Prediction of Coronary Heart Disease in Middle-Aged Adults With Diabetes

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OBJECTIVE — To determine the 10-year probability of coronary heart disease (CHD) in diabetic adults and how well basic and novel risk factors predict CHD risk.

RESEARCH DESIGN AND METHODS — We measured risk factors in 14,054 participants (1,500 with diabetes) initially free of CHD in the Atherosclerosis Risk in Communities study from 1987 to 1989 and followed them prospectively for CHD incidence through 1998. We used proportional hazards regression models and receiver operating characteristic (ROC) curves for CHD risk prediction.

RESULTS — Based on our model using basic risk factors (age, race, total and HDL cholesterol, systolic blood pressure, antihypertensives, and smoking status), ~61% of diabetic women and 86% of diabetic men had a predicted 10-year CHD probability ≥10%. This CHD risk-prediction model had an area under the ROC curve of 0.72 in diabetic women and 0.67 in diabetic men. Novel risk factors or subclinical disease markers individually added only modest predictivity, but the addition of multiple markers (BMI, waist-to-hip ratio, Keys dietary score, serum albumin and creatinine, factor VIII, white blood cell count, left ventricular hypertrophy determined by electrocardiogram, and carotid intima-media thickness) increased the area under the curve by ~10%.

CONCLUSIONS — Although all diabetic adults are at high risk for CHD, their variation in CHD risk can be predicted moderately well by basic risk factors. No single novel risk marker greatly enhanced absolute CHD risk assessment, but a battery of novel markers did. Our model can provide estimates of CHD risk for the primary prevention of this disease in people with type 2 diabetes.

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Using multivariable risk assessment to define the likelihood of a coronary heart disease (CHD) event has become a cornerstone of preventive cardiology. The Framingham Study provided the most widely used CHD risk equation (1), which generalizes fairly well to other healthy populations (2). The Framingham model includes a variable for diabetes status (yes/no), but the U.K. Prospective Diabetes Study recently provided a multivariable CHD risk equation specifically for people with diabetes (3).

People with diabetes are at particularly high risk of CHD, so much so that the National Cholesterol Education Program (NCEP) now recommends that diabetic patients do not need specific CHD risk assessment, but instead that they be managed as if they had CHD (4). Likewise, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) recommends that hypertension be aggressively managed in diabetic patients (5). However, absolute CHD risk varies within the diabetic population and further risk stratification might help in making clinical decisions about aggressiveness of preventive management. The recent American Heart Association's Prevention Conference VI reviewed various means beyond basic risk factor assessment to accomplish CHD risk assessment in diabetic patients (6). However, epidemiological data on the value of novel markers of CHD risk in people with diabetes were scarce.

Using data from the Atherosclerosis Risk in Communities (ARIC) study on risk assessment, we sought to address three questions related to risk of CHD in diabetes: *1*) How well does risk assessment, using basic risk factors, identify diabetic participants who will or will not develop CHD? *2*) Do measures of subclinical disease or novel risk factors improve prediction of CHD, when compared with basic risk factors alone, in diabetic participants? and *3*) What is the 10-year probability of CHD in middle-aged participants with diabetes at various levels of predicted risk? We also sought to provide a potentially useful equation to predict CHD risk in diabetic individuals for clinical use.

RESEARCH DESIGN AND METHODS

— The ARIC study is a prospective study of cardiovascular disease in a cohort of 15,792 people, aged 45–64 years in 1987–1989, sampled from four U.S. communities (7,8). The cohort continues to be followed for mor-

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Abbreviations: ABI, ankle-brachial index; ADA, American Diabetes Association; ARIC, Atherosclerosis Risk in Communities; AUC, area under the curve; CHD, coronary heart disease; FEV_1, forced expiratory volume in 1 s; IMT, intima-media thickness; JNC, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LVH, left ventricular hypertrophy; NCEP, National Cholesterol Education Program; PAD, peripheral arterial disease; ROC, receiver operating characteristic; WBC, white blood cell count.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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bidity and mortality, and this report includes follow-up through 1998, for a median of 10.2 years. A recent study has described CHD risk prediction in the entire cohort using basic and novel risk factors (9). For this study, participants who were not black or white ($n = 48$) and those who were black in two centers ($n = 55$) were excluded from analysis because of small numbers. Also excluded were participants who had preexisting CHD at baseline ($n = 763$), were missing data on baseline preexisting CHD ($n = 339$), or were missing data on one of the basic risk factors or BMI ($n = 533$), leaving 14,054 individuals available for analysis, 1,500 of whom had diabetes.

