

# Intensive Integrated Therapy of Type 2 Diabetes Implications for Long-Term Prognosis

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**The macro- and microvascular burden of type 2 diabetes is well established. A number of recent single risk factor intervention trials targeting hyperglycemia, dyslipidemia, hypertension, procoagulation, microalbumuria, and existing cardiovascular disorders have, however, shown major beneficial effects on long-term outcome. The results from these studies are anticipated to change the future management of type 2 diabetes, and most of the updated national guidelines for the treatment of type 2 diabetes recommend a multipronged approach driven by ambitious treatment targets. The outcome of this intensive integrated therapy has, however, only been investigated in a few studies of patients with type 2 diabetes. One of these trials, the Steno-2 Study, showed that intensive intervention for an average of 7.8 years cuts cardiovascular events as well as nephropathy, retinopathy, and autonomic neuropathy by about half when compared with a conventional multifactorial treatment. The challenge for now is to ensure that the trial experiences are widely adopted in daily clinical practice. *Diabetes* 53 (Suppl. 3):S39–S47, 2004**

**D**uring recent years, numerous prospective studies have identified several modifiable risk factors for both micro- and macrovascular complications in patients with type 2 diabetes. These factors include hyperglycemia, hypertension, dyslipidemia, microalbuminuria, a prothrombotic state, smoking, and lack of physical activity (1–6).

Even though there are no data from controlled long-term clinical trials to provide definite answers to the impact on diabetes outcome of each of the lifestyle factors, there is overwhelming epidemiological evidence that a healthy life performance helps prevent diabetes complications. Importantly, crucial information has been gained from single risk factor intervention trials in both diabetic and nondiabetic subjects. Based on the results of these interventions, the degree of cardiovascular relative risk reduction with each individual risk factor ranges from small (e.g., nonsignificant for hyperglycemia lowering us-

ing insulin or sulfonylurea in the U.K. Prospective Diabetes Study [UKPDS]) to moderate (e.g., ~10% with aspirin therapy) to substantial (e.g., 25–30% with blood pressure reduction or statin-induced lipid lowering). Also treatment with angiotensin-converting enzyme (ACE) inhibitors as secondary prevention of cardiovascular disease is convincingly demonstrated (7). Moreover, intervention against hyperglycemia (8), hypertension (9), or preventive treatment with angiotensin II receptor blockers (10,11) have shown beneficial effects on risk of microvascular events in long-term studies.

These drug trials in patients with type 2 diabetes have characteristically been carried out as single risk factor intervention studies on a background of a conventional multifactorial treatment approach. The results from these studies have changed the management of type 2 diabetes, and most national guidelines now recommend an intensified multifactorial intervention of the known modifiable risk factors for late diabetic complications with ambitious treatment goals. The outcome of this intensive approach has, however, only been investigated in a few studies of patients with type 2 diabetes. In this article, we give a critical review of the pertinent literature.

## INTENSIFIED MULTIFACTORIAL INTERVENTION IN TYPE 2 DIABETES

Three studies have evaluated the impact of long-term intervention comprising combined behavior modification and polypharmacy specifically in patients with type 2 diabetes. Two of these studies have included patients with newly diagnosed type 2 diabetes, whereas the inclusion criterion in the last study was type 2 diabetes and microalbuminuria.

In this respect several questions arise: 1) What are the benefits of intensified multiple risk factor intervention on morbidity and mortality? 2) Who will benefit the most from such an intervention? 3) What is the most powerful component in the intensified multifactorial approach to reduce complications and mortality? 4) Are there any problems with the adherence to combined aggressive lifestyle and multiple drug treatment? 5) Are there any adverse effects? 6) Do drug interactions pose a risk? 7) What are the costs of an intensified multitarget intervention at the community and patient level?

**The Diabetes Intervention Study.** The Diabetes Intervention Study was a randomized 5-year trial with the primary aim of testing the effect of intensified health education in improving metabolic regulation and reducing the level of coronary risk factors and incidence of ischemic heart disease (12). A total of 1,139 patients aged

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GP, general practitioner; UKPDS, U.K. Prospective Diabetes Study.

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30–55 years with newly diagnosed type 2 diabetes entered the study. Patients were randomized to a control group ( $n = 378$ ) receiving standard treatment at various diabetes outpatient clinics in Germany or an intervention group ( $n = 761$ ) receiving structured intensified health education, including dietary advice, antismoking and antialcohol education, and ways to increase physical activity. The health education included oral and written instructions by health care personnel about lipid-lowering diet and how to reduce overweight. Patients were given a written exercise program and had the possibility of participating in group exercise sessions, and antismoking education was conducted in groups. Guidelines for drug treatment of hyperglycemia and hypertension were in principle the same for both groups, but within the intervention group patients were also randomized to treatment with clofibric acid 1.6 g daily or placebo. Patients in the intervention group were seen every third month.

