Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes

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ABSTRACT

BACKGROUND

Cardiovascular morbidity is a major burden in patients with type 2 diabetes. In the Steno-2 Study, we compared the effect of a targeted, intensified, multifactorial intervention with that of conventional treatment on modifiable risk factors for cardiovascular disease in patients with type 2 diabetes and microalbuminuria.

METHODS

The primary end point of this open, parallel trial was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization, and amputation. Eighty patients were randomly assigned to receive conventional treatment in accordance with national guidelines and 80 to receive intensive treatment, with a stepwise implementation of behavior modification and pharmacologic therapy that targeted hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, along with secondary prevention of cardiovascular disease with aspirin.

RESULTS

The mean age of the patients was 55.1 years, and the mean follow-up was 7.8 years. The decline in glycosylated hemoglobin values, systolic and diastolic blood pressure, serum cholesterol and triglyceride levels measured after an overnight fast, and urinary albumin excretion rate were all significantly greater in the intensive-therapy group than in the conventional-therapy group. Patients receiving intensive therapy also had a significantly lower risk of cardiovascular disease (hazard ratio, 0.47; 95 percent confidence interval, 0.24 to 0.73), nephropathy (hazard ratio, 0.39; 95 percent confidence interval, 0.17 to 0.87), retinopathy (hazard ratio, 0.42; 95 percent confidence interval, 0.21 to 0.86), and autonomic neuropathy (hazard ratio, 0.37; 95 percent confidence interval, 0.18 to 0.79).

CONCLUSIONS

A target-driven, long-term, intensified intervention aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria reduces the risk of cardiovascular and microvascular events by about 50 percent.

PATIENTS WITH TYPE 2 DIABETES MELLI-tus have a risk of death from cardiovascular causes that is two to six times that among persons without diabetes, and among white Americans, the age-adjusted prevalence of coronary heart disease is twice as high among those with type 2 diabetes as among those without diabetes.[1-4] The cardiovascular events associated with type 2 diabetes and the high incidence of other macrovascular complications, such as strokes and amputations, are a major cause of illness and an enormous economic burden.

Multiple modifiable risk factors for late complications in patients with type 2 diabetes, including hyperglycemia, hypertension, and dyslipidemia, increase the risk of a poor outcome.[5] Randomized trials that investigated the effect of intensified intervention involving a single risk factor in patients with type 2 diabetes demonstrated benefits in terms of both macrovascular and microvascular complications in kidneys, eyes, and nerves.[6-10] On the basis of the results of these trials, recent guidelines from the American Diabetes Association and other national guidelines recommend an intensified multifactorial treatment approach, although the effect of this approach has not been confirmed in long-term studies.

We undertoook a randomized study — the Steno-2 Study — to evaluate the effect on cardiovascular disease of an intensified, targeted, multifactorial intervention comprising behavior modification and polypharmacologic therapy aimed at several modifiable risk factors in patients with type 2 diabetes and microalbuminuria; we compared this approach with a conventional intervention involving multiple risk factors.

METHODS

PATIENTS AND STUDY DESIGN

The study protocol specified two major analyses, a microvascular analysis in which the development of diabetic nephropathy after four years of intervention was the primary end point and a macrovascular analysis in which a composite end point for macrovascular disease after eight years of intervention was the primary end point. The results of the original microvascular part of the study have been reported elsewhere, together with detailed information about the study design and base-line phenotypic data.[11] Patients with persistent microalbuminuria were selected, since microalbuminuria is a well-established

independent risk factor for cardiovascular disease (the primary end point) as well as for nephropathy, retinopathy, and neuropathy (secondary end points).[12,13] All patients provided written informed consent. The protocol was in accordance with the Declaration of Helsinki and was approved by the ethics committee of Copenhagen County, Denmark.

The study was a randomized, open, parallel trial (Fig. 1). Randomization was performed with the use of sealed envelopes. Eighty patients were randomly assigned to receive conventional treatment for multiple risk factors from their general practitioner, according to the 1988 recommendations of the Danish Medical Association (which were revised in 2000) (Table 1), with the possibility of being referred to specialists.[14] The remaining 80 patients were randomly assigned to undergo intensive multifactorial intervention involving strict treatment goals (Table 1), to be achieved through behavior modification and a stepwise introduction of pharmacologic therapy overseen by a project team (doctor, nurse, and dietitian) at the Steno Diabetes Center. On average, patients in the intensive-therapy group were offered individual consultations every third month during the eight-year follow-up. All hospital admissions in the conventional-therapy group occurred at the request of the patients' personal physicians.

