changes related to reduced kidney function and/or immunologic effects of CKD) also warrant further examination in future studies. Immune dysfunction among patients with renal insufficiency is well characterized,[8] and may influence risk of both renal and urothelial cancers.[9]

Another important area of continued research following up on these findings is whether the relationship between CKD and RCC differs by race or ethnicity. The prevalence of CKD is higher, and impairment of renal function is likely to be more severe among African Americans than among non-Hispanic whites.[10] Two recent studies suggest that the magnitude of the association between ESRD and RCC risk is greater among African Americans than among whites.[11,12] Additional research is warranted to evaluate whether such racial differences in CKD might contribute to the observed excess incidence of RCC among African Americans.[1]

Currently, there are no established screening protocols for kidney cancer (with the exception of those for patients with certain hereditary conditions, such as von Hippel-Lindau disease) or for bladder cancer in asymptomatic adults.[13,14] It is possible, as noted by Lowrance *et al.*,[7] that their findings may have implications for targeted cancer screening among some patients with CKD. However, the magnitude of the observed associations between eGFR and renal and urothelial cancers is smaller than that generally considered acceptable for screening purposes.[15] As such, additional research would be needed to identify specific high-risk groups of patients with CKD and to evaluate the potential benefits and harms of screening in these populations.

In summary, this report by Lowrance *et al.*[7] is an important step forward in characterizing the relationship between CKD and risk of RCC and other malignancies. Studies such as this further support an etiologic role of impaired renal function in the development of RCC.

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DISCLOSURES

None.

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See related article, "CKD and the Risk of Incident Cancer," on pages 2327–2334.

Are Post-Trial Observational Studies Useful?

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For more than two centuries, the measurement of urinary proteins has been a standard tool for nephrologists to diagnose

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kidney disease. Renal disease is characterized by changes in the glomerular filtration barrier leading to increased urinary excretion of proteins, the main protein of which is albumin. This was later called *macroalbuminuria* and appeared to be associated with an increased risk of progressive renal function loss.[1] In the 1980s, novel methods were introduced that enabled the measurement of small quantities of albumin in the urine, called *microalbuminuria*. The introduction of these techniques encouraged endocrinologists and diabetologists to measure urinary albumin in their patients with diabetes (at that time, this comprised predominantly patients with type 1 diabetes). To note, these small quantities of albumin also predicted the risk of developing progressive renal disease in patients with type 1 diabetes.[2] In recent decades, attention on albuminuria as a predictor of renal risk has shifted mainly to patients with type 2 diabetes, likely because of the worldwide increased prevalence of this disease. Studies in populations with type 2 diabetes confirmed the important role of macroalbuminuria in the progression of renal disease, as also found in nondiabetic renal disease.[3] In addition, the success of renoprotective interventions was shown to associate with and often depend on the albuminuria-lowering effect: The greater the reduction in albuminuria in the first months of treatment, the greater the subsequent renal risk reduction.[4,5]

The study by de Boer *et al.* in this issue of *JASN* brings the role and importance of macroalbuminuria in the type 1 diabetes population to our attention and provides important insights into the long-term renal outcomes in a contemporary cohort of patients with type 1 diabetes and macroalbuminuria.[6] This study analyzed data from the Diabetes Control and Complication Trial (DCCT) and its observational Epidemiology of Diabetes Intervention and Complication (EDIC) follow-up study. The analysis included 159 individuals who developed incident macroalbuminuria over a 25-year follow-up period. The wealth of data of such long-term follow-up is enormous and a lot can be learned. First, de Boer *et al.* showed that despite the improvement in treatments over the years, the incidence of progression to macroalbuminuria is still high and is surprisingly similar to that reported in type 2 diabetes. Second, de Boer *et al.* found that macroalbuminuria is associated with a marked risk of progression in renal disease, as evidenced by an eGFR loss of -5.4 ml/min per 1.73 m^2 per year and a high risk for developing an eGFR$<$60 ml/min per 1.73 m^2. Because of the resemblance of such risk data with those data observed in type 2 diabetes, we cannot escape the notion that the treatment of type 1 diabetes should receive more attention, particularly in the prevention of macroalbuminuria. In addition, data on type 2 diabetes in patients with macroalbuminuria and compromised eGFR show an extremely high risk for ESRD (which leads to death in the case of no dialysis or transplantation) or death, which is higher than that of all treated cancers.[7] de Boer *et al.* report that the use of renin-angiotensin-aldosterone system inhibition (RAASi) increased over time, macroalbuminuria regressed, and the risk of renal disease progression decreased. These findings are intuitively compelling and could lead to the conclusion that RAASi may have played a role in either preventing macroalbuminuria or exerting renal protective effects by lowering albuminuria and slowing progression of eGFR decline if macroalbuminuria was present.

