Epidemiologic Relationships Between A1C and All-Cause Mortality During a Median 3.4-Year Follow-up of Glycemic Treatment in the ACCORD Trial

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OBJECTIVE — Randomized treatment comparing an intensive glycemic treatment strategy with a standard strategy in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was ended early because of an unexpected excess of mortality in the intensive arm. As part of ongoing post hoc analyses of potential mechanisms for this finding, we explored whether on-treatment A1C itself had an independent relationship with mortality.

RESEARCH DESIGN AND METHODS — Participants with type 2 diabetes (n = 10,251 with mean age 62 years, median duration of diabetes 10 years, and median A1C 8.1%) were randomly assigned to treatment strategies targeting either A1C <6.0% (intensive) or A1C 7.0–7.9% (standard). Data obtained during 3.4 (median) years of follow-up before cessation of intensive treatment were analyzed using several multivariable models.

RESULTS — Various characteristics of the participants and the study sites at baseline had significant associations with the risk of mortality. Before and after adjustment for these covariates, a higher average on-treatment A1C was a stronger predictor of mortality than the A1C for the last interval of follow-up or the decrease of A1C in the first year. Higher average A1C was associated with greater risk of death. The risk of death with the intensive strategy increased approximately linearly from 6–9% A1C and appeared to be greater with the intensive than with the standard strategy only when average A1C was >7%.

CONCLUSIONS — These analyses implicate factors associated with persisting higher A1C levels, rather than low A1C per se, as likely contributors to the increased mortality risk associated with the intensive glycemic treatment strategy in ACCORD.

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Type 2 diabetes is associated with increased risk of cardiovascular events (1–3) in part because hypertension, dyslipidemia, and other risk factors are associated with diabetes. Epidemiological analyses also suggest that each 1% higher A1C is associated with 15–20% greater cardiovascular risk (4–7). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was designed to test whether intensive intervention to control hyperglycemia to a nearly normal range in patients with type 2 diabetes can reduce cardiovascular risks (8–10). It also included randomized comparisons of two targets for blood pressure control and two regimens for control of plasma lipid levels.

The aim of an intensive glycemic strategy was to reduce A1C to <6.0%, whereas the aim of a standard strategy was for a more conventional target range (10). Because of an unexpected finding, the intensive treatment strategy was discontinued early, after 3.4 years (median) rather than the planned 5.6 years of follow-up. All-cause mortality was greater with the intensive strategy (1.4 vs. 1.1% per patient-year [257 vs. 203 total deaths during follow-up], resulting in a hazard ratio [HR] of 1.22, P = 0.04). Initial analyses did not identify any specific cause for this finding (11). Several potential mechanisms have been suggested, including hypoglycemia, weight gain, and individual drugs, drug combinations, or drug dosages (12–14). In addition, the effects of rapid lowering of glucose levels or maintenance of nearly normal levels are of great interest. Although the ACCORD trial compared treatment strategies rather than actual levels of A1C, the question arises whether A1C values <7% may, independent of other circumstances, pose an unacceptable risk of death for any high-risk person with type 2 diabetes. To clarify this relationship between glycemic control and mortality, we performed post hoc analyses using data obtained at baseline and during randomized treatment.

RESEARCH DESIGN AND METHODS

— The rationale, study design, and entry criteria for the ACCORD trial are described elsewhere (8–10). The ACCORD trial was conducted at 77 clinical sites in the U.S. and Canada. Between January 2001 and October 2005, 10,251 participants with type 2 diabetes and either a prior cardiovascular event or other evidence of high risk were enrolled.

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They were randomly assigned to either an intensive glycemic strategy with the aim of achieving A1C <6.0% or a standard strategy with the aim of keeping A1C between 7.0 and 7.9%. Any antihyperglycemic agents approved by regulatory authorities could be used, as considered appropriate for each individual by investigators at the clinical sites, together with lifestyle interventions. The ACCORD formulary provided, free of cost to participants, at least one agent in each of the major categories of antihyperglycemic drugs. In addition, in a double two-by-two factorial design, all participants were enrolled in either a blood pressure trial comparing an intensive with a standard treatment strategy or a lipid trial comparing treatment with fenofibrate versus placebo while maintaining good control of LDL cholesterol, mainly with simvastatin. The primary end point of all components of the ACCORD trial is a composite of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke. All-cause mortality is a predefined secondary end point.

