

# The use of SGL T2 inhibitors and GLP-I receptor agonists, a worthwhile physiologic combination in managing type 2 diabetes while reducing cardiovascular risk

## Abstract

The management of type 2 diabetes has become increasingly challenging where management decision choices should be focusing on reducing hypoglycemia while reducing end organ effects, particularly cardiovascular disease, nonalcoholic fatty liver disease, and diabetes related nephropathy. Intensification of diabetes management should be exercised every 3 months according to most published consensus statements; however, hemoglobin A1c targets need to be individualized based on existing comorbidities and age. The recent revision of the consensus statement of the American diabetes Association, as well as the American Association of Clinical Endocrinologists diabetes management algorithm still advocates metformin as initial monotherapy as adjunct to diet and exercise. Options for intensification should be based on cardiovascular risk, need for weight loss, need to avoid hypoglycemia, and in those circumstances where cost may be an issue. During the development program of most of these newer agents, certain combinations have been studied including the GLP-1 receptor agonists and the SGL T2 inhibitors which seem to provide an additive benefit in curtailing the challenge of glycemic control while mitigating cardiovascular risk.

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## Core defects of hyperglycemia

Type 2 diabetes is a disorder of progressive beta cell failure. Additional therapeutic interventions will likely need to be added during the lifetime of the diabetic. Factors that can contribute toward the progressive nature of loss of glycemic control include genetics, the contribution of weight towards insulin resistance, hypertension, dyslipidemia, all of which can contribute to impaired glucose tolerance and subsequent development of overt diabetes.<sup>1</sup>

In 2009, Dr. Ralph DeFronzo elaborated further upon the triumvirate of diabetes by describing the Ominous Octet or 8 core defects responsible for hyperglycemia. In addition to impaired beta cell insulin secretion due to the progressive nature of beta cell failure, and target insulin resistance with diminished glucose uptake, there is hepatic glucose production in excess, partly driven by the alpha cell with glucagon dysregulation; the fat cell and lipoprotein toxicity where free fatty acids impair insulin secretion; the brain, in which 2 areas in particular have been described, those being the ventral medial nucleus, and the upper posterior hypothalamus where the paraventricular nuclei are located. These centers are responsible for appetite regulation with the magnitude of the inhibitory response following glucose ingestion being reduced in obese, insulin resistant individuals. It is suggested that central dopamine release is also inherently responsible for first phase insulin secretion from the beta cell. The kidney has also been described as a core defect of type 2 diabetes where there is pathologic up regulation of the SGL T2 receptor and the GLUT-2 co-transporter. Finally, there is the incretin effect/ incretin hormones, in which the magnitude of beta cell responsiveness of insulin secretion is significantly greater in those challenged with an oral glucose load relative to an IV glucose load. This difference and

insulin secretion is driven by the incretin hormones that include GLP-1, as well as GIP (glucose insulinotropic polypeptide), where these hormones have a half-life of approximately 2-1/2 minutes because of the ubiquitous enzyme dipeptidyl peptidase 4 (DPP-IV).<sup>2</sup> It has been repeatedly demonstrated that beta cell responsiveness greatly improves with supraphysiologic or pharmacologic doses of GLP-1 that are resistant to the effect of DPP-IV. There have been other core defects described in publications of recent however the additional described core defects and their contribution towards hyperglycemia have yet to be justified.

## Where GLP-I receptor agonists and SGL T2 receptor blockers are effective in these core defects

Glucocentric treatments have been implemented traditionally, first through the use of insulin at the turn of the 20<sup>th</sup> century, and then with the development and availability of insulin secretagogues, which stimulates insulin secretion from the beta cell independent of the blood glucose levels. The role of metformin as a sensitizer and reducer of hepatic glucose output was recognized and has been implemented successfully thereafter. Other agents have become available that improve insulin sensitivity at the level of the skeletal muscle, as well as having an effect on lipid metabolism (thiazolidinediones). The GLP-1 receptor agonists have been designed to be resistant to the effect of DPP-IV. They have an effect on the beta cell by inducing glucose mediated insulin secretion, leading to postprandial glycemic control that is magnified with the short acting GLP-1 receptor agonists, as well as having a suppressive effect on glucagon secretion from the alpha cell, particularly the long-acting GLP-1 receptor agonists, thus exerting an effect on hepatic glucose output which can translate into significant improvement in fasting plasma

