

# Subclinical Atherosclerosis and Estimated Glucose Disposal Rate as Predictors of Mortality in Type 1 Diabetes

JON C. OLSON, DRPH, JOHN R. ERBEY, PHD, KATHERINE V. WILLIAMS, MD, DOROTHY J. BECKER, MD, DANIEL EDMUNDOWICZ, MD, SHERYL F. KELSEY, PHD, KIM SUTTON TYRRELL, DRPH, AND TREVOR J. ORCHARD, MD

**PURPOSE:** To investigate the usefulness of ischemic resting electrocardiogram (ECG), ankle brachial index (ABI)  $<0.8$ , ankle brachial difference (ABD)  $\geq 75$  mm Hg (a marker of peripheral medial arterial wall calcification), and estimated glucose disposal rate (eGDR) (a marker for insulin resistance) for predicting mortality risk in the context of standard risk factors.

**METHODS:** Data are from participants in the Pittsburgh Epidemiology of Diabetes Complications Study of 658 subjects with childhood onset Type 1 diabetes of mean age 28 years (range 8–48) and duration of diabetes 19 years (range 7–37) at baseline. Deaths were confirmed by death certificates.

**RESULTS:** There were 68 deaths from all causes during 10 years follow-up. In univariate analysis, the mortality hazard ratios and 95% confidence intervals associated with ischemic ECG (6.7, 3.7–12.1), the lowest quintile of eGDR (i.e., the most insulin resistant) (6.7, 4.1–10.9), ABI  $<0.8$  (2.5, 1.1–5.9), and ABD  $\geq 75$  mm Hg (6.7) were only marginally less than those conveyed by pre-existing coronary artery disease (8.4, 4.7–15.2) or overt nephropathy (7.6, 4.5–12.9). Ischemic ECG and eGDR were independent mortality predictors, together with duration of diabetes, coronary artery disease, overt nephropathy, non-high density lipoprotein cholesterol, and smoking history. If serum creatinine was available, it entered, and glycosylated hemoglobin replaced eGDR.

**CONCLUSIONS:** Estimated GDR and ECG ischemia are strong predictors of mortality in type 1 diabetes and may be useful in the identification of those at risk.

*Ann Epidemiol* 2002;12:331–337. © 2002 Elsevier Science Inc. All rights reserved.

**KEY WORDS:** Type 1 Diabetes, Subclinical Atherosclerosis, Insulin Resistance, Mortality.

## INTRODUCTION

Several measures of subclinical atherosclerosis have been examined as risk factors for mortality. Isolated ischemia on electrocardiogram (ECG) is independently associated with cardiovascular disease (CVD) mortality in nondiabetic populations (1–3), but has not been fully examined in diabetes. Asymptomatic large vessel peripheral arterial disease detected by a low ratio of ankle: brachial blood pressure is associated with elevated mortality (4–6). However, data in type

1 diabetes are few. A complicating element in the measurement of peripheral arterial pressure is that medial arterial wall calcification, which is common in type 1 diabetes of long duration (7), may reduce compressibility of the artery by a cuff, leading to elevated pressure recordings (8).

Previous reports from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study have raised the possibility that insulin resistance, the hallmark of type 2 diabetes and a CVD predictor in the general population, may also relate to CVD risk in type 1 diabetes (9–10). Recently, we developed an equation for estimated glucose disposal rate (eGDR) as a marker for insulin resistance in type 1 diabetes based on euglycemic hyperinsulinemic clamp studies (11), clamps being impractical for large populations.

Because many type 1 diabetes patients die suddenly from CVD without prior CVD evidence (12), it is critical to identify those at risk if preventive measures are to be successful. Therefore, we examined the ability of eGDR, ischemic ECG, and abnormal ankle blood pressures to predict mortality in type 1 diabetes in the context of standard risk factors.

Department of Epidemiology, Graduate School of Public Health (J.C.O., J.R.E., S.F.K., K.S.T., T.J.O.); the Department of Medicine (K.V.W., D.E.); and the Department of Pediatrics (D.J.B.), Division of Endocrinology and Metabolism, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA.

Address correspondences to: Trevor J. Orchard, M.D., Second Floor, Diabetes and Lipid Research, 3512 Fifth Avenue, Pittsburgh, PA 15213. E-mail: tjo+@pitt.edu

Received 8 December 2000; revised 16 May 2001; accepted 6 June 2001.

