Canadian Geriatrics Society

DIABETES MANAGEMENT IN OLDER ADULTS WITH A SPECIAL FOCUS ON SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS (SGLT2is)

Abstract

Treatment of type 2 diabetes mellitus (T2DM) should be individualized, particularly in older adults who may be frail, functionally dependent, cognitively impaired, or have a short life expectancy. Frail older adults are more vulnerable to hypoglycemia and are more likely to suffer from hypoglycemia-related adverse effects. As such, a more flexible HbA1c target may be necessary, as aggressive glycemic control in older adults may lead to net harm. Newer clinical practice guidelines now recommend use of sodium glucose cotransporter 2 inhibitors (SGLT2is) in patients without diabetes due to proven cardiorenal benefits. What does this mean for the frail older adult? In this article we acknowledge the benefits of the newer oral antihyperglycemic agents with particular focus on the SGLT2i and potential harms associated with SGLT2i use with a hypothetical but plausible case presentation.

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KEY POINTS

1. Newer agents, such as GLP1-RAs, DPP4is, and SGLT2is, are effective, safe, and tolerable in older persons and can be considered for use in older patients.

2. SGLT2is should be considered for use in older patients with cardiovascular and/or renal disease, however, caution and close follow-up should be practiced in frail older adults, especially those with history of falls, orthostatic hypotension, malnutrition, and weight loss.

3. Antihyperglycemic agents with high risk of hypoglycemia should be avoided in older persons.

4. Addition and/or substitution of different antihyperglycemic agents depends on the older patient's functional status, comorbidities, current medications, and risks and benefits of the side effects associated with that drug – an individualized approach that will vary for each older patient.

CASE

Mrs. X is an 80-year-old single female who lives alone in an apartment with minimal social supports. She receives home care supports for bathing, otherwise she is independent for all other basic activities of daily living. Her close friend is her power of attorney who assists with finances and transportation. She manages her medications independently, however, she finds this task overwhelming. She has a history of mild dementia on donepezil, hypertension, myocardial infarction (MI), heart failure with reduced ejection fraction (HFrEF) on furosemide, bisoprolol, and perindopril, dyslipidemia on atorvastatin, T2DM with hemoglobin A1c (HbA1c) level of 7.0% on canagliflozin and saxagliptin. She had two falls in the past year related to orthostatic hypotension and mobilizes with a walker. She has also lost interest in cooking, relying on simple pre-cooked meals. She has lost 15 pounds in the past year. She presented to the hospital with acute cholecystitis and underwent an urgent, uncomplicated cholecystectomy. Post-operatively, she developed euglycemic diabetic ketoacidosis (DKA). She has no previous history of hyperglycemic emergency.

INTRODUCTION

People with T2DM form a heterogenous group, therefore, therapeutic regimens and targets should be individualized, especially in older patients with dementia, functional dependency, and frailty.[1] Numerous factors predispose older adults to hypoglycemia, one of the most feared complications in this group, including isolation, erratic appetite, skipped meals, undernutrition, polypharmacy that favors drug-drug interactions, declining renal function that increases drug levels, and more frequent intercurrent illnesses.[2] One benefit of the newer antihyperglycemic agents highlighted in the updated Diabetes Canada Clinical Practice Guidelines (CPG) is their negligible to low risk of hypoglycemia. Furthermore, some agents have proven benefit in patients with cardiovascular (CV) comorbidities. Theoretically, these agents would be preferred for the older population, as they have improved the ability to cope with the risk of hypoglycemia and CV events, the two most important drawbacks in treating older people with diabetes.[3] Unfortunately, clinical trials examining the efficacy and safety of these drugs often fail to include older adults, especially those with limited life expectancy and/or frailty.

This article aims to review the benefits, efficacy, safety, and tolerability of SGLT2i use with a specific focus on their applicability to older adults, as compared to other new agents including the glucagon-like peptide-1 receptor agonists (GLP1-RA), and dipeptidyl peptidase 4 inhibitors (DPP4is).

