Associations of Mortality and Diabetes Complications in Patients With Type 1 and Type 2 Diabetes

Early Treatment Diabetic Retinopathy Study report no. 27

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OBJECTIVE — Diabetes is a leading cause of morbidity and mortality. The purpose of this study is to assess the associations between diabetes complications and mortality in the Early Treatment Diabetic Retinopathy Study (ETDRS).

RESEARCH DESIGN AND METHODS — We examined demographic, clinical, and laboratory characteristics of the 3,711 subjects enrolled in the ETDRS, a randomized controlled clinical trial designed to evaluate the role of laser photocoagulation and aspirin therapy for diabetic retinopathy. The outcome assessed was all-cause mortality. Multivariable Cox proportional hazards regression was used to assess associations between diabetes complications and mortality for type 1 and type 2 diabetes separately.

RESULTS — The 5-year estimates of all-cause mortality were 5.5 and 18.9% for patients with type 1 and type 2 diabetes, respectively. In patients with type 1 diabetes, amputation (hazard ratio [HR] 5.08 [95% CI 2.06–12.54]) and poor visual acuity (1.74 [1.10–2.75]) remained significantly associated with mortality, after adjusting for other diabetes complications and baseline characteristics. In patients with type 2 diabetes, macrovascular disease and worsening levels of nephropathy, neuropathy, retinopathy, and visual acuity are associated with progressively increasing risks of mortality, after controlling for other baseline risk factors.

CONCLUSIONS — Amputation is the strongest predictor for mortality in patients with type 1 diabetes. All complications independently predict mortality in patients with type 2 diabetes. There is an increased risk for mortality as the degree of each complication worsens. Additional studies are needed to investigate the effectiveness of tertiary prevention to decrease mortality in these patients.

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Abbreviations: ECG, electrocardiogram; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Currently, there are ~13 million Americans with diagnosed diabetes (1) and millions more who remain unaware that they have the disease (2). This number is expected to increase to 29 million by the year 2050 (3). This presents a serious challenge to the health care system because people with diabetes have an increased mortality and a reduced life expectancy compared with those without diabetes (4). Although consistently underreported on death certificates as a cause of death (5), diabetes ranks as the sixth leading cause of death in the U.S., accounting for >71,000 deaths a year (6). Among those people with diabetes, the majority of deaths are due to the macrovascular complications of cardiovascular and cerebrovascular diseases, including myocardial ischemia and stroke (7). In addition to the increased mortality, diabetes is also associated with the morbidity of microvascular diseases, including nephropathy, neuropathy, and retinopathy. In fact, diabetes is the leading cause of end-stage renal disease (8), nontraumatic amputations (9), and adult blindness (10) in the U.S.

A number of studies have found relationships between the macrovascular (11–30) and microvascular (31–54) complications of diabetes and mortality. However, many of these studies assessed complications individually, failing to consider other putative risk factors and complications. The Early Treatment Diabetic Retinopathy Study (ETDRS) was a large, multicenter, randomized clinical trial that enrolled persons with diabetes and retinopathy to study the therapeutic effects of aspirin and laser photocoagulation on the risk of the progression of diabetic retinopathy and vision loss (55). After comprehensive baseline ocular and medical examinations with laboratory tests, patients were followed for 5–9 years. The aim of the current study is to assess the associations between the multiple complications of diabetes and mortality in a

population with extensive clinical data. These associations are clinically important to all health care providers who treat and counsel patients with early or late complications of diabetes.

RESEARCH DESIGN AND METHODS

— All subjects were participants in the ETDRS, a randomized clinical trial designed to assess photocoagulation and aspirin treatment for patients with diabetic retinopathy (55). The ETDRS enrolled 3,711 subjects aged 18–69 years from April 1980 through July 1985. Inclusion criteria included the diagnosis of diabetes and diabetic retinopathy in each eye that was defined as having mild, moderate, or severe nonproliferative diabetic retinopathy (NPDR) or mild to moderate proliferative diabetic retinopathy (PDR) with or without macular edema.

The exclusion criteria for entry into the ETDRS were contraindication to aspirin use, abnormal coagulation factor, systolic blood pressure >210 mmHg and/or diastolic blood pressure >110 mmHg, and a history of renal transplant or renal dialysis. Because of the need for long-term follow-up in this clinical trial, patients with severe renal disease or an unfavorable prognosis for 5 years were excluded from participating in the ETDRS. Informed consent was obtained from each subject before enrollment, and patients were randomly assigned to receive either 650 mg aspirin or placebo daily. Patients were followed for a minimum of 5 years and for as long as 9 years.

