The potential of sodium glucose cotransporter 2 (SGLT2) inhibitors to reduce cardiovascular risk in patients with type 2 diabetes (T2DM)☆

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Abstract

Type 2 diabetes mellitus (T2DM) significantly increases morbidity and mortality from cardiovascular disease (CVD). Treatments for patients with T2DM have the potential to reduce cardiovascular (CV) risk. This review focuses on the potential of a new class of antidiabetic agents, the sodium glucose cotransporter 2 (SGLT2) inhibitors, to reduce CV risk in patients with T2DM through reductions in hyperglycemia, blood pressure (BP), and body weight. The results of clinical trials of SGLT2 inhibitors are summarized and discussed.

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1. Introduction

Diabetes is an increasing public health problem. The UN General Assembly has recognized that diabetes poses risks to well-being worldwide and has calculated that diabetes prevalence has risen by about 7% per decade, from 8.3% in 1980 to 9.8% in 2008 among men, and from 7.5% to 9.2% among women (Tobias, 2011). The number of adults with T2DM worldwide has more than doubled in the last 30 years, rising from 153 million in 1980 to 347 million in 2008 (Danaei et al., 2011). This trend is set to continue, with predictions of 439 million cases by 2030 (Nolan et al., 2011).

T2DM is a major cause of morbidity and death worldwide, being the leading cause of kidney failure, non-traumatic lower limb amputation, and new cases of blindness among adults in the United States, as well as a major cause of heart disease and stroke (Centers for Disease Control and Prevention, 2011). Diabetes is the seventh leading cause of death in the United States, and mortality rates are projected to rise sharply over the next decade (Centers for Disease Control and Prevention, 2011).

2. Pathogenesis of T2DM and limitations of current therapies

T2DM results from progressive β-cell dysfunction in the presence of chronic insulin resistance, leading to a progressive decline in plasma glucose control (Campbell, 2009). Signaling pathways involved in glucose homeostasis are disrupted during the pathogenesis of T2DM, resulting in increased glucagon secretion, reduced incretin response, increased endogenous glucose production, increased renal glucose reabsorption, impaired expansion of subcutaneous adipose tissue, and hypoadiponectinemia (DeFronzo, Davidson, & del Prato, 2012; Nolan et al., 2011).

Most therapies available for the treatment of patients with T2DM act by increasing insulin sensitivity or by stimulating insulin secretion (Cefalu, Richards, & Melendez-Ramirez, 2009; DeFronzo, 2010). Treatment success is usually defined as achieving target levels of glycated hemoglobin (HbA1c) with low rates of hypoglycemic events (Cefalu et al., 2009). Initial management usually consists of lifestyle modifications (diet and exercise) often with metformin monotherapy at the time of diagnosis or shortly thereafter (Inzucchi et al., 2012). As the disease progresses, more complex treatment regimens, involving more than one antidiabetic agent and ultimately insulin, are required to keep plasma glucose levels at target (Inzucchi et al., 2012). This can be viewed as a “treat-to-failure” approach, and results in patients having inadequate glycemic control for much of their time on treatment (Cefalu, 2012a). Recent recommendations have focused on “individualizing” treatment for patients in the context of wider disease management (Inzucchi et al., 2012). This patient-centered approach to care goes beyond algorithms to incorporate patient attitudes and preferences, gender, race, ethnicity, risks of therapy, comorbidities, the presence of complications, and the resources and support systems available to the individual (Cefalu, 2012b).

While tight glycemic control is known to reduce the microvascular complications of T2DM, around half of all patients fail to achieve and maintain the HbA1c target of <7% recommended by the American Diabetes Association (ADA) and other bodies (American Diabetes Association, 2012; Cornell, 2011; Turner, Cull, Frighi, & Holman, 1999). Estimates of the proportion of patients achieving this goal vary considerably and depend on the type of treatment. A recent meta-analysis of 218 trials with patients with T2DM found that the

