

Impact of diabetes mellitus on long-term outcome after unstable angina and non-ST-segment elevation myocardial infarction treated with a very early invasive strategy

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Abstract

Aims/hypothesis. We sought to evaluate the impact of diabetes mellitus on long-term outcome in patients with unstable angina and non-ST-segment elevation myocardial infarction treated with a very early invasive strategy.

Methods. We carried out a prospective cohort study in 270 diabetic and 1163 non-diabetic patients with unstable angina and non-ST-segment elevation myocardial infarction. All patients underwent coronary angiography and, if appropriate, subsequent revascularisation within 24 hours of admission. The primary endpoint was all-cause mortality during follow-up for up to 60 months.

Results. Diabetic patients had less favourable baseline characteristics including more advanced coronary artery disease and more severe unstable angina and non-ST-segment elevation myocardial infarction. Percutaneous coronary intervention was performed in 53% of diabetic patients and 56% of non-diabetic patients. Coronary artery bypass grafting was done in 21% of diabetic

patients and 12% of non-diabetic patients. In-hospital mortality (4.1% vs 1.3%; hazard ratio 3.47; 95% CI: 1.57 to 7.64; $p=0.002$) and long-term mortality (9.7% vs 4.9%; hazard ratio 2.11; 95% CI: 1.33 to 3.36; $p=0.002$) were significantly higher in diabetic patients. After adjustment for differences in baseline characteristics, diabetes mellitus was no longer an independent predictor of long-term mortality (hazard ratio 1.43; 95% CI: 0.74 to 2.78; $p=0.292$).

Conclusions/interpretation. Diabetic patients treated with a very early invasive strategy for unstable angina and non-ST-segment elevation myocardial infarction have a higher in-hospital and long-term mortality that is largely explained by their less favourable baseline characteristics including more advanced coronary artery disease and more severe unstable angina and non-ST-segment elevation myocardial infarction.

Keywords Diabetes mellitus · Long-term mortality · Myocardial infarction · Revascularisation · Unstable angina

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Abbreviations: CK, creatine phosphokinase · FRISC, Fragmin and fast Revascularisation during InStability in Coronary artery disease · OASIS, Organisation to Assess Strategies for Ischemic Syndromes · TACTICS-TIMI 18, Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis In Myocardial Infarction 18 · UA/NSTEMI, unstable angina and non-ST-segment elevation myocardial infarction

Introduction

Diabetes mellitus is an important risk factor for coronary artery disease, which is associated with increased mortality and morbidity in diabetic patients as compared with non-diabetic patients [1, 2, 3]. Patients with diabetes mellitus with no history of coronary artery disease have the same risk of cardiovascular death as non-diabetic patients with a history of myocardial infarction [4]. In addition, patients with diabetes mellitus have not experienced the reduction in cardiovascular mortality rates that has recently been observed in non-diabetic subjects [5]. The number of adults with diabetes mellitus worldwide is likely to grow from 135 million in 1995 to approximately 300 million in 2025 [6]. However, only limited informa-

tion is available regarding the outcome of diabetic patients after hospital admission with unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI), the most common reason for admission to a coronary care unit [7, 8, 9, 10, 11]. The OASIS registry prospectively collected data from UA/NSTEMI patients treated with predominately medical therapy in six different countries including the United States, and reported that diabetes mellitus independently predicted mortality [11]. Overall, cumulative mortality in patients with diabetes mellitus was 19% at 24 months in the OASIS registry.

Revascularisation, irrespective of the primary success of medical therapy, has become the preferred treatment strategy in patients with UA/NSTEMI [12, 13, 14]. Current practice guidelines for the management of patients with UA/NSTEMI from the American College of Cardiology, the American Heart Association, and the European Society of Cardiology recommend an early invasive strategy for most patients [15, 16]. The long-term outcome of patients with diabetes mellitus and UA/NSTEMI treated with a very early invasive strategy remains to be assessed. We sought to determine the long-term outcome of systematic revascularisation within 24 hours in diabetic patients. In addition, we evaluated whether the prognostic impact of diabetes mellitus is different between women and men.

