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ARTICLE

Prediction and classification of cardiovascular disease risk in older adults with diabetes

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Abstract
Aims/hypothesis We sought to derive and validate a cardiovascular disease (CVD) prediction algorithm for older adults with diabetes, and evaluate the incremental benefit of adding novel circulating biomarkers and measures of subclinical atherosclerosis.
Methods As part of the Cardiovascular Health Study (CHS), a population-based cohort of adults aged ≥65 years, we examined the 10 year risk of myocardial infarction, stroke and cardiovascular death in 782 older adults with diabetes, in whom 265 events occurred. We validated predictive models in 843 adults with diabetes, who were followed for 7 years in a second cohort, the Multi-Ethnic Study of Atherosclerosis (MESA); here 71 events occurred.
Results The best fitting standard model included age, smoking, systolic blood pressure, total and HDL-cholesterol, creatinine and the use of glucose-lowering agents; however, this model had a C statistic of 0.64 and poorly classified risk in men. Novel biomarkers did not improve discrimination or classification. The addition of ankle–brachial index, electrocardiographic left ventricular hypertrophy and internal carotid intima–media thickness modestly improved discrimination (C statistic 0.68; $p=0.002$) and classification (net reclassification improvement [NRI] 0.12; $p=0.01$), mainly in those remaining free of CVD. Results were qualitatively similar in the MESA, with a change in C statistic from 0.65 to 0.68 and an NRI of 0.09 upon inclusion of subclinical disease measures.
Conclusions/interpretation Standard clinical risk factors and novel biomarkers poorly discriminate and classify CVD risk in older adults with diabetes. The inclusion of subclinical atherosclerotic measures modestly improves these features, but to develop more robust risk prediction, a better

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understanding of the pathophysiology and determinants of CVD in this patient group is needed.

Keywords Biological markers · Cardiovascular diagnostic techniques · Cardiovascular disease · Cohort · Diabetes · Regression analysis · Risk factors

Abbreviations

ABI	Ankle–brachial index
CHS	Cardiovascular Health Study
CVD	Cardiovascular disease
IMT	Intima–media thickness
MESA	Multi-Ethnic Study of Atherosclerosis
NRI	Net reclassification improvement
nt-BNP	N-terminal pro-B-type natriuretic peptide

Introduction

Diabetes (specifically type 2 diabetes) is a problem of enormous importance in older adults. The incidence and prevalence of diabetes continue to rise throughout older age until late life, resulting in an enormous burden of diabetes in older adults [1]. Diabetes is particularly strongly associated with macrovascular complications in older adults, especially in individuals with subclinical vascular disease [2].

Despite the prevalence and magnitude of cardiovascular disease (CVD) risk associated with diabetes in older adults, the determinants of CVD in this population, as well as the degree to which they can successfully identify persons at greater or lesser risk, have not been well clarified. Indeed, it is clear that in middle-aged adults with diabetes, risk varies substantially as a function of other risk factors [3, 4]. While a number of risk prediction models are available, some of the most commonly used, such as the Framingham Risk Score [5] and the Reynolds Risk Score [6], were specifically tested in adults without diabetes and, like many others, systematically excluded older adults in their derivation.

An important area of controversy in screening for CVD is the role of specialised modalities, such as electrocardiographic stress testing or computed tomography estimates of coronary calcium. Some experts have recommended electrocardiographic stress testing in at least some subgroups of patients with diabetes [7, 8], although a recent randomised trial of adenosine-stress perfusion imaging suggested this was unlikely to improve long-term outcomes [9]. However, given the high risk of CVD that diabetes confers upon older adults in the presence of subclinical atherosclerosis, older adults with diabetes may be an appropriate target for selective screening [2]. The discriminatory power of non-invasive testing has not been formally tested in older adults with diabetes, but the risk associated with subclinical disease could be high enough to improve CVD discrimination and prediction.

