New Glucose-Lowering Agents for Diabetic Kidney Disease

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Lisanne C. de Vos, Thushan S. Hettige, and Mark E. Cooper

The prevalence of diabetes mellitus is increasing and is associated with a range of complications including nephropathy. New antidiabetic agents are sought which also have positive effects to diminish diabetic complications. Examples of promising new classes of such agents are glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium-glucose cotransporter 2 inhibitors. In addition to cardiovascular protective effects such as weight loss and decreased blood pressure of some of these agents, there is evidence for renoprotective effects with these agents. This review elaborates on the main results of renoprotective effects of these 3 treatment classes. In conclusion, currently available trials have demonstrated renoprotective effects for certain glucagon-like peptide-1 receptor agonists, liraglutide and semaglutide, and the sodium-glucose cotransporter 2 inhibitors, empagliflozin and canagliflozin. Dipeptidyl peptidase-4 inhibitors did not show a significant renoprotective effect. Nevertheless, larger studies with respect to renoprotective effects of these 3 drug classes are currently being performed, and thus, no conclusions for all of these agents can yet be made.

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INTRODUCTION

Diabetes mellitus is reaching epidemic levels, with its worldwide prevalence estimated to increase to 552 million by 2030.[1] The burden of the patients is, first, metabolic in that patients must perform regular lifelong glucose monitoring and lifestyle modification to prevent acute hyperglycemic or hypoglycemic events. The second major burden relates to its complications where specifically patients have an increased risk of microvascular and macrovascular complications of diabetes, including diabetic kidney disease.

The most frequently prescribed glucose-lowering drugs from a historical perspective are metformin, sulphonylureas, and insulin. Although these drugs have been shown to be able to diminish the risk of diabetic complications, they can be associated with significant side effects such as hypoglycemia and in particular with insulin and sulphonylureas weight gain.

Over the last decade, several new glucose-lowering drugs have been introduced and have dramatically transformed the therapeutic landscape for type 2 diabetes.[2] These medications, include glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter 2 (SGLT-2) inhibitors, with some of these agents showing not only antidiabetic effects but also promising end-organ benefits. This paper reviews the current evidence regarding the efficacy and safety profile of these new antidiabetic medications, with a particular focus on their renal end points.

GLUCOSE-LOWERING DRUGS

During the last century, impressive progress has been made in the treatment of diabetes mellitus. The first patient treated with insulin was in 1922, and after commercial availability of insulin, this resulted in the survival of patients with previously fatal type 1 diabetes.[3] Currently, short- and long-acting insulin options are available to be injected intermittently or continuously with an insulin pump. Although strict glucose regulation is possible with insulin, and evidence from the Diabetes Control and Complication Trial demonstrated reduced diabetic complications after intensive glucose therapy,[4] insulin has several adverse events with hypoglycemia, the most life-threatening side effect.[5] In addition, intensified insulin therapy and specifically twice-a-day or postprandial regimens are associated with weight gain of up to 4 kg per year.[6] More than 30 years after the introduction of insulin, sulfonylureas became commercially available.[3] Sulfonylureas stimulate the β-cells of the pancreas to produce insulin. Similar to insulin, these medicines are associated with hypoglycemia and weight gain.[7] Hence, these agents are not recommended as a first choice monotherapy for type 2 diabetes. Only in 1995, the biguanide metformin was commercially available in the United States, although this drug was already more widely available outside the United States for several decades. Metformin has multiple actions, and these include inhibition of gluconeogenesis in the liver and an increase in the sensitivity of peripheral tissues to insulin.[8] In addition to its glucose-lowering effect, metformin does not induce weight gain and in some cases usage may lead to a small reduction in weight.[9] The most frequently reported side effects are gastrointestinal in nature including diarrhea, nausea, and abdominal discomfort which can occur in up to 10% of subjects requiring either drug cessation or dose reduction.[10] However,

From the Department of Diabetes, Central Clinical School, Monash University, Melbourne, Australia; and the Department of Internal Medicine, Division of Vascular Medicine, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

de Vos and Hettige contributed equally.

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Address correspondence to Mark E. Cooper, MD, PhD, 99 Commercial Road, Level 5, Melbourne, Victoria 3004, Australia. E-mail: mark.cooper@monash.edu

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metformin is excreted unchanged via the kidneys, and in patients with chronic kidney disease (CKD), metformin toxicity resulting in lactic acidosis can occur.[10] Currently, metformin is the recommended initial monotherapy in patients with type 2 diabetes mellitus but is generally avoided in subjects with reduced estimated glomerular filtration rate (eGFR) (<30 mL/min/1.73 m^2) which is often seen in aging diabetic subjects or in a subgroup with advanced nephropathy.[9]

