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Research paper

Deprescribing in type 2 diabetes and cardiovascular disease: Recommendations for safe and effective initiation of glucagon-like peptide-1 receptor agonists in patients on insulin therapy

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ABSTRACT

Select glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated cardiovascular benefits in both primary and secondary prevention populations and are recommended in multiple guidelines for cardiovascular risk reduction in people with type 2 diabetes (T2D). Despite this, uptake of GLP-1 receptor agonists in clinical practice has been lagging. While the etiology of their underuse is multifactorial, lack of comfortability in adding a GLP-1 receptor agonist to established insulin regimens is a common barrier. Adjustments to basal and bolus insulin doses upon initiation of GLP-1 receptor agonists in trials have varied. When recommending empiric dose adjustments during initiation of GLP-1 receptors agonists, the most recent A1C and the current blood glucose levels, if available, should be taken into consideration. When initiating in a person being managed with basal-only insulin regimens, an empiric 20 % dose reduction is recommended if the baseline A1C is ≤8 %. For individuals using intensive insulin regimens, empiric dose reductions of up to 25 % in basal and 50 % in bolus therapy were implemented and summarized further in this review. Overall, initiation of GLP-1 receptor agonists can decrease insulin requirements and may permit deintensification of antihyperglycemic therapy through the reduction or discontinuation of bolus insulin therapy. As a result, this simplified regimen promotes increased adherence, reduces glycemic variability and hypoglycemia, and improves overall glycemic management and quality of life. This review aims to serve as a guide for clinicians to facilitate the initiation of GLP-1 receptor agonists and deintensification of insulin by providing suggested dose adjustments based on available literature.

1. Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in people with type 2 diabetes (T2D) [1,2]. Advancements in therapeutic options for the management of T2D and the subsequent publication of cardiovascular outcomes trials for newer antihyperglycemic therapies have transformed treatment algorithms for persons with T2D with guidelines encouraging clinicians to evolve from a glucocentric to cardiometabolic approach that focuses on cardiovascular risk reduction [3–7]. Select glucagon-like peptide-1 (GLP-1) receptor agonists, dulaglutide, liraglutide, injectable and oral semaglutide have demonstrated atherosclerotic cardiovascular disease (ASCVD) benefits in both primary and secondary prevention populations and have been shown to slow the progression to macroalbuminuria [3]. As a result, the American Diabetes Association (ADA) now recommends these select GLP-1 receptor agonists as first-line therapy in persons with T2D and ASCVD or those with indicators of high cardiovascular risk, independently of baseline A1C, individualized A1C target, or metformin use. GLP-1 receptor agonists should also be considered as the initial injectable therapy for persons with T2D, regardless of cardiovascular risk, unless contraindications are present.

Due to its insidious onset and tendency for individuals with T2D to experience months-to-years of hyperglycemia prior to diagnosis, many patients present with elevated blood glucose and hemoglobin A1C levels prompting clinicians to initiate insulin as the initial antihyperglycemic therapy, with a focus on restoring euglycemia and resolving glucose toxicity. Insulin initiation, both as basal-only and intensive insulin regimens, is a common result of diagnosis and initial treatment in acute

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care settings where clinicians are more concerned about managing transient hyperglycemia and less focused on mitigating long-term cardiovascular risk. Additionally, institutional inpatient formularies and clinicians' ability to navigate outpatient medication coverage may serve as barriers to the initiation of GLP-1 receptor agonists in these settings.