Subjects and methods

Study population. From January 1996 to December 1999, consecutive patients admitted to our centre with UA/NSTEMI were treated with a very early invasive strategy. Patients were eligible for inclusion in this study if they underwent coronary angiography for symptoms of myocardial ischaemia occurring at rest (Braunwald class IIIB unstable angina) [17]. We excluded patients who had the following conditions: (i) a first case of angina pectoris during exertion, or worsening angina during exertion (Braunwald class 1A–C); (ii) persistent ST-elevation; or (iii) postinfarction angina (Braunwald class 1C, 2C, 3C). Also excluded were patients in whom angiography was not performed due to patient refusal ($n=6$) or extremely severe concomitant disease ($n=9$ with severe dementia or advanced malignancy). The study was carried out in accordance with the Declaration of Helsinki and approved by the institutional review board. Informed consent was obtained from all participating patients. Diabetes was defined as the patient having a known history of diabetes mellitus treated currently with either diet intervention, oral glucose-lowering agents or insulin. Irrespective of the presence or absence of diabetes, strict glycaemic control was observed in all patients. Upon hospital discharge, all patients were instructed to follow a low-cholesterol diet, and statins were recommended to achieve an LDL cholesterol lower than 2.6 mmol/l during follow-up. All patients received aspirin and beta blockers unless contraindicated.

Very early invasive strategy. Patients with persistent chest pain underwent immediate coronary angiography. In patients asymptomatic while on medical therapy, coronary angiography was performed within 24 hours of admission. Whenever possible, coronary stenting of the culprit lesion was done directly

after angiography. Stenting was not restricted to patients with one- and two-vessel disease, but also favoured in patients with three-vessel disease, if the target lesion seemed accessible. If percutaneous coronary intervention was not possible (unprotected left main disease, diffuse three-vessel disease) but revascularisation seemed necessary, patients were scheduled for urgent coronary artery bypass grafting.

Follow-up. All patients were scheduled for outpatient visits at 6 months. In addition, patients were contacted by questionnaire in September 2000, 4 years and 9 months after enrolment of the first patient. For patients reporting cardiac symptoms, at least one clinical and ECG examination was performed in the outpatient clinic or by the referring physician. All information derived from contingent hospital re-admission records and that provided by the referring physician or by the outpatient clinic was reviewed and entered into the computer database.

Endpoints and statistical analysis. The pre-specified primary endpoint was defined as death from all causes. As secondary endpoints we assessed non-fatal myocardial infarction and the composite of death and non-fatal myocardial infarction. Myocardial infarction was defined as typical chest pain at rest followed by an increase in creatine phosphokinase (CK and CK-MB more than two times the upper limit of normal, and more than five times the upper limit of normal after coronary artery bypass grafting) or new Q waves in the ECG. To meet this endpoint criterion, patients who initially had myocardial infarction had to develop ST-segment changes and an increase in CK of at least 50% over the previous trough level in at least two samples reaching at least three times the upper limit of normal.

Follow-up events were adjudicated by a clinical events committee. All patients received ECG recordings directly after percutaneous coronary intervention or coronary artery bypass grafting and on the following morning. In addition, cardiac markers (CK and CK-MB) were determined between 8 and 24 hours after the intervention, and additionally whenever ischaemic symptoms developed. The statistical analyses were performed using the SPSS/PC (version 11.0; SPSS, Chicago, Ill., USA) software package. Discrete variables were expressed as percentages (95% CI) and continuous variables were expressed as means \pm SD. A p value of 0.05 or less was considered statistically significant. For the rarer outcomes, confidence intervals were calculated using the Wilson method. Comparisons were made using ANOVA for independent samples and chi square tests as appropriate. All hypothesis testing was two-tailed. Cox proportional hazards regression analysis was used as the appropriate method throughout. Multivariate Cox regression analysis was performed to identify independent predictors of death. Baseline characteristics, ECG findings, markers of inflammation and myocardial necrosis, and the angiographic extent of coronary artery disease were entered into the model. The cumulative survival curves were constructed by the Kaplan–Meier method.

