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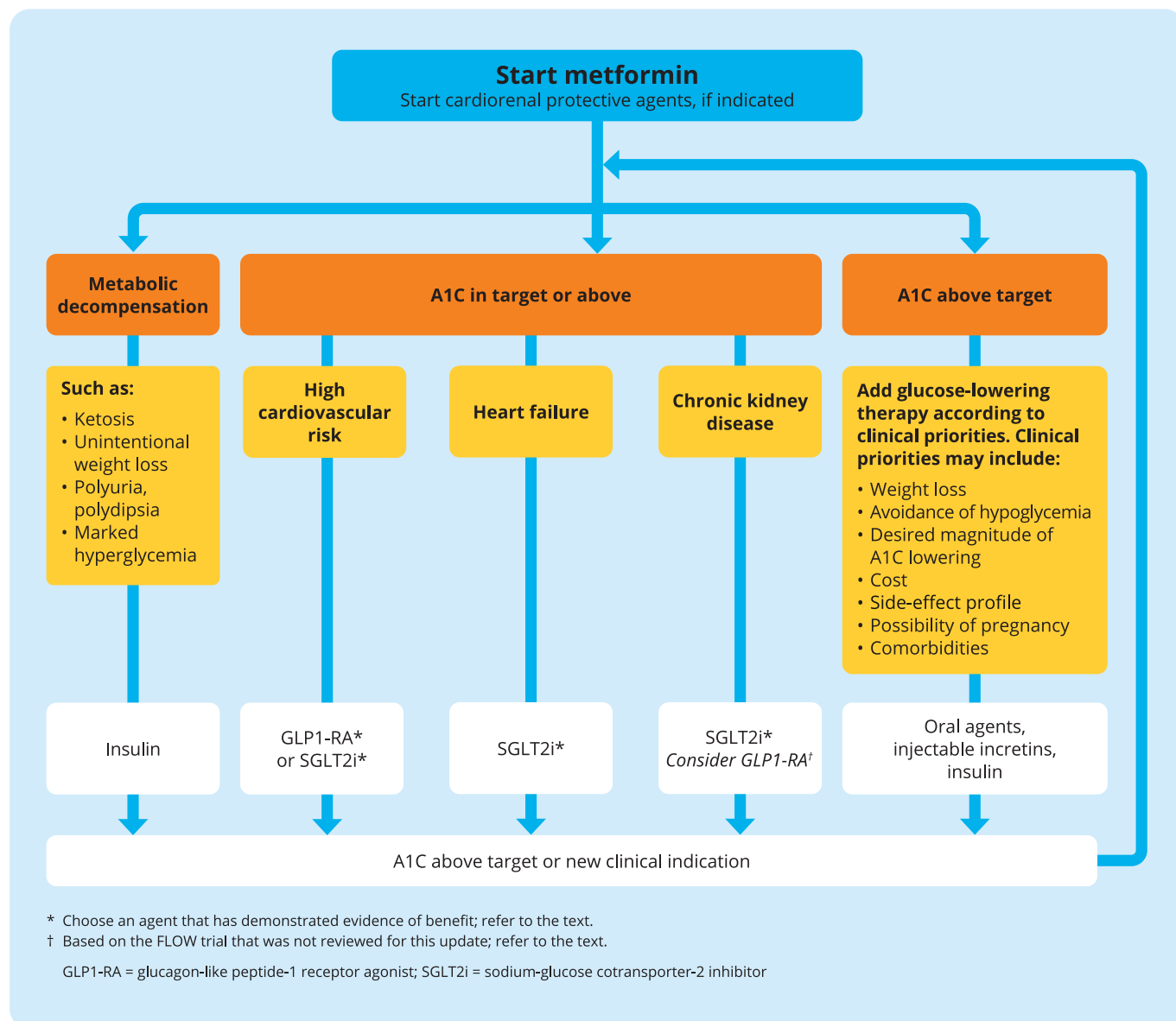
Figure 1. Pharmacotherapy for type 2 diabetes, to reach glycemic targets and optimize cardiorenal risk. *A1C*, glycated hemoglobin.

