Reducing Cardiovascular Complications of Type 2 Diabetes

A complex but achievable and affordable task

Cardiovascular disease (CVD) remains the cause of death in 60–70% of type 2 diabetic patients in industrialized countries and a major cause of morbidity, especially among the elderly (1–3). Furthermore, evidence indicates that diabetic patients have not benefited as much as the nondiabetic population from the reduction of CVD mortality rates in the U.S. (4). Other recent findings suggest that CVD complication rates associated with diabetes can be considerably reduced through intensified treatment of abnormalities in nonglycemic CVD risk factors (e.g., high blood pressure and dyslipidemia) often associated with diabetes (5,6). The article by Herman et al. (7) in this issue of *DiabetesCare* provides additional evidence that the benefits of such treatments may be achieved at little or no cost above that of conventional therapy.

Microvascular complications are clearly related to the degree of glucose control in both type 1 and type 2 diabetes. Much effort has been expended to evaluate the effects of glucose control on CVD rates among diabetic patients. Unfortunately, intensive control of hyperglycemia, a difficult task for both health care professionals and patients, is not as effective at lowering CVD rates as it is at reducing rates of microvascular complications (8). This suggests that interventions in addition to glycemic control are needed to minimize macrovascular complications. In the recently completed U.K. Prospective Diabetes Study (UKPDS), improved glycemic control led to a clear reduction of microvascular complications, but to only a borderline reduction in macrovascular complications (8). In contrast, a substudy of hypertension control in the UKPDS showed a benefit of blood pressure treatment on macrovascular complications (5). A clear benefit of treatment of isolated systolic hypertension was also found in an analysis of the diabetic subgroup in the Systolic Hypertension in the Elderly Program (9). More limited evidence is also available for the benefits of reducing LDL cholesterol levels in patients with diabetes. Although the number of diabetic patients was small, the greatest benefit was seen in the Scandinavian Simvastatin Survival Study (4S), but positive results have also been found in the Cholesterol and Recurrent Events Trial and the Long-term Intervention with Pravastatin in Ischemic Disease study (6,10,11).

The cost minimization analyses by Herman et al. (7) demonstrate that hospital utilization for CVD was significantly reduced by simvastatin therapy and, among diabetic patients, there may even be a cost savings associated with lipid-lowering therapy. Although this is an important finding, some caution is in order. The analysis of diabetic patients is a post hoc subgroup analysis. Patients already had clinical CVD and the effect on primary prevention is not known. The number of diabetic patients studied was small, so confidence limits of the rate estimates are wide. In 4S, patients with diabetes had a greater percent reduction in CVD hospitalization than those without. CVD rates among diabetic patients receiving simvastatin approached those of the nondiabetic patients treated with simvastatin. In future larger studies that include diabetic patients with milder dyslipidemia and without preexisting clinical CVD, the benefits of lowering lipid levels in diabetic patients may be less than those observed in 4S. Furthermore, while Herman et al. correctly declare a private single-payer direct-cost perspective, certain direct costs (notably, outpatient utilization) are not included in the analyses.

Despite these reservations, Herman et al. provide an important analysis whose central finding, that CVD hospitalizations can be substantially reduced with simvastatin therapy in diabetic patients at a cost not greatly different from that of conventional therapy, has important clinical and public health implications. Evidence now indicates that lipid reduction may be added to blood pressure reduction as another way to reduce the morbidity and mortality associated with CVD among diabetic patients. In managing patients with type 2 diabetes, it is crucial to consider interventions on other CVD risk factors as well as on hyperglycemia as part of a long-term plan to minimize chronic vascular complications.

The expectation that lowering cholesterol with simvastatin or other hydroxymethylglutaryl-CoA reductase inhibitors will produce a cost savings among people with diabetes may be "too good to be true." It is safe to assume that the economic benefit of this therapy is likely to be greater among those with diabetes than those without: this is because the CVD event rate among people with diabetes is substantially higher, leading to a higher absolute benefit even if the relative benefit is similar to that in those without diabetes (6). In general, other studies of blood pressure and lipid control among diabetic patients have shown percent reductions closer to those of the general nondiabetic population than those seen in 4S. With limited data reported so far from patients with diabetes, this may provide a more conservative basis for cost and benefit estimates. The argument that economic benefits of lipid control are greater for those with diabetes than for those without could be advanced more persuasively with an analysis of the cost per life-year gained from simvastatin therapy, similar to the cost-effectiveness analysis of the overall 4S cohort (12).

The economic value of blood pressure and lipid control is likely to be in the promising range for people with diabetes. In an era of finite resources, the issue will invariably be one of "opportunity cost," which is the health benefit forgone by an alternative use of the same resources. Though it would be folly to accept the principle that the least expensive care is the most appropriate, recommended interventions should be implementable at a cost that is reasonable and at least comparable to that of alternative ways of achieving the same health benefit. This means that it is not enough to simply know the impact of a single intervention on a narrow set of outcomes. Rather, we need to know the value of the interventions relative to each other so that the same resources may be most efficiently allocated to maximize net health gain.

To get to this point for interventions against CVD among people with diabetes will require two steps. First, the incremental CVD benefits of various potential interventions will need to be rigorously tested in large clinical trials. Second, the economic impact of these interventions should be prospectively evaluated in those trials by means of a societal prospective and common measure of benefit, such as life-years gained or quality adjusted life-years gained (13).

Before we are able to prevent or cure diabetes, we will have several effective and potentially affordable therapies to reduce the chronic complications of the disease. Many of these will involve multiple drugs and require considerable efforts from both health care providers and diabetic patients to achieve their benefits. Efforts will be necessary to improve compliance with drug regimens and to identify and potentially concentrate on the most important risk factors for individual patients. Maintaining health and quality of life with available resources will be our greatest challenge.

PETER J. SAVAGE, MD
K.M. VENKAT NARAYAN, MD

From the Division of Epidemiology and Clinical Applications (P.J.S.), National Heart, Lung, and Blood Institute, Bethesda, Maryland; and the Division of Diabetes Translation (K.M.V.N.), Division of Diabetes Translation, Centers for Disease Control and Prevention, Atlanta, Georgia.

Address correspondence to Peter J. Savage, MD, Room 8104, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Rockledge II, 6700 Rockledge Dr., Bethesda, MD 20817-7938. E-mail: savagep@nih.gov.

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