Open access • Journal Article • DOI:10.1056/NEJMOA0806359

Long-term follow-up after tight control of blood pressure in type 2 diabetes

Rury R. Holman, Sanjoy K. Paul, M. Angelyn Bethel, H. Andrew W. Neil ...+1 more authors

Institutions: Churchill Hospital

Published on: 09 Oct 2008 - The New England Journal of Medicine (Massachusetts Medical Society)

Topics: United Kingdom Prospective Diabetes Study

ORIGINAL ARTICLE

Long-Term Follow-up after Tight Control of Blood Pressure in Type 2 Diabetes

Rury R. Holman, F.R.C.P., Sanjoy K. Paul, Ph.D., M. Angelyn Bethel, M.D., H. Andrew W. Neil, F.R.C.P., and David R. Matthews, F.R.C.P.

ABSTRACT

BACKGROUND

Post-trial monitoring of patients in the United Kingdom Prospective Diabetes Study (UKPDS) examined whether risk reductions for microvascular and macrovascular disease, achieved with the use of improved blood-pressure control during the trial, would be sustained.

METHODS

Among 5102 UKPDS patients with newly diagnosed type 2 diabetes mellitus, we randomly assigned, over a 4-year period beginning in 1987, 1148 patients with hypertension to tight or less-tight blood-pressure control regimens. The 884 patients who underwent post-trial monitoring were asked to attend annual UKPDS clinics for the first 5 years, but no attempt was made to maintain their previously assigned therapies. Annual questionnaires completed by patients and general practitioners were used to follow patients who were unable to attend the clinic in years 1 through 5, and questionnaires were used for all patients in years 6 to 10. Seven prespecified aggregate clinical end points were examined on an intention-to-treat basis, according to the previous randomization categories.

RESULTS

Differences in blood pressure between the two groups during the trial disappeared within 2 years after termination of the trial. Significant relative risk reductions found during the trial for any diabetes-related end point, diabetes-related death, microvascular disease, and stroke in the group receiving tight, as compared with less tight, blood-pressure control were not sustained during the post-trial follow-up. No risk reductions were seen during or after the trial for myocardial infarction or death from any cause, but a risk reduction for peripheral vascular disease associated with tight blood-pressure control became significant ($P=0.02$).

CONCLUSIONS

The benefits of previously improved blood-pressure control were not sustained when between-group differences in blood pressure were lost. Early improvement in blood-pressure control in patients with both type 2 diabetes and hypertension was associated with a reduced risk of complications, but it appears that good blood-pressure control must be continued if the benefits are to be maintained. (UKPDS 81; Current Controlled Trials number, ISRCTN75451837.)

From the Diabetes Trials Unit (R.R.H., S.K.P., M.A.B.) and the Division of Public Health and Primary Health Care (H.A.W.N.), and the National Institute of Health Research (NIHR) School for Primary Care Research (H.A.W.N.), Oxford Centre for Diabetes, Endocrinology, and Metabolism (R.R.H., S.K.P., M.A.B., H.A.W.N., D.R.M.); and the NIHR Oxford Biomedical Research Centre (R.R.H., H.A.W.N., D.R.M.) — both in Oxford, United Kingdom. Address reprint requests to Dr. Holman at the Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology, and Metabolism, Churchill Hospital, Headington, Oxford OX3 7LJ, United Kingdom, or at rury.holman@dtu.ox.ac.uk.

This article (10.1056/NEJMoa0806359) was published at www.nejm.org on September 10, 2008.

N Engl J Med 2008;359:1565-76.

The United Kingdom Prospective Diabetes Study (UKPDS) was a randomized, prospective, multicenter trial that indicated that improved glucose control in patients with newly diagnosed type 2 diabetes mellitus reduces the risk of clinically evident microvascular complications, with a relative risk reduction for myocardial infarction of 16% (P=0.052).[1] From 1987 to 1991, UKPDS patients with hypertension were, in addition, randomly assigned in a factorial manner to a tight blood-pressure control regimen involving an angiotensin-converting–enzyme (ACE) inhibitor or a beta-blocker or to a less-tight blood-pressure control strategy that excluded these agents.[2] For tight as compared with the less-tight control of blood pressure, there were relative risk reductions of 24% for any diabetes-related end point, 32% for diabetes-related death, 44% for stroke, and 37% for microvascular disease.[3]

A postinterventional benefit with regard to both microvascular and macrovascular complications of diabetes has been reported in the Steno-2 Study.[4] Over a period of 5.5 years after multifactorial risk intervention, persistent reductions in the rates of death from any cause, death from cardiovascular causes, and progression of microvascular disease were reported, despite diminutions in the within-trial differences in glucose, blood-pressure, and lipid control, suggesting that there may be a persistent effect of earlier improved management of risk factors.[4]

We report here the results of a 10-year, postinterventional follow-up of the survivor cohort of the UKPDS blood-pressure study that examined whether a continued benefit of earlier improved blood-pressure control was evident and, if so, the degree to which it persisted. In a companion article in this issue of the *Journal*, we report the results of the post-trial monitoring in the glycemic intervention groups of the UKPDS patients.[5]

Methods

Patients

Details on recruitment of patients for the UKPDS and the protocols, methods,[2,6] and post-trial monitoring procedures[5] have been reported previously. The embedded Hypertension in Diabetes Study (HDS)[2] involved randomization of 1148 of 1544 UKPDS patients with hypertension (blood pressure, ≥160/90 mm Hg or ≥150/85 mm Hg if the patient was receiving antihypertensive treatment) in a factorial manner, over a 4-year period beginning in 1987, to a tight blood-pressure control regimen (with randomized assignment to up to 50 mg of captopril [Capoten, Bristol-Myers Squibb] twice daily or up to 100 mg of atenolol [Tenormin, Hoechst] once daily) or to a less-tight blood-pressure control regimen (without the use of ACE inhibitors or beta-blockers). A total of 144 patients declined to participate in the blood-pressure study. A total of 252 other patients were excluded because they already required strict blood-pressure control (owing to previous stroke, accelerated hypertension, cardiac failure, or renal failure) or beta-blockade (owing to myocardial infarction in the previous year or current angina), had severe vascular disease or a severe concurrent illness, had contraindications to the use of beta-blockers, or were pregnant. The 1148 patients had a mean (±SD) age of 56.4±8.1 years and 56% were male; 87% reported that they were white, 4% Asian Indian, and 7% Afro-Caribbean.

