Cardiogenic shock in acute myocardial infarction: clinical outcome and predictors

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The Impact of Multivessel Disease With and Without a Coexisting Chronic Total Occlusion on Short and Long Term Mortality in ST-elevation Myocardial Infarction Patients With and Without Cardiogenic Shock.

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ABSTRACT

AIMS
To evaluate the impact of multivessel disease (MVD) with and without a chronic total occlusion (CTO) on early and late mortality in ST-elevation myocardial infarction (STEMI) patients with and without cardiogenic shock (CS).

METHODS AND RESULTS
5018 STEMI patients were treated with primary percutaneous coronary intervention and stratified according to the presence of CS and the extent of coronary artery disease into single vessel disease (SVD), MVD without a CTO and MVD with a CTO. We performed a landmark mortality analysis up to 5-year follow-up with a landmark set at 30 days. In patients without CS (n=4409), only MVD with a CTO was an independent predictor for 30-day (HR:2.8,p<0.01) and 5-year mortality (HR:1.7,p<0.01), whereas MVD without a CTO was not associated with increased mortality. In CS patients (n=609), MVD with and without a CTO were independent predictors for 30-day mortality (HR:2.2,p<0.01, HR:1.8,<0.01). In 30-day CS survivors, only MVD with a CTO was associated with a trend towards increased mortality (HR:1.7,p=0.06).

CONCLUSION
In non-CS STEMI patients with MVD, the presence of a coexisting CTO in a non-IRA drives early and late mortality. In patients with CS, MVD with and without a CTO were predictors for short term mortality.
INTRODUCTION

Angiography in the setting of primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) exposes the extent and severity of coronary artery disease. Around half of these patients suffer from multivessel disease (MVD). Patients with MVD have a worse prognosis compared to patients with single vessel disease (SVD). The clinical management of these non-culprit lesions remains debatable as robust evidence on MVD management in the setting of primary PCI for STEMI is lacking. Moreover, no clear beneficial effect has been shown in patients treated with multivessel PCI compared to culprit lesion PCI only. As a result, additional PCI for STEMI patients without cardiogenic shock (CS) is not recommended in the current ACC/AHA guidelines (class III). For hemodynamically compromised patients, the guidelines state that if the stenotic artery perfuses a large area of myocardium and the procedure can be done efficiently, complete revascularization may improve long term prognosis.

Recently our research group has shown that the prognostic value of MVD is almost completely driven by the presence of a chronic total occlusion (CTO) in a non-infarct related artery (IRA). This novel concept has been confirmed in other STEMI datasets. For patients presenting in CS, the impact of MVD with and without a coexisting CTO is less clear. In a subgroup of CS patients, we reported that MVD with a coexisting CTO was an independent predictor for 1-year cumulative mortality, while MVD without a CTO was borderline non significant. These results were limited by a small sample size, especially with respect to CS patients.

In the present study, we sought to investigate an even longer follow-up time point and to assess the prognostic importance of MVD with or without a CTO in patients with STEMI according to the presence or absence of CS at time of index myocardial infarction. Prognosis was assessed with respect to left ventricular ejection fraction (LVEF) as well as crude mortality at follow-up. In order to distinguish early events, we performed a landmark mortality analysis at the 30 day time-point with a total follow-up period to 5 years.

METHODS

From January 1997 through December 2008, a total of 5307 consecutive and unselected STEMI patients treated with primary PCI in our hospital were entered in a
dedicated database. Acute STEMI was diagnosed when patients had symptoms of an acute myocardial infarction lasting 30 minutes to 12 hours, accompanied by an electrocardiogram with ST-segment elevation >1 mm (0.1 mV) in ≥ 2 contiguous leads. Patients were immediately transported to the cardiac catheterization laboratory and underwent coronary angiography with a view to perform primary PCI. PCI was performed by standard techniques, if the coronary anatomy was suitable. In our institution we only perform culprit lesion PCI, with only a rare exceptions for patients with CS.

