SGLT2 Inhibitors in Treatment of Type 2 Diabetes

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Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of oral hypoglycemic agents which increase urinary glucose excretion by suppressing glucose reabsorption at the proximal tubule in the kidney. SGLT2 inhibitors lower glycated hemoglobin (HbA1c) by 0.6–0.8% (6–8 mmol/mol) without increasing the risk of hypoglycemia and induce weight loss and improve various metabolic parameters including blood pressure, lipid profile and hyperuricemia.

sodium-glucose cotransporter 2 inhibitor | type 2 diabetes | cardiovascular outcome trial | cardiorenal protection

1. Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of oral hypoglycemic agents (OHA). They have been developed based on the discovery of phlorizin, a natural product with SGLT inhibitory activity which was extracted from the bark of the apple tree in 1835, and advances in understanding of the mechanisms of glucose transport, resulting in the identification of SGLTs and their functional properties in the 1980–1990s [1]. In Japan, the first SGLT2 inhibitor, ipragliflozin, was marketed in 2014, and currently six SGLT2 inhibitors, ipragliflozin, dapagliflozin, canagliflozin, empagliflozin, luseogliflozin, and tofogliflozin, are available for the treatment of type 2 diabetes (T2DM) (**Table 1**). Ipragliflozin and dapagliflozin have also been approved for the treatment of type 1 diabetes (T1DM) in Japan.

Table 1. Sodium-glucose cotransporter 2 (SGLT2) inhibitors available in Japan.

Generic Name	Dosage	SGLT1/2 Selectivity	Half-Life ($t_{1/2}$)	Indication
Ipragliflozin	50–100 mg once daily	254:1	15 h	Type 1 and type 2 diabetes
Dapagliflozin	5–10 mg once daily	1242:1	8–12 h	Type 1 and type 2 diabetes

Generic Name	Dosage	SGLT1/2 Selectivity	Half-Life ($t_{1/2}$)	Indication
Canagliflozin	100 mg once daily	155:1	12 h	Type 2 diabetes
Empagliflozin	10–25 mg once daily	2680:1	14–18 h	Type 2 diabetes
Luseogliflozin	2.5–5.0 mg once daily	1770:1	9 h	Type 2 diabetes
Tofogliflozin	20 mg once daily [50]	2912:1 [50]	5 h	Type 2 diabetes [2]

2. Mechanisms of Action of SGLT2 Inhibitors

In the kidney, approximately 180 g of glucose per day is excreted in the primitive urine through glomerular filtration. Most of the glucose in the primitive urine is however completely reabsorbed by SGLT2 and SGLT1 expressed in the proximal tubule, and glucose is not normally excreted in the urine.

SGLT activity mediates apical sodium and glucose transport across cell membranes. Cotransport is driven by active sodium extrusion by the basolateral sodium/potassium-ATPase, thus facilitating glucose uptake against an intracellular up-hill gradient. Basolaterally, glucose exits the cell through facilitative glucose transporter 2 (GLUT2). In humans, six SGLT isoforms have been identified [1][3].

SGLT2 is responsible for glucose reabsorption in the proximal tubule segment 1 and 2 (S1/2), wherein it reabsorbs more than 90% of the filtered glucose load, while normally SGLT1 reabsorbs the residual glucose in the proximal tubule segment 3 (S3). However, in SGLT2 knockout mice, SGLT1 compensated and reabsorbed up to 35% of the filtered glucose load [1][3]. Glucose resorption by SGLT2 is increased by 30% in the setting of hyperglycemia [4], although it remains unclear whether SGLT2 expression is increased in patients with diabetes [5].

SGLT2 inhibitors suppress reabsorption of glucose by inhibition of SGLT2, and thereby increase urinary glucose excretion by approximately 60–80 g per day and ameliorate hyperglycemia [6]. Excretion of 60–80 g of excess glucose corresponds to 240–320 kcal of energy loss from the body, promoting weight loss. Improvement of obesity/overweight, especially abdominal fat accumulation promotes amelioration of insulin resistance and results in improvement of metabolic parameters such as blood pressure, lipid profile, and serum uric acid level (**Figure 1**).

