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CORONARY ARTERY DISEASE

Original Studies

Impact of Diabetes Mellitus Status on Coronary Pathoanatomy and Interventional Treatment: Insights From the Euro Heart Survey PCI registry

Timm Bauer,[1*] MD, Helge Möllmann,[1] MD, Franz Weidinger,[2] MD, Uwe Zeymer,[3] MD, Ricardo Seabra-Gomes,[4] MD, Franz Eberli,[5] MD, Patrick Serruys,[6] MD, Alec Vahanian,[7] MD, Sigmund Silber,[8] MD, William Wijns,[9] MD, Matthias Hochadel,[3] PhD, Holger M. Nef,[1] MD, Christian W. Hamm,[1] MD, Jean Marco,[10] MD, and Anselm K. Gitt,[3] MD

Objectives: The present analysis was performed to evaluate the impact of diabetes mellitus (DM) status on the severity of coronary artery disease (CAD) and current approaches in interventional treatment. Background: Little is known about the effect of DM treated with diet, oral agents, or insulin on lesion characteristics and anatomical pattern of CAD and their interventional treatment. Methods and results: Patients (n = 46,779) of the contemporary Euro Heart Survey PCI registry with known DM status were included in this analysis. Nondiabetics (n = 35,280, 75.4%) were compared with diabetics treated with diet (n = 1,533, 3.3%), oral agents (n = 7,222, 15.4%), and insulin (n = 2,744, 5.8%). Diabetic patients were older, suffered more frequently from comorbidities and presented more often with cardiogenic shock. The number of severely stenosed (≥70%) segments incrementally increased from nondiabetics to insulin-requiring diabetics. The location of lesions did not differ between patients with and without DM. The ratio stenosed/treated segments progressively rose among the four patient cohorts. The severity of DM negatively correlated with the extent of complete revascularization. After adjustment for confounding variables no significant differences in hospital mortality could be observed between patients without DM and diabetics treated with diet, but a significantly higher rate of death was seen in diabetic patients with oral medication and insulin therapy. Conclusions: Although CAD was more severe in patients with DM the percentage of treated segments with ≥70% stenosis was lower. Adjusted hospital mortality was increased among diabetics treated with oral medication or insulin, but not among those treated with diet. © 2011 Wiley Periodicals, Inc.

Key words: PCI; percutaneous coronary intervention; ANGO; angiography; coronary; CATH; diagnostic cardiac catheterization

[1]Kerckhoff Heart Center, Bad Nauheim, Germany
[2]Krankenhaus Rudolfstiftung, Vienna, Austria
[3]Herzzentrum Ludwigshafen, Institut für Herzinfarktforschung Ludwigshafen an der Universität Heidelberg, Germany
[4]Instituto do Coração, Lisbon, Portugal
[5]Stadtspital Triemli, Zurich, Switzerland
[6]Thorax Center, Erasmus MC, Rotterdam, Netherlands
[7]Bichat Hospital, Paris, France
[8]Kardiologische Gemeinschaftspraxis und Praxisklinik, Munich, Germany
[9]Cardiovascular Center, Aalst, Belgium
[10]Centre Cardiothoracique de Monaco, Monaco

The members of the ESC Board Committee for the Euro Heart Survey Programme 2006–2008 are as follows: Anselm K. Gitt (Chairperson) (Germany), Hector Bueno (Spain), Nicolas Danchin (France), Kevin Fox (UK), Peter Kearney (Ireland), Aldo Maggioni (Italy), Keith McGregor (France), Gregorsz Opolski (Poland), Ricardo Seabra-Gomes (Portugal), and Franz Weidinger (Austria).

