CARDIOVASCULAR MEDICINE

Long-term impact of multivessel disease on cause-specific mortality after ST elevation myocardial infarction treated with reperfusion therapy

R J van der Schaaf, J R Timmer, J P Ottervanger, J C A Hoorntje, M-J de Boer, H Suryapranata, F Zijlstra, J-H E Dambrink

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See end of article for authors' affiliations

Correspondence to:
Dr Jan-Henk E Dambrink,
Isala klinieken, locatie
Weezenlanden,
Department of Cardiology,
Groot Wezenland 20,
8011 JW Zwolle, The
Netherlands; v.r.c.derks@
isala.nl

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Objectives: To investigate the long-term impact of multivessel coronary artery disease (MVD) on cause-specific mortality in patients with ST elevation myocardial infarction (STEMI) treated with reperfusion therapy.

Methods and results: Patients with STEMI (n = 395) treated with primary angioplasty or thrombolysis in the setting of a randomised clinical trial were enrolled in the study. Follow up was 8 (2) years. For patients who died all available records were reviewed to assess the specific cause of death. MVD was present in 57% of patients. Patients with MVD were older and more of them had diabetes and previous myocardial infarction. Compared with the non-MVD group, residual left ventricular ejection fraction was lower (45.9% v 49.6%, p = 0.001) and total mortality was higher in patients with MVD (32% v 19%, p = 0.002). After adjustment for potential confounders this association was not significant (hazard ratio 1.4, 95% confidence interval (CI) 0.9 to 2.2). When the specific cause of death was considered, sudden death was comparable between patients with and without MVD (10% v 8%, p = 0.49) but death caused by heart failure was significantly higher in patients with MVD (hazard ratio 7.4, 95% CI 1.7 to 32.2).

Conclusion: Patients with STEMI and MVD have a higher long-term mortality than do patients with non-MVD. MVD is not an independent predictor of long-term total mortality or sudden death. However, MVD is a very strong and independent predictor of long-term death caused by heart failure.

The goal in ST elevation myocardial infarction (STEMI) is the restoration of antegrade perfusion in the infarct-related coronary artery, to preserve myocardial function and to improve survival.^{1,2} More than half of the patients presenting with STEMI have multivessel coronary artery disease (MVD) and their characteristics may differ from those of patients with single-vessel disease (non-MVD), as age and the frequency of diabetes, hypertension and previous myocardial infarction increase with the severity of disease.³ Patients with MVD treated with reperfusion therapy have a worse outcome than do patients without MVD. Left ventricular ejection fraction (LVEF) at discharge is lower and short-term mortality is higher.² Although patients with MVD have been reported to have acceptable in-hospital survival and long-term outcome after primary percutaneous coronary intervention (PCI), other studies have reported a clearly worse long-term prognosis in patients with MVD than in patients without MVD.⁴⁻⁹

It is unclear whether the potentially increased mortality is due to an increased incidence of sudden death or whether mortality is related to progressive heart failure.

To determine the association of MVD with long-term cause-specific mortality, we reviewed the data of 395 consecutive patients admitted with STEMI, all of whom were treated with reperfusion therapy by either thrombolysis or primary PCI.

METHODS

Between 1990 and 1995, 395 patients were enrolled in the Zwolle trial, in which primary PCI was compared with thrombolysis as reperfusion therapy for STEMI. Methods of this study have been described in detail.¹⁰ Briefly, patients with STEMI were randomly assigned to primary PCI or

thrombolysis. Patients were enrolled if they had no contraindications for thrombolytics, had symptoms of an acute myocardial infarction lasting longer than 30 min accompanied by an ECG with ST segment elevation of more than 1 mm (0.1 mV) in two or more contiguous leads and presented within 6 h, or between 6 and 24 h if there was evidence for continuing ischaemia.

