A practical approach and algorithm for intensifying beyond basal insulin in type 2 diabetes

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1 | INTRODUCTION: THE NEED FOR INTENSIFICATION BEYOND BASAL INSULIN

Although the early phases of type 2 diabetes can in some cases be successfully managed with healthy behavioural changes and non-insulin antihyperglycaemic agents, the chronic decline in β-cell function and insulin secretion will, for many, culminate in the need for insulin therapy. Most international diabetes clinical practice guidelines are aligned in recommending basal insulin as the initial insulin therapy for individuals with type 2 diabetes whose fasting plasma glucose (FPG) and glycated haemoglobin (HbA1c) levels are persistently suboptimal.1-4

Current basal insulin options include neutral protamine Hagedorn, glargine 100, detemir, glargine 300 and degludec.5 Compared to their
predecessors, the newest human basal insulin analogues (glargine 300, degludec) offer longer durability with less glycaemic variations which, in turn, translate to improved glycaemic control with lower risk of nocturnal hypoglycaemia.6 That said, higher doses of glargine 300, relative to traditional basal insulins, are usually required.7 While the vast majority of the basal insulin treat-to-target trials with type 2 diabetes cohorts have typically targeted an FPG that is below 6.0, 5.5 or even 5.0 mmol/L, the mean end-of-study FPG in all of these studies was greater than the FPG goals.8–14 That the mean end-of-study HbA1c levels in the same trials were usually above 7.0% (53 mmol/mol) underscores the point that basal insulin titration alone does not, in most cases, adequately lower HbA1c to goal levels.8–14 Indeed, a meta-analysis of 48 basal insulin analogue trials revealed that only 41% of study participants attained an HbA1c of less than 7.0% (53 mmol/mol).15 In accord, three independent retrospective analyses of data sourced from electronic medical record and claims databases suggest that over 60% of those treated with basal insulin are unable to meet guideline-recommended HbA1c targets.16–18

Continual titration of basal insulin with the goal of reaching an FPG between 4.0 and 5.5 mmol/L may, in some cases, improve overall glycaemia. However, this approach is limited by the risk of nocturnal hypoglycaemia. Despite the lack of consensus on what the maximum dose of basal insulin should be, therapy intensification typically moves beyond basal insulin once the basal insulin dose transitions from 0.5 to 1.0 U/kg/d or higher.1,2,19 Of note, beyond basal insulin strategies are most appropriate if the HbA1c remains above 7.0% (53 mmol/mol) or perhaps above an individualized target of 8.0%, despite optimal FPG levels, and especially, if postprandial glucose (PPG) readings are routinely over 10 mmol/L.1–3,19

The upsurge in the number of novel antihyperglycaemic agents over the last decade has transformed diabetes management and has afforded more opportunities for improved and often value-added personalized therapy. Current alternatives for intensification beyond basal insulin include mealtime rapid-acting insulin analogues administered 1 to 3 times daily, a less preferred option of premixed insulin 2 or 3 times daily or, if not already being used, non-insulin antihyperglycaemic agents such as metformin, dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide 1 receptor agonists (GLP-1RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2i). However, despite the constant revisions of clinical practice guidelines and the plethora of anti-hyperglycaemic agents available, real world evidence suggests that clinical inertia for intensification beyond basal insulin remains a global burden. To this point, a recent study reported that the treatment regimen was intensified in less than 40% of the cohort using basal insulin with an HbA1c of 7.5% (58 mmol/mol) or higher and, of further concern, the median time to therapy intensification was 3.7 years.20 The intensification beyond basal insulin algorithm from the American Diabetes Association1 focuses on injectable options. In contrast, the algorithm from the American Association of Clinical Endocrinologists recommends both non-injectable and injectable options but provides little guidance for the clinician to decide which path to follow.2 A practical clinical algorithm may, therefore, be warranted, to assist clinicians in the effective implementation of intensification beyond basal insulin in a safe and simple fashion, and accordingly, may contribute to more patients achieving glycaemic targets. Our group held a meeting in January 2018 to review the evidence for intensification beyond basal insulin, with the goal of producing a practical algorithm on this topic. Herewith, we review the major evidence for intensification with insulin options and non-insulin options such as DPP-4i, GLP-1RA and SGLT2i and present our recommended algorithm for intensification beyond basal insulin. Thiazolidinediones and sulphonylureas are not included in this review. Given that thiazolidinediones have been associated with a higher frequency of heart failure and oedema, combination therapy with insulin is not recommended.21,22 Hypoglycaemia is a major concern with sulphonylurea use; thus, although they are often concomitantly prescribed with basal insulin, it may be prudent to avoid insulin-sulphonylurea strategies. In fact, the combination of sulphonylureas with multiple daily injections of insulin is not recommended.4