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		$$
DPP4 inhibitors: Block the enzyme DPP4 which breaks down incretin hormones, thereby enhancing the effect of endogenous incretins: stimulating glucose-dependent insulin secretion; slowing gastric emptying; inhibiting glucagon release.	• Linagliptin • Saxagliptin • Sitagliptin	↓	↔	Negligible risk	• Pancreatitis reported in case reports, but not seen in larger studies [123]	• Avoid using with other incretins • Caution with saxagliptin in people with heart failure [124,125]	$$
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	$$$$
GLP1 receptor agonists: Mimic the incretin hormone GLP1 that stimulates glucose-dependent insulin secretion; slows gastric emptying; inhibits glucagon release; enhances satiety.	• Dulaglutide • Liraglutide • Lixisenatide • Semaglutide (oral) • Semaglutide (subcutaneous)	↓↓ to ↓↓↓	↓↓ to ↓↓↓	Negligible risk	• GI: Nausea, vomiting, diarrhea, constipation [12] • Worsening retinopathy seen with rapid A1C lowering [60] • Pancreatitis reported in case reports, but not seen in larger studies [123,126]	• Avoid using with other incretins • Contraindicated with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2	$$$$
Insulins: Activate insulin receptors to regulate metabolism of carbohydrates, fat, and protein, and promote absorption of glucose by tissues; reduce glucose production and release by the liver.	**Basal Insulins** *Intermediate-acting* • NPH *Long-acting analogues* • Degludec U-100 • Degludec U-200 • Glargine U-100 • Glargine U-300 • Icodec† **Bolus (prandial) Insulins** *Short-acting* • Regular U-100 • Regular U-500 *Rapid-acting analogues* • Aspart • Aspart (faster-acting) • Glulisine • Lispro U-100 • Lispro U-200 **Premixed Insulins** • Premixed regular-NPH • Biphasic insulin aspart • Lispro/lispro protamine suspension	↓ to ↓↓↓	↑ to ↑↑	Significant risk		• Potentially greatest A1C reduction and no maximum dose • Numerous formulations and delivery systems allow for regimen flexibility	$ to $$$$
Secretagogues: Activate sulfonylurea receptors on pancreatic B-cells to stimulate endogenous insulin secretion.	**Sulfonylureas** • Gliclazide • Gliclazide modified-release • Glimepiride • Glyburide **Meglitinides** • Repaglinide	↓↓	↑	Minimal/ moderate risk		• Relatively rapid glucose-lowering response • Meglitinides reduce postprandial hyperglycemia with minimal, if any, reduction in fasting hyperglycemia • Gliclazide preferred over glyburide due to lower risk of hypoglycemia • Repaglinide contraindicated when co-administered with clopidogrel or with gemfibrozil	$ to $$
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 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)

eGFR (mL/min/1.73 m²)	Biguanides: Metformin	Incretins — DPP4 Inhibitors: Linagliptin	Saxagliptin	Sitagliptin	GIP/GLP1-RA	GLP1-RA	SGLT2 Inhibitors: Canagliflozin	Dapagliflozin	Empagliflozin	Secretagogues	Others	Insulins
≥60	2,550 mg (2,000 mg)*	5 mg	5 mg	100 mg	Tirzepatide 15 mg‡	Dulaglutide 4.5 mg‡ Liraglutide 1.8 mg Semaglutide SQ 2 mg‡ Semaglutide PO 14 mg	300 mg	10 mg	25 mg	Gliclazide 320 mg; (120 mg)* Glimepiride 8 mg Glyburide 20 mg Repaglinide 12mg	Acarbose 300 mg Pioglitazone 45 mg	No maximum daily dose
45-59							100 mg†	No dose change†	10 mg†	Gliclazide, Glimepiride, Repaglinide - No dose change Avoid Glyburide		
30-44	1,000 mg		2.5 mg	50 mg								Dose reduction may be needed
25-29	500 mg			25 mg			Do not initiate but can continue†			Dose reduction may be needed		
20-24								Do not initiate but can continue†			Pioglitazone - No dose change Acarbose - Limited data available	
15-19									Do not initiate but can continue†			
<15 or Dialysis	Avoid		Avoid		Limited data available	Limited data available				Avoid		

Increase frequency of monitoring renal function

Legend: ■ Dose reduction ■ Avoid ■ Limited data available ■ Do not initiate but can continue

* 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.
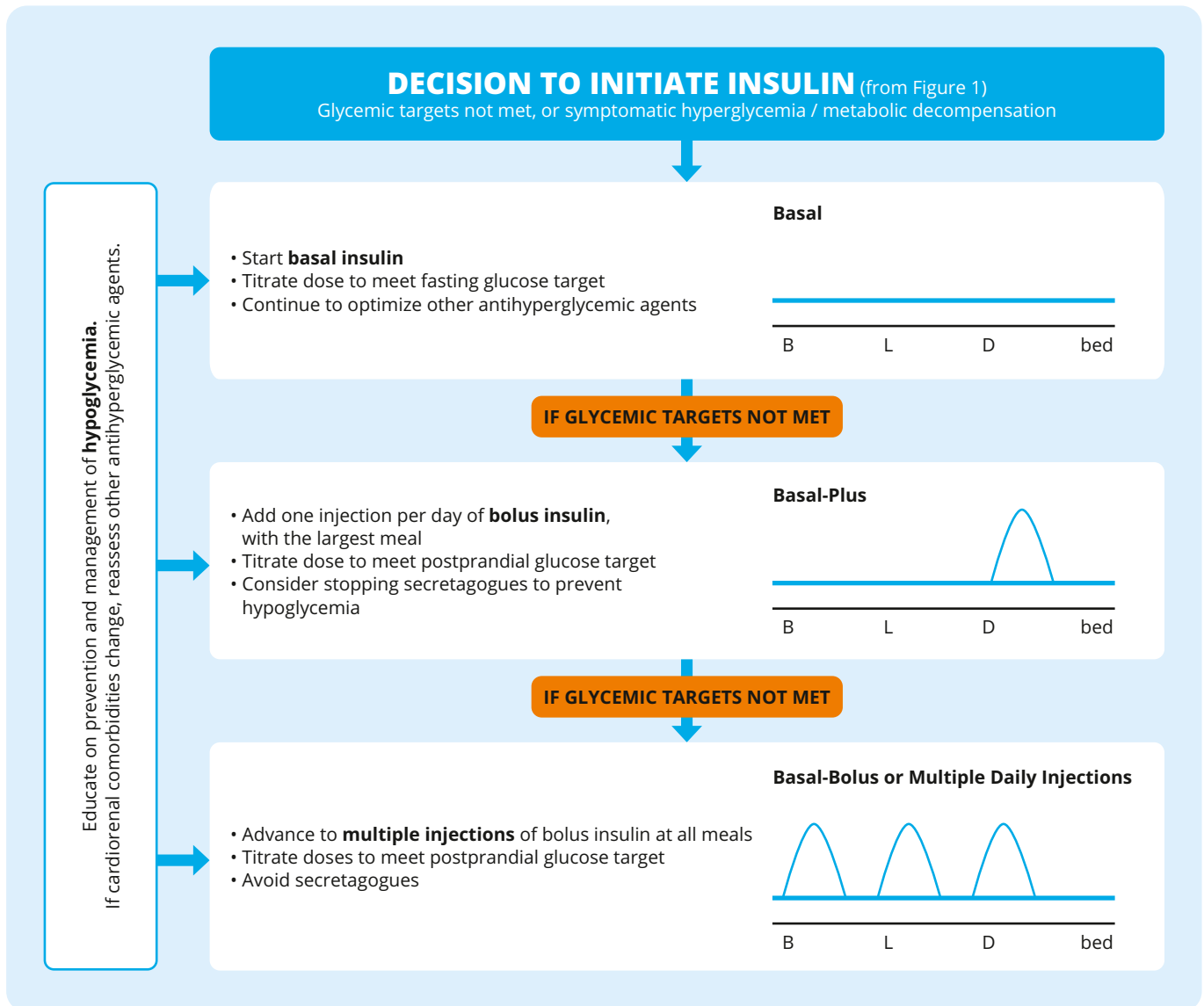
Lower rates of hypoglycemia have been observed in some studies of individuals with type 2 diabetes treated with rapid-acting insulin analogues compared to those treated with short-acting (regular) insulin [104–107]. Use of long-acting basal insulin analogues reduces the relative risk of symptomatic and 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

