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SGLT2 inhibition with dapagliflozin

A novel approach for the management of type 2 diabetes

Background
Because of the progressive nature of the disease, most patients with type 2 diabetes mellitus eventually require multiple treatments to achieve glycaemic targets. The majority of available therapies are insulin dependent, aiming to decrease insulin resistance and increase insulin secretion. Sodium glucose co-transporter 2 (SGLT2) inhibitors, a new class of antidiabetic agents, limit renal glucose reabsorption promoting urinary excretion of glucose, thereby reducing plasma glucose.

Objective
This article explores the mechanism of action and clinical data surrounding SGLT2 inhibitors, with a particular focus on dapagliflozin.

Conclusion
Clinical trials have shown dapagliflozin to be effective in reducing glycosylated haemoglobin, weight and fasting plasma glucose, either as monotherapy or as add-on therapy to metformin, sulphonylurea and insulin. Other SGLT2 inhibitors are currently under investigation.

Keywords
diabetes mellitus, type 2; hypoglycaemic agents; sodium-glucose transport proteins/antagonists and inhibitors; dapagliflozin

The prevalence of diabetes in Australia has increased by approximately 8% per annum since 2000. By 2017, the number of people with diabetes in Australia will be in excess of 3.6 million.[1] The multifactorial management of these patients will place an unprecedented burden on the healthcare system and society in general.[1]

A major focus of diabetes management is optimal glycaemic control.[2] This involves the prevention and management of transient or sustained hyperglycaemia, as well as the avoidance of hypoglycaemia, without adversely affecting quality of life. What is 'optimal' glycaemic control must be individualised according to patient preferences, needs and tolerances, and considering a range of factors such as age, comorbidities, self monitoring, risk of significant side effects and complexity of treatment regimens.[2] Achieving and sustaining individual treatment goals represents the greatest fundamental challenge of diabetes care.[3,4]

The majority of patients with type 2 diabetes mellitus (T2DM) will require one or more different types of medication to manage their glucose levels. Until very recently this invariably involved the use of metformin and/or sulphonylureas. Failure of oral therapy was then followed by the introduction of basal or mixed insulins. Though effective, this strategy has a number of limitations, including beta-cell exhaustion,[5] weight gain[6] and hypoglycaemia,[7] which often lead to therapeutic inertia and compromise of targets for glycaemic control.

Over the past decade, a number of new agents have been introduced for the management of diabetes. Most of the current therapies for T2DM tend to aim at decreasing insulin resistance or increasing insulin secretion (*Table 1*).[5] However, a new class of drugs that enhance urinary glucose excretion, inhibiting glucose reabsorption via the sodium glucose co-transporter 2 (SGLT2), is now available.[5,7,8]

This article reviews the pharmacological and clinical data surrounding dapagliflozin, the first SGLT2 inhibitor to be approved by the Australian Therapeutic Goods Administration (TGA), as a model example. A number of other SGLT2 inhibitors are under investigation, including empagliflozin, canagliflozin and ipragliflozin. In addition, a non-selective SGLT inhibitor (LX4211) is in advanced clinical trial development. It is likely that these and other agents that share similar pharmacodynamic properties may become available over the next few years.

Renal glucose reabsorption

In healthy adults, approximately 180 g of glucose is freely filtered through the glomeruli of the kidney daily.[3,5,7] Almost all of this filtered load is reabsorbed by sodium-coupled active transport in

Table 1. Mechanisms of action of antidiabetic therapies[5]

Therapy	Mechanism of action
Metformin	Decreases hepatic glucose production Improves glucose clearance through an improvement of hepatic insulin sensitivity Decreases fatty acid oxidation, and increases glucagon-like peptide 1 (GLP-1)
Sulphonylureas	Inhibit pancreatic beta-cell K_{ATP} channels and enhance insulin secretion
Thiazolidinediones	Increase the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin, indirectly reducing hepatic glucose production by altering adipose tissue lipid metabolism
Meglitinides	Bind to the beta-cell K_{ATP} channel (at a different site to sulphonylureas), and stimulate insulin secretion
GLP-1 mimetics	Reduce postprandial hepatic glucose production and enhance peripheral glucose uptake
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Prevent the degradation of endogenous GLP-1, thereby prolonging its insulinotropic activity
Alpha-glucosidase inhibitors	Non-insulin dependent Reduce the breakdown of oligosaccharides to monosaccharides in the proximal small intestine, thereby lowering postprandial glucose levels
Insulin	Directly stimulates the insulin receptor

