ORIGINAL ARTICLE

Follow-up of Blood-Pressure Lowering and Glucose Control in Type 2 Diabetes

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ABSTRACT

BACKGROUND

In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) factorial trial, the combination of perindopril and indapamide reduced mortality among patients with type 2 diabetes, but intensive glucose control, targeting a glycated hemoglobin level of less than 6.5%, did not. We now report results of the 6-year post-trial follow-up.

METHODS

We invited surviving participants, who had previously been assigned to perindopril–indapamide or placebo and to intensive or standard glucose control (with the glucose-control comparison extending for an additional 6 months), to participate in a post-trial follow-up evaluation. The primary end points were death from any cause and major macrovascular events.

RESULTS

The baseline characteristics were similar among the 11,140 patients who originally underwent randomization and the 8494 patients who participated in the post-trial follow-up for a median of 5.9 years (blood-pressure–lowering comparison) or 5.4 years (glucose-control comparison). Between-group differences in blood pressure and glycated hemoglobin levels during the trial were no longer evident by the first post-trial visit. The reductions in the risk of death from any cause and of death from cardiovascular causes that had been observed in the group receiving active blood-pressure–lowering treatment during the trial were attenuated but significant at the end of the post-trial follow-up; the hazard ratios were 0.91 (95% confidence interval [CI], 0.84 to 0.99; P=0.03) and 0.88 (95% CI, 0.77 to 0.99; P=0.04), respectively. No differences were observed during follow-up in the risk of death from any cause or major macrovascular events between the intensive-glucose-control group and the standard-glucose-control group; the hazard ratios were 1.00 (95% CI, 0.92 to 1.08) and 1.00 (95% CI, 0.92 to 1.08), respectively.

CONCLUSIONS

The benefits with respect to mortality that had been observed among patients originally assigned to blood-pressure–lowering therapy were attenuated but still evident at the end of follow-up. There was no evidence that intensive glucose control during the trial led to long-term benefits with respect to mortality or macrovascular events. (Funded by the National Health and Medical Research Council of Australia and others; ADVANCE-ON ClinicalTrials.gov number, NCT00949286.)

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Post-trial follow-up studies involving patients with diabetes have previously shown long-term beneficial effects of earlier periods of intensive glucose control, but not blood-pressure lowering, on a range of outcomes, including mortality and macrovascular events.[1-3] The Epidemiology of Diabetes Interventions and Complications (EDIC) study, an extension of the Diabetes Control and Complications Trial (DCCT) involving young patients with type 1 diabetes and no history of cardiovascular disease, hypertension, or hypercholesterolemia, showed a lower risk of macrovascular events, as well as a sustained benefit with respect to microvascular complications, beyond the period of intensive glucose control.[1] The post-intervention follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) also showed long-term beneficial effects of intensive glucose control in patients with newly diagnosed type 2 diabetes.[2] Among patients formerly assigned to intensive therapy as compared with conventional therapy, the reduced risk of microvascular events was maintained, and previously nonsignificant estimates of the effect of intensive therapy on the end points of death and myocardial infarction became significant with extended follow-up.[2] In contrast, no long-term benefits were detected with improved blood-pressure control in the UKPDS.[3]

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial assessed the effects of routine blood-pressure lowering and intensive glucose control in a broad cross section of patients with type 2 diabetes.[4,5] Routine administration of a single-pill (fixed-dose) combination of perindopril and indapamide was associated with a reduction in the risk of the primary composite end point of major macrovascular or microvascular events. Reductions in the risks of death from any cause, death from cardiovascular causes, and nephropathy were also observed.[4] Intensive glucose control was associated with a reduction in the risk of the primary composite end point of major macrovascular or microvascular events, owing primarily to a reduction in the incidence of new or worsening nephropathy.[5] This benefit with respect to nephropathy included a reduction in the incidence of end-stage renal disease but not of death from renal disease.[6] No clear protective or harmful effects of intensive glucose control with respect to death from any cause or major macrovascular events were identified.[5] We now report the results from the post-trial follow-up of the ADVANCE-Observational Study (ADVANCE-ON), which was designed to test the hypotheses that there would be long-term benefits of the two active interventions.

Methods

Randomized Trial

Details of the recruitment of patients and the study design and methods have been published previously.[7] In brief, 11,140 patients, 55 years of age or older, with type 2 diabetes and at least one additional risk factor for cardiovascular disease were enrolled between 2001 and 2003 at 215 centers in 20 countries. The study had a 2-by-2 factorial design. Patients were randomly assigned to a single-pill (fixed-dose) combination of perindopril (4 mg) and indapamide (1.25 mg) or matching placebo, after a 6-week active run-in period, and were also randomly assigned to a gliclazide (modified release)–based intensive glucose-control regimen, targeted to achieve a glycated hemoglobin level of 6.5% or lower, or to standard glucose control, with targets and regimens based on local guidelines. There were no inclusion or exclusion criteria related to blood pressure, and no blood-pressure targets were specified. The use of concomitant treatments during the trial, including other blood-pressure–lowering and glucose-control therapy, was at the discretion of the responsible physician. The last trial visits for the randomized blood-pressure–lowering comparison were completed in June 2007 after a median follow-up period of 4.4 years, at which time patients resumed their usual care for blood-pressure control.[4] The randomized glucose-control regimen continued for an additional 6 months, to ensure adequate study power in the context of a smaller-than-anticipated separation in glycated hemoglobin levels between the groups. The last trial visits for the glucose-control comparison were completed in January 2008 after a median follow-up period of 5.0 years.[5] At this time, all the patients discontinued their randomly assigned intervention and returned to the care of their usual physician for all aspects of treatment.

Post-Trial Follow-Up

ADVANCE-ON was a post-trial follow-up study involving all surviving patients from the ADVANCE

Table 1. Baseline Characteristics of All Participants in the Randomized Trial and of the Subgroup That Participated in the Post-Trial Follow-up, According to Assignment in the Randomized Trial.*

