Newer Glucose-Lowering Therapies in Older Adults with Type 2 Diabetes

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KEYWORDS

• Type 2 diabetes • Older adults • DPP-4 inhibitors • GLP-1 receptor agonists
• SGLT-2 inhibitors • Tirzepatide • Diabetes subtypes • Precision medicine

KEY POINTS

- Diabetes is prevalent in older adults, affecting more than 25% of the population above the age of 65.
- It is especially important to personalize diabetes management in older individuals, taking into consideration the heterogeneity in the disease as well as the presence of comorbidities, diabetic complications, geriatric syndromes, functional and cognitive status, and life expectancy when setting glycemic targets and choosing treatments.
- Hypoglycemia is a particular risk among older individuals with diabetes. Newer glucose-lowering drugs with a decreased risk of hypoglycemia are preferred in older adults.
- Newer glucose-lowering therapies such as dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter 2 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1RA) can be safely used in older patients.
- Recent guidelines suggest early initiation of specific cardiorenoprotective glucose-lowering agents (in SGLT-2i and GLP-1RA classes) irrespective of glycemic status or age among those at high risk for atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease.

INTRODUCTION

As life expectancy increases around the world, clinicians are increasingly faced with the formidable task of managing older adults with multiple diseases. Diabetes is common in the older adult population, affecting one in four people over 65 years of age.[1] The global epidemic of diabetes, combined with increases in life expectancy, means that the population of older adults with diabetes will continue to grow in the

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foreseeable future. Indeed, by the year 2045, over 276 million older adults are projected to have diabetes.[2] Older adults with diabetes have a shortened life expectancy, dying 4.6 years earlier on average, develop disability 6 to 7 years earlier and spend one to two more years in a disabled state than adults without diabetes.[3]

The advent of new glucose-lowering drugs in recent years, including dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1RA), and sodium-glucose cotransporter 2 inhibitors (SGLT-2is), has provided clinicians with many more effective and safe treatment options to care for their older patients with diabetes. However, it is essential to know the advantages and disadvantages of these newer classes of glucose-lowering drugs in the aging population when incorporating them into an individualized treatment regimen. Certain SGLT-2i and GLP-1RAs have demonstrated benefits and are indicated to reduce the risk for cardiovascular disease (CVD), heart failure (HF), and chronic kidney disease (CKD) progression in high-risk patients with diabetes, including older adults. Thus, the incorporation of these drugs into individualized treatment regimens to improve long-term outcomes should be considered for selected older individuals with type 2 diabetes (T2D) who are likely to benefit.

Diabetes in Older Adults

Heterogeneity of diabetes in older adults

Diabetes is a heterogeneous disease in the older adult population. For example, older individuals could have type 1 diabetes (T1D) that developed in childhood with a correspondingly long duration of disease, or they might have developed autoimmune diabetes in their later years and have a relatively short duration of the disease. Similarly, they might have developed T2D as a young adult in their 30s or 40s and have a relatively long duration of the disease or, not uncommonly, they could have developed it as an older adult and have had diabetes for only a few years. The pathogenesis of T2D is complicated, with multiple metabolic abnormalities including insulin resistance and insulin secretory defects contributing to hyperglycemia (**Fig. 1**). Recent studies indicate that even among adults who would ordinarily be classified as having "typical" T2D, there exists heterogeneity, with at least five subgroups differing in pathogenesis and risk for complications. Ahlqvist and colleagues conducted cluster analyses on several thousand patients with new-onset diabetes and found that they could be divided into five clusters: (1) a Severe Autoimmune Insulin-Deficient Diabetes (SAID) cluster, generally corresponding to T1D and characterized by early-onset disease, relatively low body mass index (BMI), poor metabolic control, insulin deficiency, and the presence of Glutamic Acid Decarboxylase (GAD) antibodies; (2) a Severe Insulin-Deficient Diabetes (SIDD) cluster which was similar to the SAID cluster but with negative GAD antibodies and early signs of diabetic retinopathy; (3) a Severe Insulin-Resistant Diabetes (SIRD) cluster characterized by insulin resistance (high HOMA2-IR index) and high BMI that had the highest risk of developing of CKD, macroalbuminuria, and end-stage renal disease (ESRD); (4) a Mild Obesity-Related Diabetes cluster that was associated with obesity but without marked insulin resistance and finally, and especially relevant for this review; and (5) a Mild Age-Related Diabetes cluster that was characterized by older age of onset with relatively mild metabolic derangements and a low risk for complications.[4] These clusters have been replicated in multiple different populations around the world, including populations with a longer duration of diabetes. Although classification schemes are not yet incorporated into clinical practice, it is useful to appreciate that this heterogeneity exists, as it can help to predict risk for complications. Furthermore, an evolving body of evidence suggests that the different clusters

