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WHAT PHYSICIANS NEED TO KNOW ABOUT SGLT-2 INHIBITORS

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KEY MESSAGES

- With the introduction of SGLT-2 inhibitors, a novel class of anti-diabetic agents, treatment options have expanded beyond targeting insulin resistance and β-cell function
- SGLT-2 inhibitors block the renal reabsorption of glucose, which offers benefits in terms of low rates of hypoglycaemia, blood pressure-lowering effects and weight loss
- Critical to the value of SGLT-2 inhibitors is their cardiovascular and renal protection which has led to the prominent inclusion of these medications in the most recent ADA/EASD guidelines for the treatment of type 2 diabetic patients with atherosclerotic cardiovascular disease, heart failure and chronic kidney disease.

Overview of the pathophysiology of type 2 diabetes

Treatment options for type 2 diabetes have historically addressed two major pathophysiological features of type 2 diabetes – β-cell dysfunction and insulin resistance, while lifestyle changes and weight reduction, including bariatric surgery and GLP-1 receptor agonists, seek to address the role of obesity in the development of type 2 diabetes.

Both β-cell dysfunction and insulin resistance occur many years before diagnosis. In fact, it has been estimated that 50% of β-cell function has already been lost prior to clinical diagnosis (Figure 1).[1-3]

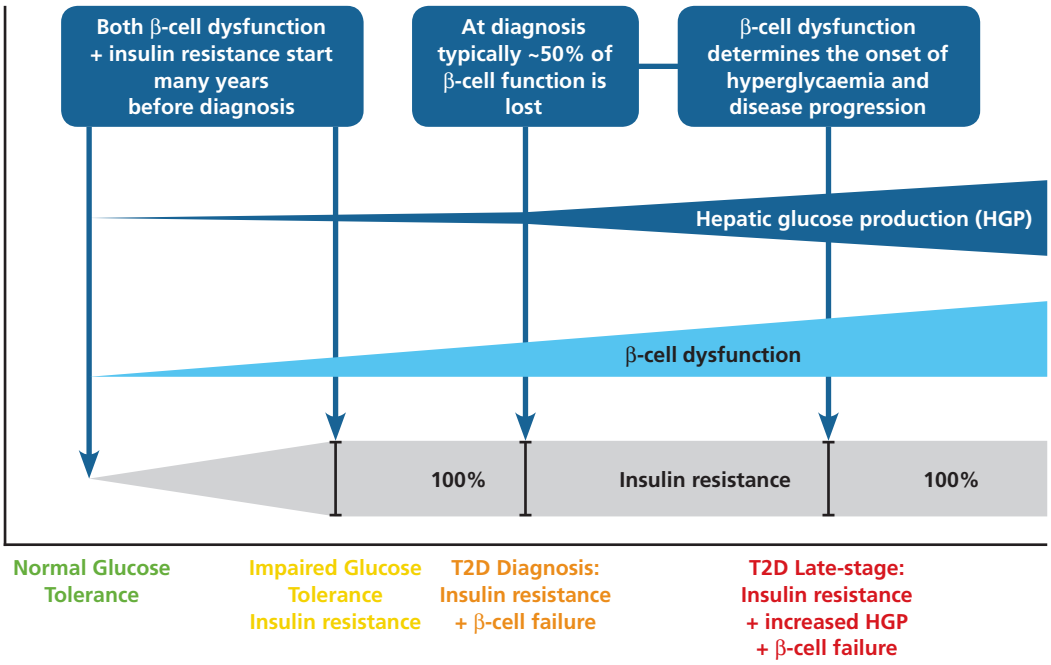

Figure 1. Relative contributions of diabetic pathophysiologies over time[1-3]

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Novel mechanism of SGLT-2 inhibitors

SGLT-2 inhibitors are old 'new drugs', known since 1886 to occur naturally in the bark of pear, apple and cherry trees and to have the ability to lower glucose. The SGLT-2 inhibitors have a novel mode of action and act as competitive inhibitors of SGLT-2 receptors, thereby reducing the re-absorption of glucose from the proximal tubule of the kidney. This results in an increase in the excretion of urinary glucose. The action of SGLT-2 inhibitors is therefore glucose dependent; an entirely different attribute not found in other oral antidiabetic drugs (OADs). This 'glucose-dependent' feature of SGLT-2 inhibitors results in a low risk of hypoglycaemia, reduction in blood pressure due to osmotic diuresis and a reduction in body weight due to calorie loss of around 200-400 Kcal/day. The urinary excretion of glucose with SGLT-2 inhibitors occurs during hyperglycaemia, not when glucose levels are low, minimising the risk of hypoglycaemic events.