the brush border membrane of the proximal tubule.[8] More than 90% is reabsorbed by a low affinity, high capacity system in the early convoluted segment of the proximal tubule controlled by SGLT2.[8] Reabsorption of the remaining filtered glucose is performed by a high affinity, low capacity system in the straight segment of the descending proximal tubule regulated by SGLT1.[5,8] The result of these highly efficient reabsorption pathways is that only tiny amounts of glucose appear in the urine in non-diabetic individuals.[9]

However, the capacity for reabsorption is limited. If plasma glucose levels rise and the filtered load exceeds the capacity for glucose reabsorption, then glucose (and the water held with it) will spill over into the urine. This produces the classic symptoms of polyuria, frequency and polydipsia that characterise uncontrolled hyperglycaemia. The threshold at which glucosuria occurs is usually between 10 and 11 mmol/L, but this can vary significantly from person to person. Moreover, in response to chronic hyperglycaemia, the glucose reabsorption capacity from the proximal tubule is up-regulated, retaining extra glucose at a time when plasma glucose levels are already elevated, instead of allowing it to pass into the urine. Consequently, these renal changes also contribute to the development of glucose intolerance in T2DM individuals[10] and provide a rationale for these reabsorption pathways to be targeted in the management of diabetes.

What happens when you block SGLT?

Some individuals lose increased amounts of glucose into their urine in the absence of hyperglycaemia due to an inherited impairment of renal glucose reabsorption. The most common form involves a mutation in the SLCA2 gene that reduces the expression and/or activity of SGLT2. Despite this, familial glucosuria is a benign condition,[11] suggesting that inhibition of SGLT2, which is almost exclusively expressed in the kidneys, may represent a safe long-term strategy in humans.

Unlike SGLT2, SGLT1 is also expressed in the brain, the heart, and in the intestinal epithelium, where it is involved in water and glucose uptake.[5,7,8] Mutations in the SLC5A1 gene encoding SGLT1 may be associated with glucose-galactose malabsorption and must be managed by restricting glucose and galactose in the diet. This makes SGLT1 a less appealing target.

In the late 19th century it was demonstrated that phlorizin – a non-selective SGLT inhibitor derived from the bark of apple trees – induced glucosuria in otherwise healthy people[12] and lowered the serum glucose levels in animals and patients with diabetes.[13] However, phlorizin has poor oral bioavailability and also inhibits glucose transport via SGLT1.[7] Consequently, a number of pharmaceutical companies have developed more selective metabolically stable chemicals that selectively block SGLT2, including dapagliflozin.

Dapagliflozin

Dapagliflozin is a selective reversible inhibitor of SGLT2 in the kidney, and the first of this novel class of glucose-lowering agents to be made available in Australia. The selectivity of dapagliflozin for SGLT2 is 1 000–3 000-fold greater than that for SGLT1.[14]

Pharmacodynamics

By reducing the capacity for tubular glucose reabsorption and lowering the threshold for spillover into the urine, dapaglifozin results in urinary glucose wasting in both healthy volunteers and patients with diabetes.[15] However, total urinary glucose losses are proportional to the ambient plasma glucose level, so that absolute losses are greater in patients with hyperglycaemia. On average, a 10 mg daily dose of dapagliflozin will increase the amount of glucose excreted in the urine of a patient with T2DM by 50–80 g/day. This effect is seen with the first dose and, with chronic treatment, this increase in glucose excretion may be sustained for at least 2 years.[16]

Pharmacokinetics/metabolism

Dapagliflozin is rapidly and extensively absorbed after oral administration. The oral bioavailability of a 10 mg dose is ≥75%.[14] Food has a modest effect on the pharmacokinetics, slowing the time to achieve maximum concentration.[14] However, this interaction is not clinically significant, meaning that dapagliflozin can be administered with or without food.