---

**Selected Abbreviations and Acronyms**

ABD = ankle brachial difference  
ABI = ankle brachial index  
AER = albumin excretion rate  
CAD = coronary artery disease  
CVD = cardiovascular disease  
DERI = Diabetes Epidemiology Research International  
ECG = electrocardiograph  
EDC = epidemiology of diabetes complications  
eGDR = estimated glucose disposal rate  
HbA<sub>1</sub> = hemoglobin A<sub>1</sub>  
HDLc = high-density lipoprotein cholesterol  
LDLc = low-density lipoprotein cholesterol  
LL = log likelihood  
MC = Minnesota Code  
ON = overt nephropathy  
SBP = systolic blood pressure  
WBC = white blood cell

---

---

**MATERIALS AND METHODS**

**Study Population**

Subjects were participants in the Pittsburgh EDC Study, a 10-year prospective study of risk factors for complications of type 1 diabetes. EDC participants were recruited from the Children's Hospital of Pittsburgh registry of type 1 diabetes, which is representative of the Allegheny County population (13). Subjects diagnosed with type 1 diabetes at Children's (or seen there within a year of diagnosis) before age 17 between 1950 and 1980 were eligible for the EDC study. Recruitment has been described previously (14).

658 subjects met eligibility criteria and participated in the first of six biennial EDC examinations from 1986 to 1988. Subjects who refused to attend a particular examination were invited to complete and return a mailed questionnaire concerning their medical history. Home visits were attempted for subjects unable to attend the clinic. Through the EDC examination cycle in 1996 to 1998 (10-year follow-up), follow-up data were available on all but three subjects, who were excluded yielding a sample size of 655.

**Clinical Evaluation and Procedures**

Before attending each clinic, participants completed a questionnaire concerning demographic information, medical history, depressive symptoms if aged 18+ years (Beck Depression Inventory) (15), and physical activity. An ever smoker was defined as 100+ lifetime cigarettes.

**Subclinical measures.** Resting ankle/arm systolic blood pressures were taken using a Doppler blood-flow detector with the subject supine. Starting with the right arm and proceeding to the same side tibialis posterior and dorsalis pedis arterial pressures, then the opposite side ankle arteries and ending with the right arm again. The ankle-brachial

ratios were calculated using the arm pressure taken closest in time to the ankle pressure. An ankle-brachial index (ABI) of <0.8 for any of the four vessels was defined as ABI <0.8. Because the relationship of ABI <0.8 to mortality was stronger than ABI <0.9, only ABI <0.8 is reported. An ankle-brachial difference (ABD) of  $\geq 75$  mm Hg for any of the four vessels was considered positive for peripheral arterial calcification (8), based on a radiographic validation study.

A 12-lead electrocardiogram was obtained. The baseline ECGs were coded using the Minnesota Code (MC) (16). Q-wave myocardial infarction was defined as MC 1.1-1.2, and ischemic ECG as MC 1.3, 4.1-4.3, 5.1-5.3, or 7.1 (17). The QT interval was derived from a single waveform in ECG lead II and heart rate from an average of 5 R-R distances. The QT interval was corrected for heart rate according to Bazett's formula:  $QT_c = QT/\sqrt{R-R}$  (18).

**Clinical measures.** Height was measured with the clinic stadiometer. Body mass index was calculated as weight (kg)/height<sup>2</sup> (m<sup>2</sup>). Two waist measurements were made midway between the upper iliac crest and lower costal margin, and two hip measurements at the maximum hip circumference. Averages of each were used to derive the waist to hip ratio.

Sitting blood pressures were measured according to the Hypertension Detection and Follow-up Program protocol (19) using a random zero sphygmomanometer. The mean of the second and third readings was used. Hypertension was defined as blood pressure  $\geq 140/90$  mm Hg or taking anti-hypertensive medication.

**Laboratory methods.** Fasting blood samples were taken. For the first 18 months of the study, hemoglobin A<sub>1</sub> (HbA<sub>1</sub>) was measured in saline-incubated samples by microcolumn cation-exchange (Isolab, Akron, OH). Thereafter, HbA<sub>1</sub> was measured using automated high-performance liquid chromatography (HPLC) (Diamat, Bio-Rad, Hercules, CA). Extensive duplicate samples were run with both techniques, and no systematic differences were seen. Readings with the two methods were shown to be almost identical ( $r = 0.95$ ; Diamat HbA<sub>1</sub> =  $0.18 + 1.00$  Isolab HbA<sub>1</sub>). The absolute difference was 0.158 (% HbA<sub>1</sub>). The methods produced almost identical results ( $r = 0.95$ ). Cholesterol and triglycerides were measured enzymatically (20,21). High-density lipoprotein cholesterol (HDLc) was determined using a modification of the Lipid Research Clinic's method by a heparin and manganese procedure (22). Low-density lipoprotein cholesterol (LDLc) was calculated using the Friedewald equation (23), which has been previously validated in this type 1 diabetic population (24). Non-HDLc was calculated as total cholesterol-HDLc.

Apolipoprotein A-1 was determined by immunoelectrophoresis (25,26). Serum fibrinogen levels were determined with a biuret colorimetric procedure and a clotting method.

White blood cell (WBC) counts were determined using the Coulter S-Plus IV. Serum creatinine was measured enzymatically (Kodak Ectachem®) and fibrinogen by abuiert colorimetric procedure and a clotting method.