To address these questions, we examined the risk of CVD in older adults with diabetes who were enrolled in the Cardiovascular Health Study (CHS) [10]. The CHS is a population-based longitudinal study of CVD and its risk factors in 5,888 community-dwelling older adults from four regions throughout the USA. After deriving a risk score and examining the incremental benefit of adding novel biomarkers and subclinical disease measures, we validated the model in the Multi-Ethnic Study of Atherosclerosis (MESA) [11], a population-based cohort of adults free of CVD.

Methods

Study population and design The CHS is a prospective study of men and women aged 65 years or older, who were recruited from Medicare-eligibility lists in Pittsburgh, PA, Sacramento, CA, Hagerstown, MD, and Forsyth County, NC, all in the USA. Participants were not institutionalised or wheelchair-dependent, did not require a proxy for consent, were not under treatment for cancer at the time of enrolment and were expected to remain in their respective regions for at least 3 years. Between 1989 and 1990, 5,201 participants were recruited and examined (the original cohort); from 1992 to 1993 an additional 687 African-American participants were recruited and examined.

The CHS study design and objectives have been published previously [10]. The baseline examination included standardised medical history questionnaires, physical examination, resting ECG and laboratory examination; these procedures were generally repeated in the original cohort between 1992 and 1993 when the African-American cohort was added. Follow-up contact occurred every 6 months, alternating between telephone calls and clinic visits through to 1999; contact was by phone calls thereafter.

The MESA is a population-based sample of 6,814 men and women, who were free of clinical CVD, aged 45 to 84 years and were recruited from Forsyth County, NC, Northern Manhattan and the Bronx, NY, Baltimore County, MD, St Paul, MN, Chicago, IL, and Los Angeles County, CA, all in the USA. Approximately 38% of the recruited participants are white, 28% African-American, 22% Hispanic and 12% Asian, predominantly of Chinese descent.

As previously described [11], MESA participants underwent an extensive baseline examination between 2000 and 2002, which included questionnaires, physical examination, laboratory examination and several measures of subclinical vascular disease. Subclinical measures overlapping with CHS measures include: carotid ultrasonography, ECG and measurement of the ankle–brachial index (ABI). Participants are contacted every 9 to 12 months throughout the study to assess CVD events.

Neither study performed formal categorisation of type of diabetes, and data on duration of diabetes was not available

for every participant, but it is likely that participants with diabetes in both cohorts had type 2 diabetes.

In both the CHS and the MESA, participants gave written informed consent upon enrolment. The institutional review boards at each field centre and the central data coordinating centre approved the respective studies.

Determination of diabetes In the CHS, fasting glucose was measured between 1989 and 1990, and 1992 and 1993 in all participants who attended the clinic examination. Medication use for diabetes was ascertained yearly with a validated medication inventory [12–14]. Prevalent diabetes was defined at both examinations as fasting blood glucose ≥7.0 mmol/l, non-fasting blood glucose ≥11.1 mmol/l (if participants had failed to fast; $n=6$) or the use of glucose-lowering agents; at baseline in the CHS, only first- and second-generation sulfonylureas and insulin were in use. An identical approach was used in the MESA to identify diabetic participants, who reported their medication use and underwent fasting blood glucose measurement at the baseline examination.

Determination of incident CVD All cases of myocardial infarction, stroke and death in the CHS are adjudicated by central committees. Details of the protocols for adjudication and confirmation of these events, including the algorithms used for classification, have been published [15, 16]. In brief, participants reported incident CVD events at annual clinic visits and interim telephone interviews when questioned about hospitalisations and other acute events. Discharge summaries and diagnoses were obtained for all hospitalisations. For all potential incident events, additional information, such as cardiac enzyme levels, serial ECGs and cranial imaging studies was collected. To be categorised as a stroke, a new neurological deficit had to have persisted for 24 h; for deficits persisting for less than 24 h, a lesion appropriate to the clinical deficit had to have been detected on brain imaging studies. In these analyses, we used a primary composite outcome that included incident myocardial infarction, stroke, and death from coronary or cerebrovascular causes. In sensitivity analyses, we also included adjudicated incident congestive heart failure as an endpoint.