Uptake of GLP-1 receptor agonists in clinical practice has been lagging even with guideline recommendations, endorsements from multiple endocrinology and cardiology societies, and positive results in reducing major adverse cardiovascular event (MACE) endpoints in cardiovascular outcomes trials. Observational studies conducted in the United States found that <8 % of individuals with T2D and clinical ASCVD were prescribed a GLP-1 receptor agonist [8–10]. The etiology of this clinical inertia is multifactorial, including unfamiliarity with these agents, their administration and dose escalation requirements; lack of experience in adjusting the current medication regimen for individuals with T2D when adding other antihyperglycemic agents; fear of inducing hypoglycemia; belief that initiating and adjusting medications approved for diabetes is outside of the scope of practice for cardiology; and lack of care integration with the primary care and endocrinology teams [6,10]. Approaches to GLP-1 receptor agonist prescribing for the cardiology care team have been described; however, there is limited discussion around the de-intensification of antihyperglycemic therapy, specifically, hypoglycemia-inducing agents, such as secretagogues (e.g., sulfonylureas or meglitinides) and insulin, to improve comfortability with adding GLP-1 receptor agonists to reduce cardiovascular risk [10]. Despite prescribing information recommending lowering the dose of secretagogues and insulin to mitigate the risk of hypoglycemia when adding a GLP-1 receptor agonist to these agents, formal guidance on the amount and timing of the dose reduction is limited. Multiple trials have provided recommendations for the adjustment of basal insulin doses during GLP-1 receptor agonist initiation [11–18]; however, less robust data exists for their addition to intensive insulin regimens (i.e., multiple daily injection [MDI] and pre-mixed insulin). This review aims to summarize initial dose adjustments to insulin regimens during initiation of GLP-1 receptor agonists from previous clinical trials and offers practical guidance for clinicians aiming to optimize cardiometabolic, renal, and glycemic outcomes for their patients through the addition of these antihyperglycemic agents.

2. Methods

PubMed was used to identify prospective, randomized, controlled, parallel group trials that evaluated GLP-1 receptor agonist therapy initiated in persons with T2D using intensive insulin regimens. Investigators' primary aim was to summarize these study protocols to identify best practices when adding these agents to basal-bolus or premixed insulin regimens. PubMed was searched using “GLP-1 agonist”, “glucagon-like peptide receptor”, and “intensive insulin”, filtered by randomized controlled trials in humans. All relevant full texts and related articles as well as manuscripts identified by authors through clinical practice that met criteria were selected and summarized in a narrative fashion.

3. Literature Review

3.1. Literature evaluating the addition of GLP-1 receptor agonists to basal insulin

If insulin is required for the management of T2D, the ADA recommends a GLP-1 receptor agonist be used in combination with insulin for greater efficacy, durability of treatment effect and to reduce cardiovascular risk [3]. Adjustments to basal insulin doses upon initiation of GLP-1 receptor agonists in clinical trials have varied. Protocols from several studies evaluating the addition of short-acting GLP-1 receptor agonists versus placebo implemented an initial 20 % reduction in the basal insulin dose for participants with a baseline A1C of 7.5–8 % or less [11–15]. Clinical trials studying long-acting GLP-1 receptor agonists in patients inadequately controlled on basal insulin, both with and without metformin, also implemented a 20 % dose reduction in basal insulin if participants' baseline A1C was 8 % or less [16,17]. In studies of oral semaglutide versus placebo added to patients with moderate renal impairment not meeting glycemic targets (mean baseline A1C 8.0 %), basal insulin doses were reduced by 20 % regardless of baseline A1C [18]. The addition of a GLP-1 receptor agonist to basal insulin therapy consistently resulted in significant improvements in A1C in these studies [11–18], and most trials demonstrated similar rates of hypoglycemia [12–14,16–18]. An empiric 20 % decrease in basal insulin dose for individuals' with a baseline A1C of 8 % or less was largely consistent across randomized, placebo-controlled clinical trials evaluating the initiation of a short- or long-acting GLP-1 receptor agonist.

