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Declining In-Hospital Mortality and Increasing Heart Failure Incidence in Elderly Patients With First Myocardial Infarction

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Objectives The purpose of this study was to examine the long-term incidence of heart failure (HF) in elderly patients with myocardial infarction (MI).

Background In-hospital HF is common after MI and is associated with poor short-term prognosis. Limited data exist concerning the long-term incidence or prognosis of HF after MI, particularly in the era of coronary revascularization.

Methods A population-based cohort of 7,733 patients ≥65 years of age hospitalized for a first MI (International Classification of Diseases-9th Revision-Clinical Modification code 410.x) and without a prior history of HF was established between 1994 and 2000 in Alberta, Canada, and followed up for 5 years.

Results During the index MI hospitalization, 2,831 (37%) MI patients were diagnosed with new HF and 1,024 (13%) died. Among hospital survivors who did not have HF during their index hospitalization (n = 4,291), an additional 3,040 patients (71%) developed HF by 5 years, 64% of which occurred in the first year. In total, 5,871 (76%) elderly patients who survived their first MI developed HF over 5 years. Among those who survived the index hospitalization, the 5-year mortality rate was 39.1% for those with HF during the index MI hospitalization compared with 26.7% among those without HF ($p < 0.0001$) during the index MI hospitalization. Over the study period, the 5-year mortality rate after MI decreased by 28%, whereas the 5-year rate of HF increased by 25%.

Conclusions In this large cohort of elderly patients without a history of HF, HF developed in three-quarters in the 5 years after their first MI; this proportion increased over time as peri-MI mortality rates declined. New-onset HF significantly increases the mortality risk among these patients. (J Am Coll Cardiol 2009;53:13–20) © 2009 by the American College of Cardiology Foundation

The incidence and prevalence of heart failure (HF) in adults is increasing. Given the high prevalence of cardiovascular risk factors, an increasing global burden of HF, in both developed and developing countries, seems assured (1,2). In the U.S. alone, HF accounted for approximately 727,000 emergency department visits, 1 million hospital admissions, and an estimated overall annual cost of $29 billion for 2006 (3,4). Whereas the poor prognosis of HF patients is established, less is known concerning the events that precede the development of HF.

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Although ischemic heart disease is well recognized as a principal cause of HF, the incidence, prevalence, and time course for the development of HF after myocardial infarction (MI) is unclear. In patients presenting with an MI and concurrent in-hospital HF, early (i.e., within 6 months) post-discharge mortality is nearly 4-fold higher than in those without HF (5). An Australian study showed that patients younger than 65 years of age presenting with their first MI in whom HF developed early (<28 days from index MI) had a greater likelihood of HF admission or mortality over the next decade (6). Surprisingly, the incidence of

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme

HF = heart failure

MI = myocardial infarction

STEMI = ST-segment elevation myocardial infarction

late-onset HF was strikingly low; only 9% were hospitalized for HF in the next decade, leading to speculation of under-reporting of HF. An earlier study of all Albertans who survived their first MI between 1994 and 1999 found that HF developed in 29% over 32 months; however, that study included patients of all ages and did not have access to medication data (7). Few studies have examined the effect of the sentinel event of developing HF in long-term follow-up post-MI. Data from 200 MI patients in the original Framingham cohort showed a 14% incidence of HF post-MI over the next 5 years: nearly one-half of those patients subsequently died (8). Few patients age 65 years or older have been enrolled in clinical trials or registries, despite their increased risk for complications or mortality after MI (9). Given the modest sample size and advances in medical care, a more contemporary cohort not limited to those in a select registry or clinical trial is required to best address the question of whether advances in MI care have increased or reduced the subsequent incidence of HF.

We describe the incidence and temporal trends of HF during and after MI, and the subsequent risk for death after developing HF are described using a 6-year community-based cohort of all patients age 65 years or older with an acute MI hospitalized in a large geographic region with universal health care coverage.