The blood-pressure target for the tight-control group was less than 150/85 mm Hg, and the target for the less-tight–control group was less than 180/105 mm Hg, with therapies added as necessary in the following recommended sequence: 20 mg of furosemide daily (maximum, 40 mg twice daily), 10 mg of slow-release nifedipine daily (maximum, 40 mg), 250 mg of methyldopa daily (maximum, 500 mg), and 1 mg of prazosin thrice daily (maximum, 5 mg). The median duration of follow-up for the comparison of tight control with less-tight control was 8.4 years,[2] and within the tight-control group, the duration was 8.6 years for the comparison of ACE inhibitors with beta-blockers.

Post-Trial Monitoring

When the interventional trial closed on September 30, 1997, the survivor cohort entered a 10-year post-trial monitoring program planned to coincide with a projected 50% mortality rate. In September 1998,[3,7] after publication of the UKPDS results, patients and clinicians were advised to aim for the lowest feasible blood-glucose and blood-pressure levels. Patients returned to their usual physicians, with no attempt to maintain previously randomized therapies, and were seen annually for 5 years in UKPDS clinics. Standardized collection of end-point data was continued, as were measurements of blood pressure, levels of fasting plasma glucose, glycated hemoglobin, and plasma creatinine; calculation of the albumin-to-creatinine ratio; and clinical examinations ev-

ery 3 years. Questionnaires — the European Quality of Life–5 Dimensions (EQ-5D) instrument[8] and a questionnaire on health-resource use — were administered annually. Patients who were unable to attend clinics were mailed the EQ-5D and health-resource questionnaires, and additional questionnaires were sent to their general practitioners to capture possible end points. During years 6 to 10, because of funding constraints, these questionnaires were used to follow all patients remotely. After the censoring date of post-trial monitoring (September 30, 2007), final questionnaires were sent to all remaining patients.

CLINICAL OUTCOMES

The study administrator obtained full documentation from hospitals and general practitioners for all putative end points, whether reported at a clinic visit or on a questionnaire. The vital status of patients was obtained from the U.K. Office of National Statistics. End points were adjudicated exactly as they had been during the trial and by the same end-point committee, the members of which were unaware of the treatment assignments. The seven prespecified UKPDS aggregate clinical end points[2] 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 (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycemia or hypoglycemia, or sudden death), death from any cause, myocardial infarction (sudden death, fatal or nonfatal myocardial infarction), fatal or nonfatal stroke, peripheral vascular dis-

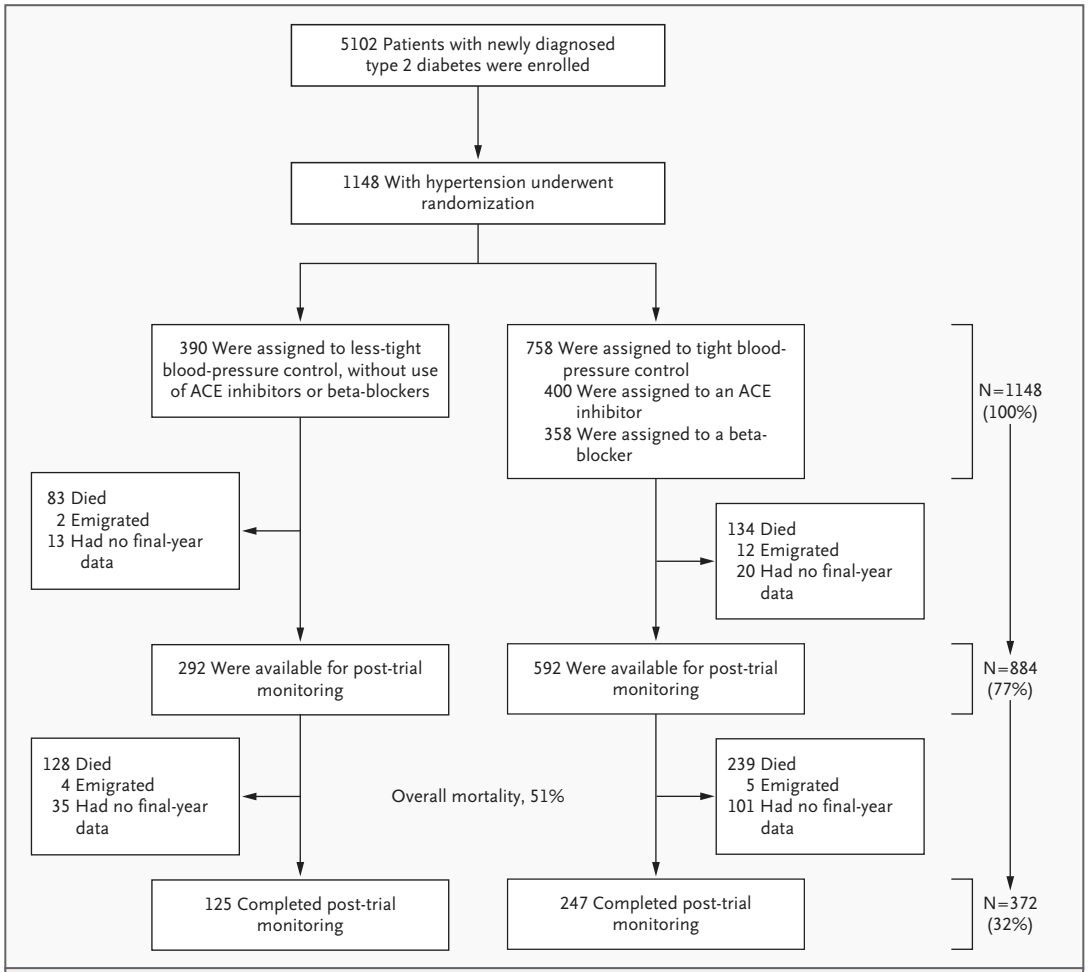


Figure 1. Enrollment, Randomization, and Follow-up of Study Participants.
ACE denotes angiotensin-converting enzyme.

