Original Research Article

Updated risk factors should be used to predict development of diabetes

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Authors' Contributions

MAB and KH researched the data and drafted the manuscript. ARC, PD, GRF, RRH, TJ, NSL, JJVM, and EB reviewed the manuscript. SMH reviewed/edited the manuscript and contributed to the writing. LT and JLS analyzed and researched the data and contributed to the description of the statistical methods. MAB takes responsibility for the manuscript. All authors approved the final manuscript.

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Abstract

Aims: Predicting incident diabetes could inform treatment strategies for diabetes prevention, but the incremental benefit of recalculating risk using updated risk factors is unknown. We used baseline and 1-year data from the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial to compare diabetes risk prediction using historical or updated clinical information.

Methods: Among non-diabetic participants reaching 1 year of follow-up in NAVIGATOR, we compared the performance of the published baseline diabetes risk model with a "landmark" model incorporating risk factors updated at the 1-year time point. The C-statistic was used to compare model discrimination and reclassification analyses to demonstrate the relative accuracy of diabetes prediction.

Results: A total of 7527 participants remained non-diabetic at 1 year, and 2375 developed diabetes during a median of 4 years of follow-up. The C-statistic for the landmark model was higher (0.73 [95% CI 0.72–0.74]) than for the baseline model (0.67 [95% CI 0.66–0.68]). The landmark model improved classification to modest (<20%), moderate (20%–40%), and high (>40%) 4-year risk, with a net reclassification index of 0.14 (95% CI 0.10–0.16) and an integrated discrimination index of 0.01 (95% CI 0.003–0.013).

Conclusions: Using historical clinical values to calculate diabetes risk reduces the accuracy of prediction. Diabetes risk calculations should be routinely updated to inform discussions about diabetes prevention at both the patient and population health levels.

Keywords: diabetes risk prediction, impaired glucose tolerance

1. Introduction

The use of diabetes risk prediction tools is advocated to identify high-risk individuals who should be screened more frequently for the development of diabetes or who may benefit from intensive diabetes prevention strategies [1-3]. The available risk calculators and outcome prediction tables use a given set of risk factors to model the likelihood of developing diabetes over a defined follow-up period. There is little consensus as to which risk prediction tool is most appropriate, and most have limited applicability due to the small size or limited ethnic variability in the populations from which they were derived.

With the rising global incidence of diabetes, there is interest in improving the performance of risk prediction tools, at both an individual and a population health level. Some have sought to improve prediction by adding additional genetic [4], laboratory [5, 6], or clinical [7] parameters to the traditional sociodemographic risk factors of ethnicity, family history of diabetes, personal history of gestational diabetes, and physical inactivity. Comparatively little is known about the impact of change in common risk factors over time on risk prediction [8]. Using data from the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study (ClinicalTrials.gov NCT00097786), we investigated the incremental benefit to diabetes risk prediction of updating risk factors after 1 year of follow up [9-11].

2. Materials and Methods

The NAVIGATOR study design and results have been previously published [9-11]. Briefly, 9306 participants with impaired glucose tolerance (IGT) and cardiovascular disease or cardiovascular risk factors were enrolled from 40 countries between January 2002 through January 2004. Subjects were randomized to nateglinide and/or valsartan in a balanced 2 × 2

factorial design; all participants received a study-specific lifestyle modification program. After randomization, fasting plasma glucose was measured every 6 months for 3 years and annually thereafter. Oral glucose tolerance tests (OGTTs) were performed annually. HbA_{1c} was measured only at baseline. Progression to diabetes occurred if the participant had a fasting plasma glucose level ≥126 mg/dL (≥7.0 mmol/L) or ≥200 mg/dL (≥11.1 mmol/L) 2 hours after a glucose challenge, confirmed by OGTT within the following 12 weeks. The date of diabetes onset was the date of the first elevated glucose value. Among 183 patients, diabetes was diagnosed outside of the study but confirmed by an independent adjudication committee. Subjects were followed for a median of 5 years for the incidence of diabetes.