Estimated glucose disposal rate (11) was calculated according to the formula  $eGDR = 24.31 - 12.22 * (\text{waist to hip ratio}) - 3.29 * (\text{hypertension; yes} = 1; \text{no} = 0) - 0.568 * \text{HbA}_{1c}$ . This was derived from hyperinsulinemic euglycemic clamp studies conducted in 24 subjects selected on the basis of low/middle/high levels of risk factors associated with insulin resistance. EGDR was highly associated with glucose disposal during the clamp ( $r^2 = 0.63$ ).

**Diabetes complications.** Distal symmetric polyneuropathy was determined according to the Diabetes Control and Complications Trial clinical examination protocol (27). The presence of two or more symptoms, signs, and absent tendon reflexes was considered positive.

Overt nephropathy was defined as an albumin excretion rate (AER)  $>200 \mu\text{g}/\text{min}$  in 2 of 3 timed urine collections (24-hour, overnight, and postclinic), renal dialysis, or kidney transplant. If two timed urine specimens were not complete, a previously validated urinary albumin:creatinine (mg/mg) ratio  $>0.31$  was used to define overt nephropathy. Urinary albumin was determined immuno-nephelometrically (28). If no specimens were available, serum creatinine  $>2 \text{ mg}/\text{dl}$  was considered evidence of overt nephropathy.

Clinical coronary artery disease (CAD) was defined as a history of myocardial infarction (confirmed by ECG Q waves or hospital records, using standardized criteria) (29), coronary artery occlusion  $\geq 50\%$  by angiography, or diagnosis of angina by the EDC physician during any EDC cycle visit.

Death certificates were obtained for all reported deaths. Cause of death was classified as i) cardiovascular disease; ii) renal disease; iii) infection; iv) other diabetic; or v) other nondiabetic, according to the principles of classification of the Diabetes Epidemiology Research International (DERI) (30). A separate classification was made based on the mention of CVD or renal disease on the death certificate, regardless of the DERI classification.

### Statistical Analysis

Differences between subjects by vital status were evaluated using Student's *t*-test for continuous variables and chi-square test for dichotomous variables. Non-normally distributed variables were transformed by natural log; the Mann-Whitney test was used to compare continuous variables that could not be log-normalized.  $P < .05$  was considered statistically significant. All risk factor variables studied were obtained at baseline.

Variables that were correlated at the  $p < .05$  level with mortality were made available for Cox proportional hazards

modeling. Significance of  $p < .05$  was required to enter the model, and  $p > .10$  for exclusion from the model of a variable that had entered. eGDR was entered as a continuous variable.

Because of colinearity with diabetes duration, the age variable was not used in multivariate analyses. Presence of overt nephropathy was used in place of AER in multivariate models. Alternate models were developed using both overt nephropathy and creatinine, or excluding creatinine.

For Cox regression of cause-specific mortality, deceased subjects without the cause of death of interest were excluded from the analysis. Analysis was performed using SPSS for Windows (31).

---

## RESULTS

At baseline, the prevalences of ABD  $\geq 75 \text{ mm Hg}$  and eGDR  $<6.22 \text{ mg}/\text{kg}/\text{min}$  (lowest quintile) were 6.8 and 20%, respectively. Prevalences were significantly higher among men than women (10.4 vs. 3.1% for ABD; 26.8 vs. 12.5% for eGDR; each  $p < .001$ ). There were no significant gender differences in the prevalences of ischemic ECG, or ABI  $<0.8$ , which had overall prevalences of 5 and 4%, respectively.

Of the 68 deaths, 44% were attributed to CVD, 15% to kidney failure, 16% to infection, 9% to other diabetic causes, and 16% to other nondiabetic causes (including 2 whose cause had not yet been assigned), according to the DERI coding. CVD and renal disease were mentioned on 41% and 34% of death certificates, respectively. Among 9 subjects with fatal MI or CAD death as their first clinical evidence of CAD, 8 had ON at baseline.

Among subjects who later died, 71% of those with baseline CAD and 71% of those with ECG ischemia were assigned a DERI code for CVD death. Among subjects with any of the other markers or with eGDR  $<6.22$ , the cause of death was assigned to CVD in 47–50% of decedents, similar to subjects with smoking history (51%), hypertension (56%), neuropathy (56%), and overt nephropathy (50%).

Table 1 shows baseline risk factor levels according to vital status at 10-year follow-up. Risk factor and subclinical marker associations with mortality were similar for men and women (not shown), except that HbA<sub>1c</sub> predicted mortality in women and overall, but not in men. Only gender, body mass index, and QTc interval did not predict mortality.

