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Risk prediction of major complications in persons with diabetes: The Atherosclerosis Risk in Communities Study

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Abstract

Aims—We developed a prediction equation for 10-year risk of a combined endpoint (incident coronary heart disease, stroke, heart failure, chronic kidney disease, lower extremity hospitalizations) in persons with diabetes, using demographic and clinical information, and a panel of traditional and nontraditional biomarkers.

Materials and Methods—We included 654 persons in the ARIC Study, a prospective cohort study, with diagnosed diabetes (visit 2, 1990–92). Models included self-reported variables (Model 1), clinical measurements (Model 2), and HbA1c (Model 3). Model 4 tested the addition of 12 blood-based biomarkers. We compared models using prediction and discrimination statistics.

Results—Successive stages of model development improved risk prediction. The C-statistics (95% confidence intervals) of models 1, 2, and 3 were 0.667 (0.64, 0.70), 0.683 (0.65, 0.71), and 0.694 (0.66, 0.72), respectively ($P < 0.05$ for differences). Addition of three traditional and nontraditional biomarkers (beta-2 microglobulin, creatinine-based estimated glomerular filtration

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AUTHOR CONTRIBUTIONS

C.M.P. designed the study, analyzed and interpreted the data, and wrote the manuscript. K.M., M.W., L.E.W., and J.C. interpreted the data, and reviewed and edited the manuscript. E.S. designed the study, interpreted the data, and reviewed and edited the manuscript. E.S. is the guarantor of the work and, as such, takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

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rate [eGFR], and cystatin C-based eGFR) to model 3 significantly improved discrimination (C-statistic=0.716, P=0.003) and accuracy of 10-year risk prediction for major complications in persons with diabetes (midpoint percentiles of lowest and highest deciles of predicted risk changed from 18%–68% to 12%–87%).

Conclusions—These biomarkers, particularly those of kidney filtration, may help distinguish between persons at low versus high risk of long-term major complications.

Introduction

Diabetes is a major risk factor for coronary heart disease (CHD), stroke, heart failure, chronic kidney disease (CKD) and end-stage renal disease (ESRD), lower extremity disease, and mortality (1–5). Recent evidence suggests that persons with diabetes may have varying degrees of risk depending on the presence and severity of other risk factors and co-morbidities (6). Understanding this heterogeneity in risk and distinguishing between those persons at very low long-term risk versus those most in need of aggressive cardiovascular risk management could help personalize and improve care for persons with diabetes. Hemoglobin A1c (HbA1c), and other biomarkers not included in traditional cardiovascular risk equations, may improve cardiovascular risk prediction in diabetes (7–10).

There are several challenges in developing an accurate, clinically relevant risk score. Predicting risk of a combined endpoint, particularly combined microvascular and macrovascular events, has not been widely studied (11–13). The clinical utility of a single risk score for multiple endpoints has broad application: convenience and efficiency for the clinician; indicative of overall long-term risk; and a “rule out” approach to guide more conservative treatment decisions. Furthermore, most existing risk scores have used traditional methods, such as Cox regression, to account for loss to follow-up, but have not accounted for competing risks, which can better estimate absolute risks, which is especially important in clinical settings (14,15).

We, thus, aimed to develop a risk prediction equation for 10-year risk of a combined endpoint of major microvascular and macrovascular complications in white and black persons with diabetes, while accounting for the competing risk of death from another cause. We explored pre-determined sets of demographic and clinical information and a panel of biomarkers of hyperglycemia, cardiac function, kidney function, liver function, and inflammation.