REVIEW OF AVAILABLE ORAL ANTIHYPERGLYCEMICS

The Diabetes Canada CPG outlines an approach to prescribing antihyperglycemic therapy in patients with diabetes and reviews the currently available oral antihyperglycemic agents, available at: Diabetes Canada | Clinical Practice Guidelines - Chapter 13: Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update. Table 1, adapted from the Diabetes Canada CPG[4] and Koufakis et al.[5], outlines the advantages and disadvantages of these agents in older adults specifically.

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

Class and mechanism of action	Name of drug	Advantages in older adults	Disadvantages in older adults
Biguanide: Enhances liver and peripheral insulin sensitivity, reduces gluconeogenesis, excreted by urine	Metformin	Low risk of hypoglycemia Possible anti-aging effects[6]	No randomized trials in older patients Increased probability of GI adverse events and lactic acidosis[5] Frequent monitoring of renal function[5] Increased risk of vitamin B12 deficiency which can predispose to falls
Thiazolidinedione: Enhances liver and peripheral insulin sensitivity	Rosiglitazone Pioglitazone	Low risk of hypoglycemia	Increased incidence of edema and HF[7] Increased risk of HF, acute MI, and mortality with rosiglitazone[7] Increased risk of bone fractures in females[8]
Insulin secretagogue: Stimulates endogenous insulin production	Sulfonylureas: Gliclazide Glyburide Glimepiride Meglitinides: Repaglinide	Strong hypoglycemic effect	High risk of hypoglycemia Increased mortality risk has been reported[9] Debatable CV safety[5]
Alpha-glucosidase inhibitor: Inhibits pancreatic alpha-amylase and intestinal alpha-glucosidase	Acarbose	Modest efficacy Relatively safe	Lack of studies in older patients No studies with outcomes that show a protection against diabetic complications[2] Increased probability of GI adverse events[2]
Incretin: Increases glucose-dependent insulin release, slows gastric emptying, inhibits glucagon release	GLP1-RA: Exenatide Lixisenatide Dulaglutide Liraglutide Semaglutide	GLP1-RA: Low risk of hypoglycemia Cardiorenal benefits Potential to improve neurological outcomes[10-11] Weekly administration available	Mostly injectable therapies Increased probability of GI adverse events[5] Potential to induce significant weight loss High cost
	DPP4i: Alogliptin Linagliptin Saxagliptin Sitagliptin	DPP4i: RCTs demonstrate efficacy and safety in elderly CV and renal safety Improved sarcopenic parameters[12] Good tolerability	Increased risk of bullous pemphigoid[13-14] Risk of pancreatitis and pancreatic cancer debatable[15] Specific agents contraindicated in HF
Sodium glucose cotransporter 2 inhibitor: Reduces renal glucose reabsorption causing increased glucosuria	Canagliflozin Empagliflozin Dapagliflozin	Phase III studies show safety in elderly[16] Low risk of hypoglycemia Cardiorenal benefits	Concerns regarding increased risk of euglycemic DKA, genitourinary infections, dehydration, and fractures High cost

Abbreviations: GI: gastrointestinal; HF: heart failure; MI: myocardial infarction; RCTs: randomized controlled trials; CV: cardiovascular; GLP1-RA: glucagon-like peptide-1 receptor agonists; DPP4i: dipeptidyl peptidase 4 inhibitors; DKA: diabetic ketoacidosis.

CURRENT MANAGEMENT OF DIABETES MELLITUS IN OLDER ADULTS

In general, in those with obesity and T2DM, the primary metabolic defect is insulin resistance, but insulin secretion remains intact; appropriate initial therapy for this group should involve agents that target insulin resistance, such as metformin.[1] In a patient with T2DM who is lean, the metabolic defect is impaired glucose-induced insulin secretion; initial therapy for this group should involve agents that stimulate insulin secretion without causing hypoglycemia. DPP4is are ideal in this case, particularly in older patients.[1] Still, metformin remains the first line agent when initiating antihyperglycemic agents, according to the Diabetes Canada CPG, due to its low risk of hypoglycemia and weight gain and long-term experience with the agent.[4]