The intensive glycemic treatment strategy was stopped in February 2008. The dataset used for the present analyses comprises findings for all randomized participants from enrollment until 10 December 2007. Of the 10,251 participants in the ACCORD trial, 5,123 were randomly assigned to standard and 5,128 to intensive glycemic management.

Participants visited clinical sites every 2–4 months. At the 4-month intervals, they were asked about hypoglycemia and other medical events, were weighed, and had blood collected for A1C measurements.

Statistical analysis

Four ways of assessing each participant's glycemic levels were used. First, the overall glycemic exposure during randomized treatment was defined as a time-varying covariate of the mean of all 4-month A1C values after the baseline measurement to the end of the period covered in this dataset or until the time of death. This was called the average A1C. Second, a time-varying measure reflecting glycemic control just before each measurement was also used. This was termed the last A1C. Third, the magnitude of the early reduction of glucose levels was assessed as a time-varying covariate by subtracting the mean of A1C values in the first 12 months after initiation of glycemic treatment for each participant from the baseline value. For the first 4 months, the 0- to 4-month decrease was used, for months 4–8, the difference between baseline and the average of 4 and 8 months was used; and for months 8 and onward the difference between baseline and the average of months 4, 8, and 12. This was the 1-year decrease in A1C. Finally, the earliest changes in A1C were examined by computing 0- to 4-month decreases from baseline. This was the 4-month decrease in A1C.

Potential confounders of interpretation of the relationships between time-varying measures of A1C and occurrence of mortality from any cause included characteristics of the participants at baseline, characteristics of the clinical site at which an individual was enrolled, and selected factors related to the randomization or postrandomization experience (Table 1). Study site characteristics included the number of participants enrolled, whether the site was part of an integrated health plan, whether the principal investigator was a diabetes specialist, and whether a full-time certified diabetes educator was part of the staff. Postrandomization factors (not shown in Table 1) included incidence of hypoglycemia requiring medical assistance and weight gain or loss. Hypoglycemia requiring medical assistance was defined as a time-varying covariate of self-report of hypoglycemic symptoms requiring assistance by medical personnel on at least one occasion before death or completion of the period of treatment. The time-varying covariate is 0 until a hypoglycemic episode and 1 thereafter. Weight change from baseline was defined as a time-varying covariate and divided into loss of weight >5 kg, gain of >5 kg, and gain or loss of up to 5 kg. Factors introduced at randomization included participation in the blood pressure or lipid trial, assignment to intensive blood pressure treatment, and assignment to fenofibrate treatment (15,16). Inclusion in these treatment groups is not presented here but is included in the modeling procedure.

Unadjusted relationships of these factors with all-cause mortality were examined to identify potentially confounding variables using Cox proportional hazard models with Wald confidence intervals and tests. Factors with univariate relationships with $P < 0.25$ were used in a model selection procedure. Backwards, forwards, and stepwise approaches resulted in the same models. Baseline A1C was included in all models. Model 1 included the selected characteristics of the participants and their sites at baseline. Model 2 added severe hypoglycemia and weight change as time-varying covariates and the randomization assignments in other ACCORD trials. Model 3 included the components of model 2 plus assignment to the standard or intensive glycemic treatment strategies. Curves modeling the relationships over the range of observed A1C values (penalized B-splines) (17,18) were used to explore the linearity assumption in the Cox proportional hazards model. Figure 1 presents the linear portion of the Cox proportional hazards model [$\beta' x_i$ in $h_i(t) = h(t)e^{\beta' x_i}$). Tests of linearity of the effect of average A1C were performed by comparing models with linear terms with those with spline terms using likelihood ratio tests. Testing for differences of the nonlinear fits between intensive and standard glycemia assignment was done by comparing the nested models with one spline (same for both groups) and two splines (allowing different fits), also with likelihood ratio tests. Finally, Poisson regression provided direct estimates of mortality rates in relation to the magnitude of the 1-year change of A1C.

RESULTS

Patterns of glycemic control and mortality in the intensive and standard treatment groups

A1C values declined rapidly from the 8.1% (median) baseline in both treatment groups in the 1st year of treatment. With standard treatment, a plateau value close to 7.5% was maintained thereafter. With intensive treatment a plateau at 6.4% was established between 12 and 24 months. All-cause mortality rates were equivalent with the two strategies in the first 2 years, but in the 3rd year the rate with the intensive strategy was twice that with the standard strategy (supplementary Figure A1, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-1278/DC1).