3.2. Literature evaluating the addition of GLP-1 receptor agonists to intensive insulin regimens

The addition of GLP-1 receptor agonist therapy to intensive insulin regimens has not been well studied in clinical trials; therefore, use of these agents in addition to basal-bolus or premixed insulin regimens is not specifically addressed by clinical practice guidelines. Prospective, randomized, controlled, parallel group trials have evaluated the addition of GLP-1 receptor agonists to intensive insulin regimens in patients with long-standing T2D (mean disease duration of 14–17 years) with a range of baseline insulin requirements and this literature is summarized in Table 1 [19–24]. Lane and colleagues and Vanderheiden and colleagues studied the effect of adding a GLP-1 receptor agonist to high-dose insulin regimens (total daily insulin dose [TDD] >150 units), while three additional studies evaluated the addition of a GLP-1 receptor agonist in those with a lower mean baseline TDD [19,20,22–24]. There was variation in the empiric insulin dose adjustment algorithms; however, there were consistent themes when compared with the previously discussed basal insulin studies.

The available literature evaluating the addition of GLP-1 receptor agonists to intensive insulin regimens is primarily with liraglutide [19–21,23]. Additional studies evaluated once weekly injectable albiglutide, which is no longer commercially available, and oral semaglutide [22,24]. All study populations included those with T2D on intensive insulin regimens with or without metformin [19–24]. Additional antihyperglycemic therapy use outside of insulin and metformin was prohibited, limiting generalizability. The primary outcome in these trials was change in A1C, which was reflected in the structure of the insulin adjustment protocols including aggressive titration schemes and tight glycemic targets. Insulin doses were returned to baseline or regimens were re-intensified if patients were not meeting their glycemic targets and/or experiencing hyperglycemia after the initial GLP-1 receptor agonist initiation and titration period.

In two of the trials, empiric dose reductions were implemented if baseline A1C was 8 % or lower [19,23]. In one of these studies the bolus insulin dose was decreased by 50 % if A1C was 7 % or less and by 25 % if A1C was 7.1–8 %, while the basal dose was decreased by 25 % if A1C was 8 % or less [19]. In the other trial by Vanderheiden and colleagues, a 20 % decrease in TDD was implemented in participants with A1C 8 % or lower without delineation of how this reduction was distributed among basal, bolus, or premixed insulin doses [23]. The study conducted by Lind and colleagues included participants with a higher baseline A1C and did not empirically reduce insulin doses based on A1C; however, participants were considered for a reduction in basal or bolus insulin doses if their fasting or pre-meal blood glucose levels were consistently <126 mg/dl, respectively [20,21]. Two studies did not stratify adjustments by baseline glycemic management; Rosenstock and colleagues decreased insulin lispro doses by 50 % at randomization and discontinued insulin lispro altogether at week 4 with the option to reintroduce as necessary, while Zinman and colleagues decreased TDD by 20 % at randomization and maintained these dose reductions until

Table 1
Prospective, randomized, controlled, parallel-group trials evaluating GLP-1 receptor agonist therapy added to intensive insulin regimens.

