Effect of Intensive Glycemic Lowering on Health-Related Quality of Life in Type 2 Diabetes

ACCORD trial

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OBJECTIVE—To compare the effect of intensive versus standard glycemic control strategies on health-related quality of life (HRQL) in a substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.

RESEARCH DESIGN AND METHODS—A randomly selected subsample of 2,053 ACCORD participants enrolled in the HRQL substudy was assessed at baseline and 12-, 36-, and 48-month visits. HRQL assessment included general health status (the 36-Item Short Form Health Survey [SF-36]), diabetes symptoms (the Diabetes Symptom Distress Checklist), depression (Patient Health Questionnaire [PHQ]-9), and treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire [DTSQ]). Repeated-measures ANOVA models were used to estimate change in HRQL outcomes by treatment group over 48 months adjusting for model covariates. The effects of early discontinuation of the ACCORD intensive glycemic control arm on study results were explored.

RESULTS—A total of 1,956 (95%) completed the self-report HRQL instrument(s) at baseline. The intensive arm had a larger decrease in SF-36 physical health component score than the standard arm (−1.6 vs. −1.1, $P = 0.0345$). Treatment satisfaction (DTSQ) showed larger improvement with intensive than standard ($P = 0.0004$). There were no differences in mean scores of the Diabetes Symptom Checklist and PHQ-9. Effects of participant transition following discontinuation of the intensive arm on HRQL were not significant.

CONCLUSIONS—The ACCORD trial strategy of intensive glycemic control did not lead to benefits in HRQL and was associated with modest improvement in diabetes treatment satisfaction. Thus patient acceptability was apparently not compromised with intensive and complex interventions such as those used in ACCORD.

Diabetes Care 34:807–812, 2011

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Received 8 October 2010 and accepted 21 January 2011.
DOI: 10.2337/dc10-1926. Clinical trial reg. no. NCT00000620, clinicaltrials.gov.
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc10-1926/-/DC1.
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The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was a multicenter randomized controlled treatment trial testing independent effects of two strategies of control of blood glucose, blood pressure, and lipids on cardiovascular disease (CVD) in patients with type 2 diabetes (1). The glycemia trial randomized 10,251 participants with type 2 diabetes to intensive (goal HbA_{1c} <6%) or standard therapies (goal HbA_{1c} 7.0–7.9%). All participants were also randomized to the blood pressure or lipid trial arms. An ACCORD substudy focused on health-related quality of life (HRQL) outcomes associated with intensive versus standard glycemic control strategies (2). The rationale for the HRQL substudy was the need to consider the impact or potential benefit of intensive glycemia management from the participants' point of view. Diabetes is known to be associated with decrements in HRQL from functional limitations, restrictions in normal activities, work limitations, poor general health, and depression (3–6) and from symptom distress such as excessive thirst, frequent urination, fatigue, and neuropathies (7–11). Patients with diabetes commonly suffer from psychological disturbances such as depression, anxiety, and social withdrawal (12,13). Thus potential treatment benefits of improved diabetes control and reduced risk for vascular diseases could have broad HRQL benefit. Short-term effects of HbA_{1c} level on HRQL have been reliably shown (3); however, few longitudinal studies have examined HRQL in the context of intensive glycemic control. The potential impact of treatment complexity on daily life with diabetes is also important to consider (5,14,15). In ACCORD the intensive glycemia target of HbA_{1c} <6% places a greater burden on the patient in terms of self-management, pharmacologic intensification, and office visits. Additionally the potential for side effects must be weighed. Thus this report addresses a secondary objective of the ACCORD trial to investigate the effects

of glycemic control strategy on patient appraisal of general health, symptoms, depression, and treatment satisfaction.

