Prognostic Value of Coronary Computed Tomographic Angiography in Diabetic Patients Without Known Coronary Artery Disease

Martin Hadamitzky, md[1]
Franziska Hein, md[1]
Tanja Meyer, md[1]
Bernhard Bischoff, md[1]

Stefan Martinoff, md[2]
Albert Schömig, md[1]
Jörg Hausleiter, md[1]

OBJECTIVE — Diabetic patients have a high prevalence of coronary artery disease (CAD), but timely diagnosis of CAD remains challenging. We assessed the ability of coronary computed tomography angiography (CCTA) to detect CAD in diabetic patients and to predict subsequent cardiac events.

RESEARCH DESIGN AND METHODS — We analyzed 140 diabetic patients without known CAD undergoing CCTA; 1,782 patients without diabetes were used as a control group. Besides calcium scoring and the degree of the most severe stenosis, the atherosclerotic burden score counting the number of segments having either a nonstenotic plaque or a stenosis was recorded. The primary end point was a composite of hard cardiac events defined as all-cause death, nonfatal myocardial infarction, or unstable angina requiring hospitalization.

RESULTS — During a mean follow-up of 33 months, there were seven events in the diabetic group and 24 events in the control group. The best predictor in diabetic patients was the atherosclerotic burden score: the annual event rate ranged from 0.5% for patients with <5 lesions to 9.6% for patients with >9 lesions, resulting in a hazard ratio (HR) of 1.3 (95% CI 1.1–1.7) for each additional lesion ($P = 0.005$). For comparison, in nondiabetic patients the annual event rate ranged from 0.3 to 2.2%, respectively, resulting in an HR of 1.2 (95% CI 1.1–1.3, $P < 0.001$). The atherosclerotic burden score improved the prognostic value of conventional risk factors significantly ($P < 0.001$).

CONCLUSIONS — In diabetic patients without known CAD, CCTA can identify a patient group at particularly high risk for subsequent hard cardiac events.

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Diabetes is associated with a markedly increased risk for coronary artery disease (CAD), and CAD is the most common cause of death in diabetic adults (1). Although primary prevention measures for CAD are recommended for all diabetic patients (2), additional therapies are indicated where known CAD is present, e.g., institution of β-blocker therapy, and goals for secondary prevention are more stringent, including an LDL cholesterol target <70 mg/dl (3). For an optimized prevention regimen, early detection of CAD is therefore of significant importance in diabetic patients. Unfortunately, the sensitivity of clinical risk assessment is limited, mainly because typical symptoms of ischemia are often absent, and cardiac stress imaging tests also have a limited negative predictive value in these patients (4). By virtue of its ability to detect both coronary stenoses and calcified and noncalcified plaques, coronary computed tomography angiography (CCTA) may be a reasonable option to close this diagnostic gap.

During the last few years, CCTA has emerged as a widely used imaging modality for detection or exclusion of obstructive CAD, replacing invasive coronary angiography in certain conditions (5). In addition, several studies demonstrated the usefulness of CCTA as a prognostic tool for prediction of subsequent cardiac events (6–8).

For diabetic patients undergoing CCTA, an increased prevalence of obstructive and nonobstructive CAD was recently demonstrated (9,10), but up to now, no data are available relating to how this observation influences further clinical outcome. Therefore, the aim of this study was twofold: to assess the prevalence of CAD by CCTA in diabetic patients without known CAD and to investigate the predictive value of CCTA on incident cardiac events.

RESEARCH DESIGN AND
METHODS — The study population consisted of all consecutive patients undergoing CCTA in our institution between 1 December 2003 and 29 February 2008, for evaluation of suspected CAD. Exclusion criteria were *1*) typical angina pectoris, *2*) a history of myocardial infarction including electrocardiographic signs of a silent myocardial infarction, *3*) a history of coronary revascularization, either by percutaneous coronary intervention or bypass or otherwise known CAD, *4*) absence of stable sinus rhythm during the investigation, and *5*) a life-threatening conditions. Patients were subdivided according to the presence of diabetes, defined as current treatment with insulin or oral hypoglycemic medication or dietetic control of blood glucose levels in patients having elevated fasting blood glucose levels or an abnormal glucose tolerance test based on the World Health Organization criteria (11).

Written informed consent was obtained from all patients before examina-

tion. A structured interview was performed before examination, and information about age, patients' height and weight, history of cardiac disease, and present complaints was collected. The following cardiac risk factors were recorded: *1*) presence and degree of hypertension, *2*) diabetes (see definition above), *3*) smoking (defined as current smoker or previous smoker within the last year), and *4*) a positive family history (defined as the presence of CAD in first-degree relatives aged <55 years for male or <65 years for female). From these data, the Framingham risk score with the established categorical model using LDL cholesterol according to Wilson et al. (12) was calculated. The study design was approved by the local ethics committee.