Reference	N	Study duration	GLP-1 RA studied	Baseline A1C, %	Age, years	Algorithm for empiric insulin dose adjustments at GLP-1 RA initiation or study randomization	Baseline insulin doses, units	Change, units (% change from baseline)	A1C change from baseline, %	Incidence of hypoglycemia, %
Lane W et al. [19]	37	6 months	Liraglutide	7.8	59.7	- Basal - A1C ≤8.0 %: ↓ 25 % - A1C >8 %: no adjustment - Bolus - A1C <7.0 %: ↓ 50 % - A1C 7.1–8.0 %: ↓ 25 % - A1C >8 %: no adjustment	- GLP-1 RA - TDD: 199.0 - Basal: N/A - Bolus: N/A - Control - TDD: 171.2 - Basal: N/A - Bolus: N/A	- GLP-1 RA - TDD: −67.4 (−34) - Basal: N/A (−31) - Bolus: N/A (−38) - Control - TDD: +6.7 (+4) - Basal: N/A - Bolus: N/A - P < 0.0001 (TDD)	- GLP1: −0.65 - Control: −0.39 - P < 0.0001	CGM TBR at 6 months: GLP-1 RA: 2.81 Control: 1.63
Lind M et al. [20,21]	122	24 weeks	Liraglutide	9.0	63.7	- TDD - Mean glucose <153 mg/dl: ↓ 10–20 % - Basal - FPG <90 mg/dl or nocturnal hypoglycemia: ↓ 20–40 % - FPG 90–126 mg/dl: ↓ 20–30 % - FPG >126 mg/dl: no adjustment - Bolus - Pre-meal glucose <126 mg/dl: ↓ 10–20 % at prior meal - Daytime hypoglycemia: ↓ >20 % at prior meal	- GLP-1 RA - TDD: 105.3 - Basal: 57.2 - Bolus: 48.1 - Control - TDD: 105.6 - Basal: 59.3 - Bolus: 46.3	- GLP-1 RA - TDD: −18.1 (−17) - Basal: −6.8 (−12) - Bolus: −11.2 (−23) - Control - TDD: −2.34 (−2) - Basal: −0.5 (−1) - Bolus: −1.9 (−4) - P < 0.001 (TDD)	- GLP1: −1.54 - Control: −0.42 - P < 0.001	Symptomatic, non-severe <72 mg/dl: - GLP-1 RA: 1.29 - Placebo: 1.24 - P = 0.96 Severe: - GLP-1 RA: 0 - Placebo: 0 - P = 1.0
Rosenstock J et al. [22]	814	26 weeks	Albiglutide	7.7	58.0	- Basal - No adjustment - Bolus - ↓ 50 % - Discontinued at week 4	- GLP-1 RA - TDD: 80.3 - Basal: 41.6 - Bolus: 38.7 - Control - TDD: 82.9 - Basal: 41.6 - Bolus: 41.3	- GLP-1 RA: - TDD: −11.3 (−14) - Basal: +17.7 (+43) - Bolus: −28.9 (−75) - Control: - TDD: +47.5 (+57) - Basal: +17 (+41) - Bolus: +30.6 (+74) - P < 0.0001 (TDD, bolus)	- GLP1: −1.04 - Control: −1.10 - P < 0.0001 (noninferiority)	Any ≤70 mg/dl: - GLP-1 RA: 72.5 - Control: 86.9 - P = 0.0001 Symptomatic, non-severe ≤70 mg/dl: - GLP-1 RA: 50.8 - Control: 72.4 Severe: - GLP-1 RA: 2.3 - Control: 5.3
Vanderheiden A et al. [23]	71	6 months	Liraglutide	8.9	54.2	- TDD: - A1C ≤8 %: ↓ 20 % - A1C >8 %: no adjustment	- GLP-1 RA - TDD: 240[a] - Control - TDD: 220[a]	- GLP-1 RA - TDD: -40[a] (−17) - Control - TDD: -2[a] (−1) - P = 0.06 (TDD)	- GLP-1 RA: −0.9 - Control: 0 - P = 0.002	Any <70 mg/dl: - GLP-1 RA: 85 - Control: 71 - P = 0.25 Any <54 mg/dl: - GLP-1 RA: 55 - Control: 37 - P = 0.22
Zinman B et al. [24]	731	52 weeks	Semaglutide, oral	8.2	61	- TDD: ↓ 20 %, irrespective of A1C	- GLP-1 RA, TDD: - 3 mg: 61 - 7 mg: 63 - 14 mg: 53 - Control, TDD: 55	- GLP-1 RA, TDD: - 3 mg: +2 (+3) - 7 mg: −6 (−10) - 14 mg: −7 (−13) - Control, TDD: +10 (+18) - P = 0.0450 (3 mg); P < 0.0001 (7 mg, 14 mg)	- GLP-1 RA - 3 mg: −1.5 - 7 mg: −1.6 - 14 mg: −2.0 - Control: −0.8 - P = 0.0161 (3 mg); P = 0.0035 (7 mg); P < 0.0001 (14 mg)	Severe or symptomatic, non-severe ≤56 mg/dl: - GLP-1 RA - 3 mg: 28.3 - 7 mg: 26.0 - 14 mg: 26.5 - Control: 29.3

Data are means, unless otherwise noted. Severe hypoglycemia as defined by the American Diabetes Association classification that requires assistance of another person to actively administer carbohydrate, glucagon, or other corrective action.