Importantly, the action of SGLT-2 inhibitors is independent of the stage of the disease and they are effective throughout the course of type 2 diabetes.

SGLT-2 inhibitors – pharmacological properties of available therapies

"SGLT-2 inhibitors are old 'new drugs', known since 1886 to occur naturally in the bark of pear, apple and cherry trees and to have the ability to lower glucose."

All SGLT-2 inhibitors are given orally, once daily. The different agents display some variation in selectivity, affinity for SGLT-1 and in the amount of glucose excreted at the higher dose (Table 1).

Table 1. Pharmacological properties of available SGLT-2 inhibitors[4]

	Empagliflozin	Dapagliflozin	Canagliflozin
Therapeutic dose (mg/day)/ Starting dose	10–25 10	5–10 10	100–300 100
Administration	qd With or without food	qd With or without food	qd Before first meal
Peak plasma concentration (hours post-dose)	1.5	Within 2	1–2
Absorption (mean oral bioavailability)	≥60%	~78%	~65%
Metabolism	ß Primarily glucuronidation – no active metabolite		
Elimination (half-life, hours)	Hepatic: renal 43:57 [12.4]	Hepatic: renal 22:78 [12.9]	Hepatic: renal 67:33 [13.1]*
Selectivity over SGLT-1	1:5000	>1:1400	>1:160[1]
Glucose excretion with higher dose (g/day)	78	~70	119

*For the 300mg dose. qd, once daily; SGLT-1, sodium-glucose co-transporter-1; SGLT-2, sodium-glucose co-transporter

Source: Data provided by European Medicines Agency (www.ema.europa.eu)

The three available SGLT-2 inhibitors lower HbA1c by an expected 0.5-1% with their higher doses all being situated towards the upper end of the dose-response curve.

Body weight reductions are in a similar range and vary according to dosage and whether the agents are given as monotherapy, with metformin and sulphonylureas, or with insulin; the weight loss range is 2-4 kg.

Blood pressure reductions are comparable to what would be expected from an antihypertensive agent (2-4/5mmHg reduction) but currently no head-to-head studies of empagliflozin, canagliflozin or dapagliflozin are available for comparative purposes. SGLT-2 inhibitors are also linked to a reduction in uric acid levels.

Safety is an important attribute – the incidence of urinary tract infections in patients using empagliflozin was similar to placebo, but genital tract infections were increased relative to placebo (3-4 fold from 1-4%). It is worth noting that genital tract infections on empagliflozin usually occurred as a single event and were mild to moderate in severity and easily treated. Another potential side effect is Fournier's gangrene (necrotising fasciitis) but this is very rare with one event per one million years of patient exposure to empagliflozin. There was no increase in the risk of malignancies, bone fractures or diabetic ketoacidosis (DKA) in patients treated with empagliflozin. Therefore in everyday clinical practice, the SGLT-2 inhibitors are well tolerated.

"The urinary excretion of glucose with SGLT-2 inhibitors occurs during hyperglycaemia, not when glucose levels are low."

Time to change perspective and focus on cardiovascular and renal risk reduction

The increased risk of cardiovascular disease in patients with type 2 diabetes has been demonstrated in several epidemiological studies. However, attempts to lower cardiovascular disease mortality and all-cause mortality with a therapeutic focus on tight glycaemic control has been disappointing in a wide range of clinical trials.[5]

After the adverse cardiovascular outcome associated with rosiglitazone therapy,[6] regulatory agencies like the FDA introduced the requirement that all new therapies for type 2 diabetes show 'no adverse effect' on cardiovascular risk. The non-inferiority boundary was set as a hazard ratio of 1.3-1.8. To date, more than 150 000 patients have been investigated in cardiovascular outcome trials using the newer agents, such as the DPP4 inhibitors, GLP-1 receptor agonists and the SGLT-2 inhibitors.

In the SGLT-2 inhibitor class, empagliflozin and canagliflozin have been shown to provide cardiovascular benefit, while dapagliflozin, in headline results, has been shown to reduce the composite endpoint, cardiovascular death or hospitalisation for heart failure.[7,8]

Cardiovascular outcomes – EMPA-REG OUTCOME study

The EMPA-REG OUTCOME trial showed a 38% relative risk reduction (RRR) in cardiovascular death, with the benefit seen early on in the trial. There was no difference between the lower dose of 10mg and the 25mg dose, so the two patient groups were combined in the analysis. "The EMPA-REG OUTCOME trial of empagliflozin was the first to show not only glucose-lowering, blood pressure and weight reduction, but also substantial benefit in reducing cardiovascular death," commented Professor Pieber.