Results

Baseline characteristics. There were 270 patients with diabetes and 1163 patients without diabetes in this study. The vast majority of diabetic patients were classified as having Type 2 diabetes (261 of the 270, 97%). Besides diet and exercise, therapy included insulin in 74 (28%) of the 261 patients, and glibenclamide in 50 (19%) of the 261 patients. Baseline characteristics

Table 1. Baseline patient characteristics

	Diabetic patients (n=270)	Non-diabetic patients (n=1163)	p value
Age (years)	68±9	64±11	<0.001
Female sex	31 (25–36)	28 (26–31)	0.407
Previous myocardial infarction	41 (36–47)	31 (28–34)	0.001
Previous coronary bypass grafting	16 (11–20)	13 (11–15)	0.339
Previous coronary angioplasty	22 (17–27)	22 (20–25)	0.858
Hypercholesterolaemia	64 (58–69)	66 (63–69)	0.451
Hypertension	75 (70–80)	59 (56–62)	0.001
Smoking	14 (9–18)	25 (22–27)	0.001
Angina pectoris at rest >48 h	16 (12–20)	17 (15–19)	0.616
Angina pectoris at rest <48 h	67 (61–73)	69 (66–72)	0.522
Non-Q-wave myocardial infarction	17 (13–22)	14 (12–16)	0.167
Cardiopulmonary resuscitation	3.0 (0.9–5.0)	0.9 (0.4–1.5)	0.009
Defibrillation (only)	2.6 (0.7–4.5)	1.5 (0.8–2.3)	0.238
Cardiogenic shock	1.1 (0–2.4)	0.9 (0.3–1.4)	0.695
New ST depression at entry	14 (10–18)	10 (8–12)	0.090
New T-wave inversion	28 (23–34)	29 (27–32)	0.703
Troponin T ≥0.01 µg/l	63 (56–69)	55 (51–58)	0.047
C-reactive protein >10 mg/l	30 (24–37)	25 (22–28)	0.112
Creatinine (µmol/l)	91±74	80±59	0.016
White blood cell count (×10 ³ /µl)	9.0±3.0	8.8±8.0	0.820
Platelet count (×10 ³ /µl)	236±94	235±70	0.874

Data are expressed as means ± SD, or percentages (95% CI)

Table 2. Baseline angiographic and procedural characteristics

	Diabetic patients (n=270)	Non-diabetic patients (n=1163)	p value
Coronary vessels with ≥50% stenosis			0.001
0	7 (4–10)	15 (13–17)	0.001
1	19 (14–24)	26 (24–29)	0.023
2	21 (16–26)	24 (21–26)	0.367
3	53 (46–59)	35 (32–38)	0.001
Percutaneous coronary intervention	53 (47–59)	56 (53–59)	0.278
Proportion with stent	74 (66–82)	81 (78–84)	0.094
Proportion with abciximab	12 (6–18)	11 (9–14)	0.931
Coronary artery bypass grafting	21 (17–26)	12 (10–14)	0.001
Medical therapy	26 (21–31)	31 (29–34)	0.075

Data are expressed as percentages (95% CI)

were considerably different between diabetic and non-diabetic patients (Tables 1 and 2). Diabetic patients were older, more often hypertensive and less often smokers, and they more frequently had a previous myocardial infarction as well as cardiac arrest during the UA/NSTEMI leading to admission than non-diabetic patients. They also had a higher incidence of new ST-segment depression and raised troponin T.

Angiographic characteristics and revascularisation.

Coronary angiography revealed that coronary artery disease was more extensive in diabetic patients. More than half of the patients with diabetes mellitus had three-vessel disease compared with 35% of patients without diabetes mellitus. Conversely, non-diabetic patients were two times as likely to have no coronary vessel with a high-grade lesion as diabetic patients. Ac-

cordingly, coronary artery bypass grafting was chosen significantly more often (21% vs 12%, $p=0.001$) in patients with diabetes. However, percutaneous coronary intervention was the predominant revascularisation procedure in both groups. Percutaneous coronary intervention was performed in 53% of patients with diabetes and in 56% of patients without diabetes. Altogether, two-thirds of patients underwent revascularisation.

