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Influence of diabetes mellitus on clinical outcomes across the spectrum of acute coronary syndromes

Findings from the GUSTO-IIb Study

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Aims We examined the characteristics, outcomes, and effects of hirudin vs heparin treatment of diabetic patients across the spectrum of acute coronary syndromes.

Methods and Results We studied the 12 142 patients enrolled in the randomized GUSTO-IIb study. Diabetic patients (n=2175) were older, more often female, more often had prior cardiovascular disease, hypertension, and hyperlipidaemia, and less often were current smokers. Diabetic patients had a higher overall incidence of death or (re)infarction at 30 days (13·1% vs 8·5%, $P=0·0001$), whether they presented with ST-segment elevation (13·9% vs 9·9%, $P=0·0017$) or not (12·8% vs 7·8%, $P=0·0001$), and at 6 months (18·8% vs 11·4%, $P=0·0001$). Among diabetic patients, hirudin was associated with a tendency toward a lower risk of death or (re)infarction at 30 days (12·2% vs 13·9% with heparin) and 6 months (17·8% vs 20·2%). Diabetic patients had more major bleeding, stroke, heart failure, shock, atrioventricular block, and atrial arrhythmias, but no increased risk for ocular bleeding.

Conclusions Diabetic patients with acute coronary syndromes had worse 30-day and 6-month outcomes, particularly those without ST-segment elevation. The statistically non-significant trend toward improved outcomes with hirudin was similar among patients with and without diabetes, with a greater point estimate for the absolute difference in patients with diabetes.
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Key Words: Unstable angina, myocardial infarction, diabetes mellitus, hirudin, heparin.

Introduction

Epidemiological studies suggest that patients with diabetes mellitus have an increased prevalence of coronary artery disease, an increased incidence of acute coronary syndromes, and worse outcomes after these events compared with patients without diabetes[1–4]. Recent prospective clinical trials support these observations[5–8]. These analyses are limited by several factors, however. Most data have been derived from assessments of patients with ST-segment elevation myocardial infarction who are eligible for thrombolysis, representing only a minority of acute coronary syndrome patients. Other studies of broader cohorts are limited by their relatively small sample sizes and by the small proportions of patients with diabetes enrolled.

The Global Use of Strategies To Open Occluded Coronary Arteries in acute coronary syndromes (GUSTO-IIb) study captured the entire spectrum of acute coronary syndrome patients, including unstable angina, non-ST-segment elevation infarction, and ST-segment elevation infarction (both thrombolytic-eligible and -ineligible). The broad inclusion criteria and large proportion of patients with diabetes, paired with nearly-complete data through 6 months of follow-up, provide a comprehensive dataset from which we can describe the characteristics and outcomes of patients with diabetes after acute coronary syndromes.

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The primary objective of the GUSTO-IIb trial was to compare heparin with recombinant hirudin, a potent, direct thrombin inhibitor. Since aberrations of the coagulation system associated with diabetes may contribute to the worse clinical outcomes of patients with acute coronary syndromes, we analysed the relative efficacy of hirudin, a more potent and specific thrombin inhibitor, compared with heparin in the subset of patients with diabetes.

Methods

Patients

The GUSTO-IIb trial included 12 142 patients enrolled at 373 hospitals in 13 countries from 19 May 1994 to 17 October 1995. These patients had presented within 12 h of chest pain, consistent with acute coronary syndrome and had either transient or persistent ST-segment elevation or depression, or T-wave inversion. Details of the study design have been reported[9]. For this study, patients were considered to have diabetes if they had a prior diagnosis of diabetes, were receiving either oral hypoglycaemic agents or insulin at entry, or were diagnosed with diabetes during the index admission.

Antithrombin treatment

Patients were randomized to receive either intravenous heparin with hirudin placebo or hirudin with heparin placebo for at least 3 but not more than 5 days, with the duration left to the discretion of the treating physician[9]. Dosing was adjusted in a double-blind fashion to achieve a target activated partial thromboplastin time of 60 to 85 s.

End-points

The primary end-point was the composite incidence of death or (re)infarction within 30 days after entry. This end-point also was assessed at 6 months of follow-up. Myocardial infarctions were centrally adjudicated against standard criteria[10] by members of a clinical-events committee who were blinded to treatment assignment.