2 | INTENSIFICATION WITH INSULIN-BASED REGIMENS

There are several avenues for intensifying therapy beyond basal insulin with insulin-based regimens. These include initiating a single injection of a rapid-acting insulin analogue (basal-plus) and advancing in a stepwise fashion up to a total of three mealtime injections (basal-bolus),1–3 introducing a basal-bolus regimen immediately2,3 or replacing the basal insulin with twice-daily premixed insulin.1,13

The basal-plus regimen may be initiated as a single injection of a rapid-acting insulin analogue before the largest meal of the day,23,24 before the meal associated with the highest PPG,24–27 or before breakfast.28 The glycaemic efficacy achievable with these approaches is comparable. The starting dose of mealtime insulin can be 2, 4 or 6 U23,25,28 or 10% of the basal dose.29 Prandial insulin can be titrated at 1 U/d and should be based on the level of glucose before the next meal or that at bedtime,23–25,29 or the PPG reading, targeting either a premeal glucose level in the 4 to 7 mmol/L range or a 2-hour PPG value of less than 10 mmol/L.4 Of note, a single mealtime injection of insulin in addition to basal insulin can achieve an HbA1c target of ≤7.0% (53 mmol/mol) in between 17% and 52% of patients24,28–30 and, while the stepwise progression from 1 to 2 or 3 injections of mealtime insulin is just as efficacious as the direct to basal-bolus option in lowering HbA1c, the former is associated with less risk of hypoglycaemia and greater patient satisfaction.23 Given that weight gain is a common and undesirable concern in insulin use, and is often a primary reason for clinical inertia and poor adherence, it is worth underscoring the observation that insulin regimens that begin with basal insulin and advance to prandial insulin are associated with less weight gain than those initiated with premix or prandial insulin.31 For every additional injection of mealtime insulin, the complexity and number of injections increase the ongoing risk of hypoglycaemia and weight gain.

In some cases, it may be necessary to consider reducing the number of injections to improve adherence. Although intensifying from basal insulin to twice-daily premixed insulin may allow for fewer injections than switching to a basal-bolus regimen, and may result in degrees of HbA1c lowering, weight gain and rates of hypoglycaemia that are similar to those of a basal-bolus strategy, the premixed insulin
approach has been associated with a lower likelihood of meeting an HbA1c target of ≤7.0% (median, 39%) relative to that observed with basal-bolus therapy (median, 43%).32 Importantly, a premixed insulin regimen also provides less flexibility than a basal-plus or basal-bolus insulin regimen for dose adjustments based on meal content and meal timing, and thus, is generally best reserved for individuals who have consistent eating patterns. Initial dosing of premixed insulin before breakfast and the evening meal does not need to be complex and can follow 1 of the following 2 routines: two-thirds of the dose to be taken in the morning and one-third in the evening, or half in the morning and half in the evening.1 Insulin doses can be titrated by 1 to 2 U once or twice weekly to attain glycaemic targets, although some individuals may need to incorporate a lunchtime dose in order to meet HbA1c and FPG goals.1

When initiating mealtime or premixed insulin, it is generally good practice to discontinue any insulin secretagogues, in an attempt to lessen the rates of hypoglycaemia and weight gain.4 Table 1 summarizes the therapeutic considerations for each of the insulin-based intensification regimens.

### 3 | INTENSIFICATION WITH DPP-4I, GLP-1RA AND SGLT2I

This section will review important considerations when introducing a DPP-4i, a GLP-1RA and/or an SGLT2i to basal insulin. It is assumed that, in the absence of contraindications and intolerance, most of those using basal insulin will also be using metformin and many may also be using other non-insulin anti-hyperglycaemic agents, all of which were initiated prior to and maintained when basal insulin was introduced. The addition of the agents in the sections below assumes that patients are not already using these specific agents.

