No Racial Differences in the Association of Glycated Hemoglobin With Kidney Disease and Cardiovascular Outcomes

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OBJECTIVE—There is debate regarding the clinical significance of well-established racial differences in HbA1c. We compared the associations of diabetes diagnostic categories for HbA1c and fasting glucose with clinical outcomes in black and white persons in the community.

RESEARCH DESIGN AND METHODS—We conducted a prospective cohort analysis of participants without diabetes or cardiovascular disease from the Atherosclerosis Risk in Communities study. We examined the associations of clinical categories of HbA1c (<5.7%, 5.7–6.4%, ≥6.5%) and fasting glucose (<100, 100–125, ≥126 mg/dL) with outcomes separately among 2,484 black and 8,593 white participants and tested for race interactions.

RESULTS—Baseline characteristics differed significantly in blacks compared with whites, including HbA1c (5.8 vs. 5.4%; P < 0.001). During 18 years of follow-up, there were trends of increased risk of kidney disease, fatal and nonfatal coronary heart disease, and stroke across categories of HbA1c in both blacks and whites. The adjusted hazard ratios for each outcome across categories of HbA1c were similar in blacks and whites (P for interaction >0.05) except for all-cause mortality. Patterns of association were similar, but weaker, for fasting glucose. HbA1c and fasting glucose both were more strongly associated with all-cause mortality in whites compared with blacks, largely explained by racial differences in the rate of cardiovascular deaths.

CONCLUSIONS—HbA1c is a risk factor for vascular outcomes and mortality in both black and white adults. Patterns of association for HbA1c were similar to or stronger than those for fasting glucose. With respect to long-term outcomes, our findings support a similar interpretation of HbA1c in blacks and whites for diagnosis and treatment of diabetes mellitus.

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In a major change to clinical guidelines, the American Diabetes Association and the World Health Organization now recommend the use of hemoglobin A1c (HbA1c) for the diagnosis of diabetes (1,2). This recommendation has sparked debate regarding the strengths and weaknesses of HbA1c as a diagnostic test, particularly related to possible nonglycemic determinants of HbA1c values (3–6). A major element of this controversy has been the well-documented higher values of HbA1c in blacks compared with whites (7–10); this racial difference has not been consistently observed for fasting glucose (7). Studies demonstrating higher HbA1c values in ethnic minority populations as compared with whites have led to questions regarding the use and interpretation of HbA1c in racial minorities (3–5,10–17). Some investigators have proposed that systematically higher HbA1c values in blacks compared with whites stem from racial differences not in glucose exposure but in the propensity of hemoglobin to undergo glycation (8,9,14,15,17–19). If so, then HbA1c should be a weaker predictor of diabetic complications in blacks as compared with whites, especially relative to the prognostic value of fasting glucose. If HbA1c does not perform similarly as a marker of long-term risk in persons of different ancestry, then this could have major implications for the diagnosis and management of diabetes (18). The objective of this study was to compare the associations of diabetes diagnostic categories of HbA1c and fasting glucose with long-term clinical outcomes and to determine if risk associations differ between black and white persons in the community.

RESEARCH DESIGN AND METHODS

Study population
We analyzed data from the Atherosclerosis Risk in Communities (ARIC) study, a community-based prospective cohort study of 15,792 middle-aged adults from four U.S. communities: Jackson, Mississippi; Forsyth County, North Carolina; suburban Minneapolis, Minnesota; and Washington County, Maryland. The first examination of participants (visit 1) occurred in 1987–1989, with three follow-up visits occurring ∼3 years apart. A fourth visit is ongoing (2011–2013). The majority of black participants in the ARIC study were recruited at the Jackson field center, which exclusively enrolled blacks (N = 3,728). Some black participants also were enrolled at the Forsyth County field center (N = 483). A few black participants were enrolled at the Minneapolis (N = 22) and Washington County (N = 33) field centers.

Visit 2, which took place from 1990 to 1992 and was attended by 14,348 participants, was the baseline for the current study. We excluded participants who were not black or white; who had a history of

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diagnosed diabetes (as recorded at either visit 2 or visit 1); who had a history of coronary heart disease, stroke, or congestive heart failure; who were fasting <8 h; or who were missing information on covariates of interest. After exclusions, the study sample size was 11,077. For analysis of incident kidney disease, we further excluded participants with estimated glomerular filtration rate (GFR) <60 ml/min/1.73 m² at baseline. Thus, all analyses of incident kidney disease had a sample size of 10,800.

