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Development of a New Diabetes Risk Prediction Tool for Incident Coronary Heart Disease Events: The Multi-Ethnic Study of Atherosclerosis and the Heinz Nixdorf Recall Study

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Abstract

Objective—We develop a new diabetes CHD risk estimator using traditional risk factors plus coronary artery calcium (CAC), ankle-brachial index (ABI), high sensitivity C-reactive protein, family history of CHD, and carotid intima-media thickness and compared it with United Kingdom

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Prospective Diabetes study (UKPDS), Framingham risk and the NCEP/ATP III risk scores in type 2 diabetes mellitus (T2DM).

Methods and Results—We combined data from T2DM without clinical CVD in the Multi-Ethnic Study of Atherosclerosis (MESA) and the Heinz Nixdorf Recall Study (N=1343). After a mean follow-up of 8.5 years, 85(6.3%) participants had incident CHD. Among the novel risk markers, CAC best predicted CHD independent of the FRS [hazard ratio: HR (95% CI): log (CAC +25):1.69(1.45 – 1.97), p<0.0001; CAC categories: CAC ≤ 25 as reference, >25 and ≤ 125:2.29(0.87 – 5.95), >125 and ≤ 400: 3.87(1.57– 9.57), >400: 5.97(2.57– 13.84), respectively). The MESA-HNR diabetes CHD risk score has better accuracy for the main outcome versus the FRS or UKPDS [area under curve (AUC) of 0.76 vs. 0.70 and 0.69, respectively; all p<0.05]. The MESA-HNR risk score improved risk classification versus the FRS (net reclassification improvement (NRI) = 0.19 and integrated discrimination improvement (IDI) =0.046, p<0.05) and UKPDS (NRI=0.215 and IDI = 0.046, p<0.05). Compared with the ATP III guidelines, the MESA-HNR score has an NRI of 0.74 for the main outcome.

Conclusions—This new CHD risk estimator has better discriminative ability for incident CHD than the FRS, UKPDS, and the ATP III/NCEP recommendations in a multi-ethnic cohort with T2DM.

Keywords

Diabetes mellitus; coronary calcium score; risk assessment; coronary heart disease

Introduction

Cardiovascular disease (CVD) preventive strategies are commonly based on an assessment of the individual patient's risk using global risk scoring tools (1, 2). However, patients with type 2 diabetes mellitus (T2DM), are typically excluded from global risk scoring tools because they are considered “coronary heart disease risk equivalents” and recommended to receive the same preventive interventions as patients with known coronary heart disease (3, 4).

For example, the Adult Treatment Panel (ATP) III Guidelines exclude patients with T2DM from the risk estimation tool because they assume that diabetes automatically confers a high risk for future cardiovascular events. However, some existing risk estimation tools have attempted to stratify patients with T2DM more precisely (5, 6). Specifically, one version of the Framingham risk score (FRS) and the United Kingdom Prospective Diabetes Study (UKPDS) score classify patients with T2DM as being at low, intermediate, and high risk of CVD based on calculated scores (2,3). It is unclear how often these alternative risk estimation tools are used in clinical practice and whether they achieve reasonable discrimination and calibration for risk estimation in patients with T2DM from other race/ethnic backgrounds.

Recently, cardiovascular risk estimation tools have begun to include measures of subclinical atherosclerosis and newer markers of risk to improve risk discrimination and classification (7–9). In the Multi-Ethnic Study of Atherosclerosis (MESA) (7), the Rotterdam Study (8),

and the Heinz Nixdorf Recall (HNR) study (9), the strongest measures of risk were coronary artery calcium (CAC) score and brain natriuretic peptide (BNP), two "novel" markers excluded from the Framingham Risk Score and the UKPDS. It therefore seems reasonable to explore whether some newer markers of risk could better discriminate risk among patients with T2DM.

