Prognostic factors in primary and elective percutaneous coronary intervention
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Impact of a Chronic Total Occlusion in a Non-Infarct Related Artery on Long-Term Mortality in Patients With Diabetes Mellitus After ST Elevation Myocardial Infarction

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ABSTRACT

**Background:** Recently, a chronic total occlusion (CTO) in a non-infarct-related artery (IRA), and not multivessel disease (MVD) alone was identified as an independent predictor of mortality after ST elevation myocardial infarction (STEMI). Patients with diabetes mellitus (DM) constitute a patient group with a high prevalence of MVD and high mortality after STEMI. We studied the prevalence of a CTO in a non-IRA and its impact on long-term mortality in STEMI patients with DM.

**Methods:** Between 1997 and 2007, we admitted 4506 patients with STEMI treated with primary PCI. Patients with DM were identified. We categorized patients as having single vessel disease (SVD), MVD without CTO and CTO based on the angiogram before PCI.

**Results:** A total of 539 patients (12%) had DM. Multivessel disease with or without a CTO was present in 33% of nondiabetic patients and in 51% of diabetic patients. The prevalence of a CTO in a non-IRA was 21% in STEMI patients with DM compared to 12% in STEMI patients without DM (p<0.01). Kaplan-Meier estimates for 5-year mortality in STEMI patients with DM were 25%, 21% and 47% in patients with SVD, MVD without a CTO and MVD with a CTO in a non-IRA, respectively. A CTO in a non-IRA was an independent predictor of 5-year mortality (Hazard ratio 2.2, 95% confidence interval 1.3-3.5, p<0.01).

**Conclusion:** The prevalence of a CTO in a non-IRA was increased in STEMI patients with DM. The presence of a CTO in a non-IRA was a strong and independent predictor of 5-year mortality. These results suggest that particularly in the high-risk subgroup of STEMI patients with DM, MVD has prognostic implications only if a concurrent CTO is present.
INTRODUCTION

Patients with diabetes mellitus (DM) constitute a patient group with a high prevalence of multivessel disease (MVD) and high mortality after ST elevation myocardial infarction (STEMI). Approximately 35-45% of non-diabetic STEMI patients have MVD compared with 60-70% of patients with DM. The higher mortality of STEMI patients with DM has been suggested to be, at least partly, due to the greater extent of coronary artery disease.(1-3)

Recently, the presence of a chronic total occlusion (CTO) in a non-infarct-related artery (IRA), and not MVD alone, was reported to be an independent predictor of mortality after STEMI.(4-6) Given the greater extent of coronary artery disease in diabetic STEMI patients, we hypothesized that the prevalence of a CTO in a non-IRA would be higher in this high-risk subgroup. Moreover, the prognostic impact of a CTO in a non-IRA in diabetic STEMI patients is currently unknown. Therefore, we studied the prevalence and impact of a concurrent CTO on long-term mortality in STEMI patients with DM.

METHODS

Between 1997 and 2007, a total of 4931 consecutive and unselected patients were admitted to our hospital with STEMI. Acute STEMI was diagnosed when patients had symptoms of an acute myocardial infarction lasting 30 minutes to 6 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 immediate coronary angiography with a view to perform primary PCI. PCI was performed by standard techniques, if the coronary anatomy was suitable. All procedural decisions, including device selection and adjunctive pharmacotherapy, such as glycoprotein IIb/IIa inhibitors, were made at the discretion of the operator. All patients were treated with heparin (5000 IU) and aspirin (900 mg) prior to PCI. If a coronary stent was implanted, ticlopidine or clopidogrel was prescribed according to the guidelines.(7)

Study cohort

Data for the 4931 patients were checked for consistency and completeness. For patients who underwent >1 primary PCI during the study period (n=147), only the first intervention was included in this analysis. Patients treated with rescue PCI for failed intravenous thrombolysis (n=145), patients without confirmed diagnosis of STEMI (n=76) and patients lost to follow-up (n=57) were excluded. The remaining 4506 patients constitute the present study cohort. This cohort has been described before.(8) We subsequently identified patients with an established diagnosis of DM at time of admission from our electronic database for the current analysis.

