ESC European Society of Cardiology

European Heart Journal (2025) **46**, 1540–1550
https://doi.org/10.1093/eurheartj/ehae885

CLINICAL RESEARCH
Epidemiology, prevention, and health care policies

Incident heart failure and recurrent coronary events following acute myocardial infarction

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Received 27 March 2024; revised 12 September 2024; accepted 6 December 2024; online publish-ahead-of-print 28 January 2025

See the editorial comment for this article 'Prognosis following acute myocardial infarction', by I.B. Squire and S. Sze, https://doi.org/10.1093/eurheartj/ehaf056.

Abstract

Background and Aims Recurrent myocardial infarction (MI) and incident heart failure (HF) are major post-MI complications. Herein, contemporary post-MI risks for recurrent MI and HF are described.

Methods A total of 6804 patients with a primary discharge diagnosis of MI at 28 Baylor Scott & White Health hospitals (January 2015 to December 2021) were studied. Patient characteristics, treatment, and outcomes, including incident HF, recurrent MI, all-cause death, and all-cause and cardiovascular rehospitalizations, were assessed. Landmark approach anchored at 3 months post-discharge was used to assess 1-year outcomes.

Results Median age was 69 years, 59.7% were male, and 76.7% had non-ST-elevation MI. Comorbidities included hypertension (89%), dyslipidaemia (87%), Type 2 diabetes (48%), and chronic kidney disease (34%); 17% had a history of MI and 23% of HF; 63% underwent percutaneous/surgical revascularization. In landmark-anchored 1-year outcomes ($N = 6210$), 413 (6.7%) patients died, 1730 (27.9%) had all-cause and 735 (11.8%) cardiovascular hospitalizations, 234 (3.8%) had recurrent MI. Of patients without history of HF, 1160 (23.8%) developed incident HF [42.2%, 26.7%, and 31.1% with ejection fraction (EF) < 40%, 41–49%, and >50%, respectively) within 3 months of discharge. Patients who developed HF had higher risk of death and hospitalizations (all $P < .001$), irrespective of EF. Of 2179 patients with EF > 50% without prevalent HF or HF during index hospitalization, 257 (11.8%) developed HF and 77 (3.5%) recurrent MI within 1 year.

Conclusions In a contemporary post-MI cohort, the risk for incident HF was greater than recurrent MI, even among those with normal EF and no HF at discharge.

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Structured Graphical Abstract

Key Question

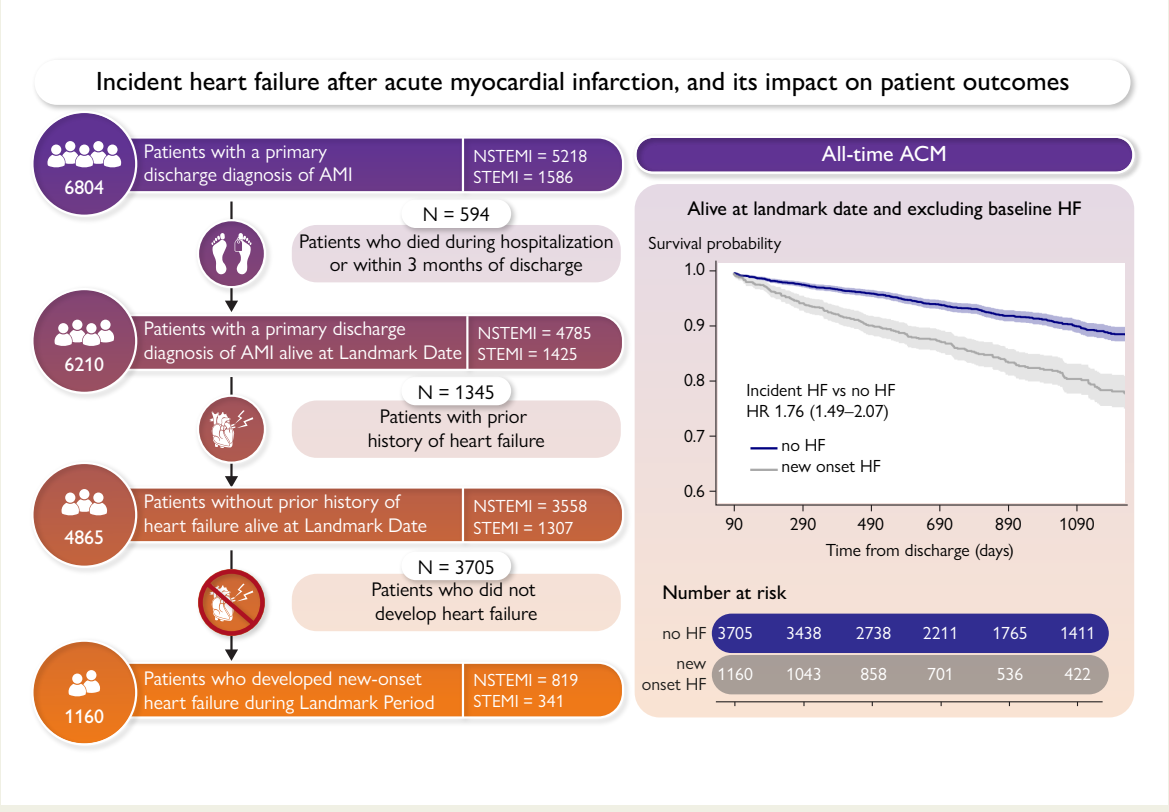
What is the risk for developing heart failure (HF) after myocardial infarction, and how does incident HF impact patient outcomes?

Key Finding

Of myocardial infarction patients without a history of HF, 23.8% developed HF. These patients had significantly increased risks of all-cause mortality, and of all-cause and cardiovascular readmissions.

Take Home Message

There is a critical need to better understand the mechanisms behind development of HF after myocardial infarction, and to develop therapeutic strategies targeting preservation of myocardial function and mitigating the risk of HF.



Incident heart failure after acute myocardial infarction and its impact on patient outcomes. ACM, all-cause mortality; AMI, acute myocardial infarction; HF, heart failure; HR, hazard ratio; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

Keywords Myocardial infarction • Heart failure • Mortality • Registry • Epidemiology

Introduction

Patients who develop post-myocardial infarction (MI) heart failure (HF) have a high risk for mortality and rehospitalizations. Reducing the risk of recurrent ischaemic events after an acute MI is a major therapeutic goal and has led to significant advances in systems of care, revascularization strategies, and drug therapy targeting secondary prevention. New onset HF is another adverse consequence complicating MI. Estimates from over a decade ago suggest that 20%–25% of patients develop HF during an MI admission or after discharge.[1,2] Several therapies have shown risk reduction for death or HF in high-risk patients following an MI, such as beta-blockers, angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs).[3] It has been two decades, however, since a drug therapy was shown to reduce the risk for HF after an acute MI. Herein, we leveraged an integrated healthcare system's data to evaluate contemporary trends in patient characteristics, and risks and outcomes related to the development of incident HF and recurrent MI in patients post-MI, to inform the need for clinical and research priorities.