Materials and Methods

Study population

The Atherosclerosis Risk in Communities (ARIC) Study is a community-based cohort of 15,792 persons recruited from four field centers in the United States: Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland (16). Visits 1 through 5 took place during 1987–89, 1990–92, 1993–95, 1996–98, and 2011–13, respectively. We used visit 2 (1990–1992) as the baseline exam in the present study as this was the first visit with relevant biomarker data available (e.g., HbA1c). Of the 14,348 participants who attended visit 2, there were 1,356 with diagnosed diabetes, defined

as self-reported physician diagnosis of diabetes or use of glucose-lowering medication at either visit 1 or 2. After exclusion of participants who were missing baseline covariate data (N=276), were fasting <8 hours (N=172), were neither black nor white (N=2), had prevalent CVD (N=227), had prevalent reduced kidney function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m²) (N=23), or had prevalent lower extremity amputation or peripheral vascular bypass (N=2), there were 654 participants eligible for our main analyses.

Covariates

All covariates were obtained at visit 2, unless otherwise specified. The following variables were assessed during the participant interview: age, sex, education level (visit 1), alcohol consumption, smoking status, and physical activity (visit 1)(17). Antihypertensive, cholesterol-lowering, and glucose-lowering medication use was assessed via self-report and a medication inventory. Recent diabetes was defined as having had diabetes at visit 2 but not at visit 1. Family history of CVD was defined as self-reported parental history of either stroke or CHD. Diastolic and systolic blood pressures were measured and recorded as the mean of the 2nd and 3rd readings. Body mass index (BMI) was calculated as measured weight (in kilograms) divided by measured height (in meters) squared.

Lipids were measured on the Roche Cobas Bio (Roche Diagnostics, Indianapolis, IN)(16); serum glucose (hexokinase method) and creatinine (Jaffe method) on a Coulter DACOS analyzer (Beckman Coulter, Inc., Fullerton, CA, USA); and HbA1c from stored whole blood in 2003–04 and 2007–08 with the Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer and Tosoh G7 Analyzer (Tosoh Bioscience, Inc., South San Francisco, CA, USA), respectively, using a high-performance liquid chromatography method, and was standardized to the Diabetes Control and Complications Trial assay (18). The following biomarkers were measured in 2012–2013 using stored serum samples from visit 2 on the Roche Modular P800 (Roche Diagnostics Corporation, Indianapolis, IN): cystatin C (Gentian immunoassay, Gentian, Moss, Norway); beta-2 microglobulin (B2M) (latex agglutination method); alanine transaminase (ALT), aspartate transaminase (AST), and gamma-glutamyl transpeptidase (GGT) (kinetic rate method); fructosamine (colorimetric method, Roche Diagnostics Corporation, Indianapolis, IN, USA); high-sensitivity C-reactive protein (hs-CRP) (immunoturbidimetric method); and glycated albumin (Asahi Kasei Lucica GA-L, Tokyo, Japan) and 1,5-AG (GlycoMark, New York, NY) (enzymatic methods). Glycated albumin was expressed as a percentage of total albumin: [(glycated albumin concentration in g/dL / serum albumin concentration in g/dL) / 1.14*100] + 2.9. N-terminal probrain natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) were also measured in 2011–13 from stored visit 2 serum (sandwich immunoassay) on a Roche Elecsys autoanalyzer (Roche Diagnostics Corporation, Indianapolis, IN).

Incident Outcomes

We created a combined endpoint for the first occurrence of CHD, stroke, heart failure, CKD, lower extremity amputation, or peripheral vascular bypass, over a maximum of 10 years of follow-up. Outcomes were ascertained via continuous surveillance of hospitalizations and death certificates, annual telephone follow-up with participants or a proxy, and/or linkage to the National Death Index. CHD was adjudicated and defined as the first occurrence of a

definite or probable hospitalized myocardial infarction, death due to CHD, or cardiac procedure (19). Stroke was adjudicated and defined as the first occurrence of a definite or probable hospitalized stroke or death due to stroke (20). Heart failure was defined as the first hospitalization listing a heart failure code (based on a 428 International Classification of Diseases, 9th Revision [ICD-9] code or an ICD, 10th Revision [ICD-10] code of 150), or death attributed to heart failure (21). Incident CKD was defined as eGFR<60 mL/min/1.73 m² and 25% decline in eGFR since visit 2, or hospitalization due to kidney disease, kidney transplant or dialysis, or death due to kidney disease (22). Incident lower extremity amputation and peripheral vascular bypass events were identified from ICD-9-CM diagnostic and procedure codes using hospitalization data.

