Predicting Six-year Mortality Risk in Patients with Type 2 Diabetes

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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.

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Objective: The objective of this study was to create a tool that predicts the risk of mortality in patients with type 2 diabetes.

Research Design and Methods: This study was based on a cohort of 33,067 patients with type 2 diabetes identified in the Cleveland Clinic electronic health record (EHR) who were initially prescribed a single oral hypoglycemic agent between 1998 and 2006. Mortality was determined in the EHR and the Social Security Death Index. A Cox proportional hazards regression model was created using medication class and 20 other predictor variables chosen for their association with mortality. A prediction tool was created using the Cox model coefficients. The tool was internally validated using repeated, random, subsets of the cohort which were not used to create the prediction model.

Results: Follow-up in the cohort ranged from 1 day to 8.2 years (median = 28.6 months) and 3,661 deaths were observed. The prediction tool had a concordance index (i.e. c-statistic) of 0.752.

Conclusions: This study successfully created a tool that accurately predicts mortality risk in patients with type 2 diabetes. The incorporation of medications into mortality predictions in patients with type 2 diabetes should improve treatment decisions.
Patients with type 2 diabetes are at an increased risk of mortality (1)(2-4) and tools for predicting overall mortality in diabetics are lacking. Tools for predicting the risk of cardiovascular disease (CVD) have been created and assist physicians in the prevention of CVD among patients with type 2 diabetes. (5-8) However, these tools do not consider the risk of all-cause mortality. Preventing a myocardial infarction is important, but not if the patient dies prematurely from Kidney Disease. Treating each disease in isolation fails to consider the overall effect to the patient. Scores have been created to adjust for diabetes severity and other comorbid conditions when studying mortality. (9, 10) However, these indices do not provide overall mortality predictions and therefore are of limited use in routine clinical practice. Furthermore, existing prediction tools do not adjust for a patient’s current therapy. Specific diabetic medications may decrease the risk of one complication, while increasing the risk of other outcomes. Tools are needed to help clinicians tailor therapy to individual patients in order to minimize mortality risk based on characteristics of the patient, their disease, and the available treatment options. The purpose of this study was to create a mortality risk calculator for patients with type 2 diabetes that can be used to aid treatment decisions.

METHODS

This study was conducted on a retrospective cohort of patients with type 2 diabetes whose data was collected for clinical and administrative purposes in the electronic health record (EHR) at the Cleveland Clinic (CC). The cohort began in 1998 and follow up data was obtained through 2006.

Eligibility Criteria at Baseline: Baseline was defined as the date of the first prescription for a qualifying oral anti-diabetic agent in an eligible patient. Since we are interested in patients with type 2 diabetes, the cohort was limited to patients at least 18 years of age with a diagnosis of diabetes. Patients with diabetes were identified if they had a single diagnosis of diabetes in the “History” or “Problem List” sections of their chart. In order to reduce the chance of misclassification due to “rule out” diagnoses, we required two occurrences of “Diabetes” for patients with diabetes identified from the “Encounter Diagnosis” section. The following codes from the International Classification of Diseases version 9 (ICD-9) were used to identify patients with diabetes: 250 through 250.99, 357.2, 362.01, 362.02, 366.41, and 648.01 through 648.04.

The cohort was further limited to patients who were prescribed a single one of the four most common types of oral hypoglycemic agents: sulfonylureas (SU), meglitinides (MEG), biguanides (BIG), or thiazolidinediones (TZD). Patients prescribed alpha glucosidase inhibitors were excluded due to an inadequate sample (n=149). Patients with prescriptions for multiple oral agents at baseline were excluded due to the substantial number of possible two-drug (10) and three-drug (10) combinations.

Exclusions: Patients with Polycystic Ovarian Syndrome (PCOS) are sometimes treated with a biguanide and could be confused with diabetes. Non-insulin, injectable medications are used infrequently in the treatment of type 2 diabetes and the patients on these medications may represent fundamentally different patients. Therefore, patients with PCOS (ICD9 256.4) and patients prescribed non-insulin, injectable diabetes medications at baseline were excluded.

