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Factors associated with failure to achieve a glycated haemoglobin target of <8.0% in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial

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Abstract

The aim of this study was to identify the clinical features of participants in the standard therapy arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) glycaemia trial who failed to reach the glycated haemoglobin (HbA1c) target. We analysed 4685 participants in the standard therapy arm, comparing participants who reached the HbA1c target of <8.0% with those whose HbA1c level was ≥8.0% 12 months after randomization. Baseline and 12-month clinical characteristics were compared. At 12 months after randomization, 3194 participants had HbA1c <8.0% and 1491 had HbA1c ≥8.0%. Black race [odds ratio (OR) 0.74, 95% confidence interval (CI) 0.61–0.89; $p = 0.002$], severe hypoglycaemia (OR 0.57, CI 0.37–0.89; $p = 0.014$) and insulin use (OR 0.51, CI 0.40–0.65; $p < 0.001$) were associated with failure to reach HbA1c goal at 12 months in the adjusted model. Even with free medications, free visits with clinicians and

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Conflict of Interest

None of the authors have any conflict of interest to disclose.

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aggressive titration of medications, >30% of participants in the standard arm of the ACCORD trial had an HbA1c $\geq 8.0\%$ at 1 year. Participants who were black, had severe hypoglycaemia and were on insulin were more likely to have an above-target HbA1c concentration after 12 months on the standard protocol.

Keywords

antidiabetic drug; clinical trial; cost-effectiveness; diabetes complications; insulin therapy; type 2 diabetes

Introduction

Achieving glycaemic control goals in patients with type 2 diabetes requires a comprehensive treatment plan. A glycated haemoglobin (HbA1c) concentration of 7.0–7.9% has been shown to be associated with a reduced risk of microvascular disease as compared with higher HbA1c targets in epidemiological analyses and in randomized clinical trials in type 1 (Diabetes Control and Complications Trial) and type 2 diabetes [UK Prospective Diabetes Study (UKPDS), Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, ADVANCE, Veterans Affairs Diabetes Trial (VADT) and the Kumamoto study], and is not associated with the increased risk of total and cardiovascular mortality seen in ACCORD participants randomized to a HbA1c target of $<6.0\%$ [1–6]. Current guidelines recommend individualized glycaemic goals based on patient comorbidities and preferences, and an HbA1c goal of 7.0–7.9% is often appropriate for middle-aged and older patients with or at high risk of cardiovascular disease [7].

Achieving the glycaemic goals recommended in current guidelines can be challenging in some patients, and identification of patients who may need additional support to achieve glycaemic targets would be of benefit to patients and caregivers alike. Many factors contribute to the failure to achieve a target HbA1c of $<8.0\%$, but clinical and demographic factors could be identified through examination of a well-characterized cohort of patients. To identify factors associated with failure to achieve a HbA1c of $<8.0\%$, therefore, we examined participants randomized to the ACCORD glycaemia trial standard therapy arm. A total of 5123 participants were randomized to the standard treatment arm, and after 12 months of therapy had an interquartile range HbA1c of 7.0–8.1% [8], showing that not all participants achieved the target. In the present report we identify baseline and on-treatment characteristics associated with failure to achieve HbA1c $<8.0\%$ in this cohort. We suggest that clinicians consider these factors in recommending a treatment plan to achieve target glycaemia and that future study be devoted to determine ways to implement successful treatment plans in patients with these characteristics.

Research Design and Methods

The rationale, study design and entry criteria for the ACCORD trial are described elsewhere [9–11]. Briefly, 10 251 participants with type 2 diabetes, HbA1c $\geq 7.5\%$, and either a prior cardiovascular event or cardiovascular risk factors were randomly assigned to either an intensive glycaemic strategy targeting an HbA1c level $<6.0\%$ or a standard glycaemic

strategy targeting an HbA1c level of 7.0–7.9%. Of the 10 251 participants, 5123 were randomly assigned to the standard therapy group. In this group, participants had glycaemia management visits every 4 months, and lifestyle and/or pharmacological therapy was intensified whenever HbA1c was $\geq 8.0\%$ [8,9]. Any antihyperglycaemic agent approved by the regulatory authorities and included in the ACCORD trial formulary could be used free of charge to the participants, although use of a thiazolidinedione was discouraged in this group [9].

We chose to analyse the standard therapy group at 12 months' follow-up from the initiation of the trial because the mean HbA1c level had reached 7.5% by that point, and then remained stable throughout the study [8].