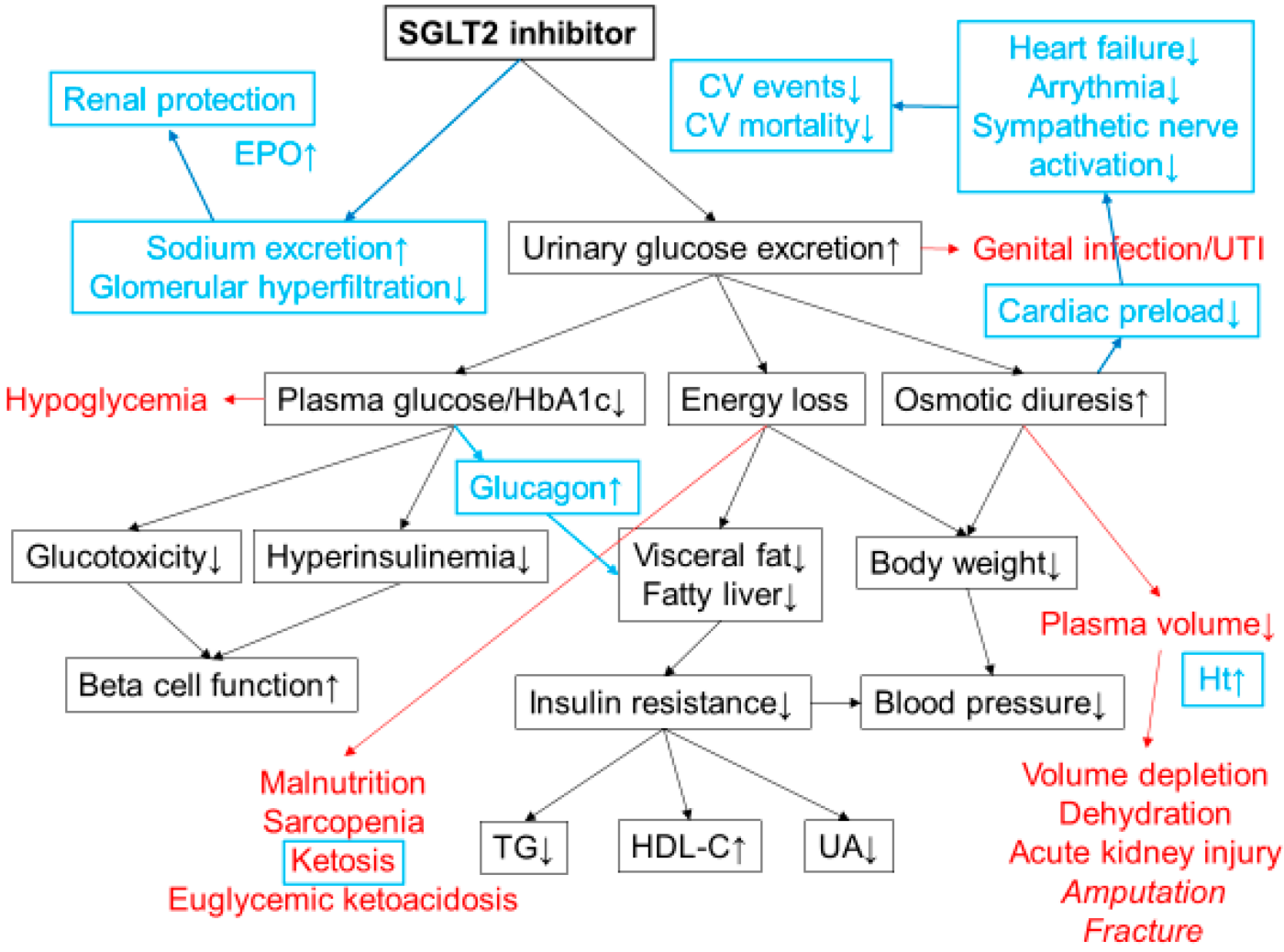

Figure 1. Mechanisms of action of SGLT2 inhibitors. SGLT2 inhibitors lower plasma glucose level by increasing urinary glucose excretion. Energy loss by SGLT2 inhibitor treatment promotes weight loss and improves insulin resistance and various metabolic parameters. Possible adverse effects are shown in red. Increased risk of lower-extremity amputation and bone fracture has been reported in a clinical trial with canagliflozin. The cardiorenal benefits shown in CVOTs have revealed additional mechanisms of action of SGLT2 inhibitors that were unknown at the time of launch (highlighted in blue). Osmotic diuresis and natriuresis are likely to be the major mechanisms of the cardiorenal benefits of SGLT2 inhibitors. Increases in blood ketone bodies and hematocrit may also contribute to the cardiorenal benefits. CV; cardiovascular, TG; triacylglycerol, HDL-C; high density lipoprotein cholesterol, UA; uric acid, Ht; hematocrit, UTI; urinary tract infection, EPO; erythropoietin.

