Predictors of Mortality Over 8 Years in Type 2 Diabetic Patients

Translating Research Into Action for Diabetes (TRIAD)

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OBJECTIVE—To examine demographic, socioeconomic, and biological risk factors for all-cause, cardiovascular, and noncardiovascular mortality in patients with type 2 diabetes over 8 years and to construct mortality prediction equations.

RESEARCH DESIGN AND METHODS—Beginning in 2000, survey and medical record information was obtained from 8,334 participants in Translating Research Into Action for Diabetes (TRIAD), a multicenter prospective observational study of diabetes care in managed care. The National Death Index was searched annually to obtain data on deaths over an 8-year follow-up period (2000–2007). Predictors examined included age, sex, race, education, income, smoking, age at diagnosis of diabetes, duration and treatment of diabetes, BMI, complications, comorbidities, and medication use.

RESULTS—There were 1,616 (19%) deaths over the 8-year period. In the most parsimonious equation, the predictors of all-cause mortality included older age, male sex, white race, lower income, smoking, insulin treatment, nephropathy, history of dyslipidemia, higher LDL cholesterol, angina/myocardial infarction/other coronary disease/coronary angioplasty/bypass, congestive heart failure, aspirin, β-blocker, and diuretic use, and higher Charlson Index.

CONCLUSIONS—Risk of death can be predicted in people with type 2 diabetes using simple demographic, socioeconomic, and biological risk factors with fair reliability. Such prediction equations are essential for computer simulation models of diabetes progression and may, with further validation, be useful for patient management.
boards at each participating site approved the study.

In 2000–2001, we administered a survey by computer-assisted telephone interview or in writing by mail. In addition, centrally trained reviewers used standardized data collection methods to abstract medical records. Each year, we obtained information on TRIAD decedents using National Death Index (NDI) Plus searches (8). Deaths were verified by matching name, date of birth, sex, and social security number of the decedent with data supplied by the NDI. The sensitivity of NDI has been shown to range from 87 to 98% (9). Different combinations of identifiers excluding social security number (available for ~52% of participants) correctly identify 83–92% of decedents and 92–99% of living individuals, making NDI an accurate means of ascertaining vital status even without social security numbers (10).

Vital status was determined for all TRIAD participants (n = 11,927) through 31 December 2007. We included TRIAD participants who had both survey and medical record review data (n = 8,820) and excluded those with type 1 diabetes defined as age at diagnosis of diabetes <30 years and treatment with insulin only (n = 486), leaving a final study population of 8,334. We excluded from the stratified analyses one decedent who had “N/A” listed as the underlying cause of death. Values for variables from the patient survey that had <15% missing, including age, sex, race/ethnicity, education, income, duration of diabetes, BMI, and smoking were imputed using single imputation with the transcan function in S-PLUS (edition 6.1; Insightful, Seattle, WA).

Outcome measure and covariates
We used the underlying cause of death ICD-10 code on the NDI file to group causes of death. The categories were as follows: diabetes (E10–E14), cardiovascular disease (I00–I99), cancer (C00–C97), renal failure (N17–19), infection (A00–B99, J10–18), external (injury-related) causes (V00–V89), and all other codes. We investigated all-cause, cardiovascular (ICD-10 codes 100–199 for underlying cause of death), and noncardiovascular mortality (all other ICD-10 codes for underlying cause of death). Time to follow-up was calculated as interview date to date of death or date censored (31 December 2007).

We assessed demographic covariates including age, sex, race/ethnicity, education, and income. We also assessed age at diagnosis of diabetes, duration of diabetes, treatment of diabetes, and BMI. We assessed clinical variables including smoking, systolic blood pressure, LDL cholesterol, hemoglobin A1C, microalbuminuria, and Charlson Index measured at baseline. The Charlson Index weights various comorbid conditions (including dementia, cardiovascular disease, chronic obstructive pulmonary disease, peptic ulcer disease, liver disease, connective tissue disease, and cancer) by the strength of their associations with mortality and was used to quantify comorbidity burden (11,12).

We assessed history of hypertension, dyslipidemia, transient ischemia attack (TIA), stroke, carotid endarterectomy, angina, myocardial infarction, other coronary heart disease, coronary angioplasty, coronary bypass, congestive heart failure, peripheral vascular disease, peripheral vascular surgery, retinopathy, nephropathy, and diabetic peripheral neuropathy. We also assessed use of aspirin, diuretic, ACE inhibitor, angiotensin receptor blocker (ARB), β-blocker, calcium channel blocker, other antihypertensive, statin, or other anticholesterol medications at baseline.

Statistical analyses
We described the percent distribution of categorical variables and the mean ± SD of continuous variables. Unadjusted hazard rate ratios (HRs) were constructed using each variable singularly in three separate Cox proportional hazards models predicting all-cause, cardiovascular, and noncardiovascular mortality. Each separate model specified the total alive population as the reference category.

To simultaneously adjust for covariates predicting mortality, we constructed fully adjusted Cox proportional hazards models. Again, all-cause mortality, cardiovascular mortality, and noncardiovascular mortality, defined by underlying cause of death, were modeled separately, using the total alive population as the reference category. We excluded age at diagnosis of diabetes and duration of diabetes from the list of potential predictors because of their high degree of collinearity with age. Continuous variables were stratified into categories to allow for interpretation of patterns and to avoid violating the multiplicative model’s linearity assumption. The Cox proportional hazards models also included a stratum statement for health plan/provider group cluster to account for the clustered study design and the correlation among participants within health plans and provider groups.