Image acquisition and analysis
The detailed multislice computed tomography scan protocol is described elsewhere (13). Images for calcium scoring were acquired by a non–contrast-enhanced sequential scan and analyzed with a commercially available software package (Siemens CalciumScore; Siemens, Erlangen, Germany). For CCTA, a bolus-timing test scan using 10–20 ml of contrast material (iomeprol, Imeron 350, iodine content 350 mg/ml; Bracco Altana Pharma, Konstanz, Germany) followed by a 50-ml saline chaser was used. After administration of 80–140 ml of contrast material individually adjusted to the selected table feed and scan range at a rate of 4–6 ml/s followed by a 50-ml saline chaser, the CCTA images were acquired. Dose reduction strategies such like electrocardiographic gated tube current modulation or reduced tube voltage were used whenever feasible.

For image analysis, the coronary artery tree was segmented according to the modified American Heart Association classification (14). Each segment with a diameter >1.5 mm was evaluated by two experienced readers (one radiologist and one cardiologist). Any disagreement was settled by consensus. The degree of stenosis was rated visually using four groups: no relevant stenosis (<25%), mild stenosis (25–49%), moderate stenosis (50–74%), and severe stenosis (≥75%). If a moderate or severe stenosis could not be excluded because of artifacts, the segment was classified as having a moderate stenosis. In addition, for each segment the presence of calcium and the presence of noncalcified and mixed plaques were assessed. Noncalcified plaques were de-

fined as any discernible structure in the coronary artery wall with a computed tomographic density less than the contrast-enhanced coronary lumen but greater than the surrounding connective tissue. Plaques meeting these criteria, but additionally showing calcification, were classified as mixed plaques. All patients with nonobstructive and obstructive CAD were advised to work vigorously to lower their cardiovascular risk profile and use of aspirin and statins was recommended, if feasible. In addition, all patients with obstructive CAD were advised to undergo invasive angiography. From the primary analysis the following CCTA parameters were calculated:

Coronary obstruction score. The most severe stenosis of any segment >1.5 mm in diameter categorized as follows: score 0: all evaluable coronary segments <25%; score 1: at least one evaluable coronary segment with mild stenosis (25–49%); score 2: at least one evaluable coronary segment with moderate stenosis (50–74%); and score 3: at least one evaluable coronary segment with severe stenosis (≥75%).

Atherosclerotic burden score. The number of segments with any stenosis ≥25% or any nonobstructive calcified, mixed or noncalcified plaques, irrespective of the degree of stenosis.

Follow-up
Follow-up information was gathered by clinical visits, telephone contact, or questionnaire sent by mail. We verified all reported events by hospital records or contact with the attending physician.

The primary end point of interest was a composite of hard cardiac events defined as all-cause death, nonfatal myocardial infarction, or unstable angina requiring hospitalization. The definition of nonfatal myocardial infarction was based on the criteria of typical acute chest pain and persistent ST-segment elevation or positive cardiac enzymes. Unstable angina pectoris was defined according to the guidelines of the European Society of Cardiology (15) as typical acute chest pain with negative cardiac enzymes, if CAD could not be excluded as the cause of symptoms.

Statistical analysis
Categorical variables are expressed as frequencies and percentages and continuous variables are expressed as means ± SD; comparisons were done by a Fisher exact test or Student *t* test. Event-free survival

was analyzed using the Cox proportional hazards model. To avoid overfitting of multivariable analysis, only parameters showing a significant correlation in univariate analysis were included into the model. To improve normal distribution, calcium scoring was included as its logarithm. Statistical significance was accepted for bilateral $P < 0.05$. The statistical package R version 2.6.1 (16) including the package Design (17) was used for statistical analysis.

RESULTS

Study population and clinical characteristics
A total of 2,021 patients met the inclusion criteria. Of these, 1,922 patients could be contacted for follow-up, resulting in a follow-up rate of 95.1%. Overall, there were 140 patients with diabetes. In 46 patients, blood glucose levels were controlled by diet, 73 patients took oral antidiabetic medication, and 21 patients were using insulin. The control group comprised the 1,782 patients without known diabetes. The mean duration of follow up was 35.2 ± 15.4 months in the diabetic group and 32.8 ± 15.1 months in the control group.

