ORIGINAL ARTICLE

10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

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ABSTRACT

BACKGROUND

During the United Kingdom Prospective Diabetes Study (UKPDS), patients with type 2 diabetes mellitus who received intensive glucose therapy had a lower risk of microvascular complications than did those receiving conventional dietary therapy. We conducted post-trial monitoring to determine whether this improved glucose control persisted and whether such therapy had a long-term effect on macrovascular outcomes.

METHODS

Of 5102 patients with newly diagnosed type 2 diabetes, 4209 were randomly assigned to receive either conventional therapy (dietary restriction) or intensive therapy (either sulfonylurea or insulin or, in overweight patients, metformin) for glucose control. In post-trial monitoring, 3277 patients were asked to attend annual UKPDS clinics for 5 years, but no attempts were made to maintain their previously assigned therapies. Annual questionnaires were used to follow patients who were unable to attend the clinics, and all patients in years 6 to 10 were assessed through questionnaires. We examined seven prespecified aggregate clinical outcomes from the UKPDS on an intention-to-treat basis, according to previous randomization categories.

RESULTS

Between-group differences in glycated hemoglobin levels were lost after the first year. In the sulfonylurea–insulin group, relative reductions in risk persisted at 10 years for any diabetes-related end point (9%, P=0.04) and microvascular disease (24%, P=0.001), and risk reductions for myocardial infarction (15%, P=0.01) and death from any cause (13%, P=0.007) emerged over time, as more events occurred. In the metformin group, significant risk reductions persisted for any diabetes-related end point (21%, P=0.01), myocardial infarction (33%, P=0.005), and death from any cause (27%, P=0.002).

CONCLUSIONS

Despite an early loss of glycemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow-up. A continued benefit after metformin therapy was evident among overweight patients. (UKPDS 80; Current Controlled Trials number, ISRCTN75451837.)

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The United Kingdom Prospective Diabetes Study (UKPDS), a randomized, prospective, multicenter trial, showed that intensive glucose therapy in patients with newly diagnosed type 2 diabetes mellitus was associated with a reduced risk of clinically evident microvascular complications and a nonsignificant reduction of 16% in the relative risk of myocardial infarction (P=0.052).[1] In patients whose body weight was more than 120% of their ideal weight[2] and who primarily received metformin, reductions in the risk of myocardial infarction of 39% (P=0.01) and of death from any cause of 36% (P=0.01) were observed. The results of the UKPDS, which were published in 1998, have appeared to be influential in subsequent diabetes management.[3,4]

In patients with type 1 diabetes, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study reported a postinterventional microvascular benefit and the emergence of macrovascular risk reduction from earlier improved glycemic control during an 8-year period.[5] The Steno-2 Study reported a similar outcome during a 5.5-year period after earlier multifactorial risk reduction among patients with type 2 diabetes.[6] In both trials, enhanced risk reductions occurred despite the loss of within-trial differences in glucose levels and, in the Steno-2 Study, diminished differences in blood pressure and lipid levels, suggesting the persistence of effects of earlier improved metabolic management.

We report here the results of a 10-year, postinterventional follow-up of the UKPDS survivor cohort that examined whether a continued microvascular benefit from earlier improved glucose control was evident and whether such therapy had a long-term effect on macrovascular outcomes.

Methods

Patients

The recruitment of patients, study protocol, and methods for the UKPDS have been reported previously.[7,8] Approval was obtained from the ethics committees at all 23 clinical centers, and the study conformed to the Declarations of Helsinki guidelines. Briefly, 5102 of 7616 patients who underwent screening were enrolled from 1977 to 1991. All patients provided written informed consent. Patients were between the ages of 25 and 65 years and had a fasting plasma glucose level of more than 108 mg per deciliter (6.0 mmol per liter) on two occasions after their general practitioners had diagnosed type 2 diabetes. By self-report, 81% of the patients were white, 10% Asian Indian, and 9% Afro-Caribbean. A total of 2514 patients were excluded because of the following conditions: ketonuria, a serum creatinine level of more than 175 μmol per liter (2.0 mg per deciliter), myocardial infarction in the previous year, current angina or heart failure, more than one major vascular event, retinopathy requiring laser treatment, malignant hypertension, uncorrected endocrine disorder, occupations precluding insulin therapy, severe concurrent illness limiting life expectancy, inadequate understanding of the study protocol, or unwillingness to enter the study.

After a 3-month dietary run-in period, patients with a fasting plasma glucose level of more than 108 mg per deciliter but less than 270 mg per deciliter (15.0 mmol per liter) were randomly assigned to receive conventional glucose control (diet) or intensive glucose control (sulfonylurea or insulin or, if more than 120% of ideal body weight, metformin[2]). All patients were seen quarterly in UKPDS clinics.[7] The median follow-up for the sulfonylurea–insulin and metformin groups was 10.0 years[1] and 10.7 years,[9] respectively.

Post-Trial Monitoring

All surviving patients entered the post-trial monitoring program after the intervention trial closed on September 30, 1997. A 10-year follow-up was planned to coincide with a projected death rate of 50%. In September 1998, when the UKPDS results were published,[10,11] patients and clinicians were advised that it was necessary to lower levels of blood glucose and blood pressure as much as possible. Patients returned to community or hospital-based diabetes care according to their clinical needs, with no attempt to maintain previously randomized therapies. They were seen annually for 5 years in UKPDS clinics, with continued standardized collection of outcome data; measurements of blood pressure, fasting plasma glucose, glycated hemoglobin, plasma creatinine, and the ratio of albumin to creatinine; and results on two questionnaires, the European Quality of Life–5 Dimensions (EQ-5D)[12] and a questionnaire on the use of health resources.

