Hemoglobin A$_{1c}$ as a Predictor of Incident Diabetes

PEIYAO CHENG, MS, MPH[1]
BRITTA NEUGAARD, PHD, MPH[1,2,3]

PHILIP FOULIS, MD, MPH[1,3]
PAUL R. CONLIN, MD[4,5]

OBJECTIVE—Several studies have suggested that HbA$_{1c}$ levels may predict incident diabetes. With new recommendations for use of HbA$_{1c}$ in diagnosing diabetes, many patients with HbA$_{1c}$ results below the diagnostic threshold will be identified. Clinicians will need to categorize risk for a subsequent diabetic diagnosis in such patients. The objective of this study was to determine the ability of HbA$_{1c}$ to predict the incidence of a diabetic diagnosis.

RESEARCH DESIGN AND METHODS—We performed a historical cohort study using electronic medical record data from two Department of Veterans Affairs Medical Centers. Patients ($n = 12,589$) were identified with a baseline HbA$_{1c}$ <6.5% between January 2000 and December 2001 and without a diagnosis of diabetes. Patients (12,375) had at least one subsequent follow-up visit. These patients were tracked for 8 years for a subsequent diagnosis of diabetes.

RESULTS—During an average follow-up of 4.4 years, 3,329 (26.9%) developed diabetes. HbA$_{1c}$ ≥5.0% carried a significant risk for developing diabetes during follow-up. When compared with the reference group (HbA$_{1c}$ <4.5%), HbA$_{1c}$ increments of 0.5% between 5.0 and 6.4% had adjusted odds ratios of 1.70 (5.0–5.4%), 4.87 (5.5–5.9%), and 16.06 (6.0–6.4%) ($P <$ 0.0001). Estimates of hazard ratios similarly showed significant increases for HbA$_{1c}$ ≥5.0%. A risk model for incident diabetes within 5 years was developed and validated using HbA$_{1c}$, age, BMI, and systolic blood pressure.

CONCLUSIONS—The incidence of diabetes progressively and significantly increased among patients with an HbA$_{1c}$ ≥5.0%, with substantially expanded risk for those with HbA$_{1c}$ 6.0–6.4%.

Diabetes Care 34:610–615, 2011

HbA$_{1c}$ is a well-established test to track long-term glucose control and the risk for developing microvascular complications in patients with diabetes (1). However, until recently, HbA$_{1c}$ was not an accepted test for diagnosing diabetes because of concerns about both lower specificity and sensitivity compared with fasting plasma glucose (2). A number of threshold values that relate HbA$_{1c}$ to a diabetic diagnosis have been proposed in the past (3–7), but none were broadly adopted. A recent report by an International Expert Committee (8) proposed that HbA$_{1c}$ ≥6.5% on two repeated tests may be used to diagnose diabetes. These recommendations were subsequently accepted by the American Diabetes Association (9). Implementation of the recommendations will increase the number and frequency of HbA$_{1c}$ tests obtained in patients at risk for diabetes. Indeed, the Expert Committee raised concerns about how to identify and manage higher risk individuals, as there is yet no accepted HbA$_{1c}$ threshold value for initiating preventive strategies.

Evidence suggests that clinicians have been using HbA$_{1c}$ in the evaluation of patients without known diabetes in the absence of clearly accepted threshold values for establishing a diagnosis. As an example, in the Veterans Health Administration (VHA) in fiscal years 2006 and 2007 there were >500,000 patients without a prior diagnosis of diabetes who had HbA$_{1c}$ tests—representing 37 and 39% of all patients having an HbA$_{1c}$ test performed in those years (P.R.C., unpublished observations).

To better understand the relationship between HbA$_{1c}$ levels and the subsequent risk of diagnosed diabetes, we identified a cohort of patients without diabetes in whom an HbA$_{1c}$ was obtained and tracked these individuals for up to 8 years for evidence of a diabetic diagnosis. We hypothesized that a baseline HbA$_{1c}$ level has predictive information for the future development of diabetes and can be used to risk stratify patients. Our data confirm the continuum of risk associated with increasing levels of HbA$_{1c}$ and also identify a HbA$_{1c}$ threshold value, below which the risk is nominal.