Enzymatic infarct size was estimated by measurement of serial lactate dehydrogenase activity. Cumulative enzyme release from five to seven serial measurements up to 72 h after symptom onset was calculated.² Global LVEF was measured by equilibrium radionuclide ventriculography between days 4 and 10 after treatment.^{2,11} In the thrombolysis group, an initial conservative approach of watchful waiting after treatment was followed by elective coronary angiography. For this study MVD was defined as > 70% stenosis of the coronary luminal diameter in at least one of the non-infarct-related epicardial arteries. Additional revascularisation procedures were performed for all patients if indicated for symptoms or signs of myocardial ischaemia.¹²

Follow-up information was obtained in September 2000. All outpatients' reports were reviewed, and general practitioners were contacted by telephone. For patients who had sustained clinical events during follow up, hospital records were reviewed.

Cardiac causes of death were divided into three categories: heart failure, sudden death, and other. A cardiologist confirmed deaths from cardiovascular causes by examining medical records obtained from hospitals and attending

Abbreviations: HR, hazard ratio; LVEF, left ventricular ejection fraction; MVD, multivessel disease; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction

physicians or from attending general practitioners if the patients died at home.

Sudden cardiac death was defined as either witnessed or unwitnessed cardiac arrest without evidence of circulatory collapse, such as hypotension, exacerbation of congestive heart failure or altered mental status, before the disappearance of the pulse or abrupt collapse occurring within 1 h of the onset of the symptoms that resulted in death.¹³ Death caused by heart failure was defined as death due to clinical end-stage heart failure during hospital admission or to exacerbation of congestive heart failure reported by an attending general practitioner. For all deaths, no probable non-cardiac cause was suggested by the history or autopsy. Baseline characteristics, clinical data, angiographic data and outcomes were recorded prospectively on a dedicated database.

Statistical analysis

Statistical analyses were two tailed and performed with SPSS V.12.0 (SPSS Inc, Chicago, Illinois, USA). Differences between group means were tested by two-tailed Student's *t* test. Univariate predictors of total mortality were calculated with χ^2 statistics, with calculation of relative risks and exact 95% confidence intervals (CIs). Significance was defined as $p < 0.05$. Cumulative survival curves were constructed according to the Kaplan–Meier method and differences between the curves were tested for significance by the log rank statistic.¹⁴ The Cox proportional hazards regression model was used to estimate the hazard ratios (HRs) of clinical variables that were significantly different in univariate analysis.¹⁵ Age (≥ 60 years) and left ventricular function (LVEF $< 40\%$) were dichotomised for the multivariate analysis.

RESULTS

Patient characteristics

In the Zwolle trial 395 patients were enrolled. Angiographic data were not available for three patients. A total of 225 patients (57%) had MVD. Table 1 presents baseline patient characteristics. Patients with MVD were older and more of them had a previous myocardial infarction or diabetes, or both. More patients with than without MVD had symptoms of heart failure on admission. More patients with than without MVD were treated with PCI.

Infarct size and left ventricular function

Data on enzymatic infarct size were available for 93% of the patients and LVEF was measured in 96% of the patients. Although enzymatic infarct size was comparable between the two groups, residual LVEF was higher in patient without MVD (49.6 (9.4)%) than with MVD (45.9 (11.6)%).

Table 1 Baseline characteristics of patients with and without MVD in the Zwolle trial

	Non-MVD (n = 167)	MVD (n = 225)	p Value
Age (years)	58 (10)	61 (10)	0.001
Primary PCI	72 (43%)	121 (54%)	0.04
Men	134 (80%)	181 (80%)	0.96
Hypertension	24 (14%)	51 (23%)	0.05
Smoking	86 (51%)	91 (40%)	0.03
Diabetes	20 (12%)	54 (24%)	0.003
Previous CAD	16 (10%)	66 (30%)	<0.001
Anterior infarction	68 (41%)	82 (36%)	0.39
Killip class $\geq$ II	10 (6%)	39 (17%)	0.001

Data are mean (SD) or number (%).

CAD, coronary artery disease; MVD, multivessel disease; PCI, percutaneous coronary intervention.

Table 2 Enzymatic infarct size and residual LVEF in the Zwolle trial in patients with and without MVD

Infarct size	Non-MVD (n = 167)	MVD (n = 225)	p Value
LDH ₀₋₇₂	1018 (910)	1164 (1005)	0.16
LVEF (%)	49.6 (9.4)	45.9 (11.6)	0.001
LVEF $< 40\%$	18 (11%)	44 (21%)	0.01

Data are mean (SD) or number (%).

