INCIDENCE AND RISK FACTORS FOR CARDIOVASCULAR DISEASE IN AFRICAN AMERICANS WITH DIABETES: THE ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) STUDY

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To determine the incidence rate of cardiovascular disease (CVD) and its association with conventional and less well-established risk factors in African Americans with diabetes, we studied 741 African Americans aged 45 to 64 years with diabetes, in the Atherosclerosis Risk in Communities (ARIC) study. Risk factors were measured from 1987 to 1989, and incident CVD (n = 143 coronary heart disease (CHD) or stroke events) was ascertained through 1998. The crude incidence rate (per 1000 person-years) of CVD was 22.5 (11.9 for CHD and 12.0 for stroke). After multivariate adjustments, total cholesterol, prevalent hypertension and current smoking were significantly and positively associated with incident CVD among these African Americans with diabetes. Among the non-conventional risk factors, serum creatinine, factor VIII, von Willebrand factor, and white blood cell count were positively and serum albumin negatively and independently associated with CVD incidence. Adjusted relative risks for highest versus lowest tertiles of these risk factors ranged from 1.77 to 2.13. This study confirms that the major risk factors (hypercholesterolemia, hypertension and smoking) are important determinants of CVD in African Americans with diabetes. In addition, several blood markers of hemostasis or inflammatory response and elevated serum creatinine also proved to be CVD risk factors in African Americans with diabetes. (*J Natl Med Assoc.* 2002;94:1025–1035.)

Key words: cardiovascular disease ◆ coronary heart disease ◆ diabetes ◆ stroke

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INTRODUCTION

It is well established that people with diabetes have an increased risk of cardiovascular disease (CVD), including coronary heart disease (CHD), stroke, peripheral vascular disease, and congestive heart failure.[1-6] The public health impact of CVD in people with diabetes is enormous and increasing as the prevalence of diabetes rises.[7] Strategies to prevent diabetes and its cardiovascular complications are urgently needed.[1] Conventional risk factors (smoking, hypertension, dyslipidemia) contribute to CVD occurrence in people with, and without, diabe-

tes.[1,8] In addition, people with diabetes have unique risk factors related to their hyperglycemia or insulin resistance, including hemostatic abnormalities and elevated circulatory inflammatory markers.[1,8]

Identification of important non-traditional CVD risk factors might motivate new strategies for CVD prevention in diabetes. Some studies have examined non-traditional CVD risk factors among patients with diabetes,[9-15] but none has focused on African Americans, who have a high prevalence of diabetes. Therefore, we examined the incidence and risk factors for CVD in the cohort of African Americans with diabetes in the Atherosclerosis Risk in Communities (ARIC) study. We specifically hypothesized that markers of hemostasis or inflammation might be independent risk factors.

METHODS

Setting and Participants

The ARIC study is an ongoing prospective study of 15,792 persons, 4,266 African American, aged 45 to 64 years at baseline examination in the 1987 to 1989 period.[16] Participants were selected by probability sampling from four US communities: Forsyth County, North Carolina; Jackson, Mississippi (African Americans only, identified from driver's license lists); the northwestern suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Jackson accounted for about 90% of the African Americans in the sample while the remainder came from Forsyth County via county-wide sampling. The sampling procedures and methods used in ARIC have been described in detail elsewhere.[16] Participants were followed up by telephone interviews annually and three triennial clinic visits.

Baseline Measurements

At baseline, information was collected by self-report on race, education level, smoking status, and alcohol use. A modified version of the questionnaire by Baecke et al.[17] was used to assess physical activity. This provided three indices of activity in sport, leisure, and work ranging from 1 (low) to 5 (high). Technicians measured body size to derive the body mass index (BMI) in kg/m^2, as well as waist-to-hip ratio (ratio of circumference of the waist [at the umbilical level] and the hips [maximum]). Hypertension was defined as systolic blood pressure of 140 mmHg or more, diastolic blood pressure of 90mmHg or more, or the current use of antihypertensive medications. Blood pressure measurements were taken by trained technicians three times using a random-zero sphygmomanometer. The mean of the last two were used for analysis.

Participants were asked to fast for at least 12 hours before blood collection. Blood samples were drawn from the antecubital vein into vacuum tubes containing sodium citrate, EDTA or serum separator gel, for hemostatic factors, lipids, glucose and blood chemistries, respectively. Samples for glucose and other blood chemistries were allowed to clot for 30 to 40 minutes and then centrifuged at 3000g for 10 minutes at 4° C. Samples for hemostatic factor and lipids were centrifuged immediately. All sample aliquots were frozen at −70° C until analyzed within two months.

