Insulin Dose and Cardiovascular Mortality in the ACCORD Trial

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OBJECTIVE

In the ACCORD trial, intensive treatment of patients with type 2 diabetes and high cardiovascular (CV) risk was associated with higher all-cause and CV mortality. Post hoc analyses have failed to implicate rapid reduction of glucose, hypoglycemia, or specific drugs as the causes of this finding. We hypothesized that exposure to injected insulin was quantitatively associated with increased CV mortality.

RESEARCH DESIGN AND METHODS

We examined insulin exposure data from 10,163 participants with a mean follow-up of 5 years. Using Cox proportional hazards models, we explored associations between CV mortality and total, basal, and prandial insulin dose over time, adjusting for both baseline and on-treatment covariates including randomized intervention assignment.

RESULTS

More participants allocated to intensive treatment (79%) than standard treatment (62%) were ever prescribed insulin in ACCORD, with a higher mean updated total daily dose (0.41 vs. 0.30 units/kg) ($P < 0.001$). Before adjustment for covariates, higher insulin dose was associated with increased risk of CV death (hazard ratios [HRs] per 1 unit/kg/day 1.83 [1.45, 2.31], 2.29 [1.62, 3.23], and 3.36 [2.00, 5.66] for total, basal, and prandial insulin, respectively). However, after adjustment for baseline covariates, no significant association of insulin dose with CV death remained. Moreover, further adjustment for severe hypoglycemia, weight change, attained A1C, and randomized treatment assignment did not materially alter this observation.

CONCLUSIONS

These analyses provide no support for the hypothesis that insulin dose contributed to CV mortality in ACCORD.

Epidemiological analyses and some interventional studies suggest that attainment of lower mean levels of A1C is associated with reduced risk of cardiovascular (CV) death as well as other medical outcomes (1,2). Other epidemiological data, however, suggest that optimal A1C may be approximately 7.5% (58 mmol/mol) and indicate higher mortality in those with both lower and higher A1C levels (3).

Recent randomized studies have failed to demonstrate reductions of all-cause or CV mortality accompanying intensive glucose-lowering therapy in people with type 2 diabetes (4–7). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, both all-cause and CV mortality were higher with intensive glycemic treatment (4,5). This observation has prompted reevaluation of potential risks associated with seeking intensive glycemic treatment goals.

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**The entire list of the ACCORD Investigators can be found in an appendix to ref. 4.*

Further analyses from ACCORD have failed to establish that differences in the rate of reduction of A1C to near-normal levels, severe hypoglycemia, or weight gain explain the increased death rate among intensively treated subjects (2,4,8–11). Instead, Riddle et al. (12) found that the excess mortality in ACCORD occurred among participants who were randomized to intensive treatment but were unable to reduce their average A1C levels during the initial year of follow-up to <7.0% (53 mmol/mol). Also, rates of severe hypoglycemia were elevated at higher levels of A1C during treatment in both the intensively treated and standard treatment groups (11).

Based on these findings, it seems possible that progressively greater use of insulin for treating persistently high A1C might have contributed to increased CV mortality in ACCORD. This possibility is supported by previous epidemiological analyses showing an association between insulin therapy and mortality (3,13–15). In the Helsinki Policemen Study, hyperinsulinemia was associated with increased all-cause and CV mortality independent of other risk factors (16). Furthermore, actions of insulin at the cellular level may favor vascular changes leading to adverse CV outcomes (17,18). It is therefore plausible that intensive treatment with increasingly higher doses of exogenous insulin fails to normalize glucose levels and yet causes adverse effects in severely insulin-resistant individuals. This hypothesis could be tested with ACCORD data because prescribed adjustments of glucose-lowering medications, including insulin, were recorded for all participants. For clarification of the relationships of exogenous insulin dose, glycemic control, and CV mortality, we performed post hoc analyses of ACCORD baseline and follow-up data.

RESEARCH DESIGN AND METHODS

ACCORD Study Design

The rationale, study design, and entry criteria for the ACCORD trial have previously been described (19–21). The ACCORD trial was conducted in the U.S. and Canada at 77 clinical sites. Between January 2001 and October 2005, 10,251 participants with type 2 diabetes and either a prior CV event or other evidence of high CV disease risk were enrolled. Participants were randomly assigned to either a standard glycemic treatment strategy (n = 5,123) with the aim of keeping A1C between 7.0% (53 mmol/mol) and 7.9% (63 mmol/mol) or an intensive strategy (n = 5,128) with the aim of achieving A1C <6.0% (42 mmol/mol). In addition, as described in detail elsewhere (19–21), participants were also allocated to interventions in the blood pressure and lipid-lowering studies that were also part of ACCORD. The primary end point of ACCORD was a composite of CV mortality, nonfatal myocardial infarction, or nonfatal stroke. All-cause mortality was a predefined secondary end point.