Diabetic patients were significantly older and more often overweight, and there were more patients with hypertension and hypercholesterolemia among diabetic patients compared with nondiabetic patients, resulting in a significantly higher Framingham risk score. Patients' sex and the prevalence of atypical chest pain or dyspnea did not differ significantly between both groups. Overall the pretest risk was significantly higher in diabetic patients. For a detailed description of the patient characteristics, see Table 1.

Results of CCTA
The results of CCTA and calcium scoring are summarized in Table 2. Of 140 diabetic patients, 19 patients (13%) had completely normal coronary arteries and in 16 patients (11%) plaques with a lumen narrowing <25% were detected. Plaques with maximum stenosis between 25 and 49% were found in 38 patients (27%), plaques with maximum stenosis between 50 and 74% were found in 53 patients (16%), and plaques with maximum stenosis ≥75% were found in 14 patients (10%). Compared with nondiabetic patients, there were significantly more patients with atherosclerotic changes (86 vs. 73%, $P < 0.001$) and sig-

Table 1—Clinical characteristics and conventional risk scores

	No diabetes	Diabetes	P value
n	1,782	140	
Age	59.0 ± 11.0	64.5 ± 8.3	<0.001
Male sex	1,215 (68)	92 (65.7)	0.57
BMI	25.5 ± 3.8	28.3 ± 4.3	<0.001
Hypertension	1,008 (57)	109 (78)	<0.001
Smoking	624 (35)	46 (33)	0.65
Hypercholesterolemia	907 (51)	86 (61)	0.018
Family history	585 (33)	44 (31)	0.78
Atypical chest pain	693 (39)	51 (36)	0.59
Dyspnea	53 (3)	6 (4)	0.44
Framingham risk score	7.6 ± 6.9	15.2 ± 11.2	<0.001
Low	622 (37)	7 (5)	
Intermediate	911 (54)	83 (63)	
High	143 (9)	43 (32)	

Data are means ± SD or n (%).

nificantly more patients with obstructive CAD (48 vs. 25%, $P < 0.001$).

In diabetic patients, there were on average 5.2 segments affected by atherosclerotic lesions: 28% with noncalcified plaques, 20% with mixed plaques, and 52% with calcified plaques. In nondiabetic patients, on average only 2.9 segments showed atherosclerotic changes: 31% with noncalcified plaques, 17% with mixed plaques, and 52% with calcified plaques. Whereas the total number of lesions was significantly higher in diabetic patients ($P < 0.001$), the plaque composition was similar ($P = 0.99$).

In diabetic patients, the Agatston score of 61 ± 56 was significantly higher than that in nondiabetic patients (Agatston score of 13 ± 11, $P < 0.001$).

Cardiac events

In the 140 diabetic patients, there were 5 deaths. In addition, 2 patients had unstable angina requiring hospitalization. Of the 1,860 patients without diabetes, 16 patients died. Two patients had nonfatal

Table 2—Computed tomographic parameters

	No diabetes	Diabetes	P value
n	1,782	140	
Obstructive CAD	457 (26)	67 (48)	<0.001
Most stenotic lesion			
Normal	483 (27)	19 (14)	
Nonstenotic plaque	298 (17)	16 (11)	
25–49% stenosis	544 (31)	38 (27)	
50–75% stenosis	381 (21)	53 (38)	
>75% stenosis	76 (4)	14 (10)	
No. lesions per patient	2.9 ± 3.2	5.2 ± 3.7	<0.001
Noncalcified	0.9 ± 0.8	1.4 ± 1.4	<0.001
Mixed	0.5 ± 1.1	1.0 ± 1.6	<0.001
Calcified	1.5 ± 2.2	2.7 ± 2.8	<0.001
Vessels affected			<0.001
One-vessel disease	213 (12)	24 (17)	
Two-vessel disease	140 (7.86)	23 (16)	
Three-vessel disease	93 (5)	20 (14)	
Calcium (Agatston) score	13 ± 11	61 ± 56	<0.001
0	658 (39)	22 (17)	
1–100	579 (34)	45 (34)	
100–400	270 (16)	31 (23)	
>400	188 (11)	35 (26)	

Data are means ± SD or n (%).

myocardial infarctions and 6 patients had unstable angina requiring hospitalization.

There was a significant difference in the event rate between diabetic and nondiabetic patients with respect to the primary end point of all-cause death, nonfatal myocardial infarction, and unstable angina requiring hospitalization. In diabetic patients, the annual event rate was 1.8% (95% CI 0.8–3.7%), whereas in nondiabetic patients it was only 0.5% (0.3–0.8%), resulting in a hazard ratio (HR) of 3.5 (1.5–8.2, $P = 0.003$).