Outcome: Mortality was determined in the EHR and with linkage to the Social Security Death Index (SSDI). Patients classified as deceased per the SSDI or the EHR, but who continued to have vital
statistics entered into the EHR were counted as alive.

**Predictor Variables:** The following variables were included in the model due to their independent associations with mortality in the literature: estimated glomerular filtration rate (GFR), hemoglobin A1c (HbA1c), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG), history of congestive heart failure (CHF), history of coronary heart disease (CHD), smoking status, use of concomitant medications (insulin, ace inhibitor / angiotensin receptor blocker, aspirin, clopidogrel, lipid lowering drug), new diabetes, gender, race, age, and oral medication class. Values for all of the predictor variables were extracted from the EHR. GFR was calculated from serum creatinine using the simplified equation from the Modification of Diet in Renal Disease Study Group (11). BMI was calculated using the standard equation (BMI = Weight (Kg) / Height² (m²)). The baseline date was defined as the date of the first prescription for an oral hypoglycemic agent in a qualified individual. The baseline value for the predictor variables was defined as the value on the baseline date or the most recent historical value. If no historical value was available then the value closest to the baseline date up to 21 days into the future was defined as the baseline. (Except for smoking, which did not have the 21 day limit). Patients were considered to be ‘new diabetics’ if they had been seen before their baseline date by either Endocrinology or Primary Care at the Cleveland Clinic and did not have a diagnosis of diabetes entered in the EHR at that time.

**Interactions:** A limited number of interactions were explored for inclusion in the predictive model, but for parsimony were only included if statistically significant (p<0.05). The following interactions were investigated in the model:

- **Medication class * GFR**
- **Medication class * Age** - The medication class interactions with age and GFR was included due to the precautions advised for using biguanides in older adults and in patients with renal dysfunction (12).
- **Gender * Race** - The interaction for gender and race was explored due to the higher risk of coronary heart disease seen in black women (13).
- **Medication class * CHF** - The interaction between medication class and heart failure was explored due to the precautions advised for using thiazolidinediones and biguanides in patients with congestive heart failure (12).

**Statistical Methods:** The analytic dataset was built using SAS version 9.1. Missing values were imputed using the Multiple Imputation by Chained Equations package version 1.16 for R. (14) Imputation was performed in order to maximize the available information and to reduce the potential bias introduced by deleting incomplete records. The imputation was performed using regression techniques that include all baseline patients and all baseline variables as predictors and without knowledge of the outcome. Linearity assumptions of the ordinal and continuous variables were relaxed by fitting the model using restricted cubic splines.

A Cox proportional hazards regression model was created with the predictor variables and interactions listed above with time to death as the outcome. Statistical analyses were performed using R for Unix version 2.3.1. (15) The coefficients from the fitted Cox model were also used to develop an interactive web based tool that calculates the predictions automatically. The web based calculator is available at: [http://infolab.umdnj.edu/simpal/RCC/RCEval.cgi?Owner=wellsb@ccf.org&RCName=Six](http://infolab.umdnj.edu/simpal/RCC/RCEval.cgi?Owner=wellsb@ccf.org&RCName=Six)
Ten-fold cross validation was used to validate our modeling approach. With this method, the data is randomly partitioned into 10 equal segments. One segment (10% of the data) is extracted prior to fitting the prediction model. The model is fitted with the remaining 90% of the data and the prediction accuracy is evaluated on the outcomes observed in the 10% sub-sample. The process is repeated (ten times) until each segment of the data has been used to assess the prediction accuracy. A calibration curve was created by plotting the quintiles of the predicted probabilities on the observed estimates for the entire cohort. The model was also evaluated through the use of the concordance index (i.e. c-statistic). In this process, the model is graded on its ability to differentiate between all possible discordant pairs of patients. (Example: Patient 1 dies after 6 months in the cohort. Patient 2 dies after 3 years in the cohort. Does the predictive model correctly show that patient 1 had a higher risk of death?) Concordance indices can vary between 0.5 (chance) and 1.0 (perfect prediction).