As SGLT1 is responsible for glucose absorption in the small intestine, SGLT2 inhibitors with low SGLT1/SGLT2 selectivity such as canagliflozin have been shown to suppress postprandial glucose excursion and increase glucagon-like peptide 1 (GLP-1) secretion in addition to increasing urinary glucose excretion [7][8].

On the other hand, given the mechanisms of action of SGLT2 inhibitors, their glucose-lowering effect is attenuated with reduced renal function. Thus, treatment with SGLT2 inhibitors is not recommended in patients with renal dysfunction, i.e., estimated glomerular filtration rate (eGFR) <45 mL/min, from the glucose-lowering point of view.

However, in view of the results of CVOTs showing a renoprotective effect of SGLT2 inhibitors among those with a wide range of renal function [9][10], currently treatment with SGLT2 inhibitors is rather also considered for patients with diabetes and renal dysfunction, i.e., eGFR ≥ 30 mL/min, to improve renal outcomes [11].

3. Clinical Efficacy of SGLT2 Inhibitors

3.1. Glucose-Lowering Effect

A meta-analysis of 45 clinical trials showed that treatment with SGLT2 inhibitors results in a HbA1c reduction of 0.79% with monotherapy and 0.61% with add-on therapy to other glucose-lowering agents in patients with T2DM [12]. SGLT2 inhibitors improve both fasting and postprandial hyperglycemia and increase time-in-range (TIR, proportion of time spent in the target glucose range between 70 and 180 mg/dL) assessed by continuous glucose monitoring (CGM) [13][14].

3.2. Body Weight, Blood Pressure, and Other Metablic Parameters

The above-mentioned meta-analysis showed that treatment with SGLT2 inhibitors in patients with T2DM reduced body weight by 1.7 kg (2.4%), and systolic and diastolic blood pressure by 4 and 2 mmHg, respectively, without increasing heart rate. Reduction in serum triacylglycerol level by 1–9% and serum uric acid level by 0.3–0.9 mg/dL, and increase in serum HDL-cholesterol by 6–9% by treatment with SGLT2 inhibitors have also been reported in patients with T2DM [12].

On the other hand, increase in LDL-cholesterol by 2–6% by treatment with SGLT2 inhibitors has been reported. However, Hayashi et al. have reported that small dense LDL-cholesterol, a more atherogenic subspecies of LDL-cholesterol, is reduced while less atherogenic large buoyant LDL-cholesterol is increased by 12-week treatment with dapagliflozin [15].

3.3. Hypoglycemia

The risk of hypoglycemia with SGLT2 inhibitors is low, and the risk of hypoglycemia is similar to placebo when SGLT2 inhibitors are used as monotherapy [12][16]. However, the risk of hypoglycemia may be increased when SGLT2 inhibitors are used in combination with insulin and/or insulin secretagogues. Therefore, the dose of insulin and/or insulin secretagogues may need to be reduced when combined with an SGLT2 inhibitor, to avoid hypoglycemia. When reducing the dosage of insulin, adjustment by within 10–20% of the total insulin dose is recommended to avoid development of diabetic ketoacidosis [17].

3.4. Beta Cell Function

Since SGLT2 inhibitors lower plasma glucose level independently of insulin, they do not increase insulin secretion but rather improve beta cell function [18][19] through amelioration of glucotoxicity and possibly reduction of beta cell workload [20][21][22]. On the other hand, glucagon secretion increases after administration of SGLT2 inhibitors,

possibly because of rapid loss of glucose from the body [23][24]. Elevated plasma glucagon level also contributes to promoting lipolysis and reducing liver fat and visceral adiposity [25]. A direct effect of SGLT2 inhibitors on alpha cells has also been proposed [26][27], though there are conflicting results [28][29] and further research is warranted.