Clinical examinations every 3 years were continued. Patients who were unable to attend clinics were sent EQ-5D and health-resource question-

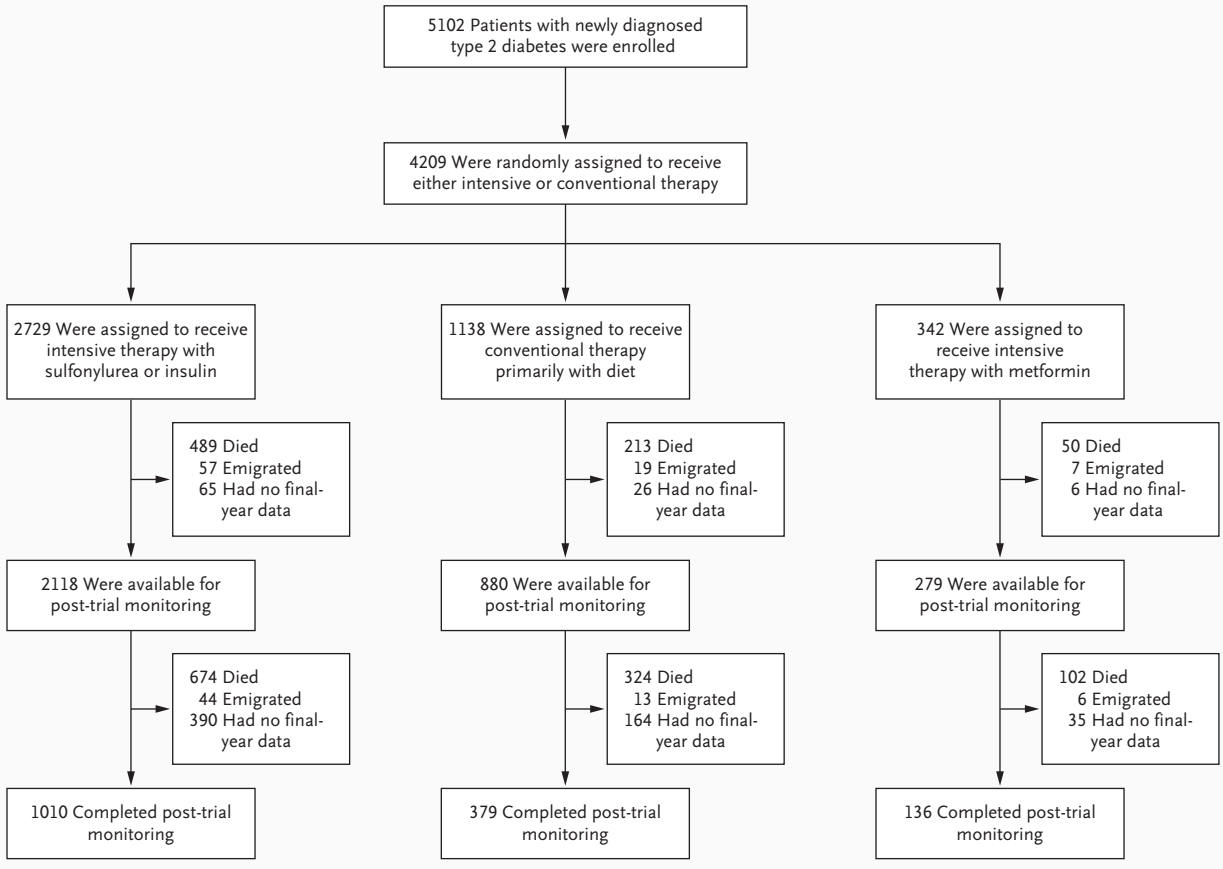


Figure 1. Enrollment and Outcomes.

Of the 4209 patients who underwent randomization in the original United Kingdom Prospective Diabetes Study, 78% entered post-trial monitoring. Of the 1138 patients who were assigned to receive conventional therapy, 411 were overweight. These were compared with the 342 overweight patients who were assigned to receive intensive therapy with metformin. Vital status was not available for any of the patients who left the United Kingdom during follow-up. For patients for whom no final-year data were available, the analysis may not have captured all nonfatal events. Overall, 3.5% of patients were lost to follow-up.

naires, and additional questionnaires were sent to their general practitioners to capture possible clinical outcomes. In years 6 to 10, these questionnaires were used to follow patients remotely, since funding for clinic visits was not available. Final questionnaires were sent to all remaining patients after the cutoff for the censoring of post-trial data on September 30, 2007.

CLINICAL OUTCOMES

The study administrator obtained full documentation for all putative outcomes from hospitals and general practitioners, whether reported at clinic visits or by means of questionnaires. The vital status for all patients who were still living in the United Kingdom was obtained from the Office of National Statistics. Members of the UKPDS end-point committee, who were unaware of assignments to study groups, adjudicated outcomes exactly as they had during the original trial. The seven prespecified UKPDS aggregate clinical outcomes[7] were any diabetes-related end point (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal myocardial infarction, angina, heart failure, fatal or nonfatal stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye, or cataract extraction), diabetes-related death (sudden death or death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycemia, or hypoglycemia), death from any cause, myocardial infarction (sudden death or fa-

