9-Year Effects of 3.7 Years of Intensive Glycemic Control on Cardiovascular Outcomes

*The ACCORD Study Group Writing Committee**

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OBJECTIVE

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, ~4 years of intensive versus standard glycemic control in participants with type 2 diabetes and other cardiovascular risk factors had a neutral effect on the composite cardiovascular outcome, increased cardiovascular and total mortality, and reduced nonfatal myocardial infarction. Effects of the intervention during prolonged follow-up were analyzed.

RESEARCH DESIGN AND METHODS

All surviving ACCORD participants were invited to participate in the ACCORD Follow-on (ACCORDION) study, during which participants were treated according to their health care provider's judgment. Cardiovascular and other health-related outcomes were prospectively collected and analyzed using an intention-to-treat approach according to the group to which participants were originally allocated.

RESULTS

A total of 8,601 people, representing 98% of those who did not suffer a primary outcome or death during the ACCORD trial, were monitored for a median of 8.8 years and a mean of 7.7 years from randomization. Intensive glucose lowering for a mean of 3.7 years had a neutral long-term effect on the primary composite outcome (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death), death from any cause, and an expanded composite outcome that included all-cause death. Moreover, the risk of cardiovascular mortality noted during the active phase (hazard ratio 1.49; 95% CI 1.19, 1.87; $P < 0.0001$) decreased (HR 1.20; 95% CI 1.03, 1.39; $P = 0.02$).

CONCLUSIONS

In high-risk people with type 2 diabetes monitored for 9 years, a mean of 3.7 years of intensive glycemic control had a neutral effect on death and nonfatal cardiovascular events but increased cardiovascular-related death.

Type 2 diabetes is a strong risk factor for cardiovascular outcomes, and the incidence of these outcomes rises with the degree of hyperglycemia (1). These clear relationships support the hypothesis that glucose lowering may reduce these outcomes. However, large randomized controlled trials have yielded mixed findings with respect to the cardiovascular effects of glucose lowering. Four of these trials explicitly tested the effect of intensive versus standard glucose lowering on cardiovascular outcomes in people with type 2 diabetes (2–5). A meta-analysis of these four trials suggested a beneficial or neutral effect on one or more cardiovascular outcomes (6).

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**A list of the members of the ACCORD Study Group Writing Committee can be found in the APPENDIX.*

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However, one of these, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial reported both increased total and cardiovascular mortality and reduced nonfatal myocardial infarction in the intensive glucose-lowering group during a mean follow-up period of 3.7 years (2). The reasons for these discrepant findings remain unknown despite many analyses. Also not known is whether the effect on mortality or myocardial infarctions was sustained or limited by time. This uncertainty was addressed by the ACCORD Follow-on (ACCORDION) study, which consented and monitored ACCORD participants for up to 7 years after the intensive glycemic intervention was stopped.

RESEARCH DESIGN AND METHODS

The design of the ACCORD trial and the effect of intensive versus standard glucose-lowering approaches on cardiovascular outcomes have been previously reported (2,7,8). Briefly, ACCORD enrolled 10,251 people whose mean age was 62 years, who had type 2 diabetes for a median duration of 10 years with a mean glycated hemoglobin (HbA_{1c}) level of 8.3%, and who had previous cardiovascular disease or cardiovascular disease risk factors. Participants in 77 sites in the U.S. and Canada were randomly assigned to intensive glucose-lowering approaches targeting a glycated hemoglobin level $<$6% or to standard glucose-lowering approaches targeting a level of 7–7.9%. Participants in both groups received education and lifestyle advice regarding diabetes management and were provided with glucose-lowering drugs at no cost from a common formulary. Achieved levels of glycated hemoglobin, adverse effects of glucose-lowering drugs, and rates of hypoglycemia were recorded regularly throughout the trial, and glucose-lowering therapies were adjusted according to each participant's randomly assigned treatment group and glycemic response to therapy. At the time of allocation to the glycemic strategy, ~4,733 ACCORD participants (54%) were also enrolled in a blood pressure trial and randomized to intensive versus standard blood pressure lowering (9). The remaining 5,518 (46%) were enrolled in a lipid trial comprising LDL lowering with a statin plus fenofibrate or placebo (10). Details regarding the findings of these trials have been reported separately (2,7–10).