At the end of follow-up, the only significant difference in diet was in the ratio of polyunsaturated to saturated fat, which increased significantly more in the intervention group. No difference was seen for daily intake of energy, cholesterol, or alcohol. Also, physical activity increased significantly more with intensive education, whereas the amount of tobacco use only decreased significantly more than the control group in the part of the intensive group that was randomized to treatment with clofibric acid. Fasting serum cholesterol increased significantly in both the control and the intervention group, which was also the case for fasting serum triglycerides. However, the increase in fasting serum triglycerides was lower in the intensive group, but not lower with clofibric acid compared with placebo. Also, both systolic and diastolic blood pressure decreased significantly more with intensive therapy compared with placebo. Similarly, although an increase in fasting blood glucose was seen over the study period in both groups, this increase was significantly lower in the intervention group with fewer patients receiving glucose-lowering drugs.

The incidence of cardiovascular disease during the study period was not lower in the intervention group with an incidence rate of 30.3 per 1,000 patients in the control group, 53.6 in the intervention group treated with placebo, and 55.6 in the intervention group treated with clofibric acid.

**Diabetes Care in General Practice.** An almost similar approach to multiple risk factor intervention was undertaken in the Danish study Diabetes Care in General Practice, which was a randomized controlled trial of structured personal care in type 2 diabetes (13). This study also included patients with newly diagnosed type 2 diabetes, but in contrast to other studies, it was the general practitioners (GPs) who were randomized to either a GP control group ( $n = 231$ ) or a GP intervention group ( $n = 243$ ). A total of 1,263 patients were enrolled in the study with 614 being followed at the GP control group (routine care) and 649 being followed at the GP intervention group (structured care). In the routine care group, doctors were free to choose any treatment and change it over time according to national guidelines. After the end of the recruitment phase the GP control group did not have any contact with the steering committee until the final exam-

inations. In the structured care group, patients were seen every third month, and, once a year, patients were screened for diabetic complications. After each consultation, a questionnaire was sent to the steering committee in which the GP together with the patient defined the best possible goals for blood glucose concentration, glycated hemoglobin, diastolic blood pressure, and lipids within three predefined categories very similar to the goals in the routine care group. The GPs were introduced to possible solutions to therapeutic problems through clinical guidelines supported by an annual half-day seminar.

At the end of follow-up after 6 years, the only differences between groups were seen for fasting plasma glucose, glycated hemoglobin, and systolic blood pressure. No differences between groups were found for diet, exercise, smoking habits, fasting serum cholesterol and triglycerides, and diastolic blood pressure. The only drug used significantly more in the structured care group was metformin.

The primary outcome of the study of overall mortality, incidence of diabetic retinopathy, urinary albumin concentration  $>15$  mg/l, myocardial infarction, and stroke did not differ between groups, nor was this the case for the secondary outcomes consisting of new peripheral neuropathy, angina pectoris, intermittent claudication, and amputation. However, the Diabetes Care in General Practice study importantly demonstrated that an intensified and structured multifactorial intervention can be implemented at the GP level, at least in a clinically controlled setting.

**Steno-2 Study.** The Steno-2 Study, which was conceived in 1992, differed from the previous two studies by recruiting a high-risk group of type 2 diabetic patients with microalbuminuria, a marker of generalized vascular damage (14,15). As a consequence, the mean known diabetes duration for the 160 patients enrolled in the study was 6 years and about one-quarter had already experienced a cardiovascular event. Patients were randomized to conventional multifactorial treatment at their general practitioner following national guidelines ( $n = 80$ ), or intensified multifactorial intervention integrating both behavior modification and polypharmacy by a diabetes team consisting of a doctor, nurse, and a clinical dietitian at Steno Diabetes Center in Copenhagen. As in the previous studies, patients in the intervention group were seen every third month. Targets for blood glucose, glycated HbA<sub>1c</sub>, systolic and diastolic blood pressure, and fasting values of serum total cholesterol, LDL cholesterol, and triglycerides were lower in the intervention group than with conventional therapy. A stepwise, target-driven approach for drug treatment was used in order to achieve these goals (Table 1). The protocol specified two major end-point analyses: a microvascular analysis after 4 years of intervention with development of diabetic nephropathy as the primary outcome (14) and development or progression in retinopathy and neuropathy as secondary end points, and a macrovascular analysis after 8 years of intervention with the incidence of a composite end point of cardiovascular mortality, myocardial infarction, stroke, revascularization, and amputation as the primary end point (15).

