ORIGINAL ARTICLE

Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes

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ABSTRACT

BACKGROUND

Intensified multifactorial intervention — with tight glucose regulation and the use of renin–angiotensin system blockers, aspirin, and lipid-lowering agents — has been shown to reduce the risk of nonfatal cardiovascular disease among patients with type 2 diabetes mellitus and microalbuminuria. We evaluated whether this approach would have an effect on the rates of death from any cause and from cardiovascular causes.

METHODS

In the Steno-2 Study, we randomly assigned 160 patients with type 2 diabetes and persistent microalbuminuria to receive either intensive therapy or conventional therapy; the mean treatment period was 7.8 years. Patients were subsequently followed observationally for a mean of 5.5 years, until December 31, 2006. The primary end point at 13.3 years of follow-up was the time to death from any cause.

RESULTS

Twenty-four patients in the intensive-therapy group died, as compared with 40 in the conventional-therapy group (hazard ratio, 0.54; 95% confidence interval [CI], 0.32 to 0.89; P=0.02). Intensive therapy was associated with a lower risk of death from cardiovascular causes (hazard ratio, 0.43; 95% CI, 0.19 to 0.94; P=0.04) and of cardiovascular events (hazard ratio, 0.41; 95% CI, 0.25 to 0.67; P<0.001). One patient in the intensive-therapy group had progression to end-stage renal disease, as compared with six patients in the conventional-therapy group (P=0.04). Fewer patients in the intensive-therapy group required retinal photocoagulation (relative risk, 0.45; 95% CI, 0.23 to 0.86; P=0.02). Few major side effects were reported.

CONCLUSIONS

In at-risk patients with type 2 diabetes, intensive intervention with multiple drug combinations and behavior modification had sustained beneficial effects with respect to vascular complications and on rates of death from any cause and from cardiovascular causes. (ClinicalTrials.gov number, NCT00320008.)

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Type 2 diabetes mellitus is associated with a high rate of complications related to cardiovascular disease and diabetic nephropathy, retinopathy, and neuropathy.[1-3] The rate of death among patients with type 2 diabetes is approximately twice as high as that among persons without the disorder.[2,3] However, trials of interventions for single risk factors have shown efficacy in reducing the development and progression of complications.[4-9] Furthermore, the risk of vascular complications was reduced by about half in the Steno-2 Study, our previous prospective, randomized, open-label, blinded trial, during an average of 7.8 years of intensified multitarget intervention aimed at concomitant risk factors.[10] The study encompassed treatment goals similar to those recommended in the current guidelines of the American Diabetes Association.[11]

Although the number of deaths was lower in the intensive-therapy group in the Steno-2 Study, the relatively small number of patients who reached that end point precluded a determination of whether this approach affected mortality. Therefore, this follow-up to the Steno-2 Study was designed to address the question of mortality, as well as whether the risk reductions already achieved for both macrovascular and microvascular diseases were maintained during follow-up in a community setting. In the follow-up study, patients were observed for a mean of 5.5 years after the initial trial had ended.

METHODS

STUDY DESIGN

Detailed information about the Steno-2 Study has been reported previously.[10,12] Briefly, in 1993, a total of 160 white Danish patients with type 2 diabetes (defined according to the criteria of the World Health Organization) and persistent microalbuminuria were randomly assigned to receive either conventional multifactorial treatment, consistent with the guidelines of the Danish Medical Association,[13] or intensified, target-driven therapy involving a combination of medications and focused behavior modification. The intensive-therapy group had defined targets consistent with the latest guidelines of the American Diabetes Association. These targets included a glycated hemoglobin level of less than 6.5%, a fasting serum total cholesterol level of less than 175 mg per deciliter (4.5 mmol per liter), a fasting serum triglyceride level of less than 150 mg per deciliter (1.7 mmol per liter), a systolic blood pressure of less than 130 mm Hg, and a diastolic blood pressure of less than 80 mm Hg. Patients were treated with blockers of the renin–angiotensin system because of their microalbuminuria, regardless of blood pressure, and received low-dose aspirin as primary prevention.[10,12] The numbers of patients who underwent randomization, were assigned to receive treatment, and completed the study and follow-up are shown in Figure 1.

STUDY POPULATION

Of the 160 patients who were enrolled in the Steno-2 Study, 27 died and 3 (including 1 patient in the intensive-therapy group) withdrew before the end-of-trial examinations in 2001. All 130 remaining patients provided written informed consent to continue participation in the observational follow-up study after the intervention study ended. The protocol for the follow-up study was in accordance with the provisions of the Declaration of Helsinki and was approved by the ethics committee of Copenhagen County, Denmark.

When the Steno-2 Study was completed, the structured treatment of patients in the intensive-therapy group stopped. However, all participating patients in both study groups were informed in detail about the benefits of intensified multifactorial treatment, and the diabetes specialists to whom the patients were referred were educated about the new national recommendations for intensified multitarget treatment on the basis of the results of the Steno-2 Study. This education took place both at regional and at national levels.[14,15] This report includes follow-up data obtained from September 1, 2006, to December 31, 2006. At follow-up examination, 84% of patients in the intensive-therapy group and 87% of those in the conventional-therapy group were still being treated at diabetes clinics.

PROCEDURES, MEASUREMENTS, AND END POINTS

End-point examinations were performed for both macrovascular and microvascular complications, and data regarding biochemical and clinical status were obtained in both study groups. The measurements were obtained by a single laboratory technician who was not aware of the original study-group assignments.

