25 (9.4%)	0.74

CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

discharged alive (N=242), 75 (28.3%) were discharged on an ACEI/ARB and 151 (57.0%) were discharged on a beta blocker. No patient with myocardial injury or T2MI were discharged on sacubitril/valsartan.

HF Hospitalizations in Follow-Up

Among those who were discharged alive (N=321), follow-up data at 1 year were available for 289 patients (90.0%) with 32 patients lost to follow-up (10%). Among those with follow-up data (N=289), 5.5% (N=16) experienced at least 1 subsequent hospitalization for acute HF within 30 days, 17.3% (N=50) within 180 days, and 22.1% (N=64) within 1 year (Figure 3). Among those with a HF hospitalization (N=64), the mean number of hospitalizations was 1.69 (±1.22) and the total number of HF hospitalizations was 108. The number of HF hospitalizations ranged from 1 to 7. Of those who had at least 1 HF hospitalization at 1 year (N=64), the diagnosis at time of index T2MI was HFpEF in 35 cases (54.7%), HFrEF in 24 cases (37.5%), and HFmrEF in 5 cases (7.8%) based on available EF data at that time (39 patients had a Transthoracic echocardiogram [TTE] during at least one of their index HF admissions, and the remaining 25 patients had a TTE within a year of their HF hospitalization). Patients with T2MI with available NT-proBNP measurements during their index admission who subsequently had a HF hospitalization within 1-year (N=59) had higher median NT-proBNP concentrations during their T2MI admission compared with 176 patients with measurable NT-proBNP values who did not have a subsequent HF hospitalization (6399 ng/mL [IQR, 3760–16 141] versus 4236 ng/mL [IQR, 983–10 842], P=0.004).

Among patients with a past history of HF or who were newly diagnosed with HF during their index T2MI admission (N=161), 34.2% (N=55) were hospitalized with HF at 1 year (Figure 3). Among T2MI who had no HF diagnosis at discharge (N=128), the 1-year HF hospitalization rate was 7.0% (N=9).

Among the myocardial injury patients who were miscoded as T2MI 208 patients had available follow-up data; the rate of HF hospitalization was 4.3% (N=9) at 30 days, 11.1% (N=23) at 180 days, and 15.4% (N=32) at 1 year. Patients with myocardial injury had a similar risk of HF hospitalization at 1 year when compared to patients with T2MI (adjusted odds ratio [aOR], 0.73, 95% CI 0.45–1.27; Figure 4). Furthermore, the risk of HF hospitalization was similar when comparing myocardial injury and T2MI patients with a history of HF (aOR, 0.97, 95% CI 0.54–1.71).