### 3.1 | Dipeptidyl peptidase-4 inhibitors

DPP-4is are orally administered incretin agents that enhance glucose-dependent insulin secretion and suppress glucagon release.1 The addition of a DPP-4i to insulin offers individuals with type 2 diabetes several advantages over other alternatives when there is a need to advance therapy beyond basal insulin. On average, the combination of a DPP-4i with insulin results in approximately a 0.4% to 0.7% lower HbA1c relative to that observed with insulin plus placebo.33–37 The same studies also revealed that the rates of hypoglycaemia and weight change are similar in the DPP-4i and placebo groups, with minimal differences in insulin usage by study end.33–36

Insulin dose was not reduced at randomization in the DPP-4i add-on to insulin trials, but could be titrated downward if hypoglycaemia became an issue.33–37 Depending on an individual’s clinical history and background therapy, a proactive 10% reduction of the insulin dose may be warranted when introducing a DPP-4i, to lower the risk of developing hypoglycaemia, especially if the baseline HbA1c is less than 8.0% (Table 2). Vilsbøll and colleagues reported that 24 weeks after sitagliptin was added to stable-dose insulin therapy, HbA1c, FPG and PPG were appreciably lower relative to the levels recorded in the group randomized to placebo.38 The incidence of symptomatic hypoglycaemia was, however, higher in the sitagliptin plus insulin arm than in the placebo plus insulin arm (16% vs 8%; P = .003).38 A subsequent study observed superior HbA1c lowering (~1.3% vs ~0.9%; P = .001) and fewer events of hypoglycaemia (25.2% vs 36.8%; P < .001) when background insulin was allowed to be titrated in a treat-to-target regimen after the addition of sitagliptin vs placebo.39 A similar benefit to HbA1c and reduction in hypoglycaemia was

<table>
<thead>
<tr>
<th>Insulin options</th>
<th>Therapeutic considerations</th>
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</table>
| Basal-plus      | Only 1 additional injection
|                 | Requires titration algorithm
|                 | Weight gain
|                 | Hypoglycaemia |
| Basal-bolus     | Requires up to 3 additional injections
|                 | Requires titration algorithm
|                 | More complex
|                 | Weight gain
|                 | Hypoglycaemia |
| Premixed        | Requires 2 to 3 injections daily
|                 | Requires titration algorithm
|                 | Little flexibility
|                 | Weight gain
|                 | Hypoglycaemia |
| Non-insulin options |                           |
| DPP-4 inhibitors| Simple
|                 | No weight gain
|                 | Neutral or increased hypoglycaemia when added to basal insulin but less hypoglycaemia relative to insulin titration
|                 | May be slightly insulin sparing
|                 | Consider for elderly and those with renal impairment
|                 | Increased cost |
| GLP-1 receptor agonists | Convenient options of injectable, including once weekly or fixed-ratio combinations with basal insulin
|                 | Weight loss
|                 | Insulin sparing
|                 | Neutral or increased hypoglycaemia when added to basal insulin but less hypoglycaemia relative to prandial insulin add-on |
|                 | Cardiovascular benefit with liraglutide and semaglutide in individuals with established cardiovascular disease
|                 | Increased cost |
| SGLT2 inhibitors | Simple
|                 | Weight loss
|                 | Neutral or increased hypoglycaemia when added to basal insulin
|                 | Insulin sparing
|                 | Caution in individuals who are insulin-deficient because of risk of SGLT2 inhibitor-associated diabetic ketoacidosis
|                 | Cardiovascular benefit with empagliflozin and canagliflozin in individuals with established cardiovascular disease and eGFR >30 mL/min/1.73 m²
|                 | Increased cost |
demonstrated in a study comparing sitagliptin add-on to insulin upti-
tration in patients using basal or basal-bolus insulin.40

Given the pharmacological profiles of DPP-4i on an insulin back-
ground, there are several populations that may especially benefit
from a DPP-4i plus insulin regimen. The safety and tolerability fea-
tures render this combination a particularly suitable approach for
erly individuals. Inzucchi and colleagues noted that when linagliptin
was added to basal insulin in individuals 70 years and older with a
baseline HbA1c of 7.0% to 10.0% (53 to 86 mmol/mol), there was a
placebo-adjusted change in HbA1c of 0.77%, as well as a concomi-
tant 39% lower incidence of overall hypoglycaemia

In short, intensification of basal insulin therapy with DPP-4i is
associated with clinically meaningful reductions in HbA1c, typically
without increasing the risk of hypoglycaemia or unwanted weight

gain. Importantly, this management strategy may be advantageous in
certain populations such as the elderly and those with impaired GFR.