The primary end point in the follow-up trial was the time to death from any cause. It is man-

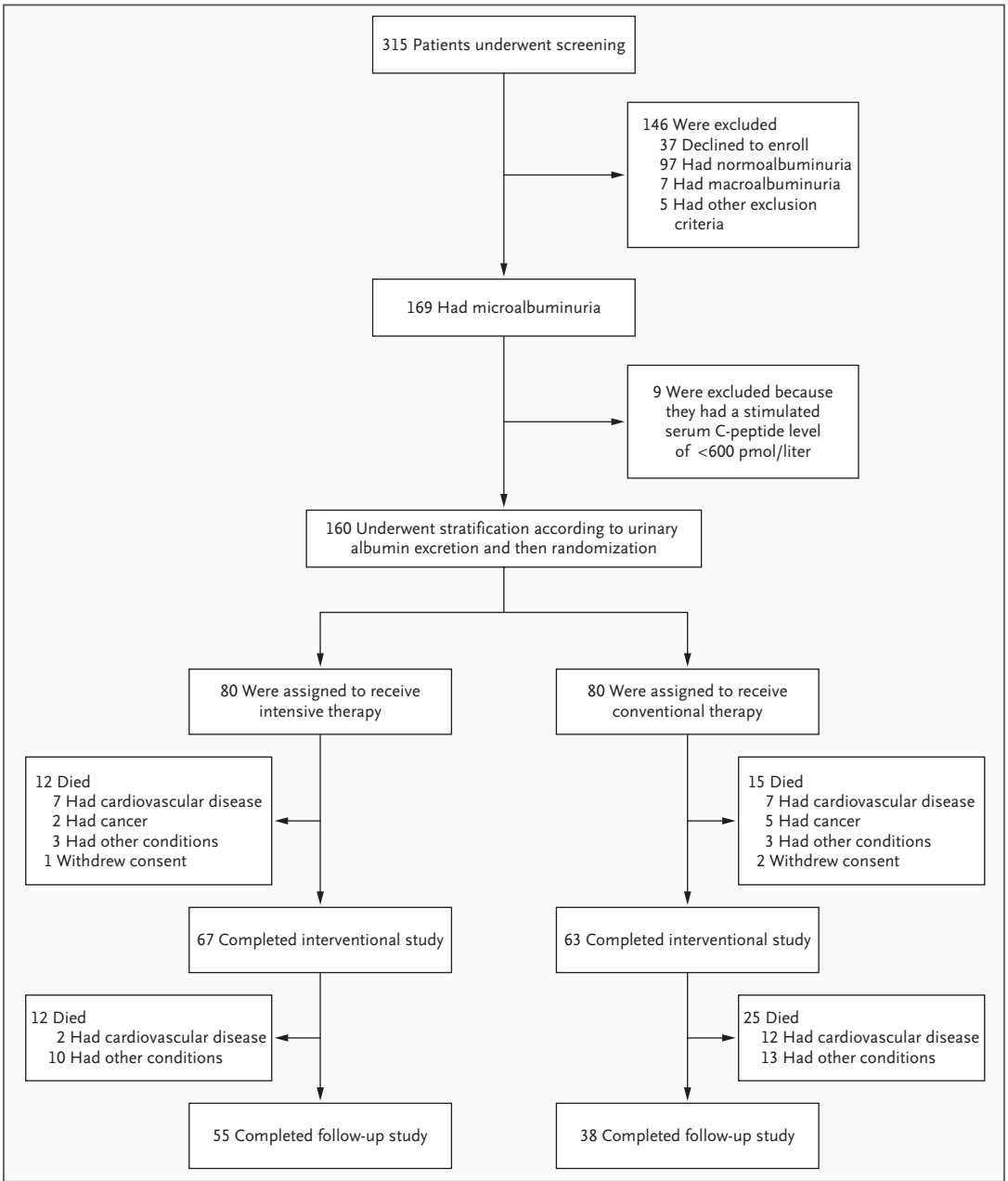


Figure 1. Enrollment and Outcomes.

Three patients withdrew during follow-up because they moved to other regions: one patient in the intensive-therapy group withdrew after 3.2 years, and two patients in the conventional-therapy group withdrew after 0.4 and 4.7 years. No other patients were lost to follow-up.

datory by law for a physician to complete a death certificate for any death occurring in Denmark; the data are coded and retained in the computerized Danish Death Registry.[16]

The secondary end points were death from cardiovascular causes and a composite of cardiovascular disease events that included death from cardiovascular causes, nonfatal stroke, nonfatal myocardial infarction, coronary-artery bypass grafting, percutaneous coronary intervention or revascularization for peripheral atherosclerotic arterial disease, and amputation because of ische-

mia.[17] An independent committee whose members were unaware of study-group assignments from the intervention portion of the Steno-2 Study adjudicated the specified end points.

The tertiary end points were incident diabetic nephropathy or the development or progression of diabetic retinopathy or neuropathy.[12] Diabetic nephropathy was defined as a urinary albumin excretion rate of more than 300 mg per 24 hours in two of three consecutive sterile urine specimens measured at baseline; after 1.9, 3.8, and 7.8 years; and at the end of the follow-up period.