Persons who did not experience a CVD, CKD, or lower extremity event and were still alive 10 years after the date of their visit 2 examination were censored at that time. Persons who died from an event other than those listed above were considered to have experienced the competing risk of death. Persons who were lost to follow-up having not experienced the event of interest and were not known to have died were censored at the time of their last contact.

Statistical analysis

We calculated descriptive statistics for demographic and clinical characteristics in the study population overall and stratified by event type (any, none, competing).

We used a 3-stage approach to evaluate prediction models for 10-year risk of any of the major complications. In stage 1, we created Model 1, which included pre-specified self-reported information (age, sex, race, education, smoking status, alcohol consumption, physical activity, family history of CVD, glucose-lowering medication use, antihypertensive medication use, cholesterol-lowering medication use, and recent onset of diabetes) plus measured BMI, which is often self-reported in other studies or some clinical settings. In stage 2, we created Model 2, which additionally included pre-specified clinical variables (LDL-c, HDL-c, triglycerides, and systolic blood pressure). In stage 3, we created Model 3, which added HbA1c, and Model 4, which additionally tested the inclusion of 12 biomarkers of hyperglycemia (fasting glucose, fructosamine, glycated albumin, 1,5-AG), cardiac damage (hs-cTnT, NT-proBNP), kidney function (serum creatinine, cystatin C, B2M), liver function (AST, ALT, GGT), and inflammation (hs-CRP). We specified the variables for inclusion in models 1 and 2 a priori. Several interactions were additionally tested in Model 2: the interaction of sex with all variables, race with all variables, antihypertensive medication use with systolic blood pressure, and cholesterol-lowering medication use with LDL-c. The following interactions were found statistically significant ($P<0.05$ using a Wald test) and were additionally included in all relevant models: sex*triglycerides ($P=0.02$), sex*glucose-lowering medication (oral, insulin, or none) ($P=0.01$), race*triglycerides ($P=0.049$), and race*BMI ($P=0.03$). All continuous variables were centered. We natural log-transformed any variables that were not normally distributed. For biomarkers that had undetectable values, we imputed the values as half of the lower limit of detection (1.5 ng/L for hs-cTnT, 2.5 pg/mL for NT-proBNP, and 2 U/L for ALT). We calculated eGFR using

creatinine (eGFR-Cr) and cystatin C (eGFR-CysC) (23), and used the inverse of B2M (1/B2M) in analyses (24), since these measures are better related to renal physiology.

We used a Fine and Gray model (25) for all analyses. We first ran Models 1 and 2, which each included pre-specified variables, and assessed whether Model 2 improved prediction. We then ran Model 3, which included the addition of HbA1c, and tested the improvement in prediction compared to Model 2. Lastly, we evaluated whether the addition of the 12 traditional and nontraditional biomarkers to Model 3 improved prediction. We added each biomarker individually to model 3 and conducted two tests: 1) a Wald test of the coefficient and 2) a comparison of the change in the C-statistic before versus after addition of the biomarker to Model 3. We then selected those biomarkers that had $P < 0.05$ for both tests, and added them to model 3 simultaneously. To determine which biomarkers to keep in the model, we assessed the P-values of each of the biomarkers from the Wald test. We removed the biomarker with the highest P-value if it was above $P = 0.05$, and re-ran the model. We continued this procedure until all biomarkers in the model had $P < 0.05$, at which point we considered this the best and final model (Model 4).