Table 1. Baseline Characteristics of the Survivor Cohort Entering Post-Trial Monitoring.*

Characteristic	Final-Year Post-Trial Monitoring Data Obtained			Blood-Pressure Control			ACE Inhibitor or Beta-Blocker for Tight Control		
	Yes (N=372)	No (N=163)	P Value	Less Tight (N=292)	Tight (N=592)	P Value	ACE Inhibitor (N=304)	Beta-Blocker (N=288)	P Value
Age — yr	63±8	63±9	0.97	65±8	65±8	0.54	65±8	64±8	0.15
Male sex — no. (%)	201 (54)	90 (55)	0.50	161 (55)	306 (52)	0.33	147 (48)	159 (55)	0.10
Race or ethnic group — no. (%)†									
White	298 (80)	145 (89)	<0.001	256 (88)	512 (86)	0.95	268 (88)	244 (85)	0.64
Afro-Caribbean	37 (10)	11 (7)		20 (7)	42 (7)		20 (7)	22 (8)	
Asian Indian	35 (9)	5 (3)		14 (5)	35 (6)		15 (5)	20 (7)	
Other	2 (1)	2 (1)		2 (1)	3 (1)		1 (<1)	2 (1)	
Weight — kg									
Median	83.0	83.0	0.63	82.0	82.0	0.58	80.0	84.0	0.01
Interquartile range	73.0–95.0	72.0–94.0		72.0–94.0	71.0–94.0		70.0–92.0	73.0–96.8	
Body-mass index‡	30.5±5.8	30.0±5.3	0.54	29.9±6.0	30.3±6.0	0.23	29.9±5.8	30.8±6.2	0.14
Blood pressure — mm Hg									
Systolic	146±20	145±18	0.86	152±22	143±20	<0.001	143±20	144±19	0.38
Diastolic	81±9	82±10	0.62	82±10	79±10	<0.001	79±10	79±9	0.51
Fasting plasma glucose — mg/dl	162±60	162±54	0.83	161±57	166±60	0.26	166±63	166±58	0.72
Glycated hemoglobin — %									
Median	7.85	8.00	0.41	7.5	8.3	0.001	8.0	8.4	0.39
Interquartile range	6.80–9.48	7.10–9.50		6.5–8.8	7.0–9.5		7.0–9.5	7.1–9.7	
Lipid profile — mg/dl									
Total cholesterol	198±39	198±38	0.72	199±39	200±39	0.66	203±39	196±39	0.04
LDL cholesterol	127±34	126±.32	0.98	126±33	128±34	0.44	131±34	125±34	0.06
HDL cholesterol	41±12	43±14	0.35	42±12	41±12	0.06	42±13	39±12	0.009
Triglycerides									
Median	134	129	0.50	131	138	0.15	138	139	0.42
Interquartile range	93–194	82–198		89–178	95–201		87–206	101–195	
Plasma creatinine — mg/dl									
Median	1.02	1.00	0.60	1.09	1.04	0.81	1.10	1.05	0.97
Interquartile range	0.89–1.17	0.91–1.15		0.92–1.23	0.92–1.12		0.95–1.23	0.91–1.20	
Albumin-to-creatinine ratio§									
Median	16.2	15.0	0.79	18.6	21.9	0.22	17.4	20.1	0.58
Interquartile range	8.2–47.9	7.5–51.6		9.2–82.6	9.4–78.5		9.3–62.9	8.9–73.9	

* Plus–minus values are means ±SD. P values were calculated with the use of the chi-square test (for categorical variables) or the Wilcoxon signed-rank test (for continuous variables). HDL denotes high-density lipoprotein, and LDL low-density lipoprotein. 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.

† Race or ethnic group was self-reported.

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

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

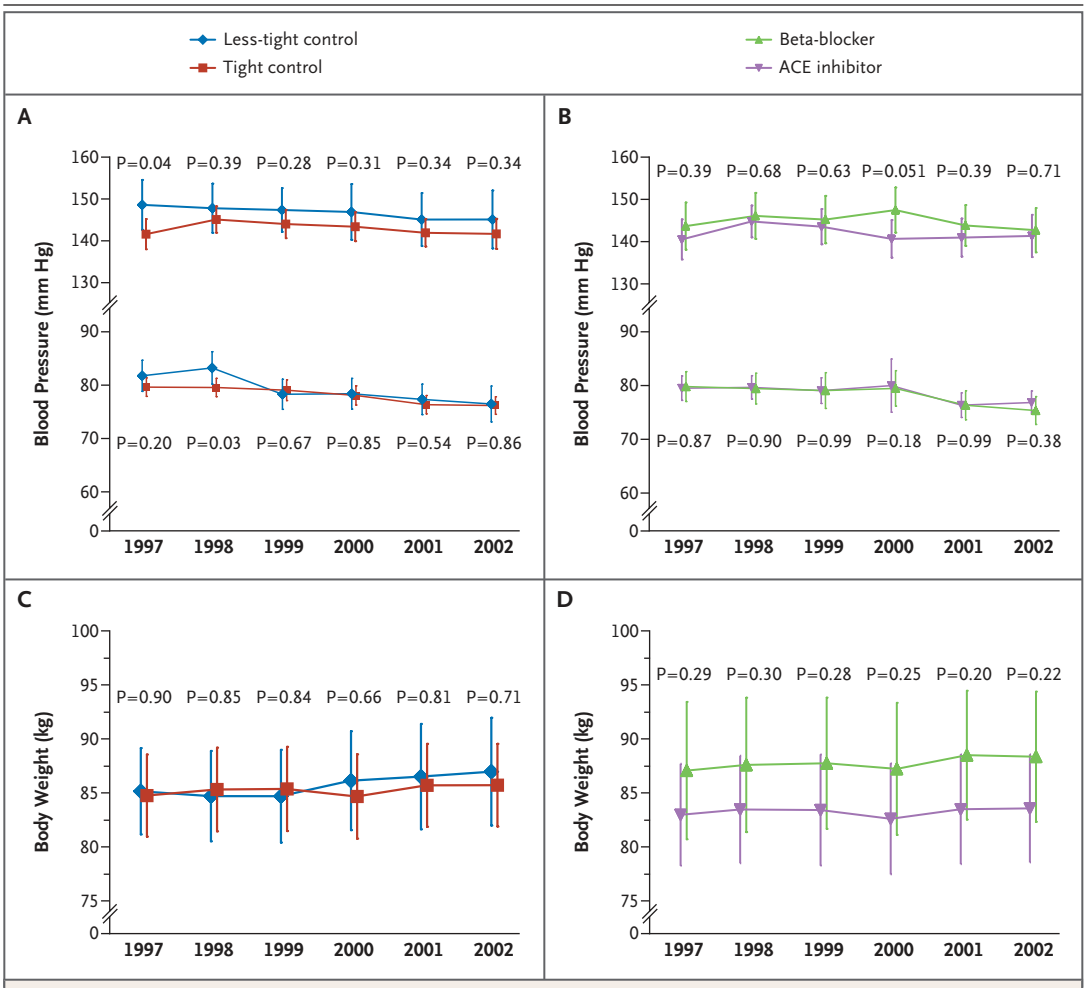


Figure 2. Mean Blood Pressures and Corresponding Body Weights, for Years 1 through 5 Only, of Patients Who Attended a UKPDS Clinic, According to Treatment Assignment.