MESA (United States) and the HNR Study (Germany) are prospective observational studies that included patients with T2DM in their enrollment and follow-up. The goals of this report are to (a) describe a newly developed "MESA-HNR" CHD risk estimator for patients with T2DM, based on a broad array of conventional and novel clinical risk factors and biomarkers, and (b) compare its prediction performance with the FRS, UKPDS and ATP III/NCEP recommendations (1–3).

Methods

Study Population and Data Collection

The MESA study design was published previously (10). In brief, MESA is a cohort study begun in July 2000 to investigate the prevalence, correlates, and progression of subclinical CVD in individuals without known CVD at baseline. The cohort includes 6814 women and men aged 45–84 years old recruited from 6 US communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan, New York; and St. Paul, Minnesota). In MESA, 38% of participants were white (n = 2624), 28% black (n = 1895), 22% Hispanic (n = 1492) and 12% Chinese (n = 803). Individuals with a history of physician-diagnosed myocardial infarction, angina, heart failure, stroke or transient ischemic attack, or who had undergone an invasive procedure for CVD (coronary artery bypass graft, angioplasty, valve replacement, pacemaker placement or other vascular surgeries) were excluded. However, patients with diabetes mellitus were included if they met other enrollment criteria.

The HNR recruited a total of 4814 Caucasians between 45 and 75 years of age from three neighboring cities in the metropolitan Ruhr area of Germany between 2000 and 2003 in a single center with a response rate of 55.8%(11). Participants were a random sample derived from mandatory citizen registries and provided to the study center. The study was certified according to DIN EN ISO 9001:2000, and re-certified in 2006. Both studies were approved by the appropriate Institutional Review Boards of each study site, and written informed consent was obtained from all participants.

Clinical Data

Demographics, medical history, anthropometric and laboratory data for this analysis were obtained in each study during the baseline examination. Body mass index (BMI; kg/m^2) was computed based on direct measurements of height and weight. All medication utilization was based on participants' self-report. Standard enzymatic methods were used to measure total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides. Low-density lipoprotein cholesterol (LDL-C) was calculated with the Friedewald equation in MESA (12) and measured directly in HNR (14). Blood samples were obtained after a 12 h

fasting in MESA. In HNR, participants were fasting 9.7+4.9 h (median 12 h) before blood sampling. In both studies, blood pressure was measured using an oscillographic method with two different systems (Dynamap, Johnson & Johnson, USA and HEM-705CP, Omron, Hoofddorp, NL). The mean values of the second and third of three measurements taken at least 2 min apart were used. Hypertension was defined in both studies as a blood pressure measurement of 140/90 mmHg or use of antihypertensive medication. In both studies, participants were considered to have diabetes mellitus if they were taking anti-diabetic medication or had a fasting glucose concentration of ≥126 mg/dl. Duration of diabetes was self –reported. Smoking history was categorized as (i) currently smoking, (ii) former, defined as not smoking within the past 30 days in MESA and as stopped smoking (a) within the past year or (b) more than 1 year ago in the HNR, and (iii) never(8,13). The use of lipid-lowering medication was documented. This included HMG CoA reductase inhibitors (`statins'), fibrates, bile acid sequestrants, and nicotinic acid derivatives. High sensitivity C-reactive protein (Hs-CRP) was measured using the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, Illinois). Analytical intra-assay coefficients of variation ranged from 2.3% to 4.4%, and inter-assay coefficients of variation ranged from 2.1% to 5.7% with a detection level of 0.18 mg/L. Family history of CHD was obtained by asking participants whether any member in their immediate family (first-degree relatives: parents, siblings, and children) experienced fatal or nonfatal myocardial infarction.

Ankle-Brachial Index

The protocol and quality control of ankle brachial index (ABI) measurement in both the MESA and HNR studies were previously published (13, 14). Briefly, ABI was measured in supine participants with systolic blood pressures measured in both arms and legs with appropriately sized cuffs. For both legs (when possible), the systolic blood pressure was measured in each posterior tibial and dorsalis pedis artery. All pressures were detected using a continuous-wave Doppler ultrasound probe. The ABI was calculated as the higher systolic blood pressure in the posterior tibial or dorsalis pedis artery divided by the higher of the arm systolic blood pressure values.

