ORIGINAL ARTICLE

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

ABSTRACT

BACKGROUND

In patients with type 2 diabetes, the effects of intensive glucose control on vascular outcomes remain uncertain.

METHODS

We randomly assigned 11,140 patients with type 2 diabetes to undergo either standard glucose control or intensive glucose control, defined as the use of gliclazide (modified release) plus other drugs as required to achieve a glycated hemoglobin value of 6.5% or less. Primary end points were composites of major macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy), assessed both jointly and separately.

RESULTS

After a median of 5 years of follow-up, the mean glycated hemoglobin level was lower in the intensive-control group (6.5%) than in the standard-control group (7.3%). Intensive control reduced the incidence of combined major macrovascular and microvascular events (18.1%, vs. 20.0% with standard control; hazard ratio, 0.90; 95% confidence interval [CI], 0.82 to 0.98; P=0.01), as well as that of major microvascular events (9.4% vs. 10.9%; hazard ratio, 0.86; 95% CI, 0.77 to 0.97; P=0.01), primarily because of a reduction in the incidence of nephropathy (4.1% vs. 5.2%; hazard ratio, 0.79; 95% CI, 0.66 to 0.93; P=0.006), with no significant effect on retinopathy (P=0.50). There were no significant effects of the type of glucose control on major macrovascular events (hazard ratio with intensive control, 0.94; 95% CI, 0.84 to 1.06; P=0.32), death from cardiovascular causes (hazard ratio with intensive control, 0.88; 95% CI, 0.74 to 1.04; P=0.12), or death from any cause (hazard ratio with intensive control, 0.93; 95% CI, 0.83 to 1.06; P=0.28). Severe hypoglycemia, although uncommon, was more common in the intensive-control group (2.7%, vs. 1.5% in the standard-control group; hazard ratio, 1.86; 95% CI, 1.42 to 2.40; P<0.001).

CONCLUSIONS

A strategy of intensive glucose control, involving gliclazide (modified release) and other drugs as required, that lowered the glycated hemoglobin value to 6.5% yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy. (ClinicalTrials.gov number, NCT00145925.)

The members of the Writing Committee of the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) Collaborative Group are listed in the Appendix. Address reprint requests to Dr. Anushka Patel at the Cardiovascular Division, George Institute for International Health, University of Sydney, P.O. Box M201, Missenden Rd., Sydney, NSW 2050, Australia, or at apatel@george.org.au.

*Members of the ADVANCE Collaborative Group are listed in the Supplementary Appendix (available with the full text of this article at www.nejm.org).

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The prevalence of diabetes is increasing worldwide, and most people with diabetes will die or be disabled as a consequence of vascular complications.[1,2] Prospective studies have shown continuous associations of blood glucose and glycated hemoglobin levels with the risks of major vascular events.[3,4] However, previous randomized trials evaluating the effects of glycemic control in patients with diabetes have provided inconsistent evidence of effects on vascular disease.[5-11] Nevertheless, current guidelines recommend a target glycated hemoglobin level of 7.0% or less for most patients with diabetes.[12-14]

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial was designed to assess the effects on major vascular outcomes of lowering the glycated hemoglobin value to a target of 6.5% or less in a broad cross-section of patients with type 2 diabetes. The part of the study that evaluated the lowering of blood pressure with the use of perindopril and indapamide, completed in June 2007, showed a reduction in the risks of major vascular events and death, regardless of the initial blood pressure.[15] Here we report the main results from the comparison of the blood-glucose-lowering strategies, completed in January 2008, which evaluated an intensive glucose-control strategy based on gliclazide (modified release) and other drugs as required to achieve the target glycated hemoglobin level.

METHODS

The ADVANCE trial is a factorial randomized, controlled trial conducted at 215 collaborating centers in 20 countries from Asia, Australasia, Europe, and North America (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). Approval to conduct the trial was obtained from the ethics committee of each study center, and all participants provided written informed consent. Detailed study methods have been published previously.[16]

The ADVANCE trial was an investigator-initiated trial that was designed, conducted, analyzed, and had data interpreted independently of both sponsors. Study data were collected and retained by the investigators and were not made available to the study sponsors. The writing committee and the management committee, whose membership did not include any sponsor representatives, had final responsibility for the manuscript preparation and the decision to submit for publication. The first five authors vouch for the validity and completeness of the reported data.

PARTICIPANTS

Eligibility criteria, as detailed previously,[16] were a diagnosis of type 2 diabetes mellitus at 30 years of age or older, an age of at least 55 years at the time of study entry, and a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease. There were no inclusion or exclusion criteria related to glycated hemoglobin. Exclusion criteria included a definite indication for, or contraindication to, any of the study treatments or a definite indication for long-term insulin therapy at the time of study entry.

STUDY TREATMENT

Potentially eligible participants entered a 6-week run-in period, during which they continued their usual methods of glucose control and received a fixed combination of perindopril and indapamide. Those who tolerated and were compliant with the treatment during the run-in period were randomly assigned, according to a factorial design, to receive continued therapy with either perindopril and indapamide or matching placebo and to undergo either a strategy of intensive blood glucose control (target glycated hemoglobin value, ≤6.5%) or a strategy of standard glucose control (with target glycated hemoglobin levels defined on the basis of local guidelines). Central, computer-based randomization was stratified according to several factors,[16] including study center and presence or absence of a history of major vascular disease.

Patients who were randomly assigned to undergo intensive glucose control were given gliclazide (modified release, 30 to 120 mg daily) and were required to discontinue any other sulfonylurea. Although the timing, selection, and doses of all other treatments were at the discretion of the treating physician, a treatment protocol was suggested (see the Supplementary Appendix). On the basis of the glycated hemoglobin level at each visit, this protocol initially advised increasing the dose of gliclazide (modified release), with the sequential addition or increase in dose of metformin, thiazolidinediones, acarbose, or insulin (advising the initial use of basal insulin, with the addition of short-acting insulin at meals for patients in whom the target glycated hemoglobin level was not achieved, despite acceptable

fasting blood glucose levels). Patients in the standard-control group who were using gliclazide (modified release) when they entered the study were required to substitute this drug with another sulfonylurea, if continued therapy was required.

FOLLOW-UP SCHEDULE

Patients in the intensive-control group were seen at week 2 after randomization; then at months 1, 2, 3, 4, and 6; and every 3 months thereafter. These patients were also encouraged to attend other, unscheduled visits to improve the monitoring and intensification of glucose control. Participants assigned to undergo standard control were seen at 3, 4, and 6 months after randomization and every 6 months thereafter. At study visits common to both groups, information was collected on blood glucose, glycated hemoglobin, blood pressure, and lipids, as well as adherence to, and tolerability of, study treatments and occurrence of study outcomes. At the 2-year, 4-year, and final visits, the ratio of urinary albumin to creatinine was measured and a retinal examination, the Mini–Mental State Examination, and quality-of-life assessment were also performed. At study visits for patients in the intensive-control group only, the information collected was limited to blood glucose, glycated hemoglobin, and glucose-lowering treatments.

