Additional Use of Glycated Hemoglobin for Diagnosis of Type 2 Diabetes in People Undergoing Coronary Angiography Reveals a Subgroup at Increased Cardiovascular Risk

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OBJECTIVE—To study the prognosis of people with newly diagnosed type 2 diabetes as per the American Diabetes Association (ADA) 2010 definition but without diabetes as per the ADA 2009 definition.

RESEARCH DESIGN AND METHODS—A total of 2,002 participants of the Ludwigshafen Risk and Cardiovascular Health (LURIC) study without a history of diabetes were studied.

RESULTS—During the follow-up of a mean duration ± SD of 7.7 ± 2.0 years, 346 people died (202 cardiovascular deaths). Subjects with type 2 diabetes as per the ADA 2009 definition ($n = 468$) had significantly increased all-cause and cardiovascular mortality compared with people without diabetes as per the ADA 2010 definition (both $P \leq 0.003$). Subjects with type 2 diabetes as per the ADA 2010 definition but without diabetes as per the ADA 2009 definition ($n = 150$) were at significantly increased risk to die of cardiovascular diseases ($P = 0.029$).

CONCLUSIONS—Use of the ADA 2010 diabetes definition may be instrumental in improving cardiovascular risk stratification in people undergoing coronary angiography.

According to the 2009 guidelines of the American Diabetes Association (ADA), subjects with increased fasting glucose (≥ 126 mg/dL) and/or post-challenge glucose (≥ 200 mg/dL) are diagnosed with diabetes (1). Using the ADA 2010 criteria, subjects with isolated elevation of glycated hemoglobin $\geq 6.5\%$ (fasting glucose <126 mg/dL, postchallenge glucose <200 mg/dL) are also considered diabetic individuals (2).

Glycated hemoglobin has been associated with macrovascular disease (3–8).

Of particular interest, recent data from the Atherosclerosis Risk in Communities (ARIC) study and the Ludwigshafen Risk and Cardiovascular Health (LURIC) study have shown that glycated hemoglobin is a better predictor for all-cause and cardiovascular mortality than fasting glucose (9,10).

The objective of the present work in 2,002 LURIC participants was to analyze whether subjects with newly diagnosed type 2 diabetes as per the ADA 2010 definition who would not have received the diagnosis as per the ADA 2009 definition are at increased risk of death from any cause and from cardiovascular diseases (10,11).

RESEARCH DESIGN AND METHODS—LURIC is a cross-sectional and prospective clinical trial that was designed to investigate cardiovascular risk factors. A total of 3,316 white subjects were recruited between July 1997 and January 2000 at the Ludwigshafen Heart Center in southwestern Germany (10,11). All participants underwent coronary angiography. The precise inclusion/exclusion criteria have been previously described (10,11). For the present analyses, subjects with known diabetes or incomplete determination of the glucometabolic phenotype (missing 75-g oral glucose tolerance test despite fasting glucose <126 mg/dL) were additionally ruled out. Information on the cause of death was missing for 11 decedents. These people were excluded when data on cardiovascular mortality were analyzed. The study was approved by the ethics committee at the Ärztekammer Rheinland-Pfalz and was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants (10). Diabetes was diagnosed according to the 2009 and 2010 criteria of the ADA (1,2). The follow-up for all-cause and cardiovascular mortality had a mean duration ± SD of 7.7 ± 2.0 years.

Laboratory analyses
The laboratory methods have been reported previously (10,11). Glucose was measured enzymatically on a Hitachi 717 analyzer (Roche, Mannheim, Germany). Glycated hemoglobin was measured with an immunoassay (hemoglobin A_{1c} UNIMATE 5; Hoffmann-LaRoche, Grenzach-Whylen, Germany).

Statistical analysis
The baseline clinical and biochemical characteristics are presented for three

groups: group A, subjects without diabetes as per the ADA 2010 definition (without diabetes); group B, subjects with type 2 diabetes as per the ADA 2010 definition but without diabetes as per the ADA 2009 definition (T2DM ADA 2010); and group C, subjects with type 2 diabetes as per the ADA 2009 definition (T2DM ADA 2009). Categorical data are expressed as numbers and percentages. In the case of continuous variables, we report means with SDs or medians with interquartile ranges. *P* values for differences in baseline characteristics among the three groups were calculated with the χ^2 test for categorical data and with ANOVA for continuous variables. Triglycerides and insulin were transformed logarithmically before being used in parametric statistical procedures. The Cox proportional hazards model was used to test the relationships of the three groups with all-cause and cardiovascular mortality. Two predefined models of adjustment were used (model 1: univariate; model 2: adjusted for sex, age, BMI, hypertension, smoking, glomerular filtration rate, triglycerides, LDL cholesterol, and HDL cholesterol). The results are presented as hazard ratios with 95% CIs. All statistical tests were two-sided and *P* < 0.05 was considered significant. The SPSS 15.0 statistical package (SPSS Inc., Chicago, IL) was used.