Composite HF Hospitalization or Cardiovascular Death

Among patients with T2MI discharged alive with available follow-up data (N=289), the incidence of cardiovascular death at 1 year was 0.7% (N=2) at 30 days, 4.8% (N=14) at 180 days, and 8.3% (N=24) at 1 year. First hospitalization for HF or cardiovascular death occurred in 17 patients at 30 days (5.9%), 60 patients at 180 days (20.8%) and 78 patients at 1 year (24.2) (Figure 5). Among patients with a past history of HF or who were newly diagnosed with HF during their index T2MI admission (N=161), 41.6% (N=67) were hospitalized with HF at least once or experience a cardiovascular death at 1 year (Figure 5). Among T2MI who had no HF diagnosis at discharge (N=128), 11 (8.6%) were hospitalized
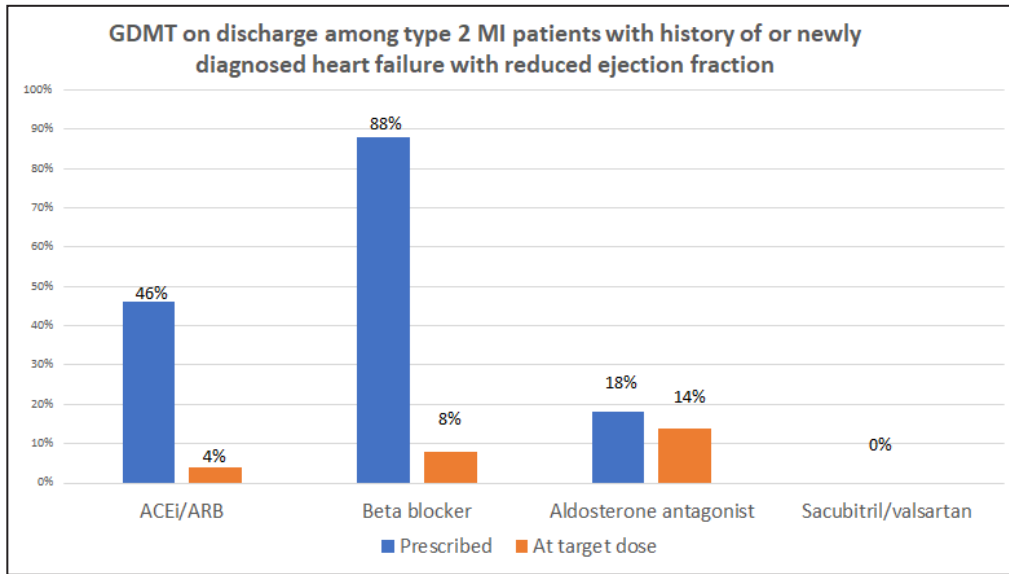
Figure 2. Guideline-directed medical therapy on discharge among patients with T2MI with a history of or newly diagnosed heart failure with reduced ejection fraction (N=50).
ACEI indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; GDMT, guideline directed medical therapy; and MI, myocardial infarction.

for HF at least once or had died from a cardiovascular death at 1 year (Figure 5).

Among patients with myocardial injury miscoded as a T2MI (N=208) with available follow-up data at 1 year, the rate of HF hospitalization or cardiovascular death at 30 days was 5.8% (N=12), 180 days was 13.5% (N=28), and 1 year was 18.3% (N=38). Patients with myocardial injury had a similar risk of HF hospitalization or cardiovascular death at 1 year when compared to patients with T2MI (aOR, 0.82, 95% CI 0.51–1.32; Figure 6). Similarly, the risk of HF hospitalization or cardiovascular death at 1 year was similar among patients with

T2MI and myocardial injury with a history of HF (aOR, 0.92, 95% CI 0.53–1.59) and those without a history of HF (aOR, 0.87, 95% CI 0.30–2.42).