In February 2008, the intensive glycemic treatment strategy was stopped owing to an increase in all-cause mortality, and intensive participants were transitioned to standard therapy. The data set used for the present analyses includes 10,163 of the 10,251 randomized participants. The remaining 88 participants were excluded because they did not have follow-up data for medications or A1C values.

Participants visited clinical sites every 2 to 4 months. At the 4-month intervals, they were asked about hypoglycemia and other medical events, were weighed, and had blood collected for A1C measurements. Follow-up visits took place between January 2001 and June 2009, with a mean of 4.97 years of follow-up per participant, representing 50,464 participant-years. Analyses were performed using all ACCORD follow-up until the closeout visits, which began in the spring of 2009.

Definition of Covariates and Exposures

Baseline Covariates

Baseline participant covariates included those used by Riddle et al. (12) in their predictive models for ACCORD mortality. These covariates are listed in Table 1.

Time-Varying Medication Exposure

We defined exposure to insulin in terms of the updated, average daily recommended (prescribed) dose in units per kilogram of body weight, calculated in a cumulative manner and updated each time a dose changed (the cumulative daily dose over time divided by the number of days of follow-up). If the information was missing at a particular visit for participants who were known to have recently been on insulin, then they were deemed to be on the same dose of insulin as their last recorded dose. The calculation of insulin dose included data from randomization until CV death or the end of follow-up. Updated, average measures for three different characterizations of insulin, including total insulin, basal insulin (including the component of premixed insulin), and bolus insulin (including the component of premixed insulin), were the main predictors of interest. Basal insulins used included glargine, detemir, and human NPH; bolus insulins included aspart, glulisine, lispro, and human regular insulin.

Other Time-Varying Covariates

Updated, average A1C during follow-up was calculated in a cumulative manner throughout follow-up and updated each time a new value was obtained (i.e., the newly obtained A1C was allocated to each follow-up day since the previously obtained A1C, and the mean of these values over all follow-up days was obtained). Weight change from baseline was defined as a time-varying covariate. Both have previously been described (12).

Statistical Analyses

Means or percentages of potential confounding variables at baseline were computed. Baseline characteristics of participants who were prescribed any type of insulin therapy during the study were compared with those who were never prescribed insulin, stratified by treatment assignment, with χ^2 tests for categorical variables and two-sample t tests for continuous variables (Supplementary Tables 1 and 2).

Unadjusted relationships of baseline factors with CV mortality were examined to identify potentially confounding variables using Cox proportional hazards models (Table 1). Hazard ratio (HR) estimates and their 95% CIs were computed and Wald tests were performed. For selection of baseline covariates for inclusion, participant covariates and clinical site characteristics were used in model selection procedures; stepwise, backward, and forward selection approaches resulted in the same models. The significance level for entering and removing a covariate from the model was 0.05. Note that the level of collinearity for all the baseline factors was inspected and all variance inflation factor

Table 1—Baseline characteristics of the study population and of the study sites at which the participants were enrolled, with univariate (unadjusted) HRs for CV mortality

