Incident Myocardial Infarction is Four-fold Higher in Subjects at High Risk for Type 2 Diabetes

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Aim

We and others have observed that subjects at high risk for developing type 2 diabetes mellitus (T2DM) have a higher incidence of primary cardiovascular disease. The aim of this study was to understand the differences between biomarkers of cardiovascular and diabetes risk.

Introduction

T2DM has been established as a major risk factor for cardiovascular disease, and a significant portion of this risk is known to occur in the prediabetic state[1]. The PreDx® Diabetes Risk Score (DRS) is a simple and accurate test based on circulating biomarkers that provides a quantitative estimate of the 5-year risk of developing T2DM[2,3]. In this study, we applied a model utilizing the circulating biomarkers of the DRS to the Inter99 study population to assess the 5-year risk of primary cardiovascular events (CVE) for subjects at low, moderate and high risk for T2DM. We compared the cardiovascular risk factor status of high-risk individuals prior to the onset of clinical diabetes with the corresponding risk factor status of individuals who remained free of diabetes during a 5-year follow-up period. The data here show a greater incidence of primary cardiovascular events among high DRS subjects as compared to low DRS subjects, and that certain biomarkers in the DRS are strongly predictive of cardiovascular events. Careful management of cardiovascular risk for patients with a high DRS should therefore be considered.

Methods

Subjects. Subjects for this study were from the Inter99 cohort, a random population of subjects from the southwestern part of Copenhagen County, Denmark who were drawn from the Danish Civil Registration System to participate in a prevention study for cardiovascular disease[4]. Of the 6,784 subjects who participated at baseline assessment, serum samples were available for the present study from 5,764 subjects. Subjects were excluded from the present study if there was a prior history of cardiovascular disease, if necessary measures needed for the analyses were not available, or if assessment of diabetes outcomes was not available at five year follow-up. Diagnosis of T2DM was based upon criteria from the World Health Organization, defined as either a 2-h plasma glucose of ≥11.1 mmol/L [≥200 mg/dL] from an oral glucose tolerance test (OGTT) or fasting plasma glucose (FPG) of ≥7.0 mmol/L [≥126 mg/dL][5]. After applying the exclusion criteria, there were 4,202 subjects in the study. Among these, 171 developed diabetes and 76 exhibited cardiovascular events (26 myocardial infarction, 30 stroke, 31 revascularization) during the follow-up period.

Clinical measures and risk scores: At each visit, data were collected regarding lifestyle, anthropometric measures (e.g. blood pressure, waist circumference, height, weight), routine laboratory measures (e.g. HbA1c, FPG and lipids), and OGTT as described previously[4]. The multivariate algorithm for a general cardiovascular risk score (Framingham CVD) and the Reynolds Risk Score (Reynolds) was calculated as reported[6,7].

PreDx Diabetes Risk Score (DRS): The risk of developing T2DM within five years was expressed as the DRS, which was calculated from quantitative measures of seven circulating biomarkers in baseline samples[2]. Quantification of FPG, fasting serum insulin and HbA1c was determined at Steno Diabetes Center, Copenhagen, Denmark[4]. HbA1c concentrations were determined by ion exchange HPLC (BioRad, USA) with a coefficient of variation of 11%. Quantification of fasting serum adiponectin, C-reactive protein (CRP), ferritin and interleukin-2 receptor alpha (IL2-Ra) was carried out at the Tethys Clinical Laboratory, Emeryville, CA. Ferritin was

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measured using solid-phase, two-site chemiluminescent immunometric assays. CRP was measured using an immuno-turbidometric assay and adiponectin and IL2-Ra were measured using a sandwich immunoassay format. In the validation of these assays, the coefficients of variation for ferritin, IL2-Ra, CRP and adiponectin were 4.6%, 6.8%, 12.5% and 6.2%, respectively. The DRS was previously trained on a nested case-control of 799 subjects from the Inter99 population[3]. All biomarker measurements in this study were obtained from previously unused aliquots and were run in a randomized order.