4. Adverse Effects

The adverse effects of SGLT2 inhibitors other than hypoglycemia include genitourinary tract infection and dehydration and related symptoms [6][12][16]. Genital infection more frequently occurs in female patients. Cases of Fournier's gangrene associated with the use of SGLT2 inhibitors have also been reported [30]. Body weight loss induced by SGLT2 inhibitors may increase the risk of development of sarcopenia in elderly patients. Cases of diabetic ketoacidosis after the initiation of SGLT2 inhibitors have been reported [17]. Ketoacidosis can develop without hyperglycemia, i.e., euglycemic diabetic ketoacidosis. Patients should be carefully monitored for the development of ketoacidosis, especially those with T1DM and those with T2DM and insulin deficiency [17]. In the CANVAS/CANVAS-R trial, increased risk of lower-extremity amputation and bone fracture was observed in the canagliflozin group [31], although there was no significant difference in the rate of amputation or fracture in the CREDENCE trial [32].

5. Positioning of SGLT2 Inhibitors in Treatment of T2DM

Obesity is an established risk factor for the development of T2DM. SGLT2 inhibitors not only improve hyperglycemia but also induce weight loss, ameliorating the pathogenesis of T2DM. Although lifestyle modification is important for weight loss in the treatment of T2DM, it is often difficult to maintain long-term weight loss.

It can be assumed that the same effect would be obtained if patients restricted carbohydrate intake by the same amount as that excreted by SGLT2 inhibitors, i.e., 60–80 g per day (240–320 kcal). However, intensive lifestyle modification failed to improve CV outcome in the Look AHEAD (Action for Health in Diabetes) trail [33]. The impressive results observed in CVOTs with SGLT2 inhibitors [31][32][34][35] suggest that SGLT2 inhibitors promote cardiorenal protection through specific effects such as diuretic effects, apart from the effects of caloric restriction.

The ADA/EASD now positions SGLT2 inhibitors as the mainstay in the management of T2DM [11]. The use of SGLT2 inhibitors is recommended for patients with a high risk of or established atherosclerotic cardiovascular disease (ASCVD) and those with CKD or heart failure.

The target population of SGLT2 inhibitors is being expanded also in Japan. At the time of launch of the first SGLT2 inhibitor in Japan, ipragliflozin, in 2014, the target population of SGLT2 inhibitors was thought to be rather restricted to obese, younger patients with T2DM and metabolic syndrome, while about half of patients with T2DM are not obese in Japan. However, currently, treatment with SGLT2 inhibitors is also considered for patients with T2DM, and especially those with established ASCVD, heart failure, or CKD, as recommended by the ADA/EASD. Furthermore, improvement of CV outcome by treatment with dapagliflozin has been observed in patients with heart failure with reduced ejection fraction (HFrEF), irrespective of the presence or absence of diabetes [36][37], suggesting the

possibility that SGLT2 inhibitors can be used as a drug for heart failure independent of the presence or absence of diabetes. Trials evaluating the efficacy of SGLT2 inhibitors in patients with heart failure with preserved ejection fraction (HFpEF) and those with CKD and without diabetes are also under way [38][39]. Since SGLT2 inhibitors lower plasma glucose level independently of insulin, they can also be used for patients with T1DM as concomitant medication with insulin [40].

Meta-analysis suggests that the cardiorenal benefits of SGLT2 inhibitors are a class effect; however, the structure, dosage, pharmacokinetic/pharmacodynamic (PK/PD) profile, and SGLT2 selectivity are different among SGLT2 inhibitors. Further research is needed to clarify whether there is any difference in the effect on clinical outcomes among different SGLT2 inhibitors. The first dual SGLT1/2 inhibitor, sotagliflozin, has also been developed, and a CVOT with sotagliflozin is ongoing [41][42].