Carotid Intima-Media Thickness

The protocol and quality control for carotid intima-media thickness (CIMT) measurement in the MESA and HNR studies were previously published (15, 16). CIMT images were obtained using B-mode sonography at the right and left common carotid artery and measured 1 cm starting from the bulb. The mean of maximum intima-media thickness of the common carotid artery was used. The protocols for CIMT measurement were similar in both MESA and the HNR studies.

Coronary Artery Calcium (CAC) Score by Computed Tomography (CT)

Details of the MESA and HNR CT scanning and interpretation methods have been reported by Carr et al (17) and Schmermund et al (18). Briefly, for MESA sites, scanning centers assessed CAC by chest CT with either a cardiac-gated electron-beam CT scanner (Chicago, Los Angeles, and New York) or a multidetector CT system (Baltimore, Forsyth County, and St. Paul). Certified technologists scanned all participants twice over phantoms of known physical calcium concentration. A radiologist or cardiologist read all CT scans at a central

reading center (Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, California). In the HNR study, two radiology departments scanned and analyzed the CAC score in a blinded, independent way (19). In both studies, CAC was defined as a hyper-attenuating focus of at least four contiguous pixels with a CT density of >130 Hounsfield units. The area of each focus was measured and the CAC score was determined using the methods of Agatston et al (20). The total (Agatston) CAC score was computed by summing up the CAC scores of all foci in the epicardial coronary system without phantom adjustment. Agreement with regard to the presence of CAC was high in MESA (k =0.90–0.93) and interclass correlation coefficient for CAC scoring of 0.99. In the HNR study, inter-scan variability was 5–8%, and for inter-institutional readings of the two EBCT centers, a k-value of 0.94 in 250 scans was found (21).

Composite Outcome Definition

For these prediction models, we used “hard coronary heart disease” as the composite endpoint. Hard coronary event was defined as adjudicated fatal or non-fatal myocardial infarction. The adjudication processes for both studies were published previously (8, 18). Other CHD outcomes such as revascularization and angina were excluded from our composite outcome because the two studies used significantly different definitions of angina pectoris and revascularization rates.

Statistical Analysis

Based on the similarity of procedures, data from both cohorts were pooled into a single sample for analysis. Descriptive statistics were provided showing means and standard deviations on all of the candidate predictors of hard coronary heart disease (CHD) events. We then explored whether any candidate novel risk factors (CAC, Hs-CRP, ABI, CIMT, pack-years of smoking, or family history of CHD) were associated with the outcome using a Cox model conditional on the FRS. To improve variable selection, we then used Bayesian model averaging to estimate the posterior probability of a predictor of CHD events being included in a statistical model with the highest likelihood (22, 23). This approach has been used (24, 25) to select the best set of predictors of a cardiovascular outcome when predictors are correlated. Traditionally, a posterior probability of 50% or more is used to determine which variables are included in the statistical model; here, we set a more inclusive threshold of 20% to capture as many potential predictors as possible.

All missing data (<4% of a variable) were handled using multiple imputation methods, because excluding participants with missing data would induce more bias in estimation of risk scores than using an appropriate technique for missing data. Areas under the curve (AUCs) were computed for the FRS, the UKPDS, and the best-fitting model using the HNR-MESA data. The FRS and UKPDS models were refit onto the HNR-MESA data because the raw scores tended to greatly overpredict (more than double) the rate of CHD events in this relatively healthy population. By refitting, the comparison between the prediction rates of FRS and UKPDS scores with a HNR-MESA score is more directly comparable in performance.

