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Cardiovascular Disease Risk Assessment in Patients with Diabetes Mellitus

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Cardiovascular Disease Risk Assessment in Patients with Diabetes Mellitus

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ABSTRACT OF THE DISSERTATION

Cardiovascular Disease Risk Assessment in Patients with Diabetes Mellitus

by

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University of California, Los Angeles, 2020

Professor Nathan D. Wong, Co-Chair

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Patients with diabetes mellitus (DM) were generally found to have two to four times of the risk to develop cardiovascular events compared to those without DM. Accurate cardiovascular disease (CVD) risk assessment is critical for patients with DM to guide the preventive therapy. Approaches of evaluating the CVD risk for those with DM included the historical "CVD risk equivalent" approach and the current risk score approach. Some risk reclassification tools are recommended when the treatment decisions are not clear based on risk score assessment. The current study investigated all three approaches in CVD risk assessment among patients with DM.

We identified the predictors of CVD risk equivalent and redefined the CVD risk equivalent conditions in DM patients in a pooled cohort of four large US community-based cohorts. We examined the relative CVD risk comparing those with DM but no CVD history (DM+/CVD-) vs. those with no DM but a CVD history (DM-/CVD+) at baseline. Overall DM+/CVD- had 17% lower CVD risk than those with DM-/CVD+. DM+/CVD- participants with HbA1c≥7%, DM duration over 10 years, or DM medication use had similar CVD risk as those with DM-/CVD+ while those without these factors had lower CVD risk. Subgroup analysis comparing the hazard ratios (HR) of DM+/CVD- vs. DM-/CVD+ was done by conventional CVD risk factors. DM+/CVD- were found to have similar CVD risk as those DM-/CVD+ among women, those age <55 years, White race, or with high triglycerides groups. One with DM+/CVD- was defined to have CVD risk equivalent DM if his/her relative CVD risk was as high as or higher than that if he/she had DM-/CVD+. The CVD risk profile and CVD risk were compared between the CVD risk equivalent subgroups in DM+/CVD-. Among those with DM+/CVD-, 17.5% were found to have CVD risk equivalent DM, who had lower mean 10-year ASCVD risk score compared to those with non-CVD-risk equivalent DM (14.8% vs. 22.7%, $p<0.0001$) however had much higher observed CVD risk, with adjusted hazard ratios (HRs) compared to those with DM-/CVD- being 2.65 (95% CI: 2.37-2.97) vs. 1.40 (95% CI: 1.31-1.49) , respectively.

We developed and validated a set of new risk scores for DM macrovascular complications from a pooled cohort of the US population. We pooled 4,183 CVD-free adults with DM (aged 30-86 years, 45% male and 45% Black) from five US population-based cohorts. We developed 10-year Diabetes Mellitus Risk Scores (DMRS) for total CVD [myocardial infarction, cardiac revascularization, stroke, heart failure (HF) and CVD death], atherosclerotic CVD (ASCVD),

and separately for coronary heart disease (CHD), stroke and HF. Age, sex, hemoglobin A1c (HbA1c), serum creatinine, systolic blood pressure and current smoking were the most important predictors of all endpoints. DMRS had good internal discrimination and calibration (c-statistics: 0.70-0.76; calibration slopes: 1.03-1.16 comparing observed vs. predicted risk). Scores were externally validated in 6642 CVD-free subjects from the Action to Control Cardiovascular Risk in Diabetes trial Follow-on (ACCORDION) cohort and were compared with Framingham Risk Scores (FRS), UK Prospective Diabetes Study (UKPDS) risk engines and 2013 Pooled Cohort Equation (PCE) for each endpoint. In the ACCORDION cohort, DMRS showed superior performance over FRS, UKPDS and PCE (c-statistics 0.62-0.71 vs. 0.55-0.60, $p < 0.05$ for CVD comparing DMRS vs. FRS and PCE and CHD comparing DMRS vs. FRS).

In addition, we comprehensively evaluated the incremented prediction from three subclinical atherosclerosis (SA) measures, namely coronary artery calcium (CAC), carotid intima media thickness (CIMT) and ankle brachial index (ABI) beyond the DMRS in 931 CVD-free subjects with DM (mean age of 62.3 years, with 43.8% males) in the MESA cohort. CAC was found to be associated with CVD, ASCVD, CHD, HF and stroke after adjustment of DMRS (HR ranged 1.11-1.28, all $p < 0.05$). We calculated the Harrell's c-statistics and net reclassification index (NRI) in the following model comparisons for each event: (1) single SA measures + DMRS vs. DMRS; (2) pairwise comparison of three models with single SA measure + DMRS; (3) CAC+CIMT (or ABI, or CIMT+ABI)+DMRS vs. CIMT(or ABI, or CIMT+ABI)+DMRS. The Harrell's c-statistics of DMRS were 0.65, 0.66, 0.66, 0.68 and 0.65 for CVD, ASCVD, CHD, HF and stroke, respectively. CAC+DMRS increased the C-statistics to 0.70, 0.68, 0.74, 0.68 and 0.62 (p value <0.05 for CVD and CHD) while the change was minimal with the addition of

CIMT or ABI to DMRS. CAC showed superiority in c-statistics and NRI to CIMT and ABI as well as beyond CIMT, ABI or both for CVD and CHD events. The results demonstrated that CAC remained the strongest CVD risk reclassifier among CAC, CIMT and ABI for patients with DM.

The new definition of CVD risk equivalent DM and its algorithm has the potential to help pick those whose DM is more severe than other DM patients regarding the CVD risk. More importantly, the high DM-conferred CVD risk in those with CVD risk equivalent DM were not captured by the current CVD risk assessment tools like PCE which only includes DM as binary predictors and neglects all the heterogenous CVD risk associated with DM. As to the estimation of global CVD risk, our new DMRS were demonstrated to have better prediction performance than existing risk scores including PCE, FRS and UKPDS in the DM population. Given that our DMRS were not yet perfect CVD risk estimation tools, we can further use cardiac CT scanning to get CAC score, which were found to have superior reclassification and discrimination ability to CIMT and ABI, to assist the CVD risk assessment for patients with DM.

The dissertation of Yanglu Zhao is approved.

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ABBREVIATIONS AND ACRONYMS

ABI = ankle brachial index

ACCORDION= The Action to Control Cardiovascular Risk in Diabetes trial Follow-On

ARIC = Atherosclerosis Risk In Communities

ASCVD = atherosclerotic cardiovascular disease

BMI = body mass index

CAC = coronary artery calcium

CARDIA = Coronary Artery Risk Development in Young Adults

CHD = coronary heart disease

CIMT = carotid intima media thickness

CVD = cardiovascular disease

DBP = diastolic blood pressure

DM = diabetes mellitus

DMRS = Diabetes Mellitus Risk Scores

eGFR = estimated glomular filtration rate

FHS Offspring = Framingham Heart Study Offspring c ohort

FRS = Framingham Risk Score

GND test = Greeenwood-Nam-D'Agostino test

HbA1c = Hemoglobin A1c

HDL-C = high density lipoprotein cholesterol

HF = heart failure

HR = hazard ratio

Hs-CRP = high sensitivity c reactive protein

HTN = hypertension

JHS = Jackson Heart Study

LDL-C = low density lipoprotein cholesterol

LVH = left ventricular hypertrophy

MESA = Multi-Ethnic Study of Atherosclerosis

NRI = net reclassification index

PCE = Pooled Cohort Equation

PVD = peripheral vascular disease

RS = risk score

RF = risk factor

SA = subclinical atherosclerosis

SBP = systolic blood pressure

UACR = urinary acid creatinine ratio

UKPDS = UK Prospective Diabetes Study

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1. Introduction

1.1 Diabetes Mellitus and Cardioavscular Disease Prevention

Diabetes mellitus (DM) is a chronic condition that occurs when the body cannot produce enough or effectively use insulin, which are induced by a genetic predisposition plus environmental factors. [1] According to the 2020 National Diabetes Statistics Report, 34.2 million (9.4%) persons in the United States population have DM in 2018, with a total of 1.5 million new cases. [2] DM is listed as the 7th cause of death in the US, leading to 83,564 deaths in 2017. Patients with DM generally have two to four times of the risk to develop cardiovascular events compared to those without DM and cardiovascular disease (CVD) remains the leading cause of death among patients with DM. [3-5] At least 68% of people age 65 or older with DM die from some form of heart disease; and 16% die of stroke. In 2016, 1.7 million hospitalizations were related to CVD among DM patients. [2] DM-related CVD resulted in an estimated $37.3 billion spending per year. [6] In addition to an increased CVD risk and mortality, approximately one in six patients with DM experienced silent myocardial infarction before CVD becomes clinically manifested. [7] Once the CVD events occur, both the short-term and long-term prognosis are worse than those without DM. [8,9]

Although the etiology of excessive CVD risk in patients with DM is not fully known, it is shown that DM may increase CVD risk through multiple mechanisms. First of all, DM promotes atherosclerosis through exacerbation of dyslipidemia, endothelial dysfunction, oxidation, glycosylation and inflammation. In diabetes, dense and small low-density lipoprotein-cholesterol (LDL-C) is more commonly seen, which is more atherogenic than large LDL particles.

Hypertriglyceridemia is also common among DM patients, which lead to increased production of the small, dense form of LDL and to decreased high-density lipoprotein (HDL) transport of cholesterol back to the liver. [10] Insulin resistance in early preclinical stage of DM and insulin deficiency in later phase of DM increase the oxidative stress, inflammation, dysregulation of vascular tone, hypercoagulability of blood and eventually lead to vascular alternation and higher risk for vascular blockage. [11] DM also contributes to the development of heart failure through direct myocardial damage, post-myocardial infarction cardiac damage, microvascular complications, and chronic inflammation. In addition to the DM-conferred CVD risk, patients with DM are more frequently accompanied by other CVD risk factors including family history of DM and CVD, unhealthy lifestyles, hypertension, obesity and metabolic syndrome. These risk factors, together with DM itself, increase the global risk of CVD as well as its component events including myocardial infarction, stroke, peripheral vascular disease, heart failure and CVD death.

To reduce morbidity and mortality among DM patients, multifactorial preventive strategies should be applied according to one's specific risk profile. These facts yield a need for reliable and accurate CVD risk assessment to inform patient about their risk status and guide the effective and cost-saving preventive intervention. The 2018 American Heart Association (AHA)/ American College of Cardiology (ACC) guidelines on the management of blood cholesterol continue to recommend DM as one of the statin-benefit groups and any one with DM between age 40-75 is recommended to start/continue statin therapy. With indicators of higher CVD risk, such as 10-year ASCVD risk score by PCE $\geq$ 20%, multiple risk factors, or DM-specific risk enhancers, high intensity statin therapy is recommended in primary prevention population with DM. [12] The 2019 American Diabetes Association (ADA) Standards of Medical Care in

Diabetes have provided comprehensive CVD prevention guidelines specific for DM population, most of which is consistent with the AHA/ACC guidelines (Table 1-1). [13-15] The 2019 European Society of Cardiology (ESC) guidelines recommend an LDL-C target below 55 mg/dL for those with DM at very high risk and the target of 70 mg/dL to those with DM and at high CV risk [16, 17]. Although ESC has the SCORE algorithm to estimate 10-year total CVD risk, DM is not eligible to use the score and risk equations for general population is not recommended to DM population.

1.2 Is Diabetes a Cardiovascular Disease Risk Equivalent? - The Debates

Since the first guideline on DM management in 1988, different approaches have been used to define future CVD risk. These approaches can be classified into three categories: "CVD risk equivalent" approach, CVD risk scoring system approach and reclassification by novel tests. The "CHD risk equivalent" approach, or the idea of taking DM as a universally high-risk group as those who already have CHD, is among the earliest attempt as well as the most simplistic ways to evaluate future CVD risk for diabetic population.

The concept of "CHD risk equivalent" was first introduced by Haffner et al. [18] in their pioneer study. They found the incidence rates of myocardial infarction for diabetic subjects without prior myocardial infarction (MI) were comparable to that of their non-diabetic counterparts who had a history of MI. In this study, 1059 subjects with type 2 diabetes and 1378 non-diabetic subjects were followed up for seven years from 1982 in Finland. The DM group had 890 subjects without prior MI (DM+/MI-) and the 69 non-DM subjects had prior MI (DM-/MI+) at baseline.

Incidence rate of CHD were 3.2 per 100 person-years in the DM+/MI- group and 3.0 per 100 person-years in DM-/MI+ group. The hazard ratios (HR) for CHD mortality comparing DM+/MI- to DM-/MI+ to were 1.4 [95% confidence interval (CI): 0.7-2.6] adjusted for age and sex and 1.2 (95% CI: 0.6-2.4) further adjusted to other cardiovascular risk factors.

This finding, together with other studies showing the greater cardiovascular benefit of statin therapy in diabetic subjects, has influenced the target and intensity of lipid lowering therapy for DM in later amended guidelines. The 2001 *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III(ATP III)]* first time defined DM as CHD risk equivalent and include all DM patients in the high-risk population. LDL target for those high risks (CHD and CHD risk equivalent, or 10-year CHD FRS > 20%) was <100 mg/dL and drug therapy is recommended when LDL >130 mg/dL. [19] The 2004 Update of ATP III recommended an optimal LDL level < 70 mg/dL and drug therapy initiation at LDL >100 mg/dL. [20] One advantage of such recommendation is that it ensured most high-risk DM patients receive aggressive treatment to maximize the reduction of CVD risk. It also renders further steps of CVD risk estimation for DM patients unnecessary; on the other hand, it brings unfavorable psychological burden to those diabetes patients with relative low risk. It is also possible that the maximal dose of preventive therapy cannot bring as much benefit as those with real high risk and thus may be a waste of medical resources. Side effects and a potential of worse adherence may also come along with the long-term intensive therapy. Sparse evidence has been available to tackle above issues.

Haffner's study has several limitations in the contemporary knowledge and population settings. For instance, there were only 69 subjects in the non-DM with prior MI group, resulting in the large confidence range, low power of detect true difference and possibly a biased HR estimate. The whole study population were followed up in 1980s, during which statin therapy and other preventive measures was not commonly recommended to patients with DM while nowadays CVD risk reduction was a priority to most DM patients with various types of drugs being used. Given these limitations, numerous studies continue to answer the same question however inconsistent conclusion were drawn. One important opposing evidence comes from a meta-analysis which includes 13 cohort studies and 45,108 patients showed that those with diabetes have a 43% lower risk for future hard coronary artery events compared with those with a prior MI. [21] A recent study including 1.6 million Kaiser Permanente Northern California registered patients aged 30-90 years found those with DM along had 39% lower CHD risk than those with prior CHD along (HR of 0.61, 95 % CI, 0.60–0.63) over 10 years of follow-up (2002-2011). [22] The study is featured with its large, contemporary and age-and-race diverse cohort. However, other studies using large and contemporary cohorts have quite contradictory findings. One Danish study based on national registry data compared the CVD mortality between diabetics taking glucose-lowering medications and non-diabetics with and without a prior MI were compared (inclusion age ≥30 years) and showed that compared with those without a prior MI or DM, those with DM alone had similar risk increase as those with prior MI alone, regardless of sex and diabetes type. [23] One possible explanation is that taking medication is a proxy of DM severity and these DM patients may have higher risk than the overall DM population. Other evidence supporting DM is a CHD risk equivalent are from studies with longer follow-up time. [24,25]. Interestingly, almost all studies concluding DM as a CHD risk equivalent were based on

European cohorts. The predominant Caucasian ethnicity, high prevalence of DM and severe stage of DM are the possible reasons.

One issue of existing studies is that none of them recognized the importance of considering DM as risk factors for the whole cardiovascular disease spectrum and explore whether DM is a "CVD risk equivalent" by including stroke, heart failure (HF), and peripheral vascular disease (PVD) among the most important complications of DM. Besides, two questions still remain after we give the "Yes" or "No" answer to whether DM is "CVD risk equivalent". Firstly, what are the reasons for the different answers from different studies? Prior studies with subgroup analysis mostly examined if relationship is modified by age and sex but not other possible interactions. [22] In fact, each one of the studies on this topic can be seen as a subgroup of the DM population and the characteristic difference among them could be the potential effect modifier. As mentioned above, race could be one of the reasons why most studies that found DM a CVD risk equivalent were based on European cohorts. Another potential reason is the cohort effect: with the contemporary treatment, DM is no longer a CVD risk equivalent. A meta- analysis of 102 studies showed that diabetes increases CVD risk independent of other risk factors. [26] The PCE for ASCVD risk estimation uses DM as a binary factor, ignoring its heterogeneity in risks and interaction with other risk factors. [27]. Interaction of DM with other comorbidities such as hypertension, obesity and dyslipidemia is possible but has not been explored in the setting of a comparison between DM and prior CVD patients.

1.3 Cardiovascular Disease Risk Scores for Diabetes Population

CVD risk scores, sometimes called CVD risk engines or CVD risk calculators are continuous scores that integrate CVD-related risk factors with different weights and are used to estimate the risk of CVD. The Framingham risk score (FRS) was the first developed CVD risk score and since then many other CVD risk scores have been developed to predict CVD risk for different populations. [28-31] The Reynolds Risk Score was originally designed for CVD-free women [32] and the UK Prospective Diabetes Study (UKPDS) risk engine was specifically created for the diabetic population. [33] Other scores were developed for those with prior CVD. [34] Some countries usually use their own population to develop a CVD risk score instead of borrowing an outside calculator. [35, 36].

A well-constructed CVD risk score may be referenced in CVD management guidelines. In the clinic, CVD risk scores are often used by health care providers to help identify the high-risk population and further guide the preventive treatment. [12] Most of these risk scores have now been made as online risk calculators or mobile APPs that allow non-professional individuals to evaluate risk. Such self-awareness of disease risk may be a good impetus to promote risk-reduction behaviors such as smoking cessation and closer monitoring of blood pressure, glucose level and lipid profiles, etc. In research, existing risk scores are usually used as the reference model to be compared when new CVD risk model is being developed. Another important use of CVD risk scores is similar to exposure-based propensity scores to reduce the dimension of individual covariates to control confounding. [37]

1.3.1 Development and Validation of CVD Risk Score for DM Patients

There are important components and criteria for developing CVD risk scores. [38,39] D'Agostino et al. summarized the complete process of development and validation for a CVD risk score into the following 10 steps: (1) Endpoint (event/outcome); (2) At-risk population; (3) Follow-up time; (4) Risk factors; (5) Mathematical model; (6) Estimation (relative and absolute risks); (7) Performance (discrimination, calibration); (7) Internal validation; (8) External validation (performance and recalibration); (9) New markers; (10) Long-term prediction. [39] With regards to CVD risk scores for DM patients, we often observe variable methods when carrying out these steps and the choice of selection often involves different considerations.

Endpoint/Outcome

For current risk scoring systems, various endpoints have been used such as total CVD, hard CHD and hard atherosclerotic CVD. It seems that there is no best choice on whether we should include soft events in CVD endpoints among DM patients. DM patients are featured with longer asymptomatic or preclinical period for CVD and suffer more silent coronary heart events than their non-diabetic counterparts. Therefore, only counting the hard events may not catch all the true events and lead to the underestimation of the risk score and thus bad calibration. On the other hand, the softer endpoints such as percutaneous coronary interventions, bypass surgery, and coronary revascularization is more prone to be misclassified and lead to poor discrimination, and the time of occurrence of certain endpoints such as angina, angiographic disease, or coronary calcium can be quite uncertain. The FRS/UKPDS validation study in the ADVANCE cohort did find that when any CVD event was used as endpoint instead of hard CVD event, calibration was better while c-statistics (discrimination) were poorer. [40] In addition to these commonly seen endpoints, CVD mortality, HF and even microvascular complications have been used in risk

models for diabetes patients. It was found in a large DM cohort in the UK that HF is the most commonly seen first manifestation of CVD in the DM followed by peripheral vascular disease (PVD) [41], which should be included along with CHD and stroke in risk assessment.

At Risk Population

It seems that the choice of target population is obvious here, which should be patients with diabetes. However, the most commonly used CVD risk scores in clinic are usually those designed for the general population that includes both those with and without DM. Such risk scores usually include DM as a binary factor, ignoring its heterogeneity in risks and interaction with other risk factors. In contrast, CVD risk scores specifically developed for DM patients includes more DM-related variables such as HbA1c and DM duration. A study that directly compared the performance of general population vs diabetes-specific CVD risk models in DM patients showed discriminatory advantage of diabetes-specific over general population-based models for CVD risk stratification in diabetes. [42]

The type of DM also matters. In fact, there are many more CVD risk scores for T2DM patients than for all DM patients or T1DM patients. One reason is that many of these risk scores were developed using large sample-sized clinical trial cohorts, which specifically targets T2DM. [33, 43, 44] Such clinical trial data includes information on many cardiometabolic variables, thus providing great pool of candidate predictors when developing a risk score. Although observational studies include different types of DM patients, the small proportion of DM patients, missing information on DM type, and fewer DM-related variables limits the use of such data to develop risk scores for all DM patients. Given that T1DM are much fewer than T2DM in

the population, CVD risk scores for T1DM usually use data from medical record, or national health registry. [45,46]

Candidate Risk Factors

In addition to traditional risk factors seen in general population, DM severity indicators such as HbA1c, retinopathy and kidney functions measures are commonly found in CVD risk scores for DM patients. Such measures may be relatively normal among non-DM subjects and do not have as strong a predictive value as in DM patients. On the contrary, various measures that indicates the severity and complications of DM may play important role in CVD risk assessment for those with DM.

Novel risk predictors may include biomarkers. We previously reviewed the advances of these novel risk factors in risk assessment, including C-reactive protein (inflammatory biomarker), lipoprotein (a), low density lipoprotein and high density lipoprotein particles, lipoprotein-associated phospholipase A2 (lipid biomarkers) and several subclinical atherosclerosis measures. [47] Biomarkers representing pathophysiological processes of atherosclerosis, such as growth differentiation factor 15, N-terminal pro B-type natriuretic peptide and high-sensitive troponin T were also found to enhance CVD risk prediction among diabetics. [48] All these potential new risk factors were independently associated with future CVD risk, however, whether or not they can improve a risk model needs further examination.

Risk Estimation

Risk estimation involves the selection of risk factors and calculation of risk scores. A wide variety of methods have been used to select the risk factors to be included. The purpose of risk factor selection is not only to include the risk factors that are associated with CVD events and can improve the accuracy of risk scores, but also to control the total number of risk factors to avoid over-complex equation or high cost related to the tests. The most commonly used selection method is a stepwise selection based on a prespecified p value. More recently, machine learning methods have gained popularity and were increasingly used to select risk factors. The Pooled Cohort Equation adopted by current AHA/ACC guidelines used random survival forest method to determine the "importance" parameter of potential risk factors. [27]

Once the risk factors are selected, they need to be integrated into a single risk score using certain mathematical models. The early Framingham Risk Score for CHD events used logistic regression model to generate the score. [49] Logistic regression model treated event as binary outcome and neglects the timing of event. Poisson regression models have also been used alternatively to estimate incidence rates assuming homogenous risk over time. Currently the most widely used model is the Cox proportional hazard regression model, which makes no assumption about baseline risk and time. In the Cox model, a baseline survival at the target time frame, i.e. 10 years is needed. Other models involving event time such Poisson model, Weibull model and accelerated failure time model are sometimes used instead of the Cox model.

Evaluation of Risk Score Performance

Binary outcome and time-to-event outcome have a number of evaluation methods regarding prediction performance such as R2, goodness of fit test, mean squared error, C-statistics, etc. C-

statistics are routinely reported in almost all risk scores' performance evaluation stage. The Harrell's C statistic is specially designed for time-to-event outcome and is similar to area under the ROC curve for binary outcome which lies between the value of 0.5-1. The C-statistic enables the quantification of predictive ability of risk scores but is also found to be conservative in pair-wise comparison when the two compared models have large overlap of covariates or when the old model is already good enough. [50] The net reclassification index (NRI) has been frequently used since its introduction in 2008. Compared to C-statistics, the categorical NRI has greater clinical relevance and importance when two risk scores are compared. However, NRI, especially category-free NRI, sometimes suffers a false positive problem in reporting significant results. [51]

Before a CVD risk score can be used in diabetic patients, the score also needs to be tested in other external DM cohorts. Performance of a risk score is more heterogeneous and generally poorer in external validation. Since many of the CVD risk scores for the general population can also be used in DM patients, they usually serve as a reference model in head-to-head comparisons with the DM-specific CVD risk models. More importantly, all these risk scores were derived from older cohorts dated back years ago during which the baseline risk factors, disease incidence and preventive management were notably different from the contemporary population. This temporal disparity may also have a negative impact on the performance of risk scores.

1.3.2 An Update: New CVD Risk Scores for DM Patients in Different Countries

In 2012, Van Dieren et al. systematically reviewed 45 CVD risk scores that can be used for T2DM population, among which 12 were T2DM-specific CVD risk scores. [52] Here we summarize the newly emerged risk scores for both T1DM and T2DM as well as updates of the old DM-specific CVD risk scores (see Table 1-2). These new CVD risk scores have used new types of endpoints, new dataset from contemporary cohorts, or elongated follow-up from original derivation cohort.

United Kingdom

The UKPDS risk engine is the earliest and the most well-known CVD risk scoring system for patients with diabetes. The first UKPDS risk engine was dated back to 2001 and was developed to separately predict 10-year CHD and stroke instead of composite CVD events. [33,53] Post-trial follow-up of UKPDS cohort continues contributing to a new set of CVD risk scores called UKPDS Outcomes Model (UKPDS-OM). The current version of OM is OM2, which has significant distinction from the old UKPDS risk engine. [54] The OM2 predicts lifetime risk of seven primary complications of myocardial infarction, ischemic heart disease, stroke, congestive heart failure, amputation, blindness and renal failure. Additional models were also developed for total mortality, diabetic ulcer and some second events. OM2 does not provide estimate of risk for composite CVD events. The study directly compared observed vs. predicted event for internal validation. External validation showed tendency of underestimation of risk. [55]

England researchers developed a risk score as part of QDiabetes risk score for 10-year heart failure risk from 437,806 diabetic patients in general practice. [56] Unlike the OM2 for heart failure, the model can be used in both T1DM and T2DM, and in both with or without prior CVD.

The risk score included common risk predictors of age, BMI, SBP, cholesterol/HDL ratio, HbA1c, material deprivation, ethnicity, smoking, duration and type of DM, atrial fibrillation, cardiovascular disease and chronic renal disease. External validation on two large cohorts from England showed satisfactory AUC (ranged 0.76-0.78) and excellent calibration.

United States and Canada

To date, several CVD risk scores were developed for DM populations in the US and two of them have used the Atherosclerosis Risk in Communities Study (ARIC) cohort. The older one predicted CHD risk with a basic model of 8 predictors and a full model of 17 predictors. [57] The newer ARIC CVD risk score for DM estimated 10-year CVD risk and successively explored four clusters of predictors with 4 models. [58] Model 1 with 13 self-reported risk factors had C-statistics of 0.667 and Model 4 with self-report risk factors, clinical measured risk factors, HbA1c and 12 novel biomarkers reached a C-statistic of 0.714. Each inclusion of an additional set of predictors significantly improved C-statistics.

Cleveland Clinic currently has two DM complication risk scores. Both scores were developed from Cleveland Clinic patients and have not been externally validated. [59,60] One predicted 5-year risk for mortality, HF, CHD and stroke. Internal discrimination (c-statistics) was 0.73, 0.75, 0.69 and 0.72 for CHD, HF, stroke and mortality, respectively. The other set is called Individualized Diabetes Complications Risk Scores (IDC-RS), which predict total mortality, CHD, HF and diabetic nephropathy. To calculate the IDC Risk Scores, age, sex, race, smoking, BMI, SBP and DBP, HbA1c, serum creatinine, details of CVD history and CVD medication are required. C-statistics were 0.79, 0.66 0.72 and 0.73 for total mortality, CHD, HF and

nephropathy. To note, the IDC Risk Score is specifically designed for those with both T2DM and obesity and the scores were separately developed in those underwent metabolic surgery vs. received usual care.

Basu et al. developed a comprehensive risk scoring system named RECODe (Risk Equations for Complications Of type 2 Diabetes) for microvascular and macrovascular complications using the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial cohort recruited from US and Canada. [43] Multiple risk scores were developed to predict 10-year risk of each microvascular complications including nephropathy, retinopathy and neuropathy, and macrovascular endpoints of myocardial infarction, stroke, congestive heart failure and cardiovascular mortality as well as composite endpoints of ASCVD and total mortality. Internal and external validation achieved moderate discrimination and good calibration. When compared with UKPDS and PCE, statistically significant improvement in NRI was observed. [61] The RECODe risk score for ASCVD events includes CVD history as one significant predictor, therefore may be applicable to those with past history of CVD.

Another set of risk assessment models for DM was developed using the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort from 29 clinic centers in the US and Canada. [62] Although the developers claimed the models for all DM patients, the whole derivation cohort is only composed of T1DM. The risk models predict micro- and macrovascular complications as well as adverse events of hypoglycemia and ketoacidosis that are commonly seen in T1DM. External validation showed

general better performance in T1DM than T2DM with the exception of predicting long-term CVD events.

Sweden

Two CVD risk scores for T2DM and T1DM were developed in Sweden [63, 48]. The Swedish National Diabetes Registry (NDR) risk score for T2DM was featured with the wide age range from 18 to 70 years old and simple achievable risk profiles, with HbA1c as the only lab test [63] to predict first-time CVD in 5 years. An important difference of the T1DM NDR risk score is that it is applicable to T1DM patients both with and without prior CVD. In this model, CVD history was identified as an independent predictor with 7 common predictors including DM onset age, diabetes duration total cholesterol: HDL-C ratio, HbA1c, SBP, smoker and macroalbuminuria. External validation showed excellent discrimination and calibration. [48]

Germany

In Germany, a CVD mortality risk score for DM patients, called VILDIA risk score, investigated 135 potential risk factors (mostly biomarkers) and eventually selected NT-proBNP, age, male sex, renin, diabetes duration, Lp-PLA2 and 25-OH vitamin D3 using bootstrapping stepwise selection. [64] The VILDIA CVD mortality risk score showed better discrimination for CVD mortality in an external German cohort than UKPDS risk engine. Since the UKPDS risk engine and the VILDIA risk score predicted different endpoints, it is usually not recommended to make such direct comparison.

Denmark

The Steno Type 1 Risk Engine, a 5-year CVD risk score for T1DM in Denmark was developed with outpatient clinic data and have shown excellent performance. [45] It is so far the largest CVD-free T1DM cohort used to develop CVD risk score. The risk engine includes age, sex, diabetes duration, SBP, LDL-C, HbA1c, albuminuria, glomerular filtration rate, smoking, and exercise.

China

Three independent 5-year risk scores for CHD, HF and stroke were previously developed for T2DM patients using population-based data in Hong Kong. [52] Recently Hong Kong researchers developed new 5-year CVD risk scores for T2DM patients. [65] The baseline derivation cohort was in 2010 and therefore is the most recent derivation cohort among all CVD risk scores. The set of risk scores had two versions with one using fewer risk factors. In both models, age, smoking, HbA1c, SBP, TC/HDL-C ratio and eGFR were identified as predictors. The complete model additionally included diabetes duration, usage of anti-hypertensive drug and insulin, BMI, DBP, and UACR. The new model showed superior discrimination and calibration ability to other CVD risk scores for DM patients. The risk scores still need to be validated among DM patients in mainland China before being applied in the whole country.

ADVANCE Risk Score and AD-On Risk Score

The Action in Diabetes and Vascular Disease (ADVANCE) clinical trial enrolled high CVD risk participants with DM from across 20 countries in Asia, Australasia, Europe and Canada. Despite the short follow-up of main trial, ADVANCE researchers managed to develop a 4-year CVD risk score from ADVANCE participants that may be applicable to T2DM in diverse countries. [44]

Retinopathy was identified as one of the DM-related predictors in the final model. In external validation, the ADVANCE CVD risk score showed barely modest discrimination and a tendency to underestimate risk regarding calibration, partially due to the BP and glycemic intervention. [66] ADVANCE researchers also developed 5-year risk scores for early and late stage of renal disease. [67] C-statistics were 0.847 for major kidney-related events and 0.647 for new-onset albuminuria.

With the longer post-trial follow-up, ADVANCE-On Project further developed 10-year risk scores for CVD and major renal disease. [68]. In the new risk score, age, sex, SBP, antihypertensive medication, duration of diabetes, HbA1c, UCAR, eGFR, age at completion of formal education, exercise, history of diabetic retinopathy and atrial fibrillation were included. Discrimination of the 4-year and 10-year risk scores were similar for both 4-year and 10-year events. The risk scores for renal events performed better with C-statistics around 0.8 mainly due to the highly predictive renal function measures like eGFR and UACR.

1.4 Subclinical Atherosclerosis Measures as Novel Screening Modality for CVD Risk

Subclinical atherosclerosis is the early stages of atherosclerosis with no clinical manifestation. It can happen throughout the body at different vascular sites. Non-invasive techniques have been well-developed to detect and measure subclinical atherosclerosis. In addition to indicate the existence and quantify the severity of early atherosclerosis, these measures are found to have potential usefulness in improving cardiovascular risk prediction together with the traditional risk factors. [69]

1.4.1 Coronary Artery Calcium (CAC)

CAC is the calcium deposits in the coronary artery wall. [70, 71] CAC is quantified by either multidetector computed tomography (MDCT) or electron beam computed tomography (EBCT). [72] There have been several methods to calculate the CAC score, although the Agatston method is most commonly used clinically. [73] CAC is independently associated with CVD and has emerged as the strongest predictor for refining risk assessment on top of global risk assessment compared to other subclinical measures. [74, 75] In those subjects with DM, a CAC score of 0 is associated with short-term (5-year) ASCVD risks and all-cause mortality as low as persons without DM and higher CAC scores are associated with progressively higher ASCVD event rates and mortality. [76, 77] The PREDICT study [78] further examined the incremental prediction of CAC beyond UKPDS in DM subjects and showed that AUC of including CAC to UKPDS increased from 0.63 to 0.73. In one of our current MESA projects we found that the CAC has a three-category NRI of 0.25 (95% CI: 0.12-0.38) for ASCVD events compared to PCE among those subjects with DM (S Malik et al. Results not published). The Diabetes Heart Study found NRI for reclassifying CVD-death after adding CAC to FRS was 0.13 (95% CI: 0.07-0.19). [79] These results suggested that CAC has a predictive value in CVD risk re-stratification in DM population as well. In the most recent studies, different parameters of CAC including the calcium density and regional distribution calcium were examined with relation to future CVD events, which may provide even more incremental predictive information than CAC score. [80] Although CAC score is a very promising risk reclassification tool, major concern about the disadvantage of CAC test is the cost-effectiveness and potential radiation harm from CT scanning.

