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A CLINICIAN AND CLINICAL TRIALIST'S PERSPECTIVE

Does intensive therapy of type 2 diabetes help or harm? Seeking accord on ACCORD

ABSTRACT

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial tested the hypothesis that intensive glucose-lowering (with a hemoglobin A_{1c} target of less than 6.0%) would reduce the incidence of atherosclerotic disease events and death compared with standard treatment (with a hemoglobin A_{1c} target of 7.0% to 7.9%) in more than 10,000 patients with type 2 diabetes at high risk of cardiovascular events. The study was terminated early because more people had died in the intensive-treatment group than in the standard-treatment group (257 vs 203). The ACCORD results should not substantially alter our usual approach to glucose-lowering, which should still be “as low as we can get it safely” while avoiding hypoglycemia, significant weight gain, complex regimens, and, perhaps, the “stress” of maintaining glycemic control, especially in patients at high risk of coronary heart disease.

KEY POINTS

No obvious cause, including hypoglycemia proximate to death or the use of any particular medication, clearly explained the excess deaths, although hypoglycemia occurred more often in intensively treated participants.

The death rates in ACCORD were lower than in population studies and in other intervention trials. It is likely that multiple approaches to reducing the risk of cardiovascular disease contributed to this low mortality rate.

THE Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial¹⁻⁵ was designed primarily to address, in patients with type 2 diabetes at high risk of cardiovascular events, whether intensive glucose control would result in a lower risk of atherosclerotic disease events or death than would standard treatment.

It was widely expected that intensive treatment would confer either modest benefit or, at worst, no benefit. However, the glucose-lowering arm of the trial was terminated early because of a higher mortality rate in the intensively treated group. (The ACCORD trial has two other arms, which concern blood pressure and lipid-lowering, and these are continuing.)

In earlier trials in type 2 diabetes, concerns had been raised about an increased risk of cardiovascular events and possibly death associated with glucose-lowering drugs, hypoglycemia itself, or both, and these were well known when ACCORD was convened. ACCORD was very carefully designed and included careful adjudication of each cardiovascular event and death, including whether hypoglycemia might have been a proximate cause of some sudden deaths.⁵

Therefore, the surprising result of the higher mortality rate with intensive glycemic control in ACCORD will be fodder for discussion

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Is glucose
a culprit, or
does it just
run in bad
company?

in many arenas over the next several years, and it poses some challenges for physicians and patients in determining treatment goals, as well as for organizations that write clinical practice guidelines (and perhaps organizations involved in pay-for-performance based on these guidelines).

Still, I believe that the ACCORD results should not substantially change our approach to treatment goals in type 2 diabetes, although hemoglobin A_{1c} targets below 6% may not have much added value for cardiovascular risk reduction. The low overall mortality rate in all the arms of the ACCORD trial emphasizes the importance of lifestyle modification, lipid and blood pressure therapy, and encouragement of aspirin use in all patients with type 2 diabetes.

This article reflects my views as a practicing diabetologist and clinical trialist (I was an investigator in the ACCORD trial) with a long-standing interest in clinical trials and in how the results influence clinical practice. The views I express herein may not reflect the views of other ACCORD investigators, the National Heart, Lung, and Blood Institute (NHLBI), the ACCORD trial coordinating center at Wake Forest University, or its data safety and monitoring board.

■ RISK OF CORONARY DISEASE INCREASES WITH GLUCOSE

Many observational studies⁶⁻¹⁰ have shown that the risk of cardiovascular disease, especially coronary heart disease, is two to five times higher in people with diabetes mellitus than in people without diabetes. The risk appears to be continuous, so the higher one's glucose or hemoglobin A_{1c}, the higher the risk.⁶ This risk even extends to glucose values well below the threshold values currently used to diagnose diabetes mellitus.⁶ Since there is no glucose threshold for coronary heart disease, the term *dysglycemia* (rather than *hyperglycemia*) has been proposed to note the relationship between glucose and coronary heart disease. (The glucose threshold for microvascular complications of diabetes, such as retinopathy and nephropathy, appears to be between 110 and 126 mg/dL).