RESULTS—The clinical and biochemical characteristics of the study participants and data on mortality are shown in Table 1. A total of 346 (17.3%) deaths occurred during the follow-up. Among these, 202 (58.4%) were accounted for by cardiovascular diseases. Compared with subjects without diabetes, people with T2DM ADA 2009 (hazard ratio 2.02 [95% CI 1.61–2.53]; *P* < 0.001) and those with T2DM ADA 2010 (1.54 [1.05–2.26]; *P* = 0.028) had increased all-cause mortality. After multivariate adjustment, this association remained significant for individuals with T2DM ADA 2009 (1.62 [1.28–2.04]; *P* < 0.001) but turned insignificant for those with T2DM ADA 2010 (1.34 [0.91–1.97]; *P* = 0.141). There was no significant difference in all-cause mortality between subjects with T2DM ADA 2009 and people with T2DM ADA 2010 (*P* = 0.360, model 2). Compared with subjects without diabetes, subjects with T2DM ADA 2009 (1.99 [1.48–2.69]; *P* < 0.001) and those with T2DM ADA 2010 (1.98 [1.25–3.13]; *P* = 0.003) more frequently died of cardiovascular diseases. These associations

remained significant after multivariate adjustment for both subjects with T2DM ADA 2009 (1.62 [1.18–2.21]; *P* = 0.003) and subjects with T2DM ADA 2010 (1.67 [1.05–2.65]; *P* = 0.029). There was no significant difference in cardiovascular mortality between subjects with T2DM ADA 2009 and subjects with T2DM ADA 2010 (*P* = 0.894, model 2).

CONCLUSIONS—The current study shows that LURIC participants with newly diagnosed T2DM ADA 2010 have increased cardiovascular mortality compared with those without diabetes. Of importance, there were no differences in mortality rates for cardiovascular disease between LURIC participants with T2DM

ADA 2009 and those with T2DM ADA 2010. In agreement, subjects with T2DM ADA 2009 and people with T2DM ADA 2010 had a similar cardiovascular risk factor profile.

There is broad evidence that type 2 diabetes will increase the risk of cardiovascular death (12–14). Thus far, only subjects with elevated fasting or postchallenge glucose were diagnosed with diabetes (1). However, fasting and postchallenge glucose have high intraindividual variability (15). Hence, the sensitivity of these tests to select subjects with disturbance of glucose metabolism is not optimal.

Our data support that the use of glycated hemoglobin at a cut point of ≥6.5% as an additional criterion for the

Table 1—*Baseline characteristics according to diabetes definition*

	No diabetes as per ADA 2010 definition	T2DM ADA 2010	T2DM ADA 2009	*P* value*
n	1,384	150	468	—
Male sex	1,012 (73.1)	113 (75.3)	342 (73.1)	0.839
Age (years)	60.6 ± 10.8	62.7 ± 9.2	64.6 ± 9.5	<0.001
Fasting glucose (mg/dL)	98 ± 10	103 ± 11	125 ± 28	<0.001
Glucose 2 h (mg/dL)†	125 ± 33	137 ± 30	233 ± 65	<0.001
Fasting insulin (mU/L)	8 (6–12)	9 (6–12)	12 (8–21)	<0.001‡
Hemoglobin A_{1c} (%)	5.7 ± 0.4	6.8 ± 0.5	6.5 ± 1.0	<0.001
BMI (kg/m^2)	27.1 ± 3.8	28.0 ± 4.3	28.2 ± 4.0	<0.001
Waist circumference (cm)§	97 (12)	101 (11)	101 (11)	<0.001
Systemic hypertension	920 (66.5)	112 (74.7)	379 (81.0)	<0.001
Blood lipid level (mg/dL)				
Total cholesterol	196 ± 38	189 ± 37	193 (40)	0.073
LDL cholesterol	120 ± 35	117 ± 31	116 ± 34	0.097
HDL cholesterol	40 ± 11	38 ± 10	37 ± 10	<0.001
Triglycerides	137 (103–190)	140 (108–187)	158 (120–222)	<0.001‡
Glomerular filtration rate (mL/min/1.73 m^2)	84 ± 17	80 ± 18	81 ± 18	<0.001
Smoking				0.074
Never	501 (36.2)	48 (32.0)	153 (32.7)	—
Former smoker	597 (43.1)	64 (42.7)	232 (49.6)	—
Current smoker	286 (20.7)	38 (25.3)	83 (17.7)	—
Coronary artery disease (50% stenosis)	869 (62.8)	102 (68.0)	344 (73.5)	<0.001
Medication use				
β-Blocker	889 (64.2)	88 (58.7)	303 (64.7)	0.369
ACE inhibitor	667 (48.2)	78 (52.0)	258 (55.1)	0.031
Calcium antagonist	180 (13.0)	19 (12.7)	87 (18.6)	0.010
Diuretic	250 (18.1)	43 (28.7)	166 (35.5)	<0.001
Statin	656 (47.4)	75 (50.0)	234 (50.0)	0.561
Acetyl salicylic acid	983 (71.0)	118 (78.7)	322 (68.8)	0.068
Mortality				
All-cause death	194 (14.0)	30 (20.0)	122 (26.3)	—
Cardiovascular death‖	111 (8.1)	22 (14.8)	69 (14.9)	—

Data are *n* (%) in cases of categorical data and means ± SDs or medians (25th–75th percentiles) in cases of continuous variables. *χ^2 test and ANOVA for categorical and continuous data, respectively. †*n* = 1,384/150/238. ‡ANOVA of logarithmically transformed values. §*n* = 1,363/149/461. ‖*n* = 1,378/149/464.

diagnosis of diabetes may improve cardiovascular risk stratification in subjects referred for coronary angiography. Future studies should attempt to answer the question whether measurement of glycated hemoglobin will obviate the need for oral glucose tolerance testing.

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