ORIGINAL ARTICLE

Long-Term Effects of Intensive Glucose Lowering on Cardiovascular Outcomes

The ACCORD Study Group*

ABSTRACT

The members of the writing group (Hertzel C. Gerstein, M.D., McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada; Michael E. Miller, Ph.D., Wake Forest University School of Medicine, Winston-Salem, NC; Saul Genuth, M.D., Case Western Reserve University, Cleveland; Faramarz Ismail-Beigi, M.D., Ph.D., Case Western Reserve University, Cleveland; John B. Buse, M.D., Ph.D., University of North Carolina, Chapel Hill; David C. Goff, Jr., M.D., Ph.D., Wake Forest University School of Medicine, Winston-Salem, NC; Jeffrey L. Probstfield, M.D., University of Washington, Seattle; William C. Cushman, M.D., Memphis Veterans Affairs Medical Center, Memphis; Henry N. Ginsberg, M.D., Columbia University College of Physicians and Surgeons, New York; J. Thomas Bigger, M.D., Columbia University College of Physicians and Surgeons, New York; Richard H. Grimm, Jr., M.D., Ph.D, University of Minnesota, Berman Center for Outcomes and Clinical Research, Minneapolis; Robert P. Byington, Ph.D., Wake Forest University School of Medicine, Winston-Salem, NC; Yves D. Rosenberg, M.D., National Heart, Lung, and Blood Institute, Bethesda, MD; and William T. Friedewald, M.D., Columbia University College of Physicians and Surgeons, New York) assume responsibility for the content of this article. Address reprint requests to Dr. Gerstein at McMaster University, Department of Medicine, HSC 3V38, 1200 Main St. W., Hamilton, ON L8N 3Z5, Canada, or at gerstein@mcmaster.ca.

*Members of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group are listed in the Supplementary Appendix, available at NEJM.org.

BACKGROUND

Intensive glucose lowering has previously been shown to increase mortality among persons with advanced type 2 diabetes and a high risk of cardiovascular disease. This report describes the 5-year outcomes of a mean of 3.7 years of intensive glucose lowering on mortality and key cardiovascular events.

METHODS

We randomly assigned participants with type 2 diabetes and cardiovascular disease or additional cardiovascular risk factors to receive intensive therapy (targeting a glycated hemoglobin level below 6.0%) or standard therapy (targeting a level of 7 to 7.9%). After termination of the intensive therapy, due to higher mortality in the intensive-therapy group, the target glycated hemoglobin level was 7 to 7.9% for all participants, who were followed until the planned end of the trial.

RESULTS

Before the intensive therapy was terminated, the intensive-therapy group did not differ significantly from the standard-therapy group in the rate of the primary outcome (a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) (P=0.13) but had more deaths from any cause (primarily cardiovascular) (hazard ratio, 1.21; 95% confidence interval [CI], 1.02 to 1.44) and fewer nonfatal myocardial infarctions (hazard ratio, 0.79; 95% CI, 0.66 to 0.95). These trends persisted during the entire follow-up period (hazard ratio for death, 1.19; 95% CI, 1.03 to 1.38; and hazard ratio for nonfatal myocardial infarction, 0.82; 95% CI, 0.70 to 0.96). After the intensive intervention was terminated, the median glycated hemoglobin level in the intensive-therapy group rose from 6.4% to 7.2%, and the use of glucose-lowering medications and rates of severe hypoglycemia and other adverse events were similar in the two groups.

CONCLUSIONS

As compared with standard therapy, the use of intensive therapy for 3.7 years to target a glycated hemoglobin level below 6% reduced 5-year nonfatal myocardial infarctions but increased 5-year mortality. Such a strategy cannot be recommended for high-risk patients with advanced type 2 diabetes. (Funded by the National Heart, Lung and Blood Institute; ClinicalTrials.gov number, NCT00000620.)

TYPE 2 DIABETES MELLITUS IS A STRONG, independent risk factor for cardiovascular disease and death,[1] and many epidemiologic analyses have identified a progressive relationship between hyperglycemia and these outcomes.[2-5] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was designed to determine whether a strategy of targeting normal glycated hemoglobin levels (i.e., <6.0%) would reduce the risk of serious cardiovascular events in middle-aged and elderly people with type 2 diabetes mellitus, glycated hemoglobin levels of 7.5% or more, and additional cardiovascular risk factors.[6] However, on the basis of a mean of 3.5 years' worth of data, the independent data and safety monitoring board recommended termination of the intensive glucose-lowering regimen because of the finding of higher mortality in the intensive-therapy group. Therefore, we applied the approaches that were used in the standard control group to participants assigned to the intensive-therapy group, for up to 17 months of additional follow-up. We report the clinical outcomes at 5 years of follow-up in response to a mean of 3.7 years of an intensive glycemia strategy.

METHODS

STUDY DESIGN

The design and major results of the trial have been published previously.[6,7] Briefly, we recruited male and female volunteers from 77 clinical centers in the United States and Canada. The participants were 40 to 79 years of age, had type 2 diabetes mellitus and a glycated hemoglobin level of 7.5% or more, and had previous evidence of cardiovascular disease or risk factors for cardiovascular disease. Participants were randomly assigned to receive either intensive glucose-lowering therapy targeting a glycated hemoglobin level of less than 6.0% or standard glucose-lowering therapy targeting a level of 7 to 7.9%. All participants received counseling about lifestyle and education about the management of diabetes. Glucose-lowering drugs were chosen from a common formulary according to the participant's study-group assignment and response to therapy.[7] Glycated hemoglobin levels were audited regularly according to treatment group and study center, and feedback was provided to facilitate the attainment of the target glycated hemoglobin levels.