The MESA uses similar procedures, with events adjudicated by a central Morbidity and Mortality Committee. In the MESA, we used a composite endpoint of incident myocardial infarction, stroke and death from CVD in order to achieve comparability with the CHS.

Potential covariates To develop a risk score in the CHS, we used covariates assessed at the time of diabetes ascertainment, whether 1989 to 1990 or 1992 to 1993. Seated systolic and diastolic blood pressure, weight, waist circumference and standing height were measured by trained field centre staff. Smoking was reported in three categories (current, former, never). Laboratory values measured at the University of Vermont Central Laboratory included total, HDL- and LDL-cholesterol, triacylglycerol, glucose, creatinine, C-reactive protein, fibrinogen, albumin, factor VII coagulant activity, leucocyte count, cystatin C, lipoprotein a, potassium and uric acid [17]. N-terminal pro-B-type natriuretic peptide (nt-BNP) and HbA_{1c} were also available in subsets of participants at baseline [18, 19]. Family histories of stroke and heart disease were reported at baseline. We categorised the duration of diabetes in original cohort participants identified in 1992 and 1993 and in all African-American cohort participants as: newly diagnosed, >0 to 3 years, and >3 years.

Subclinical vascular disease measures included electrocardiography, which underwent standardised coding for major and minor electrocardiographic abnormalities as previously described [20, 21]. Carotid ultrasonography was conducted to evaluate intima–media thickness (IMT) and maximum stenosis for the internal and common carotid arteries [22]. The ABI was assessed bilaterally with a standardised protocol [23], using the ratio of the average of two blood pressure measurements in the right arm and the lower of two leg measurements, one in the right and one in the left leg.

To validate the models in the MESA, we adopted a similar approach, using those covariates from the baseline MESA examination that were selected for model inclusion in the CHS derivation cohort.

Statistical analysis In Stata 11 (Stata, College Station, TX, USA), we conducted multivariable Cox proportional hazards analyses to examine the associations between potential covariates and the composite CVD outcome variable in the CHS; we also evaluated a second outcome that added congestive heart failure. Follow-up was ended at 10 years to reduce misclassification in predictor variables and to concord most closely with previous risk stratification models. Because sex did not conform to the proportional hazards assumption, we stratified baseline hazards by sex and tested other predictors for interaction with age, sex and race.

We evaluated potential predictors of CVD with three successive models, retaining significant predictors (at $p<0.05$) at each stage. Our first model examined standard risk factors for CVD that are easily measured in routine clinical settings. These included: age, sex, race, smoking, blood pressure, use of antihypertensive or hypoglycaemic medication, total, HDL- and LDL-cholesterol, BMI, weight, waist circumference, glucose, creatinine, atrial fibrillation, family history of stroke and family history of heart disease. We grouped all hypoglycaemic medications because first- and second-generation sulfonylureas and insulin conferred similar risks in our analyses. The second model examined whether easily collected laboratory data would improve the

baseline model; these values included: C-reactive protein, fibrinogen, albumin, factor VIIc, leucocyte count, cystatin C, potassium [24], uric acid, lipoprotein (a) and triacylglycerol. Finally, we examined a third model that included possible measures of subclinical vascular disease, such as: major and minor electrocardiographic abnormalities, IMT and stenoses from carotid ultrasound, and ABI. Successive models were nested (i.e. additional predictors added to previous ones without replacement) to facilitate formal comparison.

Missing data at baseline in the CHS (other than for diabetes or CVD) were imputed as previously reported [25]. All continuous covariates were explored with splines, quintiles, standard cutpoints (e.g. BMI categories for overweight and obesity) and $\log_e$ transformation (where skewed) to ascertain optimal forms of these variables. Smoothed plots indicated that a threshold in creatinine above 110.5 μmol/l was the best model form for this variable; this cutpoint was previously identified as a risk factor for stroke in the full CHS population [26]. We also found that a small incremental risk was associated with systolic blood pressure above 160 mmHg, ABI below 1 or internal carotid IMT above 3 mm; hence these variables were Winsorised at those cutpoints.