DECISION TO INITIATE INSULIN (from Figure 1)
Glycemic targets not met, or symptomatic hyperglycemia / metabolic decompensation

Educate on prevention and management of **hypoglycemia.**
If cardiorenal comorbidities change, reassess other antihyperglycemic agents.

Basal
- Start **basal insulin**
- Titrate dose to meet fasting glucose target
- Continue to optimize other antihyperglycemic agents

B   L   D   bed

IF GLYCEMIC TARGETS NOT MET

Basal-Plus
- Add one injection per day of **bolus insulin**, with the largest meal
- Titrate dose to meet postprandial glucose target
- Consider stopping secretagogues to prevent hypoglycemia

B   L   D   bed

IF GLYCEMIC TARGETS NOT MET

Basal-Bolus or Multiple Daily Injections
- Advance to **multiple injections** of bolus insulin at all meals
- Titrate doses to meet postprandial glucose target
- Avoid secretagogues

B   L   D   bed

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 step-wise 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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Author Disclosures

References

[1] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352(9131):837–53.
[2] Sigal RJ, Armstrong MJ, Bacon SL, Boule NG, Dasgupta K, Kenny GP, et al. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Physical activity and diabetes. Can J Diabetes 2018;42(Suppl. 1):S54–63.
[3] Sievenpiper JL, Chan CB, Dworatzek PD, Freeze C, Williams SL. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Nutrition therapy. Can J Diabetes 2018;42-(Suppl. 1):S64–79.
[4] Sherifali D, Berard LD, Gucciardi E, MacDonald B, MacNeill G. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Self-management education and support. Can J Diabetes 2018;42(Suppl. 1):S36–41.
[5] Wharton S, Pedersen SD, Lau DJR, Sharma AM. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Weight management in diabetes. Can J Diabetes 2018;42(Suppl. 1): S124–9.
[6] Imran SA, Agarwal G, Bajaj HS, Ross S. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Targets for glycemic control. Can J Diabetes 2018;42(Suppl. 1):S42–5.
[7] Berard LD, Siemens R, Woo V. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Monitoring glycemic control. Can J Diabetes 2018;42(Suppl. 1):S47–53.
[8] Lega IC, Yale JF, Chadha A, Paty B, Roscoe R, Snider M, Steier J. Hypoglycemia in adults. Can J Diabetes 2023;47(7):548–59.
[9] MacKay D, Chan C, Dasgupta K, Dominy C, Gagner M, Jin S, Kim J, et al. Remission of type 2 diabetes. Can J Diabetes 2023;46(8):753–61.
[10] UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–65.
[11] Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–43.
[12] Maruthur NM, Tseng E, Hutfless S, Wilson LM, Suarez-Cuervo C, Berger Z, Chu Y, Iyoha E, Segal JB, Bolen S. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: A systematic review and meta-analysis. Ann Intern Med 2016;164:740–51.
[13] Hong J, Zhang Y, Lai S, Lv A, Su Q, Dong Y, Zhou Z, Tang W, Zhao J, Cui L, Zou D, Wang D, Li H, Liu C, Wu G, Shen J, Zhu D, Wang W, Shen W, Ning G; SPREAD-DIMCAD Investigators. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care 2013;36:1304–11.
[14] Palmer SC, Mavridis D, Nicolucci A, Johnson DW, Tonelli M, Craig JC, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: A meta-analysis. JAMA 2016;316:313–24.
[15] Phung OJ, Sobieraj DM, Engel SS, Rajpathak SN. Early combination therapy for the treatment of type 2 diabetes mellitus: Systematic review and meta-analysis. Diabetes Obes Metab 2014;16:410–7.
[16] Rosenstock J, Chuck L, Gonzalez-Ortiz M, Merton K, Craig J, Capuano G, Qiu R. Initial combination therapy with canagliflozin plus metformin versus each component as monotherapy for drug naive type 2 diabetes. Diabetes Care 2016;39:353–62.
[17] Gao W, Dong J, Liu J, Li Y, Liu F, Yang L, et al. Efficacy and safety of initial combination of DPP-IV inhibitors and metformin versus metformin monotherapy in type 2 diabetes: A systematic review of randomized controlled trials. Diabetes Obes Metab 2014;16:179–85.
[18] Milder TY, Stocker SL, Abdel Shaheed C, McGrath-Cadell L, Samocha-Bonet D, Greenfield JR, et al. Combination therapy with an SGLT2 inhibitor as initial treatment for type 2 diabetes: A systematic review and meta-analysis. J Clin Med 2019;8(1):45.
[19] Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S; VERIFY study group. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy

in newly diagnosed type 2 diabetes (VERIFY): A 5-year, multicentre, randomised, double-blind trial. Lancet 2019;394(10208):1519—29.

[20] Frias JP, Zimmer Z, Lam RLH, Amorin G, Ntabadde C, Iredale C, et al. Double-blind, randomized clinical trial assessing the efficacy and safety of early initiation of sitagliptin during metformin uptitration in the treatment of patients with type 2 diabetes: The CompoSIT-M study. Diabetes Obes Metab 2019;21(5):1128—35.

[21] Hadjadj S, Rosenstock J, Meinicke T, Woerle HJ, Broedl UC. Initial combination of empagliflozin and metformin in patients with type 2 diabetes. Diabetes Care 2016;39:1718—28.

[22] Garber AJ, Larsen J, Schneider SH, Piper BA, Henry D; Glyburide/Metformin Initial Therapy Study Group. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. Diabetes Obes Metab 2002;4:201—8.

[23] Rosenstock J, Goldstein BJ, Vinik AI, O'Neill MC, Porter LE, Heise MA, Kravitz B, Dirani RG, Freed MI; RESULT Study Group. Effect of early addition of rosiglitazone to sulphonylurea therapy in type 2 diabetes patients (>60 years): The Rosiglitazone Early vs. SULphonylurea Titration (RESULT) study. Diabetes Obes Metab 2006;8:49—57.

[24] Rosenstock J, Rood J, Cobitz A, Huang C, Garber A. Improvement in glycaemic control with rosiglitazone/metformin fixed-dose combination therapy in patients with type 2 diabetes with very poor glycaemic control. Diabetes Obes Metab 2006;8:643—9.

[25] Rosenstock J, Rood J, Cobitz A, Biswas N, Chou H, Garber A. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. Diabetes Obes Metab 2006;8:650—60.

[26] Bloomgarden ZT, Dodis R, Viscoli CM, Holmboe ES, Inzucchi SE. Lower baseline glycemia reduces apparent oral agent glucose-lowering efficacy: A meta-regression analysis. Diabetes Care 2006;29:2137—9.

[27] Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The effect of oral antidiabetic agents on A1C levels: A systematic review and meta-analysis. Diabetes Care 2010;33:1859—64.

[28] Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: Progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999;281:2005—12.

[29] Paul SK, Klein K, Thorsted BL, Wolden ML, Khunti K. Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. Cardiovasc Diabetol 2015;14:100.

[30] Mearns ES, Sobieraj DM, White CM, Saulsberry WJ, Kohn CG, Doleh Y, Zaccaro E, Coleman CI. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: A network meta-analysis. PLoS One 2015;10:e0125879.

[31] Mishriky BM, Cummings DM, Tanenberg RJ. The efficacy and safety of DPP4 inhibitors compared with sulfonylureas as add-on therapy to metformin in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract 2015;109:378—88.

[32] Foroutan N, Muratov S, Levine M. Safety and efficacy of dipeptidyl peptidase-4 inhibitors vs sulfonylurea in metformin-based combination therapy for type 2 diabetes mellitus: Systematic review and meta-analysis. Clin Invest Med 2016;39:E48—62.

[33] Chubb B, Gupta P, Gupta J, Nuhoho S, Kallenbach K, Orme M. Once-daily oral semaglutide versus injectable GLP-1 RAs in people with type 2 diabetes inadequately controlled on basal insulin: Systematic review and network meta-analysis diabetes therapy. Res Treat Educ Diabetes Relat Disord 2021;12(5):1325—39.

[34] Clar C, Gill JA, Court R, Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2012;2:e001007.

[35] Hartley P, Shentu Y, Betz-Schiff P, Golm GT, Sisk CM, Engel SS, Shankar RR. Efficacy and tolerability of sitagliptin compared with glimepiride in elderly patients with type 2 diabetes mellitus and inadequate glycemic control: A randomized, double-blind, non-inferiority trial. Drugs Aging 2015;32:469—76.

[36] Zhong X, Lai D, Ye Y, Yang X, Yu B, Huang Y. Efficacy and safety of empagliflozin as add-on to metformin for type 2 diabetes: A systematic review and meta-analysis. Eur J Clin Pharmacol 2016;72:655—63.

[37] Zhou JB, Bai L, Wang Y, Yang JK. The benefits and risks of DPP4-inhibitors vs. sulfonylureas for patients with type 2 diabetes: Accumulated evidence from randomised controlled trial. Int J Clin Pract 2016;70:132—41.