DISCUSSION

In this longitudinal study that closely examines the relationship between T2MI and HF, we report several important findings. First, T2MI and HF often coexist. Half of patients with T2MI in our study had prevalent HF; the majority had HFpEF. Patients with T2MI who had a history of HF also had more prevalent cardiovascular
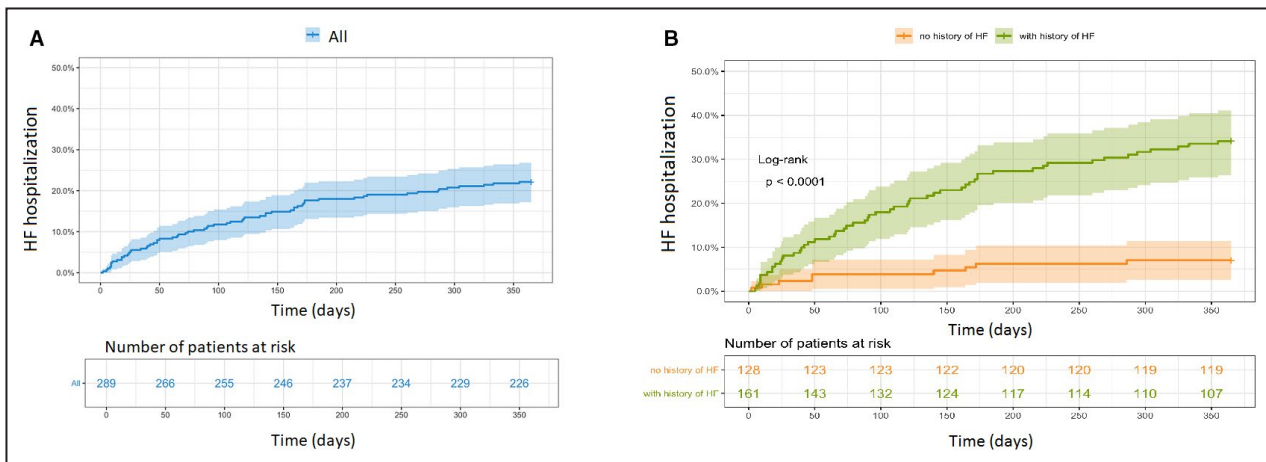
Figure 3. Kaplan-Meier survival curves illustrating time-to-first HF hospitalization among (A) all patients with type 2 MI discharged alive with available follow-up data at 1 year (N=289) and (B) patients with type 2 MI without a diagnosis of heart failure at discharge (N=128) vs those with a diagnosis of heart failure (N=161).