Comparisons between models

We used the following measures of discrimination to assess incremental improvements in prediction between Models 1 and 2, Models 2 and 3, and Models 3 and 4: 1) Harrell's C-statistic, which accounts for censoring in survival analysis; 2) the overall net reclassification improvement (NRI) (continuous and categorical, split at a 25% predicted risk threshold) to quantify upward and downward reclassification, and the event and nonevent NRI separately, to determine the amount and direction of reclassification separately in people who did and did not experience an event; and 3) the relative integrated discrimination improvement (IDI) to assess the improvement in average sensitivity (26–32). For the NRIs and relative IDI, we reported bias-corrected bootstrapped 95% confidence intervals (CIs).

To assess the calibration of each of the final models, we calculated the observed risk (proportion of persons who experienced the event of interest) within each decile of predicted risk. We plotted the median predicted risk against the observed risk within each decile of predicted risk to visually assess their agreement. We excluded persons who had a competing risk event from this assessment of model calibration.

We conducted several secondary analyses. We applied the models we developed to the same population, but extended the follow-up time to a maximum of 20 years, and compared prediction of the 4 models for 20-year risk. We then developed two separate models for prediction of 10-year risk of macrovascular complications (CVD or lower extremity event) and 10-year risk of CKD; and calculated predictive statistics to compare models 1–4 for each of these outcomes.

Results

Of the 654 persons with diagnosed diabetes followed for a maximum of 10 years, 296 had a major complication: 141 CVD events (9 fatal, 132 non-fatal), 152 CKD events (4 ESRD cases), and 3 lower extremity disease hospitalizations. There were 331 participants who did

not experience any event of interest (9 were lost to follow-up) and 27 who died without experiencing any event of interest during follow-up. Compared to persons who did not experience any of the major complications during 10 years of follow-up, those who did were older and had a higher BMI, and a higher proportion were male, had hypercholesterolemia, had hypertension, or were on any glucose-lowering medication (Table 1).

The following three biomarkers were selected and included in Model 4: 1/B2M, eGFR-Cr, and eGFR-CysC. We report the beta coefficients and corresponding subhazard ratios and P-values for each term included in the final models in eTable 1. The baseline 10-year survival ($S_0(t)$, where $t=10$) for Models 1, 2, 3, and 4 were 0.55, 0.65, 0.61, and 0.53, respectively.

Compared to Model 1, the C-statistic was higher for Model 2 ($P=0.032$) and improved further after the inclusion of HbA1c ($P=0.021$); and improved again after the inclusion of 1/B2M, eGFR-Cr, and eGFR-CysC in Model 4 ($P=0.003$) (Table 2). The improvements in the continuous NRI and relative IDI followed patterns similar to those observed for the C-statistic. Both persons who did and did not experience the event of interest were better classified in successive models according to the continuous NRI, and nearly all improvements were statistically significant (Table 2). Improvements in the categorical NRI (using a cut-point of 25%) were driven by correct reclassification of participants who did not experience a major complication (Table 2). Furthermore, all models were well-calibrated (Figure 1).

In a secondary analysis, we compared prediction of the 4 models for 20-year risk of major complications. There were 383 events of interest and 77 competing risk events (deaths) over a maximum of 20 years of follow-up (eTable 2). Improvements in risk prediction between models were similar to those from the 10-year risk prediction equation (eTable 3).

We developed two additional prediction models for macrovascular and microvascular complications, separately. We observed 180 incident macrovascular events (33 competing events). 1/B2M was included in this final model. The addition of each HbA1c and 1/B2M resulted in statistically significant improvements in prediction of macrovascular events (eTables 4 and 5). There were 184 incident CKD events (69 competing events). The model we developed for 10-year risk prediction of CKD included the addition of 1/B2M and eGFR-creatinine. The addition of HbA1c did not statistically significantly improve prediction of CKD (eTables 6 and 7).

Discussion

We successfully constructed a prediction model for 10-year risk of major complications in middle-aged persons with diabetes in the community-based ARIC Study. Including HbA1c, 1/B2M (a novel biomarker of kidney filtration), and eGFR-Cr and eGFR-CysC (biomarkers of kidney function) significantly improved model performance. The final model that included these biomarkers had overall good discrimination ($C\text{-statistic}=0.716$) and was well-calibrated. Furthermore, this model correctly re-classified a substantial number of persons using a risk threshold of 25%, particularly among those who did not experience a major complication in 10 years. Correct reclassification of persons who did not experience an event

during this time period is quite important for identifying those at low long-term risk of multiple major complications.