Prior to PCI, all patients were treated with heparin (5000 IU) and aspirin (500 mg). Adjunctive treatment with glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. Post PCI ticlopidine or clopidogrel was prescribed according to the guidelines. Duplicate patients due to recurrent STEMI (n=192), patients with missing admission hemodynamic status (n=68) and patients lost to follow-up (n=29) were excluded, resulting in a final cohort of 5018 patients.

The final STEMI cohort was divided into patients with and without cardiogenic shock. Subsequently, all patients were stratified into three groups: patients with SVD, MVD without a CTO, and MVD with a coexisting CTO.

DATA COLLECTION
Baseline characteristics, including demographic, clinical presentation and angiographic data, and hospital procedures were collected prospectively in the abovementioned dedicated database. Information on vital status was obtained from the Dutch national population registry (Statistics Netherlands, Voorburg, the Netherlands) per February 9, 2011. Patient data were checked for inconsistency and completeness. In case of conflicting or missing data outpatient files were reviewed and/or general practitioners were contacted by telephone.

DEFINITIONS
Multivessel disease was defined as at least 1 stenosis ≥ 70% in a non-infarct related epicardial artery or a stenosis ≥ 50% in the left main coronary artery. A CTO was defined as a 100% luminal narrowing in a non-IRA before PCI without antegrade flow or with antegrade or retrograde filling through collateral vessels. The degree of stenosis was determined by the operator by visual assessment of the diameter on
angiography. Cardiogenic shock state was determined by the attending operator guided by a definition similar to the SHOCK trial, i.e. a systolic blood pressure persistently < 90 mm Hg or vasopressors required to maintain blood pressure > 90 mm Hg, evidence of end organ hypoperfusion (e.g. urine output < 30 ml or cold/diaphoretic extremities or altered mental status), and evidence of elevated filling pressures. In addition shock was considered present when an intra aortic balloon pump (IABP) or other circulatory support device was inserted for hemodynamic instability.

**LEFT VENTRICULAR FUNCTION**

The left ventricular ejection fraction (LVEF) was assessed by global visual estimation on echocardiography. Baseline LVEF was assessed within 10 days after the index event. The LVEF was dichotomized as either > 40% or ≤ 40%.

**PRIMARY OUTCOME**

The primary outcome for the present analysis was all-cause 30-day and five-year mortality in 30-day survivors in patients with and without CS. The secondary outcome was left ventricular ejection fraction (LVEF) after STEMI in patients with and without CS.

**STATISTICAL ANALYSIS**

Cumulative event-rates of all-cause death were estimated using the Kaplan-Meier method and compared using the Log Rank statistic. Follow-up for mortality was censored at the date of last follow-up by checking vital status in the Dutch population registry, or at five years, whichever came first. We performed a ‘landmark mortality analysis’ with a landmark set at 30 days, in patients with and without cardiogenic shock. Hazard ratios for all-cause mortality were calculated using time extended Cox proportional hazard regression analyses after verification of the proportional hazards assumption. The multivariable model was built by stepwise backward variable selection with entry and exit criteria set at the p = 0.1 level. The following variables were included into the model: male gender, age (continuous), diabetes mellitus, hypertension, positive family history of cardiovascular disease, current smoking, hypercholesterolemia, previous myocardial infarction (MI), cardiogenic shock, left anterior descending (LAD) coronary artery-related MI, MVD without a
## TABLE 1 Baseline Clinical, Angiographic and Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total N=5018</th>
<th>Non Shock n=4409 (87.9%)</th>
<th>Shock n=609 (12.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SVD n=3199</td>
<td>MVD n=1153</td>
<td>CTO n=666 value</td>
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<tr>
<td>Male (%)</td>
<td>70.5</td>
<td>71.1</td>
<td>63.5</td>
</tr>
<tr>
<td>Age in years (median, IQR)</td>
<td>59 (50-69)</td>
<td>58 (49-69)</td>
<td>61 (52-71)</td>
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<tr>
<td>Hypertension (%)</td>
<td>28.7</td>
<td>29.0</td>
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<td>Smoker (%)</td>
<td>47.6</td>
<td>48.8</td>
<td>34.2</td>
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<td>Hypercholesterolemia (%)</td>
<td>21.2</td>
<td>22.0</td>
<td>12.6</td>
</tr>
<tr>
<td>Family history of CVD (%)</td>
<td>41.0</td>
<td>42.6</td>
<td>23.1</td>
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<td>Previous MI (%)</td>
<td>8.1</td>
<td>8.0</td>
<td>8.8</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>8.9</td>
<td>9.0</td>
<td>8.1</td>
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### ANGIOGRAPHIC CHARACTERISTICS

