Clinical considerations when adding a sodium-glucose co-transporter-2 inhibitor to insulin therapy in patients with diabetes mellitus

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A B S T R A C T
A consensus meeting was held to discuss add-on therapy of sodium-glucose co-transporter-2 (SGLT2) inhibitors in patients with diabetes mellitus treated with insulin. The objectives were to affirm the efficacy and safety of SGLT2 inhibitors as an add-on to insulin, empower clinicians to minimise the risk of adverse events, and provide clinical guidance. Administration of SGLT2 inhibitors as an add-on therapy to insulin is associated with significant reductions compared with placebo in glycosylated haemoglobin A1c, fasting plasma glucose, insulin dose, and body weight without an increased risk of hypoglycaemia. Compared with traditional therapies, SGLT2 inhibitors have shown cardiovascular and renal benefits. Adding an SGLT2 inhibitor to insulin increases the risk of urinary tract and genital tract infections. The use of SGLT2 inhibitor is also associated with a slightly increased incidence of diabetic ketoacidosis. Patients who may benefit most from add-on therapy with SGLT2 inhibitors include those with established atherosclerotic cardiovascular disease, heart failure, chronic kidney disease, high insulin doses, obesity, and metabolic syndrome. Routine monitoring for diabetic ketoacidosis is controversial, and patient and clinician education is essential to minimise risk. The decision to adjust insulin dose when adding an SGLT2 inhibitor is dependent on patient factors, but the insulin dose should not be reduced beyond 20% prior to the first dose of SGLT2 inhibitor. Patients should temporarily discontinue SGLT2 inhibitors during fasting, acute illness, or low/reduced carbohydrate intake. If ketonuria is detected, SGLT2 inhibitors but not insulin should be immediately discontinued and medical advice sought.

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are an important therapeutic option in the management of type 2 diabetes mellitus (T2DM). These oral agents treat hyperglycaemia by blocking the reabsorption of glucose in renal tubules, which results in increased urinary glucose excretion. As monotherapy, SGLT2 inhibitors have been shown to significantly lower glycated haemoglobin A1c (HbA1c), fasting glucose, and postprandial glucose compared with placebo in subjects with T2DM that was inadequately controlled with diet and exercise. The significant and consistent reduction in HbA1c observed with SGLT2 inhibitors is similar to or better than that produced by metformin, sulfonylureas, and dipeptidyl peptidase-4 (DPP-4) inhibitors, with a minimal risk of hypoglycaemia. These SGLT2 inhibitors can also bring about reductions in body weight and blood pressure. Sodium-glucose co-transporter-2 inhibitor therapy is associated with an elevated risk of genital tract infections (GTIs) and, to a lesser degree, urinary tract infections (UTIs). In addition, in rare cases, SGLT2 inhibitors have been associated with diabetic ketoacidosis (DKA) and euglycaemic ketoacidosis.
Many patients with T2DM fail to achieve glycaemic goals despite receiving two or more antidiabetic drug classes that target different core defects of the disease. Whereas the majority of antidiabetic drugs have an insulin-dependent mode of action, SGLT2 inhibitors have an insulin-independent mode of action, suggesting that the use of these drugs could offer therapeutic synergy when used in combination. Randomised controlled trials (RCTs), as well as real-world studies, have confirmed the efficacy and tolerability of SGLT2 inhibitors when used as monotherapy and as an add-on therapy to insulin. At the time of writing, SGLT2 inhibitors are not approved for use in type 1 diabetes mellitus (T1DM); however, there are RCTs providing evidence of a potential role for SGLT2 inhibitors in patients with T1DM. 

A meeting of esteemed endocrinologists in Hong Kong was held in August 2018 to develop a consensus on the role of add-on therapy with SGLT2 inhibitors in insulin-treated patients with diabetes mellitus. The expert panel considered all evidence relating to T2DM and also considered T1DM where possible. All statements pertaining to T1DM should be interpreted carefully given the paucity of data available for this condition and not construed as recommendations for off-label use. Herein we present the consensus findings of the expert panel, with the major objectives of this review summarised as follows: (1) to summarise the clinical approach and rationale for intensifying insulin therapy with SGLT2 inhibitors (2) to affirm the efficacy and safety of SGLT2 inhibitors in insulin-treated patients; (3) to empower clinicians to minimise the risk of hypoglycaemia and DKA; (4) to provide practical clinical guidance on adding SGLT2 inhibitors in insulin-treated patients; and (5) to guide clinicians on patient selection.