In-hospital and long-term outcome. Patients with diabetes mellitus had a significantly higher in-hospital mortality rate than patients without diabetes mellitus (4.1% vs 1.3%; hazard ratio 3.47; 95% CI: 1.57 to 7.64). In addition, non-fatal Q-wave myocardial infarction and the combined endpoint of death or myocardial infarction was recorded more frequently during the initial hospitalisation in patients with diabetes mellitus (Table 3).

Table 3. Association between diabetes mellitus and outcome

	Diabetic patients (n=270)	Non-diabetic patients (n=1163)	Hazard ratio (95% CI)	p value
In-hospital				
Death	4.1 (2.1–7.2)	1.3 (0.7–2.1)	3.47 (1.57–7.64)	0.002
Death or myocardial infarction ^a	7.8 (4.9–11.6)	3.7 (2.7–4.9)	2.41 (1.40–4.15)	0.002
Q-wave myocardial infarction	1.1 (0.2–3.2)	0.3 (0.1–0.8)	4.44 (0.90–21.99)	0.068
Non-Q-wave myocardial infarction	2.6 (1.0–5.3)	2.2 (1.5–3.3)	1.34 (0.54–3.32)	0.535
During follow-up				
Death	9.6 (6.4–13.8)	4.9 (3.7–6.3)	2.11 (1.33–3.36)	0.002
Death or myocardial infarction ^a	13.7 (9.8–18.4)	8.6 (7.1–10.4)	1.76 (1.20–2.59)	0.004
Myocardial infarction	4.4 (2.3–7.6)	4.0 (3.0–5.3)	1.21 (0.62–2.36)	0.570

Data are expressed as percentages (95% CI) unless otherwise stated. ^a Counting only one event per patient

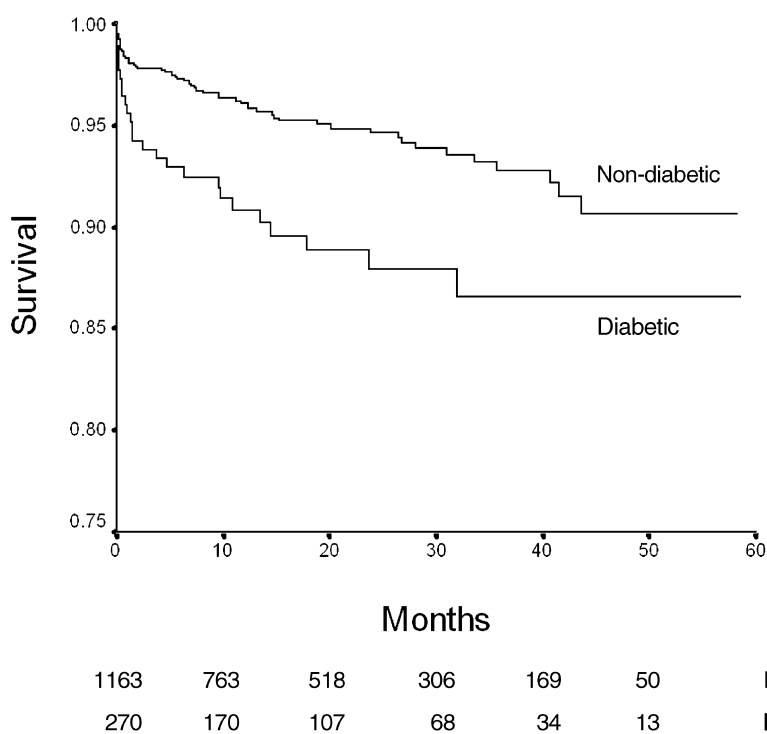


Fig. 1. Cumulative survival in diabetic and non-diabetic patients during long-term follow-up. $p=0.0016$ by log-rank

The mean interval between admission and last patient contact or death was 19 months in diabetic patients and 20 months in non-diabetic patients. During follow-up, mortality was significantly higher in patients with diabetes mellitus than in patients without diabetes mellitus (Fig. 1). Kaplan–Meier analysis revealed a cumulative survival rate of 86.6% for diabetic patients and 92.8% for non-diabetic patients at 36 months. The incidence of non-fatal myocardial infarction was similar in the two groups.

