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CLINICAL PRACTICE UPDATE IN
ENDOCRINOLOGY & DIABETES

Injectable Medications:
Promising Combinations to Ease the Discussion

The next class of combination therapies in T2D will mix basal insulin and GLP-1 into a single injection. Two products will likely become available in Canada in 2018, **iGlarLixi (Soliqua™) and iDegLira (Xultophy™)**. Both are titratable fixed-ratio combinations of insulin glargine plus lixisenatide, and insulin degludec plus liraglutide, respectively. The efficacy and safety of both products have been studied in their individual phase 3 clinical trial programs.

LixiLan (iGlarLixi)'s phase 3 clinical trial program evaluated participants with T2D using basal insulin and metformin and showed a greater HbA1c benefit for iGlarLixi compared with iGlar (–1.1% vs. –0.6%, p<0.0001) in 736 participants over 30 weeks, reaching a mean final HbA1c of 6.9% compared with 7.5%, respectively. Importantly, mean body weight decreased by 0.7 kg with iGlarLixi and increased by 0.7 kg with iGlar (1.4 kg difference, p<0.0001). Documented symptomatic hypoglycemia (≤3.9 mmol/L) was low and comparable between both groups, which had been titrated to fasting plasma glucose <5.6 mmol/L up to a maximum dose of 60 units/day.

A more recent trial, evaluating the efficacy and safety of iDegLira vs. basal-bolus therapy in participants with T2D (DUAL VII), shifted the traditional paradigm of treatment escalation after basal insulin. A single injection of iDegLira was compared to 4 daily injections of a basal-bolus insulin approach (iGlar-100 and iAsp) and similarly showed reduced HbA1C at 26 weeks, equal in both groups but with lower hypoglycemia rates (1.07 vs. 8.17), weight loss instead of weight gain (-0.93kg vs. +2.64kg), and needing less than half the units of insulin (40U vs. 84U).

iDegLira (Xultophy™) and iGlarLixi (Soliqua™) are not yet approved in Canada, but we can still apply the principles of the these trials to the individual components pending their eventual release. Not surprisingly, achieving adequate glycemic control

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while sparing insulin use appears to have a distinct advantage in reducing hypoglycemic events and weight gain. Thus, the combination of GLP-1 and basal insulin appears to be superior when compared to insulin alone. It has also been shown to be safe, effective, convenient and flexible, and eventually may likely become the generally accepted standard when we initiate basal insulin for our patients.

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GLP-1 Receptor Agonists:
Latest Perspectives

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Because type 2 diabetes (T2D) is a progressive disease, most of our patients eventually require medication to maintain adequate glycemic control and prevent diabetes-related complications. Patients are often initially treated with oral medications, and we usually reserve insulin for later in the disease course, often against significant patient resistance due to fear of injections, potential weight gain, risk of hypoglycemia, and associated stigma. However, we all face an ongoing need to adopt an earlier and more aggressive treatment paradigm that reduces overall disease burden long-term.

A relatively new class of injectable agents, the glucagon-like peptide-1 receptor agonist (GLP-1) is an approved treatment for T2D. In Canada, we have several approved human GLP-1 analogues (dulaglutide, liraglutide, albiglutide and semaglutide) and exendin-based therapies (exenatide, exenatide LAR and lixisenatide). Thus far, the GLP-1 class has shown benefit over DPP-4 inhibitors in efficacy and weight reduction, and has seen superior cardiovascular (CV) outcome trial results. Comparable and head-to-head trials have shown more favourable results with the first group, the human GLP-1 analogue group.

Although we still tend to reserve GLP-1 therapies for until later in the disease course, these CV benefits, plus their demonstrated A1C reductions of 0.7-1.5%, with only rare hypoglycemia, and with a weight loss benefit of 2.6-6.1kg over 52-56 weeks in phase 3 trials, must now press us to consider this class earlier. The collection of these latter 3 benefits has been coined the "composite index" in Canada, and should be an important goal for most of our overweight patients.

Additionally, the recently released 2018 Diabetes Canada Clinical Practice Guidelines advises us to prioritize antihyperglycemic agents with demonstrated CV benefit for patients with established CV disease, and subsequently to consider the avoidance of hypoglycemia and/or weight gain before other clinical considerations.

The advent of weekly dosing in newer GLP-1 arrivals has significantly facilitated the challenging discussion with patients who may be fearful of injections and reluctant to add to their medication burden. We explore the recent impact of some of these agents, landmark trials, and their relevance in today's practice.