Baseline characteristic	Value	HR (95% CI)	*P*	Overall *P*
Age (years)	62.2 ± 6.8	1.07 (1.05, 1.08)	<0.001	
Female	3,906 (38.4)	0.57 (0.44, 0.73)	<0.001	
Race/ethnicity				0.097
African American	1,927 (19.0)	0.90 (0.68, 1.19)	0.466	
Hispanic	727 (7.2)	0.83 (0.53, 1.30)	0.424	
Other	1,110 (10.9)	0.59 (0.39, 0.90)	0.015	
Non-Hispanic white	6,399 (63.0)	1		
Diabetes duration (years)				<0.001
≤5	2,988 (29.4)	1		
6–10	2,914 (28.7)	0.85 (0.62, 1.17)	0.316	
11–15	1,942 (19.1)	0.98 (0.70, 1.37)	0.905	
≥16	2,319 (22.8)	1.68 (1.27, 2.23)	<0.001	
History of CV disease (yes vs. no)	3,576 (35.2)	3.11 (2.49, 3.88)	<0.001	
Prior myocardial infarction (yes vs. no)	471 (4.6)	2.87 (2.05, 4.00)	<0.001	
Heart failure/congestive heart failure (yes vs. no)	491 (4.9)	4.57 (3.43, 6.09)	<0.001	
Retinal surgery (yes vs. no)	890 (8.8)	1.56 (1.13, 2.15)	0.007	
Amputation (yes vs. no)	184 (1.8)	3.32 (2.06, 5.33)	<0.001	
Education				<0.001
Less than high school	1,501 (14.8)	2.30 (1.65, 3.21)	<0.001	
High school graduate	2,682 (26.4)	1.39 (1.00, 1.93)	0.048	
Some college	3,330 (32.8)	1.34 (0.98, 1.84)	0.068	
College graduate or more	2,643 (26.0)	1		
Smoking				0.001
Former	4,492 (44.2)	1.56 (1.23, 1.98)	<0.001	
Current	1,411 (13.9)	1.30 (0.92, 1.85)	0.140	
Never	4,260 (41.9)	1		
Alcohol use				0.348
1–6 drinks/week	1,963 (19.3)	0.82 (0.61, 1.09)	0.171	
≥7 drinks/week	470 (4.6)	1.09 (0.67, 1.78)	0.733	
No drinks/week	7,725 (76.0)	1		
Insulin use (yes vs. no)	3,559 (35.0)	1.69 (1.36, 2.10)	<0.001	
ACE inhibitor (yes vs. no)	5,397 (53.1)	1.18 (0.95, 1.47)	0.135	
Angiotensin receptor blockers (yes vs. no)	1,618 (15.9)	0.67 (0.47, 0.95)	0.024	
Statins (yes vs. no)	6,311 (62.1)	1.16 (0.93, 1.46)	0.194	
Metformin (yes vs. no)	6,080 (59.8)	0.90 (0.73, 1.12)	0.360	
Sulfonylureas (yes vs. no)	5,092 (50.1)	0.77 (0.62, 0.96)	0.021	
Thiazolidinediones (yes vs. no)	1,967 (19.4)	0.76 (0.57, 1.03)	0.077	
BMI (kg/m^2)	32.2 ± 5.5	1.01 (0.99, 1.03)	0.382	
Systolic blood pressure (mmHg)	136.3 ± 17.1	1.00 (1.00, 1.01)	0.365	
Diastolic blood pressure (mmHg)	74.9 ± 10.6	0.98 (0.97, 0.99)	<0.001	
Visual acuity				<0.001
<20/40	2,310 (23.8)	3.22 (2.06, 5.04)	<0.001	
20/20–20/40	5,906 (60.8)	1.97 (1.28, 3.04)	0.002	
≥20/20	1,502 (15.5)	1		
Peripheral neuropathy (yes vs. no)	4,328 (42.7)	1.86 (1.49, 2.31)	<0.001	
Heart rate	72.6 ± 11.7	1.00 (0.99, 1.01)	0.847	
Q-T index	101.7 ± 5.2	1.06 (1.04, 1.07)	<0.001	
A1C in % (mmol/mol)	8.3 ± 1.1 (67 ± 1)	1.19 (1.09, 1.31)	<0.001	
Fasting plasma glucose (mg/dL)	175.3 ± 56.2	1.00 (1.00, 1.00)	0.258	
LDL (mg/dL)	104.9 ± 33.9	1.00 (1.00, 1.00)	0.515	
HDL (mg/dL)	41.8 ± 11.6	0.98 (0.97, 0.99)	<0.001	
Triglycerides (mg/dL)	190.3 ± 148.7	1.00 (1.00, 1.00)	0.928	
Serum creatinine (mg/dL)	0.9 ± 0.2	4.04 (2.81, 5.82)	<0.001	

Continued on p. 2003

Table 1—Continued

Baseline characteristic	Value	HR (95% CI)	*P*	Overall *P*
Urinary albumin-to-creatinine ratio (mg/mg)				<0.001
<30	6,937 (68.8)	1		
30 to ≤300	2,481 (24.6)	1.96 (1.54, 2.49)	<0.001	
>300	670 (6.6)	3.71 (2.73, 5.04)	<0.001	
Integrated health plan (yes vs. no)	4,050 (39.9)	1.41 (1.13, 1.75)	0.002	
Endocrinologist or diabetologist (either vs. other physician)	5,664 (55.7)	0.81 (0.65, 1.00)	0.052	
Certified diabetes educator on staff at randomization	3,927 (38.6)	0.78 (0.62, 0.98)	0.030	
Site size				0.978
<100	1,568 (15.4)	0.99 (0.72, 1.37)	0.969	
100–150	3,027 (29.8)	1.02 (0.80, 1.31)	0.848	
>150	5,568 (54.8)	1		

Values are means ± SD or *n* (%).

measures were <2.2, tolerance measures were >0.45, and condition index measures were <3.2; thus, we did not see collinearity as an issue in our analyses.

Comparisons of updated, average insulin doses between the two intervention groups were performed using two-sample *t* tests. The association between updated, average A1C and updated, average insulin dose (total, basal, and bolus) was examined using linear regression models (Fig. 1). For each type of insulin, the updated, average insulin dose was the dependent variable and the updated, average A1C was the independent variable. The treatment assignment was included in the model. To check whether the association was the same in both treatment assignment groups, we included an interaction between treatment assignment and updated, average A1C.

