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Special Article

Pharmacologic Glycemic Management of Type 2 Diabetes in Adults—2024 Update

Diabetes Canada Clinical Practice Guidelines Expert Working Group:

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Key Messages

- Metformin should be the initial agent of choice in most people with type 2 diabetes who require pharmacotherapy to reach glycemic targets.
- Insulin should be initiated immediately, with or without metformin, in individuals with metabolic decompensation and/or severe symptomatic hyperglycemia.
- When glycated hemoglobin (A1C) is more than 1.5% above target, other antihyperglycemic agents in combination with metformin may be needed.
- Certain glucagon-like peptide-1 receptor agonists (GLP1-RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors should be used for cardiorenal protection in people with high cardiovascular (CV) risk, heart failure (HF), or chronic kidney disease (CKD). These medications should be initiated if these comorbidities or complications are already present at diagnosis or if they develop over the person's lifetime, even if the A1C is in target.
- Choice of additional antihyperglycemic agents, when treatment intensification is required to improve glycemia, should consider individual priorities, preferences, and comorbidities. Clinical priorities may include weight loss, avoidance of hypoglycemia, desired magnitude of glucose lowering, cost, side-effect profile, possibility of pregnancy, and comorbidities.
- Insulin regimens in type 2 diabetes should be tailored to the individual to reach individualized glycemic levels and minimize the risk of hypoglycemia. Insulin should be introduced in a stepwise approach, and other antihyperglycemic agents should be continued and/or initiated to further improve glycemia and reduce insulin dose requirements.

Key Messages for People Living With Diabetes

- Most people who have type 2 diabetes will need glucose-lowering medications to reach their personal glucose targets.
- Metformin is generally the first choice because of its effectiveness, mild side effects, safety track record, and low cost.
- Multiple medications that work in different ways may be needed if glucose levels are very high, or if they remain high with just 1 medication. The decision about which other medications to use depends on many factors, including glucose levels, other health problems, and medication costs.
- Certain medications have specific benefits on the heart and the kidneys for people who have these problems already. Therefore, these medications should be used by anybody with these problems, even if their glucose levels are already good.
- Sometimes, people with type 2 diabetes also need insulin. Different types of insulin may be needed at different times of day. Other glucose-lowering medications are usually continued because they can reduce the amount of insulin needed.
- People with type 2 diabetes should discuss the pros and cons of different treatment plans with their health-care providers to decide together on what approach is best.

Introduction

The United Kingdom Prospective Diabetes Study (UKPDS) established the importance of glycemic management to reduce the risk of long-term complications in people with type 2 diabetes [1]. More recently, clinical trials have demonstrated that certain glucose-lowering medications can reduce cardiac and renal complications of diabetes in certain populations, beyond the effects of glucose lowering alone. We conducted a thorough review of the existing evidence to support people living with type 2 diabetes and their health-care providers in the selection of glucose-lowering agents. This review spanned the period from June 2020 to February 2023, and updates the last guideline published in 2020.

This chapter focusses exclusively on pharmacologic glycemic management for type 2 diabetes in adults. Physical activity [2], nutrition therapy [3], self-management education and support [4], and weight management [5] are other important components of glycemic management for type 2 diabetes, and are discussed in their own chapters. Similarly, related topics, such as targets for glycemic management [6], glucose monitoring [7], management of hypoglycemia [8], and remission of type 2 diabetes [9], are addressed in other chapters.

Initiating Pharmacotherapy

After counselling and support for health behaviour modification is provided, pharmacotherapy may be required to reach glycemic