We examined several features of the three successive CHS models. First, we present hazard ratios for each of the included covariates. Second, we examined receiver-operating characteristic curves and C statistics as measures of discrimination, using Harrell's *c* for right-censored data [27]. Third, we present Bayes' and Akaike's information criteria and the Hosmer–Lemeshow test as measures of model fit. Fourth, we visually examined the predicted and observed cumulative incidence curves separately, in tertiles of predicted risk in men and women. To generate predicted curves, we first categorised individuals into tertiles on the basis of predicted risk from the basic model; we then computed the average value of covariates within each tertile; and finally we used those values, along with the original regression coefficients and baseline hazard function from the basic model [28]. The observed curves were produced using the Kaplan–Meier method. Finally, we calculated the net reclassification improvement (NRI), which evaluates the number of individuals with and without events who are recategorised into lower or higher risk categories as new covariates are included [29]. Because no standard risk thresholds exist in this older population of people with diabetes, we tested models of 10 year cumulative incidence with two cutpoints at 30% and 45% (approximately tertiles).

We validated the results in the MESA in two steps, using 7 years of follow-up, the longest currently available. First, to evaluate whether the strengths of the associations identified were similar in the MESA and the CHS, the coefficients (i.e. hazard ratios) for all variables chosen from each of the three models in the CHS were refitted to the MESA population; we excluded five MESA participants with missing data on some variables in the base model (mainly total cholesterol), none of whom sustained an event. Second, we used the coefficients from the CHS models based on 7 years of follow-up and recalibrated them to the baseline survival of the MESA, in order to perform model tests similar to those conducted in the CHS, including visual examination of the observed and predicted risk, and tests of incremental change in C statistics and NRI (using cutpoints of 5% and 10%, also approximately tertiles) across the three models.

Results

Derivation in the CHS We identified 782 older adults who had diabetes and were free of prevalent CVD, congestive heart failure and atrial fibrillation at the 1989–1990 and 1992–1993 baseline examinations. The characteristics of these 426 women and 356 men are shown in Table 1.

During follow-up, 131 incident cases of CVD occurred among women and 134 cases among men. The estimated 10 year cumulative incidence of CVD reached 35% in women and exceeded 40% in men (data not shown). The most common first CVD event overall was stroke, accounting for 60 cases in women (plus two others with concurrent myocardial infarction) and 41 cases in men (plus seven others with concurrent myocardial infarction).

Table 2 shows the results of our three successive models. The final basic model included standard cardiovascular risk factors such as smoking, lipids and systolic blood pressure, along with the prescription of glucose-lowering medication and kidney function. This model performed modestly overall, but less well in men, with C statistics of 0.67 in women and 0.60 in men; the observed risk was similar in men in the 2nd and 3rd tertiles of predicted risk (electronic supplementary material [ESM] Fig. 1b).

We next examined a model that included novel circulating biomarkers representing a wide variety of potential pathways (C-reactive protein, fibrinogen, albumin, factor VIIc, leucocyte count, cystatin C, potassium [24], uric acid, lipoprotein a and triacylglycerol). Of these, only C-reactive protein was associated with risk when added to the basic model, but did not improve discrimination (Table 2) or reclassification (NRI 0.02, $p=0.44$).

Our final model identified ABI, internal carotid wall thickness and electrocardiographic left ventricular hypertrophy as being additionally associated with risk of CVD. This model demonstrated a larger gain in indices of model fit and discrimination, with a significant increase in the C statistic ($p=0.002$). The increase was particularly marked in men (C statistic 0.68 in women, 0.67 in men), although the overall C statistic remained below 0.7.

