Type 2 diabetes is a progressive, chronic metabolic disease characterized by hyperglycemia. Beyond being a diagnostic marker, elevated glucose is a key factor in the two abnormalities that are at the core of type 2 diabetes: pancreatic β-cell failure and insulin resistance. Chronic hyperglycemia can induce apoptosis of β-cells that is not countered by a compensatory increase in β-cell neogenesis and can lead to decreased insulin gene transcription. The detrimental effect of excessive glucose concentrations is referred to as "glucotoxicity."

Despite therapeutic advances, the incidence and prevalence of diabetes continue to surge. An estimated 25.8 million people in the United States have diabetes. The incidence could triple to one in three by 2050. Worldwide, the number of individuals with diabetes is projected to rise from 366 million in 2011 to 552 million by 2030, which is the equivalent of approximately three new cases being diagnosed every 10 seconds.

Type 2 diabetes doubles the risk of cardiovascular disease, and macrovascular complications (myocardial infarction and stroke) are a common cause of death in patients with type 2 diabetes. The U.K. Prospective Diabetes Study showed that every 1% absolute decline in mean A1C was associated with a 37% reduction in the risk of microvascular complications and a 21% reduction in the risk of any diabetes-related complication or death. Diabetes also exacts a tremendous economic burden; in the United States, direct and indirect costs totaled $174 billion in 2007.

Meeting treatment goals is elusive for many people with diabetes. Data from the National Health and Nutrition Examination Survey from 2003 to 2006 showed that only 57.1% of adults with diagnosed diabetes achieved an A1C < 7%, 45.5% had a blood pressure level < 130/80 mmHg, and 46.5% had an LDL cholesterol level < 100 mg/dl. Only 12.2% of people with diabetes reached all three goals.

There are multiple barriers to achieving optimal glycemic control. The pathophysiology of diabetes is complex and involves multiple defects: β-cell failure (decreased insulin secretion); insulin resistance in muscle, brain, and liver; increased glucagon secretion in α-cells; increased lipolysis in adipose tissue; incretin deficiency and resistance in the gastrointestinal (GI) tract; and increased glucose reabsorption in the kidney. Other obstacles include clinical inertia, or the failure to start or intensify therapy when clinically indicated. There is some evidence that patients with type 2 diabetes who have lower medication adherence are less likely to undergo treatment intensification. Reaching glycemic targets may also be hampered by aversion to adding insulin or implementing lifestyle changes. Barriers such as cost and formulary restrictions also present challenges.

Current medications for type 2 diabetes have potential adverse effects; sulfonylureas and insulin, for example, can cause hypoglycemia and weight gain. Thus, the search continues for novel therapeutic agents that can help patients avoid these limiting side effects while providing glycemic control.

Although the concept of the kidney playing a significant role in glucose balance is not new, only recently has this organ been considered a potential therapeutic target. Sodium-glucose cotransporters (SGLTs), namely SGLT-1 and SGLT-2, facilitate reabsorption of glucose back into the plasma. Inhibiting this process promotes glucosuria and thus reduces blood glucose. This review describes the mechanism of action of this new mechanism of action.
class of treatment for type 2 diabete
es, as well as published data on its
efficacy and safety.

Role of the Kidney in Glucose
Homeostasis
Despite wide fluctuations in the daily
supply of glucose and the body’s
demand for it, homeostatic mecha
nisms maintain plasma glucose levels
within a narrow range, with average
levels of 90–100 mg/dl in a 24-hour
period. The kidney’s crucial role in
maintaining glucose balance was first
described as early as 1938. Along
with the liver, the kidney supplies
glucose during periods of fasting. The
renal contribution to gluconeogenesis
is 15–55 g/day, or 20–25% of the
glucose released into the circulation
after an overnight fast.

The reabsorption of glucose
filtered into the glomerular filtrate is
the primary mechanism by which the
kidney influences glucose homeosta
sis. Glucose excretion in urine is the
net difference between the amount
of glucose filtered by the kidney and
the amount reabsorbed. In healthy
individuals, the kidney contributes
significantly to glucose homeostasis
by reabsorbing essentially all of the
180 g of glucose that it filters per
day. Individuals without diabetes
thus have very little or no glucose
present in the urine.