TERMINATION OF INTENSIVE REGIMEN AND ASSESSMENT OF OUTCOMES

Recruitment occurred in two phases, from January to June 2001 and from February 2003 to October 2005. On February 5, 2008, participants were informed of the decision to discontinue the intensive glucose-lowering regimen, after a mean treatment period of 3.7 years. Participants in the intensive-therapy group subsequently were switched to standard glycemic therapy, and their target glycated hemoglobin level of less than 6% was changed to a target level of 7 to 7.9%. Since participants had also been assigned to receive treatment either to control lipid levels or to lower blood pressure,[8,9] they continued to be followed at least every 4 months until the originally planned end of the trial (June 2009). Thus, data on clinical outcomes, including the primary outcome (a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) and death from any cause (a secondary outcome), continued to be collected and adjudicated for an additional 17 months by a central committee whose members were unaware of study-group assignments.

INTERVENTION EFFECTS

The effects of the glycemic intervention during a mean of 3.5 years (until December 10, 2007), which provided the basis for the data and safety monitoring board's recommendation to discontinue the intensive regimen, have been reported previously.[6] Here we report the effect of the intervention during an additional 0.2 years (i.e., until February 5, 2008), which was when participants were informed of the change in approach. We also report on outcomes that occurred before February 5, 2008, that were not reported to the coordinating center as of December 10, 2007. Therefore, we used intention-to-treat analyses to report on the effect of a mean of 3.7 years of an intensive glycemic intervention on cardiovascular disease, followed by a mean of 1.2 years of standard glycemic therapy. Also reported are the effects of the glycemic intervention until the transition date and until the end of the overall trial for both the blood-pressure and lipid trials. The treatment effects of the lipid and blood-pressure interventions were reported separately.[8,9] All primary and secondary outcomes were adjudicated centrally by two adjudicators who were unaware of treat-

ment-group assignments, and in addition, deaths were reviewed by two diabetes experts (who were unaware of treatment-group assignments) to determine whether they were due to hypoglycemia. The ACCORD trial was sponsored by the National Heart, Lung, and Blood Institute (NHLBI), and the protocol (available with the full text of this article at NEJM.org) was approved by an NHLBI review panel and by the ethics committee at each center. All participants provided written informed consent. All authors vouch for the accuracy and completeness of the reported data. The donors of medications and devices had no role in the study design, data accrual and analysis, or manuscript preparation.

STATISTICAL ANALYSIS

All statistical analyses were conducted at the coordinating center with the use of S-Plus software, version 8.0 (Insightful), or SAS software, version 9.2 (SAS Institute). Baseline characteristics of the participants were summarized with the use of means, standard deviations, and percentages. Median glycated hemoglobin levels were calculated monthly (by calendar month) to show the effect of the switch from intensive therapy to the standard approach. Exposure to glucose-lowering drugs was summarized as the number of participants who were prescribed a medication at the last visit before the transition date and at the trial termination. The incidence of key safety outcomes was expressed as the percentage of events per follow-up year, taking into account censoring of follow-up data. Kaplan–Meier estimates were used to calculate the percentage of participants who had an event during follow-up.

Primary and secondary outcomes were analyzed with the use of Cox proportional-hazards regression analyses according to the intention-to-treat principle, and between-group comparisons of the outcomes were performed with the use of hazard ratios and 95% confidence intervals derived from these models. These analyses were performed for events occurring from randomization until the date of transition (February 5, 2008) and from randomization until the final visit (between the beginning of March and the end of June 2009). An additional post hoc analysis was performed for the primary outcome and death from any cause with the use of data from the post-transition phase only.

For analyses of outcomes, data from participants without final follow-up data were censored

as of the time of their last completed 4-month visit in both the intensive-therapy and standard-therapy groups. Data on mortality for participants in the United States who were not followed for the full follow-up period and who were not known to be deceased were censored as of the most recent date they were known to be alive or January 1, 2008, on the basis of the National Death Index.

Silent myocardial infarctions were identified on the basis of electrocardiograms obtained every 2 years and were considered to have occurred at the midpoint of the dates between the electrocardiogram showing a new myocardial infarction and the previous electrocardiogram. Information from electrocardiograms obtained after the transition date were not known to the data and safety monitoring board or investigators at the time of the transition. Therefore, new silent myocardial infarctions detected after the transition date that would have been assigned to the period before transition were deemed to have occurred on the date of transition; this occurred for 29 participants.

Cox models for the primary outcome contained a term representing study-group assignments plus terms accounting for the following prespecified stratifying variables: assignment to the blood-pressure trial or lipid trial; assignment to the intensive blood-pressure intervention in the blood-pressure trial; assignment to receive fibrate in the lipid trial; the seven clinical center networks; and the presence or absence of previous cardiovascular disease. For all secondary outcomes, an a priori decision was made to drop the clinical center networks from this model, because fewer events were expected than for the primary outcomes. The consistency of the effect of the study-group assignment on death from any cause and on the primary outcome in the blood-pressure trial and the lipid trial was assessed with the use of statistical tests of interactions between the treatment effect and the subgroup within the Cox models.