References

1. Ghezzi, C.; Loo, D.D.F.; Wright, E.M. Physiology of renal glucose handling via SGLT1, SGLT2 and GLUT2. Diabetologia 2018, 61, 2087–2097.
2. Abdul-Ghani, M.A.; DeFronzo, R.A.; Norton, L. Novel hypothesis to explain why sglt2 inhibitors inhibit only 30-50% of filtered glucose load in humans. Diabetes 2013, 62, 3324–3328.
3. Poulsen, S.B.; Fenton, R.A.; Rieg, T. Sodium-glucose cotransport. Curr. Opin. Nephrol. Hypertens. 2015, 24, 463–469.
4. DeFronzo, R.A.; Hompesch, M.; Kasichayanula, S.; Liu, X.; Hong, Y.; Pfister, M.; Morrow, L.A.; Leslie, B.R.; Boulton, D.W.; Ching, A.; et al. Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. Diabetes Care 2013, 36, 3169–3176.
5. Norton, L.; Shannon, C.E.; Fourcaudot, M.; Hu, C.; Wang, N.; Ren, W.; Song, J.; Abdul-Ghani, M.; DeFronzo, R.A.; Ren, J.; et al. Sodium-glucose co-transporter (sglt) and glucose transporter (glut) expression in the kidney of type 2 diabetic subjects. Diabetes Obes. Metab. 2017, 19, 1322–1326.
6. Nagahisa, T.; Saisho, Y. Cardiorenal protection: Potential of sglt2 inhibitors and glp-1 receptor agonists in the treatment of type 2 diabetes. Diabetes Ther. 2019, 10, 1733–1752.
7. Polidori, D.; Sha, S.; Mudaliar, S.; Ciaraldi, T.P.; Ghosh, A.; Vaccaro, N.; Farrell, K.; Rothenberg, P.; Henry, R.R. Canagliflozin lowers postprandial glucose and insulin by delaying intestinal glucose absorption in addition to increasing urinary glucose excretion: Results of a randomized, placebo-controlled study. Diabetes Care 2013, 36, 2154–2161.
8. Takebayashi, K.; Hara, K.; Terasawa, T.; Naruse, R.; Suetsugu, M.; Tsuchiya, T.; Inukai, T. Effect of canagliflozin on circulating active glp-1 levels in patients with type 2 diabetes: A randomized

trial. Endocr. J. 2017, 64, 923–931.

9. Neuen, B.L.; Young, T.; Heerspink, H.J.L.; Neal, B.; Perkovic, V.; Billot, L.; Mahaffey, K.W.; Charytan, D.M.; Wheeler, D.C.; Arnott, C.; et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: A systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2019, 7, 845–854.
10. Jardine, M.J.; Zhou, Z.; Mahaffey, K.W.; Oshima, M.; Agarwal, R.; Bakris, G.; Bajaj, H.S.; Bull, S.; Cannon, C.P.; Charytan, D.M.; et al. Renal, cardiovascular, and safety outcomes of canagliflozin by baseline kidney function: A secondary analysis of the credence randomized trial. J. Am. Soc. Nephrol. 2020, 31, 1128–1139.
11. Buse, J.B.; Wexler, D.J.; Tsapas, A.; Rossing, P.; Mingrone, G.; Mathieu, C.; D'Alessio, D.A.; Davies, M.J. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the american diabetes association (ADA) and the european association for the study of diabetes (EASD). Diabetologia 2020, 63, 221–228.
12. Vasilakou, D.; Karagiannis, T.; Athanasiadou, E.; Mainou, M.; Liakos, A.; Bekiari, E.; Sarigianni, M.; Matthews, D.R.; Tsapas, A. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: A systematic review and meta-analysis. Ann. Intern. Med. 2013, 159, 262–274.
13. Nishimura, R.; Osonoi, T.; Kanada, S.; Jinnouchi, H.; Sugio, K.; Omiya, H.; Ubukata, M.; Sakai, S.; Samukawa, Y. Effects of luseogliflozin, a sodium-glucose co-transporter 2 inhibitor, on 24-h glucose variability assessed by continuous glucose monitoring in japanese patients with type 2 diabetes mellitus: A randomized, double-blind, placebo-controlled, crossover study. Diabetes Obes. Metab. 2015, 17, 800–804.
14. Henry, R.R.; Strange, P.; Zhou, R.; Pettus, J.; Shi, L.; Zhuplatov, S.B.; Mansfield, T.; Klein, D.; Katz, A. Effects of dapagliflozin on 24-hour glycemic control in patients with type 2 diabetes: A randomized controlled trial. Diabetes Technol. Ther. 2018, 20, 715–724.
15. Hayashi, T.; Fukui, T.; Nakanishi, N.; Yamamoto, S.; Tomoyasu, M.; Osamura, A.; Ohara, M.; Yamamoto, T.; Ito, Y.; Hirano, T. Dapagliflozin decreases small dense low-density lipoprotein-cholesterol and increases high-density lipoprotein 2-cholesterol in patients with type 2 diabetes: Comparison with sitagliptin. Cardiovasc. Diabetol. 2017, 16, 8.
16. McGill, J.B.; Subramanian, S. Safety of sodium-glucose co-transporter 2 inhibitors. Am. J. Cardiol. 2019, 124, S45–S52.
17. Danne, T.; Garg, S.; Peters, A.L.; Buse, J.B.; Mathieu, C.; Pettus, J.H.; Alexander, C.M.; Battelino, T.; Ampudia-Blasco, F.J.; Bode, B.W.; et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium–glucose cotransporter (sglt) inhibitors. Diabetes Care 2019, 42, 1147–1154.

