Clinical outcome in high-risk STEMI patients with multivessel disease: towards recanalization of CTOs following primary PCI
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Chapter 4

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

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Abstract

**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 thrombolytic therapy in the setting of a randomized clinical trial were included in the study. Follow-up was 8±2 years and in 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 often had diabetes and previous myocardial infarction. Compared with SVD residual left ventricular ejection fraction (LVEF) was lower (45.9% vs 49.6%, p=0.001) and total mortality was higher in patients with MVD (32 vs 19%, p=0.001). After adjusting for potential confounders this association was not statistically significant (HR 1.4; 95%CI 0.9 – 2.2). When the specific cause of death was considered, sudden death was comparable between patients with and without MVD (10% vs 8%, p=0.49), but death due to heart failure was significantly increased in patients with MVD (HR 7.4; 95%CI 1.7 – 32.2).

**Conclusion:** STEMI patients with MVD have a higher long-term mortality compared with patients with SVD. 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 due to heart failure.
Introduction

The aim 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. More than half of the patients presenting with STEMI have multivessel disease (MVD) and their characteristics may differ from patients with single vessel disease (SVD) as age, the frequency of diabetes, hypertension and previous myocardial infarction is increasing with the severity of disease. Patients with MVD treated with reperfusion therapy have a worse outcome compared with patients with SVD. Left ventricular ejection fraction (LVEF) at discharge is lower and short term mortality is increased. Although it has been reported that after primary percutaneous coronary intervention (PCI) patients with MVD have an acceptable in-hospital survival and long-term outcome, other studies have reported a clearly worse long-term prognosis in patients with MVD compared with patients with SVD.

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 treated with reperfusion therapy by either thrombolysis or primary PCI.

Methods

Between 1990 and 1995, 395 patients were included 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. Briefly, patients with STEMI were randomised to primary PCI or thrombolytic therapy. Patients were enrolled if they had no contraindications for thrombolytic therapy, had symptoms of an acute myocardial infarction lasting longer than 30 min, accompanied by an electrocardiogram 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 (LDH) activity. Cumulative enzyme release from 5 to 7 serial measurements up to 72 hours after symptom onset (LDH_{72}) was calculated. The global left ventricular ejection fraction (LVEF) was measured by equilibrium radionuclide ventriculography between days 4 and 10 after treatment. In the thrombolysis group, an initial conservative approach of watchful waiting after treatment was followed by elective coronary angiography. For the purpose of 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.
Follow-up information was obtained in September 2000. All outpatients' reports were reviewed, and general practitioners were contacted by phone. 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 physicians or from attending general practitioners if the patients died at home.

Sudden cardiac death was defined as either witnessed, or un-witnessed, 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 one hour of the onset of the symptoms that resulted in death.\textsuperscript{13} Death due to heart failure was defined as death due to clinically end-stage heart failure during hospital admission or by 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 in a dedicated database.

Statistical Analysis

Statistical analysis were two-tailed and performed using SPSS 12.0. Differences between group means were tested by two-tailed Student's t-test. Univariate predictors of total mortality were calculated with chi-square statistics, with calculation of relative risks and exact 95\% confidence intervals (CI). Statistical significance was defined as a p-value of less than 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.\textsuperscript{14} The Cox proportional-hazards regression model was used to estimate the hazard ratios (HR) of clinical variables that were significantly different in univariate analysis.\textsuperscript{15} Age (\(\geq 60\) years) and left ventricular function (LVEF < 40\%) were dichotomised for the purpose of the multivariate analysis.

Results

Patient characteristics

In the Zwolle trial 395 patients were included. Angiographic data were not available for 3 patients. A total of 225 patients (57\%) had MVD. Baseline patient characteristics are presented in table 1. Patients with MVD were older, more often had a previous myocardial infarction and/or diabetes. Patients with MVD more often had symptoms of heart failure on admission, compared with patients with SVD. They were more often treated with PCI than SVD patients.
Table 1 Baseline characteristics. Patients with and without multivessel disease in the Zwolle trial

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>SVD (n=167)</th>
<th>MVD (n=225)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>58 ± 10</td>
<td>61 ± 10</td>
<td>0.001</td>
</tr>
<tr>
<td>Primary PCI</td>
<td>72 (43%)</td>
<td>121 (54%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Male</td>
<td>134 (80%)</td>
<td>181 (80%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24 (14%)</td>
<td>51 (23%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Smoking</td>
<td>86 (51%)</td>
<td>91 (40%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20 (12%)</td>
<td>54 (24%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Previous CAD</td>
<td>16 (10%)</td>
<td>66 (30%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>68 (41%)</td>
<td>82 (36%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Killip class ≥ 2</td>
<td>10 (6%)</td>
<td>39 (17%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CAD=coronary artery disease; MVD=multivessel disease; PCI=percutaneous coronary intervention; SVD=single vessel disease.