Association between diabetes mellitus and sex. As shown in Figures 2 and 3, the impact of diabetes mellitus on long-term outcome was considerably dif-

ferent between men and women ($p=0.001$ for association). While diabetic men showed a marked reduction in survival rate compared with men without diabetes (83.7% vs 92.4% at 36 months), diabetic women showed a very similar survival rate to women without diabetes mellitus (93.9% vs 93.7% at 36 months).

Diabetes mellitus and very early percutaneous coronary intervention. The long-term survival rate in patients undergoing very early revascularisation with percutaneous coronary intervention was excellent, irrespective of the presence or the absence of diabetes mellitus (Fig. 4). At 36 months, the cumulative survival rate was 92.4% in diabetic patients and 92.0% in non-diabetic patients.

Multivariate Cox regression analysis. After adjustment for baseline characteristics, ECG findings, mark-

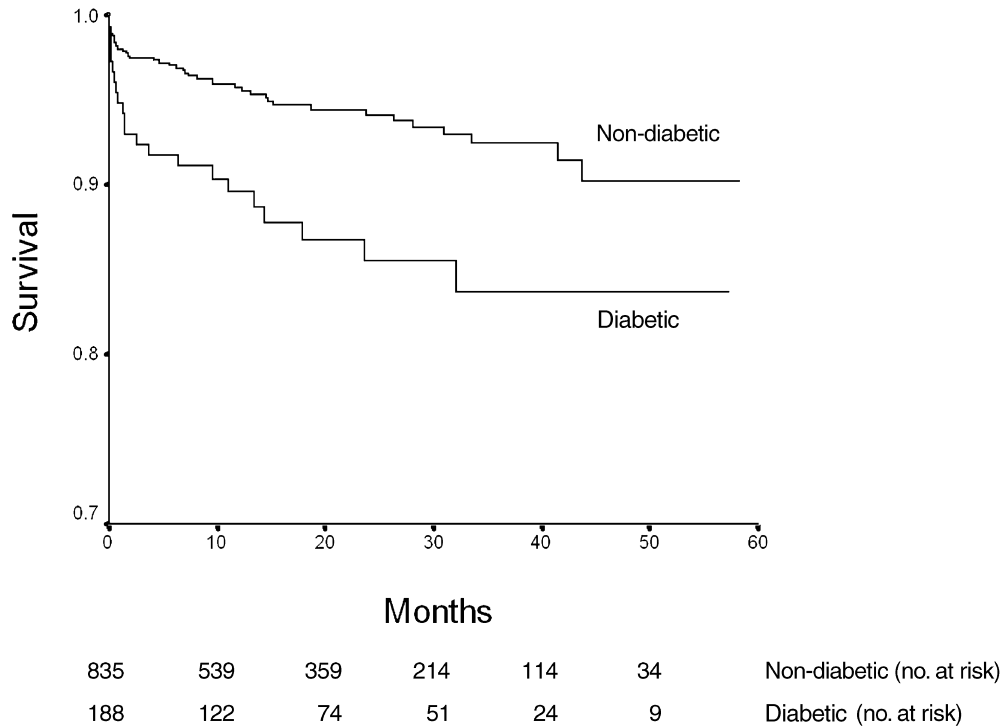


Fig. 2. Cumulative survival in diabetic and non-diabetic men. $p=0.0010$ by log-rank