LABORATORY MEASUREMENTS

All measurements were performed in local laboratories, and each glycated hemoglobin measurement was standardized (see the Supplementary Appendix).[17] Blood glucose measurements were performed on samples of venous or capillary blood, depending on local practice.

END POINTS

The primary study outcomes were a composite of macrovascular events and a composite of microvascular events, considered both jointly and separately. Macrovascular events were defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Microvascular events were defined as new or worsening nephropathy (i.e., development of macroalbuminuria, defined as a urinary albumin:creatinine ratio of more than 300 μg of albumin per milligram of creatinine [33.9 mg per millimole], or doubling of the serum creatinine level to at least 200 μmol per liter [2.26 mg per deciliter], the need for renal-replacement therapy, or death due to renal disease) or retinopathy (i.e., development of proliferative retinopathy, macular edema or diabetes-related blindness or the use of retinal photocoagulation therapy).

Prespecified secondary outcomes were death from any cause, death from cardiovascular causes, major coronary events (death due to coronary heart disease [including sudden death] or nonfatal myocardial infarction), total coronary events (major coronary events, silent myocardial infarction, coronary revascularization, or hospital admission for unstable angina), major cerebrovascular events (death due to cerebrovascular disease or nonfatal stroke), total cerebrovascular events (major cerebrovascular events, transient ischemic attack, or subarachnoid hemorrhage), heart failure (death due to heart failure, hospitalization for heart failure, or worsening New York Heart Association class), peripheral vascular events, all cardiovascular events, new or worsening nephropathy, new or worsening retinopathy, development of microalbuminuria (urinary albumin:creatinine ratio, 30 to 300 μg per milligram [0.34 to 33.9 mg per millimole]), visual deterioration, new or worsening neuropathy, decline in cognitive function (reduction in the Mini–Mental State Examination score by at least 3 points, as compared with the baseline score), dementia (satisfying the criteria in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*), and hospitalization for 24 hours or more. Hypoglycemia was defined as a blood glucose level of less than 2.8 mmol per liter (50 mg per deciliter) or the presence of typical symptoms and signs of hypoglycemia without other apparent cause. Patients with transient dysfunction of the central nervous system who were unable to treat themselves (requiring help from another person) were considered to have severe hypoglycemia.

An independent End Point Adjudication Committee, unaware of the group assignments, reviewed source documentation for all suspected primary end points and deaths. An independent data and safety monitoring committee reviewed the unblinded data at regular intervals.

STATISTICAL ANALYSIS

The ADVANCE trial was originally designed to have a statistical power of 90% to detect a relative risk reduction of 16% or more for intensive control, as compared with standard control, for each of the primary outcomes, with the use of a two-tailed test with an alpha level of 5%. After a mean of approximately 3 years of follow-up, it be-

came apparent that the event rates (in the two groups combined) were lower than expected. Thus, in a manner blinded to any results of the effects of intervention, two changes were made to the protocol to increase the power of the study: joint (as well as separate) analysis of the primary outcomes was prespecified, and the period of treatment and follow-up was extended by 12 months for the part of the study that evaluated the lowering of blood pressure and by 18 months for the part that evaluated the control of blood glucose.

All analyses were conducted according to the intention-to-treat principle. Effects of treatment on study end points were estimated with the use of unadjusted Cox proportional-hazard models, involving survival time to the first relevant end point in any individual patient. Data for patients were censored at their date of death, date of last visit (for those still alive at the end of the follow-up period), or date when last known to be alive (for those with unknown vital status). Differences in continuous variables between the two study groups during the follow-up period were estimated with the use of linear mixed models. The numbers needed to treat were calculated as reciprocals of the absolute differences in risk with their normally approximated 95% confidence intervals.[18] All P values were two-sided, and P values less than 0.05 were considered to indicate statistical significance. No adjustment for multiple statistical testing was made.[19]

The homogeneity of treatment effects across subgroups (none of which were prespecified) was tested by adding interaction terms to the relevant Cox models. Interaction between the blood-pressure intervention and the blood-glucose intervention in the ADVANCE trial was assessed with the use of the database locked at the end of the period

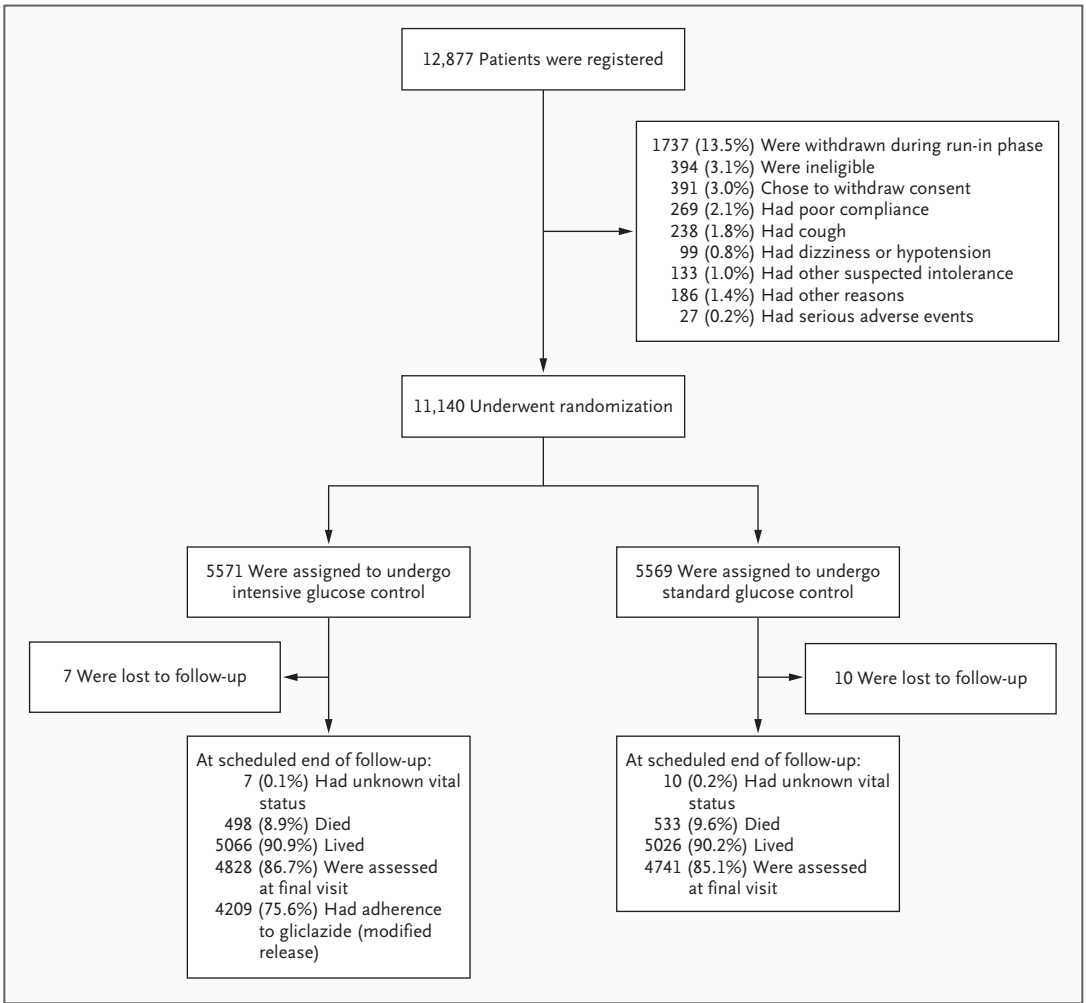

Figure 1. Enrollment, Randomization, and Follow-up of Study Participants.