SGLT2is are a game-changing addition to the therapeutic arsenal of T2DM. In addition to lowering HbA1c with minimal hypoglycemic risk, they have been shown to have cardiorenal protective properties in large scale cardiovascular outcome trials (CVOTs).[5] The efficacy profile of SGLT2is versus placebo is unchanged by age.[17]

Table 2. Major possible side effects/adverse events and benefits with the use of SGLT2i agents in older patients

Possible side effects/adverse events	Considerations in older adults
Volume depletion	May cause orthostatic hypotension Adjust antihypertensive therapies, especially loop diuretics, before starting SGLT2i therapy[18]
Amputation	Canagliflozin associated with higher risk of lower limb amputations in CANVAS trial[19] Overall, SGLT2is are not associated with increased risk of amputation operations, even among high-risk groups, including elderly aged 65 years or older and those with peripheral arterial disease[20]
Fractures	Canagliflozin associated with higher risk of bone fractures in CANVAS trial[19] – high CV risk and use of diuretics in this trial suggests fracture incidence may be related to fall events[21]
Renal function	Transient decline in eGFR with initiation similar in younger patients[21] Compromised renal function may contraindicate SGLT2i use[22] May be slightly less effective at reducing HbA1c in setting of CKD, but efficacy and safety profiles have been demonstrated in mild to moderate CKD[18] Delays progression of CKD and reduces clinically significant renal events[19,23-24] Superior in reducing risk of albuminuria and risk of ESRD compared to DPP4is[25]
Genitourinary infections	Tend to occur more frequently in females[22] Increased risk of genital mycotic infections, but not UTIs, compared to DPP4is[26]
Gastrointestinal events	Not associated with increased risk of GI side effects, even when used with metformin[27]

Possible side effects/adverse events	Considerations in older adults
Cancer	Debatable risk of bladder cancer[28]
Euglycemic DKA	Higher rate of DKA compared to DPP4is[29] Overall, DKA incidence in clinical trials was low and did not appear to increase according to age[21] Strategies to help prevent DKA occurrence include avoiding excessive reduction or interruption of insulin; suspending SLGT2i use at least 72 hours before surgery or during times of illness or infection; avoiding alcohol consumption or ketogenic diets

Abbreviations: SGLT2i: sodium glucose cotransporter 2 inhibitor; CANVAS: CANagliflozin cardioVascular Assessment Study; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin; CKD: chronic kidney disease; ESRD: end-stage renal disease; DPP4i: dipeptidyl peptidase 4 inhibitor; UTI: urinary tract infection; GI: gastrointestinal; DKA: diabetic ketoacidosis.

While the safety profiles of SGLT2is (e.g., empagliflozin,[30] dapagliflozin,[31] canagliflozin,[32] and ertugliflozin[16]) in those aged 65 years or older are considered good,[33] there remains hesitance in prescribing these drugs to older adults in clinical practice, which may be due to the concern for increased potential for adverse events.[34] Table 2 reports some of these possible adverse events to be aware of. However, pooled analysis results from phase II/III studies have demonstrated that two-year long treatment with dapagliflozin was well tolerated in older people with T2DM; between older and younger populations, the rates of hypoglycemia, genital infections, and urinary tract infections were comparable, there were low rates of volume depletion for older patients, and there was no increased risk of bone fractures in older patients.[35]

SGLT2is can be used as add-on therapy in select and relatively healthy older patients with T2DM but dedicated randomized controlled trials (RCTs) assessing both efficacy and safety of this drug class in older patients, aged 75 years or older specifically, are lacking. The studies use participants without complex comorbidities, so the outcomes in frailer older patients are unclear. Due to a larger body of evidence with DPP4is (e.g., alogliptin, linagliptin, saxagliptin, and sitagliptin) in this older group, the Diabetes Canada CPG recommends they should generally be used before SGLT2is as add-on therapy after metformin in older patients.[1] However, there is one scenario where an SGLT2i can be considered as second-line after metformin; if the patient is an older adult younger than 75 years old with evidence of CV disease, adequate renal function, and no other complex comorbidities, then empagliflozin can be considered.[1] Considering the recently updated NICE clinical guidelines for management of T2DM in adults, which recommends SGLT2i as first-line treatment in certain individuals with heart failure (HF), established atherosclerotic cardiovascular disease (ASCVD), or are at high risk of developing CV disease, it is likely SGLT2is will be more widely prescribed.[36]