Serum glucose was measured using a modified hexokinase/glucose-6-phosphate dehydrogenase method. Insulin level was assessed by radioimmunoassay (iodine 125-labeled Insulin [732] Kit; Cambridge Medical Diagnostics Inc., Billerica, Mass). Serum magnesium was assessed using the metallochromic dye calmagite (1-[1-hydroxy-4-methyl-2-phenylazo]-2-naphthol-4-sulfonic acid) according to the procedure of Gindler and Heth.[17] Albumin was measured using a bromocresol green colorimetric assay.[19] Creatinine was measured by using an alkaline picarate colometric assay.[20]

Total cholesterol[21] and triglycerides[22] were measured by enzymatic methods; HDL cholesterol was measured after dextra-magnesium precipitation.[23] The lipid laboratory also measured HDL3 cholesterol[24] and calculated HDL2 cholesterol values; apolipoproteins A-I and B were measured by radioimmunoas-

say.[25-27] Lipoprotein(a) was measured as its apolipoprotein by using a double-antibody enzyme-linked immunosorbent assay technique.[28]

Factors VII and VIII activities were assessed by determining the ability of the tested sample to correct the clotting time of human factor VII or factor VIII-deficient plasma obtained from George King Biomedical. Fibrinogen was measured by using the thrombin-time-titration procedure. Antithrombin III activity was measured by using a chromogenic substrate method. von Willebrand factor antigen and protein C were assessed by enzyme-linked immunosorbent assays. White blood cell count was measured using automated cell counters in laboratories in each ARIC center.[29]

Prevalent CHD was defined as a reported history of physician-diagnosed heart attack, prior cardiovascular surgery or coronary angioplasty, or a prior MI determined by ECG. Prevalent stroke was defined as a reported history of a physician-diagnosed stroke. Diabetes was defined as fasting serum glucose level of 7.0 mmol/L (126 mg/dL) or more,[30] nonfasting glucose level of at least 11.1mmol/L (200 mg/dL), current use of medication for diabetes, or a self-reported history of medically diagnosed diabetes. Names of current medications were obtained from participants at the baseline examination, and for this analysis diabetes treatment status was classified into three mutually exclusive categories: no pharmacological treatment; oral hypoglycemic treatment; and insulin treatment.

Ascertainment of Incident CVD

For the purpose of this article, incident CHD and incident stroke were combined into a single composite endpoint of "incident CVD." The methods used to ascertain CHD[31,32] and stroke events[33] have been described in detail previously. Incident CHD was defined as a first definite, probable, or silent myocardial infarction or definite CHD death following published criteria.[32] Incident MI was defined by combinations of chest pain, cardiac enzyme values, and electrocardiographic changes. Silent MI was defined by the appearance between the first and subsequent ARIC examinations of a major Q wave, or a minor Q wave with ischemic ST-T changes, or an MI by computerized NOVACODE[34] criteria, confirmed by side-by-side visual ECG comparison. CHD death criteria used medical history, symptoms, and death certificate data.

Stroke was defined as the sudden or rapid onset of neurologic symptoms lasting >24 hours or leading to death, in the absence of a nonstroke cause.[33] Incident stroke was the first occurrence of definite or probable hospitalized stroke, fatal or nonfatal.

Statistical Analysis

For our main analyses, we excluded hierarchically individuals with any of the following: race other than African American (n = 11526); free of diabetes at baseline (n = 3325); prevalent CHD, stroke or both at baseline (n = 171); or missing values on baseline exposures (n = 29). After these exclusions, the study sample comprised 741 African Americans with diabetes initially free of CVD. For a subsidiary analysis we included, for comparison, 897 whites with diabetes. Participants were followed until December 31, 1998. Follow-up time was from the baseline clinic visit to the time of the first CVD event for clinically recognized cases. Date of silent myocardial infarction was assigned as the midpoint between the time an infarction was detected by ECG and the visit immediately before the detection. The follow-up time for participants who remained free of CVD lasted until the day of death, loss of contact, or to the end of 1998.

Age, ARIC field center, and sex-adjusted mean values for risk factors were compared between those *with* versus those *without* incident CVD using analysis of covariance. Values of triglycerides and lipoprotein(a) were transformed by taking logarithms because of skewed distributions. Age, ARIC field center, and sex-adjusted incidence rates were calculated for CVD and specifically for stroke and CHD using Poisson regression. Adjusted hazard rate ratios

for risk factors, with 95% confidence intervals, were determined using Cox proportional hazards models after checking the proportional hazards assumption (testing for interaction with follow-up time). Risk factors were represented in categories or tertiles as dummy variables. A *p*-value for the trend was computed across groups using a variable with an ordinal value (1, 2 or 3) assigned to each tertile.