*Correspondence to: Timm Bauer, MD, Kerckhoff Heart Center, Department of Cardiology, Benekestr, 2-8, 61231 Bad Nauheim, Germany. E-mail: Bauer-Timm@gmx.de

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INTRODUCTION

Patients with diabetes mellitus (DM) have a two- to fourfold increased risk for the development of coronary artery disease (CAD) [1]. Compared with their nondiabetic counterparts, CAD is more severe and associated with a higher morbidity and mortality [2–5]. Percutaneous coronary intervention (PCI) is an established treatment option in CAD, but postinterventional outcome is worse among those with DM [6–12]. This is partly due to platelet and endothelial dysfunction causing accelerated atherosclerosis and plaque instability [13]. Within the diabetic population, differences in the anatomical patterns of CAD and clinical outcomes could be observed between insulin dependent and noninsulin dependent patients [14–16]. Although many studies on DM and PCI have already been carried out, little is known about the impact of DM treated with diet, oral agents, or insulin on lesion characteristics and anatomical pattern of CAD and their interventional treatment. In particular, there is a lack of information about differences between noninsulin-dependent diabetics treated with diet only and those with oral medication. We therefore evaluated the effect of DM status on coronary pathoanatomy and treatment with PCI within the contemporary Euro Heart Survey (EHS) PCI Registry.

METHODS

The PCI-Registry of the EHS Programme

The PCI-Registry is a prospective, multicentre, observational study on current practice of unselected patients undergoing elective or emergency PCI. Consecutive patients with acute coronary syndrome (ACS) or stable coronary artery disease (CAD) were recruited within the period from May 2005 to April 2008. The participating hospitals were located throughout Europe (176 centres in 33 ESC-countries) and included university hospitals, community hospitals, specialist cardiology centres and private hospitals all providing PCI. The mean annual PCI volume of the participating facilities was approximately 1,000.

During specified periods all patients treated with PCI were prospectively registered and followed during their clinical course to document patient characteristics, adjunctive medical treatment, procedural details, and in-hospital outcomes.

Data Collection

On admission, data on patient characteristics were recorded, including age, gender, cardiovascular risk factors, concomitant diseases, prior myocardial infarction, prior stroke, prior cardiovascular interventions, and chronic medical treatment, as well as data on symptoms and prehospital delay. Data on electrocardiographic findings, biochemical markers, procedural details and adjunctive therapy were documented. At discharge, major cardiovascular, cerebrovascular adverse events, puncture site complications, and recommended medical treatment were recorded.

Every participating centre was committed to include every consecutive patient undergoing PCI during selected time periods. If continuous enrolment was not feasible due to high annual numbers of PCI, these centers were asked to recruit consecutive patients from day 1 to 7 of every calendar month during the entire study period. All patients gave written informed consent for processing their anonymous data. Electronic case report forms were used for data entry and transferred via the web to a central database located in the European Heart House, where they were edited for missing data, inconsistencies and outliers. Additional editing of the data as well as the statistical analyses for this publication was performed at the Institut fuer Herzinfarktforschung Ludwigshafen an der Universitaet Heidelberg, Germany. The study was approved by the ethics committees responsible for the participating centres as required by local rules.

Study Population

A total of 47,407 patients were prospectively enrolled in the EHS PCI registry. Of these, patients with known DM status at admission ($n = 46{,}779$) were analyzed and stratified into four groups: no DM, DM treated with diet, oral agents, or insulin. For the classification prescription drug plans, anamnestic data, previous discharge letters, and other documents were used. Hemoglobin A1c (HbA1c) and blood glucose levels were not routinely measured and not recorded at admission or during the index hospital stay.

Definitions

In patients without initial myocardial infarction, clinical signs of ischemia and relevant increases of cardiac biomarkers were defined as postprocedural myocardial infarction. Postprocedural reinfarction was diagnosed if patients had signs of recurrent ischemia and an additional relevant increase of cardiac biomarkers. Bleeding complications were classified as major when the patient had an intracranial bleed or an overt clinical bleeding with a drop in hemoglobin of greater than 5 g/dl. Chronic renal failure was diagnosed by any of the following: serum creatinine >2 mg/dl or 200 μmol/l in the past, on dialysis or history of renal transplantation. The American Heart Association 15-segment model was used to describe the location of lesions in native

