Impact of Overbasalization on Clinical Outcomes in Patients With Type 2 Diabetes: A Post Hoc Analysis of a Large Randomized Controlled Trial

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The American Diabetes Association's *Standards of Medical Care in Diabetes* emphasize the need for awareness regarding overbasalization (basal insulin doses >0.5 units/kg/day without bolus insulin) in the treatment of type 2 diabetes. However, outcomes data on the impact of overbasalization are limited. This post hoc analysis of a large randomized controlled trial suggests that an insulin therapy regimen involving overbasalization compared with a basal-bolus insulin regimen that avoids overbasalization is less effective at lowering A1C and may be associated with increased cardiovascular risk. Clinicians should consider alternative approaches to glycemic control before increasing basal insulin doses to >0.5 units/kg/day.

Thirty million people in the United States have type 2 diabetes, and diabetes-related complications continue to place strain on the health care system and on patients. Among many others, two major risk factors associated with diabetes-related complications are elevated A1C and obesity (1). Ultimately, many patients will require insulin to achieve glycemic control and, in turn, possibly avoid complications (2,3). As basal insulin is titrated, it is necessary to avoid "overbasalization," which is defined as titration of basal insulin beyond an appropriate dose in an attempt to achieve glycemic targets (3,4). However, a definitive dose of basal insulin beyond which prandial therapy should be initiated has not been well studied or defined. Indeed, insulin resistance is variable, and the optimal basal insulin dose may vary between patients. However, out of concern for hypoglycemia, weight gain, and the potential for reaching glycemic targets, the American Diabetes Association (ADA) now recommends assessing patients for overbasalization once their basal insulin dose reaches ~0.5 units/kg/day (3).

Although overbasalization has not been not well studied, a universal definition for its identification in clinical practice has been debated (5,6). One recent study found that 38% of patients with type 2 diabetes using basal insulin experienced overbasalization (7), although no large studies have assessed the association of overbasalization with clinical outcomes. The objective of this study was to assess the association of overbasalization with clinical outcomes via a post hoc analysis of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (8). The hypothesis was that overbasalization is independently associated with negative clinical outcomes.

Methods

ACCORD was a double-blind, double two-by-two factorial randomized controlled trial (8). All patients were assigned to either intensive or standard glycemic management. Half of the patients were assigned to intensive or standard blood pressure management, whereas the other half were required to be receiving simvastatin and were then assigned to receive either fenofibrate or placebo. ACCORD included patients with type 2 diabetes who had an A1C ≥7.5% and one of two cardiovascular risk profiles: either age 40–79 years with cardiovascular disease (CVD) or age 55–79 years with anatomically evident significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two risk factors of four

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(dyslipidemia, hypertension, current smoking, and obesity). People were excluded from ACCORD if they had recent or frequent serious hypoglycemia, were unwilling to use insulin or monitor blood glucose, had a BMI >45 kg/m^2 and/or a serum creatinine level >1.5 mg/dL, or had any other serious illness.

The current study assessed the presence or absence of overbasalization at the 12-month visit. This time point was chosen to assess overbasalization as a treatment strategy used to control blood glucose. In the original ACCORD trial, many medication changes were made from baseline to the 1-month visit, as would be expected based on the study's protocol (8). Moreover, A1C plateaued after 12 months, indicating that the primary clinical strategies implemented to control blood glucose were completed. Finally, there was a predetermined 12-month study visit for all arms of the ACCORD trial; thus, assessment at this time point minimizes the proportion of patients with missing data.

Accordingly, we sought to assess the impact of overbasalization, assessed at the 12-month study visit, as a treatment strategy to control A1C. Based on our prior work and guidance in the ADA's *Standards of Medical Care in Diabetes*, overbasalization was defined as a basal insulin dose >0.5 units/kg/day (3,7). Any patients meeting this description were considered "overbasalized." Patients in this analysis could have been taking any combination of noninsulin therapies but were divided into five groups for analysis based on their insulin use strategy: *1*) no insulin therapy, *2*) basal insulin only—not overbasalized, *3*) basal insulin only—overbasalized, *4*) basal-bolus insulin—not overbasalized, and *5*) basal-bolus insulin—overbasalized. Commensurate with this delineation, patients with missing insulin data, those taking any premixed insulin (because of unavailability of patient-level insulin formulation ratios), and those taking only bolus insulin were excluded. Consequently, of the original 10,251 patients in the ACCORD trial, 9,321 were included in the present analysis.

