Intensified Multifactorial Intervention and Cardiovascular Outcome in Type 2 Diabetes: The Steno-2 Study

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We recently published the results of the Steno-2 study, which evaluated the benefits of intensified integrated behavior modification and targeted polypharmacy. The results provide abundant evidence that an ambitious treatment strategy is superior to a conventional one. The study involved 160 high-risk type 2 diabetic patients with microalbuminuria—a strong risk factor of both macrovascular and microvascular complications—aged 55.1 years, who were randomly assigned to a conventional or an intensive, multifactorial intervention for a period of 7.8 years. In the intensive group, a stepwise treatment plan was adopted involving both continuous lifestyle education and motivation and an ambitious goal-oriented pharmacological treatment of known modifiable risk factors. The conventional group was treated in accordance with national guidelines for type 2 diabetes with less stringent goals. The specific significant group differences in the degree of change in key clinical and biochemical variables at the end of the study were (in the intensive group): lower systolic and diastolic blood pressures, hemoglobin A_{1c} (HbA_{1c}), fasting serum total and low-density lipoprotein (LDL) cholesterol, fasting serum triglycerides, and 24-hour urine albumin excretion, as well as increased carbohydrate and decreased fat intake as percentage of total energy. There was no difference in weight gain between groups during follow-up and no other major side effects were reported. The primary end point was a macrovascular outcome: a composite of death from cardiovascular causes, nonfatal myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, nonfatal stroke, amputation for ischemia, or vascular surgery for peripheral arterial atherosclerosis. The differences between groups in surrogate end points translated into the following significant group differences in final clinical end points: 44% of patients in the conventional group had a cardiovascular event compared with 24% in the intensive group, ie, a relative risk reduction of about 50%. Also, the relative risk of nephropathy, retinopathy, and autonomic neuropathy (secondary end points) was diminished by about 60% in the intensively treated group. In conclusion, an intensified and goal-oriented multipronged approach to the treatment of type 2 diabetes reduces cardiovascular events, as well as nephropathy, retinopathy, and autonomic neuropathy, by about half. The challenge is to ensure that this experience is widely adopted in daily practice.

MANY CASES of type 2 diabetes mellitus were until about 2 decades ago thought to be innocent and benign disorders. Since then, epidemiological research has provided insights that type 2 diabetes is in fact a severe vascular disease characterized by a 2- to 6-fold increased risk of cardiovascular disease and death, and by a life expectancy which in high-risk patients may be shortened by 5 to 10 years.[1] Apart from macrovascular complications, diabetic nephropathy, retinopathy, and neuropathy, collectively termed microvascular complications, also constitute a major challenge in patients with type 2 diabetes mellitus.

Once type 2 diabetic patients have developed severe vascular complications, the 5-year survival is comparable to that of many malignant disorders. The epidemic growth worldwide in the incidence of type 2 diabetes and the severe vascular complications make it an enormous burden to the affected patients and to national health budgets.

During recent years, numerous prospective studies have, however, identified a series of potentially modifiable risk factors for ischemic vascular complications.[1] These factors include hyperglycemia, hypertension, dyslipidemia, microalbuminuria, a proinflammatory state, and smoking. Also, crucial information has been gained from single risk factor–intervention trials in both diabetic and nondiabetic subjects. The degree of relative risk reduction with each individual risk factor target ranges from borderline for hyperglycemia-lowering in the United Kingdom Prospective Diabetes Study (UKPDS), through moderate (eg, ~10% with asprin therapy), to substantial (eg, 25% to 30% with blood pressure reduction or statin-induced lipid-lowering). Moreover, in long-term studies, intervention against hyperglycemia or hypertension has shown beneficial effects on the risk of microvascular events. Against the background of these trials, many national diabetes associations recommend a multiple risk factor–intervention approach from the very time at which the clinical diagnosis of type 2 diabetes is made. The approach appears reasonable; however, it involves considerable effort and expense on the part of the patient, as well as the health care providers, and the efficacy of this "gold standard" of multifactorial therapy has never previously been validated in a prospective trial.

INTENSIFIED MULTIFACTORIAL INTERVENTION: THE EVIDENCE-BASED THERAPEUTIC PACKAGE PAYS OFF

Recently, we published the results of the Steno-2 study,[2] which evaluated the benefits of integrated intensive behavior modification and intensive targeted and individually tailored polypharmacy. The results provide abundant evidence that the combined and intensified treatment strategy is clearly superior to a conventional one.