[38] Min SH, Yoon JH, Hahn S, Cho YM. Comparison between SGLT2 inhibitors and DPP4 inhibitors added to insulin therapy in type 2 diabetes: A systematic review with indirect comparison meta-analysis. Diabetes Metab Res Rev 2016;33.

[39] Liu SC, Tu YK, Chien MN, Chien KL. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: A network meta-analysis. Diabetes Obes Metab 2012;14:810—20.

[40] Mearns ES, Saulsberry WJ, White CM, Kohn CG, Lemieux S, Sihabout A, et al. Efficacy and safety of antihyperglycaemic drug regimens added to metformin and sulphonylurea therapy in type 2 diabetes: A network meta-analysis. Diabet Med 2015;32:1530—40.

[41] Lee CMY, Woodward M, Colagiuri S. Triple therapy combinations for the treatment of type 2 diabetes—a network meta-analysis. Diabetes Res Clin Pract 2016;116:149—58.

[42] Lozano-Ortega G, Goring S, Bennett HA, Bergenheim K, Sternhufvud C, Mukherjee J. Network meta-analysis of treatments for type 2 diabetes mellitus following failure with metformin plus sulfonylurea. Curr Med Res Opin 2016;32:807—16.

[43] Feig D, Berger H, Donovan L, Godbout A, Kader T, Keely E, Sanghera R. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Diabetes and pregnancy. Can J Diabetes 2018;42(Suppl. 1):S255—82.

[44] Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Riesmeyer JS, Riddle MC, Rydén L, Xavier D, Atisso CM, Dyal L, Hall S, Rao-Melacini P, Wong G, Avezum A, Basile J, Chung N, Conget I, Cushman WC, Franek E, Hancu N, Hanefeld M, Holt S, Jansky P, Keltai M, Lanas F, Leiter LA, Lopez-Jaramillo P, Cardona Munoz EG, Pirags V, Pogosova N, Raubenheimer PJ, Shaw JE, Sheu WH, Temelkova-Kurktschiev T; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): A double- blind, randomised placebo-controlled trial. Lancet 2019;394:121—30.

[45] Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311—22.

[46] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834—44.

[47] Neal B, Perkovic V, Neal B, Perkovic V, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644—57.

[48] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117—28.

[49] Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE—TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347—57.

[50] Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, Charbonnel B, Frederich R, Gallo S, Cosentino F, Shih WJ, Gantz I, Terra SG, Cherney DZI, McGuire DK; VERTIS CV Investigators. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383(15):1425—35.

[51] Sattar N, Lee MM, Kristensen SL, Branch KR, Del Prato S, Khurmi NS, Gerstein HC. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A systematic review and meta-analysis of randomised trials. The lancet Diabetes Endocrinol 2021;9(10):653—62.

[52] Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, McMurray JJ. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol 2019;7(10):776—85.

[53] Giugliano D, Scappaticcio L, Longo M, Caruso P, Maiorino MI, Bellastella G, et al. GLP-1 receptor agonists and cardiorenal outcomes in type 2 diabetes: An updated meta-analysis of eight CVOTs. Cardiovasc Diabetol 2021;20:1—11.

[54] Mannucci E, Dicembrini I, Nreu B, Monami M. Glucagon-like peptide-1 receptor agonists and cardiovascular outcomes in patients with and without prior cardiovascular events: An updated meta-analysis and subgroup analysis of randomized controlled trials. Diabetes Obes Metab 2020;22(2):203—11.

[55] D'Andrea E, Kesselheim AS, Franklin JM, Jung EH, Hey SP, Patorno E. Heterogeneity of antidiabetic treatment effect on the risk of major adverse cardiovascular events in type 2 diabetes: A systematic review and meta-analysis. Cardiovasc Diabetol 2020;19(1):154.

[56] McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZ, Dagogo-Jack S, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: A meta-analysis. JAMA Cardiol 2021;6(2):148—58.

[57] Rahman H, Khan SU, Lone AN, Ghosh P, Kunduru M, Sharma S, et al. Sodium-glucose cotransporter-2 inhibitors and primary prevention of atherosclerotic cardiovascular disease: A meta-analysis of randomized trials and systematic review. J Am Heart Assoc 2023;12(16):e030578.

[58] Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247—57.

[59] Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, Maggioni AP, Marso SP, Öhman P, Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228—39.

[60] Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, Jeppesen OK, Lingvay I, Mosenzon O, Pedersen SD, Tack CJ, Thomsen M, Vilsbøll T, Warren ML, Bain SC; PIONEER 6 Investigators. Oral

semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381:841—51.

[61] McMurray JJ, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2021;381(21):1995—2008.

[62] Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Zannad F. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383(15):1413—24.

[63] Solomon SD, McMurray JJ, Claggett B, de Boer RA, DeMets D, Hernandez AF, Langkilde AM. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2022;387(12):1089—98.

[64] Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Packer M. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385(16):1451—61.

[65] Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, Solomon SD. SGLT2 inhibitors in patients with heart failure: A comprehensive meta-analysis of five randomised controlled trials. Lancet 2022;400(10354):757—67.

[66] Cardoso R, Graffunder FP, Ternes CM, Fernandes A, Rocha AV, Fernandes G, Bhatt DL. SGLT2 inhibitors decrease cardiovascular death and heart failure hospitalizations in patients with heart failure: A systematic review and meta-analysis. eClinicalMedicine 2021;36.