Average on-treatment A1C showed substantial overlap for individuals in the two groups (supplementary Figure A2). With the intensive strategy, average A1C was ≤6% at 4.4% of the participants' visits, between 6.0 and <7.0% at 55.1%, and ≥7.0% at 40.5%. With the standard strategy, corresponding values were 0.2, 9.0, and 90.8%. Deaths from both cardiovascular and noncardiovascular causes occurred over a wide range of A1C values with both treatment strategies, with considerable overlap between the strategies. Approximately half of the deaths were due to cardiovascular causes (135 of 257

Table 1—*Characteristics of the study population at baseline and of the study sites at which they were enrolled, with univariate HRs for all-cause mortality*

Baseline characteristic	Value	HR (95% CI)	*P* value	Overall *P* value
Age (years)	62.2 ± 6.8	1.08 (1.06−1.09)	<0.0001	
Female	3,952 (38.6)	0.64 (0.52−0.78)	<0.0001	
Race/ethnicity				0.001
African-American	1,952 (19)	0.81 (0.63−1.03)	0.0821	
Hispanic	738 (7.2)	0.71 (0.47−1.06)	0.09	
Other	1,117 (10.9)	0.51 (0.35−0.74)	0.0004	
Non-Hispanic white	6,444 (62.9)	1		
Diabetes duration				0.002
6–10 years	2,931 (29.3)	0.88 (0.68−1.14)	0.3,422	
11–15 years	1,958 (19.6)	0.86 (0.64−1.15)	0.3,041	
≥16+ years	2,341 (23.4)	1.33 (1.05−1.7)	0.0203	
≤5 years	2,776 (27.7)	1		
History of cardiovascular disease	3,608 (35.2)	2.07 (1.72−2.48)	<0.0001	
Prior myocardial infarction	475 (4.6)	1.44 (0.99−2.09)	0.0592	
Heart failure/congestive heart failure	494 (4.9)	3.18 (2.42−4.17)	<0.0001	
Retinal surgery	879 (8.6)	1.67 (1.28−2.17)	0.0001	
Amputation	185 (1.8)	2.64 (1.71−4.09)	<0.0001	
Education				0.0028
Less than high school	1,521 (14.8)	1.64 (1.23−2.19)	0.0007	
High school graduate	2,704 (26.4)	1.42 (1.1−1.85)	0.0079	
Some college	3,357 (32.8)	1.18 (0.91−1.53)	0.218	
College graduate or more	2,662 (26)	1		
Smoking				<0.0001
Former	4,527 (44.2)	1.78 (1.44−2.21)	<0.0001	
Current	1,429 (14)	2.13 (1.62−2.8)	<0.0001	
Never	4,282 (41.8)	1		
Alcohol use				0.0589
1–6 drinks/week	1,975 (19.3)	0.75 (0.59−0.97)	0.0282	
7+ drinks/week	470 (4.6)	1.15 (0.76−1.72)	0.5,065	
No drinks/week	7,801 (76.1)	1		
Insulin use	3,579 (34.9)	1.4 (1.17−1.69)	0.0003	
ACE inhibitor	5,433 (53)	1.27 (1.05−1.52)	0.0131	
Angiotensin receptor blockers	1,639 (16)	0.79 (0.59−1.04)	0.0928	
Statins	6,363 (62.1)	0.92 (0.76−1.1)	0.3534	
Metformin	6,135 (59.8)	0.84 (0.7−1.01)	0.0665	
Secretagogues	5,273 (51.4)	0.79 (0.66−0.95)	0.0105	
Thiazolidinediones	1,982 (19.3)	0.85 (0.67−1.09)	0.204	
BMI (kg/m^2)	32.2 ± 5.5	1 (0.984−1.017)	0.9773	
Systolic blood pressure (mmHg)	136.4 ± 17.1	1.003 (0.997−1.008)	0.3316	
Diastolic blood pressure (mmHg)	74.9 ± 10.7	0.975 (0.966−0.984)	<0.0001	
Visual acuity				<0.0001
<20/40	2,337 (23.9)	3.36 (2.26−5)	<0.0001	
20/20–20/40	5,948 (60.7)	2.16 (1.47−3.18)	<0.0001	
≥20/20	1,510 (15.4)	1		
Peripheral neuropathy	4,356 (42.6)	1.83 (1.52−2.2)	<0.0001	
Heart rate	72.7 ± 11.8	1 (0.992−1.008)	0.9311	
Q-T index	101.8 ± 5.2	1.05 (1.03−1.06)	<0.0001	
A1C (%)	8.3 ± 1.1	1.04 (0.96−1.14)	0.3252	
Fasting plasma glucose (mg/dl)	175.3 ± 56.2	1 (0.998−1.001)	0.6445	
LDL (mg/dl)	104.9 ± 33.9	0.998 (0.995−1.001)	0.119	
HDL (mg/dl)	41.9 ± 11.6	0.988 (0.98−0.996)	0.0054	
Triglycerides (mg/dl)	190.1 ± 148.4	1 (0.999−1.001)	0.9412	