RESEARCH DESIGN AND METHODS

—The ACCORD glycemia treatment trial methods and design have been previously reported (16,17). Briefly, this was a randomized controlled clinical trial of treatment for type 2 diabetes, conducted in 77 clinical centers across the U.S. and Canada. Central laboratory measures of HbA_{1c} were used to reflect level of glycemic control. A total of 10,251 participants were recruited and randomly assigned to either intensive glycemia management with a target HbA_{1c} <6.0% or standard glycemia management with a target HbA_{1c} between 7.0 and 7.9%. To be eligible for ACCORD, participants had to have a confirmed diagnosis of type 2 diabetes; an HbA_{1c} between ≥7.5 and 11%; and be either *1*) age 40–79 years with cardiovascular disease or 2) age 55–79 years with anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for CVD (dyslipidemia, hypertension, current status as a smoker, or obesity). Key exclusion criteria included frequent or recent serious hypoglycemic events, unwillingness to do home glucose monitoring or inject insulin, a BMI of more than 45 kg/m^2, a serum creatinine level of greater than 1.5 mg/dL, or other serious illness. The ACCORD study protocols were approved by the institutional review board or ethics committee at each ACCORD site or coordinating center as well as by an ethics review panel at the National Heart, Lung, and Blood Institute. All patients provided written informed consent.

HRQL substudy

The ACCORD HRQL study was designed to detect meaningful change from baseline in HRQL associated with glycemic control treatment arms. Specifically, the prespecified objectives were to test potential treatment benefits from intensive glycemic versus standard therapy in terms of less symptom distress, improved general health (physical and psychological wellbeing), and improved treatment satisfaction. The impact of the intervention on depression, based on data from the Patient Health Questionnaire (18), is reported here as a secondary outcome.

Of the 10,251 patients enrolled in the ACCORD trial, a randomly selected subsample of 2,053 was enrolled in the ACCORD HRQL substudy. Of these, N = 1,024 had been randomized to intensive glycemic control and N = 1,029 to standard control.

Study outcomes and covariates

Four distinct measures, general health, treatment satisfaction, diabetes-related symptoms, and depression, were used to measure HRQL. Data were collected by self-report questionnaire administered at the ACCORD baseline, 12-, 36-, and 48-month visits. General health status was assessed using the 36-Item Short Form Health Survey, Version 2 (SF-36) (19), where aggregate physical health (PH) and mental health (MH) component scores were calculated. The component scores are weighted combinations of individual items and have a general population norm of 50 and a standard deviation of 10, with higher scores representing better health. The PH component refers to ratings of limitations in physical, social, and role activities; severe bodily pain; fatigue; and self-rated health. The MH component refers to psychological distress, social and role disability as a result of emotional problems, and self-rated health.

A 60-item version of the Diabetes Symptoms Distress Checklist (DSC) (7) was used to assess the presence and severity (impact on functional status) of diabetes-related symptoms. Participants report whether or not they had experienced the given symptom or feeling and rate symptom distress on a scale of 0–4 (0 = not at all, 1 = somewhat, 2 = moderately, 3 = very much, 4 = extremely).

Satisfaction with diabetes treatment was assessed using the eight-item World Health Organization Diabetes Treatment Satisfaction Questionnaire (WHO-DTSQ), an authorized version identical to the DTSQ status version widely used in diabetes clinical trials (20). The DTSQ includes an overall six-item measure of satisfaction with the diabetes regimen with scores ranging from 0 to 36, with higher scores indicating higher satisfaction. For a subset of participants (ACCORD vanguard phase), only five satisfaction items were measured; therefore we converted the DTSQ score to a range from 0 to 100. In addition to the six-item measure, there were also two standard questions assessing perceived frequency of hyperglycemia and hypoglycemia ranging from 0 to 6, with higher scores indicating more frequent perception of high or low blood glucose.

Depression was assessed using the 9-item depression measure from the Patient Health Questionnaire (PHQ-9). The PHQ-9 is the self-report version of the PRIME-MD, a well-validated psychiatric diagnostic interview for use in primary care settings (18). Scores range from 0–27, and the score is treated as a continuous variable.

Data analysis

All statistical analyses were conducted using SAS software Version 9 (SAS Institute, Cary, NC). Statistical significance was defined as P value <0.05. Descriptive analyses of baseline clinical and HRQL characteristics were used to assess the representativeness of the HRQL subsample in relation to the ACCORD study population and to illustrate successful randomization of the HRQL substudy participants. Baseline characteristics of the two study groups were compared using χ^2 tests, t tests, and Wilcoxon tests.