Table 1. Baseline Characteristics of the Patients.*

Variable	Data Available in Final Year of Post-Trial Monitoring			Sulfonylurea–Insulin Group			Metformin Group		
	Yes (N=1525)	No (N=705)	P Value†	Conventional Therapy (N=880)	Intensive Therapy (N=2118)	P Value†	Conventional Therapy (N=309)	Intensive Therapy (N=279)	P Value†
Age — yr	62±8	60±9	0.002	63±9	63±9	0.78	63±9	64±9	0.56
Male sex — no. (%)	892 (58.5)	391 (55.5)	0.22	532 (60.5)	1248 (58.9)	0.44	142 (46.0)	127 (45.5)	0.92
Race or ethnic group — no. (%)‡			<0.001			0.59			0.42
White	1161 (76.1)	564 (80.0)		710 (80.7)	1717 (81.1)		262 (84.8)	235 (84.2)	
Afro-Caribbean	143 (9.4)	51 (7.2)		58 (6.6)	159 (7.5)		23 (7.4)	28 (10.0)	
Asian Indian	209 (13.7)	84 (11.9)		105 (11.9)	230 (10.9)		21 (6.8)	12 (4.3)	
Other	12 (0.8)	6 (0.8)		7 (0.8)	12 (0.6)		3 (1.0)	4 (1.4)	
Weight — kg			0.97			0.01			0.42
Median	81.0	81.00		79.0	80.0		87.0	86.0	
Interquartile range	71.00–92.00	70.00–91.00		69.0–90.0	71.0–92.0		76.0–97.0	75.0–95.8	
Body-mass index	29.4±5.5	29.4±5.4	0.86	28.7±5.6	29.3±5.5	0.005	32.2±5.7	31.7±5.4	0.34
Blood pressure — mm Hg									
Systolic	137±19	137±19	0.98	138±21	139±20	0.52	139±22	141±18	0.43
Diastolic	77±10	78±10	0.22	77±10	77±10	0.06	77±10	78±10	0.22
Fasting plasma glucose — mg/dl	164±59	168±61	0.34	178±58	161±61	<0.001	182±55	177±64	0.12
Glycated hemoglobin — %			0.25			<0.001			0.12
Median	8.0	8.1		8.5	7.9		8.9	8.4	
Interquartile range	6.9–9.4	7.0–9.6		7.3–9.7	6.8–9.2		7.5–10.0	7.2–9.7	
Cholesterol — mg/dl									
Total	198±39	198±37	0.66	197±37	197±39	0.63	200±37	204±41	0.37
Low-density lipoprotein	127±34	127±32	0.81	126±32	126±34	0.92	129±32	130±36	0.98
High-density lipoprotein	42±12	43±13	0.87	43±12	42±13	0.23	40±12	42±13	0.08

Triglycerides — mg/dl			0.60			0.97			0.10
Median	127	132		128	127		143	157	
Interquartile range	84–184	88–190		88–180	85–182		103–203	107–231	
Plasma creatinine — mg/dl			0.87			0.61			0.03
Median	1.00	0.98		1.02	1.02		0.96	1.03	
Interquartile range	0.87–1.15	0.89–1.14		0.89–1.17	0.90–1.17		0.83–1.11	0.85–1.23	
Ratio of albumin to creatinine§			0.99			0.42			0.48
Median	12.3	12.7		14.9	14.3		19.9	19.8	
Interquartile range	6.2–33.9	5.8–36.7		6.5–49.7	6.8–43.8		8.1–82.8	8.0–61.2	

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

† P values were calculated with the use of the chi-square test for categorical variables and the Wilcoxon signed-rank test for continuous variables.

‡ Race or ethnic group was self-reported.

§ Albumin was measured in milligrams, and creatinine was measured in grams.

tal or nonfatal myocardial infarction), stroke (fatal or nonfatal stroke), peripheral vascular disease (amputation of at least one digit or death from peripheral vascular disease), and microvascular disease (vitreous hemorrhage, retinal photocoagulation, or renal failure).

STATISTICAL ANALYSIS

We performed the analyses according to the intention-to-treat principle, with descriptive statistics presented as numbers and percentages or appropriate measures of central tendency and dispersion. Continuous and categorical study variables were compared between the conventional-therapy group and the intensive-therapy groups with the use of nonparametric tests. Kaplan–Meier time-to-event analyses were used for aggregate clinical outcomes, with log-rank tests used for differences between previous study-group assignments. Since recruitment was performed during a 14-year period, patients could have been in the interventional trial for 6 to 20 years. Since there was no common time from randomization to the start of post-trial monitoring, we used serial hazard-ratio plots with confidence intervals (after checking that proportional-hazards assumptions were not violated) to illustrate possible changes in post-trial relative risks, with P values calculated only at the end of follow-up. Absolute risk rates are expressed as the number of events per 1000 person-years.

Post-trial monitoring was initiated by the investigators and was sponsored for 5 years by the Medical Research Council and then by the University of Oxford. The investigators designed and conducted the study, analyzed the data, and prepared the manuscript, independently of any funding bodies. The investigators vouch for the completeness and accuracy of the data.

RESULTS

PATIENTS

A total of 4209 patients were randomly assigned to receive either conventional therapy or intensive therapy (Fig. 1). Of these patients, baseline characteristics for the 3277 patients who entered post-trial monitoring are shown in Table 1. In the sulfonylurea–insulin group, patients who had been assigned to receive intensive therapy had lower levels of mean glycated hemoglobin and fasting plasma glucose than those who received conventional therapy (P<0.001 for both comparisons)

but had a higher median weight (P=0.01) and mean body-mass index (P=0.005). More patients who had initially been assigned to receive intensive therapy were receiving a combination of oral and insulin therapy (64%) than were those who had originally been assigned to receive conventional therapy (46%). No significant differences were observed for any variables between patients for whom final-year data were available and those for whom final-year data were not available, except that patients for whom such data were available were 2 years older (P=0.002) and were less likely to be white (P<0.001) (Table 1).