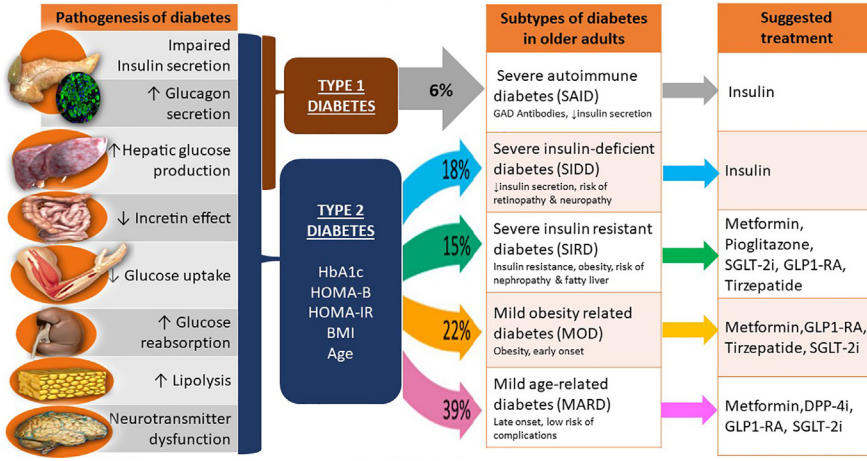

Fig. 1. Pathophysiology, subtypes, and suggested treatment options for patients with diabetes. BMI, body mass index; DPP-4i, dipeptidyl peptidase -4 inhibitor; GLP-1RA; glucagon-like peptide-1 receptor agonist; HOMA-B, homeostasis model assessment of beta-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; SGLT-2i, sodium-glucose co-transporter 2 inhibitor.

benefit from certain therapeutic interventions more than others. For example, the SIDD cluster, which tends to have a higher hemoglobin A1c (HbA1c) at presentation, fails metformin monotherapy earlier than other groups (except for the SAID cluster), and more often requires insulin (like the SAID cluster). This is consistent with the putative underlying pathophysiologic defect in insulin secretion that drives hyperglycemia in this group. Thus, heterogeneity in the pathogenesis and duration of diabetes, as well as the variable risk for complications, coupled with other comorbidities and the pharmacotherapies needed to manage multiple diseases, makes management of diabetes in older adults especially challenging.

Systemic Effects of Aging and Complications of Diabetes

Human aging is characterized by pathophysiological changes in virtually every organ system that can increase risk for diabetes, impact the selection of therapies to control hyperglycemia, and increase the risk of complications and comorbidities. For example, a progressive loss of beta-cell insulin secretory capacity and the development of insulin resistance related to obesity and physical inactivity with aging are thought to contribute to the age-related increase in the incidence and prevalence of diabetes. People with diabetes are at an increased risk of developing microvascular and macrovascular complications, including diabetic retinopathy, neuropathy, nephropathy, coronary artery disease, HF, stroke, peripheral vascular disease, and lower-limb amputations that can be disabling and life-threatening.[5] The risk of diabetic complications is increased with poor glycemic control and long-standing diabetes and is higher in older adults with diabetes. The presence of complications should be carefully assessed as this can impact goal setting as well as selection of specific-glucose lowering medications.

Cardiovascular aging and cardiovascular disease complications of diabetes

Age-related changes in the cardiovascular system include limited cardiomyocyte regeneration capacity, myocardial fibrosis,[6] amyloid deposition,[7] increased vasculature stiffness,[8,9] and left ventricular remodeling which markedly increase risk for

CVD and HF in older adults with diabetes.[10] Therefore, cardiovascular aging, though considered normal, tends to lower the threshold for development of CVD.[11]

There is a two- to four-fold increased risk of CVD in patients with T2D compared with the general population.[12] The prevalence of HF is significantly increased with age,[13] and patients with T2D have a two- to five-fold increased risk of developing HF compared with their counterparts without diabetes, irrespective of age, hypertension, coronary artery disease and hypercholesteremia.[14,15] Furthermore, diabetes is a predictor of poor outcomes in HF patients. Some newer glucose-lowering drugs are indicated to reduce the risk of CVD (GLP-1RAs, SGLT-2i) and HF (SGLT-2i).

Renal aging

With aging, the kidneys undergo progressive structural changes and functional decline.[16–19] After 35 years of age, the glomerular filtration rate (GFR) falls by about 5% to 10% per decade.[20,21] Owing to gradual impairment of renal functional reserve, older adults are increasingly susceptible to acute kidney injury (AKI) and are at increased risk for CKD, ESRD, and drug-related nephrotoxicity.[22,23]

Diabetes is also associated with nephron loss, oxidative stress, and autophagy, which accelerates the GFR decline with aging and further increases risk for AKI, CKD, and mortality.[24] Over 40% of patients with T2D will develop CKD during their lifetime.[25]

Older adults with diabetes should be routinely screened for CKD with at least annual measurements of GFR (eGFR) and urine albumin creatinine ratio. Management of CKD should focus on risk factor identification and control, including hyperglycemia and hypertension, as well as early initiation of renoprotective pharmacologic therapies such as Renin Angiotensin Aldosterone System (RAAS) blockers and mineralocorticoid receptor antagonists.[26] GLP-1RAs decrease the progression of microalbuminuria, whereas SGLT-2is decrease the progression of microalbuminuria and slow the eGFR decline and are indicated to decrease the risk of progression of CKD.[27] Importantly, the progressive loss of kidney function over time can affect the clearance of some glucose-lowering medications, such as metformin, sulfonylureas, certain DPP-4i, certain GLP-1RAs, and SGLT-2is, requiring dose adjustment of these medications in patients with CKD.[26,28] Thus, it is important to assess renal function when evaluating older adults with diabetes to gauge their risk of subsequent cardiovascular and kidney complications and to choose therapies to decrease the risk of these complications from among the many possible options.