Variable	Blood-Pressure–Lowering Comparison				Glucose-Control Comparison			
	Clinical Trial		Post-Trial Follow-up		Clinical Trial		Post-Trial Follow-up	
	Active Drug (N=5569)	Placebo (N=5571)	Active Drug (N=4278)	Placebo (N=4216)	Intensive Control (N=5571)	Standard Control (N=5569)	Intensive Control (N=4283)	Standard Control (N=4211)
Age — yr	66±6	66±7	66±6	66±6	66±6	66±6	65±6	66±6
Female sex — no. (%)	2366 (42.5)	2367 (42.5)	1842 (43.1)	1806 (42.8)	2376 (42.6)	2357 (42.3)	1867 (43.6)	1781 (42.3)
Age at diagnosis of diabetes — yr	58±9	58±9	58±9	58±9	58±9	58±9	58±9	58±9
Previous vascular disease — no. (%)								
Major macrovascular disease	1798 (32.3)	1792 (32.2)	1296 (30.3)	1279 (30.3)	1794 (32.2)	1796 (32.2)	1274 (29.7)	1301 (30.9)
Major microvascular disease	570 (10.2)	585 (10.5)	404 (9.4)	396 (9.4)	571 (10.2)	584 (10.5)	385 (9.0)	415 (9.9)
Blood glucose assessment								
Glycated hemoglobin — %†								
Mean	7.5±1.6	7.5±1.6	7.5±1.5	7.5±1.5	7.5±1.6	7.5±1.5	7.5±1.5	7.5±1.5
Median (interquartile range)	7.2 (6.5–8.3)	7.2 (6.4–8.2)	7.2 (6.5–8.2)	7.2 (6.4–8.1)	7.2 (6.5–8.2)	7.2 (6.5–8.2)	7.2 (6.5–8.2)	7.2 (6.5–8.2)
Fasting blood glucose — mmol/liter	8.5±2.8	8.5±2.7	8.5±2.7	8.4±2.7	8.5±2.8	8.5±2.8	8.4±2.7	8.5±2.7
Blood-pressure assessment								
Systolic — mm Hg	145.1±21.8	144.9±21.3	144.1±21.3	144.0±21.0	145.0±21.7	145.0±21.4	143.9±21.3	144.2±21.0
Diastolic — mm Hg	80.7±11.0	80.6±10.8	80.4±10.8	80.1±10.6	80.8±11.0	80.5±10.8	80.3±10.8	80.2±10.6
Current treatment for hypertension — no. (%)	3802 (68.3)	3853 (69.2)	2802 (65.5)	2784 (66.0)	3816 (68.5)	3839 (68.9)	2783 (65.0)	2803 (66.6)
Assessment of other major risk factors								
LDL cholesterol — mmol/liter	3.1±1.0	3.1±1.0	3.1±1.0	3.0±1.0	3.1±1.0	3.1±1.0	3.1±1.0	3.1±1.0
Urinary albumin-to-creatinine ratio‡								
Mean	52.8±115.0	52.2±115.0	48.7±107.0	48.3±108.0	52.0±113.0	53.0±117.0	47.8±103.0	49.2±111.0
Median (interquartile range)	15.0 (7.1–39.8)	15.0 (7.1–39.8)	14.4 (7.1–36.9)	14.7 (7.1–36.9)	15.0 (7.1–39.0)	14.9 (7.1–39.8)	15.0 (7.1–37.1)	14.1 (7.1–36.2)
Serum creatinine — μmol/liter	87±25	87±26	85±22	85±23	86±24	87±27	84±22	85±22
Body-mass index§	28±5	28±5	28±5	28±5	28±5	28±5	28±5	28±5
Current smoking — no. (%)	804 (14.4)	878 (15.8)	598 (14.0)	638 (15.1)	860 (15.4)	822 (14.8)	630 (14.7)	606 (14.4)

* Plus–minus values are means ±SD. Baseline (prerandomization) characteristics were recorded at the first (registration) visit of the randomized Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE). The follow-up study (ADVANCE–Observational Study [ADVANCE-ON]) involved participants in ADVANCE who contributed data after the end of the trial (see Fig. S1 and S2 in the Supplementary Appendix). During the ADVANCE trial, the active-drug group in the blood-pressure–lowering comparison received the fixed combination of perindopril and indapamide. To convert the values for blood glucose to milligrams per deciliter, divide by 0.05551. To convert the values for low-density lipoprotein (LDL) cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for creatinine to milligrams per deciliter, divide by 88.4.

† Glycated hemoglobin values were standardized for the ADVANCE trial but not for the ADVANCE-ON analysis.

‡ For the urinary albumin-to-creatinine ratio, urinary albumin was measured in micrograms, and creatinine in milligrams.

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

trial. A detailed description of the original study protocol has been published previously, and the current protocol, including the statistical analysis plan (which was completed before the end of the follow-up period), is available with the full text of this article at NEJM.org. ADVANCE-ON was an investigator-initiated study that was designed, conducted, analyzed, and interpreted independently of the funders, including the commercial sponsor (Servier International). Servier International was given the opportunity to comment on the final draft of the manuscript but had no role in the decision to submit the manuscript for publication. The first two authors wrote all drafts of the manuscript. The writing committee (i.e., all the authors) and the management committee (see the Supplementary Appendix, available at NEJM.org), neither of which included representatives of the sponsors, had final responsibility for the manuscript and for the decision to submit it for publication.

Two years after completion of the final ADVANCE trial visits, all local trial sites were invited to participate in the follow-up study, and 172 of 215 (80%) agreed. After approval of the study by the ethics review board at each site, all surviving trial patients were invited to participate in the post-trial follow-up. In January 2010, annual post-trial visits commenced. At the first post-trial visit, all the participants provided written informed consent and completed a standardized questionnaire on the occurrence of all study outcomes of interest and all medications they were taking. A random subgroup of 2000 patients, balanced across regions and across the prior randomized study groups, were also invited to undergo assessment of the glycated hemoglobin level, fasting blood glucose level, blood pressure, weight, serum creatinine level, and urinary albumin-to-creatinine ratio at the first post-trial visit, to determine whether differences observed during the trial (in-trial period) persisted. For patients known to have died after the final in-trial visit, the cause and date of death were recorded. For patients unwilling or unable to attend study visits in person, follow-up assessments were conducted by telephone or home visit, or information was provided by the primary care physician, other health care providers, or next of kin. At annual visits, patients completed a questionnaire on medication taken and study outcome events. In addition, at the final visits, which occurred between January 1, 2013, and February 28, 2014, patients attending visits in person were invited to undergo an assessment of the glycated hemoglobin level, fasting blood glucose level, weight, blood pressure, serum creatinine level, and urinary albumin-to-creatinine ratio, regardless of whether they had undergone these assessments at the first visit.

STUDY OUTCOMES

The two prespecified primary outcomes for the present study were death from any cause and major macrovascular events (a composite, as in the randomized trial, of nonfatal myocardial infarction, nonfatal stroke, or death from any cardiovascular cause). The prespecified secondary outcomes were death from cardiovascular causes, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, major clinical microvascular events (a composite of end-stage renal disease, defined as requirement for renal-replacement therapy; death from renal disease; requirement for retinal photocoagulation; or diabetes-related blindness in either eye), the separate components of this composite outcome, and major hypoglycemia (as defined in the original trial protocol[5]). It was not possible to replicate the outcomes, "major microvascular events" and "new or worsening nephropathy," as defined in the original trial, because levels of serum creatinine and urinary albumin were measured in only a subgroup of participants during the post-trial follow-up. Outcomes occurring during the post-trial follow-up period were as reported by investigators at the study centers, according to prespecified definitions and criteria, and were not centrally adjudicated.