Definitions

Patients with DM were categorised according to preadmission treatment: either with oral medication or diet controlled (non-insulin dependent DM [NIDDM]) or with insulin (insulin dependent DM [IDDM]). 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. 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. Shock was defined according to the clinical criteria used in the “SHould we emergently revascularize Occluded Coronaries for cardiogenic shock?” (SHOCK) trial.(9)

Baseline data

All patients undergoing PCI at our institution were prospectively followed. Baseline clinical, angiographic, and procedural information was entered by qualified cardiac catheterization laboratory personnel and interventional cardiologists in a dedicated electronic database.

Follow up

Information on the vital status was obtained from the institutional follow-up database of PCI patients. Patients were surveyed one year after primary PCI using a mailed, self-administered
questionnaire. Information on mortality was synchronized with the computerized records from the national population registry (Statistics Netherlands, Voorburg, the Netherlands) and was verified until January 1, 2009. We reviewed the outpatient files and contacted general practitioners by telephone in the case of conflicting or missing data.

Primary outcome

The primary outcome for the present analysis was all-cause five-year mortality.

Statistical Analysis

Statistical analysis was performed with SPSS statistical software, version 17.0 (SPSS, Inc., Chicago, Illinois). Discrete variables were summarized as frequencies and percentages. Differences in baseline characteristics between the three groups were tested for significance by the \( \chi^2 \) test. Statistical significance was defined as a \( p \) value <0.05.

Cumulative event-rates of all-cause death were estimated using the Kaplan-Meier method. Follow-up for mortality was censored at the date of last follow-up by checking vital status in the Dutch population registry, or at 5 years, whichever came first. The Log Rank statistic was used to test for significant differences in mortality between the groups. Hazard ratios for all-cause death were calculated using Cox proportional hazard regression analyses after verification of the proportional hazards assumption. We constructed 2 multivariate Cox regression models. We used a categorical variable consisting of 3 groups to classify patients as having SVD, MVD without CTO or MVD with CTO. The first model included variables for MVD with CTO and MVD without CTO, with SVD as the reference. The second model included variables for MVD with CTO and SVD, with MVD without CTO as the reference. The following covariates were included in both models: age (as a

TABLE 1 Baseline characteristics for ST elevation myocardial infarction patients with and without diabetes mellitus

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Patients without Diabetes Mellitus</th>
<th>Patients with Diabetes Mellitus</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>73%</td>
<td>63%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td>49%</td>
<td>66%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28%</td>
<td>50%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoker</td>
<td>45%</td>
<td>32%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>20%</td>
<td>33%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Family history of cardiovascular disease</td>
<td>40%</td>
<td>33%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>12%</td>
<td>23%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Shock</td>
<td>7.6%</td>
<td>10%</td>
<td>0.04</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;40%*</td>
<td>16%</td>
<td>25%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Angiographic characteristics

| LAD related myocardial infarction         | 44%                               | 44%                            | 0.86    |
| MVD                                       | 33%                               | 51%                            | <0.01   |
| MVD without CTO                          | 21%                               | 30%                            | <0.01   |
| MVD with CTO                              | 12%                               | 21%                            | <0.01   |
| Post-Procedural TIMI flow grade 3         | 88%                               | 87%                            | 0.23    |

Procedural characteristics

| Thrombolysis performed                    | 32%                               | 25%                            | <0.01   |
| Intra-aortic balloon pump                 | 8.4%                              | 11%                            | 0.04    |
| Stent placement                           | 75%                               | 69%                            | <0.01   |
| Glycoprotein IIb/IIla inhibitor used      | 26%                               | 26%                            | 1       |

* Left ventricular ejection fraction was available for 1844/4506 patients.