In a cardiovascular outcome trial (CVOT) with sitagliptin (TECOS),
23% of the participants were using insulin at baseline, and major
cardiovascular events and hospitalization for heart failure events were
similar in individuals who received sitagliptin and those who received
placebo for this subgroup.43,44 In a CVOT with saxagliptin (SAVOR-
TIMI 53), 41% of the cohort were treated with insulin at baseline and,
while the primary composite cardiovascular outcome was neutral in
this population for saxagliptin vs placebo, there was an increase in
hospitalization for heart failure among the insulin-treated individuals
who were randomized to saxagliptin.45,46 The cardiovascular impact
of linagliptin in combination with insulin will be revealed by the results
of the CARMELINA trial, where 58% of the 6980 participants were
being treated with insulin at baseline.47 The linagliptin label in Canada48
states that linagliptin is not recommended for use with
insulin because of concerns related to higher rates of cardiovascular

### Table 2: Insulin adjustments when initiating non-insulin
anti-hyperglycaemic agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Insulin adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 inhibitors</td>
<td>• Downtitrate if hypoglycaemia occurs&lt;br&gt;• Consider a 10% reduction in basal insulin dose at initiation, especially if HbA1c is less than 8.0%</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>• Downtitrate if hypoglycaemia occurs&lt;br&gt;• Consider a 10% to 20% reduction in basal insulin dose at initiation, especially if HbA1c is less than 8.0%</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>• Downtitrate if hypoglycaemia occurs&lt;br&gt;• Consider a 10% reduction in basal insulin dose for fasting plasma glucose 6.0 to 8.0 mmol/L and a 20% reduction for fasting plasma glucose less than 6.0 mmol/L&lt;br&gt;• Exert caution with aggressive dose reduction&lt;br&gt;• Increased risk of SGLT2 inhibitor-associated diabetic ketoacidosis in individuals who are insulin-deficient</td>
</tr>
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### Table 3: Meta-analyses of non-insulin anti-hyperglycemic agents vs placebo as add-on to insulin