Diabetic retinopathy was graded according to the six-level grading scale of the European Community-funded Concerted Action Programme into the Epidemiology and Prevention of Diabetes (EURODIAB) by two independent eye specialists who were unaware of the patients' study-group assignments (see the table in the Supplementary Appendix, available with the full text of this article at www.nejm.org).[18] Progression of retinopathy was defined as an increase of at least one level in the EURODIAB grading scale in either eye, as reported previously.[12] The need for laser treatment of either proliferative retinopathy or macular edema was evaluated by ophthalmologists at the eye clinic of the Steno Diabetes Center, who were unaware of study-group assignments. Blindness was defined according to the criteria of the World Health Organization as a maximally corrected visual acuity of less than 6/60 in either eye (less than 20/200 on the Snellen visual-acuity scale).

Peripheral neuropathy was measured with a biothesiometer. The diagnosis of autonomic neuropathy was based on a measurement of the RR interval on an electrocardiogram obtained during paced breathing and on an orthostatic-hypotension test, with progression defined as reported previously.[12]

STATISTICAL ANALYSIS

The protocol for the follow-up trial specified that no analyses of death from any cause would be performed until at least 60 patients had died, as verified by online death registration, and until at least half the patients in either the intensive-therapy group or the conventional-therapy group had died. It was estimated that this plan for analyzing death from any cause would provide a statistical power of 0.75 and a type I error rate of 0.05 in detecting a reduction in the relative risk of death of 40% in the intensive-therapy group. Continuous reporting from the Danish Death Registry to the Steno Diabetes Center confirmed that this milestone was reached in June 2006.

All end points were analyzed according to the intention-to-treat principle. For the primary and secondary end points, event curves for the time to the first event were based on Kaplan–Meier analysis, and treatments were compared by means of the log-rank test. The hazard ratio for the comparison of intensive with conventional therapy and 95% confidence intervals were estimated with the use of a proportional-hazards model. We determined whether the hazard ratio at the end of the formal intervention subsequently changed. If so, the time since randomization was used as the time scale in an adjusted model.[19] Data regarding tertiary end points were censored according to prespecified intervals and analyzed with the use of a proportional-hazards model, with adjustment for age, duration of diabetes, sex, and microvascular status at baseline; these results are expressed as relative risks. Changes in measured variables within groups were compared by means of analysis of covariance, with baseline values as covariates. The Mann–Whitney test was used for any instances of non-Gaussian distribution. A chi-square test was performed to compare categorical variables. All reported P values are two-sided.

RESULTS

PATIENTS

Behavioral, clinical, and biochemical characteristics of the patients at baseline, at the end of the trial (at 7.8 years), and at the end of the follow-up period (at 13.3 years) are shown in Table 1. The two study groups were similar at baseline but differed significantly at the end of the intervention period, indicating that intensive therapy was superior to conventional therapy in controlling the level of glycated hemoglobin; fasting serum levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides; systolic and diastolic blood pressures; and rate of urinary albumin excretion (Table 1). At the end of the follow-up period, the differences in risk factors between the groups had narrowed, primarily because of intensified treatment among patients in the original conventional-therapy group (Fig. 1A). In contrast, risk factors in the intensive-therapy group remained the same as they had been during the original trial, except for systolic blood pressure, which increased

Table 1. Clinical, Demographic, Biochemical, and Other Characteristics of the Patients.*

Characteristic or Variable	At Baseline		At End of Intervention Study		At End of Follow-up	
	Intensive Therapy (N=80)	Conventional Therapy (N=80)	Intensive Therapy (N=67)	Conventional Therapy (N=63)	Intensive Therapy (N=55)	Conventional Therapy (N=38)
Clinical and demographic						
Age (yr)	54.9±7.2	55.2±7.2	62.1±7.2	63.1±6.8	66.0±7.0	66.1±6.8
Duration of follow-up (yr)	NA	NA	7.8±0.4	7.8±0.3	13.3±0.4	13.3±0.4
Body-mass index						
Men	29.3±3.6	30.3±5.3	30.0±4.3	30.8±5.6	31.1±4.6	30.2±5.7
Women	31.1±4.5	28.9±3.8	33.8±6.8	30.0±4.4	34.7±7.0	33.4±4.3
Waist circumference (cm)						
Men	105±10	107±14	108±10	112±14	112±11	110±17
Women	100±14	101±13	108±14	107±11	112±13.7	115±10.5
Blood pressure (mm Hg)						
Systolic	146±11	149±19	131±13	146±18†	140±14	146±18
Diastolic	85±10	86±11	73±11	78±10†	74±8	73±7
Current smoker (%)	40	35	31	27	22	18
Daily dietary intake						
Median (kcal)	2257	2137	2213	2111	2148	1944
Range (kcal)	1390–3764	1350–6062	1314–3563	1346–3277	1285–3686	1426–2587
Composition of intake (%)						
Protein	15.4±2.5	15.6±2.0	17.0±2.5	16.9±2.3	17.2±1.8	18.1±1.7
Carbohydrates	37.2±6.3	38.6±6.1	46.4±6.5	43.7±6.7†	45.8±5.2	43.9±5.0†
Alcohol	6.3±9.2	4.0±6.6	5.9±7.5	4.4±7.0	3.8±5.7	3.6±5.7
Fat	41.1±6.4	41.8±6.5	30.6±5.1	35.0±7.0†	32.6±4.7	34.3±5.3‡
Saturated fatty acids	17.5±3.4	17.4±4.0	10.6±3.1	12.7±3.7†	12.1±3.4	12.8±3.3
Exercise duration (min/wk)						
Median	120	105	144	90	120	60
Range	0–725	0–900	0–930	0–630	0–1050	0–645
Biochemical						
Fasting plasma glucose (mg/dl)	182±56	189±54	129±45	178±71†	160±55	170±61
Glycated hemoglobin (%)	8.4±1.6	8.8±1.7	7.9±1.2	9.0±1.8†	7.7±1.2	8.0±1.4
Fasting serum C peptide (pmol/liter)						
Median	846	863	676	751	704	630
Range	294–1655	300–1686	117–2524	59–3650	80–3030	183–3495
Stimulated serum C peptide (pmol/liter)						
Median	1438	1514	1140	1090	1310	912
Range	680–3315	644–3170	141–3930	84–5418	217–3560	291–4270
Fasting serum cholesterol (mg/dl)						
Total	210±41	233±50	159±34	216±50†	147±34	155±32
Low-density lipoprotein	133±36	137±37	83±30	126±36†	71±29	77±28
High-density lipoprotein	40±9	39±11	47±16	45±12	51±15	47±15