The clustering of multiple coronary risk factors such as obesity, dyslipidemia, and hy-

pertension has always raised the question of whether glucose is a culprit in coronary risk or whether it simply "runs in bad company."

■ EARLIER CLINICAL TRIALS SUGGEST INTENSIVE TREATMENT RAISES RISK

Even though it has been widely believed that intensive glucose-lowering would reduce cardiovascular risk in type 2 diabetes, there have been hints in previous studies that some intensive-treatment regimens might increase risk.

Two large randomized clinical trials and one small one (discussed below) addressed whether glucose control would reduce the risk of atherosclerotic vascular disease events. In each of them, an increased risk of cardiovascular events and possibly of death was seen in at least one intensively treated group.

In the following discussion, I have calculated all of the death rates as the number of deaths per 1,000 patients per year, based on published study results. In this way, we can compare the rates in the various studies (including ACCORD), regardless of the trial duration.

The University Group Diabetes Program: Controversy about tolbutamide therapy

The University Group Diabetes Program (UGDP)¹¹⁻¹⁶ included about 1,000 participants randomized to five treatments: tolbutamide (Orinase, a sulfonylurea), insulin in a fixed dose based on body weight, insulin in adjusted doses based on fasting glucose levels, placebo, and (later) phenformin.

In the 1970s, when the UGDP was carried out, randomized clinical trials were uncommon. Like other trials from that era, the UGDP was underpowered by today's standards and did not have a data safety and monitoring board.

Rates of cardiovascular events and deaths (per 1,000 patient-years):

- 25 (tolbutamide group)
- 12 (placebo group).

The two insulin groups did not differ from the placebo group in their rates of cardiovascular events or death.¹⁵ The tolbutamide arm was stopped, and the ensuing controversy about how to interpret the trial results lasted for more than a decade. It also resulted in a

black-box warning for tolbutamide and all subsequent sulfonylureas.

United Kingdom Prospective Diabetes Study: Method of glucose-lowering an issue

The United Kingdom Prospective Diabetes Study (UKPDS)¹⁷⁻²⁷ was launched in 1977. A cohort of 5,102 patients (mean age 54 years) with newly diagnosed type 2 diabetes mellitus followed a “prudent diet” for the first 3 to 4 months. Then, if their fasting glucose levels were in the range of 6.1 to 15 mmol/L (110–270 mg/dL), they were randomized to receive various treatments.

Patients who were not obese were randomized to receive either intensive treatment or conventional treatment. The intensive-treatment group received either insulin or a sulfonylurea (chlorpropamide [Diabinese], glibenclamide, or glipizide [Glucotrol]); the conventional-treatment group received diet therapy. The sulfonylurea arm was included partly to address the UGDP results.

Patients who were obese were randomized to receive one of three treatments: intensive treatment (with the agents listed above), conventional treatment, or metformin (Fortamet, Glucophage).

The mean in-trial hemoglobin A_{1c} level in the intensive-treatment group was 7.0%, compared with 7.9% in the conventional-treatment group.

After a mean follow-up of more than 10 years, the incidence of myocardial infarction was 16% lower in the intensive-treatment group, but the difference was not statistically significant ($P = .052$).

Rates of death from all causes among nonobese subjects (per 1,000 patient-years):

- 18.2–20.5 (intensive-treatment group)
- 19.9 (conventional-treatment group).

In the obese patients who received metformin, the incidence of myocardial infarction was lower than in the conventional-treatment group but not the intensive-treatment group.

Rates of death among obese patients (per 1,000 patient-years):

- 13.5 (metformin group)
- 18.9 (intensive-treatment group)
- 20.6 (conventional-treatment group).