18. Takahara, M.; Shiraiwa, T.; Matsuoka, T.A.; Katakami, N.; Shimomura, I. Ameliorated pancreatic beta cell dysfunction in type 2 diabetic patients treated with a sodium-glucose cotransporter 2 inhibitor ipragliflozin. Endocr. J. 2015, 62, 77–86.
19. Polidori, D.; Mari, A.; Ferrannini, E. Canagliflozin, a sodium glucose co-transporter 2 inhibitor, improves model-based indices of beta cell function in patients with type 2 diabetes. Diabetologia 2014, 57, 891–901.
20. Saisho, Y. Changing the concept of type 2 diabetes: Beta cell workload hypothesis revisited. Endocr. Metab. Immune Disord. Drug Targets 2019, 19, 121–127.
21. Saisho, Y. Beta cell dysfunction: Its critical role in prevention and management of type 2 diabetes. World J. Diabetes 2015, 6, 109–124.
22. Saisho, Y. How can we develop more effective strategies for type 2 diabetes mellitus prevention? A paradigm shift from a glucose-centric to a beta cell-centric concept of diabetes. EMJ Diabet 2018, 6, 46–52.
23. Ferrannini, E.; Muscelli, E.; Frascerra, S.; Baldi, S.; Mari, A.; Heise, T.; Broedl, U.C.; Woerle, H.J. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J. Clin. Investig. 2014, 124, 499–508.
24. Merovci, A.; Solis-Herrera, C.; Daniele, G.; Eldor, R.; Fiorentino, T.V.; Tripathy, D.; Xiong, J.; Perez, Z.; Norton, L.; Abdul-Ghani, M.A.; et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J. Clin. Investig. 2014, 124, 509–514.
25. Sheu, W.H.H.; Chan, S.P.; Matawaran, B.J.; Deerochanawong, C.; Mithal, A.; Chan, J.; Suastika, K.; Khoo, C.M.; Nguyen, H.M.; Linong, J.; et al. Use of sglt-2 inhibitors in patients with type 2 diabetes mellitus and abdominal obesity: An asian perspective and expert recommendations. Diabetes Metab. J. 2020, 44, 11–32.
26. Bonner, C.; Kerr-Conte, J.; Gmyr, V.; Queniat, G.; Moerman, E.; Thevenet, J.; Beaucamps, C.; Delalleau, N.; Popescu, I.; Malaisse, W.J.; et al. Inhibition of the glucose transporter sglt2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat. Med. 2015, 21, 512–517.
27. Saponaro, C.; Mühlemann, M.; Acosta-Montalvo, A.; Piron, A.; Gmyr, V.; Delalleau, N.; Moerman, E.; Thévenet, J.; Pasquetti, G.; Coddeville, A.; et al. Interindividual heterogeneity of sglt2 expression and function in human pancreatic islets. Diabetes 2020, 69, 902–914.
28. Suga, T.; Kikuchi, O.; Kobayashi, M.; Matsui, S.; Yokota-Hashimoto, H.; Wada, E.; Kohno, D.; Sasaki, T.; Takeuchi, K.; Kakizaki, S.; et al. Sglt1 in pancreatic alpha cells regulates glucagon secretion in mice, possibly explaining the distinct effects of sglt2 inhibitors on plasma glucagon levels. Mol. Metab. 2019, 19, 1–12.
29. Kuhre, R.E.; Ghiasi, S.M.; Adriaenssens, A.E.; Wewer Albrechtsen, N.J.; Andersen, D.B.; Aivazidis, A.; Chen, L.; Mandrup-Poulsen, T.; Orskov, C.; Gribble, F.M.; et al. No direct effect of

sglt2 activity on glucagon secretion. Diabetologia 2019, 62, 1011–1023.

