**Positioning SGLT2 Inhibitors / Incretin Based Therapies in the Treatment Algorithm**

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**Summary**

Sodium glucose co-transporter 2 (SGLT2) inhibitors are the most recent addition to the therapeutic options available for the treatment of type 2 diabetes, and became available after introduction of incretin-based therapies, dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor agonists (GLP-1 RA). 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 T2DM (i.e. improvement in beta cell function and insulin sensitivity). They do, however, have some adverse effects, notably nausea with GLP-1 receptor agonists and genital tract infections and potential for volume depletion with SGLT2 inhibitors. Whether incretin-based therapies are associated with an increased risk of pancreatitis is unclear. Most recently, diabetic ketoacidosis has been reported with SGLT2 inhibitors. 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 to 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 stems from the observation that the effect of oral glucose to stimulate 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 (7-36 amide) (GLP-1); 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 type 2 diabetes. However, near-normalisation of blood glucose levels with insulin therapy has been demonstrated to improve the beta 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 hypoglycaemia when used as monotherapy or in combination with an insulin sensitizer (6; 7). GLP-1 is part of the physiological system signalling 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 type 2 diabetes (12). However, endogenous human GLP-1 has a short half- life (2-3 minutes) due to breakdown in the circulation by protease enzymes, notably dipeptidyl peptidase-4 (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 (GLP1-RA).

***DPP-4 inhibitors (DPP4i)***

Four oral DPP-4i are approved for use in both the United States (US) and the European Union (EU)(Sitagliptin, Saxagliptin, Alogliptin and Linagliptin) (Table 1). Vildagliptin is approved in the EU but not the US. Several other agents of this class are marketed worldwide (for example omaragliptin and trelagliptin are available only in Japan). All five DPP4i appear to have similar efficacy in terms of glucose lowering. An 18 week phase 3b, multi-centre, double-blind trial of saxagliptin vs sitagliptin has demonstrated non-inferiority as add-on therapy to metformin (13). Trelagliptin, a once weekly DPP-4i was studied against alogliptin once daily and has demonstrated non-inferiority in the Japanese population studied (14). Meta-analysis of DPP4i has shown an average HbA1c 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 RA. DPP4i can be used in combination with other oral agents or with basal insulin (17) although the reduction of HbA1c with insulin is modest (18; 19). The DPP4i are weight neutral and have a low risk of hypoglycaemia.

*DPP-4i – adverse effects*

In general, the adverse effect profile of the DPP4i is quite favourable. With the exception of linagliptin, the DPP4i require dose reduction in patients with renal impairment. Some concern has been raised about the risk of pancreatitis and pancreatic cancer, based on pre-clinical studies and reports from post-marketing surveillance studies. However, the current data do not support a likely association (20). The FDA has recently issued a warning about the possibility of joint pain developing during DPP-4 inhibitor treatment, following 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 following 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 the SAVOR trial with saxagliptin (22) but there was no associated increase in mortality. In the EXAMINE trial with alogliptin (23) and in TECOS with sitagliptin (24), the incidence of cardiovascular events was similar to the placebogroup**.**

***GLP-1 receptor agonists***

The GLP-1 RA are either analogues of human GLP-1 with addition of a fatty acid, an immunoglobulin or albumin molecule to cause resistance to DPP-IV degradation (liraglutide, dulaglutide, albiglutide) or those which are based on the exendin molecule (exenatide, lixisenatide). The duration of action of exenatide and lixisenatide range from 6-8 hrs, liraglutide is 24 hours while exenatide QR, 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 HbA1c reduction ranging from -0.8 to -1.5% at approved doses (25-27). They have a low intrinsic risk of causing hypoglycaemia, due to the “glucose-dependence” of their insulin secretory effect. GLP-1 RAs also induce satiety and produce mean weight loss of ~3 kg in clinical trials (28). However, the weight loss can be quite variable with ~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, exert a potent effect to suppress the elevated rates of hepatic glucose production (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 to the DPP4i (25; 30; 33) .

*GLP-1 RA - 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 RA from available randomised controlled trial data, but causality is yet to be proved. (20). Other concerns relate to C-cell thyroid tumours and stem from pre-clinical data from rodents (35) and may not be relevant to humans (36). GLP-1 RAs show a small, but consistent fall in in systolic blood pressure of 2-3 mmHg and a 2-3 beats per minute 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 cardiovascular outcome studies are underway, with the only reported data from the ELIXA trial with lixisenatide (38). This trial, conducted in high risk type 2 diabetic patients, showed a neutral effect on cardiovascular (CV) events.