LAD = Left anterior descending coronary artery, MVD = Multivessel Disease, CTO = Chronic total Occlusion, TIMI = Thrombolysis in Myocardial Infarction
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continuous variable, per year increment), male gender, hypertension, smoking, hypercholesterolemia, previous MI, shock, left anterior descending coronary artery-related MI, post PCI TIMI 3 flow, use of glycoprotein IIb/IIIa inhibitors, and stent use. A covariate was allowed in the model if it influenced the model with a likelihood ratio significance level of p<0.10 and removed if its significance level exceeded p=0.15.

RESULTS

Between 1997 and 2007 we treated 4506 STEMI patients with primary PCI of whom 539 (12%) had a confirmed diagnosis of DM at admission. Table 1 shows baseline, angiographic and procedural characteristics for 4506 STEMI patients with and without DM. Patients with DM were older, more often female, and more often had a previous MI and cardiogenic shock at presentation. Furthermore, 51% of patients with DM had MVD compared to 33% of patients without DM (p<0.01). Interestingly, the prevalence of a CTO in a non-IRA was 21% in STEMI patients with DM compared to 12% in patients without DM (p<0.01)(figure1).

Baseline, angiographic and procedural characteristics for the study cohort of 539 patients with DM are shown in table 2. Diabetic patients with MVD (both with and without a CTO) were older, more often had a previous MI and cardiogenic shock at presentation, were more often treated with IABP counterpulsation, and were less frequently treated with coronary stents and thrombosuction, compared with patients with SVD. Furthermore, patients with a CTO in a non-IRA more often had a previous MI and cardiogenic shock at presentation compared to MVD patients without a CTO.

Kaplan-Meier estimates of 5-year mortality were 18% and 28% in STEMI patients without and with DM, respectively. Figure 2 shows the Kaplan-Meier estimates of cumulative mortality up to 5 years for nondiabetic (2a) and diabetic (2b) STEMI patients with SVD, MVD without a CTO and CTO. In STEMI patients without DM, mortality increased significantly with increasing severity of coronary artery disease. In patients with DM, mortality was significantly higher in patients with a CTO in a non-IRA when compared to patients with SVD or MVD without a CTO (p<0.01), but there was no significant difference in mortality between patients with MVD without a CTO and patients with SVD (p=0.82).

Table 3 shows unadjusted and adjusted hazard ratios of significant predictors of 5-year mortality in STEMI patients with DM. When SVD was used as the reference category, a CTO in a non-IRA was a strong and independent predictor of 5-year mortality (adjusted hazard ratio 2.2, 95% confidence interval 1.3-3.5, p<0.01), whereas MVD without a CTO was not associated with increased 5-year mortality. When MVD without a CTO was used as the reference category, CTO in a non-IRA remained an independent predictor of 5-year mortality (adjusted hazard ratio 2.6, 95% confidence interval 1.6-4.4, p<0.01).
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DISCUSSION

In this cohort of 4506 STEMI patients of whom 539 patients had DM, the prevalence of a CTO in a non-IRA was almost twice as high in diabetic patients compared to non-diabetic patients. Moreover, a CTO in a non-IRA was a strong and independent predictor of mortality in STEMI patients with DM. This is the first study evaluating the prevalence and prognostic value of a CTO in a non-IRA in diabetic STEMI patients.

Even with contemporary mechanical reperfusion therapy mortality after STEMI in patients with DM remains high. Diabetic patients are older, have a higher prevalence of co-morbidities and more often have a history of a previous MI.(10-12) Nevertheless, the increased risk associated with DM persists after multivariate adjustment. A number of factors may cause the increased morbidity and mortality after STEMI in diabetic patients. Patients with DM are known to have higher rates of incomplete ST-segment resolution and reduced myocardial blush grade after primary PCI for STEMI, suggesting impaired reperfusion at the myocardial tissue level.(13, 14) Furthermore, longstanding hyperglycemia, hyperinsulinemia, and increased circulating free fatty acids induce adverse metabolic changes in the endothelium.(15, 16) Diabetes mellitus is also associated with intrinsic myocardial dysfunction, probably as a result of autonomic neuropathy and microvascular dysfunction.(17, 18)

Finally, the current study confirms and extends previous reports showing that patients with diabetes mellitus have more severe coronary artery disease, i.e. a higher prevalence of MVD. Interestingly, we observed that the prevalence of a CTO in a non-IRA was twice as high in STEMI patients with DM compared with patients without DM.

