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Predictors of the first heart failure hospitalization in patients who are stable survivors of myocardial infarction complicated by pulmonary congestion and/or left ventricular dysfunction: a VALIANT study

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Aims We sought to assess the incidence of and prognostic factors for heart failure (HF) hospitalization among survivors of high-risk acute myocardial infarction (MI).

Methods and results We assessed the risk of an initial hospitalization for HF in 11 040 stable MI patients (no major non-fatal cardiovascular events or deaths within 45 days of randomization) without a prior history of HF enrolled in the VALIANT trial. Multivariable models were developed to identify independent predictors of HF and HF or cardiovascular death. Of 11 040 stable post-MI patients, 1139 (10.3%) developed HF during the median 25-month follow-up at a rate of ~3.4% per year. Most patients, 824 (72.3%), did not have a symptomatic recurrent MI between randomization and the onset of HF. The most important predictors of HF were older age, antecedent diabetes, prior MI before index MI, and reduced renal function. HF markedly increased the risk of death [HR(hazard ratio) 8.22; 95% CI(confidence interval), 7.49–9.01].

Conclusion HF post high risk-MI occurs in a time-dependent fashion and is usually not directly related to re-infarction. Patients who experience HF beyond the acute phase have increased mortality. Long-term survivors of high-risk MI should be followed closely and treated aggressively beyond the acute MI period.

Keywords Myocardial infarction • Heart failure • Hospitalization • Predictors • Mortality

Introduction

Therapies for acute myocardial infarction (MI) patients continue to evolve and have resulted in improved rates of short- and long-term survival.[1] Despite this trend, the presence of signs of heart failure (HF) in the setting of acute MI continues to be associated with increased mortality.[2] Previous studies have focused primarily on identifying predictors of mortality and HF development during the acute phase following MI.[3,4] Given improvements in hospital survival and the rate of subsequent discharge, clinicians more often see outpatients who are long-term MI survivors who

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remain at risk for developing HF.[5] Strategies that identify higher risk MI patients when they present for post-discharge MI care may allow physicians to use more aggressive treatment with proven therapies, intensify risk factor control, and more closely monitor patients for early signs of adverse events.

Stable long-term survivors of MI were previously evaluated in the CARE population[5] and seven independent predictors of HF hospitalization were identified. However, there remains a paucity of knowledge regarding the predictors and time course of HF in long-term MI survivors, especially those who presented with high-risk MIs. Previous studies have demonstrated several important prognostic factors following acute MI, including older age, comorbid illnesses, and factors related to the extent of myocardial injury, such as Killip classification and left ventricular (LV) dysfunction.[6–9] However, in acute MI patients already at high risk for adverse outcomes, little is known about the persisting importance of these factors in further characterizing patients into lower and higher risk of adverse outcomes.

The aims of this analysis were: (i) to explore the initial hospitalization for HF beyond the acute phase in stable survivors of MI complicated by signs of pulmonary congestion and/or LV dysfunction; (ii) to quantitatively evaluate potential predictors of HF hospitalization in stable MI survivors who had prior pulmonary congestion and/or LV dysfunction at the time of MI; and (iii) to characterize the impact of HF hospitalization on subsequent mortality as it relates to this high risk overall population.

Methods

Study design and patient population

Details of the enrolment and exclusion criteria, follow-up, and results of the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial have been reported elsewhere.[10] Briefly, VALIANT was a multicenter, international, randomized clinical trial that enrolled 14 703 patients $\geq$18 years of age with an acute MI occurring between 12 h and 10 days prior to randomization with clinical evidence of acute HF and/or radiological evidence of HF and/or LV ejection fraction (EF) $\leq$35% as assessed by echocardiogram or left ventriculogram or LVEF $<$ 40% as assessed by radionuclide scan. Patients without clinical or radiologic evidence of HF and LVEF $>$ 40% were excluded from this study. The highest Killip classification between the qualifying MI and randomization was recorded and determined as follows: Class I: no rales over the lung fields and no S_3; Class II: rales over $\leq$50% of lung fields or presence of an S_3; Class III: rales over $\geq$50% of lung fields, Class IV: pulmonary oedema with hypoperfusion or cardiogenic shock. All enrolled patients provided informed consent and were randomized to receive captopril (up to 50 mg thrice daily), valsartan (up to 160 mg twice daily), or the combination of these two drugs (captopril up to 50 mg thrice daily and valsartan 80 mg twice daily).