RESULTS
The final cohort had a sample size of 33,067 patients. Table 1 shows the characteristics of the cohort at baseline by drug class. Overall, the patients were predominantly white with a similar proportion of males and females. Patients on biguanides were younger, had less heart failure, were more likely to be new diabetics, compared to patients on the other drugs. TZD patients were the most likely to be using insulin, while patients on MEG had the lowest levels of LDL and triglycerides.

Cumulative mortality by drug class is shown in Figure 1. There were 1,958 patients followed for at least 5 years. The median length of follow up was 28.6 months (range = 1 day to 8.2 years). The number of deaths per drug class were 799, 135, 2220, and 507 for BIG, MEG, SFU, and TZD respectively. The interaction between race and gender was not found to be statistically significant and was removed from the model for parsimony. The other interactions (Medication * GFR, Medication * Age, and Medication * CHF) were all statistically significant. The Medication * CHF interaction was the least significant of these interactions and was removed from the final model in order to reduce the size of the final nomogram.

Figures 2 and 3 show the paper based nomogram for predicting 6 year survival (model coefficients are available in online Appendix A available at http://care.diabetesjournals.org).

The biguanides were associated with the lowest risk of mortality in younger patients. Due to the interactions between medication with GFR and medication with age, the medication associated with the highest probability of survival varied according to individual patient characteristics. As expected, smoking and high levels of HbA1c were associated with lower survival. LDL had a ‘U’ shaped relationship with mortality. The lowest risk of mortality was associated with an LDL of 150mg/dl and increased with higher or lower LDL levels.

Figure 4 shows the calibration curve for the mortality prediction. The predicted survival was quite accurate at all quintiles of mortality risk. The concordance index for the survival prediction was 0.752, which indicates that the nomogram was correct 75.2% of the time in identifying which patient had the highest risk among all possible discordant patient pairs.

CONCLUSIONS
The prediction tool created in this study was accurate in predicting six-year mortality risk among patients with type 2 diabetes. The concordance index (i.e. c-statistic) of 0.752 indicates good
discrimination ability of this tool and the calibration curve shows that the prediction does not significantly overestimate or underestimate risk. If the current prediction tool performs well in other cohorts of patients with type 2 diabetes, it offers clinicians a tool for tailoring anti-diabetic treatments with the aim of improving survival among patients with type 2 diabetes.

We are unaware of other tools designed to predict mortality in patients with type 2 diabetes in the clinical setting. The recently published “Diabetes Complications Severity Index” (DCSI) will hopefully improve the ability to adjust for the severity of type 2 diabetes in future regression models predicting mortality. (9) However, the DCSI is not a stand alone prediction tool and is designed to be used as a covariate in a larger model. We did not have all of the predictors necessary to add the DCSI score to our model. The widespread use of this tool may be limited by the number of predictor variables that we included in the model and the requirement of GFR. We did not attempt to reduce the model using variable selection techniques (e.g. stepwise regression) because the omission of insignificant predictors tends to harm predictive accuracy. (16) We hope that the online version of the calculator will make the model more user friendly by calculating GFR automatically from serum creatinine and eliminating the need for the paper nomogram. The online calculator is available at: http://infolab.umdnj.edu/simpal/RCC/RCEval.cgi?Owner=wellsb@ccf.org&RCName=Six%20Year%20Mortality%20Risk%20in%20Type%202%20DM

