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The Effect of Intensive Glucose Lowering Therapy Among Major Racial/Ethnic Groups in the Veterans Affairs Diabetes Trial☆,☆☆

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ABSTRACT

Objective. To examine the effect of intensive glycemic control on cardiovascular disease events (CVD) among the major race/ethnic groups in a post-hoc analysis of the VADT.

Materials and Methods. Participants included 1111 non-Hispanic Whites, 307 Hispanics and 306 non-Hispanic Blacks randomized to intensive or standard glucose treatment in VADT. Multivariable Cox proportional hazards models were constructed to assess the effect of intensive glucose treatment on CVD events among race/ethnic groups.

Results. Mean age was 60.4 years and median follow-up was 5.6 years. By design, modifiable risk factors were managed equally well in both treatment arms and only differed modestly between race/ethnic groups. HbA_{1c} decreased significantly from baseline with intensive glucose treatment in each race/ethnic group, with a trend for a greater response in Hispanics ($P = 0.02$ for overall comparison between groups). Intensive glucose treatment was associated with reduced risk of CVD events for Hispanics but not for others (hazard ratios ranged from 0.54 to 0.75 for Hispanics whereas they were consistently close to 1 for others). Sensitivity analyses with different definitions of race/ethnicity or limited to individuals free of previous known CVD yielded similar results.

Conclusions. The results of these analyses support the hypothesis that race/ethnicity is worthy of consideration when tailoring intensive treatment for individuals with long-standing type 2 diabetes. However, additional studies are needed to confirm the findings of this post-hoc analysis.

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1. Introduction

Recent large and well conducted randomized controlled trials demonstrated that intensive glycemic control does not reduce cardiovascular disease (CVD) events in people with type 2 diabetes of moderate to long duration [1–3]. However, subsequent analyses [4–8], together with results from an earlier trial conducted in new onset diabetes [9–11], have suggested that factors such as pre-existing macrovascular disease, duration of

Abbreviations: RCT, Randomized controlled trial; CVD, Cardiovascular disease; VADT, Veterans Affairs Diabetes Trial; UKPDS, The United Kingdom Prospective Diabetes Study; HbA_{1c}, HemoglobinA_{1c}; BMI, Body mass index; HDL, High density lipoprotein; SD, Standard deviation; HR, Hazard ratio; CI, Confidence interval.

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diabetes, level of glycemic control and significant comorbidities may influence whether intensive glucose control is appropriate for patients with diabetes [1,5–7,12–14]. Many of these factors reflect the stage of the diabetes and, in particular, the individual's vascular health. Baseline levels of atherosclerosis may therefore be an important determinant of response to tight glucose control. In an ancillary study of the Veterans Affairs Diabetes Trial (VADT), we have previously reported intensive glycemic control significantly reduced the primary CVD endpoints in those with lower burden of atherosclerosis at baseline [4]. In addition, using different measures of subclinical atherosclerosis such as vascular calcium scores and carotid intima media thickness, we and others have shown Hispanics have lower atherosclerosis burden compared with non-Hispanic Whites in both diabetic and non-diabetic populations [15–19]. A similar phenomenon has been reported among Native American Indians [20], where CVD was reported as extremely rare, until overt diabetes and diabetic nephropathy became common in this population [21,22].