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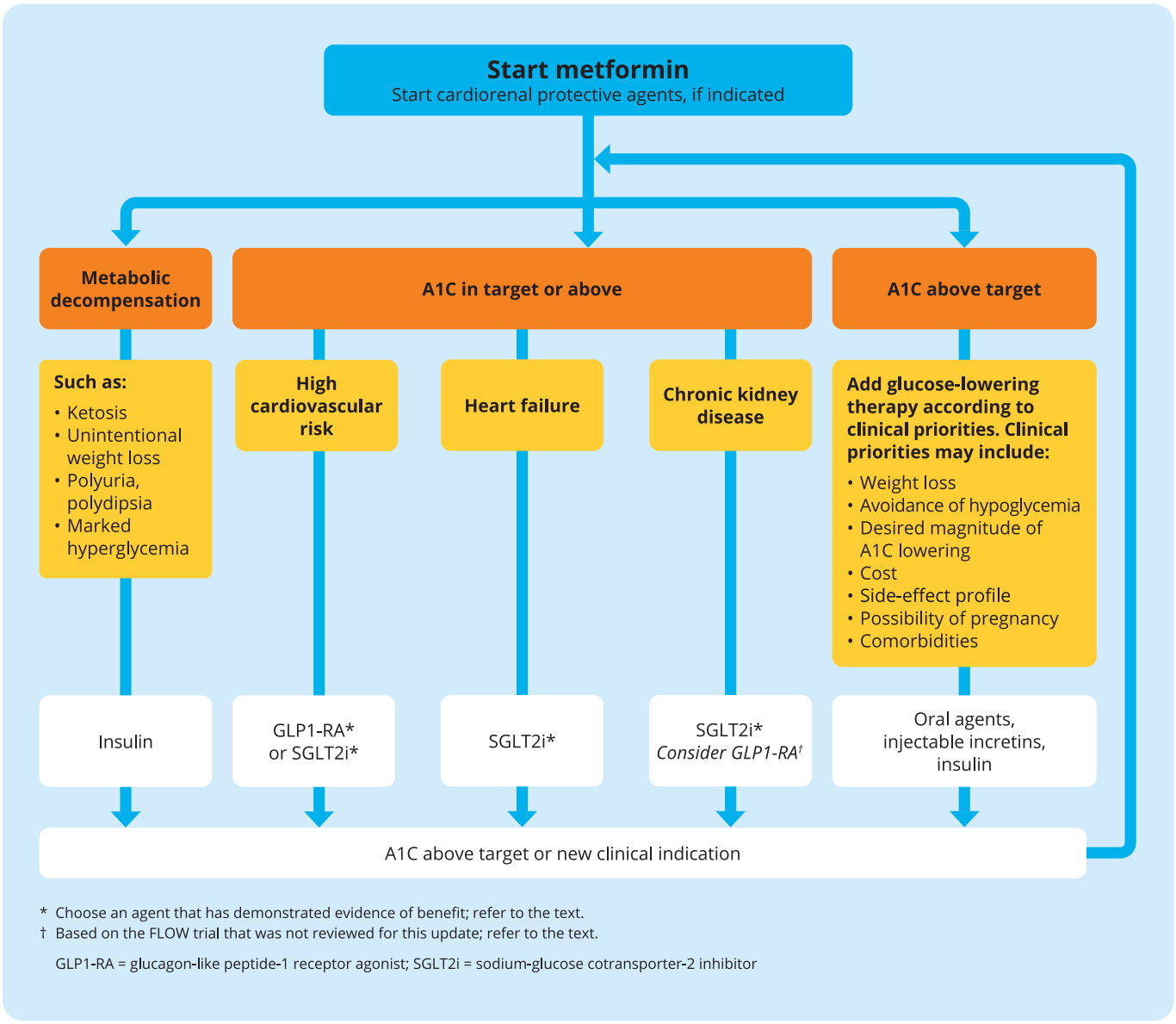


Figure 1. Pharmacotherapy for type 2 diabetes, to reach glycemic targets and optimize cardiorenal risk. *A1C*, glycated hemoglobin.

targets and to optimize cardiorenal risk (Figure 1). Metformin is the recommended first-line antihyperglycemic medication for most people. The preference for metformin as the initial agent is based on its durable efficacy in lowering A1C, absence of risk for hypoglycemia or weight gain, relatively mild side-effect profile, long-term safety track record, and affordability. Further, metformin monotherapy in newly-diagnosed participants who had overweight in the UKPDS demonstrated CV and all-cause mortality benefits [10]. Metformin monotherapy has comparable A1C-lowering effects to sulfonylureas, but better glycemic durability [11], negligible risk of hypoglycemia [12], no weight gain [12,13], and lower CV risk [13]. Metformin has better A1C lowering and weight loss than dipeptidyl peptidase-4 (DPP4) inhibitors [12,14]. To date, no studies have demonstrated superiority of SGLT2 inhibitors, GLP1-RAs, or glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonists (GIP/GLP1-RAs) over metformin as first-line therapy in people newly diagnosed with type 2 diabetes. Metformin should be started at a low dose (i.e. 250 mg or 500 mg twice daily with meals) and gradually increased over several weeks to a target dose of 2,000 mg daily. This slow increase minimizes the risk of gastrointestinal side effects. Minimal improvements in glucose occur at doses above this level. However, metformin cannot be used in everyone, such as those with a history of lactic acidosis, an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2, or severe hepatic dysfunction.

People who have evidence of metabolic decompensation (e.g. marked hyperglycemia, ketosis, hyperosmolar state or unintentional weight loss related to hyperglycemia) and/or severe symptomatic hyperglycemia (e.g. polyuria, polydipsia, or visual blurring) should be started immediately on insulin, with or without metformin, regardless of A1C level. Once stable, it may be possible to taper or discontinue insulin and replace it with other agents as required. Even in the absence of metabolic decompensation, people with marked hyperglycemia (e.g. A1C more than 1.5% above target) may require the initiation of other antihyperglycemic agents in combination with metformin at diagnosis for faster and greater improvements in glucose [15–20]. These additional agents may be able to be reduced or withdrawn over time if glycemia improves. Combining metformin with another agent at the outset lowers average A1C values by 0.4% to