Statistical Analysis

Baseline clinical, metabolic and sociodemographic characteristics were compared between those with HbA1c $<8.0\%$ and those with HbA1c $\geq 8.0\%$ at 12 months using chi-squared tests for categorical variables and two-sample t-tests for continuous variables. Logistic regression analysis was used to examine the association between participants achieving HbA1c $<8.0\%$ or $\geq 8.0\%$ at 12 months and baseline and follow-up predictors. Odds ratios (ORs) for achieving the target HbA1c were derived using maximum likelihood estimation. Covariates include ACCORD trial assignment (blood pressure trial or intensive lipid arm), secondary prevention of coronary artery disease, network (geographic distribution including western, northeast, and southeast United States, Minnesota/Iowa, Ohio/Michigan, Veteran Affairs and Canada), race, age, baseline body mass index (BMI), duration of type 2 diabetes, baseline HbA1c, weight change, hypoglycaemia, baseline medications used, medications used at 12 months, and the number of medication classes used. The interactions between race and trial assignment, race and gender, race and baseline HbA1c were also tested.

Results

Of the 5123 participants randomized to the standard group, we analysed the 4685 participants with complete data. We excluded 342 who did not have a 12-month follow-up visit, 82 with no HbA1c test at 12 months, and 14 with missing baseline data. Of the 4685 participants analysed, 3194 had HbA1c $<8.0\%$ and 1491 had HbA1c $\geq 8.0\%$ 12 months after randomization. The associations of baseline clinical and sociodemographic factors with the likelihood of reaching the HbA1c goal of $<8.0\%$ are shown in Table 1.

At 12 months, participants who reached HbA1c $<8.0\%$ had an average HbA1c of 7.2% compared with 8.8% in those whose HbA1c levels were $\geq 8.0\%$. Participants with HbA1c $\geq 8.0\%$ gained more weight compared with those with values below this level (1.01 vs -0.38 kg ; $p < 0.001$) and had more episodes of severe hypoglycaemia (3.4 vs 1.3%; $p < 0.001$). Table 2 shows the ORs for achieving a 12-month HbA1c $<8.0\%$ based on logistic regression models. Black participants (OR 0.74, 95% CI 0.61–0.89) were less likely to have a 12-month HbA1c $<8.0\%$ but Hispanic participants were not (OR 0.81, 95% CI 0.62–1.07) when compared with white people, after adjusting for other covariates. Participants who were older, had a shorter duration of diabetes, had a lower baseline HbA1c, had fewer episodes of severe hypoglycaemia, and had less weight gain were more likely to achieve

their HbA1c goal. Participants on insulin at 12 months were less likely to have a 12-month HbA1c <8.0% when compared with those not on insulin (OR 0.51, 95% CI 0.40–0.65).

Medication adherence was measured by participant self-report at each visit. Oral medications had a 96–99% adherence rate, basal insulin a 97% adherence rate and bolus insulin a 90–93% adherence rate.

Discussion

In the present analysis, we found that ACCORD participants in the standard glycaemia therapy group who failed to reach an HbA1c target <8.0% 12 months after randomization had small but significant differences in both baseline characteristics and 12-month clinical features when compared with participants who reached this HbA1c target. Younger age, female gender, higher BMI, longer duration of diabetes, higher baseline HbA1c, black race and history of cardiovascular disease event(s) were associated with a 12-month HbA1c ≥8.0%. Clinical characteristics significantly associated with a 12-month HbA1c ≥8.0% included the use of insulin both at baseline and at 12 months, episodes of severe hypoglycaemia and weight gain.

In the ACCORD study, race has already been reported to be associated with weight gain, with participants of Asian race having more weight gain over 2 years [12], but the present study is the first analysis to show the importance of race/ethnicity with regard to the ability to achieve an HbA1c target commonly used in clinical practice. When adjusting for other covariates in a logistic regression model, black participants were less likely to have a 12-month HbA1c of <8.0% compared with white participants. In the UKPDS study, no significant ethnic differences in glycaemic control were observed [13], although the UKPDS had a less diverse study population than the ACCORD trial. It has been suggested that there are racial and ethnic differences in the relationship between HbA1c and blood glucose levels from factors such as red cell survival, extracellular–intracellular glucose balance, and non-glycaemic genetic determinants of HbA1c concentration [14]. It has also been reported that among participants in the ACCORD trial, black and Hispanic people have a higher haemoglobin glycation index than white people [15].

No oral medication was significantly associated with reaching HbA1c <8.0%. Also, the use of more oral medication classes was not associated with a 12-month HbA1c <8.0%. Those who used insulin at 12 months were less likely to have an HbA1c <8.0% at 12 months. This is difficult to interpret as these participants were more likely to be on insulin at baseline, and more likely to have had intensification per protocol that could have included the initiation of insulin. Consequently, insulin use may be a surrogate for another clinical characteristic that places a participant at risk of being unable to achieve HbA1c levels of <8.0%. Despite this, the present data show that the use of insulin, even in a protocol-driven manner designed to establish lower glycaemic targets, does not guarantee reaching the HbA1c goal in this patient population. One explanation may be that participants with a 12-month HbA1c level ≥8.0% were also more likely to have episodes of severe hypoglycaemia. Also, participants with a higher haemoglobin glycation index were less likely to reach their target HbA1c and more likely to have severe hypoglycaemia [15].