A significantly larger decline in the ratio of daily intake of saturated and unsaturated fatty acids occurred at both the 4- and 8-year examinations in the intervention group, but otherwise there were no significant differences in

TABLE 1

The significant risk reduction of cardiovascular disease and microvascular complications documented by the Steno-2 Study (15) was achieved by using the following treatment algorithm

#### Dietary intervention and exercise

The aim was to reduce fat intake to <30% and saturated fatty acids to <10% of total daily energy intake and to increase the daily intake of vegetables, fruits, walnuts, almonds, and seafood. The reduction of daily energy intake was not a goal.

Exercise: light to moderate leisure time exercise of any type for at least 30 min 3–5 times a week.

#### Hyperglycemia

Target: HbA<sub>1c</sub> <6.5%

Oral antidiabetic drugs (OAD) were introduced if HbA<sub>1c</sub> was >6.5% after 3 months of dietary intervention. Overweight and obese patients were started on metformin to maximum of 2 × 1,000 mg. If contraindicated or in lean patients, a sulfonylurea (gliclazide) was prescribed.

Combination of the two drugs was considered when HbA<sub>1c</sub> target was not met.

NPH at bedtime was added when HbA<sub>1c</sub> was >7.0% despite maximal dose of both OADs. At the start of insulin treatment, obese patients stopped the sulfonylurea and the lean patients stopped metformin.

If the daily insulin dose exceeded 80 IU, or if no decrease of HbA<sub>1c</sub> was observed, patients were switched to regimens (two to four daily injections) with fast-acting and NPH insulin.

#### Hypertension

Target: <140/85 mmHg (study years 1993–1999); <130/80 mmHg (2000–2001)

ACE inhibitor as initial treatment. If side effects, angiotensin II receptor antagonists were used.

If target not achieved, combination with any of the following antihypertensive drugs was prescribed: thiazides, calcium antagonists, and β-blockers.

#### Microalbuminuria

As all patients had microalbuminuria, ACE inhibitors were prescribed irrespective of blood pressure values.

#### Dyslipidemia

Targets: total cholesterol <190 mg/dl (1993–1999) and <175 mg/dl (2000–2001); triglycerides <150 mg/dl

Treatment: atorvastatin for raised isolated fasting cholesterol or combined dyslipidemia; fibrates in isolated fasting hypertriglyceridemia (>350 mg/dl)

#### Smoking

Patients and their spouses were invited to smoking cessation courses.

#### Aspirin

Aspirin 150 mg/daily was given to all patients with known ischemia and/or peripheral artery disease.

lifestyle performance between the two groups, despite the many resources spent on intensive behavior modification (16). In contrast, a marked effect was seen on other risk factors. At 4 years of intervention the groups differed significantly for fasting blood glucose; glycated HbA<sub>1c</sub>; systolic blood pressure; fasting values of serum total cholesterol, LDL cholesterol, and triglycerides; and urinary albumin excretion rate. At the 8-year examination, this was still the case, and furthermore the difference in diastolic blood pressure between the groups was also statistically significant.

Significant effects of the intensified multifactorial intervention were found on the primary and secondary end points at both of the major end-point examinations after 4 and 8 years of intervention, respectively. After 4 years of intervention, risk reductions were seen for the development of nephropathy as well as for the development or progression in retinopathy and autonomic neuropathy. No effect of intensified intervention could be shown on peripheral neuropathy. Exactly the same result occurred after 8 years of examination. The primary end point at this time point was, however, cardiovascular disease, where we showed a significant relative risk reduction of 53% (absolute risk reduction 20%) for the composite end point with intensified multifactorial intervention. After 7.8 years the number needed to treat to prevent one event was 5.0 for macrovascular complications, 5.3 for diabetic nephropathy, 6.2 for progression in retinopathy, and 4.2 for progression in autonomic neuropathy. Figure 1 shows the distribution of cardiovascular end points in both groups. **Some strengths and shortcomings of the intensive intervention of the Steno-2 trial.** The intensively

treated patients in Steno-2 were prescribed ambitious treatment targets comparable to what now has become standard in most countries. Few of the patients in the trial achieved all treatment goals but for most patients the treatment targets for regulation of dyslipidemia, hypertension, and microalbuminuria were attainable without undue difficulties. The latter observation is encouraging, since control of these risk markers is of tremendous importance for long-term outcome. Probably the most difficult target is a glycated hemoglobin value within normal range. Only 15% of the patients in the intensive arm reached this goal (Fig. 2). However, a target is not “an all or none” phenomenon. Post hoc epidemiological analysis of UKPDS data showed a straight-line correlation between the mean value of glycated hemoglobin and the development of both micro- and macroangiopathy, suggesting that any reduction in glycemia will pay off (17).