TABLE I. Baseline Characteristics

	No DM (n = 35,280)	Diet (n = 1,533)	Oral (n = 7,222)	Insulin (n = 2,744)	P value for trend
Demographics					
Age (yr)	63.3 (54.5–72.0)	66.1 (57.8–74.0)	66.1 (58.6–73.4)	66.0 (57.7–72.9)	<0.001
Women	23.3%	30.0%	32.2%	38.3%	<0.001
BMI (kg/m^2)	27.0 (24.7–29.6)	28.1 (25.8–31.1)	28.4 (25.8–31.3)	28.8 (26.0–32.1)	<0.001
History relevant to CAD					
Prior MI	32.7%	38.1%	34.6%	42.4%	<0.001
Prior PCI	23.0%	21.3%	27.9%	30.0%	<0.001
Prior CABG	5.5%	6.2%	8.5%	10.7%	<0.001
Heart failure	11.3%	11.7%	9.5%	16.2%	<0.05
Hx of stroke	3.5%	5.8%	5.7%	7.6%	<0.001
PAD	4.9%	6.8%	8.5%	13.5%	<0.001
Chronic renal insufficiency	2.6%	5.6%	4.4%	10.7%	<0.001
Risk factors					
Hypertension	65.1%	79.0%	80.7%	82.3%	<0.001
HLP	62.0%	71.4%	70.3%	70.8%	<0.001
Current/former smoker	55.3%	49.5%	41.8%	41.8%	<0.001
Initial presentation					
Cardiogenic shock	1.5%	1.7%	1.8%	2.6%	<0.001
Resuscitation	1.6%	1.6%	1.2%	1.8%	0.48
Left ventricular function					
Ejection fraction ≤40%	11.6%	14.7%	14.2%	21.3%	<0.001

vessels. Segment 16 was defined as the most stenosed arterial bypass graft and 17 as the most stenosed venous bypass graft. Severe stenoses were defined by a stenosis degree ≥50% in the left main or ≥70% in the other segments.

Statistical Methods

Categorical data are presented as absolute numbers and percentages, metrical data as medians with 25th and 75th percentiles. These descriptive statistics were calculated from the available cases. Trends in the frequencies of binary variables across patient groups were assessed by Cochran-Armitage test.

The associations between the diabetes types, further risk factors and mortality were analysed using logistic regression models. Firstly, unadjusted odds ratios with 95% confidence intervals (CI) for death were estimated for the three types of diabetics in relation to the DM group, which was defined as reference group. Secondly, adjusted odds ratios were calculated with adjustment (1) for differences in demography (age, sex) and presentation (haemodynamic instability (cardiogenic shock and/or resuscitation) and acute ST elevation myocardial infarction (STEMI) and non ST elevation myocardial infarction (NSTEMI)), (2) additionally for high-risk features of the intervention (treatment of left main stem, bypass graft, more than one segment, type C lesion, in-stent restenosis, bifurcation lesion), (3) chronic renal failure. P values ≤0.05 were considered significant. All P values are results of two-tailed tests. The analysis was performed with the SAS© system release 9.1 on a personal computer (SAS Institute, Inc., Cary, NC).

RESULTS

Patients and Baseline Characteristics

For the present analysis 46,779 patients were stratified into four categories: 35,280 patients (75.4%) with no DM, 1,533 patients (3.3%) with DM treated with diet alone, 7,222 patients (15.4%) with DM treated with oral agents, and 2,744 patients (5.9%) with insulin-requiring DM. The baseline characteristics are shown in Table I. Nondiabetics were younger and more often male, but there was no age difference between the three DM groups. Incremental increases in comorbidity prevalence could be observed among the four patient cohorts.

Initial Assessment and Diagnosis

Diabetics more frequently presented with cardiogenic shock (Table I). They were treated more commonly for NSTE-ACS and less often for STEMI. This was particularly obvious among insulin-dependent diabetics (Fig. 1).

Angiographic and Interventional Characteristics

The number of left main stem disease, three-vessel disease, and severely stenosed segments incrementally increased from nondiabetics to insulin-dependent diabetics (Table II, Fig. 2). Type C lesions and restenoses were more frequently observed among patients with

DM (Table II). Location of lesions did not differ between patients with and without DM (Fig. 2). The proportion of severely stenosed segments that were not treated during the session progressively rose among the four patient cohorts ($P < 0.0001$ for trend) (Fig. 3).

