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Diabetes Mellitus: The Major Risk Factor in Unstable Coronary Artery Disease Even After Consideration of the Extent of Coronary Artery Disease and Benefits of Revascularization

Anna Norhammar, MD, PHD,* Klas Malmberg, MD, PHD,* Erik Diderholm, MD, PHD,† Bo Lagerqvist, MD, PHD,† Bertil Lindahl, MD, PHD,† Lars Rydén, MD, PHD, FACC,* Lars Wallentin, MD, PHD†

Stockholm and Uppsala, Sweden

OBJECTIVES This study was designed to study the influence of diabetes on the outcome of unstable coronary artery disease (CAD).

BACKGROUND Diabetes mellitus is a major contributor to CAD. Despite improvement in the management of patients with unstable coronary syndromes, this condition is still linked to a substantially increased mortality and morbidity among diabetic patients. Recent evidence advocates early revascularization in unstable coronary syndromes. Diabetic patients subjected to coronary interventions under stable conditions have a higher risk for complications and a more dismal prognosis than nondiabetic subjects. Accordingly, it is of considerable interest to obtain further information regarding the best possible management of diabetic patients with unstable CAD.

METHODS A total of 2,158 patients without and 299 with diabetes mellitus were randomized to an early invasive or a noninvasive strategy. The severity of CAD was expressed as the number and extent of vessel involvement.

RESULTS Three-vessel disease was diagnosed in 42% of diabetic and 31% of nondiabetic patients ($p = 0.006$). The percentages of patients with ST-depression and troponin-T >0.03 μg/l at admission were comparable among diabetic and nondiabetic patients. Mortality and reinfarction after 12 months were more frequent among diabetic than nondiabetic patients in both treatment groups. Diabetes remained a strong independent predictor for death and myocardial infarction in multivariable analysis. The invasive strategy reduced event rate in nondiabetic patients from 12.0% to 8.9% (odds ratio [OR] = 0.72; confidence interval [CI] 0.54 to 0.95; $p = 0.019$) and in diabetic patients from 29.9% to 20.6% (OR 0.61; CI 0.36 to 1.04; $p = 0.066$). In a multivariate analysis including the extent of CAD, diabetes remained a strong independent predictor of the combined end point (relative risk [RR] 2.40; CI 1.47 to 3.91; $p = 0.0001$) and of mortality (RR 5.43; CI 2.09 to 14.12; $p = 0.001$).

CONCLUSIONS An invasive strategy improved outcome for both diabetic and nondiabetic patients with unstable CAD. However, diabetes mellitus remained an independent and important risk factor for death and myocardial infarction in the invasive group. Thus, factors beyond the extent of flow-limiting coronary lesions are of considerable importance for outcome in diabetic subjects with unstable coronary syndromes. (J Am Coll Cardiol 2004;43:585–91)
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Among risk factors for coronary artery disease (CAD), diabetes mellitus (DM) is a major contributor, not only to the development of CAD but also to outcome following various manifestations of the disease. In fact, increasing levels of blood glucose, even below the level of established diabetes, serve as predictors of increased risk (1). Despite improvement in the management of patients with unstable coronary syndromes, unstable CAD is still linked to a substantially increased mortality and morbidity among diabetic patients, as demonstrated by the OASIS and GUSTO II trials (2,3). Because the prevalence of DM in patients with myocardial infarction (MI) is high, and the prevalence in the general population is expected to increase in coming decades (4), management of the diabetic patient cohort will substantially affect total morbidity and mortality in this disease.

Recent evidence advocates early revascularization in unstable coronary syndromes (5,6). Diabetic patients subjected to coronary interventions under stable conditions have a higher risk for complications and a more dismal prognosis than nondiabetic subjects (7–9). Diabetic patients more often have three-vessel disease and a more diffuse coronary artery involvement than their nondiabetic counterparts (10,11), factors that may contribute to the less favorable outcome following revascularization. Accordingly, it is important to determine whether the best management of

From the *Department of Cardiology, Karolinska Hospital, Stockholm, Sweden; and †Department of Cardiology, Uppsala University Hospital, Uppsala, Sweden. The FRISC II trial was supported by and organized in collaboration with the Pharmacia and Upjohn Company. The Swedish Heart-Lung Foundation supported this part of the study.