Perhaps traditional lifestyle modification remains the most important unresolved issue in the integrated intensive approach. The excuses for not quitting smoking or for not exercising were legendary in the Steno-2 Study, although various tailored educational programs were enthusiastically communicated and transiently practiced. It was far easier to have patients diminishing intake of animal fat and doubling their weekly intake of vegetables, fruit, and seafood. The latter three food items are known to have beneficial effects on cardiovascular end points beyond what is measured as changes in, for instance, energy intake or serum lipids. Thus, diets naturally high in ω-3 fatty acids (18), α-linolenic acid, and flavonoids (19) have proved beneficial as secondary prevention of cardiovascular disease, even though no effects can be seen on tradi-

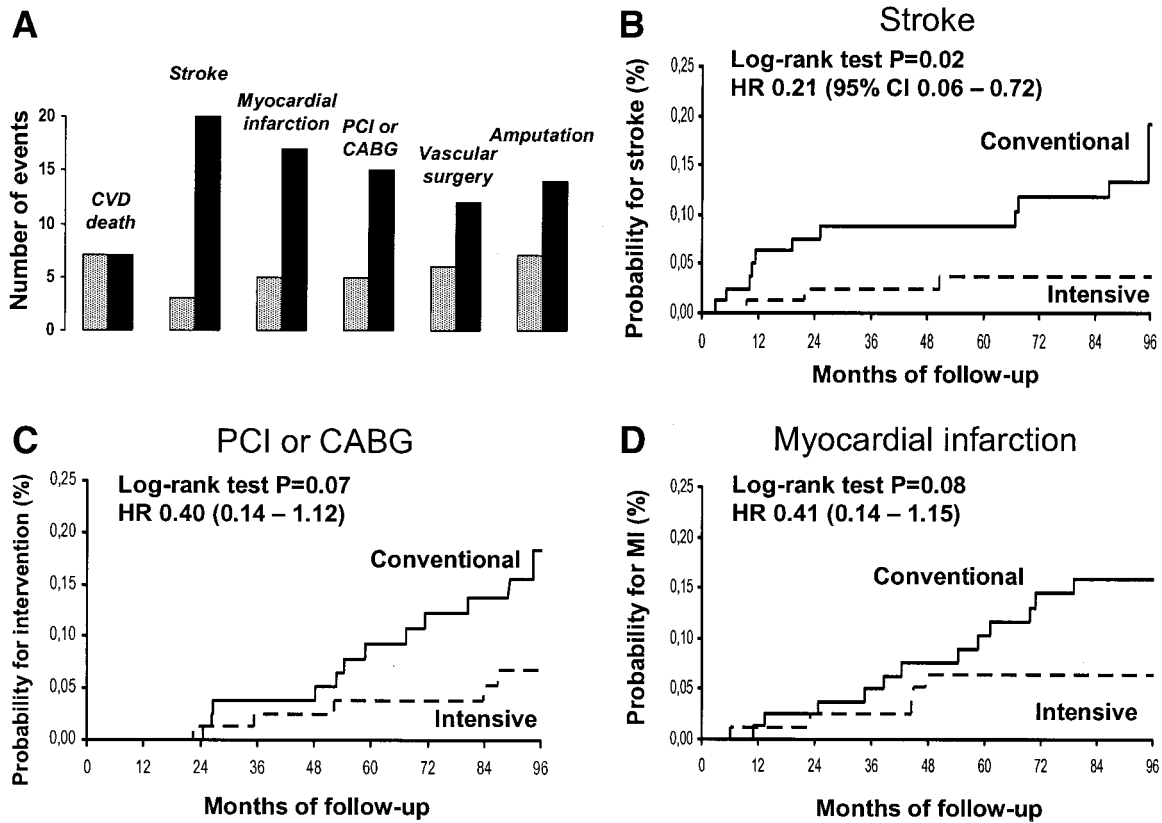


FIG. 1. A: Distribution of the total number of cardiovascular events in the intensive therapy group in the Steno-2 Study (15) (dashed line) and the conventional therapy group (solid line). B: Kaplan-Meier estimates of time to first stroke in the intensive therapy and conventional therapy group. HR, hazard ratio. C: Kaplan-Meier estimates of time to first percutaneous intervention (PCI) or coronary bypass graft (CABG) in the intensive therapy and conventional therapy group. D: Kaplan-Meier estimates of time to first myocardial infarction in the intensive therapy and conventional therapy group.

tional risk markers such as serum lipids and blood pressure.