Table 1. Characteristics of Participants at Baseline and at the End of the Follow-up Period.*

Characteristic	Baseline		End of Follow-up	
	Intensive Control (N=5571)	Standard Control (N=5569)	Intensive Control (N=4828)	Standard Control (N=4741)
Age — yr	66±6	66±6		
Female sex — no. (%)	2376 (42.6)	2357 (42.3)		
Age when diabetes first diagnosed — yr	58±9	58±9		
Duration of diabetes — yr	7.9±6.3	8.0±6.4		
Region — no. (%)				
Australia and New Zealand	744 (13.4)	741 (13.3)		
Asia	2069 (37.1)	2067 (37.1)		
Europe	2538 (45.6)	2545 (45.7)		
North America	220 (4.0)	216 (3.9)		
Previous vascular disease				
History of major macrovascular disease — no. (%)	1794 (32.2)	1796 (32.3)		
Myocardial infarction	668 (12.0)	666 (12.0)		
Stroke	515 (9.2)	508 (9.1)		
Other	683 (12.3)	678 (12.2)		
History of major microvascular disease — no. (%)	571 (10.3)	584 (10.5)		
Macroalbuminuria†	189 (3.4)	215 (3.9)		
Microvascular eye disease‡	403 (7.2)	392 (7.0)		
History of microalbuminuria — no. (%)	1434 (27.0)	1423 (26.7)		
Blood-glucose control				
Glycated hemoglobin, nonstandardized level — %				
Mean ±SD	7.51±1.57	7.52±1.54	6.53±0.91	7.30±1.26
Median	7.2	7.2	6.4	7.0
Interquartile range	6.5–8.2	6.5–8.2	6.0–6.8	6.5–7.9
Glycated hemoglobin, standardized level — %				
Mean ±SD	7.48±1.65	7.48±1.63	6.49±0.99	7.24±1.38
Median	7.2	7.2	6.3	7.0
Interquartile range	6.4–8.2	6.4–8.2	5.9–6.9	6.4–7.9
Fasting blood glucose — mmol/liter				
Mean ±SD	8.51±2.78	8.48±2.76	6.56±1.88	7.75±2.34
Median	7.9	7.9	6.2	7.3
Interquartile range	6.6–9.7	6.6–9.7	5.4–7.3	6.2–8.7
Other major risk factors				
Blood pressure — mm Hg				
Systolic	145.0±21.7	145.0±21.4	135.5±17.6	137.9±18.4
Diastolic	80.8±11.0	80.5±10.8	73.5±9.8	74.3±9.9
Serum cholesterol — mmol/liter				
Low-density lipoprotein	3.12±1.04	3.11±1.02	2.64±0.97	2.65±1.06
High-density lipoprotein	1.26±0.35	1.25±0.35	1.24±0.35	1.25±0.35
Serum triglycerides — mmol/liter				
Median	1.60	1.64	1.45	1.59
Interquartile range	1.20–2.30	1.20–2.30	1.03–2.03	1.10–2.20
Serum triglycerides — μmol/liter	1.95±1.29	1.96±1.29	1.70±1.06	1.82±1.15
Serum creatinine — μmol/liter	86±24	87±27	94±37	93±41
Weight — kg	78.2±16.8	78.0±16.8	78.1±17.5	77.0±16.7
Body-mass index§	28±5	28±5	28±5	28±5
Waist circumference — cm	99±13	98±13	99±14	98±13
Current smoking — no. (%)	793 (14.2)	757 (13.6)	385 (8.3)	350 (7.8)

Table 1. (Continued.)

Characteristic	Baseline		End of Follow-up	
	Intensive Control (N=5571)	Standard Control (N=5569)	Intensive Control (N=4828)	Standard Control (N=4741)
Glucose-lowering drug				
Gliclazide (modified release) — no. (%)¶	422 (7.6)	443 (8.0)	4209 (90.5)	80 (1.6)
Other sulfonylurea — no. (%)	3578 (64.2)	3513 (63.1)	89 (1.9)	2606 (57.1)
Metformin — no. (%)	3397 (61.0)	3355 (60.2)	3455 (73.8)	3057 (67.0)
Thiazolidinedione — no. (%)	201 (3.6)	206 (3.7)	788 (16.8)	495 (10.9)
Acarbose — no. (%)	512 (9.2)	448 (8.0)	891 (19.1)	576 (12.6)
Glinide — no. (%)	103 (1.8)	84 (1.5)	58 (1.2)	127 (2.8)
Any oral hypoglycemic drug — no. (%)	5084 (91.3)	5045 (90.6)	4525 (93.7)	4001 (84.4)
Insulin — no. (%)	82 (1.5)	77 (1.4)	1953 (40.5)	1142 (24.1)
None — no. (%)	487 (8.7)	524 (9.4)	42 (1.5)	220 (6.4)
Other drugs				
Aspirin — no. (%)	2460 (44.2)	2435 (43.7)	2665 (57.0)	2503 (54.9)
Other antiplatelet agent — no. (%)	271 (4.9)	235 (4.2)	333 (7.1)	284 (6.2)
Statins — no. (%)	1554 (27.9)	1592 (28.6)	2131 (45.6)	2174 (47.7)
Other lipid-modifying drug — no. (%)	501 (9.0)	435 (7.8)	326 (7.0)	317 (7.0)
Any blood-pressure–lowering drug — no. (%)	4183 (75.1)	4182 (75.1)	4291 (88.9)	4190 (88.4)

* Plus–minus values are means ±SD. Baseline characteristics were recorded at the first (registration) visit, before the start of the active run-in period. Data are based on the number of patients who attended each visit and who had data for the characteristic. Glycated hemoglobin values were standardized as described in the Supplementary Appendix. To convert the values for blood glucose to milligrams per deciliter, divide by 0.05551. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129. To convert the values for creatinine to milligrams per deciliter, divide by 88.4.

† Macroalbuminuria was defined as a urinary albumin:creatinine ratio of more than 300 μg of albumin per milligram of creatinine (33.9 mg per millimole).