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Abbreviations and Acronyms

CABG	= coronary artery bypass graft
CAD	= coronary artery disease
CK	= creatine kinase
DM	= diabetes mellitus
ECG	= electrocardiogram
MI	= myocardial infarction
PCI	= percutaneous coronary intervention
RIKS-HIA	= Register of Information and Knowledge about Swedish Heart Intensive
RR	= risk ratio

diabetic patients with unstable CAD involves immediate revascularization or a more conservative approach based on pharmacologic therapy.

The FRISC II database offers unique opportunities to explore the best possible treatment of diabetic patients with unstable CAD. The present study describes the association between diabetes and outcome in relation to the extent of CAD and other risk factors of prognostic importance and investigates whether early revascularization improves the prognosis for patients with diabetes.

MATERIALS AND METHODS

The FRISC II invasive study was a prospective, randomized multicenter trial recruiting patients admitted to hospital because of unstable CAD. Full details on this study have been given elsewhere (12,13). Eligible patients were randomized as soon as possible, but at the latest within 72 h after the start of open-label dalteparin (or standard heparin), to one of four treatment policies: invasive strategy and long-term dalteparin, invasive strategy and long-term placebo, noninvasive strategy and long-term dalteparin, or noninvasive strategy and long-term placebo. With the invasive strategy, the target was to perform all invasive procedures within seven days after starting open-label dalteparin. The comparison of the invasive and noninvasive strategies was not blinded. Follow-up lasted 12 months.

Patients. Patients were eligible for inclusion if they had symptoms of ischemia that were increasing or occurring at rest or warranting the suspicion of acute MI, with the last episode preceding the first dose of dalteparin or standard heparin by <48 h. Furthermore, myocardial ischemia had to be verified by electrocardiogram (ECG) (ST-depression ≥0.1 mV or T-wave inversion ≥0.1 mV), or by elevation of biochemical markers (creatine kinase [CK]-MB >6 μg/l, troponin-T ≥0.10 μg/l, qualitative troponin-T test positive, or catalytic activity of CK, CK-B, or CK-MB above the local decision limit for the diagnosis of MI). The exclusion criteria included raised risk of bleeding or anemia, indication for or treatment with thrombolysis within the past 24 h, angioplasty performed within the past six months, on a waiting list for coronary revascularization procedure, other acute or severe cardiac disease, renal insufficiency (creatinine >150 μmol/l), hepatic insufficiency, known clinically relevant osteoporosis, other severe illness, hypersensitivity to randomized drugs, anticipated problems of cooperation, or participation in this or another clinical trial. Patients with previous open-heart surgery, advanced age (above 75 years), or other conditions that, in the investigator's judgment, made randomization to revascularization inappropriate were not eligible. The criteria for diabetes in this study were that the diagnosis was known to the patient and that treatment had been prescribed with diet, oral antidiabetic drugs, or insulin.

Intervention strategies. The direct invasive strategy required coronary angiography within a few days of enrollment, aiming for revascularization within seven days from the start of open-label dalteparin (or standard heparin). Revascularization was recommended in all patients with a ≥70% diameter obstruction in any artery supplying a significant proportion of the myocardium. Percutaneous coronary intervention (PCI) was recommended if there were one or two target lesions, whereas coronary artery bypass grafting (CABG) was to be preferred in patients with three-vessel or left main disease.

The noninvasive strategy included coronary angiography in patients with refractory or recurrent symptoms (despite maximal medical treatment) or severe ischemia at a predischarge symptom-limited exercise test (12). During follow-up, invasive procedures were to be considered, regardless of randomized strategy, for all patients with incapacitating symptoms, recurrence of instability, or MI.