<table>
<thead>
<tr>
<th></th>
<th>DPP-4i plus insulin vs placebo plus insulin (9 RCTs)44</th>
<th>GLP-1RA plus basal insulin vs placebo plus basal insulin (10 RCTs)77</th>
<th>SGLTI2i plus insulin vs placebo plus insulin (7 RCTs)82</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c Δ, % (mean difference)</td>
<td>-0.6 (95% CI: -0.96, -0.57)</td>
<td>-0.56 (95% CI: -0.67, -0.44)</td>
<td></td>
</tr>
<tr>
<td>Weight Δ, % (mean difference)</td>
<td>-0.04 (95% CI: -2.3, -0.6)</td>
<td>-2.6 (95% CI: -3.1, -2.2)</td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia/risk ratio</td>
<td>0.94 (95% CI: 1.16, 1.88)</td>
<td>1.07 (95% CI: 0.99, 1.15)</td>
<td></td>
</tr>
<tr>
<td>Insulin dose, U/d (mean difference) (range of results for difference)</td>
<td>-1.9 (95% CI: -1.6)</td>
<td>-8.8 (95% CI: -13.4, -4.2)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated haemoglobin; RCTs, randomised controlled trials; SGLT2i, sodium-glucose cotransporter 2 inhibitor.
individuals who are not at glycaemic goal despite using basal insulin, with or without another glucose-lowering agent (any DPP-4i should be withdrawn). Intensification with a GLP-1RA will not only lower PPG levels but will also improve the likelihood of achieving HbA1c targets, with the additional benefit of weight loss. Studies of liraglutide as add-on to a variety of background insulin regimens, including basal-bolus, premixed and insulin pump therapy, have consistently shown efficacious HbA1c lowering from baseline in the ~0.7% to ~1.9% range with relative weight losses of up to 5.6 kg and with rates of hypoglycaemia similar to or lower than those with ongoing insulin therapy, along with a significant insulin-sparing effect. In studies with observation windows ranging from 24 to 30 weeks, add-on of the short-acting GLP-1RAs exenatide and lixisenatide to basal insulin therapy culminated in placebo-corrected HbA1c lowering between 0.3% and 0.9%, with parallel weight losses of 0.4 to 2.7 kg relative to the corresponding placebo arm. Rates of hypoglycaemia in the groups randomized to the GLP-1RA were either similar or greater than those reported in the placebo groups, and the end-of-study insulin doses in the GLP-1RA groups were 2 to 7 U/d lower than those in the corresponding placebo arms. In 26- to 30-week long studies that introduced longer acting GLP-1RAs to background therapy of basal insulin, the mean placebo-corrected HbA1c levels and weight differences were ~0.7% and ~1.5 kg with exenatide once weekly (QW), ~1.2% and ~3.1 kg with lixisenatide 1.8 mg, ~0.8% and ~2.4 kg with dulaglutide 1.5 mg, ~1.4% and ~2.3 kg with semaglutide 0.5 mg and ~1.8% and ~5.0 kg with semaglutide 1.0 mg. Rates of hypoglycaemia in the groups randomized to the GLP-1RA were either similar or greater compared to those who received placebo, with relative differences in insulin dose reductions ranging from 2 to 13 U/d in favour of the GLP-1RA. There have been several studies specifically designed to compare GLP-1RAs as add-on to basal insulin against add-on prandial insulin, either as basal-plus or basal-bolus regimens. In a 26-week long study, the HbA1c-lowering efficacy of lixisenatide as add-on to basal insulin therapy was found to be superior to one injection of insulin aspart in addition to basal insulin (~0.74% vs ~0.39%, respectively) with concurrent and significant weight reductions (~2.8 kg vs ~0.9 kg, respectively), as well as lower rates of hypoglycaemia (1.0 event per patient/year vs 8.2 events per patient/year). HbA1c lowering with lixisenatide was reported to be noninferior to one injection of insulin glulisine after 26 weeks (~0.6% in both groups), with a significant weight difference of ~1.6 kg and an appreciably lower rate of symptomatic nocturnal hypoglycaemia. In 3 26- to 30-week studies comparing a GLP-1RA to thrice daily prandial insulin as add-on to basal insulin, HbA1c lowering was similar with both approaches, yielding placebo-corrected weight benefits from 1.5 to 4.6 kg and significantly lower rates of hypoglycaemia with the GLP-1RA. Studies of lixisenatide as add-on to a variety of background insulin regimens, including basal-bolus, premixed and insulin pump therapy, have consistently shown efficacious HbA1c lowering from baseline in the ~0.7% to ~1.9% range with relative weight losses of up to 5.6 kg and with rates of hypoglycaemia similar to or lower than those with ongoing insulin therapy, along with a significant insulin-sparing effect. It is notable that the FLAT-SUGAR trial demonstrated lower glycaemic variability with exenatide added to basal insulin therapy compared to the corresponding basal-bolus regimen. Fixed-ratio combinations (FRCs) of a basal insulin and a GLP-1RA provide an alternate means of intensifying basal insulin therapy with a GLP-1RA. Titration of the FRC of insulin degludec with lixisenatide (iDegLira) was compared to titrated basal insulin in 2 26-week-long studies conducted in cohorts previously treated with basal insulin. The FRC was associated with a superior 0.7% to 1.0% HbA1c lowering relative to that with basal insulin and, notably, the mean end-of-study basal insulin dose was the same in both study arms. Furthermore, the glycaemic efficacy occurred alongside weight benefits (~2.7 to ~3.2 kg), with similar or lower rates of hypoglycaemia in the FRC groups. A study comparing iDegLira to a basal-bolus insulin regimen in individuals previously treated with basal insulin plus metformin reported that HbA1c lowering was similar in each arm after 26 weeks, with a weight difference of ~3.6 kg and less hypoglycaemia with iDegLira vs the basal-bolus arm. In these iDegLira studies, the rates of nausea were relatively low (6.5%–11.1%), an outcome that was probably attributable to the moderately slow titration rate of 2 U/0.072 mg every 3 to 4 days. A 30-week study in which titration of the FRC of insulin glargine with lixisenatide (iGlarLixi) was compared to titrated insulin glargine in participants previously treated with basal insulin revealed a 0.5% lower HbA1c level with the FRC relative to insulin glargine, with the same mean insulin dose in both arms by study end. The investigators of this study reported a relative weight difference of ~1.4 kg in favour of the FRC, with similar rates of hypoglycaemia in both groups and nausea occurring in only 10.4% of the iGlarLixi participants. A meta-analysis of 10 trials that compared GLP-1RA plus basal insulin to placebo plus basal insulin demonstrated a mean improvement in HbA1c of 0.76%, a mean weight loss of 1.5 kg, with a 1.47-fold increase in hypoglycaemia (Table 3). In the same report, the investigators compared GLP-1RA plus basal insulin to basal-bolus therapy in seven studies that revealed no significant difference in HbA1c, a significant mean weight difference of ~4.7 kg and a 34% lower risk of hypoglycaemia. A more recent meta-analysis of three trials that evaluated FRC treatment vs basal insulin therapy, where basal insulin treatment was switched to an FRC, the FRC strategy was associated with 0.72% lower HbA1c, 2.4 kg lower weight, 30% less hypoglycaemia, but almost 7-fold higher rates of nausea. Across the GLP-1RA plus basal insulin trials, the insulin dose was sometimes reduced by 10% to 20% at randomization, especially if baseline HbA1c was less than 8.0%, to lessen the chance of hypoglycaemia. In other studies, the insulin dose was reduced only if hypoglycaemia became a concern (Table 2). Subgroup analyses of two large CVOTs with lixisenatide and semaglutide have suggested that adding these agents to background insulin may provide a reduction in major cardiovascular events in patients with type 2 diabetes at high-risk of cardiovascular events. The cardiovascular benefit in these trials was driven mainly by the cohort of patients with established cardiovascular disease. In summary, the addition of a GLP-1RA to basal insulin therapy is associated with efficacious glucose lowering and weight loss and is significantly insulin sparing relative to basal insulin monotherapy. GLP-1RA and basal insulin combinations involve less risk of hypoglycaemia relative to intensification to basal-bolus regimen. Finally, FRCs offer a convenient and well tolerated option for intensification beyond basal insulin.
### Sodium-glucose cotransporter 2 inhibitors