Baseline data on age, sex, race, duration of diabetes, use of insulin, use of oral hypoglycemic medications, use of antihypertensive medications, cigarette smoking status (never, former, or current), and alcohol consumption (never, <1 drink/day, or ≥1 drink/day) were obtained from an interviewer-administered questionnaire. Patients were classified as having type 1 diabetes if their age at diabetes diagnosis was ≤30 years and they started on continuous insulin use within 1 year of diagnosis or their age at diabetes diagnosis was ≤40 years, they started on continuous insulin within 1 year of diagnosis, and their percentage of desirable weight was <120%. All others were classified as having type 2 diabetes. At the baseline physical examination, the height, weight, and blood pressure of the patients were obtained. BMI was calculated from the height and weight. Baseline laboratory measurements assessed include fasting serum levels of HbA_{1c}, total cholesterol, triglycerides, fibrinogen, creatinine, hematocrit, plasma proteins (fibrinogen and albumin), and urine protein, tested once at baseline by the dipstick method. After the first 2,709 patients were enrolled, the ETDRS protocol was modified, discontinuing some baseline laboratory measures. Patients were monitored in 4-month intervals with ocular and medical examinations per the ETDRS protocol.

Baseline diabetes complications

The complications of diabetes assessed in this study included macrovascular disease, nephropathy, peripheral neuropathy, retinopathy, and visual acuity, all assessed at the baseline evaluation. Macrovascular disease was considered to be present if the patient had a history of any of the following: myocardial infarction, coronary artery disease, congestive heart failure, stroke, transient ischemic attacks, intermittent claudication, antianginal use, or an electrocardiogram (ECG) abnormality.

Nephropathy was categorized into four levels by increasing severity based on the natural history of the disease (56). None/mild proteinuria (level 1) was defined as negative or trace urine protein with serum creatinine ≤1.4 mg/dl. Moderate proteinuria (level 2) was defined as urine protein + or ++ by dipstick measurement and serum creatinine ≤1.4 mg/dl. Severe proteinuria (level 3) was defined as urine protein +++ or ++++ by dipstick measurement and serum creatinine ≤1.4 mg/dl. Increased serum creatinine (level 4) was defined as serum creatinine >1.4 mg/dl with any measurable urine protein by dipstick.

Peripheral neuropathy was categorized into four levels by increasing severity. Vibration sensation was performed using a 128-Hz tuning fork placed over the dorsum of the great toe on the boney prominence of the distal interphalangeal joint while the patient's eyes were closed. Vibration that was felt easily by the examiner's finger but not appreciated by the subject was considered diminished. Before the examination, a trial was given on the patient's fingers to be certain that the patient understood the stimulus. Normal (level 1) was defined as normal vibratory sensation and no history or presence of ulceration or amputation. Vibratory sense neuropathy (level 2) was defined as vibratory sense diminished on physical examination with a tuning fork but no history or presence of ulceration or amputation. Ulceration (level 3) was defined as normal or diminished vibratory sensation, history or presence of ulceration, but no amputation. Amputation (level 4) was defined as the history or presence of amputation of any portion of a leg, regardless of sensory loss or ulceration status.

Diabetic retinopathy status was defined at baseline by five levels of increasing severity, based on standardized grading protocol of seven-field stereoscopic fundus photographs of the eye assigned to the deferral of treatment in the ETDRS (57). The categories included the following: none/mild NPDR (level 1, ETDRS score 10–37), moderate NPDR (level 2, ETDRS score 43–47), severe NPDR (level 3, ETDRS score 53–55), mild PDR (level 4, ETDRS score 61), and moderate/high PDR (level 5, ETDRS score 65–85).

Visual acuity was measured using the standardized ETDRS letter charts (58) at 4 m, or 1 m when necessary, and results are given in logMAR units. The best-corrected visual acuity, measured in the eye assigned to the deferral of laser photocoagulation treatment, was categorized into three levels: ≥84 letters (level 1, Snellen equivalent ≥20/20), 69–83 letters (level 2, Snellen equivalent <20/20 −20/40), and <69 letters (level 3, Snellen equivalent <20/40).

Outcome measurement

The outcome in this study was time to all-cause mortality, defined as the occurrence of death of any cause at any time during the period of the study. The Mortality and Morbidity Classification Committee, composed of internists and cardiologists who were not ETDRS investigators, coded the deaths during the study.

Statistical analysis

Kaplan-Meier analyses were used to evaluate the rate of all-cause mortality separately in type 1 and type 2 diabetes in the entire ETDRS population. Categorical and continuous variables were compared using the χ^2 and Student's t test, respectively, for the baseline demographic, clinical, and laboratory characteristics among the patients with type 1 or type 2 diabetes.

