# Positioning SGLT2 Inhibitors/ Incretin-Based Therapies in the Treatment Algorithm

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**Sodium–glucose cotransporter 2 inhibitors (SGLT2i) are the most recent addition to the therapeutic options available for the treatment of type 2 diabetes and became available after the introduction of incretin-based therapies, dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RAs). These agents have potential advantages with regard to their weight loss–promoting effect, low risk of hypoglycemia, reduction in blood pressure, and reduction in cardiovascular events in high-risk patients (with empagliflozin). Apart from these clinically important outcomes, they may also correct core defects present in type 2 diabetes (i.e., improvement in β-cell function and insulin sensitivity). They do, however, have some adverse effects, notably, nausea with GLP-1 RAs and genital tract infections and potential for volume depletion with SGLT2i. Whether incretin-based therapies are associated with an increased risk of pancreatitis is unclear. Most recently, diabetic ketoacidosis has been reported with SGLT2i. Therefore, a key clinical question in relation to guidelines is whether these clinical advantages, in the context of the adverse effect profile, outweigh the additional cost compared with older, more established therapies. This article reviews the therapeutic rationale for the use of these newer drugs for diabetes treatment, considers their place in current guidelines, and discusses how this may change as new data emerge about their long-term efficacy and safety from ongoing outcome trials.**

## Incretin-Based Therapies: Rationale for Use and Clinical Summary

The development of incretin-based treatments for type 2 diabetes (T2DM) stems from the observation that the effect of oral glucose of stimulating insulin secretion is much greater than when blood glucose levels are raised to the same concentration using intravenous glucose (1). This is due to secretion of "incretin" hormones from the K cells (located in the duodenum and jejunum) and L cells (located in distal small bowel and large intestine). The known incretin hormones in humans are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) (7-36)amide; GLP-1 is the most biologically active incretin (2). In T2DM, stimulated GLP-1 and GIP responses have been reported to be normal, decreased, or increased (3). In contrast, the glucose-stimulated insulin response to GIP (even at pharmacological doses) is attenuated (4), suggesting that loss of the incretin response may be a primary pathophysiological abnormality in the development of T2DM. However, near normalization of blood glucose levels with insulin therapy has been demonstrated to improve the β-cell responsiveness to both GIP and GLP-1 (5). It also is important to note that the insulin secretory response to GLP-1 is glucose dependent, in that insulin secretion is only stimulated at glucose concentrations above ~3.5–4.0 mmol/L. Therefore, GLP-1–based treatment is unlikely to result in hypoglycemia when used as monotherapy or in combination with an insulin

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sensitizer (6,7). GLP-1 is part of the physiological system signaling satiety (8,9), reduces food intake and promotes weight loss in humans (10), and delays gastric emptying (11). Early studies showed that continuous subcutaneous GLP-1 infusion effectively lowered fasting and postprandial glucose levels and promoted weight loss in patients with T2DM (12). However, endogenous human GLP-1 has a short half-life (2–3 min) due to breakdown in the circulation by protease enzymes, notably, dipeptidyl peptidase (DPP)-4, which cleaves the molecule to leave the inactive GLP-1 (9-36). Hence, native GLP-1 has limited therapeutic efficacy. Pharmaceutical development took two routes: inhibition of the DPP-4–degrading enzyme and prolongation of the biological half-life by developing DPP-4–resistant GLP-1 receptor agonists (GLP-1 RAs).

#### *DPP-4 Inhibitors*

Four oral DPP-4 inhibitors (DPP-4i) are approved for use in both the U.S. and the European Union (sitagliptin, saxagliptin, alogliptin, and linagliptin) (Table 1). Vildagliptin is approved in the European Union but not the U.S. Several other agents of this class are marketed worldwide (for example, omaragliptin and trelagliptin are available only in Japan). All five DPP-4i appear to have similar efficacy in terms of glucose lowering. An 18-week, phase 3b, multicenter, double-blind trial of saxagliptin versus sitagliptin has demonstrated noninferiority as add-on therapy to metformin (13). Trelagliptin, a once-weekly DPP-4i, was studied against alogliptin once daily and has demonstrated noninferiority in the Japanese population studied (14). Meta-analysis of DPP-4i has shown an average $HbA_{1c}$ reduction ($-0.74\%$) (15) that is slightly less efficacious than sulfonylureas when used as monotherapy and similar to metformin and pioglitazone (16) but inferior to GLP-1 RAs. DPP-4i can be used in combination with other oral agents or with basal insulin (17), although the reduction of $HbA_{1c}$ with insulin is modest (18,19). The DPP-4i are weight neutral and have a low risk of hypoglycemia.

#### *DPP-4i: Adverse Effects*

In general, the adverse effect profile of the DPP-4i is quite favorable. With the exception of linagliptin, the DPP-4i require dose reduction in patients with renal impairment. Some concern has been raised about the risk of pancreatitis and pancreatic cancer, based on preclinical studies and reports from postmarketing surveillance studies. However, the current data do not support a likely association (20). The U.S. Food and Drug Administration (FDA) has recently issued a warning about the possibility of joint pain developing during DPP-4i treatment after review of 33 cases reported over the past 8 years. However, the potential mechanism(s) are uncertain and a causal link is unproven, although symptoms appear to resolve after treatment withdrawal (21). Several large cardiovascular (CV) outcome trials have been completed, comparing these agents with placebo on the background of standard diabetes care (Table 2), and have shown a neutral effect on CV outcomes. An increase in hospitalization for heart failure was reported in Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI) with saxagliptin (22), but there was no associated increase in mortality. In Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) with alogliptin (23) and in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) with sitagliptin (24), the incidence of CV events was similar to that in the placebo group.