1.4.2 Carotid Intima-Media Thickness (CIMT)

CIMT is an indicator of atherosclerosis on carotid artery which measures the combined thickness of the intima and media with ultrasound. Although CIMT is related to higher CVD event risk [74,75,81], meta-analysis and pooled cohort studies showed the addition of common CIMT to traditional risk models was only associated with a modest improvement and is unlikely to be of clinical importance (NRI of 0.8% for general population). [82,83] Similar findings in a cohort of 4,220 DM patients demonstrated that common CIMT did not add predictive value to the Framingham Risk Score during a median follow-up of 8.7 years. [84] Therefore, CIMT is not considered as a supplementary risk stratification tool as CAC and ABI for patients with DM in current guidelines [85], except that CIMT plus carotid plaque detection test is currently recommended in the European Society of Cardiology guidelines to general population with intermediate risk.

1.4.3 Ankle Brachial Index (ABI)

ABI is a measure of peripheral vascular blockage and is defined as the ratio of the higher systolic blood pressure of dorsalis pedis or posterior tibial arteries and the brachial arteries in the supine position. Reduction of blood flow into lower limbs causes the ABI value to drop and ABI < 0.9 is an indicator of peripheral artery disease. ABI is also found to be independently associated with CVD. [75,86,87] However, many studies in various population types including the DM found no significant increase of AUC or NRI when ABI was added to conventional risk scores. [74,75,86,88] One of the few exceptions is the ABI collaboration pooled cohort study of 18 cohorts with 44,752 subjects. The study compared FRS and model incorporating FRS + ABI and

found ABI has borderline significant NRI of 4.3% (95% CI 0.0 to 7.6%, p = 0.050) in men and significant NRI of 9.6% (95% CI 6.1 to 16.4%, p < 0.001) in women. [89] Interestingly, when FRS is replaced by multiple risk factors in FRS, NRI of ABI become non-significant again. This may be explained by the potential collinearity of ABI and some risk factors or due to the better fitted model using individual risk factors than FRS. In addition, most studies have included ABI in the model in original form or as dichotomous variable (ABI< 0.9 vs >0.9) while some excluded subjects ABI >1.4. This may attenuate the impact of high ABI on CVD risk and may be a potential cause of underestimated prediction ability of ABI.

1.4.4 Myocardial Perfusion Imaging (MPI)

The Detection of Ischemia in Asymptomatic Diabetics (DIAD) clinical trial failed to demonstrate the effect of MPI screening on improving clinical outcomes [90] even though the participants demonstrate resolution of ischemia upon repeat testing. [91] Other studies show contradictory results. One meta-analysis evaluated the prognostic value of normal stress myocardial perfusion single-photon emission computed tomography (MPS) for future CHD among patients with DM. The study has included a total of 14 studies recruiting 13,493 DM patients. The negative predictive value (NPV) for non-fatal myocardial infarction and cardiac death of normal MPS was 94.92% (95% confidence interval 93.67-96.05), therefore can relatively safely exclude those without CAD and validly define the “low risk” group among the DM ones. [92] Such new evidence may alter the screening modality of CVD among the DM population.

1.4.5 Coronary Computed Tomography Angiography (CCTA)

CCTA is an invasive assessment of non-obstructive disease, coronary stenosis and proportion of occlusion, plaque characterization and calcification, etc. [93] Similar to MPI, a recent meta-analysis examined the results of CCTA (obstructive CAD, non-obstructive CAD, or no CAD) in relation with future events (all-cause mortality or other CVD events) among DM patients. The final sample included 8 studies and 6,225 participants (56% male; weighted age, 61 years) with a follow-up period ranging from 20 to 66 months, finding that obstructive and non-obstructive CAD were associated with an increased HR of 5.4 and 4.2, respectively. [94] This meta-analysis may provide comparably strong evidence against prior studies and may change the role of CCTA in risk assessment for those with DM. Several studies have compared the predictive value of CCTA vs. CAC however findings were not consistent. [95-98] In particular, Min et al. found various measures from CCTA, including maximal stenosis, number of obstructive vessels and segment stenosis score added predictive value to CAC. [96]

1.5 Summary

Refining risk estimates in DM patients may help implementing prevention strategies in an efficient and cost-saving manner as well as reducing the potential side effect of intensive therapy including statin and antiplatelet medication. Two meta-analyses of statin trials have shown that statin use may increase the risk of hyperglycemia [91,92]. For those DM patients with low-to-intermediate risk, preventive statin therapy may provide limited protective benefit but impact the hypoglycemia drug effect. In such patients, risk assessment and the following statin initialization or intensification needs be tailored. Despite the fact that accurate risk estimation is the first step of effective preventive strategy, problems remain in each of the CVD risk assessment approach

among patients with DM. The dissertation contains three distinct projects on each approach of CVD risk assessment. The first project *Identification of "cardiovascular disease risk equivalent" among patients with diabetes mellitus* tried to answer the question of whether DM is a "CVD risk equivalent" beyond "Yes" or "no" and identify the subgroup of DM population whose CVD risk is as high as or higher than that if he/she had no DM but prior CVD history. The second project was the development and validation of a set of DM Risk Scores (DMRS) for macrovascular complications, including CVD, ASCVD, CHD, HF and stroke from a pooled cohort of US population. The last project examined the incremental predictive ability of three subclinical atherosclerosis measures, including CAC, CIMT and ABI beyond the DMRS in patients with DM, with an emphasis on the necessity and test order of each measure either individually or combined. The three distinct projects have a common theme of improving the current CV risk prediction paradigm for DM patients and better fit an increasing need of "precision medicine" and "evidence-based medicine".

1.6 Tables and Figures

Table 1-1. Comparisons of AHA/ACC, ADA and ESC Guidelines on CVD Risk Management for DM Patients.

		AHA/ACC guidelines	ADA guidelines	ESC guidelines	Common features
CVD risk assessment	CVD risk calculator	PCE for ASCVD	PCE for ASCVD	Not recommended	• Classification includes extreme high /high /intermediate
	Possible Risk groups	• Very high-risk: prior CVD, or PCE ≥20% • High-risk: multiple RFs • Moderate risk	• High risk: PCE ≥20% (ASCVD risk equivalent), or multiple RFs or prior ASCVD • Moderate risk	• Very-high-risk: prior CVD, organ damage, T1DM >20 years, ≥3 RFs • High-risk: 1 RF, or DM duration ≥10 years • Moderate risk	
	Novel risk assessment tools	• DM-specific risk enhancer [a] • CAC scanning	Not recommended.	• Arterial Plaque detection • CAC and coronary angiography • ABI	
BP management	Diagnosis Target	≥130/80 mmHg 130/80 mmHg	≥140/90 mmHg • Individualized targets • 130/80mmHg for the high-risk	≥140/90 mmHg • Individualized targets • 130/80mmHg: younger and tolerated	• Life style change is Class I recommendation • Aspirin is recommended to those with both prior CVD and DM.
Lipid management	Statin intensity	• High intensity: very-high/high-risk DM • Intermediate intensity: all other DM	• High intensity: high risk group • Intermediate intensity: 40+ years old and no high risk	• LDL-C <55 mg/dL: very-high-risk • LDL-C<70 mg/dL: high-risk • LDL-C<100 mg/dL: moderate-risk	
	Novel therapies	Ezetimibe or PCSK9i: very-high-risk group [b]	Ezetimibe or PCSK9i: to those with prior ASCVD	Ezetimibe: when goal is not reached	

Blood sugar management	Target Medication to reduce CVD risk	HbA1c <7% First- line: metformin Uncontrolled DM with other RFs: SGLT-2 orGLP-1R	Generally HbA1c <7% DM with prior CVD: SGLT-2 orGLP-1R An emphasis on HF risk	HbA1c <7% SGLT-2 and metformin for HF

a. DM-specific risk enhancers include: Long duration (⩾10 years for type 2 diabetes mellitus, or ⩾20 years for type 1 diabetes mellitus), Albuminuria ⩾30 mcg of albumin/mg creatinine, eGFR <60 mL/min/1.73 m2, Retinopathy, Neuropathy, ABI <0.9

b. Novel therapies are recommended beyond statin therapy when patients do not tolerate statin dose or do not reach treatment goals.

Table 1-2. Cardiovascular Risk Prediction Scores in Diabetes

Author and Year	Name of Score	Country	Derivation Cohort	Outcome(s)[a]	# of Predictors[b]	Features
Hayes et al. 2013	UKPDS-OM2	United Kingdom	5,102 T2DM participants in UKPDS trial	Life-time risk of 7 primary endpoints, total mortality, diabetic ulcer and repeated events	11	•30 years of follow-up •Inclusion of time varying risk factors •Estimation of life expectancy and quality-adjusted life years
Hippisley-Cox et al. 2015	QDiabetes (Heart Failure) [c]	England	437,806 DM subjects in general practice	10-year HF risk	13	•Large derivation and validation cohorts •Online risk calculator •Easy-to-get predictors •
Parrinello et al. 2016	New ARIC risk score for DM	US	654 subjects with DM in ARIC study	10-year CVD risk	13-30	•Successive examination of risk factors based on accessibility
Basu, et al. 2017	RECODe [c]	US and Canada	9,635 T2DM subjects from ACCORD study	10-year risk for CVD and its components, microvascular event, total mortality	14	•Contemporary and large derivation cohort •Composite and individual complication events
Lagani, et al. 2015	DCCT/EDIC risk score	US and Canada	1,441 T1DM subjects in DCCT/EDIC cohort	micro- and macrovascular complications, hypoglycemia, ketoacidosis	7	•Prediction for adverse events of hypoglycemia and ketoacidosis

a. Some risk scores include several separate algorithms for different endpoints.
b. Mean or range of the number of predictors are reported if multiple models were developed.

Table 1-2 (cont'd). Cardiovascular Risk Prediction Scores in Diabetes

Author and Year	Name of Score	Country	Derivation Cohort	Outcome(s)[a]	# of Predictors[b]	Features
Cederholm, et al. 2011	NDR risk score for T1DM [c]	Sweden	3,661 T1DM with and without CVD	5-year CVD risk	8	•Excellent performance in external validation
Goliasch, et al. 2017	VILDIA score [c]	Germany	864 DM patients from German LURIC study	10-year CVD mortality	7	•Prediction of CVD mortality •Large selection pool of potential predictors, including multiple novel biomarkers
Vistisen, et al. 2016	The Steno Type 1 Risk Engine	Denmark	4,306 T1DM in STENO cohort	5-year CVD risk	10	•Excellent performance in external validation •Contemporary and large derivation cohort
Wan, et al 2018	Chinese CVD risk score for T2DM	China	137,935 T2DM patients In Hong Kong	5-year CVD risk	6-12	•Contemporary and large derivation cohort •A web calculator and color-coded chart
Woodward, et al. 2016	AD-on score	20 Countries	6,951 T2DM subjects from ADVANCE-On trial	10-year CVD risk 10-year renal disease risk	13	•Region-specific calibration of risk scores •Potential to be applied to various countries

a. Some risk scores include several separate algorithms for different endpoints.
b. Mean or range of the number of predictors are reported if multiple models were developed.

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2. Study Data Sources

The three projects used the following 6 data sources either individually or as pooled cohort. Among the 6 cohorts, 5 were NIH-funded, large prospective observational cohorts. A summary of the five cohorts are show in Table 2-1. The 6th data source ACCORDION is a secondary clinical trial data.

2.1 ARIC

The Atherosclerosis Risk in Communities Study (ARIC), sponsored by the National Heart, Lung, and Blood Institute (NHLBI) is a prospective epidemiologic study conducted in four U.S. communities ((Washington County, MD; Forsyth County, NC; Jackson, MS; and Minneapolis, MN)). ARIC is designed to investigate the causes of atherosclerosis and its clinical outcomes, and variation in cardiovascular risk factors, medical care, and disease by race, gender, location, and date. ARIC includes two parts: the Cohort Component and the Community Surveillance Component. In the current projects, the Cohort Component was used.

The ARIC Cohort Component began in 1987, and each ARIC field center randomly selected and recruited a cohort sample of approximately 4,000 males and females between 45-64 years old from a defined population in their community, to receive extensive examinations, including medical, social, and demographic data. The first exam was conducted between 1987-1989, finally including 15,792 subjects. These participants were re-examined every three years, with the second exam conducted between 1990-1992 (N=14,348 subjects). The second exam had relatively complete DM-related data including HbA1c and therefore was used as the baseline in

Project 1 and Project 2 as parts of the pooled cohort. Because the baseline of ARIC was approximately 10 years older than all other cohorts, ARIC was separately analyzed in Project 1 and Project 2.

Follow-up occurred semi-annually, by telephone, to maintain contact and to assess health status of the cohort till Dec 2016. Content of follow-up included an extensive of CVD and non-CVD outcomes including but not limited to: death cause and date, CHD, stroke/TIA, hoptalizations, intermittent claudication, angina, cardiovascular procedures, medication use, cancer, diabetes, hypertension, pumonary disease, etc. Most CVD events (except for HF before 2005) were collected from wide sources of interview, hospitalization/medical records, national death index, follow-up examination and were adjudicated by ARIC reviewers.

2.2 CARDIA

The Coronary Artery Risk Development in Young Adults (CARDIA) Study focused the development and determinants of clinical and subclinical cardiovascular disease. It began in 1985-1986 with a total sample of 5115 males and females aged 18-30 years. Caucasians and African Americans were included. The participants were selected with similar age, sex, race and education distribution in each of 4 centers: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. Follow-up examinations occurred during 1987-1988 (Year 2), 1990-1991 (Year 5), 1992-1993 (Year 7), 1995-1996 (Year 10), 2000-2001 (Year 15), 2005-2006 (Year 20), 2010-2011 (Year 25), and 2015-2016 (Year 30). At Year 20 Exam (2005-2006) HbA1c levels were first measured and Year 20 Exam was used as baseline exam in Project 2 (N=3,547).

During their scheduled study examinations and yearly telephone interviews, participants or designated proxy was asked about interim hospital admissions, outpatient procedures, and deaths till Dec 2017. Two physicians of the CARDIA Endpoints Committee independently reviewed medical records to adjudicate each possible CVD event or underlying cause of death using specific definitions and a detailed manual of operations (http://www.cardia.dopm.uab.edu). If disagreement occurred between the reviewers, the case was reviewed by the full committee.

2.3 FHS Offspring

The Framingham Heart Study (FHS) is an epidemiologic study begun in Framingham in 1948 with 5,209 residents in Framingham, Massachusetts. After World War II, US witnessed a rapid increase of heart disease and there was need to increase the understanding CVD etiology. So far the entire FHS has recruited five distinct cohorts including the Original Cohort, Offspring Cohort, Omni One Cohort, Generation Three Cohort, New Offspring Spouse Cohort and Omni Two Cohort. FHS was maintained under the conjunct effort of of Boston University and the NHLBI.

The Offspring Study was initiated in 1971-1975 when the need for establishing a prospective epidemiologic study of young adults was recognized. A sample of 5,124 men and women, consisting of the offspring of the Original Cohort and their spouses was recruited. Repeated examinations were done every four years. HbA1c was measured at Exam 7 (1998 – 2001, N=3,539) and was used as baseline exam for Project 1 and Project 2. All events for FHS Offspring participants are adjudicated periodically by a panel of 3 physicians who evaluate all medical and hospital records. Follow-up lasted till December 2013.

2.4 JHS

The Jackson Heart Study (JHS) is a single-site, community-based epidemiologic study of environmental and genetic factors associated with cardiovascular disease among African Americans. The JHS is funded by the NHLBI and the National Institute on Minority Health and Health Disparities (NIMHD) and is conducted in Jackson, Mississippi. JHS has included the widest age range from 21-84 years old among all cohorts used in this dissertation. HbA1c was measured at Exam 1 (2000-2002), which was the baseline used in Project 1 and Project 2. The JHS expand the Jackson Field Center of the ARIC study in the African American population so 1,622 out of the 5,302 JHS participants are also ARIC participants. In both projects where JHS and ARIC were used as parts of the pooled cohort, the 1,626 JHS subjects were excluded from analysis. JHS has used similar study protocols as ARIC.

JHS participants are contacted annually by telephone to update personal and health information including vital status, interim medical events, hospitalizations, functional status and sociocultural information. Ongoing cohort surveillance for cardiovascular events (i.e., CHD and related procedures, HF, and stroke) and deaths also involves data linkage with hospital discharge lists of JHS catchment area hospitals and the NDI. Medical records of cardiovascular disease related hospitalizations and death certificates are abstracted and used for adjudication of cardiovascular events and related deaths.

2.5 MESA

The Multi-Ethnic Study of Atherosclerosis (MESA) is a study of the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. It is a population-based, prospective cohort study involving 6,814 persons aged 45 - 84 years old free of clinical CVD at baseline []. Participants were recruited and underwent the first exam during 2000 and 2002 in six US field centers (Baltimore; Chicago; Forsyth County, North Carolina; Los Angeles; New York; and St Paul, Minnesota) from four race/ethnic groups of Caucasian (38%), African American (28%), Hispanic American (22%), or Chinese American (12%). HbA1c was only available at MESA Exam 2 (2003-2004) and therefore were used as baseline for Project 1 and Project 2.

The cohort was followed till the end of year 2017. At intervals of 9-12 months, a telephone interviewer inquired about interim hospital admissions, cardiovascular diagnoses, and deaths. MESA obtained medical records for about 98% of hospitalized events and information about 95% of outpatient cardiovascular diagnoses. Follow-up telephone interviews were completed in 92% of living participants. An adjudication committee received copies of all death certificates and medical records for hospitalizations and outpatient cardiovascular diagnoses and conducted next-of-kin interviews. Two physicians independently classified and assigned incidence dates. For disagreements, a full mortality and morbidity review committee made the final classification.

2.6 ACCORD

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was specifically designed to determine whether a therapeutic strategy targeting normal glycated hemoglobin levels (i.e., below 6.0%) would reduce the rate of cardiovascular events, as compared with a strategy targeting glycated hemoglobin levels from 7.0 to 7.9% in middle-aged and older people with type 2 DM and either established cardiovascular disease or additional cardiovascular risk factors. ACCORD was sponsored by the NHLBI and conducted in 77 clinical centers across the United States and Canada.

Volunteers with a HbA1c ≥ 7.5% and age of 40 - 79 years with cardiovascular disease or age of 55 - 79 years with anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, current status as a smoker, or obesity) were recruited. The finding of higher mortality in the intensive-therapy group led to a decision to terminate the intensive regimen in February 2008, 17 months before the scheduled end of the study. In addition to the main hypoglycemic trial, the entire cohort was split to two equal samples, one to investigate effect the intensive vs. standard anti-hypertensive treatment and the other for intensive vs. standard lipid-lowering treatment. So 1/4 of the entire ACCORD trial received completely standard treatment.

Although terminated early, the ACCORD managed to extend follow-up to a maximal of 13 years as ACCORD Follow-On study (ACCORDION). The ACCORDION data was used as external validation cohort in Project 2.

2.7 Table

Table 2-1. Cohort Summary

	ARIC	**MESA**	**CARDIA**	**JHS**	**FHS Offspring**
Original Baseline exam	1987-1989	2000-2002	1985-1986	2000-2002	1971 - 1975
Original Baseline Age	45-64	45-84	18-30	21-84	5 - 70
Original Sample Size	15,792	6,814	5,115	5,302	4,095
Baseline in the project [a]	**1990-1992 (Exam 2)**	**2003-2004 (Exam 2)**	**2005-2006 (Year20 Exam)**	**2000-2002 (Exam 1)**	**1998-2001 (Exam 7)**
Sample size in the project	13454	6233	3547	3680	3539
Race/Ethnicity	Caucasian African-American	Caucasian African-American Hispanic Asian	Caucasian African-American	African-American	Caucasian
Center locations	MD, NC, MS, MN	MN, IL, MD, NY, NC, CA	AL, MN, IL, CA	Jackson, MS	Framingham, MA

a. Baseline of cohort in the projects were determined by the exams when HbA1c were first measured.

3. Identification and Predictors for Cardiovascular Disease Risk Equivalents among Adults with Diabetes Mellitus

Short title: CVD risk equivalent among adults with diabetes

3.1 Abstract

Background: It is unknown whether diabetes mellitus (DM) is a cardiovascular disease (CVD) risk equivalent when accounting for DM severity and other CVD risk factors. We aimed to investigate the factors that influence DM-related CVD risk equivalence.

Methods: We pooled 4 US community-based cohorts (ARIC, JHS, MESA, FHS Offspring) and classified subjects into DM-/CVD-, DM+/CVD-, DM-/CVD+ or DM+/CVD+ at baseline. DM+/CVD- were further classified by DM duration, HbA1c control or DM medication. Adjusted hazard ratios (HRs) were estimated for CVD during a median follow-up of 14 years. Subgroup analysis comparing the HR of DM+/CVD- vs. DM-/CVD+ was done by age, sex, race, hypertension, dyslipidemia, obesity, etc. We defined one with DM+/CVD- as CVD risk equivalent DM if his/her relative CVD risk was as high or higher than if he/she had DM-/CVD+. The CVD risk profile and CVD risk were compared between the CVD risk equivalent subgroups in DM+/CVD-.

Results: The pooled cohort included 27,732 adults (mean age of 58 years, 45% males). CVD event rates per 1000 person-years were 16.3, 33.3, 40.9 and 69.0 among those with DM-/CVD-, DM+/CVD-, DM-/CVD+ and DM+/CVD+, respectively. DM participants with HbA1c≥7%, DM duration over 10 years, or DM medication use had similar CVD risk as those with DM-/CVD+ while those without these factors had lower CVD risk. DM+/CVD- had similar CVD risk as

those DM-/CVD+ among woman, age <55 years, White race, or high triglycerides groups. Among those with DM+/CVD-, 17.5% were found to have CVD risk equivalent DM. But these persons had lower 10-year ASCVD risk (14.8% vs. 22.7%) however much higher observed CVD risk, with adjusted HRs compared to DM-/CVD- of 2.65 (2.37-2.97) vs. 1.40 (1.31-1.49) for those with DM but not at CVD risk equivalent status.

Conclusion: Among CVD-free adults with DM, we show fewer than 20% are actually CVD risk equivalent DM. Poor HbA1c control, long DM duration, and current diabetes medication use were identified as predictors of CVD risk equivalent status. Moreover, we showed DM to be more detrimental for CVD risk if one is woman, younger age, White, or with high triglycerides. Intensified treatment should be considered for these populations.

3.2 Introduction

The concept of the "coronary heart disease (CHD) risk equivalent" was first introduced by Haffner et al. [1] In this landmark study, the investigators observed that the myocardial infarction (MI) incidence rate for diabetic subjects without prior MI (DM+/MI-) was as high as that of those who had a history of MI but no DM (DM-/MI+), which demonstrated that diabetic patients had a CHD risk comparable to the secondary prevention population and should be given similar approach to manage CVD risk. Many subsequent studies have kept exploring the question "Is DM a CHD or cardiovascular disease (CVD) risk equivalent?" however, the results have been inconsistent. [2-7] A meta-analysis of 13 cohort studies comprised of 45,108 participants showed that those with diabetes had 43% lower risk for future CAD events (fatal or non-fatal myocardial infarction) compared with those with a prior MI. [5] A study of 1.6 million Kaiser Permanente Northern California patients aged 30-90 years found those with DM but no history of CHD had a 39% lower 10-year CHD risk than those with CHD and no history of diabetes. [6]

Multiple reasons could potentially contribute to the different conclusions among these studies. [7,8] For instance, compared to the studies concluding that DM is not a CHD risk equivalent, the studies supporting DM as CHD risk equivalent tended to include more severe DM with longer duration, or to be more Caucasian, or to have longer follow-up time. [2-4] In addition, contemporary DM populations substantially differ from the historical cohorts in aspects of diagnosis algorithm, treatment strategies, and DM severity, all of which influence the answer to the question, "Is DM a CVD risk equivalent for global CVD events?". Some of the studies failed to adjust for other CVD risk factors, making the CVD risk comparison between DM only vs. CVD only subjects potentially influenced by comorbidities. [2,9] In addition, no prior studies

have been done to systematically evaluate what factors makes the DM in a person a "true" CVD risk equivalent. Addressing this gap in the literature has important clinical implications as intensified therapeutic intervention may be warranted in those adults with diabetes at highest CVD risk

We aimed at evaluating overall CVD risk burden among those with DM compared to those with no DM but prior CVD and identifying what factors, including DM-specific risk factors (DM duration, HbA1c control and medication use) and non-DM specific risk factors such as age, sex, dyslipidemia, etc. would influence the CVD risk among DM compared to those with prior CVD and no DM in a large pooled, contemporary cohort from the US population. In addition, we integrated the identified factors to define one as having "CVD risk equivalent" DM if his/her relative CVD risk was as high as or higher than that had he/she had no DM but CVD history. Finally, we compared the CVD risk profile and actual CVD risk between the CVD risk equivalent DM vs. non-CVD risk equivalent DM subjects.

3.3 Methods

Study Sample

We pooled four US cohorts on cardiovascular studies with diverse ethnic, geographical and temporal backgrounds: the Atherosclerosis Risk In Communities (ARIC) Study, Multi-Ethnic Study of Atherosclerosis (MESA), Jackson Heart Study (JHS) and Framingham Heart Study Offspring cohort (FHS Offspring). [10-13] Because HbA1c is one of the current DM diagnosis criteria, our study used as baseline exams in each cohort when HbA1c measure was first available instead of the original baseline [Exam 2 (1990-1991) for ARIC, Exam 2 (2003-2004)

for MESA, Exam 1 (2000-2002) for JHS and Exam 7 (1998-2001) for FHS Offspring] which leads to us having a more contemporary cohort than if the original baseline exams were used. Subjects between ages of 30-84 were included. Participants from both JHS and ARIC were excluded from the JHS cohort with the ARIC exam used instead as their baseline.

Participants were classified into four groups: no DM or prior CVD (DM-/CVD-), having DM and no prior CVD (DM+/CVD-), having no DM but prior CVD (DM-/CVD+) and having both DM and prior CVD (DM+/CVD+). DM was defined as having at least one of the following before or at baseline: (1) use of diabetes medication; (2) self-report of DM; (3) fasting blood glucose of ≥ 6.99 mmol/l (126 mg/dL); (4) 2h post-challenge glucose ≥11.1 mmol/l (200 mg/dL); or (5) A HbA1c ≥6.5% (48 mmol/mol). Prevalent CVD at baseline is defined as having at least one of below before the baseline exam: myocardial infarction, cardiac revascularization, stroke, heart failure, or peripheral vascular disease. Participants with DM+/CVD- were further classified by: (1) DM duration: Newly diagnosed DM, DM duration <10 years and DM duration 10+ years; (2) HbA1c control: <7% vs.≥7%; (3) DM medication use: yes vs. no. In sensitivity analysis, HbA1c level were classified as <7%, 7% - <9% and ≥9%.

Baseline Risk factors

We collected the following baseline information: age, sex, race/ethnicity, family history of premature CVD, smoking status, alcohol use, body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) diabetes duration, hemoglobin A1c (HbA1c), DM medication; high sensitivity C-reactive protein (hs-CRP), high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), triglycerides, total cholesterol, serum

creatinine atrial fibrillation, left ventricular hypertrophy (LVH), lipid-lowering medication and anti-hypertensive treatment. Estimated glomerular filtration rates (eGFR) were calculated from the MDRD equation. 10-year ASCVD risk scores were calculated by the Pooled Cohort Equation (PCE) among those without prior CVD. [14] All variables had less than 7% missing data. Missing data on risk factors were filled in with multiple imputation, more specifically, fully conditional specification methods. Continuous variables with skewness >1 were log transformed and used in multiple imputation. Complete case analysis was done as sensitivity analysis.

Follow-Up and Endpoint Definitions

Our primary endpoint of interest was incident CVD, a composite endpoint including myocardial infarction, cardiac revascularization, stroke, heart failure (HF), peripheral vascular disease (PVD and CVD death. Time to event was recorded as the time from our baseline exam to the first of above events or time to death, loss to follow-up or the last date of follow-up if no events occurred. The adjudication process for events involved a panel to review hospitalization and death data per study protocols previously published. [10-13] According to the designated baseline exam in the project, the maximum follow-up time was 26.9 years for ARIC, 13.8 years for MESA, 17.4 years for JHS and 13.3 years for the FHS Offspring cohort.

Statistical Analysis

All continuous variables were compared among the DM/CVD groups using ANOVA. Continuous variables with skewness >1 were log transformed to get a normal distribution. The Chi-square test was used to compare categorical variables. Baseline risk profiles were further compared between those with DM+/CVD- vs. DM-/CVD+. CVD event rates per 1000 person-

years were calculated in each DM+/CVD- groups and further by CVD risk factor groups or cohort.

Cox proportional hazards regression was used to calculate the HR of CVD risk for DM-/CVD+ (overall and by duration, HbA1c control, DM medication use) vs. DM-/CVD+ group when: (1) unadjusted; (2) adjusted for age, sex and race; (3) adjusted for all risk factors. Subgroup analysis comparing the HR of DM+/CVD- vs. DM-/CVD+ was done by age (<55 years, 55-65 years, 65+years), sex, race (white, black, other races), cohorts (ARIC vs. other cohorts), family history of CVD, current smoking, hypertension, triglycerides dyslipidemia (≥ 200mg/dL vs. < 200mg/dL), HDL-C dyslipidemia (< 40mg/dL for men or < 50mg/dL for women vs. ≥ 40mg/dL for men or ≥ 50mg/dL for women), obesity (BMI ≥ 30kg/m^2 vs. < 30kg/m^2), hs-CRP levels (≥2 mg/L vs. < 2mg/L), and chronic kidney disease (eGFR >90 ml/min/1.73m^2, 60-89 ml/min/1.73m^2, <60 ml/min/1.73m^2). In sensitivity analysis, we redid subgroup analysis for triglycerides as <150mg/dL, 150-200 mg/dL and ≥ 200mg/dL, BMI as <25 kg/m^2, 25-<30 kg/m^2, and ≥ 30kg/m^2.

To define the CVD risk equivalent DM in the DM+/CVD- group, we integrated relative log risk of DM+/CVD- by summing the beta coefficients for all the variables that impact HR of the DM+/CVD- vs. DM-/CVD+ in the Cox regression model. In the Cox model, the DM/CVD variable was dummy coded using those with DM-/CVD+ as the reference group. Beta coefficients were defined as β_1 for DM+/CVD- variable, and β_{1X} for statistically significant interaction of DM+/CVD- variable and other variables X in the model. For anyone from the

DM+/CVD- group with a comparable/higher CVD risk than that if he/she had DM-/CVD+, his/her risk factor value X would satisfy the equation:

$$1 - S_t^{e^{(\beta 1 * 1 + \sum \beta 1X * 1 * X + \beta hba1c * HbA1c + \sum \beta x * X)}} \geq 1 - S_t^{e^{(\beta hba1c * (6.5 \text{ or } HbA1c) + \sum \beta x * X)}}$$

So we get:

$$\beta_1 + \sum \beta_{1X} * X + \beta_{HbA1c} * HbA1c \geq \beta_{HbA1c} * (6.5 \text{ if } HbA1c \geq 6.5 \text{ or } HbA1c \text{ if } HbA1c < 6.5)$$

Similarly, if one with DM+/CVD- does not qualify the CVD risk equivalent, his/her risk profiles would satisfy:

$$\beta_1 + \sum \beta_{1X} * X + \beta_{HbA1c} * HbA1c < \beta_{HbA1c} * (6.5 \text{ if } HbA1c \geq 6.5 \text{ or } HbA1c \text{ if } HbA1c < 6.5)$$

Those with DM+/CVD- was reclassified as a non-CVD risk equivalent DM vs. CVD risk equivalent DM subgroups. We further compared the risk factor profile and incident CVD risk among the above two risk categories in subjects with DM.

Statistical analysis was done using SAS (version 9.4; SAS Institute, Cary, NC). A two-sided p value <0.05 (and p value <0.1 for interaction test) was considered statistically significant.

3.4 Results

Baseline Risk Factors

In a total of 27,732 study participants, 3,735 (13.5%) had DM only, 2,563 (9.2%) had prior CVD only and 1,135 (4.1%) had both DM and prior CVD. At baseline, those with DM+/CVD-, DM-/CVD+ and DM+/CVD+ has poorer non-modifiable or untreated risk factors such as age, sex, family history of CVD, and hs-CRP, etc. Modifiable and treated risk factors like SBP and LDL-

C had smaller disparities among the groups. Compared to those with DM+/CVD-, those with DM-/CVD+ were slightly older, with more male, more white race, more smokers and alcohol consumers, more with family history of CVD, more LVH and Afib, higher LDL-C and serum creatinine however with lower SBP, BMI, triglycerides, hs-CRP and higher HDL. Lipid and blood pressure medication uses were similar between the two groups (Table 3-1).

CVD Risk among DM/CVD Groups

During a median follow-up of 13.9 years, there were 5105 (25.2%), 1566 (41.9%), 1293 (50.5%) and 707 (62.3%) incident CVD events that occurred among those with DM-/CVD-, DM+/CVD-, DM-/CVD+ and DM+/CVD+, respectively. Corresponding CVD event rates per 1000 person-years were 16.3, 33.3, 40.9 and 69.0, respectively. Event rates per each study are presented in Supplemental Figure 3-1. We examined the relative CVD risk by HRs by DM/CVD status at three levels of covariate adjustment (Figure 3-1). The unadjusted HRs for DM+/CVD-, DM-/CVD+ and DM+/CVD+ vs. DM-/CVD- were 2.22 (95%CI: 2.10-2.35), 2.89 (95%CI: 2.71-4.71) and 5.10 (95%CI: 4.71-5.52), respectively. With full adjustment of non-DM specific CVD risk factors, the HRs for all three groups were attenuated to different extents. Regardless of levels of adjustment, there was stepwise increase of CVD risk among those with DM-/CVD-, DM+/CVD-, DM-/CVD+ and DM+/CVD+.

CVD Risk Comparing Those with DM+/CVD- (and Its Severity Groups) vs. DM-/CVD+

We classified those with DM+/CVD- according to DM severity indicated by HbA1c control, DM duration or medication use and examined their CVD risk vs. that in DM-/CVD+. Overall, those with DM+/CVD- had a 17% lower CVD risk than those with DM-/CVD+ independent from

other CVD risk factors [HR: 0.83 (95%CI: 0.76-0.89), p<0.0001]. In Table 3-2, it is shown that among CVD-free DM subjects, HbA1c ≥7% or DM medication use had CVD risk comparable to that among those with DM-/CVD+ [HR: 1.06 (95%CI: 0.96-1.16) and 1.03 (95%CI: 0.94-1.13), p=NS]. When those with DM+/CVD- and uncontrolled HbA1c was further classified as <9% vs. ≥ 9%, HRs were 0.94 (95%CI: 0.84-1.04) and 1.30 (95%CI: 1.14-1.47) compared to those with DM-/CVD+. Having a DM duration 10 years or more was associated with a 17% higher risk than the DM-/CVD+ group [HR: 1.17 (95%CI: 1.04-1.32), p<0.05] while newly diagnosed DM had a 39% lower CVD risk [HR: 0.61 (95%CI: 0.54-0.67), p<0.0001].