glucose.<sup>3</sup> Furthermore, GLP-1 has an effect on gastric emptying that is usually self-limited and depending on the size of the molecule, can penetrate the blood brain barrier exerting an effect on energy intake facilitating a beneficial effect on weight.<sup>4,5</sup> Inhibition of the enzyme DPP -IV may allow endogenously produced GLP-1 to remain longer than the 2-1/2 minute half-life, however, we've come to learn from physiologic studies that beta cell responsiveness in type 2 diabetes is more robust when pharmacologic or supraphysiologic levels of GLP-1 are provided exogenously.

The SGL T2 inhibitors exert their effect through inhibition of glucose reabsorption via the SGL T2 receptor where 90% of glucose is reabsorbed, as well as the SGL T-1 receptor, which is not as plentifully distributed in the nephron but rather, in the GI tract. This is where the remaining 10% is absorbed. Unfortunately, sole SGL T1 inhibition is not as useful a target due to reported GI intolerance.<sup>6</sup> It has been demonstrated that significant reduction in circulating glucose burden may have a beneficial effect on beta cell function and beta cell sparing.<sup>7,8</sup>

### Review of cardiovascular outcomes studies of both SGL T2 receptor inhibitors and GLP-1 receptor agonists

In 2008, the United States FDA provided guidance requesting that all antidiabetic agents in development undergo cardiovascular

risk assessment designated clinical trials with the focus on higher risk populations of patients with established cardiovascular disease. Of those intensively studied were the DPP-IV inhibitors, SGL T-2 receptor blockers, as well as GLP-1 receptor agonists. Significant benefit was noted in the majority of these agents demonstrating either safety in those at increased risk of cardiovascular events or benefit, either in the form of reduced heart failure hospitalizations or overall cardiovascular mortality. It is important for the reviewer to take into consideration that while the endpoints may have been similar in most of these trials, study designs were not.

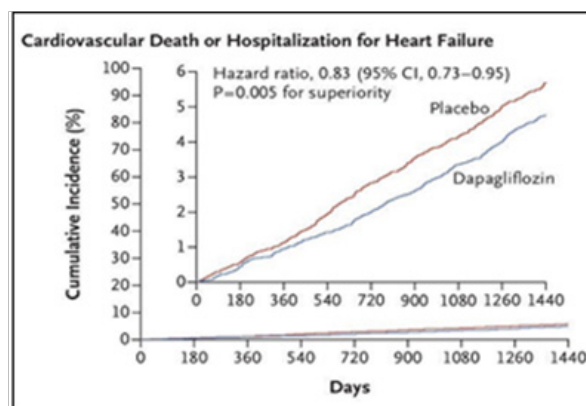
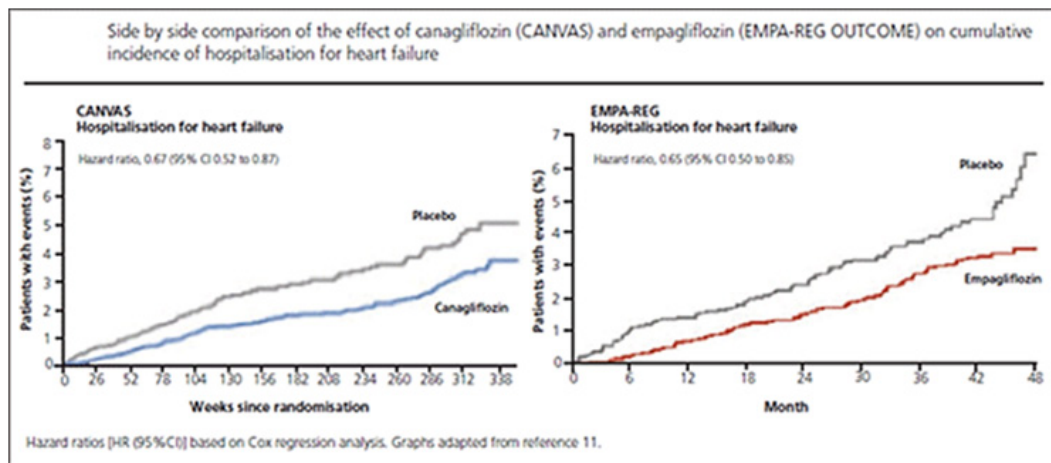
Most notable in the GLP-1 receptor agonist trials included studies for the exendin 4-based molecule exenatide via continuous delivery utilizing an implantable bio pump, which is currently under FDA review, exenatide LAR, dosed once weekly, lixisenatide, a short acting GLP-1 agonist dosed once daily, and the GLP-1 analogs, which include once daily liraglutide, once weekly albiglutide, once weekly dulaglutide, and once weekly semaglutide. Injectable semaglutide was reviewed in a smaller preapproval cardiovascular study, as well as the once daily *oral* version of the same molecule in a separate similarly designed smaller preapproval study. The populations involved in these trials varied with respect to cardiovascular risk and most of the studies, at the very least, demonstrated noninferiority or reduction in major adverse cardiovascular events as depicted in the figure below, with their respective hazard ratios and confidence intervals.