Reabsorption occurs in the
proximal convoluted tubule (PCT)
and is carried out by two isoforms of
SGLT. SGLT-2 is located in the S1
and S2 segments of the PCT and has
a high capacity but low affinity for
glucose transport. In healthy indi
viduals, it reabsorbs 90% of filtered
glucose (Figure 1). SGLT-1 governs
glucose transport in the S3 segment
and is a low-capacity, high-affinity
glucose transporter that reabsors
the remaining 10% of the filtered
glucose. The active transport of
glucose is linked to downhill sodium
transport, which is maintained by
active extrusion of sodium across the
basolateral surface into the intracel
lular fluid (Figure 2). Facilitated
glucose transporters (GLUTs) carry
glucose across the basolateral mem
brane by facilitated diffusion.

Glucose reabsorption in the PCT
increases with rising plasma glucose
levels until the transport maximum
for glucose (Tmax) is reached. The
Tmax is usually considered to occur
at a glomerular filtration rate of
260–350 mg/min/1.73 m². The renal
glucose threshold (RT) is the
plasma glucose concentration above
which the SGLT capacity becomes
saturated and urinary glucose excre
tion (UGE) occurs. It is estimated to
occur at a plasma glucose concen
tration of 200 mg/dl (Figure 3). The
actual threshold is not abrupt
and differs from the theoretical
threshold for both the reabsorption
and excretion curves (Figure 3). One

Figure 1. Renal glucose handling. In healthy individuals, the vast majority of the
glucose filtered by the kidney is reabsorbed by SGLT-2 in the S1 and S2 segments
of the proximal convoluted tubule, and the remaining glucose is reabsorbed by SGLT-1
in the S3 segment.

Figure 2. SGLT-2 mediates glucose reabsorption in the kidney. SGLT-2 catalyzes
the active transport of glucose (against a concentration gradient) across the luminal
membrane by coupling it with the downhill transport of Na+. The inward Na+ gradi
ten across the luminal epithelium is maintained by active extrusion of Na+ across
the basolateral surface into the intracellular fluid. Glucose diffuses out of the cell
down a concentration gradient via the basolateral facilitative transporter GLUT2.
Adapted from Ref. 20.
reason for this splay, or difference in thresholds, is physiological variation among individual nephrons.

The rate of renal glucose reabsorption is elevated in people with type 2 diabetes; the $T_{\text{max}}$ is increased by 20–40% compared to healthy individuals.21 What was once an adaptive response to ensure sufficient caloric intake thus becomes the opposite: a maladaptive action that fuels further increases in plasma glucose. Both expression and function of SGLT-2 are upregulated in people with type 2 diabetes.22,23

Introduction to SGLT-2 Inhibitors

In the 2nd century, the Greek physician Areataeus postulated that diabetes was caused by a derangement in the kidney.24 Phlorizin, the first known SGLT inhibitor, was isolated from the root bark of apple trees.25 Interes in the compound was dormant until the 1970s, with discovery of the location of the transporters.

Phlorizin nonsel ectively blocks both SGLT-2 and SGLT-1, leading to UGE. When administered to diabetic rats, phlorizin normalized both fasting and postprandial plasma glucose concentrations and completely eliminated insulin resistance.26 The safety of chronic UGE is supported by a benign genetic condition termed familial renal glucosuria (FRG). This genetic disorder involves loss-of-function mutations in the gene coding for SGLT-2 that cause UGE ranging from 20 to 200 g/day.27,28 Individuals with FRG do not experience hypoglycemia, are asymptomatic, do not exhibit evidence of renal tubular dysfunction or renal insufficiency, and have a normal life expectancy.27,28

Phlorizin was not developed for use in humans because of its low bioavailability (~15%) and its action on SGLT-1, which can result in GI side effects, including diarrhea. Other SGLT-2 inhibitors, such as sergliflozin, did not reach advanced stages of clinical development for reasons related to their pharmacokinetic profiles (i.e., their susceptibility to hydrolysis by GI tract enzymes resulted in relatively short half-lives and poor bioavailability).29,31 Canagliflozin has been approved in the United States, and dapagliflozin has been approved in Europe. Several other SGLT-2 inhibitors are in development (Table 1).