(continued)

Table 1—*Continued*

Baseline characteristic	Value	HR (95% CI)	*P* value	Overall *P* value
Serum creatinine (mg/dl)	0.91 ± 0.23	2.44 (1.72−3.46)	<0.0001	
Urinary albumin-to-creatinine ratio (mg/mg)				<0.0001
30–≤300	2,501 (24.6)	1.7 (1.39−2.09)	<0.0001	
>300	673 (6.6)	2.9 (2.2−3.81)	<0.0001	
<30	6,998 (68.8)	1		
Integrated health plan	4,078 (39.8)	1.39 (1.16−1.68)	0.0004	
Endocrinologist or diabetologist	5,706 (55.7)	0.84 (0.7−1)	0.0556	
Certified diabetes educator on staff at rand	3,960 (38.6)	0.94 (0.78−1.14)	0.5429	
Site size				0.894
<100	1,583 (15.4)	0.94 (0.72−1.24)	0.6837	
100–150	3,049 (29.7)	0.97 (0.78−1.19)	0.7385	
>150	5,619 (54.8)	1		

Values are means ± SD, *n* (%), or HR (95% CI).

with the intensive strategy and 109 of 203 with the standard strategy).

Characteristics of the participants and study sites and relationships with mortality

Table 1 shows the composition of the study population and the unadjusted relationships between all-cause mortality and baseline characteristics of the participants and their study sites.

Associations between A1C and mortality without and with adjustment for characteristics of the participants and study sites and selected postrandomization events

Results of the proportional hazards regression models adjusting for the effects of potentially confounding variables are summarized in Table 2. Of the three A1C measures, average A1C had the strongest association with mortality. A 1% higher average A1C was associated with HRs of 1.20 ($P = 0.0002$) unadjusted, 1.22 ($P = 0.0001$) after adjustment for baseline, site-related, and some postrandomization factors, and 1.45 ($P < 0.0001$) after full adjustment including adjustment for assignment to the standard or intensive treatment strategy. The last A1C showed no association with mortality in the unadjusted analysis or in models 1 and 2, but after adjustment for treatment assignment in model 3, a significant association was apparent (HR 1.14, $P < 0.003$). No relationships between the 1-year or 4-month decreases of A1C from baseline and subsequent mortality were found before adjustment for covariates, but model 3 demonstrated a significant relationship for the 1-year change (HR 0.85, $P < 0.013$). With average and last A1C, a higher on-treatment A1C value was associated with a greater risk of death. The 1-year decrease in A1C analysis in model 3 showed that a greater decrease of A1C was associated with a lower risk of death.

Adjusted risk of all-cause mortality over the observed range of average A1C

The relationship between average A1C and mortality was examined within the intensive and standard treatment strategies separately, as well as their interaction, using the fully adjusted regression model 3. Different relationships were apparent ($P_{\text{interaction}} = 0.0007$). The HR for 1% higher A1C for the intensive strategy