Methods

Databases. The Alberta Elderly MI cohort was created by identifying the first MI hospitalization and following up the patient's physician visits, emergency department visits, and hospitalizations for 5 years. The database was created by linking 5 separate databases maintained by Alberta Health and Wellness in Alberta, Canada: 1) the Discharge Abstract Database, which records information (including dates, diagnoses, and procedures) on all admissions to any of the acute care facilities in Alberta; 2) the Ambulatory Care Database, which records all visits to hospital-based physicians' offices and all emergency departments; 3) the Physician Claims Database, which records all claims for service (by diagnostic code) made by physicians for the outpatient care of patients in physicians' offices; 4) the Alberta Health Care Insurance Registry, which tracks the vital status of all Albertans; and 5) the Blue Cross Medication Database, which includes hospital discharge and outpatient prescription medication data on all patients 65 years of age or older. Data on aspirin use (because of its availability over the counter in Alberta) or therapy with thrombolytic agents, heparin, or other acute in-hospital agents are not available. Each individual has a unique health care number by which patient information can be followed up through each of the databases. Deaths were identified using the Alberta Health Care Insurance Registry and the Discharge Abstract Database, which provide the details on date of death and location (in or out of hospital).

The cohort consists of patients ≥65 years of age who had been hospitalized for a primary diagnosis of acute MI (International Classification of Diseases-9th Edition-Clinical Modification [ICD-9-CM] 410.x) between April 1, 1994, and March 31, 2000. Patients with a prior admission for MI or HF in the last year were excluded. The patients were followed up until death or 5 years after the initial MI hospitalization, with the follow-up ending on April 1, 2005.

Definitions of outcomes and covariates. Concurrent HF was defined as HF developing as a complication of the index MI; subsequent HF was defined as a hospitalization or physician claim for HF (ICD-9-CM 428.x; previously validated with specificity of 95% to 96% vs. chart audit gold standard [10,11]) occurring after the index MI. Time to HF was defined as the time of discharge if the HF occurred as a complication of the index MI or the time of subsequent admission for subsequent hospitalizations.

Identification of comorbidity was performed using the ICD-9-CM codes at the incident hospitalization or if there was an additional hospitalization or physician claim in the next 30 days. The 30-day window was selected to enrich the data over that acquired during the index hospitalization while mitigating survivor bias. The accuracy of our data acquisition, the use and accuracy of discharge coding to identify cases and comorbidities, and hospital and specialist information have been described elsewhere (12–14). Location of death was divided into hospital or out-of-hospital as done previously (15); cause of death was unavailable.

To describe other non-HF hospitalizations, intercurrent hospitalizations (with clinical relevance and an incidence of >1%) during the first year are provided for descriptive purposes for patients discharged alive after the index MI. The primary diagnosis for hospitalization is provided in 4 categories: alive and did not develop HF, alive and developed HF, died after developing HF, and died without developing HF.

Evidence-based medications for the index MI were defined as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins). Per prior studies using these administrative databases, a window of 30 days after the hospital discharge was used to identify prescriptions that could be linked to the hospital visit after discharge. Because our primary interest was development of subsequent HF, information regarding medications is provided on those patients discharged alive after their index MI.

Statistical analyses. Continuous baseline variables were compared using standard estimation methods, using mean (SD) and *t* tests or medians with interquartile ranges and Wilcoxon tests for continuous data where appropriate. Count data were summarized using percentages, relative

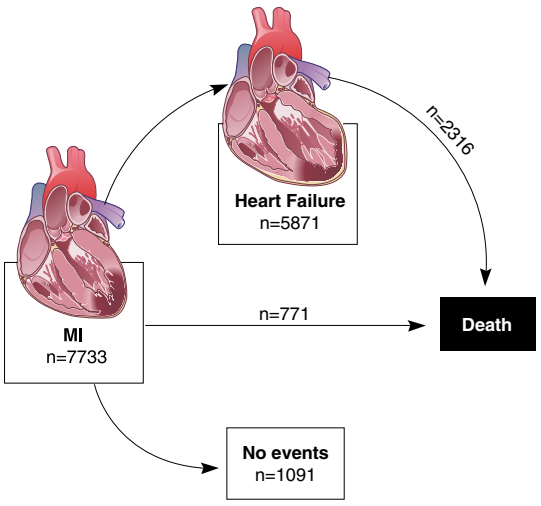

Figure 1 **Multistate Model of Transitions for Patients Through 3 Clinically Important States: The Index MI Hospitalization, Subsequent Heart Failure, and Death**

MI = myocardial infarction. Figure illustration by Rob Flewell.