Unless otherwise indicated, nominal P values, unadjusted for the multiple tests performed for this report or for monitoring by the data and safety monitoring board, are reported. Since we conducted 46 statistical tests of hypotheses related to secondary end points and subgroups, there was a 91% chance (i.e., $1-[1-0.05]^{46}$) that at least one of these tests would be significant at an alpha level of 0.05, assuming independence between tests.

820

The effect of the study-group assignment on the primary outcome or mortality after the transition in participants who had not had a primary outcome and who were alive at the transition date was explored with the use of Kaplan–Meier curves and Cox regression models. Further post hoc exploratory analyses to identify factors associated with higher mortality in the intensive-therapy group have examined baseline characteristics,[10] the achieved glycated hemoglobin level and the rapidity of its decline,[11] and hypoglycemic events.[12,13]

RESULTS

Baseline characteristics of the participants have been reported previously.[6] Table 1 shows these characteristics before the transition date and at the final visit. Figure 1 in the Supplementary Appendix (available at NEJM.org) shows the completeness of follow-up in the two study groups. Median glycated hemoglobin levels before the transition date in the intensive-therapy and standard-therapy groups were 6.4% and 7.5%, respectively. After the transition date, therapy was relaxed (i.e., fewer drugs or lower doses were used) for a particular indication at least as often in the intensive-therapy group as in the standard-therapy group. For example, at the first post-transition visit, relaxation of therapy was indicated in 94% of participants in the intensive-therapy group and 69% of those in the standard-therapy group. At the final visit, median glycated hemoglobin levels were 7.2% in the intensive-therapy group and 7.6% in the standard-therapy group (Fig. 2 in the Supplementary Appendix). By the final visit, the numbers of participants who were receiving metformin, secretagogues, thiazolidinediones, insulin, and combination therapy with insulin and oral agents were similar in the two groups (Table 1 in the Supplementary Appendix). Rates of severe hypoglycemia and other adverse events within the two groups were similar after the transition (Table 2 in the Supplementary Appendix).

Figure 1 shows the incidence of the primary outcome and death from any cause from randomization until the time of transition, from randomization until the end of the whole study, and from the transition date until the termination of the trial. Figure 2 shows the effect of intensive glucose-lowering therapy on all the major outcomes, from randomization until the end of the active treatment period and until the end of the study. Before the transition, the incidence of the primary outcome among the participants in the intensive-therapy group was 2.0% per year, as compared with an incidence of 2.2% per year among the participants in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.03; nominal P=0.132, and P=0.134 after adjustment for repeat testing by the data and safety monitoring board) and remained nonsignificant throughout the entire period of observation (hazard ratio, 0.91; 95% CI, 0.81 to 1.03; P=0.12).

The intensive therapy had different effects on two of the key components of this primary outcome. At the time of the transition, the rate of nonfatal myocardial infarction in the intensive-therapy group was lower than that in the standard-therapy group (1.08% vs. 1.35%; hazard ratio, 0.79; 95% CI, 0.66 to 0.95; P=0.01), but the rate of death from cardiovascular causes was nonsignificantly higher (0.71% vs. 0.55%; hazard ratio, 1.27%; 95% CI, 0.99 to 1.63; P=0.07). These divergent effects were retained at the end of the study, with a rate of nonfatal myocardial infarction in the intensive-therapy group that was lower than that in the standard-therapy group (1.18 vs. 1.42; hazard ratio, 0.82; 95% CI, 0.70 to 0.96; P=0.01) and a rate of death from cardiovascular causes that was higher (0.74 vs. 0.57; hazard ratio, 1.29; 95% CI, 1.04 to 1.60; P=0.02).

Finally, at the time of the transition, there was a 21% higher rate of death from any cause in the intensive-therapy group than in the standard-therapy group (1.42 vs. 1.16; 95% CI, 1.02 to 1.44; nominal P=0.030 and P=0.036 after adjustment for repeat testing by the data and safety monitoring board) and a 19% higher rate at the end of the study (1.53 vs. 1.27; 95% CI, 1.03 to 1.38; P=0.02) (Fig. 1 and 2). The causes of death are listed in Table 2. There was no clear difference between study groups in any other predefined cardiovascular outcomes.

Table 3 lists the annual incidence of the primary and secondary outcomes in the two treatment groups after the transition date, and Figures 1C and 1F show the corresponding Kaplan–Meier curves for the primary outcome and death from any cause. Hazard ratios in the post-transition period were not significantly different from those in the pretransition period for either the primary outcome (ratio of pretransition to post-transition hazard ratios, 0.95; 95% CI, 0.72 to 1.26; P=0.72) or death from any cause (ratio of pretransition

Table 1. Characteristics of the Participants at Baseline, before the Transition, and after the Transition.*