To obtain the most parsimonious model (defined as the best prediction model with the least number of variables), we used stepwise Cox proportional hazards models to model all-cause, cardiovascular, and noncardiovascular mortality separately, again with each compared with the total alive population. Variables that were significant at P < 0.05 were entered and remained in the model. No variables were excluded from entry into the models; however, for some variables that we had previously categorized (age, BMI, and Charlson Index), we now entered them into the models as continuous variables. The significance of the variables in each of the models was assessed by the Wald χ² test, and we present the estimated HRs and 95% CIs. We then used logistic regression to determine the parameter estimates for the 8-year prediction equations (the last column of Tables 1, 2, and 3). We tested for overfitting using the method of Harrell et al. (13). A shrinkage estimate of <0.85 would suggest overfitting (13). The fit of the equations was assessed by the −2 log-likelihood test and the Hosmer-Lemeshow goodness of fit χ² test. We also assessed the discrimination of the equations, defined as their ability to correctly identify those who died, quantified by the concordance index (i.e., the c-statistic) (13). Our final three prediction equations provide estimates of a subject’s likelihood of dying over 8 years expressed as a probability between 0 and 1.0.

We also conducted 10-fold cross-validation of the prediction models. We randomly partitioned the data into 10 equal segments and extracted one 10% segment before the prediction model was fitted. The model was fitted with the remaining 90% of the data and we calculated sensitivity, specificity, and positive predictive value (PPV) for the 10% subsample. This process was repeated 10 times until each segment of the data was used. We report average sensitivity, specificity, and PPV for each prediction model. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS—Of the 8,334 individuals included in our analyses, 1,616 (19%) died before 1 January 2008. The average length of follow-up was 6.2 years. One percent of decedents were 25–44 years of age, 22% 45–64 years of age, 65% 65–84 years of age, and 12% ≥85 years of age. Fifty-three percent of decedents were
Table 1—Unadjusted, fully adjusted, and stepwise Cox proportional hazards regression models and final equations predicting all-cause mortality in the TRIAD population adjusted for health plan/provider group cluster (N = 8,334), 2000–2007