TRIAL	MACE	CV DEATH	NON-FATAL MI	NON-FATAL STROKE	Subjects with Established CVD	OBSERVATIONS
LEADER <sup>23</sup> 9340 patients	0.87 (0.378,0.97) p=0.010	.78 (0.66,0.93) p=0.007	0.88(0.75,1.03) p=0.007	0.89 (0.72,1.11) p=0.30	~81%	3 pt. MACE driven by sig. ↓CV death
ELIXA <sup>9</sup> 6068 patients	1.02 (0.89,1.17) p=NS 4-point MACE	0.98(0.78,1.22)	1.03(0.87,1.22)	1.12(0.79,1.58)	100%	NA
EXSCEL <sup>10</sup> 14752 patients	0.91(0.83,1.0) p=0.06 NS	0.88(0.76,1.02)	0.97(0.85,1.10)	0.85(0.70,1.03)	~73%	Barely missed sig. by .01
HARMONY <sup>11</sup> 9463 patients	0.78(0.68,0.90)	0.93(0.73,1.19) p=0.57	0.75(0.61,0.90) p=0.003	0.86(0.66,1.14) p=0.300	100%	3 pt. MACE driven by sig. ↓Fatal and Non-Fatal MI
SUSTAIN 6 <sup>12</sup> 3297 patients	0.74(0.58,0.95) p<0.0001 non inferior	0.98(0.65,1.48) p=0.92	0.74(0.51,1.08) p=0.12	0.61(0.38,0.99) p=0.04	~83%	3 pt. MACE driven by sig. ↓ non-fatal CVA
REWIND <sup>14</sup> 9901 patients	0.88(0.79,0.99) p=0.026	0.91(0.78,1.06) p=0.21	0.96(0.79,1.16) p=0.65	0.76(0.61,0.95) p=0.017	~31%	3 pt. MACE driven by sig. ↓ non-fatal CVA
PIONEER 6 <sup>13</sup> 3183 patients	0.79	0.49 p=0.03	1.18 p=NS	0.74 p=NS	~85%	3 pt MACE driven by sig. ↓CV death

There has been some interest on the basis of observed trial results where EXENDIN 4-based GLP-1 receptor agonist molecules demonstrated non-inferior results for cardiovascular benefit where as those GLP-1 preparations that were analogs of endogenous GLP-1 demonstrating consistent benefit. Perhaps more research may need to be conducted to determine whether or not metabolic byproducts of these molecules following cleavage by either DPP-IV or NEP(neprolysin) may offer an anti-inflammatory effect or other reason for the observed benefit. In vivo studies using rodent models demonstrated cardio- protection when GLP-1 (28-36) amide, a byproduct of NEP metabolism of native GLP-1, was infused for 30minutes with recovery of left ventricular pressures and reduced infarct size following ischemic injury.<sup>8</sup> Nonetheless, the studied GLP-

1 agonists that were EXENDIN 4 based are all short acting agents with the exception of exenatide LAR dosed once weekly. In that particular trial, there was a particularly low risk population of patients and a high dropout rate, which ultimately affected the hazard ratio and calculation of statistical significance unfavorably.