STATISTICAL ANALYSIS

All analyses were performed according to the initial study-group assignment. Treatment effects were examined with the use of cumulative-incidence survival curves and Cox proportional-hazards models. Data were censored at the time of the first relevant end point, the date of the patient's death, the date of the patient's last visit (for those still alive), or, for patients whose vital status was unknown at the end of the study (February 28, 2014), the date the patient was last known to be alive. Hazard ratios were estimated for the in-trial period and over the entire period of follow-up according to the intention-to-treat principle. We also performed a nonrandomized,

Table 2. Primary and Secondary Outcomes during the Randomized Trial and Overall in the Blood-Pressure–Lowering Cohort and the Glucose-Control Cohort.*

Study Cohort and Outcome	In-Trial Period				Overall Follow-up			
	Active Drug (N=5569)	Placebo (N=5571)	Hazard Ratio (95% CI)	P Value	Active Drug (N=5569)	Placebo (N=5571)	Hazard Ratio (95% CI)	P Value
	no. (%)				*no. (%)*			
Blood-pressure–lowering cohort								
Death from any cause	408 (7.3)	471 (8.5)	0.86 (0.75–0.98)	0.03	1092 (19.6)	1173 (21.1)	0.91 (0.84–0.99)	0.03
Major macrovascular events	480 (8.6)	520 (9.3)	0.92 (0.81–1.04)	0.16	1050 (18.9)	1116 (20.0)	0.92 (0.85–1.00)	0.06
Death from cardiovascular causes	211 (3.8)	257 (4.6)	0.82 (0.68–0.98)	0.03	466 (8.4)	522 (9.4)	0.88 (0.77–0.99)	0.04
Myocardial infarction	161 (2.9)	168 (3.0)	0.95 (0.77–1.18)	0.65	349 (6.3)	373 (6.7)	0.92 (0.79–1.06)	0.24
Stroke	212 (3.8)	218 (3.9)	0.97 (0.80–1.17)	0.73	474 (8.5)	494 (8.9)	0.94 (0.83–1.07)	0.35
Major clinical microvascular events†	212 (3.8)	189 (3.4)	1.12 (0.92–1.36)	0.26	417 (7.5)	390 (7.0)	1.05 (0.92–1.21)	0.47
End-stage renal disease	13 (0.2)	8 (0.1)	1.61 (0.67–3.89)	0.29	43 (0.8)	39 (0.7)	1.08 (0.70–1.66)	0.74
Death from renal causes	15 (0.3)	13 (0.2)	1.14 (0.54–2.40)	0.72	52 (0.9)	49 (0.9)	1.04 (0.70–1.53)	0.86
Retinal photocoagulation or diabetes-related blindness	193 (3.5)	173 (3.1)	1.11 (0.91–1.37)	0.31	349 (6.3)	320 (5.7)	1.07 (0.92–1.25)	0.35
Major hypoglycemia	113 (2.0)	90 (1.6)	1.26 (0.95–1.65)‡	0.10	414 (7.4)	404 (7.3)	1.03 (0.90–1.17)‡	0.71
	Intensive Control (N=5571)	Standard Control (N=5569)	Hazard Ratio (95% CI)	P Value	Intensive Control (N=5571)	Standard Control (N=5569)	Hazard Ratio (95% CI)	P Value
	no. (%)				*no. (%)*			
Glucose-control cohort								
Death from any cause	498 (8.9)	533 (9.6)	0.93 (0.83–1.06)	0.28	1139 (20.4)	1126 (20.2)	1.00 (0.92–1.08)	0.91
Major macrovascular events	557 (10.0)	590 (10.6)	0.94 (0.84–1.06)	0.32	1089 (19.5)	1077 (19.3)	1.00 (0.92–1.08)	0.93
Death from cardiovascular causes	253 (4.5)	289 (5.2)	0.88 (0.74–1.04)	0.12	490 (8.8)	498 (8.9)	0.97 (0.86–1.10)	0.63
Myocardial infarction	190 (3.4)	188 (3.4)	1.01 (0.83–1.24)	0.92	368 (6.6)	354 (6.4)	1.02 (0.89–1.19)	0.75
Stroke	236 (4.2)	245 (4.4)	0.96 (0.81–1.15)	0.68	491 (8.8)	477 (8.6)	1.01 (0.89–1.15)	0.82
Major clinical microvascular events†	212 (3.8)	246 (4.4)	0.86 (0.72–1.03)	0.11	390 (7.0)	417 (7.5)	0.92 (0.80–1.05)	0.23
End-stage renal disease	7 (0.1)	20 (0.4)	0.35 (0.15–0.83)	0.02	29 (0.5)	53 (1.0)	0.54 (0.34–0.85)	0.007
Death from renal causes	17 (0.3)	20 (0.4)	0.85 (0.45–1.62)	0.62	48 (0.9)	53 (1.0)	0.89 (0.60–1.31)	0.56
Retinal photocoagulation or diabetes-related blindness	195 (3.5)	216 (3.9)	0.90 (0.74–1.09)	0.29	332 (6.0)	337 (6.1)	0.97 (0.83–1.13)	0.69
Major hypoglycemia	150 (2.7)	81 (1.5)	1.85 (1.42–2.42)‡	<0.001	445 (8.0)	373 (6.7)	1.19 (1.04–1.36)‡	0.009

* In the blood-pressure–lowering group, the median in-trial period was 4.4 years, and the median overall follow-up period was 9.9 years; in the glucose-control group, the median in-trial period was 5.0 years, and the median overall follow-up period was 9.9 years. The hazard ratio is for the active-therapy (perindopril–indapamide) group as compared with the placebo group for the blood-pressure-lowering cohort and for the intensive-glucose-control group as compared with the standard-glucose-control group for the glucose-control cohort.

† The definition of major clinical microvascular events was based on the ADVANCE-ON trial protocol, which included in that category a requirement for renal-replacement therapy, death from renal disease, and development of severe diabetes-related eye diseases.

‡ This is the relative risk rather than the hazard ratio. The relative risk was estimated with the use of a log-binomial model.

observational analysis of incident events during the post-trial period alone. Serial hazard ratios with 95% confidence intervals were estimated at the end of each calendar year of post-trial follow up. Each hazard ratio was obtained from a Cox model that included all the data collected up to the end of that calendar year. The interaction between the effects of intensive glucose control and blood-pressure lowering and the homogeneity of treatment effects in prespecified subgroups were tested by adding an interaction term to the relevant Cox models. A sensitivity analysis that included data only from sites that were able to follow at least 85% of surviving patients was performed for the entire period of follow-up.

The analyses were performed with the use of SAS software, version 9.2. All tests were two-sided, and P values of less than 0.05 were considered to indicate statistical significance. The protocol prespecified that no adjustments would be made for the multiple statistical testing.[8] In light of this, the findings were interpreted with caution.

RESULTS

FOLLOW-UP

Of the 10,261 participants who were alive when the blood-pressure–lowering comparison was completed and the 10,082 patients who were alive when the glucose-control comparison was completed, 8494 (83% and 84%, respectively) enrolled in the post-trial follow up; 5131 of the 7279 patients who were alive at the end of the follow-up period (70%) completed a visit during the final year of the follow-up study (Fig. S1 and S2 in the Supplementary Appendix). The first post-trial visits occurred a median of 3.5 years after the final trial visit for the blood-pressure–lowering comparison and 2.9 years after the final trial visit for the glucose-control comparison. The median in-trial, post-trial, and total follow-up periods were 4.4 years, 5.9 years, and 9.9 years, respectively, for the blood-pressure–lowering comparison and 5.0 years, 5.4 years, and 9.9 years, respectively, for the glucose-control comparison.

