Should we as a nephrology community merely assume that because of these worse outcomes (high event rates), the benefit of therapy would be equivalent in patients with CKD and those with normal kidney function? The 4D trial suggested that this may not be a safe assumption. Arguably, it is more likely than not that these treatments provide at least some benefit to the CKD population; however, the extent of the benefit still should be defined. Clearly, there are more aggressive and nontraditional aspects of the atherosclerotic process among people with CKD that are not factors in those with normal kidney function. In assuming that traditional treatments offer the same benefit, are we missing opportunities to note potentially poorer therapeutic effects and test strategies more focused on our patients’ unique pathobiology?

The CKD population is expanding, patients with CKD bear a heavy burden of cardiovascular morbidity and mortality, and therapies in this group of patients remain unproved. This incongruity should be a call to arms. More randomized trials are desperately needed, and we as a medical community should feel an ethical responsibility to establish the efficacy of available treatments in this sizable and growing minority of patients. What proportion of the worse outcomes in CKD can be attributed to the health services delivery problem of decreased use of secondary prevention as compared with the potentially flawed assumption of efficacy equivalent to those with normal kidney function? Without squarely asking that question, we cannot consider ourselves to be practicing true evidence-based medicine.

DISCLOSURES

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REFERENCES


See related article, “Renal Impairment Predicts Long-Term Mortality Risk after Acute Myocardial Infarction,” on pages 141–150.

Cardiovascular Disease, Chronic Kidney Disease, and Type 2 Diabetes Mellitus: Proceeding with Caution at a Dangerous Intersection

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Type 2 diabetes carries an unequivocal risk for cardiovascular disease. Patients with diabetes have the same risk for future cardiovascular events as survivors of myocardial infarction. Morbidity and mortality in diabetes is largely driven by atherosclerotic complications. Just the presence of diabetes has a fundamental, pervasive effect on the vasculature; for example, erasing the gender benefit seen in women in terms of cardiovascular disease and making all patients with diabetes less likely to benefit from advances in cardiovascular therapeutics. Given this grim picture, one could ask: Can it get much worse for the patient with diabetes and cardiovascular disease? Unfortunately, the answer is yes.

In this issue of JASN, Schneider et al. offer more evidence that even within this dangerous intersection of cardiovascular disease and diabetes, chronic kidney disease (CKD) confers a significant further increased risk for recurrent cardiovascular events, at least as seen within the Prospective Pioglitazone Clinical Trial in Macrovascular Events Study (PROactive). PROactive studied 5238 patients with type 2 diabetes and well-established cardiovascular disease: approximately 50% had a prior myocardial infarction and approximately 50% had a second qualifying cardiovascular event (stroke, peripheral vascular disease, coronary disease, or coronary intervention). Among the 5154 patients with renal data, 11.6% with an estimated GFR (eGFR) <60 ml/min per 1.73 m² had a primary composite end point of 27.5% versus 19.6% in those with normal eGFR.

A new chapter is thus emerging in our understanding of cardiovascular risk—the impact of CKD. Adding diabetes to CKD only amplifies cardiovascular risk. Many of the metabolic abnormalities thought to promote atherosclerosis in type 2 diabetes (e.g., elevated triglycerides, low HDL, visceral adiposity, hypertension, hypercoagulability, inflammation) are also common in CKD. Indeed, microalbuminuria may well be a missing component in the definition of metabolic syndrome. CKD promotes atherosclerosis by worsening these metabolic abnormalities. Impaired kidney function has been linked to proatherosclerotic mechanisms such as oxidative stress, inflammation, endothelial dysfunction, and activation of the renin-angiotensin system. Hypertriglyceridemia, common in CKD, may foster lipid accumulation in renal cells, instigating pathological responses. Levels of asymmetric dimethylarginine (ADMA), which promotes endothelial dysfunction, are also elevated in CKD. Because ADMA inhibits nitric oxide synthase, other perturbations in renal nitric oxide pathways may contribute to atherosclerosis in CKD. Increased vascular calcification has also been invoked in cardiovascular disease among patients with renal disease.

PROactive was a double-blind, randomized, placebo-controlled study that investigated the effect of pioglitazone, a peroxisome proliferator-activated receptor gamma (PPARγ) activating thiazolidinedione, on a combined end point of vascular events. In PROactive, the decline in the primary end point (approximately 10%) was not statistically significant. A secondary end point of nonfatal myocardial infarction, death, and stroke was reduced by 16% (P < 0.027). The ramifications of PROactive have been intensely discussed. Many factors may have limited pioglitazone’s impact in PROactive, including a late-stage cardiovascular disease cohort, a shorter study duration (34.5 mo) than planned, and inclusion of elective (revascularization) and refractory peripheral vascular disease outcomes in the combined primary end point. Schneider et al. point out a slower overall decline in GFR among PROactive subjects than what is typically seen in diabetes, raising yet another potential offsetting variable at work in the PROactive results.