risks, and chi-square tests. Temporal trends were examined using the Cochran-Armitage test. A further analysis was performed using age in 3 categories (65 to 69 years of age, 70 to 75 years of age, and older than 75 years of age) equivalent to the 25th and 50th percentile of age in the study cohort. A multistate model was constructed based on the work of Putter et al. (16). Inclusion of factors for the multistate model from the univariate analysis was done if $p < 0.20$. The multistate model was developed by first identifying 3 clinically important states: the index MI hospitalization, subsequent HF, and death. The transitions to be modeled are from MI to HF development with death without HF as a competing risk, and then a third to allow the modeling of prognostic indicators of death among those who have developed HF. The schematic for this model with the patient numbers from our study are given in Figure 1. This model allows the estimation of prognostic factors both for each transition separately or as a single unit if the factor has a similar effect regardless of transition. Additionally, by using the clock-forward method (16), patients in the HF group are left-censored until they enter the state, allowing patients to enter the HF state (when they develop HF) and leave if they die or reach the end of the 5-year follow-up. To further explore potential bias inherent in the model we created, the analysis was then repeated on a subset of patients (n = 4,291) who left the hospital alive after their index MI who had not developed in-hospital HF as a complication of their MI. Results are presented as odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) with 95% confidence intervals (CIs) where appropriate; a p value of <0.05 was taken as statistically significant. All analyses were done using R version 2.6.1 (17) and SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

Results

A total of 11,479 elderly patients were identified with MI between April 1, 1994, and March 31, 2000. Patients with prior HF were excluded from the cohort (n = 2,523, 21.9%), as were those with prior MI (n = 1,688, 14.7%), resulting in a final study population of 7,733 patients (median age 75 years, 60.0% male) with a first MI and no prior HF who were followed up for up to 5 years.

Index hospitalization. During the index MI hospitalization, 2,831 (36.7%) patients were diagnosed with HF. Patients developing HF during the index hospitalization were more likely to be older, to be male, and to have hypertension, diabetes, other vascular disease, chronic obstructive pulmonary disease, and renal disease (Table 1). Medical therapy and invasive revascularization also differed between these 2 groups (Table 2). Patients who developed

Table 1 **Baseline Characteristics of All Patients at Index Myocardial Infarction**

Variable	At Index Myocardial Infarction		Relative Risk for Developing HF During the Index Hospitalization	p Value
	No HF	Developed HF		
n (%)	4,902 (63.4%)	2,831 (36.6%)		
Age, yrs, median (IQR)	74.5 (69.7–80.3)	75.5 (70.5–81.1)		<0.001
Female	41.3	37.8	0.86 (0.78–0.95)	0.0022
Diabetes	16.7	23.2	1.51 (1.35–1.70)	<0.0001
Hypertension	35.3	42.3	1.40 (1.27–1.54)	<0.0001
Cardiac arrhythmia	23.1	36.5	1.91 (1.73–2.11)	<0.0001
Atrial fibrillation	9.6	20.4	2.43 (2.13–2.77)	<0.0001
Peripheral arterial disease	2.7	6.5	2.49 (1.98–3.13)	<0.0001
Cerebrovascular disease	4.9	7.4	1.55 (1.28–1.88)	<0.0001
Acute renal disease	1.9	4.5	2.45 (1.87–3.21)	<0.0001
Chronic renal disease	1.5	5.9	4.24 (3.20–5.62)	<0.0001
COPD	12.9	16.9	1.37 (1.21–1.56)	<0.0001
Cancer	2.3	3.4	1.50 (1.14–1.98)	0.004

Values are percents unless otherwise stated.
COPD = chronic obstructive pulmonary disease; HF = heart failure; IQR = interquartile range.

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Table 2 Medical Therapy and Invasive Coronary Revascularization Within 30 Days of Index Myocardial Infarction

Variable	At Index Myocardial Infarction		
	No HF	Developed HF	p Value
n (%)	4,902 (63.4%)	2,831 (36.6%)	
Any invasive coronary revascularization	12.4	16.8	<0.0001
Stent	6.0	8.7	<0.0001
PCI	10.6	13.9	<0.0001
CABG	1.9	3.2	0.0006
ACE inhibitor	31.8	39.3	<0.0001
ARB	1.4	2.7	0.0003
Beta-blocker	58.7	49.6	<0.0001
Calcium-channel blocker	3.6	3.4	0.796
Statin	12.7	10.5	0.007
Nitrates	64.0	53.4	0.0002
Sublingual	47.5	40.3	<0.0001
Pill or patch	27.0	30.1	0.008
Warfarin	8.6	12.4	<0.0001
Diuretics	10.8	23.0	<0.0001

Values are percents unless otherwise stated. Medication data only for those who survived index hospitalization.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; HF = heart failure; PCI = percutaneous coronary intervention.