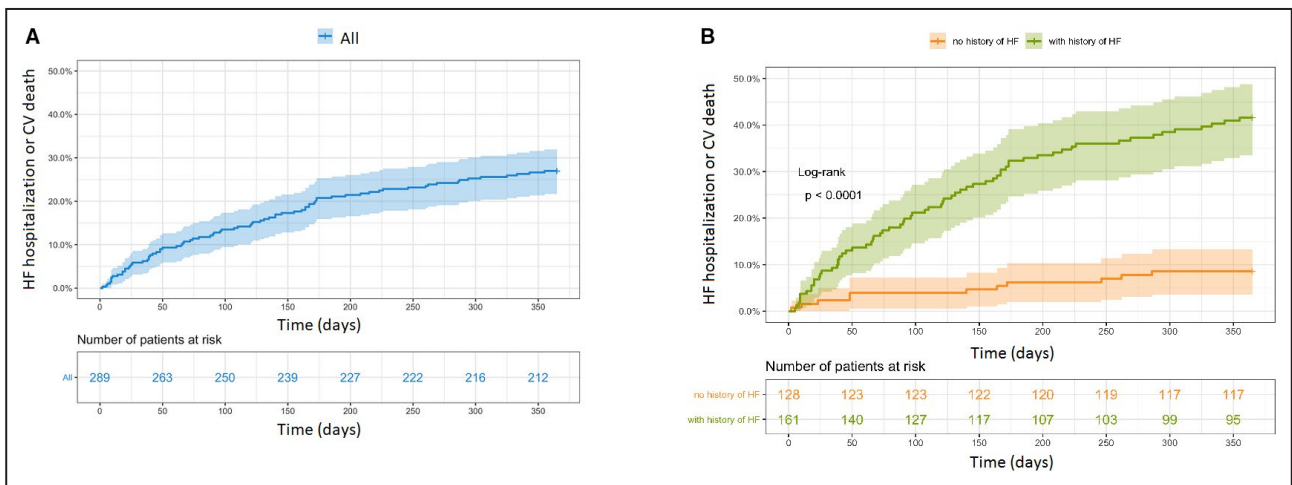Presented with 95% pointwise CI calculated by log transformation. HF indicates heart failure; MI, myocardial infarction.
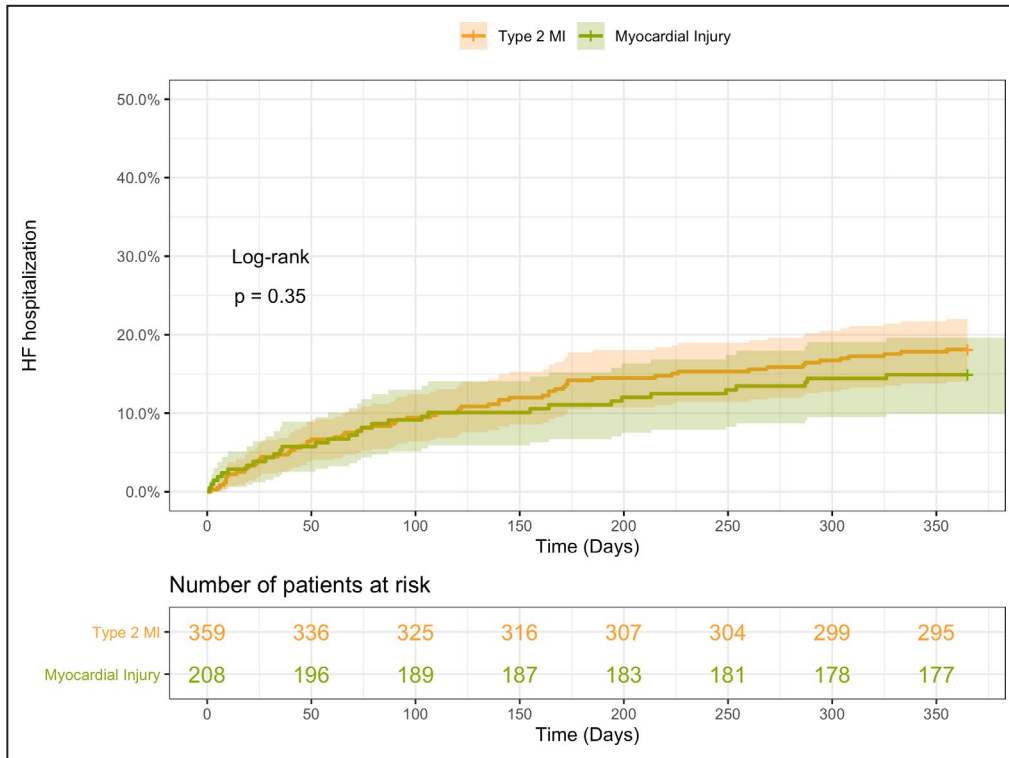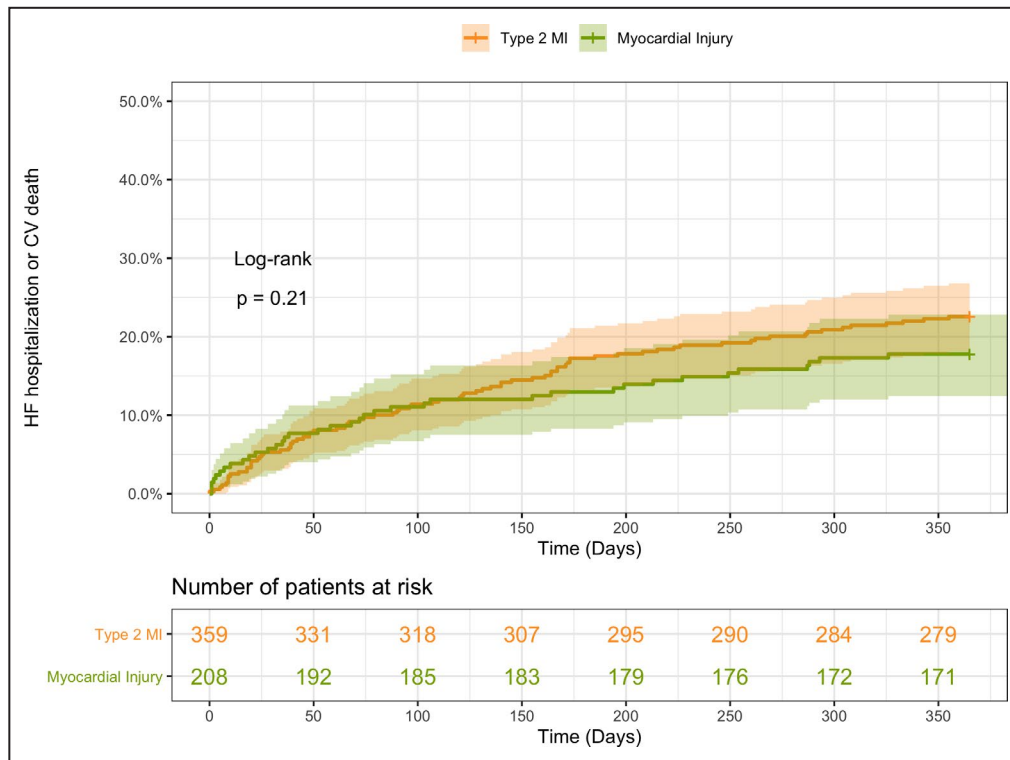
Figure 4. Kaplan-Meier survival curves illustrating time-to-first HF hospitalization among patients with type 2 MI discharged alive with available follow-up data at 1 year (N=289) and patients with myocardial injury (N=208).
Presented with 95% pointwise CIs calculated by log transformation. HF indicates heart failure; and MI, myocardial infarction.