‡ Microvascular eye disease was defined as proliferative diabetic retinopathy, retinal photocoagulation therapy, macular edema, or blindness thought to be caused by diabetes in at least one eye.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ The use of gliclazide (modified release) at baseline in the intensive-control group is reported for the first (registration) visit; at the randomization visit, 99% of patients in this group were given the drug.

of follow-up for the blood-pressure-lowering part of the study (average duration of follow-up, 4.3 years). All analyses were performed with the use of SAS software, version 9.1 (SAS Institute).

RESULTS

ENROLLMENT AND BASELINE CHARACTERISTICS OF PARTICIPANTS

Between June 2001 and March 2003, a total of 12,877 potentially eligible participants were registered, 1737 (13.5%) were withdrawn during the run-in period, and 11,140 (86.5%) underwent randomization (Fig. 1). The median duration of follow-up was 5.0 years. The two groups had similar characteristics at baseline (Table 1, and Table 1 in the Supplementary Appendix). The mean baseline glycated hemoglobin was 7.5%, and the mean fasting blood glucose level was 8.5 mmol per liter (153 mg per deciliter). At baseline, 91% of patients were receiving oral hypoglycemic agents.

EFFECTS ON GLYCATED HEMOGLOBIN AND FASTING BLOOD GLUCOSE

At the end of the follow-up period, the mean glycated hemoglobin values were 6.5% in the intensive-control group and 7.3% in the standard-control group. During the follow-up period, the time-weighted average glycated hemoglobin level was reduced by 0.67 percentage point and the fasting blood glucose level by 1.2 mmol per liter (21.9 mg per deciliter) among patients undergoing intensive control as compared with those undergoing standard control (Fig. 2).

EFFECTS ON OTHER RISK FACTORS

Table 1 describes the levels of other risk factors among study participants. At the end of the follow-up period, the mean systolic blood pressure was lower in the intensive-control group than in the standard-control group (135.5 vs. 137.9 mm Hg; average difference, 1.6 mm Hg; P<0.001) (Table 1). This difference was apparent at the first common

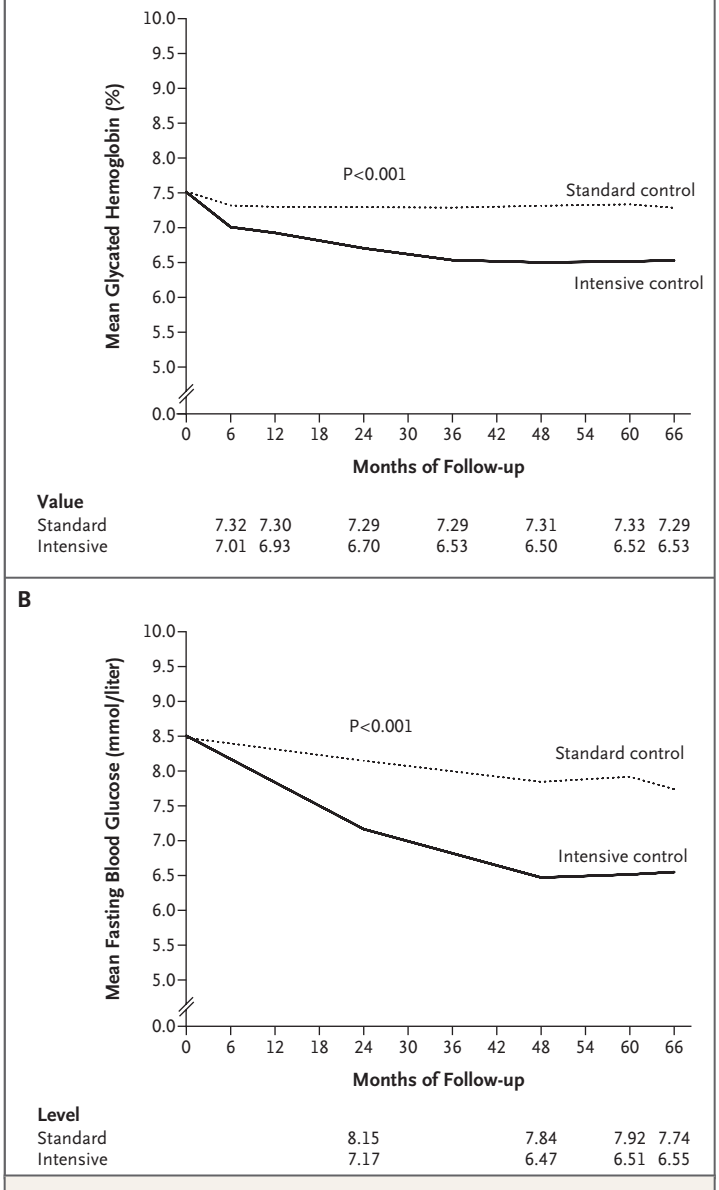

Figure 2. Glucose Control at Baseline and during Follow-up, According to Glucose-Control Strategy.

Data are shown for mean glycated hemoglobin (Panel A) and mean fasting blood glucose (Panel B). The average difference between the intensive-control group and the standard-control group for the follow-up period was 0.67 percentage point (95% confidence interval [CI], 0.64 to 0.70) for glycated hemoglobin and 1.22 mmol per liter (21.9 mg per deciliter) (95% CI, 1.15 to 1.28 [20.8 to 23.0]) for fasting blood glucose.

post-randomization visit (at 3 months) and all subsequent common visits (Fig. 1 in the Supplementary Appendix). The mean body weight during the follow-up period was 0.7 kg greater in the intensive-control group than in the standard-control group (P<0.001).

USE OF GLUCOSE-LOWERING THERAPY AND OTHER TREATMENTS

On average, each patient in the intensive-control group attended 31 study visits, as compared with 11 for each patient in the standard-control group, over the course of the trial period. During the follow-up period, the use of most classes of oral hypoglycemic drug and of insulin had increased to a greater degree in the intensive-control group than in the standard-control group (Table 1, and Table 1 in the Supplementary Appendix). In the intensive-control group, 90% of patients attending the final visit were still receiving gliclazide (modified release), 70.4% of whom were taking 120 mg of the drug daily. Insulin was prescribed for 40.5% and 24.1% of patients in the intensive-control group and the standard-control group, respectively, by the end of the follow-up period. At the final visit, 16.8% of patients undergoing intensive glucose control and 10.9% of those undergoing standard glucose control were receiving thiazolidinediones. The use of blood-pressure–lowering, lipid-modifying, and antiplatelet treatments was similar between the two groups during the follow-up period.

