EDITORIAL

# Reducing Cardiovascular Risk in Type 2 Diabetes

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Mortality from cardiovascular disease is increased by a factor of two to three in persons with diabetes as compared with the general population.[1] Cardiovascular disease develops earlier in the presence of diabetes and occurs as often in diabetic women as in diabetic men. To reduce this increased risk, a multifactorial approach to the management of type 2 diabetes has been advocated. The American Diabetes Association, for example, recommends not only good glycemic control but also identification and aggressive treatment of associated cardiovascular risk factors, with more stringent target levels for lipids and blood pressure than those recommended for the general population (Table 1).[2] Such a strategy requires considerable effort on the part of physicians and patients, and strong evidence of its benefits is therefore critical. Yet data have been lacking on the effects of such a multifactorial approach.

In this issue of the *Journal*, a report by Gæde and colleagues clearly demonstrates that a multifactorial strategy reduces the risk of cardiovascular disease among patients with type 2 diabetes.[3] The investigators randomly assigned 160 patients with type 2 diabetes and microalbuminuria to receive conventional care or intensive treatment. Conventional care was delivered according to the recommendations of the Danish Medical Association. (These recommendations were revised in 2000, and several targets for both groups were subsequently lowered.) Patients in the intensive-therapy group were treated with a stepwise introduction of lifestyle and pharmacologic interventions intended to maintain glycosylated hemoglobin values below 6.5 percent, blood pressure below 130/80 mm Hg, cholesterol levels below 175 mg per deciliter (4.5 mmol per liter), and triglyceride levels below 150 mg per deciliter (1.7 mmol per liter). Recommended lifestyle interventions included reduced intake of dietary fat, regular participation in light or moderate exercise, and cessation of smoking. All participants in the intensive-therapy group were also advised to take aspirin and a dietary supplement that included vitamins E and C, folic acid, and chrome picolinate. In addition, patients in the intensive-therapy group were given an angiotensin-converting–enzyme (ACE) inhibitor (or, if contraindicated, an angiotensin II–receptor antagonist), regardless of blood pressure, to slow the progression of renal disease; after 2000, these medications were also routinely prescribed for patients in the conventional-therapy group.

After a mean follow-up of 7.8 years, one or more cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction or stroke, coronary- or peripheral-artery revascularization, or amputation as a result of ischemia) had occurred in

**Table 1. Target Levels of Risk Factors in Patients with Diabetes.***

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| Blood pressure below 130/80 mm Hg |
| Low-density lipoprotein cholesterol below 100 mg/dl (2.6 mmol/liter) |
| Triglycerides below 150 mg/dl (1.7 mmol/liter) |
| High-density lipoprotein cholesterol above 40 mg/dl (1.1 mmol/liter)† |
| Glycosylated hemoglobin below 7 percent |

* The recommendations are from the American Diabetes Association.[2] To achieve targets, lifestyle interventions (diet and exercise) are recommended first, followed by pharmacologic interventions, if necessary. Details are available at http://care.diabetesjournals.org/cgi/content/full/26/suppl_1/s33.

† In women, a level above 50 mg per deciliter (1.3 mmol per liter) may be appropriate.

44 percent of patients in the conventional-therapy group but in only 24 percent of those in the intensive-therapy group. The risk reduction was similar when revascularization procedures were excluded. Rates of nephropathy, retinopathy, and autonomic neuropathy were also markedly reduced in the intensive-therapy group — findings that are consistent with those reported after a shorter follow-up period in the same population.[4]

That a multifactorial approach substantially reduced cardiovascular risk is not in itself surprising. Previous studies have shown benefits of several components of this approach. For example, subgroup analyses of diabetic participants in large clinical trials have demonstrated reductions in major cardiovascular events on the order of 25 percent with statin therapy,[5] 15 percent with aspirin therapy,[6] and 50 percent with blood-pressure reduction (to a diastolic pressure of 80 mm Hg or less).[6] But the study conducted by Gæde et al. provides the best evidence to date of the magnitude of the benefit that can be derived from instituting several interventions. As the authors acknowledge, the design of their study did not allow them to identify which intervention or combination of interventions was responsible for the benefits, or to what extent. Certainly, there is good justification for aggressive treatment of elevated lipid levels and blood pressure in diabetic patients with these risk factors and for the use of aspirin in those with cardiovascular disease or other cardiovascular risk factors. But is there evidence to support the other interventions?