Table 2 shows the percentage mortality and univariate hazard ratios for mortality of subclinical markers, CAD, and overt nephropathy. Subjects with baseline CAD experienced the highest mortality (54%), followed by ischemic ECG (45%), ABD 75+ (44%), eGDR  $<6.22$  (30%), overt nephropathy (28%), and ABI  $<0.8$  (23%). The hazard ratios for ischemic ECG, ABD 75+, and eGDR  $<6.22$  were similar to each other, and 10–20% lower than prevalent

**TABLE 1.** Baseline risk factor levels for mortality, EDC 10-year follow-up

Variable	n	Alive	Dead
Total population	655	587	68
Sex (% male)	655	50.1	55.9
Age (yrs)	655	26.8 ± 7.7	33.8 ± 6.7***
Diabetes duration (yrs)	655	18.6 ± 7.4	25.3 ± 5.8****
Subclinical measures			
Ischemic ECG (%)	637	3.0	21.2***b
ABI < 0.8 (%)	646	3.5	8.8*b
ABD 75+ (%)	646	4.2	27.9***b
ABI < 0.8 or ABD 75+ (%)	646	7.6	35.3***b
eGDR < 6.22 (mg/kg/min) (%)	645	15.4	57.6***a
<sup>1</sup> HbA <sub>1c</sub> (%)	651	10.3 ± 1.8	10.9 ± 1.8*
Fibrinogen (mg/dl)	645	283.5 ± 88.2	348.7 ± 94.1****
WBC × 10 <sup>3</sup> /mm <sup>2</sup>	648	6.5 ± 1.9	7.8 ± 2.1****c
Triglycerides (mg/dl)	615	101.5 ± 77.4	186.8 ± 143.2****a
LDLc (mg/dl)	601	113.3 ± 33.3	142.5 ± 38.0****c
non-HDLc (mg/dl)	648	133.0 ± 39.5	177.4 ± 52.7****c
HDLc (mg/dl)	648	54.3 ± 12.2	49.5 ± 12.7**
ApoA1/HDLc	639	2.6 ± 0.5	3.0 ± 0.6***
Serum Creatinine (mg/dl)	651	0.9 ± 0.6	2.2 ± 2.4****a
Log median AER (μg/min)	650	3.4 ± 1.9	5.8 ± 2.0****a
SBP (mm Hg)	655	112.1 ± 13.7	128.7 ± 24.6****a
DBP (mm Hg)	655	72.3 ± 10.5	78.8 ± 13.7****c
QTc (Bazett)	617	409.5 ± 29.9	403.0 ± 28.7
Body mass index (kg/m <sup>2</sup> )	652	23.5 ± 3.2	23.8 ± 3.3
Waist to hip ratio	649	0.82 ± 0.07	0.87 ± 0.09****
Beck Depression Inventory	529	7.0 ± 6.4	10.3 ± 6.4****a
Smoke ever (%)	627	34.4	63.6***
Hypertension (%)	655	12.6	51.5***
CAD (%)	655	2.0	20.6***b
Neuropathy (%)	652	24.3	73.1***b
Overt nephropathy (%)	655	20.8	70.6***b

Values are given as mean ± SD or prevalence (%). 7.77 is the mean eGDR; 6.22 is the lowest quintile.

<sup>a</sup>Mann-Whitney.

<sup>b</sup>Fisher's exact.

<sup>c</sup>Log-transformed before *t*-test.

Comparisons by vital status: \**p* < .05; \*\**p* < .01; \*\*\**p* < .001.

<sup>1</sup>Significant only in women (*p* < .01) when examined gender-specifically.

baseline CAD (8.4) or overt nephropathy (7.6) for mortality risk. The prediction of subclinical markers and eGDR for total mortality is further explored by gender in Figure 1, where it can be seen that eGDR is more predictive in men. Though HR and specificity are generally quite high, sensitivity, only for ischemic ECG in men, does exceed 50%.

In multivariate modeling in which all univariate predictors in Table 1 were available (except age because of collinearity with duration) and creatinine (vide infra), prevalent CAD, duration, eGDR (modeled as a continuous variable), overt nephropathy, ischemic ECG, smoking history, and non-HDLc predicted mortality (Table 3a). When serum creatinine was available, it entered the model in addition to overt nephropathy, resulting in a significantly better model (Table 3b; probability  $\chi^2_{(1)} \geq 10.3$  *p* < .005), and HbA<sub>1c</sub> (a component of the eGDR) replaced eGDR. Excluding creatinine and complications (CAD, overt nephropathy) from

**TABLE 2.** Association of baseline status with mortality, univariate prediction, EDC 10-year follow-up

Clinical and subclinical markers	n	Percentage dying (n)	Mortality HR (95% CI) <sup>1</sup>
CAD	26	54 (14)	8.4 (4.7-15.2)
Overt nephropathy	170	28 (18)	7.6 (4.5-12.9)
eGDR < 6.22 mg/kg/min	127	30 (40)	6.7 (4.1-10.9)
Ischemic ECG	31	45 (14)	6.7 (3.7-12.1)
ABD 75+ mm Hg	43	44 (19)	6.7 (3.9-11.4)
ABI < 0.8	26	23 (6)	2.5 (1.1-5.9)
ABI < 0.8 or ABD 75+ mm Hg	68	35 (24)	5.4 (3.3-8.9)

eGDR median = 8.06, mean = 7.74, interquartile range = 6.66-9.12.

