Fueled by a global pandemic of obesity, diabetic kidney disease is a pressing public health challenge. Diabetic kidney disease is the most common cause of chronic kidney disease, leading to premature death and end-stage renal disease (ESRD) in the developed and developing worlds. Remarkably, the excess risk of death from any cause in type 1 or 2 diabetes is associated almost entirely with the presence of kidney disease. In the absence of diabetic kidney disease, the risk of death among persons with diabetes is similar to that in the general population.1,2

The management of diabetic kidney disease focuses on the treatment of hyperglycemia and hypertension with a foundation of inhibition of the renin–angiotensin–aldosterone system.3 The incidence of ESRD that is attributable to diabetes has stabilized during the past decade, which has been heralded as therapeutic success. However, the overall number of people with diabetic kidney disease continues to rise in parallel with the prevalence of type 2 diabetes.4

Clinical trials intensifying the control of conventional risk factors have not shown improved outcomes. Intensifying the management of glycemia to lower glycated hemoglobin targets in older people with type 2 diabetes (glycated hemoglobin, <6.0 to 6.5% in persons typically >60 years of age, depending on the study) produced small reductions in the risk of albuminuria onset or progression but has been associated with episodes of severe hypoglycemia that occur two to four times as frequently as with conventional glycemic management; in addition, these targets have not decreased the risk of death, cardiovascular disease, or ESRD.5 Another disappointment has been maximal inhibition of the renin–angiotensin–aldosterone system. Dual-blockade strategies (an angiotensin-converting–enzyme inhibitor plus an angiotensin-receptor blocker or one of those agents plus a renin inhibitor) have lowered the risk of albuminuria but have increased the risk of adverse events without reducing the risk of ESRD.6 Thus, new therapeutic agents are urgently needed.

Abundant experimental evidence indicates that oxidative stress and inflammation are important mediators in diabetic kidney disease. Bardoxolone methyl is a small molecule that activates nuclear 1 factor (erythroid-derived 2)—like 2 factor (Nrf2), a transcription factor regulating antioxidant genes. In 2011, the results of the phase 2 52-week Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes trial showed that bardoxolone methyl increased the estimated glomerular filtration rate in participants with moderate-to-severe diabetic kidney disease.7 However, the bardoxolone methyl groups had an increased rate of albuminuria, unintended weight loss, and more adverse events than the placebo group.

The results of the phase 3 Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus: the Occurrence of Renal Events (BEACON) trial, which involved patients with advanced diabetic kidney disease, are now reported in the Journal.8 The BEACON trial was terminated prematurely on the recommendation of the independent data and safety monitoring committee, after achieving full enrollment but with only a median of 9 months of follow-up. The reasons for termination were the strong adverse safety signals associated with bardoxolone methyl treatment, as compared with placebo, including increased rates of heart failure and cardiovascular events; higher levels of blood pressure, heart rate, and albuminuria; unintentional weight loss; and anemia.
loss; and more gastrointestinal and muscle-related symptomatology. The reasons for these adverse events are unclear. The authors speculate that fluid retention, increased afterload, and higher heart rate contributed to heart failure in patients in the bardoxolone methyl group. In addition, direct toxic effects are possible.

What lessons can be learned from the bardoxolone methyl studies? First, more extensive analysis of preclinical data might have led to greater caution before clinical trials were conducted with this agent. Notably, in one study, the administration of bardoxolone analogues to diabetic rats was associated with increased occurrences of kidney injury, hypertension, proteinuria, and weight loss, which is analogous to some clinical trial findings. However, these data were published only after the BEACON trial was terminated. Second, it is not surprising that a potent activator of a transcription factor might have off-target effects. In addition to Nrf2, bardoxolone methyl activates peroxisome proliferator–activated receptor γ, which may contribute to fluid retention and heart failure, especially in persons with advanced diabetic kidney disease. Third, caution should be exercised whenever any drug for diabetic kidney disease increases, rather than decreases, the degree of albuminuria.

Unfortunately, the failure rate of new drug therapies in clinical trials is extraordinarily high, exceeding 90% overall; even in phase 3 trials, it is still approximately 50%. In addition to bardoxolone methyl, a series of other new therapies for diabetic kidney disease have founedered over the course of drug development. Examples include inhibitors of advanced glycation end products, aldose reductase inhibitors, sulodexide, antifibrotic treatments, and inhibitors of protein kinase C. Increasing the success rate for drug development requires reengineering how we translate discovery science into clinical trials. Efforts are under way to increase thorough reporting of preclinical studies, and the development of new tools such as human “organs on microchips” may augment the assessment of potential off-target toxic effects. Additional key areas for focus are rigorous evaluations of dosing, suitable biomarkers for disease processes and therapeutic responses, and business and regulatory environments that foster innovation. If new therapies for diabetic kidney disease are to benefit patients, fresh approaches will be critical. Given the escalating human and societal costs of diabetic kidney disease, efforts to find new safe and effective therapies remain vital.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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