The primary outcome was adjusted change in A1C from baseline to 12 months. The secondary outcome was adjusted change in body weight from baseline to 12 months. Exploratory outcomes included the ACCORD trial's primary composite outcome of three-point major adverse cardiovascular events (MACE) (first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) and the ACCORD's expanded macrovascular outcome (first occurrence of the primary three-point MACE outcome plus heart failure [HF] hospitalization and revascularization), as well as total mortality and congestive heart failure (CHF) death or hospitalization.

χ^2 Tests were used to compare categorical variables, and one-way ANOVA with post hoc Tukey comparisons were used for continuous variables. Univariate ANOVA was used to assess the impact of insulin use strategy on change in A1C from baseline to 12 months (adjusted for age, baseline A1C, and trial arm assignment) and change in body weight (adjusted for age, baseline body weight, and trial arm assignment).

Univariate and multivariate binary logistic regressions were used to assess the association between insulin use strategy and outcomes, summarized as odds ratios (ORs) with 95% CIs. The insulin use strategy of basal insulin only—overbasalized was set as the reference group for regression analyses and univariate ANOVA analyses to facilitate comparisons to all other insulin use strategies. Multivariable regression analyses assessing exploratory outcomes were adjusted for sex, age, race, BMI, HF, CVD, estimated glomerular filtration rate (eGFR), and trial arm assignment. Patients with missing data were excluded from specific analyses. The analysis was hypothesis driven, and models were determined by the investigators based on expected associations. Data were analyzed using SPSS, v. 27, statistical software (IBM Corp., Armonk, NY).

The study was determined exempt by the University of South Florida Institutional Review Board. Data are available through request to the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center.

Results

The study included 9,321 patients (Table 1). Of those, 8,503 patients had complete data assessing the primary outcome of change in A1C from baseline to 12 months and 9,207 patients had complete data for multivariable assessment of change in body weight from baseline to 12 months. Additionally, 9,321 patients had complete data for univariate logistic regressions, and 9,182 patients had complete data for multivariate logistic regressions. Overall, patients were most commonly White, older (mean age >60 years in all groups), with obesity, and predominately male (>60%). One notable exception is that half of the patients categorized with a treatment strategy of basal insulin only—overbasalized were female. Mean A1C at baseline was >8% in all groups, although it was lowest among patients not receiving

TABLE 1 Patient Characteristics

Baseline	No Insulin Therapy (n = 6,530)	Basal Insulin Only—Not Overbasalized (n = 992)	Basal Insulin Only—Overbasalized (n = 258)	Basal-Bolus Insulin—Not Overbasalized (n = 896)	Basal-Bolus Insulin—Overbasalized (n = 645)	P
Age, years	62.8 ± 6.6	62.2 ± 6.6	62.2 ± 6.1	63.8 ± 7.0	61.8 ± 6.5	<0.001
Female sex	2,478 (37.9)	382 (38.5)	129 (50)	322 (35.9)	254 (39.4)	0.001
Race/ethnicity						<0.001
White	4,097 (62.7)	637 (64.2)	139 (53.9)	621 (69.3)	441 (68.4)	
Black	1,157 (17.7)	205 (20.7)	72 (27.9)	131 (14.6)	109 (16.9)	
Hispanic	472 (7.2)	60 (6.0)	29 (11.2)	49 (5.5)	39 (6.0)	
Other	804 (12.3)	90 (9.1)	18 (7.0)	95 (10.6)	56 (8.7)	
Baseline BMI, kg/m^2	32.0 ± 5.36	32.2 ± 5.33	32.9 ± 5.08	32.1 ± 5.25	34.0 ± 5.33	<0.001
Baseline body weight, kg	93.0 ± 18.4	93.8 ± 18.0	93.2 ± 17.8	93.5 ± 17.5	99.0 ± 18.7	<0.001
Baseline A1C, %	8.19 ± 1.03	8.40 ± 1.05	8.72 ± 1.05	8.44 ± 1.00	8.69 ± 1.07	<0.001
Diabetes duration, years	9.8 ± 7.2	10.4 ± 7.0	13.8 ± 7.8	14.2 ± 8.0	14.6 ± 8.0	<0.001
Cigarette smoking	877 (13.4)	152 (15.3)	38 (14.7)	114 (12.7)	83 (12.9)	0.43
Baseline comorbidities						
CVD	2,113 (32.4)	352 (35.5)	93 (36.0)	373 (41.6)	309 (47.9)	<0.001
HF	233 (3.6)	51 (5.1)	10 (3.9)	54 (6.0)	78 (12.1)	<0.001
eGFR, mL/min/1.73 m^2*	91.6 ± 27.4	92.5 ± 27.7	92.7 ± 29.5	87.0 ± 26.3	88.9 ± 26.9	<0.001
Trial arm						<0.001
Standard glycemia/intensive blood pressure	855 (13.1)	79 (8.0)	36 (14.0)	61 (6.8)	48 (7.4)	
Standard glycemia/standard blood pressure	863 (13.2)	81 (8.2)	20 (7.8)	67 (7.5)	40 (6.2)	
Intensive glycemia/intensive blood pressure	609 (9.3)	154 (15.5)	29 (11.2)	148 (16.5)	113 (17.5)	
Intensive glycemia/standard blood pressure	651 (10.0)	156 (15.7)	30 (11.6)	155 (17.3)	88 (13.6)	
Standard glycemia/lipid fibrate	1,041 (15.9)	74 (7.5)	33 (12.8)	65 (7.3)	57 (8.8)	
Standard glycemia/lipid placebo	1,041 (15.9)	86 (8.7)	34 (13.2)	52 (5.8)	47 (7.3)	
Intensive glycemia/lipid fibrate	745 (11.4)	172 (17.3)	33 (12.8)	183 (20.4)	111 (17.2)	
Intensive glycemia/lipid placebo	725 (11.1)	190 (19.2)	43 (16.7)	165 (18.4)	141 (21.9)	
Medications at 12-month visit						
ACE inhibitor	3,461 (53.9)	576 (58.9)	154 (60.4)	531 (59.7)	390 (61.0)	<0.001
Angiotensin receptor blocker	1,375 (21.4)	199 (20.3)	60 (23.5)	215 (24.2)	156 (24.4)	0.11
Statin	4,958 (77.3)	750 (76.1)	201 (78.8)	706 (79.8)	512 (80.1)	0.17