In line with a reduced burden of atherosclerosis in Hispanics, a number of studies have reported lower rates of CVD mortality, despite a higher burden of risk factors in Hispanics compared with non-Hispanic Whites [23–28], which led to the notion of a "Hispanic Paradox". Consistent with this, the most recent National Vital Statistics reported that Hispanics have lower age-adjusted mortality rates compared with non-Hispanic White and non-Hispanic Black populations [29]. The concept of "Hispanic Paradox" is complex and has become controversial, in part because of the recognition that Hispanics are a diverse and heterogeneous population, and the hypothesis has been contested in several prospective cohort studies [30–32]. Nevertheless, there is greater appreciation that several characteristics such as social support, optimism, and strong familial and social ties are common among Hispanics, all of which are thought to be stress buffering and may potentially be protective among Hispanics despite their higher risk profile [33]. There is also growing recognition for the role of gene polymorphisms among different ethnic populations influencing disease outcomes and drug response [34,35]. Particularly relevant support for this concept comes from a recent UKPDS study that reported different rates of CVD events and mortality in people with new onset diabetes across various race/ethnic groups, in line with the idea that race/ethnic specific cardiovascular protective mechanisms may exist [36]. A recent comprehensive review of the literature from the science advisory from the American Heart Association [33] promotes the need to develop a culturally tailored and targeted approach for the goal of CVD risk reduction among Hispanics. However, the data on consequences of CVD risk reduction strategies in different race/ethnic groups, in particular in patient with type 2 diabetes, are lacking. Therefore, in this post-hoc analysis of the VADT we sought to determine the association between intensive glycemic control and CVD events among major race/ethnic groups.

2. Materials and Methods

2.1. Study Population

The VADT study design, exclusion/inclusion criteria, and study measures and activities have been described in detail [37]; further study information is provided in supplementary material on-line. In brief, the VADT included 1791 military veterans at 20 VA medical centers with poorly controlled type 2 diabetes who were randomized to receive either intensive or standard glucose treatment for a median duration of 5.6 years. The primary outcome was the time to the first occurrence of any one of a composite of CVD events (myocardial infarction, stroke, death from cardiovascular causes, new or worsening congestive heart failure, surgical intervention for cardiac, cerebrovascular, or peripheral vascular disease, inoperable coronary artery disease, and amputation for ischemic gangrene) adjudicated by an end-point committee that was unaware of treatment assignment. Optimal control of blood pressure and dyslipidemia, daily aspirin use, dietary advice, and diabetes education were uniformly provided to both treatment arms. Protocol and consent forms were approved by the institutional review board at each of the 20 participating sites and all patients provided written informed consent. The current analysis included 1724 VADT participants whose responses to standard NIH-format questions concerning race and ethnicity [38] allowed categorization into one of the 3 major race/ethnic groups: non-Hispanic White, non-Hispanic Black and Hispanic. We categorized as Hispanic those reporting Hispanic ethnicity as long as such individuals did not report Black race. Similarly, individuals who reported Black race were categorized as non-Hispanic Blacks as long as Hispanic ethnicity was not reported and irrespective of other races that were reported. The non-Hispanic White group included those who reported only White race and non-Hispanic ethnicity.

2.2. Statistical Analyses

Descriptive statistics, including mean ± SD, median (25th–75th percentiles), and frequencies were calculated for all variables. Between group differences were evaluated with analyses of variance or unpaired t-tests for normally distributed variables, with Kruskal–Wallis analysis of variance and Mann–Whitney U test for variables with skewed distributions, and with chi square tests for proportions. To determine whether longitudinal responses to treatment (i.e. hemoglobinA_{1c} (HbA_{1c}) changes during the study) differed among race/ethnic groups, a linear mixed effects model was used (details provided in Supplementary Material). Statistical significance was recognized for two-sided P values <0.05.

Cox proportional hazards risk analysis was used to determine associations between treatment assignment and CVD events independent of other risk factors. As our study aim was to assess treatment effects within different race/ethnic groups, and recognizing that smaller sample sizes in Hispanic and Black groups provided limited power to detect modifications of the overall treatment effect by race/ethnic groups, we performed exploratory subgroup analyses. We then assessed whether the results were consistent by performing sensitivity analyses with a series of Cox proportional hazards models within strata defined by different definitions of race/ethnic group. Sensitivity analyses included: 1) categorizing all participants into Hispanics vs. non-Hispanics regardless of race, 2) excluding individuals of mixed race from the three race/ethnic groups, 3) excluding individuals of mixed race and with prior CVD.