American Heart Association/American College of Cardiology guidelines recommend that all persons with diabetes between 40 and 75 years of age with LDL-c 70–189 mg/dL be treated with moderate intensity statin therapy for primary prevention of CVD. They also recommend considering higher intensity statin therapy in those at 10-year CVD risk $\geq 7.5\%$ using the 10-year Pooled Cohort Equation for atherosclerotic CVD (33). Our risk prediction equation for a combined endpoint could help identify middle-aged individuals at lowest risk for multiple major complications who might benefit most from a more conservative treatment approach. Given the notable heterogeneity of risk in persons with diabetes (from roughly 10% to 90% 10-year risk of the combined outcome), we may want to think about the potential over- or under-treatment of risk factors. Identification of high-risk persons in whom aggressive treatment may be most appropriate could be a second step in this process, and could include tailoring therapy based on predicted risk of individual outcomes.

Standard approaches to survival analysis (i.e., Kaplan-Meier method and Cox proportional hazards regression) overestimate cumulative incidence when competing risks are present; in particular it is important to treat death as a competing risk rather than a censoring event. These standard approaches may therefore affect the calibration of the risk prediction model, more so even than the discrimination (14,15). The Fine and Gray method that we used in this analysis may more accurately assess both discrimination and calibration. Accurate determination of absolute risk is vital for clinical prognosis and treatment decisions.

Whereas risk prediction equations developed in persons with diabetes may better predict risk than those developed in the general population (34), many of these have performed poorly when applied to external populations of persons with diabetes (35). For instance, the United Kingdom Prospective Diabetes Study (UKPDS) risk engine, a risk prediction tool for CHD and stroke in persons with newly-diagnosed diabetes (36,37), has been shown to greatly overestimate risk by up to five-fold in external populations (38). The risk score we developed had better discrimination and was better calibrated than many risk scores that have been developed for CVD risk prediction in persons with diabetes (39). Most risk scores have been developed in white European populations (40), which may limit their generalizability. Having to use multiple risk scores to predict risk of diabetes complications is burdensome for practitioners (41,42), whereas a risk prediction tool that comprehensively predicts risk of multiple diabetes complications may be convenient for clinical use. Two recent studies developed risk prediction models for multiple endpoints that included micro- and macrovascular complications, and found that combining these outcomes improved classification of persons into low- and high-risk groups (11,13). Although very few risk scores have included HbA1c (43) in their risk prediction algorithm, even fewer have comprehensively evaluated and compared a panel of traditional and nontraditional biomarkers of hyperglycemia, cardiac damage, kidney filtration, liver function, or inflammation (40). The biomarkers evaluated here were selected because they are markers of physiological damage in the pathway to the clinical endpoints that we included, and have been associated with increased risk of complications in persons with diabetes (10,44–52). Our model extends the findings of a previous ARIC study that developed a risk score for 10-

year prediction of a single endpoint of CHD in persons with diabetes. Although HbA1c data were unavailable at the time, they found that adding a panel of novel markers to traditional basic risk factors improved prediction (53).