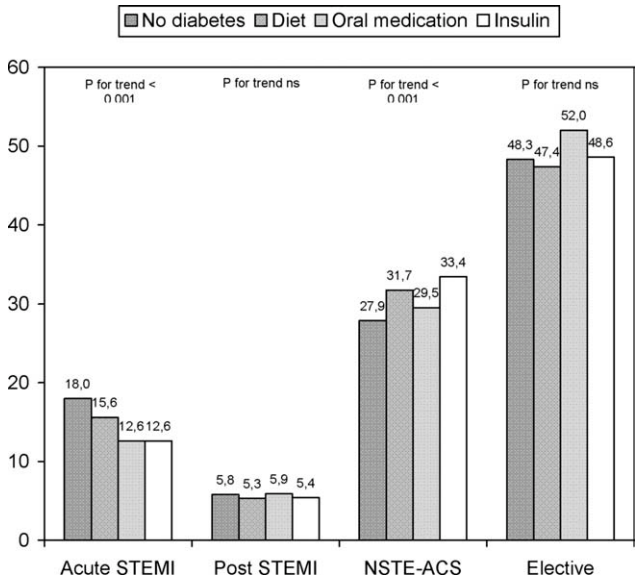

Fig. 1. PCI indication according to diabetes mellitus status.

Diabetics more commonly underwent PCI of left main stem, bypass grafts and more than one segment. The stenting rate was similar among the four groups, but the use of drug-eluting stents (DES) was higher among diabetics treated with oral medication and insulin. Maximum stent/balloon size was smaller among patients with drug-treated DM. The proportion of stent length >20 mm increased among the four cohorts. There were no major differences in procedural success and periprocedural complications among the different patient cohorts (Table II).

Antithrombotic Medication

The use of GP IIb/IIIa antagonists was higher among non-diabetics. Apart form that there were no major differences in the antithrombotic medication (Table II).

Hospital Complications

The incidence of hospital death gradually increased among the four patient cohorts. In comparison with nondiabetics mortality was almost doubled among insulin-requiring patients (Fig. 4). After adjustment for confounding variables no significant differences in hospital mortality could be seen between patients without

TABLE II. Angiographic and Interventional Characteristics

	No DM ($n = 35,280$)	Diet ($n = 1,533$)	Oral ($n = 7,222$)	Insulin ($n = 2,744$)	P value for trend
Stenosed vessels (≥50%)					
Left main stem	4.4%	4.4%	4.7%	5.9%	0.001
Three-vessel disease	19.2%	26.4%	27.1%	29.7%	<0.001
Treated vessels					
Left main stem	2.7%	2.2%	2.6%	3.2%	0.67
Bypass	1.5%	1.5%	2.5%	3.0%	<0.001
>1 segment	30.9%	30.1%	34.6%	33.9%	<0.001
Lesion characteristics					
Type C	27.7%	31.1%	30.0%	32.5%	<0.001
In-stent restenosis	6.3%	6.5%	7.9%	9.9%	<0.001
Bifurcation	15.6%	17.2%	16.2%	14.7%	0.83
Stent details					
Stent implantation	94.2%	93.8%	93.5%	91.7%	<0.001
Bare-metal stent	57.8%	61.8%	46.3%	43.5%	<0.001
Drug-eluting stent	41.3%	36.3%	52.4%	52.7%	<0.001
Max. stent/balloon size ≤3 mm	55.0%	55.9%	62.7%	64.5%	<0.001
Stent length >20 mm	34.7%	35.4%	35.9%	37.1%	<0.001
Procedural success					
TIMI 3 flow after PCI	93.3%	93.4%	93.7%	92.6%	0.90
<50% Stenosis after PCI	95.3%	95.1%	94.9%	94.1%	<0.01
Antithrombotic treatment before or during PCI					
ASA	81.1%	82.2%	77.1%	76.2%	<0.001
Clopidogrel	78.7%	85.2%	74.7%	77.0%	<0.001
Ticlopidine	4.4%	3.2%	3.6%	3.2%	<0.001
GP IIb/IIIa antagonist	25.4%	20.7%	22.2%	22.4%	<0.001
Antiplatelet therapy at discharge					
ASA	92.6%	97.0%	89.4%	92.4%	<0.001
Clopidogrel	90.1%	92.4%	90.7%	90.9%	<0.05
Ticlopidine	5.7%	4.0%	4.6%	4.6%	<0.001