To address the primary aim of identifying predictors of new-onset HF hospitalization, patients with prior history of HF ($n = 2174$) were excluded from this analysis. In addition, patients who died or experienced a non-fatal cardiovascular event (including HF) within the first 45 days were also excluded ($n = 1489$), leaving 11 040 patients eligible for this analysis.

Endpoints

Hospitalization for HF was the primary endpoint of this analysis and combination of hospitalization for HF or cardiovascular mortality was the secondary endpoint. The clinical adjudication committee reviewed all deaths and HF hospitalizations in a blinded fashion. Hospitalization for HF was defined as the unplanned treatment of new or worsening HF requiring the use of intravenous diuretics, inotropes, or vasodilators during any hospital admission or overnight stay in a healthcare facility. Patients with a concomitant MI must have experienced HF that became a significant component of the hospitalization or prolonged the hospital stay. Patients with transient signs of HF would not have met the criteria. Deaths were classified as cardiovascular vs. non-cardiovascular, and underlying causes of death were further classified. MI was centrally adjudicated by the same committee and was defined as *either* typical ischaemic symptoms or electrocardiographic changes consistent with infarction *and* marker elevation.

Statistical analysis

Continuous baseline variables were summarized as mean $\pm$ standard deviation, except where noted, and were compared among groups using *t*-tests where data were normally distributed and Wilcoxon rank sum tests otherwise. Categorical variables were summarized as percentages and were compared using χ^2 tests. Event-free survival curves were generated using Kaplan–Meier estimates.

A total of 39 baseline variables (including demographic features, cardiac risk factors and medical history, characteristics of index MI, vital signs, and laboratory values) and 14 variables between the index MI and randomization (including arrhythmias, acute renal failure, new hypertension and diabetes, and revascularization) were identified as candidate variables by the VALIANT investigators. An additional 15 variables present at 45 days post randomization (including blood pressure, heart rate revascularization, and New York Heart Association class) were considered bringing the total variables to 68. As patients with HF were not eligible for the analysis, this variable represents the only deviation from the standard candidate variables in other VALIANT models.[11] Restricted cubic splines were used to estimate the non-linearity of continuous variables. When these factors were found to be non-linear, appropriate transformations were applied and the -2 log likelihood test for the model with the transformed choice vs. restricted cubic spline estimated the appropriateness of the choice. Most transformations resulted in linear piecewise estimates or truncations. Estimated glomerular filtration rate (GFR), one of the candidate predictors, was calculated using the Modification of Diet in Renal Disease equation.[12]

A multivariable Cox proportional hazards model was developed using stepwise selection to determine independent predictors of HF from among the candidate predictors just described. The selected set of predictors was then applied to the composite endpoint of HF or cardiovascular death, and the estimates assessed for their similarity between the two models to rule out any survivor bias in the HF model. Factors in the final models were significant in predicting both HF and HF or cardiovascular death. We tested the proportional hazards assumptions using factor $\times$ time time-dependent interaction, and the proportional hazards assumption was met for each factor. The HF models were also applied to patients for whom LVEF values were assessed and imputed ($n = 11\ 040$) to try to rule out any possible bias from excluding patients with imputed values. Of these patients, 2458 (22%) did not have a measured LVEF. A sensitivity analysis with imputed and non-imputed LVEF data did not significantly change the parameter estimates. Thus, the final cohort for the multivariable model comprised the remaining 8582 patients with available LVEF

(mean 5 days post-MI) and without a clear pre-existing history of HF or clinical events in the first 45 days following acute MI. To validate the final Cox model, we used the bootstrapping re-sampling technique with 200 distinct samples, refitting the model with each repetition.[13] Any variable chosen >50% of the time was deemed to be validated. The model's discrimination ability was assessed using the c-statistic. The bootstrapping was also used to correct the c-index for over-optimism. Finally, an integer-based risk score was developed using the parameter estimates of the 8 strongest predictors. A plot of the score and the actual event rate was developed.