Abbreviations: CGM, continuous glucose monitoring; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; TBR, time below range; TDD, total daily dose.

[a] Vanderheiden et al. reported total daily insulin doses as medians.

week 8 of the study [22,24].

The addition of a GLP-1 receptor agonist contributed to a significant decrease in TDD of insulin compared to the control in multiple studies. The reduction in TDD from baseline to study conclusion in the GLP-1 receptor agonist groups ranged from 6 to 67 units or a 10 % to 34 % decrease overall [19,20,22,24]. Three of the studies reported final changes in basal and bolus doses with the initiation of a GLP-1 receptor agonist; bolus doses decreased from baseline in all studies, ranging from 23 to 75 %, while basal dose changes ranged from a 31 % decrease to 43 % increase from baseline [19,20,22]. The trial in which the mean basal insulin dose increased throughout the study period was likely secondary to an extensive decrease in bolus insulin doses [22].

The initiation of a GLP-1 receptor agonist resulted in significant reductions in A1C in multiple studies without an increased risk for hypoglycemia [19,20,23,24]. The incidence of hypoglycemia was not significantly different between groups in the studies by Lind and Vanderheiden [20,23]. Lane and colleagues used continuous glucose monitoring (CGM) and reported a decrease in time in hypoglycemia from baseline in both groups at 6 months [19]. Rosenstock and colleagues reported a statistically significant difference between the GLP-1 receptor agonist and control groups, with higher incidence of hypoglycemia in the control group [22]. Rates of hypoglycemia were similar between groups in the Zinman trial, with the highest incidence, again, occurring in the control group [24].

4. Discussion

Cardiovascular disease is the leading cause of death in people living with diabetes and individuals with diabetes are twice as likely to have ASCVD than those without diabetes. Guidelines from the American College of Cardiology and ADA, as well as other subsequent publications have developed guidance to improve prescribing and comfortability among cardiology team members with using GLP-1 receptor agonists in people with T2D to reduce their cardiovascular risk [3,6,10]. Despite increased guidance on GLP-1 receptor agonist use, clinical uptake remains low [8–10]. To better understand the reason for the delayed integration of GLP-1 receptor agonists into clinical practice, an evaluation of prescribing patterns by clinical specialty was performed. Endocrinologists prescribe these agents more frequently than cardiologists and primary care providers; however, the number of cardiology and primary care providers greatly outnumbers endocrinologists nationwide and people with T2D and cardiovascular disease are four times more likely to see a cardiologist than endocrinologist in the outpatient setting [25]. This highlights the need for members of the cardiology care team to take a more active role in using these cardiovascular risk-reducing agents for people with T2D.

Efforts at increasing GLP-1 receptor agonist use have primarily focused on educating clinicians on the cardiovascular benefit, identifying appropriate candidates for therapy, considerations, and contraindications to use, initiation and titration, counseling points, education, monitoring, and follow-up. There is minimal literature reviewing how to deprescribe other antihyperglycemic agents to reduce the risk of hypoglycemia, which may be a deterrent to prescribing GLP-1 receptor agonists in clinical practice [6,10].