Clinical approach and rationale

Statement 1.1: The decision to add an additional therapy or intensify insulin therapy is dependent on individual patient factors that contribute to inadequate control

Because T2DM is a progressive disease, many patients will need intensification of therapy. If the patient has experienced an episode of severe hypoglycaemia while on insulin therapy, then the addition of another therapy with a low risk of hypoglycaemia may be a better option compared with intensifying insulin therapy. Patient preference is an important consideration. Intensifying insulin heightens the potential risks for weight gain and hypoglycaemia, especially at high insulin doses. Moreover, a large proportion of patients with T2DM have co-morbid obesity and/or metabolic syndrome, with the latter characterised by hypertension and dyslipidaemia.

in addition to poor glycaemic control. Intensifying insulin in these patients could contribute to a vicious cycle of increasing appetite, further weight gain, and increasing insulin resistance.

Statement 1.2: Sodium-glucose co-transporter-2 inhibitors offer weight loss and cardiovascular-renal benefits with a low risk of hypoglycaemia compared with other oral agents

Sodium-glucose co-transporter-2 inhibitors offer the benefit of improving glycaemic control without increasing the risks of hypoglycaemia or weight gain in insulin-treated patients. Compared with most other therapies, SGLT2 inhibitors have shown cardiovascular benefits in patients with established atherosclerotic cardiovascular disease, which appears to be a class effect. Because of their insulin-independent mechanism, SGLT2 inhibitors are often effective in patients in whom other therapies have failed. Add-on therapy with an SGLT2 inhibitor may have particular benefits in obese patients, as insulin intensification or add-on therapy with sulfonylurea or thiazolidinedione may exacerbate weight gain. Treatment with SGLT2 inhibitors can improve metabolic syndrome through reductions in weight and blood pressure while counteracting insulin resistance and improving insulin sensitivity. Continuous glucose monitoring studies have shown improvement in glucose excursions after initiating SGLT2 inhibitor therapy. In patients with T1DM, the patients who mainly benefit from SGLT2 inhibitor
therapy are those on high insulin doses and those in whom features of T2DM—including excessive weight, high blood pressure, and other indices of metabolic syndrome—have accrued.

**Efficacy and safety**

Statement 2.1: Administration of sodium-glucose co-transporter-2 inhibitors as add-on therapy to insulin in type 2 diabetes mellitus is associated with significant reductions in haemoglobin A1c, fasting plasma glucose, insulin dose and body weight

The efficacy of SGLT2 inhibitors as add-on therapy to insulin in T2DM has been demonstrated in randomised, placebo-controlled trials, with significant reductions in HbA1c, fasting plasma glucose, total daily insulin dose, and body weight compared with placebo achieved over periods of up to 24 weeks (Table).\(^9\) So far, no head-to-head trials have compared SGLT2 inhibitors and DPP-4 inhibitors as an add-on therapy to insulin. Indirect comparison via network meta-analysis has suggested that SGLT2 inhibitors showed better glycaemic control and greater weight reduction than DPP-4 inhibitors in patients with T2DM that was inadequately controlled with insulin (Table).\(^20\) In addition, SGLT2 inhibitors have proven cardiovascular-renal benefits, while most DPP-4 inhibitors have only achieved cardiovascular safety.