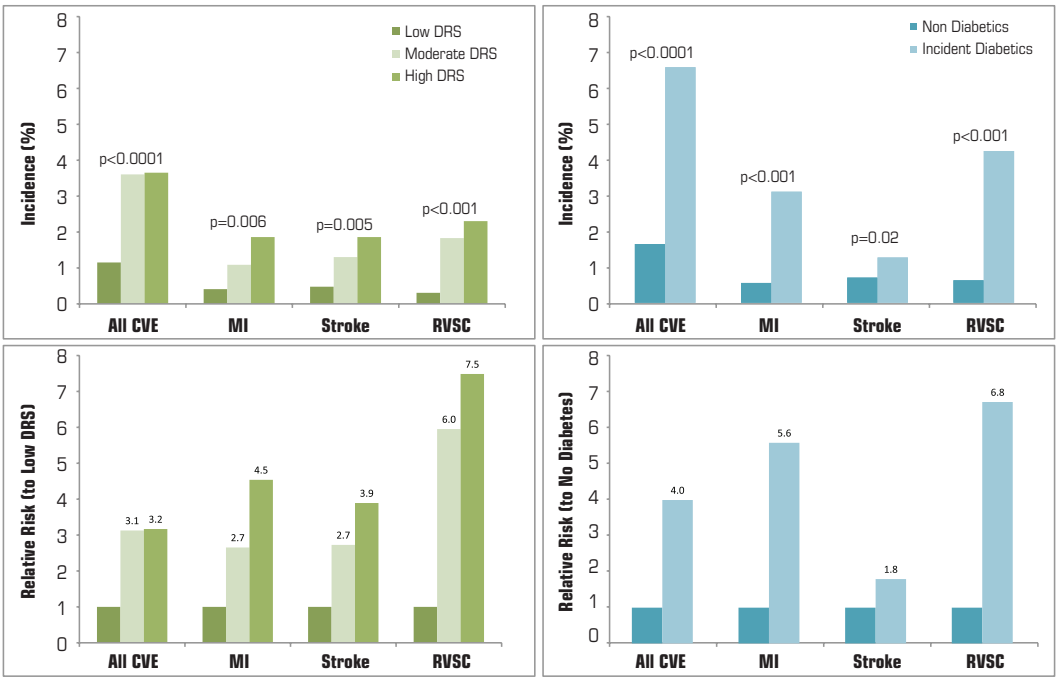
Table 1: Selected Characteristics of the Study Population

General characteristics of DRS risk classes and Diabetes classes were calculated based on 5 year outcomes. The DRS risk classes are stratified from the non-diabetic baseline population as described[3]. For the diabetes classes, Non-diabetics did not meet diabetes criteria at any time during the study; incident diabetics were non-diabetic at baseline, but converted within 5 years; diabetics were diabetic at baseline. The components of the Framingham CVD, Reynolds and the DRS are shown. Cardiovascular events are primary, subjects with a history of cardiovascular disease were excluded from the analysis. All the variables are significant except as indicated in bold. Values are medians (IQR) for quantitative variables and counts (% of Class) for discrete variables. P values were estimated with a Kruskal-Wallis test for quantitative variables and a Fisher's exact test for the discrete variables.