Methods

Study design

Electronic health records for patients admitted with MI within the Baylor Scott & White Health system, which composes of over 50 hospitals and 1000 outpatient care sites, between January 2015 and December 2021 were assessed. Institutional Review Board approval was obtained.

Informed consent was waived based on the retrospective and de-identified nature of the study.

Study population

All patients 18 years or over with a primary discharge diagnosis of MI between January 2015 and December 2021 from 28 hospitals were included. These 28 hospitals were chosen based on the availability of data on the same electronic health record platform during the entire study period. Patients were identified using International Classification of Diseases Tenth Edition (ICD-10) codes for a primary discharge diagnosis of MI; a comprehensive list of codes is provided in Supplementary data online, *Table S1*. Patients were included regardless of left ventricular ejection fraction (LVEF) measurement at index MI admission.

Data collection

Baseline characteristics recorded included age, sex, race, ethnicity, estimated glomerular filtration rate, atrial fibrillation, hypertension, prior history of MI, HF, chronic kidney disease (CKD), Type 2 diabetes (T2D), smoking status, dyslipidaemia, cerebrovascular disease, and peripheral artery disease. Data were obtained on type of MI [ST-elevation MI (STEMI) or non-STEMI (NSETMI)] and last LVEF before discharge at index hospitalization as well as LVEF nearest to HF diagnosis, within 6 months. Data were collected on therapy at the time of MI presentation and at discharge, including antiplatelet agents, beta-blockers, ACEi/ARB/angiotensin receptor–neprilysin inhibitors, MRA, lipid-lowering therapies, sodium-glucose co-transporter-2 inhibitors, anti-glycaemic drugs, and diuretics. Diagnostic evaluation assessed included echocardiography, stress testing (exercise stress testing, myocardial perfusion imaging, or stress echocardiography), and coronary angiography. Revascularization data with thrombolytics and percutaneous or surgical revascularization were assessed. The date of the last follow-up was determined by the latest documented encounter with the healthcare system or date of death.

Study endpoints

The main study endpoints were recurrent MI, all-cause death, and all-cause and cardiovascular (CV) rehospitalizations. Incident HF diagnosis was determined by the first diagnosis of HF within 3 months after discharge or first HF diagnosis during index hospitalization with a subsequent HF diagnosis within 3 months after discharge to account for possible myocardial stunning following MI, which could lead to temporarily reduced LVEF or HF signs and symptoms. These data were obtained through review of patient's initial encounter and subsequent encounters in the institution's electronic health records.

Statistical analysis

Baseline characteristics were assessed. Continuous data are reported as medians and interquartile range (IQR) or means and standard deviation. Categorical data are reported as frequencies and percentages. Proportion of patients with STEMI and NSTEMI, and those with prior history of HF were assessed. Drug therapy at discharge for beta-blockers, ACEi/ARB, and MRA was assessed for the overall population and in those with an American Heart Association/American College of Cardiology Class 1 indication.[4] Patients who developed incident HF were reported after the exclusion of patients with prior HF and divided based on LVEF (measured at first diagnosis of HF or within 6 months of diagnosis) into ≤40%, 41–49% vs. ≥50% to assess HF with reduced, mildly reduced, and preserved ejection fraction (HFrEF, HFmrEF, and HFpEF), respectively, and were compared.

Outcomes were assessed for 1-year event rates using a landmark approach where patients were included only if they were alive at 3 months post-discharge. This was done to account for patients requiring a post-discharge HF encounter if the first diagnosis was made during an index MI to account for possible stunned myocardium, thereby avoiding accounting for outcomes before ascertaining diagnosis. Secondary analyses were also performed for all patients discharged alive and are presented in Supplementary data online, *Tables S2* and *S3*.

Rate and time to the first event for incident HF, recurrent MI, all-cause death, and all-cause and CV rehospitalizations were assessed. The mean length of index admission was recorded. Outcomes were assessed in the overall cohort, in those with STEMI and NSTEMI, with and without prior history of HF, and in those without prior HF, who developed incident HF. χ^2 and Wilcoxon rank-sum tests were used to compare incidence and time to the first event, respectively. The average number of rehospitalizations was assessed.

Cumulative outcomes were assessed using Kaplan–Meier estimates for the entire follow-up for incident HF or all-cause death in the overall population and among those with STEMI vs. NSTEMI. Patients with prevalent HF were excluded. Kaplan–Meier survival estimates were also compared for patients who developed HF with LVEF ≤ 40%, 41–49%, and ≥50%. Cox proportional hazard regression was used to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) of all-cause death, incident HF, and recurrent MI among STEMI vs. NSTEMI, and in those with incident HF with LVEF ≤ 40%, 41–49%, and ≥50%, adjusting for age, sex, obesity, and T2D. Cumulative outcomes were assessed using Kaplan–Meier estimates for the entire follow-up for incident HF and recurrent MI and stratified by LVEF subgroups and MI type (NSTEMI vs. STEMI).

The study included patients with primary discharge diagnosis of MI to focus on Type 1 MI. It is, however, possible that patients with Type 2 NSTEMI may have been coded as Type 1 MI as primary discharge diagnosis, or patients initially coded for Type 1 MI were deemed to have Type 2 NSTEMI during hospitalization. Therefore, separate analyses were performed assessing recurrent MI and incident HF among patients with STEMI only. Analysis was also performed among patients with recorded LVEF ≥ 50% during index hospitalization, no prior history of HF, or new onset HF during index MI hospitalization, to assess the incidence of new onset HF and recurrent MI within 12 months of discharge in patients with normal LVEF post-MI.

No imputation was performed, and all missing data were handled using complete-case analysis. All statistical analyses were performed using SAS software Version 9.4 (SAS Institute, Cary, NC, USA) and a *P*-value of <.05 was used to denote statistical significance.

Results

Baseline characteristics

A total of 6804 patients were included. There were 986 patients who were admitted from another facility. This included 555 patients who were transferred between facilities within the Baylor Scott and White health system. The median age was 69 (IQR 59, 78) years and 59.7% were men. Baseline comorbidities included hypertension (89.3%), dyslipidaemia (87.2%), T2D (47.8%), CKD (33.6%), atrial fibrillation/flutter (23.4%), peripheral artery disease (21.7%), and stroke (18.1%). Overall, 76.7% of MI were NSTEMI and 23.3% of patient had previous history of HF and 16.8% of MI. The median follow-up was 722 (IQR 365, 1315) days for the total cohort, 750 (386, 1344) days for those discharged alive, and 702 (347, 1306) days for those included in the landmark analysis. Further baseline characteristics are described in *Table 1*. *Figure 1* describes the sub-populations studied.