Table 3 shows the results for net reclassification comparing the basic model with the one that adds subclinical

Table 1 Baseline characteristics of CHS and MESA participants who had diabetes and were free of CVD

Characteristic	CHS		MESA	
	Women	Men	Women	Men
n	426	356	399	444
Age (years)	72.6 (5.6)	73.0 (5.3)	65.0 (9.5)	64.6 (9.4)
Race				
White	307 (72.1)	289 (81.2)	62 (15.5)	95 (21.4)
Black	115 (27.0)	64 (18.0)	162 (40.6)	163 (36.7)
Chinese-American	0	0	50 (12.5)	53 (11.9)
Hispanic	0	0	125 (31.3)	133 (30.0)
Current smoking	48 (11.3)	33 (9.3)	39 (9.8)	71 (16.0)
Systolic blood pressure (mmHg)	141 (21)	140 (23)	135 (23)	131 (21)
Diastolic blood pressure (mmHg)	70 (12)	73 (12)	69 (10)	75 (10)
Use of antihypertensive medications	269 (63.1)	188 (52.8)	271 (67.9)	267 (60.1)
Weight (Kg)	74.8 (15.0)	84.4 (13.6)	79.4 (19.2)	88.0 (17.2)
Waist circumference (cm)	101 (14)	102 (11)	106 (16)	104 (13)
BMI (kg/m^2)	29.5 (5.6)	28.0 (4.1)	31.6 (6.6)	29.6 (4.8)
Total cholesterol (mmol/l)	5.69 (1.11)	5.05 (0.98)	5.05 (0.99)	4.72 (1.04)
LDL-cholesterol (mmol/l)	3.50 (1.03)	3.05 (0.88)	2.97 (0.88)	2.83 (0.86)
HDL-cholesterol (mmol/l)	1.35 (0.34)	1.15 (0.30)	1.30 (0.34)	1.09 (0.28)
Triacylglycerol (mmol/l)	1.97 (1.23)	1.94 (1.20)	1.77 (1.32)	1.90 (1.81)
Fasting glucose (mmol/l)	9.30 (3.01)	9.14 (2.91)	8.67 (2.92)	9.00 (3.43)
Use of oral hypoglycaemic agents	156 (36.6)	135 (37.9)	288 (72.2)	293 (66.0)
Use of insulin	48 (11.3)	44 (12.4)	58 (14.5)	58 (13.1)
Creatinine (μmol/l)	79.8 (24.1)	104.2 (29.3)	75.3 (31.3)	97.3 (59.7)
C-reactive protein (nmol/l)	40.4 (107)	28.7 (114)	30.3 (64.3)	18.0 (50.6)
ECG left ventricular hypertrophy	22 (5.2)	11 (3.1)	3 (0.7)	12 (2.7)
ABI	1.04 (0.18)	1.07 (0.21)	1.06 (0.15)	1.12 (0.15)
Common carotid IMT (mm)	1.07 (0.21)	1.17 (0.25)	0.90 (0.19)	0.97 (0.19)
Internal carotid IMT (mm)	1.40 (0.53)	1.62 (0.63)	1.21 (0.68)	1.32 (0.71)

Values are *n* (%) for categorical variables and mean (SD) for continuous variables, except C-reactive protein (geometric mean [SD])

disease measures, using three categories of risk. There was a significant improvement in classification, although this was driven primarily by downward classification of adults who did not experience events.

We performed two additional sensitivity analyses. First, we evaluated these three models with a composite outcome that further included congestive heart failure, resulting in 354 events. The overall performance and incremental gain from the addition of subclinical disease measures were very similar, with C statistics of 0.64, 0.65 and 0.68, and Hosmer–Lemeshow *p* values of $p=0.93$, $p=0.07$ and $p=0.35$, respectively, across the three models. Interestingly, HDL-cholesterol was significantly inversely associated with risk in this model, but not in the original model (hazard ratio per mmol/l 0.63; 95% CI 0.44, 0.90). Second, we tested the addition of nt-BNP in the subset of 723 participants for whom this measure was available, reducing the events from 265 to 231. Although nt-BNP was significantly associated with risk in the model that included novel biomarkers (hazard ratio for a 1-unit increase in $\log_e$ [nt-BNP] 1.16; 95% CI 1.01, 1.32), it only increased the C statistic from 0.64 to 0.65. Moreover, nt-BNP was not significantly associated with risk in the model that included subclinical disease measures. In similar analyses, neither HbA_{1c} (hazard ratio per percentage point 1.06; 95% CI 0.97, 1.17), nor categorical duration of diabetes ($p=0.55$) was associated with risk.