RESEARCH DESIGN AND METHODS

Study population
This historical cohort study included 12,589 patients at two Department of Veterans Affairs (VA) Medical Centers who had at least one HbA$_{1c}$ test <6.5% between 1 January 2000 through 31 December 2001 (baseline HbA$_{1c}$). Institutional review board approval was obtained at both study sites before initiating the study.

Patient records were evaluated for 12 months before the baseline HbA$_{1c}$ to assure that they had at least one ambulatory care visit, no HbA$_{1c}$ ≥6.5%, and no diagnosis of diabetes. A diagnosis of diabetes was defined as: at least one inpatient diagnosis of diabetes mellitus (ICD-9 code of 250.*), two or more outpatient diagnoses of diabetes mellitus (ICD-9 code of 250.*), or a prescription for any medication used in diabetic treatment. This method to ascertain diabetic status has been previously validated within the

VA (10). Participants with more than one HbA_{1c} test during the baseline period had their first test result used as the baseline. Patients were required to have at least one ambulatory care visit at any time during the follow-up period (from date of baseline HbA_{1c} test to 31 December 2008) or until a diabetic diagnosis was made. After the above exclusion criteria were applied, 12,375 patients were classified without diabetes and were entered into the follow-up period. The period of follow-up for a given patient varied based on when they had clinic visits during the follow-up period.

Data were abstracted electronically from the patients' medical records. Information was collected on outpatient clinic visits, admissions, vital signs, outpatient prescriptions, comorbid diagnoses, patient demographics, and laboratory tests. Because our clinical laboratories do not label glucose measurements as fasting or nonfasting, we recorded glucose levels obtained between 0600 and 1100 h as a proxy for the fasting state. The ICD-9 codes used for the comorbid conditions were as follows: cardiovascular disease (CVD) (coronary heart disease 410–414; stroke 430–438; heart failure 428; cardiac arrest 427.1, 472.4, 427.5; inflammatory heart disease 429.01, 429.1, 420–425; and hypertension 401–405). Race and ethnicity were self-reported by patients. The study end point was whether a diagnosis of diabetes mellitus occurred during the follow-up period.

During the study, both facilities used the same methodology for measuring HbA_{1c} levels, which used a nonporous ion-exchange high-performance liquid chromatography to separate HbA_{1c} from other hemoglobin fractions and is certified by the National Glycohemoglobin Standardization Program. This method is fairly immune to the presence of hemoglobinopathies or carbamylated hemoglobin as a result of high urea concentrations. Abnormal concentrations of hemoglobins that may falsely elevate HbA_{1c} are clearly recognized.

Statistical analysis

The distribution of baseline HbA_{1c} levels was analyzed using univariate procedures and stratified into five groups (1): <4.5% (2), 4.5–4.9% (3), 5.0–5.4% (4), 5.5–5.9% (5), and 6.0–6.4%. The lowest group, with HbA_{1c} <4.5%, was treated as the reference group and all other groups were compared with the reference for risk calculation.

Data were analyzed using SAS 9.1 (SAS Institute, Cary, NC). Descriptive statistics were conducted on the study sample at baseline: median and range were calculated for the continuous variables; frequency and proportion were calculated for the categorical variables. The study also compared the baseline characteristics for patients who developed diabetes with patients who did not develop diabetes in the follow-up period. The nonparametric Wilcoxon rank-sum test was used to compare medians for continuous variables, and the χ^2 test was used to compare proportions for categorical variables. Given the large sample size, a P value of <0.0001 was used to determine statistical significance. Both logistic regression models and Cox proportional hazards models were used to compare the risk of developing diabetes with baseline HbA_{1c} level as the main effect (HbA_{1c} <4.5% as reference group). Based on the univariate results, a stepwise selection method (using an α of 0.05) was used for further evaluation of the confounders in the multiple logistic regression. Both unadjusted odds ratio/hazard ratio and multivariable adjusted odds ratio/hazard ratio were calculated. The Kaplan–Meier method was used to calculate survival probability with time, and a diabetic event probability versus time plot was developed and stratified by baseline HbA_{1c} groups. All of the 12,375 patients were included in the survival analysis, including those patients who died before developing diabetes. Date of entry was the date on which the initial HbA_{1c} measurement was obtained. For those patients who died, we used their date of death as the censor time. For patients who survived without developing diabetes, we used the last visit date as their censor time in the survival analysis calculation.

