

Predictors and prognostic impact of recurrent myocardial infarction in patients with left ventricular dysfunction, heart failure, or both following a first myocardial infarction

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Aims

Recurrent myocardial infarction (MI) is common after a first MI and is associated with increased morbidity and mortality. Predictors and prognosis of a recurrent MI with contemporary management are not well known.

Methods and results

We assessed the predictors and prognostic impact of a first recurrent MI in 10 599 patients with left ventricular dysfunction, heart failure, or both following a first MI from the Valsartan in Acute Myocardial Infarction Trial (VALIANT) cohort. During a median follow-up of 27.4 months, 861 patients (9.6%) had a recurrent MI. The median time to recurrence was 136 days (quartiles 35–361 days), with a declining rate of recurrent MI within the first 3 months. The strongest predictors of recurrent MI were reduced estimated glomerular filtration rate, unstable angina, diabetes, and age. Mortality was markedly elevated (20.5%) within the first 7 days of a recurrent MI. Patients who survived 7 days after a recurrent MI continued to be at increased risk of death compared with patients without a recurrent MI and the risk of death remained elevated more than two-fold a year after the recurrent MI (adjusted hazards ratio 2.4, 95% confidence interval 1.7–3.2). One-year mortality for the entire VALIANT cohort was 10.3%, whereas 38.3% of the patients were dead 1 year after recurrent MI. Early reinfarctions (within 1 month) was associated with significantly higher 30-day mortality than later reinfarctions.

Conclusion

Even in the context of contemporary treatment, a recurrent MI confers a significantly increased risk of death in patients following a high-risk first MI. Strategies aimed at reducing recurrent MI will thus likely prolong survival in post-MI survivors.

Keywords

Myocardial infarction • Mortality • Epidemiology

Introduction

Patients who have survived the early phase of a myocardial infarction (MI) are at risk for subsequent cardiovascular adverse events that will impact their long-term survival, including rehospitalization for heart failure, ventricular arrhythmias and sudden death, and

recurrent MIs. Recurrent MI has been associated with increased mortality both in the pre-thrombolytic and thrombolytic era.^{1–4}

The prognostic importance of recurrent MI needs to be reassessed as the biomarker assays used to diagnosis MI become more sensitive and therapy of MI progresses.^{5–7} We utilized data from the multicentre Valsartan in Acute Myocardial Infarction (VALIANT)

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trial to assess the predictors of and prognostic implications of recurrent MI on mortality in patients with a high-risk first MI on contemporary therapy.

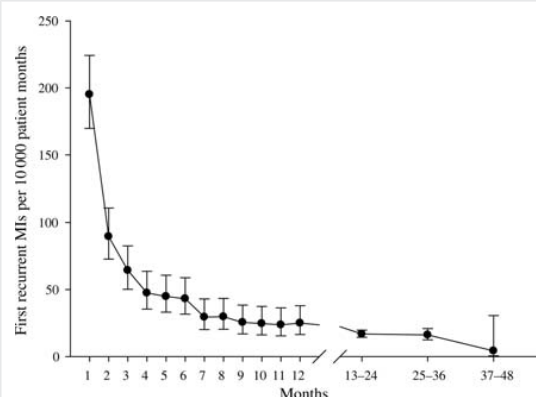


Figure 1 Rates of first recurrent myocardial infarction.

Methods

VALIANT randomized 14 703 patients with left ventricular systolic dysfunction, heart failure, or both to receive either captopril, valsartan, or the combination.⁸ There were no differences in mortality observed between the three treatment arms.⁹ We limited this analysis to the 10 599 patients with a first MI. Patients were randomized a median of 116 h (4.9 days) following the onset of their index MI (range: 12 h–10 days). The inclusion period ran from December 1998 through June 2001 and the median follow-up was 27.4 months.