Dapagliflozin is extensively metabolised into inactive conjugates, predominantly dapagliflozin 3-O-glucuronide, and then eliminated by the kidneys.

The glucosuric efficacy of dapagliflozin is dependent on renal function, meaning its efficacy is reduced in patients with renal impairment. Therefore, dapagliflozin should not be used in patients with moderate to severe renal impairment (estimated glomerular filtration rate, eGFR)

<60 mL/min/1.73 m^2).[14] No dose adjustment is necessary for patients with mild or moderate hepatic impairment. However, dapagliflozin exposure may be increased in patients with severe hepatic impairment and therefore should not be used in this setting.[14]

No clinically significant pharmacokinetic interactions have been demonstrated between dapagliflozin and other agents used in the routine management of diabetes, including sulphonylureas, nor with statins, warfarin and digoxin.

Glucose lowering following SGLT2 inhibition

Urinary loss of glucose has the potential for improving glycaemic control, including glycosylated haemoglobin (HbA_{1c}), fasting plasma glucose (FPG) and postprandial glucose (PPG) levels, in patients with T2DM[17–22] through a mechanism independent of insulin secretion and action.

The efficacy of dapagliflozin has been studied in a number of phase 2 and 3 trials. In 12 and 24 week double-blind, placebo controlled, randomised trials in patients with T2DM, dapagliflozin 10 mg/day, either as monotherapy or as add-on therapy to metformin, glimepiride, or insulin, significantly reduced HbA_{1c}, FPG, and, in some cases, body weight compared with placebo (*Table 2*).[17–22] A total of 5693 patients with T2DM were treated in 11 double-blind, controlled clinical studies conducted to evaluate the safety and glycaemic efficacy of dapagliflozin; 3939 patients in these studies were treated with dapagliflozin up to a maximum duration of exposure of 102 weeks.[14]

A 52 week double-blind, multicentre, non-inferiority study compared dapagliflozin with the sulphonylurea glipizide as add-on therapy in patients inadequately controlled on metformin or metformin plus one other oral anti-diabetic drug.[23] Patients were randomised to dapagliflozin or glipizide, up-titrated over 18 weeks, based on glycaemic response and tolerability, to 10 mg/day or 20 mg/day, respectively. While the initial efficacy was greater with glipizide, it progressively waned during the maintenance period. On the other hand, glucose control remained stable in those treated with dapagliflozin at 52 weeks. The adjusted mean change in HbA_{1c} was not significantly different between the two groups (–0.52%).

Safety and tolerability

Dapagliflozin has been generally well tolerated in clinical trials of 1 or 2 years duration and in extension studies of up to approximately 2 years.[8]

Polyuria, frequency, nocturia and thirst may be experienced symptomatically by some patients taking dapagliflozin, as glucose spill over causes an osmotic diuresis, similar to that observed with uncontrolled diabetes. Additional fluid loss with dapagliflozin is between 300–400 mL/day (approximately equivalent to a can of soft drink or one extra void). This is well tolerated by most patients, especially with morning dosing.[19] However, patients with pre-existing bladder dysfunction may experience more problems. Dapaglifozin is not recommended for use in patients on loop diuretics.

Genital infections are more common in patients receiving dapagliflozin, consistent with the favourable growth environment for micro-organisms

Table 2. Results for dapagliflozin 10 mg/day in 12 and 24 week randomised, double-blind, placebo controlled trials in patients with type 2 diabetes mellitus[17–22]