Table 1
Antihyperglycemic agents for use in type 2 diabetes

Class and mechanism of action	Drug	A1C lowering*	Weight	Hypoglycemia	Other adverse events	Other therapeutic considerations	Cost
First Line for Most People							
Biguanides: Decrease hepatic glucose production; increase insulin sensitivity and glucose uptake by muscles and tissues; reduce intestinal glucose absorption.	• Metformin • Metformin extended-release	↓↓	↔	Negligible risk	• GI side effects, such as diarrhea, abdominal pain, nausea, vomiting [12] • Vitamin B12 deficiency [116–118]	• Diarrhea tends to resolve over time and is minimized with starting low dose, slow titration, taking with meals, and using extended-release preparation [119–122] • Assess vitamin B12 levels periodically or with symptoms of impaired proprioception or peripheral neuropathy	$
Second Line (in alphabetical order)							
Alpha-glucosidase inhibitors: Inhibit pancreatic amylase and intestinal glucosidase, which delays the breakdown and absorption of complex carbohydrates.	• Acarbose	↓	↔	Negligible risk	• GI side effects (e.g. flatulence, diarrhea) common • May elevate ALT		$$
Incretins — **DPP4 inhibitors:** Block the enzyme DPP4 which breaks down incretin hormones, thereby enhancing the effect of endogenous incretins: stimulating glucose-dependent insulin secretion; slowing gastric emptying; inhibiting glucagon release.	• Linagliptin • Saxagliptin • Sitagliptin	↓	↔	Negligible risk	• Pancreatitis reported in case reports, but not seen in larger studies [123]	• Avoid using with other incretins • Caution with saxagliptin in people with heart failure [124,125]	$$
Incretins — **GIP/GLP1 receptor agonists:** Potently activate GLP1 signaling pathway to stimulate glucose-dependent insulin secretion through activity at the GIP receptor and the GLP1 receptor.	• Tirzepatide	↓↓↓	↓↓↓	Negligible risk	• GI: Nausea, vomiting, diarrhea, constipation • Worsening retinopathy seen with rapid A1C lowering	• Avoid using with other incretins • Contraindicated with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2	$$$$
Incretins — **GLP1 receptor agonists:** Mimic the incretin hormone GLP1 that stimulates glucose-dependent insulin secretion; slows gastric emptying; inhibits glucagon release; enhances satiety.	• Dulaglutide • Liraglutide • Lixisenatide • Semaglutide (oral) • Semaglutide (subcutaneous)	↓↓ to ↓↓↓	↓↓ to ↓↓↓	Negligible risk	• GI: Nausea, vomiting, diarrhea, constipation [12] • Worsening retinopathy seen with rapid A1C lowering [60] • Pancreatitis reported in case reports, but not seen in larger studies [123,126]	• Avoid using with other incretins • Contraindicated with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2	$$$$
Insulins: Activate insulin receptors to regulate metabolism of carbohydrates, fat, and protein, and promote absorption of glucose by tissues; reduce glucose production and release by the liver.	**Basal Insulins** *Intermediate-acting* • NPH *Long-acting analogues* • Degludec U-100 • Degludec U-200 • Glargine U-100 • Glargine U-300 • Icodec† **Bolus (prandial) Insulins** *Short-acting* • Regular U-100 • Regular U-500 *Rapid-acting analogues* • Aspart • Aspart (faster-acting) • Glulisine • Lispro U-100 • Lispro U-200 **Premixed Insulins** • Premixed regular-NPH • Biphasic insulin aspart • Lispro/lispro protamine suspension	↓ to ↓↓↓	↑ to ↑↑	Significant risk		• Potentially greatest A1C reduction and no maximum dose • Numerous formulations and delivery systems allow for regimen flexibility	$ to $$$$
Secretagogues: Activate sulfonylurea receptors on pancreatic B-cells to stimulate endogenous insulin secretion.	**Sulfonylureas** • Gliclazide • Gliclazide modified-release • Glimepiride • Glyburide **Meglitinides** • Repaglinide	↓↓	↑	Minimal/moderate risk		• Relatively rapid glucose-lowering response • Meglitinides reduce postprandial hyperglycemia with minimal, if any, reduction in fasting hyperglycemia • Gliclazide preferred over glyburide due to lower risk of hypoglycemia • Repaglinide contraindicated when co-administered with dopidogrel or with gemfibrozil	$ to $$
SGLT2 inhibitors: Inhibit SGLT2 protein 2, thereby reducing glucose reabsorption by the kidney, leading to increased urinary glucose excretion, responsible for glucose-lowering effects; favourable impacts on renal and heart failure outcomes likely related to renal and systemic hemodynamic effects.	• Canagliflozin • Dapagliflozin • Empagliflozin	↓↓ Efficacy declines as eGFR declines	↓	Negligible risk	• Genital mycotic infections. [12, 40, 89] Women are at higher risk • Rare but important risk for euglycemic diabetic ketoacidosis [127] • Increased risk of fractures with canagliflozin [68, 128, 129] • Increased risk of lower extremity amputation with canagliflozin • No increased risk of urinary tract infection [130, 131]	• To prevent euglycemia DKA, SGLT2 inhibitors should be held or not used if fasting, if consuming a low-carbohydrate diet, if at risk for volume depletion (diarrhea, sepsis), or prior to major surgery • Caution in those at risk of volume depletion (e.g., loop diuretics) • Dapagliflozin not to be used with bladder cancer	$$ to $$$
Thiazolidinediones: Activate the gamma isoform of the peroxisome proliferator-activated receptor; enhance insulin sensitivity in the liver, muscles, and adipose tissues.	• Pioglitazone • Rosiglitazone	↓↓	↑	Negligible risk	• May induce edema and/or congestive heart failure, especially in combination with insulin [132] • Rare occurrence of macular edema • Higher occurrence of fractures • Decrease in triglyceride with pioglitazone	• Pioglitazone not to be used with bladder cancer • Controversy regarding MI risk for rosiglitazone	$$

* Maruthur et al 2016 (19); Mearns et al 2015 (24); Liu et al 2012 (23).
† Recently approved by Health Canada, but not included in the literature review for this update.