Age- and sex-adjusted Cox proportional hazards models were used to estimate the associations between mortality

Table 1—*Baseline demographics and laboratory values by diabetes type and all-cause mortality*

Characteristic	Type 1 diabetes		Type 2 diabetes	
	Survivors	Nonsurvivors	Survivors	Nonsurvivors
n	1,324	120	1,681	586
Age (years)	33.0 ± 10.2	41.4 ± 11.8*	54.4 ± 8.8	58.8 ± 6.7*
Sex (female)	38.1	34.2	47.4	46.6
Race (white)	93.8	81.7*	64.8	68.9
Duration of diabetes (years)	18.1 ± 6.2	19.4 ± 7.2	13.5 ± 6.8	14.5 ± 7.2*
BMI (kg/m^2)	23.4 ± 3.4	23.7 ± 4.0	28.8 ± 5.6	29.2 ± 6.2
HbA_{1c} (%)	10.0 ± 1.9	10.5 ± 2.8	9.4 ± 2.2	9.6 ± 2.3†
Systolic blood pressure (mmHg)	127 ± 18	137 ± 24*	145 ± 22	148 ± 23*
Diastolic blood pressure (mmHg)	80 ± 10	81 ± 12	84 ± 10	84 ± 11
Total cholesterol (mg/dl)	212 ± 48	248 ± 71*	232 ± 50	253 ± 75*
Triglycerides (mg/dl)	124 ± 119	183 ± 213*	196 ± 209	241 ± 292*
Fibrinogen (mg/dl)	262 ± 64	306 ± 87*	308 ± 77	341 ± 98*
Cigarette smoking				
Never	46.8	30.8*	52.5	46.6†
Former	21.2	25.0	30.7	34.5
Current	32.0	44.2	16.8	18.9
Alcohol consumption				
Never	41.5	55.0*	69.4	70.3
<1/day	47.5	41.7	25.5	24.7
≥1/day	10.9	3.3	5.1	5.0
Diuretic use	9.8	18.3*	31.9	44.0*
Daily use of insulin	99.9	100	73.0	75.6
Hypoglycemic use	0.2	0	23.9	22.2
Antihypertensive use	4.8	10.8*	24.2	30.2*
Assigned to aspirin treatment	48.9	44.2	51.7	49.0

Data are means ± SD or percent.*Significantly different at $P \leq 0.01$; categorical and continuous variables were compared within each type of diabetes using the χ^2 and Student's *t* test, respectively; †significantly different at $P \leq 0.05$.

and each of the complications of diabetes (model 1). We then examined Cox proportional hazards models predicting mortality with each of the following baseline covariates: race, BMI, systolic and diastolic blood pressure, duration of diabetes, type of diabetes, assignment to aspirin therapy, use of insulin, use of oral hypoglycemic medications, use of antihypertensive medications, use of diuretics, cigarette smoking status (never, former, or current), alcohol consumption (never, <1 drink/day, or ≥1drink/day), HbA_{1c}, total cholesterol, triglycerides, and fibrinogen. If the baseline covariate was significant at the $P < 0.05$ level, it was added to the age- and sex-adjusted Cox proportional hazards models to estimate the associations between mortality and each of the complications of diabetes (model 2). Finally, all diabetes complications with statistically significant covariates were considered in a final Cox proportional hazards model to predict mortality (model 3). Statistical analyses were performed using SAS 8.2 for Windows (SAS Institute, Cary, NC).

RESULTS — Of the total ETDRS population ($n = 3,711$), the 5-year Kaplan-Meier probability estimates of all-cause mortality during the course of the study were 5.5% (95% CI 4.3–6.7) and 18.9% (17.2–20.6) for patients with type 1 and type 2 diabetes, respectively. Baseline characteristics, laboratory values, and diabetes complications of patients, based on type of diabetes and the mortality outcome, are shown in Tables 1 and 2. Those subjects with type 2 diabetes lacking complete baseline laboratory data only differed with regard to race (36.6% white and 43.1% nonwhite; $P = 0.0025$) from those with complete data. Subjects with type 1 diabetes and incomplete laboratory values did not significantly differ from those with complete data.

Of the ETDRS participants with type 1 diabetes ($n = 1,444$), ~8.3% ($n = 120$) died over a mean follow-up time of 6.0 ± 1.5 years. The most common cause of death in patients with type 1 diabetes was an acute coronary event (55%) followed by infection (11%). Those who died were more likely to be older, nonwhite, use diuretic and antihypertensive medications, and have higher levels of the following: systolic blood pressure, total cholesterol, triglycerides, and fibrinogen. Patients with type 1 diabetes who died also had significantly different proportions of cigarette use, alcohol use, macrovascular disease, nephropathy, neuropathy, and visual acuity compared with those who survived.