The SGLT2is are unique among the current anti-hyperglycaemic agents in that they act via insulin-independent inhibition of glucose reabsorption in the kidneys. SGLT2is trigger robust and clinically meaningful reductions in FPG and PPG, with the additional benefits of blood pressure lowering and weight loss in as little as 4 weeks after therapy initiation. Accordingly, intensification of basal insulin with SGLT2i in individuals who are not at glycaemic goal may obviate the use of higher insulin doses, more frequent injections of insulin and the potential of greater weight gain. A recent meta-analysis that included 7 placebo-controlled trials of 12 weeks or more duration described a mean HbA1c reduction of 0.56%, a mean weight loss of 2.6 kg, a neutral impact on hypoglycaemia and a mean reduction in insulin dose of 8.8 U. In a pre-specified insulin sub-study of the 52-week long CANVAS trial, the higher canagliflozin dose of 300 mg on an insulin background was associated with a placebo-corrected 0.73% reduction in HbA1c, a 3.5% weight loss and a 6.2 mm Hg decline in systolic blood pressure, with numerically greater rates of hypoglycaemia and higher rates of genital mycotic infections. The SGLT2i arm of a longer 104-week study that compared dapagliflozin to placebo as add-ons to insulin therapy showed a relative HbA1c reduction of 0.8%, with no increase in hypoglycaemia, a relative weight loss of 3.2 kg and a stable dose of insulin vs an increase of 18.3 U in the placebo arm. However, these benefits were accompanied by higher incidences of genital infection in the dapagliflozin-treated group (14.3% vs 3%). In a 52-week study where empagliflozin or placebo was added to titrated basal-bolus insulin therapy, empagliflozin treatment resulted in a 0.46% reduction in HbA1c, with a concomitant weight loss of 2.5 kg and 11 U less insulin at study end; rates of hypoglycaemia were similar across groups and genital infections were more widespread among those randomized to empagliflozin. Among the studies concerning SGLT2i add-on to insulin therapy, the insulin dose was generally not reduced unless hypoglycaemia became a concern. A practical approach is to consider a 10% reduction upon initiation if the FPG is in the range of 6 to 8 mmol/L, and a 20% reduction if the FPG is less than 6 mmol/L (Table 2). Caution should be exercised with regard to aggressive reduction of insulin dose because there is the potential risk of SGLT2i-associated diabetic ketoacidosis. Table 1 summarizes the therapeutic considerations when adding an SGLT2i to basal insulin therapy.