Current guidelines which address deprescribing primarily focus on the older adult population. The ADA has created an algorithm outlining the simplification of intensive insulin regimens in older adults and provides guidance on transitioning individuals off basal-bolus and premixed insulin regimens through the addition of non-insulin agents [3]. For older adults using basal and bolus insulin, a 50 % reduction in the bolus insulin dose may be considered when initiating a non-insulin antihyperglycemic agent if using >10 units per dose at baseline, and for patients using 10 units per dose or less, it is reasonable to discontinue the bolus insulin altogether. While these general recommendations may offer guidance to simplify intensive insulin regimens in older adults, the recommended dose adjustments may not be appropriate in younger patients, those with extensively elevated A1C values, or those receiving more potent non-insulin antihyperglycemic therapy, such as GLP-1 receptor agonists. Expert opinion from Artigas and colleagues suggested an initial 30–40 % reduction in bolus insulin and 10 % reduction in basal insulin with the initiation of GLP-1 receptor agonist therapy; however, these recommendations were derived from heterogeneous clinical trials of short-acting GLP-1 receptor agonists added to insulin therapy and based on the final insulin dose reductions reported after GLP-1 receptor agonist initiation and titration [26]. In addition, these recommendations were published before the widespread use of more potent and long-acting agents and the publication of additional prospective, randomized, controlled studies evaluating the addition of GLP-1 receptor agonist therapy to intensive insulin regimens.

4.1. *Clinical integration of GLP-1 receptor agonists in individuals using insulin*

Recommendations for empiric dose adjustments to insulin therapy upon initiation of GLP-1 receptor agonist therapy based on the available literature and the authors' clinical experience are summarized in Table 2.

4.1.1. *Adjusting basal insulin regimens*

The authors suggest that when initiating a GLP-1 receptor agonist in patients established on basal insulin therapy, with or without oral antihyperglycemic therapy, one may consider an empiric 20 % decrease in the basal insulin dose when the A1C is 8 % or less. Initial basal insulin dose reductions for patients with an A1C >8 % at GLP-1 receptor agonist initiation may be considered in the presence of extensive glycemic variability, frequent hypoglycemic episodes, or hypoglycemia unawareness; however, in the absence of these factors, an adjustment to the basal insulin dose may not be necessary. A subsequent 20 % basal insulin dose reduction may also be considered at each GLP-1 receptor agonist dose titration depending on the most recent glycemic trends.

4.1.2. *Adjusting intensive insulin regimens*

Approaches to the empiric adjustment of intensive insulin regimens upon GLP-1 receptor agonist initiation varied among prospective, randomized, controlled trials [19–24]. The objective of these studies differs in comparison to the ADA recommendations for deprescribing in older adults; the focus is on change in A1C and glycemic management as opposed to de-intensifying bolus insulin and optimizing non-insulin medication use. Nevertheless, the data provides guidance that is not addressed in clinical practice guidelines. The study protocols highlight the importance of glycemic trends in guiding adjustments in practice and the importance of considering when the specific GLP-1 receptor agonist will reach steady state, which will be longer for the weekly agents (e.g., ~3–5 weeks), such as dulaglutide and semaglutide, compared to liraglutide (e.g., ~3 days) [27]. Each agent's half-life and

Table 2
Recommendations for empiric basal and bolus insulin dose reductions during GLP-1 receptor agonist initiation.

Glycemic control or characteristics at baseline	Basal dose reduction (%)	Bolus dose reduction (%)
A1C <7.0 % (or average FPG <130 mg/dl)	20 %	50 %
A1C 7.1–8.0 % (or average FPG 130–200 mg/dl)	10–20 %	25 %
A1C >8.0 % (or average FPG >200 mg/dl) *with* glycemic variability, hypoglycemia unawareness or severe hypoglycemic events	10 %	25 %
A1C >8.0 % (or average FPG >200 mg/dl) *without* glycemic variability, hypoglycemia unawareness or severe hypoglycemic events	No adjustment	10–20 %

Abbreviations: FPG, fasting plasma glucose.

time to full effect should be taken into consideration, in addition to A1C and the most current blood glucose levels, if available, when recommending empiric dose adjustments upon initiation of GLP-1 receptors agonists and the opportune timing of follow-up for future adjustments.