Subgroup Analysis

In subgroup analysis, we examined the HRs of DM+/CVD- vs. DM-/CVD+ according to other CVD risk factors. Unadjusted event rates were presented in Supplementary Figure 3-2. We found that female, white race, age <55 years old and elevated triglycerides tended to have similar CVD risks as those with DM-/CVD+ (HRs close to 1 with non-significant p values), while male, Black or other races, Age ≥55 years or those with triglycerides < 200 mg/dL had lower CVD risk than those with DM-/CVD+, with HRs ranging from 0.58-0.80 (Figure 3-2). We also examined the HRs of DM+/CVD- vs. DM-/CVD+ in the combined age, sex, race groups (Supplemental Figure 3-3) and it was found that there is linear trend of HRs by age in females but not in males.

Given the baseline of ARIC was about 10 years earlier than the other four cohorts, we investigated the potential cohort effect in sensitivity analysis. In ARIC (N=14,331), DM+/CVD- had CVD HR of 0.96 (95%CI: 0.88-1.06, p=0.44) compared to DM-/CVD+; while in the pooled non-ARIC cohort (N=13,401), the corresponding HR was 0.66 (95%CI: 0.56-0.77, p<0.0001).

The subgroup analysis according to other risk factors was presented in Supplemental Table 3-1. Three-category BMI subgroup analysis found those normal weighted ones and obese ones tended to be CVD risk equivalent while the over weighted had 23% lower CVD risk than those with DM-/CVD+ [HR= 0.77(95% CI: 0.68-0.88). Those with triglycerides levels between 150-200 mg/dL has similar HRs as those with triglycerides < 150mg/dL.

In the above subgroup analysis, we did not adjust for DM severity variables in the Cox regression model. Therefore, the heterogenous HRs of DM+/CVD- vs. DM-/CVD+ by sex, race, age categories or triglycerides categories could be potentially contributed the DM severity itself. Therefore, we explored percentage of subjects with HbA1c ≥7%, or DM duration ≥ 10 years, or DM medication in each of the sex, race, age or triglycerides groups (Table 3-3). It was observed that females had slightly more severe DM than males at baseline and those with triglycerides ≥200 mg/dL had higher proportion of uncontrolled HbA1c than those with triglycerides < 200 mg/dL (53.2% vs. 42.2%, p <0.0001). However, in younger subjects and white subjects, DM were generally less severe, except that younger DM patients had poorer HbA1c control rate.

Defining CVD Risk Equivalent among Those with DM+/CVD-

Given the above findings, we constructed the algorithm to define CVD risk equivalent DM in DM+/CVD- group as: β1*(DM+/CVD1-) + β2* (DM+/CVD-)*age +β3* (DM+/CVD-)*sex + β4* (DM+/CVD-)*sex*age+ β5* (DM+/CVD-)*white +β6* (DM+/CVD-)*triglycerides +β7*HbA1c +β8* DM duration over 10 years + β9* DM medication use. Corresponding beta coefficients were estimated from the Cox model adjusted for other risk factors and other two DM/CVD categories. Based on the comparison of Σbeta*X vs. Σ beta*X' , where X was the

variable value of an DM+/CVD- individual and X' was the variable value had he/she had DM-/CVD+, an individual was classified to have a CVD risk equivalent DM when $\Sigma beta*X \geq \Sigma beta*X'$ or non-CVD risk equivalent DM when $\Sigma beta*X < \Sigma beta*X'$. We presented beta coefficient with an individual example to illustrate the classification process (Supplemental Table 3-3).

Among the 3,735 subjects with DM+/CVD-, 652 (17.5%) were found to have CVD risk equivalent DM according to the above definition. Table 3-4 showed the comparison of baseline risk factors between those with CVD risk equivalent DM vs. non-CVD risk equivalent DM. Those with CVD risk equivalent DM were significantly younger, with more women and obviously with higher HbA1c, longer DM duration as well as more frequent DM medication use. They also had a poorer lipid profile, especially higher triglycerides and higher CRP; however, slightly better BP control. We calculated the PCE for 10-year ASCVD risk in the two groups and found those with non-CVD risk equivalent DM had mean PCE of 22.7% while CVD risk equivalent DM group had mean PCE of 14.3% ($p<0.0001$). Actual CVD event rates per 1000 person-years were 31.0 vs. 44.9 among those with non-CVD risk equivalent DM vs. CVD risk equivalent DM. Compared to those with DM-/CVD-, those with non- CVD risk equivalent DM had a HR of 1.40 (95%CI: 1.31-1.49, $p<0.0001$), while those with CVD risk equivalent DM had a HR of 2.65 (2.37-2.97, $p <0.0001$) when adjusted for age, sex, race and other non-DM specific risk factors.

Complete-Case Analysis

We included 2,2096 subjects with complete information on related baseline variables and events follow-up. For continues baseline variables, the relative difference of complete case analysis vs. main analysis samples was less than 1%, with the exception of glucose (relative mean difference= -2.2%) and hs-CRP (relative mean difference= -5.2%). For categorical baseline variables, the difference complete case analysis vs. main analysis samples was less than 2.2%.

We re-ran main analysis in the sample with complete information. The fully adjusted HRs for those with DM+/CVD-, DM-/CVD+ and DM+/CVD+ vs. DM-/CVD- were 1.52 (95%CI: 1.42-1.63), 1.88 (95%CI: 1.73-2.03) and 2.40 (95%CI: 2.15-2.68), respectively. Overall, those with DM+/CVD- had 19% lower CVD risk than those with DM+/CVD- (HR= 0.81, 95% CI= 0.74-0.89). CVD HRs of DM severity groups vs. DM-/CVD+ were similar in complete case analysis vs. main analysis (Supplementary Table 3-4). Subgroup analysis of HRs of DM+/CVD- vs. DM-/CVD+ were also similar to those in main analysis (Supplementary Table 3-4).

3.5 Discussion

In our pooled study of four large US community-based cohorts, we found that there is stepwise increase of CVD risk among those with DM-/CVD-, DM+/CVD-, DM-/CVD+ and DM+/CVD+. All CVD-free DM is not CVD risk equivalent with an average 17% lower CVD risk than those with DM-/CVD+. Among those with DM+/CVD-, poor HbA1c control, long DM duration or current diabetes medication use were found to be CVD risk equivalents. In addition, those with DM+/CVD- had similar CVD risk to that of those with DM-/CVD+ if one is a woman, younger age, white, or with elevated triglycerides, indicating that having DM is more detrimental in these subgroups. When we aggregated above factors to define the CVD risk equivalent DM among

subjects with DM, about one-fifth of DM subjects were found to have CVD risk equivalent DM, whose DM-conferred CVD risk is equal or higher than that if he/she had no DM but prior CVD. They tended to have better CVD risk profiles (except for DM severity) than other non-CVD equivalent DM and even lower 10-year CVD risk score, yet their actual CVD risk remain higher than Non-CVD risk equivalent DM.

It has been widely accepted that DM individuals have heterogenous CVD risk and having DM does not guarantee CVD risk equivalence. Our current study confirms earlier findings showing the primary prevention population with DM to have a lower CVD risk than secondary prevention population without DM. In the contemporary era, early detection and diagnosis of DM, emerging hypoglycemic medication with cardiovascular protective effect and the overall improved DM management all contribute to the reduced CVD risk among DM. Our analysis also shows a cohort effect that the DM+/CVD- tended to be CVD risk equivalent in the 1990s cohort of ARIC but not in 2000s cohort pooled from JHS, MESA and FRS offspring. This is consistent with Haffner's earlier findings indicating DM to be a CHD risk equivalent from Finnish men studied in the 1990's. [1]

It is known that DM severity affects CVD risk. In the current study, we found that those DM subjects with poor HbA1c, long DM duration, and glucose-lowering medication use tended to be risk equivalents for future CVD events. These results are consistent with several prior studies. Schramm et al. reported that DM patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk. [2] Both Rana's study using the 16000+ North California Kaiser Permanente data and Wannamethee et al. reported that

diabetes duration of at least 10 years was a CVD risk equivalent. [6,15] Mondesir et al. defined severe DM as insulin use and/or with albuminuria (urinary albumin-to-creatinine ratio⩾30 mg/g) [16] and found only those with severe DM were CHD risk equivalent.

In addition to the DM severity indicators, sex, race, age and triglyceride levels also modified the effect of DM on CVD risk. It is well established that greater DM is associated with greater relative CVD risk among women than among men. [17] The FINAMI study found in women with DM suffered similar MI risk as women with prior MI but not in men. [9] Another study found that females with known DM had higher even higher CHD risk than those with DM-/CHD+ among the young Middle East population. [18] Kautzky-Willer et al. reviewed the sex/gender difference of DM complications and pointed out that reproductive factors, symptoms, psychosocial stress, comorbidities, greater "cardiometabolic load," and inflammation all contributed to the unfavorable CV outcomes in DM women than DM men. [19] In addition, DM onset at younger age indicated early insulin resistance and DM at younger age was found to be associated with higher relative CVD risk than late onset DM. [20-22] The age-specific association of HbA1c and CVD also shows consistent results in that HRs of HbA1c for CVD were higher at younger age. [23] Our findings that DM+/CVD- has similar CVD risk to DM-/CVD+ among white helps explain why most European studies on the topic concluded that DM is a CVD risk equivalent [3,4] while US studies with diverse race groups tended to refute the conclusion. [6,24] In addition, we found that females and those with high triglycerides tended to have more severe DM, which explain why DM were more of a CVD risk equivalent to woman or hypertriglyceridemia population. It has been found that insulin resistance can cause hypertriglyceridemia as the most commonly seen dyslipidemia among DM patients and there is

positive correlation between HbA1c and triglycerides levels [25, 26]. In the current study we also found that although high triglycerides were not necessarily related DM duration or DM medication use, it is associated with significantly higher frequency of poor HbA1c control, which may explain the high CVD risk conferred by DM in the high TG patients. However, younger DM and the white do not seem to have more severe DM and the detrimental effect of DM looks like more intrinsic irrespective of the DM severity measures.

We classified those with DM+/CVD- into non-CVD risk equivalent DM vs. CVD risk equivalent DM based on their HbA1c, DM duration, DM medication, age, sex, race and triglycerides level. Only a small proportion of subjects had sufficiently severe DM as a CVD risk equivalent while holding other risk factors unchanged. It is worth noting that this group of subjects had lower 10-year ASCVD risk scores, yet their DM-conferred CVD risk is almost twice as high as that in those with non-DM CVD risk equivalent DM. Given the current risk stratification criteria [27], most of the subjects with CVD risk equivalent DM did not reach the 20% high risk threshold yet their observed CVD risk was estimated to be equivalent or even higher than the secondary prevention population.

Our data support the need for consideration of more intensified clinical management for those with CVD risk equivalent DM. For instance, aspirin is not currently recommended to all DM patients given the limited CVD benefit and potentially increased bleeding risk, but has been recommended for those with DM at higher risk or with pre-existing CVD. [28] With the identification of CVD risk equivalent DM among DM patients, effect of aspirin can be re-evaluated for those where the benefit would overweigh the harm. Similar consideration can be

given for considering more intensified treatment targets (or thresholds that should be reached) as in the case of secondary prevention, and where additional non-statin therapy may be indicated. Further, in clinical trials, the CVD risk equivalent DM can be more precisely included as a high-risk primary prevention population to maximize treatment effects; current approaches often involve identifying higher risk persons by a count of risk factors that is less precise. Another important clinical implication of our study is to point out the problem of current CVD risk assessment tool which includes DM as binary predictor and neglect all the DM-related factors. Risk scores like FRS and PCE cannot accurately depict the DM-associated CVD risk and can even lead to underestimation of CVD risk as is shown in our study. There is need to develop DM-specific risk scores to include DM-specific predictors and use DM-specific predictor weight in risk calculator. DM-specific CVD risk scores including UKPDS OM2, RECODE score and IDC Risk Scores newly developed from Cleveland DM patient cohort may have better performance than those for the general population. [29-31]

We should note our classification of DM+/CVD- into CVD risk equivalents vs. non-CVD risk equivalents does not indicate the overall CVD risk burden but is more of an indicator for the CVD risk conferred by DM. In other words, we tried to identify whether a person with DM but no CVD had CVD risk comparable to that if he/she had no DM but prior CVD while his/her other risk profiles remain unchanged instead of whether a person with DM but no CVD had CVD risk comparable to the overall DM-/CVD+ population. Our study is not intended and not able to take over the work of a risk calculator -- to evaluate the overall CVD risk caused by other comorbidities such as hypertension and dyslipidemia. Although the 2019 ADA guidelines defined DM patients with one or more ASCVD risk factors or 10-year ASCVD risk ≥20% as

"ASCVD risk equivalent", i.e. similar ASCVD risk as those with prior ASCVD, this approach may have limitations because the ASCVD risk in those with ASCVD constantly changes and their 10-year risk cannot always be 20%. [28] We have used the term 'CVD risk equivalent" to define if one's DM is a CVD risk equivalent or not, rather than if a DM patient is CVD risk equivalent or not. By saying this, we do not mean to neglect the overall CVD risk of those with DM; on the contrary, we recommend intensified treatment in those with CVD risk equivalent DM who may be neglected by conventional CVD risk assessment, especially in risk scores that rely on a binary DM predictor are used such as the PCE or FRS. [32]

Our study has several key strengths. We included whole spectrum of CVD events, including HF and PVD within our primary endpoint, which is important given the predominance of these conditions as first CVD manifestations in those with DM. [33] Our pooled cohort was all community-based with diverse race/ethnicity and a wide age range. Meanwhile, our findings should be interpreted with the following limitations. First, the endpoint definition of PVD was slightly different across cohorts. Also, since incident PVD was not common as the first incident CVD in our cohorts, it may have limited impact. Another limitation is that we did not examine the CVD risk equivalent for individual CVD endpoint while many of previous studies focused on whether DM may still be CVD risk equivalent for a variety of endpoints including stroke, PVD, total mortality and even healthcare cost. [34-37] At last, MESA was CVD-free at exam 1 so at our baseline (exam 2) MESA had fewer subjects with prior CVD than the other cohorts. However, the combined distribution of prevalent DM and prevalent CVD in our pooled cohort were similar to many of prior studies indicating a well-represented cohort that allows the generalizability of the study findings.

To conclude, our study found that DM is heterogenous and does not automatically confer CVD risk equivalence. Those adults with diabetes with poor HbA1c control, DM duration over 10 years, DM medication use, younger age, female sex, white race and elevated triglycerides tended to have CVD risk equivalent DM. Our definition of CVD risk equivalent DM can pick out those whose DM is as harmful as those with prior CVD but no DM which is not addressed by conventional risk assessment procedures. Those identified to have CVD risk equivalent DM warrant greater attention to optimize management to reduce CVD risk.

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3.6 Tables and Figures

Table 3-1. Baseline Characteristics by DM/CVD Groups

	DM-/CVD- N=20,299	DM+/CVD- N=3,735	DM-/CVD+ N=2,563	DM+/CVD+ N=1,135	p value [a,b]
Age, years	57.6 ± 9.5	60 ± 9.1	61.5 ± 10.7	63.6 ± 9.4	<0.0001
Male	8899 (43.8%)	1714 (45.9%)	1210 (47.2%)	546 (48.1%)	0.302
Race					<0.0001
White	12670 (62.4%)	1683 (45.1%)	1727 (67.4%)	590 (52%)	
Black	5989 (29.5%)	1620 (43.4%)	809 (31.6%)	525 (46.3%)	
Other races	1640 (8.1%)	432 (11.6%)	27 (1.1%)	20 (1.8%)	
Education level					0.0001
Less than high school	2925 (14.4%)	957 (25.6%)	646 (25.2%)	403 (35.5%)	
High school graduate	5440 (26.8%)	1007 (27%)	803 (31.3%)	313 (27.6%)	
Above high school	4875 (24%)	848 (22.7%)	486 (19%)	205 (18.1%)	
Smoking status					<0.0001
Never	8419 (41.5%)	1581 (42.3%)	884 (34.5%)	398 (35.1%)	
Prior	8331 (41%)	1569 (42%)	1052 (41%)	513 (45.2%)	
Current	3549 (17.5%)	585 (15.7%)	627 (24.5%)	224 (19.7%)	<0.0001
Alcohol use	11789 (58.1%)	1595 (42.7%)	1304 (50.9%)	393 (34.6%)	<0.0001
Family History of CVD	8524 (42%)	1634 (43.7%)	1420 (55.4%)	625 (55.1%)	<0.0001
SBP, mmHg	121.8 ± 18.6	129.7 ± 19.9	124.5 ± 19.6	130.5 ± 20.7	<0.0001
DBP, mmHg	72.6 ± 10.1	73.2 ± 10.4	72.4 ± 10.6	71.6 ± 10.7	0.005
BMI, kg/m^2	27.9 ± 5.5	31.4 ± 6.5	28.6 ± 6.2	31.5 ± 7.6	<0.0001
Heart rate, bpm	64.8 ± 9.9	69 ± 11.3	64.8 ± 11	69.7 ± 12.5	<0.0001
HbA1c, %	5.4 ± 0.4	7.3 ± 1.8	5.5 ± 0.5	7.6 ± 2	<0.0001
Fasting glucose, mg/dL	96.8 ± 12.1	156.2 ± 66.9	99.8 ± 12.6	167.7 ± 73.4	<0.0001
Cholesterol, mg/dL	202.5 ± 37.7	200.8 ± 42.4	205.4 ± 40.3	208.1 ± 48.4	<0.0001
LDL-C, mg/dL	126.1 ± 35.4	123.5 ± 38.3	130.2 ± 37.3	131.4 ± 43.4	<0.0001
HDL-C, mg/dL	52.2 ± 16.3	46.0 ± 14.2	49.0 ± 16.3	43 ± 14.2	<0.0001
Triglycerides, mg/dL	122.6 ± 74.5	162.1 ± 124.1	132.6 ± 78	175.9 ± 119.4	<0.0001
	105 [75-148]	133 [93-192]	113 [82-159]	146 [99-218]	
hs-CRP, mg/L	4.0 ± 6.7	5.9 ± 9.7	5.3 ± 7.9	7.9 ± 13.4	0.003

	2.0 [0.9-4.7]	3.2 [1.4-6.7]	2.9 [1.3-6.2]	4.3 [1.8-8.9]	
Serum creatinine, mg/dL	1.0 ± 0.3	1.1 ± 0.5	1.2 ± 0.6	1.2 ± 0.8	<0.0001
	1.0[0.9-1.2]	1.0 [0.9-1.2]	1.1 [1.0-1.2]	1.1 [0.9-1.3]	
Left ventricular hypertrophy	571 (2.8%)	149 (4%)	174 (6.8%)	127 (11.2%)	<0.0001
Atrial fibrillation	99 (0.5%)	19 (0.5%)	89 (3.5%)	60 (5.3%)	<0.0001
Lipid-lowering medication	1940 (9.6%)	706 (18.9%)	482 (18.8%)	294 (25.9%)	0.924
Hypertension medication	5905 (29.1%)	2133 (57.1%)	1526 (59.5%)	910 (80.2%)	0.055
DM medication	0 (0%)	1764 (47.2%)	0 (0%)	598 (52.7%)	<0.0001

a. p values specifically compares the difference between DM+/CVD- vs. DM-/CVD+ by t-test and chi2 test.
b. p values comparing the difference among all four groups (ANOVA or chi2 test) were all <0.001.
Continuous variables were presented as mean+-SD (and median [IQR] with skewed distribution); categorical variables were presented as frequency (percentage).

Table 3-2. Hazard Ratios of DM Severity Groups vs. DM-/CVD+

	Unadjusted HR	Age, sex and race adjusted HRs	Fully adjusted HRs
Overall DM+/CVD- vs. DM-/CVD+	0.77 (0.72-0.83) §	0.84 (0.78-0.90) §	0.83 (0.76-0.89) §
DM duration subgroups vs DM-/CVD+			
Newly diagnosed DM	0.61 (0.54-0.67) §	0.67 (0.61-0.75) §	0.67 (0.60-0.74) §
DM duration 0- <10 years	0.79 (0.72-0.86) §	0.86 (0.78-0.94) ‡	0.86 (0.78-0.94)†
DM duration 10+ years	1.11 (0.99-1.25)	1.13 (1.01-1.28)*	1.17 (1.04-1.32)*
HbA1c control subgroups vs DM-/CVD+			
HbA1c < 7%	0.64 (0.58-0.70) §	0.69 (0.63-0.75) §	0.70 (0.64-0.76) §
HbA1c ≥ 7%	0.97 (0.89-1.06)	1.07 (0.98-1.18)	1.06 (0.96-1.16)
DM medication use subgroups vs DM-/CVD+			
Not on DM medication	0.63 (0.58-0.69) §	0.71 (0.65-0.78) §	0.72 (0.65-0.78) §
On DM medication	1.00 (0.91-1.09)	1.03 (0.94-1.13)	1.03 (0.94-1.13)

Fully adjusted HRs were adjusted for age, sex, race, family history of CVD, education, smoking, alcohol use, SBP, BMI, triglycerides, HDL-C, hs-CRP, serum creatinine, lipid lowering medication, HTN medication, and other two DM/CVD groups.

*p<0.05, †p<0.01, ‡p<0.001, §p<0.0001

Tables 3-3. Frequency (%) of Poor HbA1c Control, Long DM Duration or DM Medication Use in Subgroups among Those with DM+/CVD-

	HbA1c ≥7%	DM duration 10+ years	DM medication use
Sex			
Female	945(46.76 %)	396(19.59 %)	985(48.74 %)
Male	725(42.3 %)	284(16.57 %)	779(45.45 %)
p value	0.006	0.02	0.05
Race			
White	621(36.9 %)	305(18.12 %)	581(34.52 %)
Black	837(51.67 %)	291(17.96 %)	882(54.44 %)
Other Races	212(49.07 %)	84(19.44 %)	301(69.68 %)
p value	<0.0001	0.772	<0.0001
Age groups			
<55 years	520(47.19 %)	131(11.89 %)	461(41.83 %)
55- <65 years	681(45.1 %)	278(18.41 %)	654(43.31 %)
≥ 65 years	469(41.76 %)	271(24.13 %)	649(57.79 %)
p value	0.03	<0.0001	<0.0001
Triglycerides levels			
≥ 200 mg/dL	1221(42.23 %)	536(18.54 %)	1354(46.84 %)
< 200 mg/dL	449(53.2 %)	144(17.06 %)	410(48.58 %)
p value	<0.0001	0.33	0.37

p values were calculated from chi2 test.

Table 3-4. Risk Factor Comparison by the CVD Risk Equivalent DM Condition in Those with DM+/CVD-

	Non-CVD risk equivalent DM N=3,083	CVD risk equivalent DM N=652	p value
Age, years	61.2±8.9	54.1±7.4	<0.0001
Male	1542 (50%)	172 (26.4%)	<0.0001
Race			<0.0001
White	1404 (45.5%)	279 (42.8%)	
Black	1289 (41.8%)	331 (50.8%)	
Other races	390 (12.7%)	42 (6.4%)	
Education			0.002
Less than high school	810 (26.3%)	147 (22.5%)	
High school graduate	808 (26.2%)	199 (30.5%)	
Above high school	678 (22.0%)	170 (26.1%)	
Smoking status			<0.0001
Never	1250 (40.5%)	331 (50.8%)	
Prior	1365 (44.3%)	204 (31.3%)	
Current	468 (15.2%)	117 (17.9%)	
Alcohol use	1352 (43.9%)	243 (37.3%)	0.002
Family history of CVD	1314 (42.6%)	320 (49.1%)	0.0025
SBP, mmHg	130.2±19.9	127.4±19.6	0.001
DBP, mmHg	73.3±10.5	72.7±9.9	0.189
BMI, kg/m2	31±6.2	33.4±7.5	<0.0001
HbA1c, %	6.8±1.2	9.9±2.1	<0.0001
Fasting glucose, mg/dL	139±44.4	237.4±91.4	<0.0001
DM onset age, years	56.6±10.3	45.5±9.5	<0.0001
DM duration, years	4.6±7.3	8.7±8	<0.0001
Cholesterol, mg/dL	197.7±40.4	215.4±48.1	<0.0001
LDL-C, mg/dL	122.1±37.4	130.2±41.6	<0.0001
HDL-C, mg/dL	46.4±14.2	44.6±14.3	0.003
Triglycerides, mg/dL	149.5±88.9	221.5±216.1	<0.0001
hs-CRP, mg/L	5.5±9.4	7.8±10.6	<0.0001
Serum creatinine, mg/dL	1.1±0.5	1.0±0.3	<0.0001
10-year ASCVD risk	22.7±15.5	14.8±12.4	<0.0001
Left ventricular hypertrophy	116 (3.8%)	33 (5.1%)	0.124
Atrial fibrillation	17 (0.6%)	2 (0.3%)	0.425
Lipid-lowering medication	594 (19.3%)	112 (17.2%)	0.216
Hypertension medication	1768 (57.3%)	365 (56%)	0.522
DM medication	1210 (39.2%)	554 (85%)	<0.0001

Continuous variables were presented as mean+-SD (and median [IQR] with skewed distribution); categorical variables were presented as frequency (percentage).

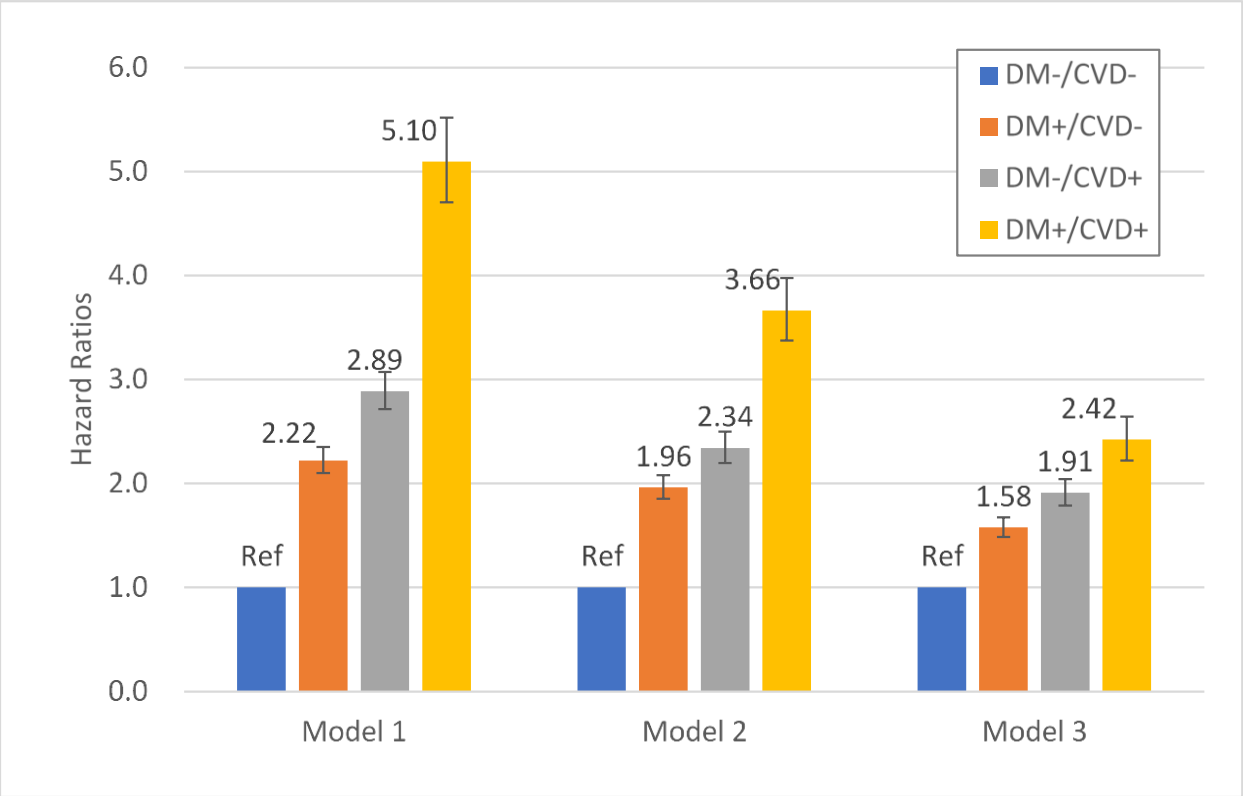


Figure 3-1. Hazard Ratios of DM/CVD Groups (DM-/CVD- as Reference)

Model 1 was crude HRs.
Model 2 was adjusted for age, sex and race.
Model 3 was adjusted for age, sex, race, education, smoking status, SBP, BMI, triglycerides, HDL-C, hs-CRP, serum creatinine, alcohol use, family history of CVD, LVH, Afib, lipid lowering medication, HTN medication.
Regardless of levels of adjustment, there was stepwise increase of CVD risk among those with DM-/CVD-, DM+/CVD-, DM-/CVD+ and DM+/CVD+. With full adjustment of non-DM specific CVD risk factors, the HRs for all three groups were attenuated to different extents.

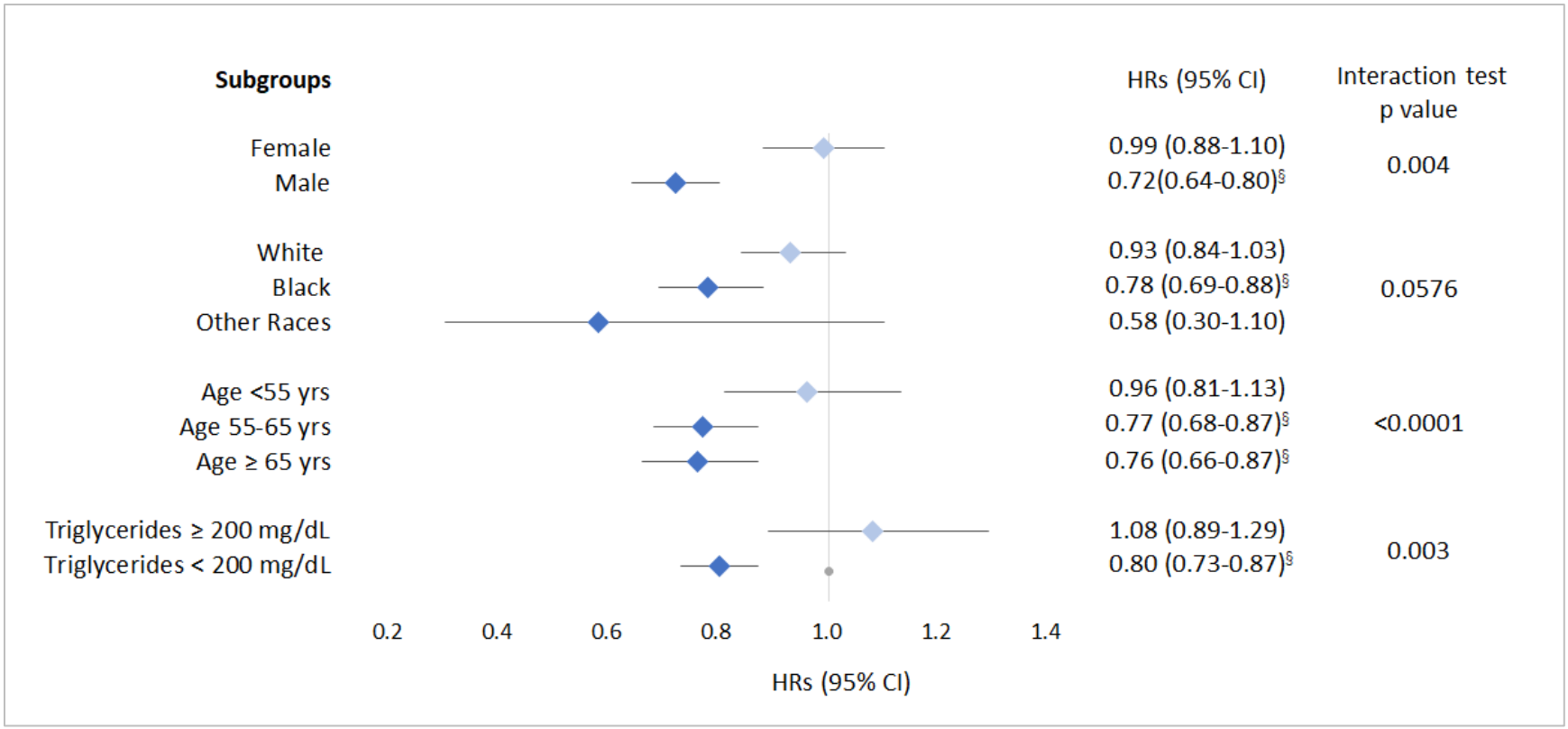


Figure 3-2. Hazard Ratios of DM+/CVD- vs. DM-/CVD+ in Subgroups

HRs were adjusted for age, sex, race, family history of CVD, education, smoking, alcohol use, SBP, BMI, triglycerides, HDL-C, hs-CRP, serum creatinine, lipid lowering medication, HTN medication, and other two DM/CVD groups.
*$p<0.05$, †$p<0.01$, ‡$p<0.001$, §$p<0.0001$
Female, white race, age <55 years old and elevated triglycerides tended to have similar CVD risks as those with DM-/CVD+ (HRs close to 1 with non-significant p values), while male, Black or other races, Age ⩾55 years or those with triglycerides < 200 mg/dL had lower CVD risk than those with DM-/CVD+.