Continued on p. 150 »

« Continued from p. 149

TABLE 1 Patient Characteristics (Continued)

Baseline	No Insulin Therapy (n = 6,530)	Basal Insulin Only—Not Overbasalized (n = 992)	Basal Insulin Only—Overbasalized (n = 258)	Basal-Bolus Insulin—Not Overbasalized (n = 896)	Basal-Bolus Insulin—Overbasalized (n = 645)	P
Cholesterol absorption inhibitor	95 (1.5)	15 (1.5)	4 (1.6)	18 (2)	14 (2.2)	0.55
Aspirin	3,724 (58.7)	582 (59.9)	147 (58.3)	563 (64.1)	400 (63.2)	0.012
Sulfonylurea	3,988 (61.5)	649 (65.4)	121 (46.9)	303 (33.9)	160 (24.8)	<0.001
Meglitinide	890 (13.7)	274 (27.6)	67 (26.0)	69 (7.7)	36 (5.6)	<0.001
Biguanide	5,316 (82.0)	822 (82.9)	191 (74.0)	606 (67.7)	423 (65.7)	<0.001
Thiazolidinedione	3,607 (55.7)	693 (69.9)	125 (48.4)	529 (59.1)	306 (47.5)	<0.001
Other noninsulin antidiabetic agent	35 (0.5)	10 (1.0)	0 (0)	1 (0.1)	10 (1.6)	0.0012

Data are mean ± SD or n (%). *Calculated with four-variable Modification of Diet in Renal Disease equation.

insulin. CVD and HF were most common at baseline among patients using a basal-bolus insulin regimen who were concurrently overbasalized. Diabetes duration increased within each successive insulin use strategy group.

Unadjusted change in A1C from baseline to 12 months was not significantly different among groups (Table 2). Notably, patients with the insulin use strategy of basal insulin only—overbasalized had numerically the smallest A1C reduction. In the primary outcome, univariate ANOVA adjusted for baseline A1C, age, and trial arm assignment, the insulin use strategy of basal insulin only—overbasalized resulted in significantly less A1C reduction than all other strategies (Table 2).

Unadjusted change in body weight from baseline to 12 months numerically increased with each insulin use strategy (Table 2). Compared with patients with the insulin use strategy of basal insulin only—overbasalized, patients not using insulin gained significantly less weight (unadjusted mean difference 1.9 kg [95% CI 1.0–2.9 kg]). Conversely, patients with the insulin use strategy of basal-bolus insulin—overbasalized gained significantly more weight (unadjusted mean difference −1.2 kg [95% CI −2.3 to −0.2]). These associations remained significant in univariate ANOVA adjusted for baseline body weight, age, and trial arm assignment (Table 2).