Of those with type 2 diabetes ($n = 2,267$), ~25.8% died over a mean follow-up time of 5.4 ± 1.8 years. The most common cause of death in patients with type 2 diabetes was an acute coronary event (56%) followed by chronic coronary disease (7%). In general, those who died were more likely to be older, use diuretics and antihypertensive medications, and have higher levels of the following: systolic blood pressure, HbA_{1c}, total cholesterol, triglycerides, and fibrinogen. Patients with type 2 diabetes who died also had significantly different proportions of cigarette use, macrovascular disease, nephropathy, neuropathy, retinopathy, and visual acuity compared with those who survived.

Associations of mortality with diabetes complications

The 5-year life mortality rates by age and sex are presented in Table 3. Age- and sex-adjusted survival plots based on each diabetes complication are shown in Fig. 1. Results of the Cox regression models are summarized in Table 4. After adjusting for age and sex (model 1), the presence of macrovascular disease (HR 1.96 [95% CI 1.33–2.89]), severe proteinuria (2.23 [1.11–4.49]), increased serum creatinine (4.53 [2.64–7.77]), diminished vibratory sense (1.51 [1.00–2.28]), amputation (3.98 [1.84–8.59]), and poor visual acuity (2.25 [1.55–3.25]) in patients with type 1 diabetes were associated with a statistically significant increased risk in all-cause mortality. After adjustment for other statistically significant covariates and other diabetes complications (model 3), amputation (5.08 [2.06–12.54]) and poor visual acuity (1.74 [1.10–2.75]) remained significantly associated with mor-

Table 2—*Baseline diabetes complications by diabetes type and all-cause mortality*

	Type 1 diabetes		Type 2 diabetes	
Baseline complication	Survivors	Nonsurvivors	Survivors	Nonsurvivors
n	1,324	120	1,681	585
Macrovascular disease*				
Absent	83.2	61.7†	60.9	35.7†
Present	16.8	38.3	39.1	64.3
Nephropathy				
None/mild proteinuria	70.0	56.3†	75.7	48.7†
Moderate proteinuria	22.2	20.5	16.2	24.9
Severe proteinuria	5.0	8.0	2.6	5.8
Increased serum creatinine	2.8	15.2	5.5	20.6
Peripheral neuropathy				
Normal	62.4	37.8†	45.9	30.3†
Vibratory sense diminished	32.3	49.6	44.2	52.7
Ulceration	3.8	5.9	6.5	9.6
Amputation	1.5	6.7	3.5	7.4
Diabetic retinopathy				
None/mild NPDR	12.6	15.0	20.5	13.7†
Moderate NPDR	40.9	36.7	55.3	56.3
Severe NPDR	19.1	18.3	13.3	16.0
Mild PDR	13.6	12.5	6.4	6.3
Moderate/high PDR	13.8	17.5	4.6	7.7
Visual acuity				
≥20/20	73.6	50.8†	48.8	34.6†
20/20–20/40	24.6	46.7	39.9	44.2
<20/40	1.7	2.5	11.4	21.2

Data are percentages. *Macrovascular disease indicates a baseline history of myocardial infarction, coronary artery disease, congestive heart failure, stroke, transient ischemic attacks, intermittent claudication, antianginal use, or an ECG abnormality; †significantly different at $P \leq 0.01$; categorical variables were compared within each type of diabetes using the χ^2 test.

tality. Statistically significant covariates included in models 2 and 3 for patients with type 1 diabetes included race, duration of diabetes, HbA_{1c}, systolic blood pressure, total cholesterol, triglycerides, fibrinogen, cigarette smoking, alcohol consumption, and use of diuretic and antihypertensive medications.

In patients with type 2 diabetes, macrovascular disease was significantly associated with mortality (HR 2.00 [95% CI 1.69–2.38]) after adjusting for age and sex (model 1). The HRs (95% CI) for increasing severity levels of nephropathy were 2.17 (1.77–2.67), 3.08 (2.13–4.45), and 3.96 (3.17–4.94). The HRs (95% CI) for increasing severity levels of neuropathy were 1.31 (1.09–1.59), 1.87 (1.38–2.52), and 2.25 (1.60–3.15). The HRs (95% CI) for increasing severity levels of retinopathy were 1.37 (1.07–1.75), 1.70 (1.26–2.30), 1.55 (1.04–2.29), and 2.23 (1.55–3.22). Visual acuity <20/40 was also significantly associated with mortality after adjustment for age and sex (1.54 [1.22–1.94]). After adjusting for statistically significant covariates and other complications (model 3), macrovascular disease, all levels of nephropathy and neuropathy, and the poorest levels of retinopathy and visual acuity remained statistically significantly associated with mortality. Statistically significant covariates included in models 2 and 3 for patients with type 2 diabetes included BMI, HbA_{1c}, total cholesterol, triglycerides, fibrinogen, cigarette smoking, use of diuretic and antihypertensive medications, and daily use of insulin.