Measurement of glucose and HbA1c
Serum glucose was measured as part of the original ARIC protocol using a hexokinase method on a Coulter DACOS (Coulter Instruments). We measured HbA1c from stored whole blood samples from all participants at ARIC visit 2 using high-performance liquid chromatography (Tosoh HbA1c 2.2 and Tosoh G7; Tosoh) (20). All values were standardized to the Diabetes Control and Complications Trial HbA1c assay.

Outcomes
For all analyses, we used standard outcome definitions in the ARIC study. Data for validated cardiovascular events were ascertained via active community-wide surveillance of hospitalizations and deaths with follow-up to 1 January 2010 (21,22). We examined adjudicated incident cases of definite or probable myocardial infarction, any definite or probable stroke, and definite or probable ischemic stroke. Congestive heart failure cases were identified from death certificates or first heart failure hospitalization with ICD-9/10 codes 428 or 150 in any position on the discharge list. Incident chronic kidney disease was defined as GFR <60 ml/min/1.73 m² estimated from serum creatinine measured at visit 4 (1996–1998) using the Chronic Kidney Disease Epidemiology Collaboration equation (23) or a kidney disease–related hospitalization or death identified during active surveillance (24). End-stage renal disease comprised the subset of hospitalizations indicating kidney transplant or dialysis (25).

Covariates
Methods for measurement of plasma lipids (26), BMI (kg/m²), waist-to-hip ratio (27), and blood pressure (28) are described elsewhere. Hypertension was defined using the mean of two blood pressure readings at the visit with cut-points of systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or hypertension medication use. Participants self-reported education level (less than high school, high school or equivalent, college or education beyond college). Smoking and alcohol drinking status were both categorized as current, former, or never. Physical activity was assessed using the Baecke questionnaire from ARIC visit 1 (29).

Institutional Review Boards at each clinical site approved the study, and written informed consent was obtained from all participants.

Statistical analyses
Baseline characteristics of the study population are shown by black or white race/ethnicity overall and by categories of HbA1c at baseline. We conducted race-stratified analyses of each clinical outcome by clinical categories of HbA1c (<5.7%, 5.7–6.4%, ≥6.5%) and fasting glucose (<100, 100–125, ≥126 mg/dl) at baseline (30). For analysis of incident

| Table 1—Baseline characteristics of the study population of persons without history of cardiovascular disease or diagnosed diabetes according to race and clinical categories of HbA1c in the ARIC study, 1990–1992 |
|---------------------------------------------------------------|
| **HbA1c, %, mean (SD)** | **<5.7%** | **5.7 to <6.5%** | **≥6.5%** | **Overall** |
| **Race** |
| White (N = 7,126) | Black (N = 1,338) | White (N = 1,238) | Black (N = 896) | White (N = 2,250) | Black (N = 2,484) |
| Fasting glucose, mg/dL, mean (SD) | 5.28 (0.27) | 5.35 (0.31) | 5.96 (0.17) | 6.02 (0.18) | 7.34 (1.23) | 7.40 (1.53) | 5.4 (0.5) | 5.8 (0.8) |
| BMI, kg/m², mean (SD) | 100.6 (9.6) | 101.4 (10.7) | 109.0 (13.7) | 115.8 (14.2) | 149.3 (54.9) | 153.6 (55.0) | 103.9 (16.0) | 108.9 (25.0) |
| Age, years, mean (SD) | 56.6 (5.6) | 55.1 (5.7) | 56.7 (5.7) | 56.7 (5.7) | 56.8 (5.7) | 56.8 (5.7) | 55.2 (5.6) | 55.2 (5.6) |
| LDL cholesterol, mg/dL, mean (SD)* | 131.2 (35.4) | 129.6 (37.1) | 139.5 (40.6) | 137.7 (40.6) | 142.7 (38.3) | 142.3 (38.3) | 132.8 (35.6) | 133.8 (38.8) |
| HDL cholesterol, mg/dL, mean (SD) | 51.1 (16.8) | 57.2 (17.9) | 44.5 (13.7) | 51.6 (15.4) | 49.1 (10.8) | 48.3 (14.3) | 49.9 (16.5) | 54.3 (17.0) |
| Triglycerides, mg/dL, mean (SD) | 126.6 (63.2) | 95.5 (45.6) | 147.3 (65.4) | 112.4 (53.4) | 184.7 (76.4) | 125.4 (55.9) | 131.1 (64.9) | 104.6 (51.0) |
| BMI, kg/m², mean (SD) | 26.6 (4.5) | 28.7 (5.8) | 28.5 (5.3) | 30.5 (6.4) | 31.5 (5.7) | 33.4 (6.6) | 27.0 (4.8) | 29.8 (6.3) |
| Waist-to-hip ratio, mean (SD) | 0.91 (0.1) | 0.89 (0.1) | 0.90 (0.1) | 0.92 (0.1) | 0.97 (0.1) | 0.94 (0.1) | 0.92 (0.1) | 0.91 (0.1) |