A model using baseline characteristics to predict 5-year incident diabetes has been previously published [12]. Here, we compared the performance of the baseline model to a Cox proportional hazards regression model whose inputs included information obtained after 1 year of trial follow-up (referred to as updated values). This model (hereafter referred to as the landmark model) predicts 4-year incident diabetes among patients who survived to 1 year without developing diabetes. The selection of predictors followed that used for creation of the baseline model: 10 baseline variables were forced into the model, selected according to clinical judgment rather than statistical significance (age, sex, race, body mass index [BMI], systolic blood pressure, family history of diabetes, history of cardiovascular disease, fasting glucose, 2-hour glucose, and HbA_{1c}). Subsequently, candidate variables were added by forward selection with a *P*-value of <0.05. Where updated risk factor measurements (collected at 1 year) were available, they replaced the baseline variables. Updated measurements were available for history of cardiovascular events, BMI, systolic blood pressure, fasting and 2-hr glucose levels, and platelet count. Updated risk factor measurements were not available for time constant covariates

(e.g., race, region), HbA_{1c}, LDL, or HDL. In addition, wherever both baseline and 1-year risk factor measurements were available, the change from baseline to 1 year (calculated as the baseline value minus the 1-year value) was a candidate variable.

Because the baseline model was developed in a different population, possibly hindering its performance relative to the landmark model, we also refitted the baseline model covariates to the 1-year follow-up population, resulting in a model that used only baseline data but was calibrated to the population of interest. For a sensitivity analysis, we repeated the comparisons using this alternative baseline model. The competing risk of death was handled by modeling the cause-specific hazard of diabetes progression, with censoring at the time of death. This methodology mirrors that used for analyzing the diabetes endpoint for the primary trial.

As previously reported, less than 3% of data were missing for baseline covariates except HbA_{1c}, which had 15% missing [12]. For the 1-year updated values, the highest missing rate was 10% for platelet count. The missing data were handled by multiple imputation, and the final model results, standard errors, C-indices, and predicted probabilities reflect the combined results from five imputed data sets. Baseline and landmark models were compared according to the C-index, which is a measure of a model's ability to discriminate risk ranging from 0.5 (poor) to 1 (perfect) [13]. Model calibration was assessed graphically with observed event rates plotted against predicted event rates over deciles of predicted risk.

As a second comparison of model performance, risk classification tables were created to compare the baseline and landmark models for predicting transition to diabetes. Participants were classified by risk of progression to diabetes: modest risk (0–5%/year or 0–20% 4-year risk), moderate risk (>5–10%/year or >20–40% 4-year risk), or high risk (>10%/year or >40% 4-year risk). This clinically motivated classification paradigm is identical to that previously described

and is based on the annual diabetes risk seen in the placebo groups of other diabetes prevention studies [9]. Risk reclassification tables show the differences in classification, when compared to observed Kaplan-Meier event rates. Net reclassification index (NRI) and the integrated discrimination index (IDI) are also reported, using methods for censored data [14, 15].

SAS statistical software (Version 9.2, SAS Institute, Cary, NC, USA) was used for all statistical analyses.

3. Results

The population for this analysis included 7527 participants who did not die, convert to diabetes, or drop out of the study before the 1-year landmark time point (Table 1). Within this population, 2375 converted to diabetes within the next 4 years of follow-up. The results of prediction in the baseline and landmark population are shown in Table 2 (see Supplemental Material for predictive equation). The C-index of 0.73 (95% CI 0.72–0.74) indicates improved discrimination of 4-year incident diabetes in the landmark model compared with the baseline model (C-index 0.67 [95% CI 0.66–0.68]), although both had good calibration (not shown). All of the updated values made significant contributions to the model, with the exception of updated history of cardiovascular disease and platelet count. Change variables for fasting and 2-hour glucose and BMI made significant contributions to the model, but change in systolic blood pressure, the history of cardiovascular disease, platelet count, and hemoglobin did not.