Baseline examination

Details of ARIC measurements have been reported elsewhere (7–9), including the sports index (10) and Keys scores from diet (11). Residual forced expiratory volume in 1 s (FEV_1) was calculated as the difference between the observed FEV_1 and FEV_1 predicted from age, height, and sex. A 12-lead electrocardiogram (ECG) was used to define left ventricular hypertrophy (LVH) using the Cornell score (12). The ankle-brachial index (ABI) was measured, and peripheral arterial disease (PAD) was defined as ABI ≤0.90 for men and ≤0.85 for women. ARIC's carotid ultrasound measurements used a scanning protocol common to the four field centers (13) and standardized central reading of scans (14). Analyses are based on mean intima-media thickness (IMT) of the far wall for 1-cm lengths of the carotid bifurcation and the internal and common carotid, right and left. The means at the six sites were combined in an unweighted average to produce an overall mean IMT. High IMT was defined as mean IMT ≥1.0 mm.

Prevalent diabetes was defined according to American Diabetes Association (ADA) criteria (15) as a fasting glucose level ≥126 mg/dl, nonfasting level ≥200 mg/dl, self-reported physician diagnosis of diabetes, or pharmacological treatment for diabetes. Among people who knew they had diabetes, 96% reported onset after age 30 years, so most ARIC diabetic participants presumably have type 2 diabetes.

Ascertainment of incident events

CHD incidence in ARIC was ascertained as previously described (8,16). A CHD event was defined as a validated definite or probable hospitalized myocardial infarction, a definite CHD death, an unrecognized myocardial infarction defined by ARIC ECG readings, or coronary revascularization.

Statistical methods

Descriptive statistics were computed by the level of each basic risk factor, including age-adjusted CHD event rates calculated from Poisson regression. From the coefficients of a proportional hazards model of time to incident CHD, a CHD risk score was calculated for each person by multiplying each model coefficient times the person's level for the risk variable associated with that coefficient, then summing these products. The CHD risk score was created two ways: *1*) by sex-specific regression modeling within the whole population, including diabetes status in the risk score (similar to the Framingham Study) (1), and *2*) by performing sex-specific regression modeling separately for those with and without diabetes (similar to the U.K. Prospective Diabetes Study) (3). Thus, for men and women, the former predicted CHD risk in the full ARIC cohort, giving diabetic participants the higher predicted CHD risk because of their diabetes, and the latter predicted CHD risk based on the cohort with diabetes separate from the cohort without diabetes.

Our measure of individual risk predictivity of a model was the area under the receiver operating characteristic (ROC) curve (AUC) (17), which ranges between 0.5 and 1 and represents the probability that a person who had an incident event by a given follow-up time had a higher risk score than a person who did not have an event by that time. The area is a function of time; we used 10 years throughout and used Kaplan-Meier-like methods to calculate the relevant probabilities of event by that time in the face of censoring. Because many potential risk factors were studied and some parsimony was desirable, we used a 0.0025 change in AUC, in any subgroup, to include (Tables 2 and 3) or exclude (Table 4) a risk factor from the prediction model. The hypothesis "risk score A yields a higher AUC than risk score B" was tested via bootstrapping (17,18). The AUC for the basic model varied slightly among Tables 2–4 because of different sets of missing data.

We present graphs of the predicted probability of a CHD event within the first 10 years of follow-up by decile of risk score. The predicted probability of incident CHD within 10 years of follow-up was calculated by decile as the mean predicted probability at 10 years over all persons in the decile. Improved prediction was indicated by moving more of the predicted events out of the lower deciles of risk score into the upper deciles. All models showed good agreement between observed and expected number of events by decile of risk score, using the Hosmer-Lemeshow statistic (19).

RESULTS

— Among ARIC participants aged 45–64 years with diabetes at baseline, 47% reported taking glucose-lowering medication (21% insulin, 26% other), 44% were untreated but met glucose criteria for diabetes, and 19% reported physician-diagnosed diabetes, but were normoglycemic on the day of examination. Among the diabetic participants, 55% were white and 45% were black.

CHD rates in relation to diabetes

Incidence rates of CHD were ~4 times higher in diabetic than nondiabetic women and 2.5 times higher in diabetic than nondiabetic men (Table 1). However, absolute differences in CHD rates between diabetic and nondiabetic participants were greater for men than for women. CHD rates were greater for diabetic than nondiabetic participants within each level of basic risk factors and subclinical disease markers (Table 1).