Open and double-blind dalteparin treatment. On admission, the patients were initially treated with either subcutaneous dalteparin or APTT-adjusted standard heparin infusion. From randomization, all patients received dalteparin, 120 IU/kg/12 h subcutaneously (maximal dose 10,000 IU), for at least five days, and always until invasive procedures. Thereafter, the patients received twice-daily subcutaneous injections of either dalteparin or placebo for three months (12).

Concomitant therapies. Aspirin was administered to all patients on admission in an initial dose of 300 to 600 mg followed by a maintenance dose of 75 to 320 mg once daily. Beta-blockers was given unless contraindicated. Organic nitrates and calcium antagonists could be added as required. Cholesterol lowering with statins, angiotensin-converting enzyme inhibitors for left ventricular dysfunction, and aggressive antidiabetic treatment were recommended, according to modern European treatment guidelines. The use of the glycoprotein IIb/IIIa receptor inhibitor abciximab during PCI was encouraged. Ticlopidine was recommended for three to four weeks after stent placement. All ECGs and exercise tests were sent to a core laboratory for evaluation.

Extent of CAD. Based on the coronary arteriographic findings, the extent of CAD was expressed in two ways. The first was a simple classification in one-, two-, and three-(including left main) vessel disease. In the second a coronary "atheroma score" was constructed by dividing the coronary arteries from each patient, depending on differences in

anatomy, into a maximum of 15 segments (14). Each segment was visually analyzed for atheromatosis and the extent of stenosis and given a score based on the maximum degree of narrowing (0 for no stenosis, 1 for stenosis <50%, 2 for 50% to 70% obstruction, 3 for >70% to <100%, and 4 for total occlusion). An "atheroma score" (0 to 1) was subsequently derived for each patient as the sum of observed scores divided by the theoretical maximum score (corresponding to total occlusion in all evaluable segments).

Efficacy end points. The primary end point was a composite end point of death or MI. Myocardial infarction was based on the presence of two out of the conventional three criteria: typical chest pain, diagnostic ECG recording (mainly new Q-wave), or elevation of biochemical markers of myocardial damage. The decision levels for biochemical markers of myocardial damage in relation to nonprocedural and procedure-related MI have previously been detailed (13). Only new Q-waves were used for the diagnosis of MI in association with CABG. Autopsy was recommended to establish cause of death. During the first six months, all reported deaths, MIs, elevation of biochemical markers in relation to PCI procedures, and new Q-waves reported by the ECG core laboratory were adjudicated by an independent clinical event committee. After this period, information on further events was evaluated by the local investigator on the basis of outpatient visits or telephone contacts with all surviving patients and, in the case of readmission to hospital, on hospital records. The cause of death during this period was based either on hospital records or on death certificates.

Statistics and data management. All statistical analyses were performed on an intention-to-treat basis. The efficacy analyses were based on events occurring from the start of open-label dalteparin treatment until 12 months. Analyses were also performed in predefined subgroups. The efficacy analyses of the one-year follow-up were point estimates including only patients with an adjudicated event or with recorded absence of the evaluated event until at least day 365 of follow up. Student's *t* test or Pearson chi-squared test was used to test the significance between patients with and without DM. The Mantel-Haenszel chi-square test was used to determine the significance of the overall degree of association. The results are presented as the risk ratio with 95% confidence interval. No adjustment was made for multiple comparisons. Graphs of the Kaplan-Meier estimate of the survival function were used without statistical analysis. The occurrence of possible interactions between the randomized invasive strategy and other factors was evaluated by logistic multiple regression analysis. The coordinating investigators, using the SPSS 10.1 statistical program for personal computer, performed the data processing and statistical analyses. The study complied with the Declaration of Helsinki, and all local ethics committees approved the protocol.