### TABLE. Efficacy and safety of SGLT2 inhibitors as add-on therapy to insulin

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Weighted mean difference* vs comparator (95% CI)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 2 diabetes mellitus: SGLT2 inhibitors vs DPP-4 inhibitors(^{20})</strong> †</td>
<td></td>
<td></td>
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<tr>
<td>HbA1c (%)</td>
<td>-0.24 (-0.43 to -0.05), P=0.02</td>
<td>Baseline: 8.3%-9.3%</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>-18.0 (-28.5 to -7.6), P=0.003</td>
<td>-</td>
</tr>
<tr>
<td>TDD insulin (IU)</td>
<td>-2.82 (-11.78 to 6.14), NS</td>
<td>NS; baseline: 22.6-93.1 IU</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>-2.38 (-3.18 to -1.58), P&lt;0.001</td>
<td>Baseline (BMI): 23.9-35.5 kg/m²</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>RR=1.19 (0.78 to 1.82)</td>
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| **Type 2 diabetes mellitus: SGLT2 inhibitors vs placebo\(^{20}\)** ‡ | | |
| HbA1c (%) | -0.56 (-0.67 to -0.44), P<0.001 | Baseline: 8.2-8.9% |
| FPG (mg/dL) | -0.95 (-1.21 to -0.70), P<0.001 | - |
| TDD insulin (IU) | -8.79 (-13.4 to -0.22), P<0.001 | Baseline: 29.6-92 IU |
| Body weight (kg) | -2.63 (-3.10 to -0.16), P<0.001 | - |
| Hypoglycaemia | RR=1.07 (0.99 to 1.15), P=0.050 | NS; incidence: 53.5% vs 49.1% |
| UTI | RR=1.29 (1.05 to 1.59), P=0.249 | Incidence: 9.1% vs 7.2% |
| Genital infections | RR=4.57 (3.47 to 6.02) | Incidence: 10.2% vs 2.1% |

| **Type 1 diabetes mellitus: SGLT2 inhibitors vs placebo\(^{20}\)** § | | |
| HbA1c (%) | -0.40 (-0.46 to -0.35), P<0.001 | Baseline: 7.6-10.5% |
| FPG (mmol/L) | -1.14 (-1.47 to -0.80), P<0.001 | Baseline: 8.4-9.8 mmol/L |
| TDD insulin (IU) | -6.0 (-7.1 to -4.9), P<0.001 | Baseline: 45-56 IU |
| Body weight (kg) | -2.68 (-3.36 to -2.00), P<0.001 | Baseline (weight): 75-80 kg Baseline (BMI): 26-30 kg/m² |
| Mean BG variation (mmol/L) | -1.07 (-1.31 to -0.84), P<0.001 | - |
| MAGE (mmol/L) | -1.45 (-2.12 to -0.78), P<0.001 | - |
| Hypoglycaemia | OR=1.01 (0.99 to 1.03) | NS |
| UTI | OR=0.97 (0.65 to 1.46) | NS |
| Genital infections | OR=3.44 (2.34 to 5.07) | - |
| DKA | OR=3.38 (1.74 to 6.56) | - |

Abbreviations: BG = blood glucose; BMI = body mass index; CI = confidence interval; DKA = diabetic ketoacidosis; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; HbA1c = glycosylated haemoglobin A1c; MAGE = mean amplitude of glucose excursions; NS = difference not significant; OR = odds ratio; RR = risk ratio; SGLT2 = sodium-glucose co-transporter2; T2DM = type 2 diabetes mellitus; T1DM = type 1 diabetes mellitus; TDD = total daily dose; UTI = urinary tract infection

* Data are weighted mean differences for efficacy parameters and either risk ratios or odds ratios for safety parameters
† Data are derived using indirect comparisons from a meta-analysis of 5 SGLT2 inhibitor studies and 9 DPP-4 inhibitor studies
‡ Data are from a meta-analysis of placebo-controlled trials of SGLT2 inhibitors as add-on to insulin therapy in T2DM
§ Data are from a meta-analysis of placebo-controlled trials of SGLT2 inhibitors as add-on to insulin therapy in T1DM

In patients with T2DM, the use of SGLT2 inhibitors as add-on therapy to insulin is associated with a similar incidence of hypoglycaemia to placebo (Table).15 However, SGLT2 inhibitors are associated with higher risks of UTIs and GTIs compared with placebo.19

Statement 2.3: Administration of sodium-glucose co-transporter-2 inhibitors as add-on therapy to insulin in type 1 diabetes mellitus is associated with significant reductions in haemoglobin A1c, fasting plasma glucose, daily total insulin dose, body weight, and glycaemic excursions.