CHD risk prediction in diabetic participants

Our first question noted above concerning how well basic risk factors identify diabetic participants who will or will not develop CHD was addressed using the AUC of ROC curves. We first predicted CHD using a "basic" risk score based on all ARIC participants and included a term to indicate diabetes or not. For comparison, we then predicted CHD in diabetes-specific models using the same basic risk factors. For participants with diabetes, particularly men, the specific model (AUC = 0.72 for women and 0.67 for men) was better than the combined model (AUC = 0.71 for women and 0.65 for men) at predicting CHD. Therefore, the remaining results focus on diabetes-specific models.

As shown in Table 2 (*row 7*) , using diabetes status−specific "basic" risk scores alone, predictivity was lower in di-

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Table 1—*Person years, number of events, and age- and race-adjusted 10-year CHD incidence rates (per 100 person years) by category of selected risk factors or subclinical disease markers in ARIC participants aged 45–64 years*

	Women						Men					
	Diabetes (n = 861)			No diabetes (n = 7,122)			Diabetes (n = 639)			No diabetes (n = 5,432)		
Risk Group	PY	No. events	Rate	PY	No. events	Rate	PY	No. events	Rate	PY	No. events	Rate
Overall												
Blood pressure*	7,809	108	13.8	71,041	237	3.3	5,506	149	27.1	51,688	570	11.0
Optimal	2,561	27	11.1	38,282	77	2.2	1,749	38	19.8	24,257	205	8.5
Normal	1,687	24	14.7	13,731	49	3.6	1,194	37	28.1	11,547	135	11.3
High normal	1,372	16	12.1	8,832	41	4.6	1,084	32	28.5	7,631	90	11.5
Hypertension stage I	1,490	23	16.5	7,927	38	4.6	998	30	30.5	6,212	106	16.7
Hypertension stage II–IV	699	18	30.4	2,268	32	13.6	479	12	25.0	2,040	34	17.9
Total cholesterol (mg/dl)												
<200	2,355	18	8.4	25,775	54	2.4	2,258	45	19.1	21,581	169	8.0
200 to <240	2,904	44	16.0	26,703	88	3.4	1,855	59	30.5	19,630	229	11.5
240 to <280	1,632	24	15.1	13,535	62	4.4	1,080	33	29.3	8,135	138	16.5
≥280	918	22	24.3	5,027	33	6.1	313	12	39.5	2,342	34	14.8
HDL cholesterol (mg/dl)												
<35	920	19	20.5	2,924	26	9.4	1,739	55	29.8	10,592	179	17.0
35 to <45	2,380	37	16.3	11,302	53	4.8	1,805	61	32.1	17,956	204	11.2
45 to <50	1,218	19	16.1	8,127	44	5.6	645	10	16.0	7,247	67	9.3
50 to <60	1,798	22	13.1	18,485	60	3.2	873	17	20.1	9,502	84	8.6
≥60	1,492	11	8.2	30,203	54	1.8	443	6	14.2	6,391	36	5.4
Current smoker												
No	6,222	71	11.7	53,688	119	2.2	4,182	112	25.1	38,124	372	9.4
Yes	1,586	37	25.4	17,353	118	7.2	1,324	37	29.1	13,563	198	15.2
Carotid IMT†												
<1 mm	6,319	83	15.2	64,671	194	3.4	4,407	97	24.4	44,497	435	10.6
≥1 mm	398	19	52.7	2,305	26	10.1	664	34	48.4	3,955	99	23.2
PAD												
No	7,071	89	13.5	66,739	217	3.5	5,199	140	26.4	49,187	518	11.0
Yes	342	16	50.1	1,977	8	4.1	167	7	43.2	726	24	30.9

Overall rate is crude, other rates are age and race adjusted. *JNC V category (38). †Exclusions for missing IMT led to rates higher than the overall rate. PY, person-years.

abetic than in nondiabetic women (AUC = 0.72 vs. 0.79). In contrast, predictivity of basic risk factors was similar in diabetic and nondiabetic men (AUC = 0.67 vs. 0.69). Table 2 (*rows 3–6*) also indicates that the basic risk factors whose contribution to predictivity would most be missed, if removed, were smoking, total cholesterol, and blood pressure in diabetic women, and total and HDL cholesterol in diabetic men. When we used more restrictive definitions of diabetes (i.e., only drug-treated diabetes or only physician-diagnosed or -treated diabetes), the AUC values for the basic model were slightly lower for diabetic women (AUC = 0.70 for both restrictive definitions) and slightly higher for diabetic men (AUC = 0.75 and 0.72, respectively).