Bleeding events were categorized according to defined criteria[10,11]. Bleeding was classed as severe if it involved intracranial haemorrhage or haemodynamic compromise requiring intervention. Moderate bleeding required transfusion but did not include haemodynamic compromise.

Statistical analysis

Continuous variables were summarized as median (25th, 75th percentiles) and categorical variables as percentages. Statistical analyses were performed according to the intention-to-treat principle. Differences in baseline characteristics were assessed using the Cochran–Mantel–Haenszel test for categorical variables and the Wilcoxon test for continuous variables. All *P*-values are two-sided. Logistic regression methods were used to assess differences with respect to the primary and secondary endpoints. Kaplan–Meier methods were used to generate event curves.

Results

Baseline characteristics

Of the 12 142 patients enrolled in the study, 2175 (18%) were diabetic (Table 1). Among the diabetic group, 668 patients had ST-segment elevation and 1507 did not. Diabetic patients were older, more often female and hypertensive, less often smokers, and had a higher prevalence of previous infarction. At entry, 26·9% of patients with diabetes were receiving insulin therapy. Patients with diabetes presented, on average, 30 min later in the course of symptoms, but among patients who received thrombolytic therapy, the symptom-to-thrombolytic time did not differ significantly between patients with and without diabetes.

Study medications and procedures

Diabetic patients more often received calcium blockers, nitrates, angiotensin-converting enzyme (ACE) inhibitors, and lipid-lowering agents and less often received thrombolytics or beta-blockers during hospitalization (Table 2). Swan-Ganz catheters and intra-aortic balloon counterpulsation were used more often among patients with diabetes. The rates of angiography and revascularization were comparable between the diabetic and non-diabetic groups.

Effect of diabetes on clinical outcomes

Diabetes was associated with a higher risk of death or (re)infarction at 30 days (13·1% vs 8·5%, $P=0·0001$) (Table 3). This difference remained significant after adjustment for age, pulse, and blood pressure on arrival; Killip class; ST-segment status; and history of hypertension, angina, infarction, and peripheral vascular disease (odds ratio [OR]: 1·34, 95% confidence interval [CI] 1·15–1·56).

Diabetic patients also had higher risks at 30 days for death alone (6·9% vs 4·1%, $P=0·0001$) and (re)infarction (8·2% vs 5·3%, $P=0·0001$). Among patients with

Table 1 Baseline clinical and demographic characteristics

	Diabetes* (n=2175)		No diabetes (n=9956)
	Hirudin (n=1030)†	Heparin (n=1145)	
Age (years)	67 (60, 73)	67 (60, 74)	64 (54, 73)
Female sex	39·7	36·6	28·4
Weight (kg)	79 (69, 91)	79·4 (69, 91)	75·7 (67, 85)
Current smoking	17·9	20·5	34·1
Prior angina	74·9	74·7	64·8
Prior infarction	35·7	33·0	25·1
Prior bypass surgery	14·5	14·5	8·6
Prior angioplasty	11·9	10·4	8·2
Prior congestive heart failure	11·2	9·6	4·4
Prior cerebrovascular disease	3·8	4·4	2·3
Peripheral vascular disease	12·9	15·3	6·7
Hypertension	60·3	59·7	42·1
Hypercholesterolemia	42·3	43·1	38·2
Body-mass index (kg . m^{2-1})	27·7 (25, 31)	27·7 (25, 31)	26·2 (24, 29)
US Sites	29·3 (26, 33)	29·3 (26, 33)	26·8 (24, 30)
Other Sites	27·0 (25, 30)	27·2 (25, 30)	26·0 (24, 29)
Systolic blood pressure (mmHg)	140 (122, 152)	140 (120, 155)	134 (120, 150)
Diastolic blood pressure (mmHg)	80 (70, 88)	80 (70, 90)	80 (70, 90)
Heart rate (per min)	79 (67, 91)	78 (68, 90)	73 (63, 84)
Killip class ≥II	18·1	18·4	11·2
Coronary artery disease (>2 vessels)	65·7		51·2
Ejection fraction	52 (41, 61)		55 (45, 65)
Treated with insulin	26·8	27·0	—
U.S. sites	37·1	36·1	
Other sites	20·5	21 5	
Hours from symptoms to treatment	2·7 (1·3, 6·0)	2 5 (1·1, 5·5)	2 3 (1·1, 4·8)
Hours from symptoms to thrombolysis‡	2·9 (1·9, 4·3)	2·9 (1·9, 4 5)	3·2 (2·1, 5·0)
Peak creatine kinase (IU . l^{-1})§	740 (331, 1695)	749 (338, 1856)	882 (394, 1875)
Serum creatinine (mg . dl^{-1})	1·03 (0·9, 1·23)	1·02 (0·9, 1·21)	1·02 (0·9, 1·20)