To examine the effects of glycemic control treatment arm before the end of the glycemia trial on study outcomes of general health, treatment satisfaction, diabetes-related symptoms, and depression, each outcome measure was considered in three separate sets of repeated-measures linear models. We used data up until 5 February 2008, when the ACCORD glycemia trial was stopped. Each set modeled the change in the HRQL measure, and each set included the following terms: glycemia intervention, secondary trial assignment, prior CVD at baseline, the baseline HRQL measure, time, and a time-by-glycemia interaction term. A first set, as specified in the protocol, included only these measures. The second set added age, race, and sex. The final set added the set of covariates listed above.

We report the overall test of the glycemia term across all visits. We visually examined the estimated change in HRQL measure across the three time points in plots. Because it is possible that intensive glucose control increases, decreases, or leaves unchanged patients' HRQL, we used two-sided P values to determine statistical significance as is conventional in clinical trial reports. Our prespecified α-level was 0.05. Although no formal adjustments for multiple comparisons were made, given the number of tests performed we estimate the probability of finding at least one model with a P value less than 0.05 to be 70.5%.

Early discontinuation of ACCORD intensive glycemia treatment

The glycemia intervention of ACCORD study was stopped early on 5 February 2008 because of higher mortality in the intensive group (21). All patients were

transitioned to the standard glycemia-regimen and continued in the ACCORD blood-pressure and lipid studies for their planned durations of at least 4 years of follow-up. To assess potential effects of the transition to standard therapy on HRQL outcomes, we conducted an additional set of analyses including the HRQL data collected after the end of the glycemia trial. Not all participants had post-transition HRQL measures, and those that did have measures were at the months 36 and 48 visits. We added a term to the model to indicate whether the measure was post-transition and added an interaction term for post-transition and glycemia arm.

RESULTS

Baseline sample characteristics

Table 1 presents the characteristics of the 2,053 participants who were included in the ACCORD HRQL substudy. There were no statistically significant differences in any of the characteristics examined by study sample. Clinical status of the HRQL substudy group at baseline was a mean HbA_{1c} of 8.3 ± 1%; means for weight and BMI were 94 kg and 32 kg/m^2, respectively, and the average duration of diabetes was 10 years (vs. 9 years in those not in the HRQL study, $P = 0.0536$), with ~37% already on an insulin treatment regimen at baseline. A comparison of Table 1 covariates on ACCORD treatment group status of intensive glycemia (goal HbA_{1c} <6%) versus standard therapy (goal HbA_{1c} 7.0–7.9%) found no statistically significant results (data not shown).

Among ACCORD HRQL study participants, the analytic sample included 1,956 (95%) who completed one or more instruments within the baseline HRQL assessments (974/1,024 for intensive glycemia, and 982/1,029 for standard therapy). Sample sizes available for repeated-measures analysis of the HRQL follow-up at 12, 36, and 48 months were $N = 921$, $N = 549$, and $N = 208$ for intensive treatment and $N = 937$, $N = 583$, and $N = 208$ for standard therapy.

Table 2 presents baseline HRQL scores by ACCORD glycemia treatment group status. At baseline, ACCORD HRQL study participants reported lower physical health (PH component score) than the general population norm of 50.0 (means = 38.0 and 37.4 per treatment group), whereas psychological well-being was similar to the general population norm of 50.0 reported by Ware et al. (19). HRQL study participants in the intensive treatment group had statistically significantly higher physical health component score mean (i.e., somewhat better HRQL) and lower (i.e., somewhat worse) MH component score mean than those assigned to standard therapy, although these differences were very small. The mean number of nonzero diabetes-related symptoms assessed on the Diabetes Symptoms Distress Checklist total symptoms reported in the intensive and standard glycemia treatment groups was 17.2 and 16.9, respectively, with a mean symptom distress rating of ~1.5, or the midpoint in the scale between somewhat and moderately. For the purposes of this study, diabetes treatment satisfaction assessed with the DTSQ treatment satisfaction scale, transformed to a percentage scale (0 to 100), was 72.5 vs. 74.0 and for the single item frequency ratings was a mean of ~1.3 for perceived hypoglycemia and 3.6 for perceived hyperglycemia.