The first regression model examined each risk factor, one at a time, with adjustment for age, ARIC field center, and sex. In "the fully adjusted" model, each of the conventional risk factors (total cholesterol, triglycerides, HDL cholesterol, BMI, hypertension, cigarette smoking, alcohol consumption, physical inactivity) was further adjusted for treatment status for diabetes and also for each other. The associations of the following putative nontraditional risk factors with incident CVD events were examined one at a time: HDL cholesterol subfractions, waist-to-hip ratio, lipoprotein(a), apolipoprotein A-I and B, magnesium, creatinine, protein C, antithrombin III, fibrinogen, factors VII and VIII, von Willebrand factor, white blood cell count, and albumin.

Although this analysis focused on African Americans with diabetes, we also tested whether similar associations existed for whites with diabetes. African Americans and whites were pooled and an interaction term was included in the Cox regression models predicting CVD. This was done for each risk factor, one at a time. All statistical analyses were performed using SAS software 6.12.

RESULTS

The cohort comprised 741 African Americans with diabetes, of whom 34% were men; 661 lived in Jackson and 80 in Forsyth County. At baseline, the mean age was 55 years, and 34% were newly diagnosed with diabetes. Insulin was used by 30%, 26% reported taking oral hypoglycemic medications, and 44% did not have any history of pharmalogic treatment of diabetes.

Over a mean of 8.5 years of follow-up, there were 143 incident CVD events (n = 65 for stroke only, n = 65 for CHD only, and 13 had both). The crude incidence rate (per 1000 person years) was 22.5 for CVD (12.0 for stroke and 11.9 for CHD). After adjusting for age and ARIC field center, the sex-specific rates of CVD were not different between men with diabetes and women with diabetes (26.1 versus 20.1 per 1000 person years, respectively, *p* value = 0.18).

As shown in Table 1, the age, ARIC field center, and sex-adjusted baseline levels of total cholesterol and triglycerides, and the prevalence of hypertension were significantly higher in participants with diabetes who sustained incident CVD events compared to those who did not. The prevalence of hypertension was very high: 78.3% for those who developed CVD and 70.1% for those who did not. Mean levels of lipoprotein(a), apolipoprotein B, fibrinogen, factor VIII, von Willebrand factor, and WBC count were significantly higher and albumin was lower in those with CVD. Diabetes treatment status in participants with, versus without, incident CVD was also significantly different; insulin use was more common among those who subsequently had events.

Among conventional risk factors (Table 2), levels of total cholesterol, triglycerides, physical inactivity, prevalent hypertension and current smoking were significantly associated ($p \leq 0.06$) with increased CVD incidence after adjusting for age, ARIC field center, and sex. When each of these was further adjusted for the other conventional risk factors, only total cholesterol, prevalent hypertension, and current smoking remained statistically associated with incident CVD. The adjusted relative risk of the highest compared to the lowest tertiles of total cholesterol was 1.87 (95% CI 1.19–2.95), and the relative risks for hypertension and smoking were 1.54 (95% CI 1.02–2.34) and 1.77 (95% CI 1.16–2.71), respectively.

Waist-to-hip ratio, lipoprotein(a), creatinine, fibrinogen, factor VIII, von Willebrand factor, and WBC count were positively associated, and albumin negatively and significantly associated

Table 1. Baseline Characteristics* in African Americans with Diabetes Aged 45 to 64 years in the Atherosclerosis Risk in Communities (ARIC) Study by Incident Cardiovascular Disease (CVD) Status†

Risk factors	CVD events		p values
	Yes n = 143	No n = 598	
Age, mean, years	55.7	54.9	0.18
Men, %	38.5	33.3	0.24
Education, %			0.14
11 years or less	58.7	50.9	
High school graduate	25.2	26.0	
Post-high school	16.1	23.1	
Cigarette smoking status, %			0.11
Current	29.3	23.1	
Former	23.8	24.9	
Never	46.9	52.0	
Alcohol use, %			0.12
Current	24.5	20.1	
Former	29.4	28.8	
Never	46.1	51.1	
Hypertension‡, %	78.3	70.1	0.05
Diabetes treatment status, %			0.001
Insulin	46.9	25.6	
Oral	21.0	27.9	
None or unknown	32.1	46.5	
Physical activity (sport index score, mean)	2.22	2.24	0.57
Body mass index, Kg/m^2	30.8	31.3	0.37
Waist-to-hip ratio	0.974	0.964	0.10
Total cholesterol, mmol/L	5.96	5.54	0.0004
HDL cholesterol, mmol/L	1.21	1.26	0.19
Triglycerides, mmol/L§	2.77	2.53	0.004
HDL_2 cholesterol, mmol/L	0.34	0.36	0.35
HDL_3 cholesterol, mmol/L	0.87	0.90	0.27
Lipoprotein(a), μg/mL§	137.0	111.1	0.01
Apolipoprotein A-I, mg/L	1282	1312	0.28
Apolipoprotein B, mg/L	1076	975	0.002
Magnesium, mmol/L	0.75	0.76	0.18
Creatinine, μmol/L	116	111	0.65
Albumin, g/L	0.037	0.039	0.001
White blood cell count, 10^9 cell/L	6.68	6.06	0.001
Fibrinogen, g/L	3.52	3.28	0.003
Factor VII, %	127	121	0.07
Factor VIII, %	185	165	0.0005
von Willebrand factor, %	174	147	<0.0001
Antithrombin III, %	27.98	28.34	0.23
Protein C, μg/mL	3.31	3.24	0.31