A series of Cox proportional hazards regression models was computed to explore the association between each category of insulin and CV mortality (Table 2). Model 1 adjusted for the baseline factors identified in the selection procedures, with the exception of baseline insulin use, since this variable would be highly confounded with the initial dose of insulin. Model 2 added indicators representing assignment to either blood pressure or lipid substudy groups and within blood pressure/lipid substudy treatment assignments, in addition to time-dependent measures of severe hypoglycemia, and weight change. Model 3 added updated, average A1C as a time-dependent covariate. Model 4 added the variable representing glycemic treatment assignment. Each model was fit three times including a single updated, average insulin variable at a time (i.e., separate models for total insulin, basal insulin, and bolus insulin) to explore the association with CV mortality. Furthermore, interactions between each insulin exposure and both duration of diabetes (≤10 years vs. >10 years) and baseline history of CV disease were tested within model 1, and the interactions between glycemic treatment assignment and each insulin exposure were tested using model 4.

For identification of which baseline characteristics were most responsible for the observed association between CV mortality and insulin dose in the unadjusted model, an additional series of Cox proportional hazards models was fitted using three separate approaches. HRs for total insulin dose were estimated: *1*) in the presence of each baseline covariate by itself, *2*) when the covariate was the only potential confounder not included, and *3*) based on a stepwise approach that enters variables based on the size of the *P* value. For the stepwise approach, the confounding variable in model 1 that was most significantly associated with CV mortality was entered in the unadjusted model, with the second most significantly associated confounding variable being subsequently entered and so forth until the significance of the HR between CV mortality and insulin dose disappeared (Supplementary Table 3).

For exploration of the linearity assumption between updated, average A1C and the insulin variables relative to CV mortality, smoothing curves (penalized B-splines) were fitted to the relationships over the range of updated, average A1C levels and insulin variables (Fig. 2). The curves were calculated based on the linear portion of the Cox proportional hazards models with full covariate adjustment (model 4). Tests of linearity of the effects of updated, average A1C and insulin variables on CV mortality were performed by comparing models containing linear terms with those containing spline terms using likelihood ratio tests. The linearity tests were performed within each treatment group. Tests of differences of the nonlinear fits between two glycemic treatment assignment groups were performed by comparing the nested models with one spline (i.e., using the same lines for both intervention groups) and two splines (i.e., allowing different lines within intervention groups) using a likelihood ratio test.

RESULTS

Baseline Characteristics and CV Mortality

Our comparison between the baseline characteristics of those prescribed insulin postrandomization and those never prescribed insulin (within intervention groups) identified several statistically significant differences between the two groups in both arms (Supplementary Tables 1 and 2). Factors associated with prescription of insulin during ACCORD included, but were not limited to, race/ethnicity, diabetes duration, history of CV disease, smoking, diabetes-related complications, the type of health plan the participant was enrolled in, and whether the site was led by an endocrinologist or diabetologist rather than another type of medical practitioner. Thus, these results illustrate some of the confounding between participant characteristics and future prescription of insulin.

There were 328 total CV deaths observed in ACCORD (*N* = 10,163). Several of the baseline characteristics were