3.7 Supplementary Materials

Supplementary Table 3-1. Hazard Ratios of DM+/CVD- vs. DM-/CVD+ in Subgroups (with Non-Significant Interaction Test)

Subgroups		Hazard Ratios [a] (95% CI)
Family history of CVD	Yes	0.86 (0.78-0.95)†
	No	0.81 (0.72-0.91) ‡
Current smoker	Yes	0.65 (0.53-0.78) §
	No	0.63 (0.56-0.69) §
Hypertension	Yes	0.89 (0.81-0.98)*
	No	0.80 (0.69-0.91)†
Obesity	Yes	0.92 (0.82-1.04)
	No	0.80 (0.72-0.89) §
Low HDL-C [b]	Yes	0.88 (0.79-0.98)*
	No	0.80 (0.72-0.90) ‡
CRP levels	≥ 2mg/L	0.90 (0.82-0.99)
	< 2 mg/L	0.72 (0.63-0.82)
Chronic kidney disease	eGFR >90 mL/min/1.73m^2	0.80 (0.58-1.10)
	eGFR 60-89 mL/min/1.73m^2	0.79 (0.71-0.88) §
	eGFR ≤ 60 mL/min/1.73m^2	0.92 (0.82-1.04)

a. HRs were adjusted for age, sex, race, family history of CVD, education, smoking, alcohol use, SBP, BMI, triglycerides, HDL-C, hs-CRP, serum creatinine, lipid lowering medication, HTN medication, and other two DM/CVD groups.
b. Low HDL-C were defined as HDL-C <40 mg/dL for men and HDL-C < 50 mg/dL for women.
p values for interaction test of DM/CVD and subgroups were all > 0.1.
*p<0.05, †p<0.01, ‡p<0.001, §p<0.0001

Supplementary Table 3-2. Individual Example of whether a Patient Had CVD Risk Equivalent DM

Parameter	Beta	X	X'[a]	Beta*X	Beta*X'
DM+/CVD- (yes=1, no=0)	0.7338	1	0	0.73378	0
DM+/CVD- (yes=1, no=0)* age (years)	-0.0225	60	0	-1.3494	0
DM+/CVD- (yes=1, no=0) * sex (male=1, female=0)	-0.9369	1	0	-0.93685	0
DM+/CVD- (yes=1, no=0) * age (years)*sex (male=1, female=0)	0.0133	60	0	0.795	0
DM+/CVD- (yes=1, no=0) * white (white=1, nonwhite=0)	0.1588	1	0	0.15875	0
DM+/CVD- (yes=1, no=0)* triglycerides (mg/dL)	0.000536	180	0	0.096426	0
Hba1c (%) [b]	0.1069	8	6.5	0.8552	0.69485
DM duration 10+ years (yes=1, no=0)	0.13323	0	0	0	0
DM medication (yes=1, no=0)	0.21609	1	0	0.21609	0
Sum of beta*individual X				0.5690	0.6949
Difference of $\Sigma\ \text{beta} * X$ and $\Sigma\ \text{beta} * X'$				-0.125854	

The example is a 60-year old white male. He has a triglyceride of 180 mg/dL with HbA1c of 8.0 with DM medication and a DM duration of 3 years.

$\Sigma\ \text{beta} * X - \Sigma\ \text{beta} * X'$ represents the log risk difference of an DM+/CVD- individual vs. had he/she had DM-/CVD+. In the example, the difference is less than 0, indicating that this person, who had DM but no CVD would have lower CVD risk than the situation when he had no DM but CVD and thus his DM should not be considered as CVD risk equivalent DM.

a. X' is the covariate value if the same subject had no DM but prior CVD

b. if one had actual HbA1c (X) $\geq$ 6.5 %, corresponding X' for HbA1c is 6.5. if one had actual HbA1c (X) less than 6.5%, corresponding X' for HbA1c is the same as X for HbA1c.

Supplemental Table 3-3. Hazard Ratios of DM Severity Group vs. DM-/CVD+ in Complete Case Analysis

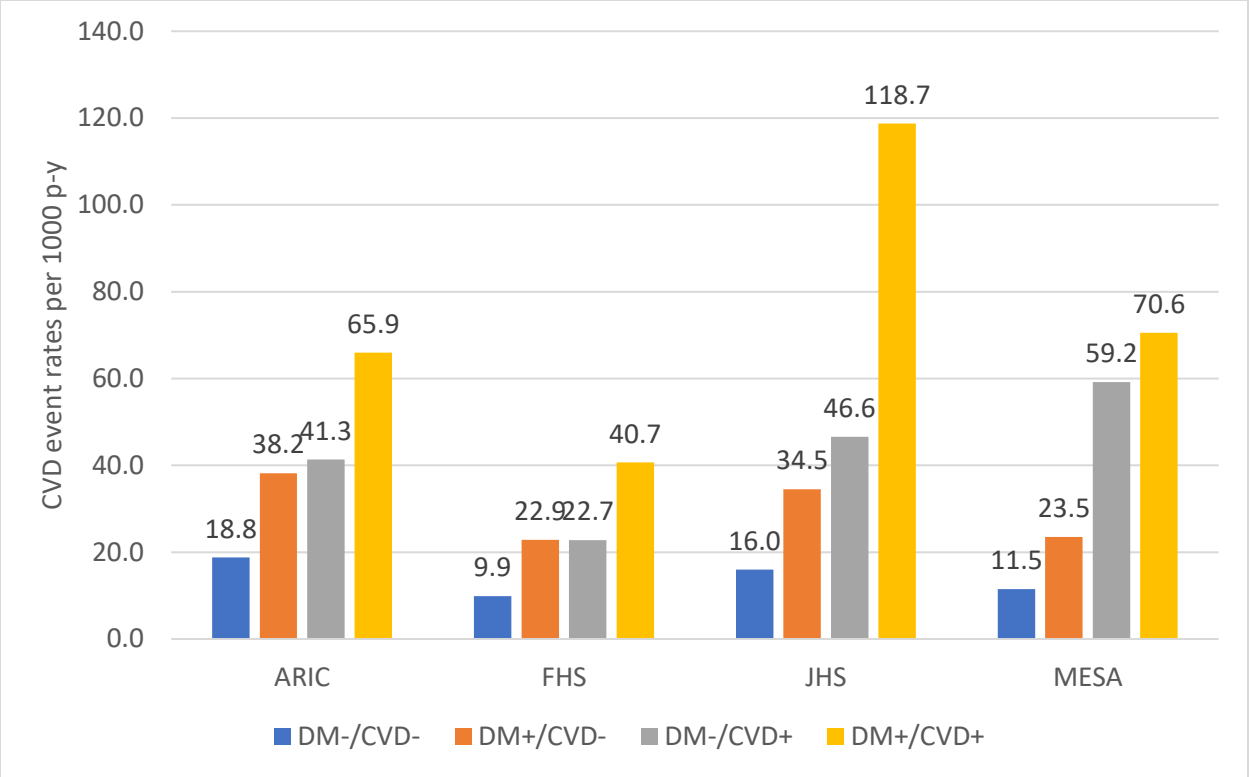
	Complete case analysis	Main analysis
DM duration subgroups vs DM-/CVD+		
Newly diagnosed DM	0.65 (0.57-0.73) §	0.67 (0.60-0.74) §
DM duration 0- <10 years	0.84 (0.75-0.94)†	0.86 (0.78-0.94)†
DM duration 10+ years	1.17 (1.02-1.35)*	1.17 (1.04-1.32)*
HbA1c control subgroups vs DM-/CVD+		
HbA1c < 7%	0.69 (0.62-0.77) §	0.70 (0.64-0.76) §
HbA1c ≥ 7%	1.03 (0.93-1.16)	1.06 (0.96-1.16)
DM medication use subgroups vs DM-/CVD+		
Not on DM medication	0.69 (0.62-0.77) §	0.72 (0.65-0.78) §
On DM medication	1.01 (0.91-1.13)	1.03 (0.94-1.13)

Fully adjusted HRs were adjusted for age, sex, race, family history of CVD, education, smoking, alcohol use, SBP, BMI, triglycerides, HDL-C, hs-CRP, serum creatinine, lipid lowering medication, HTN medication, and other two DM/CVD groups.
*p<0.05, †p<0.01, ‡p<0.001, §p<0.0001

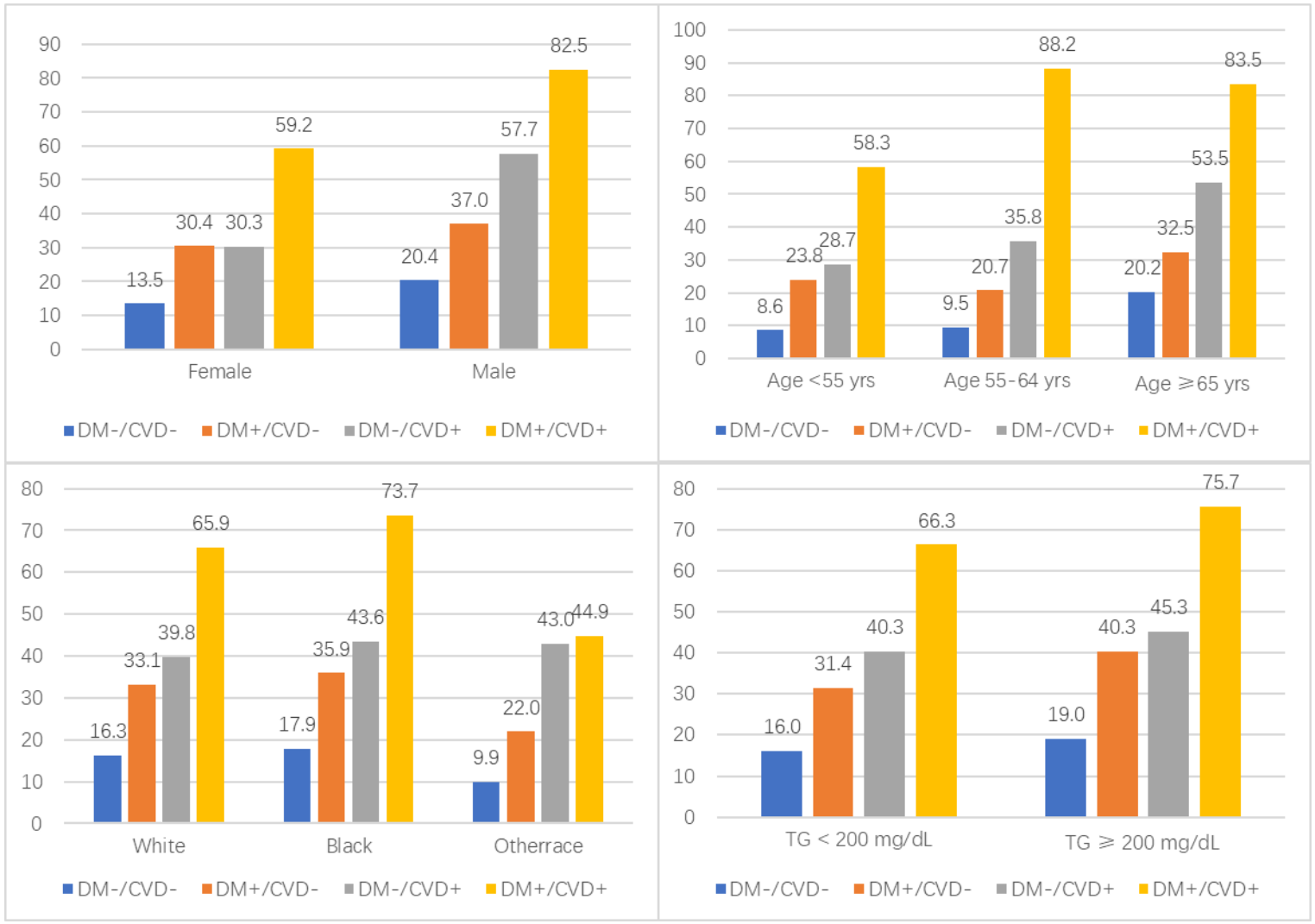
Supplemental Table 3-4. Hazard Ratios of DM+/CVD- vs. DM-/CVD+ in Subgroups (Complete Case Analysis)

	Complete case analysis	Main analysis
Sex		
Female	0.91 (0.79-1.04)†	0.99 (0.88-1.10)
Male	0.75 (0.66-0.85) §	0.72(0.64-0.80) §
Race		
White	1.01 (0.89-1.14)	0.93 (0.84-1.03)
Black	0.66 (0.56-0.76) §	0.78 (0.69-0.88) §
Other Races	0.44 (0.24-0.84)*	0.58 (0.30-1.10)
Age groups		
<55 years	0.97 (0.80-1.18)	0.96 (0.81-1.13)
55-65 years	0/74 (0.64-0.86) §	0.77 (0.68-0.87) §
≥ 65 years	0.78 (0.66-0.92)†	0.76 (0.66-0.87) §
Triglycerides levels		
≥ 200 mg/dL	1.14 (0.91-1.43)	1.08 (0.89-1.29)
< 200 mg/dL	0.77 (0.69-0.85) §	0.80 (0.73-0.87) §

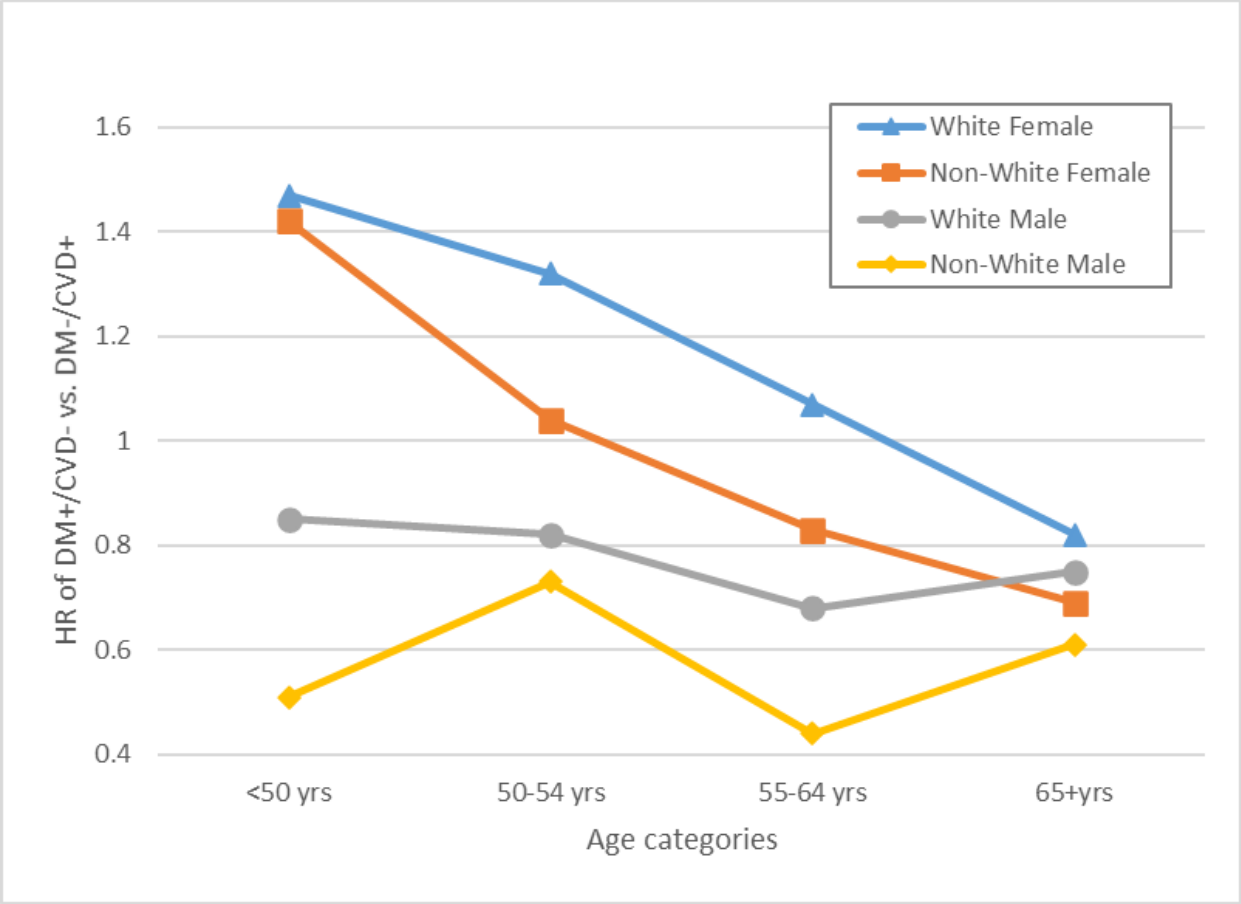
HRs were adjusted for age, sex, race, family history of CVD, education, smoking, alcohol use, SBP, BMI, triglycerides, HDL-C, hs-CRP, serum creatinine, lipid lowering medication, HTN medication, and other two DM/CVD groups.
*p<0.05, †p<0.01, ‡p<0.001, §p<0.0001



Supplementary Figure 3-1. CVD Event Rates by DM/CVD and Cohorts



Supplementary Figure 3-2. CVD Event Rates by DM/CVD and Age, Sex, Race, or Triglycerides Levels



Supplementary Figure 3-3. Hazard Ratios of DM+/CVD- vs. DM-/CVD+ for CVD Events in Each Age, Sex and Race Categories

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4. Development and Validation of New Cardiovascular Disease Risk Scores for Patients with Diabetes Mellitus from a Pooled Cohort of the US Population

Running Title: Pooled Cohort Cardiovascular Risk Score for Diabetes

4.1 Abstract

Background: Cardiovascular disease (CVD) risk scores used in diabetes mellitus (DM) patients have been previously derived from single cohorts or clinical trial samples, or designed for one endpoint. We developed a set of risk scores for total CVD and its separate components of coronary heart disease (CHD), stroke and heart failure (HF) for US adults with DM.

Methods: We pooled CVD-free adults with DM from five US population-based cohorts: Atherosclerosis Risk in Communities Study, Coronary Artery Risk Development in Young Adults Study, Framingham Heart Study Offspring Cohort, Jackson Heart Study, and the Multi-Ethnic Study of Atherosclerosis. We developed 10-year Diabetes Mellitus Risk Scores (DMRS) for total CVD (myocardial infarction, cardiac revascularization, stroke, HF and CVD death), atherosclerotic CVD (ASCVD), and separately for CHD, stroke and HF. Scores were externally validated in the ACCORD Follow-on (ACCORDION) cohort without prior CVD and compared with the corresponding Framingham Risk Scores (FRS), UKPDS risk engines and 2013 AHA/ACC Pooled Cohort Equation (PCE) for each endpoint.

Results: We included 4,183 adults with DM aged 30-86 years (45% male and 45% Black) with a median follow-up of 13 years. Age, sex, HbA1c, serum creatinine, systolic blood pressure and current smoking were the most important predictors of all endpoints. The mean predicted 10-year risks were 21.5%, 13.6%, 15.1%, 7.5% and 10.3 % for CVD, ASCVD, CHD, stroke and HF,

respectively. Our DMRS had good internal discrimination and calibration (c-statistics: 0.70-0.76; calibration slopes: 1.03-1.16 comparing observed vs. predicted risk). In the ACCORDION cohort, our scores showed superior performance over FRS, UKPDS and PCE (c-statistics 0.62-0.71 vs. 0.55-0.60, $p < 0.05$ for CVD comparing DMRS vs. FRS and PCE and CHD comparing DMRS vs. FRS).

Conclusions: Our DMRS based on pooled-data from five US cohorts with DM subjects demonstrated good predictive performance and may be useful for assessing the risk of CVD and its components in US adults with DM.

4.2 Introduction

Diabetes mellitus (DM) was historically assumed as a coronary heart disease (CHD) risk equivalent for future CHD events [1], which was one of the earliest attempts for cardiovascular disease (CVD) risk assessment. Recent studies showed patients with DM have a wide heterogeneity in CHD risk, further indicating all DM patients are not necessarily "CHD risk equivalents" and suggesting the need for risk stratification in those with DM. [2-4]

Current risk assessment for DM patients in the US is mainly based on risk scores derived from the general population, such as the Framingham Risk Score (FRS) for CVD or the 2013 AHA/ACC Pooled Cohort Equation (PCE) for hard atherosclerotic cardiovascular disease [5,6], where the highest risk patients with DM are recommended for more intensive lipid management [7], or are from other countries, such as the U.K. Prospective Diabetes Study (UKPDS) risk engine [8]. These risk scores were found to have not good enough calibration or discrimination in external validation, with a tendency to overestimate the risk in modern populations. Validation of FRS and UKPDS in the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) cohort showed that two different FRS overestimated the risk of major coronary heart disease by 146% and 289% and UKPDS overestimated the risk by 198%, respectively. [9] Another study examining the PCE found that PCE also substantially overestimated the 5-year CVD risk among diabetes patients in the high risk group (expected risk >5%), with an observed risk of 5.5% vs. expected risk of 13.8% and poorer discrimination than the non-diabetic patients (c-statistics 0.64 in DM vs. 0.74 in non-DM). [10] Similar problems exist for predicting individual CVD endpoints. The UKPDS risk engine for myocardial

infarction overestimated actual risk by approximately 130% to 290% and the UKPDS stroke risk engine overestimated observed risk by approximately 50% and showed moderate discrimination ability in external validation study (AUC:0.70-0.72). [11] In particular, a heart failure risk model is relatively rare for patients with DM.

Several potential reasons may contribute to the unsatisfactory performance (discrimination and calibration) of available scores. First and the most often implicated is the selection of study population. Different studies on the validation of risk scores tend to agree that the higher spatial, racial, and temporal similarity between validation cohort and derivation cohort will yield to better calibration. [12] That the UKPDS Risk Engine was based on the UK population where the predominant participants included were Caucasians, making it inappropriate to be used in the US population with different baseline risk profiles and racial diversity. More importantly, many of the risk scores were derived from early cohorts in which the exposure to risk factors, disease incidence, screening tests and preventive management of CVD were notably different from the more contemporary population, making the existing risk calculator outdated without a recalibration. The choice of endpoint also matters. It seems that there is no best choice on whether we should include soft events in CVD endpoints among DM patients since there is tradeoff between calibration (due to missing events) and discrimination (due to misclassified events). In the current risk scoring systems, various endpoints have been used such as total CVD, hard CHD and hard atherosclerotic CVD. DM patients are featured with longer asymptomatic or preclinical period for CVD and suffer more silent coronary heart events than their non-diabetic counterparts. Therefore, only counting the hard events may not catch all the true events and lead to the underestimation of risk score and thus bad calibration. On the other hand, the softer

endpoints such as percutaneous coronary interventions, bypass surgery, and coronary revascularization is more prone to be misclassified and lead to poor discrimination. Actually the FRS/UKPDS validation study in the ADVANCE cohort did find that when any CVD event was used as endpoint instead of hard CVD event, calibration was better while c-statistics were poorer. [9] Another reason leading to poor discrimination is the failure to include important and unique risk profiles for DM patients, such as HbA1c and DM duration. That may, at least in part, explain why UKPDS had better discrimination than FRS. Past studies used to do such comparison in an external cohort and concluded that DM-specific risk score seems discriminate the risk better than the general population risk scores. [13,14] Paynter et al. also demonstrated that including HbA1c levels improved prediction over a dichotomous term for DM in women. [15] However, most risk scores derived from the general population only include a dichotomous term of diabetes and fail to make full use of glycaemia information from diabetic patients. In addition, other risk profiles regarding lipid levels, blood pressure and obesity as well as their impact (relative risk) on CVD is also different in the DM population and should be separately evaluated in the risk prediction model.

Based on this need of tailored risk assessment, several risk engines for patients with DM have been developed in US population to predict the 10-year CVD risk. [16-19] These CVD risk scores for US DM population were either developed using single cohort with limited sample size which cannot examine other individual CVD endpoints, or developed using clinical trial or hospitalized patient data with less generalizability, or did not include external validation process. We aimed to develop a set of pooled cohort diabetes mellitus risk scores (DMRS) for total CVD, ASCVD and individually for CHD, stroke and heart failure (HF) in the US population with DM

comprising five US cohorts, each having over 10 years of follow-up and being ethnically diverse overall. We also compared the performance (discrimination and calibration) between our DMRS for different endpoints with existing risk calculators for the general population (i.e. FRS and PCE) or for those with DM (i.e. UKPDS).

4.3 Methods

Study Participants

Our derivation cohort was obtained from pooling five US prospective cohorts with diverse ethnic and geographic backgrounds: the Atherosclerosis Risk In Communities Study (ARIC), Coronary Artery Risk Development in Young Adults Study (CARDIA), Framingham Heart Study Offspring cohort (FHS Offspring), Jackson Heart Study (JHS) (excluding participants already in ARIC), and the Multi-Ethnic Study of Atherosclerosis (MESA). [20-24] We included subjects aged 30-86 years with prevalent DM and free of known CVD at baseline. DM was defined as (1) physician diagnosed DM; (2) use of insulin or oral diabetes medication; (3) a fasting blood glucose level of ≥126 mg/dL; (4) a non-fasting blood glucose level or 2-hour oral glucose tolerance test ≥200 mg/dL; and/or (5) a HbA1c ≥6.5% at the time of (or earlier than) the identified baseline visit where HbA1c and other risk factor information were available (1990-1992 in ARIC, 2005 in CARDIA, 1998-2001 for FHS Offspring, 2000-2002 in JHS, and 2003-2004 in MESA). Cohort participants were excluded if they had a history of CVD at baseline.

External validity was tested in a subgroup of CVD-free participants from the ACCORD Follow On (ACCORDION) cohort. [25] The ACCORD trial was designed to determine whether intensive vs. standard hypoglycemic treatment would reduce CVD risk in people with type 2 DM. We included participants from both trial arms, but also conducted a sensitivity analysis in those who were assigned to usual care for glucose, lipids, and blood pressure. Extended follow-up to a maximum of 13 years was available to validate our 10-year score.

Event Ascertainment and Follow-up

We defined incident CVD as non-fatal myocardial infarction (MI), cardiac revascularization, non-fatal stroke, HF or CVD death. Incident ASCVD was defined as non-fatal MI, non-fatal stroke or CVD death. Incident CHD included non-fatal MI, cardiac revascularization, or CHD death. PVD was not included due to adjudicated information on this not being available for one of the studies (JHS). The definitions of CVD, ASCVD and CHD are listed in Supplementary Table 4-1. The adjudication process for events involved a panel to review hospitalization and death data per study protocols previously published. [20-25] All events were adjudicated from medical records and death certificates for endpoint classification and assignment of incidence dates by the morbidity and mortality classification /review committees of the six studies.

Model Development

Potential risk factor candidates for our scores and collected at baseline included age, sex, race (categorized for our analysis as white, black, and other races), education level, smoking status,

alcohol consumption, family history of premature CVD (CVD < 55 years for father or < 60 years for mother), blood pressure, heart rate, atrial fibrillation, left ventricular hypertrophy (LVH), DM duration, body mass index, waist circumference, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides, high sensitivity C-reactive protein (CRP), fasting glucose, hemoglobin A1C (HbA1c), urinary albumin creatinine ratio, serum creatinine and estimated glomerular filtration rate (eGFR). Lipid-lowering medication, hypertension medication and hypoglycemic medication were also collected. Missing values of baseline risk factors were filled using multiple imputation with fully conditional specification methods. We first used elastic net regression for survival data to reduce the number of correlated risk factors. [26] Then the remaining risk factors were examined in the full model. Risk factors with $p<0.15$ in the full model remained in the final prediction model, with age, sex and race being forced in the final model. In sensitivity analysis, models with the log form of non-normal distributed risk factors and two-way interaction of risk factors were compared based on AIC and c-statistics.

The Cox proportional hazard regression model with the selected risk factors produced both relative risk as hazard ratio (HR) and an estimation of the absolute risk of an event occurring at year 10. Individual estimated absolute DMRS were calculated as:

$$R = 1 - (S_{10})^{e^{(\Sigma\, beta*X_{Individual} - Beta*X_{Mean})}},$$

where S_{10} is the population mean survival at year 10, beta is coefficient of each risk factor, $X_{individual}$ is the individual's risk factor value and X_{mean} is the population risk factor mean.

Model Validation

Internal validation was done using the bootstrap method and additionally done in ARIC vs. other four cohorts to examine potential cohort effect. External validation was done in the subgroup of ACCORDION cohort with no CVD history at baseline (n=6,642). A sensitivity analysis was done in those ACORDION participant who were in the conventional glucose lowering, lipid, or blood pressure groups (not receiving any of the intensive interventions) (n=1,660). We compared performance regarding discrimination and calibration between the DMRS and existing risk scores for CVD [FRS for total CVD, PCE for ASCVD] [5,6], ASCVD (PCE for ASCVD, FRS for total CVD) [6,5], CHD (FRS for CHD, UKPDS for CHD) [27, 7], stroke (FRS for stroke, UKPDS for stroke) [28,29] and HF (FRS for HF) [30]. We used c-statistics to examine the discrimination and Greenwood Nam-D'Agostino (GND) test for calibration. Reclassification ability was compared using net reclassification index (NRI).

Statistical analysis was done using R 3.5.3 and SAS 9.4. A two-sided p value <0.05 was considered statistically significant.

4.4 Results

Our pooled derivation cohort included 4,183 adults with DM aged 30-86 years (45% male and 45% Black). Baseline characteristics and events by study are shown in Table 4-1 and Table 4-2. During a median follow-up of 12.7 years, 1,431 total CVD, 894 ASCVD, 793 CHD, 807 HF and 376 stroke incident events occurred. Event rates were 28.0, 16.0, 14.5, 6.6 and 14.5 per 1000

person-years for CVD, ASCVD, CHD, stroke and HF, respectively. Due to age differences ARIC had the highest unadjusted CVD event rates while CARDIA had the lowest CVD event rates (37.35 vs. 6.55 per 1000 person-years). Event rates by study were shown in Supplementary Figure 4-1.

After the elastic net regression selection, DBP, BMI, heart rate, alcohol consumption, lipid lowering medication, atrial fibrillation, LVH were removed from the potential predictor list for CVD events. Removed variables by elastic net regression model for other endpoints are listed in Supplementary Table 4-2. Table 4-3 shows the final Cox regression models used to estimate the absolute 10-year risks. For the final 10-year CVD risk, age, sex, education level, current smoking, family history of CVD, systolic blood pressure (SBP), waist circumference, HbA1c, total cholesterol, HDL-C, hs-CRP, UACR, serum creatinine, diabetes duration over 10 years, hypertension medication and diabetes medication were included in the final model. We ranked predictors in each score according to their Chi-square contribution and found age, sex, HbA1c, serum creatinine, SBP and current smoking appeared most frequently in the first half of strongest predictors.

In sensitivity analyses, we evaluated comparative predicted value of the log transformed continuous measures as well as pairwise interaction terms and the models were not significantly improved based on c-statistics and AIC criteria (Supplementary Table 4-3). The corresponding adjusted hazard ratios in clinically relevant units are also listed in Table 4-2. In the derivation cohort, the average predicted 10-year risks were 21.5%, 13.6%, 15.1%, 10.3 % and 7.5% for CVD, ASCVD, CHD, HF and stroke, respectively.

We developed a risk calculator APP for the DMRS with an example demonstrated in Figure 4-1. This is the case of a 60-year black female with a DM over 10 years. She has college degree and family history of CVD but does not smoke. Her other lab measures and medical history were listed in Figure 4-1. Her predicted 10-year risks were 17.8%, 12.7%, 8.8%, 7.6% and 1.1% for CVD, ASCVD, CHD, HF and stroke, respectively. The calculation process of the predicted risk was also shown in Supplementary Table 4-4.

We evaluated the internal performance of the DMRS in bootstrapped samples overall and within each sex group. The Harrell's c-statistic was 0.71 for the CVD score. Internally the c-statistics demonstrated modest to good discrimination ability of the scores: HF risk score showed the best discrimination ability overall [C-statistics: 0.75 (0.74-0.77)], [0.74 (0.71-0.76) for men and 0.77 (0.74-0.79) for women]. Internal calibration was generally better in men than women except for stroke (Table 4-4). The calibration slopes were 1.09 for CVD and 1.06, 1.05, 1.16 and 1.03 for ASCVD, CHD, HF, and stroke respectively. The stroke score showed the best calibration that passed the GND test (chi2= 7.08, $p>0.05$). Harrell's c-statistics were comparable in ARIC and other four new cohorts; however, the newer cohorts showed lower observed event risks than the predicted risks, with calibration slopes less than 1 for all endpoints especially for stroke and HF (Supplementary Table 4-5).

We used data from 6,642 participants with type 2 DM free of CVD at baseline in the ACCORDION cohort. The validation cohort had 56% male with mean age of 62.9 years, 61% white and 21% black. Nearly half of subjects (47.2%) had DM over 10 years (Table 4-2). In

external validation, our DMRS had c-statistics of 0.62, 0.64, 0.61, 0.69 and 0.65 for CVD, ASCVD, CHD, HF and stroke; c-statistics of FRS for each corresponding endpoint were 0.60, 0.61, 0.55, 0.61 and 0.61; 2013 AHA/ACC PCE had c-statistics of 0.60 and 0.61 for CVD and ASCVD; UKPDS had c-statistics of 0.60 and 0.57 for CHD and stroke (Table 4-5). p value < 0.05 when the C-statistics of DMRS were compared to those of FRS and PCE for CVD events and for DMRS vs. FRS for CHD events. In external calibration, none of the scores passed the GND calibration tests yet the DMRS performed better on the calibration plot with calibration slopes closer to 1 (Figure 4-2 – Figure 4-6). Calibration slopes ranged 0.46-0.74 for the DMRS, 0.29 -0.78 for FRS, 0.38-0.61 for PCE and 0.02-0.17 for UKPDS. UKPDS not only severely overestimated CHD and stroke risk in the ACCORDION cohort but also showed poor discrimination in this well-treated population. Reclassification of the DMRS vs. old scores are shown in Figure 4-7. Across all the comparisons, the new scores did better in correctly reclassifying the non-events to the lower risk. Continuous NRI ranged -0.04 to 0.06 comparing the DMRS vs. FRS for each endpoint. The external performance did not differ much between the glycemic treatment arms.

We additionally ran a series of sensitivity analysis including using non-ARIC cohorts to recalibrate the DMRS and directly using the four non-ARIC cohorts as derivation cohorts and using ARIC and ACCORDION as a pooled external validation cohort for CVD events. Recalibration corrected the overestimation of scores by some extent yet the performance improvement was only modest (Supplementary Figure 4-2). Similarly, when the pooled cohort excluding ARIC were used to derive the DMRS, the scores overestimated of risk in highest decile of risk group in ACCORDION (Supplementary Figure 4-3). However, external validation

on 1,660 participants in ACCORDION with conventional glycemic, hypertension and lipid control showed the validation performance of scores was similar to that in the overall ACCORDION cohort while the calibration of the DMRS largely improved in this less aggressively treated subgroup (Supplementary Table 4-6).

4.5 Discussion

In the current study we developed a set of DM-specific risk scores for 10-year CVD and its component events that is uniquely derived from multiple pooled, large US community-based cohorts. Age, sex, HbA1c, serum creatinine, SBP and current smoking appeared to be the most important predictors of all endpoints. Moreover, our risk scores provide for further precision using ethnicity as a factor. Our scores also showed good internal discrimination and calibration, and when externally validated, superior performance over several other traditionally used risk scores.