Table 2—*HRs (95% CI) from Cox proportional hazard models*

	Association of measures of A1C with all-cause mortality						
Model includes	Unadjusted	Model 1	Model 2	Model 3	Model 3, intensive	Model 3 standard	Interaction *P* value*
Average A1C	1.20 (1.09–1.32)	1.20 (1.08–1.33)	1.22 (1.10–1.36)	1.45 (1.3–1.63)	1.66 (1.46–1.89)	1.14 (0.95–1.38)	
P value	0.0002	0.0008	0.0001	$P < 0.0001$	$P < 0.0001$	0.17	0.0007
Last A1C	1.06 (0.98–1.15)	1.05 (0.96–1.14)	1.07 (0.98–1.16)	1.14 (1.05–1.25)	1.27 (1.14–1.41)	0.98 (0.86–1.13)	
P value	0.15	0.28	0.12	0.0026	$P < 0.0001$	0.81	0.0030
1-year decrease of A1C	1.02 (0.94–1.10)	0.98 (0.87–1.10)	0.96 (0.86–1.07)	0.85 (0.75–0.97)	0.86 (0.74–1.01)	0.83 (0.71–0.97)	
P value	0.69	0.71	0.46	0.0127	0.06	0.0227	0.66
4-month decrease of A1C	1.00 (0.92–1.09)	0.98 (0.88–1.09)	0.97 (0.87–1.08)	0.90 (0.79–1.01)	0.92 (0.79–1.07)	0.88 (0.76–1.02)	
P value	0.98	0.74	0.56	0.07	0.25	0.07	0.61

Model 1 contains these baseline characteristics: age, sex, congestive heart failure, amputation, smoking, alcohol use, use of secretagogues, visual acuity, peripheral nerve function, Q-T interval, A1C, urinary albumin-to-creatinine ratio, and site in integrated health system. Model 2 adds assignment to blood pressure or lipid trial and treatment assignment within these, severe hypoglycemia, and weight change. Model 3 adds glycemic treatment strategy assignment. **P* value for interaction of treatment assignment with the A1C relationships in model 3 is shown in the column at the right.