A1C, glycated hemoglobin; BG, blood glucose; CrCl, creatinine clearance; CV, cardiovascular; DPP4, Dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP1, glucagon-like peptide-1; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; MI; myocardial infarction; SGLT2, sodium-glucose cotransporter-2.

1% more than metformin alone and increases the chances of having an A1C <7% at 6 months by 40% [14–16,20]. The initial use of multiple agents at submaximal doses has also been shown to result in fewer side effects than monotherapy at maximal doses [21–25].

Certain GLP1-RAs and SGLT2 inhibitors are demonstrated in clinical trials to have specific benefits in people with high CV risk, HF, or CKD, as discussed below. These agents should be used as initial pharmacotherapy for individuals who already have these comorbidities or complications at the time of type 2 diabetes diagnosis. In general, initiating combination therapy of these agents with metformin is recommended because the majority of participants in these trials were on concomitant metformin therapy.

A1C will typically decrease by about 0.5% to 1.5% with monotherapy, varying with the baseline A1C level and the specific agent used. In general, the higher the baseline A1C, the greater the A1C reduction observed for any given agent. However, the A1C-lowering efficacy of SGLT2 inhibitors declines with decreasing eGFR. The maximum effect of non-insulin antihyperglycemic agent monotherapy generally occurs within 3 to 6 months [26,27].

Treatment Intensification or Modification

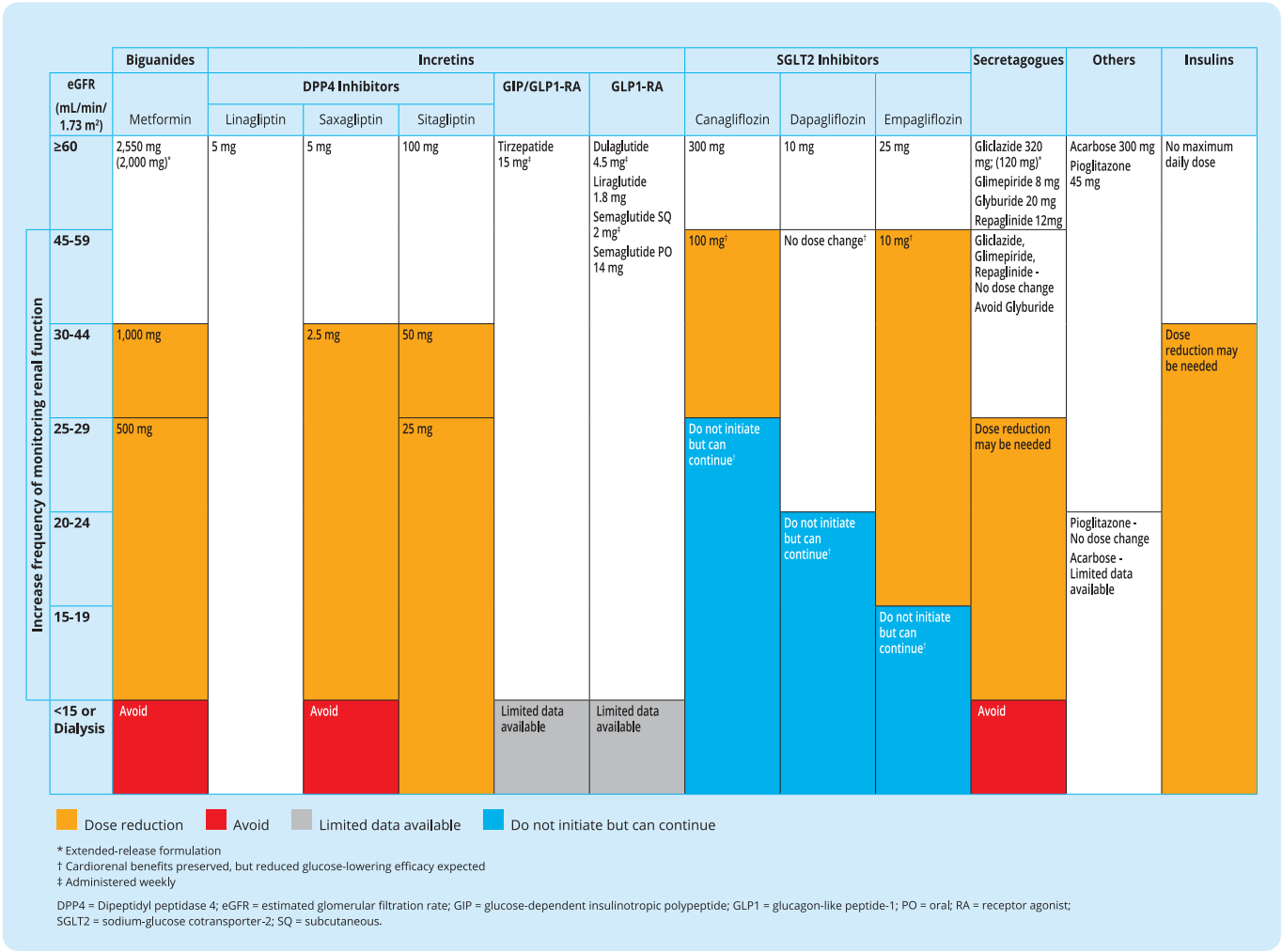
Over time, the function and number of beta cells can decline in those with type 2 diabetes, which results in higher glucose levels [28]. Thus, people with diabetes and their health-care providers need to continually monitor glycemia and consider stepwise intensification of pharmacotherapy when glycemic values rise above targets.