Hepatic aging

Aging is associated with changes in liver function which increases risk for the development of age-related cardiometabolic disease.[29] An underappreciated complication of diabetes in older patients with diabetes is the development of nonalcoholic fatty liver disease (NAFLD) or, less commonly, nonalcoholic steatohepatitis (NASH).[30] These conditions can progress to cirrhosis, liver failure, and hepatocellular carcinoma in some cases. Drugs such as the thiazolidinediones and GLP-1RAs may decrease hepatic steatosis and should be considered in older patients with NAFLD. Marked impairment of hepatic function is also important to identify as it can increase risk for hypoglycemia due to the depletion of glycogen reserves and affect the metabolism of certain glucose-lowering drugs.

Neurologic aging

The prevalence of cognitive impairment increases dramatically with aging. Diabetes is also associated with an increased risk and rate of cognitive decline and dementia.[31,32]

Both aging and diabetes increase the risk of stroke which can also lead to cognitive decline, and diabetes is associated with adverse stroke outcomes.[33] Among the newer glucose-lowering drugs, GLP-1RAs have been shown to reduce the risk of stroke in patients with T2D at high risk for CVD.[34,35]

Hypoglycemia

Hypoglycemic episodes should be ascertained and addressed in all patients with diabetes during every visit, but this is especially important in older adults with diabetes. Assessment of hypoglycemia (eg, selected questions from the Diabetes Care Profile),[36] hypoglycemic unawareness,[37] assessment of skipped meals, repeated administration of medication, and stratification of future risk of hypoglycemia with validated risk calculators (eg, Kaiser Hypoglycemia Model)[38] should be done routinely. Factors which increase the risk of treatment-associated hypoglycemia include the use of insulin/insulin secretagogues, impaired hepatic or renal function, frailty, longer diabetes duration, impaired cognition, hypoglycemic unawareness, history of severe hypoglycemic events, and polypharmacy.[39] For older adults with T1D and older adults with T2D on multiple insulin injections, continuous glucose monitoring is recommended to reduce the risk of hypoglycemia.[40,41]

TREATMENT GOALS

As suggested by American Diabetes Association (ADA), the treatment goals of older adults are different from their younger counterparts with a focus on comorbidities, complications, functional status, and life expectancy.[42] HbA1c remains the gold standard test to assess long-term glycemic control for most adults with diabetes, but in situations such as palliative care it may no longer be relevant. Furthermore, in older adults, several factors falsely raise or lower glycated hemoglobin.[43] Therefore, frequent blood glucose measurements or the use of diabetes technology such as continuous glucose monitor can provide better assessment of glycemic control in this population.

EVIDENCE-BASED DIABETES MANAGEMENT WITH NEWER GLUCOSE-LOWERING THERAPIES

In the past two decades, there has been an unprecedented increase in the number of antihyperglycemic drugs, with over 12 different classes of medications and usually multiple members of each class currently available. The mechanism of action, side effects, benefits, and pitfalls of glucose-lowering drugs are summarized in **Table 1**. Historically, older adults have been underrepresented in the clinical development programs of new drugs for diabetes, despite the high prevalence of diabetes in this segment of society. This has resulted in a critical evidence gap in understanding the risk/benefit ratio of newer diabetes drugs in this population. Thus, the safety and efficacy of these drugs in older adults has been extrapolated from data in healthier, younger populations. This is far from ideal, given the unique issues in older adults with diabetes, including their high risk of complications and high rates of comorbidities. Although this situation has improved somewhat in recent years, frail older adults with multiple comorbidities are still excluded from clinical trials due to inclusion/exclusion criteria and access to clinical research sites. Consequently, the optimal treatment approach to treatment of the older patient with diabetes, including frail older individuals with multiple comorbidities, is not known, nor are the optimal treatment approaches known in settings such as the hospital and long-term care facilities where older patients predominate.

Table 1
Glucose-lowering therapies used in older adults

Class	Reduction in HbA1c (%)	Effects on Body Weight	FDA-Approved Pharmacologic Agents	Side Effects	Benefits/Cautions in Older Adults
Biguanides	1–2	~ −1 kg	Metformin	Gastrointestinal side effects, decreased appetite	Benefits: Safe to use if no contraindications, low risk of hypoglycemia, low cost Caution: associated with weight loss, vitamin B12 deficiency, worsening neuropathy, and metformin-associated lactic acidosis in ≥ 65 year old with CKD. Contraindicated if eGFR <30 mL/min/1.73 m^2.
Sulfonylureas	1–2	~ +2 kg	Glipizide, glyburide, glimepiride	Hypoglycemia, headache, nausea, dizziness, hypersensitivity reactions, weight gain	Benefits: Low cost, consider short-acting agents like glipizide to reduce hypoglycemia. Caution: Higher risk of severe prolonged hypoglycemia with chlorpropamide, glimepiride, and glyburide. Drug interaction with some common geriatric drugs (warfarin and allopurinol). Older sulfonylureas (tolbutamide, chlorpropamide) should be avoided in older individuals.
Thiazolidinediones (TZD)	0.75–1.5	~ +4 kg	Rosiglitazone, pioglitazone	Upper respiratory tract infection, headache, sinusitis	Benefits: Low risk of hypoglycemia, can be used in impaired renal function, well tolerated and effective in reversing insulin resistance. Caution: CHF, increased bone loss and fracture risk, concern about bladder cancer. FDA black box warning: heart failure

