Long-term, cause-specific mortality after myocardial infarction in diabetes

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Aims To compare long-term, cause-specific mortality after reperfusion therapy for ST segment elevation myocardial infarction (STEMI) in patients with and without diabetes.

Methods and results Patients with STEMI ($n = 395$) were randomised to intravenous streptokinase (SK) or primary percutaneous coronary intervention (PCI). Median follow-up was 7.5 years (interquartile range 5.6–8.5). A total of 74 patients (19%) had diabetes. Reduced left ventricular ejection fraction ($<40\%$) after STEMI was more often observed in patients with diabetes (27% vs. 15%, $P = 0.02$). Patients with diabetes had a higher total mortality compared to patients without diabetes (HR 2.4; $P < 0.001$). Multivariate analysis confirmed that diabetes was an independent risk factor for long-term mortality (HR 2.3; $P < 0.001$). The incidence of sudden death was comparable in both patient groups (HR 1.6; $P = 0.23$). The increased mortality in patients with diabetes was mainly caused by heart failure (HR 3.1; $P = 0.004$). In patients with diabetes, primary PCI was associated with an improved prognosis.

Conclusions Despite reperfusion therapy, STEMI patients with diabetes have an increased long-term mortality. This is due to death by heart failure and not by an increase in sudden death. Primary PCI is associated with an improved prognosis, particularly in patients with diabetes.

Introduction

Patients with acute ST segment elevation myocardial infarction (STEMI) with diabetes have an increased mortality and morbidity when compared to patients without diabetes.\(^1\)\(^2\) There is, however, limited and contradictory information about the short-term clinical outcome of STEMI patients with diabetes treated with thrombolysis, compared to primary percutaneous coronary interven-
Materials and methods

This paper reports a sub-analysis of the Zwolle trial, in which primary PCI was compared with thrombolysis as reperfusion therapy for STEMI. Patients were enrolled if they fulfilled the following criteria: symptoms of an acute myocardial infarction lasting longer than 30 min, an accompanying 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. Exclusion criteria were a contra-indication for thrombolytic therapy, a life expectancy of less than 6 months or conditions resulting in a severe impairment of quality of life.

After informed consent had been obtained, patients were randomly assigned to undergo PCI or to receive streptokinase (SK) as the thrombolytic agent. All patients received heparin and aspirin. Patients assigned to the streptokinase group received 1.5 million units intravenously over one hour. Patients assigned to the PCI group were immediately transported to the catheterisation laboratory and if the coronary anatomy was suitable to the PCI group were immediately transported to the catheterisation laboratory and if the coronary anatomy was suitable for PCI, the procedure was performed with standard techniques. The global left ventricular ejection fraction (LVEF) was measured by equilibrium radionuclide ventriculography between days 4 and 10 after treatment. Coronary angiography was performed during follow-up in all patients to assess long-term patency of the infarct-related artery, as previously described. In the thrombolysis group, an initial conservative approach of watchful waiting after treatment was followed by elective coronary angiography. Additional revascularisation procedures were performed for all patients if indicated for symptoms or signs of myocardial ischaemia.

Patients with diabetes were defined as patients with documented diabetes using oral hypoglycaemic agents or insulin treatment at admission, or if they had a blood glucose level at admission ≥11.1 mmol/L. From August 1990 through April 1993, all presenting patients were asked to participate, and thereafter patients with marked haemodynamic instability or electrocardiographic signs of extensive infarction were excluded, as previously described. Enrollment ended in April 1995. The study population consisted of a consecutive series of patients, with only rare exceptions, as the majority of patients who presented to our hospital with STEMI agreed to participate. 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.

Non-fatal recurrent myocardial infarction was defined as the combination of chest pain, changes in the ST-segment, and a second increase in the serum creatine kinase level to more than two times the upper limit of normal. If the creatine kinase level had not decreased to normal levels, a second increase of more than 200 U/L over the previous value was regarded as indicating a recurrent infarction. 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. 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 these 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

The patient group randomised to SK was compared to the patient group randomised to PCI treatment. The primary endpoints were death and the combined incidence of death and non-fatal re-infarction (major adverse cardiac events, or MACE). For the purpose of the present study, total mortality, sudden death and MACE were also end-points for the comparison of patients with diabetes versus patients without diabetes. All outcomes were analysed according to the intention to treat principle. Statistical analyses were two-tailed and performed using SPSS 10.0. Differences between group means were tested by the two-tailed Student’s t test. Except for long-term follow-up endpoints, χ² statistics were calculated to test differences between proportions, with calculation of relative risks and exact 95% confidence intervals (CI). Differences in cause-specific mortality or MACE were tested with log-rank statistics and the estimation of hazard ratios (HR) were calculated using Cox-regression analysis. Statistical significance was defined as P < 0.05.