However, a small subset ($n = 587$) of the original group assigned to sulfonylurea therapy

whose glycemic control deteriorated during the trial were rerandomized to continue to receive a sulfonylurea alone or to have metformin added. There was a statistically significantly higher rate of cardiovascular events and a nonsignificantly higher rate of total mortality in the metformin-plus-sulfonylurea group (30.3 per 1,000 patient-years) than in the sulfonylurea-only group (19.1 per 1,000 patient-years).

These data suggested that the way glucose-lowering was achieved might be as important as the glucose levels actually achieved. However, no definite conclusions could be drawn.

In an editorial on the UKPDS, Nathan²⁶ made a comment that may have been prescient in terms of the ACCORD trial: “Professional organizations will now scramble to decide how to translate the UKPDS results... Whether the UKPDS firmly establishes the choice of any one therapy...or any combination of therapies for the long-term treatment of type 2 diabetes is more questionable.”²⁶

Veterans Administration feasibility study

A Veterans Administration feasibility study^{28,29} included 153 men (mean age 60) with type 2 diabetes (mean duration 7.8 years) who received either conventional therapy (a single daily dose of insulin) or intensive therapy (multiple doses of insulin plus a sulfonylurea). Over a mean of 27 months, the intensive-therapy group achieved a hemoglobin A_{1c} level that was 2 percentage points lower than in the conventional-therapy group.

At 2.25 years of follow-up, cardiovascular events had occurred in 24 (24%) of the intensive-therapy group and in 16 (20%) of the standard-therapy group ($P = .10$).

Rates of death from all causes (per 1,000 patient-years):

- 28.9 (intensive-treatment group)
- 17.5 (conventional-treatment group).

■ ACCORD TRIAL DESIGN

ACCORD had a double two-by-two factorial design: all of the more than 10,000 patients were randomly assigned to undergo either intensive or standard glucose-lowering therapy; in addition, approximately half were randomly assigned to receive either aggressive or stan-

Controversy over the UGDP trial lasted more than a decade

TABLE 1

Design of the ACCORD trial

GLYCEMIA TRIAL	BLOOD PRESSURE TRIAL		LIPID TRIAL ^a		TOTAL
	SYSTOLIC BLOOD PRESSURE < 120 MM HG	SYSTOLIC BLOOD PRESSURE < 140 MM HG	GROUP A	GROUP B	
Intensive therapy (hemoglobin A _{1c} < 6%)	1,178	1,193	1,383	1,374	5,128
Standard therapy (hemoglobin A _{1c} 7.0%–7.9%, inclusively)	1,184	1,178	1,370	1,391	5,123
Total	2,362	2,371	2,753	2,765	
Total		4,733		5,518	10,251

^a Treatment group assignment blinded until end of trial. Treatment group A = statin plus fenofibrate placebo; treatment group B = statin plus fenofibrate

FROM THE ACTION TO CONTROL CARDIOVASCULAR RISK IN DIABETES (ACCORD) TRIAL. WWW.ACCORDTRIAL.ORG. ACCESSED 8/18/2008.

The ACCORD cohort has had strikingly lower death rates than those in other studies

standard antihypertensive therapy, and the other half were randomly assigned to receive one of two lipid-lowering regimens (TABLE 1).

The primary outcome measured was the combined incidence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. Secondary outcomes included death from any cause. The study is also evaluating the effect of intensive treatment on microvascular disease, hypoglycemia, cognition, quality of life, and cost-effectiveness.

The ACCORD study was designed to have 89% power to detect a 15% treatment effect of intensive glycemic control compared with standard glycemic control for the primary end point.