We also developed a risk model for predicting the 5-year incidence of diabetes using logistic regression. The 5-year incidence of diabetes was defined as any patient who developed diabetes within the 5-year period after the baseline HbA_{1c} test, and patients who did not develop diabetes within the 5-year period were used as the control group. A simple risk model was developed using baseline HbA_{1c} as the only predictor, and a multivariable model was developed using baseline HbA_{1c}, age, BMI, and systolic blood pressure (SBP) as predictors. The areas under the two receiver operating characteristic (ROC) curves (indicated by C statistic) were compared using nonparametric

approaches (11). Finally, risk-calculating equations were developed from the above findings.

RESULTS—There were 12,589 individuals eligible for the study by having an HbA_{1c} test during the baseline period; 214 (1.7%) did not visit the clinic during the follow-up period and were lost to follow-up, leaving 12,375 in the study population. Baseline characteristics of the 12,375 individuals, including those who developed diabetes during follow-up, are shown in Table 1. Individuals were predominantly white men (95.4% men and 67.5% whites) with a median age of 65.9 (range 18.5– 101.5. Comparison of the demographics and clinical characteristics between these individuals and the 214 who had no follow-up visits showed no significant differences with regard to HbA_{1c}, age, glucose, SBP, creatinine, estimated glomerular filtration rate (eGFR), sex, and presence of cardiovascular disease. Those lost to follow-up were significantly lower with regard to diastolic blood pressure, albumin, BMI, and presence of hypertension.

During an average follow-up of 4.4 years and with an average of 140 (SD 194) ambulatory care visits, 26.9% developed diabetes. The criteria by which diabetes was diagnosed were: outpatient codes (59.9%), inpatient codes (5.2%), and new diabetes medication (34.9%). Blood pressure, BMI, glucose, serum creatinine, prevalent cardiovascular disease, and hypertension were significantly higher (P < 0.0001) in patients who developed diabetes. During the study period, there was a progressive decline in the number and percentage of individuals with clinic encounters in a given year. In the last year of the study period, 6,997 (56.5%) individuals had one or more clinic visits, 2,671 (21.6%) patients had no clinic visits, and 2,707 (21.9%) had died during the 8 years of follow-up.

Logistic regression was used to compare the groups for risk of developing diabetes in the follow-up period (Table 2). When compared with the reference HbA_{1c} group (<4.5%), the group with HbA_{1c} 4.5–4.9% was not significantly different, whereas risk of developing diabetes increased steadily for the higher HbA_{1c} groups ($\geq$5.0%). The point estimates for unadjusted odds ratios were 1.57 for HbA_{1c} 5.0–5.4%, 4.54 for HbA_{1c} 5.5–5.9%, and 14.93 for HbA_{1c} 6.0–6.4% compared with HbA_{1c} <4.5% (P < 0.0001).

Table 1—Baseline characteristics of study sample

	All subjects	Diabetes	Nondiabetes	P value	Odds ratio (95% CI)
n	12,375	3,329	9,046		
Age (years)	65.9 (18.5–101.5)	65.8 (26.1–90.5)	65.9 (18.5–101.5)	0.7759	
Blood pressure (mmHg)					
Systolic	139 (67–248)	141 (84–248)	138 (67–245)	<0.0001	
Diastolic	77 (50–126)	78 (50–126)	76 (50–126)	<0.0001	
BMI (kg/m^2)	29.0 (10.0–50.0)	30.0 (10.0–50.0)	28.0 (11.0–50.0)	<0.0001	
Glucose (mg/dL)	107 (42–198)	118 (49–199)	101 (31–198)	<0.0001	
Albumin (mg/dL)	4.1 (1.2–5.5)	4.0 (2.2–5.3)	4.1 (1.2–5.5)	0.0029	
Creatinine (mg/dL)	1.0 (0.2–12.0)	1.0 (0.4–8.9)	1.0 (0.2–12.0)	<0.0001	
eGFR (mL/min)	78.3 (4.5–197.5)	77.5 (6.3–189.0)	78.6 (4.5–197.5)	<0.0001	
Sex				<0.0001	1.30 (1.06–1.59)
Men	11,805 (95.4)	3,202 (96.2)	8,603 (95.1)		
Women	570 (4.6)	127 (3.8)	443 (4.9)		
Ethnicity				<0.0001	
Hispanic	323 (2.6)	138 (4.2)	185 (2.0)		
Non-Hispanic	7,383 (59.7)	2,326 (69.9)	5,057 (55.9)		
Unknown	4,669 (37.7)	865 (26.0)	3,804 (42.1)		
Race				<0.0001	
Black	712 (5.8)	208 (6.3)	504 (5.6)		
White	8,351 (67.5)	2,337 (70.2)	6,014 (66.5)		
Other	171 (1.4)	61 (1.8)	110 (1.2)		
Unknown	3,141 (25.4)	723 (21.7)	2,418 (26.7)		
Cardiovascular disease	3,911 (31.6)	1,147 (34.4)	2,764 (30.6)	<0.0001	1.19 (1.10–1.30)
Hypertension	7,251 (58.6)	2,199 (66.1)	5,052 (55.8)	<0.0001	1.54 (1.43–1.67)
eGFR <60 mL/min	2,329 (18.8)	639 (19.2)	1,690 (18.7)	0.5176	1.03 (0.93–1.14)