Table 1. (Continued.)

Characteristic or Variable	At Baseline		At End of Intervention Study		At End of Follow-up	
	Intensive Therapy (N=80)	Conventional Therapy (N=80)	Intensive Therapy (N=67)	Conventional Therapy (N=63)	Intensive Therapy (N=55)	Conventional Therapy (N=38)
Fasting serum triglycerides (mg/dl)						
Median	159	205	115	159‡	99	148
Range	48–624	56–1393	35–514	69–1931	29–1148	35–318
Urinary albumin excretion (mg/24 hr)						
Median	78	69	46	126†	69	75
Range	32–265	32–286	4–5593	3–4778	5–2838	7–5363
Urinary sodium excretion (mmol per 24 hr)						
Median	185	211	170	198	169	201
Range	25–513	46–577	32–525	53–436	23–524	68–344
Serum creatinine (μmol/liter)	78±17	76±16	102±32	111±85	100±53	105±45
Drug therapy						
No glucose-lowering drugs (%)	35	26	1	6	4	5
Metformin (%)	13	19	50	34	66	37†
Sulfonylurea (%)	53	56	50	47	40	16‡
Glitazone (%)	0	0	0	0	0	3
Any oral hypoglycemic agent (%)	59	61	74	61	84	47†
Insulin (%)	6	14	57	54	73	82
Insulin plus an oral hypoglycemic agent (%)	0	1	32	21	83	42†
Insulin dose (IU per day)						
Median	42	30	62	64	60	68
Range	10–52	14–142	12–260	12–360	16–220	30–154
ACE inhibitor or ARB (%)	20	19	97	70	91	87
Both ACE inhibitor and ARB (%)	0	0	28	0†	18	5
Diuretic (%)	21	28	58	60	82	84
Calcium antagonist (%)	14	6	36	29	42	42
Beta-blocker (%)	10	1	19	16	15	32‡
Other antihypertensive drug (%)	1	1	4	6	5	8
Any antihypertensive drug (%)	41	41	99	83†	93	100
Statin (%)	0	3	85	22†	84	82
Fibrate (%)	1	1	1	5	2	0
Aspirin (%)	14	13	87	56†	85	76

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. Stimulated serum C peptide was measured 6 minutes after intravenous injection of 1 mg of glucagon in the fasting state. 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 milligrams per deciliter, divide by 88.4. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and NA not applicable.

† P<0.01 by analysis of covariance or the Mann–Whitney test (when appropriate) for the comparison of changes between study groups.

‡ P<0.05 by analysis of covariance or the Mann–Whitney test (when appropriate) for the comparison of changes between study groups.

(P=0.001) (Fig. 2A). Time curves for risk factors showed a similar pattern for the 93 patients who were followed during the entire 13.3-year period (data not shown). No significant differences were observed between the two groups with respect to habits related to exercise and smoking, and only minor (although significant) changes were seen in the intake of carbohydrates and fat. There were also no significant differences in body weight or waist circumference (Table 1).

During the entire 13.3 years of follow-up, 24 patients (30%) in the intensive-therapy group died, as compared with 40 patients (50%) in the conventional-therapy group, which corresponded to an absolute risk reduction of 20% (P=0.02 by the log-rank test) (Fig. 3A). The hazard ratio for death in the intensive-therapy group, as compared with the conventional-therapy group, was 0.54 (95% confidence interval [CI], 0.32 to 0.89; P=0.02). There was no evidence of a change in the hazard ratio after the formal intervention was stopped (P=0.27). Deaths from cancer were as expected on the basis of data from the Danish Cancer Registry and did not differ significantly between the two study groups (two deaths in the intensive-therapy group and five in the conventional-therapy group).

Nine patients in the intensive-therapy group died from cardiovascular causes, as compared with 19 in the conventional-therapy group (P=0.03 by the log-rank test) (Table 2). The hazard ratio for death from cardiovascular causes in the intensive-therapy group was 0.43 (95% CI, 0.19 to 0.94; P=0.04). The hazard ratio for death from cardiovascular disease tended to decrease in the intensive-therapy group after the end of the original trial, but the difference between the groups did not reach significance (P=0.06). However, because of the borderline significance, we also analyzed the data according to an adjusted model that included time since randomization as the time scale. The derived results (hazard ratio, 0.43; 95% CI, 0.19 to 0.95; P=0.04) were similar to those derived from the unadjusted model.