Table 3 compares the predicted 4-year incident diabetes risk for each model with the observed risk from Kaplan-Meier probability estimates. The landmark model consistently predicts observed event rates more accurately than the baseline model, with the exception of 77 (1.0%) participants predicted to be of modest risk when the actual risk was moderate (predicted

risk <20%, observed risk 24%). The corresponding NRI was 0.14 (95% CI 0.10–0.16), and the IDI was 0.01 (95% CI 0.003–0.013). In the sensitivity analysis, where baseline data were fit to the landmark population, we saw very little difference in performance (C-index of 0.67 [95% CI 0.66–0.69], NRI 0.20 [95% CI 0.17–0.22], and IDI 0.06 [95% CI 0.05–0.06]).

4. Discussion

We have demonstrated that updating risk factor values for a few key variables improves risk prediction for incident diabetes. These key variables are typically available in routine care of at risk patients: BMI, systolic blood pressure, measures of glucose, and hemoglobin. The change over 1-year follow-up in fasting and 2-hour blood glucose and BMI is also important. Based on hazard ratios and chi-square values in Table 2, the absolute level of blood glucose (fasting or 2-hour values) is a stronger predictor of progression to diabetes than changes in glucose, but the change in BMI has a greater impact on risk prediction than the absolute level. This may imply that greater emphasis should be placed on large weight changes rather than absolute weight values when considering diabetes risk. The interim occurrence of cardiovascular events or change in systolic blood pressure does not impact prediction for diabetes.

Baseline variables shown here to be significantly associated with diabetes prediction are largely consistent with those in other predictive models. Increasing age and HDL-cholesterol levels predict decreased risk of incident diabetes, while family history of type 2 diabetes and increasing HbA1c are associated with increased diabetes risk. Of interest is our finding that higher baseline LDL-cholesterol levels are associated with a reduced risk for 4-year incident diabetes as other diabetes risk models have not identified LDL-cholesterol as an independent predictor of diabetes [3, 6, 16]. Associations between LDL-cholesterol subfractions, e.g.,

lipoprotein (a), and risk for diabetes have been inconsistent [17, 18]. However, lipid lowering with statin medications has been associated with increased diabetes risk in both epidemiological studies [19-22] and meta-analyses of prospective clinical trials [23-25]. Whether these findings and ours indicate a possible direct link with LDL-cholesterol or whether there is confounding as a result of statin therapy deserves further consideration.

Examination of the chi-square values demonstrates that glucose measures are the strongest predictors of progression, in both baseline and landmark models. The next largest chi-square values are seen for the change in fasting and 2-hour glucose. Closer examination appears to show a counterintuitive result: an increased hazard if glucose values decrease from baseline to 1 year. To understand this apparent paradox, it is important to remember that when change variables are added to the model, the effects are interpreted holding all other covariates (e.g., the absolute glucose value) constant (Figure 1). Among two people with equivalent 1-year fasting glucose, the individual whose glucose decreases over 1 year of follow-up had a higher glucose, on average, than a person who increases to the same point. Therefore, a person with higher average glucose is more likely to progress to diabetes than a person with lower average glucose. Our results suggest that the change in glucose values is important, in that it captures information about previous levels.

The reclassification table demonstrates the incremental benefit of updating risk calculations. In every case of discrepancy between the models, the observed event rates were consistent with the landmark model classification but not the baseline model classification. A striking example is the 481 patients classified as moderate risk (20-40%) by the baseline model but high risk (>40%) by the landmark model. The observed 4-year event rate in these patients was 59%. If applied across a population health setting, this degree of misclassification could

result in highly inaccurate estimates of the cost and effort required for diabetes prevention interventions to be effective.