The impact of recurrent MI post-randomization on HF hospitalization was evaluated by including MI in the HF model as a time-dependent covariate. The MI was considered to have preceded HF if it occurred at least 2 days prior to the HF event. Those MI events occurring within 2 days of the HF event were considered to occur simultaneously with HF. The impact of HF after 45 days on subsequent mortality was assessed by including HF as a time-dependent covariate in the VALIANT Cox proportional hazards model for mortality within our subset of stable MI survivors with no history of HF.

Results

The characteristics of the patient groups included and excluded from the final cohort are detailed in *Table 1*. Excluded patients were more likely to have concomitant renal failure, lung disease, antecedent hypertension, prior MI, clinical HF following VALIANT MI, and prior surgical revascularization. Among these 3663 excluded patients, a total of 1037 (28%) were hospitalized for HF, a median of 15 days post-randomization, and 720 (20%) died, of whom 178 (25%) had post-randomization antecedent HF.

Event occurrence

Of the 11 040 patients, 1139 (10.3%) were hospitalized with HF requiring intravenous therapy over median follow-up of 25.9 months (25th–75th interquartile range 20.8, 31.7 months). The cumulative incidence of HF hospitalization increased by ~3.4%/year on an average with more events occurring in the first year after the MI. HF hospitalization or cardiovascular death increased by 5.7%/year (*Figure 1*). Of stable MI patients who developed HF, the HF hospitalization was the first event after enrolment in 824 (72.3%). An additional 84 patients (7.4%) had recurrent MI prior to HF hospitalization, with MI occurrence a median of 62 days prior to HF event. The other 231 (20.3%) were hospitalized for HF simultaneously with the recurrent MI (i.e. within 2 days). Recurrent MI occurred less frequently (5.1% vs. 35.2%) among the 9901 patients who did not develop HF.

Patient characteristics

The characteristics of patients with and without HF hospitalization differed markedly (*Table 1*). Patients hospitalized for HF treatment were older and more likely female and a race other than White, were more likely to have a history of hypertension, chronic renal insufficiency, chronic lung disease, diabetes, stroke, or prior revascularization, and had a higher systolic blood pressure and worse Killip class following their index MI. Lower LVEF was also associated with increased rate of HF hospitalization. At randomization, patients who were hospitalized for HF were more likely to have been receiving angiotensin-converting enzyme (ACE) inhibitors, digoxin, intravenous inotropes, and insulin between the time of acute MI and randomization and were less likely taking beta-blockers or HMG-Co A reductase inhibitors. Older patients had a greater rate of HF hospitalization than younger patients, with <5% of patients <50 years old developing HF during the 3 year follow-up compared with >20% of patients >80 years old developing HF during the same time period (*Figure 2*).

Predictors of heart failure development

Multivariable modelling identified several independent characteristics associated with a greater risk of HF hospitalizations in survivors of complicated MI (*Table 2*). These predictors included baseline characteristics and factors evident at 45 days. The strongest predictors of HF hospitalization were of older age [HR(hazard ratio) 1.03; 95% CI(confidence interval), 1.02–1.04 for every 1 year increase in age] and antecedent diabetes (HR 1.67; 95% CI 1.47–1.89). Pulse pressure up to 30 mm Hg was independently associated with lower risk of HF hospitalization; however, a differing hazard occurred above 30 mm Hg with marked elevation in pulse pressure associated with a greater risk of HF hospitalization, though not independently. More renal impairment was also associated with a higher risk of HF hospitalization (HR 1.10; 95% CI 1.06–1.14) for every 10 cc/min/1.73 m^2 decrease in estimated GFR among those patients with GFR < 90 cc/min/1.73 m^2. Signs of HF during index MI, as measured by Killip class, also remained a powerful predictor of subsequent HF hospitalization. Among patients with a body mass index (BMI) $\geq$ 25 kg/m^2, a higher BMI was also associated with a greater risk of HF hospitalization. Several factors assessed 45 days following randomization were also predictive of subsequent HF hospitalization, including worse New York Heart Association (NYHA) class and higher heart rate. Revascularization with either angioplasty or coronary artery bypass grafting (CABG) within 45 days after randomization was associated with a lower risk of HF. All of these factors were also independently predictive of HF or cardiovascular death with similar point estimates. However, the risk of the combined HF or cardiovascular death endpoint did not increase linearly as Killip class worsened. When compared with captopril alone, there was a trend towards reduction in HF (HR 0.87; 95% CI 0.75–1.01) and HF or CV death (HR 0.89; 95% CI 0.80–1.00) among patients randomly assigned to receive combination therapy of valsartan and captopril. Non-randomized baseline medicines were not included in the multivariable model. Recurrent MI in the interim period following randomization increased the risk of subsequent HF hospitalization (HR 2.44; 95% CI 1.87–3.17; $P = 0.001$). After HF development, 434 (38.1%) patients died throughout the follow-up, with a median time to death of 67 days post HF hospitalization. This mortality is notably different from the 798 (8.1%) of the 9901 patients without subsequent HF who died during follow-up (8.1% vs. 38.1%; $P < 0.001$). The risk of death among patients hospitalized for HF was much greater than those without HF (HR 8.22; 95% CI 7.49–9.01) after adjusting for other predictors of mortality.