EFFECTS ON PRIMARY OUTCOMES

A total of 2125 participants had a major macrovascular or microvascular event: 18.1% in the intensive-control group and 20.0% in the standard-control group (hazard ratio, 0.90; 95% confidence interval (CI), 0.82 to 0.98; P=0.01) (Fig. 3). Thus, it was estimated that such an event would be averted during a 5-year period in 1 of every 52 participants (95% CI, 30 to 213) undergoing intensive control. As compared with standard control, intensive control resulted in a significant reduction in the incidence of major microvascular events (hazard ratio, 0.86; 95% CI, 0.77 to 0.97; P=0.01) but not in the incidence of major macrovascular events (hazard ratio, 0.94; 95% CI, 0.84 to 1.06; P=0.32). There was no evidence of an interaction between the blood-pressure intervention and the blood-glucose intervention in the ADVANCE trial for the primary outcomes (P>0.50 for all comparisons).

EFFECTS ON DEATH AND OTHER SECONDARY OUTCOMES

A total of 1031 participants died: 8.9% in the intensive-control group and 9.6% in the standard-control group (hazard ratio, 0.93; 95% CI, 0.83 to 1.06; P=0.28) (Fig. 3). As compared with stan-

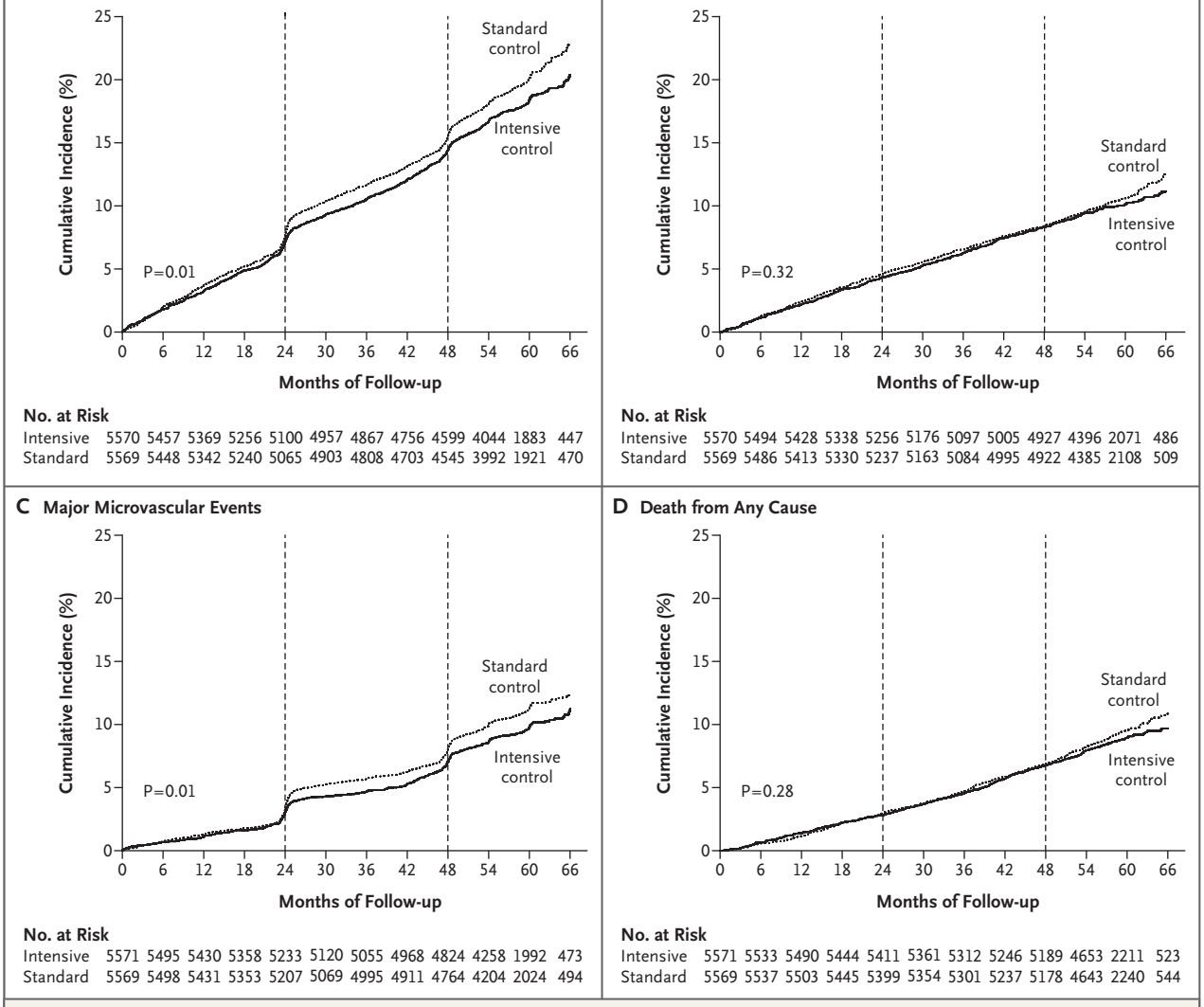

Figure 3. Cumulative Incidences of Events, According to Glucose-Control Strategy.

The hazard ratios for intensive glucose control as compared with standard glucose control were as follows: for combined major macrovascular or microvascular events, 0.90 (95% confidence interval [CI], 0.82 to 0.98) (Panel A); for major macrovascular events, 0.94 (95% CI, 0.84 to 1.06) (Panel B); for major microvascular events, 0.86 (95% CI, 0.77 to 0.97) (Panel C); and for death from any cause, 0.93 (95% CI, 0.83 to 1.06) (Panel D). The vertical dashed lines indicate the 24-month and 48-month study visits, at which additional data on microvascular events were collected, specifically the ratio of urinary albumin to creatinine and results of a retinal examination. For events relating to these data, the event time was recorded as the date of the visit. The curves were truncated at month 66, by which time 99% of the events had occurred. The effects of treatment (hazard ratios and P values) were estimated from unadjusted Cox proportional-hazard models that used all the available data.

dard control, intensive control was associated with a significant reduction in renal events, including new or worsening nephropathy (hazard ratio, 0.79; 95% CI, 0.66 to 0.93; P=0.006) and new-onset microalbuminuria (hazard ratio, 0.91; 95% CI, 0.85 to 0.98; P=0.02) (Fig. 4). The component of new or worsening nephropathy most clearly reduced through intensive glucose control was the development of macroalbuminuria (2.9%, vs. 4.1% with standard control; hazard ratio, 0.70; 95% CI, 0.57 to 0.85; P<0.001), with a trend toward a reduction in the need for renal-replacement therapy or death from renal causes (0.4% vs. 0.6%; hazard ratio, 0.64; 95% CI, 0.38 to 1.08; P=0.09) but no effect on the doubling of serum creatinine level (1.2% vs. 1.1%; hazard ratio, 1.15; 95% CI, 0.82 to 1.63; P=0.42). More patients undergoing intensive control were hospitalized