RESULTS

A total of 2,457 patients, 299 (12%) with and 2,158 (88%) without DM, were randomly allocated to either invasive or noninvasive management. Of the 299 diabetic patients, 155 were assigned to the invasive and 144 to the noninvasive branch. The corresponding figures for the nondiabetic subjects were 1,067 (invasive) and 1,091 (noninvasive), respectively. Pertinent baseline characteristics of the diabetic and nondiabetic patients are given in Table 1. The diabetic group was at higher risk with a higher prevalence of angina pectoris, previous MIs, heart failure, and peripheral vascular disease, and they were more frequently on treatment for hypertension. The occurrence of ST-depressions or elevation of troponin-T was similar in diabetic and nondiabetic patients. Diabetic patients were less often smokers. Admission blood glucose was significantly higher among the diabetic patients, 9.2 ± 3.4 mmol/l versus 5.4 ± 1.3 mmol/l ($p < 0.0001$).

Treatment instituted during hospitalization, as revealed by ongoing therapy at hospital discharge, differed between the two groups. As presented in Table 2, the diabetic patients were more frequently given calcium-channel blockers, angiotensin-converting enzyme inhibitors, and diuretics. As many as 41% of the diabetic patients were given insulin, whereas 49% were given oral agents.

Angiographic findings in the invasive group. Coronary angiography was available for 1,049 of the nondiabetic and for 151 of the diabetic patients, respectively. Figure 1 clearly demonstrates the significantly more widespread CAD among the diabetic cohort, with as many as 42% of these patients categorized either as having significant three-vessel or left main CAD compared with 31% of the nondiabetic patients ($p < 0.006$). The average "atheroma score" in nondiabetic patients was 0.18, compared with 0.24 in those with DM ($p < 0.001$). The proportion of nondiabetic

Table 1. Baseline Characteristics of Patients With and Without Diabetes Mellitus

Parameter	Patients		p Value
	No Diabetes n = 2,158	Diabetes n = 299	
Age (yrs; mean ± SD)	64 ± 9	66 ± 8	NS
Men	69% (1,492)	72% (216)	NS
Previous			
Angina pectoris	34% (733)	46% (137)	<0.001
Myocardial infarction	21% (457)	30% (89)	0.001
Heart failure	2.6% (56)	6.0% (18)	0.001
Stroke	4.4% (94)	6.0% (18)	NS
Peripheral vascular disease	2.9% (62)	7.7% (23)	<0.001
Hypertension	28% (596)	49% (147)	<0.001
PCI	3.2% (70)	3.3% (10)	NS
CABG	0.4% (8)	0.3% (1)	NS
Smoker	32% (687)	19% (58)	<0.001
ST depression	46% (969)	50% (145)	NS
Troponin T >0.03 μg/l	68% (1,389)	70% (200)	NS
Blood glucose (mmol/l ± SD)	5.4 ± 1.3	9.2 ± 3.4	<0.001

Values are percentages and numbers are within ( ).
CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

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Table 2. Treatment at Hospital Discharge in Patients With and Without Diabetes Mellitus

Treatment at Discharge	Patients: No Diabetes n = 2,158	Patients: Diabetes n = 299	p Value
Aspirin	95% (2007)	95% (265)	NS
Beta-blockers	85% (1783)	84% (234)	NS
Calcium blockers	18% (390)	24% (66)	0.045
ACE-inhibitors	16% (326)	36% (101)	<0.001
Diuretics	17% (359)	27% (76)	<0.001
Digitalis	3.6% (75)	5.7% (16)	NS
Statins	45% (937)	40% (113)	NS
Insulin	0.1% (2)	41% (115)	<0.001
Oral antidiabetic drug	0.6% (13)	49% (137)	<0.001

Values are percentages and numbers are within ( ).
ACE = angiotensin-converting enzyme.

patients that underwent coronary angiography without any subsequent coronary intervention was 21.1%, whereas 43.8% were treated with PCI and 35.2% were treated with CABG, respectively. The corresponding proportions for the diabetic cohort were 15.9%, 40.4%, and 43.7%, respectively. The proportion of patients given abciximab was 10% in the nondiabetic group and 7% among those with diabetes. The corresponding proportion of stent use was 27% and 31% of those treated with PCI.