The Steno-2 study involved 160 type 2 diabetic patients with microalbuminuria—a strong risk factor of both macrovascular and microvascular complications—aged 55.1 years, who were randomly assigned to a conventional or an intensive, multifactorial intervention for a period of 7.8 years. In the intensive group, a stepwise treatment plan was adopted involving both continuous education and motivation for adherence to a healthy

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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
HbA_{1c} (%)	<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

NOTE. 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. Data from Gæde et al.[2]

lifestyle and an ambitious goal-oriented pharmacological treatment of known risk factors. Due to the presence of microalbuminuria, all patients were prescribed an angiotensin-converting-enzyme (ACE) inhibitor or, if contraindicated, an angiotensin II (AT II)–receptor antagonist. Antihyperglycemic therapy was initiated by gliclazide (lean subjects) or metformin (obese subjects), with a combination of the 2 drugs being considered when the hemoglobin A_{1c} (HbA_{1c}) target was not met. When HbA_{1c} exceeded 7%, despite maximal dosage of gliclazide and metformin, insulin at bedtime was recommended. All patients received vitamin/mineral supplements including folic acid and aspirin in a dose of 150 mg/d. Hypertension was treated in a stepwise approach if ACE inhibitor or AT II–receptor antagonists failed to achieve targets. A combination with thiazides, calcium antagonists or β-blockers was used in these patients. Raised serum cholesterol was treated with statins, and fibrates were used to control isolated cases of hypertriglyceridemia (Table 1 shows the treatment goals of the Steno 2 study). The conventional group was treated in accordance with national guidelines for type 2 diabetes with less stringent goals.

The specific significant group differences in the degree of change in key clinical and biochemical variables at the end of the study were (in the intensive group): lower systolic and diastolic blood pressures, HbA_{1c}, fasting serum total and low-density lipoprotein (LDL) cholesterol, fasting serum triglycerides, and 24-hour urine albumin excretion (Table 2), as well as increased carbohydrate and decreased fat intake as percentages of total energy. There was no significant difference in weight gain or waist circumference between groups during follow-up and no major side effects were reported.

Table 2. Steno-2 Study: Biochemical Risk Factors at Year 7.8: Conventional Versus Intensive Therapy

Variable	Conventional *v* Intensive Therapy Values
HbA_{1c}	9.0% *v* 7.9%
Systolic blood pressure	146 *v* 131 mm Hg
Diastolic blood pressure	78 *v* 73 mm Hg
Total cholesterol	5.6 *v* 4.1 mmol/L
LDL cholesterol	3.3 *v* 2.1 mmol/L
Triglycerides	3.0 *v* 1.7 mmol/L
Urinary albumin	126 *v* 26 mg/24 h

NOTE. Data are form Gæde et al.[2]

After 7.8 years of intervention, the primary end point was a macrovascular outcome: a composite of death from cardiovascular causes, nonfatal myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, nonfatal stroke, amputation for ischemia, or vascular surgery for peripheral arterial atherosclerosis.

The differences in surrogate measures between groups translated into the following significant group differences in key end points: 44% in the conventional group had a cardiovascular event compared with 24% in the intensive group, or a relative risk reduction of about 50% (Fig 1). Also, the curves representing time to first cardiovascular event for the 2 groups continued to diverge throughout the follow-up period, suggesting the potential of an even greater effect on long-term treatment.

After 7.8 years, the relative risk of developing nephropathy, retinopathy, and autonomic neuropathy all were diminished by about 60% for the intensively treated group (Fig 2).

In the Steno-2 study, lifestyle education had only a minor measurable impact on traditional risk markers.[3] However, it

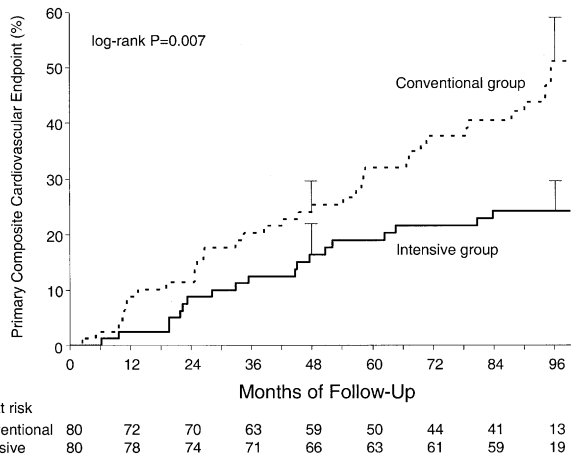

Fig 1. Steno-2 study: primary composite cardiovascular endpoint. Reprinted from Gæde et al.[2]