HF at the index MI were more likely to have undergone revascularization; more likely to receive ACE inhibitors, angiotensin receptor blockers, warfarin, or diuretics; and less likely to have received beta-blockers or nitrates.

From 1994 through 2000, there was a 28.1% relative reduction in mortality during the index hospitalization (from 18.1% to 13.0%, p = 0.01) (Fig. 2). In the same period, the incidence of in-hospital HF among survivors increased 25.1% (from 31.4% to 39.3%, p = 0.001). The mean length of stay decreased over time from 1994 (mean 8.5 days [SD 7.6]) to 2000 (mean 7.8 [SD 6.9]), p = 0.01. Medication use within 30 days of discharge increased from 1994 to 2000, for ACE inhibitors (25.3% to 45.1%), beta-blocker (44.2% to 65.6%), and statins (1.5% to 23.3%) (all p < 0.001).

Long-term follow-up. In addition to the 2,831 patients (36.6%) who were diagnosed with HF during their index MI hospitalization, an additional 3,040 of the 4,291 patients that survived the index MI without HF (70.8%) developed HF in the subsequent 5 years. Most of these patients (n = 1,612, 53.0%) developed HF in the first year, with the remainder distributed uniformly over the remaining 4 years. Thus, three-quarters of the cohort developed HF (n = 5,871, 75.9%) during the 5 years after their first MI. Mortality rate among patients who developed HF and survived their index MI was 39.1% at 5 years, compared with 26.7% among patients who did not develop HF during their index MI hospitalization (RR: 1.8, 95% CI: 1.6 to 2.0, p < 0.0001). After the index MI, death occurred more frequently in-hospital for those patients who developed HF compared with the non-HF group (64.8% vs. 30.2% respectively, p < 0.001).

As a further analysis, patients were stratified by age based on the 25th and 50th percentiles (65 to 69 years of age, 70 to 75 years of age, and >75 years of age). Of patients who were 65 to 69 years of age at the time of their first MI, 33.0% developed HF and 5.2% died at their index MI, and after discharge 50.2% who did not have in-hospital HF developed HF and 55.7% died within 5 years. Thus, 70.6% of patients age 65 to 69 years developed HF in the 5 years after their first MI. For the patients 70 to 75 years of age, 35.7% developed HF and 9.2% died at their index MI, and after discharge 57.9% of those without HF developed HF and 61.7% died. Thus, 75.1% of patients age 70 to 75 years developed HF in the 5 years after their first MI. For the patients older than 75 years of age, 39.0% developed HF and 19.6% died at their index MI, and after discharge 65.4% of those free of HF developed HF and 70.3% died. Thus, 76.8% of patients older than 75 years of age developed HF in the 5 years after their first MI. All of these comparisons were all highly statistically significant across age strata (p < 0.0001).

Intercurrent hospitalizations in the first year after being discharged alive from the index MI occurred frequently (Table 3). By the end of the first year, a substantial