Data are median (range) or n (%) unless otherwise indicated. P value and odds ratio compare both diabetic and nondiabetic groups.

The adjusted odds ratios by multivariable logistic regression showed similar trends with slight differences in point estimates and 95% confidence intervals. We assessed whether the number of outpatient visits affected a diagnosis of diabetes but found that it did not contribute to model fit and was not included in the logistic regression model.

Table 3 shows the results from the Cox proportional hazards models. Estimates of hazard ratios showed similar patterns as the odds ratio estimates with logistic regression. No significant difference was detected between the reference group and those with HbA$_{1c}$ 4.5–4.9%, but the hazard ratio increased significantly beginning with HbA$_{1c}$ ≥5.0% ($P < 0.0001$), with higher baseline HbA$_{1c}$ associated with higher risk.

We analyzed event probability (i.e., developing diabetes) during the follow-up period (Fig. 1) differentiated by baseline HbA$_{1c}$. Similar to our other analyses, the curves for incident diabetes in those with baseline HbA$_{1c}$ <5.0% intertwined, whereas those with higher baseline HbA$_{1c}$ had significantly higher probability of developing diabetes during follow-up (log-rank P value <0.0001).

Risk models for a diabetic diagnosis over 5 years were developed using HbA$_{1c}$ alone (model 1) and a multivariable model using HbA$_{1c}$, age, BMI, and SBP as predictors (model 2). For each predictor, a quadratic term was added into the model because of nonlinear association with risk (indicated by significant P values associated with quadratic terms). For model 1, the area under the ROC curve = 0.7543 (95% confidence interval 0.7429–0.7657), and for model 2, the

Table 2—Risk comparison by logistic regression for developing diabetes according to baseline HbA$_{1c}$ groups

	HbA$_{1c}$ groups					
	1 (<4.5)	2 (4.5–4.9)	3 (5.0–5.4)	4 (5.5–5.9)	5 (6.0–6.4)	P trend
N	519	1,918	4,416	3,663	1,859	—
Incident diabetes mellitus	53	190	668	1,248	1,170	—
Unadjusted odds ratio	1.00	0.97	1.57	4.54	14.93	<0.0001
95% CI	—	0.70–1.33	1.17–2.11	3.39–6.09	11.07–20.14	
Multivariable-adjusted odds ratio*	1.00	1.01	1.70	4.87	16.06	<0.0001
95% CI	—	0.70–1.45	1.21–2.36	3.49–6.79	11.40–22.65	—

*Adjusted for age, sex, ethnicity (Hispanic or Latino, not Hispanic or Latino, or unknown), race (black, white, other, or unknown), BMI, and systolic blood pressure.

Table 3—*Risk comparison by Cox proportional hazards model for developing diabetes according to baseline HbA_{1c} groups*

	HbA$_{1c}$ groups					P trend
	1 (<4.5)	2 (4.5–4.9)	3 (5.0–5.4)	4 (5.5–5.9)	5 (6.0–6.4)	
Unadjusted hazard ratio	1.00	0.90	1.41	3.69	9.62	<0.001
95% CI	—	0.66–1.22	1.07–1.87	2.80–4.86	7.30–12.67	
Multivariable-adjusted hazard ratio*	1.00	0.92	1.42	3.54	8.71	<0.001
95% CI	—	0.66–1.27	1.05–1.92	2.63–4.75	6.47–11.73	—

*Adjusted for age, sex, ethnicity, race, BMI, and systolic blood pressure.

area under the ROC curve = 0.7791 (95% confidence interval: 0.7687–0.7896). Comparison of the two areas showed significant improvement of the predictability of model 2 (*P* value <0.0001). The Hosmer and Lemeshow Goodness-of-Fit *P* value was 0.2827 for model 2, indicating good model fit.