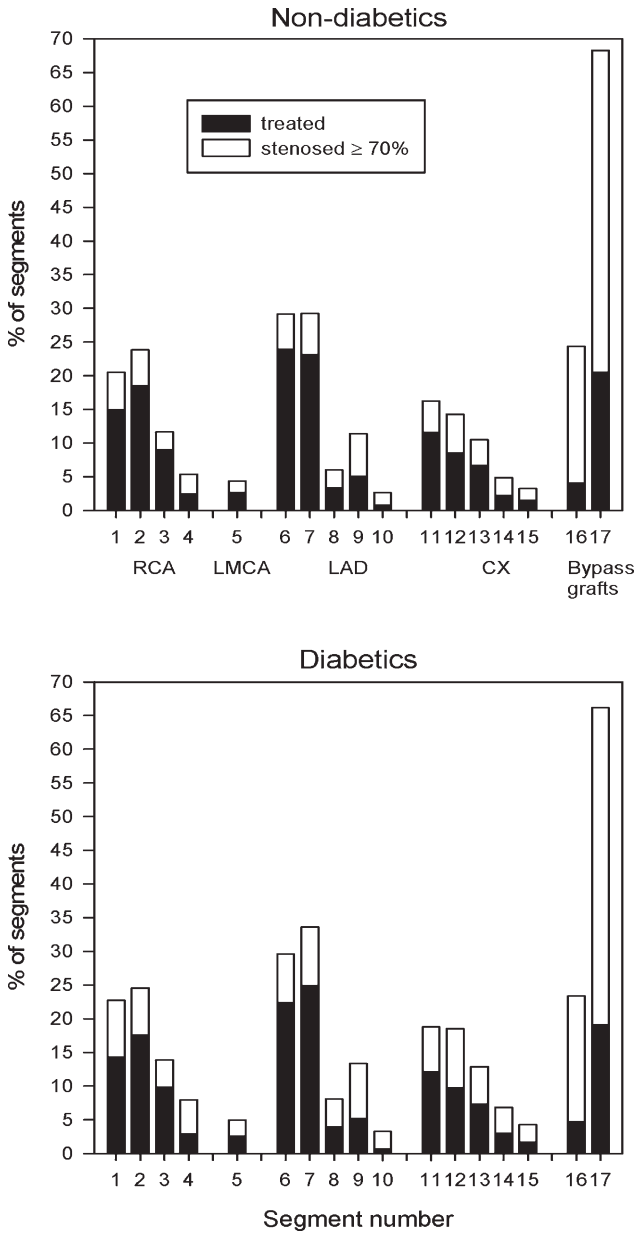

Fig. 2. Percentage of segments stenosed and treated in non-diabetics and diabetics.

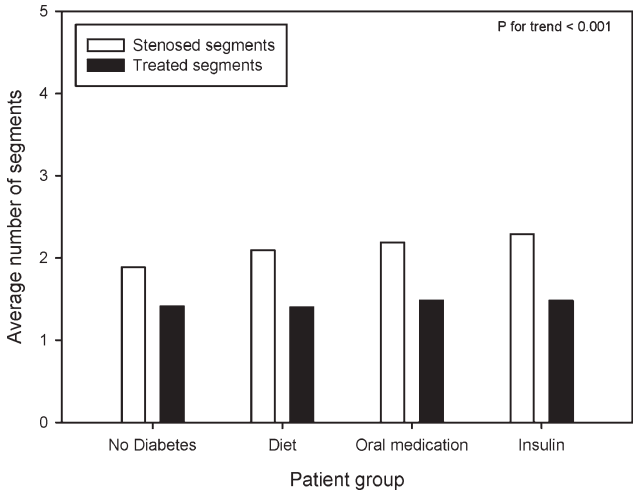

Fig. 3. Stenosed and treated segments according to diabetes status.