*Means and proportions for all variables were significantly different (P < 0.05) when comparing blacks and whites, except for LDL cholesterol levels.
kidney disease, we compared definitions using estimated GFR alone and in combination with kidney disease–related hospitalizations and deaths. Because our results were similar across different definitions of incident kidney disease, main analyses are presented using an established combined definition of estimated GFR <60 mL/min/1.73 m² or kidney-related hospitalization or death occurring during follow-up (24). We also compared the relative associations of categories of HbA1c and fasting glucose by race/ethnicity for each of the clinical outcomes using Cox proportional hazards models with adjustment for possible confounding factors. All Cox proportional hazards models were adjusted for age, sex, LDL cholesterol levels, HDL cholesterol levels, log-transformed triglyceride level, BMI, waist-to-hip ratio, hypertension (yes or no), family history of diabetes (yes or no), education (less than high school, high school or equivalent, or college or education beyond college), alcohol use (current, former, never), physical activity index, and smoking status (current, former, never). We used the likelihood ratio test to formally test for interactions (effect modification) between race and HbA1c or fasting glucose categories in the adjusted Cox proportional hazards models. Competing risks analyses were conducted using the Fine and Gray method (31). To visually display our results using a forest-style plot, we plotted the relative hazard ratio (HR) for blacks compared with whites for each of the outcomes with HbA1c or fasting glucose modeled continuously (per 1 SD). All analyses were conducted using Stata/SE version 12.1 (Stata).

### Table 2—Adjusted* HRs (95% CI) for clinical outcomes in persons without a history of cardiovascular disease or diagnosed diabetes according to clinical categories of HbA1c and stratified by race/ethnicity

| HbA1c category | Chronic kidney disease† (N = 816) | Myocardial infarction or coronary heart disease (fatal or nonfatal) (N = 882) | Fatal coronary heart disease (N = 210) | Any stroke (N = 565) | Ischemic stroke (N = 487) | Congestive heart failure (N = 1,113) | All-cause mortality (N = 2,277) |
|----------------|----------------------------------|--------------------------------------------------------------------------|----------------------------------------|----------------------|------------------------|-------------------------------------|--------------------------------|
| White          | 1.0 (ref)                        | 1.0 (ref)                                                                | 1.0 (ref)                              | 1.0 (ref)           | 1.0 (ref)              | 1.0 (ref)                           | 1.0 (ref)                       |
| Black          | 1.0 (ref)                        | 1.05 (0.78–1.41)                                                        | 1.31 (0.86–2.01)                      | 1.42 (1.02–1.97)    | 1.38 (0.97–1.96)       | 1.11 (0.86–1.43)                   | 1.11 (0.93–1.33)               |
| 5.7 to <6.5%   | 1.34 (1.10–1.64)                 | 1.65 (1.38–1.98)                                                        | 1.41 (0.97–2.06)                      | 1.58 (1.23–2.03)    | 1.50 (1.14–1.97)       | 1.42 (1.20–1.68)                   | 1.49 (1.33–1.68)               |
| ≥6.5%          | 1.82 (1.29–2.56)                 | 1.91 (1.27–2.86)                                                        | 1.99 (0.94–4.22)                      | 2.16 (1.38–3.37)    | 2.13 (1.34–3.41)       | 1.83 (1.36–2.46)                   | 1.74 (1.38–2.18)               |
| P for trend    | <0.001                           | 0.199                                                                   | <0.001                                 | <0.001              | <0.001                 | 0.047                               | <0.001                         |