Results from studies comparing SGLT2is to active comparators added to insulin therapy provide compelling reasons for intensifying beyond basal insulin with SGLT2is. A network meta-analysis of 14 12-week or longer studies comparing SGLT2is and pioglitazone as add-ons to insulin therapy revealed a similar HbA1c reduction in both groups, with the bonus of an additional 4.5 kg weight loss in the SGLT2i arm, despite lower end-of-study insulin doses with pioglitazone. When SGLT2is were evaluated in a network meta-analysis against DPP-4i as add-on to insulin therapy in studies longer than 12 weeks, the SGLT2is were found to exert a 0.24% greater reduction in HbA1c than the DPP-4i, and this was coupled with 2.4 kg more weight loss and similar incidences of hypoglycaemia.

The SGLT2i class was significantly bolstered with superior cardiovascular protection results from two large-scale cardiovascular outcome trials. Importantly, these findings led to a paradigm shift that culminated in revisions across international diabetes clinical practice guidelines that now give preference to the use of SGLT2is or GLP-1RAs, with proven cardiovascular benefit in individuals with type 2 diabetes who have pre-existing cardiovascular disease. It is noteworthy that, in both cohorts, approximately 50% of the participants were using insulin, and results from the sub-group analyses confirmed that individuals using insulin were likewise protected when randomized to either SGLT2i. Consequently, SGLT2is are a promising class for intensification beyond insulin, especially if blood pressure and weight are also concerns; however, there are important caveats with regard to renal function, which can lower the effectiveness of SGLT2is, and a prior history of genital infections. Furthermore, SGLT2is have been associated with hypotension, and canagliflozin has been shown to elevate the risk of fractures and lower extremity amputations, with the greatest absolute risk observed among those who had previously undergone an amputation.

### AN ALGORITHM FOR INTENSIFICATION BEYOND BASAL INSULIN

As discussed, traditional insulin strategies for intensification beyond basal insulin include addition of a single injection of mealtime insulin (basal-plus) before escalating to an additional 1 to 2 mealtime insulin injections (basal-bolus) or introduction of premixed insulin 2 to 3 times daily. Intensification with insulin, however, introduces significantly more complexity than does basal insulin monotherapy as it typically involves more injections, further titration algorithms, increased risk of hypoglycaemia and potential weight gain (Table 1), all of which, independently and in conjunction, may perpetuate clinical inertia and poor adherence.

Agents from the non-insulin classes of anti-hyperglycaemic agents, DPP-4i, GLP-1RA and SGLT2i, offer distinct advantages over intensification with insulin, but the cost of intensification beyond insulin may need to be a consideration, especially in certain patient groups (Table 1). The 2018 American Association of Clinical Endocrinologists algorithm for adding/intensifying insulin includes a strategy for adding non-insulin agents, including GLP-1RA, SGLT2i or DPP-4i, as therapeutic options. However, this algorithm does not provide guidance on how to best choose among these add-on agents and does not distinguish between individuals with and without established cardiovascular disease. Although the 2018 guidelines of the American Diabetes Association describe a combination injectable therapy strategy that highlights both mealtime insulin and a premixed strategy as well as the option of adding a GLP-1RA, the option of introducing SGLT2is or DPP-4is is not included in a specific basal insulin intensification algorithm. Furthermore, there is no direction in the algorithm concerning which combination injection approach to utilize. The general pharmacotherapy algorithm of the American Diabetes Association recommends agents with cardiovascular benefits (canagliflozin, empagliflozin or liraglutide,) as potential add-ons to metformin in individuals with established cardiovascular disease, based on results of the EMPA-REG OUTCOME, LEADER and CANVAS trials. Although the 2018 Diabetes Canada guidelines do not include a specific algorithm for
intensification beyond basal insulin, they do prioritize add-on therapies with demonstrated cardiovascular outcome benefit for individuals with clinical cardiovascular disease and eGFR >30 mL/min/1.73 m² whose HbA1c levels are above target. Diabetes Canada also recommends either incretin-based therapies or SGLT2is as preferred add-on agents for individuals without cardiovascular disease if lower risk of hypoglycaemia and/or less weight gain are priorities; these classes are also favoured as add-ons to insulin over insulin intensification. Recognizing the multiplicity of options for intensification beyond basal insulin, we have taken into consideration the totality of evidence available to date and have developed a clinically practical, yet user-friendly, algorithm that provides guidance on this topic (Figure 1). For individuals not at HbA1c goal with basal insulin, one should consider titration to an FPG target in the 4.0 to 5.5 mmol/L range if hypoglycaemia is not a limiting factor. For those with concerns of nocturnal or fasting hypoglycaemia, the newer longer acting basal analogues such as glargine-300 or insulin degludec are preferred, as they are associated with the lowest rates of overnight hypoglycaemia. Once FPG has been optimized, or if further titration is not possible, a series of clinical questions will help in deciding the best option for further insulin intensification.