The final Cox model was deemed valid based upon the results of 200 re-samples using the bootstrapping method with all factors remaining in the model with an exception of randomized treatment. The c-index of the original model was 0.733 and was

Table 1 Clinical characteristics of patients included or excluded from the final cohort

Characteristic	Excluded patients (n = 3663)	Included patients stable after 45 days (n = 11 040)	
	Prior HF or CV event in first 45 days	HF (n = 1139)	No HF (n = 9901)
Baseline demographics			
Age (years)	69 ± 10	70 ± 11	63 + 12
Female (%)	39.3	39.2	27.1
Non-white race (%)	6.9	8.4	6.1
BMI (kg/m^2)	27.8 ± 5	28.0 ± 5	27.9 ± 5
Risk factors and behaviours (%)			
Hypertension	68.3	63.0	49.5
Diabetes	31.5	34.8	18.7
Current smoker	20.9	26.9	36.4
Dyslipidemia	35.1	32.0	27.8
Prior renal insufficiency	4.3	1.9	0.9
Renal insufficiency post-MI	8.5	6.3	2.6
Chronic lung disease	13.5	11.7	6.4
Cardiovascular history (%)			
Prior MI	50.0	34.1	19.0
Prior surgical revascularization	12.9	9.0	4.6
Prior angioplasty	10.8	8.3	5.8
Prior stroke	10.3	8.4	4.3
Presenting characteristics			
Q-wave MI (%)	45.8	58.7	71.9
Anterior changes (%)	56.2	59.1	60.7
New LBBB (%)	6.8	7.6	3.0
Killip class III or IV post-MI (%)	34.6	33.1	18.5
Systolic BP (mm Hg)	125.1 ± 18	124.1 ± 17	121.6 ± 16
Diastolic BP (mm Hg)	72.6 ± 12	71.6 ± 11	72.3 ± 11
Heart rate (b.p.m.)	78.0 ± 14	77.3 ± 13	75.4 ± 12
Pulse pressure (mm Hg)	52.5 ± 15	52.5 ± 15	49.3 ± 13
Ejection fraction (%)	32.7 ± 10	34.5 ± 10	36.3 ± 10
Median time to randomization (h)	121	115	121
Clinical HF post-MI (%)	74.0	65.2	52.0
Primary angioplasty (%)	8.0	12.3	17.6
CABG following MI (%)	1.4	2.8	2.3
Medications at randomization (%)			
ACE inhibitors	42.4	42.2	38.2
Angiotensin receptor blocker	1.8	1.3	0.9
Beta-blockers	61.8	63.7	74.4
Digoxin	21.6	18.8	8.6
Statin	28.4	31.6	36.5
Aspirin	87.9	89.2	92.7
IIb/IIIa receptor antagonist	9.2	5.0	7.6
Insulin	18.1	19.3	10.0
Intravenous inotropes	2.8	2.5	1.4

Continuous variables presented as mean ± standard deviation, except where noted, and were compared using t-tests where data were normally distributed and Wilcoxon rank sum tests otherwise. Categorical variables are given as percent and were compared using χ^2 tests. HF, heart failure; CV, cardiovascular; BMI, body mass index; MI, myocardial infarction; LBBB, left bundle branch block; BP, blood pressure; b.p.m., beats per minute; CABG, coronary artery bypass grafting; ACE, angiotensin-converting enzyme.