Characteristic	Intensive Therapy			Standard Therapy		
	Baseline (N=5057)	Pretransition (N=5052)	Post-Transition (N=4429)	Baseline (N=5051)	Pretransition (N=5052)	Post-Transition (N=4483)
Mean weight — kg	93.6±18.6	96.7±20.7	95.6±20.9	93.6±18.6	93.7±19.8	93.8±20.1
Weight gain of >10 kg since baseline — no. (%)		861 (17.1)	699 (15.8)		426 (8.5)	452 (10.1)
Body-mass index†	32.2±5.5	33.5±6.2	33.1±6.2	32.2±5.5	32.5±5.9	32.5±6.0
Waist circumference (cm)	106.7±13.9	109.6±15.3	109.1±15.3	106.8±13.8	107.5±14.8	107.7±14.9
Blood pressure — mm Hg						
Systolic	136.2±16.9	127.7±17.2	129.3±17.4	136.4±17.2	128.5±17.4	128.5±16.5
Diastolic	74.8±10.6	67.3±10.8	68.3±10.5	75.0±10.7	68.1±10.8	67.7±10.1
Glycated hemoglobin — %						
Mean	8.3±1.1	6.6±1.0	7.4±1.2	8.3±1.1	7.7±1.1	7.8±1.2
Median	8.1	6.4	7.2	8.1	7.5	7.6
Fasting serum glucose — mg/dl	174.9±55.9	117.0±45.0	143.4±55.4	175.7±56.5	153.4±53.4	154.9±55.2
Cholesterol — g/dl						
Low-density lipoprotein	104.9±33.9	90.8±34.0	87.9±33.1	104.9±33.8	90.7±34.5	87.9±33.7
High-density lipoprotein						
Women	47.2±13.0	48.6±13.2	49.5±13.4	46.9±12.2	47.6±13.6	49.0±13.9
Men	38.4±9.5	40.1±10.8	40.4±10.4	38.8±9.7	39.6±10.8	40.5±11.2
Total	183.4±41.9	164.8±42.3	163.1±42.1	183.2±41.6	167.2±44.1	164.0±42.2
Median triglycerides — mg/dl	190.9±148.4	154.6±102.0	160.3±125.0	189.4±148.8	175.5±151.5	166.0±114.8
Potassium — mg/dl	4.5±0.4	4.4±0.4	4.4±0.4	4.5±0.7	4.4±0.5	4.4±0.5
Serum creatinine — mg/dl	0.9±0.2	1.1±0.4	1.1±0.4	0.9±0.2	1.1±0.4	1.1±0.4
Alanine aminotransferase >3 times ULN — no. (%)		52 (1.0)	27 (0.6)		77 (1.5)	21 (0.5)

* Baseline measurements include all participants who underwent randomization. Pretransition measurements are the last measurements made before the transition, on February 5, 2008, for participants with at least one measurement. Post-transition measurements are the last measurements made for participants for whom measurements were made during the post-transition period. Plus–minus values are means ±SD except where otherwise noted. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for potassium to millimoles per liter, multiply by 0.2558. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ULN denotes upper limit of the normal range.
† Body-mass index is the weight in kilograms divided by the square of the height in meters.

to post-transition hazard ratios, 1.06; 95% CI, 0.76 to 1.46; P=0.74). There was a possible difference in the effect of the intensive therapy on the pretransition primary outcome among participants with a baseline glycated hemoglobin level of 8% or less as compared with those with a level of more than 8% (P=0.03 for interaction) (Fig. 3 in the Supplementary Appendix).