The majority of patients (92 to 97%) attended UKPDS clinics in years 1 to 5. The median follow-up periods in the sulfonylurea–insulin and metformin groups were 16.8 years and 17.7 years, respectively — equivalent to 61,106 and 12,431 person-years, respectively, with 8.5 and 8.8 years of post-trial follow-up. Mortality overall was 44.0%, and leading causes of death were cardiovascular disease (51.5%) and cancer (24.2%). Baseline differences in combinations of glucose therapy disappeared by 5 years, at which time 5% of the patients were on diet alone, 46% were receiving oral therapy, and 49% were receiving insulin (with or without oral therapy). Baseline differences in mean glycated hemoglobin levels between the intensive-therapy group and the conventional-therapy group were lost by 1 year, with similar glycated hemoglobin improvements thereafter in all groups (Fig. 2A and 2B). The mean body weight did not differ at baseline or thereafter between the two groups (Fig. 2C and 2D). No significant differences in lipid levels were seen at baseline (Table 1). Levels of blood pressure and plasma creatinine and the ratio of albumin to creatinine did not differ significantly between the two groups at any

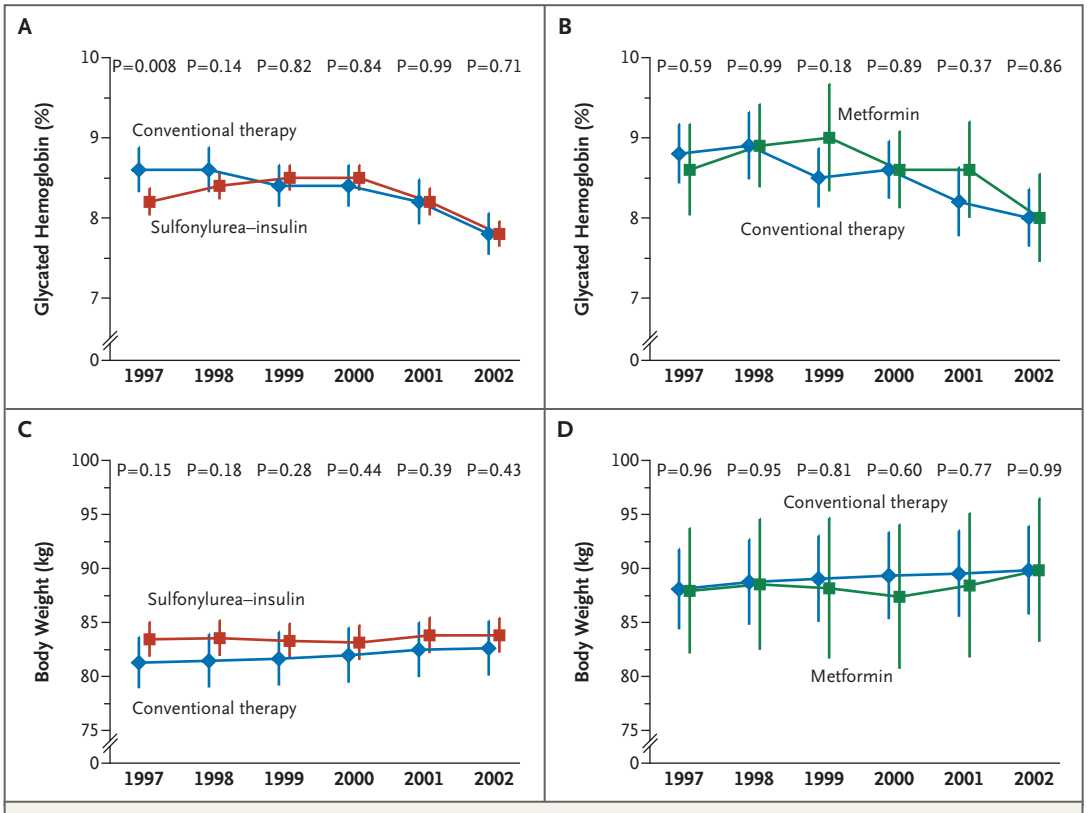


Figure 2. Mean Glycated Hemoglobin Levels and Body Weight.

Glycated hemoglobin levels for patients who were originally assigned to receive either sulfonylurea–insulin or conventional therapy (Panel A) or metformin or conventional therapy (Panel B) are shown. Panels C and D show the corresponding mean body weights in the two groups. Clinical data were not available in years 6 through 10, when questionnaires were used. The vertical bars represent 95% confidence intervals.

time, except that plasma creatinine levels in the metformin group were 15% higher on average than those in the conventional-therapy group (P<0.04) (Fig. 1 and 2 in the Supplementary Appendix, available with the full text of this article at www.nejm.org).

CLINICAL OUTCOMES

In the sulfonylurea–insulin group as compared with the conventional-therapy group, significant reductions in relative risk that had been observed during the interventional trial for any diabetes-related end point and microvascular disease were maintained. At 10 years, the risk reductions in the sulfonylurea–insulin group were 9% for any diabetes-related end point (0.04) and 24% for microvascular disease (P=0.001) (Table 2 and Fig. 3 and 4). In addition, post-trial risk reductions emerged in the sulfonylurea–insulin group for diabetes-related death (17%, P=0.01), myocardial infarction (15%, P=0.01), and death from any cause (13%, P=0.007). No significant risk reductions were observed during or after the trial for stroke or peripheral vascular disease.