At some point during follow-up, 45 patients in the conventional-therapy group (56 percent) were treated at the outpatient clinic at the Steno Diabetes Center in accordance with the national guidelines and 8 (10 percent) were referred to other diabetes clinics. The mean number of consultations at diabetes clinics per year for these 53 patients was three. Patients in the conventional-therapy group who were treated at the Steno Diabetes Center in accordance with the national guidelines did not differ from typical patients with type 2 diabetes who were seen at the center; they had a similar duration of diabetes and similar levels of hyperglycemia, blood pressure, and serum lipids after an overnight fast (data not shown). None of the patients in the conventional-therapy group were treated by the project team.

INTERVENTIONS IN THE INTENSIVE-THERAPY GROUP

The aim of dietary intervention was a total daily intake of fat that was less than 30 percent of the daily energy intake and an intake of saturated fatty acids that was less than 10 percent of the daily energy intake. Light-to-moderate exercise for at least 30 minutes three to five times weekly was recommended,

and all smoking patients and their spouses were invited to participate in smoking-cessation courses. All patients were prescribed an angiotensin-converting–enzyme (ACE) inhibitor in a dose equivalent to 50 mg of captopril twice daily or, if such a drug was contraindicated, an angiotensin II–receptor antagonist in a dose equivalent to 50 mg of losartan twice daily, irrespective of the blood pressure level. They also received a daily vitamin–mineral supplement containing 250 mg of vitamin C, 100 mg of D-α-tocopherol, 400 μg of folic acid, and 100 μg of chrome picolinate. Initially, 150 mg of aspirin per day was given as secondary prevention to patients with a history of ischemic cardiovascular disease, and after October 1999, all patients received aspirin (unless there were contraindications).

If patients were unable to maintain glycosylated hemoglobin values below 6.5 percent by means of diet and increased physical activity alone after three months, an oral hypoglycemic agent was started. As the initial step, overweight patients (defined as those with a body-mass index [the weight in kilograms divided by the square of the height in meters] above 25) received metformin (maximum, 1 g twice daily); lean patients, or overweight patients who had contraindications to metformin therapy, received gliclazide (maximum, 160 mg twice daily). As the second step, metformin was added to the regimen of lean patients and gliclazide to that of overweight patients if hyperglycemia was not controlled. If the glycosylated hemoglobin value exceeded 7.0 percent despite maximal doses of oral agents, the addition of neutral protamine Hagedorn (NPH) insulin at bedtime was recommended. When insulin was started, lean patients stopped metformin treatment and overweight patients stopped gliclazide therapy unless it was the only oral hypoglycemic agent given. The insulin dose was adjusted on the basis of the morning fasting blood glucose concentration. If the daily dose of insulin exceeded 80 IU at bedtime or there was no decrease in the glycosylated hemoglobin value, patients were switched to regimens in which regular and NPH insulin was given two to four times a day (Table 2).

Arterial hypertension was also treated with a stepwise approach. As mentioned, all patients were prescribed an ACE inhibitor or an angiotensin II–receptor antagonist because of the presence of microalbuminuria. If a patient had hypertension, thiazides, calcium-channel blockers, and beta-blockers were added as needed. The combinati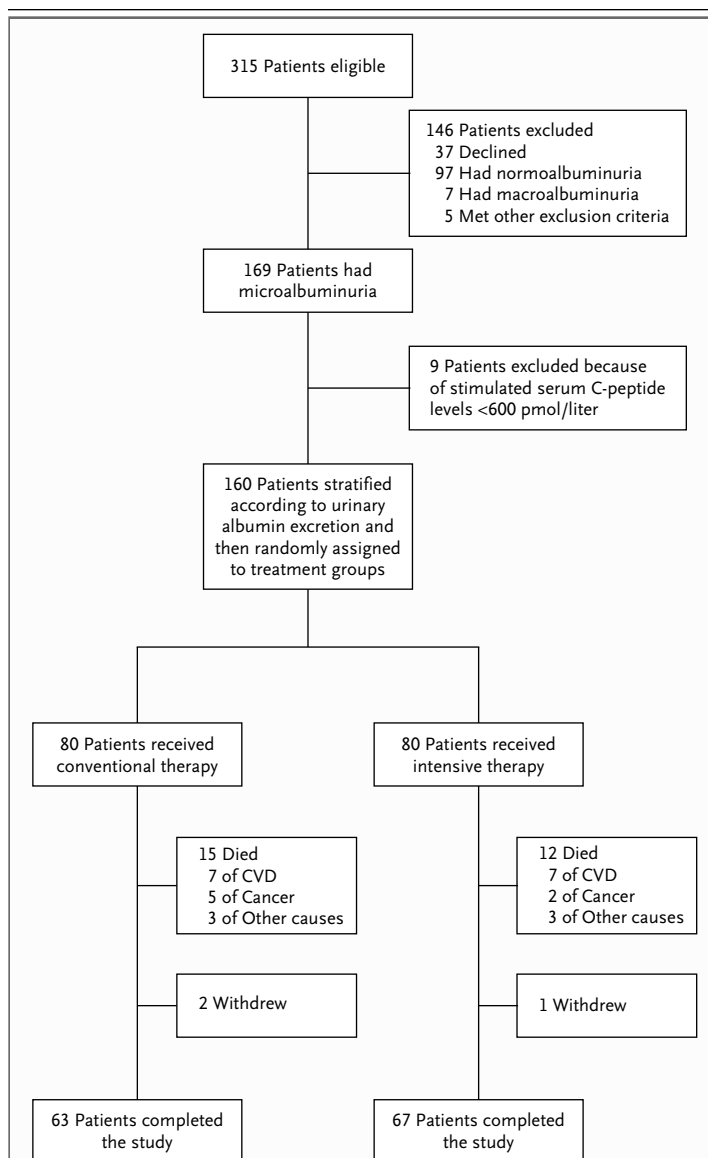on of an ACE inhibitor and an angiotensin II–receptor antagonist could also be used. Isolated instances of raised fasting serum cholesterol concentrations or combined dyslipidemia were treated with statins (atorvastatin, with a maximum of 80 mg daily, or the equivalent). Fibrates were used for isolated cases of hypertriglyceridemia, defined by a fasting serum triglyceride concentration of more than 350 mg per

