

# The Steno Diabetes Study

Reviewed by K.M. Venkat Narayan, MD, MPH, FRCP, FACP

## STUDY

Gaude P, Vedel P, Larsen N, Jensen GVH, Parving H, Pedersen O: Multifactorial interventions and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 348:383–393, 2003

## SUMMARY

**Objective.** A comparison of the effect of a targeted, intensified, multifactorial intervention with that of conventional treatment on risk factors for cardiovascular disease (CVD).

**Design.** Randomized, open, parallel trial at the Steno Diabetes Center in Denmark.

**Participants.** Eighty patients with type 2 diabetes and microalbuminuria were assigned to receive conventional treatment in accordance with national guidelines, and another 80 were assigned to receive intensive treatment with stepwise implementation of behavior modification and pharmacological therapy that treated hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, along with aspirin.

**Primary endpoints.** Death from CVD, nonfatal myocardial infarction (MI), nonfatal stroke, revascularization, and amputation.

**Results.** At a mean follow-up of 7.8 years, patients receiving the intensive therapy had a 53% (95% CI: 27–76%) lower risk of CVD, 61% (13–83%) lower risk of nephropathy, 58% (14–79%) lower risk of retinopathy, and

63% (21–82%) lower risk of autonomic neuropathy. One CVD event was prevented for every five patients treated intensively for 7.8 years.

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

## COMMENTARY

People with diabetes have two to three times the risk of CVD than those without diabetes.<sup>1</sup> Effective treatments are available to prevent the macro- and microvascular complications of diabetes. In particular, there is evidence of benefit of single-factor interventions: intensive glucose, lipid, and blood pressure control; treatment of microalbuminuria; and use of regular aspirin.<sup>2,3</sup> There is, however, scant literature on the effectiveness of multifactorial interventions, as would be applied in clinical practice, on CVD among people with diabetes.

The Steno study has attempted to close this gap in evidence by testing an intensive multifactorial intervention against conventional treatment. The intensive intervention consisted of stepwise introduction of lifestyle and pharmacological interventions aimed at keeping glycosylated hemoglobin < 6.5%, blood pressure < 130/80 mmHg, total cholesterol < 175 mg/dl, and triglycerides < 150 mg/dl. The lifestyle component of the intensive intervention included reduction in intake of dietary fat, regular exercise, and smoking cessation. Participants receiving intensive interven-

tion were also advised to take aspirin, a dietary supplement consisting of vitamins E and C, folic acid, and chromium picolinate and were given an angiotensin-converting enzyme (ACE) inhibitor, regardless of blood pressure.

After 7.8 years of follow-up, 44% of patients in the conventional arm, but only 24% in the intensive, multifactorial arm, developed CVD, representing a 53% reduction in risk. One CVD event was prevented for every five patients treated for 7.8 years with intensive, multifactorial intervention. The risks for nephropathy, retinopathy, and autonomic neuropathy were also lower in the multifactorial treatment group by 61, 58, and 63%, respectively.

From a study such as this one, it is not possible to tease out the effects of each component of the multifactorial intervention nor was this the purpose of the study. The authors were justified, based on existing evidence for CVD benefit, in including smoking cessation, physical activity promotion, lipid and blood pressure control, aspirin therapy, and ACE inhibitor therapy.<sup>3,4–7</sup> Strong evidence for microvascular benefits from glycemic control exists,<sup>8</sup> and, although not unequivocally established, glucose control may also have positive benefits on CVD. On the other hand, CVD benefits from routine vitamin or mineral supplementation have not been established, and their inclusion in a multifactorial intervention to prevent CVD is premature.

Despite these limitations, the Steno study provides evidence that an aggressive multifactorial intervention can be delivered in a real-life clinical practice

situation and can lower the risk of CVD among people with diabetes and microalbuminuria by about 50%. The quality of diabetes care remains suboptimal in the United States and elsewhere, despite the availability of effective treatments to prevent CVD.<sup>9</sup> The Steno study shows us the benefits of multifactorial interventions in practice and gives us strong reason to believe that evidence-based guidelines can be translated into clinical practice. The potential benefit to be accrued, in terms of CVD prevention, from the systematic application of current knowledge is enormous.

## REFERENCES

- <sup>1</sup>Saydah SH, Eberhardt MS, Loria CM, Brancati FL: Age and the burden of death attributable to diabetes in the United States. *Am J Epidemiol* 156:714–719, 2002
- <sup>2</sup>Narayan KM, Gregg EW, Fagot-Campagna A, Engelgau MM, Vinicor F: Diabetes: a common, growing, serious, costly, and potentially preventable public health problem. *Diabetes Res Clin Pract* 50:S77–S84, 2000
- <sup>3</sup>Narayan KM, Gregg EW, Engelgau MM, Moore B, Thompson TJ, Williamson DF, Vinicor F: Translation research for chronic disease: the case of diabetes. *Diabetes Care* 23:1794–1798, 2000
- <sup>4</sup>Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 335:1001–1009, 1996
- <sup>5</sup>Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 1755–1762, 1998
- <sup>6</sup>Hu FB, Stampfer MJ, Solomon C, Liu S, Colditz GA, Speizer FE, Willett WC, Manson JE: Physical activity and risk for cardiovascular events in diabetic women. *Ann Intern Med* 134:96–105, 2001
- <sup>7</sup>The Heart Outcomes Prevention Evaluation Study Investigators: Effect of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high risk patients. *N Engl J Med* 342:145–153, 2000
- <sup>8</sup>UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. (UKPDS 33). *Lancet* 352:837–853, 1998
- <sup>9</sup>Saaddine JB, Engelgau MM, Beckles GLA, Gregg EW, Thompson TJ, Narayan KM: A diabetes report card for the United States: quality of care in the 1990s. *Ann Intern Med* 136:565–574, 2002

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