The possibility of overfit for this analysis was considered in two separate ways. One approach was to bootstrap the sample 100 times, imputing the missing data for each bootstrap (26). We measured the mean absolute deviation of the bootstrap models fit on the main data sample as being 0.02 AUC. The second approach was to divide the data into training and validation samples. We fit the best model on the training sample and then estimated the AUC on the validation sample.

To fully demonstrate the relative fit of the different models, we computed the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) for the refit FRS, refit UKPDS, and the HNR-MESA model. Because there were very few missing data in the final set of predictors for any model, and it was unclear how to integrate these approaches with multiple imputations, we calculated the NRI and IDI on a complete case sample of the combined data. Finally, as a sensitivity analysis, we computed an alternate HNR-MESA score when CT scans were not available, testing all novel predictors for this model also. Analyses were done using a combination of SAS, STATA, and R with replication of the key parts of the analysis in multiple programming languages.

Results

Out of 1343 MESA and HNR participants with T2DM but without clinical CVD at baseline, 85(6.3%) had hard CHD after an average of 8.5 years of follow-up. Table 1 shows the demographic characteristics, CVD risk factors, and other risk markers in this combined cohort. Most participants were males and were taking antihypertensive medications during the baseline examination. Only 23% of the cohort was taking statins. Supplemental Table 1 shows the predictive value of diabetes-specific markers for hard CHD. After multiple modeling approaches, duration of diabetes and insulin use emerged as independent predictors of incident hard CHD after adjusting for the FRS variables age and sex. Log (CAC+ 25) and ankle-brachial index were independent predictors of incident hard CHD after adjusting the FRS variables in the combined cohort (Table 2).

MESA-HNR Diabetes CHD Risk Score

After Bayesian model averaging (posterior probability of selection cut-off of 20%), age, sex, systolic blood pressure, log (CAC + 25), and duration of diabetes were candidate variables for inclusion into the risk score (Supplemental Table 2). With the exception of Hispanic ethnicity (posterior probability of 40%), all other race/ethnicity had insufficient posterior probabilities for inclusion in our final model. The significant posterior probability for Hispanics was shown in further analysis to be a socioeconomic effect and hence was not included in the final model. The mean absolute deviation of the bootstrap model fit on the main data sample was 0.02 AUC, suggesting that the AUC for our primary model should be 0.74 instead of 0.76. This cross-validation approach estimated the AUC of the final risk model as 0.75. The cross-validation approach estimated the AUC of the final risk model as being 0.01 AUC lower than the estimate on the complete sample.

Neither approach suggested any important level of overfit. That is, both sensitivity analyses suggested degrees of overfit within the 95% confidence intervals of the AUC estimate.

Table 3 shows the discriminative ability of the candidate variables selected using the Bayesian model averaging (as shown in Table 4) and the improvement in discrimination from adding log (CAC +25) to the FRS and the UKPDS for incident hard CHD events. Log (CAC + 25) had better discriminative ability compared with either the refit FRS (AUC of 0.74 vs. 0.70) or the refit UKPDS (AUC of 0.74 vs.0.69). The addition of Log (CAC + 25) to the refit FRS or the refit UKPDS also improved discrimination. A model containing duration of diabetes and Log (CAC +25) had an AUC of 0.75 for incident CHD, whereas a model containing age, sex, systolic blood pressure, duration of diabetes and log (CAC + 25) had an AUC of 0.76.

Comparing MESA-HNR, Refit FRS and UKPDS Models, and ATP III /NCEP

Figure 1 shows ROC curves comparing the discriminative ability of the MESA-HNR diabetes CHD risk score (model B) with the refit models from FRS and UKPDS for incident CHD events in this cohort. The MESA-HNR score had significantly higher discriminative ability compared with either the FRS [AUC (95%CI) 0.76(0.71–0.81) vs. 0.70(0.64–0.75), $P<0.05$] or the UKPDS [AUC (95%CI) 0.76(0.71–0.81)] vs. 0.69(0.63–0.74), $P<0.05$]. The FRS and UKPDS had similar discriminative ability for incident CHD [AUC (95%CI) 0.70(0.64– 0.75) vs. 0.69(0.63–0.74), $P>0.05$]. Log (CAC + 25). Model A [duration of diabetes and log (CAC +25)] and model B [age, sex, systolic blood pressure, duration of diabetes and log (CAC + 25)] had similar discriminative abilities for incident CHD. As shown in supplemental Figure 2, there were no differences in AUC for incident CHD when all the CAC based models are compared.