Based on the above findings, we developed risk calculating equations as follows:

$$Odds = \exp(-0.4595 - 6.8111 * HbA_{1c}$$
$$+ 0.7956 * HbA_{1c}^2$$
$$+ 0.1767 * Age - 0.00144 * Age^2$$
$$+ 0.2372 * BMI - 0.00281 * BMI^2$$
$$+ 0.0330 * SBP - 0.00009 * SBP^2)$$
$$(1)$$
$$Probability = odds/(1 + odds) \quad (2)$$

where HbA$_{1c}$ is hemoglobin HbA$_{1c}$ in percentage, age is indicated in years, BMI is measured in kg/m^2, and SBP is indicated in mmHg. The first equation calculates the odds of developing diabetes mellitus in 5 years, and the second equation calculates the probability of developing diabetes mellitus in 5 years using the result from Eq. 1.

CONCLUSIONS—We found that baseline HbA$_{1c}$ was significantly predictive of the subsequent development of a diagnosis of diabetes over an 8-year period. The risk of developing diabetes increased progressively at HbA$_{1c}$ levels ≥5.0%, with an odds ratio exceeding 16 in those with HbA$_{1c}$ 6.0–6.4%. This latter group had a cumulative incidence of diabetes approaching 80%. Not surprisingly, significant predictors for diabetes incidence included clinical parameters, such as blood pressure, BMI, serum creatinine, prevalent cardiovascular disease, and hypertension. From these data, we also developed risk–calculating equations for determining the probability of developing a diabetic diagnosis within 5 years. We believe that these data will inform clinicians on how to risk–stratify individuals who are screened for diabetes using HbA$_{1c}$ but whose levels do not reach the recommended diagnostic threshold of ≥6.5%.

Several studies have evaluated HbA$_{1c}$ as a predictor of subsequent diabetes or as a tool to diagnose treatment-requiring diabetes (3–7,12–19). A number of threshold values have been previously proposed for diagnosing diabetes, such as ≥7.0% (4,7), ≥6.5% (13), >2 SD above the normal mean (i.e., >6.1%) (6). In addition, a number of HbA$_{1c}$ levels have also been proposed to identify individuals at risk for diabetes (i.e., prediabetes), such as 6.1–6.9% [7], 6.0–6.4% [8], or 5.7–6.4% [1]. The implementation of new guidelines for diagnosing diabetes using HbA$_{1c}$ will help standardize the way in which clinicians apply results from this test. However, there remains uncertainty on how to classify and whether to intervene in individuals whose levels fall below this threshold.

There is growing evidence that HbA$_{1c}$ may not only predict diabetes but also cardiovascular disease and death (12–19). Among women without diabetes, HbA$_{1c}$ levels were significantly associated with both, although the presence of other cardiovascular risk factors may contribute additionally to this risk (15,16). Selvin et al. (18) showed that, in a community-based population, HbA$_{1c}$ was significantly associated with risk of developing both diabetes and cardiovascular disease independent of fasting glucose levels. As with our results, they showed that levels ≥6.0% carried the greatest risk. Therefore, these results strongly suggest that individuals with HbA$_{1c}$ levels ≥6.0% should be targeted for prevention strategies to reduce not only incident diabetes but possibly also cardiovascular disease.
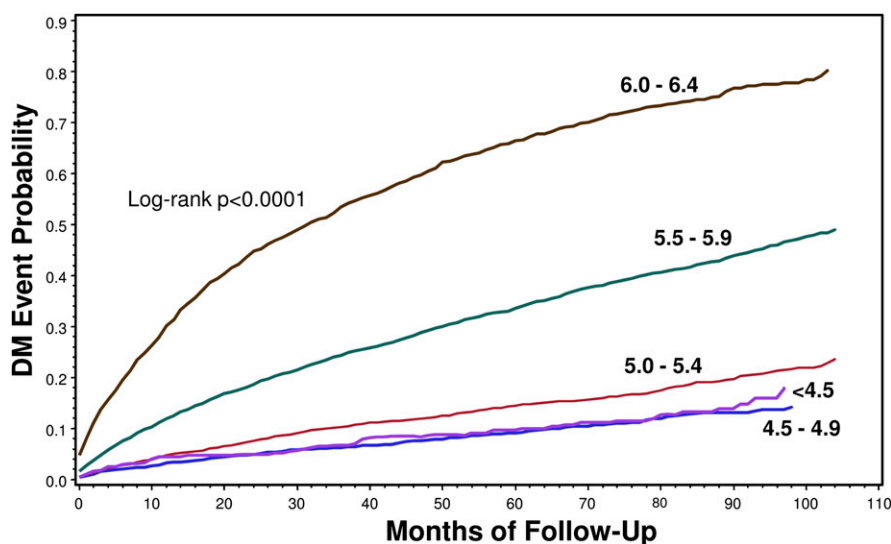