**What are the benefits of intensified multiple risk factor intervention on morbidity and mortality, and who will benefit the most from such an intervention?** All three multitarget studies demonstrated that intervention against several concomitant risk factors can be done at both the GP level and diabetes clinics, with the Steno-2 Study being the most successful, demonstrating not only reductions in a series of risk factors but also, and more

importantly, marked reductions of both cardiovascular disease and microvascular complications. This was, however, not the case for the two studies including patients with newly diagnosed type 2 diabetes. An obvious explanation for this discrepancy is the much higher number of risk factors and much larger reductions of risk factors in the Steno-2 Study.

Both of the other studies followed national guidelines with risk factor targets for the intervention groups, which were quite similar to the ones used in the control groups,

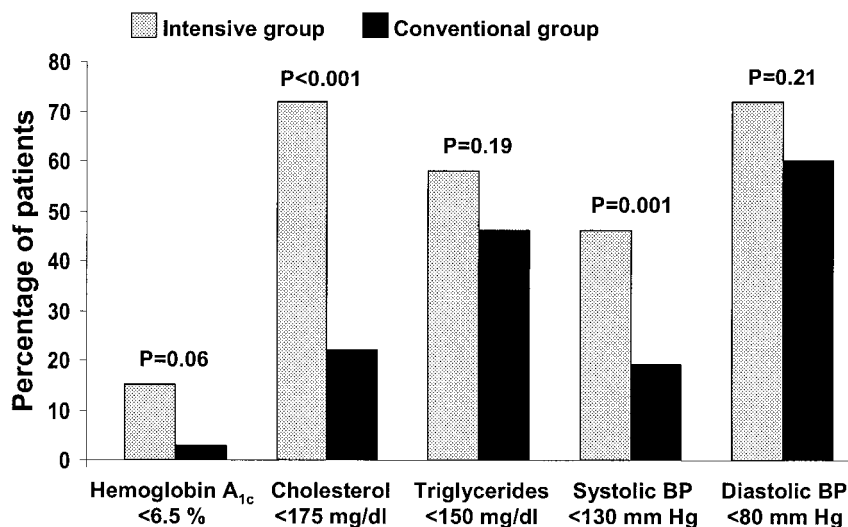


FIG. 2. The percentage of patients in each treatment group who reached the intensive treatment goals at the end of the Steno-2 Study (15).

thereby in itself diminishing the effect of intensified intervention. Also, there will always be a lag between the discovery of new treatments and their subsequent adoption as national guidelines; therefore, patients in intervention groups will not immediately receive the benefits of new knowledge. As an example, the optimal goal for fasting serum total cholesterol in the structured care group in Diabetes Care in General Practice was 230 mg/dl, although several studies published during the actual study period indicated that a much lower value should be strived for (13). Similarly, the goal for systolic and diastolic blood pressure was set relatively high in this study as well as in the Diabetes Intervention Study (12). Intervention against dyslipidemia and blood pressure have proven to induce marked risk reductions as single risk factor interventions in patients with type 2 diabetes, whereas intervention against hyperglycemia was not as effective as expected from the epidemiological studies.

As a consequence, one explanation for the lack of a significant impact of intensified multifactorial intervention in trials involving patients with newly diagnosed type 2 diabetes is that these studies have not been sufficiently powered to detect differences in primary and secondary end points. In contrast, patients in the Steno-2 study were at higher risk for both micro- and macrovascular complications than patients in the other studies, as patients in the Steno-2 Study were selected because of microalbuminuria, thereby increasing the power to detect differences in end points between the two treatment arms.

To sum up, with our present knowledge, the first and second questions asked in the beginning of this section cannot be fully answered. Clear benefits of intensified multifactorial intervention have been shown in high-risk type 2 diabetic patients with elevated urinary albumin excretion rates. These patients may comprise about one-third of patients with type 2 diabetes (20). However, further studies are needed before intensified multifactorial intervention can be recommended to patients with newly diagnosed type 2 diabetes, unless of course obvious severe risk factors are present.

**What is the strongest component of the intensive multifactorial intervention in reducing risk of complications?** The design of the Steno-2 Study did not allow conclusions to be drawn about which treatment component was the most crucial in reducing the incidence of diabetes-related complications. However, the absolute 20% reduction in the risk of cardiovascular events was higher than that in studies applying single-factor intervention strategies aimed at hyperglycemia, hypertension, or dyslipidemia (2,9,21–27). Yet, the populations studied in these trials varied considerably, as did the durations of the intervention and the composite end points.

The UKPDS, which involved 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%), with an absolute difference of 0.9% in glycated hemoglobin values (8). The study did not find significant reductions in any other macrovascular outcomes.