| Characteristic                                      | Unadjusted HR (95% CI) | Fully adjusted HR (95% CI) | Stepwise HR (95% CI) | Estimated regression coefficient |
|-----------------------------------------------------|------------------------|----------------------------|----------------------|---------------------------------|
| n                                                   | 1,616 of 8,334         | 1,100 of 5,982             | 1,100 of 5,982       | -7.0892                         |
| Intercept                                           |                        |                            |                      |                                 |
| Age (years)                                         |                        | 1.05 (1.05–1.06)           | 0.0687               |                                 |
| Age (years) (ref. <56)                              |                        | *                          | *                    |                                 |
| ≥56 to <68                                         | 2.30 (1.95–2.71)       | 1.79 (1.44–2.23)           | *                    |                                 |
| ≥68                                                 | 3.18 (4.46–6.01)       | 3.22 (2.55–4.05)           | *                    |                                 |
| Sex (female, ref. male)                             | 0.75 (0.68–0.83)       | 0.59 (0.52–0.68)           | 0.59 (0.52–0.67)     | -0.6394                         |
| Race/ethnicity (ref. non-Hispanic white)            |                        |                            |                      |                                 |
| Hispanic                                            | 0.70 (0.61–0.81)       | 0.78 (0.62–0.97)           | 0.87 (0.70–1.08)     | -0.1903                         |
| African American                                    | 0.87 (0.76–0.99)       | 0.81 (0.66–0.99)           | 0.85 (0.70–1.05)     | -0.2353                         |
| Asian/Pacific Islander                              | 0.43 (0.36–0.51)       | 0.71 (0.54–0.92)           | 0.76 (0.59–0.99)     | -0.5272                         |
| Other                                               | 0.69 (0.57–0.83)       | 0.69 (0.54–0.89)           | 0.69 (0.53–0.88)     | -0.4117                         |
| Education (ref. college graduate or more)           |                        | 2.21 (1.86–2.59)           | 1.36 (1.08–1.71)     | *                               |
| Some high school or less                            |                        | 1.38 (1.17–1.63)           | 1.11 (0.89–1.38)     |                                 |
| High school graduate                                | 1.19 (1.00–1.41)       | 1.08 (0.87–1.34)           | *                    |                                 |
| Income (ref. >$75,000)                              |                        |                            |                      |                                 |
| <$15,000                                            | 3.56 (2.91–4.37)       | 1.80 (1.36–2.38)           | 1.94 (1.49–2.54)     | 0.8428                          |
| $15,000–40,000                                      | 2.43 (1.97–2.99)       | 1.46 (1.12–1.90)           | 1.53 (1.18–1.97)     | 0.4601                          |
| $40,000–75,000                                      | 1.44 (1.14–1.81)       | 1.20 (0.91–1.58)           | 1.24 (0.94–1.63)     | 0.2327                          |
| Age at diabetes diagnosis (years) (ref. <45)       |                        |                            |                      |                                 |
| ≥45 to <56                                         | 1.30 (1.13–1.49)       | *                          | *                    |                                 |
| ≥56                                                 | 2.38 (2.10–2.69)       | *                          | *                    |                                 |
| Duration of diabetes (years) (ref. <5)             |                        |                            |                      |                                 |
| ≥5 to <10                                          | 1.11 (0.96–1.29)       | *                          | *                    |                                 |
| ≥10 to <15                                         | 1.70 (1.47–1.98)       | *                          | *                    |                                 |
| ≥15                                                 | 2.13 (1.86–2.44)       | *                          | *                    |                                 |
| Treatment of diabetes (ref. oral medication only)   |                        |                            |                      |                                 |
| Diet or exercise                                    | 1.11 (0.92–1.35)       | 1.33 (1.04–1.69)           | 1.18 (0.93–1.49)     | 0.1844                          |
| Oral medication plus insulin                        | 1.43 (1.24–1.65)       | 1.14 (0.95–1.37)           | 1.26 (1.05–1.50)     | 0.2858                          |
| Insulin only                                        | 2.07 (1.83–2.33)       | 1.24 (1.05–1.46)           | 1.30 (1.11–1.53)     | 0.3114                          |
| BMI (kg/m²) (ref. ≥25 to <30)                      |                        | 1.41 (1.23–1.62)           | 1.13 (0.95–1.36)     | *                               |
| ≥25                                                 | 0.91 (0.80–1.04)       | *                          | *                    |                                 |
| ≥35                                                 | 0.80 (0.70–0.92)       | 1.00 (0.84–1.20)           | *                    |                                 |
| Smoking                                             | 1.11 (0.98–1.26)       | 1.47 (1.25–1.73)           | 1.59 (1.35–1.87)     | 0.5816                          |
| Systolic blood pressure (mmHg) (ref. <130)         |                        | *                          | *                    |                                 |
| ≥130 to <140                                       | 0.91 (0.79–1.05)       | *                          | *                    |                                 |
| ≥140                                                | 1.20 (1.07–1.34)       | *                          | *                    |                                 |
| LDL cholesterol (mg/dL) (ref. <100)                 |                        |                            |                      |                                 |
| ≥100 to <130                                       | 0.78 (0.68–0.89)       | 0.97 (0.84–1.12)           | 0.96 (0.83–1.10)     | -0.0828                         |
| ≥130 to <160                                       | 0.86 (0.73–1.02)       | 1.12 (0.93–1.33)           | 1.08 (0.91–1.29)     | 0.1752                          |
| ≥160                                                | 1.04 (0.85–1.28)       | 1.41 (1.13–1.75)           | 1.38 (1.11–1.71)     | 0.3962                          |
| HbA1c (%) (ref. <7)                                 |                        |                            |                      |                                 |
| ≥7 to <8                                            | 0.97 (0.85–1.10)       | 1.04 (0.89–1.22)           | *                    |                                 |
| ≥8 to <9                                            | 0.90 (0.77–1.05)       | 0.98 (0.81–1.18)           | *                    |                                 |
| ≥9                                                  | 0.79 (0.69–0.91)       | 1.03 (0.86–1.24)           | *                    |                                 |
| History of retinopathy                              | 1.64 (1.46–1.84)       | 1.05 (0.90–1.23)           | *                    |                                 |
| History of nephropathy                              | 1.79 (1.61–2.00)       | 1.37 (1.16–1.61)           | 1.31 (1.12–1.53)     | 0.3207                          |
| History of microalbuminuria                         | 0.95 (0.92–1.10)       | 0.93 (0.76–1.13)           | *                    |                                 |
| History of diabetic peripheral neuropathy           | 1.67 (1.49–1.88)       | 0.99 (0.84–1.15)           | *                    |                                 |
| History of hypertension                            | 1.59 (1.41–1.80)       | 1.03 (0.86–1.24)           | *                    |                                 |
| History of dyslipidemia                             | 0.85 (0.77–0.94)       | 0.80 (0.68–0.93)           | 0.83 (0.72–0.94)     | -0.2581                         |

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**Risk factors for mortality in TRIAD**

**Table 1—Continued**

| Characteristic                                                                 | Unadjusted HR (95% CI) | Fully adjusted HR (95% CI) | Stepwise HR (95% CI) | Estimated regression coefficient |
|--------------------------------------------------------------------------------|------------------------|----------------------------|----------------------|--------------------------------|
| History of congestive heart failure                                          | 4.22 (3.78–4.71)       | 1.74 (1.48–2.05)           | 1.69 (1.43–1.99)     | 0.6382                         |
| History of TIA, stroke, or endarterectomy                                    | 2.51 (2.21–2.85)       | 1.25 (1.06–1.48)           | †                    | *                              |
| History of angina, myocardial infarction, other coronary heart disease, coronary angioplasty, or coronary bypass | 2.52 (2.28–2.79)       | 1.26 (1.09–1.46)           | 1.28 (1.11–1.49)     | 0.2536                         |
| History of peripheral vascular disease or peripheral vascular surgery         | 2.69 (2.38–3.04)       | 1.26 (1.07–1.48)           | †                    | *                              |
| Current medication use                                                        |                        |                            |                      |                                |
| Aspirin                                                                       | 1.28 (1.16–1.42)       | 0.81 (0.71–0.94)           | 0.85 (0.74–0.98)     | −0.2171                        |
| ACE inhibitors                                                                | 1.26 (1.14–1.39)       | 1.04 (0.90–1.19)           | †                    | *                              |
| ARB                                                                           | 1.14 (0.97–1.33)       | 1.05 (0.85–1.30)           | †                    | *                              |
| β-Blocker                                                                    | 1.89 (1.70–2.10)       | 1.18 (1.02–1.36)           | 1.20 (1.04–1.38)     | 0.2676                         |
| Calcium channel blocker                                                      | 1.59 (1.43–1.77)       | 1.10 (0.95–1.27)           | †                    | *                              |
| Other antihypertensive medication                                            | 1.80 (1.55–2.10)       | 1.14 (0.94–1.38)           | †                    | *                              |
| Diuretic                                                                      | 2.28 (2.07–2.52)       | 1.36 (1.18–1.57)           | 1.36 (1.18–1.55)     | 0.3949                         |
| Statin                                                                        | 1.14 (1.03–1.26)       | 1.02 (0.88–1.18)           | †                    | *                              |
| Other anticholesterol medication                                              | 1.16 (0.96–1.41)       | 1.18 (0.93–1.48)           | †                    | *                              |
| Charlson Index                                                               |                        |                            |                      | 1.18 (1.14–1.22)             | 0.2377                         |
| Charlson Index (ref. <1)                                                      |                        |                            |                      |                                |
| ≥1 to <2                                                                     | 1.16 (1.13–2.42)       | 1.80 (1.06–3.07)           | †                    | *                              |
| ≥2 to <3                                                                     | 4.41 (3.05–6.39)       | 2.61 (1.53–4.46)           | †                    | *                              |