The mean systolic (top) and diastolic (bottom) blood-pressure levels are shown for patients who were originally assigned to less-tight or tight blood-pressure control (Panel A) and, within the tight-control group, to an angiotensin-converting–enzyme (ACE) inhibitor or a beta-blocker (Panel B). Panels C and D show the corresponding body weights. P values are given for the comparison between each pair of data points for a given year. The vertical bars denote 95% confidence intervals. Clinic data were not available in years 6 through 10, when questionnaires were used. UKPDS denotes United Kingdom Prospective Diabetes Study.

ease (amputation of at least one digit or death from peripheral vascular disease), and microvascular disease (vitreous hemorrhage, retinal photocoagulation, or renal failure).

STATISTICAL ANALYSIS

Statistical analyses were performed on the basis of the intention-to-treat principle with the use of descriptive statistics presented as the number of patients (percentage) or appropriate measures of central tendency and dispersion. Continuous and categorical study variables were compared between tight and less-tight blood-pressure–control therapies by means of nonparametric tests. Kaplan–Meier time-to-event analyses were used for aggregate clinical end points, with log-rank tests used to test for differences between previous treatment assignments. Since recruitment was performed during a 4-year period, patients could have participated in the interventional trial for 6 to 10 years. Since there was no common time from randomization to the commencement of post-trial monitoring, we used serial hazard-ratio plots with confidence intervals, after checking that proportional-hazards assumptions were not violated, to estimate post-trial relative risks, with

P values calculated only at the end of the follow-up period. 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

CHARACTERISTICS OF THE PATIENTS

Baseline characteristics for the 884 patients undergoing post-trial monitoring among the 1148 patients randomly assigned to tight or less-tight blood-pressure control (Fig. 1), and for the 592 patients in the tight-control group who were randomly assigned to ACE-inhibitor or beta-blocker therapy, are shown in Table 1. As compared with patients who had been assigned to less-tight blood-pressure control, those who had been previously assigned to tight blood-pressure control during the study had a lower mean systolic blood pressure (by 9 mm Hg, P<0.001) and a lower diastolic blood pressure (by 3 mm Hg, P<0.001) but a higher median glycated hemoglobin value (by 0.8 percentage points, P=0.001). In the group undergoing tight blood-pressure control, 61% of patients were taking two or more antihypertensive agents, as compared with 36% in the group undergoing less-tight blood-pressure control. Overall, less than 2% of patients were taking lipid-lowering drugs. The two groups did not differ significantly with respect to age; sex; race or ethnic group; body weight; levels of fasting plasma glucose, lipids, or plasma creatinine; or the albumin-to-creatinine ratio (Table 1). Baseline characteristics for patients previously assigned to an ACE inhibitor or beta-blocker also did not differ significantly between the two groups, except that the beta-blocker group had a greater mean body weight, by 4 kg (P=0.01), a lower total cholesterol level, by 7 mg per deciliter (0.18 mmol per liter) (P=0.04), and a lower high-density lipoprotein (HDL) cholesterol level, by 3 mg per deciliter (0.08 mmol per liter) (P=0.009). No significant differences were found at baseline for any variable between patients with and those without available final-year data (Table 1), except that those with data were less often white (P<0.001).

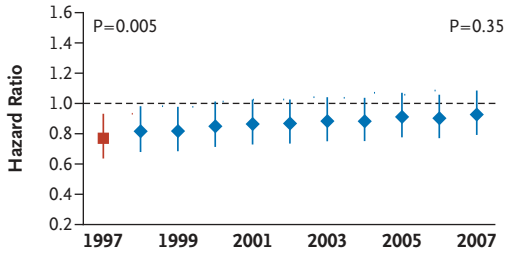
Figure 3 (facing page). Hazard Ratios for Prespecified UKPDS End Points at the End of the Trial (1997) and for Each Year of the 10-Year Post-Trial Monitoring Period, According to Treatment Assignments.

The hazard ratios are tight blood-pressure control as compared with less-tight control or for use of an angiotensin-converting–enzyme (ACE) inhibitor as compared with a beta-blocker for tight control. Hazard ratios below unity indicate a favorable outcome for tight control or ACE-inhibitor therapy. The red squares indicate data at the end of the trial[3]; the blue diamonds indicate data during the post-trial monitoring period. P values are for the end of the trial and the end of the post-trial monitoring period. Numbers of first aggregate end points accumulated in each treatment group are shown at 2-year intervals. The vertical bars denote 95% confidence intervals. UKPDS denotes United Kingdom Prospective Diabetes Study.

In years 1 through 5, the majority of patients (92 to 97%) attended a UKPDS clinic. The median duration of follow-up after randomization with regard to the comparison of the tight-control and the less-tight–control groups was 14.5 years (15,583 person-years), including a median of 8.0 years of post-trial monitoring. The median duration of follow-up after randomization with regard to the comparison of patients receiving an ACE inhibitor and those receiving a beta-blocker was 14.6 years (10,358 person-years), including a median of 7.6 years after the trial.

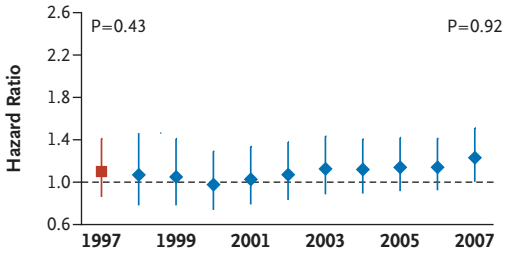
The mortality rate was 51%, with the leading causes of death being cardiovascular events (53%) and cancer (21%). The overall rate of loss to follow-up was 2%. Baseline differences between the less-tight–control group and the tight-control group in the number of antihypertensive agents taken were no longer evident by year 5 after the trial, with 73% and 75% of patients, respectively, taking two or more agents. By year 5, among all patients, 24% were receiving lipid-lowering therapy and 44% were receiving aspirin, with no significant differences between the two groups. Baseline differences between the groups in mean systolic and diastolic blood pressures were lost by year 1 and year 2, respectively (Fig. 2). There were no significant changes in body weight (Fig. 2). There were no significant differences in glycated hemoglobin, fasting plasma glucose, or