CONCLUSIONS — The ETDRS was a clinic-based study of patients with type 1 and type 2 diabetes that provides an opportunity to assess the relationships between different complications of diabetes and mortality. The majority of deaths in the ETDRS population were attributed to acute coronary events, and the 5-year mortality rate for type 2 diabetes (18.9%) was higher than that for type 1 (5.5%). In this report, we have shown that, in general, macrovascular disease and worsening levels of microvascular disease are associated with progressively increasing risks of mortality, even after controlling for other significant risk factors, in patients with type 2 diabetes. In patients with type 1 diabetes, mortality was associated with macrovascular disease, nephropathy, peripheral neuropathy, and poor visual acuity. After adjusting for other baseline characteristics and complications, amputation and poor visual acuity remained statistically significantly associated with mortality in patients with type 1 diabetes. Of note, our analyses re-

Table 3—*Five-year all-cause mortality rates by age-group and sex*

	5-year mortality rate			
	Type 1 diabetes		Type 2 diabetes	
	Male	Female	Male	Female
Age (years)				
18–29	2.7 (1.0–4.4) [342]	1.2 (0.0–2.5) [267]	No deaths [10]	No deaths [7]
30–39	5.0 (2.5–7.4) [314]	6.8 (2.7–10.8) [157]	4.1 (0.00–9.7) [53]	2.6 (0.0–7.7) [38]
40–49	8.3 (3.6–13.0) [148]	6.9 (1.1–12.8) [74]	8.4 (4.6–12.2) [218]	12.6 (7.3–18.0) [166]
50–59	15.3 (6.5–24.0) [69]	10.3 (0.7–19.8) [39]	15.6 (12.4–18.9) [495]	16.1 (12.7–19.6) [466]
60–69	28.8 (10.7–46.9) [25]	12.5 (0.0–35.4) [9]	29.4 (24.9–33.9) [422]	27.8 (23.2–32.4) [392]
Total	6.2 (4.5–7.8) [898]	4.4 (2.6–6.2) [546]	18.5 (16.3–20.8) [1198]	19.3 (16.8–21.8) [1069]

Data are means (95% CI) [*n*].