<table>
<thead>
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<th>Total N=5018</th>
<th>Non Shock n=4409 (87.9%)</th>
<th>Shock n=609 (12.1%)</th>
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<tr>
<td>LAD related MI (%)</td>
<td>46.8</td>
<td>45.7</td>
<td>59.6</td>
</tr>
<tr>
<td>Pre-Procedural TIMI flow grade 3 (%)</td>
<td>17.8</td>
<td>18.4</td>
<td>10.8</td>
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<tr>
<td>Post-Procedural TIMI flow grade 3 (%)</td>
<td>87.1</td>
<td>88.3</td>
<td>73.5</td>
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### PROCEDURAL CHARACTERISTICS

<table>
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<th>Total N=5018</th>
<th>Non Shock n=4409 (87.9%)</th>
<th>Shock n=609 (12.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosisation (%)</td>
<td>33.7</td>
<td>33.6</td>
<td>34.6</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitor used (%)</td>
<td>26.5</td>
<td>25.5</td>
<td>38.5</td>
</tr>
<tr>
<td>Stent placement (%)</td>
<td>78.9</td>
<td>78.8</td>
<td>80.4</td>
</tr>
</tbody>
</table>

Abbreviations: CTO=chronic total occlusion, CVD=cardiovascular disease, IQR=inter-quartile range, MI=myocardial infarction, MVD=multivessel disease, LAD=left anterior descending coronary artery, TIMI=thrombolysis in myocardial infarction.
CTO, MVD with a coexisting CTO, pre-procedural thrombolysis in myocardial infarction (TIMI) flow grade 3. Interaction terms between cardiogenic shock and the extent of the coronary artery disease with respect to the outcome variable all-cause mortality was tested by using the likelihood ratio statistic. Discrete variables were summarized as frequencies and percentages. Differences in baseline characteristics and left ventricular function between the groups were tested for significance by the $\chi^2$ test. Skewed-distributed continuous variables were compared with the Kruskal-Wallis test. Statistical significance was defined as a p-value <0.05.

**RESULTS**

**BASELINE CHARACTERISTICS**
Between January 1997 and December 2008, 5018 STEMI patients were treated with primary PCI. A total of 4409 (88%) STEMI patients presented without CS and 609 patients (12%) presented with CS. Of the total cohort, 3199 (64%) had SVD, 1153 (23%) had MVD without CTO and 666 (13%) had MVD with a coexisting CTO in a non-IRA. Of the non-CS STEMI patients, 2939 (67%) had SVD, 978 (22%) had MVD without CTO and 492 (11%) had MVD with a coexisting CTO in a non-IRA. Of the 609 patients with CS, 260 (43%) had SVD, 175 (29%) had MVD without a CTO; and 174 (29%) had MVD with a coexisting CTO in a non-IRA. Table 1 shows baseline clinical angiographic and procedural characteristics.

In the total cohort and non-CS cohort, patients with MVD (with and without a CTO) were older, had a higher prevalence of hypertension and diabetes, whereas they had a lower incidence of current smoking. The prevalence of hypercholesterolemia and a previous MI increased with the extent of coronary artery disease. In the CS cohort, MVD patients with a coexisting CTO in a non-IRA were older and had a higher prevalence of hypercholesterolemia and diabetes. The prevalence of a previous MI increased with the extent of coronary artery disease. Patients with SVD more frequently suffered from a LAD-related MI.

**MORTALITY IN ALL PATIENTS**
Median follow-up duration was 3.3 years (IQR:2.0-5.0 years). Figure 1A shows the Kaplan-Meier estimates for mortality for the three categories at 30 days and for the
# Table 2: Predictors of Mortality in STEMI patients treated with primary PCI.