*All $P<0·05$ for patients with vs without diabetes, except for diastolic blood pressure and serum creatinine ($P=0·35$ and 0·28, respectively). †All $P>0·05$ for hirudin vs heparin in patients with diabetes. Hypercholesterolaemia=total cholesterol >240 mg . dl or on lipid-lowering treatment. ‡Among patients receiving thrombolytic therapy. §Among patients with myocardial infarction at enrolment.

ST-segment elevation, diabetes was associated with a higher incidence of the composite 30-day end-point (13·9% vs 9·9%, $P=0.002$), as it was among those presenting without ST elevation (12·8% vs 7·8%, $P=0·0001$). Among patients presenting with ST-segment elevation, the difference in the composite end-point was driven mostly by a 2·9% absolute increase in mortality in patients with diabetes (8·4% vs 5·5%, $P=0·004$), with a 1% absolute increase in (re)infarction rates (6·3% vs 5·3%, $P=0·30$). Diabetic patients without baseline ST elevation also had a 2·9% absolute increase in mortality (6·2% vs 3·3%, $P=0·0001$). In this subset, there was also a 3·7% absolute increase in the rate of (re)infarction (9·0% vs 5·3%, $P=0·0001$). The rate of death or (re)infarction remained higher in the diabetic group through 6 months (18·8% vs 11·4%, $P=0·0001$) (Fig. 1).

Diabetic patients treated with insulin at study entry tended to have a higher rate of death or (re)infarction than those treated with oral or dietary therapy at 30 days (15·0% vs 12·4%) and at 6 months (22·1% vs 17·9%) (Fig. 2). However, the use of insulin was not a significant predictor of 30-day outcome in univariable analysis (OR: 1.25, 95% CI 0·95–1·63).

The association of end-organ damage (previously diagnosed diabetic retinopathy, nephropathy, or neuropathy) with worse clinical outcomes was not statistically significant (OR: 1·16, 95% CI 0·78–1·71). However, serum creatinine was positively correlated with risk for the primary end-point (OR 2·59, 95% CI 1·79–3·74), a relationship that was significantly more pronounced among diabetic compared with non-diabetic patients ($P=0·013$).

Diabetic patients had higher overall rates of bleeding, but no increased risk of ocular haemorrhage (Table 4). Diabetes also was associated with a higher risk of several cardiovascular complications. Among patients surviving to discharge, there was no difference between groups in length of hospitalization. The rates of bypass surgery and percutaneous intervention were similar by diabetes status in patients with single-vessel coronary disease (Table 5). In patients with multivessel disease, however, a small but significant difference was noted in

Table 2 In-hospital medications and procedures

	Diabetes (n=2175)	No diabetes (n=9956)	*P*
Medications			
Aspirin	97·2	97·6	0·223
ACE inhibitors	43·6	28·9	0·001
Beta-blockers	68·4	72·4	0·001
Calcium-channel blockers	52·8	43·9	0·001
Nitrates	93·5	91·5	0·002
Lipid-lowering agents	17·0	13·2	0·001
Thrombolytic therapy*	69·0	74·9	0·001
Procedures			
Angiography	57·0	57·5	0·704
Angioplasty	23·8	24·0	0·883
Bypass surgery	12·2	11·5	0·357
Intra-aortic balloon pump	4·6	3·4	0·009
Swan-Ganz catheterization	6·0	3·6	0·001

*Percentage of eligible patients. ACE=angiotensin converting enzyme.

management, with diabetic patients being less likely to undergo either type of revascularization.

