Management of type 2 diabetes in patients with frailty

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Clinical question

How can we use newer therapeutic agents to help manage type 2 diabetes in patients living with frailty?

Bottom line

Diabetes management should be individualized.[1] Newer antihyperglycemic agents (Table 1) such as glucagonlike peptide-1 receptor agonists (GLP1-RAs), dipeptidyl peptidase 4 inhibitors (DPP4Is), and sodium-glucose cotransporter-2 inhibitors (SGLT2Is) are therapeutic options for older patients due to these agents' low hypoglycemic risk and benefits beyond glycemic control.[2-8] This paper summarizing key points from an article published in the *Canadian Geriatrics Society Journal of CME* focuses on SGLT2Is given their evolving indications.[8]

Evidence

- A concern for older patients is hypoglycemia; risk factors include isolation, erratic meals, poor renal function, polypharmacy, and intercurrent illnesses.[9] Newer therapeutic agents are associated with lower risk.
- In pooled analyses, 10 mg of dapagliflozin was well tolerated in people aged 65 and older with type 2 diabetes, with frequency of hypoglycemia and rates of genitourinary infections comparable to those among younger study participants.[10] Rates of adverse events related to volume depletion (hypotension, hypovolemia, or dehydration) were low across all age and treatment groups, with only slightly higher rates among patients taking dapagliflozin versus placebo (<65 years: 1.7% vs 1.2%, respectively; ≥65 years: 2.3% vs 1.7%; and ≥75 years: 3.1% vs 2.6%) and among patients 75 years and older, and there was no increased risk of fracture with dapagliflozin use.[10] Unfortunately, older patients with frailty are not always included in clinical trials.
- Cardiovascular outcomes with SGLT2I use are consistent across age groups.[11]

Approach

In patients with type 2 diabetes mellitus and obesity, the primary metabolic defect is insulin resistance; appropriate therapy for this group should target insulin resistance (eg, metformin).[1] In lean individuals, the main metabolic defect is impaired insulin secretion; initial therapy for this group should involve agents that stimulate insulin secretion (eg, DPP4Is). Diabetes Canada guidelines recommend metformin as the first-line agent for patients with type 2 diabetes.[1]

Due to a larger body of evidence for DPP4I use in older people, Diabetes Canada guidelines recommend DPP4Is be used before using SGLT2Is as add-on therapy.[1] Empagliflozin, an SGLT2I, is specifically mentioned in the guidelines for consideration as second-line treatment after metformin in older adults younger than 75 years with cardiovascular (CV) disease, adequate renal function, and no complex comorbidities.[1] Canadian guidelines also include GLP1-RAs for consideration in older adults (≥60 years) with at least 2 CV risk factors, with strongest evidence supporting the use of dulaglutide, liraglutide, and semaglutide.[12] This drug class is mostly available as injectable medications, representing a potential challenge for some older adults.

Sodium-glucose cotransporter-2 inhibitors are an important addition to the therapeutic arsenal. In addition to lowering hemoglobin A_{1c} with minimal hypoglycemic risk, they have cardiorenal protective properties.[2] The efficacy profile of SGLT2Is does not change with patient age.[11] To our knowledge, DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) is the only trial that has examined the efficacy and safety of SGLT2I therapy (dapagliflozin) according to frailty status; it found treatment efficacy was not diminished in patients with a greater degree of frailty, and improvement in health-related quality of life was greater in patients with higher degrees of frailty.[13] Placebo-corrected improvements in Kansas City Cardiomyopathy Questionnaire overall summary scores (ranging from 0 to 100) at 4 months were 0.3 (95% CI -0.9 to 1.4) in individuals without frailty, 1.5 (95% CI 0.3 to 2.7) in patients with low frailty, and 3.4 (95% CI 1.7 to 5.1; $P_{\text{interaction}}$=.021) in patients with higher frailty.[13] The proportion of patients who discontinued dapagliflozin or experienced adverse events increased with increasing frailty, but adverse events were not more common compared with patients receiving placebo, irrespective of frailty class.[13] The risk versus benefit balance related to frailty was favourable for dapagliflozin—a finding that could challenge clinicians' reluctance to start this drug in frail patients. More randomized controlled trials looking at SGLT2I use in patients older than 75 years are needed.

A 2022 Canadian Cardiovascular Society guideline recommends using SGLT2Is to treat patients with heart failure (HF) or chronic kidney disease (CKD) even if they do not have diabetes.[14] This guideline's systematic review and meta-analysis indicated that in patients with HF and left ventricular ejection fraction less than

Table 1. Advantages and disadvantages of newer antihyperglycemic agents in older patients

