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Incretin-Based Therapies in Complex Patients: Practical Implications and Opportunities for Maximizing Clinical Outcomes: A Discussion with Dr. Vivian A. Fonseca

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ABSTRACT

Elderly patients and patients with renal impairment present unique challenges in the management of diabetes mellitus. Impaired renal function is a common comorbidity (or complication) associated with type 2 diabetes, as well as a complicating factor in the treatment of the disease. Renal insufficiency, which can result in elevated plasma concentrations of pharmaceutical agents, may preclude the use of some antihyperglycemic medications and require that the dosages of others be reduced. Failure to select and dose medications carefully in these patients may increase the risk of hypoglycemia and other adverse effects. For example, elevated plasma concentrations of some sulfonylureas may increase the risk of hypoglycemia. Because patients with chronic renal insufficiency tend to retain fluids, treatment with a thiazolidinedione—a class of agents associated with fluid retention—may exacerbate the risk of edema. Older patients with type 2 diabetes—like patients with renal insufficiency an important and populous subgroup—also have issues with therapy selection and dosing regimens. As a result of the effects of aging on kidney function, older patients may also be subject to elevated plasma levels with consequent additional risk of hypoglycemia and other adverse events. Because older patients tend to be treated with multiple medications for multiple comorbidities, it becomes challenging to design regimens that avoid or reduce the risk of drug–drug interactions. For both older patients and patients with chronic renal insufficiency, the most important drug-related adverse effect to avoid is hypoglycemia. Accordingly, incretin-based agents have an advantage because they are unlikely to cause hypoglycemia.

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KEYWORDS: renal impairment; elderly patients; type 2 diabetes mellitus; glucagonlike peptide-1; dipeptidyl peptidase

The majority of patients diagnosed with type 2 diabetes mellitus, or who have had the disease for a time, have or develop complications and comorbidities. Hypertension and dyslipidemia, cardiovascular disease, and, as a consequence of chronic hyperglycemia, retinopathy, neuropathy, and nephropathy, are all commonly observed in patients with type 2 diabetes.[1–5] Renal insufficiency and chronic kidney disease are also quite common in patients with type 2 diabetes, usually as a consequence of the disease but occasionally coincidental.[6] Data from the United Kingdom Prospective Diabetes Study (UKPDS) indicate that approximately 30% of patients with type 2 diabetes will develop renal impairment.[7,8] An analysis of National Health and Nutrition Examination Survey (NHANES) data found that nearly 40% of adult patients with type 2 diabetes have some degree of renal insufficiency or chronic kidney disease.[9] At the point in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial when patients in the intensive therapy group were transitioned to standard therapy, similar numbers of patients in the intensive therapy (443 of 5,107) and standard therapy (444 of 5,108) groups had experienced the prespecified first composite outcome of dialysis, renal transplantation, or high serum creatinine (>291.7 μmol/L), or retinal photocoagulation or vitrectomy.[10] In the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial, 43% of patients had evidence of kidney dysfunction at baseline, with albuminuria present in 33%

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and reduced estimated glomerular filtration rate (eGFR) present in 21%.[11]

One of the consequences of impaired renal function, and related comorbidities and complications, is that therapies for hyperglycemia—and also for these comorbid conditions—are not as effective as they otherwise might be. For example, patients with end-stage renal failure on dialysis are not protected from cardiovascular events by 3-hydroxy-3-methyl-glutaryl coenzyme A reductase therapies (statins). It is possible that even patients with more moderate degrees of renal insufficiency, who have vascular stent implants as a treatment for coronary disease, are not protected from such events.[12,13] Clinical trials of most established treatments, such as metformin, have excluded such patients, and thus there are many unknowns about the benefits and risks of treatments in such patients. A further challenge in the treatment of patients with type 2 diabetes with renal failure is that many are poorly controlled across a range of clinical targets, specifically glucose, blood pressure, and lipids.[14,15] In addition, there are contraindications/limitations to some diabetes medications, and those that can be used have changes in their pharmacodynamics, making management difficult. For example, the duration of action of insulin can change significantly based on metabolic changes associated with renal insufficiency due to disease- and/or age-related changes (Table 1[16–34]).