Dipeptidyl peptidase-4 inhibitors (DPP-4i)	0.5–1	Weight neutral	Alogliptin, sitagliptin, saxagliptin, linagliptin	Headache, nasopharyngitis, pancreatitis, myalgia, muscle weakness, muscle spasm	Benefits: Low risk of hypoglycemia, once daily pill formulation is well tolerated in elderly, frail population. Caution: Dose adjustment in patients with CKD (except linagliptin). Increased risk of HF (saxagliptin, alogliptin) inflammatory bowel disease, skin lesions (saxagliptin), and severe joint pains.
Glucagon-like peptide-1 receptor agonists (GLP-1RAs)	0.5–1.5	~ −5 kg	Exenatide, lixisenatide, liraglutide, semaglutide, dulaglutide	Nausea, vomiting, diarrhea, pancreatitis	Benefits: Consider in overweight patients, low risk of hypoglycemia, beneficial effects in patients with atherosclerotic CVD Caution: Gastroparesis, medullary thyroid cancer or MEN 2A or 2B, renal impairment (exenatide, lixisenatide, liraglutide, dulaglutide), hypoglycemia with insulin secretagogues, acute kidney injury, diabetic retinopathy,increased satiety, high cost, injectable formulations (except oral semaglutide) may cause unintentional weight loss in frail people. FDA black box: Risk of thyroid C-cell tumors in rodents, human relevance not determined.

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Class	Reduction in HbA1c (%)	Effects on Body Weight	FDA-Approved Pharmacologic Agents	Side Effects	Benefits/Cautions in Older Adults
GIP/GLP-1 receptor co-agonist	~2	~ −11 kg	Tirzepatide	Nausea, vomiting, diarrhea, decreased appetite, constipation, abdominal discomfort/pain, pancreatitis	Benefits: Consider in overweight patients, once weekly dosing Caution: Same as GLP-1RAs
Sodium-glucose cotransporter 2 inhibitors (SGLT-2i)	0.5–1	~ −2 kg	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Genital mycotic infections, urinary tract infections, increased urination, volume depletion	Benefits: Low risk of hypoglycemia, beneficial effects in patients with atherosclerotic CVD, CHF. Protects against progression of renal disease. Caution: Associated with weight loss, hypotension, dehydration, elevated LDL cholesterol, low bone mineral density, genitourinary infections, foot ulcerations, lower limb amputations (canagliflozin), Fournier's gangrene, euglycemic DKA. Contraindicated in dialysis or if eGFR <45 mL/min/1.73 m^2 (dapagliflozin, ertugliflozin) or <30 mL/min/1.73 m^2 (empagliflozin, canagliflozin).
Alpha-glucosidase inhibitor	0.5–1	~ −1 kg	Miglitol, acarbose	Flatulence, diarrhea, abdominal discomfort	Benefits: Lower postprandial glucose without increased hypoglycemic risk Caution: GI side effects.

Meglitinides	1–2	~+1 kg	Repaglinide, nateglinide	Upper respiratory tract infections, headache, sinusitis, weight gain, three times/day dosing, hypoglycemia	Benefits: Dose can be skipped if meal is skipped so may be useful in older adults with variable eating patterns. Caution: Multiple doses causing pill burden. Use with caution with gemfibrozil, and NPH-insulin
Insulin	Dose-dependent	~+2 kg	Rapid-acting (lispro, aspart, glulisine); short acting (Regular); intermediate acting (NPH); long-acting (glargine, detemir, degludec), premixed, inhaled	Weight gain, hypoglycemia, injection site reaction, lipodystrophy, pruritus, rash, hypokalemia	Benefits: Once daily basal insulin is effective. Caution: Hypoglycemia risk, avoid complex regimen, sliding scale regimen with short- or rapid-acting insulin.
Others					
Dopamine D2 receptor agonists	0.5–1	Weight neutral	Bromocriptine	Nausea, rhinitis, headache, asthenia, dizziness, constipation	Benefits: Low risk of hypoglycemia. Caution: Orthostatic hypotension, psychosis, hallucinations, somnolence. Use with caution with thiazolidinedione, insulin, and other dopamine receptor agonists

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Table 1
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Class	Reduction in HbA1c (%)	Effects on Body Weight	FDA-Approved Pharmacologic Agents	Side Effects	Benefits/Cautions in Older Adults
Bile acid sequestrants	0.5–1	Weight neutral	Colesevelam	Constipation, dyspepsia, nausea	Benefits: Reduces LDL Caution: Increase TG, decrease absorption of fat-soluble vitamins, not recommended in patients prone to bowel obstruction.
Amylin analog	0.5–0.7	~ −4 kg	Pramlintide	Hypoglycemia, nausea, headache, anorexia, abdominal pain	Benefits: Approved for T1D and T2D as adjunct treatment Caution: Gastroparesis, hypoglycemia unawareness. FDA black box: Severe hypoglycemia when used in conjunction with insulin

Abbreviations: HF,heart failure; CKD, chronic kidney disease; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; GI, gastrointestinal; GIP, gastric inhibitory polypeptide; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; MEN, multiple endocrine neoplasia; NPH-insulin, neutral protamine hagedorn insulin; T2D, Type 2 diabetes; TG, triglycerides.