ABD median = 22.0, mean = 29.4, interquartile range = 12.0-32.0.

ABI median = 1.02, mean = 1.03, interquartile range = 0.96-1.09.

<sup>1</sup>Referent group in those without the specified risk factor.

the model, the mortality predictors were eGDR, log AER, duration, ischemic ECG, and smoking (not shown).

The independent CVD mortality predictors (DERI) were creatinine, baseline CAD, diabetes duration, ischemic ECG, non-HDLc, and smoking history; that is, the same as all-cause mortality but without overt nephropathy and HbA<sub>1c</sub>. The independent predictors of renal disease death were eGDR, ischemic ECG, WBC, CAD, and duration. Similar results were obtained using any mention of CVD or of renal disease in place of the DERI classifications.

Because 75% of the deceased subjects had CAD or overt nephropathy at baseline, we examined how well the subclinical markers and eGDR predicted mortality (*n* = 17) in the 474 subjects without these complications at baseline. Estimates were less stable due to small numbers. Ischemic ECG had a high mortality hazard ratio (14.5; 95% confidence interval [CI] 4.1-50.9), with three of the eight subjects dying (two from CAD and the third from overt nephropathy). For ABI/ABD and for eGDR, though the hazard ratios were increased (2.6 and 2.1, respectively), the confidence intervals included unity. Each of the subclinical markers and eGDR <6.22 had specificity >90% for mortality. At an HbA<sub>1c</sub> level with comparable specificity; however, HbA<sub>1c</sub> (≥12%) was not associated with increased mortality risk. Both deceased subjects with baseline HbA<sub>1c</sub> ≥12% and 2 of 3 in the lowest quintile of eGDR developed overt nephropathy or CAD if they did not have these complications at baseline.

## DISCUSSION

These results support the use of eGDR, ischemic ECG, and ABI <0.8 in conjunction with ABD 75+ in identifying type 1 diabetic adults at increased mortality risk. Strikingly, eGDR in the lowest quintile, ischemic ECG, and ABD 75+ each increased mortality risk sevenfold, a degree only slightly less than that seen for pre-existing CAD or overt nephropathy. In models that included CAD and overt

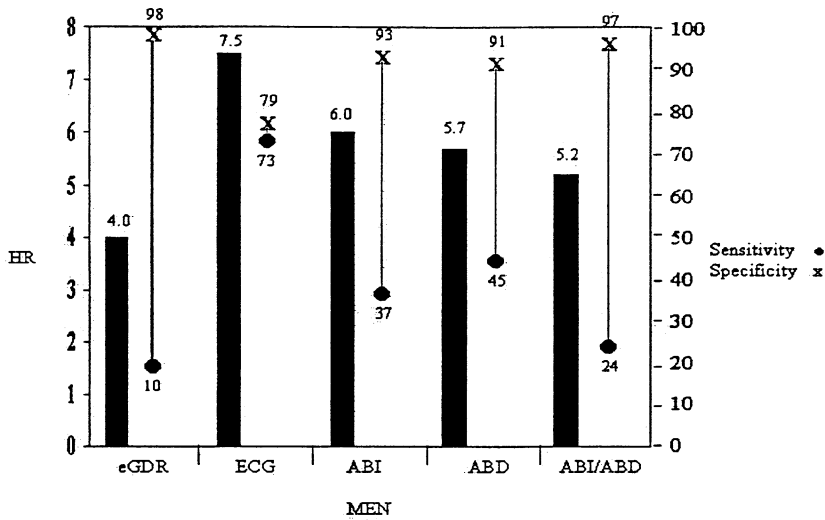
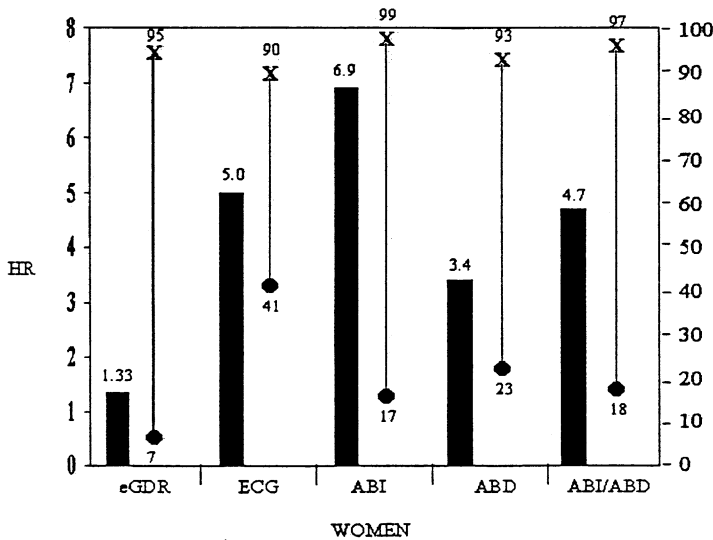