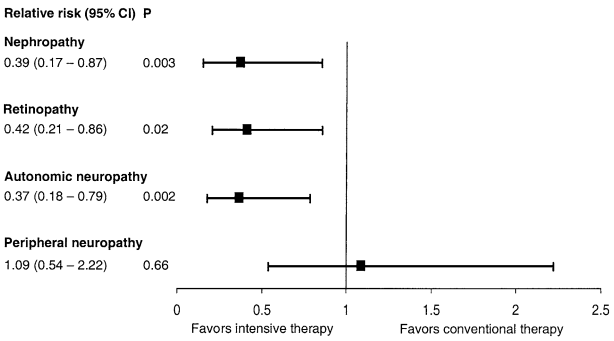

Fig 2. Steno-2 study: Secondary microvascular endpoints. Reprinted from Gæde et al.[2]

should be emphasized that compared with the conventional group the intensive group was prescribed a diet with considerably more vegetables and fish, food items that may have beneficial effects on cardiovascular endpoints beyond what is measured as changes in, for example, energy intake or serum lipids. Thus, diets that are naturally high in omega-3 fatty acids, α-linolenic acid, and flavonoids have proved beneficial as secondary prevention of cardiovascular disease even though no effects were seen on traditional risk markers such as serum lipids and blood pressure.[4,5]

The unsuccessful intervention against risk factors in the conventional group despite national treatment guidelines with well-defined goals and despite universal health coverage in our country is, indeed, provocative and suggests that the major challenge in the care of the patient with type 2 diabetes of today is likely to be continued education and motivation of both the physician and the patient. Any reminiscence of therapeutic nihilism should enthusiastically be fought against.

KEY LESSONS FROM THE STENO-2 STUDY

For the physician who provides care for patients with type 2 diabetes, the imperative from the Steno-2 study is that early and continuous application of an ambitious, targeted, multiple risk factor–intervention approach is a *sine qua non* in high-risk patients, that is, micro/macroalbuminuric patients or patients identified through health risk assessment tools. Annual screening for microalbuminuria, which is present in about one third of the type 2 diabetic population, is easy and inexpensive and should be considered *a must* of good practice for diabetes care. Given the poor prognosis of high-risk diabetic patients without an intensive treatment program that also involves continued support and treatment prioritization with regular intervals, it might be considered reasonable to refer high-risk type 2 diabetic patients to diabetes specialists.

The lesson from the Steno-2 study by no means confines the physician to a specific treatment algorithm. Obviously, it might be possible to achieve even greater benefits using supplementary evidence-based approaches.

Although systematic cost-benefit analysis of multifactorial intervention in patients with type 2 diabetes has not yet been evaluated, the cost-effectiveness of single risk factor intervention against hyperglycemia, hypertension, and dyslipidemia has been demonstrated in diabetes.[6-8] Thus, the message for the health care policymakers is pretty straightforward: multiple risk factor intervention in high-risk patients with type 2 diabetes is evidence-based, validated, and cost-effective.

The intensified multifactorial treatment approach in patients with type 2 diabetes is further justified by the accumulating results from single risk factor–intervention trials, as well as from insights gained from prospective studies. A short overview of some of the pertinent data is given.

EVIDENCE FOR THE TREATMENT EFFECT OF HYPERGLYCAEMIA

Hyperglycemia and Microvascular Complications

The combined results of the UKPDS and Kumamoto studies illustrate the importance of normalizing the blood glucose values in type 2 diabetic patients in order to prevent the prevalence and progression of microangiopathy.[9-11] Neither the UKPDS nor the Kumamoto study found any evidence to support the existence of a threshold value for blood glucose. In other words, for all increased HbA_{1c} levels, there is something to be gained by lowering the HbA_{1c} level in the form of reduced risk of microvascular complications. The UKPDS study found that the relative risk reduction for complications per 1% reduction in HbA_{1c} is similar for all levels of HbA_{1c}. In this connection, it should be noted that during intensified insulin treatment in a group of patients with type 2 diabetes, the decline in HbA_{1c} was 3 times higher for a group of patients with an average HbA_{1c} of 13% compared with a group of patients with an average HbA_{1c} of 9%. This means that the advantage of intervening against hyperglycemia in a patient with seriously dysregulated glucose metabolism will be a greater absolute risk reduction for microangiopathy than in a relatively well-regulated patient.