Study	Regimen	Duration (weeks)	Change from baseline					
			HbA_{1c} (%)		FPG (mmol/L)		Body weight (kg)	
			Placebo	Dapa 10 mg	Placebo	Dapa 10 mg	Placebo	Dapa 10 mg
Wilding et al, 2009[22] (Phase 2)	Add-on to 50% of prestudy insulin dose	12	n=19 +0.09	n=23 –0.61 *p* value NR	n=22 +0.99	n=23 +0.13 *p* value NR	n=22 –1.9	n=23 –4.5 *p* value NR
List et al, 2009[20] (Phase 2)	Monotherapy	12	n NR –0.18	n NR –0.85 *p*<0.001	n NR –0.33	n NR –1.17 *p*=0.002	n NR –1.07	n NR –2.32 *p* value NS
Ferrannini et al, 2010[19] (Phase 3)	Monotherapy	24	n=75 –0.23	n=70 –0.89 *p*<0.0001	n=75 –0.23	n=70 –1.59 *p*<0.001	n=75 –2.2	n=70 –3.2 *p* value NS
Bailey et al, 2010[18] (Phase 3)	Add-on to metformin	24	n=134 –0.3	n=135 –0.84 *p*<0.0001	n=136 –0.33	n=132 –1.30 *p*<0.0001	n=136 –0.9	n=133 –2.9 *p*<0.0001
Strojek et al, 2011[21] (Phase 3)	Add-on to glimepiride	24	n=143 –0.13	n=154 –0.82 *p*<0.0001	n=143 –0.11	n=154 –1.58 *p*<0.0001	n=145 –0.72	n=151 –2.26 *p*<0.0001
Wilding et al, 2010[17] (Phase 3)	Add-on to insulin	24	n=193 –0.30	n=194 –0.90 *p*≤0.0001	n=193 +0.18	n=194 –1.20 *p*≤0.0001	n=193 +0.02	n=194 –1.67 *p*≤0.0001

Dapa = dapagliflozin; FPG = fasting plasma glucose; HbA_{1c} = glycosylated haemoglobin; NR = not reported; NS = not significant

afforded by glucosuria. In a placebo-pooled analysis (mean duration of treatment 453.7 days for dapaglifozin 10 mg and 409.3 days for placebo) the proportion of patients with events of genital infections was 8.2% (63/768) in dapagliflozin 10 mg and 1.3% (9/694) in placebo.[14] Infections typically occur in postmenopausal women, in whom an oestrogen-deficient atrophic vaginal epithelium and diabetes confers an increased susceptibility.[16] However, balanitis has also been reported in uncircumcised men. Most of these genital infections are mild-to-moderate in intensity and either resolve with self treatment or readily respond to conventional interventions without disruption to treatment.[7] Urinary tract infections were also more frequently reported for dapaglifozin 10 mg compared to control in a placebo-pooled analysis up to 24 weeks (4.3% vs 3.7%, respectively). However, severe infections or pyelonephritis were uncommon and presented in similar frequencies for dapaglifozin and control groups.

Weight control

In most clinical trials, dapagliflozin has been associated with modest reductions in body weight (2–3 kg), while weight gain has been experienced by patients receiving sulphonylureas, meaning an absolute between-group mean difference of 4–5 kg.[6,16,23] This may be attributable to the loss of calories and lower insulin levels rather than loss of fluid.

Hypoglycaemia

Hypoglycaemia is a major limitation of sulphonylurea, glinide, and insulin-based therapies for managing diabetes. When used as monotherapy or dual therapy with metformin, dapagliflozin is not associated with an increased risk of hypoglycaemia (*Table 3*),[17–22] as insulin production is not stimulated by these agents[3] and counter-regulatory response mechanisms controlling gluconeogenesis are not impeded. Furthermore, as plasma glucose levels fall, glucosuria is reduced.[7] However, the rates of hypoglycaemia may be increased when dapagliflozin is used in combination with sulphonylurea or insulin.

Blood pressure

A mild natriuretic effect has been observed with dapagliflozin. In keeping with this observation, dapagliflozin has been associated with a modest reduction in systolic blood pressure (1–2 mmHg).[16]

Bone density

Increased flux of urine in patients with diabetes may be associated with loss of minerals into the urine. Small short-term studies have demonstrated no significant effects of dapagliflozin on markers of bone formation, bone resorption and/or bone mineral density.[24] The assessment of long-term effects of dapagliflozin on bone health is currently being conducted and reported as a condition of TGA registration.

Cardiovascular safety

The adverse cardiovascular outcomes described following the use of rosiglitazone in patients with diabetes[25] has heightened monitoring of cardiovascular safety in all new agents for the management of T2DM. The results of a prespecified meta-analysis on cardiovascular safety from the development program for dapagliflozin suggest that dapagliflozin is not associated with increased cardiovascular risk in the short term.[26] However, longer term studies in high-risk patients remain to be completed.[27] The cardiovascular safety of dapagliflozin is currently being studied in the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI 58).