Figure 1. Design of the Trial.

Three patients withdrew during follow-up because they moved to other regions: the two patients in the conventional-therapy group withdrew after 0.4 and 4.7 years of follow-up, respectively, and the patient in the intensive-therapy group withdrew after 3.2 years. CVD denotes cardiovascular disease.

Table 1. Treatment Goals for the Conventional-Therapy Group and the Intensive-Therapy Group.*

Variable	Conventional Therapy		Intensive Therapy	
	1993–1999	2000–2001	1993–1999	2000–2001
Systolic blood pressure (mm Hg)	<160	<135	<140	<130
Diastolic blood pressure (mm Hg)	<95	<85	<85	<80
Glycosylated hemoglobin (%)	<7.5	<6.5	<6.5	<6.5
Fasting serum total cholesterol (mg/dl)	<250	<190	<190	<175
Fasting serum triglycerides (mg/dl)	<195	<180	<150	<150
Treatment with ACE inhibitor irrespective of blood pressure	No	Yes	Yes	Yes
Aspirin therapy				
For patients with known ischemia	Yes	Yes	Yes	Yes
For patients with peripheral vascular disease	No	No	Yes	Yes
For patients without coronary heart disease or peripheral vascular disease	No	No	No	Yes

* To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. ACE denotes angiotensin-converting enzyme.

All end points specified in the protocol were adjudicated by an independent committee whose members were unaware of the patients' treatment assignments. Secondary end points indicative of microvascular disease, which have previously been described in detail,[11] were the incidence of diabetic nephropathy or the development or progression of diabetic retinopathy or neuropathy. Diabetic nephropathy was defined as a urinary albumin excretion of more than 300 mg per 24 hours in two of three consecutive sterile urine specimens. 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 by two independent ophthalmologists who were unaware of the patients' treatment assignment.[15] Peripheral neuropathy was measured with a biothesiometer, and the diagnosis of autonomic neuropathy was based on a measurement of the RR interval on the electrocardiogram during paced breathing and on an orthostatic-hypotension test conducted by a laboratory technician who was unaware of the patients' treatment assignments.

deciliter (4.0 mmol per liter), or were added to statin treatment if the fasting serum triglyceride concentration was also elevated (350 mg per deciliter).

PROCEDURES, MEASUREMENTS, AND END POINTS

The macrovascular study ended as planned in December 2001. Biochemical and clinical data were obtained every third month in the intensive-therapy group. End-point examinations for both macrovascular and microvascular complications were performed and biochemical and clinical status was determined after four and eight years of intervention in both groups.[11]

All blood samples were obtained at 8 a.m. after an overnight fast and before the morning medication. Blood pressure was measured twice after 20 minutes' rest while patients were supine, with use of a Hawksley random-zero sphygmomanometer. The measurements were obtained by a laboratory technician who was unaware of the patients' treatment assignment.