FIGURE 1. Measures of Subclinical Atherosclerosis and Insulin Sensitivity as Predictors (Hazard Ratios, 95% CI) of Mortality in type 1 diabetes by Gender, 10 Year Follow-up Data, Pittsburgh EDC Study



nephropathy, ischemic ECG and eGDR (or HbA<sub>1c</sub>) were independent mortality predictors, largely because they also predicted subsequent CAD and overt nephropathy. This sequence is also supported by a link between baseline ischemic ECG and CVD mortality in multivariate modeling. Ischemic ECG was a particularly strong mortality predictor among subjects free of baseline CAD or overt nephropathy.

In previous reports from the EDC study with 4-6 years follow-up, glycosylated hemoglobin failed to predict nonfatal CAD in type 1 diabetes (10,32); whereas, an association with fatal CAD was suggested (10). With longer follow-up, the Wisconsin Epidemiologic Study of Diabetic Retinopa-

thy found a borderline association between glycosylated hemoglobin and CAD mortality after adjusting for age and sex (95% CI 1.00-1.40) (33).

HbA<sub>1c</sub> was an independent mortality predictor in the present study if serum creatinine was also in the model. The eGDR, which includes HbA<sub>1c</sub>, was itself an independent mortality predictor if creatinine was not available, and an independent predictor of renal disease mortality. These data are consistent with insulin resistance and blood glucose control impacting survival through pathways in addition to CVD, notably renal disease. The multivariate model with HbA<sub>1c</sub> and creatinine was better than that with eGDR

**TABLE 3.** Significant predictors of 10-year mortality, Cox Proportional Hazards Models

Variables	HR	(95% CI)	p
3a. Excluding creatinine			
CAD	2.89	(1.46-5.75)	.002
Duration	1.64	(1.20-2.23)	.002
eGDR	0.66	(0.50-0.87)	.003
Overt nephropathy	2.60	(1.34-5.05)	.005
ECG Ischemia	2.60	(1.27-5.32)	.009
Ever smoke	2.07	(1.20-3.58)	.009
non-HDLc	1.29	(1.01-1.67)	.032
3b. All Variables Available			
CAD	3.68	(1.84-7.34)	< .001
Serum creatinine	1.35	(1.19-1.52)	< .001
Duration	1.67	(1.22-2.27)	.001
ECG Ischemia	2.90	(1.44-5.87)	.003
Ever smoke	2.19	(1.25-3.83)	.006
Overt nephropathy	2.52	(1.27-4.99)	.008
non-HDLc	1.35	(1.19-1.52)	.009
HbA1	1.39	(1.05-1.85)	.021

Hazard ratio (HR) yes/no or change per standard deviation (SD).  
SD duration = 7.5 years.  
eGDR = 1.93 mg/kg/min.  
Creatinine 1.0 mg/dl.  
HbA<sub>1</sub> 1.84 mg%.  
Non-HDLc 43.0 mg/dl.  
EGDR entered as a continuous measure.

(Tables 3a and 3b), but eGDR was a better mortality predictor than HbA<sub>1</sub> among subjects free of baseline CAD or overt nephropathy. The strong predictive power of eGDR for overt nephropathy (34), provides further evidence that nephropathy in type 1 diabetes is an insulin resistance complication (35). This also reflects the close association between hypertension (a component of the eGDR) and nephropathy.

Nephropathy is a major pathway between diabetic control and mortality (12,36). However, the predictive power of eGDR and of HbA<sub>1</sub> for mortality persisted even though overt nephropathy and CAD were in the multivariate models, because eGDR and HbA<sub>1</sub> predicted development of these complications.

ABI is a less accurate measure of lower extremity atherosclerosis in type 1 diabetes, because of peripheral arterial calcification. Prognostic usefulness was considerably improved by combining ABI <0.8 with ABD ≥75 mm Hg. ABI and ABD are derived from measurements obtained through the same procedures. Therefore, we recommend that they be used together in screening patients with type 1 diabetes.

In a recent conference on the primary prevention of CAD, the presence of ST-segment changes on resting ECG was classified as a CAD risk factor (37). Relative risks of 2-3 for fatal CHD and CVD have been reported (1,2), which are compatible with our results for all-cause mortality, in which the adjusted relative risk was 2.5. Ischemic

ECG was associated with high mortality risk even in the absence of CAD or overt nephropathy, while maintaining 99% specificity and thus seems the most useful of the sub-clinical markers. In terms of other markers, serum creatinine has been reported before and in addition to representing vessel disease, may also reflect generalized vascular disease in the kidney (38).

WBC count, a marker for inflammation in atherosclerosis, may also have an etiologic role by participating in endothelial injury and clogging capillaries and thereby reducing blood flow (see Ref.42). In shorter follow-up from the EDC study, WBC count was an independent predictor of CAD mortality (10), but perhaps because of small numbers, only a univariate predictor of total mortality (12).