ACCORD RESULTS

Participants in ACCORD were between the ages of 40 and 82 at randomization and were generally at high risk of coronary heart disease on the basis of having multiple risk factors or a prior event. TABLE 2 summarizes their baseline characteristics.³

At 1 year, the median hemoglobin A_{1c} value had fallen from 8.1% at baseline to 6.4% in the intensive-treatment group and to 7.5% in the standard-treatment group, and these values remained stable throughout the rest of the trial (FIGURE 1).¹

At a median of 3.4 years, the primary outcome (nonfatal myocardial infarction, nonfa-

tal stroke, or death from cardiovascular causes) had occurred in 6.9% of the intensive-therapy group compared with 7.2% of the standard-therapy group (hazard ratio [HR] 0.90, 95% confidence interval [CI] 0.78–1.04, $P = .16$) (FIGURE 2).¹ The difference was primarily due to a lower rate of nonfatal myocardial infarction in the intensive-therapy group ($n = 186$, 3.6%) than in the standard-therapy group ($n = 235$, 4.6%; HR 0.76, 95% CI 0.62–0.92, $P = .004$).¹

However, on February 6, 2008, the ACCORD trial announced that 257 (5%) of the patients in the intensive-treatment group had died, compared with 203 (4%) of the standard-treatment group, a 20% difference ($P = .04$) (FIGURE 3).¹

Rates of death from any cause (per 1,000 patient-years):

- 14 (intensive-treatment group)
- 11 (standard-treatment group).

Although this difference was relatively small by some standards, it was statistically significant ($P = .04$).¹ The number needed to harm was 333 patients for 1 excess death. The difference was attributable to cardiovascular deaths (TABLE 3).¹

In the analyses available at the time that this study arm closed, the excess mortality was not attributable to any particular treatment regimen. In particular, rosiglitazone (Avandia) use did not contribute to the excess mortality.

TABLE 2

ACCORD trial patient characteristics at baseline

Mean age	62 years
Mean duration of diabetes	10 years
Existing cardiovascular disease	35%
Female	39%
Racial or ethnic minorities	27%
Hemoglobin A _{1c} (mean)	8.3%
Hemoglobin A _{1c} (median)	8.1%
Mean body mass index	32 kg/m ²
Mean systolic blood pressure	136 mm Hg
Mean LDL-C	105 mg/dL

ADAPTED FROM BUSE JB, BIGGER JT, BYINGTON RP, ET AL. ACTION TO CONTROL CARDIOVASCULAR RISK IN DIABETES (ACCORD) TRIAL: DESIGN AND METHODS. AM J CARDIOL 2007; 99:21–33i.

(Of note, 91.2% of the intensive-treatment group and 57.5% of the conventional-treatment group had been treated with rosiglitazone, with more than 19,000 patient-years of rosiglitazone exposure). The excess mortality was also not attributable to hypoglycemia immediately proximate to the death.

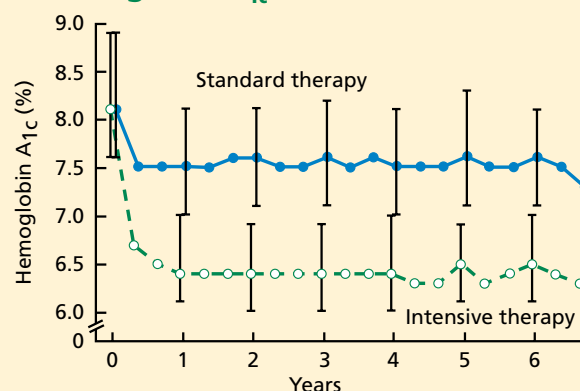
The ACCORD trial's data safety and monitoring board recommended that this arm of the study be discontinued for safety reasons, and this recommendation was accepted by the NHLBI project office. All participants were notified by letter before the trial results were announced publicly, and all intensive-therapy group participants are now being treated by the protocol used in the standard-therapy group.¹

FEWER DEATHS IN ACCORD THAN IN OTHER STUDIES IN DIABETES

The mortality rates in both arms of ACCORD were much lower than in other observational studies and clinical trials in type 2 diabetes.