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proportion meeting an HbA1c target of <7% ranged from 26% with α-glucosidase inhibitors to 63% with exenatide (Esposito, Chiiodini, Bellastella, Maiorino, & Giugliano, 2012). In the short term, the glucose-lowering efficacy of the various monotherapies recommended in the early stages of the disease is similar and other risks and benefits (e.g. risk of hypoglycemia, effect on weight) are considered in treatment choice (Scherthanner et al., 2010). Side effects of current therapies, including hypoglycemia, weight gain, fluid retention, and gastrointestinal effects, can limit their use and reduce patients’ adherence to medication (Scherthanner et al., 2010), making patients less likely to reach glycemic targets. A study of new users of oral antidiabetic treatments found that patients who did not comply with treatment were 20% less likely to achieve glycemic targets than those who did (Penning-van Beest et al., 2008), while an internet survey of 1984 patients with T2DM found that both hypoglycemia and weight gain were associated with reduced quality of life (Marrett, Stargardt, Mavros, & Alexander, 2009). Newer therapies aim to address these limitations. An ideal glucose-lowering agent should maintain glycemic control, preserve β-cell function, be weight-neutral or even promote weight loss, and have a low incidence of hypoglycemic events (Tahrani, Piya, Kennedy, & Barnett, 2010).

3. T2DM and CVD risk

T2DM confers an increased risk of vascular disease, with diabetes-induced micro- and macrovascular complications being the major causes of morbidity and mortality in patients with T2DM (Madonna & De Caterina, 2011). A meta-analysis of 102 studies found that T2DM was associated with a 2-fold increased risk of vascular diseases such as coronary heart disease and stroke, independent of other risk factors including age, sex, smoking, body mass index (BMI), and systolic BP (The Emerging Risk Factors Collaboration, 2010).

Large clinical studies of the effects of intensive glucose lowering on mortality and CV outcomes in patients with T2DM have not proved to be straightforward, suggesting that the relationship between the two is complex and not only related to control of hyperglycemia. Recent data (e.g. from the ACCORD, VADT and ADVANCE trials) have demonstrated modest but significant microvascular benefits with aggressive glucose control. However, in these same studies, aggressive glucose control did not reduce macrovascular outcomes in patients with characteristics such as long-standing disease, advanced age and frailty, low awareness of hypoglycemia, significant comorbidities, and/or pre-existing macrovascular disease (ACCORD Study Group, 2008; ADVANCE Collaborative Group, 2008; Ismail-Beigi et al., 2010; Kelly et al., 2009;erry, Ravarikar, Chokrungvaran, & Reaven, 2012). The timing of glucose control may also be important, with the “metabolic memory” hypothesis suggesting that tight control during the early stages of T2DM may have a legacy effect, with benefits on CV and microvascular disease in the long term (Holman, Paul, Bethel, Matthews, & Neil, 2008).

In addition to hyperglycemia, many patients with T2DM have co-morbid conditions that increase the risk of CVD. These co-morbidities include obesity, hypertension, and dyslipidemia, and are inter-related epidemiologically, clinically, and metabolically (Kabakci, Koylan, Ilerigelen, Kozan, & Buyukozturk, 2008). It has been estimated that approximately 90% of T2DM cases are attributable, at least in part, to excess body weight (Gregg, Cheng, Narayan, Thompson, & Williamson, 2007) and obesity increases the risk of CVD in patients with T2DM (Cornell, 2011). Hypertension is also common in patients with T2DM and is a significant risk factor for CVD in this patient group (Ferrannini & Cushman, 2012). Atherosclerosis and T2DM both lead to vascular damage and share common causative mechanisms (including inflammation) and risk factors, including hypertension and dyslipidemia (DeSouza & Fonseca, 2009).

As T2DM is a multifactorial disease, the effects of antidiabetic agents on pathophysiological abnormalities other than hyperglycemia may warrant greater consideration than they have received to date (Scherthanner et al., 2010). Some CV risk factors (e.g. hypertension) are modifiable with intervention and represent a legitimate strategy for addressing the high CV mortality in patients with T2DM (Tahrani et al., 2010). However, it is important to note that the effects of antidiabetic therapies on CV risk factors may have either a positive (e.g. reduction in BP, weight loss) or negative (e.g. weight gain, increased hypoglycemia) effect (Table 1).

4. Modulation of renal glucose reabsorption as a mechanism for improving glycemic control in T2DM: the SGLT2 inhibitors

The kidney plays an important role in glucose homeostasis, normally accounting for more than 10% of total glucose utilization in the body, up to 20% of all glucose production via gluconeogenensis, and, most importantly, mediating the reabsorption of glucose from the glomerular filtrate (Gerich, 2010; Mather & Pollock, 2011). T2DM augments all of these functions of the kidney. A three-fold increase in overall glucose production has been observed in patients with T2DM, with both the liver and the kidneys contributing to this increase via gluconeogenensis (Mather & Pollock, 2011). In addition, renal glucose reabsorption is increased (Gerich, 2010).