Effect of hirudin on clinical outcomes among patients with diabetes

The treatment effect of hirudin vs heparin on the primary end-point was similar to that observed in the overall population for patients with diabetes, at 30 days (12·2% vs 13·9%) and at 6 months (17·6% vs 19·8%) (Table 6, Fig. 3). There was no evidence of a significantly different treatment effect of hirudin for the 30-day end-point by diabetes status ($P=0.58$). There was no difference in the estimate of the treatment effect on mortality between the diabetic and non-diabetic groups at 30 days [1·04 (95% CI 0·75–1·45) vs 0·94 (95% CI 0·77–1·15)] or 6 months [0·94 (95% CI 0·73–1·21) vs 0·98 (95% CI 0·83–1·15)].

Discussion

This study reports the short- and intermediate-term clinical outcomes of diabetic patients representing the complete clinical spectrum of acute coronary syndromes. Previous studies have suggested an increased risk for reinfarction or death associated with diabetes ranging from 1·5- to 4-fold after acute coronary syndromes[1–7]. In the current study, diabetes was associated with a 1·8-fold higher risk of death or (re)infarction, with similarly increased risks for each component event.

Diabetes was associated with a higher risk of death or (re)infarction regardless of ST-segment status on presentation. Although ST elevation was associated with more death and (re)infarction among patients without diabetes, diabetic patients presenting without ST elevation did just as poorly as those who had ST elevation (Table 3, Fig. 1). This is largely due to a remarkable 3·7% absolute increase in the rate of infarction associated with diabetes among the non-ST-elevation subgroup. The increased cardiovascular risk associated with diabetes, especially for the recurrence of unstable coronary syndromes, likely reflects several factors.

Predictors of worse outcomes after acute coronary syndromes are more prevalent in the diabetic population, including advanced age, increased heart rate, reduced blood pressure, and congestive heart failure on arrival; and a history of hypertension, angina, infarction, and peripheral vascular disease[5–7]. The current data support both the increased prevalence of these factors and a significant increase in the odds of the primary end-point for patients with diabetes even after adjusting for them. There are probably other, unidentified characteristics of the diabetic condition that

Table 3 Primary and selected secondary efficacy end-points at 30 days by diabetes status

	Diabetes	No diabetes	Odds ratio (95% CI)	*P*
All patients	(n=2175)	(n=9958)		
Death	6·9	4·1	1·75 (1·5–2·1)	0·0001
(Re)infarction	8·2	5·3	1·59 (1·3–1·9)	0·0001
Death or (re)MI	13·1	8·5	1·63 (1·4–1·9)	0·0001
ST elevation	(n=668)	(n=3455)		
Death	8·4	5·5	1·57 (1·2–2·1)	0·0042
(Re)infarction	6·3	5·3	1·20 (0·9–1·7)	0·2983
Death or (re)MI	13·9	9·9	1·48 (1·2–1·9)	0·0017
No ST elevation	(n=1507)	(n=6503)		
Death	6·2	3·3	1·94 (1·51–2·50)	0·0001
(Re)infarction	9·0	5·3	1·76 (1·43–2·16)	0·0001
Death or (re) MI	12·8	7·8	1·74 (1·5–2·1)	0·0001

MI=myocardial infarction.