In the DMRS model development, traditional risk factors including SBP, total cholesterol and HDL-C were found to be predictive for future CVD. We also identified some other risk factors that need more attention in adults in DM. Among them serum creatinine and UACR were found even more strongly related to CVD risk than well-known risk factors. Our findings are consistent with others showing increased CVD risk with poorer kidney function. [31,32] Existing evidence implies the need for measuring kidney function in estimating CVD risk among DM patients.

Our DMRS showed modest to good discrimination ability internally and externally in a contemporary DM cohort. By including the DM specific risk factors in the score equation, the

new scores were able to better separate the high risk from the low risk subjects than the FRS, PCE and UKPDS prediction models. When the score was validated in the conventional treatment group of the ACCORDION cohort, calibration greatly improved, demonstrating the validity of the score in current treatment algorithm. On the contrary, UKPDS overestimated the contemporary CHD risk among DM patients by up to 500%. With the change in DM diagnosis, as well as wider use of preventive therapy and emerging new therapies, CVD risk among those with DM may have declined over time, suggesting the potential usefulness of recalibration in providing the most up-to-date risk estimation. [33] A recent meta-analysis on the recalibration of 4 CVD risk scores in 86 cohorts demonstrated that simple recalibration effectively improved the performance of existing risk scores. [34] The poor calibration of old scores were also potential reasons for the small NRI, consistent with a prior simulation study showing that poorly calibrated models may overestimate the value of added risk factors when evaluated by NRI. [35]

The discrimination performance of our scores was somewhat consistent with some of the other risk scores specifically for DM population: The external c-statistics for CVD and ASCVD were generally modest (ranged 0.6-0.7, mostly around 0.63); c-statistics for HF were often seen to be higher than that of composite CVD endpoint; and the c-statistics of CVD risk scores designed for DM population is generally lower than those for the general population. Several reasons contribute to the difference. Firstly, the DM population are generally more frequently treated for CVD risk factors including SBP, LDL-C and HbA1c so the predictive value of baseline variables is reduced compared to general population where the risk factors largely remain untreated. The problem could exacerbate when clinical trial cohort was used as external validation cohort. Some

novel predictors might be of help to improve the overall discrimination performance however were not able to be included due to unavailability in the pooled cohort.

Accurate CVD risk assessment for patients with DM based on individual risk profiles is essential to guide CVD preventive strategies. Although the whole DM population was previously considered as a homogeneous entity regarding macrovascular risk and defined as a "CHD risk equivalent", contradictory evidence suggests an overall lower CHD risk among patients with DM compared to those without DM but with a prior CHD, possibly due to the changing definition of DM, earlier diagnosis and more aggressive preventive treatment. [2,36,37] Within those with DM, CVD risk may vary by severity of DM as well as the comorbidities, suggesting the importance of including these factors in CVD risk evaluation. [36,38]

Our study had several strengths over the existing risk scores. To our knowledge this is the first pooled project using exclusively US cohorts to develop DM-specific risk scores for macrovascular complications. The primary CVD endpoint also included HF, which is very important to include having been recently found to be among the most common first clinical manifestations of CVD among DM. [39] In our study, the "weights" (measured by the beta coefficients) of some common risk factors were similar among different endpoints, indicating a homogenous predictive value across the whole spectrum of CVD events. In addition, we made head-to-head comparisons of the new scores and popular existing risk scores for each outcome in the external cohort and demonstrated modestly better performance of the new scores than the old ones.

Our new DMRS needs to be interpreted in light of some study limitations. Subsets of the external validation ACCORDION cohort were treated with intensive hypoglycemic therapy, blood pressure lowering, and/or fibrate therapies for 3.7 years from the baseline, which potentially reduced CVD risk compared to real-world cohorts, especially when the estimated risk was very high; The continuous treatment after baseline also reduce the predictive ability of baseline predictors, leading to a decreased accuracy of the DMRS in the trial cohort. It would be preferable to have external cohort from the contemporary community rather than clinical trial. However, our sensitivity analysis limited to the subset of ACCORDION participants on conventional treatments showed the robustness of validation using this study and improved calibration of the DMRS. Due to the limited number of available variables in the pooled cohort sources, some potential predictors, including subclinical atherosclerosis measures or biomarkers such as lipoprotein (a) were not able to be examined as candidate variables. Finally, since peripheral arterial disease was not adjudicated in one of our derivation cohorts, we could not utilize this within our composite or as a separate outcome.

To conclude, we created 10-year DMRS for CVD, ASCVD and individual CVD components (CHD, stroke and HF) using pooled data from five US prospective studies. Our DMRS showed better predictive discrimination than existing scores including PCE, FRS and UKPDS. Our risk score may be useful clinically for efficient estimation of the risk of key CVD outcomes in persons with DM. Further evaluation in more recent US DM cohorts would be useful for further validation.

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4.6 Tables and Figures

Table 4-1. Baseline Characteristics of Individual Cohorts

	ARIC N=1,859	CARDIA N=379	FHS Offspring N=406	JHS N=516	MESA N=1,023
Age, years	57.8±5.7	45.7±3.7	63.6±8.5	53.9±10.2	65.7±9.5
Male	850 (45.7%)	144 (38.0%)	199 (49.0%)	169 (32.8%)	521 (50.9%)
Race groups					
White	1086 (58.4%)	148 (39.1%)	406 (100%)	0 (0%)	228 (22.3%)
Black	770 (41.4%)	231 (61.0%)	0 (0%)	516 (100%)	367 (35.9%)
Other races	3 (0.2%)	0 (0%)	0 (0%)	0 (0%)	428 (41.8%)
Above high school education	697 (37.5%)	265 (69.9%)	210 (51.7%)	326 (63.2%)	545 (53.3%)
Current smokers	382 (20.6%)	72 (19.0%)	65 (16.0%)	63 (12.2%)	104 (10.2%)
Alcohol consumption	831 (44.7%)	265 (69.9%)	205 (50.5%)	220 (42.6%)	376 (36.8%)
Family history of CVD	1036 (55.7%)	101 (26.7%)	90 (22.2%)	262 (50.8%)	293 (28.6%)
SBP, mmHg	128.3±19.7	118.7±16.1	133.3±19.1	129.8±16.2	130.7±22.0
DBP, mmHg	73.2±10.6	75.2±11.4	74.5±9.8	76.7±8.6	70.6±10.6
BMI, kg/m2	30.8±6.0	34.9±9.7	30.9±6.5	35.0±7.5	30.7±6.1
Waist circumstances, cm	105.9±14.4	103.4±17.7	108.0±15.8	109.1±15.9	104.7±15.0
Total cholesterol, mg/dL	213.2±43.0	183.2±39.8	195.5±37.7	197.7±41.7	184.1±36.7
HDL-C, mg/dL	44.4±14.7	48.8±15.8	47.5±15.7	47.4±13.6	47.2±13.3
LDL-C, mg/dL	135.9±38.8	108.3±35.9	114.8±33.6	123.2±38.5	106.7±32.2
Triglycerides, mg/dL	169.9±135.1	135.9±101.4	173.0±109.1	140.3±101.3	156.1±102.4
hs-CRP, mg/L	6.4±6.7 3.6[1.5-7.5]	4.8±6.6 2.4[1.0-6.0]	5.8±7.1 3.3[1.5-6.9]	6.6±8.7 3.8[1.7-7.4]	4.5±5.7 2.5[1.1-5.7]
Creatinine, mg/dL	1.2±0.5	0.9±0.2	0.9±0.3	0.9±0.5	1.0±0.4
eGFR, mL/min*1.73m^2	62.5±13.0	102.6±25.9	79.8±19.3	96.6±23.5	78.5±19.6
UACR, mg/g	94.3±91.1[a] 10.5[4.0-28.6]	28.4±68.7 7.4[4.3-17.6]	62.2±233.3 10.0[4.6-29.3]	79.3±170.6 9.1[4.0-26.4]	63.0±217.7 10.0[5.1-30.0]

HbA1c, %	7.4±2.0	6.8±1.8	7.0±1.5	7.6±1.9	7.1±1.6
Fasting glucose, mg/dL	171.4±76.5	134.4±56.5	143.8±49.3	143.0±57.1	140.9±51.1
DM onset age, years	53.3±9.0	38.4±9.5	55.2±9.9	48.0±11.6	60.4±11.4
Heart rate, bpm	69.4±11.4	80.6±12.8	68.7±12.4	69.5±11.5	68.1±11.0
Atrial fibrillation	5 (0.3%)	1 (0.3%)	16 (3.9%)	0 (0%)	0 (0%)
Lipid-lowering medication	135 (7.3%)	89 (23.5%)	117 (28.8%)	105 (20.4%)	351 (34.3%)
HTN medication	904 (48.6%)	158 (41.7%)	223 (54.9%)	380 (73.6%)	679 (66.4%)
Hypoglycemic medication	599 (32.2%)	186 (49.1%)	161 (39.7%)	318 (61.6%)	702 (68.6%)
Follow-up, years	18.9±7.1	9.6±1.2	10.6±2.9	12.1±2.9	11.4±2.6
Events during follow-up					
CVD	997 (53.6%)	23 (6.1%)	88 (21.7%)	89 (17.3%)	234 (22.9%)
ASCVD	612 (32.9%)	21 (5.5%)	70 (17.2%)	52 (10.1%)	139 (13.6%)
CHD	557 (30.0%)	10 (2.6%)	42 (10.3%)	38 (7.4%)	146 (14.3%)
CHF	261 (14.0%)	13 (3.4%)	24 (5.9%)	28 (5.4%)	50 (4.9%)
Stroke	639 (34.4%)	3 (0.8%)	29 (7.1%)	44 (8.5%)	92 (9.0%)
Death	1140 (61.3%)	23 (6.1%)	88 (21.7%)	100 (19.4%)	246 (24.1%)

Continuous variables were presented as mean ± SD (and median [IQR] with skewed distribution); categorical variables are presented as frequency (%).

a. UACR was not measure in ARIC 1990-1992, the current reported statistics are from multiple imputation data.

Percentages of missing values were 49.4% for UACR and 15.4% for CRP; all other baseline variables had missing value less than 7%.

Table 4-2. Baseline Characteristics of Derivation and Validation Cohorts

	Pooled Cohort N= 4,183	ACCORDION N=6,642
Age, years	58.7±9.5	62.9±5.9
Male	1883 (45.0%)	3713 (55.9%)
Race groups		
White	1868 (44.7%)	4025(60.6%)
Black	1884 (45.0%)	1370(20.6%)
Other races	431 (10.3%)	1247(18.8%)
Above high school education	2043 (48.8%)	3938(59.3%)
Current smokers	686 (16.4%)	875(13.2%)
Alcohol consumption	1897 (45.4%)	1615(24.3%)
Family history of CVD	1782 (42.6%)	2978(44.8%)
SBP, mmHg	128.7±19.9	136.4±16.2
DBP, mmHg	73.3±10.5	75.7±9.9
BMI, kg/m2	31.7±6.9	32.3±5.5
Waist, cm	106.0±15.3	106.3±13.7
Total cholesterol, mg/dL	199.7±42.6	186.5±39.9
HDL-C, mg/dL	46.2±14.5	43.0±11.5
LDL-C, mg/dL	122.6±38.7	107.6±33.1
Triglycerides, mg/dL	160.1±119.1	182.7±113.7
hs-CRP, mg/L	5.8±6.9 3.1 [1.4-6.8]	/ [a]
Creatinine, mg/dL	1.0±0.5	0.9±0.2
eGFR, mL/min*1.73m^2	76.0±23.1	91.0±22.3
UACR, mg/g	75.7±158.0 9.8[4.3-27.5]	75.4±222.7 14.0[7.0-50.0]
HbA1c, %	7.3±1.8	8.3±1.0
fasting glucose, mg/dL	154.4±66.3	174.0±53.0
DM onset age, years	53.2±11.7	52.5±8.5
Heart rate, bpm	70.1±12.0	70.5±11.1
Atrial fibrillation	22 (0.5%)	74(1.1%)
Lipid-lowering medication	797 (19.1%)	3749(56.4%)
HTN medication	2344 (56.0%)	5311(80.0%)
Hypoglycemic medication	1966 (47.0%)	6251(94.1%)
Follow-up, years	14.6±6.4	9.3±2.2
Events during follow-up		
CVD	1431 (34.2%)	1641(25.2%)
ASCVD	894 (21.4%)	857(12.9%)
CHD	793 (19.0%)	811(12.2%)
CHF	376 (9.0%)	267(4.0%)

Stroke	807 (19.3%)	273(4.1%)
Death	1597 (38.2%)	1007(15.2%)

Continuous variables were presented as mean ± SD (and median [IQR] with skewed distribution); categorical variables are presented as frequency (%).
a. CRP was not measured at ACCORDION baseline examination
Percentages of missing values were 49.4% for UACR and 15.4% for CRP; all other baseline variables had missing value less than 7%.

Table 4-3. Diabetes Mellitus Risk Score (DMRS) Equations for CVD and Its Components with Coefficients and Hazard Ratios (HR) [a]

Predictors	CVD		ASCVD		CHD		Stroke		HF	
	Beta	HR	Beta	HR	Beta	HR	Beta	HR	Beta	HR
Age, per 10 years	0.0328	1.39 §	0.0301	1.35 §	0.0286	1.33 §	0.0247	1.28 ‡	0.0477	1.61 §
Male	0.3816	1.47 §	0.3803	1.46 §	0.4882	1.63 §	0.2427	1.28*	0.2228	1.25†
White race	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Black race	-0.1599	0.85†	0.0012	1.00	-0.2977	0.74 ‡	0.2305	1.26*	-0.1179	0.89
Other races	-0.3904	0.68 ‡	-0.2156	0.81	-0.1562	0.86	-0.3594	0.70	-0.6285	0.53 ‡
Above high school education	-0.2084	0.81 ‡	-0.2103	0.81†	-0.2192	0.80†	-0.2667	0.77*	-0.3746	0.69 §
Current smoking	0.5286	1.70 §	0.5507	1.73 §	0.4625	1.59 §	0.3496	1.42†	0.5355	1.71 §
Family history of CVD	0.2046	1.23 ‡	0.2562	1.29 ‡	0.2427	1.28 ‡	0.2494	1.28*	0.1981	1.22†
SBP, per 10 mmHg	0.0100	1.11 §	0.0121	1.13 §	0.0089	1.09 §	0.0155	1.17 §	0.00769	1.08 §
Waist circumference, per 10cm	0.0059	1.06†	/	/	/	/	/	/	0.01417	1.15 §
HbA1c, per 1%	0.1188	1.13 §	0.1511	1.16 §	0.0966	1.10 §	0.0186	1.20 §	0.1505	1.16 §
Total cholesterol, per 10mg/dL	0.0029	1.03 §	0.0042	1.04 §	0.0048	1.05 §	0.0026	1.03*	0.00219	1.02*
HDL-C, per 10 mg/dL	-0.0061	0.94†	-0.0116	0.89 §	-0.0145	0.87 §	/	/	/	/
hs-CRP, per 1 mg/L	0.0088	1.01 ‡	/	/	/	/	0.0115	1.01	0.0192	1.02 §
UACR, per 100 mg/g	0.0003	1.03†	0.0003	1.03	/	/	0.0005	1.05*	0.000668	1.07 §
Serum creatinine, per 1 mg/dL	0.2901	1.34 §	0.3424	1.41 §	0.3108	1.36 §	0.3038	1.36 §	0.3357	1.40 §
DM duration over 10 years	0.1859	1.20†	0.2716	1.31†	0.2602	1.30†	/	/	/	/
HTN medication	0.1990	1.20 ‡	0.1856	1.20*	/	/	/	/	0.2908	1.34 ‡
DM medication	0.2310	1.26 ‡	/	/	0.3262	1.39 ‡	/	/	0.3359	1.40 §
Other parameters in the equation [b]	Beta*X_{Mean}	5.8685		5.51919		4.4423		5.8827		7.7471
	S_{10}	0.8166		0.9100		0.8947		0.9700		0.9542

a. HR are presented in clinically relevant unit following the predictor name; beta coefficients are presented in variables' original units.

b.10-year DMRS is calculated as: $R = 1 - (S_{10})^{e^{(\Sigma\, beta * X_{Individual} - Beta * X_{Mean})}}$, where $\Sigma\, beta * X_{individual}$ is the sum of beta coefficient*individual's predictor values.

* p<0.05, † p<0.01, ‡ p<0.001, §p<0.0001.

"/" means the component is not part of the risk score equation.

Table 4-4. Internal Validation in Total Sample [a] and by Sex

		Total	Male	Female
CVD	Harrell's C-statistics	0.71(0.69-0.72)	0.68(0.66-0.70)	0.72(0.70-0.74)
	Calibration (slope/intercept/chi2)	1.091/-0.021/32.13 ‡	0.994/0.012/9.35	1.102/-0.030/47.42 §
ASCVD	Harrell's C-statistics	0.72(0.70-0.73)	0.68(0.66-0.71)	0.73(0.71-0.75)
	Calibration (slope/intercept/chi2)	1.056/-0.008/17.8*	1.048/-0.002/3.34	1.136/-0.020/10.30
CHD	Harrell's C-statistics	0.70(0.68-0.72)	0.67(0.64-0.69)	0.71(0.68-0.73)
	Calibration (slope/intercept/chi2)	1.046/-0.006/29.7 ‡	1.052/0.001/14.91*	0.93/-0.003/31.63 §
Stroke	Harrell's C-statistics	0.71(0.68-0.74)	0.69(0.65-0.74)	0.72(0.69-0.76)
	Calibration (slope/intercept/chi2)	1.028/-0.003/7.08	1.116/-0.005/5.87	0.998/-0.004/10.68
HF	Harrell's C-statistics	0.75(0.74-0.77)	0.74(0.71-0.76)	0.77(0.74-0.79)
	Calibration (slope/intercept/chi2)	1.159/-0.016/52.67 §	1.044/-0.003/12.38*	1.266/-0.024/30.18 §

a. Internal validation was done in 200 bootstrap samples.
* $p<0.05$, † $p<0.01$, ‡ $p<0.001$, § $p<0.0001$

Table 4-5 External Validation of the Diabetes Mellitus Risk Score (DMRS) and Other Scores in the ACCORDION Cohort

		DMRS	FRS	PCE	UKPDS
CVD	Harrell's C-statistics	0.62	0.60*	0.60†	/
	Calibration (slope/intercept/chi2)	0.742/0.057/39 §	0.514/0.104/233 §	0.617/0.131/127 §	/
ASCVD	Harrell's C-statistics	0.64	0.61	0.61	/
	Calibration (slope/intercept/chi2)	0.658/0.028/71 §	0.338/0.030/1757 §	0.380/0.054/530 §	/
CHD	Harrell's C-statistics	0.61	0.55 §	/	0.60
	Calibration (slope/intercept/chi2)	0.514/0.043/155 §	0.311/0.109/331 §	/	0.173/0.0726/3316 §
Stroke	Harrell's C-statistics	0.65	0.61	/	0.57
	Calibration (slope/intercept/chi2)	0.530/0.013/58 §	0.285/0.018/385 §	/	0.023/0.040/12289 §
HF	Harrell's C-statistics	0.69	0.61	/	/
	Calibration (slope/intercept/chi2)	0.460/0.003/267 §	0.780/0.024/44 §	/	/

* $p<0.05$, † $p<0.01$, ‡ $p<0.001$, § $p<0.0001$ compared to the DMRS

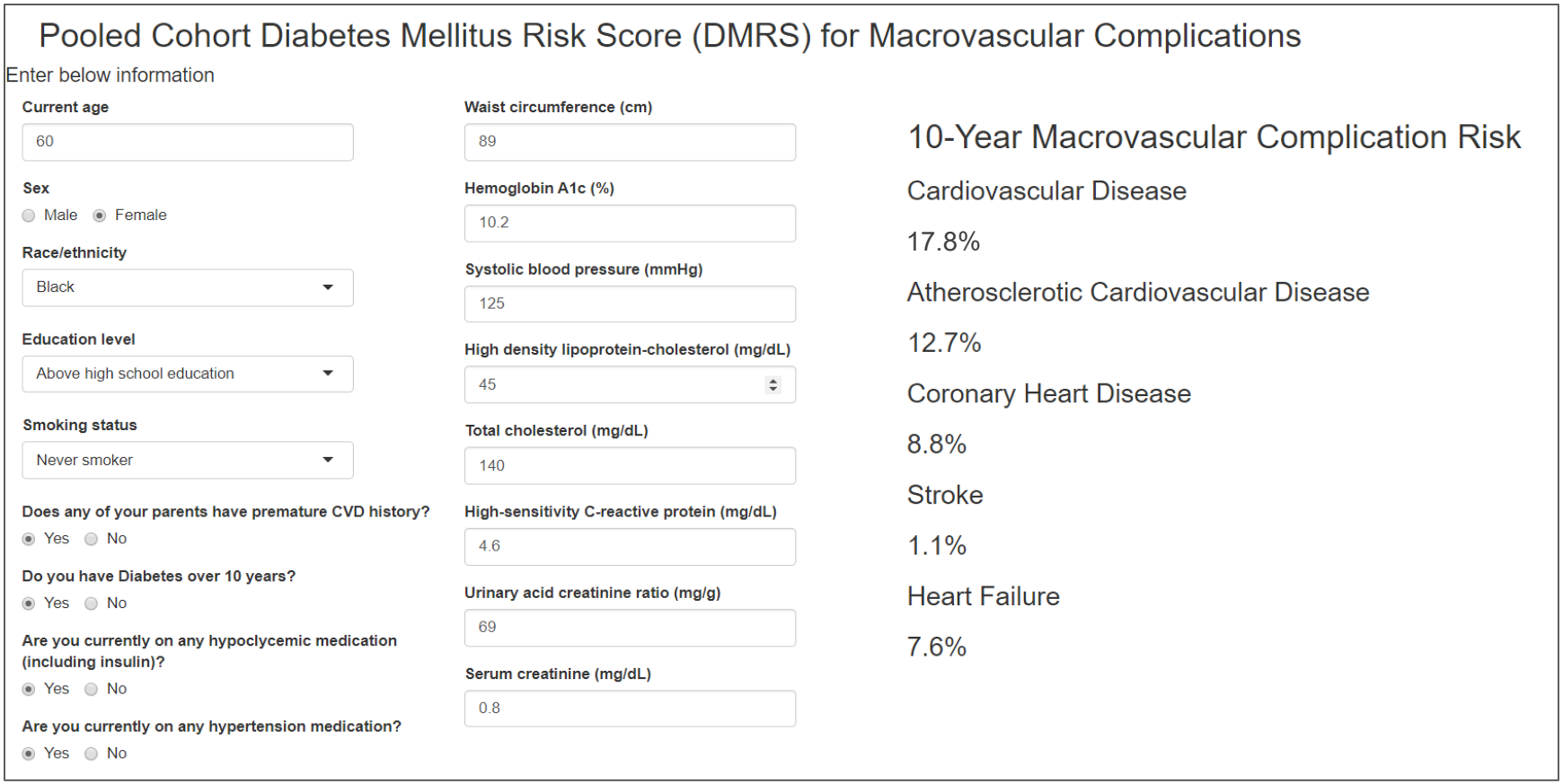


Figure 4-1. User-Friendly APP for the Diabetes Mellitus Risk Score (DMRS)