A CTO in a non-IRA has previously been reported to be a predictor of both short- and long-term mortality after STEMI treated with primary PCI.(19-21) Furthermore, a CTO in a non-IRA was associated with reduced LVEF during the index hospitalization and a further reduction in LVEF.
within the first year thereafter. We recently demonstrated that mortality in STEMI patients with cardiogenic shock and MVD is mainly driven by the presence of a CTO in a non-IRA. Interestingly, in the present study, diabetic patients with MVD without a CTO had a 5-year mortality rate which was comparable to diabetic patients with SVD and comparable to nondiabetic patients with MVD without a CTO.

Moreover, in our multivariate Cox regression models the adjusted hazard ratio for 5-year mortality of a CTO in a non-IRA was quite similar when we used SVD as the reference or MVD without CTO as the reference category (2.2 and 2.6, respectively). These results suggest that particularly in the high-risk subgroup of STEMI patients with DM, MVD has prognostic implications only if a concurrent CTO is present.

**Clinical Implications**

An aggressive multivessel PCI strategy during and after primary PCI for STEMI has not improved outcome in MVD patients both with and without DM. In fact, studies reported that treatment of non-culprit lesions in STEMI patients with MVD is associated with a higher post-procedural

**Figure 2** Kaplan-Meier estimates of 5-Year mortality in ST elevation myocardial infarction patients treated with primary percutaneous coronary intervention
As in our previous reports, the findings of the present study suggest that additional revascularization strategies should perhaps be more focussed at treating total occlusions rather than stenoses in non-IRAs. Treating a CTO in a non-IRA during the primary procedure does not seem feasible, given the complexity of CTO angioplasty which requires a skilled and experienced operator and is associated with an increased use of contrast medium, and longer fluoroscopy time. A staged PCI procedure to revascularize a CTO in a non-IRA after STEMI seems to be a more sensible approach. We have therefore recently initiated the randomized controlled multicenter Evaluating XIENCE V and LVF in PCI on occLusiOns afteR STEMI (EXPLORE) trial investigating the effects of opening a CTO in a non-IRA in a staged procedure within one week after primary PCI on left ventricular function and remodeling. (27)

**Study Limitations**

Several limitations of the current study should be mentioned. The study cohort is comprised of patients with a known diagnosis of DM at admission. We did not routinely measure haemoglobin A1c or test for DM during admission. Furthermore, detailed information on peri- and post-procedural medication (including glucose-regulating medication) was not available. Therefore we were not able to assess differences in glycemic control or adherence to guideline-based post-STEMI therapies. Moreover, we did not routinely store information on pre- or post-PCI renal function in our PCI database. Finally, some overestimation of non-culprit lesions may have occurred as non-culprit lesion stenosis severity was assessed in the acute setting on the infarct angiography by the performing cardiologist. (28)

**CONCLUSION**

Compared to STEMI patients without DM, the prevalence of a CTO in a non-IRA is increased in...
STEMI patients with DM. In patients with DM, 5-year mortality was comparable between patients with SVD and patients with MVD without a CTO. The presence of a CTO in a non-IRA is a strong and independent predictor of 5-year mortality in diabetic STEMI patients treated with primary PCI. These results suggest that particularly in the high-risk subgroup of STEMI patients with DM, MVD has prognostic implications only if a concurrent CTO is present.

Reference List

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