During an 8-year period in the UKPDS, intensive treatment of hypertension in patients with newly diagnosed

diabetes, which decreased systolic and diastolic blood pressure by 10 and 5 mmHg, 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% (2). 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 (21). Treatment of systolic hypertension for 4.7 years in the Systolic Hypertension in the Elderly Program and for 2 years in the Systolic Hypertension in Europe Trial reduced the absolute risk of cardiovascular events by 8% (22) and that of death from cardiovascular causes by 5% (23).

Subgroup analysis showed a large reduction in the absolute risk of cardiovascular events (19%) among diabetic patients with elevated serum total cholesterol concentrations who took statins for 5.4 years for secondary cardiovascular prevention (28). Other subgroup analyses in secondary prevention trials of statins or fibrates have not been associated with such marked effects (24–27).

Taken together, we suggest from the evidence of interventional trials that—concerning pharmacological treatment in the Steno-2 trial—statins and blood pressure-lowering medications might have had the major impact on cardiovascular risk reduction followed by the impact of blood glucose-lowering agents and aspirin. When similar estimates are done based on epidemiological evidence, lipid-lowering treatment appears to account for the major reduction of cardiovascular events (Fig. 3). In the case of prevention of microvascular complications, experiences from UKPDS and other trials would suggest that antihypertensive and antihyperglycemic treatments have been major determinants for the outcome of the Steno-2 Study. **Adherence to intensified treatment.** Patients are often required to take two different pills plus insulin for control of blood glucose, one or two pills for dyslipidemia, and three or four pills for hypertension, in addition to a low-dose aspirin each day. That equates to eight or more drugs each day for each intensively treated type 2 diabetic patient, which does not include any necessary drug treatment of concomitant diseases. No wonder then that patients exposed to life-long intensive treatment of type 2 diabetes need continued and personalized education about indications, mechanisms of actions, and potential side effects of the prescribed medications in order to maintain their motivation. Likewise, an annual consultation centered at an individual risk assessment and a treatment prioritization is a must. Thus, the success of polypharmacological therapy depends on the patient's knowledge and will to accept the prescribed treatment as well as on possible physician barriers to the prescription of treatment. One of the latter obstacles might be that some physicians still consider type 2 diabetes as a benign disease (30). Obviously, side effects and cost of treatment will also greatly influence drug adherence.

In this context, it is a major concern that only 50–70% of the prescribed medication is actually taken by diabetic patients (31,32). Several factors seem to be important to drug adherence. Many of the therapies given in an intensified multifactorial intervention approach are given as

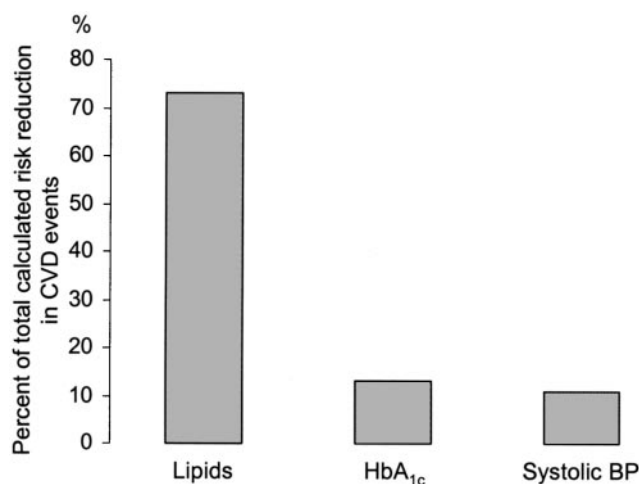


FIG. 3. The UKPDS risk engine (29) is an epidemiological tool calculating the risk for cardiovascular events in patients with type 2 diabetes on the basis of patients' age, fasting serum cholesterol and HDL cholesterol levels, systolic blood pressure, glycemic control, and smoking habits. Data are derived from the Steno-2 Study (15). Average risk factor profiles for patients in the intensive therapy group at baseline and at the end of the study have been calculated, thus giving an opportunity to differentiate the cardiovascular risk reduction into each of the entered variables (29).

preventive treatments irrespective of the presence of symptoms, and therefore patients without symptoms may find that the treatment interferes more with daily life than the disease itself. In this respect, it is worth noting that patients may find that a change in lifestyle and diet can lead to a larger reduction in the quality of life than taking drugs and thus become a barrier for adherence to treatment (31). Even in the case of symptoms, the start of a treatment may not relieve these, thereby in itself being a risk factor for nonadherence to treatment (33). The complexity of the drug regimen also seems to be of importance, especially the number of dosages per day, with decreased adherence being associated with the higher the number of dosages (34–36). To facilitate drug adherence several pharmaceutical companies now market combined drugs (e.g., combinations of oral hypoglycemic agents and combinations of blood pressure-lowering medications).