Factors related to failure to reach a 12-month HbA1c of <8.0% in this setting include: race, age, poorer baseline glucose control, insulin use, severe hypoglycaemia and weight gain. Patients with these characteristics may need special support and innovative treatment strategies to achieve the level of glycaemic control necessary to reach target HbA1c levels and reduce the microvascular and macrovascular consequences of the disease. It may be that such patients have additional factors associated with their health that makes them less responsive to insulin use; future study should be directed to address this question. The fact that participants assigned to the intensive glycaemic control arm of ACCORD reached lower HbA1c levels suggests that visits more frequently than every 4 months, intensive patient education strategies, and ongoing support from case managers or other care providers may be strategies to consider for the ~30% of patients who were unable to otherwise reach their HbA1c goal.

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Baseline characteristics of participants in the standard therapy arm of the glycaemia trial who achieved glycated haemoglobin <8.0 or 8.0% by 12 months.

Table 1.

Demographics	HbA1c <8.0%	HbA1c 8.0%*	p
No. of participants, %	3194 (68.18)	1491 (31.82)	
Mean (s.d.) age, years	62.72 (6.75)	61.25 (6.74)	<0.001
Mean (s.d.) BMI, kg/m ²	32.11 (5.38)	32.50 (5.58)	0.020
Mean (s.d.) duration of diabetes, years	10.43 (7.62)	12.05 (7.88)	<0.001
Mean (s.d.) baseline HbA1c, %	8.13 (0.97)	8.66 (1.10)	<0.001
Female, n (%)	1170 (36.6)	592 (39.7)	0.043
Race, n (%)			
Hispanic	241 (6.7)	132 (8.9)	<0.001
Black	494 (15.5)	326 (21.9)	
White	2129 (66.7)	859 (57.6)	
Other	357 (11.2)	174 (11.7)	
History of cardiovascular disease event, n (%)	1058 (33.1)	561 (37.6)	0.003
Managed by endocrinologist/diabetologist investigator, n (%)	1848 (57.9)	855 (57.3)	0.740
Metformin use at baseline, n (%)	1913 (60.0)	870 (58.6)	0.338
Secretagogues use at baseline	1017 (31.91%)	467 (31.43%)	0.741
Thiazolidinediones use at baseline	624 (19.58%)	275 (18.51%)	0.386
Bolus insulin use at baseline	373 (11.70%)	277 (18.64%)	<0.001
Premixed insulin use at baseline	275 (8.63%)	167 (11.24%)	0.005
Basal insulin use at baseline	739 (23.19%)	533 (35.87%)	<0.001
Number of oral medication classes used at baseline	1.12 (0.88)	1.09 (0.86)	0.288

BMI, bodymass index; HbA1c, glycated haemoglobin; s.d., standard deviation.

* p values were calculated using chi-squared tests for categorical variables and two-sample t-tests for continuous variables.

Table 2.Odds ratios for achieving target glycated haemoglobin concentration ^{*}.

	OR (CI)	p
Female	0.89 (0.77–1.04)	0.145
Race		
Hispanic [†]	0.81 (0.62–1.07)	0.136
Black [†]	0.74 (0.61–0.89)	0.002
Other [†]	0.80 (0.63–1.01)	0.062
Age, years	1.03 (1.02–1.04)	<0.001
Baseline BMI, kg/m ²	0.99 (0.98–1.01)	0.449
Duration of diabetes, years	0.99 (0.98–1.00)	0.018
Baseline HbA1c, %	0.67 (0.63–0.72)	<0.001
Weight change, kg	0.97 (0.95–0.98)	<0.001
Severe hypoglycaemia	0.57 (0.37–0.89)	0.014
Insulin use at 12 months	0.51 (0.40–0.65)	<0.001
Metformin use at 12 months	1.76 (0.82–3.78)	0.146
Secretagogue use at 12 months	1.10 (0.52–2.37)	0.797
Thiazolidinedione use at 12 months	1.73 (0.81–3.73)	0.158
Number of oral medication classes [‡]	0.62 (0.29–1.30)	0.206

BMI, body mass index; CI, confidence interval; HbA1c, glycated haemoglobin; OR, odds ratio.

^{*} Logistic regression was used to adjust for trial arm, secondary prevention, network, race, age, baseline BMI, duration of type 2 diabetes, baseline HbA1c, weight change, hypoglycaemia, baseline medications used, medications used at 12 months, and the number of medication classes used.

[†] Using race-white as a reference.

[‡] Oral medication classes: metformin, secretagogues, thiazolidinediones, α -glucosidase inhibitors and incretins.