There are important limitations to these findings. First, the NAVIGATOR population was constrained at entry by baseline glucose values. To be eligible, participants were required to have either IGT or fasting plasma glucose of at least 95 mg/dL (5.3 mmol/L) but <126 mg/dL (7.0 mmol/L). Therefore, our models are only generalizable to populations first identified to have elevated fasting glucose or IGT and then followed forward for 1 year. This is a particularly important limitation given the strength of the fasting and 2-hour glucose levels as predictors in both the baseline and landmark models. By definition, there is a wider distribution of glucose values in the population at the 1-year time point, potentially contributing to the improved discrimination seen in the landmark model. Another limitation is that, due to the study design, updated 1-year values were not available for all variables (e.g., LDL, HDL), but it seems unlikely that the impact of these variables would outweigh that seen for the glucose variables.

Lifestyle modification [26, 27] and metformin treatment [26] have proven efficacy for diabetes prevention. However, patients often find it difficult to implement and maintain the changes in diet and exercise required to reap the benefits. Furthermore, although recommended by the American Diabetes Association and other international guidelines [28], metformin is not formally approved for diabetes prevention, causing some payers not to reimburse its use for patients with IGT. These barriers, combined with poor uptake of screening for diabetes in many health care systems, decrease the ability to cope with the growing incidence of diabetes worldwide. Diabetes prediction tools could help to better target individuals at highest risk of conversion to diabetes for receipt of diabetes prevention interventions. However, our findings demonstrate that using historical data to inform diabetes risk calculations may underestimate the

true magnitude of the problem. In a cohort with IGT followed in clinical practice, diabetes risk calculations should be routinely updated to inform discussions about diabetes prevention at both the patient and population health levels.

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Table 1 – Baseline characteristics of the overall NAVIGATOR population and those included in the landmark analysis. Categorical variables are presented as n/N, and proportion and continuous variables are presented as N, median (25^{th} - 75^{th} percentile).

Characteristic	Baseline Value (All Navigator patients) (N=9306)	Baseline Value (Patients in 1-year model) (N=7527)	Year 1 Value (Patients in 1-year model) (N=7527)
Age	9306, 63.0 (58.0-69.0)	7527, 63.0 (58.0-69.0)	
Female	4711/9306 (50.6%)	3815/7527 (50.7%)	
Race[a]			
White	7734/9306 (83.1%)	6212/7527 (82.5%)	
Black	236/9306 (2.5%)	175/7527 (2.3%)	
Oriental	613/9306 (6.6%)	537/7527 (7.1%)	
Other	723/9306 (7.8%)	603/7527 (8.0%)	
Region			
Asia	552/9306 (5.9%)	487/7527 (6.5%)	
Europe	4909/9306 (52.8%)	3958/7527 (52.6%)	
Latin America	1406/9306 (15.1%)	1176/7527 (15.6%)	
North America	2146/9306 (23.1%)	1658/7527 (22.0%)	
Other	293/9306 (3.1%)	248/7527 (3.3%)	
Family History of Diabetes	3547/9306 (38.1%)	2845/7527 (37.8%)	
Prior Cardiovascular Disease[b]	7838/9306 (84.2%)	6346/7527 (84.3%)	222/7527 (2.9%)
BMI kg/m^2	9303, 29.7 (26.8-33.3)	7524, 29.5 (26.7-33.1)	7408, 29.3 (26.4-33.0)
Systolic BP, mmHg	9282, 140.0 (128.0-150.0)	7510, 140.0 (128.0-150.0)	7419, 133.5 (122.5-144.0)
Fasting Glucose, mmol/L	9300, 6.1 (5.7-6.4)	7522, 6.1 (5.7-6.4)	7358, 5.9 (5.5-6.3)
Two Hour Glucose, mmol/L	9301, 9.0 (8.4-9.9)	7523, 9.0 (8.3-9.9)	6953, 7.9 (6.6-9.3)
HbA1c, %	7905, 5.8 (5.6-6.1)	6481, 5.8 (5.5-6.1)	1146, 5.8 (5.5-6.1)
LDL, mmol/L	8890, 3.2 (2.6-3.9)	7200, 3.2 (2.6-3.9)	206, 3.1 (2.5-3.6)
HDL, mmol/L	9146, 1.2 (1.0-1.5)	7401, 1.2 (1.0-1.5)	215, 1.2 (1.0-1.5)
Platelet, $10^{-9}/L$	9050, 251.0 (212.0-294.0)	7323, 251.0 (212.0-295.0)	6760, 246.0 (207.0-290.0)
Hemoglobin, g/L	9137, 147.0 (138.0-155.0)	7397, 146.0 (138.0-155.0)	6825, 144.0 (136.0-153.0)
Variables Not in Model			
Medical History			
Family History of Premature Coronary Heart Disease	1544/9306 (16.6%)	1229/7527 (16.3%)	
Renal Dysfunction	90/9306 (1.0%)	66/7527 (0.9%)	
Atrial Fibrillation/Flutter	356/9306 (3.8%)	272/7527 (3.6%)	
Pulmonary Embolism or Deep Vein Thrombosis	129/9306 (1.4%)	99/7527 (1.3%)	