GLP1-RAs are also included in the Canadian guidelines and can be considered in older adults aged 60 years or older with at least two CV risk factors, with the strongest evidence for dulaglutide, then liraglutide and subcutaneous semaglutide.[4] Unfortunately, this drug class is mostly available as injectables, a potential challenge for use in older adults. All SGLT2is are available as oral medications and can be taken at any time of the day.[34]

CARDIORENAL EFFECTS OF NEWER AGENTS

The Diabetes Canada CPG reviews the evidence for cardiorenal benefits of SGLT2is, GLP1-RAs, and DPP4is, available at: Diabetes Canada | Clinical Practice Guidelines - Chapter 13: Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update.

The SGLTI2i- and GLP1-RA-mediated cardiovascular and renal protection demonstrated in CVOTs has led to a paradigm shift in the care of patients with diabetes, encouraging health care providers to use these antihyperglycemics in patients with high cardiorenal risk, regardless of glucose control.[37] The benefits of SGLT2is

and GLP1-RAs are well recognized even in patients without diabetes. The 2022 Canadian Cardiovascular Society (CCS) guidelines now recommend using SGLT2is in non-diabetic patients.[38] In adults with HF and left ventricular ejection fraction (LVEF) 40% or below, SGLT2i reduces all-cause and CV mortality, hospitalization for heart failure (HHF), and a composite endpoint of significant decline in estimated glomerular filtration rate (eGFR), progression to end-stage renal disease (ESRD), or death due to kidney disease.[38] This risk reduction in CV death and HHF remains consistent for patients aged 75 years or older.[22,39] In adults with HF and LVEF above 40%, SGLT2i reduces HHF.[38] In adults with chronic kidney disease (CKD), SGLT2i reduces a composite endpoint of significant decline in eGFR, progression to ESRD, or death due to kidney disease, all-cause and CV mortality, nonfatal MI, and HHF.[38]

If utilizing SGLT2is to treat CV disease in a non-diabetic patient, caution should be used with respect to volume depletion, hypotension, active genital mycotic infection (GMI), previous critical limb ischemia; initiation of therapy should be delayed until the condition is resolved, or therapies are modified to reduce risk.[38] Ongoing monitoring for GMIs, concomitant dehydrating illnesses, volume depletion, and renal function is recommended.[38] If considering using SGLT2i in a diabetic patient, additional consideration should be given for DKA (i.e., an SGLT2i should not be started in a patient with a history of DKA) and concomitant use of insulin or an insulin secretagogue (i.e., dose reduction or drug cessation may be required).[38]

The use of GLP1-RAs is associated with a significant benefit on composite CV outcomes, major adverse cardiovascular events (MACE), all-cause mortality, MI, stroke, CV disease, peripheral artery disease, and HF, compared to other antihyperglycemic agents, except the SGLT2is.[40] They also have significant benefit on eGFR and hard renal outcomes versus other glucose-lowering drugs, except the SGLT2is.[40]

Patorno et al. notably enrolled older adults with a mean age of 72 years, approximately 10 years older than those enrolled in the CVOTs that most of the data and recommendations above are derived from.[41] This study compared SGLT2i and GLP1-RA efficacy and safety in this often-neglected subgroup of type 2 diabetic patients, and found that older adults taking an SGLT2i had a similar MACE risk but decreased HHF risk versus those taking a GLP1-RA.[41]

SHOULD WE BE ADDING OR SUBSTITUTING SGLT2i IN EVERYONE?