Predictive value of CCTA in diabetic patients

The primary end point correlated best with the atherosclerotic burden score in CCTA both in diabetic and nondiabetic patients. In diabetic patients, the annual event rate ranged from 0.5% (95% CI 0.1–3.8%) in patients with <5 lesions to 9.6% (4.0–23.1%) for patients with >9 lesions, resulting in an HR of 1.3 (1.1–1.7, $P = 0.005$) for each additional lesion. For comparison, in nondiabetic patients the annual event rate increased from 0.3% (0.1–0.6%) for patient with <5 lesions to 2.2% (0.9–5.4%) for patients with >9 lesions. The HR was 1.2 (1.1–1.3, $P < 0.001$) (Fig. 1).

In multivariable analysis of the total patient population, the atherosclerotic burden score was the only significant predictor for hard cardiac event besides patient's age (Table 3). Coronary obstruction score and calcium score were both significant in the univariate model but could not add prognostic information on top of the atherosclerotic burden score. The atherosclerotic burden score significantly improved the predictive value of a model including all conventional risk factors, increasing the likelihood ratio from 26.2 to 38.1 ($P < 0.001$).
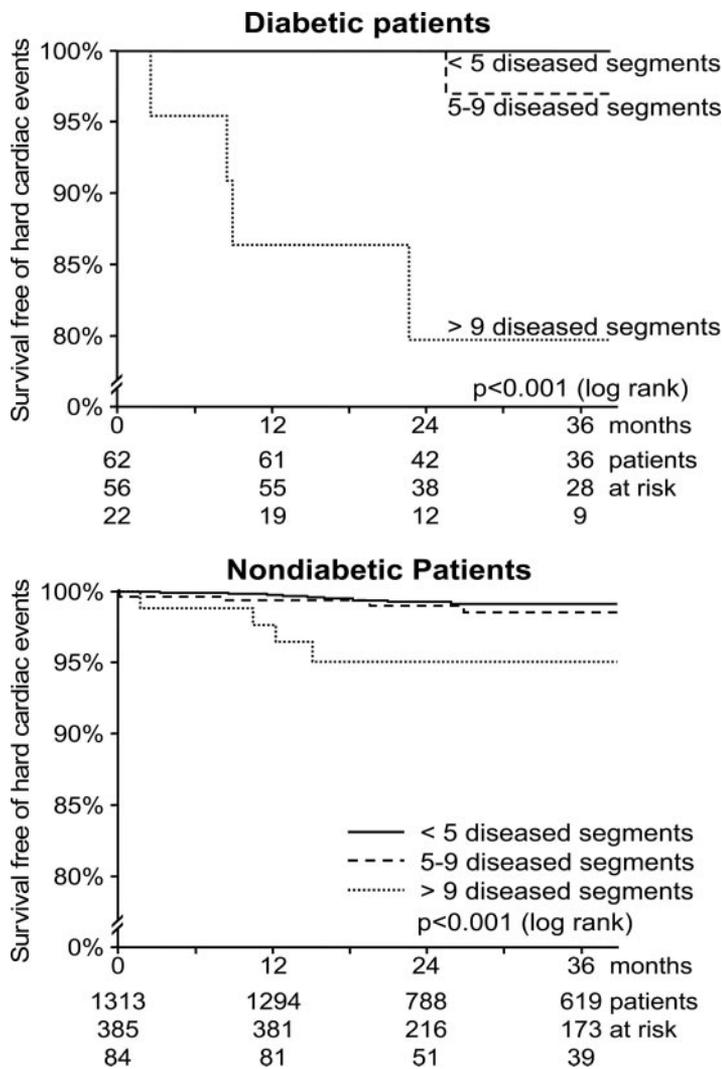
CONCLUSIONS — The principal findings of this study are that 1) the prevalence of CAD is significantly higher in diabetic patients compared than nondiabetic patients, 2) this causes a higher rate of subsequent cardiac events, and 3) CCTA has a predictive value in addition to clinical risk predictors both in diabetic and nondiabetic patients.

In line with previous publications of Zeina et al. (10) and Iwasaki et al. (9), in our study population the prevalence of CAD reached 86% in diabetic patients and was significantly higher than the prevalence of 73% in nondiabetic patients. In addition, diabetic patients had a

Diabetic patients

Nondiabetic Patients

Figure 1—*Survival free of hard cardiac events in correlation with the atherosclerosis burden score, counting the number of lesions having either nonstenotic plaques or stenoses (irrespective of degree), in patients both with and without diabetes. The numbers of patients at risk refer to the three groups analyzed (top <5, middle 5–9, and bottom >9 diseased segments).*

high number of diseased coronary segments. They showed on average 5 diseased segments, whereas nondiabetic patients had only 3. In both groups about two-thirds of all lesions had calcifications. As also described by Zeina et al. (10), there was no significant difference in plaque composition between the two groups.