CHARACTERISTICS OF THE PATIENTS

The prerandomization characteristics of the entire trial cohort and of the cohort that contributed further data during the post-trial follow-up are shown according to the original study-group assignment; the characteristics were similar in the two cohorts apart from such changes as are consistent with a healthy-survivor effect in the post-trial cohort (Table 1). The prerandomization characteristics of the subgroups that had biochemical levels measured at the first and final post-trial visits were also similar to those of the entire cohort (Table S1 in the Supplementary Appendix). In addition, the prerandomization characteristics of the patients who completed a visit in the final year of post-trial follow-up were similar to those of patients who did not (Table S2 in the Supplementary Appendix).

TREATMENT PATTERNS

After completion of the blood-pressure–lowering comparison of the trial, the use of perindopril–indapamide, other blood-pressure–lowering therapies, and other medications was well balanced between the group that had originally been assigned to perindopril–indapamide and the group that had originally been assigned to placebo (Table S3 in the Supplementary Appendix). The use of blood-pressure–lowering therapies had decreased by the first post-trial visit and then increased by the final post-trial visit, although approximately 20% of the patients remained off any such therapy.

After completion of the glucose-control comparison of the trial, the use of oral glucose-lowering therapies and insulin in the group that had originally been assigned to intensive glucose control and the group that had originally been assigned to standard glucose control converged, although some differences remained between the two groups (Table S4 in the Supplementary Appendix). The use of insulin increased more in the standard-control group than in the intensive-control group, whereas the use of sulfonylureas, including modified-release gliclazide, decreased in both groups over time.

BLOOD PRESSURE AND GLYCEMIC CONTROL

The mean between-group difference in blood pressure observed during the randomized ADVANCE trial (5.6/2.2 mm Hg, P<0.001)[4] was no longer evident 6 months after the end of that part of the trial: the blood pressures recorded at the time of the final randomized visit for the patients in the glucose-control comparison (6 months after the last visit for the blood-pressure control comparison) were 137/74 mm Hg in the perindopril–indapamide group and 136/74 mm Hg in the placebo

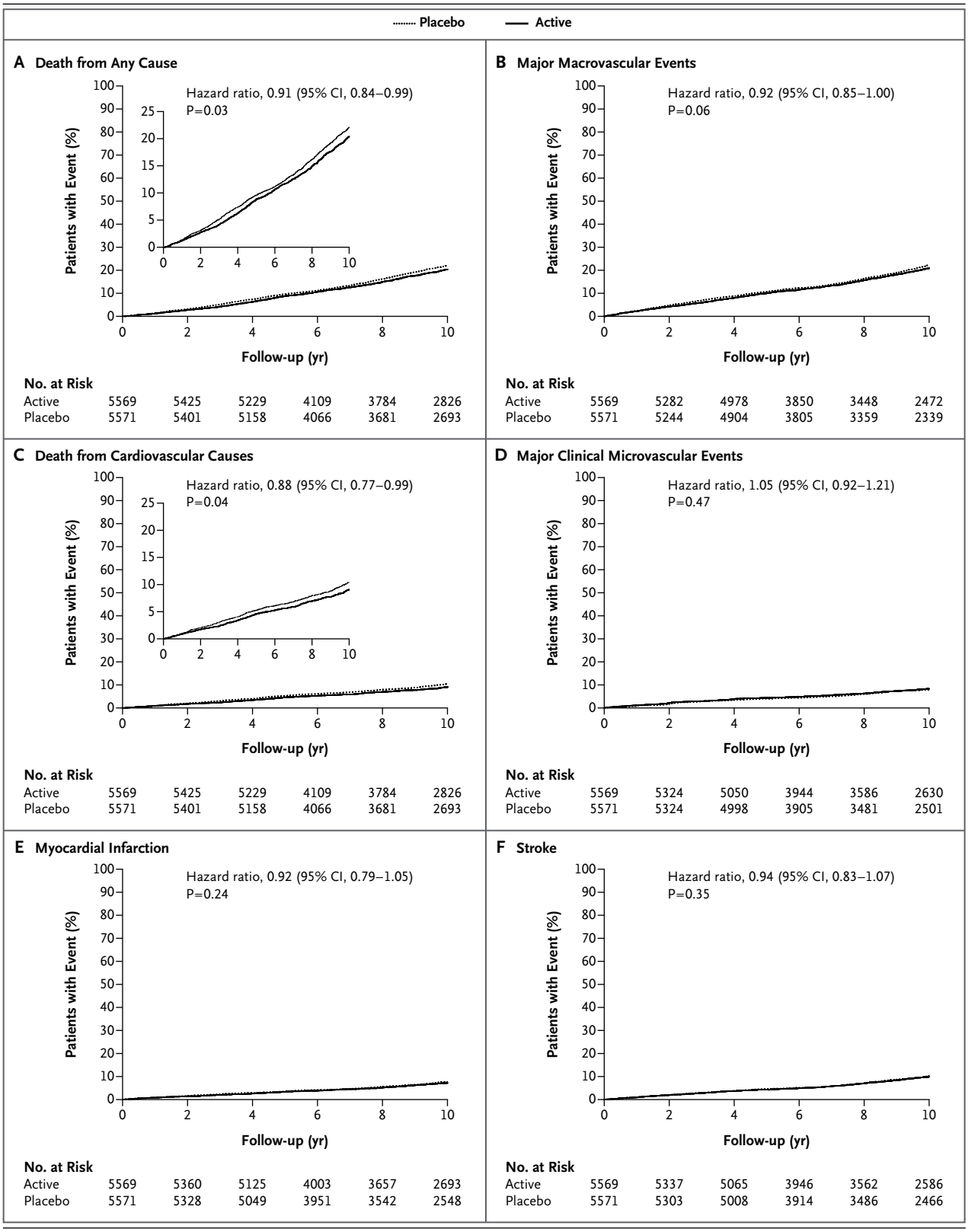


Figure 1 (facing page). Cumulative Incidence of Events, According to Blood-Pressure–Lowering Study Group.

Shown is the percentage of patients who had events at any time after the start of randomized treatment in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, according to assignment to the active-drug (perindopril–indapamide) group or the placebo group. Cumulative hazard ratios (active-drug group vs. placebo group) and P values are shown for a 12-year period from the start of randomized treatment to the end of the post-trial follow-up in the ADVANCE–Observational Study (ADVANCE-ON). The insets in Panels A and C (which show outcomes that were reduced significantly with the active drug) display the same data on an enlarged y axis.

group. The levels remained similar in the two blood-pressure–lowering study groups through the post-trial period (Table S5 in the Supplementary Appendix).

The mean between-group difference in glycated hemoglobin levels (0.67 percentage points, P<0.001)[5] observed during the randomized ADVANCE trial was no longer evident by the first post-trial visit, an average of 2.9 years later (0.08 percentage points; 95% confidence interval [CI], −0.07 to 0.22; P=0.29), and the levels remained similar at the conclusion of the post-trial follow-up (7.2% in the intensive-therapy group and 7.4% in the standard-therapy group) (Table S6 in the Supplementary Appendix).