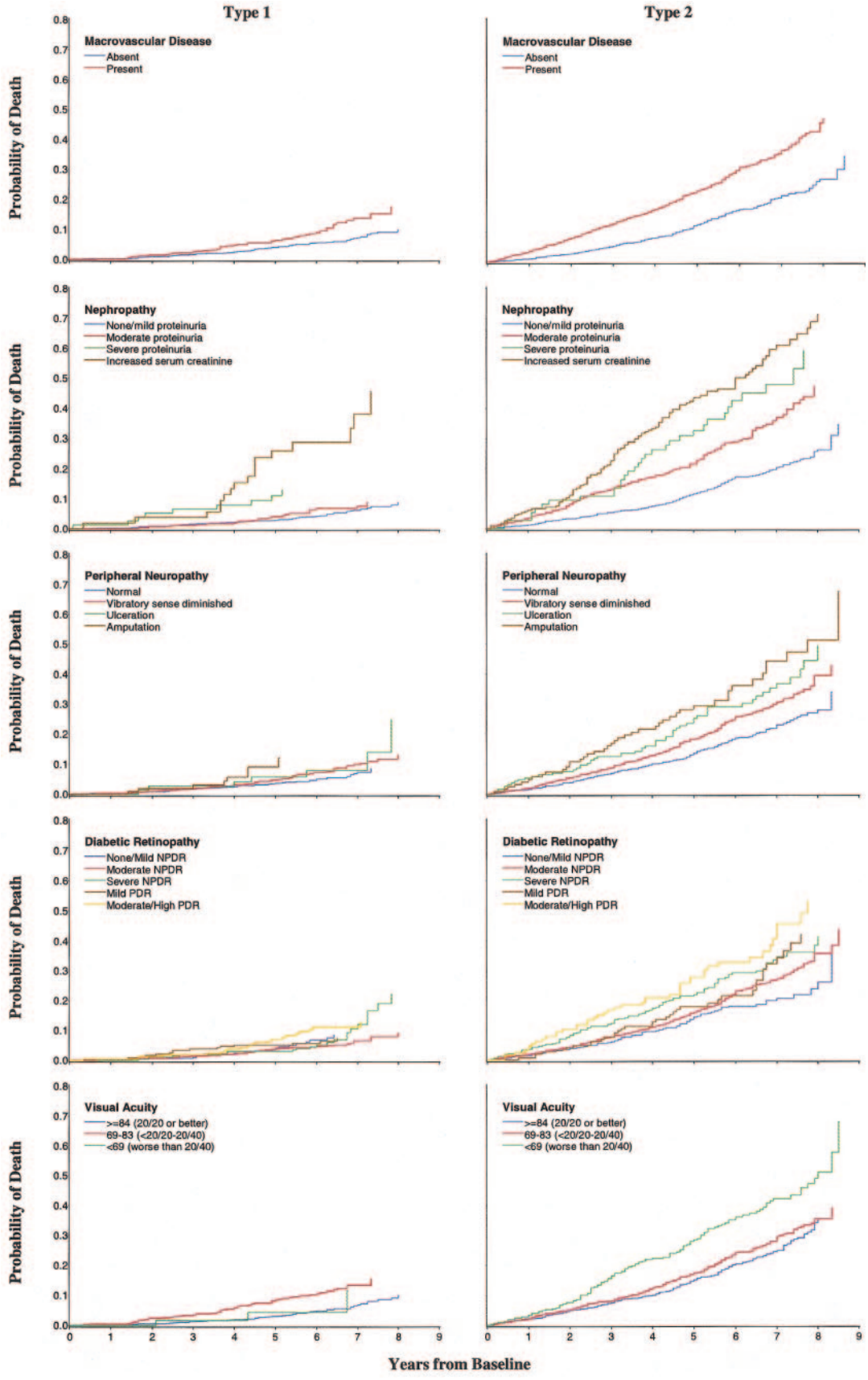

Figure 1—*Age- and sex-adjusted estimates of the probability of all-cause mortality by macrovascular disease, nephropathy, neuropathy, retinopathy, and visual acuity in patients with type 1 and type 2 diabetes.*

Table 4—*Results of Cox proportional hazards models for all-cause mortality in participants with type 1 and type 2 diabetes in ETDRS**

	Type 1 diabetes mortality			Type 2 diabetes mortality		
Complication	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Macrovascular disease†						
Absent	—	—	—	—	—	—
Present	**1.96 (1.33–2.89)**	1.43 (0.89–2.29)	1.36 (0.83–2.21)	**2.00 (1.69–2.38)**	**1.72 (1.40–2.12)**	**1.63 (1.32–2.01)**
Nephropathy						
None/mild proteinuria	—	—	—	—	—	—
Moderate proteinuria	1.25 (0.77–2.02)	0.98 (0.57–1.67)	1.02 (0.59–1.77)	**2.17 (1.77–2.67)**	**2.02 (1.59–2.56)**	**1.90 (1.49–2.42)**
Severe proteinuria	**2.23 (1.11–4.49)**	1.03 (0.44–2.40)	0.96 (0.40–2.29)	**3.08 (2.13–4.45)**	**1.90 (1.20–3.00)**	**1.89 (1.19–3.01)**
Increased serum creatinine	**4.53 (2.64–7.77)**	1.52 (0.70–3.29)	1.93 (0.89–4.18)	**3.96 (3.17–4.94)**	**2.69 (2.02–3.60)**	**2.46 (1.83–3.32)**
Peripheral neuropathy						
Normal	—	—	—	—	—	—
Vibratory sense diminished	**1.51 (1.00–2.28)**	1.39 (0.85–2.26)	1.22 (0.74–1.99)	**1.31 (1.09–1.59)**	**1.41 (1.11–1.78)**	**1.32 (1.04–1.67)**
Ulceration	1.61 (0.72–3.61)	1.44 (0.58–3.58)	1.37 (0.55–3.41)	**1.87 (1.38–2.52)**	**2.05 (1.42–2.94)**	**1.48 (1.01–2.17)**
Amputation	**3.98 (1.84–8.59)**	**5.82 (2.41–14.01)**	**5.08 (2.06–12.54)**	**2.25 (1.60–3.15)**	**2.69 (1.78–4.05)**	**2.23 (1.47–3.38)**
Diabetic retinopathy						
None/mild NPDR	—	—	—	—	—	—
Moderate NPDR	0.88 (0.51–1.53)	0.84 (0.42–1.65)	0.88 (0.43–1.80)	**1.37 (1.07–1.75)**	1.33 (0.99–1.79)	1.27 (0.94–1.72)
Severe NPDR	1.51 (0.79–2.91)	1.55 (0.71–3.37)	1.33 (0.59–2.99)	**1.70 (1.26–2.30)**	**1.77 (1.24–2.53)**	**1.48 (1.03–2.15)**
Mild PDR	1.11 (0.55–2.22)	0.71 (0.30–1.71)	0.54 (0.21–1.38)	**1.55 (1.04–2.29)**	1.54 (0.97–2.44)	1.28 (0.80–2.06)
Moderate/high PDR	1.71 (0.89–3.27)	1.35 (0.61–2.96)	1.21 (0.54–2.73)	**2.23 (1.55–3.22)**	**2.01 (1.28–3.14)**	**2.02 (1.28–3.19)**
Visual acuity						
≥20/20	—	—	—	—	—	—
20/20–20/40	**2.25 (1.55–3.25)**	**1.81 (1.17–2.83)**	**1.74 (1.10–2.75)**	1.19 (0.99–1.44)	**1.34 (1.07–1.68)**	1.24 (0.99–1.56)
<20/40	1.49 (0.47–4.77)	1.13 (0.27–4.81)	0.97 (0.22–4.19)	**1.54 (1.22–1.94)**	**1.60 (1.21–2.12)**	**1.36 (1.01–1.83)**