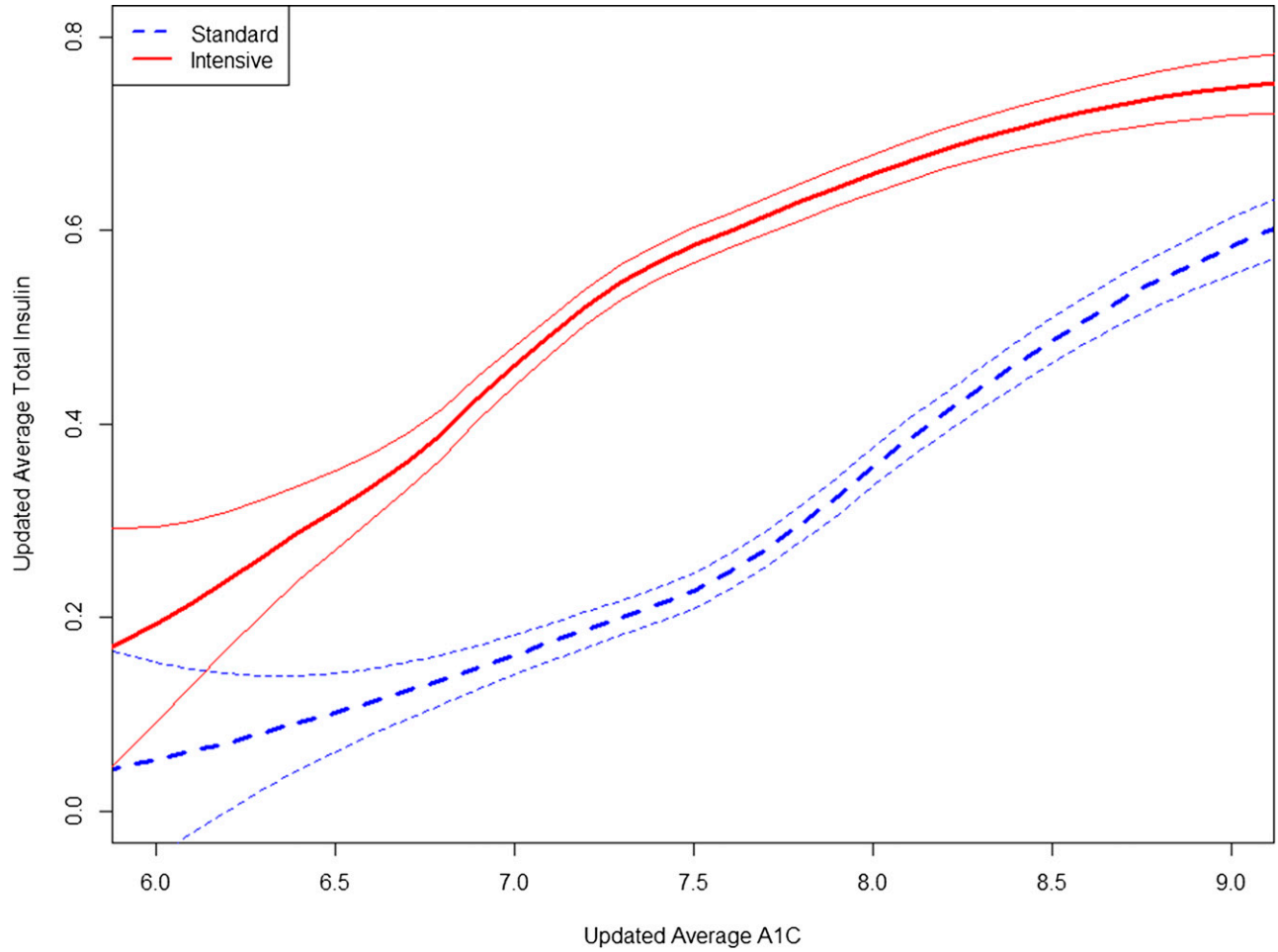

Figure 1—Smoothing curves for association between updated, average A1C (%) and updated, average total insulin dose (units/kg) for the two treatment strategies over the range of average A1C from 6.0 to 9.0% (42 to 75 mmol/mol). The bold red line represents the intensive treatment group, and the bold dashed blue line represents the standard group. The finer-colored lines represent the 95% CIs for each group. The association between A1C level and insulin dose in the intensive group was marginally different compared with the association in the standard group (P for interaction = 0.065). In the stratified analysis, an increase in updated, average A1C was associated with an increase in updated, average insulin dose within each treatment group (regression coefficient estimates are 0.20 and 0.18 for the intensive group and the standard group, respectively; both $P < 0.001$).

associated with an increased risk of CV mortality in the univariate analysis (Table 1). Those included older age; male sex; longer duration of diabetes; previous history of CV disease, myocardial infarction, congestive heart failure, and diabetes-related complications; insulin use prior to randomization; and higher A1C level, serum creatinine, and urine albumin-to-creatinine ratio.

Insulin Exposure During Intensive Versus Standard Treatment

More participants allocated to intensive treatment (79%) than standard treatment (62%) used insulin at some time during follow-up. The mean ± SD (25th percentile, median, 75th percentile) of the updated, average daily total insulin dose for all participants in the intensive arm (counting the dose in those not using insulin as 0) was 0.41 ± 0.43 units/kg body wt (0.03, 0.31, 0.65) compared with 0.30 ± 0.40 units/kg

Table 2—HRs (95% CI) and *P* values for CV mortality based on updated, average insulin dose (per 1 unit/kg) from Cox proportional hazards models

Insulin categories	Unadjusted	Model 1	Model 2	Model 3	Model 4
Total insulin	1.83 (1.45, 2.31) <0.001	1.21 (0.92, 1.60) 0.173	1.21 (0.91, 1.61) 0.191	1.12 (0.84, 1.49) 0.454	0.99 (0.74, 1.34) 0.969
Basal insulin	2.29 (1.62, 3.23) <0.001	1.30 (0.87, 1.94) 0.207	1.29 (0.85, 1.95) 0.227	1.13 (0.74, 1.72) 0.564	0.94 (0.61, 1.46) 0.796
Bolus insulin	3.36 (2.00, 5.66) <0.001	1.65 (0.88, 3.11) 0.117	1.63 (0.85, 3.12) 0.140	1.48 (0.77, 2.84) 0.237	1.23 (0.63, 2.40) 0.548

Model 1 adjusted for age, history of CV disease, heart failure, amputation, education, angiotensin receptor blockers, peripheral neuropathy, Q-T index, baseline A1C, HDL, serum creatinine, urinary albumin-to-creatinine ratio, integrated health plan, and certified diabetes educator on staff at randomization. Model 2 adds assignment to blood pressure or lipid trial and treatment assignment within these, severe hypoglycemia, and weight change. Model 3 adds updated, average A1C. Model 4 adds glycemic treatment strategy assignment.