*Adjusted for age, sex, LDL cholesterol (mg/dL), HDL cholesterol (mg/dL), log-transformed triglycerides (mg/dL), BMI (kg/m²), waist-to-hip ratio, hypertension (yes or no), family history of diabetes (yes or no), education (less than high school, high school or equivalent, or college or education beyond), alcohol use (current, former, never), physical activity index, and smoking status (current, former, never). Analytic population for analyses of chronic kidney disease also excludes persons with estimated GFR <60 mL/min/1.73 m² at baseline (N = 10,800).

**RESULTS**—In this study population of persons without a history of diabetes or cardiovascular disease, we observed significant differences in baseline risk factors between blacks and whites (Table 1). With the exception of LDL cholesterol levels, all risk factors were statistically significantly different by race. As has been previously established in the ARIC study and in many other cohorts, HbA1c levels were significantly higher in blacks compared with whites (5.8 vs. 5.4; P < 0.001) (32). Mean fasting glucose was 104 mg/dL in whites and 109 mg/dL in blacks (P < 0.001). The Pearson (Spearman) correlations between HbA1c and fasting glucose were 0.79 (0.49) in blacks and 0.67 (0.41) in whites. Compared with whites, blacks had higher mean BMI and mean HDL cholesterol and higher prevalence of hypertension, current smoking,
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less than a high school education, and family history of diabetes. Blacks had a lower mean age, activity level index, and triglyceride level, and a lower prevalence of current drinking compared with white participants. These racial differences persisted even within clinical categories of HbA1c at baseline.

During ~18 years of follow-up, there were 882 incident myocardial infarctions and fatal coronary heart disease events combined (223 in blacks), 565 fatal or nonfatal strokes of any kind (167 in blacks), and 2,277 deaths from any cause (589 in blacks). In the 10,800 participants with normal kidney function at baseline, there were 816 cases of incident kidney disease (216 in blacks), including 85 cases of end-stage renal disease (39 in blacks).

We observed similar patterns of association with outcomes comparing diagnostic categories of HbA1c with fasting glucose, with little differences in risk of clinical outcomes by race group (Tables 2 and 3). The adjusted HRs for HbA1c categories were similar across race/ethnicity for all outcomes (P for interactions >0.10) with the exception of all-cause mortality (P for interaction = 0.008). Whites with baseline HbA1c ≥6.5% were at higher risk for all-cause mortality (HR, 1.74; 95% CI, 1.38–2.18) compared with blacks with HbA1c ≥6.5% (HR, 1.31; 95% CI, 1.05–1.68). The black–white difference in the association with all-cause mortality also was present when we compared clinical categories of fasting glucose (Table 3) (P for interaction = 0.018). Whites with fasting glucose ≥126 mg/dL had a significant increase in risk of all-cause mortality (HR, 1.62; 95% CI, 1.34–1.96), whereas there was no increase in risk among blacks with elevated fasting glucose (HR, 1.00; 95% CI, 0.74–1.35).

Because previous studies have shown a higher rate of nonvascular deaths in blacks compared with whites (33), we conducted a competing risks analysis to isolate the effect of hyperglycemia on nonvascular death (death in the absence of incident cardiovascular disease defined by coronary heart disease, stroke, or heart failure). After accounting for these outcomes as competing risks in the association of HbA1c or fasting glucose with mortality, there was no interaction with race (P for interaction = 0.225 and 0.193, respectively). The adjusted HRs

Table 3—Adjusted* HRs (95% CI) for clinical outcomes in persons without a history of cardiovascular disease or diagnosed diabetes according to clinical categories of fasting glucose and stratified by race/ethnicity