Subgroup	Intensive Control (N=5571)	Standard Control (N=5569)	Hazard Ratio (95% CI)	Relative Risk Reduction (95% CI)
	number of patients (percent)			*percent*
Primary End Points				
Combined major macrovascular and microvascular events	1009 (18.1)	1116 (20.0)		10 (2 to 18)
Major macrovascular events	557 (10.0)	590 (10.6)		6 (–6 to 16)
Nonfatal MI	153 (2.7)	156 (2.8)		2 (–23 to 22)
Nonfatal stroke	214 (3.8)	209 (3.8)		–2 (–24 to 15)
Death from cardiovascular causes	253 (4.5)	289 (5.2)		12 (–4 to 26)
Major microvascular events	526 (9.4)	605 (10.9)		14 (3 to 23)
New or worsening nephropathy	230 (4.1)	292 (5.2)		21 (7 to 34)
New or worsening retinopathy	332 (6.0)	349 (6.3)		5 (–10 to 18)
Secondary End Points				
Death from any cause	498 (8.9)	533 (9.6)		7 (–6 to 17)
Major coronary events	310 (5.6)	337 (6.1)		8 (–7 to 21)
All coronary events	560 (10.1)	572 (10.3)		2 (–10 to 13)
Major cerebrovascular events	238 (4.3)	246 (4.4)		3 (–16 to 19)
All cerebrovascular events	352 (6.3)	327 (5.9)		–8 (–26 to 7)
Heart failure	220 (3.9)	231 (4.1)		5 (–14 to 21)
Peripheral vascular events	343 (6.2)	366 (6.6)		6 (–9 to 19)
All cardiovascular events	1232 (22.1)	1249 (22.4)		1 (–7 to 9)
New-onset microalbuminuria	1318 (23.7)	1434 (25.7)		9 (2 to 5)
Visual deterioration	3033 (54.4)	3015 (54.1)		0 (–5 to 5)
New or worsening neuropathy	2353 (42.2)	2311 (41.5)		–4 (–10 to 2)
Cognitive decline	895 (16.1)	911 (16.4)		2 (–7 to 11)
Dementia	61 (1.1)	48 (0.9)		–27 (–86 to 13)
Hospitalization	2501 (44.9)	2381 (42.8)		–7 (–13 to –1)

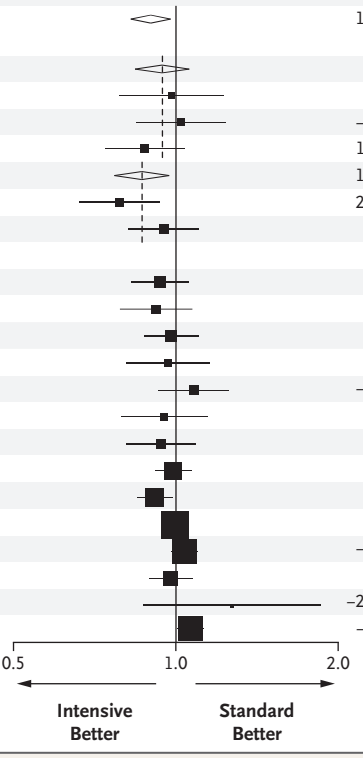

Figure 4. Relative Effects of Glucose-Control Strategy on All Prespecified Primary and Secondary Outcomes.

The diamonds incorporate the point estimates, represented by the vertical dashed lines, and the 95% confidence intervals of the overall effects within categories; for subcategories, black squares represent point estimates (with the area of the square proportional to the number of events), and horizontal lines represent 95% confidence intervals. The hazard ratios and relative risk reductions are given for intensive glucose control as compared with standard glucose control.

for any cause (44.9%, vs. 42.8% of those in the standard-control group; hazard ratio, 1.07; 95% CI, 1.01 to 1.13; P=0.03), with some of the excess of hospitalizations due to severe hypoglycemia (1.1% vs. 0.7%; odds ratio, 1.52; 95% CI, 1.01 to 2.28; P=0.04). There were no significant differences between the two groups for any of the other prespecified secondary outcomes (Fig. 4).

EFFECTS ON HYPOGLYCEMIA

Severe hypoglycemia occurred more frequently in the intensive-control group than in the standard-control group: 150 patients (2.7%) undergoing intensive control had at least one severe hypoglycemic episode, as compared with 81 patients (1.5%) undergoing standard control (hazard ratio, 1.86; 95% CI, 1.42 to 2.40; P<0.001). These included one fatal episode in the standard-control group and one episode resulting in permanent disability in each group. On average, the rate of severe hypoglycemic events was 0.7 event per 100 patients per year in the intensive-control group and 0.4 event per 100 patients per year in the standard-control group. Minor hypoglycemia also occurred more frequently in patients undergoing intensive control (120 events per 100 patients per year, vs. 90 with standard control). Approximately 47% of patients in the intensive-control group and 62% of those in the standard-control group remained free of any hypoglycemic event during the follow-up period.

EFFECTS IN SUBGROUPS OF PATIENTS

The effects of intensive control on major vascular events were consistent across participant subgroups, as defined by a range of baseline charac-

teristics (P for heterogeneity, ≥0.10 for all comparisons) (Fig. 5).

DISCUSSION

In the ADVANCE trial, an intensive glucose-control strategy involving gliclazide (modified release), and other drugs as required, lowered the average glycated hemoglobin value to 6.5% in a broad range of patients with type 2 diabetes and reduced the incidence of the combined primary outcome of major macrovascular or microvascular events. The main contributor to the 10% relative reduction in the primary outcome found with intensive control as compared with standard control was a 21% relative reduction in the risk of new or worsening nephropathy. There was no evidence of a reduction in macrovascular events.