Table 2 Enzymatic infarct size and residual left ventricular ejection fraction in the Zwolle trial Patients with and without MVD

<table>
<thead>
<tr>
<th>N=</th>
<th>SVD</th>
<th>MVD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct size</td>
<td>Mean LDHQ72 ± SD</td>
<td>1018 ± 910</td>
<td>1164 ±1005</td>
</tr>
<tr>
<td>LVEF % (± SD)</td>
<td>49.6 ± 9.4</td>
<td>45.9 ± 11.6</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF &lt; 40%</td>
<td>18 (11%)</td>
<td>44 (21%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

LDH=Lactate dehydrogenase; LVEF=left ventricular ejection fraction; MVD=multivessel disease; SVD=single vessel disease.

Infarct size and left ventricular function

Data on enzymatic infarct size were available in 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 with SVD (49.6 ± 9.4 %) compared with MVD patients (45.9 ± 11.6 %, p=0.001). Patients with MVD also more often had a reduced LVEF compared with patients with SVD (21% vs. 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) a total of 104 patients died (27%). In the MVD group 73 patients (32%) died versus 31 patients (19%) in the SVD group (p<0.001). Long-term survival curves in patients with and without MVD are shown in figure 1.

Univariate predictors of mortality were increased age (p<0.001), the presence of diabetes (p<0.001), previous coronary artery disease (p=0.01), streptokinase (SK) as
compared with PCI (p=0.03), anterior wall infarction (p=0.001), Killip class ≥ 2 on admission (p<0.001) and multivessel disease (p=0.002).

Sudden death was not significantly higher in patients with MVD compared with SVD patients (10% vs. 8%, p=0.49). Death due to heart failure was particularly higher in patients with MVD compared to those with SVD (11% vs. 1%, p<0.001). The survival curve with regard to mortality caused by heart failure is shown in figure 2. Total and cause-specific mortality is shown in table 3.

Figure 1 Overall Mortality in patients with and without multivessel disease

<table>
<thead>
<tr>
<th></th>
<th>SVD</th>
<th>MVD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause</td>
<td>31 (19%)</td>
<td>73 (32%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cardiac</td>
<td>18 (11%)</td>
<td>49 (22%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Sudden death</td>
<td>13 (8%)</td>
<td>22 (10%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>2 (1%)</td>
<td>24 (11%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

MVD=multivessel disease; SVD= single vessel disease.
Multivariate analysis

To study the independent prognostic value of MVD, multivariate analysis was performed including age, gender and all clinical variables that were significantly differently distributed between MVD en SVD patients in univariate analysis.

After multivariate analysis independent predictors of long-term total mortality were:

- Killip class ≥ 2 (HR 3.4; 95%CI: 2.1 – 5.4),
- diabetes (HR 2.1; 95%CI: 1.3 – 3.2),
- SK compared with PCI (HR 2.0; 95%CI: 1.4 – 3.1) and
- age ≥ 60 years (HR 1.1 per year; 95%CI: 1.0 – 1.1) (table 4). MVD was not independently associated with an increased long-term total mortality (HR 1.4; 95%CI: 0.9 – 2.2).

Independent predictors of death due to heart failure were:

- Killip class ≥ 2 on admission (HR 7.6; 95%CI: 3.2-17.9),
- MVD (HR 7.4; 95%CI: 1.7 – 32.2),
- SK compared with PCI (HR 5.6; 95%CI: 2.2 –14.2) and
- diabetes (HR 2.5; 95%CI: 1.1 – 5.9).