*Means and percentages are adjusted for age, ARIC field center, and sex.
†CVD defined as: CHD or stroke, see "Methods" section for description.
‡Systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or current use of antihypertensive medication.
§Values presented are geometric means.

Table 2. Adjusted Relative Risks of Cardiovascular Disease Associated with Selected Traditional Risk Factors in African Americans with Diabetes in the Atherosclerosis Risk in Communities (ARIC) Study.

		Age, ARIC field center and sex adjusted		Fully adjusted†	
Risk factors	Category*	RR (95% CI)	p value for trend	RR (95% CI)	p value for trend
Total cholesterol, mmol/L	<5.12	1.0	0.03	1.0	0.007
	5.12–6.05	1.36 (0.87–2.11)		1.58 (1.00–2.50)	
	>6.05	1.61 (1.05–2.48)		1.87 (1.19–2.95)	
HDL cholesterol, mmol/L	<1.10	1.0	0.14	1.0	0.24
	1.10–1.39	0.82 (0.54–1.22)		0.85 (0.56–1.30)	
	≥1.40	0.73 (0.48–1.11)		0.76 (0.49–1.20)	
Triglycerides, mmol/L	<1.16	1.0	0.007	1.0	0.76
	1.16–1.81	1.37 (0.88–2.15)		1.05 (0.65–1.70)	
	>1.81	1.81 (1.18–2.78)		1.08 (0.65–1.81)	
Body mass index, kg/m^2	<28.8	1.0	0.18	1.0	0.21
	28.8–33.7	1.06 (0.72–1.56)		1.12 (0.74–1.67)	
	>33.7	0.74 (0.48–1.14)		0.74 (0.46–1.18)	
Physical activity§	High vs. Low	0.68 (0.49–0.95)	0.02	0.75 (0.53–1.07)	0.11
Hypertension	Yes vs. No	1.53 (1.02–2.29)	0.04	1.54 (1.02–2.34)	0.04
Alcohol use	Never	1.0		1.0	
	Former	1.25 (0.83–1.88)	0.28	1.01 (0.66–1.57)	0.93
	Current	1.39 (0.88–2.20)	0.16	1.16 (0.71–1.50)	0.63
Cigarette smoking	Never	1.0		1.0	
	Former	1.01 (0.66–1.55)	0.95	1.17 (0.75–1.83)	0.49
	Current	1.46 (0.98–2.17)	0.06	1.77 (1.16–2.71)	0.008
Diabetes treatment status	None	1.0		1.0	
	Oral	1.06 (0.67–1.67)	0.82	1.24 (0.77–1.99)	0.37
	Insulin	2.57 (1.76–3.76)	<0.0001	3.05 (2.04–4.57)	<0.0001

*Categories for continuous variables are tertiles.
†Each variable was adjusted for the age, ARIC field center, and sex plus the other risk factors listed in the table.
§On a sports score of 1 to 5, ≤ 2 was considered low while > 2 was considered high.

with incident CVD after adjusting for sex, ARIC field center, and age (Table 3). Comparison of the highest to the lowest tertiles for these risk factors yielded relative risks for CVD in the range of 1.6 to 2.7. On further adjustment for conventional risk factors and diabetes treatment status, albumin, creatinine, factor VIII, von Willebrand factor, and WBC count all remained significantly associated with incident CVD with only a slight attenuation of the relative risks.

Comparison with Whites

As a supplemental analysis, we made comparisons with whites with diabetes. Among 897 white participants with diabetes, 182 incident CVD events occurred (n = 32 stroke, n = 150 CHD, and 16 had both). The age-adjusted CVD rates (per 1000 person-years) were similar in whites (21.6) and African Americans (22.3), p value = 0.77. The age-adjusted CHD rate was significantly higher in whites (17.5 versus 11.7 in African Americans, p = 0.004) and stroke rate was significantly higher in African Americans (11.8 versus 5.4 in whites, p value = 0.0001). There was no evidence to indicate a significant multiplicative interaction between race and any of the risk factors for CVD. This absence of interaction suggests no difference in risk factors for CVD in white and African American participants with diabetes.