Among patients in the metformin group, as compared with overweight patients in the conventional-therapy group, significant reductions in relative risk that were observed during the interventional trial for any diabetes-related outcome, diabetes-related death, myocardial infarction, and death from any cause were maintained. At 10 years, the risk reduction for any diabetes-related end point was 21% (P=0.01), for diabetes-related death 30% (P=0.01), for myocardial infarction 33% (P=0.005), and for death from any cause 27% (P=0.002) (Table 2 and Fig. 3 and 4). No sig-

Table 2. Aggregate Outcomes for Patients during Follow-up.*

Aggregate Outcome	Patients with Clinical Outcome		Absolute Risk†		P Value‡	Risk Ratio for Intensive-Therapy Regimen (95% CI)
	Intensive Therapy	Conventional Therapy	Intensive Therapy	Conventional Therapy		
	no. of patients					
Sulfonyurea–insulin group	2729	1138				
Any diabetes-related end point	1571	686	48.1	52.2	0.04	0.91 (0.83–0.99)
Diabetes-related death	618	297	14.5	17.0	0.01	0.83 (0.73–0.96)
Death from any cause	1162	537	26.8	30.3	0.007	0.87 (0.79–0.96)
Myocardial infarction	678	319	16.8	19.6	0.01	0.85 (0.74–0.97)
Stroke	260	116	6.3	6.9	0.39	0.91 (0.73–1.13)
Peripheral vascular disease	83	40	2.0	2.4	0.29	0.82 (0.56–1.19)
Microvascular disease	429	222	11.0	14.2	0.001	0.76 (0.64–0.89)
Metformin group	342	411				
Any diabetes-related end point	209	262	45.7	53.9	0.01	0.79 (0.66–0.95)
Diabetes-related death	81	120	14.0	18.7	0.01	0.70 (0.53–0.92)
Death from any cause	152	217	25.9	33.1	0.002	0.73 (0.59–0.89)
Myocardial infarction	81	126	14.8	21.1	0.005	0.67 (0.51–0.89)
Stroke	34	42	6.0	6.8	0.35	0.80 (0.50–1.27)
Peripheral vascular disease	13	21	2.3	3.4	0.19	0.63 (0.32–1.27)
Microvascular disease	66	78	12.4	13.4	0.31	0.84 (0.60–1.17)

* Shown are the numbers of patients who were followed for up to 30 years, including up to 10 years of post-trial monitoring, with aggregate clinical outcomes after assignment in the interventional phase of the United Kingdom Prospective Diabetes Study to the sulfonylurea–insulin group or the metformin group or to the corresponding conventional-therapy group.
† The absolute risk is the number of events per 1000 patient-years.
‡ P values were calculated with the use of the log-rank test.

nificant risk reductions were observed during or after the trial for microvascular disease, stroke, or peripheral vascular disease.

DISCUSSION

With more than 66,000 person-years of follow-up, this large post-trial study showed that benefits of an intensive strategy to control blood glucose levels in patients with type 2 diabetes were sustained for up to 10 years after the cessation of randomized interventions. Benefits persisted despite the early loss of within-trial differences in glycated hemoglobin levels between the intensive-therapy group and the conventional-therapy group — a so-called legacy effect. The trial showed the extended effects of improved glycemic control in patients with newly diagnosed type 2 diabetes, some of whom were followed for up to 30 years. The trial also showed that there were differences in outcomes between an intensive glucose-control strategy using sulfonylurea or insulin and that using metformin in overweight patients.

In the sulfonylurea–insulin group, the significant reduction of 25% in the risk of microvascular disease that was observed during the interventional trial in the intensive-therapy group[1] was sustained throughout the post-trial period, despite the rapid convergence of glycated hemoglobin levels in the two groups and a similar use of glucose-lowering therapies, and the reduction in the risk of any diabetes-related end point was also sustained. Clinically relevant post-trial risk reductions emerged over time for myocardial infarction (15%, P=0.01) and death from any cause (13%, P=0.007), although differences during the interventional phase of the trial were not significant.[1]

In the metformin group, which consisted of patients who were overweight, substantial risk reductions for myocardial infarction (39%, P=0.01) and death from any cause (36%, P=0.01) were observed in the intensive-therapy group during the original trial, even though the difference in glycated hemoglobin levels between the metformin group and the conventional-therapy group[9] was smaller than the difference between the sulfonylurea–insulin group and the conventional-therapy group.[1] These risk reductions were sustained throughout the post-trial period, despite similarities in glycated hemoglobin levels and in the use of glucose-lowering therapy. During the interventional phase of the trial and the post-trial period, microvascular risk reductions of 29% and 26%, respectively, were similar to those achieved in the sulfonylurea–insulin group, but neither difference was significant, probably because there were relatively few patients in this randomized comparison.

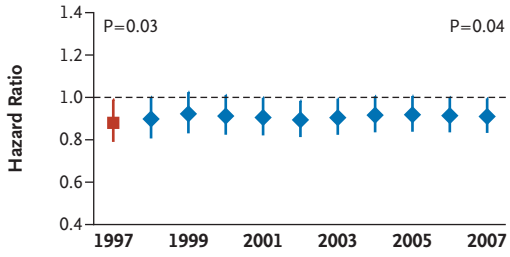
Figure 3 (facing page). Hazard Ratios for Four Prespecified Aggregate Clinical Outcomes.