#### *GLP-1 RAs*

The GLP-1 RAs either are analogs of human GLP-1 with addition of a fatty acid, an immunoglobulin, or albumin molecule to cause resistance to DPP-4 degradation (liraglutide, dulaglutide, albiglutide) or are based on the exendin molecule (exenatide, lixisenatide). The duration of action of exenatide and lixisenatide ranges from 6 to 8 h and for liraglutide is 24 h, while exenatide extended release, dulaglutide, and albiglutide are given once weekly (Table 2). Clinical trials have shown that the GLP-1 RAs effectively lower blood glucose levels when used as monotherapy or in combination with other agents, with $HbA_{1c}$ reduction ranging from $-0.8$ to $-1.5\%$ at approved doses (25–27). They have a low intrinsic risk of causing hypoglycemia, due to the "glucose dependence" of their insulin secretory effect. GLP-1 RAs also induce satiety and produce mean weight loss of $\sim$3 kg in clinical trials (28). However, the weight loss can be quite variable, with $\sim$25% of individuals failing to lose weight, 25% losing in excess of 5% of their body weight, and the remaining 50% losing an intermediate amount of weight (29). GLP-1 RAs inhibit glucagon secretion (30), which combined with the increase in insulin secretion, exerts a potent effect to suppress the elevated rates of hepatic glucose production (HGP) (31). One recent trial suggests that the GLP-1 RAs may increase insulin secretion and preserve $\beta$-cell function on a long-term basis (32). These effects on the $\beta$-cell, $\alpha$-cell, HGP, and brain (satiety/weight loss) account for their superior glycemic efficacy compared with the DPP-4i (25,30,33).

#### *GLP-1 RAs: Adverse Effects*

Their main adverse effect is nausea, which is most common at the time of treatment initiation and tends to wane over time (34). There is a small increase in pancreatitis with GLP-1 RAs from available randomized controlled trial data, but causality is yet to be proved (20). Other concerns relate to C-cell thyroid tumors and stem from preclinical data from rodents (35) and may not be relevant to humans (36). GLP-1 RAs show a small, but consistent, fall in systolic blood pressure of 2–3 mmHg and a 2–3 bpm increase in heart rate (37). The mechanisms responsible for the hemodynamic effects are not fully understood, but GLP-1 receptors are present in the vasculature and in the sino-atrial node in the heart. Several CV outcome studies are under way, with the only reported data from ELIXA (Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 [Lixisenatide]) (38). This trial, conducted in high-risk patients with T2DM, showed a neutral effect on CV events.

### Sodium–Glucose Cotransporter 2 Inhibitors: Rationale for Use and Clinical Summary

The sodium–glucose cotransporter (SGLT) 2 inhibitor (SGLT2i) class of drugs was developed as a result of research showing that inhibition of renal glucose transport using the nonspecific SGLT2/SGLT1 inhibitor, phlorizin, effectively lowered plasma glucose levels and ameliorated glucose toxicity in experimental models of diabetes (39). Under physiological conditions, the SGLT2 transporter in the renal proximal tubule reabsorbs 80–90% of the

**Table 1—Available DPP-4i**

| Drug | Dosing (mg OD) | Use in renal impairment (CrCl mL/min) | Cardiovascular outcome trials |
|---|---|---|---|
| Sitagliptin | 100<br>50<br>25 | <br>30–50<br><30 | TECOS, *n* = 14,671:<br>- December 2008–December 2014<br>- Median follow-up 3 years<br>- Inclusion criteria: documented vascular disease in coronary, cerebral, or peripheral arteries<br>- $HbA_{1c}$ 6.5–8%, age ≥50 years<br>- Primary outcome: composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina |
| Saxagliptin | 5<br>2.5 | Mild impairment: >50<br>Moderate–severe impairment: ≤50 | SAVOR-TIMI 53, *n* = 16,492:<br>- May 2010–May 2013<br>- Median follow-up 2.1 years<br>- Inclusion criteria: history of established CVD or multiple CV risk factors<br>- $HbA_{1c}$ ≥6.5%, age ≥40 years<br>- Primary outcome: composite of CV death, nonfatal MI, or nonfatal stroke |
| Linagliptin | 5 | No dose adjustment | CAROLINA (vs. glimepiride 1–4 mg OD), *n* = 6,000:<br>- October 2010–September 2018<br>- Inclusion criteria: preexisting CVD or specified diabetes<br>- End-organ damage or age ≥70 years or ≥2 specified CV risk factors<br>- $HbA_{1c}$ 6.5–8.5%, age 40–85 years<br>- Primary outcome: time to first occurrence of the composite end point (CV death, nonfatal MI excluding silent MI, nonfatal stroke, and hospitalization for UA)<br>CARMELINA (vs. placebo), *n* = 8,300:<br>- July 2013–January 2018<br>- Inclusion criteria: high risk of CV events defined by *1*) micro- or macroalbuminuria and previous macrovascular disease or *2*) impaired renal function with predefined urine albumin-to-creatinine ratio<br>- $HbA_{1c}$ ≥6.5 to ≤10%<br>- Primary outcome: time to first occurrence of any of the components of the primary composite end point: CV death, nonfatal MI, nonfatal stroke, and hospitalization for UA |
| Alogliptin | 25<br>12.5<br>6.25 | >50<br>≥30 to ≤50<br>≤30 | EXAMINE *n* = 5,380:<br>- October 2009–June 2013<br>- Median follow-up 1.5 years<br>- Inclusion criteria: acute coronary syndrome requiring hospitalization within the previous 15–90 days<br>- $HbA_{1c}$ 6.5–11%, age ≥18 years<br>- Primary outcome: composite of CV death, nonfatal MI, or nonfatal stroke |

