

CLINICAL REVIEW

GLP-1 RAs and SGLT2-Is to Lower Glucose and Reduce the Risk of Cardiovascular and Diabetic Kidney Disease

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The landscape of diabetes management has changed, such that the goal of pharmacotherapy extends beyond glucose-lowering to prioritize risk reduction of cardiovascular disease and diabetic kidney disease. Two newer classes of medications, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2-Is), have become first line therapies for many patients with type 2 diabetes to reduce cardiovascular and renal complications of type 2 diabetes. This review article will describe the mechanism of action, evidence for cardiovascular and kidney outcomes, contraindications, adverse effects, and risk mitigation strategies for the GLP-1 RA and SGLT2-I drug classes. In addition, we will provide a practical approach for primary care clinicians to prescribe, adjust, and combine these medication classes, while considering patient preference, tolerability, comorbidities, cost, and availability. (J Am Board Fam Med 2024;37:372–382.)

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Introduction

Type 2 diabetes (T2D) is a common and costly illness, affecting 1 in 10 Americans.¹ T2D is a major cause of morbidity and mortality, particularly from atherosclerotic cardiovascular disease (ASCVD), heart failure, and chronic kidney disease.² Rates of T2D and obesity are increasing, such that 30 to 40% of new cases of T2D are attributable to obesity and 89% of people with diabetes are affected by either overweight or obesity.^{3,4}

Changing Paradigms in Diabetes Treatment

Historically, glycemic control was the major focus of diabetes treatment to prevent microvascular and

macrovascular complications.⁵ Older guidelines recommended initial treatment of hyperglycemia with metformin and subsequent initiation of a variety of noninsulin medications as second- and third-line therapy.⁶ In 2008, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial found increased risk of total and cardiovascular mortality with intensive glycemic control of goal HbA1c <6.0% (median, 12-month HbA1c 6.4%) compared with 7.0 to 7.9% (median, 12-month HbA1c 7.5%) in people with long-standing T2D.⁷ Patients treated with sulfonylureas and insulin in ACCORD gained significantly more weight than the standard treatment group, potentially undermining the successful treatment of patients with both overweight or obesity and T2D.⁸ The identification of agents that also improve the cardiorenal complications of diabetes without accelerating obesity has become a major focus of research and drug development over the last fifteen years. Renewed attention has been focused on the treatment of hyperglycemia in T2D with the introduction of 2 newer classes of medications, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2-Is).⁹

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In part due to concerns regarding reports of increased myocardial infarction with the thiazolidinedione drug rosiglitazone, the Food and Drug Administration (FDA) developed new guidance in 2008 requiring manufacturers to demonstrate cardiovascular safety for new antidiabetes drugs.¹⁰ Over the last decade, multiple cardiovascular outcomes trials have demonstrated that many medications in the GLP-1 RA and SGLT2-I drug classes improve outcomes for ASCVD, heart failure, and diabetic kidney disease (DKD) as well as obesity.^{9,11} Although most of the patients in these trials had established cardiovascular disease, a minority had T2D with multiple risk factors for cardiovascular disease.¹² These cardioprotective effects come through different mechanisms of action. For SGLT2-Is this likely stems from diuretic and hemodynamic effects.¹³ And for GLP-1 RAs, it likely is due to anti-atherosclerotic and anti-inflammatory actions.¹⁴

In contrast, the medication classes of insulin and sulfonylureas were associated with increased risk of composite cardiovascular outcome of hospitalization for heart failure, stroke, ischemic heart disease or peripheral artery disease.¹⁵ These findings have changed the paradigm of treating hyperglycemia with a focus on complication prevention and treatment in addition to glucose lowering efficacy. In this review we address the 2 newer classes of medications, GLP-1 RAs and SGLT2-Is, their benefits, risks, and role in T2D management.

GLP-1 RAs

Mechanism of Action

GLP-1 RAs have high efficacy for glucose lowering, averaging 0.8-1.6% reduction in A1c.¹⁶ GLP-1 is a hormone that is secreted by the neuroendocrine cells in the gut that have 4 pathways that help with diabetes: 1) sends a signal of satiety to the hypothalamus to reduce appetite 2) slows gastric emptying 3) stimulates insulin secretion when blood glucose levels are elevated postprandially (the incretin effect) and 4) suppresses glucagon reducing gluconeogenesis and lowering fasting blood glucose.^{17,18} This helps reduce caloric intake and improve glyce-mic control.

Evidence for Cardiovascular and Kidney Outcomes

There are currently 4 GLP-1 RAs approved by the FDA: exenatide, liraglutide, dulaglutide, semaglutide.