When considering pharmacotherapy intensification, health-care providers should first assess for and address potential precipitants of increasing A1C (e.g. infection, ischemia, concomitant medications, changes in eating or physical activity). They should also explore medication adherence and barriers to adherence, such as adverse drug effects, costs, beliefs, and preferences. After these assessments, dose adjustments and/or additional antihyperglycemic medications may be considered, with a goal of meeting the glycemic target within 3 to 6 months [29]. Health behaviour interventions, including nutritional therapy and physical activity, should continue to be optimized while pharmacotherapy is being intensified. When new agents are added to improve glycemic levels, existing glucose-lowering medications should generally be continued unless contraindicated.

When selecting additional antihyperglycemic agents, agent-specific advantages and disadvantages should be considered from an individualized person-centred perspective. Factors to consider include need and desire for weight loss, risks and importance of preventing hypoglycemia, the magnitude of glucose lowering required, costs and insurance coverage, adverse effect profiles, and comorbidities (Table 1). Maximum doses are often determined by renal function (eGFR), as indicated in Table 2. Simultaneous use of agents within the same class or with similar mechanisms of action (e.g. sulfonylureas and meglitinides; or DPP4 inhibitors, GIP/GLP1-RAs and GLP1-RAs) is not recommended.

Several meta-analyses have summarized head-to-head comparisons of metformin-based combinations [12,14,30–32]. These studies showed that combinations of metformin with sulfonylureas, thiazolidinediones, SGLT2 inhibitors, DPP4 inhibitors, or GLP1-RAs have broadly comparable A1C-lowering benefits [12,30–36]. In contrast, insulin does not have a dose limit and would therefore be expected to have the greatest potential for A1C lowering, although dose increases may be limited by hypoglycemia.

Table 2
Maximum daily dose of glucose-lowering medications (regular release formulations unless specified with footnotes)



* Extended-release formulation
† Cardiorenal benefits preserved, but reduced glucose-lowering efficacy expected
‡ Administered weekly

DPP4 = Dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; GIP = glucose-dependent insulinotropic polypeptide; GLP1 = glucagon-like peptide-1; PO = oral; RA = receptor agonist; SGLT2 = sodium-glucose cotransporter-2; SQ = subcutaneous.

While glucose lowering is broadly similar across agents in combination with metformin, impacts on hypoglycemia and weight change differ. The risk of hypoglycemia is lower with incretins, SGLT2 inhibitors, and thiazolidinediones compared to sulfonylureas and insulin [12,14,30–32,37,38]. Insulin, sulfonylureas, and thiazolidinediones are associated with the most weight gain (1.5 to 5.0 kg), DPP4 inhibitors have a neutral effect on weight, while GIP/GLP1-RAs, GLP1-RAs, and SGLT2 inhibitors lead to weight loss [12,14,30–32,39–42]. For the majority of people living with type 2 diabetes, for whom weight loss is a priority, treatment intensification with a GIP/GLP1-RA or GLP1-RA may be preferred as they can induce weight loss and have negligible risk for hypoglycemia. SGLT2 inhibitors may also be preferred as they can also lead to some weight loss and have negligible risk for hypoglycemia. Where financial barriers exist, sulfonylureas are the least expensive alternative. The safety of incretin agents or SGLT2 inhibitors in pregnancy is unknown; therefore, these agents should be avoided or discontinued in women who are pregnant, planning a pregnancy, or not using a reliable contraceptive method [43].

In some subgroups of people with type 2 diabetes, individual SGLT2 inhibitors and GLP1-RAs offer specific cardiorenal benefits. These medications should be prioritized for individuals from these subgroups, and are indicated even if the A1C is in target. Evidence and recommendations for these subgroups are summarized below and in Figure 1.

Individuals at high CV risk

Randomized trials [44–50] and meta-analyses of these trials [51–57] have demonstrated the benefits of certain GLP1-RAs and SGLT2 inhibitors in people with type 2 diabetes at high CV risk. The GLP1-RAs dulaglutide [44], liraglutide [45], and subcutaneous semaglutide [46] reduce major adverse CV events (MACE) in people at high CV risk. Alongside CV disease benefits, there is evidence for reductions in microvascular disease, including renal and retinal events, with these agents. Other GLP1-RAs, such as lixisenatide [58], long-acting exenatide [59], and oral semaglutide [60], have not been shown to impact cardiorenal outcomes. Similarly, 4 landmark trials have been completed with SGLT2 inhibitors in people at high CV risk: CANVAS and CANVAS-R [47], EMPA-REG OUTCOME [48], DECLARE-TIMI 58 [49], and VERTIS-CV [50]. Both canagliflozin and empagliflozin reduce MACE outcomes in this population; dapagliflozin and ertugliflozin do not. Individual components of the MACE composite endpoint have shown inconsistent effects between trials owing to low event rates, heterogeneity of study populations, and methodological decisions. Beyond MACE, SGLT2 inhibitors have also shown reductions in HF and renal outcomes for individuals at high CV risk.