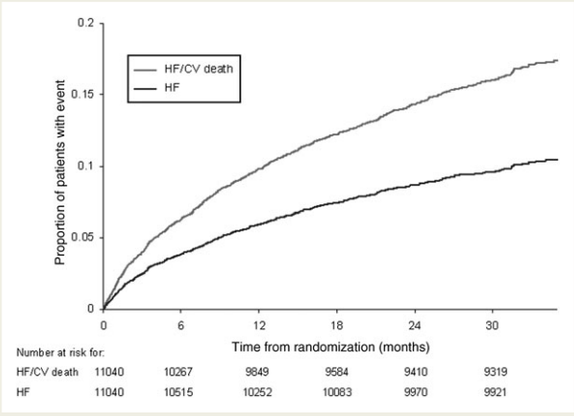

Figure 1 Heart failure hospitalization and cardiovascular death or heart failure hospitalization among stable myocardial infarction survivors without prior chronic heart failure.

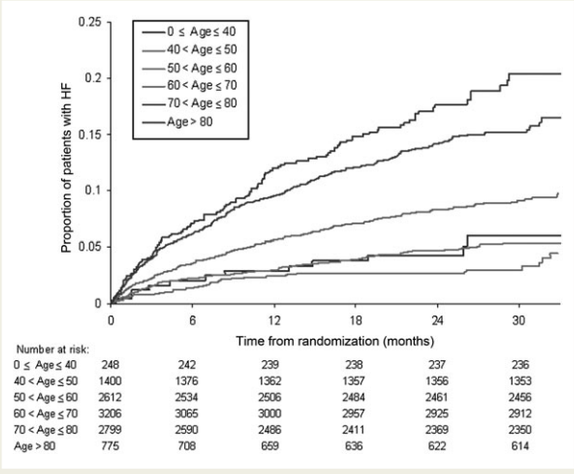

Figure 2 Heart failure hospitalization in stable myocardial infarction survivors stratified by age at randomization.

0.734 when adjusted for optimism, suggesting modest discriminatory ability. The risk score algorithm included age, race, diabetes, prior MI, peripheral arterial disease, left bundle branch block, Killip class, and New York Heart Association (*Table 3*). The scores ranged from 0 to 33. The greatest proportion of patients had a score $\leq$5. As expected, the event rate increased from 2.3% in the patients with the lowest group to 33.3% in those patients in the highest group (*Figure 3*).

Discussion

In this large, high-risk MI population with signs of congestion and/or low LVEF at randomization following MI, the majority of patients did not develop HF requiring hospitalization. The absolute risk of HF was highest in the early phase post-MI, as has been demonstrated in multiple population-based and clinical trial populations.[14–16] However, among stable survivors at least 45 days post-MI, HF hospitalization occurred in ~3.4% annually. This is slightly higher than the Framingham study with a rate of 2% annually post-MI[2] and the CARE patients who had a rate of 1.7% annually.[5] This higher rate likely reflects the greater likelihood of HF closer to the time of acute MI, the sicker VALIANT population who sustained a more complex MI event, and a greater proportion of patients with low EF. In these patients who survived the acute phase of MI, the hospitalization with HF was associated with an eight-fold increased risk of death despite comparing them with patients who had been at very high risk of mortality at baseline given their signs of pulmonary oedema and/or LV dysfunction at the time of acute MI. This mortality risk is similar to the 10-fold increased risk observed in CARE, in which patients with delayed onset HF were compared with those without HF development, in this case in a population that predominantly did not have significant HF or LV dysfunction during index MI.[5] It is notable that among those patients who died after the acute HF event, over half of the deaths occurred within ~2 months following admission for HF. This time course is much quicker than the period between hospitalization and death in an unselected HF hospitalization post-discharge.[17]

Most of the studies to date have described the risk of HF development and mortality in the acute MI phase.[18] This characterization was initially described independently by Forrester and Killip, and these classification schemes have endured almost four decades in determining risk of mortality during acute MI.[19] More recently, the GRACE registry described increased mortality both in acute MI and unstable angina patients with acute HF.[20] The Canadian Acute Coronary Registries demonstrated persistent risk out to 1 year using higher Killip class at admission for MI.[21] Given the increased survival to discharge, more emphasis is being placed on the management of these longer-term survivors of the acute MI. Identification of patients who remain at heightened risk once the acute phase of the MI passes will be important as the therapeutic options increase.