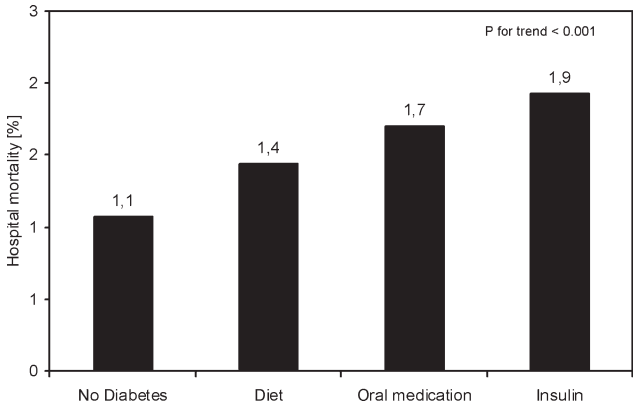

Fig. 4. Hospital mortality according to diabetes mellitus status.

DM and diabetics treated with diet, but a significantly higher rate of death was observed in patients with drug-treated DM (Table III). The incidence of nonfatal postprocedural myocardial (re-)infarction (MI) and stroke was highest among patients treated with diet (2.6% and 0.6%, respectively), followed by those with insulin (1.5% and 0.3%, respectively), nondiabetics (1.4% and 0.2%, respectively), and those with oral agents (1.1% and 0.2%, respectively). No significant difference in the occurrence of major bleedings could be observed.

DISCUSSION

This analysis of the contemporary EHS PCI Registry evaluated the impact of DM treated with diet, oral agents or insulin on coronary pathoanatomy and interventional treatment. The severity of DM negatively correlated with the extent of complete revascularization. Hospital mortality was increased among patients with drug-treated DM, but not among those treated with diet.

Baseline Characteristics

DM itself is a powerful independent risk factor for atherothrombotic events [1]. Metabolic and hematologic alterations such as hyperglycemia, insulin resistance, inflammation, and thrombophilia accelerate the atherosclerotic process and contribute to the worse prognosis. Moreover, diabetics have additional clinical

TABLE III. Unadjusted and Adjusted Odds Ratios for the Effect of Diabetes Types on In-Hospital Mortality

Comparison	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Diabetes with dietary control versus no diabetes	1.35 (0.87–2.08)	1.05 (0.65–1.70)	1.15 (0.70–1.87)
Diabetes treated by oral medication versus no diabetes	1.60 (1.31–1.97)	1.73 (1.38–2.18)	1.79 (1.39–2.28)
Diabetes treated by insulin versus no diabetes	1.82 (1.36–2.44)	1.65 (1.19–2.29)	1.55 (1.09–2.22)

[a]Adjusted for age, sex, cardiogenic shock/resuscitation, STEMI, NSTEMI.
[b]Adjusted for age, sex, cardiogenic shock/resuscitation, STEMI, NSTEMI, chronic renal failure, PCI of left main, bypass graft, more than one segment, type C lesion, in-stent restenosis, bifurcation lesion.

high-risk features. In our study they were older and suffered more often from comorbidities compared with nondiabetics. This is in line with previous observations [11,12]. However, the baseline risk profile is not identical among all diabetics. Incremental increases in comorbidity prevalence could be observed among the three DM groups. In particular, insulin-dependent diabetics have a high incidence of congestive heart failure, peripheral artery disease and chronic renal insufficiency. In comparison with nondiabetics the rate of chronic renal failure is fourfold increased among insulin-treated diabetics. Patients with chronic renal insufficiency are known to have a significant increase in cardiovascular morbidity and mortality [17]. Furthermore, patients with DM more frequently presented with cardiogenic shock. Here again, a gradual increase from nondiabetics to insulin-requiring diabetics could be observed. PCI indications were also affected by the DM status. Patients with DM were treated more commonly for NSTE-ACS and less often for STEMI. This was particularly obvious among insulin-dependent diabetics.