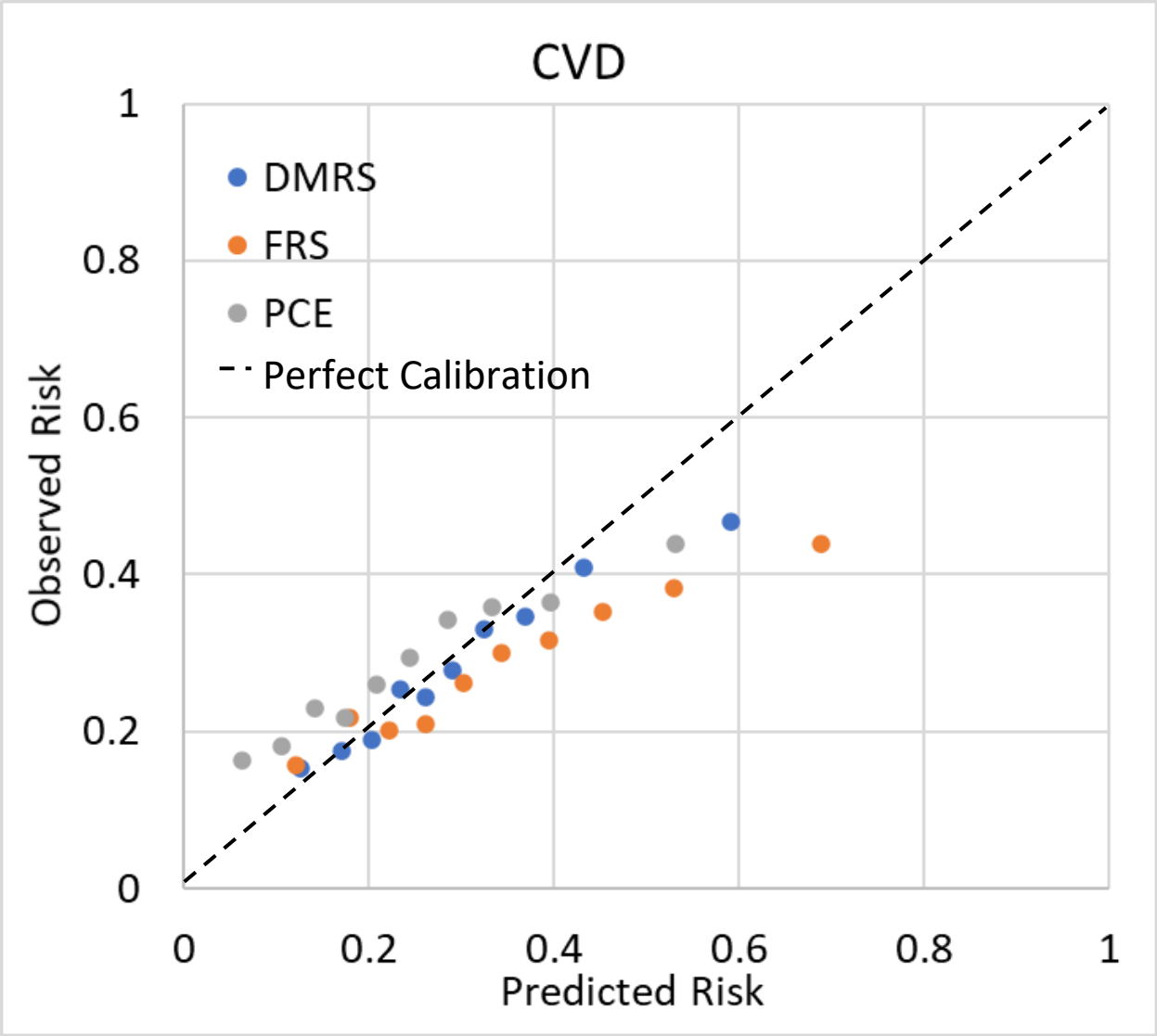


Figure 4-2. External Validation Calibration Plots for CVD

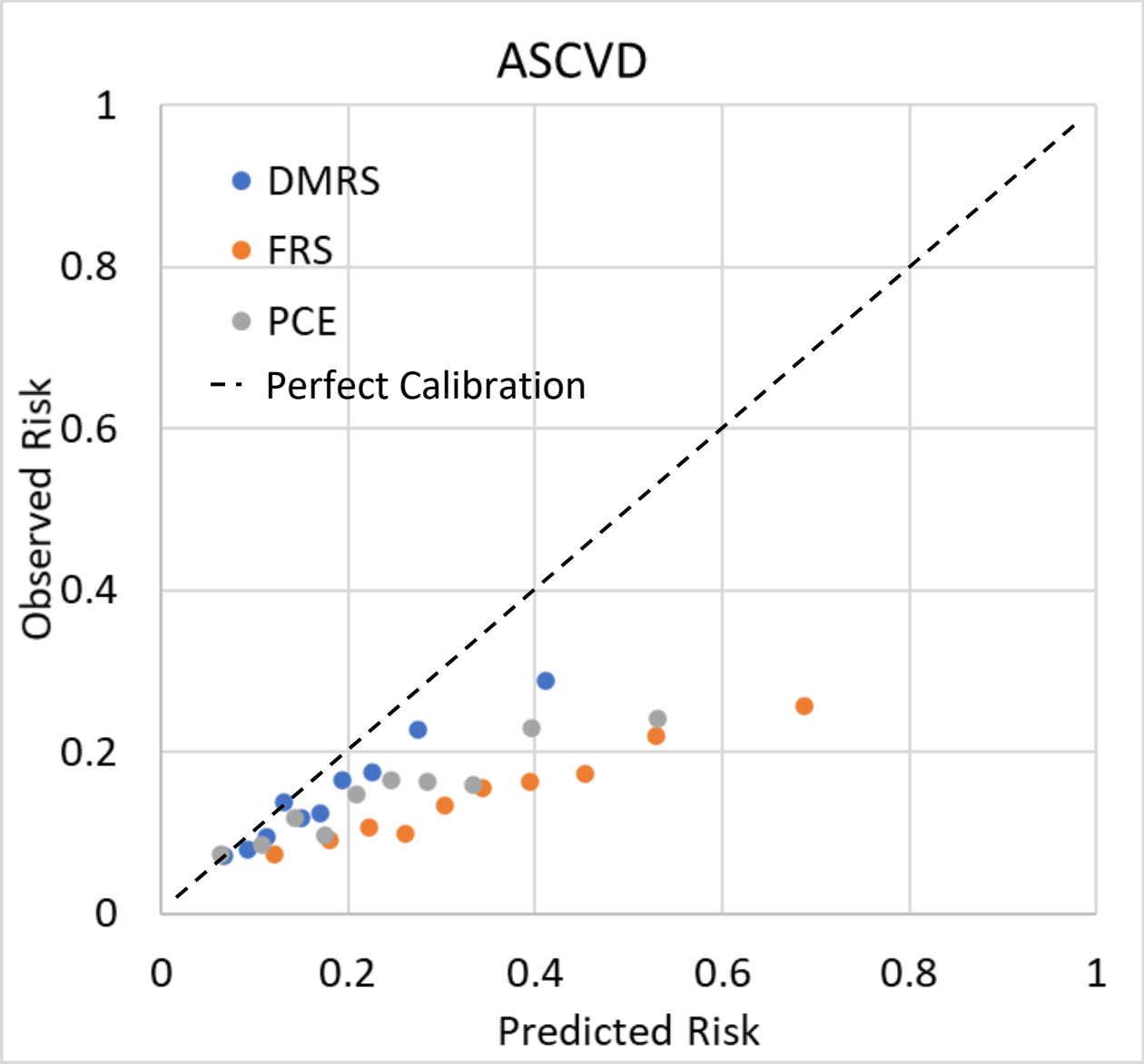


Figure 4-3. External Validation Calibration Plots for ASCVD

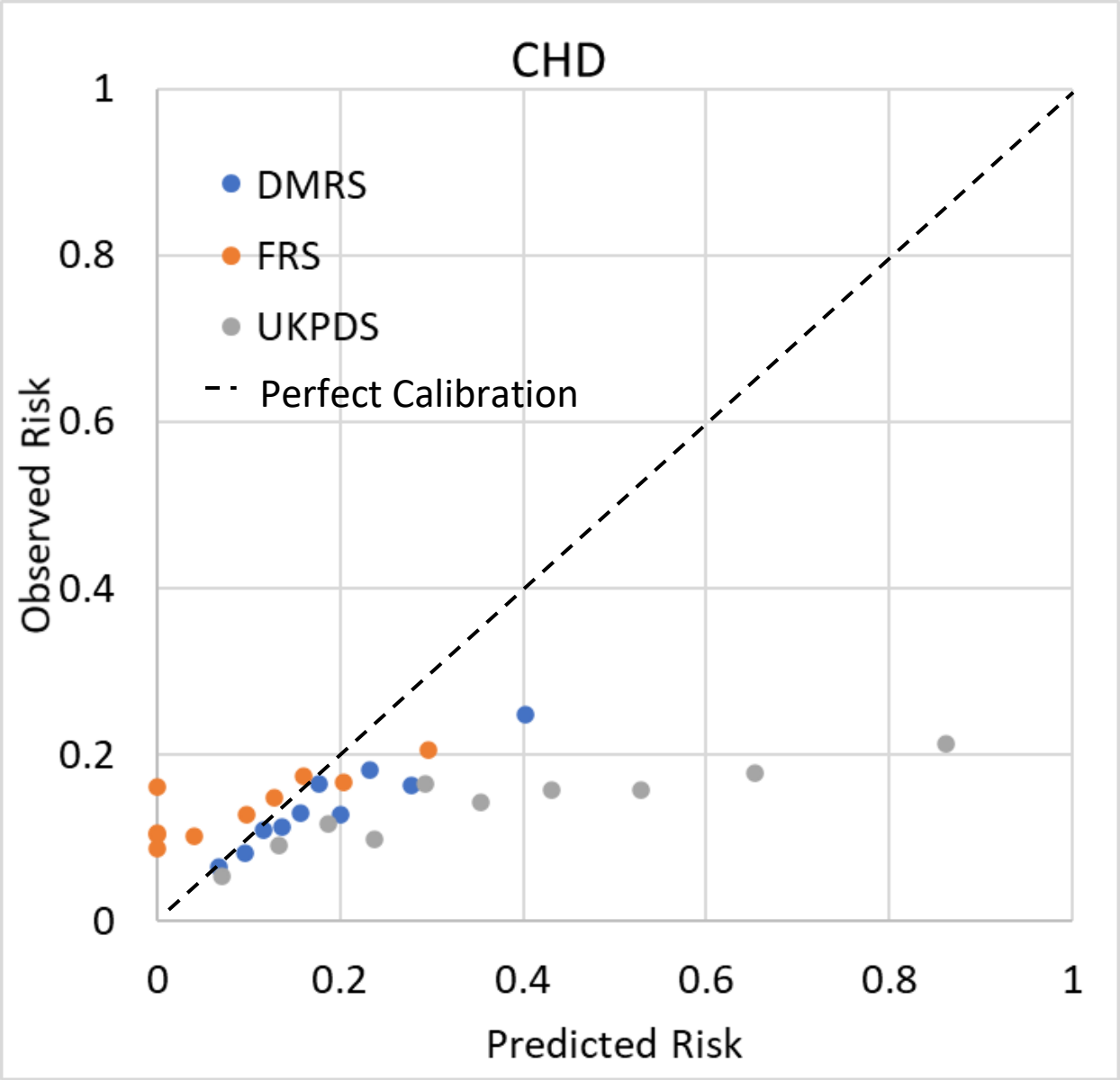


Figure 4-4. External Validation Calibration Plots for CHD

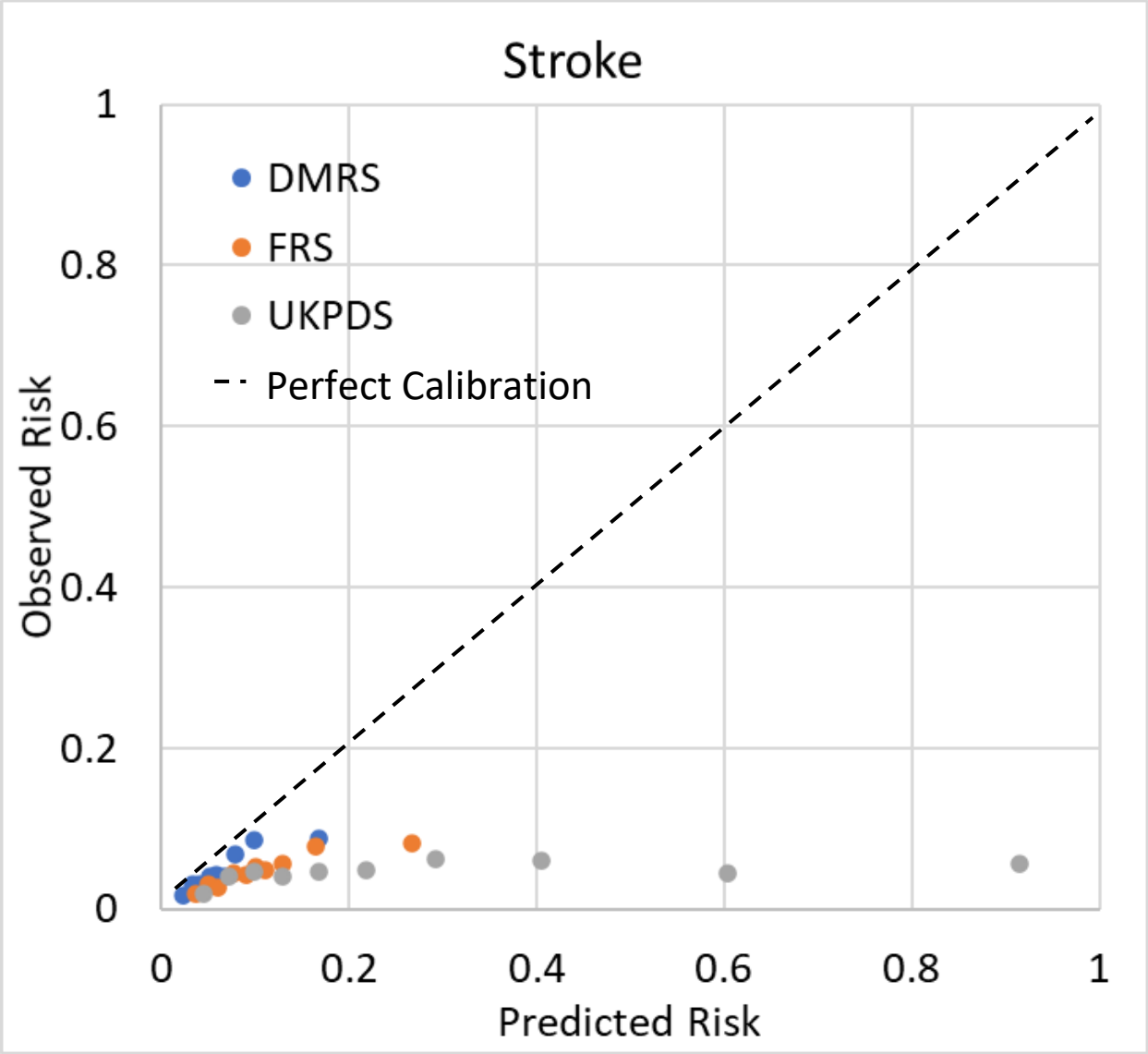


Figure 4-5. External Validation Calibration Plots for Stroke

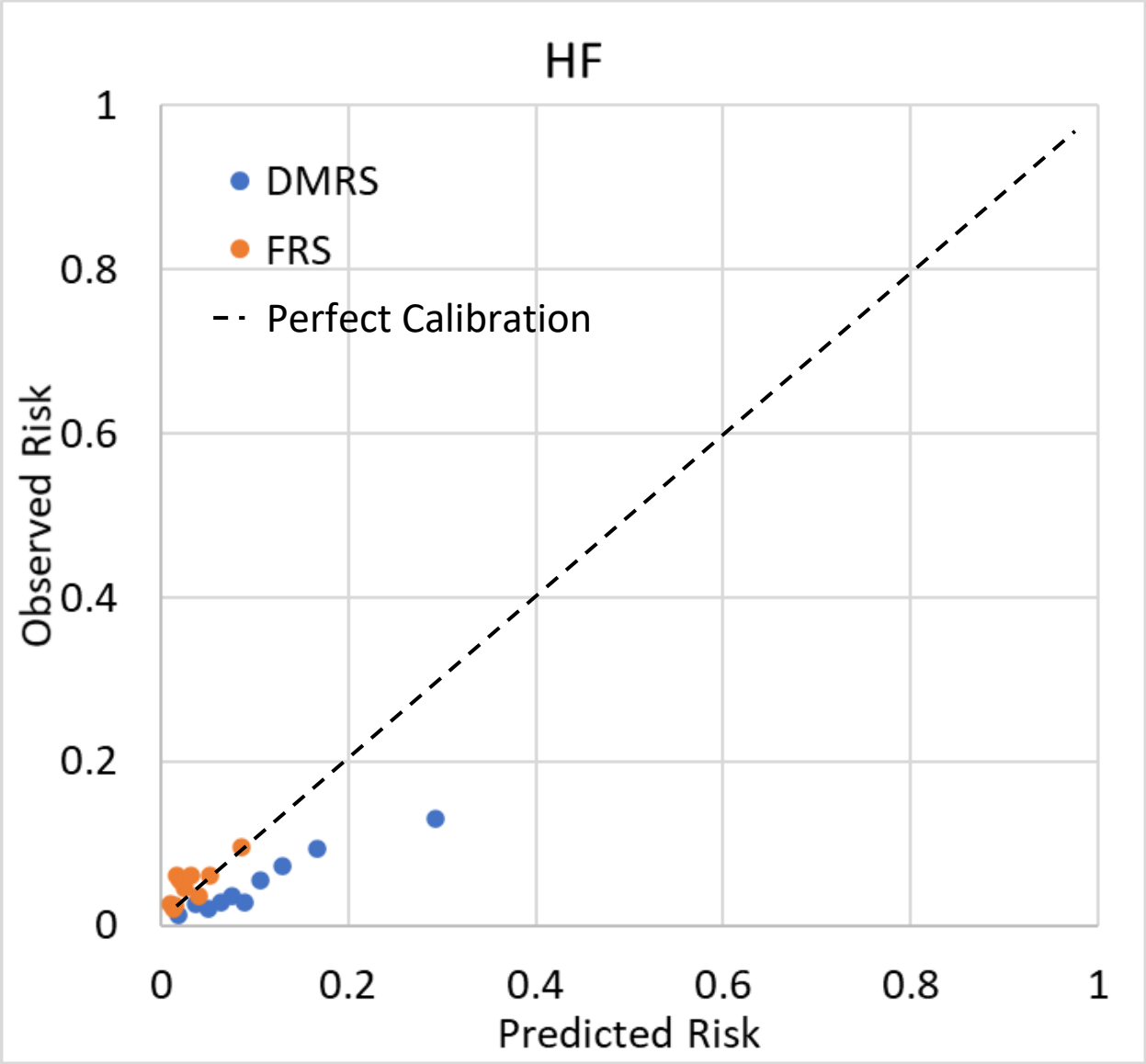


Figure 4-6. External Validation Calibration Plots for HF

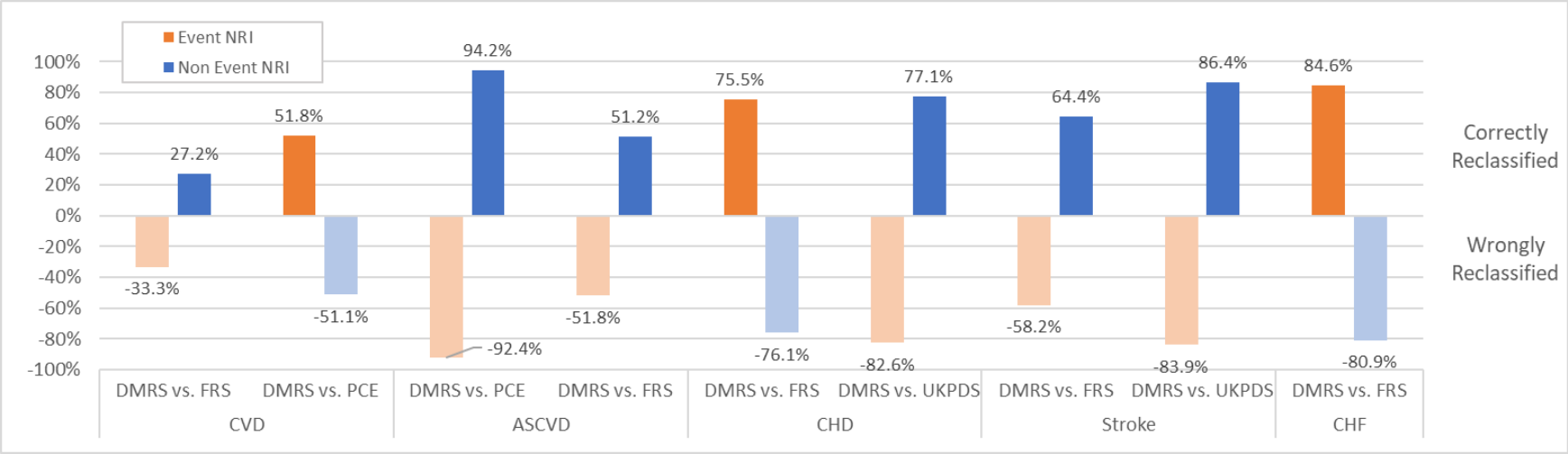


Figure 4-7. Reclassification of Risk Comparing the Diabetes Mellitus Risk Score (DMRS) vs. Old Scores for Each Endpoint

4.7 Supplementary Materials

Supplementary Table 4-1. Definition of Composite Endpoints

Endpoints	Components
CVD	Non-fatal myocardial infarction, Coronary revascularization Non-fatal Stroke HF CVD death
ASCVD	Non-fatal myocardial infarction Non-fatal stroke CHD death
CHD	Non-fatal myocardial infarction, Coronary revascularization CHD death

Supplementary Table 4-2. Predictor Selection by Elastic Net Regression Models

Endpoints	Removed variables
CVD	DBP, BMI, heart rate, alcohol consumption, lipid-lowering medication, atrial fibrillation
ASCVD	DBP, BMI, waist circumference, CRP, alcohol consumption, heart rate, lipid-lowering medication, atrial fibrillation
CHD	BMI, waist circumference, triglycerides, CRP, glucose, alcohol consumption, heart rate, lipid-lowering medication, atrial fibrillation
Stroke	DBP, waist circumference, HDL-C, CRP, glucose, heart rate, lipid-lowering medication, DM medication, DM duration over 10 years
HF	BMI, triglycerides, heart rate, lipid-lowering medication, DM duration over 10 years, atrial fibrillation

Supplementary Table 4-3. Comparison of CVD Risk Models Using Different Model Development Algorithms

	AIC	C-statistics
Model in the main analysis	22338	0.705
Model with log transformed continuous variables [a]	22291	0.707
Model with interaction terms [b]	22260	0.709
Models separately developed by sex [c]	/	0.715

a. each log transformed continuous variable from the final CVD risk prediction model was examined in replacement of original variable, i.e. ln(age) was firstly used to replace age in the model and changes of model AIC and C-statistics were recorded. Only those log transformed variables with both AIC and C-statistics improvement were remained in the final model to replace their original forms.
b. We selectively tested interaction terms of age with all other predictors, as well as medication with their corresponding risk factors in the full model. The interaction terms with $p<0.15$ were remain in this final model.
c. Models were separately constructed from the first round of predictor selection.

Supplementary Table 4-4. Example of Diabetes Mellitus Risk Score (DMRS) Calculation

		X	CVD Beta*X	ASCVD Beta*X	CHD Beta*X	Stroke Beta*X	HF Beta*X
Age, years		60	1.968	1.9218	1.6914	1.4814	2.8638
Sex, 1=Male, 0=Female		0	0	0	0	0	0
White, 1=Yes, 0=No		0	/	/	/	/	/
Black, 1=Yes, 0=No		1	-0.1599	0.0012	-0.2977	0.2305	-0.1179
Other races, 1=Yes, 0=No		0	0	0	0	0	0
Above high school education, 1=Yes, 0=No		1	-0.2084	-0.20403	-0.2059	-0.2667	-0.3746
Current smoking, 1=Yes, 0=No		0	0	0	0	0	0
Family history of CVD, 1=Yes, 0=No		1	0.2046	0.23869	0.2375	0.2494	0.1981
SBP, mmHg		125	1.25	1.3675	0.9	1.94125	0.96125
Waist circumference, cm		89	0.5251	/	/	/	1.26113
HbA1c, %		10.2	1.21176	1.454724	0.84762	0.189516	1.5351
Total cholesterol, mg/dL		140	0.406	0.539	0.6832	0.364	0.3066
HDL-C, mg/dL		45	-0.2745	-0.432	-0.62325	/	/
Hs-CRP, mg/L		4.6	0.04048	0.060444	0.06348	0.0529	0.08832
UACR, mg/g		69	0.02277	0.029325	0.0207	0.03312	0.046092
Serum creatinine, mg/dL		0.8	0.23208	0.258672	0.23952	0.24304	0.26856
DM duration over 10 years, 1=Yes, 0=No		1	0.1859	0.24959	0.2462	/	/
Taking HTN medication, 1=Yes, 0=No		1	0.199	0.19241	/	/	0.2908
Taking medication for DM, 1=Yes, 0=No		1	0.231	/	0.3274	/	0.3359
Other parameters in the equation [b]	$\Sigma Beta*X_{individual}$		5.8339	5.8846	4.2515	4.8650	8.2671
	$\Sigma Beta*X_{Mean}$	/	5.8685	5.5192	4.4423	5.8827	7.7471
	S_{10}	/	0.8166	0.9100	0.8947	0.9700	0.9542
Final Scores		/	**17.78%**	**12.71%**	**8.78%**	**1.09%**	**7.58%**

The example was a 60-year black female with a DM over 10 years. She had college degree and family history of CVD but does not smoke. Her SBP was 125 mmHg, waist circumference was 89 cm, HbA1c were 10.2%, total cholesterol was 140 mg/dL, HDL-C was 45 mg/dL, hs-CRP was 4.6 mg/L, UACR was 69 mg/g, serum creatinine was 0.8 mg/dL. She took both HTN and DM medications. Her 10-year event risk is calculated as: $R = 1 - (S_{10})^{e^{(\Sigma\, beta*X_{Individual} - Beta*X_{Mean})}}$, where $\Sigma\, beta * X_{individual}$ is the sum of beta coefficient*individual's predictor values.

Supplementary Table 4-5. Internal Validation of Diabetes Mellitus Risk Score (DMRS) in ARIC and Other Cohorts (CARDIA, FHS offspring, JHS and MESA)

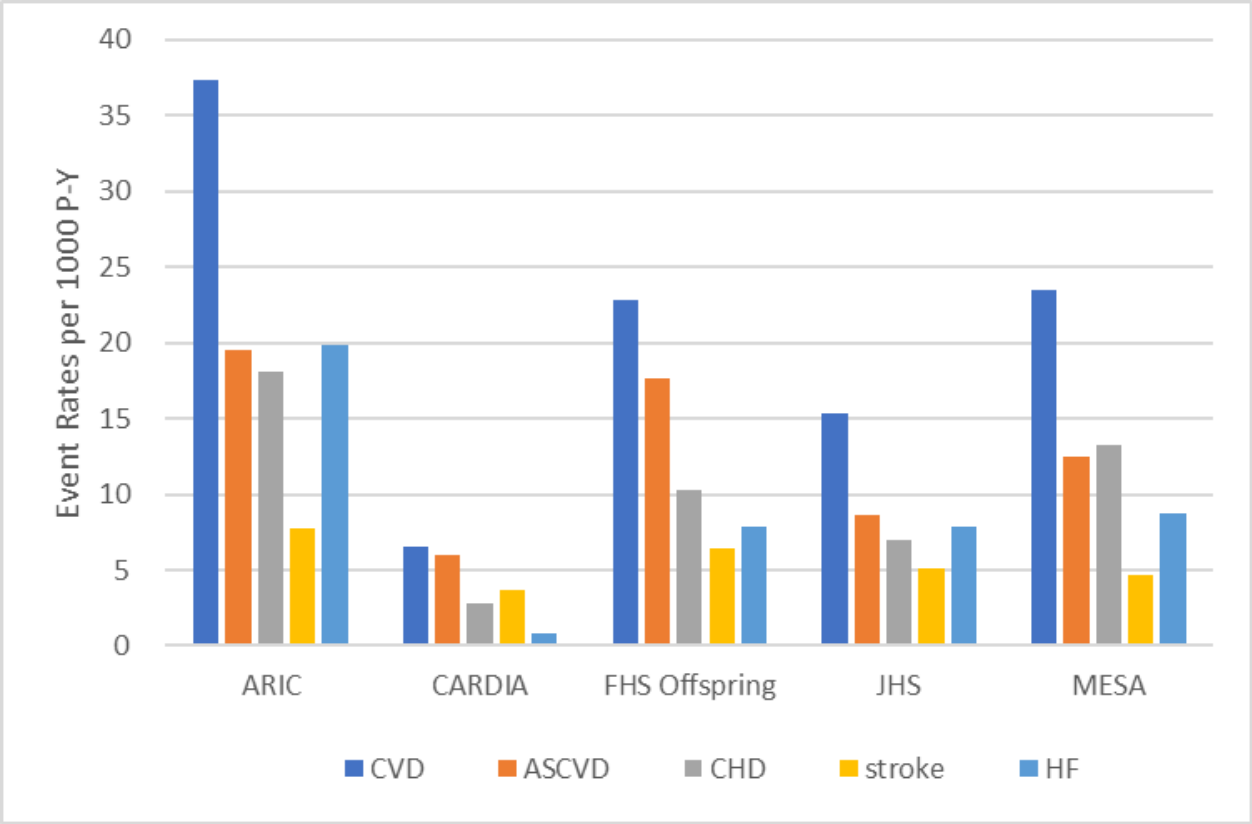
		ARIC	Other four cohorts
CVD	Harrell's C-statistics	0.69 (0.67-0.71)	0.71 (0.68-0.73)
	Calibration (slope/intercept/chi2)	1.212/-0.023/20*	0.8655 /0.001/67 §
ASCVD	Harrell's C-statistics	0.71 (0.68-0.72)	0.70(0.67-0.73)
	Calibration (slope/intercept/chi2)	1.278/-0.032/19*	0.811/0.013/18*
CHD	Harrell's C-statistics	0.68 (0.66-0.70)	0.71 (0.67-0.74)
	Calibration (slope/intercept/chi2)	1.164/-0.004/12	0.879/-0.004/39 §
Stroke	Harrell's C-statistics	0.71 (0.68-0.74)	0.69 (0.64-0.73)
	Calibration (slope/intercept/chi2)	1.418/-0.027/20†	0.743/0.010/12
HF	Harrell's C-statistics	0.74 (0.72-0.76)	0.75 (0.73-0.78)
	Calibration (slope/intercept/chi2)	1.490/-0.027/52 §	0.747/0.004/42 §

* $p<0.05$, † $p<0.01$, ‡ $p<0.001$, § $p<0.0001$

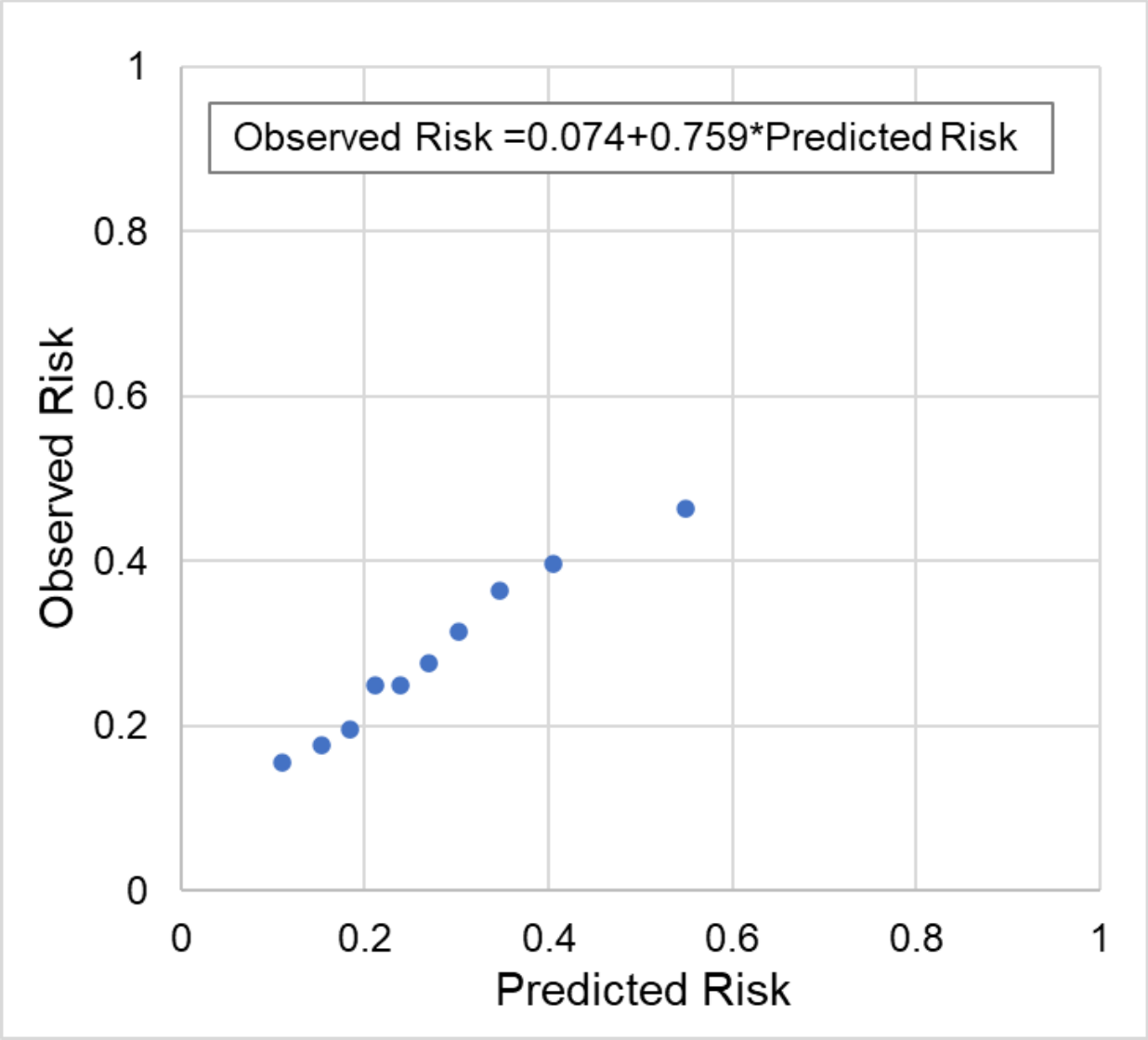
Supplementary Table 4-6. External Validation of the Diabetes Mellitus Risk Score (DMRS) and Other Scores in the Control Arm of ACCORDION Cohort

		DMRS	FRS	PCE	UKPDS
CVD	Harrell's C-statistics	0.63	0.61	0.61	/
	Calibration (slope/intercept/chi2)	0.817/0.053/7.42	0.635/0.081/32.31 ‡	0.743/0.117/34.47§	/
ASCVD	Harrell's C-statistics	0.66	0.64	0.63	/
	Calibration (slope/intercept/chi2)	0.855/0.010/12.50	0.46/0.003/344.54 §	0.52/0.036/85.10 §	/
CHD	Harrell's C-statistics	0.64	0.56 ‡	/	0.62
	Calibration (slope/intercept/chi2)	0.739/0.029/17.57*	0.432/0.125/96.24 §	/	0.173/0.0726/3316 §
Stroke	Harrell's C-statistics	0.70	0.69	/	0.57
	Calibration (slope/intercept/chi2)	0.530/0.013/58 §	0.285/0.018/385 §	/	0.023/0.037/6770.10§
HF	Harrell's C-statistics	0.69	0.58	/	/
	Calibration (slope/intercept/chi2)	0.462/0.003/97.65§	0.877/0.037/21.33 ‡	/	/

* $p<0.05$, † $p<0.01$, ‡ $p<0.001$, §$p<0.0001$ compared to the DMRS



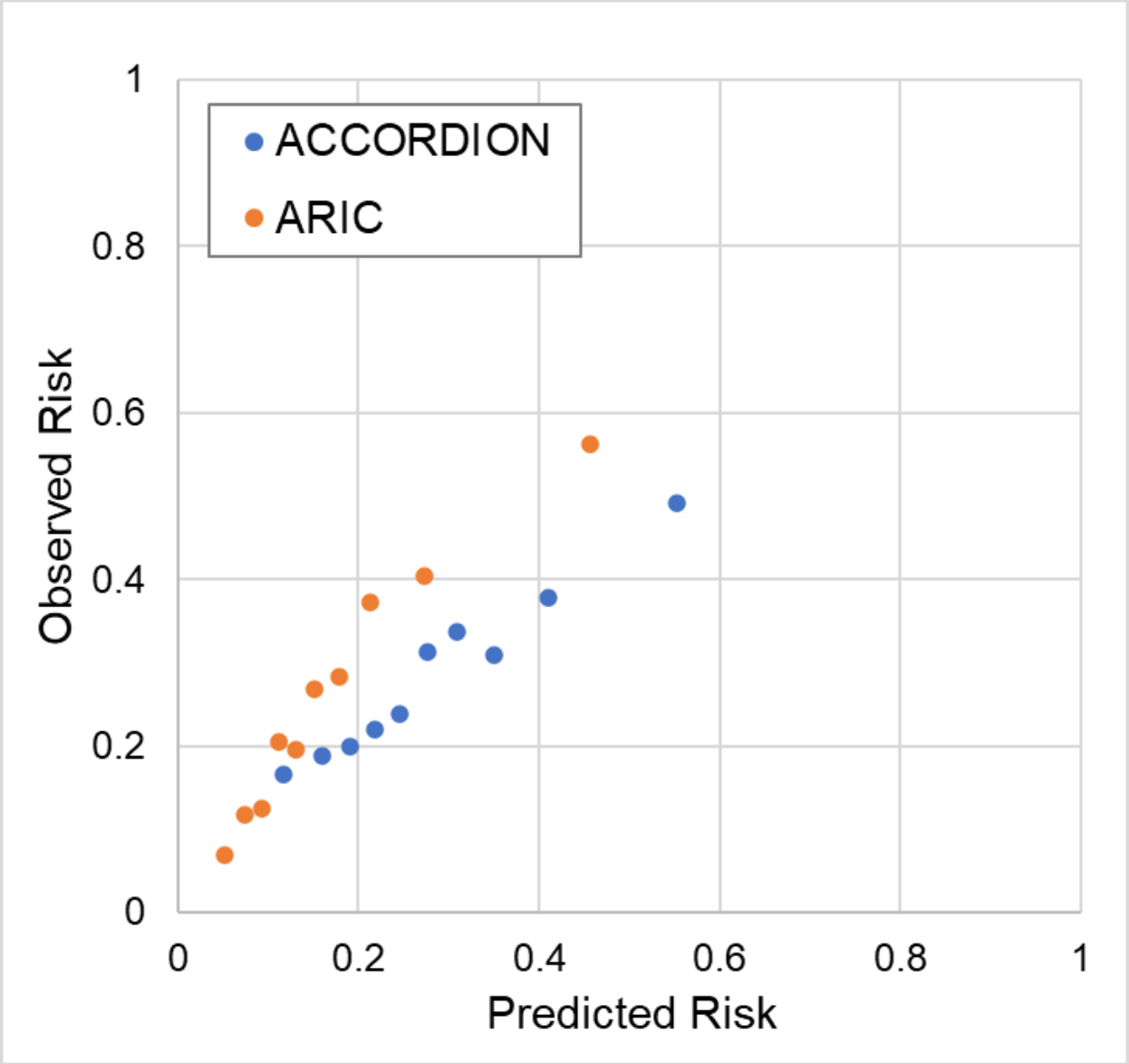
Supplementary Figure 4-1. Event Rates by Cohorts



Supplementary Figure 4-2. Recalibration of Diabetes Mellitus Risk Score (DMRS) for CVD Using the Non-ARIC Pooled Cohort and External Calibration Plot

The S_{10} (0.8166) in the original DMRS for CVD were replaced with S_{10}' (0.8287), derived from non-ARIC Pooled Cohort and Σbeta*X_{mean} were replaced with Σbeta*X_{mean}' (6.205)

GND test of recalibrated DMRS for CVD: $X^2 = 30.6$, df = 9, p =0.0003



Supplementary Figure 4-3. Diabetes Mellitus Risk Score (DMRS) for CVD Using Non-ARIC Pooled Cohort and External Validation in ACCORDION and ARIC

In ACCORDION, Observed risk = 0.067 + 0.766*Predicted Risk, GND test X2 = 30.9, df=9, p =0.0003

In ARIC, Observed risk = 0.047 + 1.233*Predicted Risk, GND test X2 = 79.7, df=9, p <0.0001

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5. Comprehensive Evaluation of the Predictive Value Increment of Subclinical Atherosclerosis Measures Beyond the New Diabetes Mellitus Risk Score: the Multi-Ethnic Study of Atherosclerosis

Running title: Predictive value of CAC, CIMT and ABI in DM

5.1 Abstract

Background: Coronary artery calcium (CAC) was found to be the single strongest predictor for cardiovascular disease (CVD) events in various populations. The comparative predictive value of CAC and other subclinical atherosclerosis (SA) measures, namely CIMT and ABI beyond the Diabetes Mellitus Risk Scores (DMRS) for the CVD and its component events was not known.

Methods: We included CVD-free subjects with diabetes mellitus (DM) from the Multiethnic Study of Atherosclerosis where CAC, CIMT and ABI measures were available at baseline. CAC, CIMT and ABI were examined in relation with CVD, Atherosclerotic CVD (ASCVD), coronary heart disease (CHD), heart failure (HF) and stroke. We examined the predictive increment of SA measures beyond DMRS using the Harrell's c-statistics and net reclassification index (NRI) in the following model comparisons: (1) single SA measures + DMRS vs. DMRS; (2) Direct comparison of each SA measure; (3) CAC+CIMT (or ABI, or CIMT+ABI)+DMRS vs. CIMT(or ABI, or CIMT+ABI)+DMRS.

Results: We included 931 subjects with DM (mean age of 62.3 years, with 43.8% males). During a median follow-up of 14.6 years, CVD and its component event rates showed stepwise increase by CAC, CIMT or ABI categories. The Harrell's C-statistics of DMRS were 0.65, 0.66, 0.66, 0.68 and 0.65 for CVD, ASCVD, CHD, HF and stroke, respectively. CAC+DMRS increased the C-statistics to 0.70, 0.68, 0.74, 0.68 and 0.62 while the change was minimal with

the addition of CIMT or ABI to DMRS. CAC showed superiority in c-statistics and NRI to CIMT and ABI as well as beyond CIMT, ABI or both for CVD and CHD events.

Conclusion: CAC remains the strongest CVD risk reclassifier among CAC, CIMT and ABI for patients with DM. Cardiac CT scanning for CAC warrants first consideration when the treatment decision is uncertain.

5.2 Introduction

Subclinical atherosclerosis (SA) represents early atherosclerotic cardiovascular disease (ASCVD) without clinical manifestation and is usually measured by non-invasive detecting techniques. SA measures not only indicate the existence and quantify the severity of early atherosclerosis but are found to have potential usefulness in improving cardiovascular risk prediction. [1] Diabetes Mellitus (DM) is a high-CVD risk condition with higher prevalence of systemic SA. [2] Detection of SA among DM population may also help better stratify their risk. Coronary artery calcium (CAC), carotid intima-media thickness (CIMT) and ankle brachial index (ABI) are the commonly used SA measures in clinic and have been extensively studied in research. All three measures are found to be independently associated with CVD risk but only CAC was shown to improve the prediction of CVD events over existing risk scores such as PCE, FRS and UKPDS in DM population. [3-11]

Studies designed for the prediction improvement of SA measures mostly involves single measure and compare it to a base model. [12,13] Fewer studies ever targeted direct comparison of two or more subclinical measures for prediction ability [14] and there is lack of evidence on whether subclinical measures are needed beyond each other in risk prediction of CVD events given their benefits and harms. The CHD risks score from Multi-Ethnic Study of Atherosclerosis and the Heinz Nixdorf Recall Study (HNR) explored traditional risk factors as well as CAC and ABI and finally included only age, sex, SBP, DM duration and CAC in the final risk calculator [15], indicating the unnecessity of ABI testing when CAC score is available. Similarly, evaluation of CIMT may not be needed beyond the CAC for risk reclassification purpose. But whether CAC

can still improve risk prediction when a patient already has ABI or CIMT tested for reclassification was not known.

There are various statistical parameters that can be used to evaluate the incremental predictive value of a new measure upon original risk score. The likelihood ratio test for beta coefficient of marker, C-statistic (AUC) and NRI are three most commonly used. An independent association between the marker and outcome is the prerequisite of possible incremental predictive value but is not a guarantee. The c-statistic enables the quantification of incremental predictive ability of new marker but is also found to be conservative when the two models have large overlap of covariates or when the old model is already good enough. [16] The most notable advantage of NRI is categorical NRI has an easy and clinically-relevant interpretation. However, NRI, especially category-free NRI, sometimes suffers false positive problem to report significant results even when the marker is not associated with the outcome. [17] Summary of pros and cons of each statistical approach is listed in Supplementary Table 5-1.

In the second project, we created a pooled cohort DM Risk Score (DMRS) for macrovascular complications and demonstrated the superior performance of DMRS over FRS, PCE and UKPDS. We aimed to examine and compare the predictive value of CAC, CIMT and ABI for CVD and its component events that DMRS predicts (CVD, ASCVD, CHD, Stroke and HF). Both c-statistics (AUC) and net reclassification index (NRI) were used to evaluate the risk prediction improvement of CAC, CIMT and ABI in DM participants from the Multi-Ethnic Study of Atherosclerosis (MESA).