The use of SGLT2 inhibitors in T1DM is currently off-label. The addition of an SGLT2 inhibitor in patients with T1DM offers therapeutic value in patients who are obese or with problems with large glucose excursions. Careful patient selection and meticulous patient education of precautions are important to minimise the risk of DKA.21 Evidence from several clinical trials showed that in patients with T1DM, dapagliplozin, or empaglibiflozin as adjunctive therapy to insulin improved glycaemic control and weight.16

Statement 2.4: Adding sodium-glucose co-transporter-2 inhibitors to insulin in type 1 diabetes mellitus does not appear to increase the risks of hypoglycaemia or urinary tract infections but increases the risk of genital tract infections.

In patients with T1DM, the use of SGLT2 inhibitor therapy is not associated with an increased risk of hypoglycaemia or UTIs compared with placebo but is associated with an increased risk of GTIs (Table).15 Evidence from the EASE trials showed that in patients with T1DM, empaglibiflozin as adjunctive therapy to insulin did not increase the risk of hypoglycaemia.16

Adverse events of special interest

Statement 3.1: The incidence of genital tract infections is higher in patients with sodium-glucose co-transporter-2 inhibitors added to insulin therapy versus other agents or placebo; however, most events are classified as mild or moderate in intensity and readily respond to therapy.

In patients with T1DM or T2DM, the addition of an SGLT2 inhibitor to insulin therapy is associated with a significantly increased risk of GTIs (Table).15,19 The estimated risk ratio ranges from 3 to 5 compared with placebo. However, treatment cessation is not necessary, and most events are mild or moderate in intensity and readily respond to therapy.

Statement 3.2: Administration of sodium-glucose co-transporter-2 inhibitors is associated with an increased, albeit low, incidence of euglycaemic diabetic ketoacidosis, a risk that is strongly associated with use of insulin.

In RCTs, the incidence of DKA among patients with T1DM or T2DM receiving SGLT2 inhibitor therapy is estimated to be <1 case per 1000, whereas in cohort studies, the incidence has been reported to be 1.6 cases per 1000 person-years.22 In patients with T1DM, the DEPICT-1,19 DEPICT-2,23 inTandem1,24 and inTandem325 trials showed a DKA incidence ranging from 1.5% to 4.0% in patients treated with selective SGLT2 inhibitors or dual SGLT1 and SGLT2 inhibitors for up to 1 year.

Statement 3.3: The risk of diabetic ketoacidosis is heightened in patients with high haemoglobin A1c levels, frail and elderly patients, those with inadequate food intake, and patients with poor disease awareness/adherence or frequent complications.

In patients with T2DM, those with HbA1c levels of ≥10% may have a higher risk of developing DKA than patients with lower HbA1c levels. Risk may also be elevated in latent autoimmune diabetes in adults, frail and elderly patients with poor disease awareness, those who are repeatedly admitted to hospital for complications, and patients with long-term diabetes with depleted β-cell reserves.

In patients with T1DM, poor glycaemic control is also indicative of heightened risk of DKA, along with insulin pump use and suboptimal adherence.26-28 Other risk groups include those taking weight loss medications, those without steady dietary control, postoperative patients, and frail or elderly patients, particularly those with cognitive impairment.

Patient selection

Statement 4.1: Sodium-glucose co-transporter-2 inhibitors have the greatest overall benefit/risk profile in patients with obesity, cardiovascular or renal diseases, high insulin requirement, or large glycaemic excursions.

