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# Managing the Diabetic Kidney Patient

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**ABSTRACT**

Diabetes mellitus (DM) is the leading cause of kidney failure in the United States, and controlling DM slows kidney failure. Thus, treatment of DM with antihyperglycemic medications is vital for patients with kidney disease. However, as kidney function and medication elimination decrease, patients are at increased risk for adverse drug reactions when medication doses are not adjusted appropriately. Dosing of antihyperglycemic medications for patients with kidney disease is an important issue for nurse practitioners and other health care providers.



## INTRODUCTION

On the basis of data from the US Renal Data System, the National Kidney Foundation estimates that 30 million Americans (14.9%) have chronic kidney disease (CKD) with 44% of new cases caused by diabetes.[1,2] Past studies have shown that lowering hemoglobin A1C reduces microvascular complications (nephropathy, neuropathy, and retinopathy) in patients with type 2 diabetes mellitus (T2DM).[3] The American Diabetes Association's Standards of Care in Diabetes (ADA SOC) recommends initiating lifestyle modifications for all patients with different levels of medication therapy based on presenting A1C. Metformin monotherapy is recommended for patients with an initial A1C $< 9\%$, dual therapy if A1C $\geq 9\%$, and consideration of insulin therapy if A1C $\geq 10\%$, fasting blood glucose $\geq 300$ mg/dL, or patient is symptomatic. In the past, dual therapy was metformin plus any of 6 other preferred treatment options, which included sulfonylureas, thiazolidinediones (TZDs), DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin. In 2018, this recommendation was changed for patients with preexisting atherosclerotic cardiovascular disease (CVD). When dual therapy is indicated, it is recommended for patients with atherosclerotic CVD to receive metformin plus an agent with evidence of cardiovascular risk reduction (ie, empagliflozin or liraglutide).[4–6] All noninsulin agents are associated with approximately a 1% reduction in A1C.[4] A French study of oral antihyperglycemic use in patients with T2DM and CKD found that roughly 40%–50% of these medications were outside the recommended doses for the patient's level of kidney disease.[7] For assistance with assessing kidney function, readers are referred to a previously published article in *TJNP*.[8] In light of the important role of antihyperglycemic agents and the risks of incorrect dosing in patients with CKD, this article discusses the commonly used agents recommended as potential first- and second-line agents for treating T2DM. The role of these agents in CKD patients with T2DM is discussed, along with dosing for various levels of kidney function.

## METFORMIN

Metformin is the only available agent in the biguanide drug class and reduces A1C by improving insulin sensitivity via 3 primary methods:

- decreasing gluconeogenesis in the liver,
- decreasing glucose absorption from the intestine, and
- increasing glucose uptake and utilization in the periphery.[9]

Because of its mechanism of action, metformin has a low risk of hypoglycemia and can result in modest weight loss. Clinical trials have also shown a 36% lower risk of all-cause mortality and lower cardiovascular mortality when metformin was used compared with sulfonylureas or insulin.[10,11]

Per the ADA SOC, metformin is recommended first-line as monotherapy and a recommended agent in both dual and triple therapy.[4] Because metformin is 100% renally eliminated and carries a low but serious risk of lactic acidosis, the original prescribing

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information contained restrictive kidney contraindications based on serum creatinine (SCr 1.4 mg/dL for women, 1.5 mg/dL for men).[9] In April 2016, the US Food and Drug Administration changed the label based on review of studies regarding the safety of metformin in patients with mild to moderate CKD.[12] The new recommendations are based upon estimated glomerular filtration rate (GFR, mL/min/1.73 $m^2$), and use is now contraindicated if GFR $< 30$ (see Table).[13] These new recommendations allow many more patients with CKD to use metformin, an inexpensive and effective first-line agent in the treatment of T2DM. Even with these labeling changes, close monitoring of renal function is warranted for all patients who are on metformin, especially those with coexisting CKD.

## SULFONYLUREAS

Sulfonylureas lower blood glucose by stimulating release of insulin from the pancreatic beta cells.[14] One of the major adverse effects of sulfonylureas is hypoglycemia, which is more likely in patients with renal impairment.[14] In a large, nested case-control study[15] in the United Kingdom, the following factors were associated with the risk of severe hypoglycemia:

- current use of insulin or sulfonylureas,
- age $\geq 75$,
- acute or chronic renal failure, and
- cognitive impairment/dementia.

First-generation sulfonylureas, chlorpropamide and tolbutamide are eliminated by the kidneys and are not recommended in patients with CKD.[16] However, the second-generation sulfonylureas are metabolized by the liver and partially eliminated in the urine. As shown in the Table, glyburide and glimepiride have decreased renal clearance of active metabolites and should be avoided or used conservatively in patients with kidney disease. However, glipizide has only inactive metabolites, making its elimination unaffected by kidney disease and the sulfonylurea of choice for CKD patients.[16,17]

## THIAZOLIDINEDIONES

The TZDs, pioglitazone and rosiglitazone, activate the proliferator-activated receptor-gamma (PPAR-Ɣ), which increases insulin-dependent glucose utilization in adipose tissue and skeletal muscle while decreasing glucose production by the liver.[18] Both agents are completely metabolized by the liver and thus do not require dose adjustments in patients with kidney disease.[17] However, TZDs are generally not used in kidney disease because of the known adverse effects of fluid retention (exacerbating heart failure), and their increased risk of fracture, anemia and bladder cancer.[16,17] For these safety reasons and due to the presence of more suitable alternatives for patients with kidney disease, TZDs are not usually recommended.

## DIPEPTIDYL PEPTIDASE-4 (DPP4) INHIBITORS

Over the past decade, several new classes of anti-hyperglycemic agents have become available, some with reduced risk of hypoglycemia and improved cardiovascular outcomes.[4] One of the first new classes was the dipeptidyl peptidase-4 (DPP-4) inhibitors (ie, alogliptin, linagliptin, saxagliptin, and sitagliptin), which can be used in patients with CKD, including end-stage kidney disease on dialysis.[19] Incretins are secreted after meals and stimulate glucose-dependent insulin secretion and then are inactivated rapidly by DPP-4.[19] Therefore, DPP-4 inhibitors increase postprandial incretin concentrations and glucose-dependent insulin secretion.

These agents have a good tolerability profile, without severe hypoglycemia or weight gain.[4,19] The glucose-lowering effect and tolerability is similar in patients with and without kidney disease, including those on dialysis. Additionally, limited data suggest that DPP-4 inhibitors might have a kidney-protective effect because they can potentially reduce the incidence of albuminuria, although more research is needed to determine whether this is solely related to improved glycemic control.[19] Available data indicate they are cardiovascular neutral agents because they have failed to demonstrate a significant difference in cardiovascular events between placebo and treatment groups.[4,19] Alogliptin, sitagliptin, and saxagliptin all require dose reductions depending on renal function, but linagliptin does not require any adjustments for any stage of renal impairment (see Table).[16]