In healthy adults, with a glomerular filtration rate (GFR) of ~125 ml/min, approximately 180 L of plasma is filtered through the kidneys every day (Gerich, 2010). A healthy adult with an average plasma glucose concentration of 5 mmol/L filters approximately 180 g of glucose per day into the glomerular filtrate (Gerich, 2010). In order to maintain glucose levels in the body, virtually all of the filtered glucose is recovered in the kidneys by sodium glucose cotransporters (SGLT1 and SGLT2). In the proximal tubule of the nephron and accounts for approximately 90% of renal glucose reabsorption (DeFronzo et al., 2012) (Fig. 1). SGLT2 operates by coupling glucose transport to an electrochemical sodium gradient to move glucose and sodium ions across the luminal surface of the epithelial cells lining the S1 and S2 segments of the proximal tubule (Mather & Pollock, 2011). Once concentrated in the epithelial cells, glucose is transported into the blood, facilitated by the glucose transporter, GLUT2 (DeFronzo et al., 2012; Wright et al., 2007). Reabsorption of glucose from the glomerular filtrate increases in proportion to the plasma glucose concentration until the maximum transport capacity of the tubules (the transport maximum for glucose [TmG]) is reached, above which excess glucose is lost in the urine (Basile, 2011; Mather & Pollock, 2011). In people with T2DM, TmG is increased by up to 20%, so urinary glucose excretion (UGE) begins to occur at normal plasma glucose levels (Gerich, 2010). Studies of renal cells isolated from urine have shown that SGLT2 and GLUT2 expression is increased in patients with T2DM (Rahmoune et al., 2005).

The kidney’s role in the reabsorption of glucose from the glomerular filtrate has led to investigation of SGLT2 as a potential therapeutic target for T2DM. SGLT2 inhibitors reduce the capacity of the proximal tubule to reabsorb glucose from the glomerular filtrate, leading to increased UGE, which reduces hyperglycemia (DeFronzo et al., 2012). Several SGLT2 inhibitors are now in Phase III clinical development (Table 2). Dapagliflozin, the first agent submitted for approval, was rejected by the US Food and Drug Administration (FDA) in January 2012. It was recommended, however, for marketing authorization by the European Medicines Agency (EMA) in April 2012 as monotherapy for the treatment of adults with T2DM in patients for whom diet and exercise do not provide adequate glycemic control and for whom metformin is considered inappropriate due to
in HbA1c of up to 0.73% have been observed when an SGLT2 inhibitor used in combination with antidiabetic agents. Additional reductions in clinical studies, demonstrating the efficacy and safety of SGLT2 inhibitors in patients with T2DM, which has been borne out in clinical studies, demonstrating the efficacy of SGLT2 inhibitors when used in combination with antidiabetic agents. Additional reductions in HbA1c of up to 0.73% have been observed when an SGLT2 inhibitor has been added to metformin (Bailey, Gross, Pieters, Bastien, & List, 2010; Nauck et al., 2011; Rosenstock et al., 2011; Rosenstock et al., 2012a; Wilding et al., 2011). When used in combination with glimepiride, dapagliflozin reduced HbA1c by up to 0.82%, compared with a reduction of 0.13% with glimepiride alone (Strojek et al., 2011), while with pioglitazone, dapagliflozin reduced HbA1c by up to 0.97%, compared to a reduction of 0.42% with pioglitazone alone (Rosenstock, Vico, Wei, Salsali, & List, 2012b). Dapagliflozin plus insulin reduced HbA1c by up to 0.96%, versus a reduction of up to 0.13% achieved with insulin alone (Wilding et al., 2009; Wilding et al., 2012), and similar results have been observed with canagliflozin (Devini et al., 2012).

SGLT2 inhibitors have been shown to reduce fasting plasma glucose (FPG). Used as monotherapy, reductions in FPG in the order of 15–65 mg/dL have been observed in clinical trials (Ferrannini et al., 2010a, 2010b; Fonseca et al., 2011; Henry et al., 2012; Kashiwagi et al., 2011; List et al., 2009; Schwartz et al., 2011). When used in combination with metformin, additional reductions of up to 32.7 mg/dL have been seen (Bailey et al., 2010; Henry et al., 2012; Rosenstock et al., 2011; Rosenstock et al., 2012a; Wilding et al., 2011). In combination with glimepiride, dapagliflozin reduced FPG by 16.7–28.4 mg/dL, compared with a reduction of 2.0 mg/dL with glimepiride alone (Strojek et al., 2011). With pioglitazone, dapagliflozin reduced FPG by 24.9–29.6 mg/dL, compared with a reduction of 5.5 mg/dL with pioglitazone monotherapy (Rosenstock et al., 2012b). A combination of dapagliflozin plus insulin reduced FPG by 15.4–27.4 mg/dL over insulin alone (Wilding et al., 2009), while canagliflozin plus insulin reduced FPG by a further 42.7–44.7 mg/dL over insulin alone (Devini et al., 2012).