Discussion

We found that patients with MVD have a higher total mortality, 8 years after reperfusion therapy for acute myocardial infarction, compared with SVD patients. MVD was not an independent predictor for total mortality, but a very strong and independent predictor of
As expected, there were several differences in baseline characteristics between patients with and without MVD. Patients with MVD were older, had more often diabetes, had more often a history of coronary artery disease and presented more often with Killip class ≥ 2 on admission. These characteristics are related to more severe disease and consistent with previous studies.3, 6, 9

Residual LVEF was more often reduced in patients with MVD and this had a strong influence on survival. Interestingly, enzymatic infarct size was comparable between the groups, therefore it is conceivable that patients with MVD would have a preexistently reduced LVEF, before the index STEMI, as a consequence of the more severe coronary artery disease. Also, residual myocardial ischemia, which is likely to be more often present in patients with MVD, may have resulted in non-contractile but viable myocardium in non-infarcted segments.18 Furthermore, patients with MVD have impaired long-term recovery of LVEF compared with SVD. Therefore not only LVEF at discharge is lower but the subsequent improvement of LVEF is reduced in MVD.19 This probably leads to an even

<table>
<thead>
<tr>
<th>Total mortality</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Killip class ≥ 2</td>
<td>3.4</td>
<td>2.1 – 5.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>2.1</td>
<td>1.3 – 3.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>1.1</td>
<td>1.0 – 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SK*</td>
<td>2.0</td>
<td>1.4 – 3.1</td>
<td>0.001</td>
</tr>
<tr>
<td>MVD vs. SVD</td>
<td>1.4</td>
<td>0.9 – 2.2</td>
<td>0.11</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.2</td>
<td>0.8 – 1.8</td>
<td>0.48</td>
</tr>
<tr>
<td>Previous CAD</td>
<td>1.2</td>
<td>0.7 – 1.9</td>
<td>0.49</td>
</tr>
<tr>
<td>Female</td>
<td>1.0</td>
<td>0.6 – 1.5</td>
<td>0.89</td>
</tr>
</tbody>
</table>

| Mortality due to heart failure |
|-----------------|------|----------|---------|
| Killip class ≥ 2 | 7.6  | 3.2 – 17.9 | <0.001 |
| MVD vs. SVD | 7.4  | 1.7 – 32.2 | 0.007  |
| SK* | 5.6  | 2.2 – 14.2 | <0.001 |
| Diabetes Mellitus | 2.5  | 1.1 – 5.9 | 0.03   |
| Age ≥ 60 years | 1.0  | 1.0 – 1.0 | 0.96   |
| Smoking | 0.5  | 0.2 – 1.3 | 0.16   |
| Previous CAD | 1.2  | 0.5 – 2.7 | 0.75   |
| Female | 1.3  | 0.5 – 3.4 | 0.54   |

*as compared with primary PCI, CAD=coronary artery disease; CI=confidence interval; HR= hazard ratios; MVD=Multivessel disease; PCI=percutaneous coronary intervention; SK=Streptokinase; SVD=single vessel disease.
larger difference in LVEF in MVD versus SVD patients and may partly explain the large
difference in mortality due to heart failure. Moreover, patients with MVD are more prone
to future coronary events and subsequent additional decrease of LV function.\textsuperscript{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 pharmacological treatment with angiotensin-
converting enzyme inhibitors, $\beta$ blockers and statins. Further studies on the possible
benefit of additional revascularization in terms of LVEF and prognosis are clearly needed.
Since we did not find a relationship between long-term mortality due to sudden death
and the presence of MVD, there may be no benefit from implantation of cardioverter
defibrillator devices in this patient group.

Finally, diabetes is associated with both diffuse coronary artery disease and a high
prevalence of heart failure, diagnostic tests to detect and treat this disease should be
performed routinely in patients with MVD.

Limitations

Our study included only 395 patients from a single centre. The patients in our study were
randomized to balloon angioplasty or to thrombolytic therapy (streptokinase). Currently,
the use of intracoronary stents, glycoprotein IIB-IIIA inhibitors, and other, more effective
thrombolytic agents have improved outcome in patients treated with reperfusion therapy
for STEMI.\textsuperscript{21, 22} It is not likely that these strategies would have selectively improved
outcome in SVD or MVD patients only. Another potential limitation of the study is the lack
of detailed information on use of medication at discharge. However, it is highly unlikely
that medication prescribed at discharge was continued without changes throughout the
8 years of follow-up, and thus 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, since other studies have shown its independent prognostic
importance.

Conclusion

Patients with STEMI and MVD have a higher long-term mortality when compared to SVD,
which could be explained by a reduced LVEF and a high prevalence of associated risk
factors in this group of patients.

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