comorbidities such as known coronary artery disease, prior revascularization, atrial fibrillation, hyperlipidemia, and chronic kidney disease compared with patients with T2MI without a history of HF. Second, acute HF is a common precipitating factor of T2MI representing

≈20% of the cases in our study. Of these cases, one-fifth represented new diagnosis of HF. Third, patients with T2MI have high rates of first and recurrent HF hospitalizations following their diagnosis. We found that 22% of patients were readmitted with HF at least once

Figure 5. Kaplan-Meier survival curve illustrating time-to-first HF hospitalization or CV death among (A) all patients with type 2 MI discharged alive with available follow-up data at 1 year (N=289) and (B) patients with type 2 MI without a diagnosis of heart failure at discharge (N=128) vs those who did (N=161).
Presented with 95% pointwise CIs calculated by log transformation. CV indicates cardiovascular; HF, heart failure; and MI, myocardial infarction.

Figure 6.   Kaplan-Meier survival curves illustrating time-to-first HF hospitalization or CV death among patients with type 2 MI discharged alive with available follow-up data at 1 year (N=289) and patients with myocardial injury (N=208).

Presented with 95% pointwise CIs calculated by log transformation. CV indicates cardiovascular; HF, heart failure; and MI, myocardial infarction.

within a year of their diagnosis, contributing to a high burden of total HF events. Most admissions were due to HFpEF (54.7%). This rate of HF hospitalization is almost 2 times higher than that has been observed after a type 1 MI (with contemporary prompt revascularization and medical management). Examining Medicare fee-for-service beneficiaries in 2010, Chen and colleagues found the number of patients hospitalized for HF within 1 year after an acute MI was 14.2 per 100 person-years in 2010.[9] Among patients with T2MI with prevalent or new HF, we found the readmission rate for HF was even higher at 34%. Additionally, and importantly, 7% of patients were newly diagnosed with HF after discharge in the year following their T2MI. However, as Chen and colleagues did not report the proportion of each subtype of MI in their study, it is therefore possible that patients with T2MI were included.

It is important to note that troponin concentrations may be elevated in patients with HF from type 1 MI, T2MI, acute myocardial injury, or chronic myocardial injury. In order to receive a diagnosis of T2MI, there must be evidence of ischemia with evidence of ischemia on ECG, new regional wall motion abnormalities in an ischemic territory on ECG, or symptoms suggestive of ischemia.[7] In our study, the Universal Definition of MI criteria was uniformly applied to diagnose T2MI.