Randomised controlled trials support the use of SGLT2 inhibitors as an add-on therapy to insulin therapy in T2DM patients with obesity, cardiovascular or renal diseases, high insulin requirement, or large glycaemic excursions in whom insulin intensification would otherwise be the next step in achieving glycaemic control.9,29-35
In patients with T1DM, SGLT2 inhibitors should only be prescribed by an endocrinologist, as the use of these therapies in T1DM is currently off-label. The use of SGLT2 inhibitors may be a useful adjunct to insulin therapy in patients with T1DM and obesity or large glycaemic variability. Hypoglycaemia unawareness is not an absolute contra-indication provided that the patient is compliant and knowledgeable about the disease. Patients should be capable of detecting insulin pump failure, and the ability to monitor urine or serum ketone levels is mandatory. In RCTs of patients with T1DM, patient selection included those aged 18 to 75 years with baseline HbA1c levels of 7.0% to 11.0% and a body mass index ≥18.5 kg/m². In the DEPICT trials, patients using insulin for ≥12 months with a total daily insulin dose ≥0.3 IU/kg for ≥3 months were selected, and patients were additionally required to have a creatinine clearance of ≥60 mL/min and C-peptide level <0.7 ng/mL. In the inTandem trials, patients were required to have treatment with insulin at a stable dose via continuous subcutaneous insulin infusion or multi-dose insulin treatment, with no change in insulin delivery within 3 months. Patients were additionally required to perform self-monitoring of blood glucose (SMBG) and have an estimated glomerular filtration rate of >45 mL/min/1.73 m².

Switching versus adding
Statement 5.1: In patients with type 2 diabetes mellitus, the decision to switch a sodium-glucose co-transporter-2 inhibitor to another oral agent or add a sodium-glucose co-transporter-2 inhibitor to an existing treatment regimen is based on factors such as efficacy, tolerability of the existing treatment, and cost

In T2DM patients on combination therapy of insulin and oral antidiabetic agents, replacing one of the oral agents with an SGLT2 inhibitor can be considered. When the effectiveness of the DPP-4 inhibitor is no longer sustained owing to its limited durability or when the patient develops fluid retention with a glitazone, patients would be expected to benefit from a switch to an SGLT2 inhibitor. Switching to an SGLT2 inhibitor might be more cost-effective compared with adding an SGLT2 inhibitor to the existing drug regimen.

Implementation
Statement 6.1: Adjustment of the insulin dose when adding a sodium-glucose co-transporter-2 inhibitor may be appropriate in some but not all patients

In patients with T2DM, the decision to adjust insulin dose upon initiation of an SGLT2 inhibitor is dependent on patient factors. If the patient is obese and insulin resistant with high HbA1c, then maintaining the insulin dose is a reasonable approach. Conversely, if a patient’s HbA1c is close to target, a reduction in insulin dose will be appropriate. For patients with frequent large glycaemic excursions, the expert panel recommends reduction of the insulin dose by up to 10% before initiating an SGLT2 inhibitor. Initiation of the SGLT2 inhibitor at the lowest available dose is also recommended.

In the DEPICT trials with T1DM, after the first dose of study drug, basal and bolus insulin were reduced symmetrically by up to 20%. In the inTandem trials, in which dual SGLT1 and SGLT2 inhibitor therapy was employed, bolus insulin was reduced by 30%, with insulin dosing subsequently adjusted according to SMBG data to meet targets. The consensus of the expert panel was that the insulin dose should not be reduced beyond 20% upon initiation of an SGLT2 inhibitor. When the patient is receiving both basal and bolus doses of insulin, the bolus dose may be reduced, with addition of the SGLT2 inhibitor as appropriate.

Monitoring
Statement 7.1: Early and regular monitoring for diabetic ketoacidosis is recommended following initiation of sodium-glucose co-transporter-2 inhibitor therapy

Patients should be monitored and closely followed after initiating an SGLT2 inhibitor. Self-monitoring of blood glucose is important, and titration of insulin may be necessary. Early follow-up in the form of telecommunication or nurse clinic instead of clinician visits may be more feasible, and monitoring of renal function within 4 weeks is recommended. Daily ketone monitoring is not practical because of the high cost and short shelf life of ketone strips. However, monitoring of ketones is recommended during acute illness. Education of patients and clinicians is essential for improved awareness, and the importance of sick day management needs to be emphasised.