All recurrent MIs were reviewed and adjudicated centrally by an independent endpoints committee. The diagnosis of non-procedure-related recurrent MI required elevated cardiac enzymes above the local diagnostic threshold along with a typical clinical presentation and/or typical electrocardiographic changes or that the patient died and the cause of death was considered to be a new MI. The diagnosis of peri-procedural MI required an increase in CK-MB greater than three times the upper limit of normal, whereas post-surgical MI required new Q-waves, CK $>5\times$ the upper limit of normal and CK-MB $>5\%$ of total CK. Only the first recurrence was counted for each patient. Comparisons between baseline demographics were done by ANOVA. Event rate for all-cause death was estimated by the Kaplan–Meier method and is reported with a 95% confidence

Table 1 Demographics

	No recurrent MI	Recurrent MI	P-value
No. of patients	9738	861	
Age	63.6 $\pm$ 11.9	67.5 $\pm$ 12.6	<0.0001
Female	3060 (31.4%)	291 (33.8%)	0.2
Smoking	3537 (36.4%)	331 (38.6%)	0.2
Systolic blood pressure	122 $\pm$ 17	124.9 $\pm$ 17.7	<0.0001
Diastolic blood pressure	72 $\pm$ 11	72 $\pm$ 12	0.3
BMI (kg/m ²)	27.9 $\pm$ 5.5	27.8 $\pm$ 5.4	0.4
eGFR	72.0 $\pm$ 21.0	65.4 $\pm$ 20.6	<0.0001
Medical history			
Heart failure	655 (6.7%)	89 (10.3%)	<0.0001
Dyslipidaemia	2315 (24.1%)	209 (24.4%)	0.8
Diabetes	1971 (20.2%)	249 (28.9%)	<0.0001
Hypertension	4939 (50.7%)	504 (58.5%)	<0.0001
Unstable angina	1400 (14.5%)	188 (21.9%)	<0.0001
Stable angina	2692 (27.9%)	321 (37.4%)	<0.0001
Peripheral vascular disease	603 (6.3%)	97 (11.3%)	<0.0001
Qualifying myocardial infarction			
Anterior location	5895 (62.4%)	483 (58.6%)	0.03
Q-wave	6880 (72.6%)	518 (63.1%)	<0.0001
CK (median and quartiles)	1329 (608–2678)	922 (499–2254)	<0.0001
Catherization without PCI/CABG	752 (7.7%)	60 (7.0%)	0.4
PCI	2710 (28.1%)	172 (20.0%)	<0.0001
CABG	216 (2.2%)	7 (0.8%)	0.005
Thrombolysis	3891 (40.0%)	291 (33.8%)	0.0004
Worst Killip's class >1	6878 (71.0%)	658 (76.9%)	0.0003
Concomitant medication			
Aspirin	8978 (92.2%)	768 (89.2%)	0.002
β -Blockade	6974 (71.6%)	590 (68.5%)	0.05
Statin	3291 (33.8%)	252 (29.3%)	0.007

interval (CI). Recurrent MIs are reported as the cumulative incidence taking into account the competing risk of all-cause death. Baseline predictors of recurrent MI were assessed by cause-specific proportional hazards regression with censoring of competing risk events. In addition, we assessed predictors of all-cause death or recurrent MI because sudden deaths might be caused by unrecognized recurrent MI and because of competing risks.¹⁰

The effect of a recurrent MI on subsequent risk of death and death or heart failure was assessed with proportional hazards regression. Multiple adjustment was performed by inclusion into the model of baseline age, gender, systolic blood pressure, body mass index, estimated glomerular filtration rate (eGFR), Killip's class >1, history of diabetes, dyslipidaemia, hypertension, heart failure, stable angina, unstable angina, peripheral artery disease, anterior index MI, Q-wave index MI, peak CK, primary percutaneous coronary intervention (PCI), and thrombolysis. Time since recurrence was treated as a time-dependent variable and modelled as a spline with 4 df.