Hence, although we identified 633 patients initially coded as T2MI, only 57% met criteria for the diagnosis when strictly adjudicated; the remainder had mostly myocardial injury as previously described.[8] Indeed, the diagnosis of T2MI can be challenging. Contributing to this is a lack of understanding among clinicians regarding the difference between non-ischemic myocardial injury and T2MI. However, beyond this, there is also subjectivity regarding the diagnosis, particularly when relying on symptoms alone.[10,11] In our study, the majority of patients were diagnosed with T2MI based on objective evidence of ischemia with <1 in 5 patients receiving a diagnosis based on symptoms alone. The DEMAND-MI (Determining the Mechanism of Myocardial Injury and Role of Coronary Disease in Type 2 Myocardial Infarction) study (NCT03338504) will provide further insights into the accuracy of T2MI diagnosis in clinical practice.

Notably, we found that the rate of HF hospitalization was similar among patients with T2MI and patients with myocardial injury who were miscoded as T2MI. This suggests that the risk of HF hospitalization may not necessarily be due to T2MI per se but rather myocardial injury. Indeed, elevations in cardiac troponin have been associated with increased risk of future development of HF in ambulatory populations,[12–14] and

an increased risk of HF events among patients with established HF.[15–18] The rate of HF hospitalization with or without cardiovascular death among patients with T2MI or myocardial injury is similar to that demonstrated by Myhre and colleagues when examining patients with HF and myocardial injury and significantly higher than patients with HF with low troponin concentrations.[19] Prior studies have also demonstrated a similar risk of major adverse cardiovascular events among patients with T2MI compared with myocardial injury.[4,20] Nevertheless, we still believe that the differentiation of T2MI from myocardial injury is important in clinical practice as the mechanism of myocardial injury differs; the former due to ischemia while the latter is often multifactorial. Accordingly, strategies targeting cardiovascular risk reduction in these groups may differ. This hypothesis warrants investigation in clinical trials.

Our study demonstrates that patients with T2MI are at high risk for new or recurrent HF admissions following their diagnosis. In patients diagnosed with T2MI, initiation of or optimization of guideline-directed medical therapy should be strongly considered among patients with a history of or new diagnosis of HF in order to modify their risk of subsequent events. In our study, we found that prescriptions of guideline-directed medical therapy were low on discharge among patients with T2MI with HFrEF. Underutilization of guideline-directed medical therapy may have contributed to the high HF event rates in our study. For patients with T2MI with and without HF co-existing cardiovascular comorbidities should be evaluated and aggressively managed. In our study, ≈40% of patients had diabetes mellitus and ≈80% had hypertension; both are known modifiable risk factors for the development of HF. Sodium glucose co-transporter-2 inhibitors (SGLT2i) have been shown to reduce the risk of HF among patients with type 2 diabetes mellitus (with or at risk for cardiovascular disease).[21] Patients with type 2 diabetes mellitus who experience a T2MI should be strongly considered for an SGLT2i to modify future risk of HF, similarly, stringent blood pressure control has been shown to prevent HF events in middle-aged and older at-risk adults.[22] The role of revascularization to reduce the incidence of HF following a T2MI is uncertain and merits investigation in a clinical trial. In this context, the rate of coronary angiography was low in our cohort with just 1 in 8 patients with T2MI undergoing a diagnostic coronary angiogram. The ACT-2 trial (Appropriateness of Coronary Investigation in Myocardial Injury and Type 2 Myocardial Infarction) is examining the role of revascularization for the treatment of T2MI and will hopefully shed light on this.

As patients with myocardial injury have an increased risk of HF events compared with those without injury,[19] patients may benefit from screening for myocardial injury to guide future risk of incident HF. The STOP-HF (St. Vincent's Screening to Prevent Heart Failure) and PONTIAC (N-terminal Pro-brain Natriuretic Peptide Guided Primary Prevention of Cardiovascular Events in Diabetic Patients) trials previously demonstrated that screening at-risk patients with natriuretic peptide measurement may alter HF risk.[23,24] Trials to assess whether measuring troponin, either alone or combined with natriuretic peptides, can alter HF risk in patients without existing HF warrant investigation in clinical trials.