Mortality and morbidity. The crude event rate as regards MI and mortality is presented in Figure 2. The diabetic patients had a higher mortality and more myocardial reinfarction than nondiabetic patients in both the invasive and the noninvasive groups. Allocation to invasive management reduced the occurrence of the primary end point among nondiabetic patients from 12% (n = 131) to 8.9% (n = 95) (invasive vs. noninvasive management, odds ratio [OR] = 0.72; confidence interval [CI] 0.54 to 0.95; p = 0.019). The corresponding event rates in the diabetic group were significantly higher, but with a larger relative as well as absolute reduction by the invasive strategy, 29.9% (n = 43) and 20.6% (n = 32), respectively (invasive vs. noninvasive management OR = 0.61; CI 0.36 to 1.04: p = 0.066). In Figure 2, there was a similar pattern concerning mortality. Mortality was reduced from 2.7% (n = 30) to 1.4% (n = 15) among nondiabetic patient and from 12.5% (n = 18) to 7.7% (n = 12) among diabetic patients. The probability of death or MI over time is shown in Figure 3, once more demonstrating that diabetic patients, both in the noninvasive and invasive groups, had a significantly higher event rate than nondiabetic patients. The proportionate improvement in outcome by the invasive strategy was, however, similar in the two groups, and there was no interaction between the diagnosis of DM and management strategy.

Multivariate analysis. Because diabetic patients are a population at higher risk than nondiabetic patients, multivariate statistics were applied to study whether diabetes as such was an independent risk predictor. In this model all parameters that differed significantly ($p \leq 0.05$) between the diabetic and the nondiabetic patient cohort as regards case history, baseline characteristics, and in-hospital management were taken into account. Independent predictors for death or MI in the combined invasive and noninvasive strategy groups are depicted in Figure 4, demonstrating that DM in fact represents an independent predictor of risk (risk ratio [RR] 2.61; CI 1.88 to 3.60; p = 0.0001). Looking at mortality only, the corresponding independent risk increase was 5.42; CI 3.12 to 9.39; p = 0.0001).

In order to study the effect of coronary artery involvement, a multivariate analysis also including the extent of CAD was performed among patients in the invasive group. When this analysis was based on categorization according to one-, two-, or three-vessel disease (Fig. 5) DM remained as an independent predictor of the combined end point (RR 2.40; CI 1.47 to 3.91; p = 0.0001) as well as for mortality (RR 5.43; CI 2.09 to 14.12; p = 0.001). In contrast, the traditional predictors of outcome in unstable CAD—ST-depression, presence of three-vessel disease and age—did not remain as significant risk predictors for death or MI in the invasively managed group underlining the importance of DM for the outcome. Expressing the severity of CAD according to the "atheroma score" resulted in an almost identical risk pattern for the combined end point (RR 2.40; CI 1.47 to 3.91; p < 0.001) as well as for mortality (RR 5.84; CI 2.27 to 15.05; p < 0.001). Although both the number of involved coronary arteries and the "atheroma score" were significantly related to the combined end point in univariable analysis (p = 0.016 and p = 0.022, respectively), they did not remain as significant independent prognostic variables (p = 0.62 and p = 0.59) after adjustment for all other variables, including diabetes, in the multivariate analysis in the invasive group.