5.3 Methods

Study Sample

We included CVD-free subjects with DM from MESA. [18] Baseline in our study is Exam 1 (2000-2002) where CAC, CIMT and ABI was available for the whole study sample. DM was defined as having at least one of following at the baseline exam: (1) physician diagnosed DM; (2) use of insulin or oral diabetes medication; (3) a fasting blood glucose level of ≥6.99 mmol/l (126 mg/dL); (4) 2h oral glucose tolerance test ≥11.1 mmol/l (200 mg/dL). HbA1c was only available at exam 2 and therefore will not be used as the diagnosis criteria (however Exam 2 HbA1c will be used ad proxy of baseline HbA1c in risk score calculation). Subjects will be excluded if one had clinical CVD events before baseline exam.

Subclinical Atherosclerosis Measures

The main CAC measure was the Agatston score. Scanning centers assessed coronary calcium with either a cardiac-gated electron-beam CT scanner (Chicago, Illinois; Los Angeles, California; and New York, New York field centers) or a multidetector CT system (Baltimore, Maryland; Forsyth County, North Carolina; and St Paul, Minnesota field centers). 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). We used the mean Agatston score and the mean CAC volume score for the 2 scans in all analyses. Intraobserver and interobserver agreements were excellent (kappa=0.93 and kappa=0.90, respectively). Since previous analyses in MESA have shown log linear relationships between CAC and CVD risk [19], the Agatston score was transformed to natural logarithm as ln(Agatston

score+1) as continuous variable. The Agatston score was classified as 0 (ref), 1-99, 100-399, 400+.

The right and left near and far walls of the internal carotid and common carotid arteries were measured by trained technicians using B-mode ultrasonography in each field center. The Logiq 700 ultrasound device (General Electric Medical Systems, Waukesha, Wisconsin) was used to record images. The ultrasound reading center measured maximal intimal medial thickness (IMT) of the internal and common carotid sites as the mean of the maximum IMT of the near and far walls of the right and left sides. The mean of maximum IMT of the common and internal carotid artery was used as final CIMT measure and was categorized into ≥1 mm vs. <1mm (reference).

ABI was measured using Doppler instrument in supine position. Systolic blood pressure measurements in the bilateral brachial, dorsalis pedis, and posterior tibial arteries were obtained in the supine position using a hand-held Doppler instrument. To avoid potential bias from subclavian stenosis, the higher of the brachial artery pressures was used as the denominator. For each lower extremity, the ABI numerator used was the highest pressure (dorsalis pedis or posterior tibial) from that leg. The leg cuff was inflated to a maximum of 300 mmHg, and if a pulse was still detected at this level the ABI was classified as "incompressible". A subset of 384 MESA participants had replicate ABI measurements that showed excellent reproducibility. ABI value was classified as <0.9, 0.9 - <1.0, 1.0 - 1.4 (reference) and > 1.4 (incompressible). ABI was examined as continuous variable.

Baseline Risk Factors

Baseline risk factors collected included age, sex, race/ethnicity, waist circumference, BMI, diabetes duration, family history of premature CVD, diabetes medication, urinary albumin/creatinine ratio, use of lipid-lowering medication, antihypertensive treatment, smoking status, serum creatinine, SBP, hs-CRP, LDL-C, HDL-C, triglycerides and total cholesterol. Since HbA1c was not collected at MESA exam 1, HbA1c from exam 2 was used as proxy of "baseline HbA1c". The above risk factors were used to calculate the following disease risk scores: the new DMRS, PCE score for ASCVD and 4 FRS for CVD, CHD, stroke and HF. [20-24] Missing values of risk factor were filled using multiple imputation. Complete-case analysis was done as sensitivity analysis when sample size allows.

Follow-Up and Ascertainment of Endpoints

We used the same definition for each endpoint corresponding to each risk score to ensure the maximal predictive value of different risk scores. For the new DMRS:

(1) CVD was defined as fatal or non-fatal MI, CVD death, cardiac revascularization, fatal or non-fatal stroke and heart failure;

(2) ASCVD was defined as fatal or non-fatal MI, fatal or non-fatal stroke, and CHD death;

(3) CHD was defined as MI, cardiac revascularization, or CHD death.

Maximum follow-up time in years was 17 years for MESA.

Statistical Analysis

(1) Descriptive analysis: All continuous variables were compared among CAC groups, or ABI groups using ANOVA and between CIMT groups using t-test. Continuous variables with skewness >1 were log transformed to get normal distribution. The chi-square test was used to

compare categorical baseline variables. Event rates per 1000 person-years were calculated in groups defined by each subclinical atherosclerosis measure.

(2) Independent association of SA and CVD (and component event) risk: The Cox proportional hazard regression models were used to calculate the HRs of each SA measure [ln(CAC+1), CIMT or ABI categories] for each endpoint when adjusted for DMRS for corresponding endpoints. In sensitivity analysis, the Cox regression models were adjusted for risk factors used in DMRS for the corresponding endpoints instead.

(3) Predictive increment of SA measures: The first step involved the construction of multiple Cox regression models with different combination of risk scores and SA measures. We called models without SA measures the "base model". Then model predictive abilities were compared using c-statistics and NRI as described below. Two models, namely a "comparison model" vs. a "reference model" were compared each time. All the prediction models are summarized in the Table 5-1.

1) Individual SA measures vs. disease risk score: The comparison model was "base model + single SA measure" and the reference model was the base model in the comparison model. For instance, to examine if CAC provides additional predictive value beyond DMRS, we compared "DMRS+CAC" vs. "DMRS" (model 4 or 5 vs model 1). To examine other risk scores, DMRS was replaced by FRS or PCE corresponding to their predicted event (model 6 vs. model 2). In sensitivity analysis, we included the risk factors of DMRS instead of the scores in the model to serve as base model and examine if predictive value of SA measures attenuated (model 7 vs model 3). Models with CIMT or ABI were examined in similar ways.

2). Head-to-head comparison of individual SA measures: To examine if one single subclinical measure is better than another, we used AUC and NRI to compare "DMRS + CAC" (model 4) vs. "DMRS + CIMT" (Model 8), "DMRS + CAC" (model 4) vs. "DMRS + ABI" (model 12) and "DMRS + CIMT" (model 8) vs. "DMRS + ABI" (model 12).

3). Incremental predictive value of CAC beyond CIMT, ABI or both: given CAC was probably the strongest risk reclassifier, we examined if CAC reclassify CVD (and component event) risk when we already knew CIMT or ABI, or both. In the part, we compared C-statistics and NRI between:

- "DMRS+CAC+CIMT" (model 15) vs. "DMRS+CIMT" (model 8),
- "DMRS+CAC+ABI" (model 16) vs. "DMRS+ABI" (model 12),
- "DMRS+CAC+CIMT+ABI" (model 18) vs. "DMRS+CIMT+ABI" (model 17).

Statistical analysis was done using SAS 9.4. A two-sided p value <0.05 was considered statistically significant.

5.4 Results

We included 931 subjects with DM from the MESA cohort (mean age of 62.3 years, with 43.8% males). More severe SA was generally associated with poorer non-modifiable or untreated risk factors such as age, sex, DM duration, hs-CRP, serum creatinine etc. They also tended to have more medication for dyslipidemia, hypertension and DM at baseline (Table 5-1, Supplementary Table 5-2, Supplementary Table 5-3).

During a median follow-up of 14.6 years, there were 265 (28.5%) CVD, 160 (17.2%) ASCVD, 157 (16.9%) CHD, 100 (10.7%) HF and 67 (7.2%) stroke incident events occurred. CVD event rates per 100 person-years were 13.7, 21.9, 32.7 and 67.0 among those with CAC of 0, 1-99, 100-399 and 400+, respectively; CVD event rates per 100 person-years were 19.9 and 33.3 among those with CIMT < 1 mm vs. ≥1 mm; CVD event rates per 100 person-years were 22.8, 35.2, 52.9 and 72.4 among those with ABI of 1.0-1.4, 0.9-0.99, <0.9 and >1.4. Other CVD component event rates also showed stepwise increase by CAC, CIMT or ABI categories (Figure 5-1).

Independent Association of SA and Incident Event Risk

Table 5-3 (and Supplementary Table 5-4) presents the association of each SA measure and each outcome at different levels of adjustment. For CAC, the unadjusted HRs per 1 unit increase of ln(CAC+1) were 1.26, 1.21, 1.32, 1.15 and 1.11 for incident CVD, ASCVD, CHD, HF and stroke events ($p < 0.05$ for stroke, $p < 0.001$ for CHF and $p < 0.0001$ for other three outcomes) (Supplementary Table 5-4). Adjustment of DMRS slightly attenuated the association between CAC, either as a continuous variable or as a categorical variable, and each endpoint (Table 5-3). CAC showed the strongest association with CHD and the weakest association with stroke among all the five endpoints. In models adjusted for DMRS risk factors, CIMT per 1 mm increase was associated with 43%, 9%, 38%, 6% and 37% higher CVD, ASCVD, CHD, HF and stroke risk. In sensitivity analysis, CIMT percentile categories (≥ 75% percentile vs. <75% percentile) were associated with similar HRs as those using absolute cutpoint of 1mm. The association was the strongest for CVD and the weakest for HF. Due to the non-linear association of ABI and CVD events, ABI was only examined as a categorical variable: ABI categories of 0.9-0.99, <0.9

and >1.4 had HRs of 1.10 (0.61-1.97), 2.06 (1.24-3.41) and 1.93 (0.6-6.18) for CVD events, respectively; HRs for other four endpoints were similar to those for CVD.

Predictive Increment of SA Measures

1) Individual SA Measures + DMRS vs. DMRS

We compared the incremental predictive value of each single SA beyond the DMRS (SA+DMRS vs. DMRS). The Harrell's C-statistics of DMRS were 0.65, 0.66, 0.66, 0.68 and 0.65 for CVD, ASCVD, CHD, HF and stroke, respectively (Table 5-4). Compared to DMRS alone, DMRS+ ln (CAC+1) increase the C-statistics for CVD events to 0.70 and CIMT and ABI categories only showed slight C-statistics improvement (C-statistics =0.66 for both CIMT and ABI, $p > 0.05$) over DMRS. For ASCVD events, all three SA measured provided non-significant C-statistics improvement beyond the DMRS, with the increase being minimal for CIMT measure. For CHD events, CAC increased the C-statistics as high as 0.74 ($p<0.0001$ for comparison) while CIMT and ABI only improved C-statistics by 0.01 ($p > 0.05$). For HF, ABI increased the C-statistics of DMRS from 0.68 to 0.71, although not statistically significant. For stroke, C-statistics increases were all non-significant for three SA measures.

When DMRS for each endpoint was replaced with FRS (or PCE for ASCVD), the Harrell's C-statistics of FRS (or PCE for ASCVD) were 0.64, 0.63, 0.61, 0.58 and 0.61 for CVD, ASCVD, CHD, HF and stroke, respectively. We evaluated the absolute and relative Harrell's C-statistics change when each SA measure was added to DMRS (Supplementary Table 5-5). As hypothesized, CAC, CIMT and ABI generally provided larger absolute and relative C-statistics improvement when DMRS were replaced with FRS. For instance, ln(CAC+1) improved C-

statistics of DMRS by 0.08 (12.1%) however improved C-statistics of FRS by 0.11 (18%) for CHD events. Meanwhile the SA measures provided smaller absolute and relative C-statistics improvement when DMRS were replaced with the risk factors used in DMRS.

The reclassification ability of CAC, CIMT and ABI compared to DMRS alone was evaluated by continuous NRI for each endpoint and additionally by categorical NRI using guideline recommended risk categories for CVD and ASCVD. Overall, CAC had the highest category-free NRI of 51.0%, 49.4% and 66.8% for CVD, ASCVD and CHD, respectively ($p<0.0001$). In addition, only CAC demonstrated both statistically significant positive event and non-event NRI for CVD, ASCVD and CHD (Table 5-5). For CVD events, ln(CAC+1) had an event NRI of 33.2% and a non-event of 17.8% over DMRS; for ASCVD events, ln(CAC+1) had an event NRI of 36.7% and a non-event of 12.7% over DMRS; for CHD events, ln(CAC+1) had an event NRI of 45.8% and a non-event of 21.0% over DMRS. For HF and stroke, CAC had the positive event NRI and close-to -zero non-event NRI. CIMT had positive non-event NRI (ranging 24.9% - 32.6%) and close to zero event NRI (ranging -1.9%-5.7%) for CVD, ASCVD, HF and stroke, making the total category-free NRI close to non-event NRI over DMRS; while for CHD, CIMT had an event NRI of 15.4% and a non-event of 30.3% over DMRS. Although ABI had overall positive NRI, its event NRI were all negative (ranging -53.4% - -31.8%) and non-event NRI were all positive and large (ranging 66.3%-78.5%). When DMRS were replaced with FRS (or PCE for ASCVD endpoint) or DMRS predictors, NRIs comparing prediction models with vs. without each SA measures were similar (Supplementary Table 5-6).

We used the 5%, 7.5% and 20% cutpoints to calculate the 4-category NRI for ASCVD events. Given total CVD event rates were about 1.5 times of ASCVD, we used 7.5%, 11.25% and 30% cutpoints for CVD events. 4-category NRI of CAC, CIMT and ABI were 21.3%, -12.8% and -11.1% for CVD events, respectively; the corresponding NRI were 3.4%, -27.4% and -26. 2% for ASCVD events (Supplementary Table 5-7). The details of reclassification by occurrence of event were presented in Figure 5-2 and Figure 5-3 where we observed that more proportion of subjects in each DMRS category were correctly reclassified by CAC than by CIMT or ABI for CVD and ASCVD events.

2) Head-to-Head Comparison of Individual SA Measures

We made pairwise comparison between the DMRS+CAC vs. DMRS+CIMT vs. DMRS+ABI using both AUC and NRI. Overall CAC showed better incremental predictive value over DMRS than CIMT and ABI for CVD, ASCVD and CHD events with the difference being largest for CHD events (Table 5-6). The difference of C-statistics were 0.04, 0.03, 0.07, 0.02 and 0.03 for CVD, ASCVD, CHD, HF and stroke comparing DMRS+CAC vs. DMRS+CIMT ($p < 0.0001$ for CVD and CHD); corresponding C-statistics difference were 0.04, 0.00, 0.07, -0.02 and -0.04 comparing DMRS+CAC vs. DMRS+ABI ($p < 0.0001$ for CVD and CHD); difference of C-statistics were all minimal and non-significant comparing DMRS+CIMT vs. DMRS+ABI for each endpoint.

Although NRIs of each pair-wise comparison were mostly positive and statistically significant, the magnitude of NRI showed consistent pattern with AUC comparison, with CAC showing superiority over CIMT and ABI for CVD, ASCVD and CHD and ABI showed superiority for

predicting HF over CIMT. The incremental predictive value for ABI was comparable with CAC for HF (C-statistics: .068 vs. 0.70 and category-free NRI = 7.5% comparing CAC +MDRS-HF vs. ABI+DMRS-HF)

3) Incremental Predictive Value of CAC Beyond CIMT, ABI or Both

We first compared CAC+CIMT+DMRS vs. CIMT+DMRS to test if CAC provided further reclassification beyond CIMT: CAC increased C-statistics by 0.04, 0.03, 0.07, 0.01 and 0.01 beyond CIMT+DMRS for CVD, ASCVD, CHD, HF and stroke events ($p < 0.001$ for CVD and CHD); corresponding NRIs were 48.7%, 52.8%, 59.8%, 30.6%, and 32.4%, respectively. When CAC was added to ABI+DMRS model, CAC increased C-statistics by 0.05, 0.01, 0.08, -0.01 and -0.03 for CVD, ASCVD, CHD, HF and stroke events ($p < 0.001$ for CVD and CHD); corresponding NRIs were 49.5%, 41.0%, 59.0%, 30.3%, and 21.5%, respectively (Table 5-7).

Then the CIMT+ABI+DMRS was set as reference model and we compared if addition of CAC improved C-statistics and NRI. Results were similar to the those above with single CIMT or ABI. If CIMT+ABI were replaced with CAC (instead of addition of CAC), C-statistics were improved to a similar extent to those of CAC+CIMT+ABI+DMRS vs. CIMT+ABI+DMRS. However, the NRI were smaller.

5.5 Discussion

In the current study, we found that CAC, CIMT and ABI were all independently associated with CVD events. In addition, CAC was independently associated with CVD component events of ASCVD, CHD, HF and stroke. When C-statistics and NRI were used to evaluate the incremental

predictive value of each SA measure, CAC showed the strongest added predictive value beyond the new DMRS for CHD events, followed by CVD, ASCVD, HF and Stroke; CIMT did not add much predictive value for any of the endpoints and ABI only tended to improve prediction for HF risk.

We made a series of comparisons between prediction models made of various combination of DMRS and SA measures. In the head-to-head comparison of predictive values, CAC was shown to have superior discrimination and reclassification ability to CIMT and ABI, except for HF comparing to ABI. CIMT was the least predictive for most of the examined endpoints; ABI had similar AUC and minimal NRI compared to CAC for HF events. Even in the presence of CIMT, ABI or both, CAC was still found to improve total CVD and CHD event risk prediction beyond CIMT, ABI or both; however even if CIMT and ABI were combined, they failed to classify CVD and its component event risk better than CAC alone.

Several previous studies compared the predictive values of SA measures for CVD (or component events) risk assessment in various populations. In the prior MESA study comparing the predictive ability of several novel predictors among intermediate risk population, CAC were found to be the strongest risk discriminator and reclassifier among coronary artery calcium, carotid intima-media thickness, ankle-brachial index, brachial flow-mediated dilation, high-sensitivity C-reactive protein (CRP), and family history of coronary heart disease [12]. The Heinz Nixdorf Recall study found CAC combined with ABI, or ABI alone, but not CAC alone or

CIMT, provided significant improvement of Harrell's C-statistics for stroke prediction in the general population. [25] For CVD prediction, CAC provided the strongest discrimination improvement among various SA measures. [26-28] To note, many of the studies also found that the improvement from CAC were especially prominent among intermediate FRS risk group and least among high risk group.

Our studies demonstrated the consistent findings with above study in the DM population. We previously found that CAC added prediction accuracy beyond FRS and PCE in both DM population and metabolic syndrome population [5]. Given that the DMRS were developed using MESA cohort as part of the derivation cohort, it is even harder for CAC to show an improvement of prediction ability. Our findings reinforced the current status of CAC scanning in guidelines that evaluation of CAC should be considered for risk assessment purpose even in the DM population. Currently CAC is recommended to intermediate risk group patients when treatment decision is uncertain; patients with CAC =0 are recommended to withhold or delay statin therapy unless the patients have DM or smoking, or having a family history of CVD; CAC=1-99 favors the statin therapy, while CAC ≥ 100 is an indicator to start statin, the highest category of CAC (≥ 400) is no longer used in the latest guideline. [29] It is noteworthy that in our analysis, we found that CAC had a higher event-NRI than non-event NRI for CVD outcome, indicating that the upward reclassification by CAC is more accurate and therefore more justified in DM patients.

To our knowledge, our study is the first to directly compare the predictive value of CAC, CIMT and ABI and the combination of them in patients with DM. In such direct comparison, we demonstrated that CAC was not only superior than CIMT, or ABI, or both but that it further improved the prediction of CIMT, ABI or both. The findings imply that (1) if a patient with DM is offered to choose from CAC, CIMT and ABI for CVD risk assessment purpose, CAC should first be considered and with CAC score available, CIMT and ABI tests may no longer be needed; (2) if a patient already has CIMT or ABI or both tested, CAC scanning still has merit as it provides further information of CVD risk assessment beyond CIMT and ABI and conventional risk assessment tools. Over the past decades, the cost of CAC scanning has been greatly reduced and is now comparable to that of CIMT and ABI tests, although neither are currently covered by the insurance plans for routine screening. A study comparing the cost effectiveness of CAC, CIMT and ABI found that CAC seems to be cost-saving especially in men. [30] The only concern specific to CAC test but not the other two is the radiation exposure, which is equal to about 3 to 4-months natural exposure and about the same dose as one mammogram.

While looking at individual CVD endpoints that DMRS predict, we observed that ABI improved the prediction of HF to a similar extent as CAC. In an ARIC study, Gupta et al. found that ABI $\leq$ 1.00 was significantly associated with an increased risk of HF independent of traditional HF risk factors. The potential pathogenesis includes the vascular stiffness that low ABI indicates and atherosclerotic microvascular dysfunction, both of which were exacerbated in the DM population. [31] Another IMPACT-ABI study used the same ABI categories as our current study and found both low and borderline low ABI were strongly associated with incident HF in HF-

free population. Although that study claimed to examine the prognostic value of ABI for HF risk, it did not provide any analysis on c-statistics or NRI. [32] The potential association of ABI and HF could be mediated by hypertension as Alves-Cabratosa et al. found that ABI had stronger association with HF than with MI or stroke in hypertensive population. [33]

Although the evaluation of predictive parameters, including Harrell's C-statistics and NRI, was not the main objective, we did observe discordance of the two measures with the predictive value indicated by HRs and likelihood ratio test. As Pepe pointed out in his simulation study, if we use the likelihood ratio test as the "gold standard" to judge predictive value, NRI would be inflated resulting in false positives, especially when category-free NRI was used [17]. How can we use NRI correctly then? First of all, we need to calculate both the event and non-event NRI and even more detailed breakdown of NRI; secondly, we may use the tests with high event-NRI for higher risk reclassification and use the tests with high non-event NRI for lower risk reclassification, i.e, withhold treatment. On the contrary, C-statistics only used rank-based information in the risk scores and tended to be conservative (more false negatives).

A strength of our study included that MESA had adjudicated CVD events and standardized SA measures. We examined both composite CVD events as well as CVD component events of ASCVD, CHD, HF and stroke. However, our results need to be interpreted with the following limitations. First, MESA had HbA1c tested 2 years after baseline exam. Given that we did not use HbA1c as a DM diagnosis criteria and only used it as proxy of baseline variable in DMRS calculation. Also, the original form of NRI cannot reflect the different consequence severity of

upward reclassification and downward reclassification. In real-world scenario, the harm of downward reclassification seems to be more severe given the consequence of missing the appropriate preventive therapy. A weighted NRI that capture cost-effectiveness, radiation exposure and other benefits and harms of the tests may be used instead to fully evaluate the comprehensive usage of each test in risk assessment. At last, future researches are still needed to demonstrate the effect of "measure-guided management strategy" on CVD outcomes. [34]

To conclude, CAC remains the strongest subclinical CVD risk stratifier among CAC, CIMT and ABI for patients with DM, providing improvement of risk discrimination and reclassification beyond the DMRS, CIMT and ABI or the combination of them. Cardiac CT scanning for CAC warrants consideration in the first place when treatment decision is uncertain.

Acknowledgement

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5.6 Tables and Figures

Table 5-1. Prediction Models for CVD and its Component Events

Base Model	Base Model + CAC	Base Model + CIMT	Base Model + ABI
1. DMRS	4. DMRS + ln(CAC+1)	8. DMRS + CIMT	/ (ABI will not be examined as a continuous variable)
	5. DMRS + CAC categories	9. DMRS + CIMT categories	12. DMRS + ABI categories
2. Old risk scores (RS)	6. Old RS + ln(CAC+1)	10. Old RS + CIMT	13. Old RS + ABI categories
3. DMRS risk factors	7. DMRS risk factors ln(CAC+1)	11. DMRS risk factors +C IMT	14. DMRS risk factors + ABI categories
Base Model with Combined SA Measures			
	15. DMRS + ln(CAC+1) + CIMT		
	16. DMRS + ln(CAC+1)+ ABI categories		
	17. DMRS + ABI categories+ CIMT		
	18. DMRS+ ln(CAC+1)+ CIMT+ ABI categories		

Old risk scores refer to FRS for CVD, CHD, Stroke and HF and PCE for ASCVD events.

Table 5-2. Baseline Risk Profiles by CAC Categories

	CAC = 0	CAC = 1-99	CAC = 100-399	CAC = 400+
Age, years	61 ± 9.3	64.9 ± 9.3	67.8 ± 8.7	69.3 ± 7.9
Male	136 (38.2%)	136 (52.7%)	100 (64.1%)	109 (67.7%)
Races				
White	41 (11.5%)	56 (21.7%)	41 (26.3%)	43 (26.7%)
Black	158 (44.4%)	93 (36%)	53 (34%)	51 (31.7%)
Other races	157 (44.1%)	109 (42.2%)	62 (39.7%)	67 (41.6%)
Above high school education	182 (51.1%)	123 (47.7%)	82 (52.6%)	84 (52.2%)
Alcohol use	159 (44.7%)	116 (45%)	92 (59%)	80 (49.7%)
Smoke status				
Never	196 (55.1%)	123 (47.7%)	64 (41%)	77 (47.8%)
Previous	110 (30.9%)	104 (40.3%)	70 (44.9%)	67 (41.6%)
Current	50 (14%)	31 (12%)	22 (14.1%)	17 (10.6%)
Family history of CVD	152 (42.7%)	126 (48.8%)	78 (50%)	82 (50.9%)
SBP, mmHg	129.7 ± 20.2	133.8 ± 22.9	136.8 ± 21.1	135.6 ± 23.7
BMI, kg/m^2	31 ± 6.1	30.7 ± 6.1	29.4 ± 5.3	30.1 ± 5.7
Waist circumference, cm	104.6 ± 14.6	105.3 ± 14.5	103.7 ± 14.3	105.2 ± 15.1
HbA1c, %	7.3 ± 1.9	7.4 ± 1.8	7.2 ± 1.5	7.1 ± 1.5
Total cholesterol, mg/dL	187.2 ± 36.8	191.2 ± 38.3	189.3 ± 45.7	186.7 ± 38.9
HDL-C, mg/dL	47.8 ± 13	45.4 ± 13	45.7 ± 14.4	46 ± 13
Triglycerides, mg/dL	151.6 ± 125.4	158.7 ± 91.8	193.7 ± 233.9	153.5 ± 84.6
UACR, mg/g	102.2 ± 444.9	85.6 ± 318.6	104.6 ± 550.6	114.8 ± 253.7
Serum creatinine, ug/dL	0.9 ± 0.3	1 ± 0.7	1 ± 0.3	1.1 ± 0.3
Hs-CRP, mg/L	4.6 ± 5.2	5.1 ± 7.5	4.4 ± 5.6	3.7 ± 5.7
DM duration, years	4.3 ± 6.1	5.5 ± 8.4	6.9 ± 9	7.7 ± 9.9
Left ventricular hypertrophy	3 (0.8%)	4 (1.6%)	4 (2.6%)	5 (3.1%)
Lipid-lowering medication	70 (19.7%)	77 (29.8%)	43 (27.6%)	64 (39.8%)
HTN medication	211 (59.3%)	155 (60.1%)	95 (60.9%)	121 (75.2%)
DM medication	272 (76.4%)	198 (76.7%)	115 (73.7%)	135 (83.9%)

Continuous variables were presented as mean ± SD; categorical variables are presented as frequency (%).

Table 5-3. Diabetes Mellitus Risk Score (DMRS) Adjusted Hazard Ratios of SA Measures for CVD and its Components Events

	CVD	ASCVD	CHD	HF	Stroke
ln(CAC+1) per 1 unit	1.21 (1.15-1.27) §	1.18 (1.11-1.26) §	1.28 (1.2-1.37) §	1.13 (1.05-1.22)†	1.11 (1.01-1.21)*
CAC = 0	Ref	Ref	Ref	Ref	Ref
CAC = 1-99	1.38 (0.97-1.97)	1.86 (1.19-2.89)†	2.49 (1.51-4.09)‡	0.79 (0.44-1.4)	1.15 (0.61-2.19)
CAC = 100-399	1.91 (1.31-2.79)‡	1.99 (1.22-3.26)†	2.52 (1.46-4.36)‡	1.6 (0.93-2.76)	1.37 (0.67-2.79)
CAC = 400+	3.7 (2.63-5.2) §	3.47 (2.22-5.41) §	6.27 (3.87-10.17) §	1.96 (1.16-3.29)*	2.09 (1.1-3.96)*
CIMT per 1 mm	1.54 (1.15-2.06)†	1.35 (0.92-1.98)	1.60 (1.11-2.32)*	1.23 (0.75-2.01)	1.69 (0.98-2.94)
CIMT < 1mm	Ref	Ref	Ref	Ref	Ref
CIMT ≥1 mm	1.34 (1.04-1.72)*	1.18 (0.86-1.62)	1.54 (1.12-2.14)†	1.29 (0.86-1.93)	1.3 (0.8-2.11)
ABI = 1.0-1.4	Ref	Ref	Ref	Ref	Ref
ABI = 0.9-0.99	1.08 (0.61-1.89)	1.25 (0.73-2.16)	1.47 (0.77-2.81)	1.21 (0.52-2.85)	1.08 (0.61-1.89)
ABI < 0.9	2.03 (1.24-3.32)†	1.83 (1.11-3.01)*	1.72 (0.91-3.24)	1.65 (0.72-3.78)	2.03 (1.24-3.32)†
ABI > 1.4	2.19 (0.7-6.88)	3.37 (1.24-9.15)*	4.91 (1.79-13.45)†	3.04 (0.74-12.5)	2.19 (0.7-6.88)

ABI had non-linear relation with CVD and was only examined as a categorical variable.
* $p<0.05$, † $p<0.01$, ‡ $p<0.001$, § $p<0.0001$

Table 5-4. C-Statistics of Prediction Models (DMRS + Single SA vs. DMRS)

		CVD	ASCVD	CHD	HF	Stroke
SA+DMRS vs. DMRS	DMRS	0.65	0.66	0.66	0.68	0.65
	DMRS + ln(CAC+1)	0.70 §	0.68	0.74 §	0.68	0.62
	DMRS + CAC cate	0.70 §	0.68	0.74 §	0.69	0.62
	DMRS + CIMT	0.66	0.65	0.67	0.67	0.60
	DMRS + CIMT cate	0.66	0.65	0.67	0.67	0.61
	DMRS + ABI cate	0.66	0.68	0.67	0.71	0.66
SA + Old RS [a] vs. Old RS	FRS (or PCE)	0.64	0.63	0.61	0.58	0.61
	FRS (or PCE) + ln(CAC+1)	0.69 ‡	0.67	0.72 §	0.62	0.62
	FRS (or PCE) + CIMT	0.64	0.63	0.64*	0.60	0.62
	FRS (or PCE) + ABI cate	0.65	0.65	0.65	0.66	0.63
SA + DMRS RFs vs. DMRS RFs	MDRS RFs	0.68	0.68	0.68	0.72	0.66
	DMRS RFs + ln(CAC+1)	0.72 †	0.70	0.74 ‡	0.73	0.66
	DMRS RFs + CIMT	0.68	0.68	0.68	0.72	0.65
	DMRS RFs + ABI cate	0.68	0.69	0.69	0.74	0.66

a. Old risk scores refer to FRS for CVD, PCE, FRS for CHD, FRS for stroke, FRS for heart failure in predicting CVD, ASCVD, CHD, Stroke and HF endpoints, respectively.
* $p<0.05$, † $p<0.01$, ‡ $p<0.001$, § $p<0.0001$

Table 5-5. Category-Free NRI Comparing Prediction Models with vs. without Single SA Measures

	NRI [a]	Event NRI	Non-Event NRI
CVD			
Ln(CAC+1) + DMRS vs DMRS	51.0% §	33.2% §	17.8% §
CIMT + DMRS vs DMRS	31.7% §	-0.9%	32.6% §
ABI categories + DMRS vs DMRS	29.8% §	-42.3% §	72.1% §
ASCVD			
Ln(CAC+1) + DMRS vs DMRS	49.4% §	36.7% §	12.7% §
CIMT + DMRS vs DMRS	26.3%†	-1.9%	28.2% §
ABI categories + DMRS vs DMRS	25.2%†	-53.4% §	78.5% §
CHD			
Ln(CAC+1) + DMRS vs DMRS	66.8% §	45.8% §	21.0% §
CIMT + DMRS vs DMRS	45.8% §	15.4% ‡	30.3% §
ABI categories + DMRS vs DMRS	35.1% §	-35.8% §	70.8% §
HF			
Ln(CAC+1) + DMRS vs DMRS	31.2%†	23.2% §	8% §
CIMT + DMRS vs DMRS	30.5%†	5.7%	24.9% §
ABI categories + DMRS vs DMRS	37.1% ‡	-31.8% §	68.9% §
Stroke			
Ln(CAC+1) + DMRS vs DMRS	29.1%*	24.9% ‡	4.2%*
CIMT + DMRS vs DMRS	27.3%*	0.3%	27.1% §
ABI categories + DMRS vs DMRS	15.8%	-50.6% §	66.3% §

a. NRI is the sum of event NRI and non-event NRI.
* $p<0.05$, † $p<0.01$, ‡ $p<0.001$, § $p<0.0001$

Table 5-6. Direct Comparison of C-Statistics and NRI between Single SA Measures

		CVD	ASCVD	CHD	HF	Stroke
CAC vs. CIMT	Difference in C-statistics [a]	0.04 [§]	0.03	0.07 [§]	0.02	0.02
	Category-free NRI	48.9% [§]	49.8% [§]	60.1% [§]	30.9%[†]	27.9%*
CAC vs. ABI	Difference in C-statistics [a]	0.04 [§]	0.00	0.07 [§]	-0.02	-0.04
	Category-free NRI	42.5% [§]	33.2% [‡]	48.8% [§]	7.5%	16.1%
CIMT vs. ABI	Difference in C-statistics [a]	0.00	-0.03	0.00	-0.04	-0.06
	Category-free NRI	20.23[†]	6.6%	21.9%*	-31.1%[†]	0.4%

a. The C-statistics of prediction models are presented in Table 5-5.
* $p<0.05$, [†] $p<0.01$, [‡] $p<0.001$, [§] $p<0.0001$

Table 5-7. Comparison of C-statistics and Category-Free NRI for Models with vs. without CAC

		CVD	ASCVD	CHD	HF	Stroke
CAC +CIMT vs. CIMT	C-statistics	0.70 vs. 0.66 §	0.68 vs. 0.65	0.74 vs 0.67 §	0.68 vs. 0.67	0.61 vs 0.60
	Category-free NRI	48.7% §	52.8%	59.8% §	30.6%+	32.4%*
CAC +ABI vs. ABI	C-statistics	0.71 vs. 0.66 §	0.69 vs 0.68	0.74 vs.0.66 §	0.68 vs. 0.69	0.63 vs 0.66
	Category-free NRI	49.5% §	41.0% §	59.0% §	30.3%+	21.5%
CAC+CIMT+ABI vs. CIMT+ABI	C-statistics	0.70 vs. 0.66 §	0.69 vs 0.66	0.74 vs.0.68 §	0.68 vs 0.68	0.61 vs0.60
	Category-free NRI	49.5% §	51.6% §	66.1% §	24.6%*	29.6%*
CIMT+ABI vs. CAC	C-statistics	0.70 vs. 0.66 §	0.68 vs. 0.66	0.74 vs. 0.68 §	0.68 vs.0.68	0.62 vs. 0.60
	Category-free NRI	41.9%	43.2%	52.0%	2.4%	8.9%

All prediction models also included DMRS.
* p<0.05, † p<0.01, ‡ p<0.001, § p<0.0001

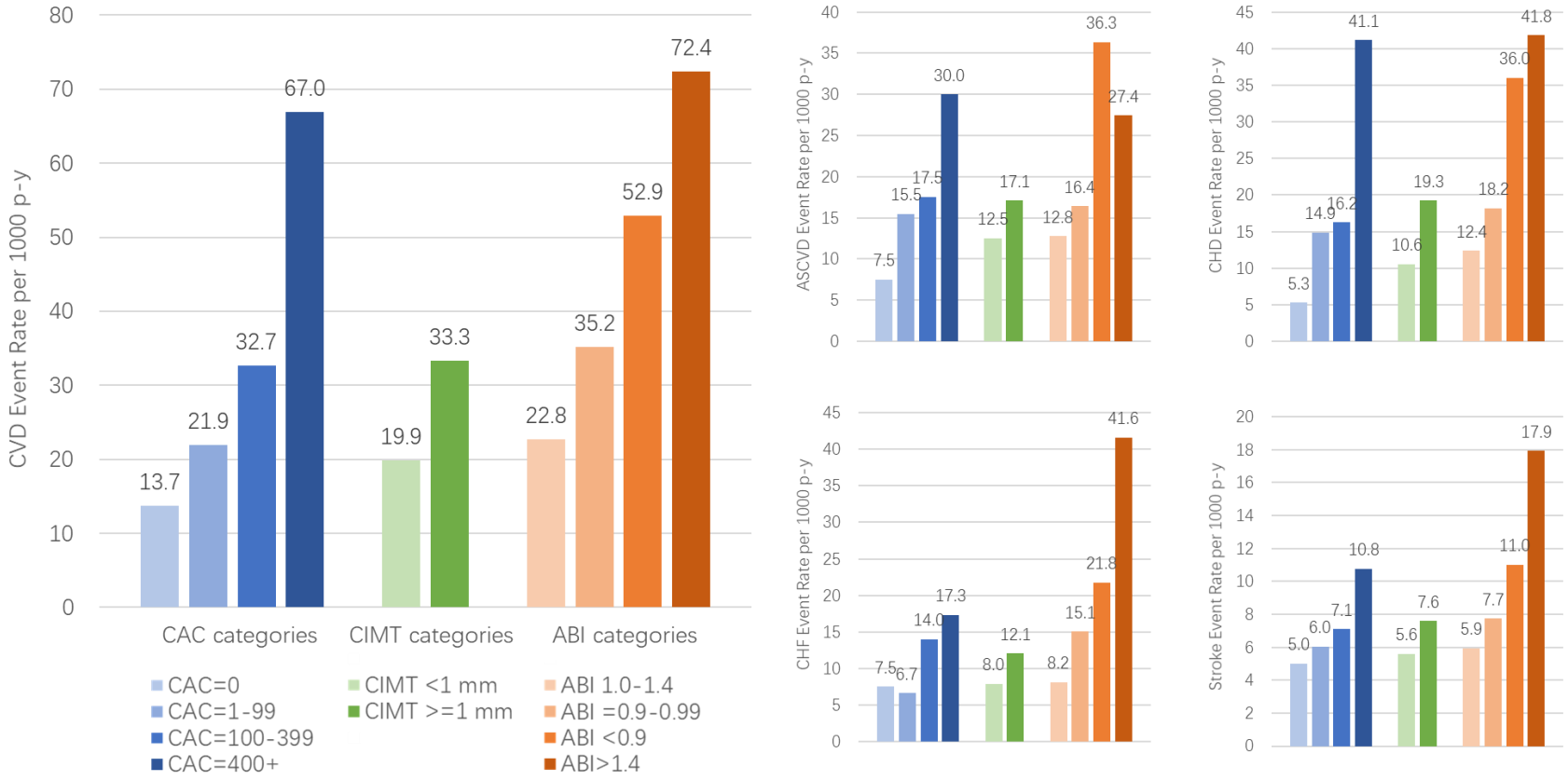

Figure 5-1. Event Rates by CAC CIMT, or ABI Categories

CVD and its component event rates showed stepwise increase by CAC or CIMT categories. CVD event rates were the lowest among ABI =1.0-1.4, followed by ABI of 0.9-<1.0, <0.9 and>1.4.