Hazard ratios for patients in the United Kingdom Prospective Diabetes Study who had any diabetes-related end point (Panels A and B), myocardial infarction (Panels C and D), or microvascular disease (Panels E and F) or who died from any cause (Panels G and H) are shown for the sulfonylurea–insulin group versus the conventional-therapy group and for the metformin group versus the conventional-therapy group. The overall values at the end of the study,[1] in 1997, are shown (red squares), along with the annual values during the 10-year post-trial monitoring period (blue diamonds). Hazard ratios below unity indicate a favorable outcome from sulfonylurea or metformin therapy. Numbers of first events in an aggregate outcome that accumulated in each group are shown at 2-year intervals. The vertical bars represent 95% confidence intervals.

Although the UKPDS conclusively showed the benefit of improved glycemic control in reducing the risk of microvascular disease, risk reductions for myocardial infarction and death from any cause were observed only with extended post-trial follow-up. Similarly, in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial (ClinicalTrials.gov number, NCT00145925),[13] in which 11,140 patients with type 2 diabetes were randomly assigned to receive either intensive glucose control or standard glucose control, patients in the intensive-control group had a mean glycated hemoglobin level that was 0.8% lower than that in the standard-control group. However, at the same time, they had a reduction in major microvascular events of 14% (95% confidence interval [CI], 3 to 33) but a nonsignificant reduction in major macrovascular events of only 6% (95% CI, −6 to 16) after a median of 5 years of follow-up.

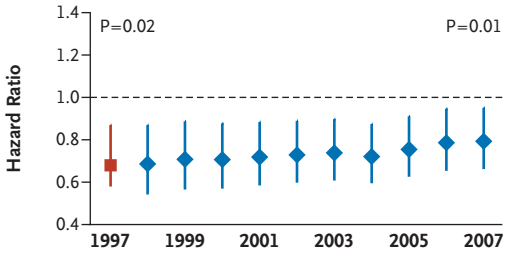
In the randomized Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (NCT00000620),[14] there was a nonsignificant

A Any Diabetes-Related End Point



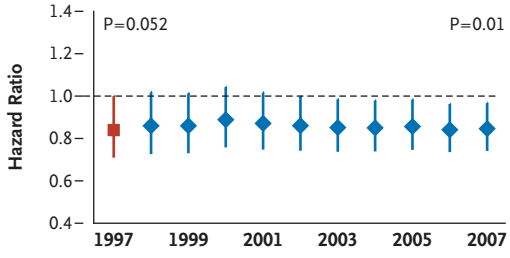
No. of Events						
Conventional therapy	438	498	571	620	651	686
Sulfonylurea–insulin	963	1151	1292	1409	1505	1571

B Any Diabetes-Related End Point



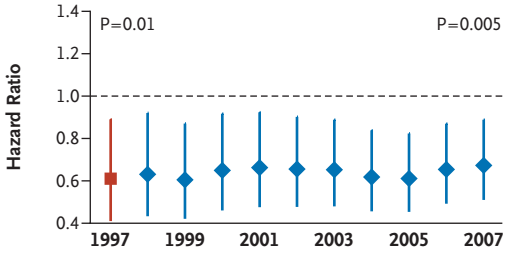
No. of Events						
Conventional therapy	160	190	220	240	252	262
Metformin	98	126	152	175	189	209

C Myocardial Infarction



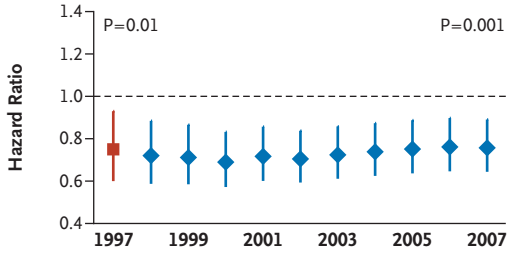
No. of Events						
Conventional therapy	186	212	239	271	296	319
Sulfonylurea–insulin	387	450	513	573	636	678

D Myocardial Infarction



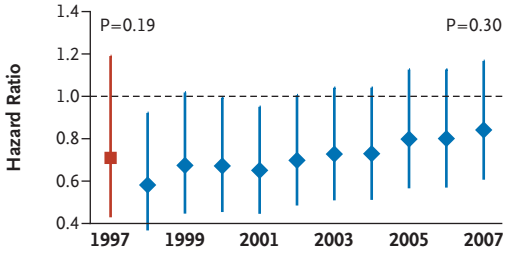
No. of Events						
Conventional therapy	73	83	92	106	118	126
Metformin	39	45	55	64	68	81

E Microvascular Disease



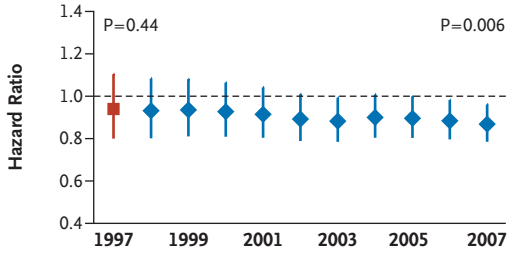
No. of Events						
Conventional therapy	121	155	187	205	212	222
Sulfonylurea–insulin	225	277	338	378	406	429

F Microvascular Disease



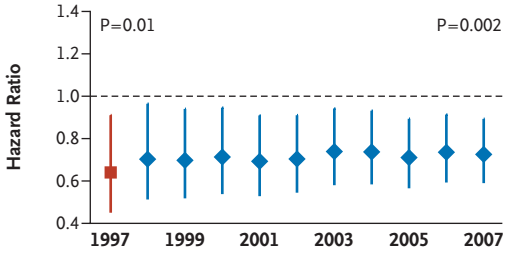
No. of Events						
Conventional therapy	38	58	70	73	74	78
Metformin	24	37	44	52	58	66