INCRETIN PATHWAY

Two of the relatively new glucose-lowering drug classes, the GLP-1 receptor agonists and the DPP-4 inhibitors, act via the incretin pathway. Incretins are hormones produced by the gastrointestinal tract and are known to influence glycemic homeostasis. The K-cells of the intestinal mucosa of the duodenum and L-cells in the distal ileum and colon produce glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, respectively.[11,12] In the case of digestion of food, GLP-1 and GIP are produced, resulting in stimulation of insulin production and secretion of this hormone by the β-cells of the pancreas. In fact, approximately 50% of insulin secretion occurs as a result of GLP-1 and GIP actions.[13] Unfortunately, both GLP-1 and GIP have short half-lives, about 2 minutes for GLP-1 and 5 minutes for GIP.[14,15] The enzyme DPP-4 induces the breakdown of these hormones. Thus, GLP-1 receptor agonists and DPP-4 inhibitors have been developed to extend the glucose-lowering effects of the incretins.

CLINICAL SUMMARY

- New classes of antidiabetic agents are desired which protect against diabetic complications.
- Glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium-glucose cotransporter 2 inhibitors have shown promising results with respect to certain diabetic complications.
- In particular, glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors appear to confer renoprotective effects in diabetes.

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

Multiple GLP-1 receptor agonists are currently available, including exenatide, liraglutide, dulaglutide, albiglutide, taspoglutide, and lixisenatide. These drugs are available as an injection, with different dosage frequency ranging from once a week to 3 times a day. Patients receiving a GLP-1 receptor agonist have improved glycemic control as reflected by decreased HbA1c and fasting glucose and also exhibit a range of improved cardiovascular risk factors including reduced body weight and lower blood pressure.[16] A meta-analysis (Evaluation of *Lixisenatide* in Acute Coronary Syndrome [ELIXA], *Liraglutide* Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER], Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes [SUSTAIN-6]) of 3 GLP-1 receptor agonists showed decreased risk of all-cause mortality, cardiovascular mortality, and severe hypoglycemia in type 2 diabetes compared to placebo.[17] However, the cardiovascular benefits were not seen in the ELIXA study. The underlying explanation for this difference is unknown, but in the ELIXA study, a shorter acting GLP-1 analog, lixisenatide, was used when compared to the other studies, LEADER and SUSTAIN-6 which examined liraglutide and semaglutude, respectively. The most frequently reported adverse events of these medicines are gastrointestinal symptoms including nausea, vomiting, and diarrhea.[16]

DIPEPTIDYL PEPTIDASE-4 INHIBITORS

At least 5 DPP-4 inhibitors are available in clinical practice, namely sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin, which are orally bioavailable and are in tablet form. A possible small reduction in blood pressure has been seen with some DPP-4 agents, but this has not been a universal finding.[18] A meta-analysis on the safety outcomes of 3 DPP-4 inhibitors (EXAMINE, SAVOR-TIMI53, TECOS) showed no benefit or risk of cardiovascular mortality. However, there is an increased risk of hypoglycemia and acute pancreatitis, but not pancreatic cancer.[17] No change in body weight occurred in comparison to metformin.[19] In the SAVOR-TIMI53 trial with saxagliptin, there was an increase in hospitalization for heart failure.[20] This was not seen with the other DPP-4 inhibitors and remains an unexpected finding.

SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS

In contrast to most glucose-lowering drugs, the SGLT-2 inhibitors exert their antidiabetic effect by increasing renal glucose excretion. The sodium-glucose cotransporters are situated in the proximal tubule of the kidney and reabsorb glucose from the glomerular filtrate. Two sodium-glucose cotransporters have been described, with SGLT-2 responsible for 97% of the glucose reabsorption, whereas SGLT-1 represents only 3% of glucose reabsorption in euglycemic mice.[21] SGLT-2 inhibitors prevent this reabsorption and therefore promote glycosuria. Currently, at least 3 SGLT-2 inhibitors are available for clinical practice including canagliflozin, dapagliflozin, and empagliflozin, all available orally as a once-daily dose. A meta-analysis of these 3 drugs showed a significant reduction in HbA1c for all the aforementioned SGLT-2 inhibitors (minimum usage of 24 weeks) compared to placebo for monotherapy and dual therapy with metformin.[22] Mean differences of HbA1c (%) ranged from −0.59 to −1.23 for monotherapy and −0.54 to −0.77 for dual therapy.[22] In addition, all these SGLT-2 inhibitors, which promote as a result of glycosuria calorie loss, led to a reduction in weight (monotherapy: −1.63 up to −3.00 kg, dual therapy: −1.62 up to −2.50 kg) and as a result of also promoting natriuresis a decrease in blood pressure (monotherapy: −2.57 up to −6.13 mmHg, dual therapy: −4.09 up to −6.60 mmHg).[22] Owing to the induced

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