Validation in the MESA The characteristics of MESA participants are shown in Table 1. Among the 843 diabetic participants at baseline, 71 CVD events occurred during 7 years of follow-up.

Table 4 shows the associations between variables selected in the CHS refit and the risk of incident CVD in the MESA. Hazard ratios were in the same direction and of comparable magnitudes in the two studies, with the exception of smoking, which, surprisingly, was not associated with risk in the MESA. Only 15 MESA participants had

Table 2 Hazard ratios and 95% CIs for 10 year risk of cardiovascular events in 782 adults from the CHS who had diabetes

Final model	Basic model	+Biomarkers	+Subclinical measures
Age (years)	1.05 (1.03, 1.08)	1.06 (1.03, 1.08)	1.03 (1.01, 1.06)
Former smoker	1.29 (0.98, 1.70)	1.25 (0.95, 1.64)	1.10 (0.83, 1.46)
Current smoker	1.64 (1.08, 2.50)	1.52 (0.99, 2.32)	1.19 (0.77, 1.84)
Systolic BP per 10 mmHg up to 160	1.15 (1.07, 1.24)	1.15 (1.07, 1.24)	1.11 (1.03, 1.20)
Total cholesterol per mmol/l	1.17 (1.05, 1.31)	1.18 (1.05, 1.33)	1.16 (1.03, 1.31)
HDL-cholesterol per mmol/l	0.79 (0.53, 1.18)	0.82 (0.54, 1.23)	0.86 (0.56, 1.30)
Creatinine >110.5 μmol/l	1.43 (1.05, 1.96)	1.36 (1.00, 1.86)	1.31 (0.96, 1.78)
Oral hypoglycaemic agent or insulin use	1.71 (1.33, 2.19)	1.73 (1.35, 2.22)	1.57 (1.21, 2.03)
CRP per 10 nmol/l up to 190 nmol/l		1.03 (1.01, 1.06)	1.03 (1.00, 1.05)
ABI <1			1.52 (1.16, 1.99)
ECG left ventricular hypertrophy			1.78 (1.08, 2.95)
Internal carotid IMT per mm up to 3			1.66 (1.35, 2.04)
Summary measures			
Akaike's information criterion	2934	2930	2898
Bayes' information criterion	2971	2972	2954
Harrell's C statistic	0.64	0.64	0.68
Hosmer–Lemeshow *p* value	0.25	0.87	0.65

CRP, C-reactive protein

electrocardiographic evidence of left ventricular hypertrophy, resulting in a significant hazard ratio but a markedly wide CI for that risk factor. Because duration of diabetes was not available in all CHS participants, we examined its inclusion in this model in MESA, where it was completely unassociated with risk (hazard ratio per year 1.01, 95% CI 0.98, 1.04; $p=0.65$).

In models recalibrated to the MESA, the C statistics were 0.65 for the basic model, 0.66 with inclusion of C-reactive protein and 0.68 with inclusion of subclinical disease measures. The gain in C statistic from models 1 to 3, although qualitatively similar to that in the CHS, was not significant ($p=0.25$). As in the CHS, the gain in model 3 occurred almost entirely in men (data not shown). A comparison of the observed and predicted cumulative incidence estimates suggested that the best calibration occurred in participants in the highest risk tertile in each of the sexes (ESM Fig. 1).

The total NRI comparing the basic model with that with subclinical disease measures was qualitatively similar to the CHS, but not significant (NRI 0.09; $p=0.25$). However, the NRI for individuals who remained free of CVD was significant at 0.19 ($p<0.001$), again demonstrating an improved identification of truly low-risk patients with the addition of measures of subclinical atherosclerosis.