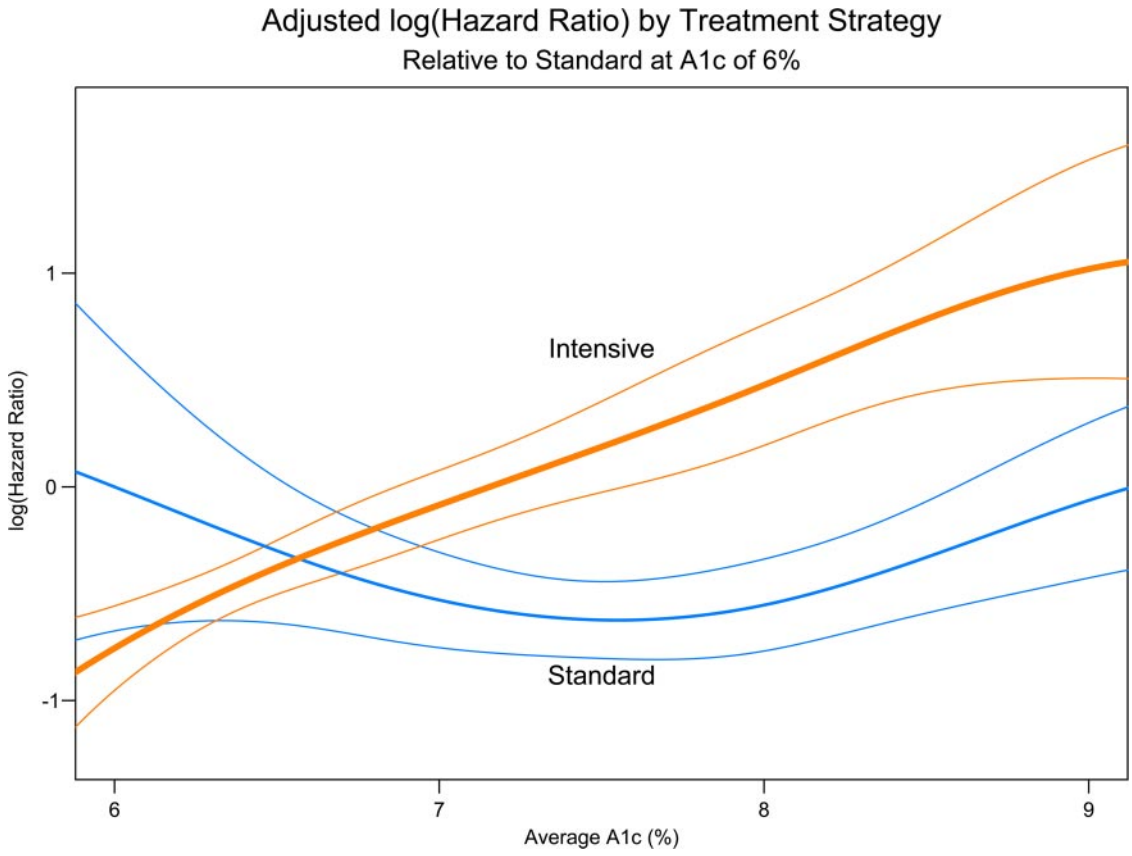

Figure 1—*Spline curves displaying the risk of all-cause mortality with the two treatment strategies over the range of average A1C from 6.0 to 9.0%. The curves represent the linear part of the proportional hazards models derived from values for intervals of average A1C from model 3. For clarity, the figure omits values <6 and >9%; ~5% of deaths are excluded from this plot at the lower end and also at the higher end of the A1C range, but these data are included in the models. The bold orange line represents the intensive treatment strategy group, the bold blue line represents the standard group, and the finer colored lines represent the 95% CIs for each group.*

was 1.66 (95% CI 1.46–1.89, $P < 0.0001$) and that for the standard strategy was 1.14 (0.95–1.38, $P = 0.17$). These relationships for the two strategies were also examined over a wide range of updated average A1C values, using smoothed spline plots and adjusting for all covariates (Fig. 1). These curves were also clearly different for the two strategies ($P_{interaction} = 0.0003$). There was marginal evidence of nonlinearity among intensive treatment participants ($P = 0.08$) but stronger evidence for nonlinearity among standard treatment participants ($P = 0.0184$). The curve for the intensive strategy showed the risk of mortality increasing steadily with higher average A1C in the range from 6.0 to 9.0%. In contrast, the lowest risk with the standard strategy was associated with average A1C between 7.0 and 8.0%. The estimates for these two curves were separated for A1C values from 7.0% to >9.0%, suggesting a possible higher risk for participants using the intensive strategy in this range. This observation is consistent with the increased risk of mortality associated with the intensive strategy using model 3, both without inclusion of average A1C as a covariate (HR 1.25, $P < 0.02$) and when average A1C was included (HR 1.82, $P < 0.0001$).

Frequency of all-cause mortality over the range of decrease of A1C in the 1st year

The effect of the initial decrease in A1C was further explored in an analysis shown in Fig. 2, which adjusted for the variables in model 3. With the standard strategy, death rates during the entire period of study did not vary over the range of 1-year A1C decrease. With the intensive strategy, the risk of death was similar to that with the standard strategy when moderate or large decreases in A1C occurred, but higher risk was suggested when little or no decrease in A1C followed initiation of treatment.

CONCLUSIONS — These post hoc analyses produced several hypothesis-generating insights. First, the 1- to 2-year delay between the initial reduction of A1C and the increase of mortality with the intensive strategy suggests that factors other than current A1C levels contributed. The broad range of average A1C values before deaths in both treatment groups also supports this view.

Second, the glycemic measure most strongly associated with death was the average A1C. Without adjustment, after adjustment for baseline factors, and after further adjustment for some postrandomization factors, a 1% greater average A1C was associated with 20, 20, and 22% increases in the risk of death. This association, not taking into consideration the glycemic treatment strategy, is similar to the 12 and 14% increments of mortality associated with 1% higher average A1C in epidemiologic analyses from other studies (6,19). In the fully adjusted analysis including glycemic treatment strategy this association was even stronger. Last A1C measurements and decreases in A1C in the 1st year of treatment showed weaker