Table 3. Adjusted Relative Risks of Cardiovascular Disease Associated with Nontraditional Risk Factors in African Americans with Diabetes in the Atherosclerosis Risk in Communities (ARIC) Study.

		Age, ARIC field center and sex adjusted		Fully adjusted†	
Risk factors*	Category	RR (95% CI)	p value for trend	RR (95% CI)	p value for trend
Waist-to-hip ratio	<0.94	1.0	0.01	1.0	0.12
	0.94–0.99	1.32 (0.86–2.04)		1.35 (0.86–2.12)	
	>0.99	1.73 (1.14–2.63)		1.45 (0.91–2.29)	
Lipoprotein(a), μg/mL	<92	1.0	0.03	1.0	0.09
	92–180	1.41 (0.91–2.21)		1.48 (0.93–2.36)	
	≥181	1.61 (1.05–2.47)		1.49 (0.95–2.35)	
Creatinine, μmol/L	<89	1.0	0.0002	1.0	0.04
	89–97	1.89 (1.12–3.16)		1.52 (0.89–2.60)	
	≥98	2.74 (1.61–4.66)		1.82 (1.04–3.19)	
Fibrinogen, g/L	<3.00	1.0	0.007	1.0	0.25
	3.00–3.56	1.34 (0.86–2.09)		1.12 (0.71–1.76)	
	≥3.57	1.82 (1.18–2.80)		1.31 (0.83–2.07)	
Factor VIII, %	<144	1.0	0.0006	1.0	0.01
	144–182	1.04 (0.65–1.65)		0.90 (0.56–1.45)	
	≥183	2.09 (1.37–3.18)		1.77 (1.14–2.76)	
von Willebrand factor, %	<123	1.0	<0.0001	1.0	0.005
	123–170	1.70 (1.07–2.71)		1.50 (0.93–2.43)	
	≥171	2.40 (1.53–3.75)		1.95 (1.23–3.10)	
WBC count, $\times 10^9$ cells/L	<5.20	1.0	<0.0001	1.0	0.002
	5.20–6.70	1.83 (1.15–2.92)		1.66 (1.02–2.69)	
	≥6.80	2.57 (1.65–4.00)		2.13 (1.33–3.41)	
Albumin, g/L	<0.036	1.0	0.0003	1.0	<0.0001
	0.036–0.038	0.58 (0.38–0.87)		0.49 (0.32–0.75)	
	≥0.039	0.46 (0.30–0.70)		0.33 (0.26–0.62)	

*The following variables had no association with incident CVD in the regression analysis and are not shown: HDL_2 and HDL_3 cholesterol, apolipoprotein A-I and B, magnesium, antithrombin III, protein C, and factor VII.
†Each variable was examined separately and adjusted for age, ARIC field center, sex, BMI, total cholesterol, HDL cholesterol, triglycerides, cigarette smoking, alcohol drinking, hypertension, physical activity, and diabetes treatment status.

DISCUSSION

This study, not unexpectedly, showed that total cholesterol, cigarette smoking, and hypertension were independently and positively associated with incident CVD in African Americans with diabetes. These traditional CVD risk factor associations are similar to those reported both in the total African American sample of ARIC[35] and in non-minority populations with diabetes.[1,8,15,36,37] They clearly emphasize the importance of traditional risk factors in the etiology and prevention of CVD in people with diabetes.

There is a belief that some unexplained effect of diabetes, or some non-conventional risk factors, also contribute to the excess CVD risk seen in people with diabetes.[8] This might include hyperglycemia by enhancing formation of advanced glycosylation products, an increased inflammatory response, hypercoagulability, or impaired fibrinolysis. We examined several markers of these processes and we found that serum creatinine, white blood cell count, factor VIII, and von Willebrand factor were positive, and serum albumin negative—independent risk factors for CVD in African Americans with diabetes. In contrast, a number of other nontraditional risk factors that we ex-

amined (apolipoproteins A-1 and B, HDL subfractions, magnesium, fibrinogen, factor VII, protein C, antithrombin III, lipoprotein(a), and waist-to-hip ratio) were not associated independently with CVD.