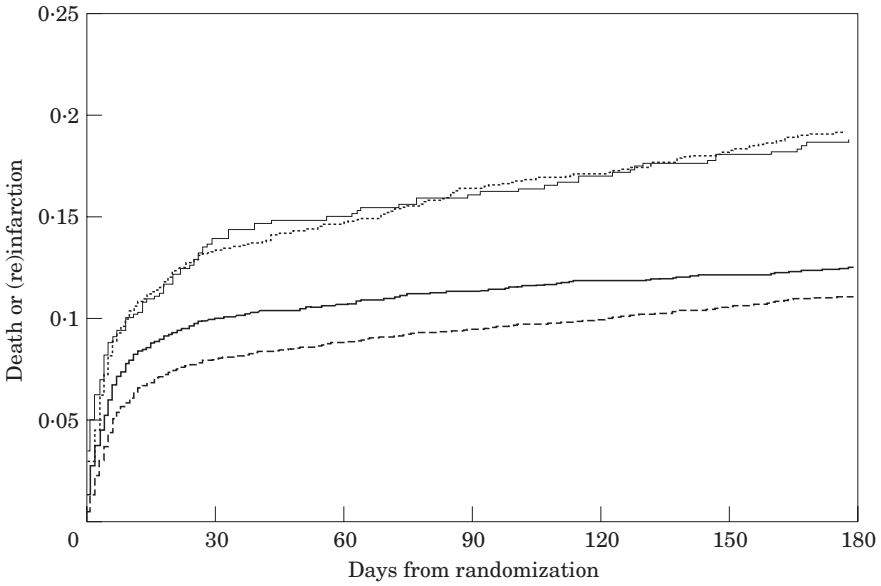

Figure 1 **Kaplan–Meier estimate of the probability of death or (re)myocardial infarction wthin 6 months after randomization according to ST segment status at the qualifying event among patients with and without diabetes. —=diabetes, ST elevation; · · · ·=diabetes, no ST elevation; ━=no diabetes, ST elevation; – – –=no diabetes, no ST elevation.**

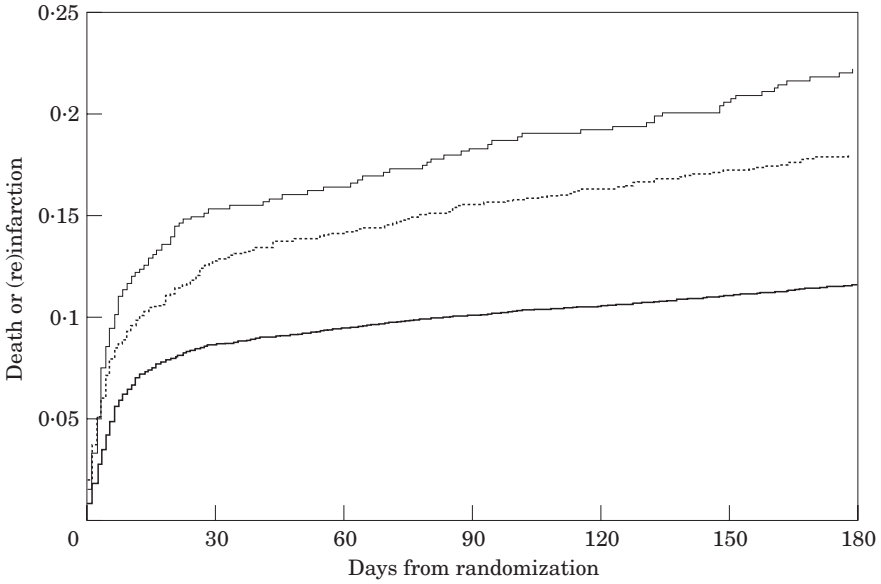

Figure 2 **Kaplan–Meier estimate of the probability of death or (re)myocardial infarction within 6 months after randomization according to insulin requirement among patients with and without diabetes. —=diabetes, insulin treatment; · · · ·= diabetes, no insulin treatment; ━=no diabetes.**

adversely affect clinical outcomes and predispose patients to recurrent ischaemic events. These include abnormalities of platelet function and the fibrino/proteolytic system, autonomic and endothelial dysfunction, possible toxicities of hypoglycaemic agents and sequelae of hypoglycaemic events, among others[12]. Continued pursuit toward a better understanding of these factors should lead to more effective cardiovascular therapies.

Differences in the use of evidence-based therapies may have contributed to the worse outcomes of diabetic patients in the study. Many studies have shown the benefits of thrombolysis, beta-blockers, and HMG-CoA reductase inhibitors ('statins') in diabetic patients with

Table 4 In-hospital clinical events

	Diabetes (n=2175)	No diabetes (n=9956)	*P*
Stroke or transient ischaemic attack	1·3	0·8	0·011
Severe bleeding	9·2	7·3	0·004
Moderate bleeding	22·0	20·1	0·044
Ocular bleeding	0·1	0·1	0·931
Congestive heart failure	7·2	3·8	0·001
Second- or third-degree heart block	4·0	2·9	0·008
Blood transfusion	11·5	8·4	0·001
Cardiogenic shock	5·2	3·0	0·001
Recurrent ischaemia	32·7	30·1	0·021
Refractory ischaemia	7·7	5·8	0·001
Atrial fibrillation or flutter	8·7	7·2	0·015
Post-enrolment infarction	5·7	4·3	0·003
Hospital stay (days)	8 (5, 13)	8 (6, 12)	0·257