Patients were enrolled into VALIANT following informed consent and the study was approved by all local institutional review boards.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

During follow-up, 861 patients had a recurrent MI [cumulative incidence 9.6% (CI 8.8–10.4%)]. Fourteen recurrent MIs occurred into the setting of PCI and four occurred in the setting of coronary artery bypass surgery. The median time to recurrence was 136 days (quartiles 35–361 days) with an exponential decline in event rate over time (Figure 1). Baseline characteristics of patients who did or did not have a recurrent MI are shown in Table 1. Patients who developed a recurrent MI had a greater prevalence of known risk factors for ischaemic heart disease and a more severe index MI. Table 2 shows the cause-specific hazards for recurrent MI and all-cause death or recurrent MI. The strongest predictors of a new recurrent MI identified in multivariable

Table 2 Multivariable proportional hazards regression of baseline predictors of first recurrent myocardial infarction and all-cause death/first recurrent myocardial infarction

	Recurrent MI		Death/recurrent MI	
	HR	χ^2	HR	χ^2
No. of events	861		1918	
Age (per 10 years)	1.13 (1.04–1.22)	8	1.27 (1.21–1.34)	82
Female gender	0.81 (0.67–0.97)	5	0.87 (0.78–0.98)	6
Smoking	0.92 (0.77–1.10)	1	0.87 (0.78–0.98)	6
Systolic blood pressure (per 10 mmHg)	1.06 (1.00–1.12)	4	0.98 (0.95–1.02)	1
Diastolic blood pressure (per 10 mmHg)	0.90 (0.83–0.98)	6	0.99 (0.94–1.05)	0
BMI (kg/m ²)	0.99 (0.98–1.01)	1	0.99 (0.98–1.00)	3
eGFR (per 10 mL/min/1.73 m ²)	0.89 (0.85–0.93)	27	0.89 (0.86–0.91)	75
Medical history				
Heart failure	0.97 (0.74–1.27)	0	1.33 (1.15–1.55)	14
Dyslipidaemia	0.90 (0.74–1.09)	1	0.91 (0.80–1.02)	3
Diabetes	1.43 (1.20–1.70)	16	1.29 (1.16–1.44)	20
Hypertension	1.17 (0.99–1.39)	3	1.22 (1.10–1.36)	13
Unstable angina	1.51 (1.24–1.82)	17	1.16 (1.02–1.32)	5
Stable angina	1.16 (0.98–1.38)	3	1.15 (1.04–1.28)	7
Peripheral vascular disease	1.29 (1.01–1.65)	4	1.23 (1.05–1.44)	7
Qualifying myocardial infarction				
Anterior location	0.99 (0.85–1.15)	3	1.14 (1.03–1.26)	7
Q-wave	0.78 (0.65–0.92)	8	0.85 (0.76–0.95)	8
CK	0.97 (0.91–1.02)	1	1.01 (0.97–1.05)	0
Catherization without PCI/CABG	0.71 (0.52–0.97)	5	1.08 (0.91–1.28)	0
PCI	0.75 (0.62–0.92)	8	0.73 (0.64–0.84)	21
CABG	0.36 (0.16–0.80)	6	0.61 (0.41–0.92)	6
Thrombolysis	0.97 (0.82–1.16)	0	0.82 (0.73–0.92)	12
Worst Killip's class >1	1.16 (0.96–1.39)	2	1.25 (1.11–1.41)	13
Concomitant medication				
Aspirin	0.88 (0.68–1.13)	1	1.03 (0.88–1.22)	0
β -Blockade	0.98 (0.83–1.16)	0	0.75 (0.68–0.83)	30
Statin	0.97 (0.81–1.16)	0	0.89 (0.79–1.00)	4

Non-significant values in italics.

proportional hazards regression were lower eGFR, a history of unstable angina, diabetes, and increasing age. No variables had an opposite effect on the combined endpoint of all-cause death or recurrent MI but history of heart failure, anterior location of the index MI, no thrombolysis, Killip's class, β -blockade, and statin therapy were associated only with all-cause death or recurrent MI, whereas blood pressure and cardiac catheterization without PCI/CABG were associated with recurrent MI only. The predictive value of eGFR was unchanged when analyses were repeated without patients whose recurrent MI was diagnosed by troponin assays.