OTHER RISK FACTORS

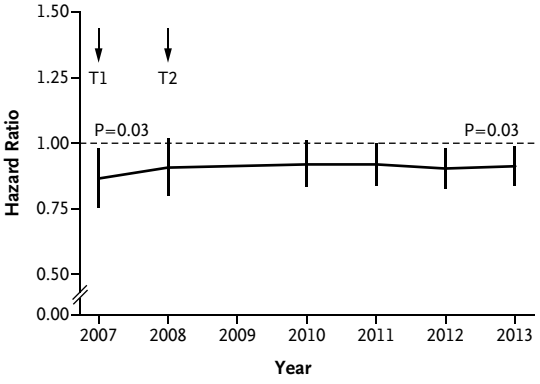
Among the patients included in the blood-pressure–lowering comparison, the incidences of other risk factors were well balanced between the perindopril–indapamide group and the placebo group (Table S5 in the Supplementary Appendix). Among the patients included in the glucose-control comparison, the small difference of 1.6 mm Hg in systolic blood pressure that had been observed, on average, between the two glucose-control groups during the trial was diminished and no longer significant at the first post-trial visit (1.2 mm Hg, P=0.17) and the final post-trial visit (0.9 mm Hg, P=0.14). The mean body weight, serum creatinine level, and urinary albumin-to-creatinine ratio were similar in the intensive and standard glucose-control groups at the final post-trial visit (Table S6 in the Supplementary Appendix).

PRIMARY OUTCOMES

During the randomized blood-pressure intervention, 879 patients died and 1000 patients had a major macrovascular event (Table 2). During the post-trial follow-up period, an additional 1386 patients died and 1166 patients had an incident major macrovascular event. Among patients assigned to perindopril–indapamide therapy, there was a significant but attenuated cumulative benefit with respect to the incidence of death from any cause that extended to the end of the overall follow-up period (hazard ratio, 0.91; 95% CI, 0.84 to 0.99; P=0.03) (Table 2 and Fig. 1A and 2A) — a finding consistent with the in-trial finding of a significant risk reduction of 14% in the rate of death from any cause among patients assigned to perindopril–indapamide therapy (hazard ratio, 0.86; 95% CI, 0.75 to 0.98; P=0.03). There was no evidence that the cumulative effects with respect to death from any cause varied according to the subgroups studied, including the subgroup defined according to assignment to intensive glucose control versus standard glucose control (P>0.20 for interaction for all subgroup analyses) (Fig. S3 in the Supplementary Appendix). There was no cumulative benefit of perindopril–indapamide with respect to major macrovascular events, and the hazard ratios for this composite outcome were similar at the end of the in-trial period and at the end of the overall follow-up period, although they were not significant at either time (Table 2 and Fig. 1B and 2B).

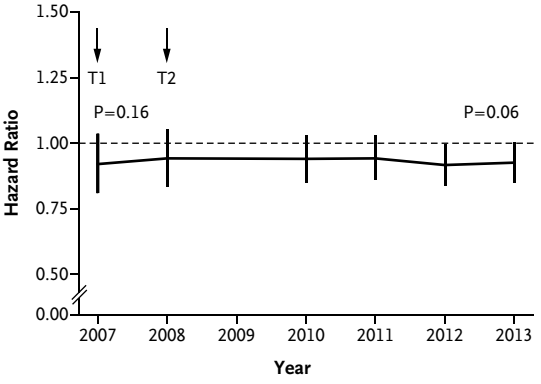
During the randomized glucose-control intervention, 1031 patients died and 1147 patients recorded a major macrovascular event (Table 2). During the post-trial period, an additional 1234 patients died and 1019 patients recorded a major macrovascular event. There were no cumulative benefits of intensive glucose control with respect to either death from any cause or major macrovascular events (Table 2 and Fig. 3A and 3B and 4A and 4B) — results that were consistent with in-trial findings. There was no evidence that the cumulative effects with respect to death from any cause varied according to the patient subgroups studied, including the subgroup defined according to assignment to active blood-pressure–lowering therapy versus placebo (P>0.10 for interaction for all subgroup analyses) (Fig. S4 in the Supplementary Appendix).

A Death from Any Cause



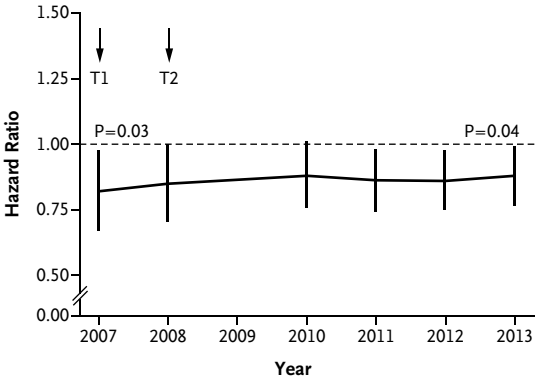
No. of Events						
Active	408	491	813	913	1007	1092
Placebo	471	540	877	984	1009	1173

B Major Macrovascular Events



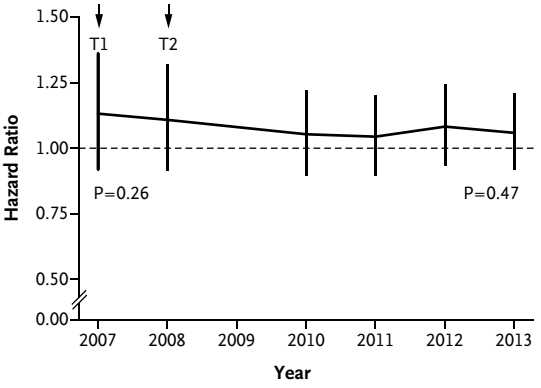
No. of Events						
Active	480	557	815	907	990	1050
Placebo	520	590	861	953	1063	1116

C Death from Cardiovascular Causes



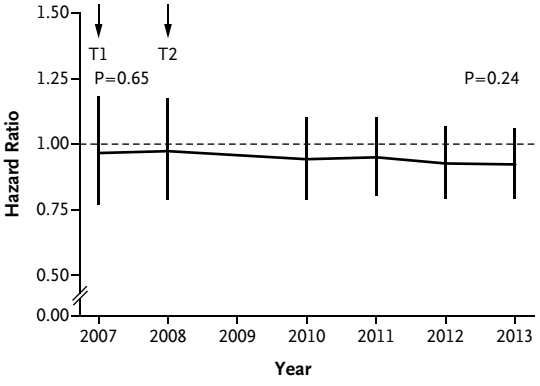
No. of Events						
Active	211	249	362	388	436	466
Placebo	257	293	409	447	500	522

D Major Clinical Microvascular Events



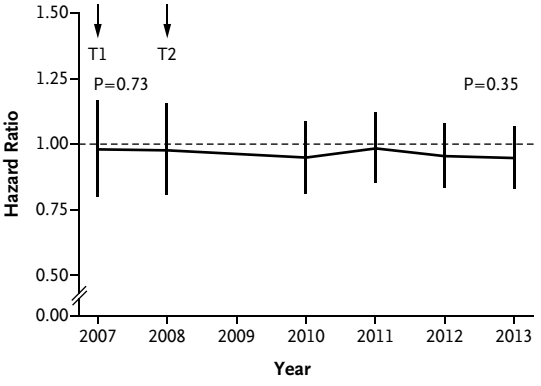
No. of Events						
Active	212	240	325	361	392	417
Placebo	189	218	309	345	360	390