The SGL T2 inhibitor works at the proximal convoluted tubule and offers a thiazide-like diuretic property and notable for decreased hospitalization due to congestive heart failure in the dedicated cardiovascular outcomes studies involving empagliflozin, canagliflozin, and dapagliflozin. Impressively noted was the rapidity in the reduction of heart failure hospitalizations during these clinical trials as demonstrated in the Kaplan Meyer curve below:



The cardiovascular outcomes study for ertugliflozin is still in progress but am confident that due to a similar mechanism of action of the currently completed cardiovascular outcomes studies involving the SGL T2 class, that a reduction in heart failure may also be noted.

End organ damage is also of importance when selecting appropriate therapies for managing diabetes. In the LEADER trial, there was a demonstrated 22% reduction in progression of nephropathy related events that was largely driven by reduction in new onset persistent macroalbuminuria, while there was a 36% reduction noted in SUSTAIN 6, using semaglutide, in new or worsening nephropathy.<sup>23-25</sup> Fatty liver and nonalcoholic steatohepatitis are also emerging health concerns in most of the patients we care for. While the body of evidence is starting to mount, it appears that there seems to be a consistent benefit of the

GLP-1 class in terms of reducing steatosis, not just in the liver but possibly in the kidney as well.

The urinary SGL T2 inhibitors have also been studied extensively with respect to cardiovascular outcomes, as well as end organ effect, particularly with preservation of renal function. Again, most of the studies all vary in terms of design, as well as percentage of individuals with established cardiac disease enrolled in their respective studies. Based on these study designs, and as depicted in the figure below, noninferiority was at least achieved in all of these studies, with the vast majority demonstrating reduction in major adverse cardiovascular events that satisfied statistical significance as well as notable reduction in the progression of nephropathy or further diminution of glomerular filtration.

TRIAL	MACE	CV DEATH	NON-FATAL MI	NON-FATAL STROKE	CHF hospitalization
EMPA REG <sup>15</sup> 7020 patients	0.86 (0.74,0.99) p=0.04	0.62 (0.49,0.77) p= <0.001	0.87 (0.70,1.09) p=0.23	1.24 (0.92,1.67) p=0.16	0.65 (0.50,0.85) p=0.002
CANVAS/CANVAS R <sup>16</sup> 10142 patients	0.86 (0.75,0.97) p<0.001 for non inferiority, p= 0.02 for superiority	0.87 (0.72,1.06) p=NS	0.85 (0.69,1.05) p=NS	0.90 (0.71,1.15) p=NS	0.67 (0.52,0.87)
DECLARE <sup>17</sup> 17160 patients	0.93 (0.84,1.03) p=0.17	0.98 (0.82,1.17) p=NS	0.89 (0.77,1.01) p=ns	1.01 (0.84,1.21) p= NS	0.73 (.61,0.88)
VERTIS CV <sup>19</sup> 8237 patients	in progress-expected results in 2019				



The exact mechanism as to why significant cardiovascular benefit was noted in these agents remains in question, but proposed theories include reduction in blood pressure, reduction in body weight, reduction in arterial stiffness, possible augmentation of myocardial function, diminution of oxygen demand, lack of sympathetic nerve activation, reduction in oxidative stress, increased glucagon secretion, reduction in circulating uric acid, effect on magnesium levels both intra- and extracellularly as well as increased levels of beta hydroxybutyrate, which is the main energy source utilized in myocardial contractility.<sup>26</sup> There has been a tremendous amount of interest in the delay of progression of renal insufficiency in type 2 diabetic patients using SGLT2 receptor antagonist therapies that is noteworthy to mention. This preservation of renal function was noted in the EMPA-REG study, CANVAS-R study as well as a dedicated study looking at renal function involving the use of canagliflozin, the CREDENCE trial, which was stopped early on the basis of significant demonstrated benefit in those in the canagliflozin group. The exact mechanism is not very well understood, but appears to perhaps be related to reduction in inflammatory markers, such as TNFR1, IL-6, MMP7 and FN1. These very markers have also been suggestive of contributing towards development of intrarenal fibrosis.<sup>27</sup>

### Review of published studies utilizing these 2 classes of agents in combination

Since the utilization of GLP-1 receptor agonists and SGL T2 receptor blockers have increased significantly over recent years, clinical trials have been concluded and reported using these classes of agents in combination either as add-on therapy to existing GLP-1 receptor agonists, or add-on therapy to SGL T2 receptor blockers.