Management during hospitalization and at discharge

In the overall cohort ($N = 6804$), echocardiography was performed in 87.4% and coronary angiography in 71.7% of patients. Revascularization was performed in 4181 patients (61.4%), of which 3626 (53.3%) underwent percutaneous and 709 (10.3%) surgical revascularizations;

Table 1 Baseline characteristics of patients

Baseline demographics	Total cohort *n* = 6804	ST-elevation myocardial infarction *n* = 1586	Non-ST-elevation myocardial infarction *n* = 5218	Without heart failure at baseline *n* = 5216	Incident heart failure within 12 months *n* = 1578
Age (years)	68.9 (58.8, 78.1)	66.4 (56.5, 75.1)	69.6 (59.6, 78.9)	67.8 (57.9, 77.0)	70.7 (60.6, 79.5)
Female sex	2741 (40.3%)	580 (36.6%)	2161 (41.4%)	2058 (39.5%)	638 (40.4%)
Smoking—current	1136 (16.7%)	329 (20.7%)	807 (15.5%)	932 (17.9%)	246 (15.6%)
Smoking—former	2106 (30.9%)	390 (24.6%)	1716 (32.9%)	1530 (29.3%)	523 (33.1%)
Smoking—never	2604 (38.3%)	541 (34.1%)	2063 (39.5%)	2016 (38.7%)	595 (37.7%)
Smoking—unknown	958 (14.1%)	326 (20.6%)	632 (12.1%)	738 (14.2%)	214 (13.6%)
Median LVEF at index (%), *N* = 5409	52.5 (41.4, 60.1)	51.0 (40.0, 58.5)	53.5 (42, 61)	54.5 (43.5, 61.2)	44.5 (35.4, 54.9)
LVEF ≤ 40%	1277 (23.6%)	341 (25.3%)	936 (23.1%)	805 (19.0%)	524 (38.28%)
LVEF 41–49%	976 (18.0%)	291 (21.6%)	685 (16.9%)	766 (18.1%)	363 (26.52%)
LVEF ≥ 50%	3156 (58.4%)	717 (53.2%)	2439 (60.1%)	2656 (62.8%)	482 (35.21%)
Median heart rate, b.p.m., *N* = 6799	81 (69, 95)	79 (68, 94)	82 (70, 95)	80 (69, 94)	85.5 (73, 99)
Median systolic blood pressure, mmHg, *N* = 6800	145 (125, 164)	138 (118, 158)	147 (128, 166)	146 (127, 164)	143 (125, 162)
Median diastolic blood pressure, mmHg, *N* = 6800	81 (70, 93)	82 (68, 95)	81 (71, 93)	82 (71, 94)	81 (70, 93)
Comorbidities					
Previous myocardial infarction	1143 (16.8%)	171 (10.8%)	972 (18.6%)	583 (11.2%)	186 (11.8%)
Prior heart failure	1588 (23.3%)	152 (9.6%)	1436 (27.5%)	0 (0%)	0 (0%)
Type 2 diabetes mellitus	3252 (47.8%)	636 (40.1%)	2616 (50.1%)	2210 (42.4%)	774 (49.1%)
Chronic kidney disease	2283 (33.6%)	330 (20.8%)	1953 (37.4%)	1312 (25.2%)	564 (35.7%)
Atrial fibrillation/atrial flutter	1593 (23.4%)	292 (18.4%)	1301 (24.9%)	940 (18.0%)	343 (21.7%)
Any cardiovascular disease	6200 (91.1%)	1457 (91.8%)	4743 (90.9%)	4671 (89.6%)	1443 (91.4%)
Hypertension	6073 (89.3%)	1327 (83.7%)	4746 (90.9%)	4552 (87.3%)	1373 (87.0%)
Peripheral artery disease	1475 (21.7%)	236 (14.8%)	1239 (23.7%)	867 (16.6%)	352 (22.3%)
Stroke	1229 (18.1%)	216 (13.6%)	1013 (19.4%)	728 (13.9%)	267 (16.9%)
Obesity/overweight	2552 (37.5%)	521 (32.8%)	2031 (38.9%)	1861 (35.7%)	544 (34.5%)
Dyslipidaemia	5934 (87.2%)	1358 (85.6%)	4576 (87.7%)	4460 (85.5%)	1386 (87.8%)
Laboratory values					
eGFR, mL/min/1.73 m^2, *N* = 3930	57 (40, 67)	61 (47, 69)	56 (38, 66)	61 (46, 70)	57 (42, 66)
BNP and/or NT-proBNP tested	4283 (62.9%)	752 (47.4%)	3531 (67.7%)	3037 (58.2%)	1127 (71.4%)
NT-proBNP, *N* = 145	2360 (328, 6699)	1608 (115, 6808)	2912.5 (674, 6699)	1511 (234, 4994)	3534 (696, 9077)
BNP, pg/mL, *N* = 4164	232 (76, 710)	148 (55, 461)	259 (81, 767)	156 (56, 503)	354 (128, 875)
Uric acid, mg/dL, *N* = 101	7.3 (6.1, 8.9)	7.2 (5.6, 8.6)	7.4 (6.1, 8.9)	7.4 (5.9, 8.6)	7.7 (6.7, 8.7)
Total cholesterol, mg/dL, *N* = 4726	157 (129, 191)	162 (135, 195)	155 (126, 190)	162 (133, 194)	156 (127, 187)
LDL cholesterol, mg/dL, *N* = 4594	89 (67, 118)	95 (70, 123)	87 (65, 116)	93 (70, 121)	88 (66, 117)