CrCl, creatinine clearance; CVD, CV disease; OD, once daily; UA, unstable angina.

filtered glucose, and the remaining 10–20% is reabsorbed by the SGLT1 transporter (40,41). SGLT2 primarily is expressed in the kidney but also is found in the α-cell (42). In contrast, SGLT1 also is found in the gut, where it is responsible for the absorption of glucose and galactose (43). Three SGLT2i (canagliflozin, dapagliflozin, and empagliflozin) (Table 3) are approved worldwide, while additional agents are approved only in Japan. The SGLT2i are given once daily, and clinical trial data show broadly similar effects on glucose lowering, with $HbA_{1c}$ reduction of 0.6–1% in individual trials, depending on the starting $HbA_{1c}$. Importantly, these drugs show similar efficacy from early stages of diabetes (44), where they can be used as monotherapy, to later stages, where they can be used in dual and triple combination with other oral agents and in combination with insulin. Because their mechanism of action is independent of the severity of insulin resistance and β-cell failure, they are effective in all individuals with T2DM as long as the estimated glomerular filtration rate (eGFR) is >45–60 mL/min · 1.73 $m^2$. In addition to their glucose-lowering effects, SGLT2i also produce weight loss of ~2–3 kg, secondary to the 280–320 kcal/day that is lost as glucose (70–80 g) (each gram of glucose equal to 4 kcal) in the urine. The weight loss plateaus after 4–6 months despite continued glycosuria. This suggests a compensatory increase in caloric intake (45,46). An additional clinical benefit of the SGLT2i is the reduction in blood pressure (3–6/1–2 mmHg systolic/diastolic) (45).

#### *SGLT2i: Adverse Effects*

The main adverse effects associated with SGLT2i are a four- to fivefold increased risk of genital fungal infections and a small increase in bacterial urinary tract infections (46). They also have a diuretic effect, and volume depletion can be a concern, particularly in patients taking loop diuretics and the elderly (47,48). SGLT2i currently are being investigated in type 1 diabetes, and some trials have reported episodes of diabetic ketoacidosis with their use (49,50). This was followed by case reports of diabetic ketoacidosis in patients with type 1 diabetes or T2DM treated

**Table 2—Available GLP-1 analogs**

| Drug | Dosing | Use in renal impairment | Cardiovascular outcome trials |
|---|---|---|---|
| Exenatide | 10 μg b.i.d. | - CrCl 30–50 mL/min (caution when escalating dose)<br>- CrCl <30 mL/min (avoid) | None |
| Exenatide QR | 2 mg weekly | - CrCl 30–50 mL/min (caution)<br>- CrCl 30 mL/min (avoid) | EXSCEL, *n* = 14,000:<br>- June 2010–April 2018<br>- Inclusion criteria: $HbA_{1c}$ ≥6.5 and ≤10.0%, age ≥18 years, and one of the following: *1*) Treatment with 0–3 oral antihyperglycemic agents and *2*) insulin therapy either alone or in combination with up to two oral agents<br>- Primary outcome: time to first confirmed CV event in the primary composite of CV death, nonfatal MI, or nonfatal stroke |
| Liraglutide | 1.2 mg OD<br>1.8 mg OD | - Mild–severe impairment<br>- No dose adjustments (use with caution) | LEADER, *n* = 9,340:<br>- August 2010–November 2015<br>- Inclusion criteria: ≥50 years old and concomitant CV, cerebrovascular, or peripheral vascular disease or chronic renal failure or chronic heart failure; ≥60 years old and other specified risk factors of vascular disease<br>- $HbA_{1c}$ ≥7%, age ≥50 years<br>- Primary outcome: time from randomization to first occurrence of composite of CV death, nonfatal MI, or nonfatal stroke |
| Lixisenatide | 10 μg OD<br>20 μg OD | - eGFR 30–50 mL/min · 1.73 $m^2$ (caution)<br>- eGFR <30 mL/min · 1.73 $m^2$ (avoid) | ELIXA, *n* = 6,000:<br>- June 2010–February 2015<br>- Median follow-up 2 years<br>- Inclusion criteria: patients with spontaneous ACS admitted to acute care facility within 180 days after ACS and prior to screening<br>- $HbA_{1c}$ 5.5–11%, age ≥30 years<br>- Primary outcome: composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA |
| Dulaglutide | 0.75 mg weekly<br>1.5 mg weekly | - No dose adjustments<br>- Caution during initiation and dose escalation | REWIND, *n* = 9,622:<br>- July 2011–April 2019<br>- Inclusion criteria: ≥50 years old with established clinical vascular disease, ≥55 years and subclinical vascular disease, or ≥60 years and at least ≥2 CV risk factors<br>- $HbA_{1c}$ ≤9.5%, age ≥50 years<br>- Primary outcome: time to first occurrence of CV death, nonfatal MI, or nonfatal stroke (composite CV outcome) |
| Albiglutide | 30 mg weekly<br>50 mg weekly | - No dose adjustments<br>- Caution during initiation and dose escalation | None |