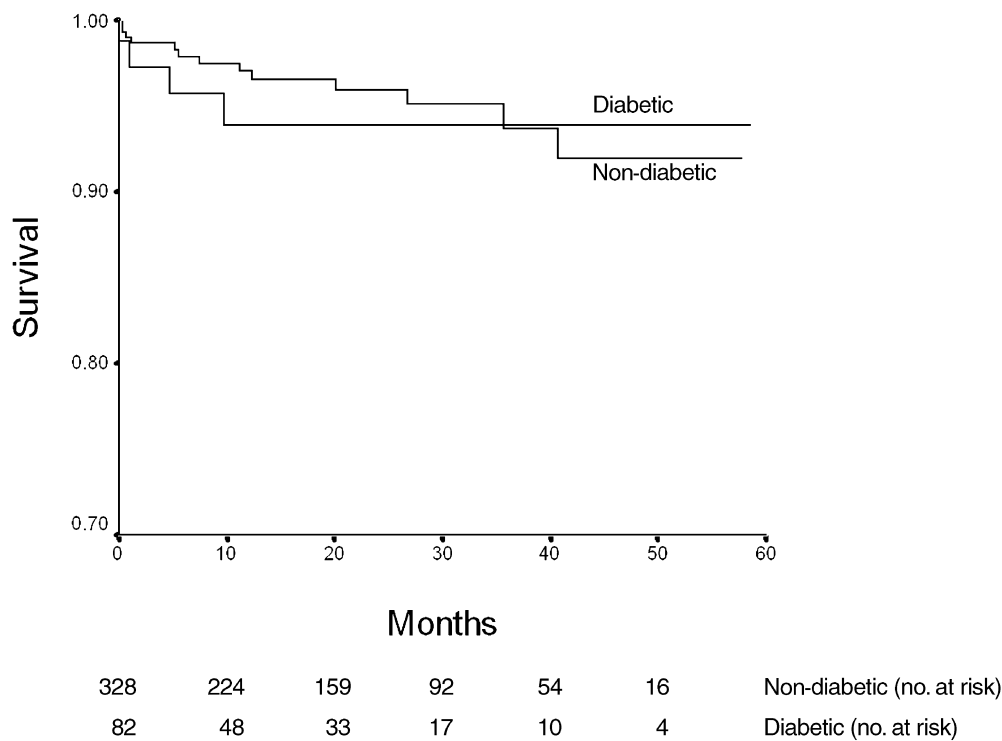


Fig. 3. Cumulative survival in diabetic and non-diabetic women. $p=0.5792$ by log-rank

ers of inflammation and myocardial necrosis, and the angiographic extent of coronary artery disease, diabetes mellitus was not found to be a significant independent predictor of long-term mortality (hazard ratio 1.43; 95% CI: 0.74 to 2.78; $p=0.292$). Adding very

early percutaneous coronary intervention as a variable to the multivariate Cox regression analysis showed that very early percutaneous coronary intervention was independently associated with a favourable outcome (hazard ratio for long-term mortality 0.50; 95% CI: 0.30 to 0.85; $p=0.011$). This association would persist if the analysis was restricted to diabetic patients only (hazard ratio 0.47; 95% CI: 0.20 to 1.09; $p=0.078$).