The other information in Tables 2–4 addresses our second study question of whether nontraditional risk factors or subclinical markers of disease improve prediction of CHD in diabetic individuals. As is shown in Table 2, based on diabetes status−specific models, single risk factors added one at a time to the "basic" model increased the AUC only modestly. For diabetic women, the addition of BMI, sport index, serum creatinine, white blood cell count (WBC), factor VIII, or the von Willebrand factor raised the AUC to ≥0.73. For diabetic men, the addition of waist-to-hip ratio, Keys score, factor VIII, or von Willebrand factor raised the AUC to >0.68. As shown in the bottom row, consideration of multiple risk factors raised these AUCs further to 0.77 (a 7% increase) in diabetic women and 0.74 (a 10% increase) in diabetic men. This gain in AUC from the basic model to the fullest model was larger in diabetic than in nondiabetic participants.

In diabetic and nondiabetic participants, the gain in AUC from adding subclinical markers one at a time to the basic risk factors was most substantial for carotid IMT (Table 3). The AUC increased to 0.72 (~2%) for diabetic women and 0.70 (~3%) for diabetic men using basic risk factors and dichotomous indicators of carotid IMT, ECG LVH, and PAD.

As shown in Table 4, using all relevant basic and nontraditional risk factors and subclinical markers, the AUC increased by ~10% in diabetic participants, a far larger increase than the increases of ≤5% for nondiabetic participants. Because the maximum AUC is 1.0, an AUC increase of the size observed also represents ~25% of the available AUC not accounted for using the basic risk factor model. Stated differently, the additional variables increased by 0.067–0.081 the probability that diabetic participants with incident CHD had a higher risk score than

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Table 2—*AUCs for various models for incident CHD with regard to risk factors by sex and diabetes status: the ARIC, 1987–1998*

	Women		Men	
Model	Diabetes	No diabetes	Diabetes	No diabetes
n	761	6,470	558	4,941
No. of CHD events	95	212	130	515
Basic − (SBP + meds)	0.696	0.751	0.670	0.668
Basic − cholesterol	0.691	0.779	0.658	0.667
Basic − HDL cholesterol	0.715	0.770	0.648	0.666
Basic − smoking status	0.691	0.748	0.671	0.679
Basic*	0.721	0.786	0.672	0.688
Basic + BMI	0.731	0.786	0.674	0.690
Basic + waist-to-hip ratio	0.723	0.786	0.689	0.689
Basic + heart rate	0.723	0.785	0.672	0.688
Basic + sport activity	0.736	0.786	0.674	0.692
Basic + residual FEV_1	0.727	0.787	0.674	0.690
Basic + Keys score	0.721	0.785	0.694	0.691
Basic + cigarette packs-years	0.726	0.786	0.672	0.693
Basic + creatinine	0.732	0.785	0.672	0.688
Basic + lipoprotein(a)	0.720	0.792	0.672	0.692
Basic + apolipoprotein AI	0.725	0.787	0.673	0.689
Basic + apolipoprotein B	0.718	0.786	0.671	0.688
Basic + albumin	0.727	0.789	0.676	0.689
Basic + fibrinogen	0.723	0.790	0.673	0.697
Basic + factor VII	0.724	0.786	0.677	0.688
Basic + WBC	0.737	0.786	0.672	0.691
Basic + factor VIII	0.747	0.786	0.696	0.688
Basic + von Willebrand factor	0.736	0.786	0.693	0.689
Basic + multiple risk factors†	0.771	0.796	0.740	0.711

Participants missing data on any of the risk factors or markers shown were excluded to ensure comparability of AUCs. *Basic model includes age, race, total cholesterol, HDL cholesterol, systolic blood pressure (SBP) use of antihypertensive medication, and smoking status. Other risk factors were either added (+) or removed (−) one at a time from this model. †Multiple risk factors include BMI, waist-to-hip ratio, lipoprotein(a), albumin, creatinine, WBC, fibrinogen, factor VIII, sport activity, residual FEV_1, Keys score, and pack-years smoking.

those without CHD (Table 4). In each subgroup, the final model provided significantly better prediction of CHD than the basic model ($P < 0.05$). For diabetic participants, however, it would be possible to drop lipoprotein(a) and fibrinogen without affecting the AUC of the final model in Table 4, thus leaving BMI, waist-to-hip ratio, sports activity, Keys score, serum creatinine, serum albumin, factor VIII, WBC, ECG LVH, and carotid IMT as the factors responsible for the increase in AUC beyond the basic model. The prediction models are presented in the APPENDIX, and an interactive user-friendly risk calculator is found at www.aricnews.net, in which one can enter a diabetic patient's risk factor levels and receive a predicted 10-year risk of CHD.