Renal disease outcomes – it is vital to reduce kidney disease in type 2 diabetes patients

Diabetes remains the most common reason for progression to end-stage renal disease in many parts of the world. "Up to 50% of patients with type 2 diabetes suffer from chronic kidney disease, up to 20% of whom are at risk of needing renal replacement therapy," Professor Pieber noted.

In the EMPA-REG OUTCOME trial, there was a 39% RRR in the risk of incident or worsening nephropathy with empagliflozin versus placebo (Figure 2).[9] Interestingly, those patients with macroalbuminuria at baseline benefited most from the sustained improvement eGFR obtained with empagliflozin therapy.[10]

"Genital tract infections on empagliflozin usually occurred as a single event, were mild to moderate in severity and were easily treated."

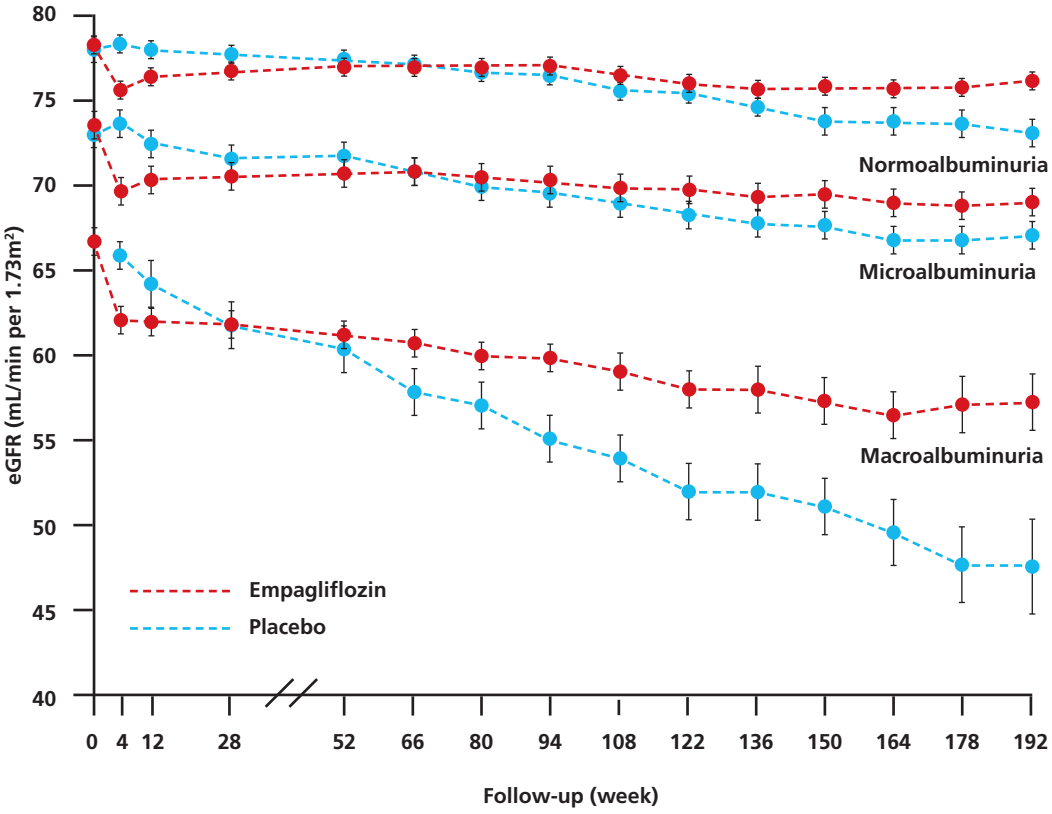


Figure 2. Sustained eGFR with empagliflozin versus placebo in patients with macroalbuminurea[9]