[67] Giugliano D, Longo M, Scappaticcio L, Bellastella G, Maiorino MI, Esposito K. SGLT-2 inhibitors and cardiorenal outcomes in patients with or without type 2 diabetes: A meta-analysis of 11 CVOTs. Cardiovasc Diabetol 2021;20:1—11.

[68] Perkovic V, Jardine MJ, Neal B, et al; Credence Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380(24):2295—306.

[69] Hiddo J, Heerspink L, Stefánsson Bergur V, Correa-Rotter Ricardo, Chertow Glenn M, et al; the DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020; 383:1436—46.

[70] The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. N Engl J Med 2023;388:117—27.

[71] Staplin N, Roddick AJ, Emberson J, Reith C, Riding A, Wonnacott A, et al. Net effects of sodium-glucose co-transporter-2 inhibition in different patient groups: A meta-analysis of large placebo-controlled randomized trials. eClinicalMedicine 2021;41:101163.

[72] Yamada T, Wakabayashi M, Bhalla A, Chopra N, Miyashita H, Mikami T, et al. Cardiovascular and renal outcomes with SGLT-2 inhibitors versus GLP-1 receptor agonists in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and network meta-analysis. Cardiovasc Diabetol 2021;20(1):14.

[73] Perkovic V, Tuttle KR, Rossing P, Mahaffey KW, Mann JFE, Bakris G, Baeres FMM, Idorn T, Bosch-Traberg H, Lausvig NL, Pratley R; FLOW Trial Committees and Investigators. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med 2024;391:109—21.

[74] Johnson JL, Wolf SL, Kabadi UM. Efficacy of insulin and sulfonylurea combination therapy in type II diabetes. A meta-analysis of the randomized placebo-controlled trials. Arch Intern Med 1996;156:259—64.

[75] United Kingdom Prospective Diabetes Study Group. United Kingdom Prospective Diabetes Study 24: A 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. Ann Intern Med 1998;128:165—75.

[76] Hemmingsen B, Christensen LL, Wetterslev J, Vaag A, Gluud C, Lund SS, Almdal T. Comparison of metformin and insulin versus insulin alone for type 2 diabetes: Systematic review of randomised clinical trials with metaanalyses and trial sequential analyses. BMJ 2012;344:e1771.

[77] Yki-Järvinen H, Kauppila M, Kujansuu E, Lahti J, Marjanen T, Niskanen L, et al. Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 1992;327:1426—33.

[78] Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T, Endahl L, Mathieu C; NN1250-3579 (BEGIN Once Long) Trial Investigators. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: A 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care 2012;35:2464—71.

[79] Rosenstock J, Schwartz SL, Clark CM Jr, Park GD, Donley DW, Edwards MB. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. Diabetes Care 2001;24:631—6.

[80] Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, Pratley RE, Haahr PM, Lange M, Brown-Frandsen K, Moses A, Skibsted S, Kvist K, Buse JB; DEVOTE Study Group. Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med 2017;377:723—32.

[81] Buse JB, Bergenstal RM, Glass LC, Heilmann CR, Lewis MS, Kwan AY, Hoogwerf BJ, Rosenstock J. Use of twice-daily exenatide in basal insulintreated patients with type 2 diabetes: A randomized, controlled trial. Ann Intern Med 2011;154:103—12.

[82] Arnolds S, Dellweg S, Clair J, Dain MP, Nauck MA, Rave K, Kapitza C. Further improvement in postprandial glucose control with addition of exenatide or sitagliptin to combination therapy with insulin glargine and metformin: A proof-of-concept study. Diabetes Care 2010;33:1509—15.

[83] Barnett AH, Charbonnel B, Donovan M, Fleming D, Chen R. Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. Curr Med Res Opin 2012;28:513—23.

[84] Vilsboll T, Rosenstock J, Yki-Jarvinen H, Cefalu WT, Chen Y, Luo E, Musser B, et al. Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. Diabetes Obes Metab 2010;12:167—77.

[85] Zinman B, Ahrén B, Neubacher D, Patel S, Woerle HJ, Johansen OE. Efficacy and cardiovascular safety of linagliptin as an add-on to insulin in type 2 diabetes: A pooled comprehensive post hoc analysis. Can J Diabetes 2016;40:50—7.

[86] Neal B, Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Ways K, Desai M, Shaw W, Capuano G, Alba M, Jiang J, Vercruysse F, Meininger G, Matthews D; CANVAS Trial Collaborative Group. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. Diabetes Care 2015;38:403—11.

[87] Rosenstock J, Jelaska A, Frappin G, Salsali A, Kim G, Woerle HJ, Broedl UC; EMPA-REG MDI Trial Investigators. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes Care 2014;37:1815—23.

[88] Wilding JP, Woo V, Rohwedder K, Sugg J, Parikh S; Dapagliflozin 006 Study Group. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: Efficacy and safety over 2 years. Diabetes Obes Metab 2014;16:124—36.

[89] Liakos A, Karagiannis T, Athanasiadou E, Sarigianni M, Mainou M, Papatheodorou K, Bekiari E, Tsapas A. Efficacy and safety of empagliflozin for type 2 diabetes: A systematic review and meta-analysis. Diabetes Obes Metab 2014;16:984—93.