Table 5 Initial treatment strategy by diabetes and severity of coronary atherosclerosis*

	Diabetes (n=2175)		No diabetes (n=9956)	
	Single-vessel diease	Multivessel disease	Single-vessel disease	Multivessel disease
Bypass surgery	16·7	34·3	16·0	36·9
Percutaneous intervention	36·4	16·8	36·5	18·1
Medical treatment	48·4	50·8	48·9	46·4

*Single-vessel=one coronary artery with >50% stenosis; multivessel=at least two coronary arteries with >50% stenoses.

coronary disease[5,614–20], whereas similar studies of calcium blockers have yielded no conclusive evidence for their use[21–24]. In the current study, patients with diabetes who presented with ST-segment elevation less often received thrombolytic therapy. The later presentation of the patients with diabetes was a likely contributor, but symptom duration before thrombolysis began did not differ significantly by diabetes status. Unwarranted concern over complications of thrombolytic therapy in diabetic patients, such as retinal haemorrhage, may have played a role in the different rates of thrombolytic use[5–7,13]. Patients with diabetes also received calcium blockers more often and beta-blockers less often. Further, although 40% of the patients with diabetes had hypercholesterolaemia, only 17% received lipid-lowering therapy. As appropriate, patients with diabetes were more likely to receive ACE inhibitors, but these drugs continue to be under-used in both groups. More effective application of evidence-based therapies would probably improve outcomes in these patients.

Differences in the use of procedures also may have contributed to the worse outcomes of patients with diabetes. The rates of angiography, angioplasty, and bypass surgery were similar between groups, but diabetic patients with multivessel disease underwent revascularization slightly less often than their non-diabetic counterparts. In fact, over 50% were treated medically. More aggressive revascularization, particularly bypass surgery, may have improved outcomes in this subset of patients[25–27], but data have been inconsistent about the optimal revascularization strategy for diabetic patients[28,29]. This issue requires further investigation.

Effect of hirudin

Diabetic status did not influence the non-significant trend toward a reduced rate of death or (re)infarction at 30 days with hirudin vs heparin observed in the overall trial ($P=0·06$). The point estimate of the absolute benefit of hirudin versus heparin was greater among patients with diabetes compared with the non-diabetic group, but was not statistically significant.

Although power was limited to detect different treatment effects among subgroups, one might have expected greater treatment effects among diabetic patients with the more potent, direct antithrombin agent, given their prothrombotic tendency. Several aberrations of the coagulation system occur in diabetes[27,30–32], including elevated levels of circulating fibrinogen, von Willebrand factor, factor VII, and plasminogen activator inhibitor (PAI)-1 and altered platelet function. Thus more potent anticoagulation and antiplatelet therapies might offer particular benefit with regard to cardiovascular

Table 6 Primary efficacy end-points at 6 months among patients with diabetes treated with hirudin versus heparin

	Hirudin	Heparin	Hazard ratio (95% CI)
All patients			
Death	10·8	11·5	0·94 (0·73–1·21)
(Re)MI	10·8	12·0	0·88 (0·68–1·14)
Death or (re)MI	17·8	20·2	0·87 (0·72–1·06)
ST elevation			
Death	10·1	13·5	0·73 (0·47–1·15)
(Re)MI	8·5	10·2	0·82 (0·49–1·38)
Death or (re)MI	16·1	21·3	0·74 (0·51–1·05)
No ST elevation			
Death	11·2	10·6	1·06 (0·78–1·44)
(Re)MI	11·8	12·8	0·90 (0·67–1·22)
Death or (re)MI	18·6	19·7	0·94 (0·74–1·18)
Insulin-treated			
Death	13·1	13·0	1·02 (0·65–1·61)
(Re)MI	13·0	15·0	0·85 (0·54–1·34)
Death or (re)MI	21·0	23·1	0·90 (0·64–1·28)
No insulin			
Death	10·0	11·0	0·90 (0·66–1·23)
(Re)MI	10·0	11·0	0·90 (0·65–1·23)
Death or (re)MI	16·7	19·1	0·86 (0·68–1·08)

MI=myocardial infarction.

