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Pharmacologic Management of Type 2 Diabetes: 2016 Interim Update

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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The process for the development of the *Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada* included provisions to update individual chapters prior to the planned published revision in 2018 in the event of significant changes in evidence supporting the recommendations (1). In the case of new recommendations or changes to existing recommendations, the process of updating would be the same as the 2013 revision, including the Independent Methodological Review (1).

Since the publication of the 2013 guidelines, several cardiovascular outcome trials have been completed, and they demonstrate the overall cardiovascular safety of 3 dipeptidyl peptidase-4 (DPP-4) inhibitors (alogliptin, saxagliptin, sitagliptin) and 1 glucagon-like-protein-1 (GLP-1) receptor agonist (lixisenatide) in patients with type 2 diabetes who are at high risk for cardiovascular events (2–5). Noninferiority of the primary cardiovascular composite endpoints was achieved, and saxagliptin demonstrated an unexpected increase in hospitalization for heart failure that has yet to be fully explained (2–5). More recently, the first cardiovascular outcome trial of the sodium glucose linked transporter 2 (SGLT2) inhibitor class was published, and it demonstrated cardiovascular superiority, thereby qualifying as a practice-changing study (6).

The Empagliflozin Cardiovascular Outcome Event Trial (EMPA-REG OUTCOME) included 7020 patients with type 2 diabetes and clinical cardiovascular disease (CVD), including prior myocardial infarction (MI), coronary artery disease, unstable angina, stroke or occlusive peripheral arterial disease and estimated glomerular filtration rate (eGFR) levels ≥30 mL/min. They were randomized to 2 different dosages of empagliflozin (10 mg or 25 mg) or placebo on top of standard care. More than 98% of the patients were receiving antihyperglycemic agents prior to randomization, and approximately 75% were taking metformin. Baseline glycated hemoglobin (A1C) levels were in the 7% to 10% range, with a mean A1C level of 8.1%, and 82% had had diabetes for more than 5 years (6). Approximately 80% were taking renin-angiotensin-aldosterone system inhibitors, statins and acetylsalicylic acid (6).

The primary outcome was a composite cardiovascular endpoint of death from cardiovascular causes, nonfatal MI or nonfatal stroke and occurred less commonly in the group taking empagliflozin (both doses combined) compared to recipients of placebo (10.5% vs. 12.1%; hazard ratio [HR], 0.86; $p<0.001$ for noninferiority, $p=0.04$ for superiority). The reduction in the primary endpoint was driven mainly by a 38% relative risk reduction ($p<0.001$) in cardiovascular death because there was no reduction in the rate of nonfatal MI or nonfatal stroke. Empagliflozin therapy was also associated with a 35% relative risk reduction ($p=0.002$) of hospitalization for heart failure and a 32% relative risk reduction ($p<0.001$) of total mortality. There were modest metabolic benefits and, overall, empagliflozin was well tolerated, although genital infections occurred at a higher rate in patients treated with empagliflozin (6).

The results of EMPA-REG OUTCOME are relevant to the management of type 2 diabetes because 40% to 60% of these individuals will die of cardiovascular disease, and the published literature to date shows little evidence that other antihyperglycemic agents provide cardiovascular benefits in patients with clinical CVD (7,8). Less than 2% of patients were drug naive, and patients typically had longstanding diabetes and were taking background antihyperglycemic therapies. The outcomes in the small number of drug-naive patients were not reported. Therefore, empagliflozin should be utilized in patients with type 2 diabetes and clinical CVD who are already taking antihyperglycemic therapy. EMPA-REG OUTCOME is the first completed cardiovascular outcome trial to include an SGLT2 inhibitor, so it is currently unknown whether the other members of this class provide the same CV benefits. CV outcome trials with the other SGLT2 inhibitors are ongoing (9,10). The management of hyperglycemia in type 2 diabetes is summarized in Figure 1, which integrates the