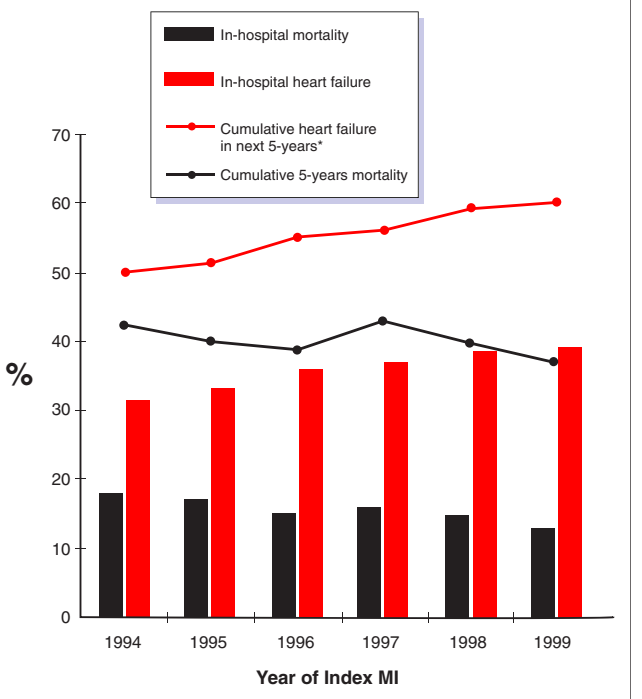

Figure 2 Temporal Trends in Mortality Rate and the Development of Heart Failure

Black bars indicate in-hospital mortality rate, and **red bars** indicate in-hospital heart failure rate. **Red line** indicates cumulative heart failure in the next 5 years for patients who survived index hospitalization, and **black line** indicates the cumulative 5-year mortality. X-axis indicates year of hospitalization for index myocardial infarction (MI).

Table 3 Intercurrent Hospitalizations in the First Year After Index Myocardial Infarction

Disease	Alive at End of First Year		Died in First Year		p Value
	No HF	Developed HF	No HF	Developed HF	
n (%)	5,300 (79.1)	707 (10.6)	488 (7.3)	206 (3.1)	
Myocardial infarction	16.5	22.5	26.6	24.3	<0.0001
Other acute ischemic heart disease	5.4	9.3	5.3	8.7	0.0002
Angina	2.8	6.1	1.4	2.9	<0.0001
Atrial fibrillation	1.4	3.1	1.0	3.4	0.0012
Ventricular arrhythmias	0.3	0.9	1.8	1.9	<0.0001
COPD	0.4	1.6	1.0	2.4	<0.0001
Cerebrovascular disease	1.0	3.5	2.9	2.4	<0.0001
Renal disease	0.2	1.7	1.4	2.4	<0.0001

Only primary hospitalized diagnoses with clinical relevance and an incidence >1% are included. Values are percents unless otherwise stated. The following International Classification of Diseases-9th Edition-Clinical Modification (ICD-9-CM) codes were used: myocardial infarction (ICD-9-CM 410), other acute ischemic heart disease (ICD-9-CM 411), angina (ICD-9-CM 413), atrial fibrillation (ICD-9-CM 427.3), ventricular arrhythmias (ICD-9-CM 427.1/4/5), chronic obstructive pulmonary disease (COPD) (ICD-9-CM 496), cerebrovascular disease (ICD-9-CM 433 to 435), and renal disease (ICD-9-CM 403, 404, 584, 585).

HF = heart failure.

proportion of patients (18.1%) had been rehospitalized for another MI. Those who were alive at the end of the first year and had developed HF were more likely to have had repeat MI, an acute ischemic event, or other intercurrent hospitalization.

Predictors of mortality or HF. The multistate model (Table 4) describes variables predictive of the development of: 1) HF, and 2) mortality (whether or not they developed HF). Similar variables predicted the development of HF and mortality. Of note, users of beta-blockers and statins after the index MI were less likely to develop HF, and ACE inhibitors, beta-blockers, and statins were associated with reduced mortality in both those patients who did develop HF post-MI and those who did not develop HF. Further, although invasive coronary revascularization (percutaneous coronary intervention with or without stent placement or bypass surgery) was not associated with the risk of developing HF in the multivariate analyses, patients who had undergone invasive coronary revascularization were less likely to die, whether or not they developed HF. In the subset of patients discharged alive from the hospital who did not develop HF as a complication of their MI, the model did not substantially change with 1 exception: ACE inhibitors were no longer associated with reduced mortality in those patients developing HF (OR: 1.04, 95% CI: 0.90 to 1.20).

