EDITORIAL (SEE NICHOLS ET AL., P. 2374)

Strategies to Reduce the Cost of Renal Complications in Patients With Type 2 Diabetes

Diabetes is a common and costly chronic disease, and diabetes-related complications are a major driver of health care costs in the United States. In 2007, 17.9 million U.S. residents were diagnosed with diabetes at a cost to the economy of $174 billion; $58 billion of which was directly attributable to diabetes-related complications (1). The most common microvascular complications include chronic kidney disease (affecting 27.8% of persons with diagnosed diabetes), foot problems (22.9%), and eye damage (18.9%) (2). The most common macrovascular complications include heart attacks (9.8%), chest pain (9.5%), and coronary heart disease (9.1%). Notably, specific racial and ethnic subgroups have higher rates of complications. For example, chronic kidney disease affects 35.2% of African Americans and 37.6% of Latinos with diabetes. Twenty-five percent of persons with diabetes report having two or more diabetes-related complications. The lifetime prevalence of these complications is much higher than these cross-sectional estimates suggest, and about 65% of those with type 2 diabetes die of a myocardial infarction or a stroke (3).

In this issue of *Diabetes Care*, Nichols, Vupputuri, and Lau report on the medical care costs associated with progression of diabetic nephropathy (4). They use administrative data from Kaiser Permanente Northwest to follow 7,758 patients with diabetes and hypertension for progression of nephropathy over an 8-year period. They found that costs increased by 37% following progression from normoalbuminuria to microalbuminuria (defined as 30–299 mg/g) and 41% following progression from microalbuminuria to macroalbuminuria (defined as >300 mg/g), after adjustment for other clinical risk factors and history of diabetes. Their study documents that among persons with the most common diabetes-related complication, chronic kidney disease, increasing disease severity is associated with increasing costs.

The clinical guidelines issued by the American Diabetes Association identify a number of clinical strategies that may delay onset or slow progression of diabetic nephropathy (5). These strategies include appropriate control of blood glucose and blood pressure, use of ACE inhibitors or angiotensin receptor blocker (ARB) medications, avoiding high-protein intake, and avoiding concomitant use of mediations that may further impair renal function.

The data presented by Nichols, Vupputuri, and Lau are observational in nature and therefore do not demonstrate that reducing levels of proteinuria will reduce costs of care. However, it is reasonable to assume that preventing onset or progression of proteinuria may keep at least some patients at lower levels of cost for various periods of time, thus avoiding some expenditures. The most powerful clinical strategies available to delay onset or slow progression of diabetic nephropathy are glucose control, blood pressure control, and use of ACE or ARB medications.

The beneficial effect of glucose control on diabetic nephropathy was well demonstrated in the ADVANCE trial, which showed that controlling A1C to a median level of 6.4%, compared with 7.5% in the standard therapy group, was associated with reductions in onset and progression of proteinuria (6). The ACCORD trial also showed that intensive glucose control delays onset and slows progression of proteinuria (7). Neither of these studies demonstrated lower rates of end-stage renal disease (ESRD) with intensive glucose control. However, these studies were of relatively short duration and were not powered to detect effects on this end point. More information may emerge from follow-up studies of these study populations.

The beneficial effect of blood pressure control using ACE medications on diabetic nephropathy was demonstrated in ADVANCE and ACCORD. ADVANCE randomized hypertensive patients to routine blood pressure care or to an intervention group that received both the ACE perindopril and the diuretic indapamide. At baseline, 26% of ADVANCE blood pressure trial patients had microalbuminuria, and 4% had macroalbuminuria. Baseline blood pressure of 145/81 was reduced to 140/73 in the standard group and to 136/73 in the intervention group, and the intervention was associated with a significant reduction in new micoralbuminuria (19.6% in the intervention group vs. 23.6% in the control group), total renal events (22.3% in the intervention group vs. 26.9% in the control group) but not with a significant decrease in new or worsening nephropathy (3.3% in the intervention group vs. 3.9% in the control group) (8). The ACCORD blood pressure trial lowered systolic blood pressure to 119.3 mmHg in the intensive treatment group and to 133.5 mmHg in the standard treatment group. This degree of blood pressure change led to lower rates of onset of microalbuminuria (20.8% in the intensive blood pressure treatment group vs. 25.0% in the standard group, $P = 0.02$) but did not significantly lower progression to macroalbuminuria (5.7% in the intensive blood pressure group vs. 7.1% in the standard group, $P = 0.09$) (9).

The beneficial effect of ARB medications on diabetic nephropathy was demonstrated in the RENAAL and IDNT trials. In the RENAAL study, patients with type 2 diabetes and microalbuminuria were randomized to treatment with losartan versus placebo with both arms also receiving conventional hypertensive therapy (10). IDNT similarly randomized patients with type 2 diabetes and microalbuminuria to treatment with irbesartan, amlodipine, or placebo. Both studies found that treatment with an ARB reduced the risks of a doubling of the serum creatinine concentration and ESRD; these effects were independent of the effect of the medications on blood pressure (11).

Most cost-effectiveness studies of diabetic nephropathy have focused on treatment with ARB medications and are based on data from RENAAL and IDNT. These studies have found that treatment of patients with type 2 diabetes and microalbuminuria with ARB medications is cost saving (12). That is, the cost of treatment is offset from reductions in cost due to delayed progression of proteinuria and

lower rates of ESRD. Cost-effectiveness studies of diabetic nephropathy based on ADVANCE or ACCORD have yet to appear. However, cost-effectiveness studies based on UKPDS have shown that intensive blood pressure control among a general population with type 2 diabetes is also cost saving (13).

It is clear that treatment of diabetic nephropathy is both clinically effective and cost-effective. It is unfortunate that a nontrivial number of patients with diabetes still progress to macroalbuminuria and ESRD. More disheartening is that fact that there are substantial disparities in diabetic nephropathy, which is more likely to occur among African Americans, Latinos, and persons with diabetes who are uninsured. Fortunately, diabetes case management is a strategy that has been proven both clinically effective in improving the quality of care among vulnerable populations and extremely cost-effective among those who are uninsured (14). Early evidence has also shown that providing diabetes case management to newly insured patients with type 2 diabetes may be cost saving (15).

Research studies suggest that the use of ACE or ARB medications and blood pressure control may be the most cost-effective approach to prevention and treatment of diabetic nephropathy among patients with type 2 diabetes, although intensive glucose control also has a clinical role to play. Nichols, Vupputuri, and Lau have done us a great service by reminding us that microvascular complications, as well as macrovascular complications, are important drivers of excess costs in type 2 diabetes.

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