In the general population, metformin remains the first-line agent in the treatment of T2DM and the Diabetes Canada CPG recommends SGLT2i as second-line if therapeutic advancement or adjustment is required in adults with T2DM and ASCVD or HFrEF or CKD with an eGFR > 30 mL/min/1.73m^2, and in adults with T2DM aged 60 years or older with at least two CV risk factors.[4] A GLP1-RA could also be considered, except for those with history of HF.[4]

According to the CCS, in patients with T2DM and either ASCVD or multiple risk factors for ASCVD without HF or CKD and irrespective of HbA1c, integration of SGLT2i or GLP1-RA is recommended to reduce cardiorenal risk.[38] Therefore, replacing, rather than adding an agent with cardiorenal benefit, would be most appropriate in the general population at or near HbA1c target.[38]

The European Society of Cardiology diabetes guideline recommends SGLT2i or GLP1-RA as first-line therapy, instead of metformin, for the general population in patients with ASCVD or at high or very high CV risk.[42] No specific trials exist showing cardiorenal benefit with these agents used as first-line therapy or as monotherapy or in newly diagnosed T2DM, but the benefit seen in CVOTs does not vary with diabetes duration, suggesting these benefits may be seen in early diabetes.[40] Furthermore, the benefits are not dependent on the presence of metformin.[38]

It should be noted, however, that these recommendations are for the general population, which does not specifically include older adults. However, post-hoc analyses of the large CVOTs examining the efficacy and safety of the SGLT2i according to age have been performed. Dapagliflozin reduces the risk of death and worsening HF and improved symptoms across all ages, even in those 75 years or older.[43] Similarly, empagli-

flozin was found to reduce the risk of CV mortality, HF, and renal outcomes across all ages.[44] Meta-analysis of EMPA-REG OUTCOMES, DECLARE TIMI 58, and CANVAS trials show that the effect of SGLT2i on CV outcomes among patients with T2DM was consistent across all age groups, with no subgroup differences.[17] Similar results were seen in another meta-analysis of EMPRA-REG OUTCOMES, DECLARE TIMI 58, and CREDENCE trials where the reduction on MACE outcomes associated with SGLT2i use was far greater in older adults than younger individuals.[45] Clearly the SGLT2is confer cardiorenal benefits in older individuals. Furthermore, the outcome benefits can be realized quickly following initiation of the drug. Dapagliflozin was associated with a reduction in the risk of CV death and HHF as early as 28 days,[46] and in another study as early as 24 days.[47] This supports the early addition of SGLT2i in patients where clinical benefits are important. On the other hand, the DAPA-CKD trial showed that in patients with CKD, regardless of the presence of T2DM or not, dapagliflozin did cause significant risk reduction in the composite endpoints, including both cardiac and renal outcome benefits, compared to placebo, but the time to outcome benefits was approximately 13 months.[48] For older adults, the benefits would likely be realized within their anticipated life expectancy, but for those who are severely frail, the benefit is unlikely to be seen within their anticipated life expectancy.[34]

CAN WE ROUTINELY APPLY THE ABOVE RECOMMENDATIONS AND EVIDENCE IN THE FRAIL OLDER ADULT?

There is a common perception that evidence-based therapies are less effective in frail individuals in addition to concerns that these patients experience more treatment intolerance and adverse side effects, often leading to discontinuation of the drug.[49] The anticipation of a less favorable risk versus benefit profile in frail individuals may cause clinicians to hesitate to initiate these therapies in these individuals. However, there is little evidence to support this assumption.[49]