Discussion

In this prospective cohort study of 782 older adults with diabetes, in which 265 cases of CVD occurred, standard

Table 3 Reclassification of CHS participants with or without CVD events among three risk groups when changing from standard Model 1 to Model 3, which adds measures of subclinical vascular disease

		Model 3 predicted risk			
		<0.30	0.30–0.44	≥0.45	Total
Participants with CVD events					
Model 1 predicted risk	<0.30	35	9	5	49
	0.30–0.44	21	36	40	97
	≥0.45	1	21	97	119
	Total	57	66	142	265
Participants without CVD events					
Model 1 predicted risk	<0.30	174	22	6	202
	0.30–0.44	70	85	40	195
	≥0.45	5	31	84	120
	Total	249	138	130	517

The NRI values calculated from this table were 0.07 for non-events ($p=0.004$), 0.04 for events ($p=0.26$) and 0.12 overall ($p=0.01$)

Table 4 Hazard ratios and 95% CIs for 7 year risk of cardiovascular events in 843 adults from the MESA who had diabetes

Final model	Basic model	+Biomarkers	+Subclinical measures
Age (years)	1.03 (1.00, 1.06)	1.04 (1.01, 1.07)	1.02 (0.99, 1.05)
Former smoker	1.24 (0.74, 2.07)	1.19 (0.71, 2.01)	1.21 (0.70, 2.10)
Current smoker	1.05 (0.45, 2.43)	1.00 (0.43, 2.33)	1.00 (0.42, 2.38)
Systolic BP per 10 mmHg up to 160	1.15 (1.00, 1.31)	1.14 (1.00, 1.30)	1.12 (0.97, 1.29)
Total cholesterol per mmol/l	1.16 (0.94, 1.44)	1.16 (0.93, 1.44)	1.11 (0.88, 1.40)
HDL-cholesterol per mmol/l	0.48 (0.21, 1.08)	0.53 (0.23, 1.19)	0.52 (0.22, 1.20)
Creatinine >110.5 μmol/l	2.15 (1.20, 3.86)	2.07 (1.15, 3.73)	1.76 (0.92, 3.39)
Oral hypoglycaemic agent or insulin use	1.89 (0.95, 3.76)	1.91 (0.96, 3.80)	1.74 (0.87, 3.48)
CRP per 10 nmol/l up to 190 nmol/l		1.03 (0.98, 1.09)	1.01 (0.95, 1.07)
ABI <1			1.88 (1.03, 3.43)
ECG left ventricular hypertrophy			5.14 (1.88, 14.1)
Internal carotid IMT per 1 mm up to 3			1.10 (0.76, 1.60)

CRP, C-reactive protein

clinical measures modestly discriminated or classified CVD risk over a 10 year follow-up period. The addition of novel circulating CVD risk factors did not improve this finding. Adding measures of subclinical atherosclerosis improved discrimination and risk classification to a modest, but significant degree, predominantly by correctly classifying individuals without subclinical CVD in lower risk categories. These findings were qualitatively similar in the MESA, a smaller and younger, but independent multi-ethnic cohort study.

Our first and second models, which incorporated standard clinical risk factors and less commonly used, but still readily available laboratory tests, share many features with existing risk scores. Classic risk factors, such as age, sex, smoking, blood pressure and lipids were all significantly associated with risk of CVD in our initial model, as they are in most traditional risk scores. Likewise, the inflammatory marker C-reactive protein entered the second model, as it did in the Reynolds Risk Score [6], but provided no gain in discrimination. Moreover, our finding that subclinical atherosclerosis significantly improves classification echoes recent findings using coronary artery calcification in the full cohort from MESA [30, 31] and internal carotid IMT in the full Framingham Offspring Study [32].

Because standard risk scores seem to poorly predict CVD risk in adults with diabetes [33, 34], similar efforts have been made to develop new CVD risk scores specific to this patient group [3, 35–38]; these efforts have generally focused on younger cohorts with fewer CVD events and drawn, in some cases, on clinical trial populations of uncertain generalisability. Our results again share many similarities with these efforts, but to our knowledge, none have independently tested their derived models in an independent population with success; moreover, none have gained widespread use in clinical practice to date. In an effort to rectify this, we focused specifically on risk factors and subclinical disease measures that would be generally available in a range of medical settings and hence could be readily applied with little modification.