A Any Diabetes-Related End Point



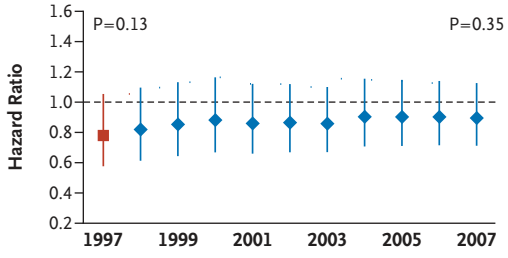
No. of Events						
Less-tight control	170	195	211	227	237	248
Tight control	259	323	371	410	441	466

B Any Diabetes-Related End Point



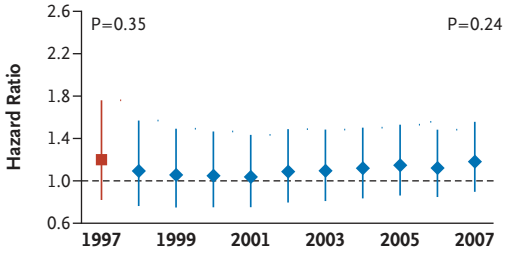
No. of Events						
ACE inhibitor	141	174	193	214	227	242
Beta-blocker	118	149	178	196	214	224

C Myocardial Infarction



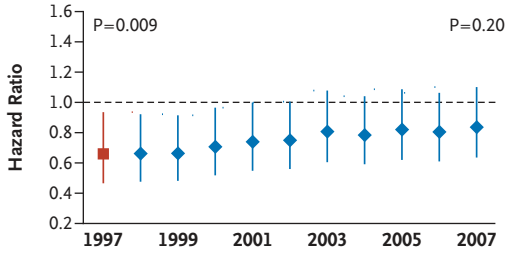
No. of Events						
Less-tight control	69	77	87	99	105	115
Tight control	107	130	148	169	189	205

D Myocardial Infarction



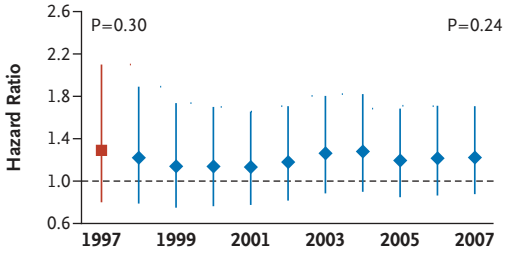
No. of Events						
ACE inhibitor	61	70	79	92	105	115
Beta-blocker	46	60	69	77	84	90

E Microvascular Disease



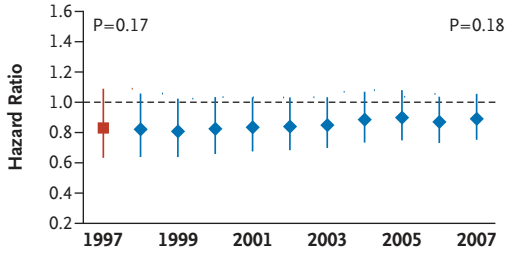
No. of Events						
Less-tight control	54	66	72	75	79	82
Tight control	68	88	108	124	133	141

F Microvascular Disease



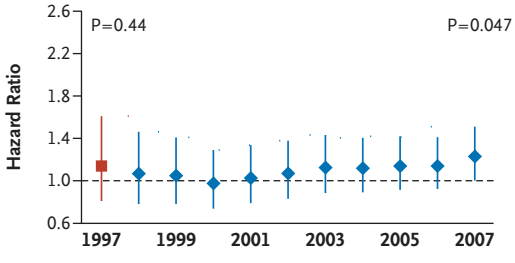
No. of Events						
ACE inhibitor	40	49	60	72	75	80
Beta-blocker	28	39	48	52	58	61

G Death from Any Cause



No. of Events						
Less-tight control	83	111	136	159	180	211
Tight control	134	177	224	267	322	373

H Death from Any Cause



No. of Events						
ACE inhibitor	75	95	119	147	177	213
Beta-blocker	59	82	105	120	145	160

plasma creatinine levels or albumin-to-creatinine ratio, at any time point, between the tight and less-tight–control groups, or between the ACE inhibitor and beta-blocker groups, with the exception of fasting plasma glucose at year 3 and glycated hemoglobin at year 4 (P=0.04 for both end points) (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

CLINICAL OUTCOMES

Among patients undergoing tight blood-pressure control as compared with those undergoing less-tight control, significant relative risk reductions seen during the trial — for any diabetes-related end point (relative risk reduction of 24%, P=0.005), diabetes-related death (32%, P=0.02), stroke (44%, P=0.01), and microvascular disease (37%, P=0.009) — were not sustained during the post-trial follow-up period. These differences diminished over time (Fig. 3), with risk reductions that were not significant at year 10 of 7% for any diabetes-related end point (P=0.31), 16% for diabetes-related death (P=0.12), 23% for stroke (P=0.12), and 16% for microvascular disease (P=0.17) (Table 2 and Fig. 4).

The nonsignificant relative risk reductions observed during the trial for myocardial infarction (21%, P=0.13) and death from any cause (18%, P=0.17) were also diminished during the follow-up period (Fig. 3). Risk reductions in the tight-control group as compared with the less-tight–control group 10 years after the trial ended were 10% for myocardial infarction (P=0.35) and 11% for death from any cause (P=0.18) (Table 2 and Fig. 4). Overall, few patients had peripheral vascular disease (8 in each group), with maintenance of the risk reduction seen during the trial (49%, P=0.17) (Fig. 4); however, the number of patients with this end point increased to 21 in each group during the post-trial monitoring period, and there was a significant risk reduction in the tight-control group at year 10 (50%, P=0.02) (Table 2 and Fig. 4). Between the patients receiving an ACE inhibitor or beta-blocker, no significant differences in aggregate end points were seen during the trial or during post-trial monitoring, apart from an emerging, nominally significant increase in the risk of death from any cause in the ACE-inhibitor group (P=0.047) (Table 2 and Fig. 3 and 4).