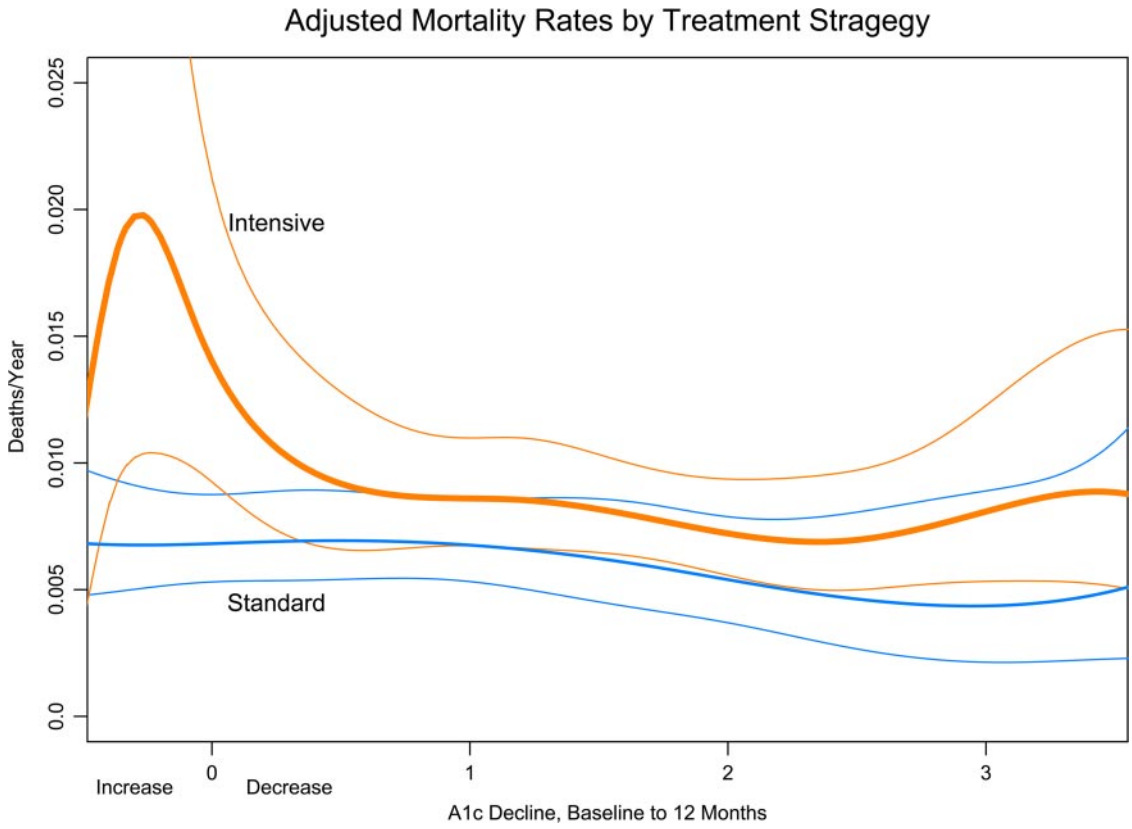

Figure 2—*Curves displaying all-cause mortality rates by treatment for the whole period of follow-up, over a range of decreases in A1C from baseline in the 1st year of treatment (as a percentage of A1C). The figure omits values <5th and >95th percentiles of A1C changes. The full range of values was from −6.8 (an increase) to 7.4% (a decrease) from baseline. The calculations used a Poisson regression model with data from model 3. The bold orange line represents the intensive treatment group, the bold blue line represents the standard group, and the finer colored lines represent the 95% CIs for each group.*

associations, which were significant only after adjustment for treatment assignment. A 1% higher last A1C was associated with 14% greater risk, and a 1% greater decrease in A1C from baseline in the 1st year with 15% lower risk.

Third, the relationships between average A1C and mortality differed between the treatment strategies. Using the fully adjusted proportional hazards regression model, higher average A1C during use of the intensive strategy was strongly associated with greater mortality (66% greater for 1% higher, $P < 0.0001$). To better understand possible differences introduced by treatment assignment, we also considered these relationships when displayed as smoothed spline plots over a range of average A1C.

With the intensive strategy, the risk of death increased continuously from 6.0 to 9.0% average A1C, whereas the curve for the standard strategy was distinctly nonlinear. The excess risk associated with intensive glycemic treatment occurred among those participants whose average A1C, contrary to the intent of the strategy, was >7%.

These observations must be interpreted cautiously, because the analyses were not defined before treatment was started, the period of follow-up was shorter than planned, and the results could have been influenced by many posttrandomization factors. However, they are relevant to the debate about which targets for glycemic control should be advised for patients with type 2 diabetes and evidence of high cardiovascular risk. These findings confirm the earlier report warning of increased risk of death associated with the intensive treatment strategy in ACCORD (11), but they suggest that low A1C is unlikely to be a primary mediator of this risk. They do not support the hypothesis that overly rapid reduction of A1C from high levels increases risk of death. In fact, the opposite relationship was observed. Participants who were unable to reduce A1C after initiation of the intensive strategy and continued to have average A1C >7% seemed to be at greater risk than those with average A1C <7% using the same strategy or than those with A1C >7% using a standard strategy.