Characteristic	Baseline Value (All Navigator patients) (N=9306)	Baseline Value (Patients in 1-year model) (N=7527)	Year 1 Value (Patients in 1-year model) (N=7527)
COPD, Emphysema, or Chronic Bronchitis	451/9306 (4.8%)	333/7527 (4.4%)	
Current Smoker	1025/9306 (11.0%)	792/7527 (10.5%)	
Height (cm)	9303, 165.0, 158.0-173.0	7524, 165.0, 158.0-173.0	
Weight (kg)	9306, 82.0, 71.5-93.5	7527, 81.8, 71.0-92.8	
Waist Circumference (cm)	9297, 100.0, 92.0-109.0	7522, 100.0, 92.0-108.0	
Diastolic BP, mmHg	9282, 82.0, 76.0-90.0	7510, 82.0, 76.0-90.0	
Pulse, bpm	9267, 70.0, 63.0-77.0	7499, 70.0, 63.0-77.0	
ECG Interpretation (N)			
Normal	4400/9061 (48.6%)	3610/7349 (49.1%)	
Clinically Insignificant Abnormality	3271/9061 (36.1%)	2634/7349 (35.8%)	
Clinically Significant Abnormality	1390/9061 (15.3%)	1105/7349 (15.0%)	
Total Cholesterol, mmol/L	9266, 5.36, 4.67-6.10	7496, 5.36, 4.68-6.10	
Triglycerides, mmol/L	9261, 1.69, 1.22-2.36	7492, 1.69, 1.22-2.35	
eGFR, mL/min per 1.73 m^2	9267, 79.7, 68.6-91.1	7497, 79.9, 68.8-91.3	
Log of Albumin/Creatinine Ratio, mg/mmol	9062, -0.22, -0.67-0.49	7344, -0.22, -0.69-0.47	

[a] Regions are defined as Asia: China (mainland), Hong Kong, Malaysia, Singapore, Taiwan; Europe: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Netherlands, Norway, Poland, Russia, Slovakia, Sweden, Switzerland, Spain, Turkey, UK; Latin America: Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Peru, Uruguay; North America: Canada, USA (incl. Puerto Rico); Other: Australia, New Zealand, South Africa.

[b] Prior cardiovascular disease: history of myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, stroke, or congestive heart failure.

Table 2 – Landmark proportional hazards model for 4-year incident diabetes.