**SGLT2 inhibitors (SGLT2i): rationale for use and clinical summary**

The SGLT2i class of drugs was developed as a result of research showing that inhibition of renal glucose transport using the non-specific SGLT2/SGLT1 inhibitor, phlorizin, effectively lowered plasma glucose levels and ameliorated glucose toxicity in experimental models of diabetes(39). Under physiologic conditions, the SGLT2 transporter in the renal proximal tubule reabsorbs 80-90% of the 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 alpha 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, 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 HbA1c reduction of 0.6-1% in individual trials, depending on the starting HbA1c. 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 beta cell failure, they are effective in all T2DM individuals as long as the eGFR is greater than 45-60 ml/min per 1.73m2. In addition to their glucose-lowering effects, SGLT2i also produce weight loss of about 2-3 kg, secondary to the 280 – 320 kcal/day that are lost as glucose (70-80g) each day (each gram of glucose = 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 SGLT2 inhibitors is a 4-5 fold 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 DKA with their use (49; 50). This was followed by case reports of DKA in both type 1 and type 2 patients treated with SGLT2 inhibitors (51).The US Food and Drug Administration (FDA) (52) and the European Medicines Agency (EMA) (53) have issued warnings about this potential complication in the context of both type 1 and type 2 diabetes. 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 both T1DM and T2DM patients, 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 PTH (parathyroid hormone) and FGF23 (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-1RAs have been demonstrated to have superior glycemic efficacy as well as beneficial effects on body weight compared to DPP-4 inhibitors. GLP-1 RA have not been compared with SGLT2 as an active comparator in clinical trials.

Empagliflozin 10 and 25 mg were compared with sitagliptin 100 mg (and placebo) in patients with T2DM with HbA1c concentrations of 7.5-10%. The changes in baseline HbA1c 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 were compared against sitagliptin in patients with T2 DM (HbA1c 7-10.5%). Canagliflozin 100 mg demonstrated non-inferiority, while canagliflozin 300 mg demonstrated superiority to sitagliptin in lowering HbA1c (0.88% vs -0.73%) at 52 weeks (60). Canagliflozin also demonstrated reduction in body weight and systolic blood pressure compared to sitagliptin while the incidence of genital mycotic infections, osmotic diuresis related adverse events and hypoglycemic episodes were higher in the canagliflozin treated patients. Canagliflozin 300mg was also compared with sitagliptin 100 mg in T2DM patients inadequately controlled with metformin and sulfonylurea combination demonstrating non-inferiority at 52 weeks and superiority in a subsequent assessment (HbA1c = -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 non-inferiority of canagliflozin 100 mg as well as superiority of canagliflozin 300 mg (HbA1c = -0.12%) (62) and empagliflozin 25 mg (-0.11%) (63) over glimepiride. Similarly, dapagliflozin 10 mg was non-inferior to glipizide at 52 weeks in terms of glycemic efficacy in patients with T2DM uncontrolled on metformin monotherapy (baseline man HbA1c of 7.7%) with advantages of reduction in body weight and less hypoglycemic episodes than glipizide (64). Superiority of dapagliflozin versus glipizide with respect to HbA1c 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-4is, GLP-1 RAs, and SGLT2is fit in current guidelines?**

HbA1c 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 HbA1c 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 cardiovascular events due to aggressive therapy (70; 72). Hence, it is important to have an individualised management approach tailoring therapy to patients’ needs and priorities (73; 74). In this review, we focus mainly on newly diagnosed type 2 diabetic patients 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 amongst 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 NICE guidelines (75) recommend the use of metformin as the initial choice of therapy and a target HbA1c of <6.5% (48mmol/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 SGLT-2i aiming for a glycemic target of <7% (53mmol/mol). For second intensification, triple therapy with metformin, a DPP-4i and sulfonylurea or metformin, pioglitazone and sulfonylurea or metformin, pioglitazone or sulfonylurea and SGLT2-i is recommended. 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 or DPP-4i and sulfonylurea or pioglitazone and sulfonylurea (first intensification). NICE recommends consideration of insulin for second intensification in this metformin intolerant (or those with contraindications) group.