Data are HR (95% CI). *Model 1 adjusts for age and sex. Model 2 adjusts for age, sex, and statistically significant ($P < 0.05$) baseline covariates. Model 3 adjusts for age, sex, statistically significant baseline covariates, and all other diabetes complications. Statistically significant HRs ($P < 0.05$) are shown in bold. Models 2 and 3 were also adjusted for the following baseline covariates in type 1 (T1) and type 2 (T2) diabetes: race (T1), duration of diabetes (T1), BMI (T2), HbA_{1c} (T1, T2), systolic blood pressure (T1), total cholesterol (T1, T2), triglycerides (T2), fibrinogen (T1, T2), cigarette smoking (T1, T2), alcohol consumption (T1), diuretic use (T1, T2), daily insulin use (T2), and the use antihypertensive medication (T1, T2); †macrovascular disease includes a history of myocardial infarction, coronary artery disease, congestive heart failure, stroke, transient ischemic attacks, intermittent claudication, antianginal use, or ECG abnormality.

vealed no statistically significant effect of aspirin use on mortality in either type 1 or type 2 diabetes. These findings regarding aspirin use are consistent with a previous study addressing mortality in the ETDRS population (59).

The association among diabetes, cardiovascular disease, and mortality is well established (11). In addition to increasing the risk of primary cardiovascular events, diabetes has also been associated with a poorer survival after such an event (12–29). In the current study, we demonstrated a relation between a history of macrovascular disease, such as cardiovascular disease, and mortality in patients with type 1 and type 2 diabetes. This association persisted in patients with type 2 diabetes after adjustment for other variables that were found to influence mortality. These findings may indicate that those with such a history have a more severe systemic disease or that the pathologic changes localized to the cardiovascular system increase the risk for death in these patients. Even in the absence of known complications, however, diabetes is considered a "coronary equivalent," because the risk of a future myocardial infarction or stroke in patients with diabetes with no previous myocardial infarction is similar to patients without diabetes who have had a prior (30) or acute (25) myocardial infarction. These findings may be explained by abnormal systolic or diastolic ventricular function, termed diabetic cardiomyopathy (60), that exists in the absence of ischemic cardiomyopathy, yet contributes to mortality in a similar manner. Futhermore, patients with diabetes are more likely to have silent myocardial ischemia (61) and painless ECG changes (62), which may also increase their risk for mortality.

A number of studies have found associations between mortality and various severities of nephropathy in patients with type 1 (31–33) and type 2 (31,32,34–42) diabetes. Although proteinuria reflects renal processes in patients with diabetes, it is also considered a marker of chronic poor health, vascular permeability, and possibly cardiovascular disease (63). Consistent with this hypothesis, we found that of the 669 patients with type 2 diabetes and at least moderate proteinuria in our study, 358 (54%) patients also had a history of macrovascular disease.

In the current study, we created categories of worsening nephropathy based on what is known of the clinical course of diabetic renal disease (56). In general, we observed statistically significant increasing risks for mortality with worsening levels of nephropathy in patients with type 2 diabetes but not type 1 diabetes. Our findings do not reflect the results of a similar study (32) in patients with type 1 diabetes that revealed nephropathy as the strongest predictor of mortality after controlling for similar

covariates and complications of diabetes. This contrast is likely the result of differences in sample size and methods to assess proteinuria between our studies. In our study of patients with type 2 diabetes, however, increased serum creatinine showed the highest HR (2.46 [95% CI 1.83–3.32]) of all diabetes complications after adjusting for all baseline covariates and other complications.

Peripheral neuropathy is a common complication of diabetes, and excess mortality has been related to diminished peripheral sensation (43), foot ulceration (44), and amputation (45–47). Our findings in patients with type 2 diabetes are consistent with these reports. We also show that amputation was the most important predictor for mortality in patients with type 1 diabetes. This is not unexpected, as the mortality rate after amputation has been reported to be two to eight times the rate of those without amputations (45–47). The increased mortality associated with the various levels of peripheral neuropathy may be related to concurrent cardiovascular autonomic neuropathy, putting the patient at higher risk for cardiovascular mortality. In the current study, the leading cause of death among those patients with a history of amputation was coronary disease with an acute event, supporting the link between severe neuropathy and cardiovascular mortality. Furthermore, we consider amputation as the most severe neuropathic complication of diabetes, when it is also an obvious marker of macrovascular disease.