We should be very careful in drawing such important conclusions from the data presented by de Boer *et al.* Why? The study design has several limitations that hamper firm conclusions, including the lack of a control group as well as indication bias and selection bias. The study by de Boer *et al.* combined data from a clinical trial with data from a post-trial observational follow-up study. Their study is thus a mixture of two different study designs. A cohort study is based on data that occur in real life without a particular interference by the investigator, whereas a randomized controlled trial does not follow real life but includes an exposure to an intervention introduced by the investigator. The extension of a clinical trial with an observational period has the advantage of assessing long-term health benefits of the original randomized intervention. After 4 years at the end of the STENO trial, intensive risk factor control did not statistically significantly decrease the risk of mortality. However, the authors performed a post-trial extension period and then discovered that after approximately a 10 year follow-up, intensive risk factor control decreased mortality risk.[8] However, the post-trial follow-up period is an observational study that is no longer based on randomized comparisons and is thus prone to bias. These biases are also present in the study by de Boer *et al.* and may lead to the erroneous conclusion that RAASi has renal protective effects by lowering albuminuria. First, and most obvious, the post-trial phase lacks a control group; thus, it is unknown whether patients who had a slower decline in eGFR did so because of RAASi or because they would have done so anyway. One could select a control group of patients who did not use RAASi at the start of the post-trial phase. However, the use of RAASi during the post-trial phase increased from 31% to 88%. Therefore, many control patients would have been treated during follow-up, which results in biased comparisons. It is noteworthy that even in contemporary medicine in which all guidelines advocate the use of RAASi in patients with macroalbuminuria, 12% of patients still did not use these drugs at the end of follow-up. A second limitation is the presence of indication bias. Indication bias relates to the phenomenon that patients at highest risk of renal function decline (*i.e.,* those with highest albuminuria levels) were more likely to receive RAASi. Indeed, RAASi was used by 88% of patients with sustained macroalbuminuria 10 years after the diagnosis, whereas it was used by 67% of patients who regressed to normoalbuminuria. Thus, individuals who had more advanced disease and were at highest risk of impaired eGFR were offered a medication that can lead to the flawed conclusion that the intervention was ineffective or even harmful compared with no treatment. Finally, selection bias may also be present. The reported association between the regression of albuminuria and the lower risk of impaired eGFR in the DCCT/EDIC cohort is not based on a

randomized comparison. It is thus possible that the lower risk of impaired eGFR among patients with regression in albuminuria was caused by selection of a subgroup of patients who had different starting eGFR levels or different other (unmeasured) confounding factors unrelated to the reduction in albuminuria. For these reasons, we recommend using caution in concluding that RAASi has renoprotective effects by decreasing albuminuria on the basis of this post-trial extension period.

In an effort to eliminate the bias without losing the fruits of long-term follow-up by the extension studies, we could consider new trial designs in diabetes that emerge in other areas of medicine. The cohort multiple randomized controlled clinical trial design is one example.[9] This design uses a natural cohort of patients with a specific disease. These patients are continuously followed and are exposed to the guideline (background) recommended therapies. New drugs/interventions are tested in a randomly selected subgroup of patients while other patients continue standard-of-care treatment. Advantages of this design include the possibility to simultaneously test multiple randomized comparisons and the improved comparability between trials.

In conclusion, post-trial observational studies such as the DCCT/EDIC are valuable and increase our understanding of long-term effects of interventions. The report by de Boer *et al.*[6] helps us to regain focus on the importance of macroalbuminuria in type 1 diabetes, including measuring it for estimation of renal and cardiovascular risk as well as reducing it by optimizing therapies. However, post-trial observational studies are cohort studies prone to bias, of which indication bias, selection bias, and unmeasured confounding are not trivial. We should all be aware of these potential biases and act accordingly by performing the proper randomized controlled trials to confirm the relevant findings. The article by de Boer *et al.* is thus meritorious and timely not only by virtue of the information it provides, but also because this article may serve as a stimulus and set the stage for appropriate randomized controlled clinical trials in this field.

DISCLOSURES

None.

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See related article, "Renal Outcomes in Patients with Type 1 Diabetes and Macroalbuminuria," on pages 2342–2350.