Beyond improving A1c in adults with type 2 diabetes, specific GLP-1 RAs have shown benefit in clinical trials for risk reduction of major adverse cardiovascular events (MACE) in adults with established cardiovascular disease (dulaglutide, liraglutide, and subcutaneous semaglutide) or multiple cardiovascular risk factors (dulaglutide),¹⁹ as well as improvements in proteinuria in adults with diabetic kidney disease with T2D.²⁰ They also have efficacy for weight loss, including very high efficacy for subcutaneous semaglutide, high efficacy for liraglutide, and intermediate efficacy for dulaglutide and exenatide.^{21,22} Liraglutide and semaglutide are currently FDA-approved for individuals with obesity at alternative doses. Oral semaglutide does not have cardiovascular or renal benefits but is effective for glucose-lowering.¹⁹

Contraindications, Adverse Effects, and Risk Mitigation

The most frequently encountered side effects associated with GLP-1 RAs are gastrointestinal (GI) related. On average, 10 to 50% of patients will experience nausea and vomiting, constipation, diarrhea, or abdominal pain. These symptoms occur when starting the medication or up titrating the dose but are most often mild and do not require discontinuation. Less than 5% of patients in GLP-1 RA clinical trials discontinued the medicine due to GI side effects, slightly lower than observed in clinical practice (5 to 10%).²³ To mitigate these effects, patients should be encouraged to take a slow and mindful eating approach, reduce portion sizes, limit alcohol intake, limit eating near bedtime, and increase water consumption. Using an antacid medication or proton pump inhibitor short term may benefit patients with symptomatic acid reflux.²⁴ If side effects are persistent or bothersome, staying on the lowest effective dose or up titrating the dose more slowly may be helpful.²⁵ GLP-1 RAs alone do not cause hypoglycemia, but other glucose-lowering medications may need to be adjusted (see “Medication Adjustment” section for details).

In randomized controlled trials, GLP-1 RAs including liraglutide, semaglutide, and dulaglutide have been shown to be associated with an increased risk of rapidly worsening diabetic retinopathy when hemoglobin A1c declines rapidly.²⁶ These data have been seen in other circumstances involving rapid decline of glucose, including intensive insulin treatment,

pancreas transplant, and bariatric surgery.²⁷ Currently focus trials on long-term effects of semaglutide specifically on diabetic retinopathy are anticipated to be completed in 2026. This data highlights the importance of yearly screening recommendations for type 2 diabetics, including yearly eye exams to assess for diabetic retinopathy, and for those with diabetic retinopathy, closer monitoring for transient worsening when started on GLP-1 RAs.

GLP-1 RAs have very few contraindications: a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia-2 syndrome and serious hypersensitivity to the medication. Patients should be screened for personal and family history of medullary thyroid cancer and multiple endocrine neoplasia-2 syndrome before prescribing GLP1-RAs and use shared decision making and patient education to ensure patients are informed about the overall risks and benefits of their treatment. Precautions include a history of pancreatitis, pancreatic cancer, and severe gastrointestinal disease.²⁵ There is insufficient data to determine drug-associated risk in pregnancy and lactation. A common barrier to GLP-1 RA use is self-administration of injections. Patient education should be offered to teach self-injection technique using either the patient's medication supply, or with a practice kit if offered by the manufacturer. This can be done by a variety of interdisciplinary team members including nurses, pharmacists, and Certified Diabetes Care and Education Specialists (CDCES). Certain brand medications (eg, Trulicity) offer injection devices that hide the needle.

GIP/GLP-1 RAs

In 2022, the FDA approved tirzepatide for T2D. This gastric inhibitory polypeptide (GIP)/GLP-1 RA has similar GLP-1 RA effect, but the GIP component is thought to further improve insulin efficiency in a fed state and decrease glucagon activation in a fasted state, which helps with glycemic control.¹⁸ The potential synergistic effect is still being investigated. Tirzepatide has a very high efficacy for weight loss.²⁸⁻³⁰ The cardiovascular outcomes trial for tirzepatide (SURPASS-COVT) is ongoing and scheduled to report outcomes in late 2024. Tirzepatide carries a similar side effect profile, contraindications, and precautions to the GLP1 RAs.