In the DURATION 8 trial, 693 subjects enrolled with background of metformin therapy would then be randomized in a double-blind fashion 1:1:1 to receive exenatide once weekly at a dose of 2mg and dapagliflozin 10mg daily, exenatide LAR with dapagliflozin matched oral placebo, and a third group with dapagliflozin and an exenatide LAR matched placebo injection. A1c reduction was noted to be 2% when dapagliflozin 10mg was added to exenatide LAR. Exenatide LAR with the dapagliflozin placebo resulted in a reduction in HBA1C of 1.6%, and the addition of dapagliflozin to exenatide LAR placebo resulted in a reduction of 1.4%. Weight benefit was also significantly noted where the dapagliflozin placebo add-on to exenatide once weekly experienced a reduction of 1.5kg, the addition of dapagliflozin to placebo exenatide experiencing a 1.4 kg reduction and dapagliflozin as add-on therapy to exenatide once weekly demonstrating a 3.4kg reduction. There was no hypoglycemia reported in this clinical trial.<sup>28</sup>

Dulaglutide at a dose of 0.75mg or 1.5mg weekly versus placebo was studied in combination with either of the currently approved urinary SGL T2 inhibitor agents at the time of the trial that included canagliflozin, dapagliflozin, or empagliflozin. The addition of dulaglutide at a dose of 0.75mg to SGL T2 inhibitors resulted in a 1.2% reduction in hemoglobin A1c and the addition of dulaglutide 1.5mg once weekly as add-on to urinary SGL T2 inhibitor resulted in a 1.3% reduction in hemoglobin A1c while placebo added onto the SGL T2 inhibitor class resulted in a 0.5% reduction in hemoglobin A1c. The weight differences were also noted to be a reduction of 2.1kg in the placebo group added on to SGL T2 inhibitor, a reduction of 2.6kg in those in which Dulaglutide 0.75mg once weekly was added on to SGL T2 inhibitors and reduction of 3.1kg in the Dulaglutide 1.5mg per week dose. Hypoglycemia was reported as 4% of the dulaglutide treatment group versus 3% in the placebo group. The hypoglycemia

differences were not statistically significant.<sup>29</sup>

Once weekly semaglutide was also studied as add-on therapy to SGL T2 inhibitor in a double blinded parallel grouped fashion. Other agents that were utilized as background therapy in this clinical trial included sulfonylureas, which were not included in the other combination therapy studies utilizing dulaglutide and exenatide LAR. Patients in the semaglutide group underwent a titration schedule according to the FDA approved product label for semaglutide every 4 weeks until a dose of 1 mg weekly was achieved. In those treated with semaglutide, the reduction in hemoglobin A1c was 1.42% with a reduction in body weight of 3.81kg. Rates of hypoglycemia reported were low albeit sulfonylureas were included in this clinical trial. Diabetic retinopathy was also reviewed in this clinical trial. The semaglutide treated group had fewer patients with a history of diabetic retinopathy relative to the placebo group and most had non-proliferative disease. Events related to diabetic retinopathy were reported in 3 patients in the semaglutide group and 8 patients in the placebo group, which was mild in severity and all were reported as non-proliferative.<sup>30</sup>

### Potential additive benefit of both of these agents in terms of mitigating cardiovascular risk

While these agents are reasonably easy to use, significant reductions in cardiovascular risk has been demonstrated across these numerous trials albeit study designs were different in all of these groups. The question is raised as to whether or not perhaps there may be an additive benefit by using 2 drugs that have been demonstrated independently to reduce cardiovascular risk. At this time, there are no published outcomes data looking at cardiovascular safety with these combinations other than the published studies in the previous section which were not powered with a high-risk cardiovascular population designed to assess cardiovascular safety. Nonetheless, it is an interesting question if combination therapy were to have an added benefit on reducing cardiovascular risk. At the very least, they seem to have a demonstrated additive benefit on weight reduction, as well as efficacy with minimal risk of hypoglycemia unless a sulfonylurea or insulin is being concomitantly utilized. While this combination demonstrates significant benefits that include weight, systolic blood pressure reduction, effect on lipids, reduction in markers of inflammation, preservation of renal function with demonstrated cardiovascular safety or cardiovascular risk reduction, this combination of agents could safely be utilized in any diabetic patient requiring more intensive control *regardless* of preexistent cardiovascular risk.