ACCORD participants were recruited between June 2001 and October 2005, managed according to their allocated strategy, and monitored for occurrence of cardiovascular and other health outcomes. The active glycemic treatment period ended on 5 February 2008 after a mean follow-up period of 3.7 years, when the National Heart, Lung, and Blood Institute accepted the independent Data and Safety Monitoring Board's recommendation to stop the glycemia trial because of excess mortality in the intensive glucose-lowering group. Subsequently, all participants were managed according to the standard glucose-lowering approach and monitored for an additional 17 months until the active lipid and active blood pressure treatment periods ended.

All surviving ACCORD participants from participating sites who could be contacted were subsequently offered the opportunity to participate in the ACCORDION study during which cardiovascular and other health related outcomes and measurements were collected and analyzed according to the group to which participants were originally allocated. No active therapies were provided by the study during this follow-up period. All participants gave written, informed consent to participate in ACCORDION.

Outcome Ascertainment

The glycemic portion of the ACCORDION study was designed to assess the effect of 3.7 years of exposure to the ACCORD intensive versus the standard glycemic glucose-lowering approach on the long-term incidence of cardiovascular outcomes. Consenting participants were seen or called by 72 sites in the U.S. and Canada on up to seven occasions between May 2011 (~1.5 years after the conclusion of the ACCORD trial) and October 2014. During four telephone and three clinic visits, the occurrence of cardiovascular outcomes, deaths, dialysis, all hospitalizations, severe hypoglycemia, medication usage, and related information was ascertained. Documentation supporting the diagnosis of myocardial infarction, unstable angina, strokes, and deaths was sought and verified by the site. Weight, height, waist circumference, blood pressure, pulse, and a neuropathy examination were conducted at each clinic visit. Glycated hemoglobin, a lipid profile, serum creatinine, alanine aminotransferase level, and a spot urine albumin-to-creatinine ratio were centrally measured at the first and third visits, during which an electrocardiogram and data concerning health-related quality of life were also collected. Deaths in the U.S. were also ascertained using the National Death Index.

As in ACCORD, the primary outcome was the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Prespecified secondary outcomes included an expanded composite outcome comprising the primary end point, any revascularization, or hospitalization for heart failure; a composite outcome comprising the primary end point or death from any cause; a coronary heart disease composite comprising fatal or nonfatal myocardial infarction, death occurring unexpectedly or after a cardiovascular procedure or noncardiovascular surgery, or unstable angina; nonfatal myocardial infarction; stroke; nonfatal stroke; all-cause mortality; cardiovascular mortality; and heart failure death or hospitalization.

All of the reported cardiovascular outcomes during the ACCORD trial were adjudicated by a masked, independent committee. Conversely, in light of evidence showing that adjudication does not materially affect the estimate of the effect size in randomized trials (11,12), only a randomly selected 10% of the reported outcomes were similarly adjudicated during the ACCORDION follow-up phase (to ensure quality control). Analyses in ACCORDION were conducted on all of the cardiovascular outcomes that occurred after randomization and that were reported by the sites during the active or follow-up period, regardless of the final adjudication status. Outcome definitions were identical to those used in ACCORD and are available online (13).

Statistical Analysis

Statistical analyses were undertaken by the ACCORD Coordinating Centre using SAS 9.4 software (SAS Institute Inc., Cary, NC), according to a prespecified plan that was finalized before any analyses began. A nominal level of significance

of $P < 0.05$ was used for all analyses without adjustment for multiple testing.