E Myocardial Infarction



No. of Events						
Active	161	186	265	300	332	349
Placebo	168	192	281	314	354	373

F Stroke



No. of Events						
Active	212	237	352	408	444	474
Placebo	218	244	371	413	461	494

Figure 2 (facing page). Hazard Ratios for Events, According to Blood-Pressure–Lowering Study Group.
Hazard ratios are shown for events that occurred from the start of randomized treatment to the end of the blood-pressuring–lowering comparison (2007), to the end of the glucose-control comparison (2008), and to the end of each year of post-trial follow-up (2010 through 2013). The hazard ratios are for the active-drug (perindopril–indapamide) group versus the placebo group. P values are for the between-group comparison at the final visit for the randomized trial in 2007 and at the end of the post-trial follow-up period. The data for 2013 include those obtained in the first 2 months of 2014, when follow-up was terminated. T1 indicates the final visit for the blood-pressure-comparison cohort, and T2 the final visit for the glucose-comparison cohort. Vertical lines indicate 95% confidence intervals.

SECONDARY OUTCOMES

In the blood-pressure–lowering cohort, an additional 520 deaths from cardiovascular causes, 393 myocardial infarctions, and 538 strokes were recorded during the post-trial period (Table 2). The in-trial reduction in the risk of death from cardiovascular causes among those assigned to perindopril–indapamide (hazard ratio, 0.82; 95% CI, 0.68 to 0.98; P=0.03) was attenuated but remained significant at the end of the overall follow-up period (hazard ratio, 0.88; 95% CI, 0.77 to 0.99; P=0.04) (Table 2 and Fig. 1C and 2C). There were no cumulative benefits with respect to any other secondary outcome, including major clinical microvascular events (Table 2).

In the glucose-control cohort, an additional 349 major clinical microvascular events were recorded during the post-trial period (Table 2). There were no cumulative benefits with respect to major clinical microvascular events (Table 2 and Fig. 3D and 4D) or severe diabetes-related eye disease (Table 2 and Fig. 3F and 4F). There was a significant cumulative benefit with respect to end-stage renal disease (hazard ratio, 0.54; 95% CI, 0.34 to 0.85; P=0.007) (Table 2 and Fig. 3E and 4E), although relatively few events were recorded. There was no cumulative benefit with respect to death from renal disease or any other secondary outcome, including death from cardiovascular causes, myocardial infarction, and stroke (Table 2).

There was no significant interaction between the effects of glucose control and blood-pressure lowering with respect to any primary or secondary outcome (P>0.10 for interaction for all comparisons). When the cumulative effects were examined with data only from sites that were able to follow at least 85% of their surviving patients, the findings were unchanged in the glucose-control cohort, and the pattern of the effects in the blood-pressure–lowering cohort remained similar (Table S7 in the Supplementary Appendix). However, the reduction in major macrovascular events observed in the perindopril–indapamide group, which was not significant in the total cohort (P=0.06) (Table 2), did become significant when only sites that were able to follow at least 85% of their surviving patients were considered (P=0.03) (Table S7 in the Supplementary Appendix). Conversely, the reduction in death from cardiovascular causes, which was significant in the total cohort (P=0.04), became nonsignificant when only sites that were able to follow at least 85% of their surviving patients were considered (P=0.06).

When the post-trial observational period was examined alone, there was no reduction in the risk of any outcome among patients assigned to perindopril–indapamide as compared with those assigned to placebo or among patients assigned to intensive glucose control as compared with those assigned to standard glucose control (Table S8 in the Supplementary Appendix). Although the rate of major hypoglycemia was low overall, the increase in that rate in the intensive-glucose-control group versus the standard-glucose-control group, which was significant during the trial, was not significant at the end of the post-trial follow-up, when only the post-trial period was considered (Table S8 in the Supplementary Appendix).

DISCUSSION

After following the current cohort for a total of 10 years, including the in-trial period and the post-trial follow-up, we observed attenuated but still significant reductions in the rates of death from any cause and from cardiovascular causes resulting from the 4.5-year period of blood-pres-

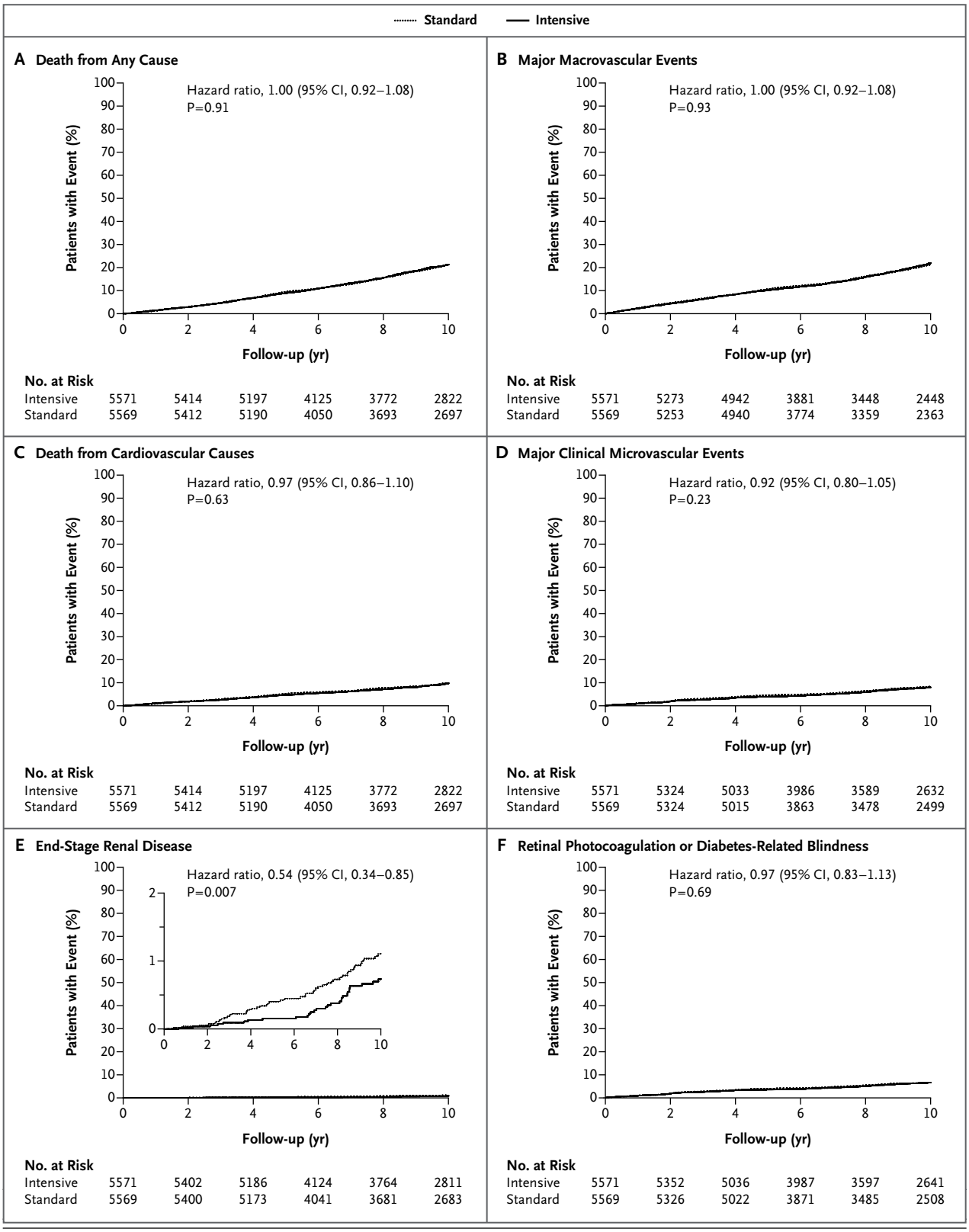


Figure 3 (facing page). Cumulative Incidence of Events, According to Glucose-Control Study Group.