Some treated diabetic participants did not fast 8 h before their blood was drawn. We therefore had to run supplemental sex-specific models on fasted participants only to consider whether baseline concentrations of serum glucose, plasma triglycerides, or treatment status (insulin, oral hypoglycemic agents, or no pharmacological therapy) added further to our CHD prediction models. Starting with the final models from Table 4, the AUC in diabetic women increased by 0.005 after adding triglycerides, but increased inconsequentially by adding treatment status or fasting glucose to the model. In diabetic men, triglycerides did not add substantially to the AUC, but treatment status added 0.017 and fasting glucose added 0.010. The multivariately adjusted relative risk of CHD for diabetic men using insulin was ~2.9 and for oral agents was ~1.6, compared with no pharmacological therapy.

Probability of CHD at various levels of risk

Figure 1 addresses our third study question about the probability of CHD at various levels of diabetes-specific risk scores. As expected, CHD risks were higher for participants with versus those without diabetes. For diabetic men and women, rates of CHD rose ~10-fold from the lowest to highest deciles of the basic risk score (Fig. 1, dotted line). About half (53%) of diabetic men and 23% of diabetic women had a predicted 10-year CHD probability ≥20%, and ~86% of diabetic men and 61% of diabetic women had a predicted 10-year CHD probability ≥10%. Based on the basic risk score, the average 10-

Table 3—*AUC for various models for incident CHD with regard to marker of subclinical disease by sex and diabetes status: the ARIC Study, 1987–1998*

	Women		Men	
Model	Diabetes	No diabetes	Diabetes	No diabetes
n	707	6,526	566	4,946
No. of CHD events	99	211	129	515
Basic*	0.711	0.777	0.680	0.679
Basic + Cornell score (continuous)	0.707	0.777	0.680	0.681
Basic + IMT (continuous)	0.723	0.781	0.699	0.701
Basic + ABI (continuous)	0.714	0.777	0.688	0.688
Basic + LVH (yes/no)	0.709	0.777	0.681	0.679
Basic + PAD (yes/no)	0.716	0.778	0.681	0.682
Basic + IMT ≥1 mm (yes/no)	0.724	0.778	0.698	0.692
Basic + multiple markers†	0.723	0.781	0.702	0.702

Participants missing data on any of the risk factors or markers shown were excluded to ensure comparability of AUCs. * Basic model includes age, race, total cholesterol, HDL cholesterol, systolic blood pressure, use of antihypertensive medication, and smoking status. †Multiple markers include IMT, LVH, and PAD.

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Table 4—*AUC for various models for incident CHD with regard to nontraditional risk factors and subclinical disease markers: the ARIC study, 1987–1998*

	Women		Men	
Model	Diabetes	No diabetes	Diabetes	No diabetes
n	687	6,396	550	4,489
No. of events	92	206	125	506
Basic*	0.709	0.779	0.682	0.680
Basic + nontraditional risk factors + subclinical disease markers†	0.776	0.792	0.763	0.716

Participants missing data on any of the risk factors or markers shown were excluded to ensure comparability of areas under the ROC curve. *Basic model includes age, race, total cholesterol, HDL cholesterol, systolic blood pressure, use of antihypertensive medication, and smoking status. †Basic risk factors plus BMI, waist-to-hip ratio, lipoprotein (a), albumin, creatinine, fibrinogen, factor VIII, WBC, Keys score, sport activity index, LVH, and IMT (continuous).

year CHD probability among diabetic participants was 26% for white men, 15% for black men, 17% for white women, and 13% for black women.

The addition of nontraditional risk factors and subclinical markers to risk scores increased the predictivity of CHD, especially among diabetic participants (Fig. 1, solid line); that is, the CHD probability became much higher in the highest deciles of risk, based on the full compared with the basic model, and correspondingly became lower for the lowest deciles. Diabetic men and women in the highest decile of the full risk score had a 10-year probability of CHD >50%.

CONCLUSIONS — People with diabetes are at high risk of CHD, so much so that the NCEP has recommended that diabetic patients not receive specific CHD risk assessment, but have their plasma lipids managed as if they had CHD (4). The NCEP appears to have based its recommendation on Finnish data suggesting that diabetic patients with no history of myocardial infarction have a risk of a future myocardial infarction similar to that of nondiabetic patients with CHD (20), a finding not confirmed in Scotland (21) or in U.S. male physicians (22). Our data verified that, compared with nondiabetic individuals, most people with diabetes have elevated risk of incident CHD (at least 1% per year). However, ~14% of diabetic men and 39% of diabetic women in ARIC had a predicted probability of CHD <1% per year when stratified by basic CHD risk score. This variation in risk may in part reflect the fact that many ARIC diabetic participants were defined by epidemiological criteria, which require only one blood glucose abnormality, and 36% were newly recognized by fasting glucose criteria alone. Yet, ARIC CHD rates are comparable to those in the U.K. Prospective Diabetes Study, where the CHD risk was ~1.5% per year (3). Taken together, these data suggest that there may still be a role for CHD risk stratification of diabetic patients in preventive medical practice. Patients with lowest CHD risk might need less aggressive intervention than those at high risk.