The primary study end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, coronary-artery bypass grafting, percutaneous coronary intervention, nonfatal stroke, amputation as a result of ischemia, or vascular surgery for peripheral atherosclerotic artery disease.

STATISTICAL ANALYSIS

Given a constant rate of events of 6 percent per year, 160 patients were needed to permit us to detect a 35 percent reduction in the relative risk of the primary composite end point with a power of 0.7 and a type 1 error rate of 0.05 during the planned mean follow-up period of eight years. The primary end point was analyzed according to the intention-to-treat principle, with event curves for the time to the first event based on Kaplan–Meier analysis, and treatments were compared with the use of the log-rank test. A Cox regression model was used to calculate the hazard ratio for the primary end point.

Since the secondary end points occurred at some point between base line and four years or between four and eight years, the rate ratio was estimated with use of a grouped survival model (binary regression with complementary log-log link). Separate effects of treatment were estimated for the two periods, whereas the effect of the control variables was assumed to be constant. Analyses were adjusted for age, the duration of diabetes, sex, and end-point status at base line. Measured variables were compared by means of analysis of covariance, with base-line values as covariates to adjust for differences between the groups at randomization. In the case of a nongaussian distribution, the Mann–Whitney test was

Table 2. Treatment in Patients with Type 2 Diabetes and Microalbuminuria.

Variable	Start of Study Period		End of Study Period		P Value*
	Conventional Therapy (N=80)	Intensive Therapy (N=80)	Conventional Therapy (N=63)	Intensive Therapy (N=67)	
Glucose-lowering treatment					
Diet alone (no. of patients)	21	28	4	1	0.15
Oral hypoglycemic agent (no. of patients)	48	47	38	50	0.14
Insulin (no. of patients)	11	5	34	38	0.91
Both agents (no. of patients)	1	0	13	22	0.14
Insulin dose (IU)					0.91
Median	30	42	64	62	
Range	14–142	10–52	12–360	12–260	
Antihypertensive treatment (no. of patients)					
ACE inhibitor†	16	15	32	53	0.002
Angiotensin II–receptor antagonist	0	0	12	31	0.002
Both	0	0	0	19	<0.001
Diuretic	17	22	39	38	0.42
Calcium-channel blocker	5	11	18	24	0.45
Beta-blocker	8	1	13	10	0.35
Other	1	1	4	3	0.61
Any	33	33	52	66	0.009
Lipid-lowering treatment (no. of patients)					
Statin	0	2	14	57	<0.001
Fibrate	1	1	3	1	0.27
Both	0	0	0	1	1.00
Aspirin (no. of patients)	11	10	35	58	<0.001
Vitamin–mineral supplement (no. of patients)	0	0	0	42	<0.001
Hormone replacement (no. of patients)	3	2	2	1	0.61

* P values are for the difference between the groups at the end of the study.
† ACE denotes angiotensin-converting enzyme.

used. A chi-square test was used to compare categorical variables.

RESULTS

The base-line demographic and clinical characteristics and biochemical status of the patients in the conventional-therapy group and the intensive-therapy group were similar (as shown in the Supplementary Appendix, available with the full text of this article at http://www.nejm.org). The mean age of the patients was 55.1 years. Changes in lifestyle (behavioral variables) and clinical and biochemical variables in the two groups and differences between groups during the mean follow-up period of 7.8 years (range, 6.9 to 8.8) are shown in Table 3. The changes in lifestyle were moderate; the only significant differences between groups were in the relative intake of carbohydrate and fat. The changes in body-mass index did not differ significantly between groups.

The groups differed significantly with respect to glycosylated hemoglobin values, fasting plasma glucose concentrations, fasting serum lipid concen-

Table 3. Changes in Clinical, Behavioral, and Biochemical Variables at the End of the Study.*