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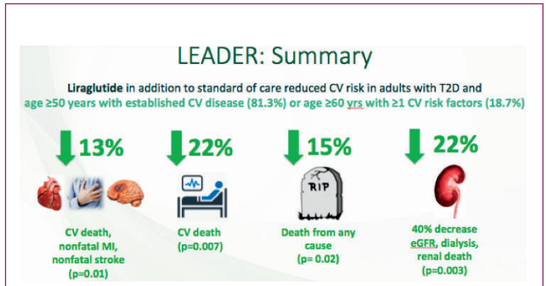
Liraglutide

Liraglutide (Victoza™) is a once-daily GLP-1 approved in Canada in 2010. The LEADER trial randomized 9340 participants with T2D, (>50 years old with CVD or >60 years old with >1 CV risk factor) to liraglutide 1.8mg daily or placebo. The primary outcome of major adverse CV events (MACE) was reduced in the liraglutide group compared to the placebo group (13.0% vs 14.9%; hazard ratio 0.87; p=0.01). The reduction in the primary endpoint was driven mainly by a 22% relative risk reduction (p<0.007) in CV death (Figure 1). **Diabetes Canada has now updated their recommended pharmacotherapy algorithm for the management of T2D, suggesting that in patients with clinical CVD who are not achieving glycemic targets, the priority should be the addition of an antihyperglycemic agent with a demonstrated CV outcome benefit.**

> "… strongly support the use of Liraglutide in T2D patients with both CV and/or renal disease."

> "The primary MACE outcome was reduced in the semaglutide group… in only 104 weeks."

FIGURE 1 - LEADER



Good for the heart, but what about the kidney?
Liraglutide has also been proven safe and effective in in patients with renal disease and in LEADER, patients were enrolled even with GFR<30 mL/min/1.73m2. Interestingly, a secondary outcome of nephropathy was significantly reduced in the liraglutide group by 22% compared to placebo (p<0.003). The LIRA-RENAL trial also showed us that in participants with T2D and moderate renal impairment (GFR 30-59 mL/min/1.73m2), liraglutide improved glycemic control (HbA1C lowering of -0.66%; p<000.1), with no increase in hypoglycemia risk and no changes in renal function. These findings strongly support the use of Liraglutide in T2D patients with both CV and/or renal disease.

Dulaglutide

Dulaglutide (Trulicity™) became the first weekly GLP-1 available in Canada in 2015. Dulaglutide's phase 3 clinical trial program AWARD (Assessment of Weekly Administration of Dulaglutide in Diabetes) has already shown a superior HbA1C reduction of once weekly dulaglutide 1.5mg with the active comparators exenatide, insulin glargine, and sitagliptin. Notably, there was a two-fold greater reduction in both A1C and weight with once weekly dulaglutide compared with sitagliptin, and superior A1C reduction with weight loss instead of weight gain when compared with insulin glargine. Weekly dulaglutide 1.5mg was non-inferior to daily liraglutide 1.8mg in AWARD-6. For patients with moderate to severe renal impairment, weekly dulaglutide 1.5mg or 0.75mg showed comparable HbA1C reduction vs. insulin glargine with greater weight loss, few episodes of hypoglycemia, greater albuminuria reduction, and markedly reduced GFR decline in the AWARD-7 trial. The dulaglutide injection pen boasts simple ease of use and teaching, is relatively painless, and has no visible sharps for those with a fear of needles; all corroborated with relatively high scores on device satisfaction questionnaires. The question of CV safety, and potentially CV benefit, is forthcoming, as the REWIND study, dulaglutide's CV outcome trial will be released in 2019.

Semaglutide

Semaglutide (Ozempic™) is the newest agent available in Canada, a weekly GLP-1 approved in 2018. The SUSTAIN series of phase 3 trials showed significantly greater HbA1C and weight reduction with semaglutide in multiple head-head comparisons including sitagliptin, weekly exenatide, and insulin glargine. The SUSTAIN-6 trial randomized 2735 participants with T2D (>50 years old with CV disease or >60 years old with >1 CV risk factor) to receive weekly semaglutide 0.5mg/1.0mg or placebo. The primary MACE outcome was reduced in the semaglutide group compared to the placebo group (6.6% vs. 8.9%; hazard ratio 0.84; p=0.02 for superiority) in only 104 weeks (Figure 2). Interestingly, the reduction in the primary endpoint was driven