DISCUSSION

This 10-year follow-up study of the survivor cohort from the UKPDS blood-pressure–intervention trial shows that the benefits seen in patients assigned to a strategy of tight blood-pressure control[3] were not maintained once the differences in blood pressure seen during the trial itself were lost. Participating patients were a hypertensive cohort recruited from among people with newly diagnosed diabetes and have been followed for over 15,000 person-years since their randomization to tight or less-tight blood-pressure control. The lower blood-pressure levels attained early in the course of diabetes did not appear to confer a legacy effect, as seen with the more sustained benefits of earlier improved blood-glucose control.[5,9]

The UKPDS blood-pressure trial showed substantial reductions in the relative risk of any diabetes-related end point, diabetes-related death, stroke, and microvascular disease associated with a strategy of tight blood-pressure control, as compared with less-tight control, that maintained systolic pressure that was 10 mm Hg lower, and diastolic pressure that was 5 mm Hg lower, over a median of 8.4 years.[3,7] After the trial, blood-pressure levels fell in the less-tight–control group and rose in the tight-control group, with no significant between-group differences after 2 years. In line with this equalization of blood pressures, the risk reductions observed were substantially smaller by year 10 after the trial, and none remained significant. No significant risk reductions were seen, during or after the trial, for myocardial infarction or death from any cause. The risk-reduction point estimate of 49%, which was not significant (P=0.17), for the small number of patients with peripheral vascular disease during the trial[3] remained unchanged, but with the accumulation of additional events during the post-trial monitoring period, the risk reduction was significant at year 10 (50%, P=0.02). No significant differences were found during or after the trial in the comparison of ACE-inhibitor therapy and beta-blocker therapy with regard to any aggregate end point, apart from a nominally significant increase in the risk of death from any cause with ACE-inhibitor use at the end of the post-trial monitoring period.

Since the publication of the UKPDS blood-pressure results, other randomized, controlled

Table 2. UKPDS End Points among Patients Followed for Up to 20 Years, Including Up to 10 Years of Post-Trial Monitoring, According to Treatment Assignments.

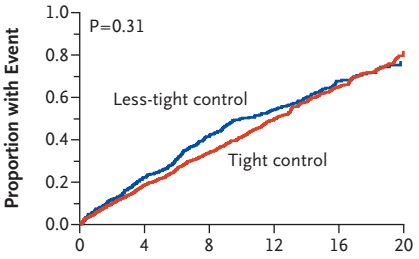
Aggregate End Point	No. of Patients with End Point		Absolute Risk of End Point		Log-Rank P Value	Relative Risk of End Point (95% CI)*
	Tight Control (N=758)	Less-Tight Control (N=390)	Tight Control	Less-Tight Control		
			no. of events/1000 patient-yr			
Tight control or less-tight control						
Any diabetes-related end point	466	248	62.1	67.2	0.31	0.93 (0.80–1.09)
Diabetes-related death	203	122	20.0	23.9	0.12	0.84 (0.67–1.05)
Death from any cause	373	211	36.0	40.4	0.18	0.89 (0.75–1.06)
Myocardial infarction	205	115	21.4	24.0	0.35	0.90 (0.71–1.13)
Stroke	90	58	9.2	12.0	0.12	0.77 (0.55–1.07)
Peripheral vascular disease	21	21	2.1	4.2	0.02	0.50 (0.28–0.92)
Microvascular disease	141	82	15.5	18.3	0.17	0.84 (0.64–1.10)
	ACE Inhibitor (N=400)	Beta-Blocker (N=358)	ACE Inhibitor	Beta-Blocker		
ACE inhibitor or beta-blocker						
Any diabetes-related end point	242	224	62.0	62.3	0.92	0.99 (0.83–1.19)
Diabetes-related death	112	91	21.1	18.7	0.34	1.14 (0.87–1.51)
Death from any cause	213	180	39.4	32.3	0.047	1.23 (1.00–1.51)
Myocardial infarction	115	90	23.0	19.7	0.24	1.18 (0.90–1.56)
Stroke	45	45	8.9	9.6	0.75	0.93 (0.62–1.41)
Peripheral vascular disease	13	8	2.5	1.7	0.33	1.55 (0.64–3.74)
Microvascular disease	80	61	17.0	13.9	0.24	1.22 (0.88–1.71)

* The relative risk is given for the tight-control group as compared with the less-tight–control group and for the angiotensin-converting–enzyme (ACE) inhibitor group as compared with the beta-blocker group.

trials have confirmed the importance of treating hypertension in patients with type 2 diabetes[10-14] and have examined blood-pressure targets lower than the UKPDS target of 150/85 mm Hg.[3] None of those subsequent studies have reported post-trial follow-up data, so the longevity of benefits observed during the trial is unknown, and we are unaware of any other blood-pressure trials that have specifically examined post-trial legacy effects. A 10-year post-trial follow-up of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS),[15] which evaluated the usefulness of enalapril for severe heart failure rather than for hypertension (and which was discontinued after 6 months), showed a significant improvement in survival for patients previously assigned to enalapril (P=0.008).[16] The Steno-2 Study, in which patients with type 2 diabetes were randomly assigned, in a nonfactorial manner, to conventional or intensive multiple risk factor interventions, showed additive benefits of improved glycemic control, the use of aspirin, and antihypertensive and lipid-lowering therapies after a median of 7.8 years.[17] Post-trial follow-up for a median of 5.5 years showed continued benefits in the intensive-therapy group as compared with the conventional group, with an overall 20% absolute reduction in the risk of death from any cause (P=0.02).[4] However, these sustained risk reductions cannot simply be regarded as a legacy effect, since favorable differences in systolic blood pressure (a difference of 6 mm Hg), low-density lipoprotein and HDL cholesterol levels, and blood glucose levels persisted beyond the trial period.[4]

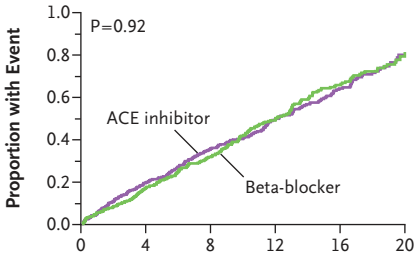
Hypertension is a major risk factor for cardiovascular disease in patients with type 2 diabetes,[18,19] conferring an age-adjusted 82% increase in the risk of diabetes-related death.[20] Hypertension is more common among those with diabetes than in the general population, as re-