*P* = 1/(1 + e^X), where X = data included in the table; ref., reference. The estimates given in the last column are for calculating the probability of death over 8 years. †Not included in the model. ^Did not enter stepwise regression because *P* value > 0.05. Boldface values represent significant at *P* < 0.05.
Table 2— Unadjusted, fully adjusted, and stepwise Cox proportional hazards regression models and final equations predicting cardiovascular mortality in the TRIAD population adjusted for health plan/provider group cluster (N = 8,334, 2000–2007)

| Characteristic                                         | Unadjusted HR (95% CI) | Fully adjusted HR (95% CI) | Stepwise HR (95% CI) | Estimated regression coefficient |
|--------------------------------------------------------|------------------------|----------------------------|----------------------|--------------------------------|
| Intercept                                              | 649 of 7,367           | 448 of 5,330               | 448 of 5,330         |                                 |
| Age (years)                                            |                        |                            | 1.08 (1.07–1.09)     | 0.0872                          |
| Age (years) (ref. <56)                                 |                        |                            |                      |                                 |
| ≥56 to <68                                            | 2.29 (1.75–3.00)       | 1.60 (1.12–2.27)           |                      |                                 |
| ≥68                                                   | 6.46 (5.07–8.23)       | 3.57 (2.47–5.16)           |                      |                                 |
| Sex (female, ref. male)                                | 0.77 (0.66–0.89)       | 0.58 (0.47–0.72)           | 0.63 (0.51–0.77)     | −0.4377                         |
| Race/ethnicity (ref. non-Hispanic white)               |                        |                            |                      |                                 |
| Hispanic                                              | 0.61 (0.48–0.78)       | 0.65 (0.45–0.94)           |                      |                                 |
| African American                                      | 0.83 (0.67–1.02)       | 0.78 (0.57–1.08)           |                      |                                 |
| Asian/Pacific Islander                                 | 0.36 (0.27–0.48)       | 0.65 (0.42–1.00)           |                      |                                 |
| Other                                                  | 0.70 (0.52–0.93)       | 0.68 (0.46–1.01)           |                      |                                 |
| Education (ref. college graduate or more)              |                        |                            |                      |                                 |
| Some high school or less                               | 2.26 (1.76–2.90)       | 1.47 (1.01–2.15)           |                      |                                 |
| High school graduate                                   | 1.32 (1.01–1.71)       | 1.18 (0.82–1.69)           |                      |                                 |
| Some college                                           | 1.25 (0.96–1.63)       | 1.22 (0.86–1.73)           |                      |                                 |
| Income (ref. >$75,000)                                 |                        |                            |                      |                                 |
| <$15,000                                               | 4.33 (3.08–6.10)       | 1.81 (1.14–2.86)           |                      |                                 |
| $15,000–40,000                                         | 3.07 (2.17–4.35)       | 1.53 (1.00–2.35)           |                      |                                 |
| $40,000–75,000                                         | 1.67 (1.14–2.45)       | 1.36 (0.87–2.13)           |                      |                                 |
| Age at diabetes diagnosis (years) (ref. <55)           |                        |                            |                      |                                 |
| ≥5 to <55                                              | 1.30 (1.05–1.61)       |                            |                      |                                 |
| ≥56                                                    | 2.50 (2.06–3.04)       |                            |                      |                                 |
| Duration of diabetes (years) (ref. <5)                 |                        |                            |                      |                                 |
| ≥5 to <10                                              | 1.12 (0.87–1.43)       |                            |                      |                                 |
| ≥10 to <15                                             | 1.99 (1.56–2.52)       |                            |                      |                                 |
| ≥15                                                    | 2.56 (2.07–3.18)       |                            |                      |                                 |
| Treatment of diabetes (ref. oral medication only)      |                        |                            |                      |                                 |
| Diet or exercise                                       | 0.95 (0.69–1.31)       | 1.09 (0.71–1.67)           | 1.07 (0.72–1.59)     | 0.0477                          |
| Oral medication plus insulin                           | 1.57 (1.26–1.95)       | 1.24 (0.94–1.65)           | 1.34 (1.02–1.77)     | 0.4411                          |
| Insulin only                                           | 2.31 (1.91–2.79)       | 1.55 (1.19–2.01)           | 1.56 (1.21–2.00)     | 0.5160                          |
| BMI (kg/m²)                                            |                        |                            |                      |                                 |
| BMI (kg/m²) (ref. ≥25 to <30)                          |                        |                            |                      |                                 |
| <25                                                   | 1.45 (1.17–1.81)       | 1.15 (0.87–1.54)           |                      |                                 |
| ≥30 to <35                                            | 0.87 (0.71–1.07)       | 1.03 (0.80–1.34)           |                      |                                 |
| ≥35                                                   | 0.84 (0.68–1.03)       | 1.09 (0.82–1.44)           |                      |                                 |
| Smoking                                               | 0.91 (0.74–1.12)       | 1.36 (1.02–1.81)           | 1.67 (1.26–2.20)     | 0.5620                          |
| Systolic blood pressure (mmHg) (ref. <130)             |                        |                            |                      |                                 |
| ≥130 to <140                                          | 0.90 (0.72–1.12)       | 0.75 (0.57–0.99)           |                      |                                 |
| ≥140                                                  | 1.22 (1.02–1.46)       | 0.85 (0.68–1.07)           |                      |                                 |
| LDL cholesterol (mg/dL) (ref <100)                     |                        |                            |                      |                                 |
| ≥100 to <130                                          | 0.80 (0.65–1.00)       | 1.06 (0.84–1.34)           | 1.03 (0.81–1.30)     | −0.0018                         |
| ≥130 to <160                                          | 0.97 (0.79–1.26)       | 1.40 (1.06–1.85)           | 1.34 (1.02–1.76)     | 0.3971                          |
| ≥160                                                  | 1.37 (1.02–1.84)       | 1.92 (1.39–2.65)           | 1.85 (1.35–2.53)     | 0.7869                          |
| HbA₁c (%) (ref. <7)                                    |                        |                            |                      |                                 |
| ≥7 to <8                                              | 0.86 (0.70–1.06)       | 0.88 (0.69–1.13)           |                      |                                 |
| ≥8 to <9                                              | 0.83 (0.65–1.05)       | 0.84 (0.62–1.13)           |                      |                                 |
| ≥9                                                    | 0.74 (0.60–0.92)       | 0.98 (0.74–1.29)           |                      |                                 |
| History of retinopathy                                | 1.66 (1.38–2.00)       | 0.97 (0.76–1.25)           |                      |                                 |
| History of nephropathy                                | 1.85 (1.56–2.11)       | 1.36 (1.05–1.77)           | 1.38 (1.08–1.76)     | 0.2727                          |
| History of microalbuminuria                           | 0.95 (0.76–1.20)       | 1.03 (0.75–1.41)           |                      |                                 |
| History of diabetic peripheral neuropathy             | 1.71 (1.43–2.06)       | 0.98 (0.76–1.25)           |                      |                                 |
| History of hypertension                               | 1.95 (1.59–2.39)       | 1.06 (0.79–1.43)           |                      |                                 |