ACS, acute coronary syndrome; CrCl, creatinine clearance; EXSCEL, EXenatide Study of Cardiovascular Event Lowering; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results—A Long Term Evaluation; OD, once daily; QR, extended release; REWIND, Researching Cardiovascular Events With a Weekly INcretin in Diabetes; UA, unstable angina.

with SGLT2i (51). The FDA (52) and the European Medicines Agency (53) have issued warnings about this potential complication in the context of both type 1 diabetes and T2DM. SGLT2 inhibition has the propensity to cause ketoacidosis due to its intrinsic metabolic effects including a shift in substrate utilization from glucose to fat oxidation and the promotion of hyperglucagonemia, which stimulates ketogenesis (54). Insulin dose reduction and stress are other important contributing factors associated with SGLT2i-induced ketoacidosis in patients with T1DM and patients with T2DM, as is stress.

Some SGLT2i have been associated with an increased risk of bone fractures; this has led to a recent FDA warning for canagliflozin (55,56). Putative mechanisms include an increase in phosphate, serum parathyroid hormone, and fibroblast growth factor 23 concentrations and small decreases in serum 1,25-dihydroxy vitamin D levels (57,58). The volume depletion associated with this class of drugs and consequent hypotension may predispose to falls, and this could be a likely contributory factor in the elderly.

#### *Available Head-to-Head Trial Data*

A comprehensive comparative review of the clinical trial data on the classes of glucose-lowering agents discussed here is outside the scope of this review. GLP-1 RAs have been demonstrated to have superior glycemic efficacy as well as beneficial effects on body weight compared with DPP-4i. GLP-1 RAs have not been compared with SGLT2 as an active comparator in clinical trials.

**Table 3—Available SGLT2i**

| Drug | Dosing | Use in renal impairment | Cardiovascular outcome trials |
|---|---|---|---|
| Canagliflozin | 100 mg OD<br>300 mg OD | - eGFR <30 mL/min · 1.73 $m^2$ (avoid)<br>- eGFR 45–60 mL/min · 1.73 $m^2$ (use 100 mg dose)<br>- eGFR 30–45 mL/min · 1.73 $m^2$ (initial use not recommended; discontinue when <45 mL/min · 1.73 $m^2$ in patients already on canagliflozin) | CANVAS, $n$ = 4,411:<br>- December 2009–April 2017<br>- Inclusion criteria: history of or high risk for CV disease (≥2 CV risk factors)<br>- $HbA_{1c}$ 7–10.5%, age ≥30 years<br>- Primary outcome: MACEs, including CV death, nonfatal MI, and nonfatal stroke |
| Dapagliflozin | 5 mg OD<br>10 mg OD | - eGFR >60 mL/min · 1.73 $m^2$ (no dose adjustment)<br>- eGFR <60 mL/min · 1.73 $m^2$ (initial use not recommended; discontinue when <60 mL/min · 1.73 $m^2$ in patients already on dapagliflozin)<br>- eGFR <30 mL/min · 1.73 $m^2$ (contraindicated) | DECLARE-TIMI 58, $n$ = 17,150:<br>- April 2013–April 2019<br>- Inclusion criteria: high risk for CV events with T2DM<br>- Age ≥40 years<br>- Primary outcome: time to first event included in the composite of CV death, MI, or ischemic stroke |
| Empagliflozin | 10 mg OD<br>25 mg OD | - eGFR ≥45 mL/min · 1.73 $m^2$ (no dose adjustment)<br>- eGFR <45 mL/min · 1.73 $m^2$ (initial use not recommended; discontinue when <45 mL/min · 1.73 $m^2$ in patients already on empagliflozin)<br>- eGFR <30 mL/min · 1.73 $m^2$ (contraindicated) | EMPA-REG OUTCOME, $n$ = 7,034:<br>- Median follow-up 3.1 years<br>- July 2010–April 2015<br>- Inclusion criteria: high CV risk<br>- $HbA_{1c}$ 7–10%, age ≥18 years<br>- Primary outcome: composite of CV death, nonfatal MI, or nonfatal stroke |

DECLARE-TIMI 58, Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; MACE, major cardiac adverse events; OD, once daily; UA, unstable angina.