Discussion

In this large cohort of elderly MI patients without a history of HF, almost three-quarters developed HF within 5 years. Importantly, this substantial HF incidence tracked a reduc-

Table 4 Multivariable Multistate Modeling for Predictors of Heart Failure or Mortality

	All Patients (n = 7,733), %	Development of HF (n = 5,871) HR (95% CI)	Mortality HR (95% CI)	
			In Those Who Developed HF (n = 2,316)	In Those Who Did Not Develop HF (n = 771)
Age, per yr		1.02 (1.02–1.02)	1.07 (1.06–1.08)	1.06 (1.05–1.07)
Female	40.0	1.07 (1.02–1.13)	1.04 (0.96–1.13)	0.83 (0.72–0.96)
Diabetes	19.1	1.21 (1.14–1.30)	1.5 (1.37–1.65)	1.17 (0.98–1.40)
Cardiac arrhythmia	28.0	1.25 (1.18–1.32)	1.24 (1.14–1.35)	1.82 (1.57–2.11)
Peripheral vascular disease	4.1	1.36 (1.20–1.54)	1.29 (1.08–1.53)	1.32 (0.91–1.90)
Cerebrovascular disease	5.8	1.13 (1.02–1.27)	1.50 (1.30–1.74)	1.66 (1.31–2.11)
Acute renal failure	2.9	1.32 (1.12–1.55)	2.21 (1.83–2.67)	2.14 (1.56–2.94)
Chronic renal failure	3.1	1.51 (1.30–1.75)	1.55 (1.29–1.85)	1.01 (0.65–1.57)
COPD	14.3	1.15 (1.07–1.24)	1.21 (1.09–1.35)	1.00 (0.81–1.24)
Cancer	2.7	1.24 (1.06–1.46)	2.63 (2.20–3.15)	1.85 (1.34–2.54)
PCI without stent	4.8	1.02 (0.91–1.16)	0.54 (0.42–0.70)	0.49 (0.29–0.83)
PCI with stent	7.0	1.08 (0.98–1.19)	0.59 (0.47–0.73)	0.75 (0.46–1.24)
CABG	2.4	1.10 (0.94–1.30)	0.45 (0.32–0.62)	0.27 (0.11–0.65)
ACE inhibitors	29.9	1.26 (1.19–1.34)	0.82 (0.75–0.90)	0.22 (0.16–0.30)
Beta-blockers	48.0	0.83 (0.79–0.89)	0.55 (0.50–0.61)	0.14 (0.11–0.18)
Statins	10.3	0.91 (0.83–0.99)	0.58 (0.48–0.72)	0.44 (0.26–0.76)
Year (1997 to 2000, reference 1994 to 1996)	51.4	1.11 (1.06–1.18)	1.06 (0.98–1.16)	1.19 (1.03–1.38)

CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; other abbreviations as in Table 2.

tion in peri-MI mortality, raising the obvious question of whether improvements in MI care were the major driver of this phenomenon. The incidence of post-MI HF we report is substantially higher than previous estimates in the literature (5–8). Further, we identified that the development of HF, even remotely after a MI, is a sentinel negatively predictive event (i.e., most of the patients who died were admitted for HF in the prior year).

Our data, indicating that concurrent in-hospital HF conferred a nearly 2-fold increase in mortality risk, supports previous published reports on the prognostic impact of MI-associated HF. However, we found a much higher rate of concurrent HF than previously reported. In the WHAS (Worchester Heart Attack Study) trial (1975 to 1995, mean age approximately 66 years), there was a decline in the incidence of peri-MI in-hospital HF from 38% to 33%. The in-hospital case fatality rate for WHAS trial patients developing HF decreased from 33% to 19% over 2 decades, yet little change occurred in the mortality rate in those without HF (7% to 9%) (18). In the NRMI-2 (Second National Registry of Myocardial Infarction) trial (1994 to 1998, mean age approximately 67 years), 19.1% of ST-segment elevation myocardial infarction (STEMI) patients had HF during their index MI hospitalization, and this was associated with an OR of 1.68 (95% CI: 1.62 to 1.75) for in-hospital mortality (19). For patients with STEMI in the GRACE (Global Registry of Acute Coronary Events) study (1999 to 2005, mean age approximately 66 years), 19.5% developed in-hospital pulmonary edema or HF in 1999, but this proportion had decreased to 11% by 2005 (20). Finally, in a prior analysis of Albertans of all ages surviving their first MI, we found that 22% developed HF during their index MI hospitalization and 7% developed HF during 32 months of follow-up; however, the mean age in that study was over a decade younger than in this current study (7). Because these studies were composed of relatively younger and select populations with prior MI or HF, they are likely less relevant to the current cohort of elderly patients with their first MI. In addition, by excluding prior MI or HF, we created an incident cohort to delineate the course of an otherwise relatively healthy but elderly population. This cohort represents a population of increasing importance that has been underrepresented in prior studies (21).