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Table 2—Continued

| Characteristic                                      | Unadjusted HR (95% CI) | Fully adjusted HR (95% CI) | Stepwise HR (95% CI) | Estimated regression coefficient |
|-----------------------------------------------------|-------------------------|----------------------------|----------------------|----------------------------------|
| History of dyslipidemia                             | 0.87 (0.75–1.02)        | 0.71 (0.56–0.90)           | 0.73 (0.59–0.90)     | −0.4408                          |
| History of congestive heart failure                 | 6.68 (5.68–7.86)        | 2.49 (1.94–3.19)           | 1.70 (1.13–3.42)     | 1.1754                           |
| History of TIA, stroke, or endarterectomy           | 3.36 (2.79–4.05)        | 1.64 (1.27–2.11)           | 1.74 (1.37–2.20)     | 0.7366                           |
| History of angina, myocardial infarction, other coronary heart disease, coronary angioplasty, or coronary bypass | 3.72 (3.19–4.33)        | 1.50 (1.18–1.91)           | 1.61 (1.28–2.02)     | 0.5142                           |
| History of peripheral vascular disease or peripheral vascular surgery | 3.63 (3.02–4.35)        | 1.48 (1.15–1.90)           | 1.54 (1.21–1.95)     | 0.4208                           |
| Current medication use                              |                         |                            |                      |                                  |
| Aspirin                                             | 1.58 (1.35–1.85)        | 0.86 (0.69–1.08)           | †                    | *                                |
| ACE inhibitors                                      | 1.41 (1.21–1.65)        | 1.09 (0.87–1.36)           | †                    | *                                |
| ARB                                                 | 1.21 (0.95–1.54)        | 1.02 (0.72–1.43)           | †                    | *                                |
| ß-Blocker                                           | 2.52 (2.15–2.95)        | 1.38 (1.10–1.72)           | 1.42 (1.15–1.77)     | 0.4364                           |
| Calcium channel blocker                             | 1.60 (1.36–1.89)        | 1.00 (0.80–1.26)           | †                    | *                                |
| Other antihypertensive medication                   | 2.19 (1.75–2.74)        | 1.41 (1.06–1.88)           | 1.35 (1.02–1.79)     | 0.4083                           |
| Diuretic                                            | 2.73 (2.34–3.19)        | 1.50 (1.20–1.88)           | 1.48 (1.19–1.83)     | 0.3625                           |
| Statin                                              | 1.33 (1.14–1.56)        | 1.12 (0.89–1.42)           | †                    | *                                |
| Other anticholesterol medication                    | 1.32 (0.99–1.76)        | 1.40 (0.99–1.96)           | 1.51 (1.08–2.11)     | 0.5052                           |
| Charlson Index                                       |                         |                            |                      |                                  |
| Charlson Index (ref. <1)                            | *                       | *                          | †                    | *                                |
| ≥1 to <2                                           | 0.54 (0.34–0.88)        | 0.73 (0.37–1.44)           | †                    | *                                |
| ≥2 to <3                                           | 0.95 (0.59–1.52)        | 0.95 (0.48–1.87)           |                      |                                  |
| ≥4                                                  | 2.88 (1.84–4.52)        | 1.08 (0.54–2.16)           |                      |                                  |