Coronary Pathoanatomy

Severity of CAD incrementally increased with regard to the different DM types. The incidence of left main, three-vessel disease, and the number of severely stenosed segments was highest in insulin-requiring patients followed by patients treated with oral agents and diet. This is partly in concordance with previous studies. Mulukutla et al. observed a higher rate of left main and three-vessel disease [16], whereas Mathew et al. found no relevant differences between non- and insulin-dependent diabetics [18]. In an investigation on multivessel PCI $\geq$3 lesions were more frequent among patients with insulin-requiring DM [15]. However, in these studies noninsulin-dependent DM was not subclassified in DM treated with diet only or oral agents.

In our analysis DM status did not have an effect on the location of lesions. They were similar among patients with and without DM. In comparison with nondiabetics every segment was more often severely stenosed among diabetics, but the distribution of proximal, mid, and distal lesions did not differ. On contrary, Henry et al. demonstrated that lesions were more frequently located on distal arteries [19]. However, another comparison of angiographic characteristics between non-insulin-requiring diabetics and nondiabetics found no difference [20].

The DM status affected lesions characteristics. In our analysis a higher rate of type C lesions and in-stent restenosis was seen in diabetics, particularly in those with insulin therapy. In a recent North-American analysis type C lesions were more often present in insulin-dependent diabetics [18]. Prior studies observed larger amounts of lipid-rich plaques and more fissured plaques in patients with DM [21,22].

Percutaneous Coronary Intervention

The DM status had a major impact on the interventional treatment. The ratio stenosed/treated segments incrementally increased from nondiabetics to insulin-dependent diabetics. Despite the lowest rate of STEMI among insulin-requiring diabetics the severity of DM negatively correlated with the extent of complete revascularization. However, we do not know why some of the severe stenoses were not treated. It is unclear whether it was impossible because of the lesion characteristics, expected low success rate or the stenosed vessel supplied infarcted regions that would not benefit from revascularization. Considering the higher incidence of renal insufficiency among diabetics staged procedure might have been planned in some of these cases.

The number of high-risk interventions gradually increased among the four groups. PCI of left main stem, bypass grafts, and more than one segment was most often conducted in insulin-requiring patients. The use of DES was high among diabetic patients with oral medication and insulin. Diabetics treated with diet less frequently received DES—almost in the same manner as non-diabetics. This is probably due to the larger reference vessel diameter. Maximum stent/balloon size among diabetics treated with diet only was as large as in nondiabetics. Patients with DM typically have coronary arteries with smaller diameters [23,24], but this might not be true for diabetics treated with diet only.

Hospital Outcome

Procedural success was high among the entire study population. Although there were no major differences

in periprocedural complications, the incidence of hospital death gradually increased among the four patient cohorts. After adjustment for baseline and interventional variables hospital mortality was significantly increased in diabetic patients with oral medication and insulin therapy, but not in those treated with diet only. Among patients undergoing PCI only drug-treated DM constitutes a high-risk variable. Gustafsson et al. also investigated the outcome in these four groups after fibrinolysis for acute myocardial infarction [25]. They also found a higher mortality in diabetics with insulin or oral hypoglycemic agents in comparison to diabetics treated with diet alone and nondiabetics. In our analysis the rate of nonfatal postprocedural myocardial infarction was surprisingly highest among those treated with diet. This is partly due to the highest rate of ACS at admission and postprocedural stent thrombosis.

Limitations

As the nature of the study is exploratory, the findings should be interpreted cautiously. In the EHS PCI registry the treatment was left to the discretion of the physician. This lead to a bias in the estimation of treatment effects, which cannot be fully eliminated even by using a multivariate analysis. As stated above, the DM status was not classified by HbA1c and blood glucose levels measured at admission. In addition, in this registry there was no differentiation between DM type 1 and 2. Furthermore, this study did not include patients treated conservatively or with coronary artery bypass grafting. The observed differences can only be applied to diabetics receiving PCI.

CONCLUSIONS

In this analysis of the EHS PCI-Registry the severity of CAD incrementally increased from nondiabetics to insulin-requiring diabetics. Location of lesions did not differ between patients with and without DM. Complete revascularization was less often achieved in insulin-dependent patients. After adjustment for baseline and interventional variables no significant differences in hospital mortality could be observed between patients without DM and diabetics treated with diet, but a significantly higher rate of death was seen in diabetic patients with oral medication and insulin therapy.

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