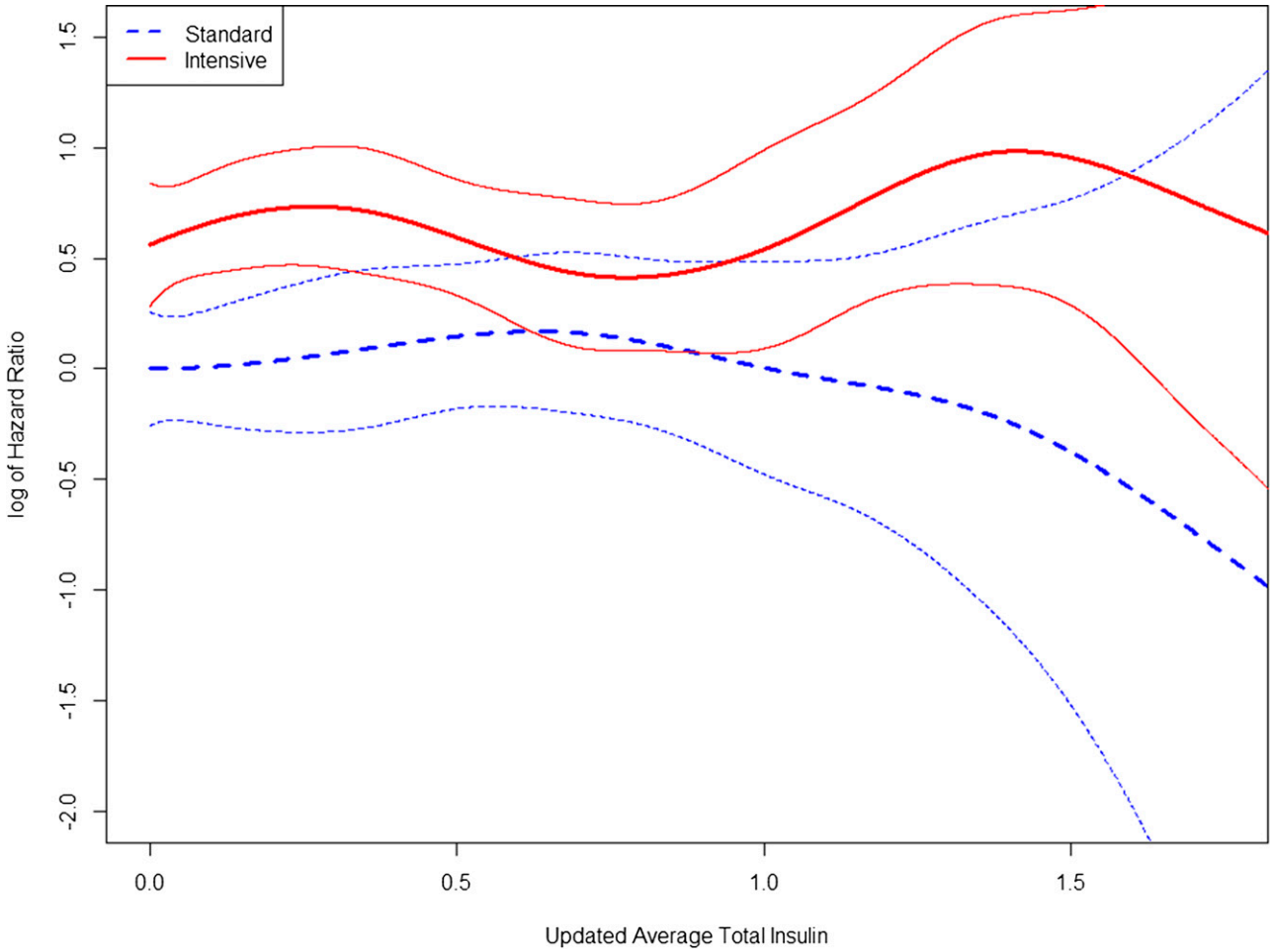

Figure 2—Spline curves displaying the risk of CV mortality with the two treatment strategies over the range of updated, average total insulin dose (units/kg). The curves represent the linear part of the Cox proportional hazards models derived from values for updated, average total insulin from model 4. The bold red line represents the intensive treatment group, the bold dashed blue line represents the standard group, and the finer-colored lines represent the 95% CIs for each group. The reference group is for an updated, average total insulin of 0 in the standard group. There was no evidence that the shape of the curves was statistically different between treatment groups (P for interaction = 0.358), and there was no evidence of nonlinearity within each treatment group (intensive P = 0.375; standard P = 0.523) or evidence of a nonzero slope within groups (intensive P = 0.975; standard P = 0.930).

body wt (0, 0.10, 0.53) in the standard arm ($P < 0.001$). The corresponding values for basal insulin were 0.30 ± 0.29 units/kg body wt (0.02, 0.24, 0.46) vs. 0.22 ± 0.28 units/kg body wt (0, 0.09, 0.38) ($P < 0.001$) and for bolus insulin were 0.12 ± 0.18 units/kg body wt (0, 0.02, 0.18) vs. 0.08 ± 0.17 units/kg body wt (0, 0, 0.10) ($P < 0.001$).