The positive associations of von Willebrand factor, factor VIII, and white blood cell count with incident CVD could reflect an important role of hemostasis in CVD etiology for people with diabetes, as in the general population.[29] Mean levels of factor VIII and von Willebrand factor have been noted to be higher in African Americans compared with whites, and in people with diabetes versus those without diabetes.[38] There is a high correlation between von Willebrand factor and factor VIII ($r = 0.73$)[38] because factor VIII is bound to von Willebrand factor in circulation. von Willebrand factor promotes platelet adhesion and aggregation, which may lead to thrombosis and eventual occlusion of cardiac or cerebral vessels. An elevated white blood cell count may mediate vascular injury or may increase the likelihood of thrombosis following an endothelial cell injury through rheological means.[39,40]

Recent evidence implicates vascular inflammation in the etiology of CVD.[41] Factor VIII, von Willebrand factor and white blood cell count may rise, and serum albumin may fall in the presence of inflammation. Thus, the association of these nontraditional risk factors with CVD may be reflective of the inflammatory component and endothelial dysfunction accompanying atherosclerosis. Prior studies have reported that elevated fibrinogen level, another inflammatory/hemostasis marker, is an independent CVD risk factor in people with diabetes.[13,14] We found in these African Americans with diabetes that fibrinogen was not a CVD risk factor after adjustment for diabetes treatment status, smoking status and other traditional risk factors.

The independent association of incident CVD with reduced serum albumin level, elevated serum creatinine, and hypertension may suggest the coexistence and poor prognosis of diabetic nephropathy, which is common in African Americans with diabetes. Microalbuminuria, which we did not measure, also has been associated with increased risk of coronary heart disease in people with diabetes.[42,43]

It was somewhat of a surprise that elevated triglycerides and low HDL cholesterol were not associated with the incidence of CVD in this cohort. In the full ARIC diabetic cohort, which included whites, there was a strong, negative, and significant association between HDL cholesterol and incident coronary heart disease.[11] African Americans have relatively higher HDL cholesterol levels than whites. Perhaps due to the limited sample size there was insufficient statistical power to detect an independent association.

Current epidemiological data suggest intensive insulin therapy may reduce CVD risk in diabetes.[44,45] Therefore, the greater incidence of CVD associated with insulin use in this study is probably because many of the diabetic participants using insulin have more severe diabetes, or they may have poorly controlled diabetes.

The age-adjusted incidence rates for CHD were lower and stroke rates were higher for African Americans with diabetes compared to white participants with diabetes. This is consistent with some previous studies of people with diabetes,[46,47] as well as those without diabetes. Previous studies also have reported the existence of similar risk factors for coronary heart disease and cardiovascular disease mortality in African Americans and whites with diabetes.[48–50] Our interaction testing likewise showed no obvious difference in risk factors for CVD in African Americans with diabetes versus whites with diabetes.

Among the strengths of the ARIC study are its abundant data on less-established CVD risk factors and detailed ascertainment of incident CVD events. While the number of African American participants, most of whom were from one field center, was relatively small, the African American cohort in ARIC is one of the largest population-based cohorts of this ethnic group ever assembled. As is appropriate for a

longitudinal study of incident CVD, participants with baseline history of CVD were excluded. A significant proportion of those excluded had diabetes, so results might have differed if a younger cohort had been studied.

The ARIC study assessed C-reactive protein, homocysteine,[50] and fibrinolytic factors, such as plasminogen activator inhibitor-1, [10] only on a small portion of the ARIC cohort; these, as well as glycosylated hemoglobin and microalbuminuria, could not be examined here. Furthermore, we could not adjust for the duration of diabetes in the analyses, because age of onset of diabetes was not available on half of subjects.

In summary, the established risk factors, total cholesterol, hypertension and cigarette smoking, were independently associated with incident CVD events in African Americans with diabetes. In addition, markers of hemostasis or inflammation (low albumin, increased von Willebrand factor, factor VIII and WBC count) or renal impairment (increased creatinine, low albumin) were independently associated with the incidence of CVD. The latter risk factors may reflect an underlying nonspecific inflammatory response to diabetes or to endothelial dysfunction and hemostatic abnormalities that are related to atherosclerosis.

The major implication of this and related studies is the need for an integrated and aggressive treatment of traditional risk factors in people with diabetes, especially African Americans.[1] In fact, the National Cholesterol Education Program now recommends that people with diabetes be managed as if they had CHD.[51] A risk reduction strategy matched to the individual diabetic patient's risk factor is imperative. Any or full armamentarium of interventions—antihypertensives, ACE inhibitors, statins and fibrates, smoking cessation, weight loss, aggressive glycemic control, and the use of aspirin[52] may be beneficial. The implementation of additional clinical intervention studies may help to further establish whether modification of risk factors can reduce the excess risk of CVD in people with diabetes.

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REFERENCES

1. Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation.* 1999;100:1134–1146.