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td><strong>Total cohort (n = 4658) Event rate = 15.3% (n = 766)</strong></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Time: 0-30 days</strong></td>
<td></td>
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<tr>
<td>MVD with CTO vs. SVD</td>
<td>4.8</td>
<td>3.8-6.1</td>
<td>&lt;0.01</td>
<td>2.7</td>
<td>2.1-3.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MVD without CTO vs. SVD</td>
<td>2.1</td>
<td>1.7-2.7</td>
<td>&lt;0.01</td>
<td>1.5</td>
<td>1.1-1.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Time: 30 days – 5 years</strong></td>
<td></td>
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<tr>
<td>MVD with CTO vs. SVD</td>
<td>2.3</td>
<td>1.8-3.0</td>
<td>&lt;0.01</td>
<td>1.4</td>
<td>1.1-1.8</td>
<td>0.02</td>
</tr>
<tr>
<td>MVD without CTO vs. SVD</td>
<td>1.4</td>
<td>1.1-1.7</td>
<td>0.01</td>
<td>1.0</td>
<td>0.8-1.3</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Non shock cohort (n = 4092) Event rate = 11.1% (n = 489)</strong></td>
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<td><strong>Time: 0-30 days</strong></td>
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<tr>
<td>MVD with CTO vs. SVD</td>
<td>3.8</td>
<td>2.7-5.3</td>
<td>&lt;0.01</td>
<td>2.8</td>
<td>1.9-4.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MVD without CTO vs. SVD</td>
<td>1.4</td>
<td>1.0-2.1</td>
<td>0.05</td>
<td>1.0</td>
<td>0.7-1.5</td>
<td>0.95</td>
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<tr>
<td><strong>Time: 30 days – 5 years</strong></td>
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<tr>
<td>MVD with CTO vs. SVD</td>
<td>2.2</td>
<td>1.7-3.0</td>
<td>&lt;0.01</td>
<td>1.7</td>
<td>1.2-2.3</td>
<td>&lt;0.01</td>
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<tr>
<td>MVD without CTO vs. SVD</td>
<td>1.4</td>
<td>1.1-1.7</td>
<td>0.02</td>
<td>1.0</td>
<td>0.8-1.3</td>
<td>0.98</td>
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<tr>
<td><strong>Shock cohort (n = 566) Event rate = 45.5% (n = 277)</strong></td>
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<tr>
<td><strong>Time: 0-30 days</strong></td>
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<tr>
<td>MVD with CTO vs. SVD</td>
<td>2.3</td>
<td>1.7-3.2</td>
<td>&lt;0.01</td>
<td>2.2</td>
<td>1.6-3.2</td>
<td>&lt;0.01</td>
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<tr>
<td>MVD without CTO vs. SVD</td>
<td>1.8</td>
<td>1.3-2.5</td>
<td>&lt;0.01</td>
<td>1.8</td>
<td>1.2-2.5</td>
<td>&lt;0.01</td>
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<tr>
<td><strong>Time: 30 days – 5 years</strong></td>
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<tr>
<td>MVD with CTO vs. SVD</td>
<td>1.8</td>
<td>1.3-3.0</td>
<td>0.04</td>
<td>1.7</td>
<td>1.0-3.0</td>
<td>0.06</td>
</tr>
<tr>
<td>MVD without CTO vs. SVD</td>
<td>1.1</td>
<td>0.6-2.1</td>
<td>0.66</td>
<td>1.1</td>
<td>0.6-2.0</td>
<td>0.83</td>
</tr>
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</table>

*adjusted for: age (continuous), hypercholesterolemia, left anterior descending coronary artery related myocardial infarction, positive family history of CVD, previous myocardial infarction and shock.

Multivariable model was built by stepwise backward variable selection with entry and exit criteria set at the p = 0.1 level. All variables known before percutaneous coronary intervention were included in the initial analysis.