Tables 4(A and B) show the net reclassification indices when the MESA-HNR diabetes CHD risk score is compared with the refit FRS (Table 4A) and refit UKPDS (Table 4B). The MESA-HNR diabetes risk score (model B) provides an improvement in discrimination over the FRS with an NRI of 0.19 and IDI of 0.046. The MESA-HNR diabetes risk score (model B) also provides an improvement in discrimination over the refit UKPDS with an NRI of 0.22 and IDI of 0.046. The ATP III/NCEP is not a risk estimator and so cannot be used to assess the individual CHD risk for each individual in this study. However, compared with the ATP III/NCEP (assuming all T2DM individuals are at high risk for CHD), the MESA-HNR CHD risk score has an NRI of 0.74.

MESA- HNR Diabetes CHD Risk Score

Supplemental Table 3 show the parameter estimate of variables in the MESA-HNR risk score (model B) for predicting incident CHD events, using a Cox proportional hazard model. Supplemental Table 4 and Table 5 show the 8-year risk estimates and a point-based 8-year risk score developed from this cohort (model B) to assess the CHD risk of individuals with T2DM.

New Pooled Equations (ASCVD risk Estimator)—We also assessed the discriminative ability of the new pooled equations (PCE) for incident atherosclerotic cardiovascular events (ASCVD) defined as a composite of CHD and stroke (excluding TIA's) in this type 2 diabetes cohort (27). The AUC of the PCE for incident ASCVD in this

cohort was 0.637. The MESA –HNR risk score had an NRI of 0.204 when compared with the PCE or ASCVD risk estimator for incident ASCVD events (Supplemental Table 5).

Discussion

The goal of this study is to develop a new diabetes CHD risk estimator with better discriminative ability using a combination of traditional risk factors and novel cardiovascular risk markers in a multi ethnic adult T2DM population. The MESA-HNR diabetes CHD risk score had better discrimination for incident CHD than the FRS, UKPDS, or the ATP III/NCEP recommendation. All three of these well-recognized risk tools (1–3) have shown only modest discriminative abilities for incident coronary heart disease in T2DM populations (28–31). Even though the ATPIII/NCEP classification of all T2DM is supported by studies such as Collaborative Atorvastatin Diabetes Study (CARDS) (32) trial, other studies, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) (33) trial, indicate that classifying all T2DM patients as being at high risk for CVD is not justified. The present study shows that a risk estimator incorporating subclinical measures of atherosclerosis, such as CAC, may help identify which patients with T2DM could benefit from statin therapy to reduce their risk of incident CHD.

The FRS was developed exclusively in Caucasians, and the elevated cardiovascular risk in people with T2DM was not recognized during the development of the FRS (2). The UKPDS (1), a risk assessment tool uniquely developed for T2DM, includes too many variables, making it too cumbersome for routine clinical use. Some have even questioned the relevance of the UKPDS, since the derivative cohort was studied over 30 years ago when most current diabetes therapies were unavailable.