A Any Diabetes-Related End Point



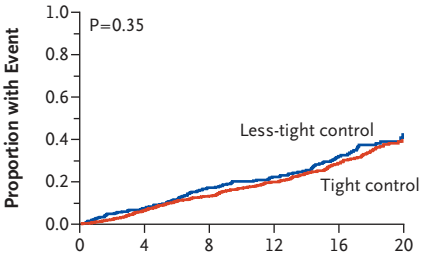
No. at Risk						
Less-tight control	390	296	214	138	68	11
Tight control	758	601	458	296	133	19

B Any Diabetes-Related End Point



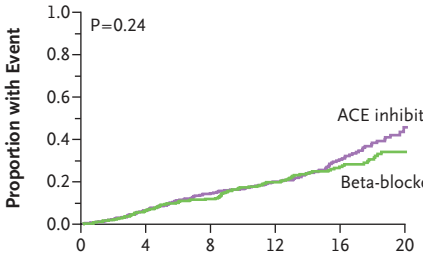
No. at Risk						
ACE inhibitor	400	310	233	155	70	9
Beta-blocker	358	291	225	141	63	10

C Myocardial Infarction



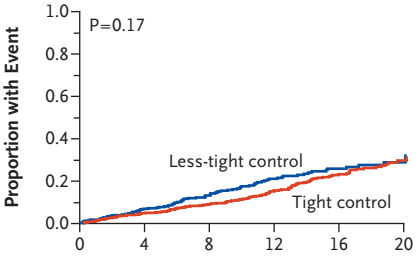
No. at Risk						
Less-tight control	390	345	288	214	131	26
Tight control	758	677	584	448	263	46

D Myocardial Infarction



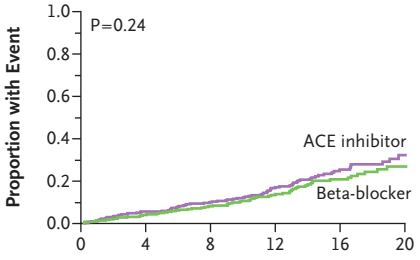
No. at Risk						
ACE inhibitor	400	355	301	237	134	23
Beta-blocker	358	322	283	211	129	23

E Microvascular Disease



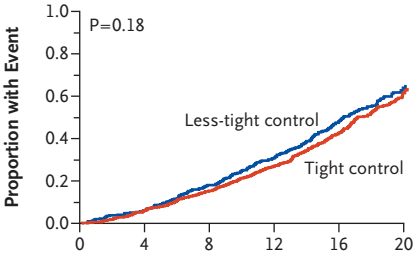
No. at Risk						
Less-tight control	390	333	272	185	104	21
Tight control	758	666	562	409	216	45

F Microvascular Disease



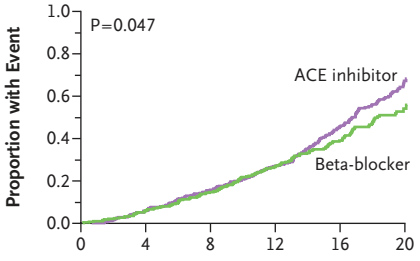
No. at Risk						
ACE inhibitor	400	346	287	212	106	24
Beta-blocker	358	320	275	197	110	21

G Death from Any Cause



No. at Risk						
Less-tight control	390	363	314	252	158	29
Tight control	758	709	631	504	313	61

H Death from Any Cause



No. at Risk						
ACE inhibitor	400	373	328	262	159	32
Beta-blocker	358	336	303	242	154	29

Figure 4 (facing page). Kaplan–Meier Cumulative-Incidence Plots and Log-Rank P Values for Prespecified UKPDS End Points during the 20-Year Period of the Trial and the Post-Trial Monitoring Period, According to Treatment Assignments.

UKPDS denotes United Kingdom Prospective Diabetes Study.

ported in the Multiple Risk Factor Intervention Trial (MRFIT), which showed that the absolute risk of death from cardiovascular causes among men with diabetes was three times that among men without diabetes.[21] The UKPDS blood-pressure trial was initiated in 1987 in recognition of the probable need to control both glycemia and blood pressure.[22] The trial showed not only the benefits of improved blood-pressure control associated with a stepwise addition of blood-pressure–lowering therapies in a treat-to-target approach but also the necessity of increasing the intensity of these therapies over time.[3,23] A more recent combined analysis of the blood-glucose and blood-pressure data from the UKPDS has confirmed the additive effects of blood glucose and blood pressure over time on the risk of complications in patients with type 2 diabetes and has shown that those assigned to strategies of both intensive glucose control and tight blood-pressure control had fewer events than those assigned to either strategy alone or to neither one.[24]

It is not surprising that the beneficial effects seen in study populations randomly assigned to blood-pressure–lowering therapies are lost once the blood-pressure differences are lost. Most trials involving lowering of blood pressure, such as the 4.5-year Systolic Hypertension in the Elderly Program (SHEP) trial demonstrating a significant reduction in the risk of stroke,[25] show an early separation of the cumulative risk of macrovascular end points between study groups. It might be expected that the relatively rapid "on-effects" of improved blood-pressure lowering on cardiovascular risk would be reflected in similarly rapid "off-effects" if blood-pressure control were to be relaxed. Alternatively, post-trial improvements in blood-pressure therapy in groups treated less aggressively during the trial would be likely to bring their cardiovascular risks into line with those treated more aggressively during the trial. In either case, no long-term differences in cardiovascular risk would be seen, as was found in our trial. This is in direct contrast to the legacy effects of earlier intensive glucose control seen in patients with type 2 or type 1 diabetes during follow-up studies of the UKPDS[5] and the Epidemiology of Diabetes Interventions and Complications (EDIC) study,[9] respectively, both of which showed extended and improved treatment benefits despite early post-trial loss of between-group glycemic differences.

Our study has certain important limitations. Questionnaires may not have captured all nonfatal end points. Biochemical and clinical measurements were not collected in years 6 to 10, although by year 3 after the trial, it was already evident that blood-pressure differences had been lost. The glucose and blood-pressure data from the trial were analyzed separately, given the factorial design, but there may have been some post-trial confounding, since at baseline the glycated hemoglobin levels were higher in patients previously assigned to tight blood-pressure control than in those assigned to less-tight control, presumably because of greater beta-blocker use and possibly the use of thiazide diuretics. The lack of detailed information on risk factors in years 6 through 10 also precludes the use of proportional-hazards analyses to assess effects of other time-dependent covariates such as microalbuminuria.