	DRS Risk Classes				Diabetes Classes		
Variable	**Low Risk (n=2956)**	**Moderate Risk (n=949)**	**High Risk (n=223)**	**P (DRS Classes)**	**Non-Diabetics (n=4031)**	**Incident Diabetics (n=171)**	**P (Diabetes Classes)**
Age (yrs)	44.9 (39.9-50)	50 (45-55)	54.9 (50-55.3)	<0.0001	45.1 (40-50.2)	50.1 (45-55)	<0.0001
BMI (kg/m^2)	24.7 (22.6-27.1)	27.2 (24.7-30.4)	29.8 (26.4-32.6)	<0.0001	25.3 (23-28)	28.6 (26-32.2)	<0.0001
DBP (mmHg)	80 (70-85)	85 (80-90)	90 (80-95)	<0.0001	80 (75-90)	86 (80-95)	<0.0001
SBP (mmHg)	125 (115-135)	132 (122-145)	140 (130-150)	<0.0001	128 (118-138)	140 (130-150)	<0.0001
Waist (cm)	82 (74-91)	93 (85-100)	97 (91-107)	<0.0001	85 (76-94)	95 (87-106.8)	<0.0001
Triglycerides (mmol/l)	0.9 (0.7-1.3)	1.3 (0.9-1.9)	1.6 (1.2-2.3)	<0.0001	1 (0.7-1.5)	1.6 (1.2-2.2)	<0.0001
High Density Lipoproteins (mmol/l)	1.4 (1.2-1.7)	1.3 (1.1-1.5)	1.2 (1-1.4)	<0.0001	1.4 (1.2-1.7)	1.2 (1-1.5)	<0.0001
Total Cholesterol (mmol/l)	5.2 (4.6-6)	5.7 (5.1-6.5)	5.9 (5.3-6.8)	<0.0001	5.4 (4.7-6.1)	5.7 (5-6.5)	<0.0001
Glucose (mmol/l)	5.3 (5-5.5)	5.8 (5.6-6.1)	6.3 (6.1-6.6)	<0.0001	5.4 (5.1-5.7)	6.1 (5.6-6.5)	<0.0001
Insulin (pmol/l)	29 (21-42)	42 (30-60)	60 (43.5-87)	<0.0001	32 (22.8-47)	54 (35.5-77.5)	<0.0001
HbA1c (%)	5.7 (5.5-6)	6 (5.7-6.2)	6.2 (5.9-6.4)	<0.0001	5.8 (5.5-6)	6 (5.8-6.4)	<0.0001
Adiponectin (ug/ml)	9.1 (7.2-11.5)	6.9 (5.6-8.7)	6.1 (4.8-7.2)	<0.0001	8.4 (6.6-10.8)	6.7 (5.4-8.5)	<0.0001
CRP (mg/l)	0.7 (0.3-1.6)	2 (0.9-4.3)	2.9 (1.5-6.8)	<0.0001	0.9 (0.4-2.4)	2.2 (1-4.1)	<0.0001
Ferritin (ng/ml)	72.8 (34.9-148)	138 (76.3-236)	195 (108.5-328)	<0.0001	90.7 (41.4-173)	150 (70.7-286.2)	<0.0001
IL2R-A (U/ml)	340.9 (276.6-428.2)	386.9 (316.5-490.1)	437.2 (348.5-560.9)	<0.0001	356.4 (285.7-446.9)	387.1 (311.3-483.4)	<0.0001
Framingham Risk	4% (2%-8%)	10%(6%-16%)	15% (9%-22%)	<0.0001	6% (3%-10%)	11% (6%-19%)	<0.0001
Reynolds Risk	1% (0%-2%)	3% (2%-7%)	6% (4%-10%)	<0.0001	1% (1%-3%)	4% (2%-%8)	<0.0001
PreDx® Diabetes Risk Score	1.8 (0.9-2.9)	5.9 (5.1-6.8)	8.6 (8.3-9)	<0.0001	2.5 (1.2-4.6)	7.1 (4.9-8.4)	<0.0001
Gender (Male)	1317 (44.6%)	588 (62%)	145 (65%)	<0.0001	1979 (49.1%)	106 (62%)	<0.0001
Family History (CVD)	**279 (9.4%)**	**71 (7.5%)**	**21 (9.4%)**	**0.1783**	**363 (9%)**	**13 (7.6%)**	**0.1932**
Smoking	756 (25.6%)	327 (34.5%)	73 (32.7%)	<0.0001	**1128 (28%)**	**52 (30.4%)**	**0.6437**
Cardio-Vascular Event	34 (1.2%)	34 (3.6%)	8 (3.7%)	<0.0001	66 (1.6%)	11 (6.6%)	<0.0001
Myocardial Infarction	12 (0.4%)	10 (1.1%)	4 (1.9%)	0.0055	22 (0.6%)	5 (3.1%)	0.0002
Stroke	14 (0.5%)	12 (1.3%)	4 (1.9%)	0.0047	28 (0.7%)	2 (1.3%)	0.0237
Revascularization	9 (0.3%)	17 (1.8%)	5 (2.3%)	<0.0001	25 (0.6%)	7 (4.2%)	<0.0001
Angina	9 (0.3%)	10 (1.1%)	1 (0.5%)	0.0158	15 (0.4%)	5 (3.1%)	0.0003
Incident Diabetes	37 (1.3%)	76 (8%)	57 (25.6%)	<0.0001	0 (0.0%)	171 (100%)	<0.0001