Relationship Between Updated, Average A1C and Updated, Average Total Insulin Dose

The updated, average total insulin dose increased linearly with increasing updated, average A1C values in both treatment arms (Fig. 1). At all A1C levels, the mean total daily insulin dose in the intensive treatment arm was higher than in the standard treatment arm.

The association between A1C level and insulin dose was not statistically different between the two glycemic treatment arms (P = 0.065). In the stratified analysis, an increase in updated, average A1C was associated with an increase in updated, average insulin dose within each treatment group (regression coefficient estimates 0.20 and 0.18 for the intensive group and the standard group, respectively, both $P < 0.001$).

Association Between Insulin Dose and CV Mortality With and Without Adjustment for Baseline and On-Treatment Characteristics

Results of the proportional hazards regression models adjusting for the effects of potentially confounding variables are summarized in Table 2. Before adjustment for covariates, a 1 unit/kg increase in average daily insulin dose was associated with significant increases in risk of CV death for all three categories of insulin use (HR 1.83 [95% CI 1.45, 2.31] for total insulin, 2.29 [1.62, 3.23] for basal insulin, and 3.36 [2.00, 5.66] for bolus insulin). After adjustment for baseline factors in model 1, HRs were attenuated and no longer statistically significant for all categories of insulin. Further adjustment for treatment allocation in the blood pressure and lipid components of ACCORD; occurrence of severe hypoglycemia; weight change; updated, average A1C; and intensive versus standard treatment assignment led to little further change in these associations (models 2, 3, and 4). In the fully adjusted model (model 4), the HRs for associations of total, basal,

and prandial insulin exposure with CV death were 0.99 (0.74, 1.34), 0.94 (0.61, 1.46), and 1.23 (0.63, 2.4), respectively.

Because most of the attenuation of the unadjusted association between insulin dose and CV mortality occurred after the inclusion of only the baseline factors in the multivariable model 1, we examined each of the 14 baseline variables separately. Both in the absence of other baseline covariates and as the last covariate adjusted for, the greatest attenuation of the HR for total insulin was after adjustment for a history of congestive heart failure. With use of a forward stepwise approach based upon sequentially adding covariates with the smallest *P* value, the greatest effect was seen with adjustment for baseline A1C, the presence of a history of congestive heart failure, peripheral neuropathy, and CV disease at baseline. Attenuation of the associations with CV mortality occurred similarly for total insulin, basal insulin, and mealtime insulin (The results for the total insulin dose are shown in Supplementary Table 3).

Investigation of differential effects of insulin dose on CV mortality within baseline levels of duration of diabetes indicated that we could not conclude that the insulin effect was different within levels ($\leq$10 years vs. $>$10 years) of baseline duration of diabetes (interaction *P* values for total, basal, and bolus insulin are $P = 0.110$, $P = 0.205$, and $P = 0.123$). Similar results were found for baseline CV history, where we found that the interactions were not significant for all the three insulin variables (interaction *P* values for total, basal, and bolus insulins are 0.876, 0.842, and 0.794, respectively).

The spline results provide no evidence that the shapes of the curves were statistically different between treatment groups ($P = 0.358$) (Fig. 2) and no evidence of nonlinearity within each treatment group (intensive $P = 0.375$; standard $P = 0.523$) or evidence of a nonzero slope within groups (intensive $P = 0.975$; standard $P = 0.930$). Assessment of basal and bolus doses separately over the observed dose ranges resulted in similar findings.

Association Between Updated, Average A1C and CV Mortality

As in prior analyses of all-cause mortality, higher updated, average A1C was associated with higher CV mortality both before (HR 1.38 [95% CI 1.22, 1.55], $P < 0.001$) and after (HR 1.49 [95% CI 1.30, 1.71], $P < 0.001$) adjustment for updated, average total insulin dose and other covariates listed in model 4 of Table 2. The associations were similar when updated, average basal and bolus insulin were used (HR 1.50 and 1.48, respectively).

CONCLUSIONS

As previously reported, insulin was used more often and at higher average doses in the intensive arm of ACCORD than in the standard arm. This was true for basal and prandial insulin separately, as well as for total daily insulin dose. These findings were not unexpected, given the policy of the ACCORD study to escalate the dose of insulin in order to attain the lower A1C target.

Within each arm of the study, there was a strong correlation between the updated, average A1C and the dose of insulin used (Fig. 1). It was also noted that, for any A1C level, participants in the intensive arm had a higher average dose of insulin than those in the standard arm. This observation is consistent with our expectation that individuals in the intensive arm who were unable to reduce A1C $<$7% (53 mmol/mol) used higher doses of injected insulin than those in the standard arm.