Practical clinical considerations for empagliflozin use – The Do's and Don'ts

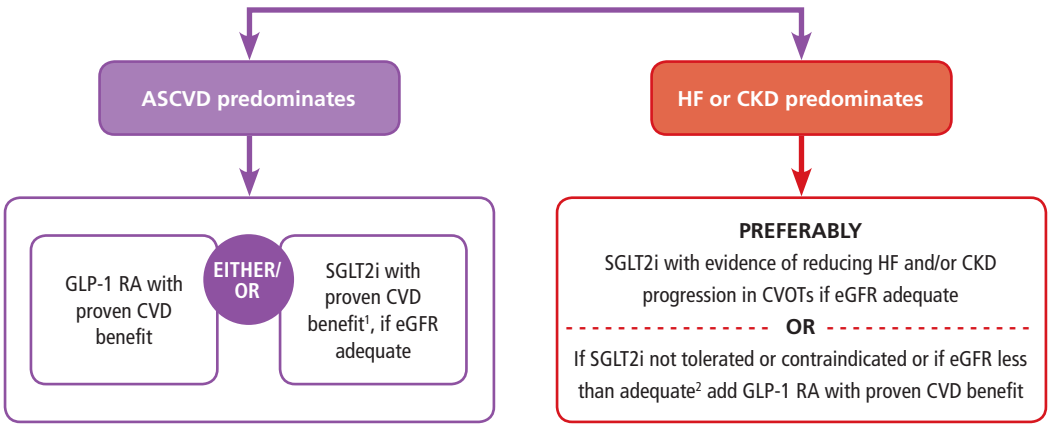
The Do's and Don'ts from these clinical trials were interpreted by Professor Pieber and are summarised in Tables 2 and 3.

The recently announced 2018 ADA/EASD treatment algorithm for type 2 diabetes has also incorporated the use of SGLT-2 inhibitors practically in patients with atherosclerotic cardiovascular disease, heart failure of chronic kidney disease, as summarised in Figure 3.

Table 2. The Do's – practical considerations for selection of empagliflozin
• Once daily oral tablet taken with or without food
• Start with 10mg. Use 25mg if greater effect on HbA1c is needed
• Advise patients to keep hydrated
• Can be used as an add-on to all therapies (OADs and insulin) – Further HbA1c reductions of 0.6-0.8% – Weight loss of 2-3kg – Up to 5mmHg reduction in blood pressure
• Check urogenital history and inform patient of UTI/GI risk
• Use with caution >75 years – dehydration risk increases
• Assess renal function -> 60ml/min to initiate
• Consider blood pressure lowering effect. Monitor patient on diuretics and reduce dosage if required
• Adjust sulphonylurea or insulin dose, advise patient of hypoglycaemia risk if used with sulphonylurea or insulin

"A substantial reduction in cardiovascular death was seen quite early in the EMPA-REG OUTCOME trial using empagliflozin."

Table 3. The Don'ts – practical considerations for non-selection of empagliflozin
• Empagliflozin is not registered for glucose-lowering in type 1 diabetic patients
• Empagliflozin is contraindicated in patients with a history of pancreatitis
• Empagliflozin is not indicated for weight loss
• Do not use if fasting for prolonged periods or hospitalised
• Do not stop insulin, but reduce dose appropriately
• Euglycaemic DKA should be considered if symptoms support assessment, regardless of blood glucose levels
• Age >85 years – do not initiate.



ASCVD = atherosclerotic Cardiovascular Disease; HF = Heart failure; CKD = chronic kidney disease; CVD = Cardiovascular disease

Figure 3. 2018 ADA/EASD treatment algorithm to reduce CVD risk

Conclusion

The SGLT-2 inhibitors offer clinicians an opportunity to direct therapy towards cardiovascular and renal risk reduction in type 2 diabetes. These medications are well tolerated and do not cause hypoglycaemia, while the reductions in blood pressure and weight are favourable attributes that add to their clinical value.

References

1. Butler AE, Janson J, Bonner-Weir S, *et al*. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes* 2003; **52**(1):102-110.
2. Del Prato S, Marchetti P. Targeting insulin resistance and beta-cell dysfunction: the role of thiazolidinediones. *Diabetes Technol Ther* 2004; **6**(5): 719-731.
3. Gastaldelli a, Ferrannini E, Miyazaki Y, *et al*. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. *Diabetologia* 2004; **47**(1): 31-39.
4. Sha S, Polidori D, Farrell K, *et al*. Pharmacodynamic differences between canagliflozin and dapagliflozin: results of a randomized, double-blind, crossover study. *Diabetes Obes Metab* 2015; **17**(2): 188-197.
5. Turnbull FM, Abraira C, Anderson RJ, *et al*. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009; **52**(11): 2288-2298.
6. Nissen SE, Wolkski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356**(24): 2457-2471.
7. Zinman B, Wanner C, Lachin JM, *et al*. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **373**: 2117-2128.
8. Neal b, Perkovic V, Mahaffey KW, *et al.* Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; **377**: 644-657.
9. Wanner C, Inzucchi SE, Lachin JM, *et al*. Empagliflozin and kidney disease progression in diabetes. *N Engl J Med* 2016; **375**: 323-334.
10. Cherney DZI, Zinman B, Inzucchi SE, *et al*. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. *The Lancet Diabetes & Endocrinology* 2017; **5**(8): 610-621.

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