Continued

Table 1 *Continued*

Baseline demographics	Total cohort *n* = 6804	ST-elevation myocardial infarction *n* = 1586	Non-ST-elevation myocardial infarction *n* = 5218	Without heart failure at baseline *n* = 5216	Incident heart failure within 12 months *n* = 1578
HDL cholesterol, mg/dL, *N* = 4726	39 (32, 48)	39 (32, 47)	39 (32, 48)	39 (32, 48)	39 (32, 49)
Triglycerides, mg/dL, *N* = 4726	116 (80, 172)	116 (81, 174)	116 (79, 171)	119 (82, 177)	107 (77, 163)
Creatine kinase, U/L, *N* = 355	204 (91, 675)	831 (238, 1863)	180 (79, 435)	269 (112, 941)	340 (112, 975)
Troponin I, ng/mL, *N* = 6458	0.32 (0.08, 1.82)	0.22 (0.03, 3.17)	0.34 (0.10, 1.64)	0.31 (0.07, 1.82)	0.5 (0.10, 2.60)
Troponin T, ng/mL, *N* = 335	0.14 (0.04, 0.65)	0.14 (0.01, 1.57)	0.15 (0.05, 0.56)	0.14 (0.03, 0.57)	0.17 (0.04, 0.63)
Serum creatinine, mg/dL, *N* = 6790	1.10 (0.89, 1.44)	1.08 (0.89, 1.31)	1.10 (0.90, 1.50)	1.05 (0.87, 1.32)	1.10 (0.90, 1.42)
Haemoglobin, g/dL, *N* = 6778	13.4 (11.7, 14.8)	14.2 (12.7, 15.4)	13.2 (11.5, 14.6)	13.7 (12.2, 15.1)	13.3 (11.7, 14.7)
Haematocrit, %, *N* = 6781	40.6 (36.1, 44.2)	42.55 (38.5, 45.9)	39.9 (35.4, 43.7)	41.4 (37.3, 44.8)	40.3 (35.9, 44.0)
Blood urea nitrogen, mg/dL, *N* = 6794	18 (14, 26)	17 (13, 22)	19 (14, 27)	17 (13.00, 23.00)	19 (14.00, 25.00)
Serum sodium, meq/L, *N* = 6794	138 (136, 140)	138 (136, 140)	138 (136, 140)	138 (136, 140)	138 (136, 140)
Serum potassium, meq/L, *N* = 951	4.1 (3.7, 4.5)	4.0 (3.6, 4.3)	4.2 (3.8, 4.6)	4.1 (3.70, 4.50)	4.1 (3.70, 4.50)
Treatments prior to index admission					
ACE inhibitor/ARB/ARNI	3946 (58.0%)	793 (50.0%)	3153 (60.4%)	2752 (52.8%)	908 (57.5%)
Beta-blocker	3305 (48.6%)	562 (35.4%)	2743 (52.6%)	2014 (38.6%)	670 (42.5%)
Mineralocorticoid receptor antagonist	619 (9.1%)	85 (5.4%)	534 (10.2%)	193 (3.7%)	69 (4.3%)
Sodium-glucose co-transporter-2 inhibitors	244 (3.6%)	57 (3.4%)	187 (3.6%)	171 (3.3%)	49 (3.1%)
Lipid-lowering drugs	4147 (61.0%)	850 (53.6%)	3297 (63.2%)	2926 (56.1%)	946 (60.0%)
Statins	3911 (57.5%)	806 (50.8%)	3105 (59.5%)	2739 (52.5%)	882 (55.9%)
Non-statins	981 (14.4%)	169 (10.7%)	812 (15.6%)	674 (12.9%)	217 (13.8%)
Antithrombotic	3164 (46.5%)	550 (34.7%)	2614 (50.1%)	1960 (37.6%)	645 (40.9%)
Antiplatelet medications	2743 (40.3%)	477 (30.1%)	2266 (43.4%)	1698 (32.6%)	553 (35.0%)
Diabetes drugs	2418 (35.5%)	445 (28.1%)	1973 (37.8%)	1601 (30.7%)	592 (37.5%)
Diuretic combinations (loop + other)	2487 (36.6%)	401 (25.3%)	2086 (40.0%)	1323 (25.4%)	502 (31.8%)
Loop diuretics	1713 (25.2%)	204 (12.9%)	1509 (28.9%)	623 (11.9%)	298 (18.9%)

Incident heart failure: defined as at least two separate encounters (outpatient or inpatient) coded for HF if patient diagnosed during index admission or at least one encounter (outpatient or inpatient) coded for HF in patients not diagnosed during index admission. Values are median (IQR).

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, inter-quartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

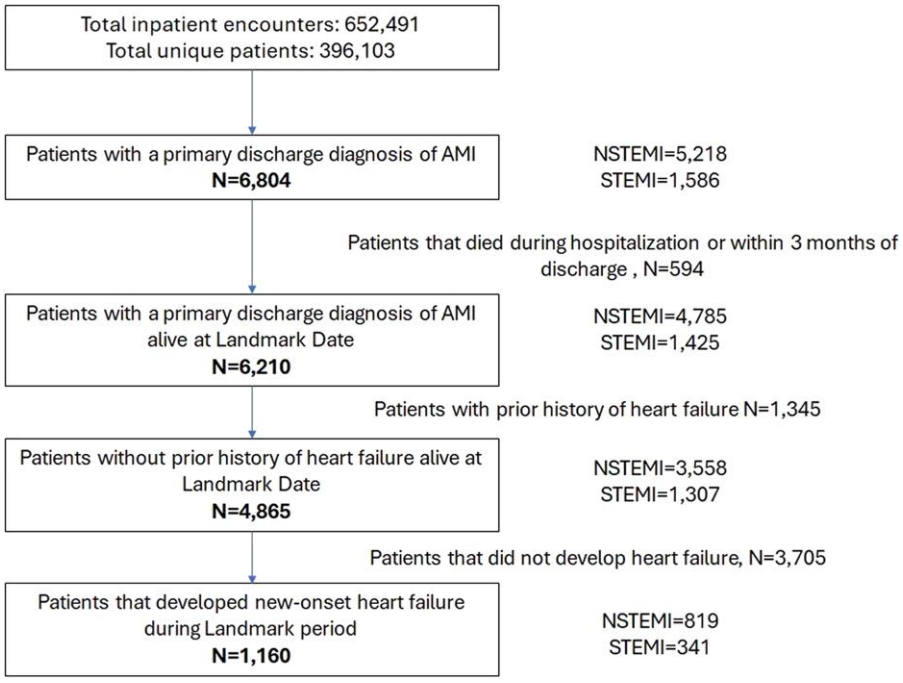


Figure 1 Consort diagram. Stepwise breakdown of patients with an acute myocardial infarction discharge diagnosis who were included in the study. Landmark date was defined as 3 months following the discharge, and landmark period was defined as the 12-month duration thereafter. AMI, acute myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction

51 (0.8%) underwent thrombolysis. Medications prescribed at discharge included antiplatelet agents (92.6%), statins (87.3%), beta-blockers (82.8%), renin–angiotensin system inhibitors (62.1%), and MRA (9.4%). At discharge, 2388 patients (35.1%) had a Class 1 indication for beta-blockers, among whom 2003 (83.9%) were prescribed beta-blocker; 5937 (87.3%) for renin–angiotensin system inhibitors among whom 3687 (62.1%) were prescribed; and 285 (4.2%) for MRA among whom 46 (16.1%) were prescribed. Treatment at admission and at discharge is shown in *Table 2*.