30. Bersoff-Matcha, S.J.; Chamberlain, C.; Cao, C.; Kortepeter, C.; Chong, W.H. Fournier gangrene associated with sodium-glucose cotransporter-2 inhibitors: A review of spontaneous postmarketing cases. Ann. Intern. Med. 2019, 170, 764–769.
31. Neal, B.; Perkovic, V.; Mahaffey, K.W.; de Zeeuw, D.; Fulcher, G.; Erondu, N.; Shaw, W.; Law, G.; Desai, M.; Matthews, D.R.; et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N. Engl. J. Med. 2017, 377, 644–657.
32. Perkovic, V.; Jardine, M.J.; Neal, B.; Bompoint, S.; Heerspink, H.J.L.; Charytan, D.M.; Edwards, R.; Agarwal, R.; Bakris, G.; Bull, S.; et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N. Engl. J. Med. 2019, 380, 2295–2306.
33. Wing, R.R.; Bolin, P.; Brancati, F.L.; Bray, G.A.; Clark, J.M.; Coday, M.; Crow, R.S.; Curtis, J.M.; Egan, C.M.; Espeland, M.A.; et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N. Engl. J. Med. 2013, 369, 145–154.
34. Zinman, B.; Wanner, C.; Lachin, J.M.; Fitchett, D.; Bluhmki, E.; Hantel, S.; Mattheus, M.; Devins, T.; Johansen, O.E.; Woerle, H.J.; et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N. Engl. J. Med. 2015, 373, 2117–2128.
35. Wiviott, S.D.; Raz, I.; Bonaca, M.P.; Mosenzon, O.; Kato, E.T.; Cahn, A.; Silverman, M.G.; Zelniker, T.A.; Kuder, J.F.; Murphy, S.A.; et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N. Engl. J. Med. 2019, 380, 347–357.
36. McMurray, J.J.V.; Solomon, S.D.; Inzucchi, S.E.; Kober, L.; Kosiborod, M.N.; Martinez, F.A.; Ponikowski, P.; Sabatine, M.S.; Anand, I.S.; Belohlavek, J.; et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N. Engl. J. Med. 2019, 381, 1995–2008.
37. Petrie, M.C.; Verma, S.; Docherty, K.F.; Inzucchi, S.E.; Anand, I.; Belohlavek, J.; Bohm, M.; Chiang, C.E.; Chopra, V.K.; de Boer, R.A.; et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. JAMA 2020.
38. Lam, C.S.P.; Chandramouli, C.; Ahooja, V.; Verma, S. Sglt-2 inhibitors in heart failure: Current management, unmet needs, and therapeutic prospects. J. Am. Heart Assoc. 2019, 8, e013389.
39. Dekkers, C.C.J.; Gansevoort, R.T. Sodium-glucose cotransporter 2 inhibitors: Extending the indication to non-diabetic kidney disease? Nephrol. Dial. Transplant. 2020, 35, i33–i42.
40. Taylor, S.I.; Blau, J.E.; Rother, K.I.; Beitelshees, A.L. Sglt2 inhibitors as adjunctive therapy for type 1 diabetes: Balancing benefits and risks. Lancet Diabetes Endocrinol. 2019, 7, 949–958.
41. Sims, H.; Smith, K.H.; Bramlage, P.; Minguet, J. Sotagliflozin: A dual sodium-glucose co-transporter-1 and -2 inhibitor for the management of type 1 and type 2 diabetes mellitus. Diabet. Med. 2018, 35, 1037–1048.

42. Cefalo, C.M.A.; Cinti, F.; Moffa, S.; Impronta, F.; Sorice, G.P.; Mezza, T.; Pontecorvi, A.; Giaccari, A. Sotagliflozin, the first dual sglt inhibitor: Current outlook and perspectives. Cardiovasc. Diabetol. 2019, 18, 20.