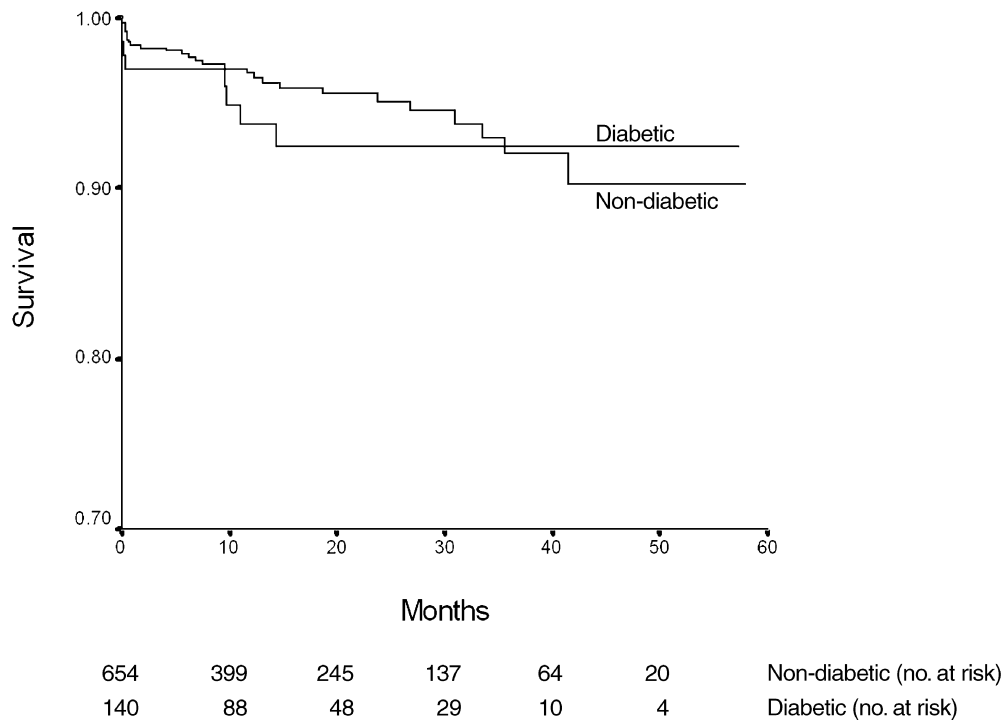


Fig. 4. Cumulative survival in diabetic and non-diabetic patients revascularised very early with percutaneous coronary intervention. $p=0.4242$ by log-rank

Discussion

Our study of 1433 consecutive patients with UA/NSTEMI treated with a very early invasive strategy showed that in-hospital and long-term mortality were significantly higher in patients with diabetes. This finding is consistent with previous studies that primarily used a conservative management strategy for UA/NSTEMI [7, 8, 9, 10, 11]. Nevertheless, as our major novel finding we were able to attribute most of this excess risk to two factors: more advanced coronary artery disease and more severe UA/NSTEMI at presentation. In fact, we could demonstrate that after adjusting for cofounders, diabetes mellitus was no longer an independent predictor of adverse outcome with this aggressive revascularisation strategy. We found important differences in baseline characteristics between diabetic and non-diabetic patients. Most importantly, diabetic patients were older and more often had previous myocardial infarction and three-vessel disease. In addition, the UA/NSTEMI seemed to be more severe in diabetic patients. Cardiopulmonary resuscitation, ST-segment depression and elevated troponin T were seen more often in diabetic patients than in non-diabetic patients. When we adjusted for these differences between diabetic and non-diabetic patients, the presence or absence of diabetes mellitus was no longer predictive of survival. As coronary angiography was performed in all patients, this study

was able to include the angiographic extent of coronary artery disease in the multivariate model to assess independent predictors of long-term mortality. We found that the association of three-vessel disease and diabetes constitutes an important component of the predictive power of diabetes by univariate analysis.

This was not a randomised trial evaluating the very early invasive strategy. Accordingly, any comparison of the outcome observed in this prospective trial with historical controls has inherent limitations and should be interpreted with considerable caution. Although very similar with respect to patient baseline characteristics and study period, our study population experienced merely two-thirds the mortality at 24 months of that observed in the OASIS registry [11]. In our study, particularly in the patients revascularised very early with percutaneous coronary intervention, there was an excellent outcome irrespective of the presence or absence of diabetes mellitus. In fact, in the subgroup receiving very early percutaneous coronary intervention, long-term survival was identical in diabetic and non-diabetic patients. This observation is supported by subgroup analyses of the TACTICS-TIMI 18 and FRISC II studies [12, 13], in which diabetic patients showed a more pronounced benefit from the early invasive strategy than non-diabetic patients. In the TACTICS-TIMI 18 study, the early invasive strategy reduced the primary endpoint of death, non-fatal myocardial infarction, or re-hospitalisation, for an acute coronary syndrome at 6 months, from 27.7% to 20.1% in diabetic patients, and from 16.4% to 14.2% in non-diabetic patients. Our finding, however, can only be used to generate hypotheses and needs to be confirmed by further study.

Excessive restriction during coronary angiography and revascularisation procedures may have contributed significantly to the dismal prognosis of patients with diabetes mellitus in earlier reports [5, 7, 11]. In a case-control study of 162 diabetic patients with unstable angina, diabetic patients less frequently underwent coronary angiography and angioplasty [7]. This observation was confirmed in the large OASIS registry. Although the diabetic patients in the registry were at clearly higher risk, having had more previous cardiovascular events including myocardial infarction, congestive heart failure and coronary artery bypass grafting, the rate of coronary angiography (37% vs 37%) and revascularisation by percutaneous coronary intervention or coronary artery bypass grafting (23% vs 20%) was not appropriately increased in patients with diabetes compared with patients without diabetes. In marked contrast, 70% of patients underwent revascularisation in this study. It is possible that at least partly as a result of this difference, 2-year mortality in patients with diabetes in the OASIS registry was increased by 50% compared with diabetic patients in our study. This hypothesis is supported by a recent study of 376 consecutive patients [5] showing that although diabetic patients with non-Q-wave myocardial infarction represented a cohort with more risk factors for poor outcome, aggressive in-hospital revascularisation with percutaneous coronary intervention resulted in excellent short-term outcome and 1-year survival similar to that in non-diabetic patients (92% vs 94%, NS). In addition, the beneficial effect of coronary stenting compared with standard balloon angioplasty on vessel patency and long-term clinical outcome in diabetic patients has now been demonstrated conclusively [18].