Empagliflozin (10 and 25 mg) was compared with sitagliptin 100 mg (and placebo) in patients with T2DM with $HbA_{1c}$ concentrations of 7.5–10%. The changes in baseline $HbA_{1c}$ were −0.74% for empagliflozin 10 mg, −0.85% for empagliflozin 25 mg, and −0.73% for sitagliptin at 24 weeks (59). Canagliflozin (100 mg and 300 mg) was compared against sitagliptin in patients with T2DM ($HbA_{1c}$ 7–10.5%). Canagliflozin 100 mg demonstrated noninferiority, while canagliflozin 300 mg demonstrated superiority, to sitagliptin in lowering $HbA_{1c}$ (0.88 vs. −0.73%) at 52 weeks (60). Canagliflozin also demonstrated reduction in body weight and systolic blood pressure compared with sitagliptin, while the incidence of genital mycotic infections, osmotic diuresis–related adverse events, and hypoglycemic episodes was higher in the canagliflozin-treated patients. Canagliflozin 300 mg was also compared with sitagliptin 100 mg in patients with T2DM inadequately controlled with metformin and sulfonylurea combination, demonstrating noninferiority at 52 weeks and superiority in a subsequent assessment ($HbA_{1c}$ −1.03 vs. −0.66%, respectively), as well as greater improvement in fasting glucose, body weight, and systolic blood pressure (61). Canagliflozin and empagliflozin were both studied against glimepiride, demonstrating noninferiority of canagliflozin 100 mg as well as superiority of canagliflozin 300 mg ($HbA_{1c}$ −0.12%) (62) and empagliflozin 25 mg (−0.11%) (63) over glimepiride. Similarly, dapagliflozin 10 mg was noninferior to glipizide at 52 weeks in terms of glycemic efficacy in patients with T2DM uncontrolled on metformin monotherapy (baseline mean $HbA_{1c}$ of 7.7%), with advantages of reduction in body weight and fewer hypoglycemic episodes than glipizide (64). Superiority of dapagliflozin versus glipizide with respect to $HbA_{1c}$ reduction and weight loss has been shown to persist for 4 years (65). In this study, more patients reported hyperglycemia on glipizide and eGFR declined more frequently in the glipizide-treated versus dapagliflozin-treated group.

### Where Do the DPP-4i, GLP-1 RAs, and SGLT2i Fit in Current Guidelines?

$HbA_{1c}$ reduction, irrespective of how it is achieved (66–71), is a major factor responsible for reducing the risk of microvascular complications and, to a lesser extent, the macrovascular complications. We believe, therefore, that $HbA_{1c}$ should be reduced to as close to normal as possible. However, the achievement of normoglycemia needs to be balanced against the potential risk of hypoglycemia, weight gain, and adverse CV events due to aggressive therapy (70,72). Hence, it is important to have an individualized management approach tailoring therapy to patients' needs and priorities (73,74). In this review, we focus mainly on patients with newly diagnosed T2DM and those with relatively short duration of disease (5–10 years) and no clinically evident CV disease. It should be emphasized that there is considerable variation to the approach to therapy among the various published guidelines.

Despite the addition of various new classes of drugs to the armamentarium, metformin still remains the first choice after lifestyle modification in most guidelines. The latest National Institute for Health and Care Excellence (NICE) guidelines (75) recommend the use of metformin as the initial choice of therapy and a target $HbA_{1c}$ of <6.5% (48 mmol/mol) for most patients. For first intensification of drug therapy (dual therapy), the recommendation is to consider metformin and a DPP-4i or pioglitazone or sulfonylurea or SGLT2i aiming for a glycemic target of <7% (53 mmol/mol). For second intensification, triple therapy with the following options are recommended: *1*) metformin, DPP-4i, and sulfonylurea; *2*) metformin, pioglitazone, and

sulfonylurea; and *3*) metformin, pioglitazone, or sulfonylurea and SGLT2i. Insulin is also recommended as an option at this stage. For patients in whom metformin is contraindicated or not tolerated, a DPP-4i or pioglitazone or sulfonylurea is recommended as initial therapy followed by combination of DPP-4i and pioglitazone, DPP-4i and sulfonylurea, or pioglitazone and sulfonylurea (first intensification). NICE recommends consideration of insulin for second intensification in this metformin-intolerant group (or those with contraindications).

NICE also recommends that GLP-1 RAs be considered in T2DM patients with BMI of $>35$ kg/m$^2$. Consideration should also be given to use GLP-1 RAs in patients with BMI $<35$ kg/m$^2$ if weight loss would help to improve other obesity-related comorbidities. The choice of GLP-1 RA is left to physician/patient preference. When more than one option is suitable, the one with the lowest cost is recommended. Continuation of GLP-1 RA therapy is recommended only if a $\geq$1% (10 mmol/mol) reduction in $HbA_{1c}$ and $\geq$3% weight loss are achieved in 6 months.

