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Impact of Microvascular Complications on Outcome After Coronary Stent Implantations in Patients With Diabetes

To the Editor: Bare metal stent implantation is less effective in patients with diabetes than in patients without diabetes (1–3). Microvascular complications have been identified as risk markers for cardiovascular events in patients with diabetes (4–7). We evaluated the impact of microvascular complications (nephropathy and retinopathy) on the outcome after elective coronary bare metal stent implantation in patients with type 2 diabetes.

A total of 283 consecutive patients with type 2 diabetes mellitus who successfully underwent their first elective bare metal stent implantation at our institution from January 2000 to June 2003 were included into the analysis. Diabetic retinopathy was detected within one week before or after the procedure. Microalbuminuria (protein excretion of 30 to 300 mg/24 h) was determined the day before the procedure.

The principal characteristics of the 283 patients are summarized in Table 1. At 12 months, major adverse cardiac events (major adverse clinical event [MACE], i.e., death of any cause, nonfatal myocardial infarction, repeat percutaneous procedure, and bypass surgery) occurred in 34 of the 161 patients (21%) in the group without microvascular complications, in 18 of the 45 patients (40%) in the nephropathy group, in 22 of the 43 patients (51%) in the retinopathy group, and in 25 of the 34 patients (73.5%) in the group with both microvascular complications ($p < 0.001$) (Fig. 1). The influence of clinical, angiographic, and procedural variables on

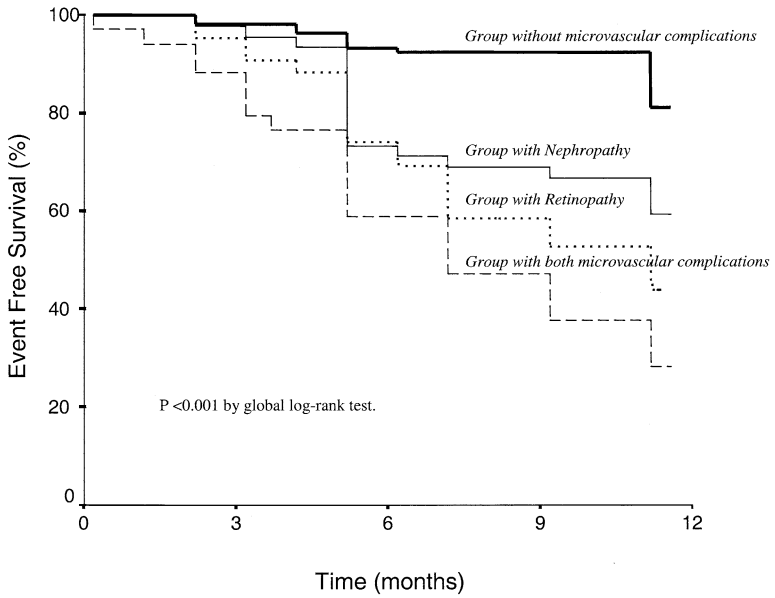

Figure 1. Kaplan-Meier event-free survival at 12 months in four groups defined according to the presence of microvascular complications.

Table 1. Characteristics of Patients According to the Presence of Microvascular Complications

	Group Without Microvascular Complications (n = 161)	Nephropathy Group (n = 45)	Retinopathy Group (n = 43)	Group With Both Microvascular Complications (n = 34)	p Value
Age	62 ± 9	62 ± 10	65 ± 12	64 ± 9	0.24
Male (%)	124 (77)	39 (87)	28 (65)	27 (79.5)	0.34
Unstable angina (%)	36 (22.5)	10 (22.5)	5 (11.5)	6 (17.5)	0.16
Diabetes treatment					<0.001
Non–insulin-requiring (%)	137 (85)	35 (78)	27 (63)	20 (59)	
Insulin-requiring (%)	24 (15)	10 (22)	16 (37)	14 (41)	
Duration of diabetes, yrs	7 ± 7	9 ± 8	14 ± 12	11 ± 8	<0.001
Left ventricular ejection fraction (%)	59 ± 8	59 ± 9	54 ± 12	54 ± 13	0.018
Previous myocardial infarction (%)	76 (47)	22 (49)	26 (60.5)	16 (47)	0.25
Systemic hypertension (%)	110 (68)	32 (71)	34 (79)	27 (79.5)	0.50
Active smokers (%)	48 (30)	13 (29)	7 (16)	10 (29.5)	0.61
Serum creatinine, mg/dl (interquartile range)	1.09 (0.96–1.25)	1.17 (1.05–1.34)	1.02 (0.56–1.24)	1.02 (0.93–1.30)	0.033
Proteinuria, mg/24 h (interquartile range)	5 (0–25)	122 (45–325)	5 (0–25)	82 (41–123)	<0.001
Glycosylated hemoglobin, %	7.4 ± 1.5	7.7 ± 1.4	8.1 ± 1.5	8.5 ± 1.7	0.003
Distribution of coronary artery disease (%)					0.090
Single-vessel	58 (36)	15 (33)	12 (28)	8 (24)	
Double-vessel	74 (46)	20 (44.5)	16 (36.5)	14 (41)	
Triple-vessel	29 (18)	10 (22)	15 (36.5)	12 (35)	
Complex lesions, B2/C (%)	161/258 (62.5)	44/67 (65.5)	42/73 (57.5)	28/54 (52)	0.85
Diameter stenosis, %					
Pre	81 ± 15	84 ± 15	82 ± 15	80 ± 15	0.75
Post	5 ± 12	6 ± 9	6 ± 9	7 ± 9	0.91
Vessel diameter, mm	2.95 ± 0.59	2.94 ± 0.54	2.83 ± 0.51	2.87 ± 0.54	0.43
Minimal lumen diameter, mm					
Pre	0.67 ± 0.51	0.67 ± 0.50	0.68 ± 0.51	0.74 ± 0.51	0.51
Post	2.88 ± 0.73	3.02 ± 0.90	2.85 ± 0.61	2.68 ± 0.65	0.18
Lesion length, mm	11 ± 5	11 ± 4	12 ± 6	12 ± 4	0.32
Complete revascularization (%)	87 (54%)	26 (57)	18 (43)	13 (39.5)	0.27
Elective IIb/IIIa inhibitors (%)	73 (45.5)	14 (32)	12 (27.5)	16 (47)	0.077