We acknowledge that the revascularisation strategy applied in UA/NSTEMI patients with three-vessel disease is controversial. In this study, coronary stenting was not restricted to patients with one- and two-vessel disease, but also favoured in patients with three-vessel disease, if the target lesion seemed accessible. It is important to note that the benefit of percutaneous coronary intervention over coronary artery bypass grafting in UA/NSTEMI patients with diabetes and three-vessel disease has yet to be proven. Although this intervention is common in well-established centres, which report an association with significantly lower morbidity, long-term outcome data from randomised trials specifically including UA/NSTEMI patients are lacking. In diabetic patients presenting with stable coronary artery disease, coronary artery bypass grafting seems to be more effective [19].

The treatment strategy applied in our patients is novel in two ways: the timing of the intervention and the preferred method of revascularisation. Coronary angiography and subsequent coronary stenting of the culprit lesion, as the primary revascularisation method, were performed within 24 hours of admission

in all patients. The percutaneous coronary intervention : coronary artery bypass grafting ratio was 4:1. In the FRISC II study, coronary angiography was performed within the first 7 days and the percutaneous coronary intervention : coronary artery bypass grafting ratio was 1:1. In addition, the FRISC II study excluded patients with previous coronary artery bypass grafting, and patients with advanced age. These differences may explain the discrepant findings in multivariate analysis with respect to the independent impact of diabetes mellitus on long-term mortality [13]. In the FRISC II study, diabetes mellitus remained an independent predictor of mortality at 12 months.

The prognostic impact of diabetes mellitus was different between women and men. Women with diabetes mellitus had similar long-term outcome to women without diabetes mellitus, whereas mortality was significantly increased in diabetic men compared with non-diabetic men. This finding is in contrast to the observation of the OASIS registry, where diabetes mellitus was of greater prognostic importance for women than for men. This may suggest that the association between diabetes mellitus and sex depends on the management strategy applied in UA/NSTEMI (very early invasive vs conservative strategy). The very early invasive strategy seems to counteract and compensate for many of the extra risk factors present in diabetic women with UA/NSTEMI. The timing of the revascularisation procedure may, at least in part, explain why diabetic women derived such a major benefit from the management strategy applied in our study compared with the management strategy applied in OASIS. Although several pathophysiological distinctions [20, 21, 22, 23, 24] have been reported between women and men, the fact that women seem to form fewer coronary collaterals than men [24] may be of great importance. Due to this lack of collaterals, women may benefit particularly from a rapid correction of the epicardial obstruction during UA/NSTEMI [25]. However, further study is necessary to confirm this hypothesis.

Our analysis has four distinguishing features: (i) it is derived from a prospective study of consecutive unselected patients rather than from a randomised trial. This eliminates selection bias and allows generalisation and extrapolation of the findings into clinical practice; (ii) it involves long-term follow-up; (iii) a uniform revascularisation strategy was applied in all patients; and (iv) the extent of coronary artery disease was quantified in all patients and included in the multivariate analysis as a potential cofounder. This enables us to investigate the impact of diabetes mellitus, independent of the extent of coronary artery disease at presentation.

In conclusion, diabetic patients with UA/NSTEMI have more advanced coronary artery disease and more severe UA/NSTEMI than non-diabetic patients. Consequently, their in-hospital and long-term mortality is higher. However, when a very early invasive strategy

is applied, and after adjustment for baseline characteristics, ECG findings, markers of inflammation and myocardial necrosis, and the angiographic extent of coronary artery disease, diabetes mellitus is no longer an independent predictor of death.

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