Recurrent myocardial infarction, all-cause death, and hospitalizations

In the landmark-anchored 1-year outcome analysis ($N = 6210$), 413 (6.7%) patients died, 1730 (27.9%) had all-cause and 735 (11.8%) CV rehospitalizations, and 234 (3.8%) had recurrent MI. Among all patients discharged alive ($N = 6556$), 663 (10.1%) died [median 89 (18, 197) days], 2306 (35.2%) had all-cause rehospitalization [median 59 (16, 164) days], and 1091 (16.6%) CV rehospitalization [median 71 (18, 185) days] and 381 (5.8%) had recurrent MI [median 91 (15, 192) days]. Outcome comparison among patients with STEMI vs. NSTEMI is shown in *Table 3* (landmark analysis) and Supplementary data online, *Table S2* (full cohort).

Incident heart failure

In the landmark-anchored analysis, 1160 (23.8%) developed incident HF within 3 months of discharge among patients without a history of HF ($n = 4865$). Baseline characteristics of patients who developed incident post-MI HF are shown in Supplementary data online, *Table S3*. A higher proportion of STEMI vs. NSTEMI (26.1% vs. 23.0%, $P = .026$) patients developed incident HF. Of all patients that developed incident HF within 3 months of discharge ($n = 1160$), 831 (71.6%) were diagnosed at index admission with subsequent confirmation at outpatient visit, and 329 (28.4%) were diagnosed after index admission (155 diagnosed at an inpatient encounter and 174 diagnosed at an outpatient encounter). Of patients diagnosed with HF within the first 3 months after index MI, median time to diagnosis was 12 days (IQR 6, 27). *Table 3* shows outcomes in landmark analysis and Supplementary data online, *Table S2* in full cohort.

Overall, 1066 of 1160 (91.9%) patients with incident HF within 3 months of index MI had a recorded LVEF at first HF diagnosis, including 450 (42.2%) with LVEF ≤ 40%, 285 (26.7%) with LVEF 41–49%, and 331 (31.1%) with LVEF ≥ 50%. Baseline characteristics of patients who did and did not develop HF, and those who developed HF with LVEF ≤ 40%, 41–49%, and ≥50%, are shown in Supplementary data online, *Table S3*. Compared with patients who did not develop HF, those who did had a higher risk of death (8.1% vs. 3.2%) and all-cause (31.2% vs. 19.0%) and CV rehospitalization (14.2% vs. 6.7%) (all $P < .001$; *Table 3*). Data for secondary analysis on all patients with full follow-up data available are shown in Supplementary data online, *Table S4*: we observed substantial differences, with older age (median 71 vs. 67 years) and higher prevalence of T2D (49% vs. 40%), CKD (36% vs. 21%), atrial fibrillation/flutter (22% vs. 16%), and peripheral artery disease (22% vs. 13%) independently among patients who developed incident HF.

Heart failure, myocardial infarction, and mortality risk over time

Figure 2 illustrates landmark analysis of death and recurrent MI risk in patients with STEMI and NSTEMI, respectively. Patients with STEMI were at a lower risk for death (HR 0.73, 95% CI 0.60–0.90), but there was no significant difference in the risk of recurrent MI (HR 0.82,

Table 2 Evaluation and treatments during index hospitalization of patients

	Total cohort $n = 6804$	ST-elevation myocardial infarction $n = 1586$	Non-ST-elevation myocardial infarction $n = 5218$	No history of heart failure $n = 5216$	History of heart failure $n = 1588$
Cardiovascular evaluation					
Echocardiography	5948 (87.4%)	1476 (93.1%)	4472 (85.7%)	4632 (88.8%)	1316 (82.9%)
Coronary angiography	4875 (71.7%)	1345 (84.8%)	3530 (67.7%)	3786 (72.6%)	1089 (68.6%)
Stress test (exercise, echocardiographic, or nuclear)	239 (3.5%)	16 (1.0%)	223 (4.3%)	153 (2.9%)	86 (5.4%)
Cardiac computed tomography	16 (0.2%)	3 (0.2%)	13 (0.3%)	14 (0.3%)	2 (0.1%)
Cardiac magnetic resonance imaging	47 (0.7%)	7 (0.4%)	40 (0.8%)	36 (0.7%)	11 (0.7%)
Reperfusion					
Thrombolysis	51 (0.8%)	16 (1.0%)	35 (0.7%)	36 (0.7%)	15 (0.9%)
Percutaneous coronary intervention	3626 (53.3%)	1232 (77.7%)	2394 (45.9%)	2949 (56.5%)	677 (42.6%)
Coronary bypass surgery	709 (10.4%)	91 (5.7%)	618 (11.9%)	597 (11.5%)	112 (7.1%)
Medications at discharge					
ACEi/ARBs/ARNI	4222 (62.1%)	1106 (69.7%)	3116 (59.7%)	3336 (64.0%)	886 (55.8%)
Beta-blocker	5634 (82.8%)	1343 (84.7%)	4291 (82.2%)	4294 (82.3%)	1340 (84.4%)
Mineralocorticoid receptor antagonist	639 (9.4%)	199 (12.6%)	440 (8.4%)	364 (7.0%)	275 (17.3%)
Sodium-glucose co-transporter-2 inhibitors	191 (2.8%)	55 (3.5%)	136 (2.6%)	139 (2.7%)	52 (3.3%)
Lipid-lowering drugs	6135 (90.2%)	1447 (91.2%)	4688 (89.8%)	4724 (90.6%)	1411 (88.9%)
Statins	5942 (87.3%)	1412 (89.0%)	4530 (86.8%)	4586 (87.9%)	1356 (85.4%)
Non-statins	1071 (15.7%)	206 (13.0%)	865 (16.6%)	802 (15.4%)	269 (16.9%)
Antithrombotic	6408 (94.2%)	1492 (94.1%)	4916 (94.2%)	4897 (93.9%)	1511 (95.2%)
Antiplatelet medications	6301 (92.6%)	1480 (93.3%)	4821 (92.4%)	4836 (92.7%)	1465 (92.3%)
Antidiabetic drugs	2567 (37.7%)	500 (31.5%)	2067 (39.6%)	1787 (34.6%)	780 (49.1%)
Diuretic combinations (loop + other)	2361 (34.7%)	362 (22.8%)	1999 (38.3%)	1369 (26.3%)	992 (62.5%)
Loop diuretics	2038 (30.0%)	303 (19.1%)	1735 (33.3%)	1083 (20.8%)	955 (60.1%)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor.