For individuals with clinical cardiovascular disease and an estimated GFR ≥ 60 mL/min/1.73 m², the recommended options are either SGLT2is (canagliflozin or empagliflozin) or GLP-1RAs (liraglutide or semaglutide), because of their proven cardiovascular benefits in this population. The Diabetes Canada guidelines suggest a higher level of evidence for empagliflozin and liraglutide (Grade A, Level 1A) than for canagliflozin (Grade C, Level 2) concerning cardiovascular benefit. If the HbA1C target remains suboptimal, it is recommended that an agent from the other class, with proven cardiovascular benefit, be added before considering mealtime insulin. Individuals with moderate renal impairment experienced cardiovascular benefit with canagliflozin, empagliflozin, liraglutide and semaglutide. As the glycaemic efficacy of canagliflozin and empagliflozin are reduced when the eGFR falls to between 30 and less than 60 mL/min/1.73 m², the GLP-1RAs (liraglutide or semaglutide) are favoured over these agents for individuals with cardiovascular disease and an estimated GFR within this range. Furthermore, despite a cardiovascular benefit in those with established cardiovascular disease, initiation of canagliflozin and empagliflozin in patients with an eGFR <60 mL/min/1.73 m² is not recommended in many product monographs. If the estimated GFR is below 30 mL/min/1.73 m², SGLT2is...
are contraindicated, rendering GLP-1RA the preferred choice, based on overall efficacy and safety, although cardiovascular benefit in patients with this level of estimated GFR is unproven because of very small numbers of such participants in the large cardiovascular outcome trials.79,80

Among individuals without clinical cardiovascular disease, a series of clinical considerations should be prioritized prior to intensifying therapy. For the elderly, DPP-4is are the preferred option, given the simplicity of prescribing, their tolerability and the low concern of hypoglycaemia, as documented in elderly-specific treatment guidelines.1,94 Although GLP-1RAs and SGLT2is can be considered for the elderly, caution is warranted, as gastrointestinal side effects have been documented for the former95 and volume-related adverse effects for the latter,96 both symptoms being more common in the elderly population. For those with an estimated GFR less than 60 mL/min/1.73 m², GLP-1RAs are preferred; GLP-1RAs followed by SGLT2is are the preferred agents for those with overweight or obesity concerns. When intensifying with incretin agents or SGLT2is, a combination of these two classes should be considered, if there are no contraindications, before advancing to mealtime insulin. The combination of a DPP-4i and a GLP-1RA is not recommended. Down-titrating the background basal insulin dose should be considered when initiating an incretin agent or an SGLT2i (Table 2). Whenever a GLP-1RA is recommended, IDegLira may be considered in place of lixisenatide plus basal insulin, and iGlarLixi in place of lixisenatide plus basal insulin. Not only will these FRCs reduce the injection burden, but they may also be better tolerated than initiation of a GLP-1RA alone. Once weekly GLP-1RA (dulaglutide, exenatide or semaglutide) also offers a convenient way to initiate GLP-1RA therapy. In all cases, cost and coverage must be considered prior to introducing incretin agents and SGLT2is.

5 | CONCLUSION

Diabetes medicine is undergoing a renaissance which is very much welcomed, given the projected escalation in the number of individuals living with diabetes and pre-diabetes, a phenomenon that is being fueled by both the rising prevalence of obesity and an aging population.57 While we have good evidence demonstrating that timely augmentation of anti-hyperglycaemic therapy yields benefits along the entire continuum of type 2 diabetes disease, achieving glycaemic targets, therapy intensification inertia, titration inertia, patient nonadherence and all of the contributory factors remain major challenges, also for those treated with basal insulin.98,99 The comprehensive algorithm provided herein, coupled with the tabulated considerations for different avenues of intensification beyond basal insulin, offer an easily accessible resource to optimize patient care and improve glycaemic target achievements.

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Conflict of interest

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Author contributions

R. M. G. conceived the idea for the expert panel and the manuscript. Every author contributed substantially to development of the recommendations as well as to the drafting and critical revision of the manuscript. The final version of the manuscript was reviewed and approved by every author, all of whom agree to act as guarantors of the work.

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