A total of 209 cardiovascular events occurred during the 13.3 years of observation (Table 2 and Fig. 3B). In the intensive-therapy group, the absolute risk reduction was 29%, with a hazard ratio of 0.41 (95% CI, 0.25 to 0.67; P<0.001). There was no evidence of a change in the hazard ratio after the formal intervention study ended (P=0.20). There were 51 events in 25 patients in the intensive-therapy group and 158 events in 48 patients in the conventional-therapy group (Table 2 and Fig. 3C). The mean number of major cardiovascular events was 0.6 in the intensive-therapy group and 2.0 in the conventional-therapy group. The average number of recurrent events among patients with cardiovascular events was 2.0 in the intensive-therapy group and 3.3 in the conventional-therapy group.

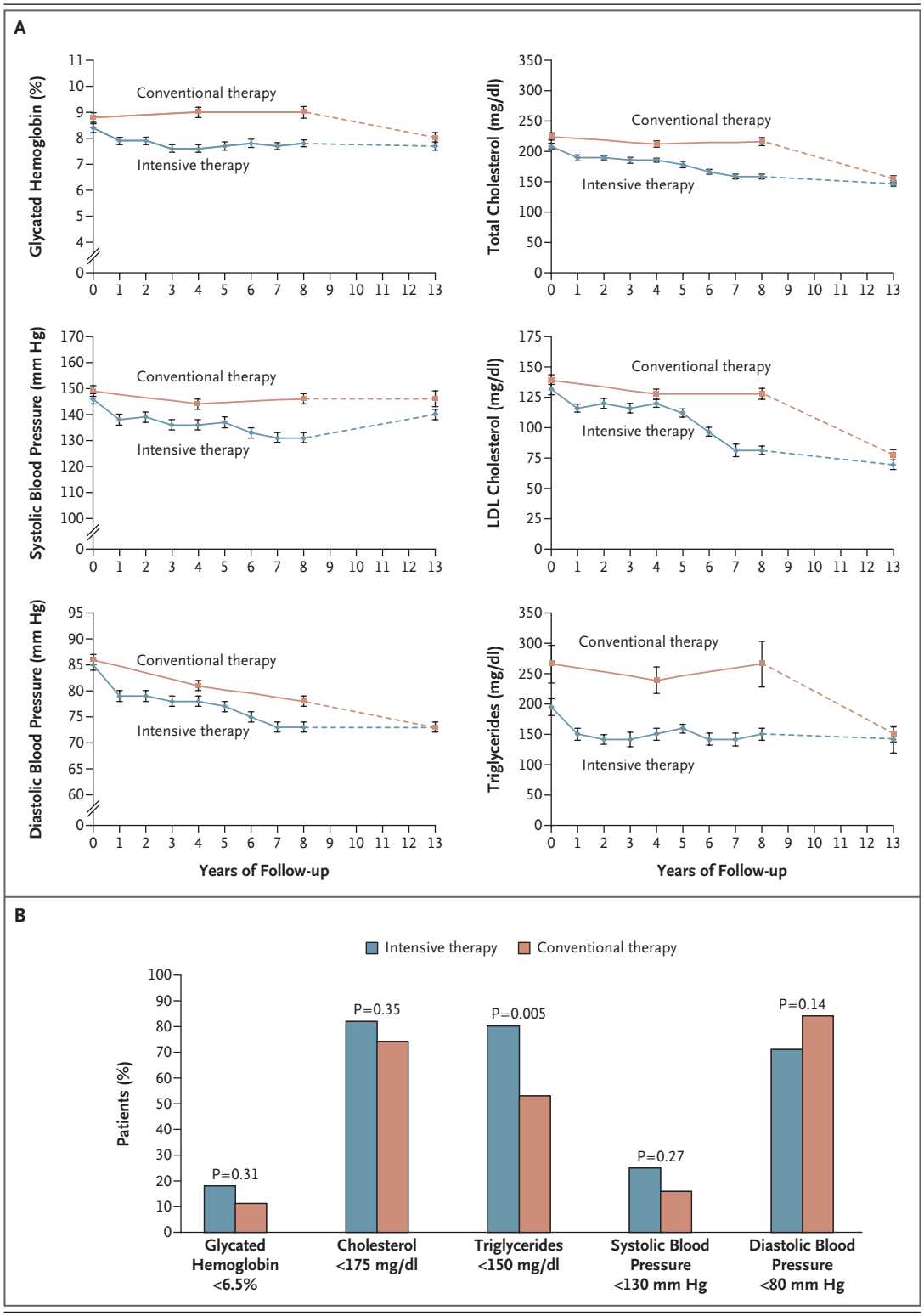
Figure 2 (facing page). Changes in Selected Risk Factors during the Interventional Study and Follow-up Period.

Panel A shows mean (±SE) values for selected risk factors during the interventional part of the study for all patients (solid lines) and during the follow-up period (dashed lines). In the conventional-therapy group, mean values were obtained at baseline, at 3.8 years, at 7.8 years, and at 13.3 years. At these intervals, the total numbers of patients in both study groups were 160, 149, 130, and 93, respectively. Panel B shows the percentage of patients in each group in whom the treatment goals for the intensive-therapy group were reached at the end of the study. Only one patient (in the intensive-therapy group) reached all five treatment goals at the end of follow-up. 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. LDL denotes low-density lipoprotein.