There are several limitations to note. The baseline for our study was in 1990–1992 and diagnostic and treatment practices for diabetes have changed since then. Compared to current guidelines, diagnostic cut-points were higher in the early to mid-1990s, and persons with diagnosed diabetes may have had more “severe” diabetes than those with diagnosed diabetes today (54). Furthermore, rates of diabetes-related complications, mainly CVD, have decreased in the past twenty years, which could be due to a variety of reasons, including improved care, but also earlier detection of diabetes due to increased screening and lower diagnostic thresholds (55). All of these factors make our analysis conservative with respect to identifying diabetics at low risk for complications. Urine was not collected at this examination, so we were unable to include albuminuria or albumin-creatinine ratio as potential biomarkers, and to determine the importance of these biomarkers in the risk prediction model. Previous studies have shown that albuminuria can significantly improve prediction of cardiovascular disease(9). Retinopathy data were not collected prospectively, and we were therefore unable to include this important complication of diabetes in our analysis. Further, while we were able to distinguish between recently diagnosed diabetes (past 3 years) from longer duration diabetes, we may not have been able to fully adjust for the impact of diabetes duration, since information on age of diagnosis was not collected at the first or second ARIC examinations. Since we restricted analyses to persons with diabetes who had no prevalent micro- or macrovascular disease at baseline, our sample size was rather small, although we were still able to develop risk prediction equations and compare risk prediction statistics with adequate precision. To note, in developing a risk prediction equation using a combined endpoint, the contribution of some predictors may vary for different endpoints. Furthermore, it assumes that the predictors contribute similarly to all outcomes included in the combined endpoint. Indeed, we found that HbA1c improved prediction of macrovascular events but not CKD, whereas eGFR improved prediction of CKD but not macrovascular events. Lastly, the clinical application of the addition of HbA1c to the risk prediction model is readily apparent. We acknowledge that including nontraditional biomarkers that may not be routinely measured in clinical practice in the risk prediction model may have more relevance for research than for clinical practice in the short-term.

Strengths of our study included the rigorous measurement of clinical and biomarker data in a large number of middle-aged persons with diagnosed diabetes in the community at a time when interventions and intensive medical treatment was less frequent. Few, if any, risk prediction models have evaluated such a comprehensive list of traditional and nontraditional variables. In particular, our results extend the current body of knowledge regarding the utility of these nontraditional biomarkers in both clinical and research settings. Long-term active surveillance of ARIC participants enabled us to capture important endpoints over a meaningful period of time.

We demonstrated that the addition of traditional and nontraditional biomarkers to a model that included clinical and demographic information substantially improved the accuracy of a

10-year risk prediction equation for major complications in persons with diabetes. Potential over- or undertreatment of cardiovascular risk factors in persons with diabetes is of current interest, and we reported improved risk reclassification, particularly in persons who did not experience an event. In particular, identifying persons with diabetes at lowest risk for major long-term complications could potentially avoid side effects from over-treatment, emphasize more conservative risk prevention approaches such as diet and lifestyle modification, and improve cost savings. Our research is a first step in focusing efforts on developing a feasible and practical risk score for clinical use in diabetes. Whereas further study of the use of these biomarkers in a clinical setting is necessary, the utility of these biomarkers for use in risk stratification is promising.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Panel A. Model 1 (Self-reported information) **Panel B. Model 2 (+ Clinical variables)**

Panel C. Model 3 (+ HbA1c) **Panel D. Model 4 (+ Additional biomarkers)** **Figure 1. Calibration of 10-year combined risk prediction models**

Observed risk (proportion experiencing the event of interest over 10 years among those at risk) vs. deciles of predicted risk (plotted at the midpoint percentile, 5th to 95th, on the X-axis). The 27 persons who experienced the competing risk event were excluded from this analysis, so the denominator is N=627.