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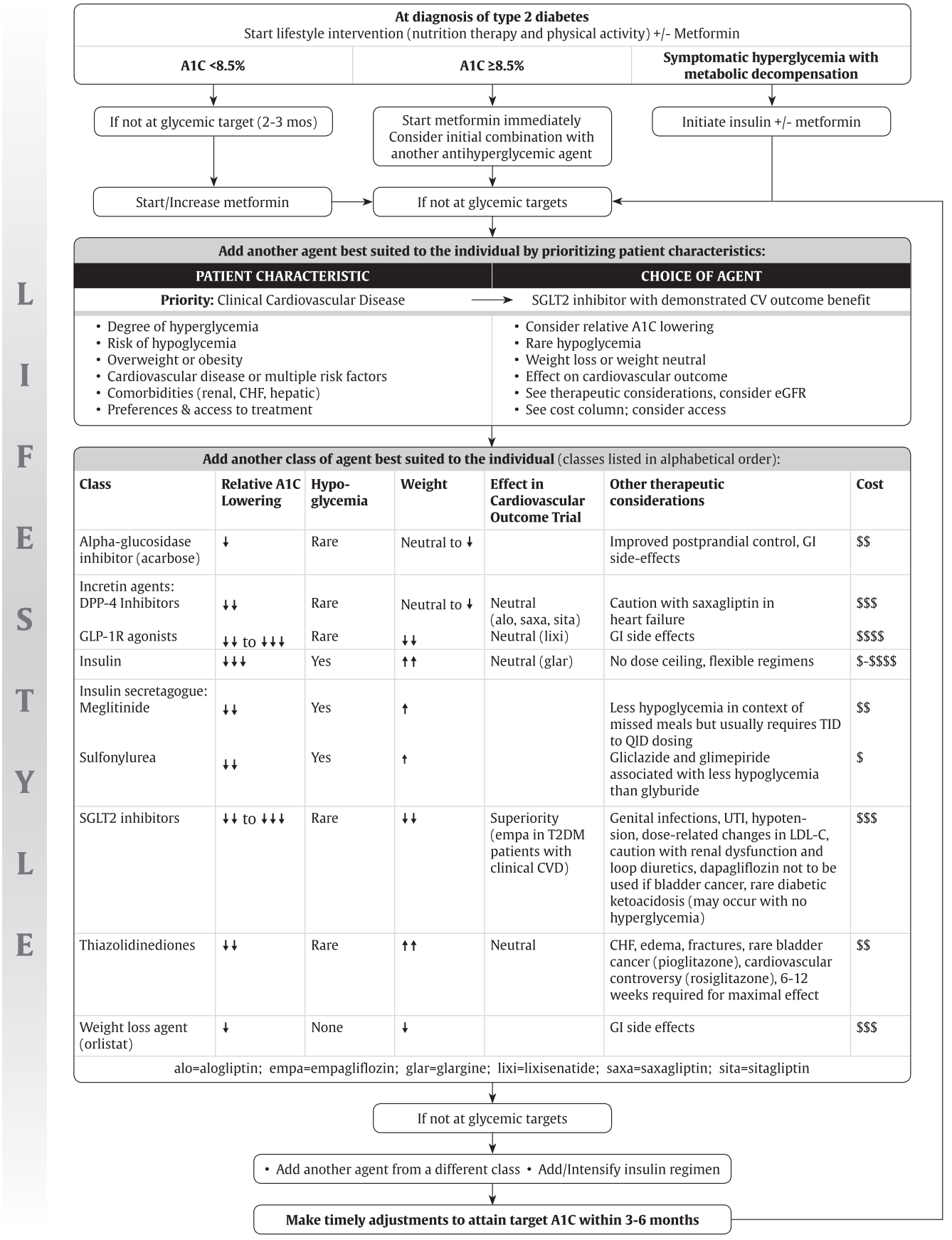

Figure 1. Management of hyperglycemia in type 2 diabetes.
CHF, congestive heart failure; *CVD,* cardiovascular disease; *DPP,* dipeptidyl peptidase; *eGFR,* estimated glomerular filtration rate; *GI,* gastrointestinal; *GLP-1R,* glucagon-like-protein-1 receptor; *LDL-C,* low density lipoprotein cholesterol; *SGLT2,* sodium glucose link transporter 2; *UTI,* urinary tract infection.