$P = 1(1+e^{-X})$, where $X$ = data included in the table, ref., reference. The estimates given in the last column are for calculating the probability of death over 8 years. *Not included in the model. †Did not enter stepwise regression because P value > 0.05. Boldface values represent significant at $P < 0.05$.

The variables that predict noncardiovascular mortality are older age, male sex, lower income, current smoking, history of nephropathy, history of congestive heart failure, use of a diuretic, and a higher Charlson Index (Table 3). The −2 log-likelihood test was 1023 ($P < 0.0001$) with 10 degrees of freedom. The max-rescaled $R^2$ was 0.24 and the Hosmer-Lemeshow goodness-of-fit test was 12.63 ($P = 0.13$) with eight degrees of freedom. There were seven variables that contributed at least 1% to the explained variance of the prediction equation. These were older age, higher Charlson Index, male sex, lower income, history of congestive heart failure, smoking, and use of a diuretic (partial $R^2 = 0.120, 0.027, 0.018, 0.013$, and 0.010, respectively). The c-statistic was 0.840 and shrinkage was 0.97. For the cardiovascular mortality prediction equation, the probability level that maximized sensitivity and specificity was 0.090, yielding a sensitivity of 73%, a specificity of 78%, and a PPV of 24%. Using 10-fold cross-validation, average sensitivity was 85%, specificity was 63%, and PPV was 18%.

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**CONCLUSIONS**—We described predictors of mortality over 8 years in an insured population with diabetes that had good access to high-quality medical care. Although cardiovascular disease was the leading cause of death in this population (40%), cancer and other diabetes-related conditions, such as infections and renal failure, were also listed frequently as the underlying cause of death. In general, the predictors of 8-year mortality in fully adjusted models are similar to predictors of 4-year mortality in TRIAD, suggesting that these models are likely generalizable enough to predict future mortality risk. Socio-demographic factors including older age, male sex, white race/ethnicity, lower income, and smoking are consistently associated with mortality. Diabetes-related variables including older age at diagnosis, longer duration of diabetes, and treatment with insulin with or without oral medications are associated with mortality in unadjusted models. In fully adjusted models, only treatment with insulin with our without oral medications remains a significant risk factor for all-cause and cardiovascular mortality. As one might expect, history of nephropathy predicts all-cause, and a PPV of 24%. Using 10-fold cross-validation, average sensitivity was 85%, specificity was 63%, and PPV was 18%.
Table 3—Unadjusted, fully adjusted, and stepwise Cox proportional hazards regression models and final equations predicting noncardiovascular mortality in the TRIAD population adjusted for health plan/provider group cluster (N = 8,334), 2000–2007