Patients who survive an acute MI complicated by pulmonary congestion or low LVEF are not necessarily destined to live with chronic HF. The majority will not be hospitalized for treatment of HF up to 3 years. This is an important message for patients who might otherwise experience depression, anxiety, and emotional distress resulting in impaired health-related quality of life as a consequence of the complexity of their acute MI.[22] Patients who develop HF beyond the acute phase may have progressive remodelling, chronic hibernating myocardium due to subclinical ischaemia, or recurrent MI,[23–25] and are classified as having Stage C chronic HF. Understanding the progression to chronic HF in this selected population will be helpful in identifying patients for more aggressive therapy, intensifying secondary prevention efforts, counselling patients on prognosis, and targeting higher risk populations for newer therapeutic strategies.

There were 19 predictors of new HF hospitalization (15 at baseline and four at 45 days) with the dominant predictors including older age, diabetes, prior MI, and renal insufficiency. With an exception of exercise routine, which was not captured in VALIANT, all of the predictors of delayed onset HF post-MI described in the CARE population were validated in the

Table 2 Independent predictors of heart failure, and heart failure or death in stable, MI survivors (n = 8582)

Predictor	HF			HF or CV death	
	HR (95% CI)	χ^2 test	*P*	HR (95% CI)	*P*
Baseline predictors					
Diabetes	1.71 (1.47–1.98)	51.1	<0.001	1.52 (1.37–1.69)	<0.001
Age (1 year increase)	1.03 (1.02–1.04)	43.8	<0.001	1.02 (1.01–1.03)	<0.001
Prior MI	1.63 (1.41–1.89)	43.4	<0.001	1.63(1.45–1.83)	<0.001
History of PAD	1.60 (1.32–1.95)	22.5	<0.001	1.53 (1.30–1.79)	<0.001
LVEF (5% decrease)	1.07 (1.03–1.11)	14.4	<0.001	1.09 (1.07–1.13)	<0.001
New LBBB	1.67 (1.28–2.19)	13.9	<0.001	1.72 (1.38–2.14)	<0.001
Race					
Black	1.84 (1.31–2.59)	12.4	<0.001	1.56 (1.17–2.07)	0.003
Other	1.41 (0.98–2.03)	3.5	0.06	1.04 (0.75–1.44)	0.807
Killip Class					
III	1.37 (1.15–1.64)	11.8	<0.001	1.44 (1.25–1.67)	<0.001
IV	1.42 (1.11–1.82)	8.0	0.005	1.31 (1.07–1.61)	0.009
GFR (10 cc/min increase)[a]	1.08 (1.03–1.12)	11.0	<0.001	1.12 (1.08–1.16)	<0.001
History of chronic lung disease	1.43 (1.16–1.77)	10.9	<0.001	1.38 (1.16–1.64)	<0.001
Clinical evidence of HF	1.32 (1.12–1.56)	10.7	0.001	1.27 (1.12–1.45)	<0.001
History of hypertension	1.28 (1.10–1.48)	10.7	0.001	1.32 (1.17–1.48)	<0.001
Pulse pressure (10 mm increase)[b]	0.44 (0.27–0.72)	10.5	0.001	0.50 (0.33–0.76)	0.001
BMI (1 kg/m^2 increase)[c]	1.01 (1.00–1.02)	8.3	0.004	1.01 (1.00–1.02)	0.024
Atrial fibrillation post-MI	1.20 (0.99–1.46)	3.6	0.06	1.25 (1.08–1.46)	0.004
Predictors at 45 days					
NYHA class					
II	1.36 (1.16–1.59)	14.8	<0.001	1.30 (1.15–1.47)	<0.001
III	1.67 (1.35–2.07)	22.7	<0.001	1.62 (1.37–1.92)	<0.001
IV	2.31 (1.13–4.70)	5.3	0.02	2.19 (1.20–4.01)	0.011
Heart rate (10 b.p.m. increase)	1.10 (1.04–1.16)	10.2	0.001	1.10 (1.06–1.16)	<0.001
CABG within 45 days	0.52 (0.33–0.84)	7.2	0.007	0.53 (0.37–0.78)	0.001
Angioplasty within 45 days	0.76 (0.54–1.07)	2.4	0.12	0.82 (0.63–1.07)	0.137
Randomized treatment					
Valsartan and captopril	0.86 (0.73–1.02)	2.9	0.09	0.89 (0.77–1.01)	0.073
Valsartan alone	0.96 (0.81–1.13)	0.28	0.60	0.98 (0.86–1.12)	0.752