Beginning in 2008, in response to concerns about the cardiovascular safety of rosiglitazone, a careful assessment of the cardiovascular safety profile of drugs in development for T2D was required by the US Food and Drug Administration (FDA).[44] Subsequently, a large number of cardiovascular outcome trials (CVOTs) have been performed to assess risk for major adverse cardiovascular events (MACE), HF, and CKD with newer glucose-lowering drugs.[45] As these trials were required to enroll high-risk participants, a large number of older individuals with comorbidities were included in these trials. These trials enrolled from 3000 to 17,000 participants who were followed from 2 to 5+ years. Typically, 40% to 60% of participants in these trials have been above the age of 65 years, and several hundred were above the age of 75 years. Thus, these trials provide an evolving and robust opportunity to evaluate the long-term safety and efficacy of newer diabetes in older adults with T2D, far outstripping the limited evidence from phase 3 clinical development programs. Data from three classes of drugs (DPP-4i, SGLT-2i, and GLP-1RA) and multiple members of each class studied as the FDA guidance are now available to guide treatment decisions in older adults with T2D.

Dipeptidyl Peptidase-4 Inhibitors

DPP-4 inactivates two incretin hormones, GLP-1 and GIP (gastric inhibitory polypeptide), which are secreted in response to the presence of nutrients in the gut. GLP-1 and GIP increase insulin secretion and decrease glucagon secretion in a glucose-dependent fashion, thereby lowering plasma glucose concentrations. DPP-4 inhibitors are orally available, small molecules that inhibit DPP-4, increasing circulating concentrations of active GLP-1 and GIP and prolonging their effect in the fasting state and postprandially. Because the effects of GLP-1 and GIP on insulin and glucagon are glucose-dependent, DPP-4 inhibitors have a low risk of hypoglycemia. Four DPP-4 inhibitors are licensed for the treatment of T2D in the United States: alogliptin, linagliptin, saxagliptin, and sitagliptin. In phase 3 clinical trials, these drugs generally produced a 0.5% to 0.7% decrease in HbA1c, were weight neutral, had a low risk of hypoglycemia (except when concomitantly used with sulfonylureas or insulin) and were very well tolerated. Of note, in head-to-head trials of 1 to 2 years duration with each of these drugs, the HbA1c lowering observed was comparable to that of sulfonylureas, but with less weight gain and a notable decrease in risk for hypoglycemia.[46] The doses of alogliptin, saxagliptin, and sitagliptin should be adjusted in patients with CKD as they are cleared, at least in part, by the kidney. Linagliptin is primarily eliminated via the enterohepatic system so no dosage adjustment is necessary and consequently it may be preferred in older adults with CKD.

The cardiovascular safety of each of these drugs was evaluated in dedicated CVOTs. In each case, there was no apparent increased risk of MACE among patients with T2D and CVD or high risk, but neither was there any apparent benefit on cardiovascular or renal outcomes, although decreased rates of albuminuria with use of DPP-4i have been reported. Prespecified subgroup analyses by age subgroup did not show any significant difference in cardiovascular safety between younger and older (>65 years) age groups treated with DPP-4i.[47–50] In general, the DPP-4i were safe and well tolerated by older individuals in these trials. A significantly increased risk of hospitalization for HF was reported in patients randomized to saxagliptin and a nonsignificant trend for an increased risk was seen with alogliptin.[51] Consequently, these drugs have label warnings about use in patients with preexisting HF. The risk of acute pancreatitis is also higher with DPP-4i, and therefore, they should be used with caution in those with a prior history of pancreatitis.[52] Collectively, the data

indicate the DPP-4i can be safely used to improve glycemic control in older individuals with T2D with a high burden of comorbidities and CVD risk.