Baseline characteristics of people randomized to the ACCORD trial and the subset that consented to subsequent passive follow-up were summarized using means, SDs, and percentages. The use of glucose-lowering drugs was summarized as the number of participants who reported taking medication at the last contact with the participant. The effect of the interventions on glycated hemoglobin levels during the active treatment phase and subsequent follow-up was estimated by calculating the median glycated hemoglobin at each follow-up visit by treatment group in monthly intervals from randomization. Follow-up for each patient was defined as the time from randomization until an outcome occurred or the last date for which the participant's health status was available.

The incidence rate and number of participants at risk for events during follow-up was determined using Kaplan-Meier estimates. Cox proportional hazards regression analyses were used to estimate the long-term effect of allocation to intensive versus standard glycemic control on the primary and secondary outcomes using a χ^2 statistic from a likelihood ratio test obtained from proportional hazards models with and without the term for intervention arm. Hazard ratios and 95% CIs were calculated using models that included independent variables that were prespecified in prior ACCORD analyses. Primary outcome model covariates included *1*) assignment to the blood pressure or lipid trials; *2*) assignment to the intensive versus standard blood pressure intervention; *3*) assignment to fibrate versus placebo; *4*) the presence or absence of previous cardiovascular disease; and *5*) the clinical center network within which the participant was monitored. Secondary outcomes were analyzed using the same list of covariates, with the exception of clinical center networks, because of the reduced number of anticipated events. All outcomes were censored on the date of the last available information, and all comparisons of intervention groups were performed according to the intention-to-treat principle. The consistency of the effect of the study group assignment on the primary outcome and mortality within prespecified subgroups (previous cardiovascular event vs. none, men vs. women, randomization age <65 or ≥65 years, randomization glycated hemoglobin ≤8% or >8%, white vs. nonwhite, and blood pressure trial vs. lipid trial) was assessed with the use of statistical tests of interactions between the treatment effect and the subgroup within the Cox models.

RESULTS

Supplementary Figure 1 displays participant follow-up during and after the ACCORD trial. Ninety percent (n = 8,601) of these living individuals, representing 98% of the 8,777 individuals without a primary outcome event during the active phase of the ACCORD trial, consented to further, posttrial follow-up. Of 10,251 randomized ACCORD participants, 9,533 (93%) were known to be alive at the end of the full ACCORD trial (when both the lipid and blood pressure interventions were discontinued), and 8,777 remained free of a myocardial infarction of stroke (i.e., the first occurrence of a nonfatal component of the primary outcome) at that time. Participants who agreed to ongoing follow-up were younger and at the time of randomization had lower serum creatinine and LDL levels, a lower prevalence of smoking and prior cardiovascular events, were less likely to be on insulin, and were more likely to be taking metformin, statins, and aspirin than the 1,650 ACCORD participants who had died or did not agree to further follow-up (Table 1).

The between-group difference in glycated hemoglobin (Supplementary Fig. 2)