Novel CVD risk markers such as CAC and ABI predicted incident hard CHD independent of the traditional risk factors in the FRS or the UKPDS in our cohort. In addition, a risk estimator incorporating CAC has better discriminative ability compared with the FRS or the UKPDS. Only one case (event) in our cohort was classified as high risk by either the FRS or the UKPDS, compared with 19 cases using the MESA-HNR score. However, even with this improved discriminative ability, 77% of cases (events) would have been misclassified as either intermediate/low risk and these individuals would not have been offered statin therapy. Using the ATP III/NCEP recommendations, all participants in the current study would have been treated with statins, without incurring the cost of a cardiac CT scan or exposure to ionizing radiation. However, using the ATPIII/NCEP guideline would have misclassified all non- cases (93% of the total cohort) as high risk and would have recommended statin therapy for them. A formal cost-effectiveness analysis is needed to definitively investigate the best approach. But given the cost of obtaining CAC; the current cost, pleiotropic effects, and safety profile of statins; and the public health impact of CHD; the ATP III/NCEP recommendation may be the favored approach for CHD risk assessment in patients with T2DM compared with FRS, UKPDS or MESA-HNR diabetes CHD risk score.

Despite the undisputed role of modifiable risk factors such as cigarette smoking and serum lipids in the pathogenesis of atherosclerosis and hence CHD events, their posterior

probability for incident CHD in this T2DM population was insufficient for inclusion in the final risk model. It appears that coronary atherosclerosis burden (such as CAC) may represent an aggregate of the risk associated with these modifiable CV risk factors. Thus irrespective of an individual's risk, smoking cessation should always be recommended. However, recommendations for lipid therapy and the use of aspirin for primary prevention should be based in an individual's global CV risk as suggested by current guidelines (3, 4).

The current study has some limitations. To generate adequate numbers for this analysis, the current cohort combined data from the MESA and HNR studies. Nonetheless, the study design, data collection, the duration of follow-up, and event adjudication process of these 2 studies were very similar. Missing data, although rare, was handled by imputation in these analyses. Sensitivity analysis showed that the imputation had no effect on the point estimates and the associations reported in this study. External validation of this MESA-HNR diabetes CHD risk estimator is still needed before it can applied for CHD risk assessment to the 366 million people worldwide with T2DM.

In conclusion, the MESA-HNR diabetes CHD risk score, which incorporates CAC, had better discriminative ability for incident CHD in T2DM compared with the FRS, UKPDS, or the ATPIII/NCEP risk approach. However, a significant proportion of T2DM participants who had CHD events were misclassified by the MESA-HNR diabetes CHD risk score. This misclassification, coupled with the current cost and safety profile of statins, may make the ATP III/NCEP recommendation a more attractive and cost-effective approach to CHD risk assessment in T2DM. This question requires additional study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Joseph Yeboah Joseph A Delaney, Robin Nance and Raimund Erbel had complete access to the data.

Joseph Yeboah: writing of MESA proposal, acting as the principal investigator, statistical analysis and manuscript preparation

Joseph A Delaney: Statistical analysis and manuscript preparation

Alain Bertoni: critical expertise, data gathering, editing

David Herrington: data gathering, statistical analysis, manuscript preparation and scientific content.

Raimund Erbel: critical expertise, data gathering, manuscript preparation

Mathew Budoff: critical expertise, data gathering, editing

Susanne Moebus: data gathering, manuscript preparation

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Nathan D Wong: data gathering, manuscript preparation

Nils Lehmann: data gathering, critical expertise

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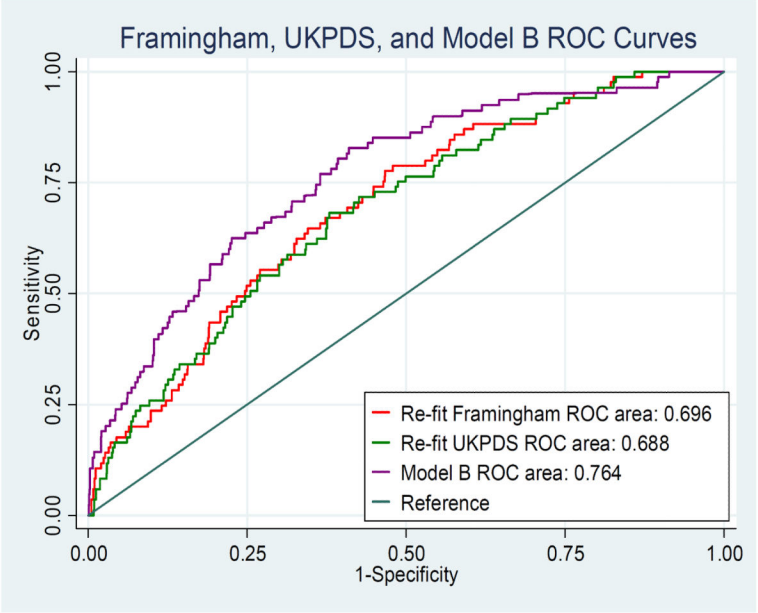