The treat-to-target strategies and algorithms for recurrent hypoglycemia to guide dose adjustments likely explain the high incidence of hypoglycemia in two of the studies [22,23]. In the Zinman study, the incidence of hypoglycemia was low overall and similar between groups; however, the highest incidence of severe events was with the initial dose of oral semaglutide in patients on intensive insulin regimens, while there were no severe events in the basal-only group [24]. This suggests that upon initiation of GLP-1 receptor agonists a more targeted approach to prioritize reduction of bolus insulin rather than a general 20 % TDD reduction may be more effective at mitigating the risk of hypoglycemia.

It is the authors' preference to prioritize empiric dose reductions in bolus insulin when initiating or titrating GLP-1 receptor agonists with permissive hyperglycemia while these agents reach steady state. Given that GLP-1 receptor agonists work directly at the pancreas to stimulate insulin release in response to a meal, it follows that exogenous insulin requirements at meal time typically decrease and the risk for hypoglycemia will be highest for persons with A1C levels closer to goal upon initiation (e.g., <7 or 8 %) [27]. In addition, the most common adverse effects of GLP-1 receptor agonists, primarily due to slowing gastric emptying, including nausea and increased satiety, perpetuate decreased appetite and smaller portions, and further supports the adjustment of bolus insulin as first priority to decrease risk of hypoglycemia. Thus, the authors recommend a 50 % reduction in bolus dose for A1C <7 % and a 25 % reduction for A1C 7.1–8 %. Another consideration of GLP-1 receptor agonist action is promotion of weight loss and improvements in insulin sensitivity; thus, larger insulin dose reductions may be required for persons with obesity. Overall, reducing the number of daily injections through initiation of a GLP-1 receptor agonist and gradual tapering of bolus insulin doses simplifies the treatment regimen which can lead to increased adherence, reductions in glycemic variability, and improved glycemic management and quality of life.

4.2. General recommendations

In addition to adjusting insulin regimens in patients with A1C values of 8 % or less or those with blood glucose values close to target at time of initiation of GLP-1 receptor agonists, empiric adjustments should be made for patients with A1C >8 % in the presence of frequent hypoglycemia, hypoglycemia unawareness, severe hypoglycemic episodes, or high glycemic variability noted on home BGM and/or CGM. The authors recommend a 25 % reduction in bolus dose in the presence of these factors, and a 10–20 % empiric reduction in the absence of these factors with permissive hyperglycemia while the GLP-1 receptor agonist reaches steady state. Blood glucose values should be used to guide adjustments more precisely, with an emphasis on fasting blood glucose readings with a goal of 80–130 mg/dl since GLP-1 receptor agonists and basal insulin both impact fasting readings. An A1C target of <8 % and corresponding fasting blood glucose goal of 90–150 mg/dl may be more appropriate in older adults with multiple comorbidities [3]. Patient education on the delayed onset and time to full effect of weekly agents is critical to promote adherence to the GLP-1 receptor agonist with reductions in insulin therapy and subsequent permissive hyperglycemia. Regardless of the clinician's decision to implement an empiric insulin dose reduction, initiating a GLP-1 receptor agonist necessitates continued BGM/CGM and coordination of close follow up to re-evaluate glycemic trends given individualized patient responses, as these recommendations are a starting point and not a one size fits all approach. In addition, assessing frequency of hypoglycemic episodes and general tolerability of the GLP-1 receptor agonist therapy is paramount for optimizing safety and efficacy of the treatment regimen.