Our data are consistent with the decreasing in-hospital mortality rate for MI over the past decade reported in large registries from other locales. For patients of all ages enrolled in the NRMI-2 trial, the in-hospital mortality rate decreased from 10.6% to 9.8% for STEMI patients and from 9.9% to 9.1% for other acute coronary syndrome patients from 1994 to 1999 (22). Other registry data from a similar time period also point to a high in-hospital mortality rate for STEMI patients (18.7%) and those with a subendocardial MI (13.6%) (23,24). A key novel finding from the current study is our demonstration that the long-term mortality decrease predominantly related to a decrease in the index admission mortality rate (5.1% absolute from 1994 to 1999), not to a further decline in post-discharge mortality over the 5 years beyond the hospital stay.

Prior studies of patients surviving an MI reported limited data on subsequent, long-term HF incidence and implications. In a post-hoc analysis of patients enrolled in the VALIANT (VALsartan In Acute myocardial iNfarcTion) trial, which enrolled patients in the same time period as our cohort, 20% of the 775 patients older than 80 years of age developed HF over the next 2 years (25). Importantly, this occurred within the context of a randomized controlled trial (mean age 65 years, mean ejection fraction 0.35, one-third with a non–Q-wave MI). These patients were not unexpectedly on a higher percentage of evidence-based medications (approximately 35% on a statin and approximately 70% on a beta-blocker) than our patients or those in cohorts enrolling patients in the same era (26). Further, the shorter follow-up precludes definitive long-term conclusions on the development of HF. In the Framingham study, a modest sample of patients (n = 546, mean age 60 years) with a Q-wave MI showed a temporal decline in the mortality rate over 40 years, but did not show a long-term decline in the incidence of HF post-MI, leading to speculation that although the acute treatment has improved for MI, longitudinal outcomes may not have changed (27). In a previous study in Olmsted County, 36% of patients (n = 1,537, mean age 66 years) with an index MI developed HF over the next 5 years, with a reduction in incident HF from 1979 to 1994 (40% to 33%), the majority of which occurred within the first 2 days, concurrent with an increase with reperfusion therapy (28). Our study is unique in showing a temporal increase in the incidence of new-onset HF post-MI offsetting the reductions observed in peri-MI mortality. Further, we have established that the long-term risk of HF in elderly MI survivors constitutes a much larger problem than previously thought, that is, 76% developed HF within 5 years. The reasons for this apparent disconnect are likely multiple: the increased comorbidity and age of patients presenting with their first MI, improved (but still suboptimal) application of revascularization, and improved chronic oral therapies for cardiovascular disease that delay but do not cure the disease.

New-onset HF not only significantly increases the mortality risk among these patients but also augments the mortality hazard associated with other prognostic factors. Hence, post-MI HF should be viewed as a sentinel event, akin to those recognized in the palliative care literature for other end-stage chronic diseases. Indeed, recent data from the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) study indicates that the first hospitalization in patients with known HF carries an adjusted 3-fold risk for death even if not previously hospitalized for HF, similar to our cohort (29). Even within the clinical trials of new therapies, the short-term mortality is low for both STEMI and non-STEMI, and HF is likely to become an increasingly important component of composite end points. In a recent trial of high-risk STEMI

patients, the 30-day death rate was 4%; HF incidence as an end point was also 4% by 30 days (30). Our long-term observations indicate that further evaluation of new therapies may benefit from a long-term assessment beyond the traditional 90- or 180-day end points.

A unique feature of our analyses was the use of a multistate model used to appropriately describe the pathway that a patient follows through multiple clinical transitions and thereby to model both the competing risks of the development of HF against death and a survival model for those patients who developed HF. In the present analysis, competing risk occurred because the majority of patients developed HF before death, highlighting an underappreciated but clinically significant event. By using the multistate model, more of the available information is used, because once HF developed, we were able to model the effects of demographics or comorbidity on subsequent death (16). For example, in this cohort, chronic obstructive pulmonary disease was associated with the development of HF and with subsequent mortality if HF developed. However, if HF did not develop, there was a neutral effect on mortality; the clinical implications of this remain to be determined for post-MI patients.