A total of 4733 participants were randomly assigned to receive either intensive or standard therapy to lower their blood pressure, and 5518 participants were randomly assigned to a statin plus either fenofibrate or placebo for control of low-density lipoprotein cholesterol. No significant interactions were noted between the glucose-lowering study and the blood-pressure study for the primary outcome, or between the glucose-lowering study and the lipid study for either the primary outcome or death from any cause. However, there was evidence of an interaction between the intensive glucose-lowering group and the intensive blood-pressure–lowering group with respect to death from any cause both before the transition (P=0.03 for interaction) and at the end of the trial (P=0.05 for interaction) (Fig. 4 in the Supplementary Appendix). Before the transition,
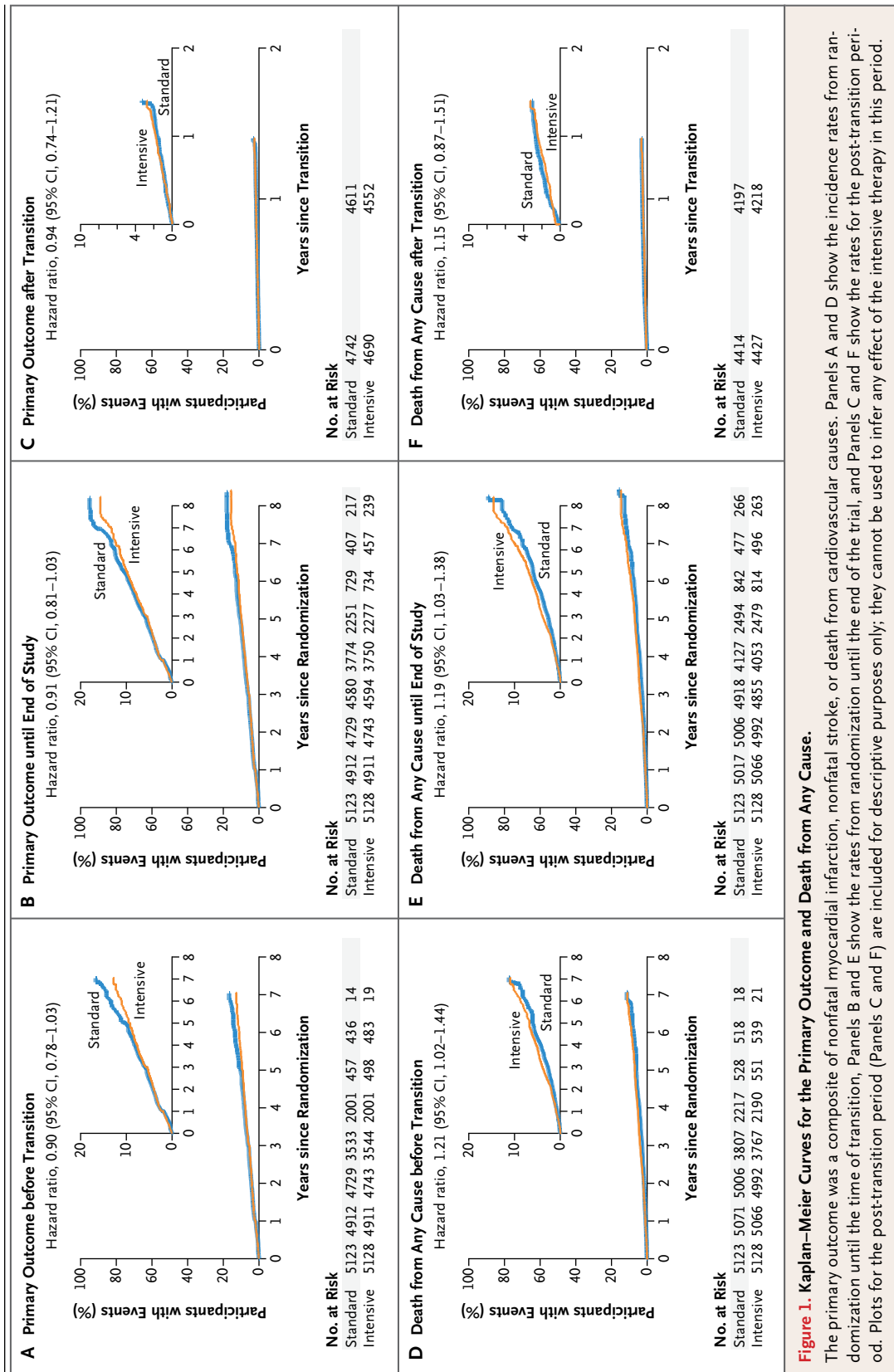
A Primary Outcome before Transition

Hazard ratio, 0.90 (95% CI, 0.78–1.03)

No. at Risk
Standard 5123 4912 4729 3533 2001 457 436 18
Intensive 5128 4911 4743 3544 2001 498 483 21

B Primary Outcome until End of Study

Hazard ratio, 0.91 (95% CI, 0.81–1.03)

No. at Risk
Standard 5123 4912 4729 4580 3774 2251 729 407 217
Intensive 5128 4911 4743 4594 3750 2277 734 457 239

C Primary Outcome after Transition

Hazard ratio, 0.94 (95% CI, 0.74–1.21)

No. at Risk
Standard 4742 4611
Intensive 4690 4552

D Death from Any Cause before Transition

Hazard ratio, 1.21 (95% CI, 1.02–1.44)

No. at Risk
Standard 5123 5071 5006 3807 2217 528 518 18
Intensive 5128 5066 4992 3767 2190 551 539 21

E Death from Any Cause until End of Study

Hazard ratio, 1.19 (95% CI, 1.03–1.38)

No. at Risk
Standard 5123 5017 5006 4918 4127 2494 842 477 266
Intensive 5128 5066 4992 4855 4053 2479 814 496 263

F Death from Any Cause after Transition

Hazard ratio, 1.15 (95% CI, 0.87–1.51)

No. at Risk
Standard 4414 4197
Intensive 4427 4218

Figure 1. Kaplan–Meier Curves for the Primary Outcome and Death from Any Cause.