G Death from Any Cause



No. of Events						
Conventional therapy	213	267	330	400	460	537
Sulfonylurea–insulin	489	610	737	868	1028	1163

H Death from Any Cause



No. of Events						
Conventional therapy	89	113	136	160	183	217
Metformin	50	70	86	110	123	152

reduction of 10% in the composite primary outcome of nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes among 10,251 patients with type 2 diabetes who were assigned either to a group with a target glycated hemoglobin level of less than 6.0% or to a group with a target level of 7.0 to 7.9% at the time the trial was stopped, after 3.5 years, because of an unexplained excess rate of death from any cause (22%, P=0.04). Both the ADVANCE and ACCORD trials involved high-risk patients who were 8 and 12 years older, respectively, than the patients in the UKPDS. In addition, at randomization in the ADVANCE and ACCORD trials, patients had been treated for diabetes for 8 and 10 years, respectively, whereas patients in the UKPDS had newly diagnosed disease. About a third of the patients in the ADVANCE and ACCORD trials had a history of macrovascular disease, as compared with 7.5% in the UKPDS.[7] Both the ADVANCE and ACCORD trials suggested that near-normal glycemia did not reduce cardiovascular events in the short term.

Our findings are consistent with those of the EDIC study,[5] which was a follow-up study involving a cohort of 1441 patients with type 1 diabetes in the DCCT.[15] In the DCCT, patients between the ages of 13 and 39 years who did not have a history of cardiovascular disease were randomly assigned to receive either intensive insulin therapy or conventional insulin therapy for a mean of 6.5 years; subsequently, 93% of the patients were followed for 11 years. At the end of that trial, the mean glycated hemoglobin level was 7.4% in the intensive-therapy group and 9.1% in the conventional-therapy group. After all major cardiovascular and peripheral vascular events were combined, patients in the intensive-therapy group had a nonsignificant reduction in the risk of macrovascular disease of 41% (95% CI, –10 to 68).[15] Nevertheless, by the end of the follow-up period, intensive therapy had significantly reduced the risk of any cardiovascular disease event by 42% (95% CI, 9 to 63; P=0.02),[5] and after 6 years, it had resulted in decreased progression of carotid intima–media thickness.[16] The EDIC study also showed a sustained reduction in the risk of progressive retinopathy 4 years after the end of the trial, despite increasing hyperglycemia,[17] and showed persistent benefits with respect to albumin excretion after 7 to 8 years.[18] A comparison of the findings of the EDIC study and those of the UKPDS suggest that improved glucose control may result in a larger cardiovascular risk reduction in patients with type 1 diabetes than among those with type 2 diabetes, which is consistent with the results of one meta-analysis.[19]

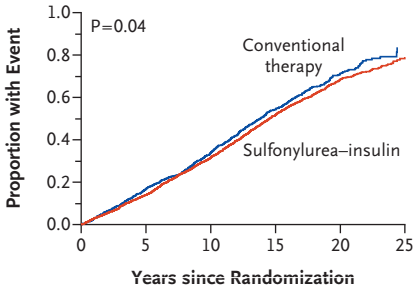
Figure 4 (facing page). Kaplan–Meier Curves for Four Prespecified Aggregate Clinical Outcomes.

The proportions of patients in the United Kingdom Prospective Diabetes Study who had any diabetes-related end point (Panels A and B), myocardial infarction (Panels C and D), or microvascular disease (Panels E and F) or who died from any cause (Panels G and H) are shown for the sulfonylurea–insulin group versus the conventional-therapy group and for the metformin group versus the conventional-therapy group. Kaplan–Meier plots for cumulative incidence and log-rank P values are shown at 5-year intervals during a 25-year period from the start of the interventional trial.

In the randomized Steno-2 Study, postinterventional benefits in patients with type 2 diabetes were reported after a 7.8-year multifactorial, intensive risk-reduction program with multiple drug combinations and behavior modification, with a follow-up of 13.3 years.[6] An overall absolute reduction in the risk of death of 20% (P=0.02) was observed, with a hazard ratio of 0.54 (95% CI, 0.32 to 0.89) for death in the intensive-therapy group, as compared with the conventional-therapy group. There was no evidence of a change in the hazard ratio once the formal intervention was stopped, but differences in glycated hemoglobin levels were maintained throughout the follow-up period. The Steno-2 Study also showed that the long-term effects of tight glycemic control and therapy with aspirin, antihypertensive agents, and lipid-lowering drugs appeared to be additive. Although persistent differences in risk-factor levels might have explained most of the benefit observed, a legacy effect could not be ruled out.