All exploratory analyses indicated a significant difference among groups, as assessed via χ^2 tests (Table 2). However, when assessed in regression analysis for significant impact of each specific insulin use strategy, no association was found between insulin use strategy and the composite outcomes of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (the ACCORD trial primary composite outcome). In the expanded macrovascular outcome (ACCORD primary outcome plus HF hospitalization and revascularization), patients without insulin use and those with the insulin use strategy of basal insulin only—not overbasalized had significantly lower odds of an event compared with those with the insulin use strategy of basal insulin only—overbasalized (ORs: no insulin 0.62 [95% CI 0.47–0.81], basal insulin only—not overbasalized 0.67 [95% CI 0.49–0.90]). These associations remained significant in the multivariable regression analysis. Additionally, the insulin use strategy of basal-bolus insulin—not overbasalized was found to have lower odds of the expanded macrovascular composite outcome versus basal insulin only—overbasalized (adjusted ORs: no insulin 0.62 [95% CI 0.46–0.83], basal insulin only—not

TABLE 2 Outcomes

	No Insulin	Basal Insulin Only—Not Overbasalized	Basal Insulin Only—Overbasalized	Basal-Bolus Insulin—Not Overbasalized	Basal-Bolus Insulin—Overbasalized	*P**
Primary outcome						
Unadjusted change in A1C, %	−1.18 ± 1.29	−1.24 ± 1.29	−1.01 ± 1.33	−1.24 ± 1.23	−1.25 ± 1.37	0.07
Adjusted change in A1C, %	−1.28 (−1.30 to −1.25)	−1.13 (−1.19 to −1.07)	−0.67 (−0.80 to −0.55)	−1.08 (−1.14 to −1.01)	−0.87 (−0.95 to −0.80)	≤0.007 for all comparisons versus basal insulin only—overbasalized
Secondary outcome						
Unadjusted change in body weight, kg	0.38 ± 5.39	1.98 ± 5.43	2.31 ± 4.59	2.35 ± 5.34	3.56 ± 5.27	<0.001
Adjusted change in body weight, kg	**0.41 (0.28–0.54)**	1.87 (1.54–2.20)	2.24 (1.59–2.88)	2.40 (2.06–2.75)	**3.41 (3.00–3.82)**	≤0.003 for marked comparisons shown in bold type versus basal insulin only—overbasalized
Exploratory outcomes						
Primary composite outcome from ACCORD trial	590 (9.0)	94 (9.5)	31 (12.0)	101 (11.3)	88 (13.6)	<0.001
Expanded macrovascular outcomes from ACCORD trial	1,399 (21.4)	225 (22.7)	79 (30.6)	239 (26.7)	209 (32.4)	<0.001
CHF hospitalization or death	220 (3.4)	44 (4.4)	18 (7.0)	54 (6.0)	61 (9.5)	<0.001
Total mortality	346 (5.3)	64 (6.5)	13 (5.0)	74 (8.3)	71 (11.0)	<0.001

Data are mean ± SD, mean (95% CI), or n (%). *P determined through χ^2 tests for exploratory outcomes.

overbasalized 0.64 [95% CI 0.47–0.89], basal-bolus insulin—not overbasalized 0.67 [0.49–0.93]). Odds of HF hospitalization or death were lower among patients not receiving insulin versus those using the insulin use strategy of basal insulin only— overbasalized in univariate and multivariate regression (OR 0.47 [95% CI 0.28–0.77], adjusted OR 0.53 [95% CI 0.31–0.89]). Finally, the odds of total mortality were significantly greater among patients with the insulin use strategy of basal-bolus insulin—overbasalized versus basal insulin only—overbasalized in univariate analysis but not in multivariate analysis (OR 2.3 [95% CI 1.3–4.3], adjusted OR 1.9 [95% CI 0.99–3.5]). All other regression comparisons to the insulin use strategy of basal insulin only—overbasalized were not significantly different.

Discussion

This study suggests that the treatment strategy of overbasalization, that is, increasing the basal insulin dose to >0.5 units/kg/day, is less effective than alternative insulin treatment strategies at reducing A1C. This finding is in line with existing literature assessing the clinical impact of overbasalization (6,9). Conversely, weight gain by insulin use strategy numerically increased as insulin therapy became progressively more intensive (Table 2), although weight gain was similar between the basal insulin only—overbasalized and basal-bolus insulin—not overbasalized strategies.