[a]Patients with GFR < 90 cc/min.
[b]Patients with pulse pressure < 30 mm Hg.
[c]Patients with BMI >25kg /m^2.
The χ^2 values are provided for the HF predictors to illustrate relative strength of predictor. HF, heart failure; CV, cardiovascular; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; PAD, peripheral arterial disease; LVEF, left ventricular ejection fraction; LBBB, left bundle branch block; GFR, glomerular filtration rate; NYHA, New York Heart Association; b.p.m., beats per minute; CABG, coronary artery bypass grafting.

VALIANT population, which had significantly more signs of HF and/or low LVEF. This suggests that these factors are important irrespective of the complexity of the MI. As more patients are surviving to discharge from these complicated infarcts, clinicians are often faced with encouraging secondary prevention efforts and medical compliance at a time when patients may have varied perceptions about the long-term consequences of their MI.

Older age and diabetes are the most powerful predictors of HF in long-term survivors of MI, consistent with other post-MI and chronic coronary artery disease populations.[26] This increased risk may be related to decreased early remodelling among patients with diabetes[27] that may lead to increased wall stress, decreased LV compliance, and earlier elevation in filling pressures leading to HF symptoms. Patients with hyperglycaemia and elevated haemoglobin A1c are more likely to develop HF post-MI;[28] however, improvements in A1c levels have not reduced HF incidence.[29] The interaction between age and diabetes may also be related to more extensive atherosclerosis and chronic renal insufficiency. Renal insufficiency is emerging as an important risk factor for adverse outcomes in both MI and HF populations independent of age and diabetes.[11,30,31] This association may be related to subsequent progressive renal disease leading to fluid retention,

Table 3 VALIANT heart failure risk score

Factor	Assign points	If patient	Points
Age	0	is 50 or younger	
	4	is 51–60 years	
	5	is 61–70 years	
	9	is 71–80 years	———
	10	is older than 80	
Race	0	is Caucasian or Asian	
	6	is African-American	———
	4	is any other race	
Diabetes	0	does not have diabetes	———
	5	has diabetes	
Prior MI	0	has not had a prior MI	———
	5	has had a prior MI	
PVD	0	does not have PVD	———
	5	has PVD	
LBBB	0	does not have new LBBB	———
	5	has new LBBB	
Killip Class	0	is Killip Class 1 or 2	———
	3	is Killip Class 3 or 4	
NYHA class at 45 days	0	is Class I	
	3	is Class II	
	5	is Class III	———
	9	is Class IV	
Total score			———

MI, myocardial infarction; PVD, peripheral vascular disease; LBBB, left bundle branch block; NYHA, New York Heart Association.

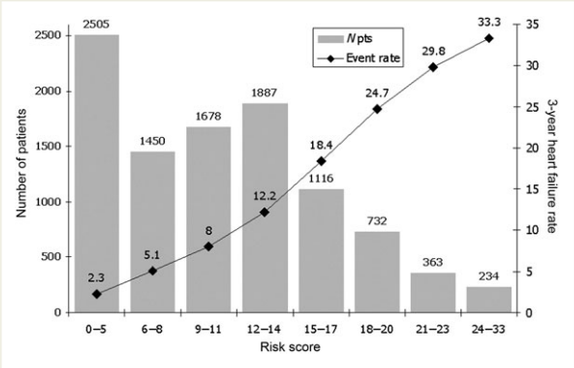

Figure 3 Distribution of scores based upon the risk score. Patients were stratified based upon their risk score; the event rate in each category is plotted and the total number of patients in each category is represented by the shaded bars