Table 1—Baseline characteristics according to follow-up

	Consent to post-ACCORD follow-up		
Baseline characteristic	No (n = 1,650)	Yes (n = 8,601)	P value
Females, n (%)	630 (38.2)	3,322 (38.6)	0.74
Age (years)	63.7 (7.7)	62.0 (6.6)	0.03
Duration of diabetes (years)	11.2 (8.3)	10.8 (7.7)	0.14
BMI (kg/m^2)	32.2 (5.5)	32.3 (5.5)	0.68
Waist circumference (cm)	107.3 (14.2)	106.7 (13.8)	0.09
Blood pressure (mmHg)			
Systolic	138 (18)	136(17)	<0.001
Diastolic	75 (11)	75 (11)	0.40
Prior cardiovascular disease, n (%)	748 (45.3)	2,861 (33.3)	<0.001
Current smoker, n (%)	292 (17.7)	1,137 (13.2)	<0.001
Postsecondary education, n (%)	844 (57.2)	5,175 (60.2)	<0.001
Ethnicity, n (%)			
White	955 (57.9)	5,438 (63.2)	
Black	414 (25.1)	1,539 (17.9)	
Hispanic	136 (8.2)	601 (7.0)	
Other	145 (8.8)	1,023 (11.9)	<0.001
Key medications, n (%)			
Insulin	628 (38.1)	2,953 (34.3)	0.004
Metformin	884 (53.6)	5,251 (61.1)	<0.001
Sulfonylurea	771 (46.7)	4,365 (50.7)	0.003
Thiazolidinedione	285 (17.3)	1,697 (19.7)	0.02
Statin	937 (56.8)	5,427 (63.1)	<0.001
ACE inhibitor or ARB	1,102 (61.9)	5,840 (67.9)	0.38
Acetylsalicylic acid	836 (50.7)	4,743 (55.1)	<0.001
Laboratory values			
HbA_{1c} (%)	8.4 (1.2)	8.3 (1.0)	<0.001
Serum creatinine (mg/dL)	0.95 (0.26)	0.90 (0.22)	<0.001
eGFR (mL/min)	90.6 (33.4)	91.1 (25.8)	0.54
Urine albumin-to-creatinine ratio	18.3 (8.0, 72.0)	12.9 (6.7, 39.8)	<0.001
Cholesterol (mg/dL)	186.1 (43.7)	182.8 (41.5)	0.005
LDL	108.1 (35.7)	104.3 (33.5)	<0.001
HDL	41.8 (12.4)	41.9 (11.5)	0.68
Triglycerides (mg/dL)	154 (102, 226)	155 (107, 229)	0.76

Cells reflect n (%), as indicated, mean (SD), or median (interquartile range). ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate.

achieved during a mean active treatment period of 3.7 years was clearly smaller but persisted well after transition of all participants to the standard glycemic treatment strategy. Thus, a mean of 1.2 years after transition (i.e., when the ACCORD trial ended), the mean (SD) glycated hemoglobin level was 7.4% (1.2%) in the intensive group and 7.8% (1.3%) in the standard group ($P < 0.001$), and at the end of the ACCORDION follow-up, these levels were 7.8% (1.4%) and 8.0% (1.4%), respectively ($P = 0.005$). This HbA_{1c} difference persisted during the ACCORDION follow-up period despite similar reported glucose-lowering regimens (Supplementary Table 1) and similar weights of 91.8 (20.4) kg and 91.2 (20.4) kg ($P = 0.4$) in people who had been allocated to the intensive and standard groups, respectively.

During the ACCORDION phase of the study, there were similar rates of severe hypoglycemia requiring medical assistance or any severe hypoglycemia in each allocated group (Supplementary Table 2).

The incidence of reported clinical outcomes and the hazard of allocation to the intensive versus the standard glucose-lowering regimen during the ACCORD trial and the full ACCORDION median follow-up period of 8.8 years are shown in Fig. 1 and listed in Table 2. Allocation to an intensive glucose-lowering regimen for a mean of 3.7 years had a neutral long-term effect on the first occurrence of the primary composite outcome comprising nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death; death from any cause; an expanded composite of nonfatal myocardial infarction, nonfatal stroke, or any death; a composite of fatal coronary heart disease, nonfatal myocardial infarction, or unstable angina; and heart failure hospitalizations. Conversely, the increase in death from cardiovascular causes that was noted at the end of the active treatment period persisted. However, as a result of similar rates after the intervention, the hazard ratio was attenuated to 1.20 (95% CI 1.03, 1.39; $P = 0.02$). Product-limit estimates of time to event for the primary outcome, death (Fig. 2), and for the three components of the primary outcome (Fig. 3) suggested that any differences in incidence were confined to the active treatment period. No differences in the long-term effect of the intervention on the primary outcome or mortality were noted for predefined subgroups (Supplementary Figs. 3 and 4).