Variable	Conventional Therapy (N=63)	Intensive Therapy (N=67)	P Value
Clinical variables			
Body-mass index			
Men	0.4±0.4	0.7±0.4	0.61
Women	1.3±1.3	2.3±1.2	0.29
Waist circumference (cm)			
Men	4±2	3±1	0.23
Women	5±5	6±3	0.81
Hip circumference (cm)			
Men	2±1	0±1	0.14
Women	−1±3	5±4	0.048
Systolic blood pressure (mm Hg)	−3±3	−14±2	<0.001
Diastolic blood pressure (mm Hg)	−8±2	−12±2	0.006
Current smoking (no. of patients)	−6	−5	0.73
Daily dietary intake			
Energy intake (kcal)			0.33
Median	−43	−57	
Range	−3706 to 999	−1610 to 1042	
Protein (% of energy intake)	1.1±0.4	1.6±0.4	0.56
Carbohydrates (% of energy intake)	4.8±0.9	9.3±0.9	0.002
Alcohol (% of energy intake)	0.9±0.9	−0.5±1.1	0.82
Fat (% of energy intake)	−6.8±0.9	−10.4±0.9	<0.001
Saturated fatty acids (% of energy intake)	−4.4±0.4	−6.9±0.5	<0.001
Exercise (min/wk)			0.38
Median	0	30	
Range	−720 to 630	−480 to 750	
Biochemical variables			
Fasting plasma glucose (mg/dl)	−18±11	−52±8	<0.001
Glycosylated hemoglobin (%)	0.2±0.3	−0.5±0.2	<0.001
Fasting serum C peptide (pmol/liter)			0.18
Median	−53	−112	
Range	−709 to 2555	−958 to 1429	
Stimulated serum C peptide (pmol/liter)			0.43
Median	−270	−332	
Range	−1309 to 3488	−1974 to 1515	
Fasting serum triglycerides (mg/dl)	9±43	−41±14	0.015
Fasting serum total cholesterol (mg/dl)	−3±7	−50±4	<0.001
Fasting serum LDL cholesterol (mg/dl)	−13±6	−47±5	<0.001
Fasting serum HDL cholesterol (mg/dl)	7±1	6±2	0.90
Serum creatinine (mmol/liter)			0.57
Median	21	24	
Range	−16 to 661	−6 to 181	
Urinary albumin excretion (mg/24 hr)			0.007
Median	30	−20	
Range	−251 to 4729	−230 to 5474	
Urinary sodium excretion (mmol/24 hr)			0.86
Median	−21	−21	
Range	−440 to 286	−225 to 302	
Glomerular filtration rate (ml/min/1.73 m²)	−32±3	−30±3	0.68

* Plus–minus values are means ±SE. To convert values for energy intake to kilojoules, multiply by 4.184. To convert values for glucose to millimoles per liter, multiply by 0.05556. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. LDL denotes low-density lipoprotein, and HDL high-density lipoprotein.

trations, systolic and diastolic blood pressure, and urinary albumin excretion rate. As shown in Figure 2A, the differences in the values of various risk factors between the two groups were maintained throughout the follow-up period. Figure 2B shows the percentage of patients in each group who achieved the various recommended treatment goals of the intensive regimen after 7.8 years of follow-up.

A total of 118 cardiovascular events occurred during follow-up. There were 85 events among 35 patients (44 percent) in the conventional-therapy group (7 deaths from cardiovascular causes, 17 nonfatal myocardial infarctions, 10 coronary-artery bypass grafts, 5 percutaneous coronary interventions, 20 nonfatal strokes, 14 amputations, and 12 surgical interventions for peripheral atherosclerotic artery disease), as compared with 33 events among 19 patients (24 percent) in the intensive-therapy group (7 deaths from cardiovascular causes, 5 nonfatal myocardial infarctions, 5 coronary-artery bypass grafts, 3 nonfatal strokes, 7 amputations, and 6 vascular surgical interventions). A breakdown of first events showed a similar distribution in the conventional-therapy group (1 death from cardiovascular causes, 8 nonfatal myocardial infarctions, 6 coronary-artery bypass grafts, 3 percutaneous coronary interventions, 11 nonfatal strokes, 3 amputations, and 3 vascular surgical interventions) and the intensive-therapy group (3 deaths from cardiovascular causes, 4 nonfatal myocardial infarctions, 4 coronary-artery bypass grafts, 3 nonfatal strokes, 2 amputations, and 3 vascular surgical interventions).

The time-to-first-event curves for the primary composite end point continued to diverge during follow-up (Fig. 3A). The unadjusted hazard ratio for the intensive-therapy group as compared with the conventional-therapy group was 0.47 (95 percent confidence interval, 0.24 to 0.73; P=0.008). Adjustment for the duration of diabetes, age, sex, smoking status, and presence or absence of cardiovascular disease at base line had no substantial effect (hazard ratio, 0.47; 95 percent confidence interval, 0.22 to 0.74; P=0.01). When a composite end point was used that excluded revascularizations so as to avoid potential physician bias in this unblinded trial, the hazard ratio was 0.45 (95 percent confidence interval, 0.23 to 0.91; P=0.02). In a hypothetical worst-case analysis in which death from any cause except cancer was included, instead of death from cardiovascular causes, the patient who withdrew consent in the intensive-therapy group was considered to have had an event, and the two patients in the con-

ventional-therapy group who withdrew were considered to have completed follow-up without events (Fig. 1), the hazard ratio was 0.50 (95 percent confidence interval, 0.29 to 0.86; P=0.01).