Results for the general linear models for repeated measures for the HRQL study outcomes through the active glycemia intervention are presented in Table 3. The results from the prespecified analyses, adjusted only for trial assignment and stratification variables, did not vary substantially from the results from a fully adjusted model including a variety of baseline covariates. After controlling for baseline covariates, change in HRQL over the 48-month duration in-trial was statistically significant for the SF-36 PH component, and DTSQ treatment satisfaction scale. For physical health, the intensive glycemic control arm had a slight (0.5 point) reduction in mean PH component change score (i.e., lowered HRQL) relative to those in the standard treatment arm (−1.6 vs. −1.1; $P = 0.0345$). For treatment satisfaction, DTSQ scores were significantly higher (i.e., greater satisfaction) than baseline in both groups, with a larger improvement in satisfaction

Table 1—*Baseline characteristics of ACCORD participants by ACCORD HRQL substudy status*

	HRQL substudy		
Baseline characteristics	Yes	No	*P* value
N	2,053	7,583	
Mean age (years)	62.2 ± 6.7	62.1 ± 6.8	0.5454
Women (%)	39.6	38.4	0.3171
Non-Hispanic white (%)	65.1	64.5	0.6520
Black (%)*	19.5	19.1	0.6818
Hispanic (%)*	6.8	7.3	0.3829
Highest level of education			0.5130
High school	13.9	14.8	
High school graduate or equivalent	26.0	26.7	
Some college or college graduate	60.1	58.5	
Living with someone (%)	80.0	79.7	0.7713
Drinking (%)	22.5	24.1	0.1358
Cigarette smoker (%)			0.1973
Current	13.3	14.5	
Previous	45.6	43.7	
Never	41.2	41.9	
Mean HbA_{1c} (%)	8.3 ± 1.1	8.3 ± 1.0	0.5014
Median HbA_{1c} (%)	8.1	8.1	0.5712
Mean fasting plasma glucose (mg/dL)	177.1 ± 57.5	174.9 ± 56.0	0.1266
Median duration of diabetes (years)	10	9	0.0536
On insulin (%)	35.9	34.8	0.3233
Mean weight (kg)	94.1 ± 18.9	93.6 ± 18.6	0.2735
BMI (kg/m)	32.4 ± 5.5	32.3 ± 5.5	0.2153
Waist circumference (cm)	107.1 ± 13.9	106.8 ± 13.9	0.4899
Peripheral neuropathy (%)	43.0	42.6	0.7782
Macroalbuminuria (%)	7.3	6.3	0.1266
Microalbuminuria (%)	30.1	31.4	0.2395
Mean SBP (mmHg)	136.2 ± 17.1	136.2 ± 17.2	0.8398
Mean DBP (mmHg)	74.5 ± 10.9	75.0 ± 10.6	0.0837

SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2—*Baseline HRQL values by ACCORD glycemia arm*

Baseline HRQL measure	Glycemia arm				
	N	Standard mean	*N*	Intensive mean	*P* value
SF-36 physical component score[a]	975	37.4	966	38.0	0.0192
SF-36 mental component score[a]	975	53.4	966	52.1	0.0197
DSC total symptom score[b]	978	16.9	973	17.2	0.5654
DSC symptom distress	966	1.5	954	1.5	0.6047
DTSQ treatment satisfaction scale[c]	966	74.0	953	72.5	0.1016
DTSQ perceived hypoglycemia[d]	976	1.2	969	1.3	0.6403
DTSQ perceived hyperglycemia[d]	978	3.6	970	3.6	0.5901
PHQ-9 depression[d]	981	5.2	972	5.6	0.0816

[a]Higher SF-36 component scores signify better HRQL; [b]DSC; [c]DTSQ transformed to scale of 0–100; [d]DTSQ ratings of hyperglycemia and hypoglycemia (range: 6 [most of time] to 0 [none of time]).

with the treatment regimen (2.4 points; $P = 0.0004$) in the intensive arm. DTSQ single-item ratings of satisfaction with high and low blood glucose showed that participants in the intensive arm reported perceived improved (less) frequency of high blood glucose (−1.7 unit reduction from baseline, $P < 0.0001$), but perceived frequency of hypoglycemia was increased (0.8 unit increase from baseline, $P < 0.0001$).