### Future direction of these combinations

#### Use in type I diabetics

There is been several clinical trials looking at GLP-1 receptor agonists as well as SGL T2 inhibitors in patients with type 1 diabetes over the recent years. The GLP-1 receptor agonist class of agents, while has been demonstrated to minimize weight gain in patients with type 1 diabetes on full physiologic replacement, has not received a label update for use in this group. Use of such agents would be considered off label, and while different GLP-1 receptor agonists have been studied, the largest body of evidence is with liraglutide.<sup>31</sup>

The urinary SGL T2 inhibitors have also been studied in type I diabetic population receiving full physiologic replacement. There is increasing body of evidence demonstrating significant usefulness in

terms of efficacy while mitigating associated weight gain with intensive insulin therapy. In Europe, dapagliflozin has gained the indication for concomitant use in the type I diabetic population. However, one needs to be wary of the possible development of diabetic ketoacidosis if the basal insulin being utilized is unable to meet the metabolic needs of the patient over the full 24 hours.<sup>32,33</sup>

In terms of the selection of either of these agents in the type I diabetic population, our opinion would likely be guided on minimizing potential complications that may be life threatening, such as ketoacidosis, which would may be less likely to occur in patients using the newer, long-acting basal insulin therapies, demonstrating 36-42 hours of duration with no stacking and lower hypoglycemic events relative to the first generation of basal insulin analogs. As a result, we would favor using the GLP-1 receptor agonist in the type I diabetic population.

### Hypoglycemia and weight benefit

Intensive management of patients with type 2 diabetes carries the risk of weight gain and increased risk of hypoglycemia, as has been demonstrated in numerous large-scale clinical trials, most notably the United Kingdom Prospective Diabetes Study and the ADOPT trial. The newer available therapies carry a reduced risk of hypoglycemia working through a glucose mediated insulin secretory response from the beta cell, those being the incretin-based therapies, or through urinary elimination of glucose via blockade of the SGL T2 receptor. Therefore, the risk of hypoglycemia with the use of these 2 classes of agents would be significantly lower unless used concomitantly with a sulfonylurea, which would mediated insulin secretion from the beta cell independent of the blood glucose or the currently available various insulin preparations. While the GLP-1 receptor agonist class has been associated with weight benefit in most patients, largely driven via central appetite suppression, the SGL T2 receptor agonists are also associated with weight loss largely driven by elimination of glucose through the urinary tubules. That being the case, each of these agents independently are associated with weight loss but even more so when used in combination establishing an interesting premise with respect to some of these expected challenges in intensive glycemic management. There are currently clinical trials in progress looking at these combinations specifically in the obesity management sector that are yet to report.

### Oral GLP-1, Co-agonist and Tri agonist agents in development

GLP-1 exists as a peptide hormone and unfortunately, succumbs to the fate of digestive enzymes which render these molecules traditionally difficult to take as an oral formulation. However, newer research and developments have enabled peptide hormones, particularly GLP-1, to be coupled with small molecule substrates functioning as a carrier allowing these peptide hormones to be taken orally. Semaglutide has completed six phase3a studies that have demonstrated significant efficacy and weight benefit as one would expect with an injectable version of GLP-1. These studies included a pre-approval cardiovascular safety study in which its primary objective of noninferiority was achieved. Secondary analysis demonstrated a 51% reduction in major adverse cardiovascular events utilizing this oral version of semaglutide. OWL833 is another oral non-peptide GLP-1 receptor agonist that is currently under evaluation. Additional research being conducted based on the understanding of the incretin affect and incretin peptide hormones has resulted in the development of new compounds that include the use of GLP-1 and

GIP in combination,<sup>34</sup> GLP-1 and glucagon in combination,<sup>35</sup> or the use of GLP-1, GIP, and glucagon as a single agent product.<sup>36</sup> Through a better mechanistic understanding, there is notable efficacy concerning hemoglobin A1c reduction and benefits on weight. In the years to come, available incretin products are likely to vary greatly, with its continued beneficial effect on efficacy, weight and cardiovascular risk.