Abbreviations: CTO=chronic total occlusion, CVD=cardiovascular disease, LAD=left anterior descending, MVD=multivessel disease, PCI=percutaneous coronary intervention, STEMI=ST-elevation myocardial infarction, SVD=single vessel disease and TIMI=thrombolysis in myocardial infarction.
FIGURE 1A
Landmark survival analysis in the total cohort

FIGURE 1B
Landmark survival analysis in patients without shock

FIGURE 1C
Landmark survival analysis in patients with shock

FIGURE 1 Landmark mortality analysis: risk of death during the first 30 days after primary PCI and thereafter in 30-day survivors for patients with SVD, MVD without a CTO or with a CTO. Abbreviations: CTO=chronic total occlusion, MVD=multivessel disease, PCI=percutaneous coronary intervention, SVD=single vessel disease.
period thereafter until 5 years in 30-day survivors. At 30 days, the Kaplan-Meier estimates for mortality increased per extent of the coronary artery disease with the highest mortality in the MVD group with a coexisting CTO. In 30-day survivors, the Kaplan-Meier estimates for 5-year mortality were comparable between SVD and MVD without a CTO whereas the mortality in the group MVD with a CTO was approximately 2 times higher in comparison to the SVD group.

After multivariate adjustment MVD with and without a coexisting CTO in a non-IRA were predictors for 30-day mortality in comparison to SVD (HR:2.7, 95% CI:2.1-3.4, p<0.01; event rates: 21.3% vs. 4.8% and HR:1.5, 95% CI:1.1-1.9, p<0.01; event rates: 10% vs 4.8%, respectively; TABLE 2). In 30-day survivors, MVD with a coexisting CTO was a significant predictor for 5-year mortality in comparison to SVD (HR:1.4, 95% CI:1.1-1.8, p=0.02; event rates: 16.6% vs. 7.5%) in contrast to MVD without a CTO (HR:1.0, 95% CI:0.8-1.3, p=0.93; event rates: 9.9% vs. 7.5%). There was a significant interaction between shock and multivessel disease with and without a CTO for mortality within 30 days but not for the period thereafter.

Mortality in patients without shock. Median follow-up duration was 3.5 years (IQR:2.1-5.0 years). The 30-day mortality and 5-year mortality in 30-day survivors in patients with MVD with a coexisting CTO was significantly higher in comparison to MVD patients without a CTO and SVD patients (FIGURE 1B). In both time periods, the mortality between MVD without a CTO and SVD was comparable.

After multivariate adjustment, MVD with a coexisting CTO was associated with 30-day (HR:2.8, 95% CI:1.9-4.0, p<0.01; event rates:11.0% vs. 3.0%) and 5-year mortality in 30-day survivors (HR:1.7, 95% CI:1.2-2.3, p<0.01; event rates:14.4% vs. 6.9%) whereas MVD without a CTO was not a predictor for early (HR:1.0, 95% CI:0.7-1.5, p=0.95; event rates: 4.3% vs 3.0%) or late mortality (HR:1.0, 95% CI:0.8-1.3, p=0.98; event rates: 9.2% vs. 6.9%, respectively; TABLE 2).

**MORTALITY IN PATIENTS WITH SHOCK**

Median follow-up duration was 2.3 years (IQR:0-4.8 years). At 30 days, the Kaplan-Meier estimates for mortality increased per extent of the coronary artery disease with the highest mortality in the MVD group with a coexisting CTO (FIGURE 1C). At 5 years, with exclusion of those who died in the first 30 days, Kaplan-Meier estimates of mortality between patients with SVD and MVD without a CTO were com-
parable throughout the entire follow-up period whereas the Kaplan-Meier estimates of mortality for the MVD group with a coexisting CTO was much higher. **FIGURE 1C** indicates a probably strong association with mortality at 3 years, which fades by 5 years as the number at risk drops.

MVD with and without a CTO were both significantly associated with 30-day mortality (HR:2.2, 95% CI:1.6-3.2, p<0.01; event rates: 50.6% vs. 25.4% and HR:1.8, 95% CI:1.2-2.5, p<0.01; event rates: 41.7% vs. 25.4%, respectively) however were not significantly associated with 5-year mortality in 30-day survivors (HR:1.7, 95% CI:1.0-3.0, p=0.06; event rates: 27.9% vs. 15.5% and HR:1.1, 95% CI:0.6-2.0, p=0.83; event rates: 16.7% vs 15.5%, respectively; **TABLE 2**).