Characteristic	Mean Glycated Hemoglobin Reduction during Follow-up (95% CI)	Intensive Control (N=5571)	Standard Control (N=5569)	Relative Risk Reduction (95% CI)
	percent	*number of patients (percent)*		*percent*
Age				
<65 yr	0.70 (0.65 to 0.75)	367 (16.1)	421 (18.7)	14 (1 to 25)
≥65 yr	0.70 (0.65 to 0.75)	642 (19.5)	695 (21.0)	8 (–3 to 17)
Sex				
Male	0.65 (0.61 to 0.69)	635 (19.9)	705 (21.9)	10 (0 to 19)
Female	0.69 (0.65 to 0.74)	374 (15.7)	411 (17.4)	10 (–3 to 22)
Systolic blood pressure				
<140 mm Hg	0.67 (0.63 to 0.72)	368 (15.7)	404 (17.1)	9 (–4 to 21)
≥140 mm Hg	0.67 (0.63 to 0.70)	641 (19.9)	712 (22.2)	11 (1 to 20)
Glycated hemoglobin				
<7.2%	0.46 (0.43 to 0.55)	387 (14.4)	430 (16.1)	10 (3 to 22)
≥7.2%	0.86 (0.81 to 0.91)	620 (21.7)	682 (23.8)	10 (0 to 20)
Blood glucose				
<7.9 mmol/liter	0.52 (0.48 to 0.55)	414 (15.2)	472 (17.3)	13 (0 to 23)
≥7.9 mmol/liter	0.81 (0.77 to 0.86)	595 (21.0)	643 (22.7)	8 (–2 to 18)
Body-mass index				
<28	0.68 (0.64 to 0.72)	558 (18.9)	663 (22.1)	15 (5 to 24)
≥28	0.65 (0.60 to 0.69)	451 (17.3)	452 (17.6)	2 (–11 to 14)
History of macrovascular disease				
No	0.67 (0.63 to 0.70)	591 (15.6)	678 (18.0)	14 (4 to 23)
Yes	0.67 (0.62 to 0.72)	418 (23.3)	438 (24.4)	4 (–10 to 16)
History of microvascular disease				
No	0.65 (0.62 to 0.68)	799 (16.0)	892 (17.9)	11 (2 to 19)
Yes	0.79 (0.69 to 0.90)	210 (36.8)	224 (38.4)	4 (–16 to 21)
Treatment with any blood-pressure–lowering drugs				
No	0.75 (0.69 to 0.81)	199 (14.3)	222 (16.0)	11 (–7 to 27)
Yes	0.64 (0.61 to 0.67)	810 (19.4)	894 (21.4)	10 (1 to 18)
Treatment with statins				
No	0.70 (0.66 to 0.73)	746 (18.6)	815 (20.5)	10 (1 to 19)
Yes	0.60 (0.55 to 0.65)	263 (16.9)	301 (18.9)	10 (–6 to 24)
Treatment with antiplatelet drugs				
No	0.70 (0.66 to 0.74)	485 (16.4)	541 (18.1)	9 (–2 to 20)
Yes	0.63 (0.59 to 0.67)	524 (20.0)	575 (22.3)	11 (0 to 21)
Overall	0.67 (0.64 to 0.70)	1009 (18.1)	1116 (20.0)	10 (2 to 18)

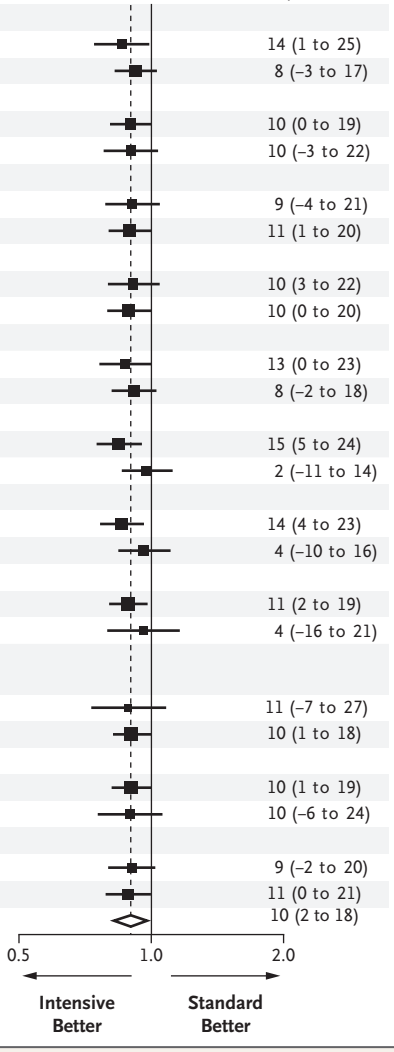

Figure 5. Effects of Glucose-Control Strategy on Combined Major Macrovascular and Microvascular Events, According to Baseline Characteristics.

The diamond incorporates the point estimate, represented by the vertical dashed line, and the 95% confidence interval of the overall effect. The hazard ratios and relative risk reductions are given for intensive glucose control as compared with standard glucose control. The P value for heterogeneity was ≥0.10 for all comparisons. Data were not available for some patients in some subgroups. The body-mass index is the weight in kilograms divided by the square of the height in meters.

Intensive glucose control was associated with an increased risk of severe hypoglycemia and an increased rate of hospitalization, as compared with standard control. There was no evidence that the effects of intensive glucose control were dependent on the baseline glycated hemoglobin or blood glucose level, age, sex, or presence or absence of a history of vascular disease.

There were no significant differences between the two study groups in the rate of death from any cause or death from cardiovascular causes. These findings contrast with the reported excess mortality that led to premature termination of the intensive glucose-control strategy in another large, randomized trial involving patients with type 2 diabetes (Action to Control Cardiovascular Risk in Diabetes [ACCORD]; ClinicalTrials.gov number, NCT00000620), in which similar levels of glucose control were achieved with the intensive-control strategy.[20,21] Mechanisms speculated to underlie the excess mortality found with intensive glucose control in the ACCORD trial include the initial level of glycated hemoglobin, the degree and pace of glucose lowering, and the treatments used to achieve such lowering.[20,22] In the ADVANCE trial, no subgroup of participants was identified to have evidence of an adverse effect of intensive glucose lowering on major vascular outcomes, including the subgroup with an initial median glycated hemoglobin value similar to that in the ACCORD study population.[21]

Intensive glucose control in the ADVANCE trial resulted in a reduction by one fifth in the development of new or worsening nephropathy and a more modest, though significant, reduction in that of new-onset microalbuminuria. In the U.K. Prospective Diabetes Study (UKPDS), the largest previously reported randomized trial of glycemic control in patients with type 2 diabetes, tighter glucose control did not reduce the incidence of major renal outcomes, although there was some evidence of a reduction in the development of microalbuminuria and overt proteinuria with a prolonged follow-up period.[6] The clear reduction in nephropathy demonstrated in the ADVANCE trial is important, because indexes of renal impairment are strongly associated with the future risk of major vascular events, end-stage renal disease, and death in patients with diabetes.[23,24]

There is no evidence that intensive glucose control in the ADVANCE trial led to reduced new or worsening retinopathy, including retinal photocoagulation. The lower rate of retinal photocoagulation in the ADVANCE trial than in previous studies of diabetes[7,25] was also reported in another recent trial.[26] This low event rate limited the power of the study to detect any moderate effects of the intervention on microvascular eye disease. However, more evidence about the retinovascular effects of intensive glucose control will be provided by the ADVANCE retinal imaging substudy.[27]

The ADVANCE trial did not show a significant effect of intensive glucose control on the risk of major macrovascular events. Although the results may indicate that lowering blood glucose levels to an average glycated hemoglobin level of 6.5% with the treatments used does not reduce the risk of macrovascular events, the results do not preclude a benefit of the size predicted by the achieved difference between the intensive-control group and the standard-control group in glycated hemoglobin levels. From observational data describing the association between glycated hemoglobin and cardiovascular events and a meta-analysis of previous randomized trials of glycemic control,[4,10] a 0.7% reduction in the glycated hemoglobin value might be expected to produce a reduction in the rate of macrovascular events by approximately one sixth. The confidence intervals for the estimate of the effect of treatment on macrovascular events in the ADVANCE trial are consistent with such a reduction, but the ADVANCE trial did not have adequate statistical power to detect such an effect reliably. The annual rate of macrovascular events (2.2%) was lower than the anticipated rate of 3.0% based on previous studies of patients with type 2 diabetes,[7,25] possibly as a consequence of the greater use of statins, blood-pressure–lowering drugs, and antiplatelet agents. Future combined analyses of the ADVANCE trial, the ACCORD trial, and other studies should provide further insight into the effects of intensive glucose control on macrovascular events.[21,28]