hypertension, alterations of the rennin–angiotensin system, or to the identification of patients at risk for recurrent MI, which could lead to further myocyte loss and eventual clinical HF. Moreover, a lower GFR may be associated with increased inflammatory activity, greater oxidative stress, and higher uric acid levels, as well as anaemia, all of which may play a role in subsequent HF development. Patients with lower GFR have excess risk factors that, though not typically captured, may confer an increased risk of HF and recurrent myocardial ischaemia. Finally, patients with lower GFR are less likely to receive therapies with known benefit in cardiovascular disease.[11] Patients who underwent revascularization, whether surgical or percutaneous, had a lower risk of developing HF. Revascularization may prevent HF by restoring blood flow, minimizing myocardial hibernation, and facilitating reverse remodelling. However, this finding also might reflect selection bias towards patients with less severe clinical presentations and better risk factor profiles.

Although the majority of patients did not suffer recurrent MI prior to HF hospitalization, it was much more common among those developing HF. Nevertheless, this possibly represents an important reversible factor that might decrease the risk of HF development. Other potentially reversible factors that may decrease HF development include attenuating the progressive decline of renal function, aggressive treatment of atrial fibrillation, control of basal heart rate with beta-blockade, improvement in LVEF by revascularization of viable myocardium, and aggressive management of diabetes. The use of valsartan and captopril in combination did not statistically reduce the risk of HF hospitalization. The inability to demonstrate a significant reduction may be related to the fact that the majority of patients do not develop chronic HF and many may have improvements in their LV function and reduction in wall stress, especially with revascularization. We did not include non-randomized medicines in the multivariable model as the use of these medicines may be more of a reflection of quality of care and/or varying practices in different regions of the world. Moreover, the use of non-randomized treatment is the result of a sophisticated interaction between the physician and patient, taking into account a variety of measured and unmeasured variables. Without fully adjusting for all of these variables, the true relevance of these medicines is questionable. The secondary preventive benefits of statins and beta-blockers have been well-described in randomized clinical trials in a post-MI population and would not add significantly to the model.[32–34]

There are several limitations to this study. First, patients with milder forms of HF not requiring hospitalization or intravenous therapy were not captured, and these patients are known to have an excess mortality.[35,36] Neither does hospitalization for HF signify the development of chronic HF in all patients although this has commonly been a surrogate measurement for HF incidence in population based studies. Secondly, VALIANT patients without a low LVEF were required to have clinical signs of congestion and this unique feature may have attenuated the relation between LVEF and subsequent HF hospitalization. Moreover, the follow-up was limited which precluded determining the predictors of HF development over a decade. Patients with 'silent MI' or subclinical or underappreciated re-infarction were not captured and patients with HF hospitalization could have suffered these events.

Our patient group was drawn from a clinical trial population, which tends to be healthier than a community-based population and many of the patients enrolled underwent revascularization, which may not be commonly done for MI survivors in certain countries. However, the patients were quite ill with signs of HF and/or low LVEF at the time of the MI, which may limit the generalizability to patients with uncomplicated MI. We did not include non-randomized medicines in the multivariable model, consistent with other VALIANT publications, and there may be important associations between medication use and prevention of HF hospitalizations. Nevertheless, this study represents one of the largest populations of complicated MI patients with HF and/or low LVEF, and identifies those risk factors that distinguish a particularly high-risk group amongst these patients who already have relatively high mortality.

In conclusion, even among patients with acute MI complicated by HF, only a minority develop HF requiring hospitalization. Stable survivors of MI remain at risk for HF and this risk appears greatest in the first 6 months and then remains relatively stable. Simple predictors at the time of MI and at initial follow-up can identify those patients at particularly high risk for developing HF. Although recurrent MI confers an increased risk of HF, most patients who are hospitalized for HF do not have a MI between the index event and the development of HF. Combination therapy with angiotensin receptor blockers and ACE inhibitors does not significantly reduce the risk of HF hospitalization. Given the excess mortality in patients who develop chronic HF, these patients at particularly high risk should be targeted for more aggressive intervention well beyond the acute phase of the MI and may benefit from more careful surveillance.

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