Figure 1—*Plot of diabetes event probability against follow-up time, differentiated by baseline HbA_{1c}. The curves for the two lowest groups substantially overlap, but groups with HbA_{1c} ≥5.0% have significantly higher probability of developing diabetes during the 8-year study period (log-rank P value <0.0001).*

Many clinicians have been attracted to using HbA$_{1c}$ as a screening test for diabetes since the test reflects longer-term glucose control, does not require fasting, has less day-to-day biologic variability, and is a well-accepted marker of risk of long-term microvascular complications (20). Such usage is evidenced by our large cohort of patients in whom HbA$_{1c}$ levels were obtained in patients without a diagnosis of diabetes. However, prior guidelines discouraged use of HbA$_{1c}$ for diagnosing diabetes, largely as a result of standardization and reproducibility issues that precluded its use in such broad settings. Current instrumentation and standardization methods (21) aligned with the Diabetes Control and Complications Trial have abrogated most of these issues. Such evidence was cited by the International Expert Committee (8) and affirmed by the American Diabetes Association (9) in their acceptance of HbA$_{1c}$ for screening and diagnosis.

Significant strengths of this study are its large population drawn from two VA medical centers in different geographic regions, the ability to query a robust electronic medical record for clinical and demographic factors, and patient follow-up for up to 8 years. Important limitations include the largely white men and older population, the reliability of the administrative data set, and the selection and ascertainment bias related to patients for whom HbA$_{1c}$ testing was performed. It is possible that HbA$_{1c}$ tests were performed in patients who were preselected for the presence of other known risk factors for diabetes. Such selective screening might bias our results toward showing a higher risk of developing diabetes for a given HbA$_{1c}$ level. To address this, our analyses controlled for many known risk factors and helped identify those factors that contribute significantly with HbA$_{1c}$ in predicting risk of diabetes. To account for the possible confounding effects from sex and age, we incorporated these two variables with several other known risk factors in our 8-year follow-up models to calculate odds ratios (hazard ratios) based on baseline HbA$_{1c}$. In our 5-year risk prediction model, the sex variable did not provide significant contribution to the predictability of the model.

Other factors may limit the generalizability of our findings. We did not have information on the prevalence of smoking in the study population, which is a known risk factor for diabetes (22) and is higher among veterans than nonveterans (23).

This might tend to inflate the risks of diabetes that we observed. Another potential bias is that a greater amount of medical care (e.g., increased number of clinic visits) might associate with a higher number of diabetes cases ascertained during the study. We adjusted for the number of medical visits but did not find that this significantly influenced the models. In addition, there were 214 individuals initially eligible to participate but who were lost to follow-up. Demographic and clinical characteristics of these individuals were quite similar to the remaining cohort. Those areas in which they differed were in a direction that paralleled those who did not develop diabetes during follow-up. Although their absence from the cohort can introduce bias in the ascertainment of both exposure and outcome, we believe that both the small number as well as the characteristics of these individuals makes it unlikely that this substantially affected the reported incidence of diabetes. Finally, we identified diagnosed diabetes based on medical record evidence that the patient was actually diagnosed by a clinician and/or treated with a diabetes medication. These criteria would exclude patients who have an unrecorded but true diagnosis of diabetes for whom no medications were prescribed, which could lead to an underestimation of the true risk of developing diabetes. However, the number of such patients should be small because of our use of multiple variables to establish a diagnosis of diabetes and the extended follow-up period.