The NICE approach is based mainly on cost-effectiveness rather than pathophysiology. However, the long-term prevention of microvascular (and macrovascular) complications that potentially can be achieved with maintenance of normoglycemia with some of the newer antidiabetes agents, especially when used in combination (76), and correction of the underlying pathophysiological abnormalities are not addressed with this approach. The NICE approach also may underestimate the risks of hypoglycemia and weight gain with sulfonylureas and risks of heart failure and fractures with glitazones. GLP-1 RAs, apart from producing durable and clinically meaningful reduction in $HbA_{1c}$, have several other advantages such as promotion of weight loss, reduction of blood pressure, and a favorable safety profile (with the exception of nausea and vomiting that wane with time) and may be beneficial at an earlier stage in the therapeutic algorithm (10,26,32,33,37,76–80). While some of the clinical trial data as well as the American Association of Clinical Endocrinologists (AACE) algorithm support early use of GLP-1 RAs, this may not be the preferred approach for all patients owing to high cost and the nature of injection therapy. The NICE guideline was produced too recently to incorporate the beneficial CV effects in high-risk patients demonstrated in the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial. (CV outcome data on other SGLT2i are awaited.) However, both clinical effectiveness and cost-effectiveness were considered important in the drafting of the NICE guidelines, and SGLT2i and GLP-1 analogs have a high acquisition cost. This approach has advantages in countries with budgetary constraints and in patients with limited financial means but may be of less relevance to populations where the cost of the newer medications can be afforded. Neither metformin nor sulfonylureas (66,81–87) prevent the progressive β-cell failure in T2DM, but other antidiabetes agents, i.e., GLP-1 RAs, which enhance insulin secretion, preserve β-cell function, and demonstrate durability of glycemic control, should be considered as first- and/or second-line therapy. Another potential drawback of NICE guidelines is the lack of consideration of combination therapy based upon the starting $HbA_{1c}$ level.

The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement (88) also allows choice from a number of options. After metformin monotherapy or in case of intolerance with metformin, it gives one of six options (sulfonylureas, pioglitazone, DPP-4i, SGLT2i, GLP-1 RAs, or basal insulin) based upon physician/patient preferences, while considering the therapeutic efficacy, risk of hypoglycemia, weight gain, adverse effects, and cost. The guidelines are flexible with respect to addition of a third agent if adequate glycemic control is not achieved and recommend basal insulin if the $HbA_{1c}$ target is not achieved after 3 months. Incorporating the available data on GLP-1 RAs, the ADA/EASD position statement allows the physician to choose between GLP-1 RAs or prandial insulin, acknowledging the advantages of the former in terms of weight loss, low incidence of hypoglycemia, and no need for dose titration. In a choice between addition of a GLP-1 RA and basal insulin, we favor the former for the following reasons: *1*) insulin causes weight gain and hypoglycemia, whereas GLP-1 RAs promote weight loss and have minimal propensity to cause hypoglycemia, and *2*) insulin requires progressive titration and frequent home capillary glucose monitoring, whereas GLP-1 RAs do not. Since combination GLP-1 RA/basal insulin therapy is at least as effective as basal/bolus insulin therapy and has advantages with respect to hypoglycemia and weight gain (89–91), we favor the former approach when postprandial glycemic control is suboptimal in patients with T2DM treated with basal insulin. Most recently, the ADA/EASD guideline has advanced SGLT2i to second-line agents or as addition to dual oral agent therapy or to insulin-treated patients with T2DM. In the latter group, addition of an SGLT2i has been shown to improve glycemic control while reducing the insulin dose and promotes weight loss without increasing the incidence of hypoglycemia (92).

The AACE/American College of Endocrinology (ACE) guidelines (93) recommend initiation of monotherapy with metformin, GLP-1 RAs, SGLT2i, DPP-4i, and thiazolidinediones (TZDs) in the corresponding order of hierarchy followed by α-glucosidase inhibitors and by sulfonylureas when the $HbA_{1c}$ is $<7.5\%$. These guidelines also recommend initial therapy with dual and triple combinations if the $HbA_{1c}$ is $>7.5\%$ and $>9.0\%$, respectively, without symptoms of hyperglycemia. The AACE/ACE comprehensive diabetes management algorithm hence presents a different approach compared with the NICE and ADA/EASD therapeutic guidelines (93). First, multiple agents with a suggested hierarchy of use are recommended as initial monotherapy or as add-on therapy to whatever agent is used to initiate treatment. Second, the AACE/ACE guidelines recommend initiating therapy with two or three agents if the $HbA_{1c}$ is $>7.5\%$ or $>9\%$, respectively. The order of preference varies slightly with GLP-1 RAs, SGLT2i, and DPP-4i followed by TZD and basal insulin for dual therapy, while for triple therapy DPP-4i are moved down after TZD and basal insulin. Third, the AACE/ACE algorithm ranks sulfonylureas lower in the hierarchy because of the propensity to cause adverse effects like hypoglycemia and weight gain.

In all the guidelines, metformin remains the first drug of choice because of its long duration of use in clinical practice, low cost, weight neutrality,

low risk of hypoglycemia, and short-term glycemic efficacy. In patients who do not attain their individualized $HbA_{1c}$ target with metformin monotherapy, the individualized treatment approach can include choosing the option of the second drug based on patient preferences, effect on body weight, hypoglycemic risk, CV risk/benefit, durability of glycemic control, ability to correct known pathophysiological abnormalities, prevention of progressive β-cell failure, and side effects. While in the NICE and ADA/EASD algorithms the GLP-1 RAs, DPP-4i, and SGLT2i are considered to be second- (dual) or third- (triple) line therapy or to be used in combination with insulin, the AACE/ACE guidelines include these agents as monotherapy options as well as part of initial dual or triple therapy depending upon the starting $HbA_{1c}$. Because the DPP-4i are less efficacious than the GLP-1 RAs and SGLT2i in reducing the $HbA_{1c}$ (25,30,33), we favor use of the latter agents.