Our study results corroborated the findings of previous large studies (23–26) for an important role of the basic risk factors in determining CHD incidence in diabetic individuals. Our data suggested,

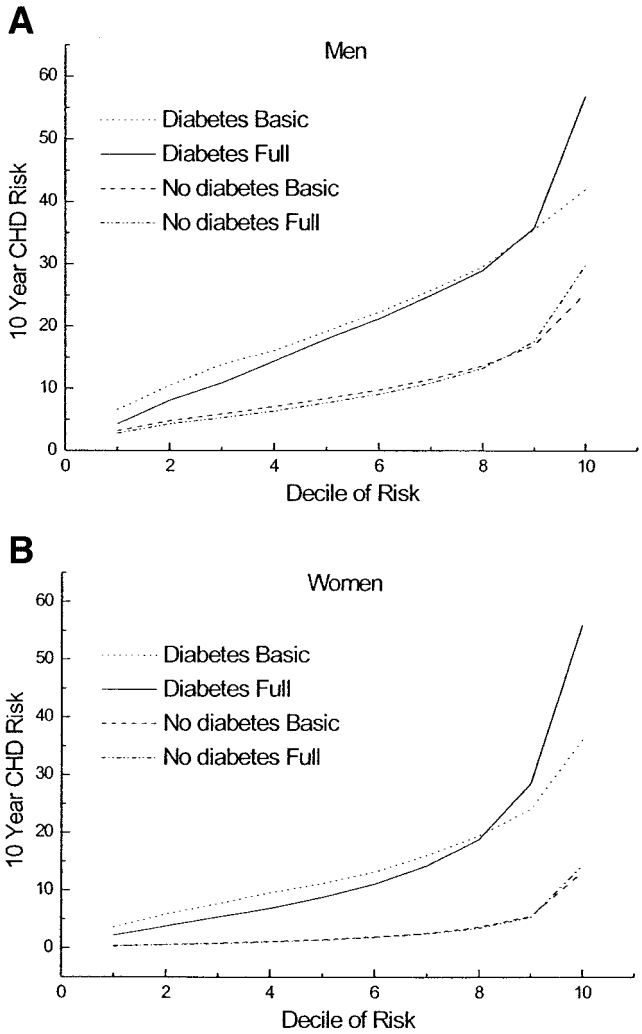

Figure 1—*Predicted 10-year risk of incident CHD, comparing the basic with the full model, by sex and diabetes status, in ARIC participants aged 45–64 years. Models performed were specific for sex and diabetes status. The basic model included age, race, total cholesterol, HDL cholesterol, systolic blood pressure, use of anti-hypertensive medication, and smoking status. The full model included basic risk factors plus BMI, waist-to-hip ratio, lipoprotein(a), albumin, creatinine, fibrinogen, factor VIII, WBC, Keys score, and carotid IMT.*

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not surprisingly, that the basic risk factors predicted CHD incidence somewhat better using a prediction model like that used in the U.K. Prospective Diabetes Study (3), derived from diabetic participants only, than using that from the Framingham study (1), a model derived from the whole ARIC sample with diabetes (yes/no) as a term in the prediction model. With increased availability of web-based or personal digital assistant calculators, risk formulas for particular patient subgroups become increasingly feasible. Indeed, the "basic" equation in the APPENDIX (Table A) has been adapted so clinicians can predict CHD risk in patients with diabetes comparable with those in ARIC (see ARIC website, www.aricnews.net). Although the basic risk factors did not predict CHD quite as well in diabetic participants as in nondiabetic participants, the absolute differences in CHD incidence across basic risk factors was greater for diabetic than nondiabetic participants, emphasizing the great potential for CHD prevention in diabetic individuals. Further rationale for control of the basic CHD risk factors in diabetic patients has been reviewed elsewhere (27).