Diabetic nephropathy developed in 31 patients in the conventional-therapy group and 16 patients in the intensive-therapy group (Fig. 3B). Three patients in the conventional-therapy group had progression to end-stage renal disease requiring dialysis, as compared with none in the intensive-therapy group.
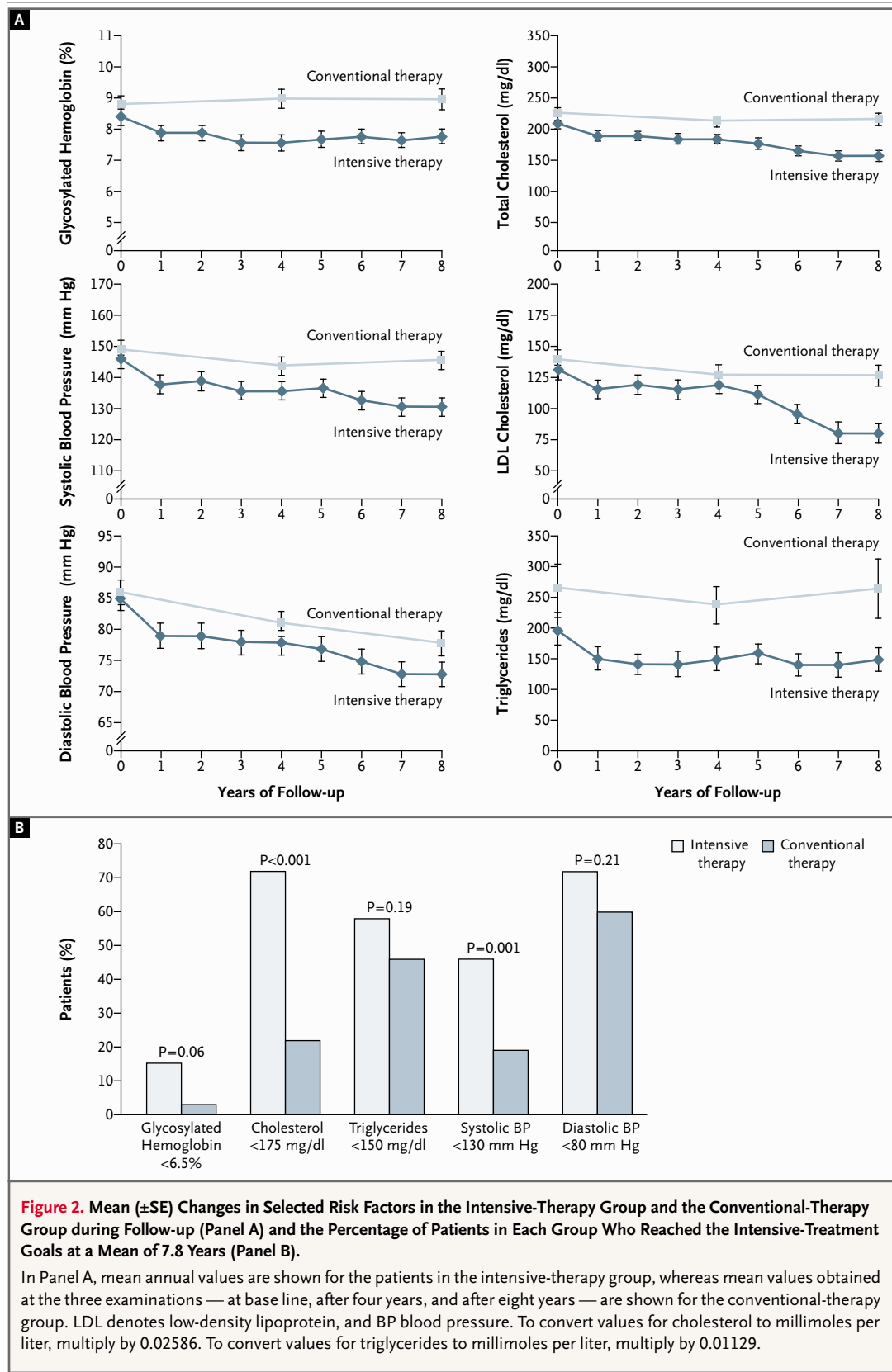
Retinopathy developed or progressed in 51 patients in the conventional-therapy group, as compared with 38 in the intensive-therapy group. The groups also differed with respect to the proportion of patients in whom retinopathy developed (38 patients in the conventional-therapy group, as compared with 27 in the intensive-therapy group; P= 0.02). Seven patients in the conventional-therapy group became blind in one eye, as compared with one patient in the intensive-therapy group (P=0.03).