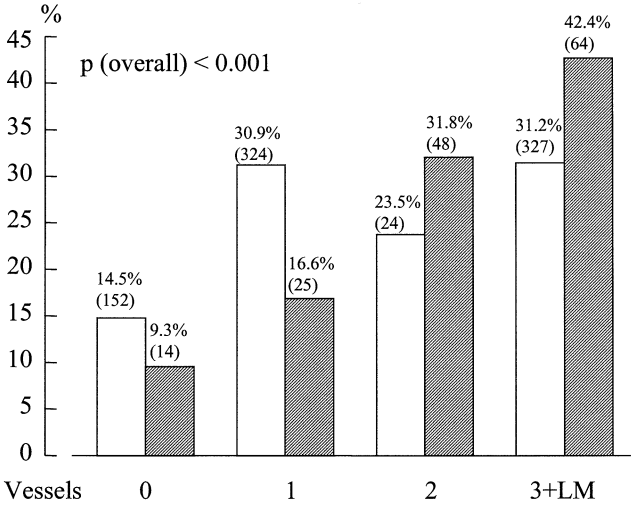

Figure 1. Number of coronary arteries with significant lesions in patients with **(hatched bars)** and without **(open bars)** diabetes mellitus. Figures within brackets represent number of patients in each group. LM = left main coronary artery.

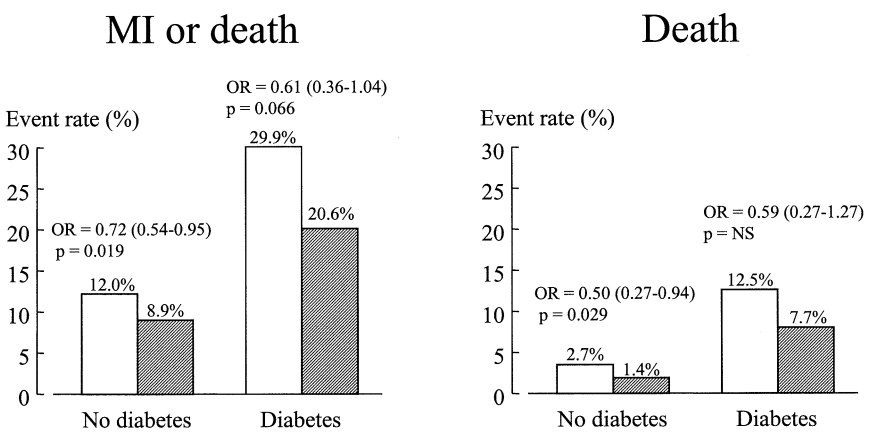

Figure 2. Crude one-year event rates as regards myocardial infarction (MI) and mortality in patients with and without diabetes mellitus subjected to an invasive **(hatched bars)** and noninvasive **(open bars)** management strategy (see text for further explanation). OR = odds ratio.

DISCUSSION

The main finding in this subgroup analysis of the FRISC II trial, investigating management strategies in unstable CAD, is that patients with DM had a significantly higher rate of death or MI than did nondiabetic patients. This was apparent both in invasively and noninvasively managed patients. The outcome for diabetic patients was considerably worse even with the invasive strategy than for noninvasively handled patients without diabetes (event rates 21% and 12%, respectively). Notably, the relative impact of an early invasive strategy was of the same magnitude in both diabetic and nondiabetic patients. This means that the absolute effect in people with diabetes was substantially larger than in the nondiabetic group: approximately 11 patients with diabetes had to be treated for one saved MI or death with an invasive strategy, compared with 32 nondiabetic patients.