During the entire observation period, diabetic nephropathy developed in 20 patients in the intensive-therapy group, as compared with 37 patients in the conventional-therapy group (relative risk, 0.44; 95% CI, 0.25 to 0.77; P=0.004) (Fig. 4). One patient in the intensive-therapy group had progression to end-stage renal disease requiring dialysis, as compared with six patients in the conventional-therapy group (P=0.04).

Progression of diabetic retinopathy occurred in 41 patients in the intensive-therapy group and in 54 patients in the conventional-therapy group (relative risk, 0.57; 95% CI, 0.37 to 0.88; P=0.01). Laser treatment for proliferative retinopathy or macular edema was administered to 14 patients in the intensive-therapy group and 27 patients in the conventional-therapy group (relative risk, 0.45; 95% CI, 0.23 to 0.86; P=0.02); blindness in at least one eye was diagnosed in 2 patients in the intensive-therapy group and in 7 patients in the conventional-therapy group (relative risk, 0.51; 95% CI, 0.17 to 1.53; P=0.23).

Autonomic neuropathy progressed in 39 patients in the intensive-therapy group and in 52 patients in the conventional-therapy group (relative risk, 0.53; 95% CI, 0.34 to 0.81; P=0.004), and peripheral neuropathy progressed in 44 and



46 patients in the two groups, respectively (relative risk, 0.97; 95% CI, 0.62 to 1.51; P=0.89).

During the 13.3 years of observation, at least one minor episode of symptomatic hypoglycemia was reported in 80% of patients in the intensive-therapy group and in 70% of patients in the conventional-therapy group (P=0.15). There was no statistical difference in major hypoglycemia epi-

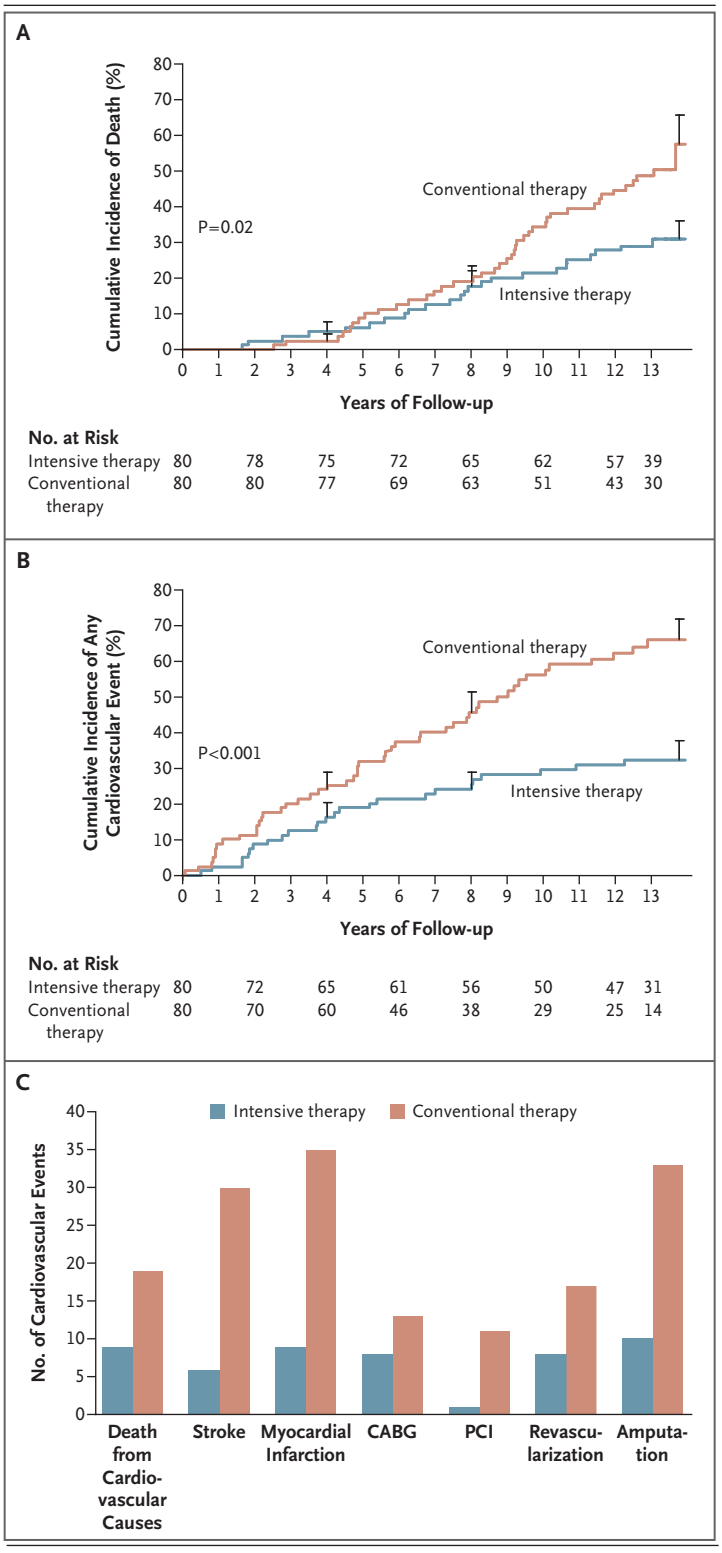


Figure 3. Kaplan–Meier Estimates of the Risk of Death from Any Cause and from Cardiovascular Causes and the Number of Cardiovascular Events, According to Treatment Group.