Hyperglycemia and Macrovascular Complications

Prospective studies of patients with type 2 diabetes have shown that the level of hyperglycemia is strongly associated with cardiovascular mortality and/or total mortality. With the exception of obese type 2 diabetic patients treated with metformin, there is no convincing evidence that blood glucose–reducing treatment of type 2 diabetes mellitus can reduce the risk of macrovascular disease and death. The lack of any significant impact on cardiovascular morbidity and mortality in the UKPDS must be seen in the light of the relatively modest HbA_{1c} reduction in the intervention group (0.9% compared with the control group). The UKPDS has hence not confirmed or excluded the beneficial effects of glucose-lowering on macrovascular outcomes. Several large clinical studies, like the Action in Diabetes and Vascular Disease Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial and the ADOPT (A Diabetes Outcome Progression Trial) study have been designed to further address this issue. It is of interest in this context that the Multiple Risk Factor Intervention Trial (MRFIT) showed that two thirds of the increased cardiovascular mortality among diabetic patients is caused by risk factors other than hyperglycemia.[12]

EVIDENCE FOR THE TREATMENT EFFECT OF HYPERTENSION

From post hoc subgroup analyses of intervention studies and the UKPDS,[13] there is evidence that intensive blood pressure–

lowering treatment reduces the risk of microvascular as well as macrovascular complications. The effect of blood pressure regulation on microvascular sequelae occurs sooner than the similar effect of blood glucose regulation. Neither type of complication proved to have a lower threshold value for blood pressure, indicating that the target for the treatment may be set at a low level. There seem to be no special advantages or disadvantages derived from the antihypertensive drugs used, although there has been some debate about whether short-acting calcium antagonists should be used. The decisive factor for measuring the effect seems to be the level of blood pressure obtained rather than the specific antihypertensive drug used. At this point, it should be repeated that the majority of hypertensive type 2 diabetic patients will require between 2 and 3 antihypertensive drugs to obtain satisfactory blood pressure regulation.

EVIDENCE FOR THE TREATMENT EFFECT OF DYSLIPIDEMIA

The most common pattern of dyslipidemia in type 2 diabetic patients is elevated serum triglyceride levels and decreased serum high-density lipoprotein (HDL) cholesterol levels. In addition, epidemiological studies show that type 2 diabetes patients without previous myocardial infarction are exposed to the same risk of myocardial infarction as nondiabetic patients with a previous infarction. Post hoc subgroup analyses of patients with type 2 diabetes mellitus and known ischemic heart disease with normal or raised fasting serum total cholesterol values or too low fasting serum HDL cholesterol values have documented the effect of secondary intervention using statin drugs or fibrates. The effect is relatively immediate. Similarly, in the recent Heart Protection Study,[14] the effect of these drugs as primary prevention of ischemic vascular disease in type 2 diabetic patients was clearly demonstrated, and the large risk reductions seen in previous secondary intervention studies was confirmed. It is important to note that patients were eligible for enrollment in this study if the fasting serum total cholesterol was above 3.5 mmol/L, thus suggesting a lowering of the treatment target for this risk factor.

EVIDENCE FOR THE TREATMENT EFFECT OF MICROALBUMINURIA

Microalbuminuria (urinary albumin excretion rate in the range 30 to 300 mg per 24 hours) is an important risk factor for the development of both microvascular and macrovascular disease.[15,16] It is known that both the treatment of hyperglycemia and hypertension can reduce the albumin excretion rate. However, treatment with ACE inhibitors seems to reduce urinary albumin excretion rate independently of the blood pressure–lowering effect of these drugs.[15] Ninety-four patients with type 2 diabetes mellitus and microalbuminuria and a blood pressure below 140/90 mm Hg were randomized to treatment with 10 mg enalapril daily or placebo. Over the study period of 5 years, 6 patients in the ACE inhibitor group and 19 in the placebo group developed diabetic nephropathy. This difference could not be attributed to differences in glycemic control, body mass index, or blood pressure values, which were similar in both groups throughout the study period. Reciprocal plasma creatinine levels as a measure for renal function decreased significantly in the placebo group as a sign of deterioration of kidney function but remained stable in the enalapril group. Similarly, treatment with the AT II-receptor antagonist irbesartan has proven effective in reducing progression to diabetic nephropathy in microalbuminuric type 2 diabetic patients during a 2-year follow-up period.[16] This effect was found to be independent of the blood pressure–lowering effect. Finally, the combination of an ACE inhibitor and an AT II-receptor antagonist (dual blockade) was significantly more effective than either drug alone in lowering blood pressure and reducing the albumin:creatinine ratio during short-term treatment for 12 weeks.

EVIDENCE FOR THE TREATMENT EFFECT OF ASPIRIN

The beneficial effect of low-dose acetylsalicylic acid as a secondary prevention of cardiovascular disease is well established in both the diabetic and nondiabetic population.