A limitation with the present investigation, as with most studies on treatment effects in patients with diabetes, is that it originates from a retrospective subgroup analysis. Even if the number of patients with diabetes were enough for comparing their outcomes to those without diabetes, from an epidemiologic perspective it may be argued that the proportion of diabetic patients, 12%, is rather low. From previous studies we know that in populations with acute MI and with unstable angina at least about 20% have DM (15–18). Thus, there may be a selection bias in FRISC II, with the implication that some diabetic patients may have been excluded despite fulfilling the inclusion criteria. At the time of patient recruitment, there may have been a hesitancy to expose diabetic patients with acute coronary syndromes to early coronary interventions. This assumption gets support from a recent survey based upon the Register of Information and Knowledge about Swedish Heart Intensive care (RIKS-HIA) (17) demonstrating that patients with DM and acute MI are significantly less often revascularized within 14 days from hospital discharge. Thus, it may very well be that the most complex diabetic patients were in fact excluded. In that case the present results will, if anything, underestimate the true risk of the combination of DM and acute coronary syndromes. It is obvious that the present data confirm previous reports on the dismal prognosis for diabetic patients with acute coronary syndromes (2,16,17). It truly underlines that non–Q-wave MIs and unstable angina are major events among people with DM.

The data from the Swedish RIKS-HIA demonstrate that patients with DM and acute MI are less often offered established, evidence-based pharmacologic treatment and are significantly less often revascularized during the immediate postinfarction period (17). The present data provide no reason for such an underutilization. Instead, the results support an increased awareness for an early invasive approach in patients with diabetes. However, it should be emphasized that despite the best available treatment strategy, diabetic patients were left with a substantially higher mortality and morbidity than their nondiabetic counterparts. Accordingly, there must also be other factors to take into account when discussing the optimal treatment of diabetic patients.

As expected and previously shown (10,11), diabetic patients had more extensive CAD. However, diabetes was an independent predictor of the primary composite end point

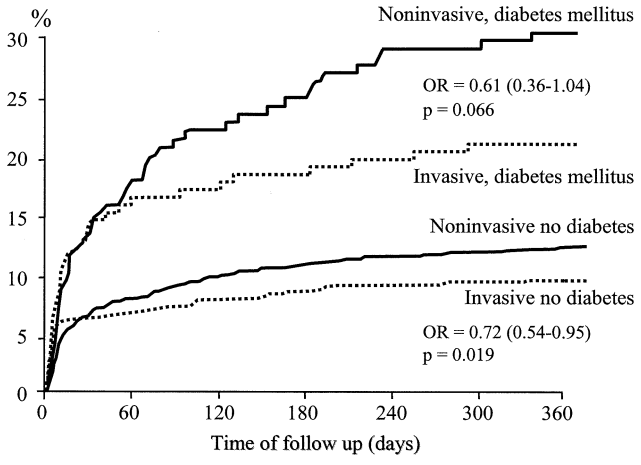

Figure 3. The probability of death or myocardial infarction over time. OR = odds ratio.

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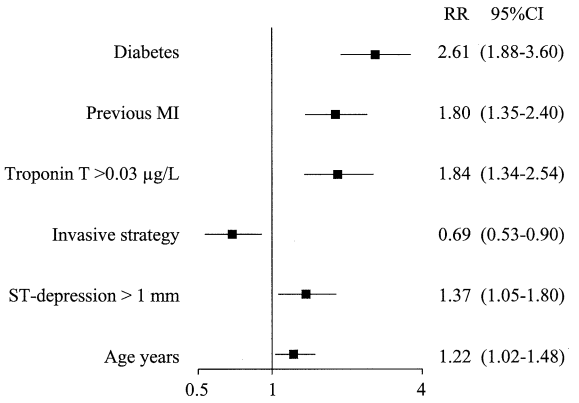

Figure 4. Independent predictors for the composite primary end point (death or myocardial infarction [MI]) in the total patient cohort (invasive and noninvasive strategy patients) according to multivariate statistics. The scale on the x-axis is logarithmic. CI = confidence interval; RR = risk ratio.