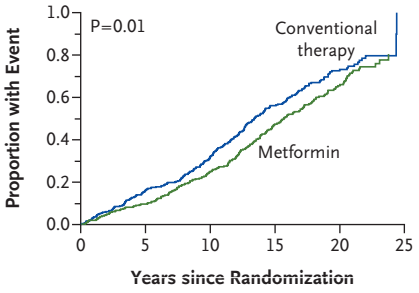
The pathophysiological mechanisms responsible for such a legacy effect of intensive glycemic control are unclear. A number of mechanisms have been proposed,[5] including increased intracellular formation of advanced glycation end products.[20] Long-term hyperglycemia is associated with a slow onset of microvascular disease, which may be mediated by the gradual accumulation of advanced glycation end products that are subsequently slowly degraded with intensive glycemic control. This mechanism may also be implicated in the development of cardiovascular disease. Thus, the sustained postinterventional benefit in

A Any Diabetes-Related End Point



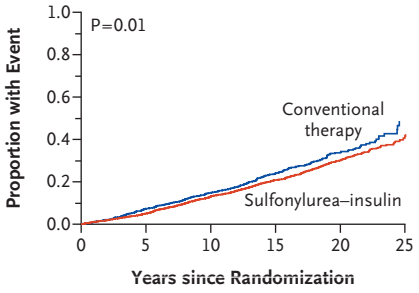
No. at Risk						
Conventional therapy	1138	913	679	370	104	5
Sulfonylurea–insulin	2729	2270	1692	933	277	32

B Any Diabetes-Related End Point



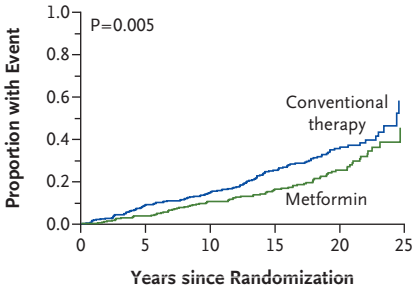
No. at Risk						
Conventional therapy	411	333	255	132	45	2
Metformin	342	300	236	144	62	7

C Myocardial Infarction



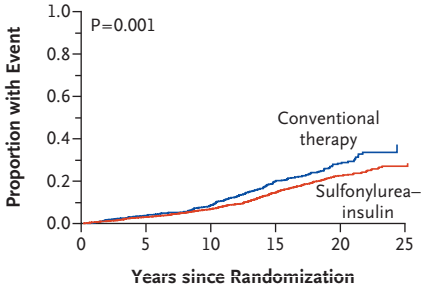
No. at Risk						
Conventional therapy	1138	1013	857	578	221	20
Sulfonylurea–insulin	2729	2488	2097	1459	577	66

D Myocardial Infarction



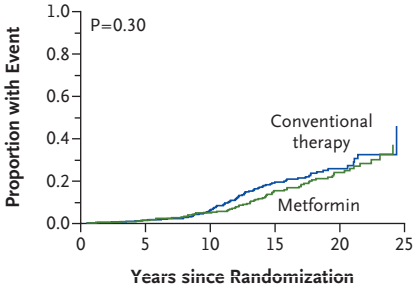
No. at Risk						
Conventional therapy	411	360	311	213	95	4
Metformin	342	317	274	214	106	16

E Microvascular Disease



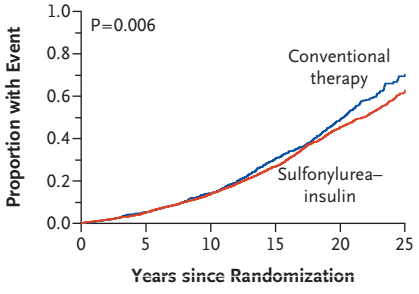
No. at Risk						
Conventional therapy	1138	1018	844	508	172	13
Sulfonylurea–insulin	2729	2465	2076	1368	488	53

F Microvascular Disease



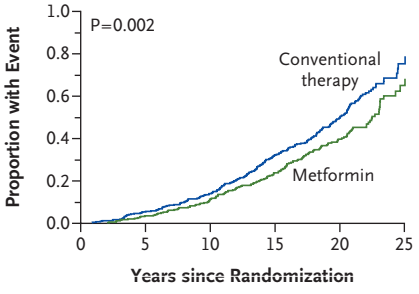
No. at Risk						
Conventional therapy	411	377	316	186	72	2
Metformin	342	319	278	197	92	16

G Death from Any Cause



No. at Risk						
Conventional therapy	1138	1066	939	665	270	28
Sulfonylurea–insulin	2729	2573	2276	1675	680	83

H Death from Any Cause



No. at Risk						
Conventional therapy	411	387	345	246	116	7
Metformin	342	328	296	239	124	11

the UKPDS might be explained in part by a lag phase before a reduction in events could occur because of improved glycemic control in the conventional-therapy group after the implementation of guidelines for stricter control on the basis of the results of the UKPDS. At the same time, the benefit of previous improved glycemic control in the intensive-therapy group would be expected to diminish only slowly.

Our study has certain limitations. Questionnaires may not have captured all nonfatal outcomes. Biochemical and clinical measurements were not collected after the fifth year, although after the first year it was already evident that differences in glycated hemoglobin levels had been lost. The absence of risk-factor information in the period between the sixth year and the 10th year precludes proportional-hazards analyses assessing possible effects of time-dependent covariates, such as microalbuminuria.

Our results show a sustained legacy effect of an intensive glucose-control strategy that appears to be longer than previously reported. These observations indicate that intensive glucose control starting at the time of diagnosis is associated with a significantly decreased risk of myocardial infarction and death from any cause, in addition to the well-established reduction in the risk of microvascular disease. On the basis of extensive trial evidence, strategies for cardiovascular risk reduction in patients with type 2 diabetes emphasize the importance of lipid-lowering therapy with statins[21] and of targeted antihypertensive treatment.[22-24] (A companion article in this issue of the *Journal* reports the 10-year, postinterventional data on blood-pressure control from the UKPDS.[25])

Our results highlight the added importance of glucose lowering in reducing the risk of coronary events and death from any cause. The findings strengthen the rationale for attaining optimal glycemic control and indicate emergent long-term benefits on cardiovascular risk.

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