Importantly, however, the definition of “high CV risk” was quite variable between these trials. Some recruited only people with established CV disease, while most enrolled both those with

established CV disease and those at older ages with multiple CV risk factors. There was significant heterogeneity across trials in the definitions of this latter group: the minimum age threshold ranged from 50 to 60; the list of eligible risk factors was variable (including risk factors like hypertension, dyslipidemia, tobacco use, microalbuminuria, left ventricular systolic or diastolic dysfunction, and longer duration of diabetes); and some trials required 2 risk factors to be present in addition to age while others only required 1. Meta-analyses of both the GLP1-RA trials [51–55] and the SGLT2 inhibitor trials [55–57] found that the benefit of these agents among those with established CV disease was clear; however, the benefit for those with multiple CV risk factors only was less certain.

In the absence of multiple CV risk factors, there is no robust evidence for the use of any specific second-line antihyperglycemic agent for the prevention of MACE.

Individuals with HF

Randomized controlled trials of dapagliflozin and empagliflozin have demonstrated cardiorenal benefits for people who have HF with either reduced ejection fraction ≤40% [61,62] or preserved ejection fraction >40% [63,64]. Approximately one-half of individuals in these trials did not have diabetes. The benefits of dapagliflozin and empagliflozin were observed in the composite outcomes of CV death or hospitalization for HF across major subgroups, including those with and without diabetes, HF with reduced or preserved ejection fraction, New York Heart Association functional class, and the presence or absence of CKD [65,66]. Furthermore, SGLT2 inhibitors may reduce MACE and renal outcomes in those with a history of HF [67].

Individuals with CKD

Several large-scale randomized controlled trials have demonstrated benefits of specific SGLT2 inhibitors on cardiorenal outcomes among people with CKD. The CREDENCE, DAPA-CKD, and EMPA-KIDNEY trials showed that canagliflozin, dapagliflozin, and empagliflozin, respectively, are associated with a reduction in the composite outcome of death from renal or CV causes, end-stage renal disease, or worsening of serum creatinine or eGFR [68–70]. Importantly, one-third of individuals in DAPA-CKD and more than one-half of individuals in EMPA-KIDNEY did not have type 2 diabetes, and subgroup analysis showed similar results between the participants with and without diabetes. These trials also showed benefits of these agents on CV and HF endpoints among people with CKD [71]. Meta-analyses of the CKD subgroups in the atherosclerotic CV disease and HF trials of SGLT2 inhibitors similarly demonstrated benefits on CV, HF, and renal outcomes. Although a similar meta-analysis of the CKD subgroups from GLP1-RA trials did not demonstrate consistent benefits [72], the recently published FLOW trial specifically examined renal outcomes for subcutaneous semaglutide in individuals with type 2 diabetes and CKD [73]. However, this trial was not included in the literature review for this update and so is not discussed here.

Insulin Treatment With Type 2 Diabetes

A combination of non-insulin antihyperglycemic agents and insulin is often effective to manage glucose levels. The insulin regimen in type 2 diabetes should be tailored to the individual to reach their individualized glycemic levels and to minimize risk of hypoglycemia. The mode of insulin administration (injections vs continuous subcutaneous infusion), the number of insulin injections (1 to 4 per day), and the timing of injections will depend on each individual's situation. Adding insulin to non-insulin antihyperglycemic agents may result in better glycemic levels with a lower dose of insulin [74], and may induce less weight gain and less hypoglycemia than that seen when non-insulin antihyperglycemic agents are stopped and insulin is used alone [75,76].

Figure 2 summarizes a stepwise approach to insulin regimens for people with type 2 diabetes. As a first step, a single daily injection of an intermediate-acting (NPH) [77] or long-acting insulin analogue (insulin glargine U-100, insulin glargine U-300, insulin detemir, or insulin degludec) [78–80] may be added, particularly for people with fasting hyperglycemia. Insulin icodec was recently approved in Canada with once-weekly dosing; however, it was not included in the literature review for this update and so is not discussed here. Incretins and SGLT2 inhibitors have been shown to be efficacious at further lowering glucose levels when combined with insulin therapy [81–94]. These agents should therefore be continued and/or initiated for people starting basal insulin. The basal insulin dose should be titrated to the fasting glucose levels; insulin requirements will likely increase as diabetes progresses, and higher doses may be needed over time.

If glycemia is suboptimal on treatment regimens that include basal insulin with other agents, bolus insulin at mealtimes (short- or rapid-acting analogues) may be added. Generally, once bolus insulin is introduced into a treatment regimen, either as a separate mealtime bolus or as part of a premixed regimen, insulin secretagogues, such as sulfonylureas and meglitinides, should be discontinued due to an increased risk for hypoglycemia. Concomitant therapy with metformin, incretins, and SGLT2 inhibitors should be continued with regimens containing bolus insulin to support glycemic management with less risk of weight gain and hypoglycemia [75,76,81–102]. Bolus insulin should be initiated using a stepwise approach, starting with 1 injection at the largest meal and then introducing additional mealtime injections later, if needed. This approach was shown to be as efficacious at A1C lowering as a full basal-bolus regimen, but is associated with less hypoglycemia and greater satisfaction after 1 year [103]. Bolus insulin doses are titrated to the postprandial glucose levels.