Of the patients who experienced a recurrent MI, 38.3% (CI 35.0–41.5%) died within a year. In contrast, 1-year mortality for

the entire cohort was 10.3% (CI 9.8–10.9%). Within 7 days of a recurrent MI, 20.5% (17.9–23.0%) of patients were dead. Patients who survived 7 days after a recurrent MI continued to be at increased risk of death compared with patients without a recurrent MI and the risk of death remained more than doubled a year after the recurrent MI (adjusted hazards ratio 2.4, 1.7–3.2), (Figure 2A). The effect of a recurrent MI on combined death or heart failure was similar to the effect on all-cause death alone (Figure 2B). Early mortality following recurrent MI (during the first month) depended on the time between index and recurrent MI, but there was no effect of the time to recurrence on mortality in the second month or later following recurrent MI (Figure 3).

Discussion

In high-risk survivors of a first MI on contemporary therapy, a recurrent MI increases the short- and long-term risk of death or development of heart failure. This increased risk initially decreases over time, but the risk of death remains more than doubled a year after the recurrent MI compared with patients without a recurrent MI. Time to recurrence is an important risk factor for mortality early after the recurrent MI but not for later mortality.

We have identified a number of factors that independently predict recurrent MI, many of which have been identified previously in smaller cohorts, including age, gender, blood pressure, diabetes, and history of unstable angina.^{1,2,11–14} Reduced renal function appears to be a particularly strong predictor of recurrent MI¹⁵ and constitutes a potential target for therapy aimed at reducing the risk of recurrent MI. Also, our results that peripheral vascular disease is predictive of cardiovascular outcomes are in line with recent data, showing an increased rate of cardiovascular events in patients with intermittent claudication.¹⁶

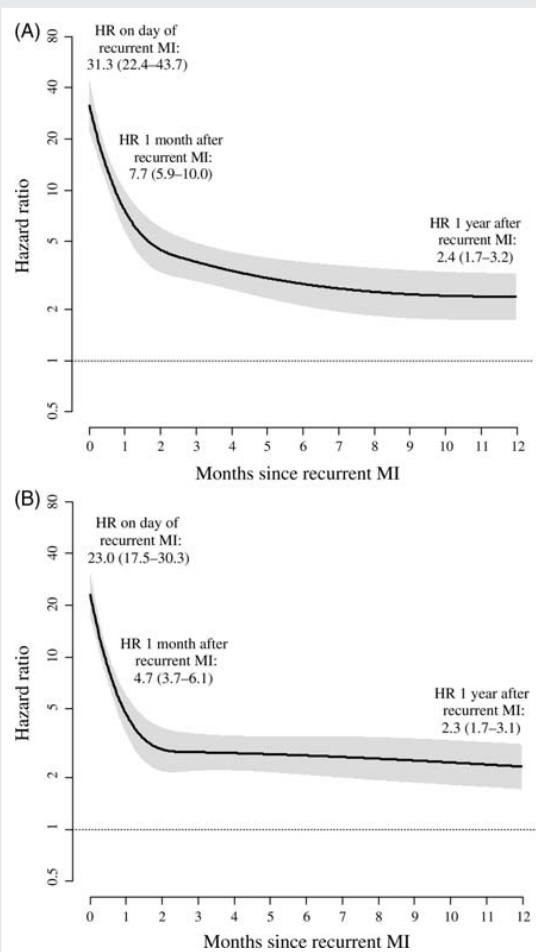


Figure 2 Effect of recurrent myocardial infarction on (A) mortality and (B) mortality or new heart failure; 95% confidence intervals in grey. Model adjusted for age, gender, systolic blood pressure, body mass index, estimated glomerular filtration rate, Killip's class > 1, history of diabetes, dyslipidaemia, hypertension, heart failure, stable angina, unstable angina, peripheral artery disease, anterior index myocardial infarction, Q-wave index myocardial infarction, peak creatine kinase, primary percutaneous coronary intervention, and thrombolysis.