NICE also recommends that GLP1 RAs be considered in T2DM patients with BMI of >35 kg/m2. Consideration should also be given to their use in patients with BMI <35 kg/m2 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 ≥1% (10 mmol/mol) reduction in HbA1c and ≥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 antidiabetic agents, especially when used in combination (76) and correction of the underlying pathophysiologic abnormalities, are not addressed with this approach. The NICE approach also may underestimate the risks of hypoglycaemia 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 HbA1c, have several other advantages such as promotion of weight loss, reduction of blood pressure and a favourable safety profile (with the exception of nausea and vomiting that wanes 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 AACE algorithm support early use of GLP-1 RAs, this may not be the preferred approach for all patients due to high cost and injectable nature of therapy. The NICE guideline was produced too recently to incorporate the beneficial cardiovascular effects in high risk patients demonstrated in the EMPA REG trial (CV outcome data on other SGLT2 inhibitors are awaited). However NICE has considered both clinical and cost-effectiveness as an important consideration while drafting their guidelines and SGLT2i and GLP-1 analogues 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 beta cell failure in T2DM, but other antidiabetic agents, i.e., GLP-1 RAs which enhance insulin secretion, preserve beta 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 HbA1c level.

The ADA/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 the six options (sulfonylureas, pioglitazone, DPP4i, SGLT2i, GLP-1 RAs or basal insulin) based upon physician/patient preferences, while considering the therapeutic efficacy, risk of hypoglycaemia, 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 HbA1c 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. When choosing between addition of a GLP-1 RA and basal insulin, we favour the former for the following reasons: (i) insulin causes weight gain and hypoglycemia, whereas GLP-1 RAs promote weight loss and have minimal propensity to cause hypoglycemia; (ii) 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 favour the former approach when postprandial glycemic control is suboptimal in T2DM patients treated with basal insulin. Most recently, the ADA/EASD guideline has advanced SGLT2 inhibitors to second line agents or as addition to dual oral agent therapy or to insulin-treated T2DM patients. In the latter group, addition of a 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/ACE guidelines (93) recommend initiation of monotherapy with metformin, GLP-1 RA, SGLT2 inhibitors, DPP-4 inhibitors and thiazolidinediones in the corresponding order of hierarchy followed by alpha- glucosidase inhibitors, and sulfonylureas when the HbA1c is <7.5%. These guidelines also recommend initial therapy with dual and triple combinations if the HbA1c is > 7.5% and >9.0% respectively, without symptoms of hyperglycemia. The AACE/ACE comprehensive diabetes management algorithm hence presents a different approach compared to 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 HbA1c is > 7.5% or >9% respectively. The order of preference varies slightly with GLP-1 RA, SGLT2i, DPP4i followed by TZD and basal insulin for dual therapy while for triple therapy DPP4i are moved down after TZD and basal insulin. Third, the AACE/ACE algorithm ranks sulfonylureas lower in the hierarchy due to the propensity to cause adverse effects like hypoglycemia and weight gain.

In all the guidelines, metformin remains the first drug of choice due to its long experience 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 individualised HbA1c 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, cardiovascular risk/benefit, durability of glycemic control, ability to correct known pathophysiologic abnormalities, prevention of progressive beta cell failure, and side effects. While in the NICE and ADA/EASD algorithms the GLP-1 RAs, DPP4i, and SGLT2i are considered to be second (dual) or third (triple) line therapy or to be used in combination with insulin, AACE/ACE guidelines includes these agents as monotherapy options as well as part of initial dual or triple therapy depending upon the starting HbA1c. Because the DPP4i are less efficacious than the GLP-1 RAs and SGLT2i in reducing the HbA1c (25; 30; 33), we favour use of the latter agents.

**Future possibilities - What new evidence might change guideline positioning?**

*Cardiovascular outcome trials*

Because of concern regarding the cardiovascular safety of some antidiabetic drugs (94), the FDA now requires a CV safety trial for all new antidiabetic 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 non-inferiority, 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 (95) . The first four trials showed non-inferiority to placebo. Of great importance, the most recently reported EMPA-REG trial met its cardiovascular outcome (95) for superiority (80% power to detect a 21.8% decrease in CV endpoint). In this trial 7020 patients with established cardiovascular disease were randomised to empagliflozin (10mg or 25mg /day) or placebo added to standard care. There was a statistically significant reduction in the primary composite outcome of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke (10.5% vs 12.1% in the empagliflozin and placebo groups respectively, 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 cardiovascular causes (HR = 0.62; 95% CI = (0.49-0.77), p<0.001), death from any cause (HR = 0.68; 95% CI 0.57-0.82, p<0.001) and hospitalization for heart failure (HR = 0.65; 95% CI 0.5-0.85, p<0.003) over a median observation time of 3.1 years. No significant the difference in rates of non-fatal MI (HR = 0.87, p = 0.23) and non-fatal stroke (HR = 1.4, p = 0.16) were observed with empagliflozin.