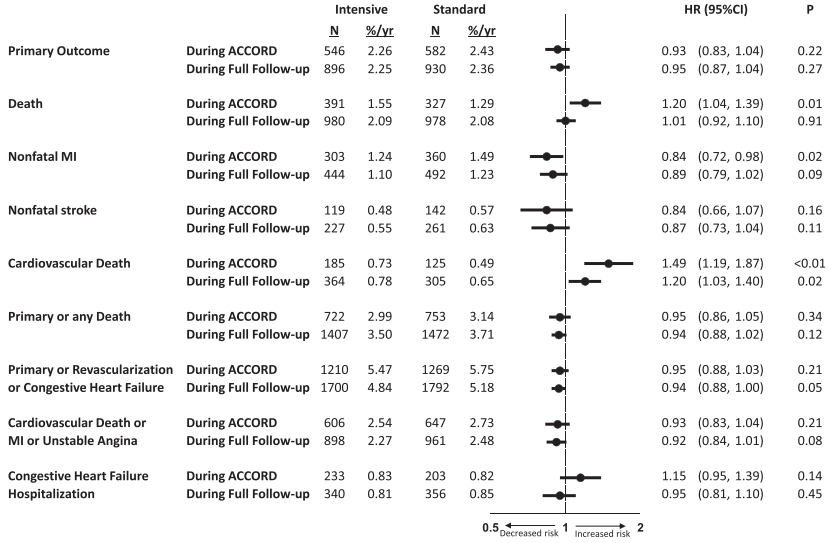

Figure 1—Hazard of outcomes during ACCORD and ACCORD/ACCORDION. The event rates and hazard ratios (HRs, ●) with 95% CIs (horizontal lines) are shown for prespecified outcomes that occurred from randomization until the end of the ACCORD trial and until the end of prolonged follow-up comprising the ACCORD and ACCORDION phase.

CONCLUSIONS

Intensive glycemic control may have long-term effects on serious health outcomes in people with type 2 diabetes. Such "legacy" effects may be beneficial or harmful and may emerge, be attenuated, or magnified with time. These data from the long-term follow-up of the ACCORD trial show that intensive glycemic control for a median of 3.7 years had a prolonged effect on HbA_{1c} levels, possibly due to some effect on β-cell function (14). At the same time, it had a neutral effect on the primary cardiovascular composite outcome of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death during a median follow-up period of 8.8 years. It also had a neutral effect on an expanded composite outcome that included death from any cause and the individual outcomes of nonfatal myocardial infarction, nonfatal stroke, and/or congestive heart failure.

Intensive glycemic control had a neutral long-term effect on all-cause mortality during this 8.8-year period, despite the higher mortality during the 3.7-year active phase of the ACCORD trial. Scrutiny of the product-limit curves (Fig. 2) and accrued data (Table 2) show that this was apparently due to clustering of the excess of cardiovascular deaths between 2 and 3 years after randomization and subsequent attenuation or reversal of this pattern. The reduction in nonfatal myocardial infarction noted during the active phase of the trial was also attenuated over the entire follow-up period.

The excess of cardiovascular-specific mortality accompanying intensive therapy that was noted during the active phase of the trial remains unexplained despite many analyses. Possible explanations that have not been supported include severe hypoglycemia (15); weight gain (R.P. Byington, unpublished analysis); the specific therapies used to lower glucose, including insulin (16) or other glucose-lowering drugs (unpublished analysis); or the differential effects of intensive control in people with underlying cardiac autonomic neuropathy (17). The degree of glucose lowering that was achieved in the intensive group was also not responsible for the mortality signal (18). Indeed, two ACCORD analyses found that the excess mortality in the intensive group was most apparent in participants whose HbA_{1c} levels remained high despite allocation to the intensive group and use of therapeutic strategies seeking nearly normal glucose levels (18,19). Other