Results for all time points grouped as pretransition and post-transition to the ACCORD standard glycemia-regimen and all data collected (not shown) revealed similar treatment group outcomes as the in-trial period results shown in Table 3, but with a somewhat larger improvement in mean DTSQ treatment satisfaction means in the intensive treatment group (pretransition: −0.8 vs. −0.8; post-transition: −0.8 vs. −1.2 for standard vs. intensive treatment groups, respectively). The difference between groups in the SF-36 PH and MH components was not statistically significant ($P = 0.1279$ and $P = 0.1414$, respectively). Group and transition (prepost) interactions for the HRQL outcomes were also tested, and none of the *P* values for interaction terms reached statistical significance.

CONCLUSIONS—The ACCORD trial included HRQL as a secondary objective to more fully understand the potential benefits of intensive glycemic control through the patient's point of view. After baseline HRQL status and clinical covariates in repeated-measures analysis were controlled, the results obtained for change in HRQL over a 48-month observation period after randomization did not show meaningful benefit between intensive glycemic control as compared with standard glycemic control strategies in domains of general health, diabetes symptoms, or depression. The pattern of no intensive treatment benefit on HRQL is consistent with the results for the ACCORD main study (1) of lack of cardiovascular benefit from intensive glycemia treatment with a target of HbA_{1c} <6%. There were no demonstrated effects upon MH simply from improved glycemic control in the intensive arm. Although there is some evidence in the literature of modest benefits to emotional wellbeing from improved glycemia, studies are mixed plausibly because of treatment variation and approach (22). In ACCORD both treatment arms had targets of improved glycemic control, with the intensive arm designed to achieve greater control albeit with potentially greater treatment complexity. Although the SF-36 PH component score was significantly different between groups, the absolute net difference of 0.5 units of change is trivial and well below a general threshold of ~3–5 points for a minimally important difference on these measures (19) and therefore clinically insignificant. The pattern of results indicates that for all HRQL study outcome measures considered, with the exception of treatment satisfaction (which had a trend toward increased satisfaction), there was a pattern of stability over time in scores for both treatment groups. The SF-36 PH and MH component scores were preplanned HRQL outcome measures in this study. A post hoc analysis of the eight individual SF-36 scale score means exploring the consistency of effects among the HRQL concepts that comprise the SF-36 component scores revealed no unusual or inconsistent influences on these summary component scores.

The finding of no decrement in treatment satisfaction, either when compared with those in standard treatment arm or over time, is notable because one source of reluctance in initiating intensive treatment regimens like the ACCORD intervention is reasonable concern over patient burden. The lack of decrement in subjective wellbeing particularly in the context of intensive glucose treatment may be related to several processes. There was increased access to providers, including both clinic visits and telephone contact in the intensive treatment arm. This may have increased perceived care quality and may have supported patient self-efficacy for managing diabetes. Patients' perception of optimal HbA_{1c} control in the intensive control arm, which sought to lower HbA_{1c} to < 6%, may also have been important in this regard. Research on treatment satisfaction in diabetes has shown that having improved blood glucose or HbA_{1c} levels is an important driver of satisfaction regardless of treatment intensity (23,24) and may influence patient appraisals of treatment effectiveness. Thus the results from this study add to the literature on treatment intensity, finding that patients may perceive intensive treatment as favorable. The finding that patients perceived hyperglycemia as a bigger problem than hypoglycemia may indicate the relative importance patients attach to hyperglycemia versus hypoglycemia.