Glucagon-Like Peptide-1 Receptor Agonists

GLP-1 receptors are distributed widely throughout the body, and therefore GLP-1RAs have multiple biological effects on different systems. In addition to increasing insulin secretion and decreasing glucagon in a glucose-dependent manner to improve glycemic control, centrally mediated effects of GLP-1RAs decrease appetite and promote weight loss. They also increase natriuresis and diuresis in the kidneys, decrease platelet aggregation and activation, decrease postprandial lipid excursions from the gut, decrease inflammation in tissues, and decrease blood pressure.[53] Approved GLP-1RAs include the short-acting agents, exenatide and lixisenatide, which are primarily effective at lowering postprandial hyperglycemia, and the long-acting agents liraglutide, dulaglutide, albiglutide, and semaglutide, which have effects on both fasting and postprandial glucose levels.[54] Liraglutide, although administered once-daily, is considered a longer acting agent because its half-life promotes 24-h glycemic control. The latter three GLP-1RAs and a depot formulation of exenatide are administered as a subcutaneous injection once-weekly.[54] Semaglutide is also available in an oral formulation, dosed once daily in the morning. Because of the pharmacokinetics of the molecule, it is also a long-acting GLP-1RA. In phase 3 and phase 4 clinical trials, GLP-1RAs have been shown to lower HbA1c to a variable degree. In general, longer acting agents are more efficacious lowering HbA1c by 1.0% to 2.0%[55] compared with the short-acting agents which lower HbA1c by 0.6% to 0.8%. Body weight loss ranges from 2 to 5 kg with various GLP-1RAs and is also variable. Even among the longer acting GLP-1RAs, efficacy is variable, with some new agents such as semaglutide showing superior HbA1c lowering and weight loss in head-to-head studies compared with earlier GLP-1RA. The GLP-1RAs are generally well tolerated, although nausea, which is usually mild to moderate, occurs in 20% to 40% of patients when initiating and titrating the medications. These symptoms generally resolve with time and can usually be managed with dietary adjustments and slower titration of the medication. Rarely, the nausea can lead to vomiting and the need to discontinue the medication. In pooled analyses, the efficacy and tolerability profile of these drugs has been similar in younger and older adults.

All of the GLP-1RAs discussed above have completed CVOTs to assess their safety and several have been associated with a reduction in MACE in patients with established CVD or high risk. A recent meta-analysis of eight CVOTs (60,080 T2D patients, 33%–75% older adults, and 8%–12% aged 75 years and above) demonstrated that GLP-1RAs as a class were associated with a significantly reduced risk of MACE (14%), CVD mortality (13%), all-cause mortality (12%), fatal and nonfatal myocardial infarction (MI) (10%), fatal and nonfatal stroke (17%), hospitalization for HF (11%), and progression of a composite kidney disease outcome (21%) compared with placebo.[56] Prespecified analyses showed consistent results across age subgroups for cardiovascular outcomes in the SUSTAIN-6 and PIONEER-6 trials (semaglutide),[57,58] and in REWIND (dulaglutide),[59] and AMPLITUDE-O (efpeglenatide).[60] A post hoc analysis of the LEADER trial showed that liraglutide significantly reduced the risk for MACE in the older population, and the benefits seemed more pronounced in patients aged 75 years or older than in those aged 60 to 74 years.[61]

In addition to their glucose-lowering indication, liraglutide and semaglutide have received an indication for decreasing the risk of MACE in people with T2D and established CVD as a result of these CVOTs. Dulaglutide has also received an indication for decreasing the risk of MACE in people with T2D and established or high risk for CVD,

based on the larger numbers of primary prevention patients in the REWIND trial. Marketing of albiglutide was discontinued in 2017, and efpeglenatide is an investigational GLP-1RA not yet approved.

Together, the data indicate that the GLP-1RAs can be used safely in older individuals with T2D and are highly efficacious. In addition, some members of the class may offer an important CV benefit, significantly decreasing the risk of MACE and stroke. Because these drugs can have potent effects on appetite, weight loss should be monitored carefully in older individuals, particularly in those who are not obese and in patients who are frail. These drugs should generally be avoided in those with unintentional weight loss.

Tirzepatide is a novel, first-in-class, dual-acting GIP and GLP-1RA co-agonist recently approved by FDA for the treatment of T2D. In clinical trials, significant decreases in HbA1c and weight have been reported[62] with no overall differences in safety or efficacy in older compared with younger patients. Tirzepatide has a half-life of 5 days and is administered as a once-weekly subcutaneous injection. Like the GLP-1RAs, gastrointestinal side effects are prominent when initiating or titrating the drug. Pooled analyses of the phase 3 trials indicate that tirzepatide is safe with respect to cardiovascular risk[63] and a dedicated CVOT is ongoing.

Sodium-Glucose Cotransporter 2 Inhibitors

SGLT-2is are orally available small molecule drugs that specifically inhibit sodium-glucose cotransporter 2 in the proximal tubule of the kidney, blocking reuptake of glucose and sodium and resulting in glucosuria and natriuresis. The increased delivery of sodium to the macula densa of the distal tubule also helps normalizes tubuloglomerular feedback, which is dysfunctional in diabetes. This is thought to play a key role in the renoprotective and possibly the cardioprotective effects of these drugs.[64] Four SGLT-2i have been approved for the treatment of T2D in the United States: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. In phase 3 clinical trials, these drugs decreased HbA1c by 0.5% to 1.0%. They also decreased weight by ~3 kg, blood pressure and plasma uric acid levels.[65] As weight loss with SGLT-2is seems to be predominantly due to visceral and subcutaneous adipose tissue loss, as opposed to lean body mass loss, this could benefit obese older adults with sarcopenic obesity.[66,67] These drugs are generally very well tolerated. Genital mycotic infections and urinary tract infections are the most common adverse events reported with the use of SGLT-2is. An increased risk for lower limb amputation was observed in the CANVAS program with canagliflozin,[68] but this was not borne out in subsequent trials with canagliflozin in high-risk patients. In people on loop-diuretics, a small, but increased risk for volume-related adverse events has been observed. A small, but increased risk of diabetic ketoacidosis (DKA) has also been reported with SGLT-2i use. Post hoc, pooled analyses of randomized controlled trials of canagliflozin (with 75 years cutoff), dapagliflozin (with 65 years and 75 years cutoffs), and ertugliflozin (with 65 years cutoff) demonstrated their safety and efficacy in improving glycemic control, body weight, and blood pressure in older individuals.[69–71] Although the prevalence of side effects and adverse events are not generally different between older and younger participants in clinical trials, volume depletion should be monitored closely in older adults, particularly in those using loop diuretics.[72]