MACE at follow-up was evaluated with a Cox regression analysis. Variables entered into the model were as follows: the presence of microvascular complications (as defined group without microvascular complications, group with nephropathy, group with retinopathy, and group with both microvascular complications), age ≥70 years, sex, insulin-treatment, duration of diabetes >7 years, small (≤2.75 mm) vessel, complex (B2/C) lesions, elective IIb/IIIa inhibitors, left ventricular ejection fraction ≤40%, complete revascularization, unstable angina, and multivessel stenting. Independent predictors of MACE at follow-up were as follows: the presence of diabetic nephropathy (hazard ratio [HR] = 1.96; 95% confidence interval [CI] = 1.03 to 3.73; p = 0.039), presence of diabetic retinopathy (HR = 3.38; 95% CI = 1.73 to 6.60; p < 0.001), presence of both diabetic microvascular complications (HR = 6.28; 95% CI = 3.33 to 11.84; p <0.001), insulin treatment (HR = 1.78; 95% CI = 1.09 to 2.92; p = 0.021), and complete revascularization (HR = 0.57; 95% CI = 0.37 to 0.96; p = 0.019).

Patients with type 2 diabetes mellitus and proteinuria or retinopathy have an increased risk of cardiovascular death (4–7). The relative risks of cardiovascular mortality and morbidity associated with the presence of microalbuminuria differ markedly according to the presence or absence of retinopathy (7). In the present study, we found that microvascular complications represent a strong predictor of MACE after bare stent implantation in type 2 diabetic patients. In particular, the presence of both nephropathy and retinopathy identifies a subgroup of diabetic patients with a worse one-year outcome after elective bare stent implantation. The results of the present study confirm and extend previous observations (8,9). Screening patients with diabetes for both nephropathy and retinopathy before coronary procedures appears to be an effective way to risk-stratify this group of patients and thus to focus preventive measures. In the era of drug-eluting stent implantation, these findings may be important to better interpret results and to appropriately stratify patients undergoing percutaneous or surgical treatments in prospective randomized trials.

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Letters to the Editor

Hibernating Myocardium, Apoptosis, and a Simple Mathematical Task

We read with extreme interest the recent report by Elsasser et al. (1). Their study reliably shows that both apoptotic and autophagic cell death occur in hibernating myocardium and may be responsible for progressive clinical deterioration and lack of functional recovery.

However, we are afraid the investigators may have made an inaccurate estimate of apoptotic cell death rate. The researchers indeed report an incidence of apoptosis of 0.002% (i.e., 1 of 50,000 cells). These data would suggest that at least 50,000 cells were counted per patient in order to ascertain whether at least one was apoptotic. But the investigators fail to clarify this issue thoroughly.

This point is particularly relevant when considering the electron microscopy data. Considering the specific limitations of electron microscopy we would imagine that the investigators evaluated not more than 100 cells at electron microscopy per case. Yet assuming 100 cells examined per case and an apoptotic rate of 1 in 50,000, the chance of randomly finding an apoptotic cell at the electron microscope level in a single case would be 1 in 500. Accordingly, the probabilty of 3 positive cases at electron microscopy would be only 1 in 125 million.

In conclusion, we find the message given by Elsasser et al. (1) extremely attractive and clinically relevant. However, we believe that they might have underestimated the incidence of apoptotic myocytes at confocal microscopy. We would greatly appreciate it if the investigators could clarify these apparent inconsistencies.

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REPLY

We thank Dr. Abbate and colleagues for their interest in our work (1). The major point of our recent publication is the fact that autophagic cell death as described previously in patients with dilated cardiomyopathy (2) is an important mechanism for killing myocytes in hibernating myocardium and that apoptosis seems to be of less importance. We are fully aware of the many technical problems that might occur when attempting a quantitative analysis of the rate of cell death, be it apoptosis, autophagic cell death, or necrosis (3). In our experience, electron microscopy is not a suitable method for determining the rate of cell death, which has been emphasized by others as well (4). Therefore, we use the confocal microscope. We analyze entire sections, and as many cells as are available from the patient's material; we count the total number of nucleated myocytes per patient and we determine the number of specifically labeled cells. This information is then statistically analyzed on the basis of individual data from each patient and ultimately expressed as a percentage. In a final stage, results are summarized for an entire group of patients, and different groups are compared by employing appropriate statistical tests. Using this procedure each patient is weighted equally, even if there are no labeled cells present.

We read with interest Dr. Abbate and colleagues' work on myocardial apoptosis in patients with unfavorable left ventricular remodeling and we noticed the unusually high rates of apoptosis reported for both infarcted myocardium and areas remote from the infarct (5). Unfortunately, a precise indication of the total number of myocytes examined is lacking from the description of methods, rendering difficult an interpretation of these results. It would have been more convincing had Dr. Abbate and colleagues used the same criteria in his own work that he requests from ours.

There is no doubt, however, that myocyte death is a major contributing factor to the deterioration of cardiac function in pathological situations in the human heart, either in postinfarction remodeling or in hibernating myocardium.

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