The variable, non-HDLc, was used so as to include 47 subjects without an LDLc value (Table 1). This proxy for LDLc independently predicted all-cause and CVD mortality.

The EDC study previously reported that a history of smoking predicted fatal CAD (18 events) in univariate analysis only (10). Klein et al.; however, reported decreased survival in current smokers with diabetes onset before age 30, with a relative risk of 2.36 after adjustment for age and sex (39). After adjusting for the same risk factors, the relative risk for ever smoking was quite similar in the present study (2.31), and smoking was an independent mortality predictor in the full model.

The QTc interval has been implicated in sudden cardiac death among patients with a history of myocardial infarction (40), and type 2 diabetes (41); however, its usefulness in type 1 diabetes is disputed, and we found no evidence that QTc predicts mortality, in agreement with Rathman and colleagues (42); whereas, Sawicki et al. reported that QTc predicted all-cause mortality, but not cardiovascular mortality, in type 1 diabetes with overt nephropathy (18).

In conclusion, the eGDR, ECG ischemia, and ABI <0.8, in combination with ABD ≥75 mm Hg, are valuable screening tools for mortality risk in adults with type 1 diabetes. As the major causes of mortality in this population are cardiovascular and renal, high-risk patients should receive medical attention to control blood glucose and lower modifiable cardiovascular risk factors.

This research was supported by NIH Grant DK34818.

## REFERENCES

1. De Bacquer D, De Bacquer G, Kornitzer M, Myny K, Doyen Z, Blackburn H. Prognostic value of ischemic electrocardiographic findings for cardiovascular mortality in men and women. *J Am Coll Cardiol.* 1998;32:680-685.
2. Hart CL, Watt GCM, Davey Smith G, Gillis CR, Hawthorne VM. Pre-existing ischemic heart disease and ischemic disease mortality in women compared with men. *Int J Epidemiol.* 1997;26:508-515.