The performance of our models was mixed when compared with studies in general populations. Thus while our C statistics did not reach 0.70 even with two measures of subclinical atherosclerosis, the full (i.e. non-diabetic) MESA cohort reported C statistics of 0.79 to 0.88 upon inclusion of coronary artery calcium score [31]. Later follow-up among non-diabetic members of the MESA cohort similarly found that the inclusion of coronary artery calcium score improved the C statistic from 0.76 to 0.81 ($p<0.001$) [30]. As a result, our results do not clearly support the introduction of any of our models for risk prediction into clinical practice among older diabetic adults. Rather, there remains much room for improvement in understanding the disease pathways underlying CVD risk in older adults with diabetes.

At the same time, our results suggest that the measurement of subclinical vascular disease significantly improves discrimination and classification in older adults with diabetes, and may eventually become relevant to their clinical care, even if we cannot recommend so now. Similar methods, such as routine myocardial perfusion imaging [9], have not been shown to improve prognosis in adults with type 2 diabetes. Nonetheless, we confirmed in the CHS and the MESA that measurement of subclinical vascular disease helps to identify a subset of adults with diabetes who are at low absolute CVD risk, a finding first suggested in the CHS over a decade ago [2]. Given our results, we suggest further evaluation of the cost-effectiveness of simple measures such as ABI and electrocardiography in older adults (and especially men) with diabetes, with a view to targeting effective but expensive drugs to those at highest risk.

Our results highlight a distinctive and potentially important feature of risk prediction and classification in older adults with diabetes. Previous risk scores have variably targeted major coronary events [5] or CVD more generally

[39, 40]. Because stroke was the single most common major CVD endpoint in the CHS, and because the addition of congestive heart failure identified ~90 additional events, both represent important and prevalent outcomes that should be included in studies with appropriately adjudicated cases.

Our study has some specific limitations. Thus although we included nearly 800 older adults with well-characterised risk profiles and a large number of events, the power to detect the risk associated with some predictors (e.g. left ventricular hypertrophy) or interactions was low, and the number of events in the MESA was quite limited. As a result, it is possible that model fit could be improved in future studies with larger numbers of events.

The CHS has information on a wealth of CVD risk factors, but, like any study, it did not measure some potentially interesting factors. For example, HbA_{1c} was not measured in all CHS participants, nor were erythrocytes stored, although a substudy at the North Carolina site found that HbA_{1c} was completely unrelated to cardiovascular events [19], a finding that we replicated. Microalbuminuria was not assessed in the CHS until 1996–1997, hence its contribution will need to be defined with further follow-up; initial evidence in the CHS suggests it may be useful [41]. Likewise, it is possible that newer measures of subclinical atherosclerosis not included in the CHS, such as cardiac computed tomography or magnetic resonance imaging, might contribute to risk identification to a greater degree than ABI and carotid ultrasonography.

We measured these biomarkers at a single point in time and evaluated their association with risk over 10 years, similarly to what has been done in other risk prediction algorithms. Although a few of these measures were assessed on more than one occasion during follow-up in the CHS, the majority have not, and hence repeated measurements might reduce misclassification and improve classification to some degree.

The CHS and MESA share many features, but also differ in important ways, most notably in the age of participants, duration of follow-up and the cumulative incidence of CVD. In addition, a greater proportion of participants in the MESA were receiving hypoglycaemic medication, a fact related to the larger number of individuals with previously undiagnosed diabetes in the CHS and to concurrent secular trends in medication use in the USA [42]. Thus, the MESA represents a useful, but imperfect population for validation, and caution is necessary when comparing values of the NRI and other tests of the risk prediction model across cohorts [43], although the similarity in the pattern of findings across the two cohorts is reassuring. In summary, standard CVD risk factors and even novel biomarkers are modestly successful at predicting cardiovascular risk in older adults with diabetes. The addition of subclinical measures of atherosclerosis has the potential to improve this problem, but our results emphasise that we have a long way to go in identifying individuals at highest risk in this vulnerable group. Further research to more clearly define the pathogenesis of CVD in older adults with diabetes and to identify new markers of risk remains an important priority against the backdrop of a worldwide diabetes epidemic and the concomitant ageing of the population in virtually all developed nations.

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