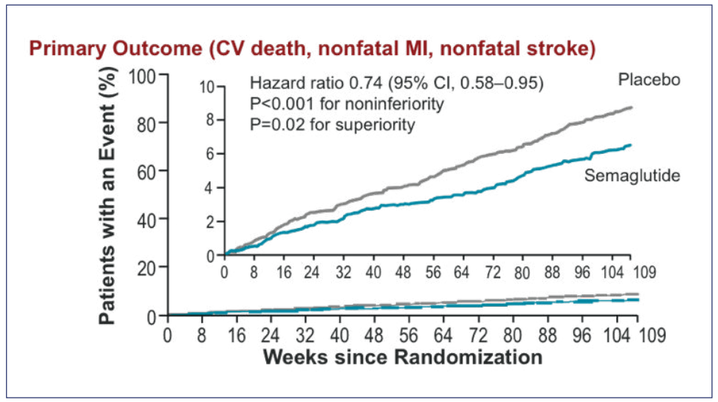


FIGURE 2 - SUSTAIN-6

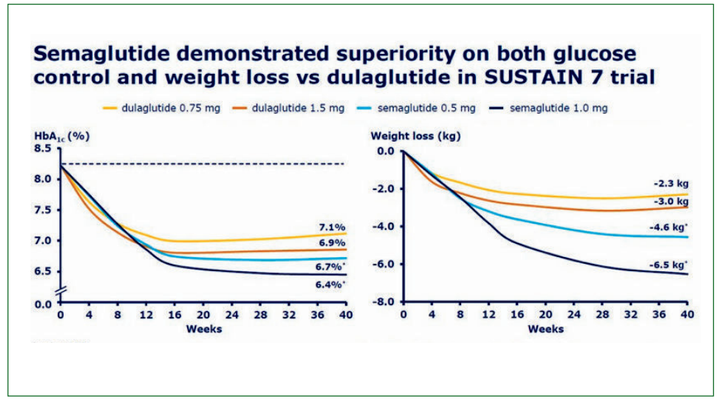


FIGURE 3 - SUSTAIN-7

mainly by a 39% relative risk reduction (p=0.04) in non-fatal stroke. Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications were unexpectedly higher (hazard ratio 1.76; p=0.02). The retinal complications were more prevalent in participants with larger reductions in HbA1C, which is a known risk for early worsening of retinopathy in T1D patients, suggesting that the problem is likely due to rapid glucose lowering in already vulnerable patients, rather than a drug-specific effect. Semaglutide's clinical trial findings thus far confirm its relative potency as an antihyperglycemic agent with CV benefit. We must consider that as agents become more potent, their initiation should remain carefully considered in the right clinical context, alongside recommended regular ophthalmologic screening.

Weekly GLP-1: Head-to-Head
Recently, SUSTAIN-7 compared the two newer weekly GLP-1 therapies and showed that both weekly doses of semaglutide (0.5mg and 1.0mg) were more effective than weekly dulaglutide (0.75mg and 1.5mg) in improving glycemic control and reducing body weight (Figures 3). Safety related adverse events and discontinuation rates were similar. We can expect that semaglutide trials underway will continue to shed new light and generate novel clinical perspectives, including upcoming comparisons with liraglutide and cangliflozin.

Summary

GLP-1 therapies are gaining more attention from healthcare providers, likely due to their demonstrated efficacy, weight reduction, safety, and CV benefit. In most trials, more participants achieved target glycemic control using GLP-1 therapies with minimal increases in hypoglycemia risk. A high relative cost and reimbursement in most provinces remain the biggest barriers to access. When we first prescribe a GLP-1 therapy, patients should be counselled about potential adverse effects, namely nausea (16.1-28%). Practical tips to reduce GI adverse effects include slowly titrating the dose, eating smaller meals, avoiding fatty and high fibre foods, and staying hydrated. Injection site reactions are extremely rare with human GLP-1 analogues. Early on in GLP-1 development, pancreatitis and pancreatic cancer had been a concern but neither was significantly increased in any of the above trials. The new option of weekly dosing also helps reduce an otherwise potentially heavy medication burden for our patients. The clinical stigma associated with injection-based therapies in diabetes must change. The use of agents with proven safety and effectiveness earlier in disease course must become part of the mainstay of individualizing treatment of T2D.