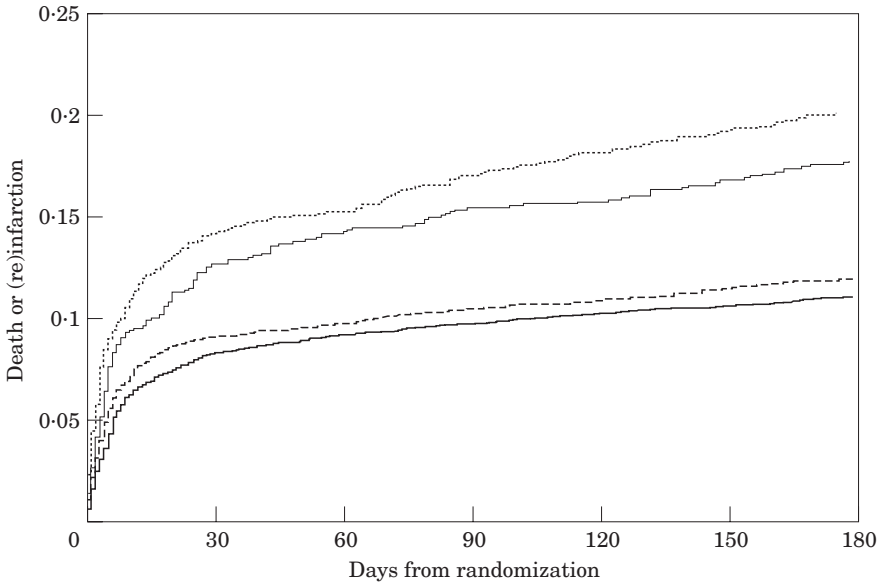

Figure 3 **Kaplan–Meier estimate of the probability of death or (re)myocardial infarction within 6 months after randomization according to treatment assignment among patients with and without diabetes. —=diabetes, hirudin; · · · ·=diabetes, heparin; ——=no diabetes, hirudin; – – –=no diabetes, heparin.**

complications in patients with diabetes. Observations of thrombolytic and platelet glycoprotein IIb/IIIa inhibitor trials support this hypothesis[5–7,33,34]. Several possible explanations exist for the lack of a more striking improvement in outcomes with hirudin vs heparin, particularly among diabetic patients. The prothrombotic state associated with diabetes may result in the need for higher anticoagulant doses, longer treatment, or both. The higher bleeding risk observed may prohibit upward titration of antithrombotic therapy among this subset of patients, however.

Influence of diabetes therapy on outcomes

Although details about diabetic management were unavailable in the database, insulin use was recorded at

enrolment. Overall, about 27% of the diabetic patients were taking insulin. Interestingly, about 37% of the diabetic patients in the U.S. were taking insulin at study entry versus about 21% elsewhere. Whether this can be explained by regional differences in patient characteristics associated with increased insulin requirements, such as the higher prevalence of obesity among the U.S. diabetic patients (Table 1), or represents international differences in practice remains unclear. These regional differences in insulin use and their potential influence on long-term outcomes warrants further evaluation.

Diabetic patients treated with insulin tended to have worse outcomes at 30 days and at 6 months than did diabetic patients treated only with oral or dietary therapy, consistent with prior studies[6,8]. Diabetic patients treated with insulin tend to be older, have had diabetes longer, more often have heart failure, and have more cardiovascular risk factors. After adjustment for these covariates in the current study, insulin treatment was not a significant predictor of adverse outcome. Although this suggests that the requirement for insulin simply is a marker of increased co-morbidity and cardiovascular risk, it is also possible that this reflects a type II statistical error.

Limitations

This study has several limitations. Although there was a prospective plan to assess outcomes and treatment effects by diabetes status, the specific analyses were defined post hoc. The definition of diabetes for this analysis is a clinical definition based on history and presenting data. In addition, we did not collect information about hypoglycaemic treatment or intensity of glycaemic control. As in any subgroup analysis, the sample sizes provide inadequate power to definitively address the relative treatment effects.

Conclusions

Diabetes is associated with worse outcomes across the spectrum of acute coronary syndromes. The statistically non-significant trend toward improved clinical outcomes with hirudin versus heparin noted in the overall trial was similar among patients with and without diabetes. Optimal use of evidence-based medical and revascularization therapy and continued efforts toward the development of more effective therapeutic strategies, especially with regard to diabetic patients, remain important and unrealized goals.

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