The American Heart Association's Prevention Conference VI concluded that data were scanty on whether nontraditional risk factors or subclinical disease markers could help further in CHD risk assessment in diabetic patients (6). That conclusion largely motivated us to explore additional risk markers in ARIC participants with diabetes, as we had in the whole ARIC cohort (9). The nontraditional risk factors or markers we examined individually contributed little to the AUC beyond the basic risk factors, but the addition of multiple markers increased the AUC by ~10%. Notably, because the AUC for the basic risk factor model was lower for diabetic than nondiabetic participants, the increase in AUC by adding nontraditional risk markers was greater for participants with diabetes than those without diabetes. Whether these nontraditional measures would be useful and cost-effective in the care of diabetic patients seems unlikely. The anthropometric, blood, and ECG measurements required by the full risk equation (APPENDIX) could be easily performed in clinical practice, but the assessment of exercise, diet, and carotid IMT require more effort and cost.

Although our study was large, prospective, and population based, and carefully assessed CHD events, it had some shortcomings. First, as mentioned above, the diagnosis was an epidemiological, not clinical, one. An oral glucose tolerance test was not performed and diabetes was defined by ADA criteria (15). Second, we measured many candidate risk markers, but not HbA_{1c}, C-reactive protein, microalbuminuria, fibrinolytic factors, or coronary vascular calcium. These may have improved prediction further. Third, some of our survival models included a large number of variables relative to the number of events, especially for diabetic participants, potentially leading to imprecise estimates of the model coefficients. We also did not have enough events in diabetic participants to split the sample and perform a test analysis on half and validation on the other half. Future studies, therefore, would be useful for comparison. Finally, the final AUCs of 0.776 in diabetic women and 0.763 in diabetic men for the full model were still far enough from perfect prediction (AUC = 1.0) that better risk markers still could be sought; however, this lack of predictivity must partly reflect imprecision in characterizing risk factors.

APPENDIX

CHD prediction equations for men and women with diabetes

Table A shows the coefficients of the risk factors for the CHD prediction equations from ARIC diabetic participants. The risk score XBETA for an individual is the sum of the products of the beta coefficients for a factor and the level of that factor for the individual. These risk scores can be converted by the following formula to prob-

Table A—*Parameter estimates for the basic and full models predicting 10-year probability of CHD in male and female ARIC participants with diabetes*

Risk variable	Overall median	Basic model		Full model	
		Women	Men	Women	Men
S_m	—	0.97507	0.93299	0.98353	0.95280
XBETAmed	—	0.99852	7.75110	2.14640	17.9811
Age (years)	55	−0.03301	0.22777	0.02914	0.42128
Age^2 (years^2)	55^2	0.00041	−0.00175	−0.00028	−0.00372
Race (white = 1, black = 0)	—	0.37361	0.49310	0.65568	0.52539
Total cholesterol (mg/dl)					
200–279 vs. <200	—	0.72618	0.46038	0.72122	0.38255
≥280 vs. <200	—	1.10225	0.90874	0.85815	0.96119
HDL cholesterol (mg/dl)					
<45 vs. ≥50	—	0.45810	0.80719	0.39395	0.79065
45–49 vs. ≥50	—	0.55162	−0.25732	0.45172	−0.29731
Systolic blood pressure (mmHg)	119	0.01314	0.00437	0.00549	0.00309
Hypertension med. (yes = 1, no = 0)	—	0.48246	−0.05461	0.43010	−0.16935
Current smoking (yes = 1, no = 0)	—	0.78920	0.15208	0.45265	−0.05033
BMI (kg/m^2)	26.74	—	—	−0.05122	−0.05070
Waist-to-hip ratio (1 unit)	0.93	—	—	3.29970	3.54309
Sport activity (1 unit)	2.25	—	—	−0.32062	−0.05680
Keys score (1 unit)	42.3	—	—	0.01014	0.03085
Serum creatinine (mg/dl)	1.1	—	—	0.06090	1.09697
Serum albumin (g/dl)	3.9	—	—	−0.78332	−0.02500
WBC (thousands/mm^3)	5.8	—	—	0.07927	0.02362
Factor VIII (%)	126	—	—	0.00637	0.00619
LVH (yes = 1, no = 0)	—	—	—	0.51805	−0.87211
IMT (mm)	0.68	—	—	1.54553	0.81442

Data are *n* or β-coefficient. Medians for continuous variables, except for age and age^2.

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abilities (P) of onset of CHD within 10 years:

$$P = 1 - S_m^{\exp(\text{XBETA} - \text{XBETAmed})},$$

where S_m is 1 minus the probability of a CHD event within 10 years for a person with 0 levels of the categorical variables in the risk score and with the median values of the continuous risk factors, and XBETAmed is the risk score calculated for such a person. The median values, S_m, and XBETAmed are given in Table A.