The early stopping of the ACCORD intensive glycemic control arm resulted in the transition of the intensively treated participants to standard glycemic control. Analysis examining HRQL outcomes of data up to glycemia trial discontinuation on 5 February 2008 and all data through to final follow-up showed that results were highly similar pre- and post-transition. Death and trial inactivity were censoring events in this repeated-measures analysis by dictating the last valid HRQL assessment point entered into analysis (last observation carried forward). In the HRQL study sample there were a total of 78 deaths over the study period; 25 of these events resulted in no valuable HRQL information (all time points missing); in 44 events, HRQL baseline and 12-month information was possible to collect, and in nine events all but the 48-month HRQL assessment was possible to collect. We examined baseline status predictors of death or inactivity in the HRQL sample from standard demographic status, lifestyle, comorbidity, diabetes, and biomarker variables. Results found higher frequency of either death or inactivity (events) was associated with older age, being a current smoker, living alone,

albuminuria, and diastolic blood pressure. In a secondary analysis (data not shown) that included predictors of events produced highly similar results to the formal analysis presented above.

There are several potential limitations to consider when interpreting these data or findings. Our sample is not representative of the entire population of patients with type 2 diabetes. ACCORD participants had a mean age of 62, diabetes duration of 10 years, risk factors for CVD, a baseline $HbA_{1c} \geq 7.5\%$, and willingness to undergo intensive treatment to control glucose, including frequent clinic visits and the use of insulin. Although we assessed a broad range of factors for their associations with HRQL, there are many other factors that could have been examined, especially in behavioral and psychosocial domains that may have been more responsive to potential burdens or risks with intensive glycemic control strategies. For example, our study did not include covariates concerning emotional state, mood, locus of control, social support, or others (5,25), limiting our ability to comment on the role of these influences. For the DTSQ measure, during ACCORD vanguard, which enrolled 1,184 patients, item 8 (recommend treatment to others) was not assessed in either treatment group. Given the high internal consistency reliability of the DTSQ ($\alpha > 0.85$) we believe that this item omission in a subset of patients would have little appreciable impact on the estimated treatment effect for this outcome. Finally, although we included known correlates of death and participant study inactivity in our models to limit their influence in treatment group comparisons, this step could not remove all potential sources of bias and neither would the alternative of imputing missing values. We studied subjective, self-reported health appraisal of participants. A health utility measurement model is an alternative approach that allows for the outcome of death to be incorporated in health scores. We neither planned nor examined a utility model with these data.

In summary, this study demonstrated no significant HRQL benefit or harm from the ACCORD intensive glycemic control strategies. Participants in the intensive treatment arm reported a greater increase in satisfaction with their diabetes treatment. The latter result suggests that new or emerging treatment strategies in diabetes that are both intensive and safe could be perceived by patients as worthwhile

Table 3—*Results of repeated-measures analyses of HRQL outcomes by glycemia arm and change in score from baseline across all visits*

	Prespecified analysis in protocol[e]						Fully adjusted model[f]					
	Standard		Intensive		Test		Standard		Intensive		Test	
Variable	Estimate[g]	95% CI	Estimate[g]	95% CI	*P* value		Estimate[g]	95% CI	Estimate[g]	95% CI	*P* value	
SF-36 physical component score	−0.2	(−0.5 to −0.2)	−0.7	(−1.1 to −0.4)	0.0242		−1.1	(−2.0 to −0.2)	−1.6	(−2.5 to −0.7)	0.0345	
SF-36 mental component score	−0.3	(−1.0 to 0.4)	0.2	(−0.6 to 0.9)	0.3361		0.8	(−1.0 to 2.6)	1.4	(−0.5 to 3.2)	0.2938	
DSC total symptom score[a]	−1.2	(−1.7 to −0.6)	−0.6	(−1.2 to −0.1)	0.2051		−0.4	(−1.9 to 1.0)	0.1	(−1.4 to 1.6)	0.1940	
DSC symptom distress	0.0	(−0.1 to 0.0)	0.0	(−0.0 to 0.0)	0.2319		−0.1	(−0.2 to 0.0)	0.0	(−0.1 to 0.1)	0.1512	
DTSQ treatment satisfaction scale[b]	11.8	(10.9–12.8)	14.0	(13.1–15.0)	0.0011		11.1	(8.6–13.5)	13.5	(11–15.9)	0.0004	
DTSQ perceived hyperglycemia[c]	−0.9	(−1.0 to −0.8)	−1.4	(−1.5 to −1.3)	<0.0001		−1.2	(−1.5 to −0.9)	−1.7	(−2.0 to −1.5)	<0.0001	
DTSQ perceived hypoglycemia[c]	0.3	(0.2–0.4)	0.7	(0.6–0.8)	<0.0001		0.4	(0.1–0.6)	0.8	(0.5–1.0)	<0.0001	
PHQ-9 continuous score[d]	−0.8	(−1.1 to −0.6)	−0.7	(−0.9 to −0.4)	0.4594		−1.0	(−1.7 to −0.4)	−0.9	(−1.5 to −0.3)	0.4414	