Table 2—First occurrence of outcomes during different study phases

	During ACCORD				Post-ACCORD Alone				Full follow-up from randomization			
	Intensive (*n* = 5,128)		Standard (*n* = 5,123)		Intensive (*n* = 4,270)		Standard (*n* = 4,331)		Intensive (*n* = 5,128)		Standard (*n* = 5,123)	
Outcome	*n*	%	*n*	%	*N*	%	*n*	%	*n*	%	*n*	%
Primary outcome	546	10.6	582	11.4	350	8.2	348	8.0	896	17.3	930	18.3
Death	391	7.6	327	6.4	589	13.8	651	15.0	980	19.1	978	19.1
Nonfatal MI	303	5.9	360	7.0	141	3.3	132	3.0	444	8.7	492	9.6
Nonfatal stroke	119	2.3	142	2.8	108	2.5	119	2.7	227	4.4	261	5.1
CVD	185	3.6	125	2.4	179	4.2	180	4.2	364	7.1	305	6.0
Primary outcome or death	722	14.1	753	14.7	685	16.0	719	16.6	1,407	27.4	1,472	28.7
Primary outcome, Revasc, CHF	1,210	23.6	1,269	24.8	490	11.5	523	12.1	1,700	33.2	1,792	35.0
Fatal CHD, MI, UA	606	11.8	647	12.6	292	6.8	314	7.3	898	17.5	961	18.8
Any stroke	128	2.5	150	2.9	114	2.7	124	2.9	242	4.7	274	5.4
CHF hospitalization	233	4.5	203	4.0	107	2.5	153	3.5	340	6.6	356	7.0
Causes of death												
Fatal MI	29	7.4	14	4.3	11	1.9	7	1.1	40	4.1	21	2.2
Fatal stroke	8	2.1	8	2.5	5	0.9	5	0.8	13	1.3	13	1.3
Unexpected, presumed CVD	82	21.0	65	19.9	47	8.0	45	6.9	129	13.2	110	11.3
CHF	22	5.6	9	2.8	21	3.6	19	2.9	43	4.4	28	2.9
Documented arrhythmia	4	1.0	3	0.9	4	0.7	2	0.3	8	0.8	5	0.5
Other cardiovascular	40	10.2	26	8.0	91	15.5	102	15.7	131	13.4	128	13.1
Cancer	95	24.3	89	27.2	68	11.5	77	11.8	163	16.6	166	17.0
Non-CVD/noncancer	95	24.3	95	29.1	0	0.0	0	0.0	95	9.7	95	9.7
Other non-CVD or unknown	10	2.6	17	5.2	227	38.5	251	38.6	237	24.2	268	27.4
Uncertain*	6	1.5	1	0.3	115	19.5	143	22.0	121	12.4	144	14.7

CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular death; MI, myocardial infarction; Revasc, revascularization; UA, unstable angina. *Identified using the National Death Index.

analyses have suggested that the excess of mortality may have been due to a harmful effect of the intervention in subgroups of individuals with peripheral neuropathy, aspirin use, or HbA_{1c} ≥8.5% at baseline (20), or in the subgroup with the highest discrepancy between baseline HbA_{1c} and the HbA_{1c} levels that would be predicted from fasting plasma glucose levels (due to higher protein glycation, higher prandial glucose levels, or other reasons) (21). Finally, that the excess mortality during ACCORD may have been a rare chance occurrence has been suggested (22). The absence of excess mortality in the active phase of the three other trials of intensive glucose control (6), the concomitant reduction in nonfatal myocardial infarction and various indices of ischemic heart disease during this phase (6,23), and attenuation of the mortality signal during the full 9 years of follow-up provide some support for this possibility.