As would be expected, the patients requiring the least intensive therapy (i.e., no insulin or basal insulin

only—not overbasalized) appeared to be at a lower risk for the outcomes assessed, except for total mortality. With regard to basal insulin only—overbasalized, the clearest therapeutic alternative insulin use strategy is basal-bolus insulin—not overbasalized. Therefore, it is a point of interest to patient care that the odds of the expanded macrovascular outcome were greater among patients receiving the insulin use strategy of basal insulin only—overbasalized versus those receiving basal-bolus insulin—not overbasalized. Notably, the association was not found in the primary composite outcome or in HF. Therefore, this finding may be spurious or may be driven by revascularization. Unfortunately, the dataset available did not assess revascularization as an individual outcome.

Overall, patients requiring insulin appear to be at higher risk for cardiovascular events versus those who do not require insulin, but not because of insulin use per se. The finding of the basal-bolus insulin—overbasalized strategy being associated with total mortality in univariate logistic regression likely points to these patients being "sicker" overall at baseline. Specifically, patients with this insulin use strategy had the longest duration of diabetes at baseline, as well as the greatest BMI, greatest prevalence of CVD, and greatest prevalence of HF. Despite the result being nearly significant with multivariable adjustment, the trend may still more likely reflect an overall higher-risk population, as all possible confounders were not included in the adjustment. Regardless, the current study suggests that the insulin use strategy of basal-bolus insulin—overbasalized identifies patients with advanced diabetes who are at significant risk for complications.

Limitations

The study's limitations include its post hoc design and the fact that it did not use the original randomization; thus, residual confounding may exist. However, with this approach, this study should not be considered an attempt to readjudicate the original ACCORD trial. Rather, the present analysis took advantage of a high-quality prospective dataset with diverse approaches to glycemic management, allowing for the comparison of various insulin use strategies.

Of note, the ACCORD trial did not include glucagon-like peptide 1 (GLP-1) receptor agonists or sodium–glucose cotransporter 2 (SGLT2) inhibitors, which are known to affect cardiovascular outcomes, reduce insulin requirements, and promote weight loss. A strength of this omission is that it resulted in fewer confounding factors between groups. Because the study found less A1C reduction, potentially increased cardiovascular risk, and numerically greater weight gain, these results point to the likely benefit of additional therapies (e.g., bolus insulin, GLP-1 receptor agonists, or SGLT2 inhibitors) versus continued basal insulin titration to >0.5 units/kg/day.

Notably, this study excluded patients using premixed insulin and bolus insulin only. Therefore, the results cannot be generalized to these populations. Additionally, the patients in the ACCORD trial had longstanding type 2 diabetes. Thus, the results cannot be extrapolated to patients with newly diagnosed type 2 diabetes, type 1 diabetes, or other types of diabetes.

Finally, some data were missing, although a robust sample size remained. Moreover, excluding patients with missing data is a conservative approach, as is using data from a high-quality randomized controlled trial, which limits the potential for misclassification bias. Additionally, a hypothesis-driven inquiry without data transformation is a robust analysis approach.

Conclusion

The treatment strategy of overbasalization, defined as basal insulin doses >0.5 units/kg/day, to reduce A1C may be less effective than alternative approaches. Moreover, in our exploratory analysis, we identified an association between overbasalization and increased cardiovascular risk. Likewise, overbasalized patients also using bolus insulin appeared to be at high risk for complications overall, although not because of insulin therapy per se.

On the basis of these findings in conjunction with the pharmacologic strategies recommended by the ADA (3), we suggest the use of alternative antihyperglycemic approaches (e.g., bolus insulin, GLP-1 receptor agonist, or SGLT2 inhibitor therapy), rather than continued titration of the basal insulin dose above 0.5 units/kg/day, to achieve glycemic control.

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DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

K.C., A.V., A.K., and N.W.C. contributed to the concept and design. K.C., A.K., A.T., and N.W.C. contributed to the acquisition and/or analysis of data. K.C., A.V., A.K., Y.S., and N.W.C. contributed to the interpretation of the data. All authors contributed to the drafting and/or critical revision of the manuscript and approved the final version of the manuscript. K.C. and N.W.C. are the guarantors of this work and, as such, had full access to all the data presented and take responsibility for the integrity of the data and the accuracy of the data analysis.

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