The risk of DKA is higher in T1DM. Urine or blood ketone monitoring should be considered during initiation of SGLT2 inhibitors and mandatory during acute stress. Education regarding optimal nutrition, situations of nausea/vomiting, and temporary cessation of SGLT2 inhibitor therapy is appropriate. Instruction on measures to reverse ketosis and prevent progression to DKA (including carbohydrates and fluid intake as well as additional correction of insulin doses) should be given. In T1DM, the STICH protocol is an appropriate strategy for mitigating DKA risk in patients receiving SGLT2 inhibitors. When DKA is suspected, the patients should stop SGLT2 inhibitor therapy, inject...
bolus insulin, consume 30 g of carbohydrates, and hydrate with water.36

Statement 7.2: Sodium-glucose co-transporter-2 inhibitor therapy should be stopped in the event of high ketone levels

In the event that a patient detects high ketone levels, they should be instructed to stop their SGLT2 inhibitor, continue insulin, ensure carbohydrate intake, and seek medical advice.

Other practical advice

Statement 8.1: Sodium-glucose co-transporter-2 inhibitor therapy should be temporarily stopped to avoid diabetic ketoacidosis during fasting or reduced intake of food, acute illness, and hospitalisation

Although there are currently no guidelines on when to discontinue SGLT2 inhibitor therapy, SGLT2 inhibitor therapy should be withheld temporarily in the following situations37:

- Fasting, reduced carbohydrate intake (withhold at onset);
- Acute illness (withhold at onset);
- Hospitalisation (withhold at onset);
- Surgery, endoscopic procedures, contrast studies requiring fasting (withhold prior to procedure, with duration depending on risk (at least 3 days prior to major surgery or prolonged fasting and/or anticipated high risk of hypovolaemia); and
- Bariatric surgery (withhold 1 to 2 weeks before initiation of ketotic diet).

Sodium-glucose co-transporter-2 inhibitors may be re-introduced when the patient is able to eat normally, with recovery of renal function following acute illness.

Further evidence to explore

Statement 9.1: Additional real-world and renal and cardiovascular outcome data in patients with type 1 diabetes mellitus are needed to further support the use of sodium-glucose co-transporter-2 inhibitors in diabetes management

Real-world data are needed to better understand long-term medication adherence and persistence, cost-effectiveness of ketone monitoring, and the role of carbohydrate intake and SMBG in the prevention of DKA. Renal and CVD outcome data are needed regarding the use of SGLT2 inhibitors in T1DM.

Concluding remarks

Sodium-glucose co-transporter-2 inhibitors are an effective and well tolerated therapeutic option as add-on therapy to insulin in patients with T2DM. Addition of SGLT2 inhibitors in this setting is associated with significant reductions in HbA1c, fasting plasma glucose, total daily insulin dose, and body weight without increasing the risk of hypoglycaemia. Sodium-glucose co-transporter-2 inhibitor use is accompanied by a slightly increased risk of UTIs and GTIs. There is a low risk of DKA (about 1 per 1000 person-years). Appropriate patient selection, education, and monitoring are helpful in mitigating this risk. The use of SGLT2 inhibitors in patients with T1DM is currently off-label and should only be attempted under the supervision of an endocrinologist in appropriately selected patients. Further research will help to clarify the role of this important oral antidiabetic drug class in both T1DM and T2DM.

Post-meeting note

The results of the EASE-2 and EASE-3 trials were published after the meeting. Data from these two trials showed that adding empagliflozin as an adjunct to insulin therapy in T1DM improved glycaemic control and weight without increasing hypoglycaemia. The rate of ketoacidosis was lower when a smaller dose of empagliflozin was used.

Author contributions

All authors have made substantial contributions to the concept or design of this study; acquisition of data; analysis or interpretation of data; drafting of the manuscript; and critical revision for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have declared no conflicts of interest.

Acknowledgement

Language editing and writing support, funded by an unrestricted educational grant from AstraZeneca Hong Kong Limited, were provided by Ben Searle and Howard Christian of MIMS (Hong Kong) Limited.

Funding/support

Editing and writing support was funded by an unrestricted educational grant from AstraZeneca Hong Kong Limited.

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