**Adverse effects to intensified polypharmacy.** Apart from being an obvious barrier to drug adherence, adverse effects may cause serious health problems. In this respect, polypharmacy with several possible drug interactions in type 2 diabetic patients has not been examined in detail. One of the interactions that have been debated is the use of acetylsalicylic acid and ACE inhibitors, which is quite common in the treatment of type 2 diabetes. Some studies have suggested that the beneficial effects of ACE inhibitors in reducing cardiovascular disease are diminished in patients taking acetylsalicylic acid (37). Although a recent metaanalysis of all the major ACE inhibitor trials concludes that the evidence for the reduced benefit is weak (38), it does stress the importance of thorough investigation of side effects and drug interactions in diabetic patients treated with polypharmacy. Another example is from the treatment of dyslipidemia, for which beneficial treatment effects of both fibrates and statins have been demonstrated in single risk factor intervention trials. Yet, the combination of these two drug classes is not recommended, and recently cerivastatin was withdrawn from

the market because of fatal side effects when used in combination with a fibrate. Further studies in this area are definitely required, although it is impossible to investigate all the possible drug combinations used in type 2 diabetes. However, this makes close follow-ups of patients even more important whenever new drugs are prescribed. One of the common side effects to treatment of hyperglycemia in single risk factor trials is weight gain. It is of interest, however, that all three multiple risk factor intervention trials in type 2 diabetes found that weight gain was, although expected, not significantly more pronounced with intensive than with conventional therapy. Similarly, hypoglycemia was not more frequent with intensified multifactorial intervention compared with the control groups, although blood glucose levels were significantly lower with intensive therapy in all three studies.

**Costs of intensified multitarget treatments.** The question of cost of treatment is a crucial one, but results on this subject have not been published from the three multifactorial intervention studies in type 2 diabetes. The direct cost of drugs for the patient can definitely be a barrier for adherence to treatment (39). In Denmark current reimbursement rules (year 2004) ensure that the direct cost of drugs cannot exceed € 485 per year. However, the cost of remedies and strips for blood glucose measurements, foot care, healthy food, etc., are not included in this amount, since special reimbursement rules exist for this area. In the Steno-2 Study all insulin-treated patients in the intensive group were urged to measure blood glucose at least once daily in order to adjust insulin dose. Yet, patient costs are only a fraction of the total cost. The total costs for an average Danish patient with type 2 diabetes have been estimated based on the assumption that most type 2 diabetic patients are followed at the GP level with an average of 3.6 consultations per year (40). These surveys also show that the typical patient is not treated according to current guidelines since, for example, the average number of eye examinations, consultations at a chiropodist, home blood glucose measurements, urinary albumin excretion rate, and measurement of blood lipids are much lower than recommended. Similarly, one-third of type 2 diabetic patients are not treated with glucose-lowering drugs, and only 14% percent of patients are receiving cholesterol-lowering drugs. Despite these shortcomings the total cost is estimated to be € 743 per year with € 173 spent on health care personnel, € 463 spent on drugs, and € 107 spent on remedies and analyses. In contrast, the estimated cost per patient in the intensive group per year in the Steno-2 Study using the same principles and prices would be € 3,168 with € 1,595 spent on drugs (based on the average doses used in the study), € 295 spent on remedies and analyses, and the rest devoted to health care personnel. The high cost for health care personnel is based on the estimate that the costs of consultation in a diabetes clinic is about 15 times higher than the costs of consultation at the GP.

If a systematic intensified multifactorial intervention, as given in the Steno-2 Study, was given at the GP level, the annual cost per patient would amount to € 2,379. In that respect it should be recalled that the number of cardiovascular events was 85 in the conventional group compared with 33 in the intensive therapy group after almost 8 years

of follow-up in the Steno-2 Study. Although the cost-effectiveness of multifactorial intervention in patients with newly diagnosed type 2 diabetes has not been evaluated, the cost-effectiveness of single risk factor intervention against hyperglycemia (41,42), hypertension (43), and dyslipidemia has been demonstrated in patients with type 2 diabetes (44,45).

Taken together, our current knowledge does not support a general use of intensified multifactorial intervention in type 2 diabetes if direct treatment costs are considered a major issue. In contrast, an intensified multifactorial approach may prove highly cost-effective in high-risk populations such as type 2 diabetic patients with increased levels of albumin excretion or with known cardiovascular disorders.