The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. Panels A and D show the incidence rates from randomization until the time of transition, Panels B and E show the rates from randomization until the end of the trial, and Panels C and F show the rates for the post-transition period. Plots for the post-transition period (Panels C and F) are included for descriptive purposes only; they cannot be used to infer any effect of the intensive therapy in this period.
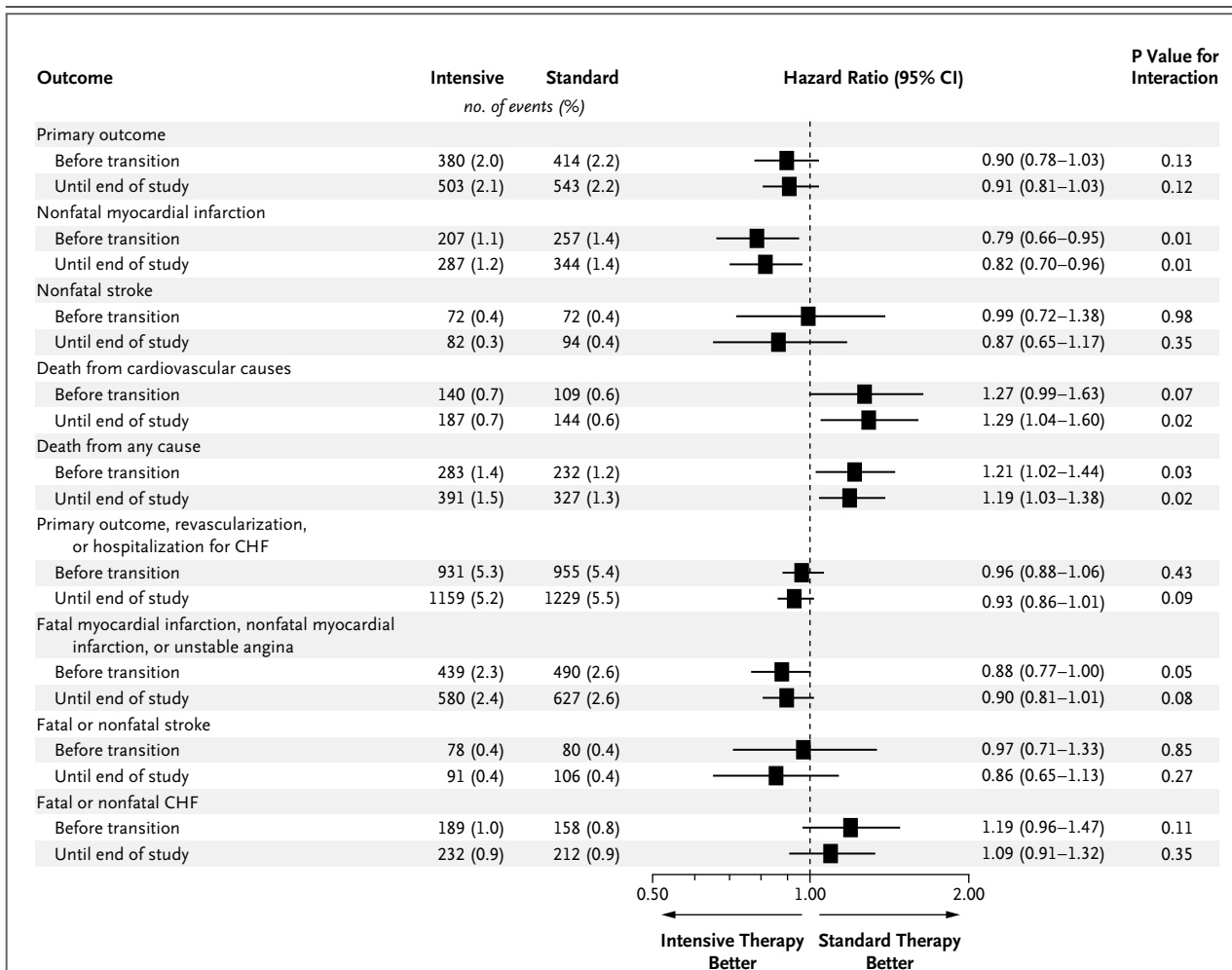
Outcome	Intensive	Standard	Hazard Ratio (95% CI)		P Value for Interaction
	no. of events (%)				
Primary outcome					
Before transition	380 (2.0)	414 (2.2)		0.90 (0.78–1.03)	0.13
Until end of study	503 (2.1)	543 (2.2)		0.91 (0.81–1.03)	0.12
Nonfatal myocardial infarction					
Before transition	207 (1.1)	257 (1.4)		0.79 (0.66–0.95)	0.01
Until end of study	287 (1.2)	344 (1.4)		0.82 (0.70–0.96)	0.01
Nonfatal stroke					
Before transition	72 (0.4)	72 (0.4)		0.99 (0.72–1.38)	0.98
Until end of study	82 (0.3)	94 (0.4)		0.87 (0.65–1.17)	0.35
Death from cardiovascular causes					
Before transition	140 (0.7)	109 (0.6)		1.27 (0.99–1.63)	0.07
Until end of study	187 (0.7)	144 (0.6)		1.29 (1.04–1.60)	0.02
Death from any cause					
Before transition	283 (1.4)	232 (1.2)		1.21 (1.02–1.44)	0.03
Until end of study	391 (1.5)	327 (1.3)		1.19 (1.03–1.38)	0.02
Primary outcome, revascularization, or hospitalization for CHF					
Before transition	931 (5.3)	955 (5.4)		0.96 (0.88–1.06)	0.43
Until end of study	1159 (5.2)	1229 (5.5)		0.93 (0.86–1.01)	0.09
Fatal myocardial infarction, nonfatal myocardial infarction, or unstable angina					
Before transition	439 (2.3)	490 (2.6)		0.88 (0.77–1.00)	0.05
Until end of study	580 (2.4)	627 (2.6)		0.90 (0.81–1.01)	0.08
Fatal or nonfatal stroke					
Before transition	78 (0.4)	80 (0.4)		0.97 (0.71–1.33)	0.85
Until end of study	91 (0.4)	106 (0.4)		0.86 (0.65–1.13)	0.27
Fatal or nonfatal CHF					
Before transition	189 (1.0)	158 (0.8)		1.19 (0.96–1.47)	0.11
Until end of study	232 (0.9)	212 (0.9)		1.09 (0.91–1.32)	0.35

Intensive Therapy Better — Standard Therapy Better

(scale: 0.50, 1.00, 2.00)

Figure 2. Hazard Ratios for the Prespecified Primary and Secondary Outcomes.