[a]DSC; [b]WHO DTSQ transformed to scale of 0–100; [c]DTSQ ratings of hyperglycemia and hypoglycemia (range: 6 [most of time] to 0 [none of time]); [d]PHQ; [e]as specified in protocol includes adjustment for the stratification variables at randomization, secondary trial, and secondary trial assignment; [f]adjusted for previous CVD, secondary trial, secondary trial assignment, age, race, sex, duration of diabetes, smoking, living alone, weight, waist circumference, BMI, baseline HbA_{1c}, fasting blood glucose, SBP and DBP, heart rate, neuropathy, retinal surgery, macro- and microalbuminuria, insulin, sulfonylureas, thiazolidinedione, β-blockers, antihypertensive medication, and triglycerides; [g]least squares mean estimated at the mean value of all continuous covariates across all time points.

and that treatment acceptability is not a limiting factor in complex interventions such as ACCORD.

Acknowledgments—The ACCORD study was supported by grants (N01-HC-95178, N01-HC-95179, N01-HC-95180, N01-HC-95181, N01-HC-95182, N01-HC-95183, N01-HC-95184, IAA-Y1-HC-9035, and IAA-Y1-HC-1010) from the National Heart, Lung, and Blood Institute; by other components of the National Institutes of Health, including the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the National Eye Institute; by the Centers for Disease Control and Prevention; and by General Clinical Research Centers.

The following companies provided study medications, equipment, or supplies: Abbott Laboratories, Amylin Pharmaceutical, AstraZeneca, Bayer HealthCare, Closer Healthcare, GlaxoSmithKline, King Pharmaceuticals, Merck, Novartis, Novo Nordisk, Omron Healthcare, sanofi-aventis, and Schering-Plough. R.T.A. is a consultant for Abbott Laboratories, Inc. D.G. is a consultant for Merck Inc. and serves as a DSMB member for Takeda Inc. J.-A.S.-H. is an investigator of clinical trials sponsored by Merck, GSK, Lilly and Abbott Laboratories through HealthPartners Research Foundation. R.C. serves as an investigator on clinical trials sponsored by Amylin, Abbott, Bayer, Daiichi Sankyo, Dexcom, Edwards Lifesciences, Eli Lilly, Hygeia, Intarcia, Johnson and Johnson/LifeScan, MannKind, Medtronic, Merck, Novo Nordisk, Quotient Diagnostics, ResMed, Roche, sanofi-aventis, Schering-Plough, Takeda, Valeritas; and serves as an Advisory Board Member for Abbott, Bayer, CeQur, Eli Lilly, Novo Nordisk, and Roche. No other potential conflicts of interest relevant to this article were reported.

R.T.A. wrote the manuscript and researched data. K.M.V.N. researched data, contributed to discussion, and edited the manuscript. P.F. contributed to discussion, conducted the statistical analyses, and co-wrote the manuscript. D.G. researched data, contributed to discussion, and reviewed and edited the manuscript. M.K.A. contributed to discussion and edited the manuscript. D.L.S. researched data and reviewed and edited the manuscript. J.-A.S.-H. contributed to discussion and reviewed and edited the manuscript. T.B. researched data and reviewed and edited the manuscript. R.C. contributed to discussion and reviewed and edited the manuscript. P.J.O. researched data, contributed to discussion, and reviewed and edited the manuscript. A.S. contributed to discussion, co-wrote the manuscript, and reviewed and edited the manuscript. P.Z. researched data, contributed to discussion, and reviewed and edited the manuscript. M.D.S. contributed to discussion, researched data, and reviewed and edited the manuscript.

The authors thank Jane Waldeck, Pennsylvania State University College of Medicine, for help with preparing the manuscript.

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