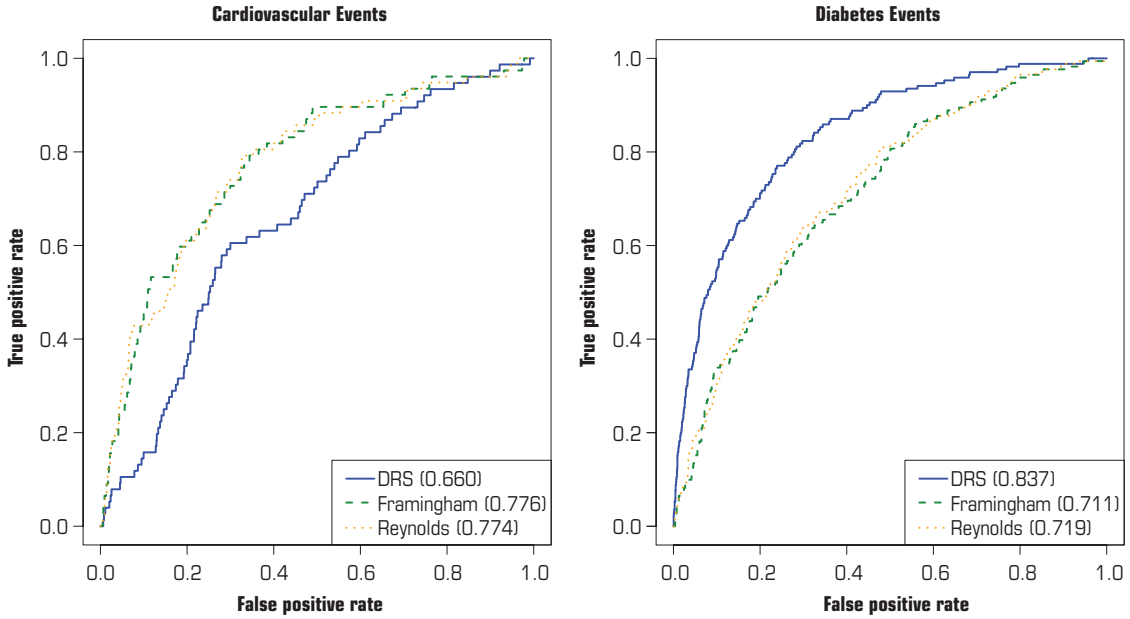
Results

Figure 1: Comparison of Cardiovascular Event Incidence and Relative Risk Among Different Diabetes Risk Groups



