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2018 Clinical Practice Guidelines

Pharmacologic Glycemic Management of Type 2 Diabetes in Adults

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Healthy behaviour interventions should be initiated in people newly diagnosed with type 2 diabetes.
- In people with type 2 diabetes with A1C <1.5% above the person's individualized target, antihyperglycemic pharmacotherapy should be added if glycemic targets are not achieved within 3 months of initiating healthy behaviour interventions.
- In people with type 2 diabetes with A1C ≥1.5% above target, antihyperglycemic agents should be initiated concomitantly with healthy behaviour interventions, and consideration could be given to initiating combination therapy with 2 agents.
- Insulin should be initiated immediately in individuals with metabolic decompensation and/or symptomatic hyperglycemia.
- In the absence of metabolic decompensation, metformin should be the initial agent of choice in people with newly diagnosed type 2 diabetes, unless contraindicated.
- Dose adjustments and/or additional agents should be instituted to achieve target A1C within 3 to 6 months. Choice of second-line antihyperglycemic agents should be made based on individual patient characteristics, patient preferences, any contraindications to the drug, glucose-lowering efficacy, risk of hypoglycemia, affordability/access, effect on body weight and other factors.
- In people with clinical cardiovascular (CV) disease in whom A1C targets are not achieved with existing pharmacotherapy, an antihyperglycemic agent with demonstrated CV outcome benefit should be added to antihyperglycemic therapy to reduce CV risk.
- In people without clinical CV disease in whom A1C target is not achieved with current therapy, if affordability and access are not barriers, people with type 2 diabetes and their providers who are concerned about hypoglycemia and weight gain may prefer an incretin agent (DPP-4 inhibitor or GLP-1 receptor agonist) and/or an SGLT2 inhibitor to other agents as they improve glycemic control with a low risk of hypoglycemia and weight gain.
- In people receiving an antihyperglycemic regimen containing insulin, in whom glycemic targets are not achieved, the addition of a GLP-1 receptor agonist, DPP-4 inhibitor or SGLT2 inhibitor may be considered before adding or intensifying prandial insulin therapy to improve glycemic control with less weight gain and comparable or lower hypoglycemia risk.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Some people who have type 2 diabetes can achieve their target blood glucose levels with nutrition guidance and physical activity alone, but most also need glucose-lowering medications. The decision about which medications are best for you depends on many factors, including your blood glucose level, symptoms, other health problems you have and affordability of medications. Your health-care provider may even combine medications that act differently on your body to help you control your blood glucose.
- Glucose-lowering medications for type 2 diabetes include:
  First-line glucose-lowering medication:
  - **Metformin:** Metformin is generally the first choice for people with type 2 diabetes because of its safety, low cost and possible heart benefits. It works by making your body respond better to insulin so that your body uses insulin more effectively. Metformin also lowers glucose production from the liver. Nausea and diarrhea are possible side effects and usually go away within 1 to 2 weeks as your body gets used to the medicine. It is associated with a low risk of hypoglycemia and does not cause weight gain.
  - If metformin and healthy behaviour changes are not enough to control your blood glucose level, other medications can be added.

  Second-line glucose-lowering medication:
  - **DPP-4 inhibitors:** These medications work to lower blood glucose by increasing insulin levels after meals and lowering glucagon levels (a hormone that raises blood glucose). They do not cause weight gain and are associated with a low risk of hypoglycemia.
  - **GLP-1 receptor agonists:** These injectable medications act when blood glucose increases after eating. They increase insulin levels, which helps lower blood glucose and lower glucagon levels (a hormone that raises blood glucose). They also slow digestion and reduce appetite. Possible side effects include nausea, which usually goes away with time. They are associated with weight loss and a low risk of hypoglycemia.
  - **SGLT2 inhibitors:** These medications work by eliminating glucose into the urine. Side effects may include genital yeast infections, urinary tract infections, increased urination and low blood pressure. They are associated with weight loss and a low risk of hypoglycemia.
  - **Insulin secretagogues (meglitinides, sulfonylureas):** These medications help your pancreas release more insulin. Possible side effects include hypoglycemia and weight gain.
  - **Thiazolidinediones:** Like metformin, these medications make the body's tissues more sensitive to insulin. Side effects include weight gain and an increased risk of heart failure and fractures.
  - **Insulin therapy:** Some people who have type 2 diabetes need insulin therapy as well. Depending on your needs, your health-care provider may prescribe a mixture of insulin types to use throughout the day and night. Often, people with type 2 diabetes start insulin use with 1 injection of long-acting insulin at night.
- Discuss the pros and cons of different treatment plans with your health-care provider. Together, you can decide which medication is best for you after considering many factors, including costs and other aspects of your health.

Conflict of interest statements can be found on page S100.

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Introduction

People with type 2 diabetes form a heterogeneous group. Consequently, treatment regimens and therapeutic targets should be individualized. The treatment of type 2 diabetes involves a multipronged approach that aims to treat and prevent symptoms of hyperglycemia, such as dehydration, fatigue, polyuria, infections and hyperosmolar states; and to reduce the risks of cardiovascular (CV) and microvascular complications (1). This includes healthy behaviour interventions (see Reducing the Risk of Diabetes chapter, p. S20; Cardiovascular Protection in People with Diabetes chapter, p. S162) and antihyperglycemic medications. This chapter provides updated recommendations for the approach to antihyperglycemic therapy and selection of pharmaceutical agents. The number of available antihyperglycemic agents is ever expanding, requiring the healthcare provider to consider many of the following factors when choosing medications: degree of hyperglycemia, medication efficacy for reducing diabetes complications (microvascular and/or CV) and lowering glucose, medication effects on the risk of hypoglycemia, body weight, other side effects, concomitant medical conditions, ability to adhere to regimen, broader health and social needs, affordability of medications, and patient values and preferences. Recommendations in this chapter are based on a rigorous and careful review of the evidence regarding the efficacy and adverse effects of available medications on clinically important outcomes.