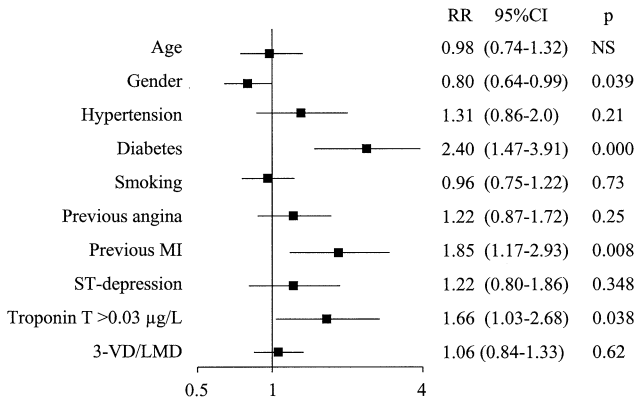

Figure 5. Independent predictors for the composite primary end point (death or myocardial infarction [MI]) in the invasive strategy group according to multivariate analysis. The scale on the x-axis is logarithmic. CI = confidence interval; LMD = left main coronary artery disease; RR = risk ratio; VD = vessel disease.

and for mortality even after statistical adjustment for all baseline dissimilarities including the extent of CAD evaluated in two different ways, signs of myocardial damage and for revascularization. In contrast to most other risk indicators, DM remained a strong predictor of a worse outcome even after elimination of the most important flow-limiting coronary lesion. The most reasonable explanation for these findings is that the diabetic state by itself is important for the final outcome. This highlights the impact of diabetes even in a revascularized group and offers support for further diabetes-specific therapy with the intention to improve outcome in these high-risk patients.

Several mechanisms may contribute to the increased risk in type 2 diabetic patients, as recently reviewed (19). Notably, thromboembolic events are promoted by a combination of increased platelet aggreggability and decreased fibrinolytic function. Endothelial dysfunction deteriorates myocardial flow reserve, and the myocardial diastolic function is often compromised in the diabetic heart, which, especially in stressful situations, is forced to an unfavorable metabolism characterized by an increased rate of beta-oxidation of free fatty acids. Many, if not all, of these perturbations may be counteracted by intense insulin-based metabolic control (20,21). It has also been noted that effective antithrombotic treatment may be of a particular value in the diabetic patient (22).

The present study did not define whether an early intervention should be a PCI or a bypass procedure (CABG). This decision was at the discretion of the physician in charge and no randomization was undertaken between the different procedures. It is therefore not possible, on the basis of FRISC II data, to elaborate on the preference of technique for the diabetic compared with the nondiabetic patient. Still, the choice of revascularization procedure, PCI or CABG, may be of great importance for the final outcome. The BARI trial clearly indicates that diabetic patients with multivessel disease benefit from CABG compared to PCI (15). The major problem with PCI in diabetic patients is the high rate of restenosis that probably translates into a decreased survival (15,23,24). The present result was obtained with limited use of stent implantations and GP IIb/IIIa infusions. It may be anticipated that modern PCI, including a more liberal use of stent implantation and GP IIb/IIIa prescription, drug-eluting stents, and new platelet-stabilizing drugs, may reduce the rate of restenosis (22,25,26), offering diabetic patients more opportunities to successful PCI.

In summary, the present data give strong support to the updated version of the European Guidelines (27) stating that diabetic patients with non–ST-elevation acute coronary syndromes should be defined as patients at high risk for mortality and new infarcts. This risk is not only linked to conventional factors such as the extent of the CAD or size of myocardial damage, but seems also to a large extent related to factors specific to the metabolic disease. Early revascularization seems to have the same relative beneficial effect in both diabetic and nondiabetic patients. Hence, an early intervention strategy might be an important part of the treatment of diabetic patients with acute coronary syndromes. This should, however, be supplemented with further therapies and strategies directed towards the many abnormalities that are associated with DM, such as endothelial dysfunction, dysglycemia, and coagulation and fibrinolytic disturbances. Key targets for additional treatment need to be evaluated in forthcoming trials in diabetic patients with and without revascularization.

Reprint requests and correspondence: Dr. Anna Norhammar, Department of Cardiology, Karolinska Hospital, 171 76 Stockholm, Sweden. E-mail: anna.norhammar@ks.se.

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