Before adjustment for baseline characteristics, which differed substantially between participants using insulin and those not using insulin, an increase in daily insulin dose by 1 unit/kg body wt was associated with a 1.8- to 3.4-fold increase in hazard of CV death, supporting the possibility that the dose of injected insulin used may have enhanced CV risk. The unadjusted HRs were similar to what has been observed in epidemiological studies linking insulin exposure with mortality (3,15).

However, after adjustment for the effects of baseline characteristics in the multivariable model 1, insulin dose was no longer significantly associated with CV mortality. Additional models were used to investigate on-treatment factors that could have possibly been related to both CV mortality and insulin dose adjustments. Notably, in model 2, which additionally adjusted for the change of weight and occurrence of severe hypoglycemia, the relationship between total insulin dose and CV mortality was unchanged from that in model 1, which only adjusted for baseline characteristics. This absence of attenuation of risk provides no support for the hypothesis that higher insulin doses lead to CV death by causing severe hypoglycemia.

Model 3 had postrandomization A1C levels added to model 2 because glycemic control could be related to prescribed insulin doses and also to severe hypoglycemia or other potential mediators of risk. Finally, model 4 had the glycemic treatment strategy assignment added to model 3 in recognition that there could be other features of the treatment strategies used, beyond those already included, that might influence outcomes. Adjustment for these postrandomization covariates in models 3 and 4 provided further, albeit modest, attenuation of the HRs, with confidence limits ranging from at least a 26% reduction to at most a 34% increase in the hazard associated with insulin use of any type. For basal and bolus insulin, the CIs are wider than for total insulin, encompassing effects for a 1 unit/kg difference in insulin dose that range from $\sim$40% reduction to a 250% increase in the risk of CV mortality. Overall, conclusions about the relationship between insulin dose and CV death were little affected by addition of the postrandomization covariates, but the width of the CIs calls attention to the need for caution in interpretation.

In a separate analysis, the baseline characteristics that contributed the most to the association between insulin dose and CV death were baseline A1C, history of congestive heart failure, peripheral neuropathy, and history of CV disease (Supplementary Table 3). Notably, the distributions of these four covariates were significantly different at baseline in the subjects who used insulin during the study versus those who did not, regardless of their assignment to the intensive versus standard treatment groups (Supplementary Tables 1 and 2). Clearly patients who used insulin differed from patients who did not use insulin in their underlying risk of CV mortality.

The results of these analyses, failing to confirm an independent relationship between insulin dose and CV mortality, are consistent with the results of the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial in which

participants were randomized to treatment with basal insulin or to standard oral step therapy as the basis for glycemic management (22). No association between basal insulin use and CV risk was found in the high–CV risk cohort studied in ORIGIN, although the ORIGIN study population had a much shorter duration of diabetes or dysglycemia and less evidence of microvascular complications of diabetes than ACCORD participants.

The lack of harmful relationship between insulin dose and CV mortality in our study is also consistent with what was observed in the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS). In the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) cohort, there were fewer CV events in the intensive arm, where subjects received higher insulin doses, than in the conventional arm (23). Similarly, in the UKPDS no increase in CV events was found among individuals assigned to treatment with insulin compared with sulfonylurea or a conventional treatment strategy based on lifestyle intervention (24).

However, the present findings differ to some extent from those in other reports, where insulin was associated with mortality (3,14–16). One reason for the difference may be the quantity and quality of data prospectively collected during >3 years of follow-up of the >10,000 participants in ACCORD, including extensive information on both the characteristics of the participants at baseline and some on-treatment factors. In addition, we were able to model details of prescribed insulin therapy, including ever use, insulin dose, and insulin type.

While recognizing these strengths of this analysis, we also acknowledge the limitations inherent in analyses of this kind. One such limitation is the fact that our study was a post hoc associational analysis. Therefore, the results should be interpreted with caution owing to the well-known statistical and other limitations of such analyses (25). Another limitation is the issue of confounding by the clinician's choices in selecting therapies and doses, i.e., confounding by indication. Also, unmeasured covariates or confounders may influence the vulnerability of a given individual to the effects of insulin. This possibility is highlighted by the differences in the known clinical characteristics at baseline in insulin-treated participants (higher A1C and increased prevalence of congestive heart failure, peripheral neuropathy, and history of CV disease), which suggest further but unapparent differences in underlying physiology or behavior that may relate to CV risk. The possibility that patients with these characteristics may, when treated with high doses of insulin, be more susceptible to mortality resulting from hypoglycemia or some other mechanism is an area that should be further explored. Also, we did not attempt to distinguish between the effects of different insulin molecules (human vs. analogs) owing to limitations of the data available.

In summary, in our analysis of ACCORD data, average daily insulin dose was not associated with increased CV mortality after adjustment for baseline covariates. These results fail to support the hypothesis that exposure to injected insulin is an independent risk factor for CV mortality in this population. However, these exploratory analyses of ACCORD do not fully lay to rest the possibility of adverse effects of insulin in particularly vulnerable individuals.

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