Panel A shows the cumulative incidence of the risk of death from any cause (the study's primary end point) during the 13.3-year study period. Panel B shows the cumulative incidence of a secondary composite end point of cardiovascular events, including death from cardiovascular causes, nonfatal stroke, nonfatal myocardial infarction, coronary-artery bypass grafting (CABG), percutaneous coronary intervention (PCI), revascularization for peripheral atherosclerotic artery disease, and amputation; Panel C shows the number of events for each component of the composite end point. In Panels A and B, the I bars represent standard errors.

sodes (13% in the intensive-therapy group and 17% in the conventional-therapy group, P=0.52). A bleeding gastric ulcer developed in one patient in the intensive-therapy group. Two patients in the intensive-therapy group and one in the conventional-therapy group reported having muscle pain after statin treatment; however, no elevation of the serum creatine kinase level was seen. Five patients in the intensive-therapy group and four patients in the conventional-therapy group reported having a cough during treatment with angiotensin-converting–enzyme inhibitors. The cough disappeared in all patients after a change to an angiotensin II antagonist. The average number of physician-prescribed drugs for type 2 diabetes or its complications in the intensive-therapy group at the end of the follow-up period was 5.5, as compared with 5.7 in the conventional-therapy group (P=0.64).

DISCUSSION

After a mean of 13.3 years (7.8 years of multifactorial intervention and an additional 5.5 years of follow-up), there was an absolute risk reduction for death from any cause of 20% among patients with type 2 diabetes and microalbuminuria who received intensive therapy, as compared with those who received conventional therapy. The absolute risk of death from cardiovascular causes was reduced by 13% among those receiving intensive therapy. During the entire follow-up period, the rate of death among patients in the conventional-therapy group was 50%, a finding that underscores the poor prognosis for such patients in the absence of intensive treatment.[20]

In comparison with the results of trials involving treatment of single risk factors in patients with type 2 diabetes, the achieved risk reductions in our trial were considerable. However, in secondary interventions, individual therapy with aspirin, anti-

Table 2. Numbers of Deaths from Any Cause, Deaths from Cardiovascular Causes, and Cardiovascular Events at 13.3 Years.*

Variable	Intensive Therapy			Conventional Therapy		
	No. of Patients	No. of Events	No. of First Events	No. of Patients	No. of Events	No. of First Events
Death from any cause	24	24		40	40	
Death from cardiovascular causes	9	9	3	19	19	3
Myocardial infarction	8	9	7	21	35	11
Stroke	6	6	4	18	30	15
Coronary-artery bypass grafting	8	8	5	13	13	7
Percutaneous coronary intervention	1	1	0	3	11	3
Revascularization	6	8	4	10	17	4
Amputation	6	10	2	14	33	5
All cardiovascular events	25	51		48	158	

* Patients could have more than one event. First events refer to the type of event for which data for a patient were censored from the proportional-hazards model after an event. Thus, the total number of first events is equal to the number of patients having a cardiovascular event during follow-up.

hypertensive agents, and lipid-lowering drugs each reduced the relative risk of cardiovascular events by about 25%, and the effects appeared to be additive.[21,22] Therefore, the reductions in risk — a 59% reduction in the relative risk and a 29% reduction in the absolute risk — in the composite of cardiovascular events fit with projections from trials involving single risk factors.[21]

Our study was not designed to identify which elements of intensive diabetes therapy contributed most to the reduction in cardiovascular risk. However, using a risk calculator based on epidemiologic and interventional data from patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study,[23] we concluded that the use of statins and antihypertensive drugs might have had the largest effect in reducing cardiovascular risk during the 7.8 years of intervention, with hypoglycemic agents and aspirin the next most important interventions.[24]

Even though the significant differences in the levels of risk factors for cardiovascular disease between the study groups at the end of our interventional study had disappeared by the end of the follow-up period (Table 1 and Fig. 2), the Kaplan–Meier curves for the time to the first cardiovascular event continued to diverge (Fig. 3B). A similar outcome was reported in the Diabetes Control and Complications Trial (DCCT),[25] involving patients with type 1 diabetes, in which the effects of intensive insulin therapy and conventional insulin therapy were compared during a 6.5-year period. After an average follow-up of 17 years, the original intensive-therapy treatment was associated with an absolute risk reduction of 2.8% for a composite cardiovascular end point. In the DCCT follow-up trial, glucose regulation deteriorated in the original intensive-therapy group and improved in the control group, resulting in a convergence of the glycemic levels in the two groups.