The effect of intensive glucose-lowering therapy is shown from randomization until the time of transition and from randomization until the end of the trial. Squares represent hazard ratios, and horizontal bars represent 95% confidence intervals. CHF denotes congestive heart failure.

this interaction was characterized by a marginally higher mortality rate in the intensive glucose-lowering group than in the standard glucose-lowering group among participants also assigned to the intensive blood-pressure–lowering group (hazard ratio, 1.45; 95% CI, 1.00 to 2.12; P=0.05) but not among those also assigned to the standard blood-pressure–lowering group (hazard ratio, 0.78; 95% CI, 0.52 to 1.18; P=0.24).

DISCUSSION

The ACCORD trial involved persons who had had diabetes for a median of 10 years, with a glycated hemoglobin level of at least 7.5%, and who had a high risk of cardiovascular disease. Our findings indicate that in a high-risk population such as this, a mean of 3.7 years of intensive therapy consisting of multiple glucose-lowering methods to target normal glycated hemoglobin levels (i.e., below 6.0%) does not result in a significantly lower number of major cardiovascular events after 5 years than does an approach that uses similar methods to target levels that are more typically achieved in persons in the United States and Canada (i.e., 7 to 7.9%). Indeed, the intensive approach led to more deaths. Effects on the primary outcome were similar during the 3.7-year glucose-

Table 2. Causes of Death.*

Cause of Death	During Pretransition Period		From Randomization until End of Study	
	Intensive Therapy	Standard Therapy	Intensive Therapy	Standard Therapy
	number (percent)			
Any	283 (5.5)	232 (4.5)	391 (7.6)	327 (6.4)
Cardiovascular disease				
Unexpected or presumed cardiovascular disease	89 (1.7)	78 (1.5)	124 (2.4)	103 (2.0)
Fatal myocardial infarction	20 (0.4)	12 (0.2)	24 (0.5)	14 (0.3)
Fatal congestive heart failure	26 (0.5)	20 (0.4)	32 (0.6)	25 (0.5)
Fatal procedure for cardiovascular disease	11 (0.2)	5 (0.1)	14 (0.3)	7 (0.1)
Fatal arrhythmia	4 (0.1)	12 (0.2)	6 (0.1)	18 (0.4)
Fatal procedure for noncardiovascular disease†	1 (<0.1)	4 (0.1)	2 (<0.1)	4 (0.1)
Fatal stroke	9 (0.2)	12 (0.2)	13 (0.3)	17 (0.3)
Other cardiovascular disease	8 (0.2)	10 (0.2)	11 (0.2)	10 (0.2)
Cancer	69 (1.3)	70 (1.4)	102 (2.0)	101 (2.0)
Condition other than cancer or cardiovascular disease	57 (1.1)	40 (0.8)	84 (1.6)	60 (1.2)
Undetermined	11 (0.2)	12 (0.2)	12 (0.2)	21 (0.4)
Identified through National Death Index	6 (0.1)	1 (<0.1)	6 (0.1)	1 (<0.1)

* Data within categories are not mutually exclusive, and persons who were classified as having more than one possible cause of death are listed in the relevant categories.
† This condition was a component of the outcome of fatal cardiovascular disease.

lowering period and the entire 5-year follow-up period; effects on mortality also were similar during the two periods. Similar effects on the primary outcome and mortality were noted in most of the predefined subgroups. The nominally positive tests for interaction with respect to the primary outcome and baseline glycated hemoglobin levels and with respect to death from any cause and the blood-pressure intervention may well have been due to chance, since a large number of statistical tests were performed. No inferences can be made about the effect of the intervention during the post-transition period, because between-group differences during this period alone are likely to have been driven by between-group differences in the characteristics of participants who survived and were followed during this period.

Reasons for the higher mortality in the intensive-therapy group during the pretransition period remain unclear. Because of the equivalent rates of hypoglycemia in the post-transition period, severe hypoglycemia cannot be implicated.

Additional analyses reported elsewhere[12] also do not implicate severe hypoglycemia. According to other analyses, the degree of reduction in glycated hemoglobin levels cannot be implicated.[11] Further analyses should explore possible explanations, such as the role of various drugs, drug combinations, or drug interactions; weight gain; the relatively short intervention period (3.7 years); and the observed interaction between the blood-pressure and glycemia trials with respect to mortality.

Strengths of our study include the randomized trial design, large sample, wide variety of clinics, frequent follow-up, high rate of complete follow-up, high rate of adherence to the study assignment, and adjudication of all events by a central committee that was unaware of the study-group assignments. The clinical relevance of the results is highlighted by the following facts: the approach used commonly available drugs, glycemia was managed within the context of good control of blood pressure and lipid levels, the recruited participants were representative of many