All SGLT-2i have completed CVOTs, and in addition, dedicated trials in participants with HF and CKD have been completed with some members of the class. In the CVOTs, a composite primary outcome of major adverse cardiovascular events including cardiovascular death, myocardial infarction, and stroke (three-point MACE) was examined. All four drugs in the SGLT-2i class demonstrated CV safety

when compared with placebo in T2D patients with CVD or high risk.[68,73–75] Empagliflozin and canagliflozin also showed a cardiovascular benefit, reducing three-point MACE compared with placebo.[68,73] In a meta-analysis of five CVOTs (46,969 T2D patients, 45%–50% aged 65 years and above, and 6%–11% aged 75 years and above), SGLT-2is were associated with significantly reduced risk of MACE (10%), cardiovascular death (15%), HF hospitalization (30%), and progression of renal disease (38%) compared with placebo.[76] In prespecified analyses of the CVOTs by age subgroup, the cardiovascular safety and benefit of the SGLT-2is was preserved in older adults.[68,74,77] Of note, in the empagliflozin CVOT, there was a significant trend for greater reduction in risk for MACE, cardiovascular death, and HF hospitalization among older adults (>65 years) compared with younger individuals.[78]

Additional outcome trials have been completed in patients with DKD (canagliflozin) and CKD (dapagliflozin). These trials have demonstrated significant reductions in composite kidney outcomes, including sustained declines in eGFR, the development of kidney failure, and kidney-related deaths of 34% to 44%.[79,80] Importantly for older adults, dedicated trials have demonstrated significant benefits of empagliflozin and dapagliflozin in patients with HF with both preserved and reduced ejection fraction.[81] The safety and efficacy of the SGLT-2is was generally similar in older participants compared with the younger participants in these trials.

As a result of the positive results in these trials, the FDA has provided label indications for empagliflozin to reduce the risk of CV death and HF (both preserved and reduced) and canagliflozin to reduce the risk of MACE and progression of DKD, in addition to the glucose lowering indication for these drugs. Dapagliflozin is also indicated to reduce the risk of hospitalization for HF and progression of DKD.

ASSESSMENT AND MANAGEMENT OF TYPE 2 DIABETES IN OLDER ADULTS

Diabetes in older adults differs in important ways from that in younger adults. Optimal management of diabetes in older adults requires regular assessment of medical, psychological, functional (self-management abilities), and social domains. Screening for diabetes complications and geriatric syndromes (ie, frailty, polypharmacy, cognitive impairment, depression, urinary incontinence, falls, and persistent pain) should be individualized, as they may affect diabetes self-management and diminish quality of life. Because of heterogeneity in the pathogenesis of diabetes, its duration and complications in this population, the selection of treatment goals, and therapeutic approaches must be personalized. For healthy older adults, an HbA1c target of less than 7.5% is recommended. Among those who have functional dependence, multiple comorbidities, impaired cognition, memory loss, frailty, polypharmacy, and diabetic complications, less stringent glycemic targets, and avoidance of overtreatment may be appropriate based on life expectancy and functional status.[42,43] In these patients, higher HbA1c targets (<8.0% or <8.5%) may be appropriate depending on personalized risk–benefit potential, risk of hypoglycemia, and life expectancy.

Historically, clinical trials had stringent exclusion criteria which resulted in limited representation of older adults, particularly those with multimorbidity, in trials and a significant gap in the evidence for selecting optimal therapies.[82] However, this situation changed with the 2008 FDA guidance on CV safety which yielded a large number of long-term trials enrolling a considerable number of older participants with multiple comorbidities. These studies provided robust data on the safety of newer glucose-lowering drugs in the older adult population. Apart from the favorable glycemic outcomes and cardiovascular safety shown in these studies, some GLP-1RA and SGLT-2is demonstrated improved clinical outcomes by decreasing risks of MACE,

HF hospitalization, and/or progression of diabetic kidney disease. This has led to a paradigm shift in the approach to selection of therapeutic options from a glucose-centric focus to one in which the prevention of cardiovascular and renal outcomes is prioritized. The accumulated data indicate that older patients are likely to derive substantial cardiovascular and renal benefits, at least equivalent to and in some cases greater than that seen in younger patients when treated with SGLT-2i or GLP-1RA.[61,72,78]