In our follow-up trial, the risk factors in the two study groups tended to converge (Fig. 2). Only the control of systolic blood pressure deteriorated in the intensive-therapy group, whereas glucose levels, lipid levels, diastolic blood pressure, and the rate of urinary albumin excretion improved in the conventional-therapy group, leaving the two study groups with similar levels of risk factors after 13.3 years. The design of our study did not allow us to estimate the exact time at which risk factors improved in the conventional-therapy group. However, since all patients were offered intensive treatment at the end of the trial, the improvement probably took place early during the follow-up period. The effect of blood-pressure reduction on cardiovascular end points usually occurs within months,[26,27] whereas the effect of lipid lowering is evident after 1 to 2 years.[8,28,29] The effect of glucose lowering on diabetes-related end points occurs even later.[4] Thus, an effect of early intervention, as compared with late intervention, may be a likely explanation for the continuing diver-

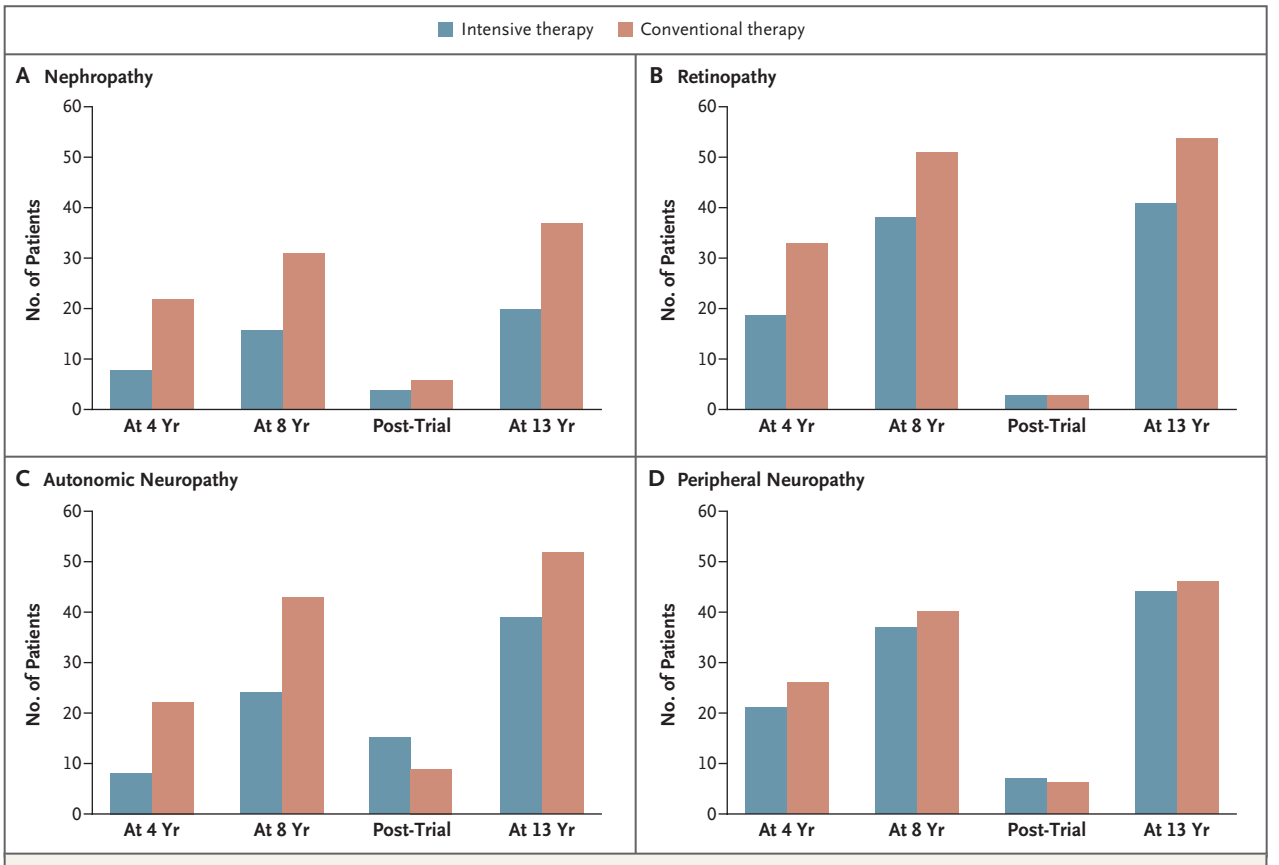


Figure 4. Patients with Development or Progression of Diabetic Nephropathy, Retinopathy, Autonomic Neuropathy, and Peripheral Neuropathy.

The bars labeled "Post-Trial" refer to the number of patients in whom the condition progressed during the period from the end of the original intervention trial to the end-point examination after an average of 13.3 years of study and follow-up.

gence in cardiovascular end points, rather than a simple time-to-effect relationship.

The drugs used in our study differed between the study groups. For instance, a larger proportion of patients in the intensive-therapy group took metformin or sulfonylurea, despite the similar levels of glycemia in the two groups. Therefore, differences in drugs or their combinations might have contributed to the long-term outcome.

Reductions in the progression of microvascular complications occurred after a mean of 3.8 years of intensified intervention,[12] changes that were maintained at 13.3 years. Indeed, during continuous follow-up, this reduction translated into a significant absolute risk reduction of 6.3% in the need for dialysis, a condition that in many parts of the world is tantamount to death.[30]

We did not monitor adverse effects continuously. However, few serious adverse effects were reported during regular interviews with patients.[10,12] In this respect, it is noteworthy that except for atorvastatin, generic drugs with well-known long-term side effects were prescribed. Whether newer and more expensive diabetes treatments would have additional beneficial long-term effects or risks remains to be determined.

Recent surveys have shown very slow progress in achieving treatment goals and in the use of recommended drugs for the prevention of diabetic vascular complications.[31,32] Therefore, since intensive, multifactorial care of patients with type 2 diabetes leads to reduced rates of death and cardiovascular disorders, the early and meticulous implementation of current treatment guidelines remains a major challenge.

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