| Chronic kidney disease† (N = 816) | <100 mg/dL | 100 to <126 mg/dL | ≥126 mg/dL | P for trend |
|-----------------------------------|------------|-----------------|-----------|-----------|
| White                             | 1.0 (ref)  | 1.08 (0.90–1.29) | 1.41 (1.03–1.94) | 0.051     |
| Black                             | 1.0 (ref)  | 1.04 (0.76–1.43) | 1.16 (0.73–1.83) | 0.782     |
| P for interaction = 0.8574        |            |                 |            |           |
| Myocardial infarction or coronary heart disease (fatal or nonfatal) (N = 882) | <100 mg/dL | 100 to <126 mg/dL | ≥126 mg/dL | P for trend |
| White                             | 1.0 (ref)  | 1.16 (0.98–1.38) | 1.26 (0.92–1.74) | 0.108     |
| Black                             | 1.0 (ref)  | 0.93 (0.68–1.27) | 1.20 (0.77–1.88) | 0.394     |
| P for interaction = 0.4678        |            |                 |            |           |
| Fatal coronary heart disease (N = 210) | <100 mg/dL | 100 to <126 mg/dL | ≥126 mg/dL | P for trend |
| White                             | 1.0 (ref)  | 0.97 (0.66–1.41) | 1.68 (0.91–3.10) | 0.116     |
| Black                             | 1.0 (ref)  | 0.73 (0.43–1.22) | 0.95 (0.43–2.09) | 0.876     |
| P for interaction = 0.6040        |            |                 |            |           |
| Any stroke (N = 565)               | <100 mg/dL | 100 to <126 mg/dL | ≥126 mg/dL | P for trend |
| White                             | 1.0 (ref)  | 0.86 (0.69–1.08) | 1.67 (1.14–2.43) | 0.025     |
| Black                             | 1.0 (ref)  | 0.94 (0.67–1.31) | 1.71 (1.09–2.69) | 0.016     |
| P for interaction = 0.9061        |            |                 |            |           |
| Ischemic stroke (N = 487)          | <100 mg/dL | 100 to <126 mg/dL | ≥126 mg/dL | P for trend |
| White                             | 1.0 (ref)  | 0.89 (0.69–1.13) | 1.68 (1.13–2.51) | 0.025     |
| Black                             | 1.0 (ref)  | 0.98 (0.68–1.42) | 1.82 (1.12–2.96) | 0.011     |
| P for interaction = 0.8844        |            |                 |            |           |
| Congestive heart failure (N = 1,113) | <100 mg/dL | 100 to <126 mg/dL | ≥126 mg/dL | P for trend |
| White                             | 1.0 (ref)  | 1.02 (0.88–1.19) | 1.28 (0.98–1.69) | 0.086     |
| Black                             | 1.0 (ref)  | 0.87 (0.67–1.13) | 0.89 (0.60–1.32) | 0.564     |
| P for interaction = 0.3324        |            |                 |            |           |
| All-cause mortality (N = 2,277)    | <100 mg/dL | 100 to <126 mg/dL | ≥126 mg/dL | P for trend |
| White                             | 1.0 (ref)  | 1.09 (0.98–1.22) | 1.62 (1.34–1.96) | <0.001    |
| Black                             | 1.0 (ref)  | 0.98 (0.81–1.18) | 0.99 (0.73–1.34) | 0.941     |

*Adjusted for age, sex, LDL cholesterol (mg/dL), HDL cholesterol (mg/dL), log-transformed triglycerides (mg/dL), BMI (kg/m²), waist-to-hip ratio, hypertension (yes or no), family history of diabetes (yes or no), education (less than high school, high school or equivalent, or college or beyond), alcohol use (current, former, never), physical activity index, and smoking status (current, former, never).†Analytic population for analyses of chronic kidney disease also excludes persons with estimated GFR <60 mL/min/1.73 m² at baseline (N = 10,800).
for categories of baseline fasting glucose with the other clinical outcomes were similar in blacks compared with whites (P for interaction >0.30). Importantly, the associations with clinical outcomes were generally stronger for HbA1c compared with fasting glucose, regardless of race.

Our results were similar (there was no strong evidence for effect modification by race) when HbA1c and fasting glucose were modeled continuously (Fig. 1), and results for incident kidney disease were similar across different case definitions (Supplementary Fig. 1). The similar patterns of risk associations in blacks and whites for HbA1c and fasting glucose diagnostic categories also can be seen in Supplementary Fig. 2, which shows the relative HRs (interaction) of blacks compared with whites for undiagnosed diabetes defined by HbA1c (≥26.5 vs. <5.7%) or fasting glucose (≥100 mg/dL vs. <100 mg/dL) for each clinical outcome.