In the part of the ADVANCE trial evaluating the lowering of blood pressure,[15] a reduction of 5.6 mm Hg in the systolic blood pressure among patients randomly assigned to receive perindopril and indapamide, as compared with those assigned to receive placebo, resulted in a relative risk reduction of 9% for the primary combined outcome. Thus, the expected relative risk reduction associated with a 1.6 mm Hg reduction in

systolic blood pressure would be less than 3%. This suggests that the lower blood pressure among patients undergoing intensive glucose control probably explains some, but no more than one quarter to one third, of the 10% reduction seen with intensive glucose control as compared with standard control. The explanation for the reduction in blood pressure in the intensive-control group is unclear. The difference in blood pressure so soon after randomization may indicate an early effect of the study treatment regimen.[29-31] However, it is also possible that the difference reflects nonspecific effects associated with more frequent contact with health care providers.

As expected, there was a significantly higher incidence of hypoglycemia in the intensive-control group (three additional severe events for every 1000 patients treated for 1 year), although the overall risk of this complication was low. Almost half of all patients undergoing intensive control remained free from any hypoglycemia (severe or minor) during the follow-up period. The proportion of patients with at least one severe hypoglycemic episode each year was about one quarter that observed in the UKPDS,[6] despite the lower glycated hemoglobin levels among the ADVANCE participants.

In the ADVANCE trial, an intensive glucose-control strategy involving gliclazide (modified release) and other glucose-lowering drugs as required reduced the glycated hemoglobin level to an average of 6.5%. There was no evidence that this treatment strategy increased mortality.[20,21] Intensive glucose control significantly reduced the primary composite outcome of major macrovascular or microvascular events, mainly as a consequence of a reduction in nephropathy. There was no separately significant reduction in major macrovascular events, although a modest benefit could not be ruled out. However, it is clear that the prevention of macrovascular complications of diabetes requires a multifactorial approach[32] addressing all major modifiable risk factors, including blood pressure[33] and blood lipids.[34] The main benefit conferred by the ADVANCE treatment regimen was a one-fifth reduction in renal complications, indicating that intensive control of glucose has an important role in the prevention of microvascular complications of type 2 diabetes.

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APPENDIX

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REFERENCES

1. Moss SE, Klein R, Klein BE. Cause-specific mortality in a population-based study of diabetes. Am J Public Health 1991; 81:1158-62.
2. Fox CS, Coady S, Sorlie PD, et al. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation 2007;115:1544-50.
3. Moss SE, Klein R, Klein BE, Meuer SM. The association of glycemia and cause-specific mortality in a diabetic population. Arch Intern Med 1994;154:2473-9.
4. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004;141: 421-31.
5. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetes patients. Diabetes Care 2000;23:Suppl 2:B21-B29.
6. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53. [Erratum, Lancet 1999;354:602.]
7. *Idem.* Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352: 854-65. [Erratum, Lancet 1998;352:1558.]
8. Abraira C, Colwell J, Nuttall F, et al. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. Arch Intern Med 1997;157:181-8.
9. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103-17.
10. Stettler C, Allemann S, Jüni P, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. Am Heart J 2006;152:27-38.
11. Meinert CL, Knatterud GL, Prout TE, Klimt CR. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes 1970;19: Suppl:789-830.
12. American Diabetes Association. Standards of medical care in diabetes — 2007. Diabetes Care 2007;30:Suppl 1:S4-S41.
13. IDF Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2005.
14. Rydén L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes and cardiovascular diseases: executive summary. Eur Heart J 2007;28:88-136.
15. Patel A, ADVANCE Collaborative Group, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829-40.
16. ADVANCE Management Committee. Study rationale and design of ADVANCE: action in diabetes and vascular disease — preterax and diamicron MR controlled evaluation. Diabetologia 2001;44:1118-20.
17. Wales External Quality Assurance Scheme home page. (Accessed May 19, 2008, at http://www.weqas.com.)
18. Woodward M. Epidemiology: study design and data analysis. 2nd ed. Boca Raton, FL: Chapman & Hall/CRC Press, 2005.
19. Schulz KF, Grimes DA. Multiplicity in randomised trials. I. Endpoints and treatments. Lancet 2005;365:1591-5.
20. National Institutes of Health. For Safety, NHLBI changes intensive blood sugar treatment strategy in clinical trial of diabetes and cardiovascular disease. 2008. (Accessed May 19, 2008, at http://www.nih.gov/news/health/feb2008/nhlbi-06.htm.)
21. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358: 2545-59.
22. Home P. Safety of very tight blood glucose control in type 2 diabetes. BMJ 2008;336:458-9.
23. Gerstein H, Mann J, Yi Q, et al. Albuminuria and risk of CV events, death, and heart failure in diabetic and non-diabetic individuals. JAMA 2001;286:421-6.
24. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-305.
25. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253-9. [Erratum, Lancet 2000;356:860.]
26. Keech AC, Mitchell P, Summanen PA, et al. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet 2007;370:1687-97.
27. Stolk RP, Vingerling JR, Cruickshank JK, et al. Rationale and design of the AdRem study: evaluating the effects of blood pressure lowering and intensive glucose control on vascular retinal disorders in patients with type 2 diabetes mellitus. Contemp Clin Trials 2007;28:6-17.
28. Abraira C, Duckworth W, McCarren M, et al. Design of the cooperative study on glycemic control and complications in diabetes mellitus type 2: Veterans Affairs Diabetes Trial. J Diabetes Complications 2003;17:314-22.
29. Fava D, Cassone-Faldetta M, Laurenti O, De Luca O, Ghiselli A, De Mattia G. Gliclazide improves anti-oxidant status and nitric oxide-mediated vasodilation in Type 2 diabetes. Diabet Med 2002;19:752-7.
30. Belcher G, Lambert C, Goh KL, Edwards G, Valbuena M. Cardiovascular effects of treatment of type 2 diabetes with pioglitazone, metformin and gliclazide. Int J Clin Pract 2004;58:833-7.
31. Wascher TC, Boes U. Forearm vascular reactivity is differentially influenced by gliclazide and glibenclamide in chronically treated type 2 diabetic patients. Clin Physiol Funct Imaging 2005;25:40-6.
32. Gæde P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580-91.
33. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prespectively designed overviews of randomized trials. Arch Intern Med 2005;165:1410-9.
34. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005;366: 1267-78. [Erratum, Lancet 2005;366:1358.]