Day 1 was defined as the day on which the patient was admitted to our hospital and included in the study. 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. The assumption of proportional hazards was assessed by division of the follow-up period into different periods analysing whether the hazard ratios were constant over time. Stratified analyses were performed to assess U or J shaped associations between age and mortality. Cox proportional-hazards regression models were used to estimate the HR of clinical variables found to be significantly different in univariate analysis. Baseline variables that were assessed in univariate analysis were age, gender, type of reperfusion, infarct location, hypertension, smoking, Killip class and multi-vessel disease. In addition to reperfusion therapy, the primary end point of the original Zwolle trial, univariate variables were also included into the multivariate analysis when they were significantly different between the groups with and without diabetes.

Results

SK versus PCI

Of the 395 patients enrolled, 201 were randomised to receive SK and 194 to undergo primary PCI. Median follow-up was 7.5 years (5.6–8.5). One patient was lost to follow-up (after 1.5 years). Mortality in the SK group was significantly higher than the PCI group (HR 1.5; P = 0.03) at the end of the follow-up period.

Clinical characteristics of patients with diabetes

In the total patient group, 32 patients (8%) had diabetes before study entry and 42 (12%) had a blood glucose level
During follow-up, mortality in patients with diabetes was generally older, female and had a greater incidence of multi-vessel disease (MVD). LVEF was measured in 67 patients of the diabetes group (91%) and in 310 patients of the non-diabetes group (97%). Patients with diabetes had a greater frequency of reduced LVEF (LVEF <40%) compared to patients without diabetes (27% vs. 15%, HR \( < 0.001 \)). The mortality rates of patients with, or without, diabetes are shown in Fig. 1. This figure shows that patients with diabetes had a higher early mortality, which also increased at a greater rate over time than non-diabetic patients. The specific causes of death are shown in Table 2. Diabetes was particularly associated with a higher incidence of death due to heart failure after short-term follow-up; this also increased during the long-term follow-up. MACE end-points were more frequent in patients with diabetes (HR 1.6; \( P = 0.009 \)), but sudden death was, however, not significantly higher in patients with diabetes.

**Reperfusion therapy in diabetes**

All patients, either with or without diabetes, more often had a reduced LVEF after treatment with SK compared to primary PCI. Patients without diabetes were found to have a higher mortality after treatment with SK compared with PCI, although the difference was not statistically significant (HR 1.5; \( P = 0.12 \)). This beneficial effect of primary PCI was more evident in patients with diabetes (HR 2.1; \( P = 0.04 \)).

**Multivariate analysis**

In order to identify independent predictors of mortality, we performed multivariate analyses and included the type of reperfusion and all clinical variables that were significantly different between the patient groups with and without diabetes. These variables were age, gender and the presence of MVD. Multivariate analysis revealed that diabetes (HR 2.3; 95% CI: 1.5–3.5, \( P < 0.001 \)), age \( \geq 60 \) years (HR 2.3; 95% CI: 1.5–3.5, \( P < 0.001 \)), treatment with SK compared to PCI (HR 1.6; 95% CI: 1.1–2.4, \( P = 0.02 \)) and MVD (HR 1.6; 95% CI: 1.1–2.5, \( P = 0.03 \)) were all independent risk factors for long-term mortality (Table 3). Independent predictors for sudden death were an age \( \geq 60 \) years and SK treatment compared to PCI as reperfusion therapy. Diabetes was not found to be an independent predictor of sudden death. There was also no independent association between occurrence of MACE and diabetes.

**Discussion**

This study confirms that STEMI patients with diabetes are a high risk group. Despite modern reperfusion therapies they had an increased long-term mortality when compared to patients without diabetes. The increase in mortality was particularly caused by death due to heart failure, whereas the incidence of sudden death was not increased in patients with diabetes. Especially in diabetic patients, primary PCI was associated with an improved survival. Although primary PCI may be the preferred method of reperfusion in patients with diabetes, other
treatment strategies for improvement of prognosis should also be investigated.