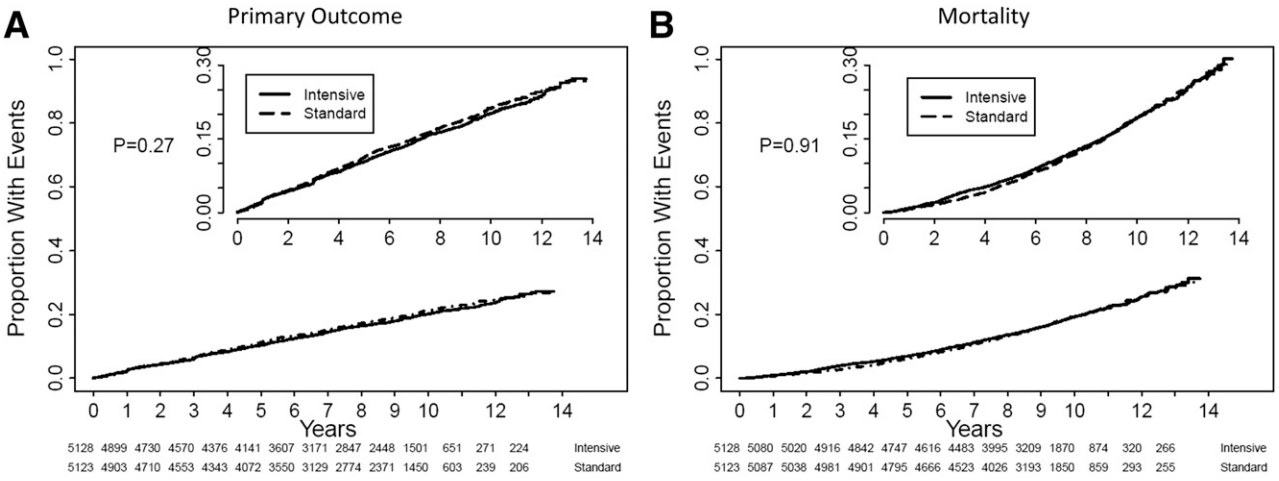

Figure 2—The Kaplan-Meier curves display the time to event for the primary outcome (*A*) and total mortality (*B*) during follow-up from randomization until the end of ACCORDION. The inset for each graph displays the same curve with a magnified *y*-axis. The numbers of individuals at risk are shown for each time point.