Mechanism of Action and Potential Advantages

By lowering the renal threshold for glucose excretion, SGLT-2 inhibitors suppress renal glucose reabsorption and thereby increase UGE.19 Hyperglycemia is thus ameliorated. However, SGLT-2 inhibitors inhibit reabsorption of only ~30–50% of the glucose filtered by the kidney.32 The reasons for this are unclear. One hypothesis is that SGLT-2 inhibitors may be actively secreted into the PCT such that the amount of SGLT-2 inhibitor in the PCT is limited by saturation of renal secretion of the inhibitor at high doses, and, depending on the site of secretion, the inhibitors may be unable to act on upstream SGLT-2.32 Another hypothesis is that SGLTs other than SGLT-2 may play a greater role in glucose reabsorption than is currently believed.32 SGLT-2 inhibition offers several putative advantages. Acting independently of insulin, these agents should not confer a risk of hypoglycemia and could be employed as monotherapy or in combination with other agents. Given their mechanism of action, these agents should be effective in patients with any degree
of insulin resistance or β-cell function. They should also be associated with weight loss resulting from the loss of glucose (calories) in urine and glucose-induced osmotic diuresis. Their mild osmotic diuretic effect could potentially also reduce blood pressure. Taken together, these effects may have a beneficial impact on cardiovascular outcomes. Inducing UGE initially appears to be a counterintuitive strategy for treatment of patients with type 2 diabetes because it employs what was once thought of only as a signal of uncontrolled diabetes. This conceptual leap from symptom to tool for studying physiology to potential treatment will be further examined.

Clinical Studies
SGLT-2 inhibitors have improved glycemic control as monotherapy in patients with type 2 diabetes in phase 2 and 3 clinical trials. Placebo-adjusted reductions in A1C of up to 1.2% have been reported in studies ranging from 4 weeks to 90 weeks in duration, in addition to decreased fasting plasma glucose and postprandial glucose. Phase 2 and 3 clinical trials of SGLT-2 inhibitors used as add-on therapy demonstrated improved glycemic control with low rates of hypoglycemia. An SGLT-2 inhibitor added to metformin, or to metformin plus a sulfonylurea resulted in absolute reductions in A1C of up to ~ 1% from a baseline of ~ 8%, A1C declined by ~ 2% in one study of dapagliflozin added to metformin, in which patients had elevated baseline A1C levels (~ 9%). Reductions in A1C have also been reported when SGLT-2 inhibitors were added to pioglitazone, glimepiride (up to 0.8%), insulin (up to 1%), or insulin plus oral antidiabetic agents (up to 0.7%).

Dapagliflozin has been shown to be effective in patients with early type 2 diabetes (i.e., treatment-naïve patients), as well as in patients dependent on insulin plus insulin sensitizers. A pooled analysis of data from five phase 3 studies of dapagliflozin demonstrated that higher baseline A1C levels were associated with greater reductions in A1C. For example, at 24 weeks, dapagliflozin lowered A1C by 0.44% (placebo-adjusted) in patients with a baseline A1C < 8.0%, by 0.54% in patients with baseline A1C ≥ 8.0 to < 9.0%, and by 1.01% in patients with baseline A1C ≥ 9%.

Because the glomerular filtration rate (GFR) is a factor in determining the extent to which SGLT-2 inhibitors can produce glucosuria, their efficacy would be expected to be reduced in patients with impaired renal function. Attenuated glucosuria associated with ipragliflozin was observed in patients with type 2 diabetes and moderate or severe renal impairment (estimated GFR [eGFR] 15–59 ml/min/1.73 m²) compared to those with mild renal impairment or normal renal function. UGE decreased by 42–90% in patients with type 2 diabetes and renal impairment (eGFR 30–89 ml/min/1.73 m²) receiving dapagliflozin compared to patients with type 2 diabetes and normal renal function.

Clinical trials of SGLT-2 inhibitors in patients with type 2 diabetes and renal impairment have shown mixed results in their ability to reduce A1C. In a study involving patients with type 2 diabetes and moderate renal impairment (eGFR 30–60 ml/min/1.73 m²), reductions in A1C were observed with dapagliflozin.
Gliflozin, 5 and 10 mg, but were not significantly different from placebo. However, in a phase 3 study of canagliflozin in patients with type 2 diabetes and moderate renal impairment (eGFR 30–50 ml/min/1.73 m²), A1C was significantly lower with canagliflozin, 100 and 300 mg, compared to placebo at week 26. Further data are required to establish the efficacy of SGLT-2 inhibitors in patients with type 2 diabetes and renal impairment.