Limitations

Although novel, our study has limitations. This was a single-center, tertiary care study and thus our T2MI patient population may not be broadly representative. Indeed, as our cohort of patients with T2MI had a higher prevalence of preexisting HF when compared with prior studies,[25–27] it is possible that this contributed to the modest rate of cases of acute HF precipitating T2MI and the subsequent high rates of HF events. All readmissions to outside institutions may not have been captured and thus our event rate may be underestimated. However, we excluded patients (only 10%) who did not have clear follow up in our healthcare system to limit this influence. As the median NT-proBNP concentration in the T2MI cohort without diagnosed HF was 4236 ng/mL, it is possible that some patients had undiagnosed HF. However, NT-proBNP elevation often predates incident HF and for this reason its measurement is recommended by the American College of Cardiology/American Heart Association guideline for the prevention of incident HF in high-risk patients.[28] Furthermore, our T2MI cohort without HF were elderly and had a high prevalence of renal failure and atrial fibrillation which have been associated with elevations in NT-proBNP in the absence of HF.[28] Further studies assessing subsequent HF hospitalization rates among patients with acute HF with/without myocardial injury versus those with T2MI are needed. Lastly, as revascularization for T2MI was uncommon in this cohort, the role of revascularization to prevent HF hospitalizations could not be explored but warrants evaluation in future clinical trials.

CONCLUSIONS

A complex intersection between T2MI and HF is present. HF is a common precipitant of T2MI and approximately 1 in 5 patients with T2MI will be readmitted for HF within 1 year of their index event. Efforts to improve primary and secondary prevention of HF events after a T2MI are needed.

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Supplemental Material

Table S1. Ischemia criteria to diagnose myocardial infarction and breakdown among patients with type 2 MI.

Ischemia criteria	N (%)
Isolated chest pain	20 (5.6)
Isolated shortness of breath	32 (8.9)
Combined chest pain and shortness of breath only	14 (3.9)
Isolated T wave inversions in an ischemic territory	49 (13.6)
Isolated ST depressions	32 (8.9)
Isolated ST elevations in an ischemic territory or new left bundle branch block	6 (1.7)
Isolated pathological Q waves	2 (0.6)
Combination of ischemic electrocardiogram features (T wave inversions in an ischemic territory, ST depressions or ST elevations, new left bundle branch block)	39 (10.9)
Isolated new regional wall motion abnormalities on echocardiogram in an ischemic territory	20 (5.6)
New regional wall motion abnormalities on echocardiogram combined with ischemic electrocardiogram changes (T wave inversions in an ischemic territory, ST depressions or ST elevations, new left bundle branch block)	34 (9.5)
Symptoms of ischemia (chest pain or shortness of breath) combined with electrocardiogram ischemic findings (T wave inversions in an ischemic territory, ST depressions or ST elevations, new left bundle branch block)	78 (21.7)
Symptoms of ischemia (chest pain or shortness of breath) combined with new regional wall motion abnormalities on echocardiogram in an ischemic territory	15 (4.2)
Symptoms of ischemia (chest pain or shortness of breath) combined with ischemic electrocardiogram changes (T wave inversions in an ischemic territory, ST depressions or ST elevations, new left bundle branch block) and new regional wall motion abnormalities on echocardiogram in an ischemic territory	18 (5)

Table S2. N-terminal pro-B-type natriuretic peptide (NT- proBNP) concentrations among study participants.

	All patients (N=289)	Type 2 MI precipitated by Heart Failure (N=73)	Type 2 MI precipitated by other causes (N=216)	p value
Median NTproBNP concentration, pg/ml (interquartile range)	5,193 (1,614-14,451)	7,698 (4,625-20,750)	4,236 (1,078-11,404)	<0.001