Lower rates of hypoglycemia have been observed in some studies of individuals with type 2 diabetes treated with rapid-acting insulin analogues compared to those treated with short-acting (regular) insulin [104–107]. Use of long-acting basal insulin analogues reduces the relative risk of symptomatic and nocturnal hypoglycemia compared to treatment with NPH insulin [104,108-110]. Insulin degludec is associated with lower rates of overall, symptomatic, nocturnal, and severe hypoglycemia compared to glargine U-100 [78,80,111–113]. There is also some evidence of lower hypoglycemia rates with glargine U-300 compared to glargine U-100 [114]. Efficacy and rates of hypoglycemia are similar between glargine U-100 and detemir [115].

Recommendations

Initial pharmacologic glycemic management

1. Physical activity, nutrition therapy, self-management education and support, and weight management are important components of glycemic management for type 2 diabetes, both at onset and throughout the course of the disease, and should be incorporated into every person's individualized care plan [Grade D, Consensus].
2. Once the decision to initiate pharmacotherapy is made, metformin is recommended as the initial antihyperglycemic medication because of its durable efficacy in lowering A1C, negligible risk for hypoglycemia or weight gain [12] [Grade A, Level 1A], relatively mild side-effect profile, long-term track record, and affordability. Initial dose should be low (250 mg or 500 mg twice daily with meals) to minimize risk of

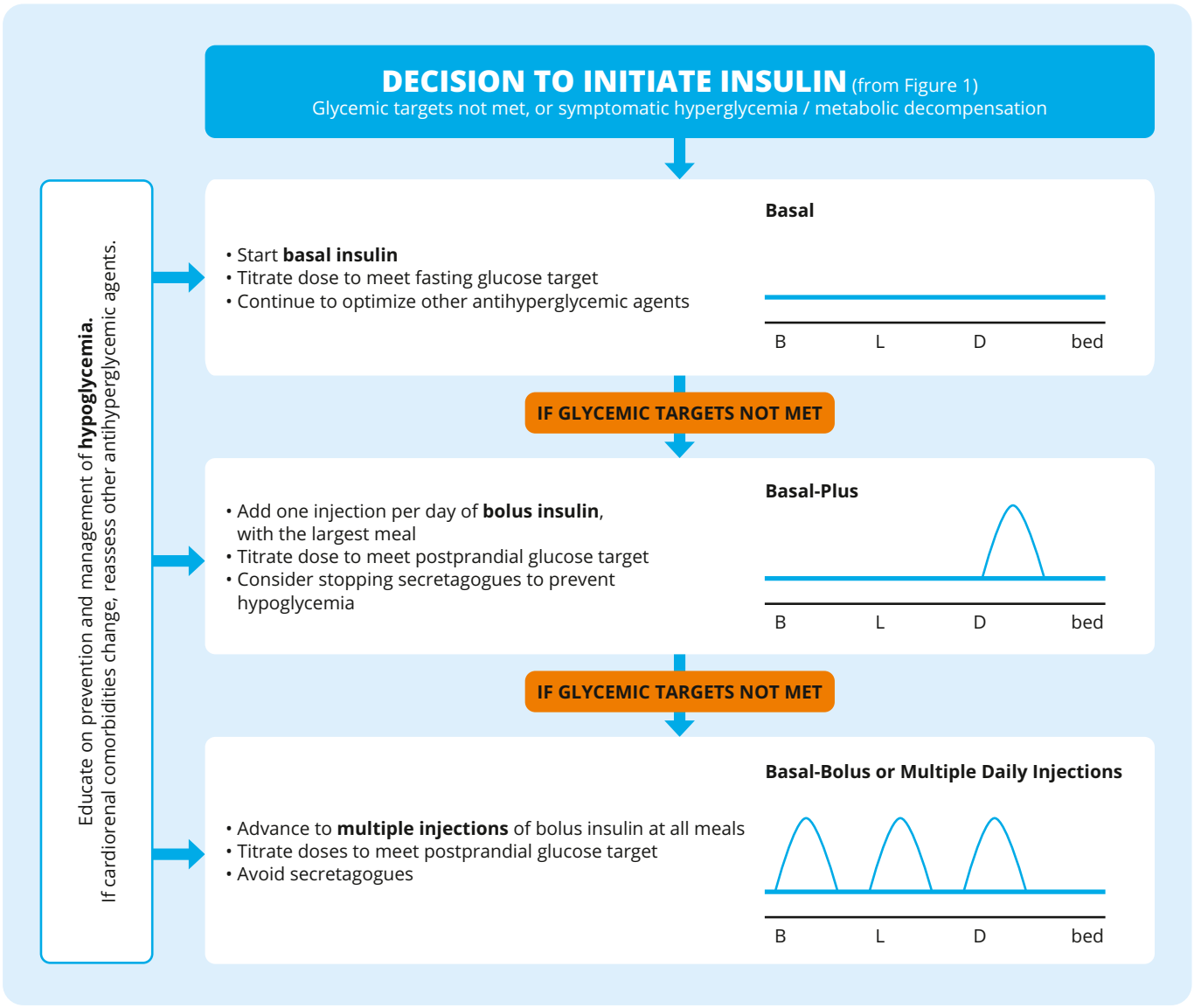


Figure 2. Stepwise approach to insulin regimens for people with type 2 diabetes. *B*, breakfast; *D*, dinner; *L*, lunch.

gastrointestinal side effects, with gradual increase to maximum dose [Grade D, Consensus].