In addition to reducing FPG, SGLT2 inhibitors reduce the postprandial spike in plasma glucose concentrations. Reductions in postprandial glucose (PPG) have been observed with SGLT2 inhibitors used as monotherapy or in combination with sulfonylurea (SU), pioglitazone or insulin therapy (List et al., 2009; Rosenstock et al., 2012b; Strojek et al., 2011; Wilding et al., 2009).

As SGLT2 inhibitors work independently of insulin, the efficacy of these drugs is independent of β-cell function or insulin resistance (Zhang, Feng, List, Kaschayanula, & Pfister, 2010). Clinical studies have shown that SGLT2 inhibitors improve glycemic control when used in patients with both early and late stages of T2DM (Devini et al., 2012).

Table 1
Effect of antidiabetic drugs on CV risk factors (Bailey, 2011; Cornell, 2011; Inzucchi, 2002; Schernthaner et al., 2010; Tahrani et al., 2010).
of females) with dapagliti
(0.04% of patients) with comparator and 9 cases of breast cancer (0.4% of patients with T2DM) resulted in loss of calories and so a reduction in body weight; initial weight loss may also re
sult from fluid loss, as UGE results in mild osmotic diuresis (Ferrannini & Solini, 2012). Reductions have also been observed when SGLT2 inhibitors were used in combination with metformin, SU, pioglitazone, or insulin (Bailey et al., 2010; DeVienie
ni et al., 2012; Nauck et al., 2011; Rosenstock et al., 2011, 2012a, 2012b; Strojek et al., 2011; Wilding et al., 2009; Wilding et al., 2011; Wilding et al., 2012; Woerle et al., 2012). In patients treated with dapagliflozin and metformin, reductions in weight began early and continued over the course of the trial; around 20% of patients had weight reductions of at least 5% after 24 weeks (Bolinder et al., 2012). Weight loss has been shown to reflect loss of both subcutaneous and visceral fat (Bolinder et al., 2012).

6.2. Blood pressure

Reductions in BP in patients who take an SGLT2 inhibitor are believed to be due, at least in part, to mild osmotic diuresis, as urine output increases due to lower reabsorption of water in the kidneys. Initial increases in urinary volume of up to 450 mL/day have been reported after dapagliflozin treatment (Bailey, 2011), representing one extra void per day, but this levels off, and signs of volume depletion such as orthostatic hypotension and tachycardia have been reported very rarely (Bailey et al., 2010; Ferrannini et al., 2010a). Reductions in weight and sodium ion excretion may also contribute to BP reductions (Bailey, 2011; Ferrannini & Solini, 2012).

Maximum mean reductions in systolic BP of −3–9 mmHg have been observed in studies of SGLT2 inhibitors used as monotherapy (Ferrannini et al., 2010a; Henry et al., 2012; Kashiwagi et al., 2011; List et al., 2009) and in combination with metformin, SU, or pioglitazone (Bailey et al., 2010; Nauck et al., 2011; Rosenstock et al., 2011; Rosenstock et al., 2012a, 2012b; Strojek et al., 2011; Wilding et al., 2011). In studies of SGLT2 inhibitors used in combination with insulin, similar reductions in systolic BP were seen (Devine
ni et al., 2012; Wilding et al., 2009; Wilding et al., 2012). Reductions in diastolic BP have been smaller and less consistent across trials (List & Whaley, 2011). Overall, better controlled studies are needed to confirm the effect of SGLT2 inhibitors on BP.

6.3. Lipids

Small lipid changes have been reported in some trials of SGLT2 inhibitors. Increases in total cholesterol and HDL-cholesterol (Bailey et al., 2010; Nauck et al., 2011; Rosenstock et al., 2012b) and a reduction in triglycerides (Bailey et al., 2010; Nauck et al., 2011) have been observed with dapagliflozin. With canagliflozin, increases in HDL-cholesterol and LDL-cholesterol have been observed, with a minimal effect on the total cholesterol:LDL-cholesterol ratio, and small and inconsistent changes in triglycerides (Cefalu et al., 2012; Gross et al., 2012; Rosenstock et al., 2012a).