#### THE RATE OF LATE COMPLICATIONS IS STILL FAR TOO HIGH IN INTENSIVELY TREATED TYPE 2 DIABETIC PATIENTS: ROOM FOR FUTURE IMPROVEMENTS

The cardiovascular complications are by far the most threatening for the long-term prognosis in patients with overt type 2 diabetes, and the high-risk microalbuminuric patients participating in the standard multitargeted intervention in the Steno-2 Study showed an event rate of the combined cardiovascular end point of 7% per year. Although the intensified multifactorial intervention cut this event rate by half, it is still more than three times as high as in the matched background population, leaving much room for improvements.

The radical fight back is obviously to intensify the primary prevention of type 2 diabetes (46–48). Perhaps a breakthrough in our understanding of the molecular pathogenesis of abdominal obesity, and thereby of targets for antiobesity drug development, will answer many of the current shortcomings in the prevention and successful treatment of the majority of type 2 diabetic patients, because abdominal obesity is known to cause insulin resistance and an atherogenic low-grade inflammatory state partially due to an excessive secretion of proinflammatory adipokines, including tumor necrosis factor- $\alpha$  (49).

Another target for major improvement is the treatment-resistant hyperglycemia of type 2 diabetic patients. The UKPDS showed a steady decline in pancreatic  $\beta$ -cell function with diabetes duration, most likely caused by an accelerated apoptosis induced by numerous factors, including chronic exposure to elevated levels of free fatty acids, glucose, and proinflammatory cytokines (50). In contrast, in the Steno-2 Study an increase in pancreatic  $\beta$ -cell function was observed in the intensive therapy group, whereas  $\beta$ -cell function remained at the baseline level in the conventionally treated group (Fig. 4). Whether these differences in  $\beta$ -cell function between diabetic patients in UKPDS and the Steno-2 Study reflect potential  $\beta$ -cell-protective effects of a more widespread use of ACE inhibitors and statins in the Steno-2 Study is unsettled. Any intervention that might prevent  $\beta$ -cell apoptosis is expected to improve glycemic control, as are treatments, (e.g., glitazones) that diminish insulin resistance and proinflammation.

Treatment targets for LDL cholesterol and triglycerides can in most cases be achieved rather easily with statins

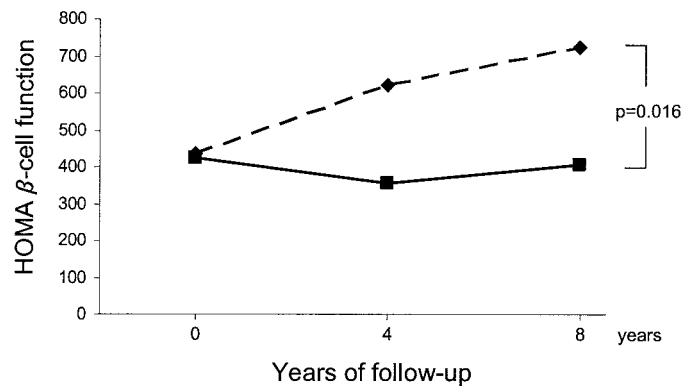


FIG. 4.  $\beta$ -Cell function during follow-up in each of the treatment groups in the Steno-2 Study (15) (dashed line, intensive therapy group; solid line, conventional therapy group).  $\beta$ -Cell function was estimated from a modified HOMA model using the formula  $\beta$ -cell function = fasting plasma C-peptide  $\times$  3.33/(fasting plasma glucose  $-$ 3.5) (51). Changes within the two groups during follow-up were compared using the Mann-Whitney test.

and fibrates. In contrast, it is much more difficult to eliminate the low serum level of HDL cholesterol as a cardiovascular risk factor.

Also, to prevent cardiovascular complications, patients with diabetes might consider to eat fatty fish and walnuts (high in  $\omega$ -3 fatty acids) several times a week (primary prevention of cardiovascular disorders), and patients with overt cardiovascular disease (secondary prevention) or autonomic neuropathy might benefit from following current guidelines from the American Heart Association recommending daily supplements of 1 g  $\omega$ -3 fatty acids (52).

Although there is evidence from epidemiological studies that elevated serum levels of homocysteine (53) and proBNP (54) are strong predictors of increased risk of cardiovascular morbidity and mortality, there is still no convincing evidence from interventional trials that lowering these risk markers (e.g., homocysteine with folic acid) will improve long-term outcome in patients with type 2 diabetes (55).

Continued smoking has disastrous effects on the progress of retinopathy and cardiovascular complications, and much more needs to be explored about how to successfully apply smoking cessation approaches.

Finally, it is anticipated that progress within the field of pharmacogenomics, identifying by genotype those patients who are responders and less responders to a given drug treatment of hyperglycemia, dyslipidemia, or hypertension, will greatly contribute to efficacious personalized interventions to improve the risk marker profile and thereby enhance the health of patients suffering from type 2 diabetes.

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