SGLT2is are a desirable option in the older patient due to their potent antihyperglycemic effect with low hypoglycemic risk and cardiorenal benefits but certainly there are numerous side effects to consider in an older patient (see Table 2). Post-hoc analysis of the DAPA-HF trial examined the efficacy of dapagliflozin according to frailty status and found that dapagliflozin reduced the risk of worsening HF or CV death in all frailty groups, with the largest absolute reductions seen in the frailer patients, and that adverse events were not higher than for placebo regardless of frailty status.[50] The DELIVER trial examined efficacy and safety of dapagliflozin according to frailty status, utilizing The Clinical Frailty Scale developed by Rockwood et al.,[51] in patients with HF with mildly reduced or preserved ejection fraction.[49] Treatment efficacy was not diminished in patients with the greatest degree of frailty and the improvement in health-related quality of life with dapagliflozin was greater in patients with greater frailty.[49] The proportion of patients who discontinued SLGT2i treatment or experienced adverse events increased with increasing frailty, but adverse events were not more common in those taking dapagliflozin compared to placebo irrespective of frailty class. Ultimately, the risk versus benefit balance related to frailty was favorable for dapagliflozin and this finding could challenge the reluctance to initiate this drug in frail patients.[49]

Weight loss is one side effect that must be strongly considered in older patients as it can be associated with falls, disability, increased morbidity, and mortality. The EMPA-ELDERLY trial will be the first RCT in older patients 65 years or older with T2DM to evaluate the effect of an SGLT2i on skeletal muscle mass, muscle strength, and physical performance.[52] SGLT2is may also be associated with volume loss due to their diuretic action. The overall incidence of volume depletion-related events is low but increases as renal function worsens in CKD[53] and may occur more frequently in patients 75 years or older.[44] This effect may be more pronounced in older adults due to their increased number of comorbidities, concomitant use of antihypertensive medications, altered thirst response, and changes in water and sodium balance that occur with ageing.[34] Special attention must be paid to orthostatic hypotension (for more on this entity see 4D-AID+-+A+Practical+Approach+to+the+Assessment+of+Orthostatic.pdf (squarespace.com)), especially in patients on antihypertensive or diuretic medication that may require dosage reduction.[54-55] The consensus on fracture risk is conflicting. Only canagliflozin has been associated with non-significant higher rates of low trauma fractures, though this may be due to a higher fall incidence, as volume-related adverse events were more frequent with canagliflozin than placebo.[56] SGLT2i use does not increase genitourinary (GU) infection incidence

in older individuals, though precaution is recommended for female patients with poorly controlled diabetes due to their high infectious risk.[55]

Though the incidence of euglycemic DKA during SGLT2i treatment is low and does not appear to increase according to age, the frequency may be double that compared to other antihyperglycemics.[53] Among reported cases, a high proportion of patients had comorbidities which may increase their susceptibility, like autoimmune diabetes (type 1 diabetes or late autoimmune diabetes of adulthood), reduction of background insulin therapy, and acute illness.[53] This risk should not preclude their use in older adults. However, avoiding predisposing factors, like carbohydrate intake restriction, excessive alcohol consumption, ketogenic diets, severe dehydration, or inappropriate reduction of insulin doses, is important.

SGLT2is act favorably on blood pressure, even in CKD patients, and may help control hypertension burden in older individuals.[57]

IF AN OLDER ADULT PATIENT WITH T2DM IS NOT ON AN SGLT2I, IS IT NECESSARY TO START ONE GIVEN THE ABOVE BENEFITS?

This raises the concern of polypharmacy, which may result in net harm in the older adult. Most patients with T2DM also have hypertension and dyslipidemia and take medications for all three conditions concurrently, where the effect of one drug could be confounded with that of another. The studies of the effect of each class of medication on survival exist, but unfortunately are not adjusted for the concurrent use of other drugs.[9]

Robust evidence supporting cardiorenal benefit of SGLT2is has led to more emphatic recommendations in diabetes treatment guidelines to prioritize using this drug class over others. The frequency of adverse events suggests there are no absolute contraindications for SGLT2i use in older patients. However, extra caution is required in real-life conditions where older individuals may be less robust than those recruited in RCTs.[18] Custódio et al. proposes an algorithm for introducing SGLT2i therapy in older patients with T2DM.[21] The "SGLT2 Rx Tool" may also be used to further understand the risks and benefits in various patient profiles.[58]

WHAT HBA1C LEVELS SHOULD WE BE TARGETING WITH THESE MEDICATIONS IN OLDER PATIENTS?