Renal safety

Dapagliflozin has no adverse effects on renal function in patients with normal renal function.

Malignancy

The proportion of subjects with malignant or unspecified tumours during clinical trials was similar between dapagliflozin-treated patients (1.47%) and placebo/comparator (1.35%). Although only small numbers of cancer events have been reported, the relative risk for some tumours (bladder, prostate, breast) was increased in patients treated with dapagliflozin. These findings led the United States Food and Drug Administration (FDA) to decline to approve dapagliflozin for use, requesting 'additional clinical data to allow a better assessment of the risk–benefit profile'.[28] However, the short time between first exposure to dapagliflozin and tumour diagnosis makes a causal relationship unlikely.[14] In addition, there does not appear to be similar concerns with other SGLT2 inhibitors currently undergoing evaluation, despite a comparable mechanism of action. Nonetheless, as a precautionary measure, dapagliflozin is not recommended for use in patients concomitantly treated with pioglitazone (epidemiological data suggested a small increased risk of bladder cancer in patients treated with pioglitazone).[14]

Conclusion

The growing epidemic of diabetes in Australia will require a multifactorial approach to achieve and maintain optimal glucose control. A number of new agents have recently become available to target different aspects of hyperglycaemia, without the limitations of hypoglycaemia and weight gain. Among these, the SGLT2 inhibitors offer a complementary approach to reduce glucose levels by promoting urinary glucose excretion. This approach has the added advantage of losing calories that may

Table 3. Incidence of hypoglycaemia in studies of dapagliflozin[17–22]

Study	Regimen	Placebo n (%)	Dapagliflozin 10 mg n (%)
Wilding et al, 2009[22]	Add-on to 50% of prestudy insulin dose	3/23 (13)	7/24 (29)
List et al, 2009[20]	Monotherapy	2 (4)	3 (NR)
Ferrannini et al, 2010[19]	Monotherapy	2/75 (3)	Morning dose 2/70 (3) Evening dose 1/71 (1)
Bailey et al, 2010[18]	Add-on to metformin	4/137 (3)	5/135 (4)
Strojek et al, 2011[21]	Add-on to glimepiride	7/146 (5)	12/151 (8)
Wilding et al, 2010[17]	Add-on to insulin	102/193 (52)	105/194 (54)

be otherwise deposited as fat, and losing sodium that may otherwise prop up blood pressure. Initially, the likely place of these agents will be as an add-on to other anti-diabetic agents to achieve and maintain targets for optimal glycaemic control in patients wanting to avoid weight gain and/or hypoglycaemia.

Other International bodies, including the United Kingdom National Institute for Health and Clinical Excellence and the US FDA currently do not recommend dapagliflozin. In addition, key limitations remain, including polyuria and genital infections which will see some patients not able to take these drugs, especially older women in whom bladder dysfunction is commonplace. Finally, whether these agents will have direct or indirect effects on long-term diabetic complications or other clinical outcomes remains to be established by comprehensive clinical trials.

Dapagliflozin indications

Dapagliflozin is indicated in Australia in patients with T2DM in the following settings:[14]

- monotherapy: as an adjunct to diet and exercise in patients whom metformin is otherwise indicated but not tolerated
- initial combination: as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycaemic control in patients when diet and exercise have failed to provide adequate glycaemic control and there are poor prospects for response to metformin therapy (eg. high HbA_{1c} levels)
- add-on combination therapy
  - with metformin, when metformin alone with diet and exercise does not provide adequate glycaemic control
  - with a sulphonylurea, when a sulphonylurea alone with diet and exercise does not provide adequate glycaemic control
  - with insulin (alone or with one or both of metformin or a sulphonylurea) when the existing therapy, along with diet and exercise, does not provide adequate glycaemic control
- Pharmaceutical Benefits Scheme listing is pending.

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Competing interests: Merlin Thomas has received payment from Sanofi-Aventis for lectures. Gary Kilov is on the AstraZeneca GP Advisory Board and education steering committee. He has also been paid for educational presentations at GPCE.

AstraZeneca provided funding for writing assistance in preparing this paper.

Provenance and peer review: Not commissioned; externally peer reviewed.

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