4.3. Clinical integration of GLP-1 receptor agonists in individuals using oral antihyperglycemic medications

While the aim of this review was to improve clinician comfortability in adding GLP-1 receptor agonists to insulin therapy, consideration must also be given in regard to how to combine GLP-1 receptor agonist therapy with other non-insulin antihyperglycemic agents. GLP-1 receptor agonists may be used concomitantly with most antihyperglycemic agents with the exception of dipeptidyl peptidase-4 (DPP-4) inhibitors. DPP-4 inhibitors represent a theoretical duplication of therapy as they also increase incretin hormones; however, DPP-4 inhibitors and GLP-1 receptor agonists are not synergistic and therefore offer no additional clinical benefit in combination [3].

GLP-1 receptor agonists, SGLT2 inhibitors, and metformin therapy should be preferred prior to sulfonylurea and meglitinide use, if tolerated [3]. Caution should be used when adding a GLP-1 receptor agonist to a sulfonylurea, such as glipizide or glimepiride, or a meglitinide (i.e., repaglinide or nateglinide), as combination therapy may increase the risk of hypoglycemia. To mitigate the risk of hypoglycemia the dose of sulfonylurea or meglitinide may need to be adjusted as the GLP-1 receptor agonist is added and should be tapered off with subsequent dose adjustments. Sulfonylureas and meglitinides are more efficacious in glucose lowering than DPP-4 inhibitors [3], and an abrupt discontinuation may create periods of unwanted hyperglycemia; therefore, the authors recommend a cross taper with GLP-1 receptor agonists. Honingberg and colleagues created a deprescribing algorithm based on A1C, recommending the sulfonylurea medication be discontinued upon initiation of GLP-1 receptor agonist therapy in those with a baseline A1C less than or equal to 7.5 %, a 50 % dose reduction in those with an A1C of 7.6 % to 8.5 % and continuing therapy with the sulfonylurea if the A1C is >8.5 % [10]. Another article recommended a 25 % or greater decrease in sulfonylurea dose if the A1C was <8 % [15]. Both sulfonylureas and GLP-1 receptor agonists have the potential to lower A1C 1–2 % depending on their dose and patients' individual response to these agents [28,29]. Since each class is considered highly efficacious in glycemic management [3], the authors recommend only discontinuing the sulfonylurea or meglitinide upon initiation of the GLP-1 receptor agonist in those meeting their A1C goal and glycemic targets, or those close to goal with frequent hypoglycemic events. In those with an A1C above goal, and infrequent episodes of hypoglycemia, the sulfonylurea or meglitinide dose should be reduced by 50 % when initiating GLP-1 receptor agonist therapy and discontinued with the first GLP-1 receptor agonist dose escalation. For individuals with A1C values >8 %, evaluation of hypoglycemic events and BGM values should be assessed before deciding to decrease the dose or discontinue the sulfonylurea or meglitinide. This will help mitigate hyperglycemic excursions that may occur upon discontinuing the sulfonylurea or meglitinide therapy prematurely before the GLP-1 receptor agonist reaches steady state and exhibits its full effect on blood glucose.

5. Conclusion

Select GLP-1 receptor agonists have demonstrated ASCVD benefit in both primary and secondary prevention populations and should be considered in people with T2D, if tolerated, to reduce their cardiovascular risk. While many clinicians have become comfortable adding GLP-1 receptor agonists to metformin therapy, or even initiating as initial therapy in the management of T2D, individuals with a longer history of T2D on intensive insulin regimens still benefit from the cardiovascular risk reduction derived from GLP-1 receptor agonist therapy. This review serves as a guide to improve clinician comfortability with initiating GLP-1 receptor agonists in persons on existing insulin regimens to help individuals with T2D improve their weight management, reduce their risk of cardiovascular disease, and ultimately improve their quality of life if they are able to reduce their overall number of injections per day and simplify their antihyperglycemic regimen.

CRediT authorship contribution statement

Elizabeth Van Dril: Conceptualization, Writing – original draft, Writing – review & editing, Supervision. **Margaret Allison:** Writing – original draft, Writing – review & editing. **Christie Schumacher:** Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Christie Schumacher is on the speaker's bureau for Abbott. All other authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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