Treatment Regimens

Newly diagnosed type 2 diabetes

Individuals presenting with newly diagnosed type 2 diabetes require a multifaceted treatment plan. This includes diabetes education by an interprofessional team (see Self-Management Education and Support chapter, p. S36), healthy behaviour interventions (diet and physical activity, smoking cessation) with a target of 5% to 10% weight loss for overweight individuals (see Weight Management in Diabetes chapter, p. S124; Cardiovascular Protection in People with Diabetes chapter, p. S162), and screening for complications. It should be emphasized to people with type 2 diabetes that healthy behaviour interventions and weight loss can lead to withdrawal of antihyperglycemic medication and even remission of type 2 diabetes in some cases (2). The Look AHEAD (Action for Health in Diabetes) trial showed that an intensive healthy behaviour intervention resulted in a significantly greater weight loss and likelihood of diabetes remission after 1 year compared to standard care, with the greatest benefit seen in persons with new-onset type 2 diabetes (21.2% remission rate) (2). Antihyperglycemic therapy with metformin may also be initiated at diagnosis, depending on the current and target glycated hemoglobin (A1C).

The treatment of hyperglycemia should begin with the establishment of a target A1C which, in most cases, will be ≤7.0% as this has been shown to reduce long-term microvascular complications in newly diagnosed people with type 2 diabetes (3). A1C targets may be higher (up to 8.5%) if the benefits of intensive glycemic control are unlikely to outweigh the risks and burden, such as in individuals with limited life expectancy, high risk of hypoglycemia, multimorbidity, or based on the values and preferences of the person with diabetes (see Targets for Glycemic Control chapter, p. S42 for recommendations). It should be emphasized to people with type 2 diabetes that reductions in A1C levels are associated with better outcomes even if recommended glycemic targets cannot be reached, and inability to achieve A1C target should not be considered a treatment failure (3,4).

If the A1C level at diagnosis is less than 1.5% above target and the person with type 2 diabetes lacks metabolic decompensation and/or symptoms of hyperglycemia, the first line of treatment should be healthy behaviour interventions (see Reducing the Risk of Diabetes chapter, p. S20). If healthy behaviour interventions are insufficient to achieve target A1C levels within 3 months, they should be combined with antihyperglycemic medications. In the face of significant hyperglycemia (i.e. A1C >1.5% above target), pharmacotherapy is usually required at diagnosis concurrent with healthy behaviour interventions. People who have evidence of metabolic decompensation (e.g. marked hyperglycemia, ketosis or unintentional weight loss) and/or symptomatic hyperglycemia should be started immediately on insulin, regardless of A1C level. Insulin may later be tapered or discontinued once stability is achieved.

In general, A1C will decrease by about 0.5% to 1.5% with monotherapy, varying with the specific agent used and the baseline A1C level. By and large, the higher the baseline A1C, the greater the A1C reduction seen for each given agent. The maximum effect of noninsulin antihyperglycemic agent monotherapy is observed by 3 to 6 months (5,6).

Initial combination therapy (with or without insulin) may be required in settings of more severe hyperglycemia and/or metabolic decompensation to provide a more rapid and larger decrease in A1C (7–11). Evidence indicates that initial combination of metformin with another agent is associated with an additional mean 0.4% to 1.0% reduction in A1C and a relative 40% higher chance of achieving A1C <7.0% after 6 months compared to metformin alone (7–9,12).

The initial use of combinations of submaximal doses of antihyperglycemic agents produces more rapid and improved glycemic control and fewer side effects compared to monotherapy at maximal doses (13–17).

Table 1 lists all the available classes of antihyperglycemic therapies. These include insulin and noninsulin therapies. Unless contraindicated, metformin should be the initial pharmacotherapy in people with type 2 diabetes. Contraindications include chronic kidney disease (CKD) stage 4 to 5 (eGFR <30 mL/min) and hepatic failure. The recommendation to use metformin as the initial agent in most people is based on its efficacy in lowering A1C, its relatively mild side effect profile, long-term safety track record, affordability, negligible risk of hypoglycemia and lack of weight gain. Compared to sulfonylureas, metformin monotherapy has comparable A1C-lowering effects, but better glycemic durability (18), a lower risk of hypoglycemia (19), less weight gain (19,20) and lower CV risk (20). Metformin is associated with less weight gain than thiazolidinediones (21), and has better A1C lowering and weight loss than DPP-4 inhibitors (19). The demonstrated CV benefit of metformin monotherapy in newly diagnosed participants who were overweight in the UKPDS trial (17) is also cited as a reason to select metformin as first-line treatment, although other evidence from a meta-analysis of metformin trials has been equivocal on this matter (21,22). Metformin should be started at a low dose and gradually increased over several weeks to minimize the risk of gastrointestinal side effects. If metformin is contraindicated or if initial combination therapy is required, then a second agent should be chosen based on individual patient characteristics and the efficacy and safety profile of other agents (see Table 1 and Figure 2). DPP-4 inhibitors, GLP-1 receptor agonists or SGLT2 inhibitors should be considered over other antihyperglycemic agents as they are associated with less hypoglycemia and weight gain (19,23–27), provided there are no contraindications and no barriers to affordability or access.

Insulin may be used at diagnosis in individuals with marked hyperglycemia and can also be used temporarily during illness, pregnancy, stress or for a medical procedure or surgery. The use of intensive insulin therapy may lead to partial recovery of beta cell function when used in people with metabolic decompensation, and studies suggest that early insulin treatment may induce remission in people