**CONCLUSIONS**—Recent reviews and editorials have speculated that racial differences in absolute values of HbA1c are an artifact and will lead to overdiagnosis of diabetes in blacks (5,11,12). Some have called into question whether HbA1c should be used for diagnosis of diabetes in blacks (12,17), and recent reviews have cited racial differences in HbA1c, as a “disadvantage” of HbA1c for diagnosis of diabetes (34–36). We found that HbA1c is a predictor of chronic kidney disease and vascular outcomes in black and white middle-aged adults in this community-based sample. We observed significant trends in risk of coronary heart disease, total stroke, and ischemic stroke across categories of HbA1c among blacks and whites. These data do not support the contention that HbA1c is a weaker predictor of outcomes compared with fasting glucose in blacks compared with whites. We previously have shown in the ARIC cohort that HbA1c is similarly associated with risk of diabetes and is more strongly associated with cardiovascular disease and mortality as compared with fasting glucose (32). The detailed analysis with updated follow-up presented here examined 2010 American Diabetes Association clinical categories of HbA1c (30,37) and focused on possible racial differences across multiple vascular outcomes and all-cause mortality. This study contributes information to the debate regarding the interpretation of HbA1c in clinical practice and implies that calls for race-specific HbA1c cut-points for diagnosis of diabetes do not reflect long-term risk associations.

Our findings support a similar interpretation of HbA1c test results in blacks and whites for diagnosis and treatment of diabetes mellitus. We hope these data will alleviate concerns regarding the use of HbA1c in blacks. As evidenced by the baseline characteristics of this study population, the majority of diabetes and cardiovascular risk factors differ substantially by race/ethnicity. It has been proposed that nonglycemic determinants of HbA1c such as erythrocyte turnover, hemoglobin characteristics, and glycation rate may differ across race groups. Nonetheless, the primary determinant of elevated HbA1c is circulating glucose (38,39). It is likely that nonglycemic factors are relatively more important at very low HbA1c levels (40,41). Our results suggest that at prediabetic and diabetic levels of HbA1c, there are no racial differences in their association with long-term risk of kidney and cardiovascular outcomes.

We observed an attenuated association between HbA1c categories and all-cause mortality in blacks compared with whites and no association between fasting glucose and mortality in blacks. We also observed similar attenuation and no association of fasting glucose categories with heart failure in blacks, although the interactions terms were not statistically significant. We found that these results may be explained by differences in rates of vascular causes of death in blacks and whites (33). The overall weaker association of elevated fasting glucose with outcomes in both blacks and whites may partially reflect the higher variability in fasting glucose compared with HbA1c (42). We previously have observed that at the same value of HbA1c at baseline, blacks are less likely than whites to receive a subsequent diagnosis of diabetes (32). This likely reflects racial differences in social, economic, and health care access factors that affect the likelihood of a diabetes diagnosis.

The results of the present analysis contradict the supposition that HbA1c differences in absolute values...
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values are artificially elevated in blacks and that such elevations are independent of the complex processes by which hyperglycemia leads to long-term complications. Our findings are reassuring and suggest that the new diagnostic cut-points for HbA1c successfully stratify persons according to long-term risk, regardless of black or white race, and even after adjustment for known risk factors. Consistent with our findings, previous work also has shown that the associations of HbA1c with microvascular outcomes, including retinopathy, do not differ by race/ethnicity (43,44). In fact, blacks in the U.S. have a higher prevalence of retinopathy than whites in the U.S. at the same level of HbA1c (45), even among persons without a history of diagnosed diabetes (46).

Limitations of this study that should be considered in the interpretation of these results include the reliance on single measurements of HbA1c and fasting glucose at baseline. Furthermore, black participants were largely enrolled in the ARIC study at two of the field centers—Jackson, Mississippi, and Forsyth County, North Carolina. Thus, we cannot definitively separate the effects of race from those of geography. Nonetheless, the ARIC study represents one of the largest cohorts of blacks for the study of these outcomes. This study benefited from the long-term follow-up, rigorous measurement of known cardiovascular risk factors, and the comprehensive surveillance for and validation of cardiovascular events.

In conclusion, our data suggest that HbA1c is a more potent predictor of long-term outcomes than fasting glucose and that the associations with kidney disease and vascular outcomes are not significantly weaker in blacks compared with whites. These data support the use of HbA1c for diagnosis and management of diabetes in black and white adults.

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