The Hypertension Optimal Treatment (HOT) trial[17] also examined the effect of treatment with acetylsalicylic acid in patients with hypertension. Of the 18,790 patients, half were randomized to 75 mg aspirin daily and the other half to placebo. No specific data for the diabetic subgroup have been published. For the whole study population, a significant 15% relative reduction in the risk of major cardiovascular events was seen, primarily due to a 36% relative reduction in the risk of myocardial infarction. Fatal bleeds were equally common in the 2 groups, but nonfatal bleeding (primarily gastrointestinal) was significantly more frequent among patients receiving acetylsalicylic acid than in those receiving placebo.

The US Physicians Health Study[18] was a primary prevention trial in which a low-dose aspirin regimen (375 mg every other day) was compared with placebo in 22,071 male physicians. There was an overall significant 44% relative risk reduction of myocardial infarction in the acetylsalicylic acid–treated group, whereas subgroup analysis in the diabetic physicians revealed a relative risk reduction of 61% for the diabetic men taking aspirin.

EVIDENCE FOR THE EFFECT OF SMOKING CESSATION

Smoking may be one of the most important risk factors for cardiovascular disease in type 2 diabetes mellitus. This is based on several epidemiological studies, where smoking is found to be a risk factor for both all-cause mortality, cardiovascular disease, and stroke in both the diabetic and nondiabetic population.

The MRFIT randomized 12,866 subjects to a control group or an intervention group with intervention against several risk factors such as diet, smoking, and blood pressure.[12] Smoking cessation programs were used with individual advice from a doctor. A 13% reduction in the number of smokers in the intervention group was seen after 6 years. However, no significant effects on total mortality or mortality from cardiovascular disease were seen in the overall analyses.

Despite these negative results from one of the most successful smoking cessation intervention programs, it is because of the epidemiological evidence recommended that all diabetic patients quit smoking.

HEALTHY FOOD AND PHYSICAL ACTIVITY: THE ESSENTIALS OF WELL-BEING

Educational programs and randomized studies of the effects of an energy-restrictive diet in obese patients with type 2 diabetes mellitus resulting in a 5% to 15% loss of body weight

have shown significant reduction in surrogate end points such as levels of blood glucose, serum lipids, and blood pressure. The results of these nonpharmacological interventions are limited by the relatively short duration of the studies and the lack of clinical end points such as microangiopathy and macroangiopathy. Besides, general clinical experience has also shown that what the patients find the most difficult is not to lose weight in itself but to maintain the weight loss in the long term.

The UKPDS, comprising more than 4,000 patients with newly diagnosed type 2 diabetes, found that 16% of the patients had normalized the fasting blood glucose level 3 months after the start of the diet intervention.[19] One year after the start of the project, however, less than half of these patients were able to maintain normal fasting blood glucose based on the diet alone despite an average weight loss of 9.4 kg.

Continued efforts to limit the diet for the purpose of losing weight might therefore be restricted to the relatively few type 2 diabetic patients who by doing so demonstrate their ability to transform their motivation into practice and maintain the desired weight loss. Hence, it is our considered opinion that the majority of obese type 2 diabetic patients should be primarily motivated to achieve and maintain a qualitative improvement of their diet as several intervention studies of nondiabetic patients have shown that a change in diet involving greater intake of vegetables and fish and less fat from dairy products and fat meat reduces the risk of developing ischemic cardiovascular diseases.[4,5] There are no results from clinically controlled studies of the effect of regular physical activity on the risk for development of microvascular or macrovascular complications in type 2 diabetes patients. However, cross-sectional studies show that physical activity in the form of moderate to strenuous physical training reduces hyperglycemia in part through an increase in insulin sensitivity.[20] Since regular physical activity also has beneficial effects on the fasting serum lipid profile, blood pressure, heart function, muscles, joints, bones, and the patients' general condition, type 2 diabetic patients are encouraged to engage in regular, light-to-moderate physical activity every day.

CONCLUSION

The available evidence from clinical trials and epidemiological studies in type 2 diabetes suggest that lowering of serum levels of lipids, as well as of blood pressure, and reduction in plasma glucose seem to be crucial to reducing cardiovascular events and microvascular complications. The Steno-2 study, which is the first validation of the integrated attack on the classical modifiable risk factors combining goal-directed tailored polypharmacy and lifestyle improvements, convincingly shows the magnitude of the benefit from this approach. The results from a study on the impact of structured education and organization of general practitioners in the care of patients with type 2 diabetes are encouraging and suggest that it is possible to transfer the Steno-2 study experience to daily practice.[21]

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