This study has several other weaknesses that should be discussed. First, there is the potential for misclassification bias surrounding the designation of the baseline oral medication. Prescriptions outside the Cleveland Clinic are unknown and we did not assess for medication changes within our system. However, in a separate analysis of this cohort, we found that approximately 75% of patients remained on the same oral diabetic medication throughout their time in the cohort. A second weakness of the study involves the substantial missing data for some predictor variables. However, the imputation techniques utilized should help to limit the potential bias caused by simply eliminating incomplete records. Thirdly, we were unable to accurately define the exact duration of type 2 diabetes. Patients who are diagnosed with diabetes on their first visit to the Cleveland Clinic will not be recognized as new diabetics. However, duration of diabetes is likely captured by the presence or absence of comorbidities and other variables such as GFR. Diabetic complications may be the most accurate reflection of diabetes duration because the disease frequently goes undetected for years after it first appears. (17) Young et al. found that duration of diabetes was not independently predictive of mortality. (9) In addition, the presence of comorbid conditions such as heart failure and stroke may be under-documented in the EHR. However, there is no reason to suggest that the documentation would vary according to drug class. In order to maximize the presence or absence of baseline conditions, we included information beyond documentation of ICD9 codes. For instance, patients with a documentation of a coronary revascularization procedure were considered to have a history of heart disease. Despite any possible lack of documentation in the EHR, the model performed very well. A final weakness could be the loss to follow up that is inevitable in this type of study. Fortunately, we were able to link participants with the SSDI, which should capture deaths in patients regardless of loss to follow-up at the Cleveland Clinic.

The major strengths of the study include the large sample size and cohort design. The good prediction accuracy obtained through the cross-validation of the
model suggests strong internal validity of these results. The web based version of this calculator provides the tool in an easily accessible format for clinical use. The current model requires external validation before the applicability of this model to other patient populations will be known.
REFERENCES
15. R Development Core Team: R: A language and environment for statistical computing., 2006
Table 1. Baseline Characteristics of Patients by Drug Class after Imputation (N=33,067)*

<table>
<thead>
<tr>
<th>Linear Variables</th>
<th>BIG N=14,708</th>
<th>MEG n=773</th>
<th>SFU n=12,606</th>
<th>TZD n=4,980</th>
<th>Missing † (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (sd)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>57.8 (13.7)</td>
<td>66.4 (13.3)</td>
<td>66.4 (13.2)</td>
<td>61.9 (12.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>33.5 (7.5)</td>
<td>30.3 (6.9)</td>
<td>31.1 (6.9)</td>
<td>33.4 (7.8)</td>
<td>13,986 (42.3)</td>
</tr>
<tr>
<td>Low Density Lipoprotein (mg/dl)</td>
<td>110.1 (39.0)</td>
<td>94.2 (36.2)</td>
<td>107.4 (39.2)</td>
<td>107.1 (40.7)</td>
<td>17,347 (52.5)</td>
</tr>
<tr>
<td>High Density Lipoprotein (mg/dl)</td>
<td>46.9 (14.0)</td>
<td>49.4 (16.3)</td>
<td>46.0 (14.4)</td>
<td>46.2 (14.1)</td>
<td>16,653 (50.4)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>203.6 (229.6)</td>
<td>169.8 (116.5)</td>
<td>202.9 (211.6)</td>
<td>207.0 (214.1)</td>
<td>16,861 (51.0)</td>
</tr>
<tr>
<td><strong>Categorical Variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6,733 (45.8)</td>
<td>418 (54.1)</td>
<td>6,961 (55.2)</td>
<td>2,600 (52.2)</td>
<td>2 (0.01)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>11,198 (76.1)</td>
<td>647 (83.7)</td>
<td>9,844 (78.1)</td>
<td>4,073 (81.8)</td>
<td>1,175 (3.6)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>431 (2.9)</td>
<td>97 (12.5)</td>
<td>1,030 (8.2)</td>
<td>255 (5.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Insulin</td>
<td>1,934 (13.1)</td>
<td>214 (27.7)</td>
<td>1,371 (10.9)</td>
<td>1,568 (31.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Aspirin</td>
<td>3,566 (24.2)</td>
<td>243 (31.4)</td>
<td>3,171 (25.2)</td>
<td>1,325 (26.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Plavix</td>
<td>929 (6.3)</td>
<td>98 (12.7)</td>
<td>1,059 (8.4)</td>
<td>516 (10.4)</td>
<td>NA</td>
</tr>
<tr>
<td>ACE / ARB</td>
<td>7,286 (49.5)</td>
<td>443 (57.3)</td>
<td>6,699 (53.1)</td>
<td>2,921 (58.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Cholesterol Medication</td>
<td>7,098 (48.3)</td>
<td>409 (52.9)</td>
<td>5,630 (44.7)</td>
<td>2,911 (58.5)</td>
<td>NA</td>
</tr>
<tr>
<td>New Diabetic</td>
<td>4,578 (31.1)</td>
<td>37 (4.8)</td>
<td>1,002 (7.9)</td>
<td>399 (8.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>1,533 (10.4)</td>
<td>147 (19.0)</td>
<td>1,791 (14.2)</td>
<td>688 (13.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Current Smokers</td>
<td>2,310 (15.7)</td>
<td>74 (9.6)</td>
<td>1,795 (14.2)</td>
<td>757 (15.2)</td>
<td>8,195 (24.8)</td>
</tr>
<tr>
<td>History of Stroke or TIA</td>
<td>591 (4.0)</td>
<td>64 (8.3)</td>
<td>715 (5.7)</td>
<td>264 (5.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Glomerular Filtration Rate (ml/min) &lt;60</td>
<td>1,875 (12.7)</td>
<td>293 (37.9)</td>
<td>3,501 (27.8)</td>
<td>1,329 (26.7)</td>
<td>10,702 (32.4)</td>
</tr>
</tbody>
</table>