In summary, we have characterized the risk of developing diabetes in patients without a diagnosis of diabetes who had a baseline HbA$_{1c}$ levels <6.5%. These data show a progressive risk for developing diabetes when HbA$_{1c}$ is ≥5.0%, with nominal risk below that level. We generated a risk calculator using HbA$_{1c}$ and other clinical data that estimate the 5-year risk of developing diabetes. Because clinicians implement HbA$_{1c}$ testing to screen for diabetes, these data may be used to help identify the risk of incident diabetes among individuals with HbA$_{1c}$ levels <6.5%.

References
1. American Diabetes Association. Standards of medical care in diabetes—2010. Diabetes Care 2010;33(Suppl. 1):S11–S61
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2009;32(Suppl. 1):S62–S67
3. Bennett CM, Guo M, Dharmage SC. HbA$_{1c}$ as a screening tool for detection of Type 2 diabetes: a systematic review. Diabet Med 2007;24:333–343
4. Peters AL, Davidson MB, Schriger DL, Hasselblad V; Meta-analysis Research Group on the Diagnosis of Diabetes Using Glycated Hemoglobin Levels. A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated hemoglobin levels. JAMA 1996;276:1246–1252
5. Ginde AA, Cagliero E, Nathan DM, Camargo CA Jr. Value of risk stratification to increase the predictive validity of HbA1c in screening for undiagnosed diabetes in the US population. J Gen Intern Med 2008;23:1346–1353
6. Rohlfing CL, Little RR, Wiedmeyer HM, et al. Use of GHb (HbA$_{1c}$) in screening for undiagnosed diabetes in the U.S. population. Diabetes Care 2000;23:187–191
7. Buell C, Kermah D, Davidson MB. Utility of A1C for diabetes screening in the 1999 2004 NHANES population. Diabetes Care 2007;30:2233–2235
8. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–1334
9. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl. 1):S62–S69
10. Miller DR, Safford MM, Pogach LM. Who has diabetes? Best estimates of diabetes prevalence in the Department of Veterans Affairs based on computerized patient data. Diabetes Care 2004;27(Suppl. 2):B10–B21
11. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–845
12. Edelman D, Olsen MK, Dudley TK, Harris AC, Oddone EZ. Utility of hemoglobin A1c in predicting diabetes risk. J Gen Intern Med 2004;19:1175–1180

13. Pendleton N, Clague JE, Cobain M, et al. Relationship between self-reported prevalence of diabetes mellitus using the Cornell Medical Index (CMI) and prevalence determined by glycosylated hemoglobin (HbA (1c)) in an elderly community-dwelling population. Arch Gerontol Geriatr 2005; 41:289–296

14. Selvin E, Zhu H, Brancati FL. Elevated A1C in adults without a history of diabetes in the U.S. Diabetes Care 2009;32:828–833

15. Pradhan AD, Rifai N, Buring JE, Ridker PM. Hemoglobin A1c predicts diabetes but not cardiovascular disease in nondiabetic women. Am J Med 2007;120:720–727

16. Blake GJ, Pradhan AD, Manson JE, et al. Hemoglobin A1c level and future cardiovascular events among women. Arch Intern Med 2004;164:757–761

17. O'Sullivan CJ, Hynes N, Mahendran B, et al. Haemoglobin A1c (HbA1C) in nondiabetic and diabetic vascular patients. Is HbA1C an independent risk factor and predictor of adverse outcome? Eur J Vasc Endovasc Surg 2006;32:188–197

18. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800–811

19. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Ann Intern Med 2004;141:413–420

20. Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan DM, Peterson CM; American Diabetes Association. Tests of glycemia in diabetes. Diabetes Care 2004; 27(Suppl. 1):S91–S93

21. Consensus Committee. Consensus statement on the worldwide standardization of hemoglobin A1c measurement: the American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation. Diabetes Care 2007;30: 2399–2400

22. Brown DW. Smoking prevalence among US veterans. J Gen Intern Med 2010;25: 147–149

23. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. BMJ 1995;310: 555–559