DRUG CLASS AND MECHANISM OF ACTION	NAME OF DRUG	ADVANTAGES IN OLDER ADULTS	DISADVANTAGES IN OLDER ADULTS
Incretin agents (GLP1-RAs and DPP4Is): increase glucose-dependent insulin release, slow gastric emptying, inhibit glucagon release	GLP1-RAs: • Dulaglutide • Exenatide • Liraglutide • Lixisenatide • Semaglutide	• Low risk of hypoglycemia • Cardiorenal benefits • Weekly administration available	• Mostly injectable therapies • Increased probability of GI adverse events[2] • Potential to induce substantial weight loss • High cost
	DPP4Is: • Alogliptin • Linagliptin • Saxagliptin • Sitagliptin	• RCTs demonstrate efficacy and safety in elderly patients • CV and renal safety • Improved sarcopenic parameters[3] • Good tolerability	• Increased risk of bullous pemphigoid[4,5] • Risks of pancreatitis and pancreatic cancer debatable[6] • Specific agents contraindicated in patients with HF[2]
SGLT2Is: reduce renal glucose reabsorption causing increased glucosuria	• Canagliflozin • Dapagliflozin • Empagliflozin	• Phase III studies show safety in elderly patients[7] • Low risk of hypoglycemia • Cardiorenal benefits	• Concerns regarding increased risk of euglycemic DKA, genitourinary infections, dehydration, and fractures • High cost

CV—cardiovascular, DDP4I—dipeptidyl peptidase 4 inhibitor, DKA—diabetic ketoacidosis, GI—gastrointestinal, GLP1-RA—glucagonlike peptide-1 receptor agonist, HF—heart failure, RCT—randomized controlled trial, SGLT2I—sodium-glucose cotransporter-2 inhibitor.
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or equal to 40%, SGLT2I use is associated with a 16% reduction in risk of all-cause mortality (95% CI 0.72 to 0.97), a 16% reduction in risk of CV mortality (95% CI 0.71 to 0.98), a 31% reduction in risk of hospitalization for heart failure (HHF) (95% CI 0.64 to 0.75), and a 41% reduction in risk of the composite end point of substantial decline in estimated glomerular filtration rate (eGFR), progression to kidney failure, or death due to kidney disease (95% CI 0.42 to 0.83).[14,15] These reductions in risk of CV death and HHF are seen in patients aged 75 years or older as well as in younger patients.[16,17] In adults with HF and left ventricular ejection fraction greater than 40%, SGLT2I use is recommended to reduce the risk of HHF.[14]

Compared with placebo in adults with CKD, SGLT2I use is associated with a 36% reduction in risk of the composite end point of eGFR decline, progression to kidney failure, or death due to CKD (95% CI 0.57 to 0.73); an 18% reduction in risk of all-cause mortality (95% CI 0.74 to 0.90); a 15% reduction in risk of CV mortality (95% CI 0.77 to 0.94); a 23% reduction in risk of nonfatal myocardial infarction (95% CI 0.62 to 0.95); and a 37% lower risk of HHF (95% CI 0.58 to 0.70).[14] The time to benefit in the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial was approximately 13 months.[18] For patients with severe frailty, life expectancy should be considered as part of prescribing decisions.[19]

When prescribing SGLT2Is for patients who do not have diabetes, caution is required with respect to volume depletion, hypotension, active genital mycotic infection, and previous critical limb ischemia.[14] In patients with diabetes, SGLT2Is should not be started in those with a history of diabetic ketoacidosis, and dose reduction or drug cessation may be required if starting an SGLT2I in a patient already using insulin or insulin secretagogue.[14] Incidence of euglycemic diabetic ketoacidosis during SGLT2I treatment is low and does not appear to increase with age, but its frequency may double with SGLT2I treatment compared with use of other antihyperglycemic agents (0.07% vs 0.03%, respectively).[20] Predisposing factors include carbohydrate restriction, excessive alcohol consumption, ketogenic diets, severe dehydration, or inappropriate reduction of insulin doses.

Weight loss is a potential side effect of SGLT2Is and is an independent risk factor for falls and increased morbidity and mortality.[20,21] Incidence of volume depletion due to SGLT2I diuretic action is low but increases as renal function worsens[20] and may occur more often in patients 75 years and older (6.8% with empagliflozin vs 5.7% with placebo)[22] due to comorbidities, antihypertensive medications, altered thirst response, and changes in water and sodium balance associated with aging.[19]

Use of SGLT2Is is not associated with higher rates of genitourinary infections in older individuals, although for female patients with poorly controlled diabetes precaution is recommended owing to inherent infection risk.[23]

Use of GLP1-RAs offers benefits related to composite CV outcomes; to risks of all-cause mortality, myocardial infarction, stroke, peripheral artery disease, and HF; and to eGFR and renal outcomes.[24]

Implementation

Canadian guidelines recommend metformin as a first-line oral agent for adults with type 2 diabetes.[1,12] For patients who also have CV disease, additional medications to prescribe could include SGLT2Is such as empagliflozin (grade A, level 1 evidence) or canagliflozin (grade C, level 2) or a GLP1-RA such as liraglutide (grade A, level 1).[1] For patients without CV disease, prescribing decisions will

depend on goals of avoiding weight gain and lowering blood glucose as well asother considerations.[1]

Starting these newer therapies for additional benefits may raise concerns about polypharmacy. Clarifying targets for glycemic control based on frailty assessment and life expectancy is a relevant consideration. Extra caution is required for prescribing these medications in real-life conditions where older individuals may be more frail than those recruited to randomized controlled trials.[25]

Custódio et al propose an algorithm for introducing SGLT2I therapy in older patients with type 2 diabetes.[26] The SGLT2 Rx Tool, developed in Canada and available from **https://www.sglt2rx.com**, may help health care providers understand the risks and benefits of these medications associated with various patient profiles.[27]

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Competing interests
None declared

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