2. Krolewski AS, Czyzyk A, Janeczko D, Kopczynski J. Mortality from cardiovascular diseases among diabetics. *Diabetologia.* 1977;13:345–350.

3. Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham Study. *Diabetes Care.* 1979;2:120–126.

4. Moss SE, Klein R, Klein BE. Cause-specific mortality in a population-based study of diabetes. *Am J Public Health.* 1991;81: 1158–1162.

5. 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.* 1997;20:935–942.

6. Gillum RF. Risk factors for stroke in blacks: A critical review. *Am J Epidemiol.* 1999;150:1266–1274.

7. Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. *JAMA.* 2001;286:1195–1200.

8. Getz GS. Report on the workshop on diabetes and mechanisms of atherogenesis. September 17th and 18th, 1992, Bethesda, MD. *Arterioscler Thromb.* 1993;13:459–464.

9. Standl E, Balletshofer B, Dahl B, et al. Predictors of 10-year macrovascular and overall mortality in patients with NIDDM: the Munich General Practitioner Project. *Diabetologia.* 1996;39:1540–1545.

10. Juhan-Vague I, Alessi MC, Vague P. Thrombogenic and fibrinolytic factors and cardiovascular risk in non-insulin-dependent diabetes mellitus. *Ann Med.* 1996;28:371–380.

11. Saito I, Folsom AR, Brancati FL, Duncan BB, Chambless LE, McGovern PG. Nontraditional risk factors for coronary disease incidence among persons with diabetes: The Atherosclerosis Risk in Communities (ARIC) Study. *Ann Intern Med.* 2000;133: 81–91.

12. Folsom AR, Ma J, Eckfeldt JH, Nieto FJ, Metcalf PA, Barnes RW. Low serum albumin: Association with diabetes mellitus and other cardiovascular risk factors but not with prevalent cardiovascular disease or carotid artery intima-media thickness. *Ann Epidemiol.* 1995;5:186–191.

13. Kannel WB, D'Agostino RB, Wilson PW, Belanger AJ, Gagnon DR. Diabetes, fibrinogen, and risk of cardiovascular disease: the Framingham experience. *Am Heart J.* 1990;120:672–676.

14. Missov RM, Stolk RP, van der Bom JG, et al. Plasma

fibrinogen in NIDDM: the Rotterdam study. *Diabetes Care.* 1996; 19:157–159.

15. Fuller JH, Stevens LK, Wang SL. Risk factors for cardiovascular mortality and morbidity: The WHO multinational study of vascular disease in diabetes. *Diabetologia.* 2001;44(Suppl 2): S54–S64.

16. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol.* 1989;129:687–702.

17. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr.* 1982;36:936–942.

18. Gindler EM, Heth DA. Colorimetric determination with bound "Calmagite" of magnesium in human blood serum [Abstract]. *Clin Chem.* 1971;17:662.

19. Doumas BT, Watson WA, Biggs HG. Albumin standards and the measurement of serum albumin with bromocresol green. *Clin Chim Acta.* 1971;31:87–96.

20. Eckfeldt JH, Chambless LE, Shen YL. Short-term, within-person variability in clinical chemistry test results. Experience from the Atherosclerosis Risk in Communities Study. *Arch Pathol Lab Med.* 1994;118:496–500.

21. Siedel J, Hagele EO, Ziegenhorn J, Wahlefeld AW. Reagent for the enzymatic determination of serum total cholesterol with improved lipolytic efficiency. *Clin Chem.* 1983;29:1075–1080.

22. Nagele U, Hagele EO, Sauer G, et al. Reagent for the enzymatic determination of serum total trigylcerides with improved lipolytic efficiency. *J Clin Chem Clin Biochem.* 1984;22:165–174.

23. Warnick GR, Benderson JM, Albers JJ. Quantitation of high-density lipoprotein subclasses after separation by dextran sulfate and Mg^{2+} precipitation [abstract]. *Clin Chem.* 1982;28: 1574.

24. Patsch W, Brown SA, Morrisett JD, Gotto AM Jr, Patsch JR. A dual-precipitation method evaluated for measurement of cholesterol in high-density lipoprotein subfractions HDL2 and HDL3 in human plasma. *Clin Chem.* 1989;35:265–270.

25. Schonfeld G, Pfleger B. The structure of human high-density lipoprotein and the levels of apolipoproteins A-I in plasma as determined by radioimmunoassay. *J Clin Invest.* 1974; 54:236–246.

26. Maciejko JJ, Mao SJ. Radioimmunoassay of alipoprotein A-I. Application of a non-ionic detergent (Tween-20) and solid-phase staphylococcus. *Clin Chem.* 1982;28:199–204.