## Future Possibilities: What New Evidence Might Change Guideline Positioning?

### *CV Outcome Trials*

Because of concern regarding the CV safety of some antidiabetes drugs (94), the FDA now requires a CV safety trial for all new antidiabetes agents. In general, these outcome trials are of relatively short duration (<3 years), recruit T2DM patients at high risk for CV disease, are designed to demonstrate noninferiority, and are placebo comparator studies. The most recently reported trials are TECOS (sitagliptin) (24), EXAMINE (alogliptin) (23), SAVOR-TIMI (saxagliptin) (22), ELIXA (38), and EMPA-REG OUTCOME (95). The first four trials showed noninferiority to placebo. Of great importance, the most recently reported EMPA-REG OUTCOME trial met its CV outcome (95) for superiority (80% power to detect a 21.8% decrease in CV end point). In this trial, 7,020 patients with established CV disease were randomized to empagliflozin (10 or 25 mg/day) or placebo added to standard care. There was a statistically significant reduction in the primary composite outcome of death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke (10.5 vs. 12.1% in the empagliflozin and placebo groups, respectively; hazard ratio [HR] 0.86 [95% CI 0.74–0.99], $P = 0.04$). More impressively, empagliflozin treatment resulted in a significantly lower risk of death from CV causes (HR 0.62 [95% CI 0.49–0.77], $P < 0.001$), death from any cause (0.68 [0.57–0.82], $P < 0.001$), and hospitalization for heart failure (0.65 [0.5–0.85], $P < 0.003$) over a median observation time of 3.1 years. No significant difference in rates of nonfatal MI (HR 0.87, $P = 0.23$) or nonfatal stroke (HR 1.4, $P = 0.16$) were observed with empagliflozin.

The profound effect size and, more unexpectedly, the rapid onset of the CV beneficial effect raise many questions for which answers are not available: *1*) What is (are) the mechanism(s) responsible for the early (within 3 months) and marked reduction in CV death and hospitalization for heart failure? *2*) Do the CV benefits represent a class effect? *3*) Can the results be generalized to all populations with diabetes, e.g., patients with T2DM with lower risk for CV complications who are at earlier stages in the natural history of the disease? Answers to the last two questions are not available. Regarding the mechanism(s) responsible for the impressive reductions in CV death and heart failure hospitalization, it is unlikely that improved glycemic controls play a significant or any role, since *1*) the CV benefit is seen early (within 3 months); *2*) $HbA_{1c}$ is a weak CV risk factor (61) and the CV benefits of $HbA_{1c}$ reduction take up to 10 years to be observed (62); *3*) intensive glycemic control in other studies, e.g., ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease: PreterAx and Diamicron MR Controlled Evaluation), and VADT (Veterans Affairs Diabetes Trial), failed to show any benefit for CV death, although a significant reduction in nonfatal MI was observed in ACCORD; and *4*) the $HbA_{1c}$ reduction in EMPA-REG OUTCOME was modest (−0.24 to 0.36% at week 206). More likely, the CV benefits result from the combined hemodynamic effects of empagliflozin to reduce blood pressure, reduce aortic stiffness, and promote intravascular volume depletion (63). The excellent safety profile of empagliflozin (no increase in urinary tract infection, volume-related side effects, or ketoacidosis along with weight loss) in conjunction with the marked reductions in CV death and heart failure is likely to elevate the SGLT2i, particularly empagliflozin, in the treatment algorithm for patients with diabetes with established CV disease. If these results are replicated in the ongoing cardiovascular outcome trial with dapagliflozin and canagliflozin, SGLT2i would merit positioning after, or even before, metformin in patients with T2DM with high-risk characteristics similar to those in T2DM patients in EMPA-REG. Other important CV outcome trials and their current status are given in Tables 1–3.

An important determining factor for the positioning of the GLP-1 RAs, DPP-4i, and SGLT2i in the therapeutic algorithm would be head-to-head CV outcome trials against active comparators. Hence, the results of CAROLINA (CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Patients With Type 2 Diabetes) (ClinicalTrials.gov identifier NCT01243424) are highly anticipated. If the results of this trial show superiority of linagliptin to glimepiride, this will influence the choice of second-line drug therapy. A second placebo-controlled trial, CARMELINA (CArdiovascular and Renal Microvascular outcomE Study with LINAgliptin in Patients With Type 2 Diabetes Mellitus at high vascular risk), with linagliptin (ClinicalTrials.gov identifier NCT01897532), is also nearing completion.

CV outcome trials with other GLP-1 RAs and SGLT2i are in progress (Tables 2 and 3), and the results of these trials will influence the place of incretin-based therapies and SGLT2i in the therapeutic algorithm.