In conclusion, these 10-year post-trial follow-up data from the UKPDS indicate that the relative risk reductions seen in the tight blood-pressure–control group did not persist when blood-pressure differences were no longer maintained. Optimal blood-pressure control is of major importance in reducing the risks of microvascular and macrovascular disease in patients with type 2 diabetes but must be maintained if these benefits are to be sustained.

Supported for the first 5 years of post-trial monitoring by the U.K. Medical Research Council, U.K. Department of Health, Diabetes UK, the British Heart Foundation, and the National Institutes of Health and for the final 5 years by Bristol-Myers Squibb, GlaxoSmithKline, Merck Serono, Novartis, Novo Nordisk, and Pfizer. The original UKDPS interventional trial was supported by the U.K. Medical Research Council, British Diabetic Association, U.K. Department of Health, U.S. National Eye Institute, U.S. National Institute of Diabetes and Digestive and Kidney Diseases, British Heart Foundation, Wellcome Trust, Charles Wolfson Charitable Trust, Clothworkers' Foundation, Health Promotion Research Trust, Alan and Babette Sainsbury Trust, Oxford University Medical Research Fund Committee, Novo Nordisk, Bayer, Bristol-Myers Squibb, Hoechst, Lilly, Lipha, and Farmitalia Carlo Erba, with consumables or logistical support from Boehringer Mannheim, Becton Dickinson, Owen Mumford, Securicor, Kodak, Cortecs Diagnostics, Glaxo Wellcome, SmithKline Beecham, Pfizer, Zeneca, Pharmacia, Upjohn, and Roche.

Dr. Holman reports receiving grant support from Asahi Kasei Pharma, Bayer Healthcare, Bayer Schering Pharma, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Merck Serono, Novartis, Novo Nordisk, Pfizer, and Sanofi-Aventis, consulting fees from Amylin, Eli Lilly, GlaxoSmithKline, Merck, and Novartis, and lecture fees from Astella, Bayer, GlaxoSmithKline, King Pharmaceuticals, Eli Lilly, Merck, Merck Serono, Novo Nordisk, Takeda, and Sanofi-Aventis, and owning shares in Glyme Valley Technology, Glyox, and Oxtech; Dr. Paul, receiving consulting fees from Amylin; Dr. Bethel, receiving grant support from Novartis and Sanofi-Aventis and lecture fees from Merck and Sanofi-Aventis; Dr. Neil, receiving consulting fees from Merck, Pfizer, Schering-Plough, and Solvay Healthcare; and Dr. Matthews, receiving lecture and advisory fees from Novo Nordisk, GlaxoSmithKline, Servier, Merck, Novartis, Novo Nordisk, Eli Lilly, Takeda, and Roche, and owning shares in OSI Pharmaceuticals and Particle Therapeutics. The Oxford Centre for Diabetes, Endocrinology, and Metabolism (OCDEM) has a Partnership for the Foundation of OCDEM, with Novo Nordisk, Takeda, and Servier. No other potential conflict of interest relevant to this article was reported.

We thank the patients and staff at the participating centers: Radcliffe Infirmary, Oxford; Royal Infirmary, Aberdeen; Selly Oak Hospital, Birmingham; St. George's Hospital and Hammersmith Hospital, London; City Hospital, Belfast; North Staffordshire City General Hospital, Stoke-on-Trent; Royal Victoria Hospital, Belfast; St. Helier Hospital, Carshalton; Whittington Hospital, London; Norfolk and Norwich Hospital, Norwich; Lister Hospital, Stevenage; Ipswich Hospital, Ipswich; Ninewells Hospital, Dundee; Northampton Hospital, Northampton; Torbay Hospital, Torquay; Peterborough District Hospital, Peterborough; Scarborough Hospital, Scarborough; Derbyshire Royal Infirmary, Derby; Manchester Royal Infirmary, Manchester; Hope Hospital, Salford; Leicester General Hospital, Leicester; and Royal Devon and Exeter Hospital, Exeter — all in the United Kingdom; the Northern Ireland General Register Office for provision of vital-status data; and John McMurray for helpful advice. We acknowledge the major contribution of the late Carole Cull and the efforts of members of the Endpoint Adjudication Committee (Charles Fox and Alex Wright).

REFERENCES

1. 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.]
2. UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. Diabetologia 1991;34:877-90.
3. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703-13. [Erratum, BMJ 1999;318:29.]
4. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580-91.
5. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.
6. UK Prospective Diabetes Study (UKPDS). XI. Biochemical risk factors in type 2 diabetic patients at diagnosis compared with age-matched normal subjects. Diabet Med 1994;11:534-44.
7. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 1998;317:713-20.
8. The EuroQol Group. EuroQol — a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.
9. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;22:2643-53.
10. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non–insulin-dependent diabetes and hypertension. N Engl J Med 1998;338:645-52.
11. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999;353:611-6.
12. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial in patients with hypertension and NIDDM. Diabetes Care 1998;21:597-603.
13. Pahor M, Psaty BM, Alderman MH, Applegate WB, Williamson JD, Furberg CD. Therapeutic benefits of ACE inhibitors and other antihypertensive drugs in patients with type 2 diabetes. Diabetes Care 2000;23:888-92.
14. Patel A, MacMahon S, Chalmers J, 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.
15. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429-35.
16. Swedberg K, Kjekshus J, Snapinn S. Long-term survival in severe heart failure in patients treated with enalapril: ten year follow-up of CONSENSUS I. Eur Heart J 1999;20:136-9.
17. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383-93.
18. Hypertension in Diabetes Study (HDS). I. Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. J Hypertens 1993;11:309-17.
19. Turner RC, Milns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ 1998;316:823-8.
20. Hypertension in Diabetes Study (HDS). II. Increased risk of cardiovascular complications in hypertensive type 2 diabetic patients. J Hypertens 1993;11:319-25.
21. Stamler J, Vaccaro O, Neaton J, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16:434-44.
22. Hypertension in Diabetes Study. III. Prospective study of therapy of hypertension in type 2 diabetic patients: efficacy of ACE inhibitor and beta-blockade. Diabet Med 1994;11:773-82.
23. Hypertension in Diabetes Study. IV. Therapeutic requirements to maintain tight blood pressure control. Diabetologia 1996;39:1554-61.
24. Stratton IM, Cull CA, Adler AI, Matthews DR, Neil HAW, Holman RR. Additive effects of glycaemia and blood pressure exposure on risk of complications in type 2 diabetes: a prospective observational study (UKPDS 75). Diabetologia 2006;49:1761-9.
25. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255-64.