Figure 1.

ROC curves comparing the discriminative ability(AUC) of the Framingham risk score, the United Kingdom Prospective Diabetes Study (UKPDS) score and the HNR-MESA Diabetes CHD score (model B) for incident hard CHD in this cohort.

Table 1

Baseline Characteristics of the study cohorts. Values as mean[standard deviation] or percentage.

Characteristics	Subjects in HNR	Subjects in MESA	All Subjects
Number of Subjects	551	792	1343
Age(years)	61[8]	64[9]	63[9]
Male	61%	53%	56%
Race - Chinese American	0%	12%	7%
African American	0%	38%	22%
Hispanic	0%	30%	18%
Total Cholesterol(mg/dL)	226[39]	189[40]	204[44]
HDL Cholesterol(mg/dL)	52[16]	47[13]	49[14]
LDL Cholesterol(mg/dL)	144[36]	112[34]	125[38]
Triglycerides(mg/dL)	189[152]	160[134]	172[143]
Systolic Blood Pressure(mmHg)	141[22]	133[22]	136[22]
Diastolic Blood Pressure(mmHg)	83[11]	72[10]	77[12]
Baseline glucose (mg/dL)	156[51]	148[54]	151[53]
Current smoker	23%	12%	16%
Pack years of cigarette smoking	32[30]	12[22]	18[26]
Family history	9%	39%	27%
Unknown family history	17%	0%	7%
Coronary Artery Calcium(mean agatston score)	309[664]	247[554]	272[601]
Duration of diabetes (years)	5.4[9.2]	5.6[8.0]	5.5[8.5]
HbA1c (%)	6.6%[1.4]	7.3%[1.7]	7.0%[1.6]
Metformin use	23%	37%	31%
Sulfonylurea use	15%	43%	32%
Insulin use	12%	13%	13%
Glitazone use	6%	10%	9%
Hypertension medication use	54%	63%	59%
Statin use	15%	28%	23%
C-Reactive Protein (mg/L)	4.1[8.0]	4.4[5.8]	4.2[6.8]
Ankle-brachial index	1.1[0.2]	1.1[0.2]	1.1[0.2]
Common Carotid Intima Media Thickness (mm)	0.71[0.13]	0.93[0.19]	0.85[0.20]
Hard Coronary Heart Disease Event	7.4%	5.6%	6.3%

HbA1C: hemoglobin A1C

Table 2

Novel Risk Factors individually modeled and adjusted for Framingham risk score (FRS) in the HNR/MESA diabetes risk group (outcome=hard coronary heart disease (CHD) events)

Parameter	Hazard Ratio	95% Confidence Interval	p-value
Log (CAC +25)	1.69	1.45 to 1.97	<.0001
CAC Categories			
Less than 25	1.00	Reference	
> 25 and ≤ 125	2.29	0.87 to 5.95	0.09
> 125 and ≤ 400	3.87	1.57 to 9.57	0.003
>400	5.97	2.57 to 13.84	<0.0001
C-Reactive Protein (mg/L)	1.02	0.98 to 1.06	0.38
Ankle-Brachial index < 0.90	1.78	1.04 to 3.06	0.04
CCA intimal medial thickness (mm)	2.10	0.74 to 5.97	0.17
Pack-years of smoking (years)	1.00	0.99 to 1.01	0.63
Family History	1.11	0.66 to 1.86	0.69
Unknown Family History	1.49	0.71 to 3.14	0.29