Shown is the percentage of patients who had events at any time after the start of randomized treatment, according to assignment to the intensive-glucose-control group or the standard-glucose-control group. Hazard ratios (intensive control vs. standard control) and P values are shown for the 12-year period from the start of randomized treatment to the end of the post-trial follow-up. The inset in Panel E (which shows an outcome that was reduced significantly with intensive glucose control) displays the same data on an enlarged y axis.

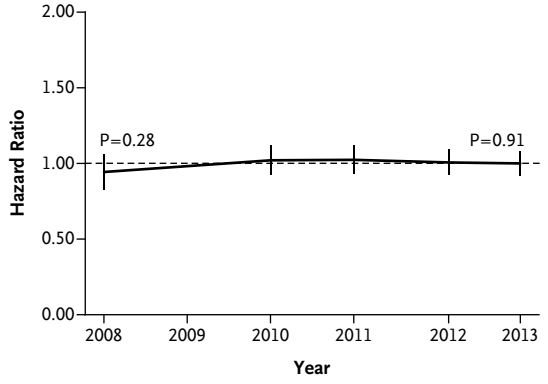
sure–lowering treatment with perindopril–indapamide (average difference in blood pressure of 5.6/2.2 mm Hg between the perindopril–indapamide group and the placebo group during the original trial). In contrast, we did not observe any significant benefits with respect to mortality, macrovascular events, or microvascular events resulting from the 5-year period of intensive glucose control (average difference in glycated hemoglobin level of 0.67 percentage points between the intensive-glucose-control group and the standard-glucose-control group during the original trial). When the prespecified components of the microvascular outcome were examined, we observed a persistent benefit of intensive glucose control with respect to end-stage renal disease but no new benefit with respect to serious eye complications.

The UKPDS post-trial follow-up study showed no persistence of the benefits of the earlier period of tight blood-pressure control with respect to macrovascular events or death. Although our blood-pressure findings appear to be different from those of the UKPDS, the point estimates for the major mortality end points are similar and are consistent with other post-trial follow-up studies of blood-pressure–lowering therapy in patients at high risk for cardiovascular events.[9-13] Indeed, a comparison of in-trial and post-trial numbers of events suggests that the cumulative reductions in mortality in the perindopril–indapamide group can be ascribed largely to a carrying forward of the effects observed during randomized treatment. It is possible that with even longer post-trial follow-up these effects might have further dissipated, as occurred in the UKPDS. The carry-forward effect and the gradual attenuation of benefits over time reinforce the importance of continuing blood-pressure–lowering medications if the benefits of treatment are to be fully realized.

The DCCT–EDIC and UKPDS post-trial follow-up studies showed the long-term beneficial effects of earlier periods of intensive glucose control with respect to macrovascular events and death.[1,2] We did not observe any such long-term benefits after post-trial follow-up. In our trial, the original benefits of intensive glucose control were due primarily to reductions in the incidence of new or worsening nephropathy, driven by reductions in the progression of albuminuria and serious renal disease requiring renal-replacement therapy.[5,6] We were unable to obtain the biochemical measurements (serum creatinine level and urinary albumin-to-creatinine ratio) required to assess the outcome of new or worsening nephropathy in all patients who entered the post-trial follow-up, so any conclusions can be based only on certain components, such as end-stage renal disease or death from renal disease. We observed benefits with respect to end-stage renal disease but no effects on the rate of death from renal disease, which may reflect the persistence of the effects observed during the trial. It is possible that the small differences in blood pressure between the intensive-glucose-control group and the standard-glucose-control group during the trial and post-trial periods contributed up to one quarter of this beneficial effect, as was reported for the benefits observed in the original trial.[5] Given the small number of events of end-stage renal disease (29 in the intensive-control group and 53 in the standard-control group), the benefits with respect to this end point should be interpreted with caution and studied further in future trials.

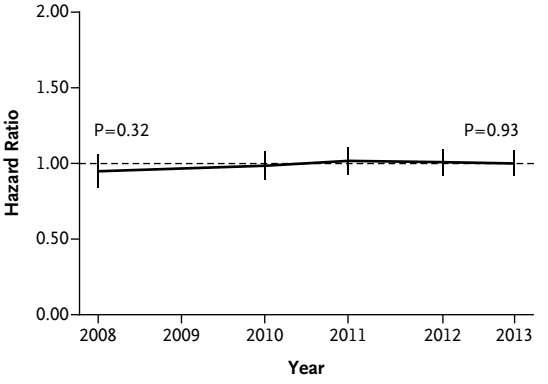
The divergent outcomes between our study and other studies of glucose control in patients with diabetes may be explained in part by differences in the response to the lowering of glucose across the trial populations. First, the younger patients with type 1 diabetes (in the DCCT–EDIC)[1] or with newly diagnosed type 2 diabetes (in the UKPDS)[2] may have been more likely to have long-term benefits from glucose lowering than the older patients with established disease who were included in our study. Second, there were differences between the studies in the in-trial levels of blood glucose, as reflected in the levels of glycated hemoglobin; the glycated hemoglobin level

A Death from Any Cause



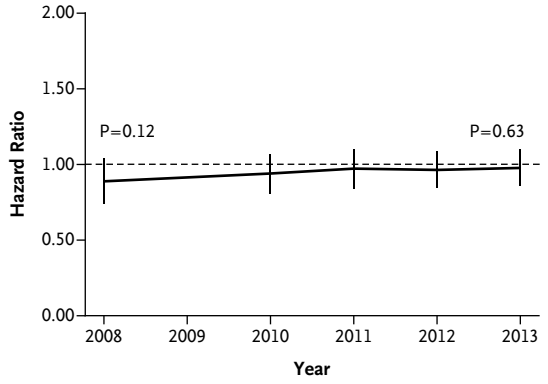
No. of Events					
Intensive	498	855	961	1060	1139
Standard	533	835	936	1046	1126