SGLT-2 inhibitors have produced weight reductions of up to 4.7 kg in phase 2 and 3 clinical trials when administered as monotherapy or as add-on therapy to metformin, a sulfonylurea, or insulin over study periods ranging from 4 to 104 weeks. Dalagliflozin also attenuates the weight gain associated with pioglitazone. Weight loss is accompanied by loss of body fat. A body composition study found that two-thirds of the 2.1 kg (placebo-adjusted) weight loss achieved with 10 mg dapagliflozin added to metformin for 24 weeks in patients with type 2 diabetes resulted from a reduction in body fat, both visceral and subcutaneous.

A lower systolic blood pressure of ~2–10 mmHg was observed in studies of SGLT-2 inhibitors in patients with type 2 diabetes. Declines in diastolic blood pressure were smaller and less consistent across clinical trials.

Patients with type 2 diabetes receiving SGLT-2 inhibitors have decreased serum uric acid levels, a potentially beneficial effect given evidence that hyperuricemia is an independent risk factor for hypertension, renal disease, and cardiovascular disease. This effect may be mediated by GLUT9 (SLC2A9b) on the apical membrane of the PCT, which exchanges glucose for urate. The high concentration of glucose in the tubule would favor the exchange of glucose for urate, resulting in increased excretion of urate in the urine.

Safety and Tolerability
Given the insulin-independent mechanism of action of SGLT-2 inhibitors, hypoglycemia would not be expected, and indeed, very low rates of hypoglycemia have been observed in clinical trials. Glucose in the urine supplies an environment that may encourage bacteria in the urinary tract to flourish and can result in infection. Some studies have shown an increased incidence of events suggestive of urinary tract infections (UTIs) in patients given SGLT-2 inhibitors. However, in many of these studies, the infections were not culture-verified, and some studies of SGLT-2 inhibitors have demonstrated a rate of UTIs similar to that with placebo.

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density, markers of bone formation, or bone resorption compared to placebo in 165 patients with type 2 diabetes inadequately controlled on metformin who were treated with dapagliflozin.57 No fractures or sex differences were noted in postmenopausal females or males.

Dapagliflozin had a largely neutral effect on blood lipids.65,76 Small increases in LDL cholesterol47,76 and HDL cholesterol47,57,76 and a small reduction in triglycerides47,76 have been observed in some placebo-controlled studies.

Outlook for SGLT-2 Inhibitors
On 19 January 2012, the U.S. Food and Drug Administration (FDA) informed Bristol-Myers Squibb and AstraZeneca that it would not approve dapagliflozin. This decision followed the agency’s Endocrinologic and Metabolic Drugs Advisory Committee recommendation against approval of dapagliflozin by a vote of nine to six. Further data from ongoing clinical trials and possibly data from new studies will be forthcoming. The Committee for Medicinal Products for Human Use of the European Medicines Agency granted marketing authorization for dapagliflozin on 12 November 2012 for use in adults with type 2 diabetes as monotherapy and as combination therapy with other glucose-lowering medicinal products including insulin, together with diet and exercise.77 On 29 March 2013, the FDA approved canagliflozin to improve glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise.78

Several clinical trials of SGLT-2 inhibitors used as monotherapy or in combination with a range of other treatments are ongoing. The largest clinical trial program in progress is for empagliflozin, involving > 14,000 patients. Very large trials of dapagliflozin, canagliflozin, and empagliflozin are ongoing to assess effects on cardiovascular outcomes. In addition, basic science and mechanistic studies are underway to provide a greater understanding of the mechanism of action of SGLT-2 inhibitors and its implications for the pathophysiological processes involved in the progression of type 2 diabetes.

Conclusion
The concept of inhibition of SGLT-2 marks a departure in how diabetes is viewed and approached for treatment. SGLT-2 inhibitors have a novel mechanism of action that is independent of insulin secretion and action. These agents block glucose reabsorption, leading to urinary glucose excretion. The advantages of this approach are reduced hyperglycemia without hypoglycemia, along with weight loss and blood pressure reduction. Data from multiple phase 3 studies of > 5,000 subjects demonstrate these findings. However, increases in UTIs and genitourinary infections have been observed in some studies. SGLT-2 inhibitors could be used as monotherapy or in combination with other medications in patients with type 2 diabetes and potentially earlier in the continuum in those with prediabetes.

Taken together, the clinical evidence to date suggests that SGLT-2 inhibitors hold promise as an important addition to the toolbox of treatment options for type 2 diabetes.

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