[90] Kim YG, Min SH, Hahn S, Oh TJ, Park KS, Cho YM. Efficacy and safety of the addition of a dipeptidyl peptidase-4 inhibitor to insulin therapy in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract 2016;116:86—95.

[91] Ahmann A, Rodbard HW, Rosenstock J, Lahtela JT, de Loredo L, Tornøe K, Boopalan A, Nauck MA; NN2211-3917 Study Group. Efficacy and safety of liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: A randomized, placebo-controlled trial. Diabetes Obes Metab 2015;17:1056—64.

[92] Rosenstock J, Guerci B, Hanefeld M, Gentile S, Aronson R, Tinahones FJ, Roy-Duval C, Souhami E, Wardecki M, Ye J, Perfetti R, Heller S; GetGoal Duo-2 Trial Investigators. Prandial options to advance basal insulin glargine therapy: Testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: The GetGoal Duo-2 trial. Diabetes Care 2016;39:1318—28.

[93] Dahl D, Onishi Y, Norwood P, Huh R, Bray R, Patel H, Rodríguez Á. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: The SURPASS-5 randomized clinical trial. JAMA 2022;327(6):534—45.

[94] Rosenstock J, Frías JP, Rodbard HW, Tofé S, Sears E, Huh R, Fernández Landó L, Patel H. Tirzepatide vs insulin lispro added to basal insulin in type 2 diabetes: The SURPASS-6 randomized clinical trial. JAMA 2023;330(17):1631—40.

[95] Mathieu C, Rodbard HW, Cariou B, Handelsman Y, Philis-Tsimikas A, Ocampo Francisco AM, et al. A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). Diabetes Obes Metab 2014;16(7):636—44.

[96] Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: A systematic review and meta-analysis. Lancet 2014;384(9961):2228—34.

[97] Maiorino MI, Chiodini P, Bellastella G, Capuano A, Esposito K, Giugliano D. Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. Diabetes Care 2017;40(4):614—24.

[98] Wysham CH, Lin J, Kuritzky L. Safety and efficacy of a glucagon-like peptide-1 receptor agonist added to basal insulin therapy versus basal insulin with or without a rapid-acting insulin in patients with type 2 diabetes: Results of a meta-analysis. Postgrad Med 2017;129(4):436—45.

[99] Pozzilli P, Norwood P, Jódar E, Davies MJ, Ivanyi T, Jiang H, et al. Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9). Diabetes Obes Metab 2017;19(7):1024—31.

[100] Rodbard HW, Lingvay I, Reed J, de la Rosa R, Rose L, Sugimoto D, et al. Semaglutide Added to Basal Insulin in Type 2 Diabetes (SUSTAIN 5): A randomized, controlled trial. J Clin Endocrinol Metab 2018;103(6):2291—301.

[101] Kesavadev J, Pillai PBS, Shankar A, Krishnan G, Jothydev S. Sitagliptin 100 mg vs glimepiride 1-3 mg as an add-on to insulin and metformin in type 2 diabetes (SWIM). Endocr Connect 2017;6(8):748—57.

[102] Ledesma G, Umpierrez GE, Morley JE, Lewis-D'Agostino D, Keller A, Meinicke T, et al. Efficacy and safety of linagliptin to improve glucose control in older people with type 2 diabetes on stable insulin therapy: A randomized trial. Diabetes Obes Metab 2019;21(11):2465—73.

[103] Rodbard HW, Visco VE, Andersen H, Hiort LC, Shu DH. Treatment intensification with stepwise addition of prandial insulin aspart boluses compared with full basal-bolus therapy (FullSTEP Study): A randomised, treat-to-target clinical trial. Lancet Diabetes Endocrinol 2014;2:30—7.

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[104] Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: A meta-analysis. CMAJ 2009;180:385–97.

[105] Anderson JH Jr, Brunelle RL, Keohane P, Koivisto VA, Trautmann ME, Vignati L, DiMarchi R. Mealtime treatment with insulin analog improves postprandial hyperglycemia and hypoglycemia in patients with non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro Study Group. Arch Intern Med 1997;157:1249–55.

[106] Anderson JH Jr, Brunelle RL, Koivisto VA, Trautmann ME, Vignati L, DiMarchi R. Improved mealtime treatment of diabetes mellitus using an insulin analogue. Multicenter Insulin Lispro Study Group. Clin Ther 1997;19:62–72.

[107] Mannucci E, Monami M, Marchionni N. Short-acting insulin analogues vs. regular human insulin in type 2 diabetes: A meta-analysis. Diabetes Obes Metab 2009;11(1):53–9.

[108] Horvath K, Jeitler K, Berghold A, Ebrahim SH, Gratzer TW, Plank J, Kaiser T, Pieber TR, Siebenhofer A. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev 2007;(2):CD005613.

[109] Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: A meta-analysis. Diabetes Res Clin Pract 2008;81:184–9.

[110] Rys P, Wojciechowski P, Rogoz-Sitek A, Niesyczyński G, Lis J, Syta A, Malecki MT. Systematic review and metaanalysis of randomized clinical trials comparing efficacy and safety outcomes of insulin glargine with NPH insulin, premixed insulin preparations or with insulin detemir in type 2 diabetes mellitus. Acta Diabetol 2015;52:649–62.

[111] Ratner RE, Gough SC, Mathieu C, Del Prato S, Bode B, Mersebach H, Endahl L, Zinman B. Hypoglycaemia risk with insulin glargine in type 2 and type 1 diabetes: A pre-planned meta-analysis of phase 3 trials. Diabetes Obes Metab 2013;15:175–84.