Baseline study population characteristics

Table 1

	Outcome Status Over Follow-up		
	Overall (N=654)	Alive and did not experience an event (N=331)	Experienced an event (N=296)
	Mean (SD) or %	Mean (SD) or %	Mean (SD) or %
Age, years	58.1 (5.7)	57.3 (5.8)	58.9 (5.4)
Male	39%	32%	46%
White	59%	59%	59%
Education			
< HS	32%	30%	35%
HS or college	40%	38%	44%
> college	28%	32%	22%
Current smoking	18%	18%	18%
Current drinking	38%	38%	37%
Physical activity	2.3 (0.7)	2.3 (0.7)	2.2 (0.7)
Family history of CVD [*]	57%	55%	57%
Hypercholesterolemia [†]	30%	25%	35%
Statin use	3%	2%	4%
BMI, kg/m ²	30.7 (5.8)	30.4 (6.1)	31.4 (5.3)
Hypertension [‡]	57%	48%	67%
Glucose-lowering medication			
Insulin	19%	17%	23%
Oral only	48%	43%	54%
None	32%	41%	23%
Recent onset of diabetes	30%	32%	27%
Died without experiencing an event (N=27)			Mean (SD) or %
			60.3 (6.4)
			41%
			67%
			22%
			33%
			44%
			33%
			56%
			2.3 (0.9)
			74%
			26%
			7%
			28.2 (6.1)
			59%
			19%
			48%
			33%
			44%

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HS, high school

^{*} Family history of CVD defined as self-reported parental history of stroke or CHD[†] Hypercholesterolemia was defined as total cholesterol 240 mg/dL or use of cholesterol-lowering medication.[‡] Hypertension was defined as systolic blood pressure 140 mmHg, diastolic blood pressure 90 mmHg, or use of antihypertensive medication.

Table 2

Predictive statistics of 10-year risk prediction models

	Continuous NRI					Categorical NRI (25% predicted risk cut-point)				
	C-statistic (95% CI)	Difference in C- statistic (95% CI)	P-value for difference	Overall NRI (95% CI) *	Event NRI (95% CI) *	Non-event NRI (95% CI) *	Overall NRI (95% CI) *	Event NRI (95% CI) *	Non-event NRI (95% CI) *	Relative IDI (95% CI) *
Model 1 (Self-reported)	0.667 (0.64, 0.70)	--	--	--	--	--	--	--	--	--
Model 2 (+ clinical variables)	0.683 (0.65, 0.71)	0.016 [†] (0.00, 0.03)	0.032 [†]	0.42 [†] (0.26, 0.56)	0.18 [†] (0.07, 0.29)	0.23 [†] (0.13, 0.34)	0.07 [†] (0.03, 0.12)	-0.02 [†] (-0.04, 0.00)	0.09 [†] (0.06, 0.14)	0.28 [†] (0.21, 0.36)
Model 3 (+ HbA1c)	0.694 (0.66, 0.72)	0.011 [‡] (0.00, 0.02)	0.021 [‡]	0.25 [‡] (0.11, 0.40)	-0.02 [‡] (-0.13, 0.10)	0.27 [‡] (0.17, 0.37)	0.02 [‡] (-0.01, 0.06)	0.01 [‡] (-0.01, 0.03)	0.02 [‡] (-0.01, 0.05)	0.08 [‡] (0.04, 0.11)
Model 4 (+ additional biomarkers)	0.716 (0.69, 0.74)	0.022 [§] (0.01, 0.04)	0.003 [§]	0.32 [§] (0.17, 0.47)	0.14 [§] (0.04, 0.25)	0.18 [§] (0.07, 0.29)	0.03 [§] (-0.02, 0.07)	-0.03 [§] (-0.06, -0.01)	0.06 [§] (0.02, 0.09)	0.15 [§] (0.09, 0.22)

* Bias-corrected 95% CIs are reported for NRI and IDI, and were obtained using bootstrap with 1,000 replications

[†] vs. Model 1

[‡] vs. Model 2

[§] vs. Model 3

Model 1 includes age, sex, race, education, smoking status, alcohol consumption, physical activity, family history of CVD, glucose-lowering medication use, antihypertensive medication use, cholesterol-lowering medication use, recent onset of diabetes, BMI, interaction of sex with glucose-lowering medication use, and interaction of race with BMI.

Model 2 additionally includes LDL-c, HDL-c, triglycerides, systolic blood pressure, interaction of sex with triglycerides, and interaction of race with triglycerides.

Model 3 additionally includes HbA1c.

Model 4 additionally includes 1/B2M, eGFR-Cr, and eGFR-CysC.