95% CI 0.63–1.07). Patients who developed incident HF had a higher risk of death (HR 1.76, 95% CI 1.49–2.07; *Figure 3A*). *Figure 3B* shows risk of death stratified by patients with incident HF with LVEF ≤ 40%, 41–49%, and ≥50%; there were no significant differences in risk between those with LVEF ≤ 40% and ≥50% (HR 1.22, 95% CI 0.89–1.68) and between 41–49% and ≥50% (HR 0.92, 95% CI 0.64–1.33) at time of first HF diagnosis.

Among 2179 patients with LVEF ≥ 50% at discharge from index hospitalization who did not have a prior history of HF and did not die or develop HF during index MI hospitalization, 257 (11.8%) developed incident HF and 77 (3.5%) developed recurrent MI in the 1 year following discharge. Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) and serum brain natriuretic peptide (BNP) measured during index acute MI hospitalization were higher among patients with incident HF including those with LVEF ≥ 50% compared with those who did not develop incident HF (see Supplementary data online, *Table S3*). The relative proportion of HF and MI risk among STEMI and NSTEMI patients was similar; these data and risk of developing both MI and HF are shown in *Table 4*.

Discussion

In this contemporary population-based real-world experience of patients following MI, we note several important findings. The risk of incident HF following MI was high and was up to six-fold higher than the risk of recurrent MI. The risk for incident HF was higher than recurrent MI among patients without a history of HF, not developing HF during index admission, and being discharged with normal LVEF. Outcomes in patients who developed post-MI incident HF were worse than those who did not. Mortality risk for patients who developed HF was comparable across LVEF groups (*Structured Graphical Abstract*). These findings highlight contemporary post-MI epidemiology suggesting a persistent high risk for HF development post-MI and a need for novel HF risk reduction strategies in this population.

Findings of high risk of HF following MI are important. These estimates are similar or higher compared with previous studies. A Norwegian study showed development of HF during an index MI in ~19% of patients.[5] Another study from Australia showed a HF prevalence within 1 year

Table 3 Patient outcomes at 1 year in the 3-month landmark anchored analysis and in select subpopulations

	Total cohort N = 6210	Myocardial infarction		P^a	History of heart failure			No history and developed incident heart failure at 3-months post-MI discharge		P^a
		ST-elevation n = 1425	Non-ST-elevation n = 4785		Yes n = 1345	No n = 4865		Yes n = 1160	No n = 3705	
Event (%)										
All-cause mortality	413 (6.7)	38 (2.7)	375 (7.8)	<0.001	199 (14.8)	214 (4.4)		94 (8.1)	120 (3.2)	<0.001
Recurrent myocardial infarction	234 (3.8)	37 (2.6)	197 (4.1)	0.008	95 (7.1)	139 (2.9)		47 (4.1)	92 (2.5)	0.005
All-cause rehospitalization	1730 (27.9)	291 (20.4)	1439 (30.1)	<0.001	664 (49.4)	1066 (21.9)		362 (31.2)	704 (19.0)	<0.001
Cardiovascular rehospitalization	735 (11.8)	114 (8.0)	621 (13.0)	<0.001	322 (23.9)	413 (8.5)		165 (14.2)	248 (6.7)	<0.001

[a]One-year event data were assessed with χ^2 tests. Time to event, number of hospitalizations, and length of stay were assessed with Wilcoxon rank-sum tests.

of MI of ~22%, of which 75% developed HF during index hospitalization. This estimate is similar to our experience.[6] Estimates from Sweden showed one-third of patients with MI developed HF over a 3-year follow-up.[7] A study from the UK over two decades ago reported ~20% of patients developed HF during index MI admission and 33% over 6 years.[8] The number of individuals who developed HF following discharge was less than those who developed HF during index admission in our study. Findings from a Canadian cohort showed that ~37% of patients developed HF during index MI admission, whereas 70% of patients that did not have HF during index admission developed HF over a 5-year follow-up.[9] Cumulative experience from these studies confirms a persistent high risk for HF post-MI.

The incidence of recurrent MI and immediate post-MI complications have decreased over the years, especially in Western countries.[10–12] Our study identified a recurrent MI rate of ~4% and death of ~7% over 1 year. The rates of post-MI 30-day survival have also improved as reported from contemporary estimates from Sweden and the UK.[13] The risk of a second MI is the highest within the first year of index MI and reduces thereafter.[14] This indicates an increasing proportion of stable post-MI patients who are at relatively higher risk of HF compared with recurrent MI. All-cause mortality was higher among patients with NSTEMI compared with those with STEMI, which corroborates prior evidence.[15,16] This finding is likely related to a higher burden of comorbidities, older age, higher prevalence of multivessel disease, and lower rates of revascularization in patients with NSTEMI compared with STEMI.[16,17] In contrast, a higher proportion of STEMI vs. NSTEMI patients developed HF in the landmark-anchored analysis (26.1% vs. 23.0%, $P < .001$). Importantly, patients who develop HF post-MI had a significantly higher rate of other adverse events compared with those who did not. Likewise, mortality and all-cause and CV rehospitalizations were significantly higher among patients who developed HF following MI. These trends underscore a need for comprehensive management of these high-risk patients and development of novel therapies further reducing the risk.

There may be several reasons that account for lower recurrent MI rates compared with incident HF. There currently exist many post-MI secondary prevention strategies including innovations in coronary revascularization, drugs targeting platelet function, lipid control, and systems of care and quality improvement efforts, all of which may provide protection from recurrent ischaemic events. However, myocardial damage and scarring secondary to the initial ischaemic event are incompletely impacted by these interventions, leading to continued myocardial dysfunction despite revascularization and in the absence of recurrent clinical ischaemic events. Renin–angiotensin system inhibitors, beta-blockers, and MRA have a mortality benefit and reverse ventricular remodelling in high-risk populations post-MI and in turn reduce the risk of HF. Our data indicated the continued suboptimal MRA use in the post-MI population, which could have contributed towards a high residual risk of HF, despite most of the patients taking ACEi/ARB and beta-blockers as indicated.