| Characteristic | Unadjusted HR (95% CI) | Fully adjusted HR (95% CI) | Stepwise HR (95% CI) | Estimated regression coefficient |
|---------------|------------------------|-----------------------------|----------------------|---------------------------------|
| n             | 967 of 7,684           | 651 of 5,533                | 651 of 5,533         | −7.2490                         |
| Age (years)   | *                      | *                           | 1.05 (1.04–1.06)     | 0.0612                          |
| Race/ethnicity (ref. non-Hispanic white) | †                      | †                           | †                    | †                               |
| Hispanic      | 0.74 (0.62–0.89)       | 0.88 (0.66–1.17)            |                      |                                 |
| African American | 0.88 (0.74–1.05)    | 0.79 (0.60–1.03)            |                      |                                 |
| Asian/Pacific Islander | 0.44 (0.33–0.55) | 0.73 (0.53–1.02)            |                      |                                 |
| Other         | 0.67 (0.52–0.83)       | 0.70 (0.49–0.94)            |                      |                                 |
| Education (ref. college graduate or more) | †                      | †                           | †                    | †                               |
| Some high school or less | 2.34 (1.90–2.88)  | 1.32 (0.99–1.77)            |                      |                                 |
| Some college   | 1.46 (1.18–1.81)       | 1.09 (0.82–1.44)            |                      |                                 |
| Income (ref. >$75,000) |                      |                              |                      |                                 |
| <$15,000      | 3.47 (2.69–4.47)       | 1.96 (1.38–2.79)            | 2.11 (1.51–2.95)     | 0.8679                          |
| $15,000–40,000| 2.21 (1.70–2.87)       | 1.52 (1.09–2.12)            | 1.61 (1.16–2.22)     | 0.4483                          |
| >=40,000–75,000| 1.33 (1.00–1.78)      | 1.13 (0.79–1.60)            | 1.19 (0.84–1.68)     | 0.1917                          |
| Treatment of diabetes (ref. oral medication only) | †                      | †                           | †                    | †                               |
| Diet or exercise | 1.22 (0.97–1.55)  | 1.55 (1.15–2.10)            |                      |                                 |
| Oral medication plus insulin | 1.39 (1.15–1.67) | 1.08 (0.85–1.38)            |                      |                                 |
| Insulin only   | 2.05 (1.75–2.40)       | 1.13 (0.90–1.41)            |                      |                                 |
| BMI (kg/m²) (ref. ≥25 to <30) |                   | †                           | †                    | †                               |
| <25           | 1.43 (1.19–1.71)       | 1.09 (0.86–1.38)            |                      |                                 |
| ≥30 to <35    | 0.94 (0.79–1.11)       | 1.08 (0.88–1.32)            |                      |                                 |
| ≥35           | 0.77 (0.64–0.92)       | 0.96 (0.76–1.22)            |                      |                                 |
| Smoking       | 1.26 (1.08–1.47)       | 1.62 (1.32–1.99)            | 1.74 (1.42–2.14)     | 0.6533                          |
| Systolic blood pressure (mmHg) (ref. <130) |                   | †                           | †                    | †                               |
| ≥130 to <140  | 0.91 (0.76–1.10)       | 0.99 (0.79–1.23)            |                      |                                 |
| ≥140          | 1.21 (1.04–1.40)       | 0.94 (0.78–1.14)            |                      |                                 |
| LDL cholesterol (mg/dL) (ref. <160) |                   | †                           | †                    | †                               |
| ≥100 to <130  | 0.76 (0.64–0.90)       | 0.94 (0.78–1.13)            |                      |                                 |
| ≥130 to <160  | 0.79 (0.64–0.98)       | 0.98 (0.77–1.23)            |                      |                                 |
| ≥160          | 0.84 (0.63–1.11)       | 1.18 (0.87–1.61)            |                      |                                 |
| HbA1c (%) (ref. <7) |                   | †                           | †                    | †                               |
| ≥7 to <8      | 1.05 (0.89–1.24)       | 1.17 (0.95–1.43)            |                      |                                 |
| ≥8 to <9      | 0.95 (0.78–1.15)       | 1.09 (0.85–1.38)            |                      |                                 |
| ≥9            | 0.80 (0.67–0.97)       | 1.06 (0.84–1.35)            |                      |                                 |
| History of retinopathy | 1.70 (1.46–1.97)  | 1.13 (0.92–1.38)            |                      |                                 |
| History of nephropathy | 1.85 (1.60–2.13) | 1.49 (1.20–1.84)            | 1.38 (1.14–1.67)     | 0.1208                          |
| History of microalbuminuria | 0.95 (0.78–1.15) | 0.82 (0.65–1.09)            |                      |                                 |
| History of diabetic peripheral neuropathy | 1.74 (1.50–2.02) | 1.02 (0.83–1.24)            |                      |                                 |
| History of hypertension | 1.46 (1.25–1.70) | 1.03 (0.81–1.32)            |                      |                                 |
| History of dyslipidemia | 0.83 (0.73–0.94) | 0.87 (0.71–1.06)            |                      |                                 |

*Continued on p. 1308*
Current medication use

| Characteristic                                                                 | Unadjusted HR (95% CI) | Fully adjusted HR (95% CI) | Stepwise HR (95% CI) | Estimated regression coefficient |
|-------------------------------------------------------------------------------|-------------------------|-----------------------------|-----------------------|--------------------------------|
| History of congestive heart failure                                         | 3.61 (3.09–4.21)        | 1.47 (1.18–1.84)            | 1.51 (1.22–1.87)       | 0.4157                         |
| History of TIA, stroke, or endarterectomy                                   | 2.27 (1.91–2.71)        | 1.11 (0.88–1.40)            | †                     | *                              |
| History of angina, myocardial infarction, other coronary heart disease, coronary angioplasty, or coronary bypass | 2.11 (1.83–2.40)        | 1.14 (0.94–1.39)            | †                     | *                              |
| History of peripheral vascular disease or peripheral vascular surgery       | 2.45 (2.07–2.90)        | 1.21 (0.97–1.50)            | †                     | *                              |
| Current medication use                                                       |                         |                             |                       |                                |
| Aspirin                                                                       | 1.14 (0.99–1.31)        | 0.76 (0.63–0.91)            | †                     | *                              |
| ACE inhibitors                                                                | 1.21 (1.06–1.37)        | 1.02 (0.85–1.22)            | †                     | *                              |
| ARB                                                                           | 1.10 (0.89–1.35)        | 1.06 (0.81–1.38)            | †                     | *                              |
| β-Blocker                                                                    | 1.63 (1.42–1.88)        | 1.07 (0.89–1.30)            | †                     | *                              |
| Calcium channel blocker                                                      | 1.64 (1.43–1.88)        | 1.20 (1.00–1.44)            | †                     | *                              |
| Other antihypertensive medication                                            | 1.68 (1.37–2.06)        | 1.02 (0.79–1.33)            | †                     | *                              |
| Diuretic                                                                      | 2.19 (1.93–2.48)        | 1.36 (1.13–1.64)            | 1.37 (1.15–1.63)       | 0.4337                         |
| Statin                                                                        | 1.04 (0.91–1.18)        | 0.91 (0.75–1.11)            | †                     | *                              |
| Other anticholesterol medication                                             | 1.07 (0.83–1.39)        | 1.06 (0.77–1.46)            | †                     | *                              |
| Charlson Index                                                               | *                       | *                           | 1.22 (1.18–1.27)       | 0.3027                         |
| Charlson Index (ref. <1)                                                     |                         |                             |                       |                                |
| ≥1 to <2                                                                     | 1.95 (1.00–3.82)        | 3.08 (1.23–7.69)            | †                     | *                              |
| ≥2 to <3                                                                     | 3.27 (1.68–6.36)        | 3.61 (1.44–9.03)            | 1.08 (0.89–1.32)       | *                              |
| ≥4                                                                            | 8.77 (4.55–16.93)       | 6.25 (2.50–15.63)           | 1.38 (1.15–1.66)       | *                              |