B Major Macrovascular Events



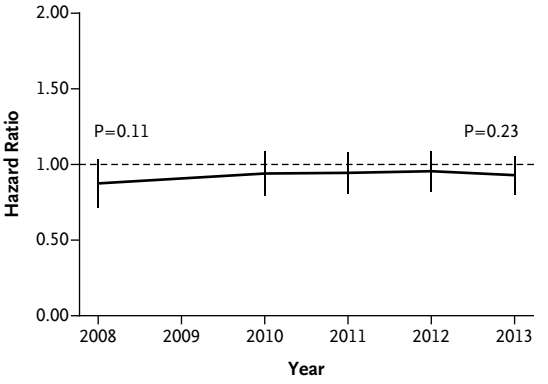
No. of Events					
Intensive	557	834	942	1035	1089
Standard	590	842	918	1018	1077

C Death from Cardiovascular Causes



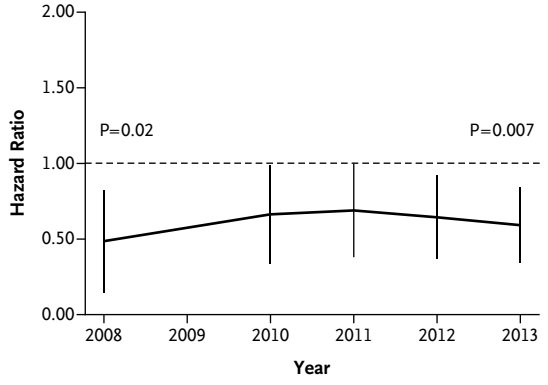
No. of Events					
Intensive	253	373	411	460	490
Standard	289	398	424	476	498

D Major Clinical Microvascular Events



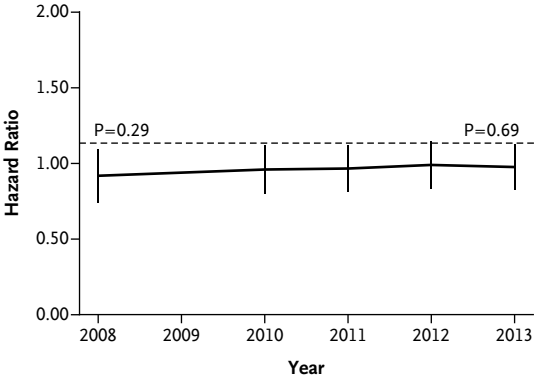
No. of Events					
Intensive	212	307	343	368	390
Standard	246	327	363	384	417

E End-Stage Renal Disease



No. of Events					
Intensive	7	21	27	29	29
Standard	20	36	43	49	53

F Retinal Photocoagulation or Diabetes-Related Blindness



No. of Events					
Intensive	195	264	291	311	332
Standard	216	277	302	314	337

Figure 4 (facing page). Hazard Ratios for Events, According to Glucose-Control Study Group.

Hazard ratios are shown for events that occurred from the start of randomized treatment to the end of the glucose-control comparison (2008) and to the end of each year of post-trial follow-up (2010 through 2013). The hazard ratios are for the intensive-control group versus the standard-control group; values less than 1.00 represent better outcomes in the intensive-control group. P values are for the between-group comparison at the final visit for the randomized trial in 2008 and at the end of the post-trial follow-up period. The data for 2013 include those obtained in the first 2 months of 2014, when follow-up was terminated. Vertical lines indicate 95% confidence intervals.

differed between study groups by an average of 0.67 percentage points over a period of 5 years in the ADVANCE trial, but the between-group difference was much larger in the DCCT (2.0 percentage points over a mean of 6.5 years during the trial) and slightly larger in the UKPDS (0.9 percentage points over a median of 10 years during the trial).[1,2,5] The baseline glycated hemoglobin levels in the patients in the DCCT and UKPDS (>8.5% in both trials) were also much higher than the baseline level in the patients in the ADVANCE trial (7.5%).[1,2,5] Moreover, during post-trial follow-up in the UKPDS,[2] the mean glycated hemoglobin level continued to decrease in both groups, whereas in our study, the level remained stable in the standard-glucose-control group and rose in the intensive-glucose-control group. Third, post-trial follow-up of our patients (5 years) was shorter than the follow-up for DCCT–EDIC and UKPDS (>10 years for both trials) and may have been insufficient for benefits to emerge. Fourth, it is possible that more widespread use of effective background preventive therapy in the ADVANCE trial masked the long-term effects. Finally, competing risk, which is a greater issue among older patients than among younger patients, may not have allowed the full effects of the glucose intervention to be observed in our study.

Our post-trial analysis has some limitations. First, our findings must be considered in the context of incomplete follow-up of the total ADVANCE cohort. Nevertheless, patients from all the original study groups who did participate in the post-trial follow-up and those who completed a visit in the final year of follow up had baseline characteristics that were similar to those in the entire trial population, allowing for the healthy-survivor effect. Second, end points recorded during the post-trial follow-up were not adjudicated; however, we have previously shown that central adjudication in the trial had little effect on the observed hazard ratios for any outcomes.[14] Third, many follow-up visits were conducted by telephone or questionnaire, with complete clinical and biochemical measurements available for only a limited subgroup of patients; therefore, we were not able to assess the possible persistence of benefits with respect to the original microvascular end point. Fourth, it should be stressed that although a comparison of outcomes across the entire follow-up period preserved the intention-to-treat principle, comparisons in the post-trial period alone are purely observational and hypothesis-generating, because they may be confounded by differences in risk profiles arising during randomized treatment. Finally, given the multiple comparisons made, the results from individual hypothesis tests must be considered with caution.

In conclusion, among patients with long-standing type 2 diabetes, blood-pressure–lowering treatment with perindopril–indapamide for an average of 4.5 years resulted in attenuated but significant long-term benefits with respect to death from any cause and from cardiovascular causes, whereas intensive glucose control for an average of 5 years did not provide any long-term benefits with respect to death or major macrovascular events.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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The authors' affiliations are as follows: the George Institute for Global Health (S.Z., J.C., B.N., L.B., Q.L., Y.H., H.A., H.M., R.J., V.P., A.R., S.M., A.P., M.W.) and Boden Institute (S.C.), University of Sydney, Sydney, the School of Public Health and Preventive Medicine, Monash University (S.Z.), Baker IDI Heart and Diabetes Institute (M.E.C.), and the University of Melbourne and Royal Melbourne Hospital (S. Harrap), Melbourne, VIC, and Bond University, Robina, QLD (P.G.) — all in Australia; the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, and Julius Clinical Research, Utrecht, the Netherlands (D.G.); Research Centre, Centre Hospitalier de l'Université de Montréal, Montreal (P.H.); University of Sheffield and Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield (S. Heller), Oxford Centre for Diabetes, Endocrinology and Metabolism (D.R.M.), and the George Institute for Global Health (S.M., M.W.), University of Oxford, Oxford, and the International Centre for Circulatory Health, Imperial College (N.P.), University College London (UCL) and the National Institute for Health Research UCL Hospitals Biomedical Research Centre (B.W.), London — all in the United Kingdom; the Chinese Hypertension League Institute, Beijing (L.L.); the University of Milan-Bicocca and Istituto Auxologico Italiano, Milan (G.M.); Hôpital Bichat–Claude Bernard and Université Paris 7, Paris (M.M.); Medical Department M, Aarhus Sygehus, Aarhus, Denmark (C.E.M.); and the Department of Epidemiology, John Hopkins University, Baltimore (M.W.).

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