LDH₀₋₇₂, cumulative lactate dehydrogenase release to 72 h after symptom onset; LVEF, left ventricular ejection fraction; MVD, multivessel disease.

$p = 0.001$). More patients with than without MVD also had a reduced LVEF (21% *v* 11%, $p = 0.01$) (table 2).

Total and cause-specific mortality

The incidence of non-cardiac death was comparable in both groups. During follow up (8 (2) years) 104 (27%) patients died. In the MVD group 73 (32%) patients died compared with 31 (19%) patients in the non-MVD group ($p = 0.002$). Figure 1 shows long-term survival curves for patients with and without MVD.

Univariate predictors of death were older age ($p < 0.001$), diabetes ($p < 0.001$), previous coronary artery disease ($p = 0.01$), streptokinase compared with PCI ($p = 0.03$), anterior wall infarction ($p = 0.001$), Killip class $\geq$ II on admission ($p < 0.001$), and MVD ($p = 0.002$).

Sudden death was not significantly higher among patients with than without MVD (10% *v* 8%, $p = 0.49$). Death caused by heart failure was particularly higher in patients with than without MVD (11% *v* 1%, $p < 0.001$). Figure 2 shows the survival curve for mortality caused by heart failure. Table 3 shows total and cause-specific mortality.

Multivariate analysis

To study the independent prognostic value of MVD, multivariate analysis of age, sex and all clinical variables that were significantly differently distributed between patients with and without MVD in univariate analysis was performed.

After multivariate analysis independent predictors of long-term total mortality were Killip class $\geq$ II (HR 3.4, 95% CI 2.1 to 5.4), diabetes (HR 2.1, 95% CI 1.3 to 3.2), streptokinase compared with PCI (HR 2.0, 95% CI 1.4 to 3.1) and age ≥ 60 years (HR 1.1 per year, 95% CI 1.0 to 1.1) (table 4). MVD was

Figure 1 Overall mortality among patients without and with multivessel disease (MVD).

Figure 2 Mortality caused by heart failure among patients without and with multivessel disease (MVD).

not independently associated with increased long-term total mortality (HR 1.4, 95% CI 0.9 to 2.2).

Independent predictors of death caused by heart failure were Killip class $\geq$ II on admission (HR 7.6, 95% CI 3.2 to 17.9), MVD (HR 7.4, 95% CI 1.7 to 32.2), streptokinase compared with PCI (HR 5.6, 95% CI 2.2 to 14.2), and diabetes (HR 2.5, 95% CI 1.1 to 5.9).

DISCUSSION

We found that patients with MVD have a higher total mortality eight years after reperfusion therapy for acute myocardial infarction than patients without MVD. This study is the first to show that the higher mortality was mainly driven by death caused by heart failure during long-term follow up. In fact, MVD was not an independent predictor for total mortality but a very strong and independent predictor of death caused by heart failure. The incidence of sudden death was comparable between the patient groups.

Our results confirm previous studies reporting a higher long-term mortality in patients with STEMI and MVD than in patients without MVD, irrespective of type of reperfusion therapy.^{4-6 8 16 17}

As expected, there were several differences in baseline characteristics between patients with and without MVD. Patients with MVD were older and more of them had diabetes, a history of coronary artery disease and Killip class $\geq$ II on admission. These characteristics are related to more severe disease and are consistent with previous studies.^{3 6 9}

More patients with MVD had reduced residual LVEF and this strongly influenced survival. Interestingly, enzymatic infarct size was comparable between the groups, and therefore patients with MVD conceivably could have had a reduced LVEF before the index STEMI as a consequence of the more severe coronary artery disease. Also, residual myocardial ischaemia, which patients with MVD are more likely to have, may have resulted in non-contractile but viable myocardium in non-infarcted segments.¹⁸ Furthermore, patients with MVD have more impaired long-term recovery of LVEF than do patients without MVD. In MVD, therefore, not only is LVEF lower at discharge but also the subsequent improvement of LVEF is smaller.¹⁹ This probably leads to an even larger difference in LVEF between patients with and without MVD and may partly explain the large difference in mortality

Table 3 Total mortality and cause-specific mortality after 8 (2) years of follow up in the Zwolle trial

Cause of death	Non-MVD (n = 167)	MVD (n = 225)	p Value
All cause	31 (19%)	73 (32%)	0.002
Cardiac	18 (11%)	49 (22%)	0.01
Sudden death	13 (8%)	22 (10%)	0.49
Heart failure	2 (1%)	24 (11%)	<0.001
Other	3	3	

MVD, multivessel disease.