Table 3. Incident Event Rates after the Transition Date.*

Outcome	Intensive Therapy		Standard Therapy	
	no. of patients (%)	*% per year*	*no. of patients (%)*	*% per year*
Primary outcome†	123 (2.8)	2.35	129 (2.9)	2.47
Secondary outcome				
Nonfatal myocardial infarction	80 (1.8)	1.51	87 (2.0)	1.64
Nonfatal stroke	10 (0.2)	0.18	22 (0.5)	0.40
Death				
Cardiovascular causes	47 (1.0)	0.84	35 (0.7)	0.62
Any cause	108 (2.3)	1.92	95 (2.0)	1.67
Primary outcome, revascularization, or hospitalization for heart failure	227 (5.8)	4.97	274 (7.0)	6.04
Fatal or nonfatal myocardial infarction or unstable angina	141 (3.2)	2.74	138 (3.2)	2.70
Fatal or nonfatal stroke	13 (0.3)	0.24	26 (0.6)	0.47
Fatal or nonfatal congestive heart failure	43 (1.0)	0.80	54 (1.2)	0.99

* Data are for descriptive purposes only and cannot be used to infer any effect of the intervention during the post-transition period alone; therefore, statistical tests are not included.
† The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.

people with diabetes who are currently receiving care in ambulatory settings, and several organizations have recommended glycemic targets of 6.5% or lower.

These findings are most applicable to middle-aged and older patients with a long duration of diabetes, a high risk of cardiovascular disease, and hyperglycemia and should be interpreted in light of the specific features of the ACCORD trial. For example, the ACCORD trial excluded people with glycated hemoglobin levels below 7.5%. Moderate heterogeneity with respect to subgroups predefined by the glycated hemoglobin level at baseline (Fig. 3 in the Supplementary Appendix) suggests that participants whose glycated hemoglobin level at baseline was 8% or lower may have had a better response to therapy than participants with higher glycated hemoglobin levels. Although this hypothesis is clearly not proved by the ACCORD trial, it is supported by a recent epidemiologic analysis of the cardiovascular effect of glucose lowering in a cohort of people with type 2 diabetes.[14]

The ACCORD trial explicitly tested whether targeting a glycated hemoglobin level below 6% by means of a large menu of glucose-lowering agents is superior to targeting a glycated hemoglobin level of 7 to 7.9%. Therefore, our findings should be interpreted in relation to these therapies and target glycated hemoglobin levels. Furthermore, targeting normal glycated hemoglobin levels (i.e., <6.0%) required the use of multiple combinations of glucose-lowering medications in ways that are not used in standard care. For example, 42% of participants in the intensive-therapy group were receiving three or more classes of oral agents, either alone (17%) or in combination with insulin (25%), whereas such combinations were used in 19% of the participants in the standard-therapy group (Table 1 in the Supplementary Appendix). Whether these unconventional combinations were responsible for the results and whether similar findings would have been observed with newer glucose-lowering therapies, different drug combinations, or different target glycated hemoglobin levels is unknown.

Finally, people with newly diagnosed diabetes may have a different response to intensive glucose-lowering therapy. A large trial involving people with newly diagnosed type 2 diabetes, in which normal glucose levels were targeted and a median glycated hemoglobin level of 7% (as opposed to 7.9%) was achieved, showed a neutral cardiovascular effect after 10 years but a reduced rate of myocardial infarction and death after 20 years.[15]

In summary, the results of the ACCORD trial show that in persons who have a high risk of cardiovascular disease and suboptimally controlled, long-standing diabetes, with good blood-pressure and lipid control, an intensive therapeutic approach targeting normal glycated hemoglobin levels with the use of multiple medications is associated with higher mortality than is a standard approach targeting higher glycated hemoglobin levels. The higher risk of death from any cause and from cardiovascular causes in the intensive-therapy group means that a therapeutic approach that targets glycated hemoglobin levels below 6% cannot be generally recommended in this population. Thus, the results of the ACCORD trial suggest a lower limit for glycemic targets, achieved with the use of multiple combinations of currently available approaches.

REFERENCES

1. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332:73-8.

2. Selvin E, Coresh J, Golden SH, Brancati FL, Folsom AR, Steffes MW. Glycemic control and coronary heart disease risk in persons with and without diabetes: the Atherosclerosis Risk in Communities study. Arch Intern Med 2005;165:1910-6.

3. Levitan EB, Liu S, Stampfer MJ, et al. HbA1C measured in stored erythrocytes and mortality rate among middle-aged and older women. Diabetologia 2008;51:267-75.

4. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800-11.

5. Gerstein HC, Swedberg K, Carlsson J, et al. The hemoglobin A1c level as a progressive risk factor for cardiovascular death, hospitalization for heart failure, or death in patients with chronic heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Arch Intern Med 2008;168:1699-704.

6. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59.

7. Gerstein HC, Riddle MC, Kendall DM, et al. Glycemia treatment strategies in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol 2007;99(12A):34i-43i.

8. The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563-74. [Erratum, N Engl J Med 2010;362:1748.]

9. *Idem.* Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575-85.

10. Calles-Escandón J, Lovato LC, Simons-Morton DG, et al. Effect of intensive compared with standard glycemia treatment strategies on mortality by baseline subgroup characteristics: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care 2010;33:721-7.

11. Riddle MC, Ambrosius WT, Brillon DJ, et al. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care 2010;33:983-90.

12. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptom-

827

atic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010;340:b4909.

13. Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. BMJ 2010;340:b5444.

14. Greenfield S, Billimek J, Pellegrini F, et al. Comorbidity affects the relationship between glycemic control and cardiovascular outcomes in diabetes: a cohort study. Ann Intern Med 2009;151:854-60.

15. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.

Copyright © 2011 Massachusetts Medical Society.