### Limitations-access and finances

While these agents may be costly based on variability of insurance coverage and access, it appears that the weight benefits, coupled with cardiovascular risk reduction makes this a highly desirable combination, which in the long run may offer significant savings on the health system as a whole by reducing cardiovascular events, and in the case with the SGLT2 inhibitors, reduction in heart failure admissions. Worthwhile mentioning were data from the CREDENCE trial which explored the use of canagliflozin at a dose of 100mg daily versus placebo in this double-blind randomized trial where type II diabetic patient with chronic kidney disease with a GFR between 30-90 with documented albuminuria on background renin-angiotensin system blockade.<sup>18</sup> The study's independent data monitoring committee for this phase 3 clinical trial discontinued the trial early on the basis of favorable chronic kidney disease outcomes in those that were treated with canagliflozin on the basis of achieving the pre-specified criteria for the primary composite endpoint of end-stage renal disease, doubling of serum creatinine, and renal or cardiovascular death when used in combination with standard of care. Such a benefit on renal function was also noted in the EMPA REG study during the post HOC analysis review. There was a slight decline in GFR noted with dapagliflozin in the DERIVE study, which involved CKD3a patients which returned back to baseline at the conclusion of the study, suggesting that this agent in particular is not harmful to renal function.<sup>37</sup> The LEADER trial and SUSTAIN 6 also demonstrated favorable effects on renal function in those enrolled in study drug cohort. It is still poorly understood as to why these 2 classes of agents demonstrated favorable effect on renal function and very likely, additional studies looking at the mechanism of nephroprotection may be underway.

With these agents, the reduction in hypoglycemia risk is most certain unless treatment being rendered includes a sulfonylurea or insulin. In the more recent years, formulary changes have made these agents more accessible, with anticipated continued improvements in coverage. For those who would truly benefit from these agents and still may be challenged financially, the respective manufacturing companies may offer savings programs for those particular individuals through direct contact.

### Conclusion

The management of type 2 diabetes has become increasingly complex with the availability of many different agents for glucose lowering currently available, all with their specific benefits and caveats. The advent of the need for demonstration of cardiovascular safety has resulted in numerous clinical trials published involving incretin-based therapies and the SGLT2 inhibitors. While currently approved DPP-IV inhibitors have demonstrated cardiovascular neutrality or a heart failure signal in select agents, the GLP-1 receptor agonists have at the very least demonstrated no increased cardiovascular risk to at most reduction in major adverse cardiovascular events, as has the urinary SGL T2 inhibitors. The combination of GLP-1 receptor agonists and SGL T2 inhibitors may have an additive effect on addressing the core defects responsible for hyperglycemia and have demonstrated significant efficacy when used in combination with tremendous

weight benefit. However, it still is unclear if there may be additive cardiovascular risk reduction. The availability in the years to come of GLP-1 in an oral form make further stimulate use of this peptide hormone in the diabetic community because of its multiple attributes and may pave the way for future availability of combination oral agents that might include both GLP-1, SGL T2, as well as a possible triple pill with the 2 aforementioned agents in combination with metformin. This novel combination of agents is an attractive method of intensification for those not at target while practicing lifestyle intervention and background metformin therapy, with mitigation of cardiovascular risk.

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## Authorship

All named authors meet the International Committee of Medical General Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published

## Disclosures

Dr. Javier Morales is on the speakers Bureau of Novo-Nordisk, Eli Lilly and company, Boehringer Ingelheim, Janssen pharmaceuticals, Mylan pharmaceuticals, and Abbott Laboratories, and serves as consultant, as well as having participated in advisory board meetings for the above-named entities.

Dr. Mercedes Assumpcao-Morales has nothing to disclose

## Compliance with ethics guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the offers of this publication.

## Conflicts of interest

Author declares there are no conflicts of interest towards the article.

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