The National Health and Nutrition Education Survey (NHANES),³⁰ conducted from 1971 to 1975, included 14,374 people with diabetes between the ages of 25 and 74. Many of them were younger than the ACCORD patients, but two NHANES age-groups overlapped

ACCORD trial results: Lower hemoglobin A_{1c} with intensive treatment



No. at risk

Intensive therapy	5109	4774	4588	3186	1744	455	436
Standard therapy	5119	4768	4585	3165	1706	476	471

FIGURE 1. Median hemoglobin A_{1c} levels at each study visit in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Bars denote interquartile ranges.

FROM GERSTEIN HC, MILLER ME, BYINGTON RP, ET AL. EFFECTS OF INTENSIVE GLUCOSE LOWERING IN TYPE 2 DIABETES. N ENGL J MED 2008; 358:2545–2559. COPYRIGHT 2008, MASSACHUSETTS MEDICAL SOCIETY. ALL RIGHTS RESERVED.

the ACCORD cohort. Rates of death from any cause at 22 years (per 1,000 patient-years):

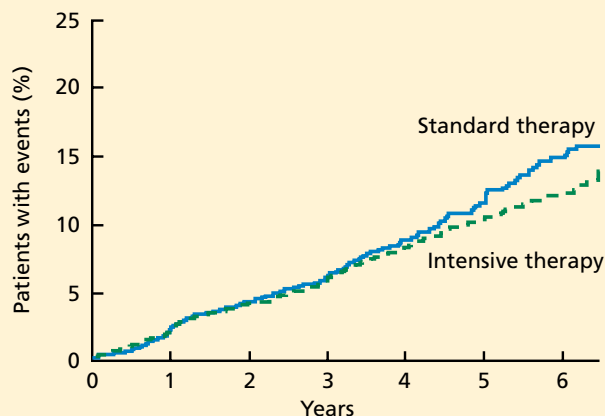
- 39.7 (ages 45–64)
- 89.7 (ages 65–74).

The NHANES cohort would not have been treated as vigorously for coronary risk and other common causes of death.

UGDP, UKPDS. Death rates in the glucose-lowering trials of type 2 diabetes mellitus cited above were typically in the range of 20 deaths per 1,000 patient-years but were as high as 30 deaths per 1,000 patient-years in the UGDP tolbutamide group¹⁶ and the UKPDS sulfonylurea-plus-metformin group.^{20,22,26}

Steno-2.³¹ Half of 160 patients with type 2 diabetes were randomized to intensive strategies for controlling glucose, lipids, and blood pressure and for taking aspirin and angiotensin-converting enzyme inhibitors and following a healthy lifestyle. The other half received conventional therapy. Even in the intensive-treatment group, the mortality rate at 13 years was higher than in ACCORD. Rates of death from any cause (per 1,000 patient years):

ACCORD results: A lower rate of the combined primary outcome with intensive treatment



No. at risk

Intensive therapy	5128	4843	4390	2839	1337	475	448
Standard therapy	5123	4827	4262	2702	1186	440	395

FIGURE 2. Kaplan-Meier curves for the combined primary outcome (the first occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes) in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.

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- 22.5 (intensive-treatment group)
- 37.6 (conventional-treatment group).

After the ACCORD results were presented, two other trials addressing the question of whether lower hemoglobin A_{1c} would reduce cardiovascular risk in type 2 diabetes have reported their outcomes:

The ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation),^{32,33} with 11,140 patients, had a target hemoglobin A_{1c} of 6.5% in an intensive-treatment group and 7.3% in a usual-treatment group. The intensive-treatment group showed no difference in the rates of major macrovascular events (HR 0.94, 95% CI 0.84–1.06, *P* = .32) or all-cause mortality (HR 0.93, 95% CI 0.83–1.06, *P* = .32). The overall death rate in ADVANCE (about 18 deaths per 1,000 patient-years) was

higher than in ACCORD.

The **Veterans Administration Diabetes Trial** included 1,791 patients.³⁴ Like the ADVANCE trial, it also found no difference in major cardiovascular outcomes (HR 0.868, *P* = .11) or cardiovascular mortality rates (HR 1.258, *P* = .36) with intensive therapy vs conventional therapy, ie, achieved hemoglobin A_{1c} levels of 6.9% vs 8.4% (presented at the American Diabetes Association 2008 Scientific Sessions). Hypoglycemia was associated with an increased risk of death in the standard-treatment group.