findings of EMPA-REG OUTCOME by prioritizing the presence of clinical cardiovascular disease when adding an antihyperglycemic and choosing an SGLT2 inhibitor with demonstrated CV benefits in this patient population. As part of individualized pharmacotherapy management for all patients with type 2 diabetes, the presence of CVD or multiple risk factors and the effect of antihyperglycemic agents on CV outcomes should also be considered; hence, the addition of the column titled "Effect in Cardiovascular Outcome Trial" to the pharmacotherapy table. Only data from prospective randomized controlled trials of CV outcomes with a specific antihyperglycemic agent were included in this column. Therefore, in addition to the data from recent trials of incretin and an SGLT2 inhibitor, the new column includes the CV neutrality of insulin glargine (11) and thiazolidinediones (12,13) in CV outcome trials. As future cardiovascular outcome trials of antihyperglycemic agents are published, the guidelines committee will continue to assess new evidence and update as appropriate.

Recommendations (Changes from 2013 are in bold-face type)

1. In people with a **new diagnosis** of type 2 diabetes:
   i. Metformin may be used at the time of diagnosis, in conjunction with lifestyle management (Grade D, Consensus).
   ii. **If A1C <8.5%** and glycemic targets are not achieved using lifestyle management within 2 to 3 months, antihyperglycemic agent therapy **with metformin** should be initiated (Grade A, Level 1A) (14).
   iii. If A1C levels are ≥8.5%, antihyperglycemic agents should be initiated concomitantly with lifestyle management, and consideration should be given to initiating combination therapy with 2 agents, 1 of which may be insulin (Grade D, Consensus)
   iv. Individuals with symptomatic hyperglycemia and metabolic decompensation should receive an initial antihyperglycemic regimen containing insulin **with or without metformin** (Grade D, Consensus).
2. Metformin should be the initial drug used **in monotherapy** (Grade A, Level 1A) (15,16) for overweight patients; Grade D, Consensus for nonoverweight patients).
3. Other classes of antihyperglycemic agents, including insulin, should be added to metformin, or used in combination with each other, if glycemic targets are not met, taking into account the information in Figure 1 and the table available at http://guidelines.diabetes.ca/cdacpg_resources/Ch13_Table1_Antihyperglycemic_agents_type_2_2016.pdf (Grade D, Consensus), and these adjustments to and/or additions of antihyperglycemic agents should be made in order to attain target A1C levels within 3 to 6 months (Grade D, Consensus).
4. **In people with clinical cardiovascular disease in whom glycemic targets are not met, an SGLT2 inhibitor with demonstrated cardiovascular outcome benefit should be added to antihyperglycemic therapy to reduce the risk for cardiovascular and all-cause mortality (Grade A, Level 1A for empagliflozin)** (6).
5. **Choice of additional pharmacologic treatment agents should be individualized by patient's characteristics, taking into consideration (Grade D, Consensus):**
   - Degree of hyperglycemia
   - Risk of hypoglycemia
   - Overweight or obesity
   - Cardiovascular disease or multiple risk factors
   - Comorbidities (renal, congestive heart failure, hepatic, etc.)
   - Preferences of the patient
   - Access to treatment
6. When basal insulin is added to antihyperglycemic agents, long-acting analogues (detemir or glargine) may be used instead of intermediate-acting Neutral Protamine Hagedorn (NPH) to reduce the risk for nocturnal and symptomatic hypoglycemia (Grade A, Level 1A) (17–19).
7. When bolus insulin is added to antihyperglycemic agents, rapid-acting analogues may be used instead of regular insulin to improve glycemic control (Grade B, Level 2) (20) and to reduce the risk for hypoglycemia (Grade D, Consensus).
8. All individuals with type 2 diabetes currently using or starting therapy with insulin or insulin secretagogues should be counselled about the prevention, recognition and treatment of drug-induced hypoglycemia (Grade D, Consensus).

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