Table 4 Independent predictors of total and cause-specific mortality in the Zwolle trial

	HR	95% CI	p Value
Total mortality			
Killip class $\geq$ II	3.4	2.1 to 5.4	<0.001
Diabetes mellitus	2.1	1.3 to 3.2	0.001
Age $\geq$ 60 years	1.1	1.0 to 1.1	<0.001
Streptokinase v pPCI	2.0	1.4 to 3.1	0.001
MVD v non-MVD	1.4	0.9 to 2.2	0.11
Smoking	1.2	0.8 to 1.8	0.48
Previous CAD	1.2	0.7 to 1.9	0.49
Female sex	1.0	0.6 to 1.5	0.89
Mortality from heart failure			
Killip class $\geq$ II	7.6	3.2 to 17.9	<0.001
MVD v non-MVD	7.4	1.7 to 32.2	0.007
Streptokinase v pPCI	5.6	2.2 to 14.2	<0.001
Diabetes mellitus	2.5	1.1 to 5.9	0.03
Age $\geq$ 60 years	1.0	1.0 to 1.0	0.96
Smoking	0.5	0.2 to 1.3	0.16
Previous CAD	1.2	0.5 to 2.7	0.75
Female sex	1.3	0.5 to 3.4	0.54

CAD, coronary artery disease; HR, hazard ratio; MVD, multivessel disease; pPCI, primary percutaneous coronary intervention.

caused by heart failure. Moreover, patients with MVD are more prone to future coronary events and a subsequent additional decrease of left ventricular function.²⁰

Clinical implications

As heart failure appears to be the primary cause of long-term mortality in patients with MVD, most benefit is to be expected from interventions targeted towards prevention and treatment of heart failure. This may include treatment with angiotensin-converting enzyme inhibitors, β blockers and statins. Further studies on the possible benefit of additional revascularisation on LVEF and prognosis are clearly needed. As we did not find a relationship between long-term mortality due to sudden death and the presence of MVD, implantation of cardioverter-defibrillator devices may not benefit this patient group.

Lastly, as diabetes is associated with both diffuse coronary artery disease and a high prevalence of heart failure, patients with MVD should routinely have diagnostic tests to detect and treat diabetes.

Limitations

Our study enrolled only 395 patients from a single centre. The patients in our study were randomly assigned to balloon angioplasty or to thrombolysis (streptokinase). The use of intracoronary stents, glycoprotein IIb/IIIa inhibitors and other, more effective thrombolytic agents has improved the outcome of patients treated with reperfusion therapy for STEMI.^{21 22} These strategies probably would not have selectively improved the outcome of patients either without or with MVD. Another potential limitation of the study is the lack of detailed information on the use of drugs at discharge.

However, it is highly unlikely that a drug prescribed at discharge was continued without changes throughout the eight years of follow up, and thus drugs prescribed at discharge may not be a reliable predictor of mortality. The fact that MVD was not an independent predictor of total mortality may have been due to the sample size of the study, as other studies have shown its independent prognostic importance.

Conclusion

Patients with STEMI and MVD have a higher long-term mortality than those without MVD, which can be explained by a smaller LVEF and a high prevalence of associated risk factors in this group of patients.

MVD is a very strong and independent predictor of death caused by heart failure, but not sudden death, during long-term follow up. Studies to evaluate the effect of aggressive additional revascularisation are warranted.

Authors' affiliations

R J van der Schaaf, J R Timmer, J P Ottervanger, J C A Hoorntje, M-J de Boer, H Suryapranata, J-H E Dambrink, Department of Cardiology, Isala klinieken, locatie Weezenlanden, Zwolle, The Netherlands
F Zijlstra, Department of Cardiology, Thoraxcenter, University Medical Center, Groningen, The Netherlands

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