6.4. Uric acid

Small reductions (approximately 1 mg/dL) in serum uric acid have been reported in trials of SGLT2 inhibitors used as monotherapy (Henry et al., 2012; List et al., 2009), and in combination with metformin (Bailey et al., 2010; Nauck et al., 2011; Rosenstock et al., 2012a), pioglitazone (Rosenstock et al., 2012b), SU (Strojek et al., 2011) or insulin (Wilding et al., 2009; Wilding et al., 2012). Reductions in serum uric acid levels may be mediated by GLUT9 (SLC2A9), a facilitative glucose transporter found in the proximal tubule. GLUT9 functions as a high-capacity urate transporter and is believed to secrete uric acid into the tubule in exchange for luminal glucose (Cheeseman, 2009). Thus, an increased glucose concentration in the proximal tubule would be expected to increase secretion of uric acid.
Table 3
Summary of ongoing CV outcomes trials with SGLT2 inhibitors (www.clinicaltrials.gov).

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Treatment groups</th>
<th>Patient population</th>
<th>No. of patients</th>
<th>Treatment duration</th>
<th>Primary endpoint</th>
<th>Secondary CV endpoints</th>
<th>Estimated completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01032629</td>
<td>Canagliflozin and placebo</td>
<td>Patients with T2DM and high CV risk</td>
<td>4400</td>
<td>4 years</td>
<td>Time to first occurrence of CV death, non-fatal MI, or non-fatal stroke</td>
<td>None</td>
<td>April 2013 (event driven)</td>
</tr>
<tr>
<td>NCT01131676</td>
<td>Empagliflozin and placebo</td>
<td>Patients with T2DM and high CV risk</td>
<td>7000</td>
<td>4 years</td>
<td>Time to first occurrence of CV death, non-fatal MI, or non-fatal stroke</td>
<td>Composite of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina Incidence of silent MI</td>
<td>March 2018 (event driven)</td>
</tr>
</tbody>
</table>

acid into the urine and reduce serum uric acid. A reduction in serum uric acid could have beneficial effects on CV risk, given the increasing evidence that elevated serum uric acid levels are an independent risk factor for CV disease (Zoppini et al., 2009).

6.5. Overall effect on CV risk

The data submitted to the FDA as part of the application for registration of dapagliflozin contain the most comprehensive analysis to date of the effect of an SGLT2 inhibitor on CV outcomes. Fourteen clinical trials were analyzed: three 12-week Phase IIb studies, ten 24-week Phase III studies, and one 52-week study, with extensions of some of these trials of up to 156 weeks. Dapagliflozin was not associated with excess CV risk, with an overall hazard ratio of 0.67 relative to comparators for the primary composite of CV death, myocardial infarction, stroke, and hospitalization for unstable angina (FDA Briefing Document, 2011).

Long-term data on the effects of SGLT2 inhibitors on CV outcomes in patients with T2DM are not yet available. In the absence of such data, the magnitude of CV protection provided by SGLT2 inhibitors in patients with T2DM can only be estimated based on anticipated reductions in HbA1c, BP, and body weight. Based on meta-analyses of randomized clinical trials, a 0.8% reduction in HbA1c would reduce CV risk by 8%, a 4 mmHg reduction in systolic BP would provide at least the same level of protection, and jointly these effects would be expected to reduce vascular risk by about 15% (Foote, Perkovic, & Neal, 2012). Such reductions in HbA1c and BP might be regarded as conservative based on the results of clinical trials of SGLT2 inhibitors and it is possible that reductions in body weight and serum uric acid might add to the CV protection that SGLT2 inhibitors provide. Several large long-term CV outcome studies are ongoing (Table 3).

7. Conclusions

T2DM increases the risk of CV morbidity and mortality and is associated with co-morbidities that increase CV risk. SGLT2 inhibitors are a new class of treatment for T2DM that acts independently of insulin and can be used either early or late in the disease process to reduce hyperglycemia by reducing renal glucose reabsorption and increasing UG. Clinical trials have shown that in addition to reducing HbA1c, SGLT2 inhibitors reduce body weight, systolic BP and serum uric acid. Inhibiting SGLT2 and exposing the nephron to an increased sodium and glucose load may have a greater impact on CV risk than presently perceived. Large studies are underway to elucidate the effects of SGLT2 inhibitors on CV outcomes, the results of which are eagerly awaited.

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