We also observed that even among patients without a prior history of HF or new onset HF at the index MI hospitalization who had a normal LVEF (≥50%), the incidence of HF in the subsequent 12 months remained substantial at 11.8%. This was more than three times the risk of recurrent MI (3.5%). These findings indicate that despite the preservation of cardiac function after an MI, other contributing mechanisms like coronary microvascular dysfunction persist and modulate the future development of HF.[18–20] The possibility of underlying microvascular dysfunction is supported by our finding that among patients with a normal LVEF, post-infarction levels of NT-proBNP/BNP were several folds higher in patients who developed HF, as compared with those who did

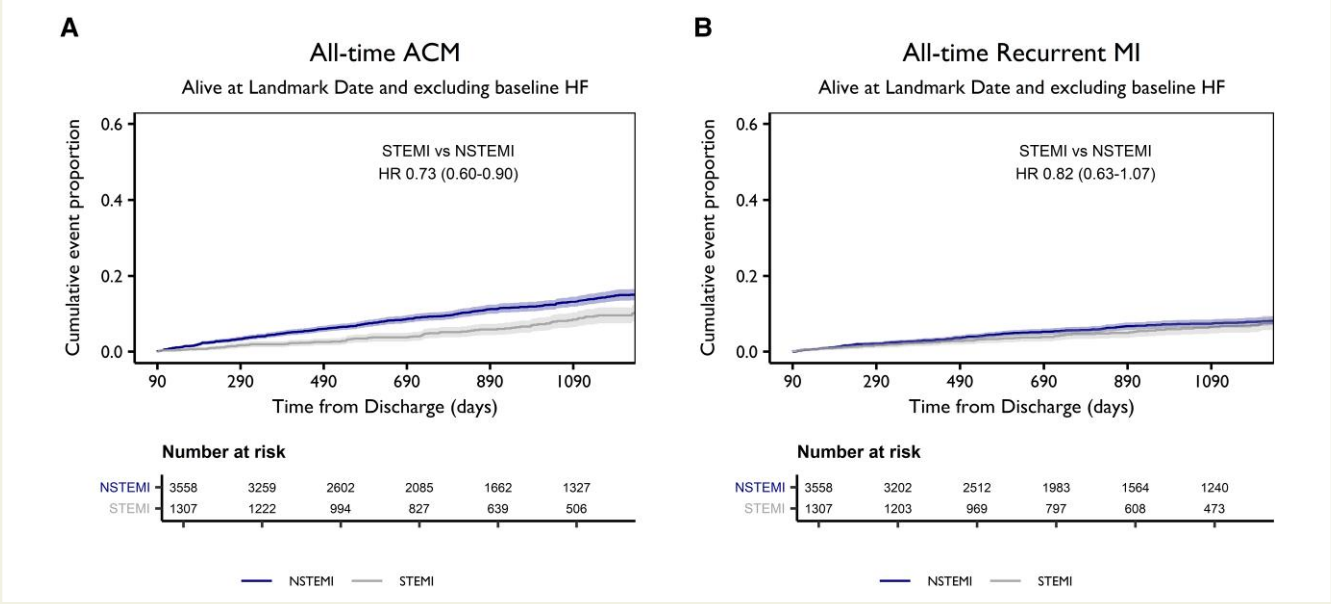


Figure 2 Outcomes after ST-elevation and non-ST-elevation myocardial infarction. Kaplan–Meier cumulative incidence estimates for (*A*) all-cause mortality excluding myocardial infarction patients with baseline history of heart failure in patients with ST-elevation myocardial infarction vs. non-ST-elevation myocardial infarction and (*B*) recurrent myocardial infarction excluding baseline history of heart failure in patients with ST-elevation myocardial infarction vs. non-ST-elevation myocardial infarction. ACM, all-cause mortality; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction

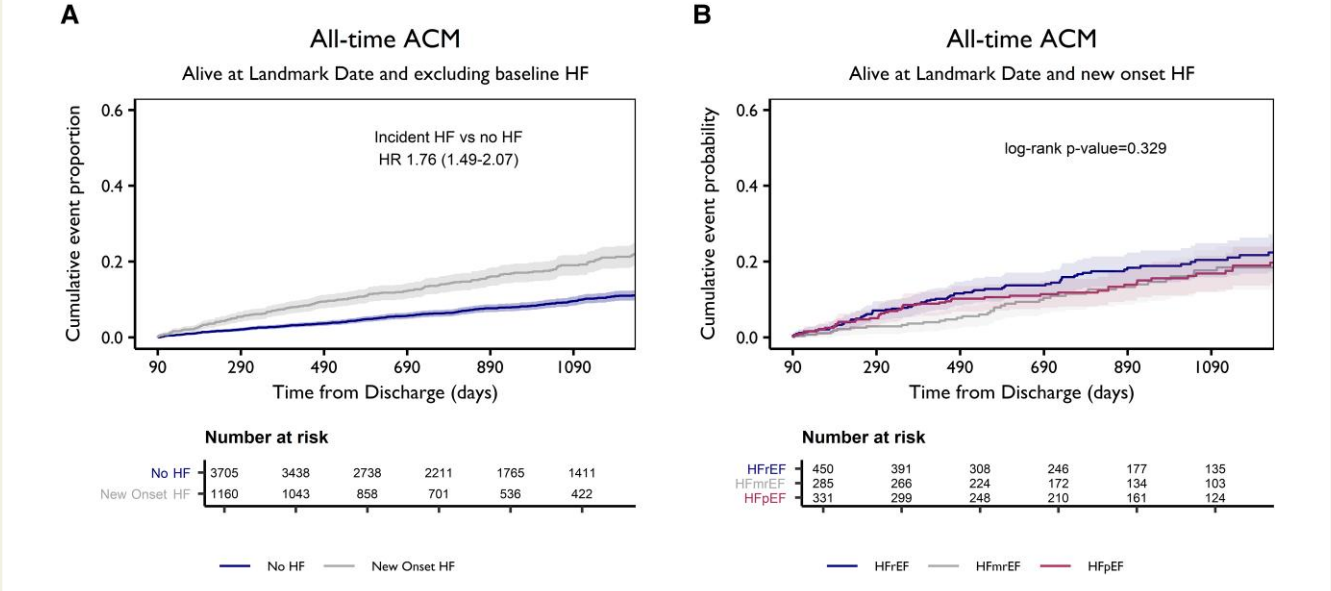


Figure 3 Mortality risk in relation to heart failure post-myocardial infarction. Kaplan–Meier cumulative incidence estimates for (*A*) all-cause mortality (ACM) in patients with and without incident heart failure, and (*B*) ACM in patients with heart failure and reduced, mildly reduced, and preserved ejection fraction. ACM, all-cause mortality; HF, heart failure; HFrEF, HF with reduced ejection fraction; HFmrEF, HF with mildly reduced with ejection fraction; HFpEF, HF with preserved ejection fraction; HR, hazard ratio; MI, myocardial infarction

not (see Supplementary data online, *Table S3*).[21] Microvascular dysfunction is largely unaffected by first-line secondary prevention drugs or revascularization strategies and is known to contribute towards endothelial impairment, arteriolar remodelling, interstitial fibrosis, and microinfarction commonly manifesting as chronic stable angina and progressive ventricular dysfunction.[22,23] Evidence also suggests that microvascular angina and HF (especially HFpEF) represent two ends of a disease continuum mediated by a common underlying mechanism involving coronary