Autonomic neuropathy progressed in 43 patients in the conventional-therapy group, as compared with 24 in the intensive-therapy group; peripheral neuropathy progressed in 37 and 40 patients, respectively.

The groups did not differ significantly with respect to the number of patients who reported at least one minor episode of hypoglycemia at the four- or eight-year examination (39 in the conventional-therapy group and 42 in the intensive-therapy group, P=0.50). Twelve patients in the conventional-therapy group and five in the intensive-therapy group had at least one major hypoglycemic event that impaired consciousness and required help from another person (P=0.12). More than 75 percent of major events occurred in insulin-treated patients. One patient in the intensive-therapy group was hospitalized for a bleeding gastric ulcer. Otherwise, no major adverse events were reported.

DISCUSSION

We found that a targeted, long-term (mean, 7.8 years), intensified intervention involving multiple risk factors reduced the risk of cardiovascular events among patients with type 2 diabetes and microalbuminuria. The continued divergence in the rates of the primary end point suggests that therapy for even longer periods may result in an even better prognosis. Our data suggest that five patients need to be treated for this length of time to prevent one

Figure 2. Mean (±SE) Changes in Selected Risk Factors in the Intensive-Therapy Group and the Conventional-Therapy Group during Follow-up (Panel A) and the Percentage of Patients in Each Group Who Reached the Intensive-Treatment Goals at a Mean of 7.8 Years (Panel B).

In Panel A, mean annual values are shown for the patients in the intensive-therapy group, whereas mean values obtained at the three examinations — at base line, after four years, and after eight years — are shown for the conventional-therapy group. LDL denotes low-density lipoprotein, and BP blood pressure. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.
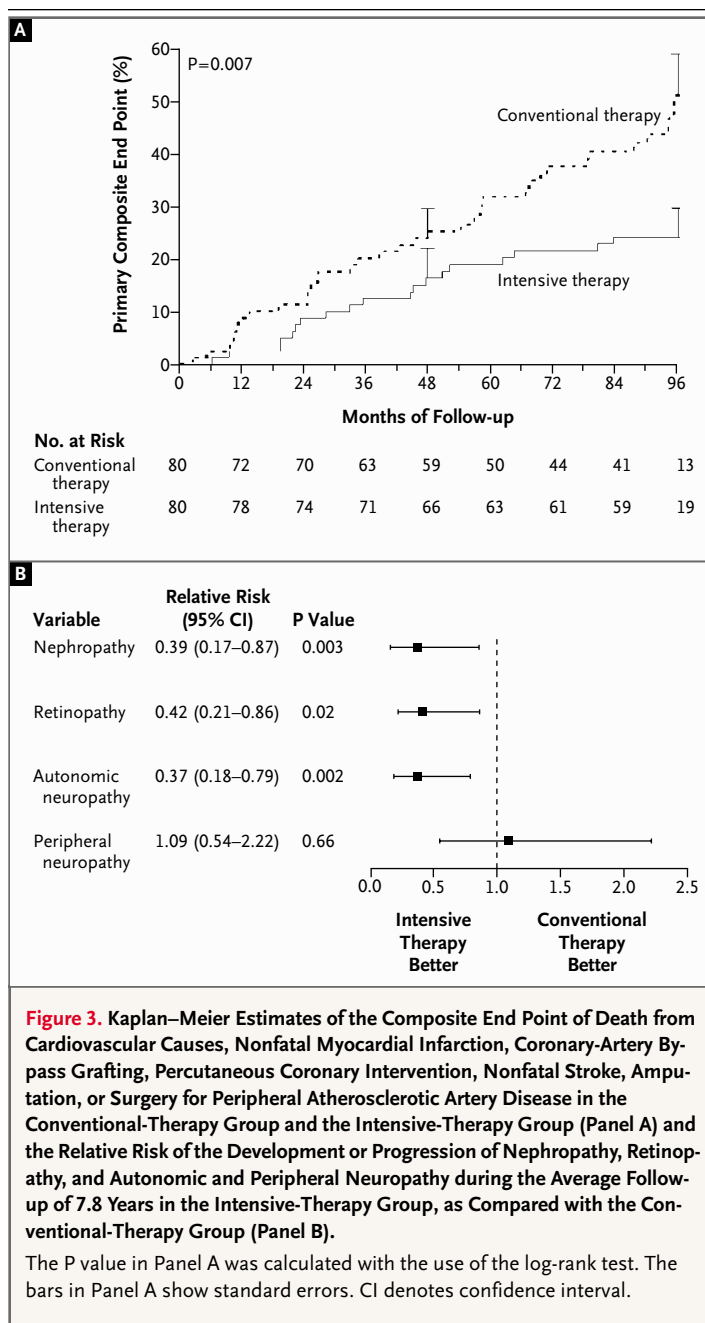
cardiovascular event. In addition, the reductions in the risk of nephropathy, retinopathy, and autonomic neuropathy obtained after four years of the intervention were maintained at eight years.[11] Serious adverse events were few. The study design precludes us from drawing conclusions about which treatment component was the most crucial in reducing the incidence of diabetes-related complications.