The importance of comorbid cardiovascular and noncardiovascular conditions requiring hospitalizations is worthy of note. For patients who were discharged after their index MI, nearly one-fourth were rehospitalized for MI or other acute ischemic events within the year. Other vascular disease also played an important role; between 1% and 3.5% were admitted to the hospital for a stroke or transient ischemic event. Clearly, recognition and management of the global vascular risk of these patients should be at the forefront.

Two therapeutic interventions were associated with a lower mortality in our cohort: revascularization and medical therapy. Medication prescription rate at discharge was consistent with previous reports from this time period, highlighting the similarity between this cohort and other detailed registries (22). Indeed, the associations we found for beta-blockers, statins, and ACE inhibitors mirrored the randomized trial evidence for each agent. Patients who underwent revascularization at the index hospitalization did not have a reduced incidence of HF; however, if it developed, they had a lower mortality risk. For example, we found statin use was associated with a decreased incidence of HF and, whether or not it developed, a lower mortality. In the 4S (Scandinavian Simvastatin Survival Study) trial testing simvastatin versus placebo, a 30% relative reduction in mortality and a 21% relative reduction in new-onset HF was seen in the statin arm (31). However, in the Controlled Rosuvastatin Multinational Trial in Heart Failure (median age 77 years, ejection fraction <35%), HF patients treated with a statin did not have a lower all-cause mortality despite a 44% reduction of low-density lipoprotein to 1.96 mmol/l (32). Reconciliation of these disparate results may hinge at least in part on the difference between preventing HF from developing and treating the HF once it is evident.

Study limitations. We used the first MI as the entry point into our cohort; however, administrative coding did not separate out STEMI from non-STEMI for the time frame of this study. Given this limitation, it is possible that inclusion of a lower-risk population of patients with unstable angina will have underestimated the frequency of subsequent HF in patients with higher-risk non-STEMI or STEMI. In the 1993 to 1995 cohort of the Cooperative Cardiovascular Project of Medicare patients using the 410.x administrative code for MI, 44% of patients were noted to have a subendocardial MI (23). The refinement of biomarkers including troponin also took place concurrently with our cohort, and although it is unclear what impact this had on the identification of cases in our cohort, it seems reasonable to hypothesize that this may have led to an underestimation of the frequency of HF because outcomes in higher-risk patients with non-STEMI or STEMI would be diluted by the lower event rates in lower-risk patients with only minor troponin elevations. On the other hand, these limitations also mean that it is likely that a population spanning all risk strata was included in our study, thereby enhancing the applicability of our findings to a general MI population. Similarly, renal failure is an important comorbidity and is under-represented in our analysis because of the lack of access to estimated glomerular filtration rate. Likewise, information on potential eligibility for thrombolytic therapy for patients with STEMI is unavailable in our database because the number of hours from chest pain, or whether there was an indication or contraindication to thrombolytics, is not recorded in administrative data.

Left ventricular dysfunction as identified by quantitative methods for estimating ejection fraction was not available; rather, we relied on HF coding from the clinical diagnosis of HF. In the VALIANT trial and other analyses, ejection fraction did not predict future HF hospitalization (25). We did not include 90 patients (0.8%) with no prior HF diagnosis but a pulmonary edema ICD-9-CM administrative code on the index MI hospitalization because this code has not been prospectively validated for subsequent HF hospitalizations. The 428.x ICD-9-CM administrative code has been shown to be accurate for identifying patients with symptomatic HF (11). In the TRACE (Trandolapril Cardiac Evaluation) trial, 54% of patients had clinical HF, of which 76% had left ventricular systolic dysfunction by imaging, leading us to speculate that the true incidence of left ventricular systolic dysfunction with or without HF symptoms is possibly greater than that reported by us (33).

Conclusions

In an elderly cohort of patients with their first MI, the in-hospital mortality improved over 6 years, but the incidence of in-hospital and subsequent HF increased. Subsequent HF is very common after MI in the elderly, particularly in the first year, and confers a substantial risk for death. Mechanisms to risk stratify and identify elderly patients at

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risk for HF and to institute appropriate medical therapies and close follow-up constitute a large unmet need.

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