An analysis suggested that patients with a shorter duration of diabetes may have had cardiovascular benefit from intensive glucose-lowering, while those who had had it longer may have had increased risk associated with the more intensive therapy. The rate of death from all causes appears to have been higher than in ACCORD, but this could not be determined accurately from the presentations.

Comment. Thus, the ACCORD cohort as a whole has had strikingly lower death rates than in these other studies. The fact that all participants had lower glucose levels on therapy than at baseline may possibly contribute to these lower death rates. In addition, all ACCORD participants in the lipid arm received a statin; all participants in the blood pressure arm had their blood pressure lowered to levels below those commonly seen in clinical practice; participants were encouraged to exercise regularly; most participants were given diet instruction; and other healthy behaviors such as aspirin use, regular follow-up with primary care physicians, and recommendations about smoking were encouraged throughout the study. These comprehensive strategies may represent better care and thus result in lower death rates than in other studies.

POSSIBLE EXPLANATIONS FOR THE ACCORD OUTCOMES

The ACCORD trial has already stimulated fierce debate about the reasons for the higher mortality rate in the intensive-treatment group. With longer follow-up, some new risk factors for death may be identified that are not evident in the analyses of the current 460 deaths. What follows are some of my thoughts,

with the caveat that they are not confirmed (supported statistically) by any currently available analyses from ACCORD.

It seems unlikely that lower glucose values as reflected by lower hemoglobin A_{1c} values in the intensive-treatment group are an a priori explanation for the observed differences in mortality rates—especially since the mortality rates were lower than in the NHANES and clinical trial data sets cited above. If we assume that a type 1 statistical error (finding a difference where no difference actually exists) does not explain the findings, then at least four reasonable postulates exist:

Hypoglycemia may have some adverse effect, either acutely or from recurrent events that trigger a catecholamine response with associated risk for arrhythmia or increased coronary heart disease risk. However, the investigators analyzed each death to determine whether hypoglycemia was a contributing cause, and they found no statistically significant relationship between hypoglycemia and death in the intensive-treatment group.

Weight gain is common with intensive therapy. Obesity may be associated with greater cytokine production, higher concentrations of clotting factors, higher levels of free fatty acids, and other potential contributors to the risk of coronary heart disease and death. Currently, the ACCORD analyses do not suggest that weight gain explains the higher death rate.

Medications such as rosiglitazone, sulfonylureas, and the combination of a sulfonylurea plus metformin have been previously associated with increased death rates in some observational and intervention trials. These studies had some serious methodologic limitations (eg, absence of risk adjustment, events not adjudicated, small study cohorts, wide variation in study cohort characteristics) and small numbers of events.^{11–13,16,26,35} ACCORD analyses have not shown that any single glucose-lowering agent—including rosiglitazone—or combination of agents explains the death rates.

The stress of maintaining glycemic control has been speculated to have in some way contributed to an increased risk. To achieve intensive control, patients had to have frequent contact with their health care providers, they were often told that their hemoglo-

ACCORD results: More deaths from any cause with intensive treatment

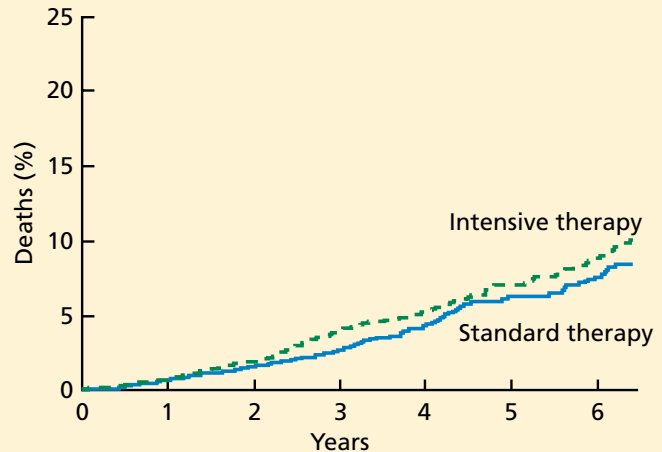


FIGURE 3. Kaplan-Meier curves for death from any cause in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.