The absolute 20 percent reduction in the risk of cardiovascular events is higher than that in studies applying single-factor intervention strategies aimed at hyperglycemia, hypertension, or dyslipidemia.[7,16-23] Yet, the populations studied in these trials varied considerably, as did the durations of the intervention and the composite end points. The United Kingdom Prospective Diabetes Study, involving intensive treatment of hyperglycemia in patients with newly diagnosed type 2 diabetes over a 10-year period, found an absolute reduction in the risk of myocardial infarction of borderline significance (3 percent), with an absolute difference of 0.9 percent in glycosylated hemoglobin values.[6] The study did not find significant reductions in any other macrovascular outcomes.[6]

Intensive treatment of hypertension in patients with newly diagnosed diabetes during an eight-year period, which decreased systolic and diastolic blood pressure by 10 and 5 mm Hg, respectively, significantly reduced both the absolute risk of stroke and the combined end point of diabetes-related death, death from vascular causes, and death from renal causes by 5 percent.[7] The Hypertension Optimal Treatment Study, which treated elevations in diastolic blood pressure for an average of 3.7 years, reported similar reductions in the risk of composite end points for macrovascular disease in subgroup analyses of patients with type 2 diabetes.[17] Treatment of systolic hypertension for 4.7 years in the Systolic Hypertension in the Elderly Program trial and 2 years in the Systolic Hypertension in Europe Trial reduced the absolute risk of cardiovascular events by 8 percent[18] and that of death from cardiovascular causes by 5 percent.[19] Subgroup analysis showed a large reduction in the absolute risk of cardiovascular events (19 percent) among diabetic patients with elevated serum total cholesterol concentrations who took statins for 5.4 years for secondary cardiovascular prevention.[8] Other subgroup analyses in secondary-prevention trials of statins or fibrates have not been associated with such marked effects.[20-23]

In our study, the reductions in the risk of mi-

Figure 3. Kaplan–Meier Estimates of the Composite End Point of Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, Coronary-Artery Bypass Grafting, Percutaneous Coronary Intervention, Nonfatal Stroke, Amputation, or Surgery for Peripheral Atherosclerotic Artery Disease in the Conventional-Therapy Group and the Intensive-Therapy Group (Panel A) and the Relative Risk of the Development or Progression of Nephropathy, Retinopathy, and Autonomic and Peripheral Neuropathy during the Average Follow-up of 7.8 Years in the Intensive-Therapy Group, as Compared with the Conventional-Therapy Group (Panel B).

The P value in Panel A was calculated with the use of the log-rank test. The bars in Panel A show standard errors. CI denotes confidence interval.

crovascular complications after eight years of intervention were similar to the reductions seen after four years of intervention, demonstrating long-term beneficial effects of continuous intervention in terms of diabetic nephropathy, retinopathy, and autonomic neuropathy. The fact that more than half the patients in the conventional-therapy group were referred to specialists at some point during follow-up may have diminished the degree of separation in

risk factors between the two treatment groups. As a consequence, the reported reductions in the risk of cardiovascular as well as microvascular complications may be conservative.

Our findings have considerable implications for the treatment of type 2 diabetes. An approach such as the one we used, involving a focused, multifactorial intervention with continued patient education and motivation and strict targets and individualized risk assessment, should be offered to patients with type 2 diabetes and microalbuminuria who are at increased risk for macrovascular and microvascular complications. Such patients may represent about one third of the population of patients with type 2 diabetes.[24]

Since many national guidelines for the treatment of type 2 diabetes recommend reducing the risk of multiple factors through the use of protocols and therapeutic targets similar to ours, it may be difficult to replicate our findings in other controlled clinical trials. However, future studies might address several key questions, including which type of care organization is most effective in implementing this approach to treatment. Taken together, these data suggest that a long-term, targeted, intensive intervention involving multiple risk factors reduces the risk of both cardiovascular and microvascular events by about 50 percent among patients with type 2 diabetes and microalbuminuria.

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