Gæde et al. did not specifically assess the effects of ACE inhibitors on cardiovascular risk, since these agents were ultimately prescribed routinely for patients in both groups. In the Heart Outcomes Prevention Evaluation Study, treatment with an ACE inhibitor reduced the rate of cardiovascular events by one fourth in patients with diabetes who had at least one other cardiovascular risk factor, regardless of whether they had microalbuminuria.[7] These data suggest that, barring contraindications, treatment with ACE inhibitors should be considered for high-risk patients with diabetes, even in the absence of hypertension and microalbuminuria.

It is questionable whether glucose control in isolation can reduce cardiovascular risk. Although poor glycemic control is associated with an increased risk of cardiovascular events, in the United Kingdom Prospective Diabetes Study, intensive blood glucose control with insulin or a sulfonylurea drug resulted in a nonsignificant reduction in the risk of myocardial infarction and no reduction in the risk of stroke, as compared with conventional therapy.[8] A secondary analysis suggested that metformin, when used as the sole hypoglycemic agent, reduced the risk of myocardial infarction by a third[9]; however, no benefit was observed when metformin was combined with a sulfonylurea drug. A reasonable conclusion is that targeting associated risk factors is much more likely to be cardioprotective than controlling the glucose level. Nonetheless, good glycemic control is warranted to reduce the risks of nephropathy, retinopathy, and neuropathy.

There is stronger evidence that lifestyle interventions, particularly cessation of smoking, have a cardiovascular benefit. The risk of cardiovascular events is increased by a factor of at least two in diabetic patients who smoke, and it declines after cessation of smoking. Regular exercise should also be encouraged. Observational data show a strong inverse association between regular physical activity — even an increased walking pace — and cardiovascular events in persons with diabetes.[10]

Diet is likewise important, but the best diet for reducing cardiovascular risk remains uncertain. The intensive-therapy group in the study by Gæde et al. was encouraged to follow a diet low in both total and saturated fats. Emerging evidence, however, suggests greater benefits from replacing saturated fats (and trans fats) with unsaturated fats and making other dietary changes — for example, increasing the intake of whole grains, fruit, and vegetables, and reducing the intake of refined carbohydrates — than from reducing total fats.[11] A cardiovascular benefit of routine vitamin or mineral supplementation has not been substantiated; recent clinical trials have shown no significant reductions in the rates of coronary events in association with the use of vitamin E[12] or a combination of vitamins E and C and beta carotene.[13]

Despite the benefits of a multifactorial strategy, making it routine practice is not easy. Interventions similar to those implemented by Gæde et al. are currently recommended[2] but are underused for several reasons. They require education and time on the part of physicians. In addition, patients must be willing to follow a schedule of regular office visits and blood tests and often to take multiple medications, which may have side effects, at substantial expense for those who lack prescription-drug coverage. In a recent study of nearly 2 million Medicare beneficiaries with diabetes, almost 50 percent had not undergone lipid testing in the preceding

two years[14]; rates as low or lower have been reported with other recommended components of a multifactorial approach to care. Furthermore, target levels for coronary risk factors and glycemic control are achieved in only a minority of patients who undergo the recommended testing. Participants in trials are particularly motivated, yet at the conclusion of the current study, the target systolic blood pressure was reached in less than half the patients in the intensive-therapy group, and target glycosylated hemoglobin levels were achieved in less than a fifth. Although these findings point to the difficulty of achieving the targets in the real world, they also suggest the possibility of even greater benefits if the targets can be met more frequently.

The study by Gæde and colleagues builds on recent data demonstrating that lifestyle or pharmacologic interventions may substantially reduce the risk of diabetes.[15] Surely the most effective way to reduce cardiovascular risk associated with diabetes would be to prevent diabetes itself. But for patients who already have diabetes or in whom it will develop, the advantages of a multifactorial approach to the reduction of cardiovascular risk are clear. The challenge is to ensure that this approach is widely adopted.

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