The strong association between poor glycemic control, risk of complications, and increased mortality remains consistent across all age groups, with some data suggesting a trend towards greater all-cause and cause-specific mortality among patients aged 65 years or older with HbA1c 8.0% or greater.[5] On the other hand, a U-shaped relationship between mortality and HbA1c was demonstrated in diabetic patients aged 80 to 89 years old, with the lowest mortality observed among those with HbA1c 7.0 to 7.4% and significantly higher mortality rates in subjects with strict glycemic control (HbA1c 6.0% or less) or poor glycemic control (HbA1c 8.5% or more).[59] Attempts to achieve intensive glycemic control may lead to net harm in older adults with T2DM.[60]

In functionally independent older patients with normal cognition and life expectancy long enough to benefit from treatment, HbA1c target should be 7.0% or below, just like the younger population. In those with multiple chronic diseases, mild to moderate cognitive impairment, or shortened life expectancy, HbA1c target should be 7.1 to 8.0%. In older patients with diabetes and advanced diabetic complications, significant health problems, short life expectancy, fragility, less functionality, or have limited cognitive capacity, the target should remain flexible, but still an HbA1c 8.5% or below is recommended.[3] The Diabetes Canada CPG Chapter 37 emphasizes considering functional status in determining target HbA1c in older people with T2DM.[1] In fact, the guidelines incorporate The Clinical Frailty Scale, briefly mentioned above, to recommend glycemic targets based on the patient's frailty index; a more flexible target of 7.1 to 8.0% is recommended for a patient with a frailty index of 4-5, a target of 7.1 to 8.5% is recommended for a patient with a frailty index of 6-7, and measuring HbA1c at all is not recommended for those with a frailty index of 8-9.[1]

SUMMARY

The GLP1-RAs, DPP4is, and SGLT2is, with their unique characteristics of cardiorenal benefits, independent of glycemic control, efficacy in patients with or without cardiorenal disease, and low hypoglycemic risk, offer ideal therapeutic choices for older patients. The cardiorenal benefit extends to include even very old patients aged 75 years or older.[54] This may supersede the choice to use metformin as a first-line agent. Age should not be a barrier to using these agents and, SGLT2is in particular should be considered as a valid therapeutic option for older frail adults with T2DM, HF, or CKD.[34]

Safety considerations for these drugs are essential. All individuals with T2DM currently using or starting therapy with insulin secretagogues (GLP1-RA or DPP4i) must be counselled on the prevention, recognition, and treatment of hypoglycemia.[4] If an individual develops an acute illness associated with dehydration or has an upcoming procedure associated with risk of acute kidney injury, their metformin and/or SGLT2i should be temporarily held and their insulin secretagogue dose should be reduced or held entirely if oral intake is reduced.[4] SGLT2i must be held before major surgeries and/or during acute infections or serious illnesses to reduce the risk of DKA, particularly in people who follow low carbohydrate diets or with suspected insulin deficiency[4]. Implementation of these safety considerations is imperative in our vulnerable older population.

Ultimately, selection of therapy depends on the patient, their preferences, comorbidities and current medications, tolerability, and the individualized glycemic target. In the older person with T2DM, functional status is key in determining the HbA1c target. Management beyond pharmacotherapy, including self-management education and support programs, are also vital aspects of diabetes care in this population. Further dedicated studies involving this older population with these new antihyperglycemic therapies are warranted.

CASE CONCLUSION

Mrs. X had reduced oral intake leading to an admission to the hospital. She was kept on nil per os (NPO) status prior to surgery, followed by suboptimal oral intake post-operatively. Dehydration in combination with surgery and canagliflozin use likely precipitated euglycemic DKA. She was also found to have postural hypotension. Given her frail status, history of weight loss, poor nutrition, orthostatic hypotension, increased fall risk, recent HbA1c of 7.0%, canagliflozin was discontinued as associated risks of SGLT2i would outweigh benefits in her case.

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