In addition to their higher absolute risk of CVD events, HF, and CKD, older adults with diabetes are at higher risk of hypoglycemia due to advanced age, hypoglycemic unawareness, impaired renal function, polypharmacy, multiple comorbidities, dementia, and insulin deficiency necessitating insulin administration.[42,83,84] Hypoglycemia is particularly concerning in older adults as it can precipitate cardiovascular events, worsen cognition, and increase risk of falls/fractures. Therefore, drugs with hypoglycemic potential like insulin and insulin secretagogues should be used with caution. Newer anti-glucose-lowering drugs have been shown to improve glycemic control without necessarily increasing the risk of hypoglycemia and, therefore, may be preferred in this population. Cost may be a significant limitation when prescribing these drugs for older adults on fixed incomes. When cost is a concern, metformin, thiazolidinediones, and alpha glucosidase inhibitors may be offered to improve glycemic control without increasing hypoglycemia risk. Insulin should be used with caution in older adults, however, in many cases, it is necessary to achieve glycemic targets. When included in the therapeutic regimen, a simple insulin regimen, such as a once-daily basal insulin with lower risk of hypoglycemia and an improved pharmacokinetic profile is preferred.

Finally, when selecting the optimal therapeutic regimen, the unique risks of each class of glucose-lowering drugs must be considered. For the newer glucose-lowering drugs, this includes the rare risks of pancreatitis with DPP-4i, DKA, volume depletion, genitourinary infections, and possible bone fractures with SGLT-2i and nausea and weight loss with GLP-1RAs. An approach to selecting glucose-lowering drugs to optimize outcomes and minimize risk in older individuals with T2D, based on the available evidence, is presented in **Fig. 2**.

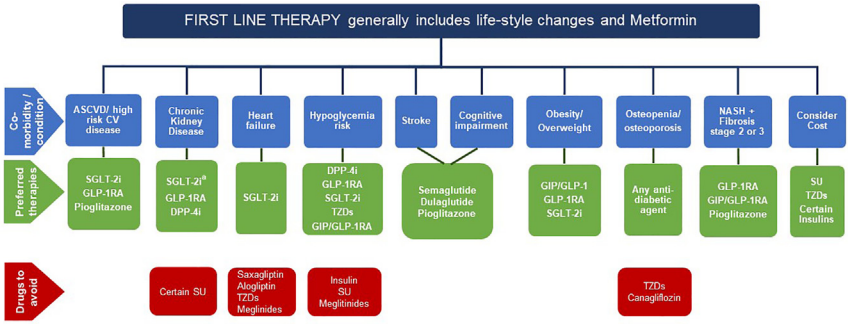

Fig. 2. Preferred pharmacotherapies in type 2 diabetes patients with associated comorbidities and conditions. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; NASH, nonalcoholic steatohepatitis; SGLT-2i, sodium-glucose co-transporter 2 inhibitor; SU, sulfonylurea; TZDs, thiazolidinediones; [a]See package insert for eGFR limitations.

SUMMARY

Diabetes management is complicated in older adults and requires a multifaceted, personalized treatment plan. Assessment of multimorbidity, diabetic complications, geriatric syndromes, and cognition is essential for tailoring the diabetes regimen. In older patients with diabetes, less stringent glycemic targets may be considered depending on life expectancy, functional and cognitive status. Limited research and guidelines are available for very old people (>75 years) with diabetes and for frail older adults, particularly those residing in long-term care facilities. Newer antihyperglycemic agents provide better safety and efficacy and less risk of hypoglycemia and in some cases are associated with cardiovascular and kidney benefits in older adults with T2D. As a result, guidelines have evolved to focus on the selection of treatments that can reduce the risk of CVD, HF, and CKD. As these comorbidities are common in older individuals with T2D, it is especially important to personalize therapy in this population.

CLINICS CARE POINTS

- Heterogeneity of diabetes in older adults requires personalized glycemic goals and an individually tailored care plan.
- Hypoglycemia in older adults is associated with worse outcomes and should be avoided by the use of newer glucose-lowering drugs that do not cause hypoglycemia and simplification of insulin regimens.
- Dipeptidyl peptidase-4 inhibitors, sodium-glucose co-transporter 2 inhibitors (SGLT-2is), and glucagon-like peptide-1 receptor agonists (GLP-1RAs) can be safely used for effective glycemic control in older patients with multiple comorbidities and high risk for cardiovascular disease.
- Certain GLP-1RAs (dulaglutide, liraglutide, and injectable semaglutide) have been granted additional Food and Drug Administration indications for decreasing the risk of major adverse cardiovascular events (including cardiovascular death, nonfatal MI, and/or nonfatal stroke) in type 2 diabetes (T2D) people with CV disease and high risk similarly in older versus younger individuals.
- In high cardiovascular risk patients with T2D, certain SGLT-2is (empagliflozin, canagliflozin, and dapagliflozin) reduce major adverse cardiovascular events, hospitalizations for heart failure, end-stage renal disease, and CV death irrespective of age.
- In patients with heart failure and CKD, SGLT-2i can be used to reduce the progression of these comorbidities irrespective of glycemic status.

DISCLOSURE

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