The higher mortality in diabetic patients could have been caused by the older age or the higher prevalence of multi-vessel disease. After adjustment for differences in baseline variables, however, diabetes was still associated with an increased long-term mortality. Patients with diabetes had a greater reduction in LVEF after STEMI compared to patients without diabetes. This could also have had a major impact on survival. The decreased LVEF observed in diabetes could have been the result of glycometabolic disturbances, including an increased utilisation of free fatty acids, and impaired pre-conditioning causing myocardial cells to be more prone to ischaemic and reperfusion injury.21 22 The presence of MVD is also associated with a limited recovery of myocardial function after STEMI.23 Besides the reduced LVEF, pro-thrombotic disturbances in the coagulation system, unfavourable lipid levels and a higher prevalence of co-morbidity such as renal disease may also contribute to the adverse prognosis of diabetic patients.24 25

This study showed that heart failure was increased in patients with diabetes. Extensive coronary artery disease, autonomic dysfunction and a high prevalence of hypertension have all been linked with diabetes and heart failure.26 Furthermore, endothelial dysfunction resulting in increased vascular resistance, is not only associated with congestive heart failure but also with diabetes and glucose disturbances in the sub-diabetic range.27 Diabetic cardiomyopathy, which is induced by various mechanisms, also predisposes to heart failure.28 Interestingly, sudden death was not higher in patients with diabetes. This is in contrast to past speculation, thus suggesting a pro-arrhythmic effect of autonomic dysfunction in patients with diabetes.29

Several explanations for our findings are possible, however, including a selection bias regarding sudden death due to patients only being included if they survived their STEMI. Diabetes in healthy men is also a known risk factor for sudden death.30 However, Whang et al.31 did not find any increased arrhythmia in diabetic patients with reduced LVEF after coronary artery bypass grafting (CABG). It is possible that diabetic patients with coronary artery disease are not more susceptible to sudden death than their non diabetic counterparts. This could partly be due to the use of glibenclamide, an oral hypoglycaemic agent, which appears to reduce cardiac arrhythmia.32

### Implications for treatment

Concerning long-term mortality, our study showed a remarkable benefit of primary PCI over thrombolysis in diabetic patients. Therefore, primary PCI should be the preferred method of reperfusion in STEMI patients with diabetes. Possible mechanisms of this benefit are a higher rate of open infarct-related arteries and improvement of microvascular flow associated with PCI.33 However, although primary PCI improves outcome, mortality remains high. Further therapeutic strategies for patients with diabetes should therefore be investigated. Modulation of glyco-metabolic disturbances during STEMI through administration of glucose-insulin-potassium infusion may reduce mortality.34 35 The DIGAMI trial showed a reduction in mortality in STEMI patients with diabetes treated with insulin-glucose infusions followed by multi-dose subcutaneous insulin.36 As a substantial part of the increased mortality in our study occurred at a later stage, during the follow-up period, revascularisation beyond the initial admission might also be beneficial. Patients with diabetes have an increased risk of restenosis after PCI, but the use of coronary stents, particularly drug-eluting, may reduce this problem.37 38 Implantable cardiac defibrillators may also reduce mortality in certain patients after myocardial infarction.39

Our findings suggest, however, that the additional benefit of this therapy for diabetic patients is limited because the majority of patients with diabetes died due to heart failure and not sudden death. It is likely that strategies aimed at preservation of LVEF and prevention of heart failure are more effective in diabetic patients. As there is a relation between glyco-metabolic dysregulation and heart failure, a meticulous regulation of glucose levels should be aimed for which may result in improvement in endothelial function and a more efficient myocardial substrate utilisation. Furthermore, a more widespread use of ACE-inhibitors and β-blockers may also lead to improvement in outcome.40 It must be stressed that optimal treatment of diabetes patients should not be confined to dealing with acute coronary events only. A broad, long-term and multi-disciplinary approach aimed at multiple risk factors is necessary and can accomplish an impressive reduction in cardiovascular complications in patients with diabetes.41

### Limitations of the study

Our study included only 395 patients from a single centre. During the study period, intra-coronary stenting and treatment with glycoprotein Ilb—Ilia inhibitors or clopidogrel were not available. These new therapy modes may well have a profound effect on clinical outcome42 and may also improve clinical outcome in patients with diabetes when treated with PCI.47 Although there were few exclusion criteria, patients in this trial may have been subject to a selection bias. No routine tests etc. to detect diabetes were performed during the follow-up period, therefore no data on the development of new diabetes can be given.
Conclusion

Despite the use of modern reperfusion therapies, STEMI patients with diabetes had larger infarct sizes and an increased long-term mortality when compared to patients without diabetes. Diabetes was not associated with an increase in sudden death. Furthermore, the use of primary PCI versus thrombolysis was associated with an improved prognosis, particularly in diabetes.

Appendix A

The Zwolle Myocardial Infarction Study Group Investigators: Dr. M.J. de Boer, Dr. J.-H.E. Dambrik, Dr. A.T.M. Gosselink, Dr. A.W.J. van 't Hof, Dr. J.C.A. Hoornjtje, Dr. J.P. Ottervanger, Dr. H. Suryapranata, Prof. Dr. F. Zijlstra.

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