Moreover, patients with diabetes will often need multiple therapies: combinations of agents to treat hyperglycemia, and combinations of agents to treat hypertension and hyperlipidemia. The complexity is further compounded when renal insufficiency is added into the mix. Metformin, which is an effective first-line agent for the treatment of type 2 diabetes, will need to be discontinued, despite its glucose-lowering benefit, if creatinine levels rise above 1.5 mg/dL in males or 1.4 mg/dL in females (1 mg/dL = 88.4 μmol/L) or if the eGFR falls below 40 mL/min, indicating moderately severe renal impairment.[35,36] This is because plasma lactate concentrations increase with metformin treatment. Lactate is normally excreted by the kidney, and this does not happen in the context of chronic renal insufficiency, leading to a risk of lactic acidosis.[8,37]

PATIENTS WITH TYPE 2 DIABETES MELLITUS AND RENAL INSUFFICIENCY

The plasma concentrations of other drugs may be increased in patients with impaired renal function, and these increases may have consequences such as hypoglycemia or unknown side effects.[38] For example, among second-generation sulfonylureas, glyburide undergoes oxidation by the liver to 3 major metabolites, 1 of which has approximately 15% of the potency of glyburide itself and which is excreted in urine, thus increasing the risk for hypoglycemia in patients with renal insufficiency/kidney disease.[39]

The presence of renal insufficiency may affect the clinical indications, efficacy, and safety of agents used to treat comorbidities. Antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers must be used with caution in patients with renal impairment, as they increase the risk of hyperkalemia, which may be fatal.[40,41] Other possible drug–drug interactions may occur; for example, the combination of dipeptidyl peptidase–4 (DPP–4) inhibitors may increase the risk of ACE inhibitor-associated angioedema.[42]

Patients with chronic renal insufficiency also tend to retain fluid. Treating these patients with a thiazolidinedione (TZD) may result in additional fluid retention and an elevated risk of edema.[43–45] As discussed above, insulin is metabolized and cleared by the kidneys. So, impaired kidney function in conjunction with agents that are designed to increase plasma insulin concentrations—including, of course, insulin itself—increases the risk for hypoglycemia in patients with type 2 diabetes.[46]

Treatment choices for patients with type 2 diabetes with chronic renal insufficiency are greatly reduced compared with patients without renal impairment. Sulfonylureas that are either not metabolized by the kidney or also undergo metabolism in other organs (e.g., the liver), such as glimepiride and glipizide, could be safely used. Alternatively, due to their shorter half-lives, meglitinides may cause less hypoglycemia. Some of the newer incretin-based agents may have a role here, although some caveats and cautions remain.[47] The DPP-4 inhibitor vildagliptin has not been tested in patients with chronic renal insufficiency, so it is not known if the dosage needs to be adjusted.[48,49] Approval of vildagliptin in the United States was delayed pending submission of additional safety data, requested by the US Food and Drug Administration (FDA), concerning its effects on liver enzyme levels in patients with renal insufficiency.[50] Novartis announced in 2009 that it currently has no plans to resubmit for US approval.[51] Renal impairment studies had been completed for the DPP-4 inhibitors saxagliptin and sitagliptin; those studies did show some degree of drug accumulation in the patient with type 2 diabetes and renal insufficiency. Accordingly, dose adjustments are required. Patients prescribed sitagliptin who have mild-to-moderate renal impairment require a 50% dose reduction. If renal impairment is severe, the sitagliptin dose should be reduced to 25% of the normal dose.[32,52,53] The case is similar with saxagliptin, although there is just a single step of dose reduction of 50% in patients with renal insufficiency. The FDA recommended that the saxagliptin dose be 2.5 mg (the highest dose is 5 mg) daily in patients with moderate-to-severe renal insufficiency.[31,54]

The theoretical problem with plasma accumulation of DPP-4 inhibitors due to poor renal clearance is not hypoglycemia, but rather that exposure to very high levels of these agents may carry risks as yet unknown. DPP-4 is a ubiquitous enzyme that regulates the activity of a large number of peptides that have a range of metabolic, immunoprotective, and nociceptive functions—peptides like neuropeptide Y and substance P, for example. Extremely high levels of DPP-4 inhibition may have potential side effects that are as yet unknown or that have not been widely noted.[55–57] (For additional information, see