To our knowledge, no data exist at the moment relating to how these findings correlate with prognosis. In our study population, diabetic patients had a more than threefold higher incidence of 1.8% per year for hard cardiac events compared with nondiabetic patients, who had an annual event rate of 0.5%. The parameter correlating best with these events both in the overall population and in diabetic patients in particular was the atherosclerotic burden score counting the diseased coronary segments. This good correlation, paired with the fact that the atherosclerotic burden score remains the only significant predictor in a multivariable analysis, suggests that by directly visualizing the atherosclerotic burden, CCTA might be able to identify exactly those diabetic patients who are at high risk for having cardiac events.

The high prevalence of atherosclerotic lesions combined with the good predictive value of the atherosclerotic burden score makes CCTA particularly useful in diabetic patients. CCTA can detect atherosclerotic changes early, well before coronary obstruction and ischemia occur; it can also detect both calcified and noncalcified plaques and can distinguish between obstructive and nonobstructive plaques. This features allow a very comprehensive assessment of diabetic pa-

Table 3—*Multivariable analysis for prediction of hard cardiac events in all patients*

	No cardiac events	Cardiac events	Univariate model		Multivariate model	
			HR (95% CI)	P value	HR (95% CI)	P value
Diabetes	133 (7)	7 (26)	3.5 (1.5–8.2)	<0.001		
Hypertension	1,097 (58)	21 (68)	1.5 (0.7–3.2)	0.3		
Hypercholesterolemia	973 (51)	20 (65)	1.6 (0.8–3.3)	0.21		
Smoking	661 (35)	10 (32)	0.9 (0.4–1.8)	0.68		
Family history	622 (33)	7 (23)	0.6 (0.2–1.3)	0.2		
Age	58.5 ± 10.9	66.2 ± 8.4	1.1 (1–1.1)	<0.001	1.05 (1.02–1.09)	0.006
Male sex	1,284 (68)	24 (77)	1.5 (0.7–3.6)	0.32		
Atypical chest pain	736 (39)	9 (29)	0.7 (0.3–1.5)	0.34		
Dyspnea	57 (3)	2 (6)	1.9 (0.5–8)	0.38		
Atherosclerotic burden score	3.0 ± 3.2	6.6 ± 4.3	1.3 (1.2–1.4)	<0.001	1.2 (1.1–1.3)	<0.001
Coronary obstruction score	0.9 ± 0.9	1.7 ± 0.9	2.5 (1.7–3.8)	<0.001		
Calcium score	1.1 ± 1.0	2.2 ± 2.1	2.5 (1.6–3.8)	<0.001		

Data are means ± SD or *n* (%) unless otherwise indicated. The HR for the calcium score is calculated for a 10-fold increase.

tients: patients with limited disease have a quite good prognosis of an ~0.5% annual event rate and could continue to receive conventional medical therapy and patients with more extended disease could benefit from a vigorous treatment of both diabetes and CAD. In particular, in patients with very extended CAD (>9 coronary segments affected) having a risk of nearly 10% per year for having a severe cardiac event, the effort and risks of a intensive blood glucose control combined with a secondary prevention regimen for CAD might be justified even in the absence of cardiac symptoms. In addition, obstructive CAD can be detected or ruled out with high accuracy (5), circumventing both the limitations of myocardial stress imaging and the risks of invasive angiography but providing valuable information for the selection of patients who could benefit from timely coronary revascularization.

Whether an approach such as this is actually better than the current concepts and whether CCTA can replace myocardial perfusion imaging as a gatekeeper for revascularization still need to be assessed in larger studies, but this study clearly demonstrates that CCTA has the potential to identify patients with a particularly high risk for hard cardiac events in a group of diabetic patients without known coronary artery disease.

This study has some limitations. It is an observational study, and the result of the investigation guided further treatment, both interventional and medical. Because most of the patients were referred from outside cardiologists in private practice, valid information regarding diabetic control or changes of medication after the investigation is not available. In addition, the number of diabetic patients is small in this unrestricted patient population.

In summary, diabetic patients without known CAD undergoing CCTA have an increased prevalence of both coronary plaques and obstructive CAD compared with nondiabetic patients. This result is in keeping with an increased risk for hard cardiac events.

A CCTA atherosclerotic burden score based on the number of diseased coronary segments (irrespective of the degree of stenosis) correlates best with events during follow-up and can significantly improve the risk stratification over and above that of conventional risk factor assessment. This procedure allows the identification of a patient group of particular high risk for incident cardiac events.

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