**LEFT VENTRICULAR FUNCTION**

Of the 5018 STEMI patients, echocardiography within 10 days was present in 32%, nonCS cohort: n=1428 with a median time to echo of 3 days (IQR: 2-4) and CS-cohort: n=177 with a median time to echo of 3 days (IQR: 1-6). The proportion of
non CS patients with a LVEF $\leq 40\%$ was 15% for SVD, 14% for MVD without a CTO and 23% for MVD with a CTO, Figure 2A. The proportion of CS patients with a LVEF $\leq 40\%$ was 24% for SVD, 44% for MVD without a CTO and 42% for MVD with a CTO, Figure 2B. In patients without CS, MVD with a coexisting CTO was more often associated with LVEF $\leq 40\%$ in comparison to patients with MVD without a CTO or SVD whereas in patients with CS, MVD with and without a CTO were both more often associated with LVEF $\leq 40\%$ in comparison to patients with SVD, Figure 2A and B).

To investigate whether the long inclusion period could potentially introduce bias to our results due to changes in both medical and interventional therapies, we divided the cohort into two time periods: 1997-2002 and 2003-2008. The hazard ratios seen in these two time periods were comparable for the total and the non-CS cohort, except for late mortality in the CS cohort where the presence of MVD with a coexisting CTO seems to have a larger effect on mortality between 2003-2008 in comparison to 1997-2002. However, the event rate for late mortality in 30-day survivors is too low to explore a reliable association. In each cohort, time was not a significant confounder as the addition of time to the multivariate model had no important influence on the hazard ratios of MVD with and without a CTO.

**DISCUSSION**

The present analyses show that in STEMI patients without cardiogenic shock, MVD is only associated with short- and long-term mortality when a coexisting CTO is present. In these non shock patients, only MVD with a coexisting CTO was associated with a reduced LVEF after STEMI in comparison to MVD without a CTO and SVD. In patients with cardiogenic shock, MVD with and without a coexisting CTO were both associated with 30-day mortality. However, both variables lost its predictive value in 30-day survivors up to 5 years of follow-up in comparison to SVD, although for MVD with a CTO, the association was only borderline non significant. Finally, in the shock cohort, MVD with and without a coexisting CTO were associated with a reduced LVEF after STEMI in comparison to SVD patients which is different from patients without CS.

This analysis is of additional value to our previous reports, in a smaller STEMI patient cohort, concerning the impact of MVD with and without a CTO. Our pre-
vious studies led us to the hypothesis that MVD with and without a CTO might have a different impact on short and long term mortality when stratified by hemodynamic instability. It is likely that the important increase of our study cohort has better revealed the impact of MVD with and without a CTO in CS STEMI patients, as in the present analysis MVD with and without a coexisting CTO are both important predictors for short term mortality. However, in 30-day survivors, MVD without a CTO lost its predictive value on long-term mortality. After multivariate analysis, the presence of a CTO showed a trend towards increased late mortality. Due to the high 30-day mortality rate (50%), a filtering effect potentially reduces power to detect a significant difference for late mortality.

The impact of MVD with a concurrent CTO in STEMI patients have been confirmed in several other registries and sub-analysis of randomized trials.\(^9\)\(^,\)\(^10\)\(^,\)\(^12\)\(^,\)\(^16\) Besides our research group, only one paper performed a landmark analysis with a landmark set on 30 days.\(^12\) The presence of a CTO was an independent predictor for early and late mortality, whereas MVD without a CTO was borderline significant for early mortality with a p-value of 0.0495. In this trial cardiogenic shock was not an exclusion criterion however the percentage of included CS patients was low, possibly explaining the borderline effect of MVD without a CTO in the total cohort. To our knowledge, the current paper is the first to report on the effect in CS and non-CS STEMI patients. The impact of MVD with and without a coexisting CTO on early and late mortality could be due to reduced LVEF after STEMI. In patients without CS, the LVEF was significantly lower in the MVD group with a coexisting CTO in comparison to the MVD without a CTO and the SVD group. When a CTO is present, the underlying myocardium is perfused through collateral circulation which can be endangered when the donor artery is blocked in case of STEMI. The area at risk would then be much larger resulting in an extent of final infarct size.