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bin A_{1c} values were “too high” even when they were well below those in the American Diabetes Association guidelines, and they had to follow complex glucose-lowering regimens.

Semiquantitative measures of overall attitudes about health exist (eg, the “Feeling Thermometer” scale), but stress was not measured quantitatively in the ACCORD trial.

IMPLICATIONS OF ACCORD

In practice, most clinicians believe that the target glucose level in patients with type 2 diabetes should be as low as safely possible. This approach does not need to be modified on the basis of current information from ACCORD.

To be safe, regimens should be associated with a low risk of hypoglycemia and a low risk of weight gain. Use of combinations of medications that work by different mechanisms is still prudent. Agents should be used that may have favorable effects on other cardiovascular risk factors (eg, lipids, blood pressure, visceral fat).

For now, strategies that lower glucose with low risk of hypoglycemia or weight gain are appropriate

TABLE 3

Causes of death in the ACCORD trial

	INTENSIVE THERAPY (N = 5,128)	STANDARD THERAPY (N = 5,123)
Any cause	257	203
Cardiovascular	135	94
Unexpected or presumed cardiovascular disease	86	67
Myocardial infarction	19	13
Congestive heart failure	23	16
Fatal procedure		
For cardiovascular disease	10	3
For condition other than cardiovascular disease	1	3
Arrhythmia	4	10
Stroke	9	11
Other cardiovascular disease	8	10
Cancer	65	63
Condition other than cancer or cardiovascular disease	50	35
Undetermined	7	11

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Hemoglobin A_{1c} targets below 7% are not precluded in all patients on the basis of the ACCORD results, though values lower than 6% may not have much added benefit for cardiovascular risk reduction. We should note that hemoglobin A_{1c} was reduced in all ACCORD participants and that death rates were lower than in many other type 2 diabetic cohorts. Pending data on other outcomes in ACCORD (nephropathy, retinopathy, dementia, fracture risk), I believe it is premature for or-

ganizations to change their proposed hemoglobin A_{1c} targets,^{36,37} as none have proposed values as low as the target in the ACCORD intensive-treatment group. At present, no class of glucose-lowering agents needs to be excluded from consideration on the basis of the ACCORD data.

The overall low rates of death in this population at high risk of coronary heart disease deserve comment. Not only are they lower than in other glucose-lowering trials, but they are also lower than in a number of studies of mortality in diabetes cohorts. As noted above, multiple risk factors for coronary heart disease and death were (and are) addressed in the ACCORD study participants, including repeated recommendation for lifestyle modification, intervention arms with lipid and blood pressure therapy, encouragement of aspirin use, and regular follow-up with health care providers for risk factors not managed by the ACCORD trial protocol. It is likely that multiple approaches to reducing the risk of cardiovascular disease contributed to this low mortality rate and that similar approaches will reduce the risk of coronary disease and death in regular clinical practice.

The ACCORD lipid and blood pressure arms are continuing, with results expected in 2010. The future results from ACCORD as well as from several glucose-lowering trials currently in progress (ADVANCE,^{32,33} Veteran's Administration,³⁴ Bypass Angioplasty Revascularization Investigation 2 Diabetes [BARI-2D]³⁸) will likely help refine our understanding of the effects of glucose-lowering, glucose-lowering strategies and targets, and multiple interventions on coronary events and all-cause mortality.

For now, any strategy that lowers glucose and is associated with a low risk of hypoglycemia and does not cause excessive weight gain should be considered appropriate in patients with type 2 diabetes. ■

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