3. Daviglius ML, Liao Y, Greenland P, et al. Association of nonspecific ST-T abnormalities with cardiovascular mortality. The Chicago Western Electric Study. *JAMA*. 1999;281:530-536.
4. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med*. 1992;326:384.
5. Kornitzer M, Dramaix M, Sobolski J, Degre S, De Backer G. Ankle/arm pressure index in asymptomatic middle-aged males: An independent predictor of ten-year coronary heart disease mortality. *Angiology*. 1995;46:211-219.
6. Leng CG, Fowkes FGR, Lee AJ, Dumbart J, Housley E, Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: A cohort study. *BMJ*. 1996;313:1440-1444.
7. Maser RE, Wolfson SK, Stein EA, Drash AL, Becker DJ, Dorman JS, Ellis D, Orchard TJ. Cardiovascular disease and arterial calcification in insulin-dependent diabetes mellitus: Interrelationships and risk factor profiles. *Pittsburgh Epidemiology of Diabetes Complications Study-V*. *Arterioscler Thromb*. 1991;11:958-965.
8. Orchard TJ, Strandness DE. Assessment of peripheral vascular disease in diabetes. *Diabetes Care*. 1993;16:1199-1209.
9. Erbey JR, Kuller LH, Becker DJ, Orchard TJ. The association between a family history of type 2 diabetes (NIDDM) and coronary artery disease in a type 1 diabetes (IDDM) population. *Diabetes Care*. 1998;21:610-614.
10. Forrest KTZ, Becker DJ, Kuller LH, Wolfson SK, Orchard TJ. Are predictors of coronary heart disease and lower extremity arterial disease in type 1 diabetes the same? A prospective study. *Atherosclerosis*. 2000;148:159-169.
11. Williams KV, Erbey JR, Becker D, Arslanian S, Orchard TJ. Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes*. 2000;49:626-632.
12. Portuese EI, Kuller L, Becker D, Ellis D, Lloyd CE, Orchard TJ. High mortality from unidentified CVD in IDDM: Time to start screening? *Diabetes Res Clin Pract*. 1995;30:223-231.
13. Wagener DK, Sacks JM, Laporte RE, MacGregor JM. The Pittsburgh study of insulin-dependent diabetes mellitus: Risk for diabetes among relatives in IDDM. *Diabetes*. 1982;31:136-144.
14. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Drash AL, Ellis D, LaPorte RE, Kuller LH. Prevalence of complications in IDDM by sex and duration: Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes* 1990;39:1116-1124.
15. Beck AT, Garbin MG. Psychometric properties of the Beck Depression Inventory: 25 years of evaluation. *Clin Psychol Rev*. 1988;8:77-100.
16. Prineas RJ, Crow RS, Blackburn H. The Minnesota Code Manual of Electrocardiographic Findings. Standards and Procedures for Measurement and Classification. Littleton, MA: John Wright; 1982.
17. Marmot MG, Smith GD, Stansfield S, Patel C, North F, Head J, White I, Brunner E, Feeny A. Health inequalities among British civil servants: The Whitehall II Study. *Lancet*. 1991;337:1387-1393.
18. Sawicki PT, Dahne, Bender R, Berger M. Prolonged QT interval as a predictor of mortality in diabetic nephropathy. *Diabetologia*. 1996;39:77-81.
19. Borhani NO, Kass EH, Langford HG, Payne GH, Remington RD, Stamler J. The hypertension detection and follow-up program. *Prev Med*. 1976;5:207-215.
20. Bucolo G, David H. Quantitative determination of serum triglycerides by use of enzymes. *Clin Chem*. 1973;19:476-482.
21. Allain C, Poon LS, Chan CSG, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. *Clin Chem*. 1974;470-475.
22. Warnick GR, Albers JJ. Heparin/Mn++ quantification of high-density-lipoprotein cholesterol: an ultrafiltration procedure for lipemic samples. *Clin Chem*. 1987;24:900-904.
23. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499-502.
24. Cruickshanks KJ, Orchard TJ, Becker DJ. The cardiovascular risk profile of adolescents with insulin-dependent diabetes mellitus. *Diabetes Care*. 1985;8:118-124.
25. Mendoza SG, Zerpa A, Carrasco H, Colmenares O, Rangel A, Gertsides PS, Kashyap ML. Estradiol, testosterone, apolipoproteins, lipoprotein cholesterol, and lipolytic enzymes in men with premature myocardial infarction and angiographically assessed coronary occlusion. *Artery*. 1983;12:1-13.
26. Stein EA, Pesce JA. Enzyme-linked immunoassays for apolipoproteins: Advantages, problems, and prototype assay. In: Lippel K, ed. *Proceedings of Workshop on Apolipoprotein Quantification*. Washington, DC: US Dept. of Health and Human Services; 1983:319-331 (NIH Publ. 83-1266).
27. DCCT Research Group. *Manual of Operations for the Diabetes Control and Complications Trial*. Washington, DC: US Dept. of Commerce; 1987.
28. Ellis D, Buffone GJ. New approach to evaluation of proteinuria states. *Clin Chem*. 1977;23:666-670.
29. Orchard TJ, the CCSP Investigators. Validation of coronary heart disease mortality data: The Community Cardiovascular Surveillance Project pilot experience. *Am Heart Assoc Cardiovasc Dis Epidemiol Newslett*. 1985;157:46.
30. DERI Mortality Study Group. Sex differences in the mortality associated with insulin-dependent diabetes mellitus in four countries. The Diabetes Epidemiology Research International (DERI) Study. *Am J Epidemiol*. 1991;133:577-584.
31. SPSS for Windows release 9.0.1. SPSS Inc. 233 S. Wacker Drive, 11th floor. Chicago, IL, 60606.
32. Lloyd CE, Kuller LH, Becker DJ, Ellis D, Wing RR, Orchard TJ. Coronary artery disease in IDDM: Gender differences in risk factors, but not risk. *Arterioscler Thromb Vas Biol*. 1996;16:720-726.
33. Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care*. 1995;18:258-268.
34. Erbey JR. Insulin sensitivity in insulin-dependent diabetes mellitus: The potential for double diabetes and the development of cardiovascular disease. Ph.D. Dissertation, University of Pittsburgh, 1998.
35. Yip J, Mattock MB, Morocutti A, Sethi M, Trevisan R, Viberti G. Insulin resistance in insulin-dependent diabetic patients with microalbuminuria. *Lancet*. 1993;342:883-887.
36. American Diabetes Association Consensus Development Conference on Insulin Resistance. *Diabetes Care*. 1998;21:310-314.
37. Smith SC, Greenland P, Grundy SM. Prevention conference V. Beyond secondary prevention: Identifying the high-risk patient for primary prevention. *Circulation*. 2000;101:111-116.
38. Shulman NB, Ford CE, Hall WD, Blaufox MD, Simon D, Langford HG, Schneider KA. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Cooperative Group. *Hypertension*. 1989;13(suppl. 5):180-193.
39. Klein R, Moss SE, Klein BEK, DeMets DL. Relation of ocular and systemic factors to survival in diabetes. *Arch Int Med*. 1989;149:266-272.
40. Puddu PE, Bourassa MG. Prediction of sudden death from QTc interval prolongation in patients with chronic ischemic heart disease. *J Electrocardiol*. 1986;19:203-211.
41. Ewing DJ, Boland O, Neilson JMM, Cho CG, Clarke BF. Autonomic neuropathy, QT interval lengthening, and unexpected deaths in male diabetic patients. *Diabetologia*. 1991;34:182-185.
42. Rathman W, Ziegler D, Jahnke M, Haastert B, Gries FA. Mortality in diabetic patients with cardiovascular autonomic neuropathy. *Diabetic Med*. 1993;10:820-824.