At present, the factors that lead to increased risk associated with A1C averaging >7% during use of an intensive treatment strategy remain unknown. Characteristics of the participants that were not measured may be involved. Among these are behavioral issues such as lack of adherence to medical advice, depression or other psychiatric conditions, abnormal cognitive function, and social or financial crises. Emergence of serious medical problems other than diabetes itself might interfere with treatment of hyperglycemia and at the same time increase the risk of mortality. Finally, the potential effects of hypoglycemia, weight gain, and various drugs require further attention. We also await data on ocular, renal, and cognitive function, as well as on mortality and cardiovascular events during longer follow-up, which may contribute to the balance of risks versus benefits.

In summary, these analyses confirm that excess risk of all-cause mortality was associated with the intensive glycemic treatment strategy used in the ACCORD trial. They suggest that factors associated with A1C persisting at >7%, rather than lower A1C, were associated with this risk. They are also consistent with other epidemiological analyses, which suggest a continuous gradient of risk of mortality, increasing from lower to higher A1C levels.

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References

1. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. JAMA 1979;241:2035–2038
2. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16:434–444
3. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–234
4. Wei M, Gaskill SP, Haffner SM, Stern MP. Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality. The San Antonio Heart Study. Diabetes Care 1998;21:1167–1172
5. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events: a meta regression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999;22:233–240
6. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412
7. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004;141:421–431
8. Goff DC, Gerstein HC, Ginsberg HN, Cushman WE, Margolis KL, Byington RP, Buse JB, Genuth S, Probstfield JL, Simons-Morton DG, ACCORD Study Group. Prevention of cardiovascular disease in persons with type 2 diabetes mellitus: current knowledge and rationale for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol 2007;99(Suppl.):4i–20i
9. The ACCORD Study Group. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. Am J Cardiol 2007;99(Suppl.):21i–33i
10. Gerstein HC, Riddle MC, Kendall DM, Cohen RM, Goland R, Feinglos MN, Kirk JK, Hamilton B, Ismail-Beigi F, Feeney P, ACCORD Study Group. Glycemia treatment strategies in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol 2007;99(Suppl.):34i–43i
11. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Bergi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
12. Dluhy RG, McMahon GT. Intensive glycemic control in the ACCORD and ADVANCE trials. N Engl J Med 2008;358:2630–2633
13. Hirsch IB. Piecing the puzzle together: ACCORDing to whom? J Clin Endcrinol Metab 2008;93:1161–1163
14. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, Howard BV, Kirkman MS, Kosiborod M, Reaven P, Sherwin RS. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care 2009;32:187–192
15. Cushman WC, Grimm RH Jr, Cutler JA, Evans GW, Capes S, Corson MA, Sadler LS, Alderman MH, Peterson K, Bertoni A, Basile JN, ACCORD Study Group. Rationale and design for the blood pressure intervention of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol 2007;99(Suppl.):44i–55i
16. Ginsberg HN, Bonds DE, Lovato LC, Crouse JR, Elam MB, Linz PI, O'Connor PJ, Leiter LA, Weiss D, Lipkin E, Fleg JL, ACCORD Study Group. Evolution of the lipid trial protocol of the Action to Control Cardiovascular Risk in Diabetes

(ACCORD) trial. Am J Cardiol 2007; 99(Suppl.):56i–71i
17. Eiler PH, Marx BD. Flexible smoothing with B-splines and penalties. Stat Sci 1996;11:89–121
18. Hurvich CM, Siminoff JS, Tsai C-L. Smoothing parameter selection in non-parametric regression using an improved Akaike information criterion. J R Stat Soc Ser B 1998;60:271–293
19. Gerstein HC, Pogue J, Mann JF, Lonn E, Dagenais GR, McQueen M, Yusuf S, HOPE Investigators. The relationship between dysglycaemia and cardiovascular and renal risk in diabetic and non-diabetic participants in the HOPE study: a prospective epidemiologic analysis. Diabetologia 2005;48:1749–1755