Of all of the complications of diabetes, retinopathy presents the physician with the unique opportunity to directly visualize and grade the actual pathology of the disease. We chose to include visual acuity in our investigation of diabetes complications to assess the parallel relationship between ocular function and ocular pathology with respect to mortality. Our results in patients with type 2 diabetes are consistent with other studies that have shown associations between mortality and various severities of retinopathy (48–56) and poor visual acuity (48,50–52). Similar to another study (52), we found that visual impairment but not degree of retinopathy is related to mortality in patients with type 1 diabetes after controlling for covariates. Our findings support the hypothesis that ocular disease may reflect comorbidities and the general health status of the patient.

The generalizability of our study is limited by the fact the ETDRS population was recruited from major ophthalmic clinical centers based on certain ocular criteria. Also, at the time of the ETDRS, patients with diabetes generally had poorer control of glycemia, because the mean HbA_{1c} in ETDRS was 10.1 and 9.4% for patients with type 1 and type 2 diabetes, respectively. Furthermore, the use of aspirin, antihypertensive medications, especially ACE inhibitors, and cholesterol-lowering medications has become more standard in the care of patients with diabetes since the ETDRS was performed. Although we did not address the effects of aspirin on morbidity in this study, our analyses did not reveal a statistically significant effect of aspirin use on mortality. This confirms the findings in a previous report of the same study population (59).

We acknowledge certain limitations in our study. There is some debate as to the exact criteria for the classification for type 1 or type 2 diabetes. We chose to classify diabetes type based on duration of diabetes, age at diagnosis, BMI, and insulin use. A previous report (64) in a sample of ETDRS subjects revealed that our clinically derived definitions provide good discrimination between the two types of diabetes.

One of the limitations with regard to our assessment of nephropathy is that proteinuria was evaluated with the dipstick method, a single semiquantitative measurement of urine protein, which may limit our ability to accurately distinguish between levels of proteinuria and may attenuate the true strength of any association between proteinuria and mortality. However, a recent study has shown that dipstick grades 0 to 4+ of proteinuria can predict severity levels of the urine protein-to-creatinine ratio (65), which reflect the level of protein excretion in the presence of a stable glomerular filtration rate. Therefore, we believe that our categories created for the renal complications of diabetes accurately represent broad levels of worsening nephropathy. This is further supported by our results, which revealed a general trend of increasing odds of mortality with worsening levels of nephropathy, as we would expect.

In the current study, subclinical peripheral neuropathy was primarily assessed through the quantitative sensory testing technique using vibration as a stimulus. The more severe levels of peripheral neuropathy were assessed by history and comprehensive physical examination of the patients' lower extremities for ulcerations or amputations. Although there are other diagnostic methods to evaluate peripheral neuropathy, such as nerve conduction studies and electromyography, we believe that the methods used in this study reflect clinical practice. Furthermore, we believe that these levels of peripheral neuropathy reflect increasing severity of disease, as foot ulcers usually precede amputation and are caused by several underlying problems, including vibratory sense neuropathy (66).

In summary, the results from our study suggest that the common complications of diabetes are independently associated with subsequent mortality. It is important to note that, in general, these complications are markers of the severity of the disease state of the individual, and although more severe complications can be temporarily managed with local therapies (angioplasty, renal dialysis or transplant, foot care, and laser photocoagulation), the underlying risk factors such as hyperglycemia, hypertension, and hyperlipidemia must be controlled to prevent continued progression of these complications. Therefore, the care of patients with diabetes should first focus on the primary prevention of diabetes complications through the control of modifiable risk factors. The Diabetes Control and Complications Trial (67) and the U.K. Prospective Diabetes Study (68) demonstrated the importance of glycemic and blood pressure control in reducing the risk for microvascular end points in persons with diabetes. In addition, specific recommendations have been made with respect to the prevention and early treatment of nephropathy (69) and peripheral neuropathy (70). In patients with diabetes and coronary artery disease, guidelines have emphasized the use of antiplatelet agents, ACE inhibitors, β-blockers, lipid-lowering agents, and glycemic control to lower long-term mortality (71). To further investigate optimal care in these patients, studies are now investigating the role of coronary revascularization procedures and insulin-sensitizing drugs to decrease insulin resistance (72). Further trials are needed to determine the effectiveness of tertiary prevention on mortality in patients with advanced complications of diabetes.

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