* All of these baseline characteristics showed significant differences when stratified by drug class.
† Number of missing values prior to imputation
Figure 1. Mortality Curve over Time
Figure 2. Nomogram for Predicting 6-year Probability of Survival (Part I)

Abbreviations for Nomogram
TZD = Thiazolidinediones  
BIG = Biguanides  
MEG = Meglitinides  
SFU = Sulfonylureas  
ARB = Angiotensin Receptor Blocker  
ACE = Angiotensin Converting Enzyme

Instructions for using the nomogram: Estimate the patient’s GFR from their most recent serum creatinine. Locate the value of the patient’s age according to baseline medication and GFR in Part I, draw a line straight upwards to the points axis to determine the number of points contributed by age. Repeat this process for the other variables in the model. Sum the points achieved for each predictor in Part I. Repeat this process on Part II of the nomogram. Sum the points obtained in both parts of the nomogram and find this total on the Total Points axis at the bottom of Part II. Draw a straight line down from the Total Points axis to determine the probability of 6-year survival.

Important points about nomograms:
U-Shaped Relationship—The Low Density Lipoprotein (LDL) predictor variable has a “U” shaped relationship with the probability of survival. This is presented in the nomogram by having the direct relationship on one side of the scale and the indirect relationship on the other side of the scale. LDL levels from 150-0 are shown under the scale and have a direct relationship with survival, while LDL values from 150-450 are shown on the top of the scale and have an indirect relationship with survival. In other words, a patient with an LDL of exactly 150 has the highest probability of survival and as the LDL goes up or down from 150 the risk of mortality increases.
Figure 3. Nomogram for Predicting 6-year Probability of Survival (Part II)

Nomogram Example: A 50-year old male with type 2 diabetes presents today for his first visit at the Cleveland Clinic. The physician caring for the patient would like to know the risk of mortality for this specific patient over the next six years if he prescribes a biguanide (BIG). Here are the characteristics for this patient along with the calculation using the survival nomogram in Figures 2 and 3: Age 50, on BIG, GFR=60 (18 points); Hba1c=10.0 (3 points); BMI=35 (0 points); SBP=140 (0 points); DBP=80 (3 points); HDL=35 (6 points); LDL=100 (1 point); TG=200 (1 point); Gender=Male (3 points); Caucasian=Yes (7 points); Heart Disease=No (0 points); Heart Failure=No (0 points); Smoking=No (0 points); On Insulin=No (0 points); ACE/ARB=No (5 points); New Diabetic=No (10 points); Aspirin=Yes (0 points); Clopidogrel=No (0 points); Lipid Drug=No (0 points). Total Points=51. Probability of 6-Year Survival~0.94.
Figure 4. Validation of the survival prediction

- Vertical Bars represent the 95% Confidence Intervals by quintile.
- The 45 degree line represents a perfect prediction.