The profound effect size and more unexpectedly, the rapid onset of the cardiovascular beneficial effect raises many questions for which answers are not available: (i) What is (are) the mechanisms responsible for the early (within 3 months) and marked reduction in cardiovascular death and hospitalization for heart failure? (ii) Do the cardiovascular benefits represent a class effect? (iii) Can the results be generalized to all diabetic populations, i.e. type 2 diabetic patients with less high risk cardiovascular complications who are earlier 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 cardiovascular death and heart failure hospitalization, it is unlikely that improved glycemic controls plays a significant or any role since: (i) the cardiovascular benefit seen early within three months, (ii) HbA1c is a weak risk factor cardiovascular (61) and the cardiovascular benefits of HbA1c reduction take up to 10 years to be observed (62); (iii) intensive glycemic control in other studies, e.g. ACCORD, ADVANCE, VADT failed to show any benefit on cardiovascular death, although a significant reduction in non-fatal MI was observed in ACCORD (iv) the HbA1c reduction in EMPA-REG was modest (-0.24 to 0.36% at week 206). More likely, the cardiovascular benefits result from the combined hemodynamic effects of empagliflozin to reduced 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, ketoacidosis along with weight loss) in conjunction with the marked reductions in cardiovascular death and heart failure are likely to elevate the SGLT2 inhibitors, particularly empagliflozin, in the treatment algorithm for diabetic patients with established CV disease. If these results are replicated in the ongoing CVOT with dapagliflozin and canagliflozin, SGLT2 inhibitors would merit positioning after, or even before, metformin in T2DM with similar high risk characteristics as these in EMPA-REG. Other important CV outcome trials and their current status are given in the tables 1-3.

An important determining factor for the positioning of the GLP-1 RAs, DPP4i, and SGLT2i in the therapeutic algorithm would be head-to-head CV outcome trials against active comparators. Hence, the results of CAROLINA (Cardiovascular Outcome Study 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, with linagliptin (ClinicalTrials.gov Identifier: NCT01897532) also is nearing completion.

Cardiovascular outcome trials with other GLP-1 RAs and SGLT2i are in progress (Tables 2 & 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 type 2 diabetes has progressed from the TRIUMVIRATE (beta cell failure, 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 HbA1c reduction than drugs that do not correct the basic pathophysiologic disturbances. A recent study (76) has compared a pathophysiologic approach using initial combination therapy with exenatide which corrects 5 components of the Ominous Octet (impaired insulin secretion, excessive glucagon secretion, increased hepatic glucose production, incretin resistance, appetite dysregulation/weight gain) plus pioglitazone which corrects 4 components of the Ominous Octet (insulin resistance in muscle, liver, adipocytes and progressive beta cell failure) plus metformin which corrects one component of the Ominous Octet (excessive HGP) versus the previous ADA/EASD algorithm which employs the stepwise addition of metformin, then a sulfonylurea (corrects none of the components of the Ominous Octet), and then insulin (represents replacement therapy for a failed beta cell). It should be noted that this stepwise addition of metformin, then sulfonylurea, and then insulin represents the most commonly used approach worldwide, including the US and Europe. In contrast to the stepwise approach, the pathophysiologic approach produced superior HbA1c reduction with markedly less hypoglycemia and weight loss versus weight gain over a two year period (76). With respect to the pathophysiologic approach, combination therapy with a SGLT2 inhibitor plus DPP-4i (98; 99) and, even better, a GLP-1 RA, has the potential to produce robust reductions in HbA1c 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 HbA1c levels (102) and this makes them an attractive option for use in poorly controlled T2DM patients. The efficacy of GLP-1 analogues to reduce glucagon and stimulate 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 SGLT2 inhibitors*

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 the EMPA-REG outcomes trial 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). The CANVAS-R trial (Clinicaltrials.gov identifier NCT01989754) is investigating the effect of canagliflozin on the progression of albuminuria and GFR in T2DM patients (n=5700) and the CREDENCE trial (Clinical trials.gov identifier NCT02065791) is examining the effect of canagliflozin on renal/cardiovascular endpoints in diabetic subjects (n=3627) with stage 2 and 3 CKD. 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 Receptor Agonists (GLP-1 RA) and Preservation of Beta Cell Function.* GLP-1 RAs effectively reduce the HbA1c, 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 beta cell function and maintain the reduction in HbA1c 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 T2DM patients who required additional glycemic control. Further, studies with liraglutide have documented that this beneficial effect on the beta cell can be observed within 8 hours (108). If this promising data is confirmed in other studies, the long-term protective effect of the GLP-1 RAs on beta cell function may warrant their future consideration as first line therapy in T2DM patients.

