bleeding rate, 2.9 vs. 23.3 events; P<0.001), and 63% of the emicizumab group had no bleeding events during the trial. In the third trial group, emicizumab prophylaxis resulted in a bleeding rate that was 79% lower than the rate with previous bypassing-agent prophylaxis (annualized bleeding rate, 3.3 vs. 15.7 events; P<0.001). These differences in bleeding rates are clinically highly significant.

The treatment of this very challenging patient group with potent hemostatic bypassing agents has always been accompanied by concern about the development of thrombotic complications. Thus, the documentation of unusual thrombotic events in five participants in this trial, in which combinations of procoagulant agents were used, may not be so unexpected. All events (thrombotic microangiopathy in three participants and cavernous sinus thrombosis and skin necrosis–superficial thrombophlebitis in one participant each) were associated with the coincident administration of emicizumab and repeated high doses of activated prothrombin complex concentrate. No thrombotic events were recorded with emicizumab alone or with coincident treatment with recombinant factor VIIa.

The results of this phase 3 trial are extremely important for the hemophilia treatment community, which has battled the hemostatic calamity of factor VIII inhibitor formation with the same bypassing therapies for the past 30 years. Although the preferred treatment of the infrequent events of breakthrough bleeding during the administration of emicizumab is not clear, it is obvious that repeated high doses of activated prothrombin complex concentrate should be avoided. Similarly, how emicizumab prophylaxis will be integrated with current schedules for the induction of immune tolerance to factor VIII remains to be evaluated.

In the meantime, weekly subcutaneous emicizumab prophylaxis appears to offer a marked reduction in bleeding rates and improvement in quality of life for this very challenging patient group. Additional studies are already in progress to determine the benefit of emicizumab prophylaxis in pediatric patients with hemophilia with inhibitors, and a study involving patients with hemophilia A without inhibitors is planned. These are extraordinary times for innovation in hemophilia therapy,[9,10] and the introduction of emicizumab represents a major contribution toward achieving an enhanced standard of care for this lifelong bleeding disorder.

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From the Department of Pathology and Molecular Medicine, Queen's University, Kingston, ON, Canada.

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A New Chapter for Diabetic Kidney Disease

Ian H. de Boer, M.D.

Many clinical outcomes have improved over the past two decades for people living with diabetes.[1] However, relatively little progress has been made in the treatment of diabetic kidney disease. Among adults with diabetes in the United States, the prevalence of diabetic kidney disease

has remained steady, near 26%,[2] and, depending on the data source, rates of end-stage renal disease (ESRD) have either remained stable or decreased only slightly.[1]

Why has diabetic kidney disease proved so difficult to prevent and treat? In part, the successes of preventing atherosclerotic complications and prolonging life mean that people with diabetes are exposed to longer cumulative durations of hyperglycemia and superimposed stresses of aging. However, a lack of effective therapies targeting diabetic kidney disease is another part of the problem. Inhibitors of the renin–angiotensin–aldosterone system effectively slow the progression of established proteinuric diabetic kidney disease, but these agents do not prevent diabetic kidney disease. A substantial residual risk of progression of kidney disease remains, and other classes of medication have not proved effective.[3]

Now some recently developed medications that control glycemia in patients with type 2 diabetes appear to have opened a new chapter for the prevention and treatment of diabetic kidney disease. Specifically, glucagon-like peptide 1 (GLP-1) agonists, dipeptidyl peptidase 4 inhibitors, and sodium–glucose cotransporter 2 (SGLT2) inhibitors may help prevent and treat diabetic kidney disease by allowing tighter and safer control of the blood glucose level and by exerting beneficial direct effects on the kidney. Exciting data on these agents have come from large clinical trials that have been mandated by regulatory authorities to ensure cardiovascular safety.[4-8] Although all these trials have focused primarily on cardiovascular outcomes, some have provided valuable information on kidney effects as secondary outcomes.

In this issue of the *Journal*, Mann et al.[9] report the kidney outcomes of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial. In the LEADER trial, 9340 participants with type 2 diabetes and high cardiovascular risk were randomly assigned to receive liraglutide (a GLP-1 agonist) or placebo, added to standard diabetes treatments, including renin–angiotensin system inhibitors (used in 83% of the participants). Liraglutide resulted in an incidence of a composite renal outcome of persistent macroalbuminuria (urinary albumin excretion >300 mg per day), persistent doubling of the serum creatinine level, ESRD, or death from renal disease that was 22% lower than the incidence with placebo. This result was driven by a lower incidence of new-onset persistent macroalbuminuria, which is known to be strongly associated with subsequent ESRD, cardiovascular events, and death, in the liraglutide group than in the placebo group. There was no significant effect on the incidence of the doubling of the serum creatinine level or ESRD, but liraglutide was associated with a slower decline in the estimated glomerular filtration rate (GFR) over time, particularly in subgroups of patients who had evidence of kidney damage at baseline.

In other cardiovascular outcomes trials with GLP-1 agonists, semaglutide resulted in a rate of a nearly identical composite renal outcome that was 36% lower than the rate with placebo,[7] and lixisenatide significantly reduced urinary albumin excretion over a period of 2 years.[5] Such results suggest a class effect of GLP-1 agonists, although detailed renal outcomes in these trials have not yet been published, and the renal effects of other GLP-1 agonists are not clear. Furthermore, two SGLT2 inhibitors (empagliflozin and canagliflozin) have shown impressive renal effects, including markedly lower rates of decline in the estimated GFR in addition to lower rates of albuminuria.[8,10] Importantly, liraglutide, semaglutide, empagliflozin, and canagliflozin each resulted in a significantly lower incidence than placebo of cardiovascular events, evaluated as primary outcomes — effects that were similar regardless of the presence or absence of kidney disease at baseline.[4,6-8]

Taken together, these trial results suggest that the use of GLP-1 agonists and SGLT2 inhibitors may ultimately help to reduce the incidence of diabetic kidney disease. But there are several caveats. First, additional outcome trials with primary kidney outcomes would strengthen the evidence of renal benefit. Second, evidence that GLP-1 agonists slow a decline in the GFR, the process leading most directly to ESRD, is currently limited. Third, class effects are uncertain. Fourth, the impressive cardiovascular and renal benefits that have been observed in trial participants who are at high cardiovascular risk, who are often also at high risk for kidney disease, may not extrapolate to the broader population of

patients with type 2 diabetes. Finally, cost may be a major barrier to widespread use of these drugs.

For patients with type 2 diabetes and prevalent kidney disease, the existing data suggest that GLP-1 agonists and SGLT2 inhibitors may slow the progression of kidney disease. Trials with primary renal outcomes and longer-term follow-up in populations of patients with prevalent kidney disease are required in order to address this question, and some are ongoing or planned. Currently, it is logical to consider including a GLP-1 agonist or SGLT2 inhibitor in the glucose-lowering regimen of patients with type 2 diabetes and mild-to-moderate diabetic kidney disease, with the anticipation of salutary renal and, particularly, cardiovascular effects. Data from ongoing studies will help to refine such an approach and address other important questions, such as how to combine glucose-lowering drugs and whether drugs targeting nonglycemic pathways can further improve renal outcomes. Overall, the new data on GLP-1 agonists, SGLT2 inhibitors, and kidney outcomes suggest a hopeful change in story line in which, over time, the incidence and progression of diabetic kidney disease may be reduced and its cardiovascular sequelae mitigated.

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From the Division of Nephrology and Kidney Research Institute, University of Washington, and the Veterans Affairs Puget Sound Health Care System — both in Seattle.

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