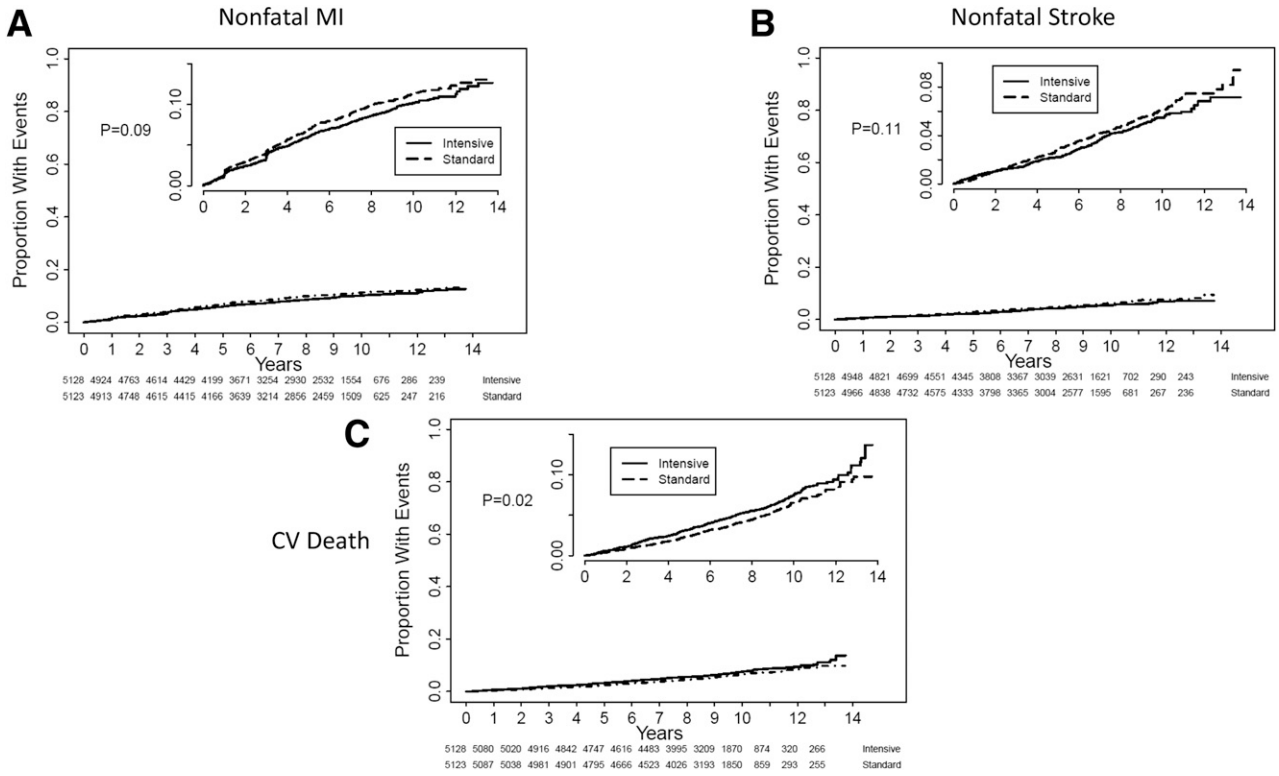

Figure 3—The Kaplan-Meier curves display the time to event for the three components of the primary outcome, including nonfatal myocardial infarction (MI) (*A*), nonfatal stroke (*B*), and cardiovascular (CV) death (*C*) during follow-up from randomization until the end of ACCORDION. The inset displays the same curve with a magnified *y*-axis. The numbers of individuals at risk are shown for each time point.

The 10- to 20-year effect of up to 6 years of intensive glycemic control on cardiovascular outcomes has also been reported in the three other large outcomes trials of intensive glucose control. In the United Kingdom Prospective Diabetes Study (UKPDS), 10 years of active therapy achieving a median HbA_{1c} difference of 0.9% reduced the 18-year incidence of myocardial infarction by 15% and death by 13% in people with newly diagnosed type 2 diabetes (24). Similarly, 6 years of active therapy achieving an HbA_{1c} difference of 1.5% reduced the 10-year incidence of cardiovascular outcomes by 17% in male veterans who participated in the Veterans Administration Diabetes Trial (VADT) (25). The Action in Diabetes and Vascular Disease (ADVANCE) trial, with a lesser glycemic difference, reported that 5 years of intensive glycemic control had a neutral effect on cardiovascular outcomes during 10 years of follow-up (26). Two of these posttrial intention-to-treat follow-up analyses reported a neutral effect on mortality, and one reported a reduction. A meta-analysis of the odds ratios for death from ACCORDION and these other three studies using a fixed-effects variance estimate (27) with heterogeneity assessed using the I^2 statistic (28) (Supplementary Table 3) yields an overall mortality odds ratio of 0.98 (95% CI 0.92, 1.04).

Taken together, the findings of ACCORDION demonstrate neither a beneficial legacy effect of 3.7 years of intensive glucose-lowering therapy on cardiovascular end points nor a continued excess of all-cause mortality. The unexplained 20% higher relative risk of cardiovascular death in ACCORDION corresponds to an absolute risk difference of ~0.13%/year or 1.3% over 10 years. When deciding on therapy for an individual patient, these findings need to be balanced against a neutral effect on overall mortality and a large reduction in eye disease in response to intensive glucose lowering (29). These findings suggest that for people with type 2 diabetes and additional cardiovascular risk factors, the main benefits of intensive glycemic control are noncardiovascular. They also support current recommendations (30,31) to tailor the degree of glucose control to the overall health status of individual patients, taking their overall frailty and burden of other illnesses into account.

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Author Contributions. H.C.G., A.G.B., J.T.B., J.B.B., W.C.C., R.H.G., S.G., F.I.-B., J.P. and W.T.F. designed and led the study, researched the data, contributed to the discussion, and reviewed and edited the manuscript. VF, N.L.G., S.J.G., I.H., C.R.L.J., R.K., M.C.R., and E.R.S. researched the data, contributed to the discussion, and reviewed and edited the manuscript. D.P.B. and T.E.C. did the statistical analyses. H.C.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix

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