**Summary and Conclusions**

Incretin-based therapies and SLGT2 inhibitors are relatively new treatments for type 2 diabetes, but have become well established in clinical use. Because of their attributes (efficacy in reducing HbA1c, weight loss, blood pressure reduction, low propensity to cause hypoglycemia, good safety profile, improvement in cardiovascular outcomes with empagliflozin, correction of multiple pathophysiologic abnormalities present in T2DM), we believe that these agents should be used early in natural history of T2DM. Their ultimate place in guidelines will be strongly influenced by the results of ongoing cardiovascular and renal outcome trials, novel combination studies and considerations of comparative efficacy and cost compared to older, “more established”, but less effective agents when long-term durability of glycemic control is considered.

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**Table 1- Available DPP4 inhibitors**

|  |  |  |  |
| --- | --- | --- | --- |
| Drug | Dosing | Use in renal impairment | Cardiovascular Outcome Trials  |
| Sitagliptin | 100 mg OD |  | TECOS n=14,671 December 2008-December2014Median follow-up:3 yrsInclusion criteria: Documented vascular disease in coronary, cerebral or peripheral arteriesHbA1c 6.5%-8%, age ≥ 50 yrsPrimary outcome: composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina |
| 50 mg OD | CrCl 30-50 ml/minute |
| 25 mg OD | CrCl <30 ml/minute |
| Saxagliptin | 5 mg OD | Mild impairment CrCl >50 ml/minute | SAVOR-TIMI 53 n=16,492 May2010- May 2013Median follow-up:2.1yrsInclusion criteria: history of established CVD or multiple CV risk factorsHbA1c ≥ 6.5%, age ≥ 40yrsPrimary outcome: composite of CV death, non-fatal MI or non-fatal stroke |
| 2.5 mg OD | Moderate-severe renal impairment CrCl≤50 ml/minute |
| Linagliptin | 5 mg OD | No dose adjustment | CAROLINA (vs glimepiride 1-4 mg OD), n=6000Oct2010-Sep 2018Inclusion criteria: pre-existing CV disease or specified diabetes end-organ damage or ≥70 years or ≥2 specified CV risk factorsHbA1c 6.5%-8.5%, age 40-85 yrsPrimary outcome: Time to first occurrence of the composite endpoint: CV death, non-fatal MI(excluding silent MI),non-fatal stroke and hospitalization for UACARMELINA (vs placebo),n=8300July 2013- Jan 2018Inclusion criteria: High risk of CV events defined by 1)micro or macroalbuminuria and previous macrovascular disease and/or 2) impaired renal function with predefined urine albumin creatinine ratioHbA1c ≥6.5% to ≤ 10%Primary outcome: Time to first occurrence of any of the components of the primary composite endpoint: CV death, non-fatal MI, non-fatal stroke and hospitalization for UA |
| Alogliptin | 25 mg OD | CrCl>50 ml/minute | EXAMINE n=5380Oct 2009-June 2013Median follow-up:1.5 yrsInclusion criteria: Acute coronary syndrome requiring hospitalization within the previous 15-90 daysHbA1c 6.5%=11%, age ≥ 18 yrsPrimary outcome : composite of CV death, non-fatal MI or non-fatal stroke |
| 12.5 mg OD | CrCl≥30 to≤50 ml/minute |
| 6.25 mg OD | CrCl≤30 ml/minute |