Main NAVIGATOR Model Variable	HR (95% CI)	Chi-Square	P Value
Age (per 10 years) [a]	0.89 (0.83–0.94)	13.53	0.0002
Female sex [a]	1.11 (1.00–1.23)	3.83	0.051
Region (vs. North America) [b]			
Asia	0.94 (0.77–1.13)	0.48	0.49
Europe	0.87 (0.77–0.97)	6.48	0.011
Latin America	0.96 (0.83–1.11)	0.35	0.56
Other	0.87 (0.68–1.11)	1.22	0.27
Race (vs. White) [a]			
Other	0.95 (0.80–1.13)	0.30	0.59
Black	0.90 (0.68–1.19)	0.57	0.45
Family history of type 2 diabetes mellitus [a]	1.13 (1.04–1.23)	7.66	0.0056
LDL (mmol/L)	0.93 (0.89–0.98)	8.57	0.0034
HDL (mmol/L)	0.76 (0.66–0.87)	15.51	<0.0001
HbA_{1c} (%)[a]	1.71 (1.54–1.89)	101.77	<0.0001
Values at 1 year			
Fasting glucose (mmol/L) [a]	1.68 (1.59–1.79)	298.54	<0.0001
2-hour glucose (mmol/L) [a]	1.43 (1.37–1.49)	250.88	<0.0001
BMI (kg/m^2) [a]	1.01 (1.00–1.02)	5.24	0.022
Prior cardiovascular disease, baseline/1 year [a,c]	1.07 (0.98–1.17)	2.09	0.15
Systolic BP (per 10 mm Hg) [a]	1.03 (1.01–1.06)	5.31	0.021
Hemoglobin (per 10 g/L)	1.08 (1.04–1.12)	16.06	<0.0001
Change from baseline to 1 year[d]			
Fasting glucose (mmol/L)	1.35 (1.23–1.49)	38.50	<0.0001
2-hour glucose (mmol/L)	1.22 (1.17–1.28)	78.91	<0.0001
BMI (kg/m^2)	0.88 (0.85–0.91)	53.11	<0.0001

For each dataset: N=7527, Event=2375, C-index=0.73.

[a] Forced into model.

[b] Regions are defined as Asia: China (mainland), Hong Kong, Malaysia, Singapore, Taiwan; Europe: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Netherlands, Norway, Poland, Russia, Slovakia, Sweden, Switzerland, Spain, Turkey, UK; Latin America: Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Peru, Uruguay; North America: Canada, USA (incl. Puerto Rico); Other: Australia, New Zealand, South Africa.

[c] Prior cardiovascular disease: history of cardiovascular disease includes myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, stroke, or congestive heart failure.

[d] Change is calculated as the baseline minus 1-year value. Therefore, an increase in the change value reflects improvement in the clinical situation.

Table 3 – Reclassification table for baseline versus landmark diabetes prediction models.

Baseline Model	**Landmark Model**			
	Modest risk (<20%)	Moderate risk (20–40%)	High risk (>40%)	Total
Modest risk (<20%)	2071[a] (0.09)	648[b] (0.25)	58[b] (0.60)	2777
Moderate risk (20–40%)	948[b] (0.15)	1795[a] (0.29)	481[b] (0.59)	3224
High risk (>40%)	77[b] (0.24)	648[b] (0.37)	801[a] (0.62)	1526
Total	3096	3091	1340	7527

Kaplan-Meier (KM) estimates of the 4-year risk of diabetes progression. In each cell, the number of individuals in each risk category is shown, followed by the observed 4-year incident diabetes risk according to KM probability estimates. C index from baseline model 0.67, from landmark model 0.73.

[a] KM rates are consistent with the landmark and baseline model classifications.

[b] KM rates are consistent with the landmark model classification, but not the baseline.

Figure 1 – Clinical example illustrating interpretation of change values for fasting glucose. Change values in the model are interpreted holding all other variables constant. Therefore, among two individuals with an equivalent 1-year fasting plasma glucose (FPG), Individual A, whose fasting glucose decreases over time, had a higher baseline glucose value than an individual whose glucose increases to the same point. Therefore, Individual A carries a higher overall risk for developing diabetes. The change value captures information about the absolute change in glucose level and some information about the baseline value as well.