Table 4 Heart failure and myocardial infarction risk among all patients with normal ejection fraction (≥50%) and no heart failure at discharge or at baseline

	Overall *N* = 2179 *N* (%)	STEMI *N* = 571 *N* (%)	NSTEMI *N* = 1608 *N* (%)
Incident heart failure only	228 (10.5)	56 (9.8)	172 (10.7)
Recurrent myocardial infarction only	48 (2.2)	14 (2.5)	34 (2.1)
Recurrent myocardial infarction followed by incident heart failure	4 (0.2)	0 (0)	4 (0.2)
Incident heart failure followed by recurrent myocardial infarction	4 (0.2)	1 (0.2)	3 (0.2)
Recurrent myocardial infarction and incident heart failure at the same time	21 (1.0)	5 (0.9)	16 (1.0)

microvascular dysfunction.[18] Identification of therapeutic targets related to microvascular dysfunction may mitigate in part the residual risk of HF in the post-MI population.

The incidence of HF with LVEF ≤ 40% constituted 38% of incident HF. Historically, HFrEF has been the predominant phenotype of HF post-MI, although contemporary evidence suggests an evolving shift in post-MI HF phenotypes with rising trends in post-MI patients who develop HFpEF.[24] This may be attributed to improved revascularization and secondary prevention therapies that allow limiting infarct size and risk reduction for systolic dysfunction. Nevertheless, HFrEF accounted for over one-third of all new onset HFs in our study. LVEF phenotype post-MI was less important from a prognostic perspective as mortality risk was comparable for all HF patients across the LVEF categories. Prior studies have reported similar findings of excess mortality of post-MI HF patients across all subsets of acute coronary syndrome and LVEF subgroups.[25,26] These data underscore the need to develop HF risk reduction strategies across the spectrum of LVEF.

These results should be interpreted considering several limitations. Due to the retrospective nature of the analysis, unmeasured confounders were not accounted for and lost to follow-up could not be reliably assessed. Heart failure and MI diagnosis was based on ICD coding. We attempted to minimize the proportion of Type 2 NSTEMI patients by not including codes for Type 2 MI as the primary discharge diagnosis; however, there may still be residual cohort of patients with Type 2 MI who were included due to coding. Nine patients had insufficient follow-up to be considered for landmark analysis; however, they were included in the baseline and 12-month post-discharge analyses. There may have been a cohort of patients with incident HF diagnosed at index admission with repeated encounters for HF within the first 3 months post-discharge but died within 3 months of discharge and were subsequently excluded from the landmark analysis. These patients would, however, have been captured in the results reported for all follow-up in Supplementary data online, *Tables S2* and *S3*. Data on LVEF were not available for 21% of the total cohort and 8% of patients with incident HF on landmark analysis. The method of LVEF quantification was through the extraction of routine echocardiographic data from the electronic medical health records, which may not accurately represent LVEF estimates. There was no difference in outcomes across LVEF subgroups; however, this analysis is limited due to the potential lack of statistical power to detect a statistically significant difference. While the absolute indications and contraindications for various post-MI therapies were accounted for when assessing medical therapy, intolerance and other factors related to documentation were not assessed. Considering the vast geographic area covered, including both inpatient and outpatient care, from which these estimates are drawn, these data likely represent an accurate estimate of events and risks. Like all observational data, however, the possibility of underestimating risk due to patients seeking care at other institutions cannot be ruled out.

In conclusion, we found a high risk of incident HF post-MI. The risk of HF was several folds higher than that for recurrent MI. The patients who developed post-MI HF had significantly worse prognosis than those who did not, and these outcomes were comparable regardless of LVEF category. The risk of HF was considerable and higher than MI even in those without history of HF and who were discharged from index admission without HF and with normal LVEF. These data underscore a need to better understand the mechanisms behind the development of HF post-MI, especially among those with normal LVEF, and to develop therapeutic strategies targeting the preservation of myocardial function and mitigating the risk of HF following MI.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

J.B. is a consultant to Abbott, American Regent, Amgen, Applied Therapeutic, AskBio, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, Cardiocell, Cardior, CSL Bearing, CVRx, Cytokinetics, Daxor, Edwards, Element Science, Faraday, Foundry, G3P, Innolife, Impulse Dynamics, Imbria, Inventiva, Ionis, Lexicon, Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Owkin, Novartis, Novo Nordisk, Pharmacosmos, PharmaIN, Pfizer, Prolaio, Regeneron, Renibus, Roche, Salamandra, Sanofi, SC Pharma, Secretome, Sequana, SQ Innovation, Tenex, Tricog, Ultromics, Vivor, and Zoll. A.A., N.S., C.Z., and M.M.T. are employees of Boehringer Ingelheim. M.P. is affiliated with 89bio, AbbVie, Actavis, Altimmune, Alnylam, Ardelyx, Attralus, Biopeutics, Boehringer Ingelheim, Caladrius, Casana, CSL Behring, Cytokinetics, Imara, Lilly, Medtronic, Moderna, Novartis, Pharmacosmos, Reata, Regeneron, and Salamandra. R.L.G. reports grants or contracts to his institution from Alnylam Pharmaceuticals, Astra Zeneca, Bristol Myers Squibb, CareDx, Eli Lilly, Gilead, Johnson & Johnson, Pfizer, Regeneron, and Roivant Sciences (Kinevant Sciences), participation on advisory boards and/or consulting

fees from AbbVie, Astra Zeneca, Eli Lilly, Gilead Sciences, GSK Pharmaceuticals, and Roche, honoraria and travel support for lectures/presentations from Gilead Sciences, speaker bureau for Alnylam and Pfizer Sciences and Pfizer, de minimis investment in AbCellera, and a gift-in-kind to his institution from Gilead Sciences to facilitate an academic-sponsored clinical trial (NCT03383419). R.W. is a speaker and consultant from Abbott Vascular, Advisor, Medtronic and Philips, Proctor, and Gore. M.M., K.H., K.M.T., M.M.B., J.V.A.B., J.A.E., E.L.P., N.S., and C.N.S. have nothing to disclose. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors did not receive payment related to the development of the manuscript. Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

Data Availability

The data used to support the findings of this study are included within the article. Further data are available on request from the corresponding author (J.B.).

Funding

This study was funded by the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance.

Ethical Approval

Ethical approval for this project was provided by Baylor Scott & White IRB.

Pre-registered Clinical Trial Number

None supplied.

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