In patients with CS, MVD with and without a CTO were associated with reduced LVEF compared with SVD. CS patients have reduced cardiac output and coronary blood flow which may increase the functional importance of non occlusive MVD lesions, resulting in myocardial ischemia in other perfusion areas than that of the culprit lesion. Interestingly, in non-CS patients only MVD with a coexisting CTO was associated with reduced LVEF.

The current study identified the presence of a CTO as a unique marker for worse
short term prognosis in non shock patients and identified MVD with and without a CTO as markers for worse short term prognosis in shock patients. These markers may be a target for additional revascularization in the sub acute STEMI phase. Current ACC/AHA guidelines on primary PCI for STEMI state that in hemodynamic stable STEMI patients only culprit lesion PCI should be performed and that PCI of non-infarct lesions is not recommended (class III, level of evidence C). This recommendation was recently confirmed by several meta-analyses.4, 5 However, revascularization of non-culprit lesions could be beneficial in patients who are hemodynamically compromised.6 The recommendation for additional revascularization in CS patients is derived from the SHOCK trial that aimed for complete revascularization.7 Our data show that MVD with and without a CTO are both predictors for mortality in CS patients. As mentioned, additional PCI for MVD in non-CS patients is not recommended and in our report its impact is clearly driven by the presence of a CTO. However, large randomized controlled trials are needed to evaluate the possible beneficial effect of CTO revascularization in STEMI patients without CS and complete revascularization in STEMI patients with CS. Therefore we initiated a global multicenter randomized controlled trial in non-CS STEMI patients, to investigate a possible beneficial effect of opening a CTO in a non-IRA in a staged PCI procedure within one week after STEMI on LVEF and left ventricular dimensions: the EXPLORE (Evaluating XIENCE V and LVF in PCI on Occlusions after STEMI) trial.17 CTO revascularization during the primary procedure is not feasible as its success depends largely on the operator’s skills, lengthens the procedure considerably with also increased use of contrast media and fluoroscopy time. Therefore, we scheduled the procedure in the semi-acute phase.

In the elective setting, only observational data is available comparing successful versus unsuccessful PCI of CTO. Successful PCI of CTO is associated with improved quality of life, LVF and survival.18-21 Another suggested theoretical benefit of CTO revascularization in the elective setting is the protective effect during future events by providing collateral circulation to the IRA. The EXPLORE trial will also address this hypothesis.17

LIMITATIONS
Several limitations of the present study should be mentioned. The study concerns a
single center study, reflecting local skills and practice. Therefore the results cannot be extrapolated to other centers. Nevertheless, several other studies have observed the same impact of CTO in STEMI patients in general. Non-culprit lesion stenosis severity was assessed at the infarct angiography in the acute setting and by the performing cardiologist. Therefore, some overestimation of non-culprit lesions might have occurred. Furthermore, detailed information about the medical treatment and revascularization of non-culprit lesions during the follow-up period was not available. Also, during this time period, no information was available on kidney function or history of heart failure and therefore could not be corrected for during multivariate adjustment. In addition, the LVEF was not routinely assessed during admission and therefore information about LVEF was not available in all patients. Information about time of symptom onset to treatment was not available in all patients and could therefore not be included in the analyses. However, no differences were observed in that proportion of the patients for which time to treatment data were available.

**CONCLUSION**

In non-CS STEMI patients with MVD, the presence of a coexisting CTO in a non-IRA drives early and late mortality. In patients with CS, MVD with and without a CTO were predictors for short term mortality.
REFERENCES


17 van der Schaaf RJ, Claessen BE, Hoebers LP, et al. Rationale and design of EXPLORE: a randomized, prospective, multicenter trial investigating the impact of recanalization of a chronic total occlusion on left ventricular function in patients after primary percutaneous coronary intervention for acute ST-elevation myocardial infarction. Trials 2010;11.