### *Evidence About New Combination Therapies*

Our understanding of the pathophysiology of T2DM has progressed from the "triumvirate" (β-cell failure and insulin resistance in liver and muscle) (96) to the "ominous octet" (97). One would expect that combination therapies with drugs that target the underlying pathophysiological abnormalities present in T2DM would produce a more efficacious and durable $HbA_{1c}$ reduction than drugs that do not correct the basic pathophysiological disturbances. A recent study (76) has compared a pathophysiological approach using initial combination therapy with exenatide, which corrects five components of the ominous octet (impaired insulin secretion, excessive glucagon secretion, increased HGP, incretin

resistance, and appetite dysregulation/weight gain), plus pioglitazone, which corrects four components of the ominous octet (insulin resistance in muscle, liver, and adipocytes and progressive β-cell failure), plus metformin, which corrects one component of the ominous octet (excessive HGP) versus the previous ADA/EASD algorithm, which uses the stepwise addition of metformin, then a sulfonylurea (which corrects none of the components of the ominous octet), and then insulin (which represents replacement therapy for a failed β-cell). It should be noted that this stepwise addition of metformin, then sulfonylurea, and then insulin represents the most commonly used approach worldwide, including in the U.S. and Europe. In contrast to the stepwise approach, the pathophysiological approach produced superior $HbA_{1c}$ reduction with markedly less hypoglycemia and weight loss versus weight gain over a 2-year period (76). With respect to the pathophysiological approach, combination therapy with an SGLT2i plus DPP-4i (98,99) and, even better, a GLP-1 RA, has the potential to produce robust reductions in $HbA_{1c}$ and weight loss without causing hypoglycemia and would have a large impact on the clinical decision-making process. Since renal glycosuria due to SGLT2 inhibition is accompanied by a "paradoxical" increase in endogenous glucose production (EGP) (100,101) due to hyperglucagonemia (42), declining insulin level, and other as-of-yet unexplained mechanisms and since incretin-based therapies (especially GLP-1 RAs) inhibit glucagon secretion, increase insulin secretion, and inhibit endogenous (both liver and kidney) production (74), combination therapy with a GLP-1 RA should prevent the increase in EGP due to SGLT2 inhibition. As with other glucose-lowering drugs, the glycemic efficacy of SGLT2i is greater at higher $HbA_{1c}$ levels (102), and this makes them an attractive option for use in patients with poorly controlled T2DM. The efficacy of GLP-1 analogs at reducing glucagon and stimulating insulin secretion is much greater than that of the DPP-4i (30), and whether these effects can overcome the compensatory increase in EGP with SGLT2 inhibition needs to be tested. Another potential advantage of combination SGLT2i/GLP-1 RA therapy is additive weight loss, but this has yet to be demonstrated in a clinical trial.

#### *Renoprotection With SGLT2i*

Hyperfiltration and the intrarenal hemodynamic changes responsible for the hyperfiltration play a central role in the development of diabetic nephropathy (103). The SGLT2i decrease glomerular hyperfiltration (50,104) and have shown promise in preclinical studies in preventing diabetic kidney disease (105,106). Recent data from EMPA-REG OUTCOME suggested significant reductions in the rate of the composite outcome of doubling of serum creatinine, end-stage renal disease, and renal death with empagliflozin treatment (107). CANVAS-R (CANagliflozin cardioVascular Assessment Study: A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus) (ClinicalTrials.gov identifier NCT01989754) is investigating the effect of canagliflozin on the progression of albuminuria and glomerular filtration rate in patients with T2DM ($n$ = 5,700), and CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) (ClinicalTrials.gov identifier NCT02065791) is examining the effect of canagliflozin on renal/CV end points in subjects with diabetes ($n$ = 3,627) with stages 2 and 3 chronic kidney disease. Results are expected in 2017 and 2019, respectively. If these trials yield positive outcomes, the combined advantages of renoprotection, reduced CV events, blood pressure reduction, and weight loss would be a unique feature of this class of drugs and place the SGLT2i at the top of the therapeutic algorithm.

#### *GLP-1 RAs and Preservation of β-Cell Function*

GLP-1 RAs effectively reduce $HbA_{1c}$, promote weight loss, and correct multiple components of the ominous octet (78). An important, and underappreciated, effect of the GLP-1 RAs is their potential to augment insulin secretion in a glucose-dependent fashion and to preserve β-cell function and maintain the reduction in $HbA_{1c}$ on a long-term basis (76). Using state-of-the-art techniques to quantitate the insulin secretion/insulin resistance (disposition) index, Bunck et al. (32) demonstrated normalization/near normalization of insulin secretion for 3 years in metformin-treated patients with T2DM who required additional glycemic control. Further, studies with liraglutide have documented that this beneficial effect on the β-cell can be observed within 8 h (108). If these promising data are confirmed in other studies, the long-term protective effect of the GLP-1 RAs on β-cell function may warrant their future consideration as first-line therapy in patients with T2DM.

## Summary and Conclusions

Incretin-based therapies and SGLT2 inhibitors are relatively new treatments for T2DM but have become well established in clinical use. Because of their attributes (efficacy in reducing $HbA_{1c}$, weight loss, blood pressure reduction, low propensity to cause hypoglycemia, good safety profile, improvement in CV outcomes with empagliflozin, and correction of multiple pathophysiological abnormalities present in T2DM), we believe that these agents should be used early in the natural history of T2DM. Their ultimate place in guidelines will be strongly influenced by the results of ongoing CV and renal outcome trials, novel combination studies, and considerations of comparative efficacy and cost compared with older, "more established," but less effective agents when long-term durability of glycemic control is considered.

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