To apply this risk score to a new population, even though the score may still properly rank individuals in the new population for CHD risk, one would need to calibrate P to the overall 10-year risk level in the new population. An approximate way to do this is to replace XBETAmed with a corresponding value calculated still at zero values of categorical variables but at the new population's medians for the continuous variables, and to replace S_m with

$$\exp(-rt\{\exp(\text{XBETAmed} - \text{mean (XBETA)}\}),$$

where XBETAmed is for the new population, r is the average annual event rate for the new population, t is the years at which the risk probability is to be calculated, and mean (XBETA) is the mean risk score for the new population. The latter is estimated from summing the β-coefficients multiplied times the estimated means of the associated risk factors in the new population.

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References

1. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB: Prediction of coronary heart disease risk using risk factor categories. *Circulation* 97:1837–1847, 1998
2. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P: Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* 286:180–187, 2001
3. Stevens RJ, Kothari V, Adler AI, Stratton IM: The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin Sci* 101:671–679, 2001
4. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of The 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). *JAMA* 285: 2486–2497, 2001
5. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. *JAMA* 289:2560–2572, 2003
6. Redberg RF, Greenland P, Fuster V, Pyorala K, Blair SN, Folsom AR, Newman AB, O'Leary DH, Orchard TJ, Psaty B, Schwartz JS, Starke R, Wilson PW: Prevention Conference VI: diabetes and cardiovascular disease. Writing Group III: risk assessment in persons with diabetes. *Circulation* 105:e144–e152, 2002
7. The ARIC Investigators: The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol* 129: 687–702, 1989
8. Folsom AR, Szklo M, Stevens J, Liao F, Smith R, Eckfeldt JH: A prospective study of coronary heart disease in relation to fasting insulin, glucose, and diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care* 20:935–942, 1997
9. Chambless LE, Folsom AR, Sharrett R, Sorlie P, Couper D, Szklo M, Nieto J: Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) Study. *J Clin Epidemiol*. In press
10. Baecke JAH, Burema J, Frijters JER: A short questionnaire for the measurement of habitual physical activity in epidemiologic studies. *Ann J Clin Nutr* 36:936–942, 1982
11. Keys A, Anderson TT, Grande F: Prediction of serum cholesterol responses of man to change in fats in the diet. *Lancet* ii:959–966, 1957
12. Crow RS, Prineas RJ, Rautaharju P, Hannan P, Liebson PR: Relation between electrocardiography and echocardiography for left ventricular mass in mild systolic hypertension (results from Treatment of Mild Hypertension Study). *Am J Cardiol* 75:1233–1238, 1995
13. Bond MG, Barnes RW, Riley WA, Wilmoth SK, Chambless LE, Howard G, Owens B: High-resolution B-mode ultrasound scanning methods in the Atherosclerosis Risk in Communities Study (ARIC). *J Neuroimaging* 1:68–73, 1991
14. Riley WA, Barnes RW, Bond MG, Evans G, Chambless LE, Heiss G: High-resolution B-mode ultrasound reading methods in the Atherosclerosis Risk in Communities Study (ARIC). *J Neuroimaging* 1:168–172, 1991
15. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
16. White AD, Folsom AR, Chambless LE, Sharrett AR, Yang K, Conwill D, Higgins M, Williams OD, Tyroler HA: Community surveillance of coronary heart disease in the ARIC Study: methods and initial two years experience. *J Clin Epidemiol* 49: 223–233, 1996
17. Campbell G: General methodology. I. Advances in statistical methodology for the evaluation of diagnostic and laboratory tests. *Stat Med* 13:499–508, 1994
18. DiCiccio TJ, Efron B: *Bootstrap Confidence Intervals*. Stanford, CA, Stanford University, 1995 (Tech. Rep. no. 175)
19. Hosmer DW, Lemeshow S: *Applied Logistic Regression*. New York, Wiley, 1989
20. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229–234, 1998
21. Evans JM, Wang J, Morris AD: Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. *BMJ* 324: 939–942, 2002
22. Lotufo PA, Gaziano JM, Chae CU, Ajani UA, Moreno-John G, Buring JE, Manson JE: Diabetes and all-cause and coronary heart disease mortality among US male physicians. *Arch Intern Med* 161:242–247, 2001
23. Adlerberth AM, Rosengren A, Wilhelmsen L: Diabetes and long-term risk of mortality from coronary and other causes in middle-aged Swedish men: a general population study. *Diabetes Care* 21:539–545, 1998
24. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
25. Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR: Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ* 316:823–828, 1998
26. Fuller JH, Stevens LK, Wang SL: Risk factors for cardiovascular mortality and morbidity: the WHO Multinational Study of

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Vascular Disease in Diabetes. *Diabetologia* 44 (Suppl. 2):S54–S64, 2001
27. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC Jr, Sowers JR: Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 100:1134–1146, 1999

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