 **Table 2- Available GLP-1 analogues**

|  |  |  |  |
| --- | --- | --- | --- |
| Drug | Dosing | Use in renal impairment | Cardiovascular Outcome Trials |
| Exenatide | 10 mcg bd | CrCl 30-50 ml/minute(caution when escalating dose)CrCl<30 ml/minute(avoid) | None |
| Exenatide QR | 2mg weekly | CrCl 30-50 ml/minute(caution)CrCl30ml/minute(avoid) | EXSCEL n=14,000 June 2010-April 2018Inclusion criteria: HbA1c of ≥ 6.5 % and ≤ 10.0% and is on one of1) 0-3 oral antihyperglycemic agents 2) insulin therapy, either alone or in combination with up to two oral agents, Age 18- 130 yrsPrimary outcome: Time to first confirmed CV event in the primary composite of CV death, non-fatal MI or non-fatal stroke |
| Liraglutide | 1.2 mg OD1.8 mg OD | Mild-severe impairmentNo dose adjustmentsUse with caution | LEADER n=9340Aug 2010- Nov 2015Inclusion criteria: ≥50 yrs and concomitant cardiovascular, cerebrovascular or peripheral vascular disease or chronic renal failure or chronic heart failure ; ≥60 yrs and other specified risk factors of vascular diseaseHbA1c ≥ 7%, age ≥ 50 yrsPrimary outcome: Time from randomisation to first occurrence of composite of CV death, non-fatal MI or non-fatal stroke |
| Lixisenatide | 10mcg OD20 mcg OD | eGFR 30-50 ml/min•1.73m2(caution)eGFR<30 ml/min•1.73m2(avoid) | ELIXA n=6000 June 2010-Feb 2015Median follow-up 2 yearsInclusion criteria: patients with spontaneous ACS admitted to acute care facility within 180 days following ACS and prior to screeningHbA1c 5.5-11%, age ≥ 30 yrsPrimary outcome: composite of CV death, non-fatal MI, non-fatal stroke or hospitalization for UA |
| Dulaglutide | 0.75mgweekly1.5mg weekly | No dose adjustmentsCaution during initiation and dose escalation | REWIND n=9622 July 2011-April 2019Inclusion criteria: ≥50 years with established clinical vascular disease, or ≥55 years and subclinical vascular disease or ≥60 years and at least 2 or more cardiovascular risk factorsHbA1c ≤ 9.5%, age ≥ 50 yrsPrimary outcome: Time to first occurrence of CV death, non-fatal MI or non-fatal stroke (composite CV outcome) |
| Albiglutide | 30mg weekly50mg weekly | No dose adjustmentsCaution during initiation and dose escalation | none |

 **Table 3- Available SGLT2 inhibitors**

|  |  |  |  |
| --- | --- | --- | --- |
| Drug | Dosing | Use in renal impairment | Cardiovascular Outcome Trial  |
| Canagliflozin | 100 mg OD300 mg OD | eGFR<30mlmin•1.73m2(avoid)eGFR45-60 ml/min/1.73m2(use 100 mg dose)eGFR30-45 (initial use not recommended & discontinue when eGFR <45 on patients who are already on Cana) | CANVAS n=4411Dec 2009- April 2017Inclusion criteria: history of or high risk for CV disease (≥ 2 CV risk factors)HbA1c 7%-10.5%, age ≥ 30 yrsPrimary outcome: MACE, including CV death, non-fatal MI and non-fatal stroke |
| Dapagliglozin | 5 mg OD10 mg OD | eGFR>60 ml/min•1.73m2(no dose adjustment)eGFR<60 ml/min•1.73m2(initial use not recommended & discontinue when eGFR <60 on patients who are already on dapagliflozin)eGFR<30 ml/min•1.73m2(contraindicated) | DECLARE-TIMI58 n=17,150April 2013-April 2019Inclusion criteria: high risk for CV events with type 2 diabetesAge 40-130 yearsPrimary outcome: Time to first event included in the composite of CV death, MI or ischemic stroke |
| Empagliflozin | 10 mg OD25 mg OD | eGFR≥45 ml/min•1.73m2(no dose adjustment) eGFR<45 mlmin•1.73m2(initial use not recommended & discontinue when eGFR <45 on patients who are already on empagliflozin)eGFR<30 ml/min•1.73m2(contraindicated) | EMPA-REG n=7034Median follow-up 3.1 yearsJuly 2010-April 2015Inclusion criteria: high CV riskHbA1c 7%-10%, age ≥ 18 yrsPrimary outcome: composite of CV death, non-fatal MI or non-fatal stroke |

TECOS: The trial to Evaluate Cardiovascular Outcomes after treatment with Sitagliptin; SAVOR-TIMI 53: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus; EXAMINE: EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome; CAROLINA: CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes; CARMELINA: Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus

EXSCEL: EXenatide Study of Cardiovascular Event Lowering Trial; LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results; ELIXA: Evaluation of cardiovascular outcomes in patients with type 2 diabetes after acute coronary syndrome during treatment with LIXisenatide; REWIND: Researching cardiovascular Events with a Weekly Incretin in Diabetes

CANVAS: CANagliflozin cardioVascular Assessment Study; DECLARE-TIMI58: Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; EMPA-REG : Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients

CV: cardiovascular; MACE: major cardiac adverse events; MI: Myocardial Infarction; UA: Unstable Angina