27. Schonfeld G, Lees RS, George PK, Pfleger B. Assay of total plasma apolipoprotein B concentration in human subjects. *J Clin Invest.* 1974;53:1458–1467.

28. Gaubatz JW, Ghanem KI, Guevara J Jr, Nava ML, Patsch W, Morrisett JD. Polymorphic forms of human apolipoprotein(a): inheritance and relationship of their molecular weights to plasma levels of lipoprotein(a). *J Lipids Res.* 1990;31:603–613.

29. Folsom AR, Wu KK, Rosamond WD, Sharrett AR, Chambless LE. Prospective study of hemostatic factors and incidence of coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation.* 1997;96:1102–1108.

30. Anonymous. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care.* 1997;20:1183–1197.

31. Prineas RJ, Crow RS, Blackburn H. The Minnesota Code Manual of Electrocardiographic Findings: Standard and Procedures for Measurement and Classification. Littleton, Mass: John Wright; 1982.

32. White AD, Folsom AR, Chambless LE, et al. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) study: methods and initial two years' experience. *J Clin Epidemiol.* 1996;49:223–233.

33. Rosamond WD, Folsom AR, Chambless LE, et al. Stroke incidence and survival among middle-aged adults: nine-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke.*1999;30:736–743.

34. Rautaharju PM, Warren JW, Jain U, Wolf HK, Nielsen CL. Cardiac infarction injury score: an electrocardiograghic coding scheme for ischemic heart disease. *Circulation.* 1981;64:249–256.

35. Jones DW, Chambless LE, Folsom AR, et al. Risk factors for coronary heart disease in African-Americans: The Atherosclerosis Risk in Communities study, 1987–1997. *Arch Intern Med.* 2002; in press.

36. Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study. *BMJ.* 1998; 316:823–828.

37. 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.* 1993:16;434–444.

38. Conlan MG, Folsom AR, Finch A, et al. Associations of factor VIII and von Willebrand factor with age, race, sex, and risk factors for atherosclerosis. The Atherosclerosis Risk in Communities (ARIC) study. *Thromb Haemost.* 1993;70:380–385.

39. Morigi M, Angioletti S, Imberti B, et al. Leukocyte-endothelial interaction is augmented by high glucose concentrations and hyperglycemia in a NF-kB-dependent fashion. *J Clin Invest.* 1998;101:1905–1915.

40. Ernst E, Hammerschmidt DE, Bagge U, Matrai A, Dormandy JA. Leukocytes and the risk of ischemic diseases. *JAMA.* 1987;257:2318–2324.

41. Kinlay S, Selwyn AP, Libby P, Ganz P. Inflammation, the endothelium, and the acute coronary syndromes. *J Cardiovasc Pharmacol.* 1998;32[suppl 3]:S62–S66.

42. Stehouwer CD, Nauta JJ, Zeldenrust GC, Hackeng WH, Donker AJ, den Ottolander GJ. Urinary albumin excretion, cardiovascular disease, and endothelial dysfunction in non-insulin-dependent diabetes mellitus. *Lancet.* 1992;340:319–323.

43. Mattock MB, Barnes DJ, Viberti G, et al. Microalbuminuria and coronary heart disease in NIDDM: an incident study. *Diabetes.* 1998;47:1786–1792.

44. Turner RC, Holman RR, Cull CA, et al. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352:837–853.

45. Malmberg K. Prospective randomised study of intensive insulin treatment on longterm survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) study group. *BMJ.* 1997;314:1512–1515.

46. Harris MI. Noninsulin-dependent diabetes mellitus in black and white Americans. *Diabetes Metab Rev.* 1990;6:71–90.

47. DeStefano F, Newman J. Comparison of coronary heart

disease mortality risk between black and white people with diabetes. *Ethnicity Dis.* 1993;3:145–151.

48. Geiss LS, Herman WH, Smith PJ. Mortality in non-insulin-dependent diabetes. In: National Diabetes Data Group, ed. Diabetes in America. Bethesda, MD: US Dept. of Health and Human Services, Public Health Service, National Institutes of Health:1995:233–257.

49. Tull ES, Roseman JM. Diabetes in African Americans. In: National Diabetes Data Group, ed. Diabetes in America. Bethesda, MD: US Dept of Health and Human Services, Public Health Service, National Institutes of Health;1995:613–630.

50. Stehouwer CD, Gall MA, Hougaard P, Jakobs C, Parving HH. Plasma homocysteine concentration predicts mortality in non-insulin-dependent diabetic patients with and without albuminuria. *Kidney Int.* 1999;55:308–314.

51. 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.* 2001;285:2486–2497.

52. Colwell JA. Aspirin therapy in diabetes. *Diabetes Care.* 1997;20:1767–1771.

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