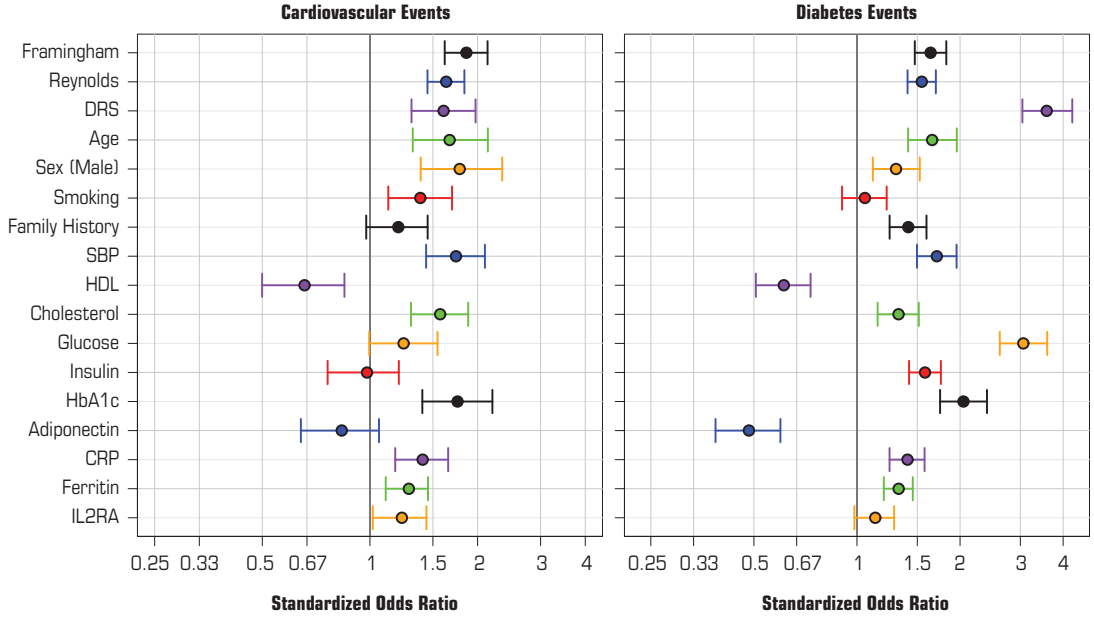
Subjects with high DRS have a significantly greater incidence of total cardiovascular events (CVE), myocardial infarction (MI), stroke and revascularization (RVSC) than those with low DRS. For comparison, the same analysis was done looking at subjects who remained diabetes free throughout the study (Non Diabetics) and subjects who developed diabetes during the study (Incident Diabetics). Similarly, greater risk of all cardiovascular events was observed among subjects with incident diabetes as compared to non-diabetic subjects. P-values were calculated by Fisher's exact test.

Figure 2: Receiver operator characteristic (ROC) curves for the DRS, Framingham CVD, and Reynolds risk score for cardiovascular and diabetes events.



All three models were predictive of both cardiovascular and diabetes events. The Framingham CVD and Reynolds risk scores were the best predictors of cardiovascular events, and the DRS was the strongest predictor of diabetes events.

Figure 3: Standardized Odds Ratios of Combined and Univariate Risk Factors for Cardiovascular and Diabetes Event Outcomes



The risk factors are charted as standardized odds ratios (OR) for incident CVE and incident T2DM independently. Among individual risk factors, strong OR (>1.5 or <0.67) of incident CVE were contributed by age, gender, SBP, HDL, cholesterol and HbA1c. Incident diabetes was predicted by age, SBP, HDL, glucose, insulin, HbA1c and adiponectin, sharing only 4 of the 9 risk factors with CVE. The multivariate risk scores typically had the largest ORs. Two of the markers had stronger ORs for incident CVE (gender and smoking), three markers had stronger ORs for incident diabetes (glucose, insulin and adiponectin).

Conclusions

- High DRS subjects show a greater incidence of primary cardiovascular events as compared to low DRS subjects.
- There are clear differences in the contribution of the constituent risk factors to predicting incident CVD and T2DM events.
- Among the biomarkers in the DRS, HbA1c, adiponectin and CRP were the strongest predictors of cardiovascular risk. By comparison, insulin and glucose were more predictive of diabetes than cardiovascular events.
- Cardiovascular and diabetes event outcomes share overlapping risk factors, consistent with the theory that these two diseases are part of a complex, cardiometabolic disorder.
- The incidence and relative risk of primary cardiovascular events suggests that intensive control of cardiovascular risk factors should be considered for patients at high risk for T2DM.

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