P = 1/(1+e^{-X}), where X = data included in the table; ref., reference. The estimates given in the last column are for calculating the probability of death over 8 years. *Not included in the model. †Did not enter stepwise regression because P value >0.05. Boldface values represent significant at P < 0.05.

cardiovascular, and noncardiovascular mortality. Charlson Index is not associated with cardiovascular mortality, and history of macrovascular disease is not associated with noncardiovascular mortality.

To our surprise, we found that history of dyslipidemia is associated with a decreased risk of all-cause and cardiovascular mortality. We hypothesize that this might be related to our inclusion of dyslipidemia and LDL cholesterol levels and use of cholesterol-lowering medications in the models. If history of dyslipidemia is an indicator of cholesterol-lowering medication use, this would tend to attenuate the association between dyslipidemia and mortality. Confounding by indication might also explain the associations between antihypertensive medication use and cardiovascular mortality. Higher rates of mortality are observed for those using diuretics, β-blockers, and other antihypertensive medications but those medications are more likely prescribed for those with longer duration and more severe hypertension and for those with cardiovascular disease and congestive heart failure.

A previous study predicting all-cause mortality in people with diabetes was performed for 33,067 individuals included in the Cleveland Clinic electronic health record (14). This study only included patients initially prescribed a single oral hypoglycemic agent, whereas our study included all people identified as having type 2 diabetes regardless of medication use. Both studies found that older age, male sex, white race, smoking, insulin use, history of heart disease, history of heart failure, and not using aspirin predicted greater risk of death. However, our study did not assess glomerular filtration rate, oral diabetes medication class, diastolic blood pressure, HDL, triglycerides, new diagnosis of diabetes, or clopidogrel use. We include an indicator for history of diabetic nephropathy, which was significant in the most parsimonious model. Although we included BMI, HbA1c, systolic blood pressure, LDL, ACE inhibitor or ARB use, and use of lipid-lowering drugs as possible variables, none of these entered the most parsimonious models.

Our findings were also similar to the results of a study conducted in Hong Kong. In that study, older age, male sex, history of peripheral vascular disease, and insulin use were associated with higher risk of all-cause mortality (15). We allowed for a continuous measurement of HbA1c and BMI in our model but neither was significant in multivariate analyses. Our study did not investigate albumin-creatinine ratio or glomerular filtration rate, although we did include history of microalbuminuria, nephropathy, and Charlson Index, two of which were significant in the most parsimonious models. The measures of area under the curve, sensitivity, and specificity for our prediction equation were very similar to those for the equation developed in the Hong Kong study.

Our study has several limitations. First, we sought to develop prediction equations to optimally discriminate the outcome of interest (mortality). As a result, we did not seek to develop causal models. The fact that a variable enters an equation does not mean that it is causally important. Similarly, variables that do not enter an equation are not necessarily unimportant in the chain of causation. We conducted a sensitivity analysis and found that stepwise selection and backward elimination models align well. For all-cause mortality, 14 of the 17 variables were the same in the stepwise and backward elimination models. For the cardiovascular mortality model, all the significant variables were the same.
For the noncardiovascular mortality model, 8 of the 13 variables were the same. It is not surprising that the noncardiovascular disease model did not align as well as the others because many different risk factors may contribute to mortality related to cancer, infections, etc.

Another limitation of our study is the use of data from people enrolled in managed care plans; our results may not be generalizable to those outside of managed care, or even those in managed care plans with different levels of access to care or quality of care. Indeed, the fact that our population had good access to high-quality care may have attenuated the impact of biological risk factors on mortality. In addition, our sample did not include people with newly diagnosed diabetes. Everyone had physician-diagnosed diabetes for at least 18 months before the survey, which might have resulted in higher mortality rates.

In conclusion, we created three prediction equations with good discrimination and high sensitivity and specificity. Although our equations need to be validated in other populations, they highlight the importance of specific demographic and biological risk factors for mortality in people with type 2 diabetes and provide a quantitative assessment of risk. These prediction equations may be incorporated into computer simulation models of disease progression. After further validation, clinicians may also use such equations to inform patients about their risk for mortality and to target the most modifiable risk factors for intervention.

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L.N.M. researched data, contributed to discussion, and wrote, reviewed, and edited the manuscript. A.J.K., B.E.W., J.C.C., D.G.M., C.M.M., and W.H.H. researched data, contributed to discussion, and reviewed and edited the manuscript. L.N.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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