CAC: coronary artery calcium score; CCA: common carotid artery

Table 3

Discrimination, as measured by area under the receiver operating characteristic (ROC) curves for various different predictive models for incident coronary heart disease event in T2DM

		AUC
	Model:	**Imputation**
A	Duration of diabetes, log(CAC+25)	0.7547
B	Age, sex, systolic bp, duration of diabetes, log(CAC+25)	0.7637
C	Framingham risk score (as reported)	0.6797
D	Framingham risk score refit*	0.6964
E	Framingham score refit* plus log(CAC+25)	0.7575
F	UKPDS score refit**	0.6878
G	UKPDS score refit** plus log(CAC+25)	0.7575
H	Log(CAC+25)	0.7412

AUC = Area under the curve, UKPDS = United Kingdom Prospective Diabetes Study, CAC = coronary artery calcium, bp= blood pressure,

Table 4a

Net Reclassmcation Improvement (NRI) table comparing the MESA-HNR score versus the Framingham Risk Score for incident coronary heart disease events.

Risk in MESA-HNR Score						
Risk in Refit FRS Score	**<6%**	**6–20%**	**≥20%**	**Overall**	**Reclassified as Higher Risk**	**Reclassified as Lower Risk**
<6%						
No. of participants	623	131	12	766		
No. of events	16	7	2	25	9	NA
No. of non-events	607	124	10	741	134	NA
6–20%						
No. of participants	272	241	54	567		
No. of events	15	28	16	59	16	15
No. of non-events	257	213	38	508	38	257
≥20%						
No. of participants	1	5	4	10		
No. of events	0	0	1	1	NA	0
No. of non-events	1	5	3	9	NA	6
Overall						
No. of participants	896	377	70	1343		
No. of events	31	35	19	85	25	15
No. of non-events	865	342	51	1258	172	263

n	NRI*	Standard Error NRI	P-value NRI
1343	0.190	0.076	0.013

*NRI= Net Reclassification Index

Table 4b

Net Reclassification Improvement (NRI) table comparing the MESA-HNR score versus the United Kingdom Prospective Diabetes Study (UKPDS) score for incident coronary heart disease events.

Risk in MESA-HNR Score						
Risk in Refit UKPDS Score	**<6%**	**6–20%**	**≥20%**	**Overall**	**Reclassified as Higher Risk**	**Reclassified as Lower Risk**
<6%						
No. of participants	629	126	15	770		
No. of events	18	7	2	27	9	NA
No. of non-events	611	119	13	743	132	NA
6–20%						
No. of participants	267	245	51	563		
No. of events	13	28	16	57	16	13
No. of non-events	254	217	35	506	35	254
≥20%						
No. of participants	0	6	4	10		
No. of events	0	0	1	1	NA	0
No. of non-events	0	6	3	9	NA	6
Overall						
No. of participants	896	377	70	1343		
No. of events	31	35	19	85	25	13
No. of non-events	865	342	51	1258	167	260

n	NRI*	Standard Error NRI	P-value NRI
1343	0.215	0.074	0.004

*NRI= Net Reclassification Index

Table 5

Points-based 8 year MESA-HNR diabetes coronary heart disease risk score.

8 Year Risk: Add points from the 5 categories	
Age:	
>=65 years	+4 points
Sex:	
Male	+4 points
Systolic bp:	
>=135	+2 points
Duration of Diabetes:	
>0 years	+3 points
CAC:	
<25	−2 points
25 to <125	0 points
125 to <400	+4 points
>=400	+16 points

*less than 1 point indicates less than 1% risk, otherwise 1 point is ~ 1 % risk of 8 year coronary heart disease event