[112] Wysham C, Bhargava A, Chaykin L, de la Rosa R, Handelsman Y, Troelsen LN, Kvist K, Norwood P. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes. The SWITCH 2 Randomized Clinical Trial. JAMA 2017;318(1):45–56.

[113] Heller SR, DeVries JH, Wysham C, Hansen CT, Hansen MV, Frier BM. Lower rates of hypoglycaemia in older individuals with type 2 diabetes using insulin degludec versus insulin glargine U100: Results from SWITCH 2. Diabetes Obes Metab 2019;21(7):1634–41.

[114] Clements JN, Bello L. Insulin glargine 300 units/mL: A new basal insulin product for diabetes mellitus. Am J Health Syst Pharm 2016;73:359–66.

[115] Zhuang YG, Peng H, Huang F. A meta-analysis of clinical therapeutic effect of insulin glargine and insulin detemir for patients with type 2 diabetes mellitus. Eur Rev Med Pharmacol Sci 2013;17:2566–70.

[116] de Jager J, Kooy A, Lehert P, Wulffelé MG, van der Kolk J, Bets D, Verburg J, Donker AJ, Stehouwer CD. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: Randomised placebo controlled trial. BMJ 2010;340:c2181.

[117] Aroda VR, Edelstein SL, Goldberg RB, Knowler WC, Marcovina SM, Orchard TJ, Bray GA, Schade DS, Temprosa MG, White NH, Crandall JP; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the diabetes prevention program outcomes study. J Clin Endocrinol Metab 2016;101:1754–61.

[118] Niafar M, Hai F, Porhomayon J, Nader ND. The role of metformin on vitamin B12 deficiency: A meta-analysis review. Intern Emerg Med 2015;10:93–102.

[119] Blonde L, Dailey GE, Jabbour SA, Reasner CA, Mills DJ. Gastrointestinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: Results of a retrospective cohort study. Curr Med Res Opin 2004;20:565–72.

[120] Ali S, Fonseca V. Overview of metformin: Special focus on metformin extended release. Expert Opin Pharmacother 2012;13:1797–805.

[121] Jabbour S, Ziring B. Advantages of extended-release metformin in patients with type 2 diabetes mellitus. Postgrad Med 2011;123:15–23.

[122] Levy J, Cobas RA, Gomes MB. Assessment of efficacy and tolerability of once daily extended release metformin in patients with type 2 diabetes mellitus. Diabetol Metab Syndr 2010;2:16.

[123] Li L, Shen J, Bala MM, Busse JW, Ebrahim S, Vandvik PO, Rios LP, Malaga G, Wong E, Sohani Z, Guyatt GH, Sun X. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: Systematic review and meta-analysis of randomised and non-randomised studies. BMJ 2014;348:g2366.

[124] Udell JA, Cavender MA, Bhatt DL, Chatterjee S, Farkouh ME, Scirica BM. Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: A meta-analysis of randomised controlled trials. Lancet Diabetes Endocrinol 2015;3:356–66.

[125] Li L, Li S, Deng K, Liu J, Vandvik PO, Zhao P, Zhang L, et al. Dipeptidyl peptidase-4 inhibitors and risk of heart failure in type 2 diabetes: systematic review and meta-analysis of randomised and observational studies. BMJ 2016;352:i610.

[126] Caparrotta TM, Templeton JB, Clay TA, Wild SH, Reynolds RM, Webb DJ, Colhoun HM. Glucagon-like peptide 1 receptor agonist (GLP1RA) exposure and outcomes in type 2 diabetes: A systematic review of population-based observational studies. Diabetes Ther 2021;12(4):969–89.

[127] Colacci M, Fralick J, Odutayo A, Fralick M. Sodium-glucose cotransporter-2 inhibitors and risk of diabetic ketoacidosis among adults with type 2 diabetes: A systematic review and meta-analysis. Can J Diabetes 2022;46(1):10–5.

[128] Alba M, Xie J, Fung A, Desai M. The effects of canagliflozin, a sodium glucose co-transporter 2 inhibitor, on mineral metabolism and bone in patients with type 2 diabetes mellitus. Curr Med Res Opin 2016;32:1375–85.

[129] Bilezikian JP, Watts NB, Usiskin K, Polidori D, Fung A, Sullivan D, Rosenthal N. Evaluation of bone mineral density and bone biomarkers in patients with type 2 diabetes treated with canagliflozin. J Clin Endocrinol Metab 2016;101:44–51.

[130] Puckrin R, Saltiel MP, Reynier P, Azoulay L, Yu OHY, Filion KB. SGLT-2 inhibitors and the risk of infections: A systematic review and meta-analysis of randomized controlled trials. Acta Diabetol 2018;55:503–14.

[131] Dave CV, Schneeweiss S, Kim D, Fralick M, Tong A, Patorno E. Sodium-glucose cotransporter-2 inhibitors and the risk for severe urinary tract infections: A population-based cohort study. Ann Intern Med 2019;171:248–56.

[132] Shi Q, Nong K, Vandvik PO, Guyatt GH, Schnell O, Rydén L, Marx N, et al. Benefits and harms of drug treatment for type 2 diabetes: Systematic review and network meta-analysis of randomised controlled trials. BMJ 2023;381:e074068.