3. Insulin, with or without metformin, is recommended as initial pharmacologic therapy for individuals with metabolic decompensation (e.g. marked hyperglycemia, ketosis, hyperosmolar state, or unintentional weight loss related to hyperglycemia) and/or severe symptomatic hyperglycemia (polyuria, polydipsia, visual blurring). Once metabolically stable, it may be possible to taper or discontinue insulin and replace it with other agents, as required [Grade D, Consensus].
4. Even in the absence of metabolic decompensation, combination therapy is recommended as initial pharmacologic therapy for people with marked hyperglycemia (e.g. A1C more than 1.5% above target) [15,17,18] [Grade B, Level 2].
   a. Choice of the second agent to start alongside metformin should be based on the individual's priorities, preferences, and comorbidities [Grade D, Consensus].
5. For individuals with cardiovascular or renal comorbidities at the time of diabetes diagnosis, specific GLP1-RAs and/or SGLT2 inhibitors should also be used as initial pharmacotherapy for cardiorenal protection (see recommendation #10).

Ongoing assessment

6. Dose adjustments, substitutions, and/or addition of other antihyperglycemic medications should be made in order to reach the target A1C within 3 to 6 months [Grade D, Consensus].
7. Cardiovascular and renal status should be reviewed at least annually to determine if treatment intensification or modification is required [Grade D, Consensus].
8. Before intensifying pharmacologic therapy, assess for potential precipitants of increasing A1C, such as infection, ischemia, concomitant medications, or changes in eating or physical activity. Explore medication adherence and barriers to adherence, such as adverse drug effects, costs, beliefs, and preferences [Grade D, Consensus].

Treatment intensification or modification

9. For individuals who do not have CV or renal comorbidities, choice of an antihyperglycemic medication when treatment

intensification is required should be based on the individual's priorities, preferences, and comorbidities (see Figure 1 and Table 1) [12]. Clinical priorities may include weight loss, avoidance of hypoglycemia, desired magnitude of glucose lowering, cost, side-effect profile, possibility of pregnancy, and comorbidities [Grade D, Consensus].

10. Priority should be given to medications with specific cardiorenal benefits for certain subgroups of individuals, regardless of the A1C level.
    a. A GLP1-RA and/or SGLT2 inhibitor with demonstrated evidence of benefit is recommended for individuals at high CV risk [44–48,51–57] [Grade A, Level 1A for dulaglutide, liraglutide, or subcutaneous semaglutide; Grade A, Level 1A for empagliflozin; Grade B, Level 2 for canagliflozin].
    b. An SGLT2 inhibitor with demonstrated evidence of benefit is recommended for individuals with HF with reduced ejection fraction [61,62] or HF with preserved ejection fraction [63,64] [Grade A, Level 1A for dapagliflozin or empagliflozin].
    c. An SGLT2 inhibitor with demonstrated evidence of benefit is recommended for individuals with CKD [68–70] [Grade A, Level 1A for canagliflozin, dapagliflozin, or empagliflozin].

Adding insulin to current antihyperglycemic therapy

11. All individuals starting insulin should receive education on the prevention and management of hypoglycemia [Grade D, Consensus].
12. A single daily injection of a basal insulin is recommended as the initial insulin regimen when adding to current antihyperglycemic therapy (see Figure 2), with dosing titrated to reach the fasting glucose target [Grade D, Consensus].
    a. Long-acting insulin analogues should be considered over NPH insulin to reduce the risk of hypoglycemia [104,108–110] [Grade A, Level 1A].
    b. Insulin degludec or insulin glargine U-300 may be considered over other long-acting insulin analogues to reduce the risk of nocturnal hypoglycemia [78,80,111–114] [Grade B, Level 2 for individuals with risk factors for hypoglycemia; Grade C, Level 3 for other individuals].
13. An incretin and/or SGLT2 inhibitor should be continued or initiated when introducing basal insulin [81–102] [Grade A, Level 1A].
14. If bolus insulin is required, it should be initiated using a stepwise approach [103], starting with 1 injection at the largest meal and then introducing additional mealtime injections later if needed (see Figure 2). Dosing should be titrated to reach postprandial glucose targets [Grade B, Level 2].
    a. Rapid-acting insulin analogues may be considered over short-acting (regular) insulin to reduce the risk of hypoglycemia [104–107] [Grade B, Level 2].
    b. Insulin secretagogues (sulfonylureas and meglitinides) should be discontinued to reduce the risk of hypoglycemia [Grade D, Consensus].

External Reviewers

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