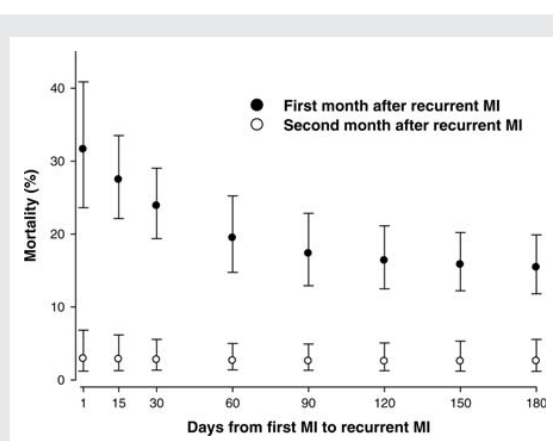


Figure 3 Mortality following recurrent myocardial infarction as a function of time to the recurrence; bars indicate 95% confidence intervals. Models adjusted for age. The figure illustrates how mortality in the first month following a recurrent myocardial infarction (filled circle) decreases with time elapsed between baseline and recurrent myocardial infarction as opposed to mortality later than the first 1 month after recurrent infarction (open circle) which is constant.

Given that a high proportion of patients with sudden cardiac death may have had an acute MI,¹⁰ we performed the analysis both by looking at recurrent MI alone and by using the combined endpoint of all-cause death or recurrent MI. History of heart failure, Killip's class, β -blockade, and the absence of reperfusion therapy were strongly associated with the risk of all-cause death or recurrent MI but not with recurrent MI alone.

There are several reasons to reaffirm the prognostic consequences of a recurrent MI in a contemporary setting. The absolute mortality following a recurrent MI has been declining over the past two decades.¹⁷ One previous report from the PAMI database of patients treated with primary angioplasty found that 2.1% (77 patients) developed a reinfarction within 1 month and this was associated with increased 6-month mortality.¹⁸ The introduction of new diagnostic criteria based on sensitive enzyme assays can result in the diagnosis of MI with smaller amounts of myocardial necrosis, which may tend to reduce the apparent mortality following a recurrent MI. In addition, current therapies, including aggressive early intervention, are associated with a decreased mortality following a recurrent MI as is the case for first MIs. Moreover, the effect of contemporary treatment on the incidence of recurrent MI itself remains unknown.^{19–21}

The present study confirms the negative prognostic impact of a recurrent MI in high-risk patients receiving contemporary therapy including inhibition of the renin–angiotensin system. The 1-year mortality following a recurrent MI was four-fold the 1-year mortality of the index MI. By allowing for the changing effect of a recurrent MI over time, we have demonstrated the very high initial relative risk of death with a gradual decline. Although the bulk of the increased risk disappeared a month following recurrence, patients who have survived a year since their recurrent MI remain at a substantially increased risk. In patients with a low-risk acute coronary syndrome, the effect of a recurrent MI similarly decreases over time.²² The impact of a recurrent MI on mortality is greatest for early recurrent MIs but the effect of time to recurrence is present only in the first month following the recurrent MI. If the patient survives the first month following a recurrent MI, the subsequent mortality does not depend on time between first and recurrent MI.

The present study is characterized by a number of strengths and limitations. The definition of recurrent MI was based on prospectively defined criteria using contemporary cardiac markers, and all recurrent MIs were centrally adjudicated by an independent committee. The settings of a large clinical trial allowed for a comprehensive collection of baseline data that could be included in a multivariable model. Nevertheless, data on the type of recurrent MI (ST-elevation vs. non-ST-elevation) or coronary anatomy were not systematically collected and left ventricular ejection fraction was not obtained for all patients. Also there was no clinical data available from the time of recurrent MI and statistical adjustment was hence performed with baseline variables. The 29% revascularization rate prior to randomization in VALIANT is likely to resemble contemporary practice as the 30-day revascularization rate following MI in the USA has increased only from 41% in 1999 to 47% in 2008.²³ The present analysis is based on a high-risk post-MI cohort and the results may not apply to all patients with a previous MI.

In conclusion, despite contemporary treatment, a recurrent MI confers a significantly increased risk of morbidity and mortality in patients with left ventricular dysfunction, heart failure, or both following a first MI. Even a year after a recurrent MI, the risk of death is more than doubled compared with patients without a recurrent MI. These data provide further evidence that aggressive post-MI intervention aimed at reducing risk factors in accordance with guidelines²⁴ may help reduce overall mortality by decreasing the risk of a recurrent MI.

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Conflict of interest: none declared

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