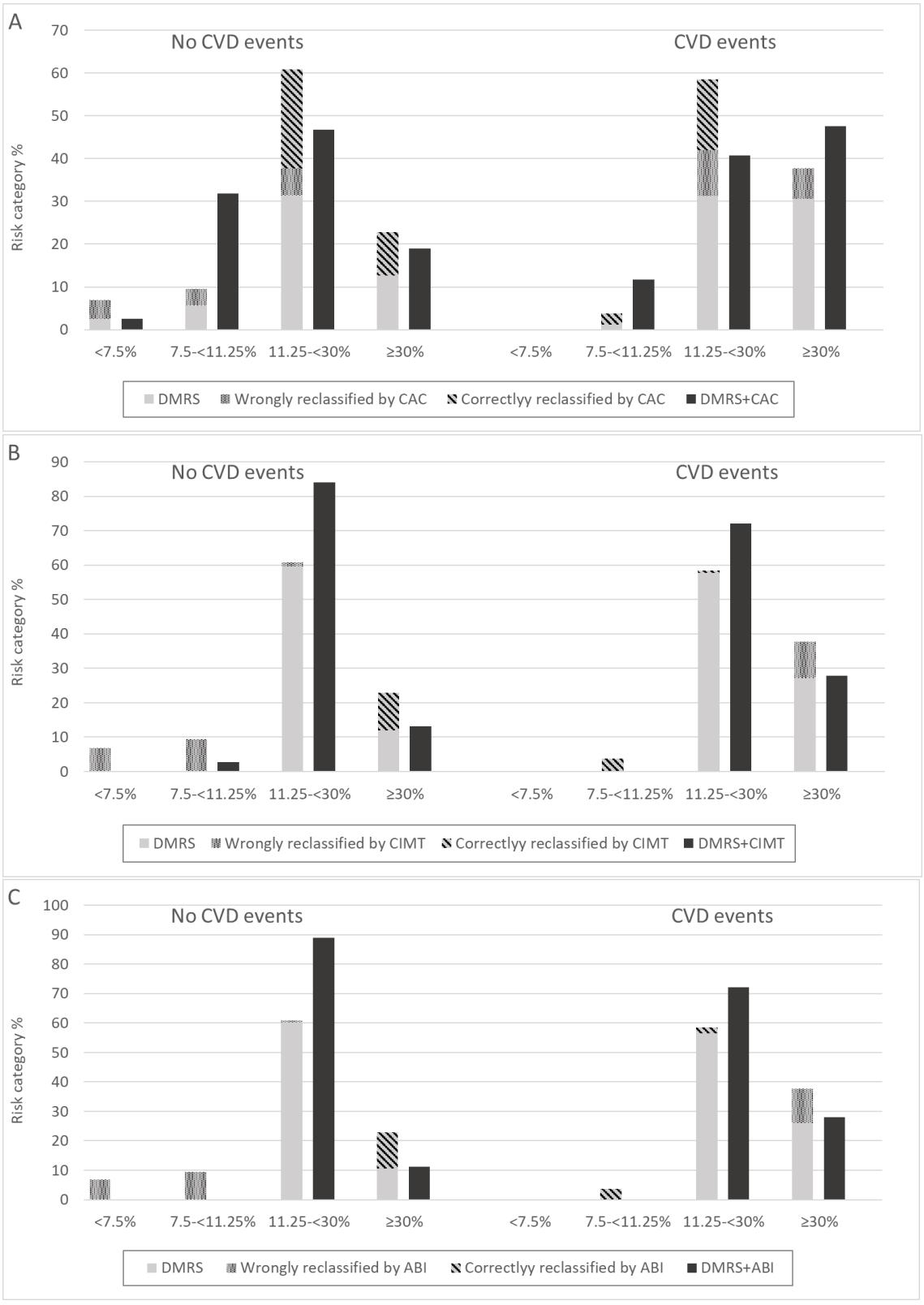

Figure 5-2. CVD Risk Restratification by CAC (A), CIMT (B) or ABI (C)

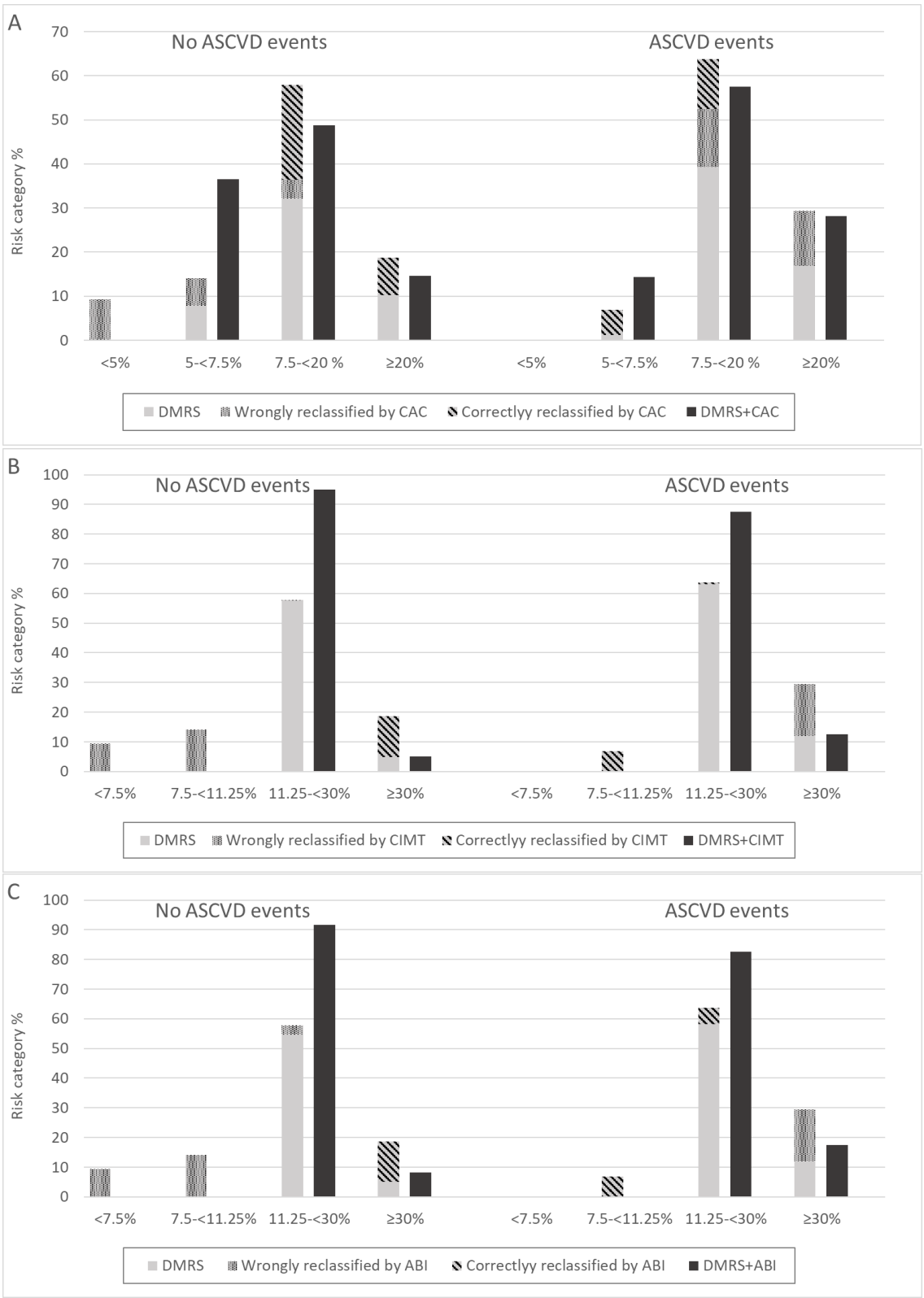

Figure 5-3. ASCVD Risk Restratification by CAC (A), CIMT (B) or ABI (C)

5.7 Supplementary Materials

Supplementary Table 5-1. Pros and Cons of Statistical Methods in Assessing Predictive Accuracy of Risk Prediction Models

	Pros	Cons
Likelihood ratio test of beta	• High power	• No quantification of the predictive improvement • Lack of clinical meaning
C-statistics	• Valid in non-nested model comparison • Provide single quantification of predictive value	• Low power when models are nested or overlapped • ROC curve does not explicitly display predicted risk
Net Reclassification Index	• Easy to interpret and understand • Clinical relevance of categorical NRI • Reclassification table provides details of reclassification information	• Inflated false positive results

Supplementary Table 5-2. Baseline Risk Profiles by CIMT Categories

	CIMT < 1mm	CIMT ≥ 1 mm
Age, years	62.1 ± 9.7	67.3 ± 8.6
Male	219 (46.1%)	262 (57.5%)
Races		
White	83 (17.5%)	98 (21.5%)
Black	169 (35.6%)	186 (40.8%)
Other races	223 (46.9%)	172 (37.7%)
Above high school education	230 (48.4%)	241 (52.9%)
Alcohol use	217 (45.7%)	230 (50.4%)
Smoke status		
Never	263 (55.4%)	197 (43.2%)
Previous	153 (32.2%)	198 (43.4%)
Current	59 (12.4%)	61 (13.4%)
Family history of CVD	211 (44.4%)	227 (49.8%)
SBP, mmHg	130 ± 20.2	136.3 ± 23.2
BMI, kg/m^2	30.8 ± 6.3	30.2 ± 5.5
Waist circumference, cm	104.9 ± 15.1	104.6 ± 14.1
HbA1c, %	7.3 ± 1.8	7.3 ± 1.7
Total cholesterol, mg/dL	189 ± 40.8	188.2 ± 37.4
HDL-C, mg/dL	46.5 ± 13	46.5 ± 13.5
Triglycerides, mg/dL	166 ± 157.8	155.7 ± 112.5
UACR, mg/g	78.8 ± 344.7	122.4 ± 461.7
Serum creatinine, ug/dL	0.9 ± 0.3	1 ± 0.6
Hs-CRP, mg/L	4.6 ± 5.9	4.5 ± 6.3
DM duration, years	5 ± 7.6	6.3 ± 8.6
LVH	4 (0.8%)	12 (2.6%)
Lipid-lowering medication	104 (21.9%)	150 (32.9%)
HTN medication	277 (58.3%)	305 (66.9%)
DM medication	360 (75.8%)	360 (78.9%)

Continuous variables were presented as mean ± SD; categorical variables are presented as frequency (%).

Supplementary Table 5-3. Baseline Risk Profiles by ABI Categories

	ABI=1.0-1.4	ABI=0.9-0.99	ABI <0.9	ABI>1.4
Age, years	63.8 ± 9.4	66.6 ± 8.9	71.5 ± 8.5	65.7 ± 10.2
Male	408 (53.1%)	30 (38.5%)	34 (45.9%)	9 (81.8%)
Races				
White	149 (19.4%)	13 (16.7%)	15 (20.3%)	4 (36.4%)
Black	280 (36.5%)	38 (48.7%)	36 (48.6%)	1 (9.1%)
Other races	339 (44.1%)	27 (34.6%)	23 (31.1%)	6 (54.5%)
Above high school education	404 (52.6%)	34 (43.6%)	30 (40.5%)	3 (27.3%)
Alcohol use	378 (49.2%)	34 (43.6%)	32 (43.2%)	3 (27.3%)
Smoke status				
Never	383 (49.9%)	38 (48.7%)	34 (45.9%)	5 (45.5%)
Previous	292 (38%)	27 (34.6%)	27 (36.5%)	5 (45.5%)
Current	93 (12.1%)	13 (16.7%)	13 (17.6%)	1 (9.1%)
Family history of CVD	359 (46.7%)	40 (51.3%)	33 (44.6%)	6 (54.5%)
SBP, mmHg	131.1 ± 20.5	142.6 ± 23.6	143.7 ± 28.6	132.9 ± 15.1
BMI, kg/m^2	30.6 ± 5.8	30.6 ± 6.3	29.3 ± 6.5	32.1 ± 5.7
Waist circumference, cm	104.9 ± 14.3	103.3 ± 15.4	103.4 ± 17	113.5 ± 11.7
HbA1c, %	7.3 ± 1.8	7.2 ± 1.7	7.2 ± 1.5	7.2 ± 1.3
Total cholesterol, mg/dL	187.8 ± 38.6	197.9 ± 45.8	190.5 ± 36	160.8 ± 30.8
HDL-C, mg/dL	46.3 ± 13.1	47.9 ± 13.4	47.4 ± 15.5	42.6 ± 10.8
Triglycerides, mg/dL	161.5 ± 137.6	168.6 ± 176.5	151.3 ± 92.2	133.5 ± 57.1
UACR, mg/g	74.2 ± 266.6	228.9 ± 824.4	243.3 ± 771.6	39.4 ± 79
Serum creatinine, ug/dL	0.9 ± 0.3	1 ± 0.4	1.3 ± 1.3	1 ± 0.2
Hs-CRP, mg/L	4.3 ± 5.7	5.7 ± 8.2	5.1 ± 6.9	6.7 ± 5.4
DM duration, years	4.9 ± 7.3	7.8 ± 8.9	9.9 ± 11.3	10.5 ± 14.4
LVH	15 (2%)	0 (0%)	1 (1.4%)	0 (0%)
Lipid-lowering medication	189 (24.6%)	31 (39.7%)	28 (37.8%)	6 (54.5%)
HTN medication	459 (59.8%)	55 (70.5%)	61 (82.4%)	7 (63.6%)
DM medication	587 (76.4%)	65 (83.3%)	61 (82.4%)	7 (63.6%)

Continuous variables were presented as mean ± SD; categorical variables are presented as frequency (%)

Supplementary Table 5-4. Hazard Ratios of single SA measures for CVD and its Component Events at Different Levels of Adjustment

	CVD	ASCVD	CHD	HF	Stroke
Unadjusted HRs					
ln(CAC+1)	1.26 (1.2-1.32) §	1.21 (1.14-1.29) §	1.32 (1.24-1.41) §	1.15 (1.07-1.24) ‡	1.11 (1.02-1.21)*
CAC = 0	Ref	Ref	Ref	Ref	Ref
CAC = 1-99	1.59 (1.12-2.26) †	2.06 (1.32-3.2)†	2.83 (1.72-4.64) §	0.88 (0.5-1.56)	1.2 (0.63-2.28)
CAC = 100-399	2.37 (1.64-3.43) §	2.34 (1.44-3.81) ‡	3.1 (1.81-5.33) §	1.86 (1.08-3.19)*	1.42 (0.7-2.88)
CAC = 400+	4.84 (3.48-6.74) §	4.03 (2.6-6.27) §	7.91 (4.91-12.74) §	2.28 (1.36-3.82)†	2.15 (1.13-4.07)*
CIMT per 1 mm	1.96 (1.5-2.55) §	1.61 (1.13-2.31)†	1.96 (1.39-2.77) ‡	1.54 (0.98-2.43)	1.77 (1.04-3.03)*
CIMT < 1mm	Ref	Ref	Ref	Ref	Ref
CIMT ≥1 mm	1.66 (1.3-2.12) §	1.37 (1-1.87)*	1.82 (1.32-2.51) ‡	1.52 (1.02-2.25)*	1.36 (0.84-2.2)
ABI = 1.0-1.4	Ref	Ref	Ref	Ref	Ref
ABI = 0.9-0.99	1.28 (0.73-2.22)	1.46 (0.85-2.5)	1.83 (0.97-3.46)	1.3 (0.56-3.02)	1.28 (0.73-2.22)
ABI < 0.9	2.89 (1.86-4.49) §	2.92 (1.87-4.53) §	2.67 (1.5-4.74) ‡	1.87 (0.85-4.12)	2.89 (1.86-4.49) §
ABI > 1.4	2.15 (0.68-6.76)	3.36 (1.24-9.13)*	5.06 (1.85-13.85)†	3 (0.73-12.31)	2.15 (0.68-6.76)
Age, Sex and Race Adjusted HRs					
ln(CAC+1)	1.22 (1.16-1.29) §	1.17 (1.09-1.25) §	1.29 (1.2-1.39) §	1.12 (1.03-1.22) †	1.07 (0.97-1.18)
CAC = 0	Ref	Ref	Ref	Ref	Ref
CAC = 1-99	1.45 (1.01-2.07)*	1.84 (1.17-2.88)†	2.59 (1.56-4.28) ‡	0.8 (0.44-1.42)	1.06 (0.55-2.05)
CAC = 100-399	2.03 (1.38-2.99) ‡	1.94 (1.17-3.22)*	2.67 (1.52-4.69) ‡	1.57 (0.89-2.77)	1.16 (0.55-2.45)
CAC = 400+	3.98 (2.78-5.71) §	3.15 (1.96-5.08) §	6.57 (3.94-10.95) §	1.81 (1.03-3.18)*	1.66 (0.82-3.35)
CIMT per 1 mm	1.55 (1.16-2.07)†	1.23 (0.84-1.81)	1.51 (1.04-2.18)*	1.20 (0.73-1.96)	1.49 (0.84-2.65)
CIMT < 1mm	Ref	Ref	Ref	Ref	Ref
CIMT ≥1 mm	1.35 (1.05-1.75)*	1.10 (0.79-1.52)	1.49 (1.07-2.08)*	1.24 (0.82-1.88)	1.16 (0.70-1.92)
ABI = 1.0-1.4	Ref	Ref	Ref	Ref	Ref

ABI = 0.9-0.99	1.33 (0.76-2.35)	1.60 (0.92-2.78)	1.70 (0.89-3.27)	1.31 (0.55-3.12)	1.33 (0.76-2.35)
ABI < 0.9	2.61 (1.64-4.16) §	2.72 (1.71-4.33) §	2.24 (1.22-4.1)†	1.68 (0.74-3.83)	2.61 (1.64-4.16) §
ABI > 1.4	1.86 (0.59-5.88)	2.86 (1.05-7.78)*	5.18 (1.88-14.27)†	2.77 (0.67-11.46)	1.86 (0.59-5.88)
		DMRS Predictors Adjusted HRs			
ln(CAC+1)	1.21 (1.15-1.28) §	1.16 (1.08-1.24) §	1.28 (1.19-1.38) §	1.12 (1.03-1.22) †	1.06 (0.95-1.17)
CAC = 0	Ref	Ref	Ref	Ref	Ref
CAC = 1-99	1.38 (0.97-1.97)	1.86 (1.19-2.89) †	2.49 (1.51-4.09) ‡	0.79 (0.44-1.4)	1.15 (0.61-2.19)
CAC = 100-399	1.91 (1.31-2.79) ‡	1.99 (1.22-3.26) †	2.52 (1.46-4.36) ‡	1.6 (0.93-2.76)	1.37 (0.67-2.79)
CAC = 400+	3.7 (2.63-5.2) §	3.47 (2.22-5.41) §	6.27 (3.87-10.17) §	1.96 (1.16-3.29)*	2.09 (1.1-3.96)*
CIMT per 1 mm	1.43 (1.06-1.94)*	1.09 (0.72-1.63)	1.38 (0.94-2.04)	1.06 (0.63-1.8)	1.37 (0.74-2.51)
CIMT < 1mm	Ref	Ref	Ref	Ref	Ref
CIMT ≥1 mm	1.25 (0.97-1.62)	0.99 (0.71-1.38)	1.38 (0.98-1.93)	1.12 (0.74-1.71)	1.03 (0.62-1.72)
ABI = 1.0-1.4	Ref	Ref	Ref	Ref	Ref
ABI = 0.9-0.99	1.10 (0.61-1.97)	1.35 (0.77-2.37)	1.35 (0.69-2.67)	1.14 (0.47-2.77)	1.10 (0.61-1.97)
ABI < 0.9	2.06 (1.24-3.41)†	2.08 (1.25-3.47)†	1.64 (0.86-3.14)	1.36 (0.57-3.24)	2.06 (1.24-3.41)†
ABI > 1.4	1.93 (0.6-6.18)	3.16 (1.14-8.8)*	4.94 (1.75-13.99)†	2.55 (0.6-10.84)	1.93 (0.6-6.18)

ABI had non-linear relation with CVD and was only examined as a categorical variable.
* p<0.05, † p<0.01, ‡ p<0.001, §p<0.0001

Supplementary Table 5-5. Absolute and Relative [a] Change of C-Statistics of Prediction Models with vs. without SA Measures

		CVD	ASCVD	CHD	HF	Stroke
SA+DMRS vs. DMRS	ln(CAC+1)	0.05 (7.7%)	0.02 (3%)	0.08 (12.1%)	0 (0%)	-0.03 (-4.6%)
	CIMT	0.01 (1.5%)	-0.01 (-1.5%)	0.01 (1.5%)	-0.01 (-1.5%)	-0.05 (-7.7%)
	ABI groups	0.01 (1.5%)	0.02 (3%)	0.01 (1.5%)	0.03 (4.4%)	0.01 (1.5%)
SA + Old RS [b] vs. Old RS	ln(CAC+1)	0.05 (7.8%)	0.04 (6.3%)	0.11 (18.0%)	0.04 (6.9%)	0.01 (1.6%)
	CIMT	0 (0%)	0 (0%)	0.03 (4.9%)	0.02 (3.4%)	0.01 (1.6%)
	ABI groups	0.01 (1.6%)	0.02 (3.2%)	0.04 (6.6%)	0.08 (13.8%)	0.02 (3.3%)
SA + DMRS RFs vs. DMRS RFs	ln(CAC+1)	0.04 (5.9%)	0.02 (2.9%)	0.06 (8.8%)	0.01 (1.4%)	0 (0%)
	CIMT	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-0.01 (-1.5%)
	ABI groups	0 (0%)	0.01 (1.5%)	0.01 (1.5%)	0.02 (2.8%)	0 (0%)

a. Relative changes of C-statistics were calculated as (C-statistics of Models with SA - C-statistics of Models without SA)/C-statistics of Models without SA

b. Old risk scores refer to FRS for CVD, PCE, FRS for CHD, FRS for stroke, FRS for heart failure in predicting CVD, ASCVD, CHD, Stroke and HF endpoints, respectively.

Supplementary Table 5-6. Category-Free NRI Comparing Prediction Models with vs. without Single SA

	SA Measures	NRI	Event NRI	Non-Event NRI
CVD				
SA + Old RS vs. Old RS	CAC	50.8% §	31% §	19.9% §
	CIMT	36.6% §	6.6%	30% §
	ABI	30.7% §	-41.1% §	71.9% §
SA+DMRS RFs vs. DMRS RFs	CAC	55.7% §	33% §	22.7% §
	CIMT	27.7% ‡	0.1%	27.6% §
	ABI	17.4%†	-68.6% §	86.1% §
ASCVD				
SA + Old RS vs. Old RS	CAC	25.2%†	-53.4% §	78.5% §
	CIMT	25.2%†	-53.4% §	78.5% §
	ABI	25.2%†	-53.4% §	78.5% §
SA+DMRS RFs vs. DMRS RFs	CAC	46.0% §	31.1% §	14.9% §
	CIMT	14.0%	-7.4%	21.5% §
	ABI	19.3%†	-67.1% §	86.4% §
CHD				
SA + Old RS vs. Old RS	CAC	-50.4% §	-47.2% §	-3.2%
	CIMT	-50.4% §	-47.2% §	-3.2%
	ABI	-50.4% §	-47.2% §	-3.2%
SA+DMRS RFs vs. DMRS RFs	CAC	59.5% §	38.1% §	21.4% §
	CIMT	19.5%*	-5.3%	24.8% §
	ABI	23.8%†	-63% §	86.8% §
HF				
SA + Old RS vs. Old RS	CAC	31%†	23.5% §	7.5% §
	CIMT	30.9%†	6%	24.9% §
	ABI	37.1% ‡	-31.4% §	68.4% §
SA+DMRS RFs vs. DMRS RFs	CAC	30.7%†	19.1% ‡	11.6% §
	CIMT	18.4%	-3.8%	22.2% §
	ABI	33.9% ‡	-37.1% §	70.9% §
Stroke				
SA + Old RS vs. Old RS	CAC	29.2%*	24.4% ‡	4.8%†
	CIMT	24.4%	0%	24.3% §
	ABI	15.7%	-50.3% §	65.9% §
SA+DMRS RFs vs. DMRS RFs	CAC	28.1%*	21%†	7.1% §
	CIMT	32.4%*	7.6%	24.8% §
	ABI	18.1%	-58.7% §	76.8% §

Old risk scores refer to FRS for CVD, PCE, FRS for CHD, FRS for stroke, FRS for heart failure in predicting CVD, ASCVD, CHD, Stroke and HF endpoints, respectively.
* $p<0.05$, † $p<0.01$, ‡ $p<0.001$, § $p<0.0001$

Supplementary Table 5-7. 4-Category NRI [a] Comparing SA+DMRS vs. DMRS for CVD and ASCVD

			NRI	Event NRI	Non-Event NRI
CVD					
	SA+DMRS vs. DMRS	CAC	21.3%	1.1%	20.2%
		CIMT	-12.8%	-6.8%	-6.0%
		ABI	-11.1%	-7.0%	-4.1%
ASCVD					
	SA+DMRS vs. DMRS	CAC	3.4%	-6.8%	10.2%
		CIMT	-27.4%	-17.4%	-10.0%
		ABI	-26.2%	-12.8%	-13.4%

a. Risk categories were < 7.5%, 7.5% - <11.25%, 11.25% - <30% and ≥ 30% for CVD and < 5%, 5%-<7.5%, 7.5% - <20% and ≥ 20% for ASCVD.
p value >0.05 for all category NRI.

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6. Summary and Public Health Implications

For patients with diabetes mellitus (DM), cardiovascular (CVD) risk assessment is as important as it is for the general primary prevention population without DM. However, CVD risk assessment, usually the very first crucial step in CVD prevention, is not sufficiently emphasized in guidelines or in everyday healthcare practice for patients with DM. Various reasons have contribution such neglection of importance of CVD risk evaluation in DM: many primary healthcare providers and some specialized cardiologists and endocrinologists still consider DM as a coronary heart disease (CHD) or CVD risk equivalent that does not need further CVD risk evaluation but should be given universally intensive preventive treatment. Actually, even some of current medical resident training books/materials still list DM "CHD risk equivalent". Such outdated knowledge will remain at bedside for long time before the new researches turn into guidelines and finally goes where it should serve – the daily healthcare practice.

With the availability of more modern, large, pooled data that better represent the US population, we once again demonstrated that DM is not a CVD risk equivalent. More importantly, multiple factors (HbA1c control, DM duration, medication use, age, sex, race, triglycerides) were identified to potentially contribute to the relative CVD risk of DM when compared to the secondary prevention population without DM. It turned out that among those with DM and without CVD, only one in five is truly "CVD risk equivalent", defined as someone with a comparable CVD risk as that if he/she had no DM but prior CVD. With the early detection of DM by lab tests and better prevention strategies, CVD risk conferred by DM will continue dropping and the future proportion of CVD risk equivalent DM is anticipated to be lower than

what we have shown in Project 1. With our algorithm to define CVD risk equivalent, we can easily identify anyone who has CVD risk equivalent DM based on his/her own DM profiles. These CVD risk equivalent DM patients should be considered not only as high-risk entity in need of more comprehensive, intensive treatment, but also as a special population whose high CVD risk is most closely related to DM. Glucose-lowering medications, especially those with cardioprotective effect such as glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter type 2 (SGLT2) inhibitors may be potentially recommended first to this particular "CVD risk equivalent DM" population with great need to reduce the DM-conferred CVD risk. With the abundance of secondary clinical trial data on various CVD prevention treatment, subgroup analysis of treatment effect is needed according the CVD risk equivalent conditions among those primary prevention population with DM.

In the first project, we found an important limitation of existing CVD risk scores used on DM patients: those patients with CVD risk equivalent DM had a large underestimated CVD risk using the Pooled cohort Equation (PCE) which failed to include DM-severity factors or interaction of DM and other CVD risk factors. To estimate the global CVD risk - the overall absolute CVD risk associated not only with DM but also all other CVD risk factors - we then developed and validated a set of risk scores for CVD, atherosclerotic CVD, CHD, heart failure (HF) and stroke for the US diabetes population. The scores have shown superior accuracy to a number of existing risk scores including the FRS, PCE and UKPDS. As several other DM-specific CVD risk scores, HbA1c, DM durations, DM medication, serum creatinine and C-reactive protein were identified as important risk predictors in addition to conventional risk factors such as age, sex and SBP. Yet in the external validation, the improvement of prediction

accuracy is not large enough to replace PCE in the current guidelines attributed to various reasons mentioned in Project 2. These limitations provide several future research directions, including the exploration of novel biomarkers, external validation in observational cohorts, more reliable validation parameters as well as the use of big data and time-varying variables in model development.

Among the above directions, we chose to examine how subclinical atherosclerosis (SA) measures improve the prediction of the newly developed risk score set. It is found that coronary artery calcium (CAC) improved CVD and CHD risk prediction most among CAC, carotid intima media thickness (CIMT) and ankle brachial index (ABI) have provided similar risk reclassification as CAC for HF events. More importantly, we demonstrated that CAC improved CVD risk prediction even when the CIMT and ABI were available but not vice versa. Currently CAC was not conventionally recommended to DM patients. Our study has demonstrated the usefulness of CAC in risk reclassification among those with DM compared to CIMT and ABI.

CVD risk assessment for patients with DM should be a dynamic process instead of a one-time effect. For researchers, it means the continuous exploration to improve assessment accuracy from all aspects. There is always a need for the use of the most contemporary derivation cohort, the application of the most updated algorithms, an inclusion of novel risk predictors etc. For physicians and policy makers, the dynamic process means updates of risk CVD assessment in guidelines and an unrelentless efforts on bench-to-bedside translation. It is also a physician's duty to help patients correctly interpret some "scientific breaking news" in the patient-centered

discussion. While the researchers have provided “evidence”, how the physicians use it in the “evidence-based medicine” can be much more complicated. For patients, the dynamic CVD risk assessment means initial evaluation and re-evaluation for the entire life based on the most current risk profiles. Now all types of CVD risk assessment tools were only used to guide initiation of preventive strategies. However, it should be more useful than that: it could be potentially a stimulus for healthy lifestyle advocation; the reevaluation may be used for comprehensive treatment effect of multiple modifiable risk factors; a detailed breakdown of risk assessment may even help identify the most important culprit among all risk predictors and make preventive treatment more targeted and more efficient.