Whatever the risk reduction seen with pioglitazone in PROactive, it did come at the expense of some increased edema, nonfatal congestive heart failure, and weight gain. In spite of the ongoing wrestling with data, regarding thiazolidinediones and cardiovascular disease, it is worth noting that no similar PROactive-like effort currently exists for any other commonly employed antidiabetic drugs. In their post hoc study, Schneider et al. also found that pioglitazone significantly lowered cardiovascular events more than placebo among those with impaired eGFR: 25% for the primary end point (nonsignificant) and 34% for a more objective clinical cardiovascular end point (significant). Interestingly, other PROactive subgroup analyses reveal more clear-cut risk reductions in myocardial infarction (fatal and nonfatal) and acute coronary syndrome as well as prior stroke than was evident in the whole study.

How might PPARγ agonists reduce cardiovascular events among CKD patients? CKD might simply identify patients with significant atherosclerosis and inflammation, with the greater benefits seen among CKD patients being independent of any specific renal effect of pioglitazone or PPARγ activation. Pioglitazone-treated PROactive patients did enjoy increased HDL levels, lower triglycerides, slightly better glucose control, and the small but significant known thiazolidinedione reduction in BP—all despite a blinded study that sought matched glucose control and active cardiovascular therapies in both arms. Improvement in any one of these parameters may have contributed to outcomes in CKD patients. Alternatively, PPARγ is expressed in the kidney, raising the possibility of direct renal pioglitazone effects. PPARγ expression in the distal collecting duct and its effects on sodium (ENaC) channels has been implicated in thiazolidinedione-mediated volume expansion.

Pioglitazone may also directly influence atherosclerosis through mechanisms that link cardiovascular disease and CKD, including modulation of the renin-angiotensin system,
inflammation, oxidative stress, nitric oxide, or ADMA levels.\textsuperscript{13,14} Indeed, previous work suggests pioglitazone lowers ADMA levels in rats.\textsuperscript{15} Of note, in PROactive, pioglitazone also caused edema and increased admission for nonadjudicated heart failure, side effects not expected to track with cardiovascular benefits in CKD. These findings further support the notion that pioglitazone-induced heart failure has different implications than true cardiogenic heart failure seen with cardiovascular events in diabetes.

One particularly puzzling aspect to these studies was the greater decline seen in eGFR among pioglitazone-treated subjects. This observation contrasts with prior reports that thiazolidinediones may afford renal protection.\textsuperscript{16} Both pioglitazone and rosiglitazone reportedly decreased urinary albumin/protein excretion while lowering BP. Thiazolidinediones also lower levels of glucose and insulin, two mediators of renal injury. In the study as a whole, no difference in urinary albumin excretion was noted,\textsuperscript{4} suggesting either that the previous smaller studies were misleading and that thiazolidinediones do not improve protein excretion, or that the PROactive cohort differed in some way. Mechanistically, PPAR\(\gamma\) activation may alter glomerular hyperfiltration and microalbuminuria through vasodilatation at the expense of decreasing GFR, as invoked with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.\textsuperscript{17} Pioglitazone reduces glomerular and Bowman’s capsule volume ratios in early stages of diabetic nephropathy in mice.\textsuperscript{18} It remains possible that pioglitazone could also cause a true deterioration in renal function even if offset by declining cardiovascular risk through other mechanisms.

Debates continue to wage over thiazolidinediones as a drug class, a possible signal for increased cardiovascular events with rosiglitazone, and differences between pioglitazone and rosiglitazone as PPAR\(\gamma\) agonists.\textsuperscript{8,9} In contrast, an extensive and evolving basic science literature establishes the importance of PPAR\(\gamma\) as a transcriptional regulator involved in insulin sensitivity, adipogenesis, atherosclerosis, and inflammation.\textsuperscript{11} Encouraging subgroup studies like the one reported here also reinforce PPAR\(\gamma\) as a potential drug target worthy of additional study and argue for careful analyses of other existing and emerging data regarding thiazolidinediones.

The intersection of cardiovascular disease, CKD, and diabetes is a dangerous one. If we are to help patients navigate this complicated convergence, there is no doubt we need to proceed with deliberate caution—paying careful attention to clinical risk, optimal management strategies, and drug safety while also avoiding the dismissal of signals of potential benefit.

\textbf{REFERENCES}


\textbf{DISCLOSURES}

None.