SGLT2-Is

Mechanism of Action

SGLT2-Is derive their name from the sodium-glucose cotransporter-2 located in the proximal tubule of the kidney. They work by selectively blocking the SGLT2 transporter – the main site for glucose reabsorption in the nephron – and lowering the renal threshold for glucose. Glucose is then excreted in the urine, with higher rates of glycosuria occurring during periods of hyperglycemia, leading to lowered plasma glucose concentrations. SGLT2-Is have modest to high A1c-lowering effects, with an average 0.5-1.0% reduction.³¹

Evidence for Cardiovascular and Kidney Outcomes

There are currently 5 SGLT2-Is approved by the FDA for treatment of T2D: bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. All but bexagliflozin are also available in combination form with metformin, and some SGLT2-Is have additional combinations. In addition to glucose lowering, cardiovascular outcome trial evidence supports the benefit of specific SGLT2-Is for reducing risk of MACE (canagliflozin and empagliflozin)^{3,32} and progression of diabetic kidney disease (canagliflozin, dapagliflozin, and empagliflozin), the latter defined variably over trials including doubling of serum creatinine, progression to urinary albumin-to-creatinine ratio >300 mg/g creatinine, end stage renal disease, or death from end stage renal disease.^{32,33} A meta-analysis of 5 trials supports SGLT2-I therapy for reduced risk of cardiovascular mortality and hospitalization for heart failure (HHF), irrespective of ejection fraction or care setting,³⁴ and clinical trial data shows that dapagliflozin and empagliflozin demonstrate benefit in both heart failure with reduced ejection fraction and preserved ejection fraction.^{32,34,35} FDA labeling varies across the SGLT2-I class, with Canagliflozin and Dapagliflozin including the indication of reduced risk of HHF in adults with T2D and Empagliflozin including the indication of reduced risk of HHF in adults with heart failure. Ertugliflozin does not list any indications for HHF. Medication guides change frequently with the publication of new trials and study data.

Contraindications, Adverse Effects, and Risk Mitigation

Given the mechanism of urinary excretion of glucose, patients are at increased risk of genital

mycotic infections (GMIs) and urinary tract infections with SGLT2-I use. GMI risk may be reduced with appropriate hygiene, wearing cotton underwear, and use of topical or systemic antifungal treatment.^{36,37} In the majority of cases, discontinuation of SGLT2-Is is unnecessary as infections are often mild and resolve with appropriate treatment.^{31,32,37} Serious complicated urinary tract infection, urosepsis, ketoacidosis (even euglycemic), and necrotizing fasciitis of the perineum (Fournier's gangrene) are rare but providing anticipatory guidance is important.³¹ The FDA describes warning signs of necrotizing fasciitis of the perineum as "pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise."³⁸ The FDA recommends against SGLT2-I use during the second and third trimesters of pregnancy, or while breastfeeding, due to potential adverse renal effects.

SGLT2-Is have osmotic diuretic effects, therefore, diuretic therapy should be proactively reduced in elderly persons at risk for hypovolemia to avoid volume depletion.³⁹ Similarly, patients should be advised to hold SGLT2-I therapy when they have diminished oral intake or in preparation for procedures that require fasting.^{32,39} To avoid nocturia, patients can take the medication in the morning, and may be educated to drink an extra glass of water daily to prevent dehydration in the appropriate clinical scenarios. Although SGLT2-Is decrease progression of diabetic kidney disease long-term, clinicians should be aware of the potential for a reversible decline in eGFR within the first 4 weeks of SGLT2-I therapy (3 to 6 mL/min per 1.73 m²).⁴⁰ Reductions in eGFR greater than this may represent acute kidney injury (traditionally >30% from baseline) and should prompt evaluation for alternative causes.⁴⁰ Experts recommend eGFR and blood pressure monitoring 3 months after SGLT2-I initiation, followed by annually (eGFR >60 mL/min per 1.73 m²) or every 3 months (eGFR 30 to 60 mL/min per 1.73 m²).⁴¹ Although the eGFR threshold for initiating SGLT2-Is to prevent the progression of CKD has become more liberal (eGFR ≥20 mL/min per 1.73 m²),³³ their glucose-lowering effect is minimal at such a low eGFR.⁴² See Table 1 for eGFR thresholds for initiation of SGLT2-Is for glycemic benefit, as well as other indications.

Guideline Recommendations regarding GLP1-RA and SGLT2-I in Context

The American Diabetes Association (ADA) Standards of Care and the ADA/European Association for the

Study of Diabetes (EASD) Consensus Report recommend a person-centered approach to the selection of antidiabetic agents that accounts for an assessment of each patient's risk factors and diabetes complications, and the relative benefits of each medication class, risks, side effects, and cost.^{9,25} The ADA Standards no longer recommend metformin as initial therapy for every patient with T2D.⁹ Rather, they recommend an SGLT2-I or a GLP-1 RA as initial therapy for patients with T2D and ASCVD or high risk for ASCVD, heart failure, or chronic kidney disease to reduce cardiorenal risk. The ADA Standards make a strong recommendation for patients with established cardiovascular disease and a weaker recommendation for patients with risk factors for cardiovascular disease.

This "weaker" recommendation is supported by data from a 2020 meta-analysis that demonstrated a 14% risk reduction of composite major cardiovascular events in patients with established cardiovascular disease (HR 0.86, 95% CI 0.80-0.93 for GLP-1 RA and HR 0.86, 95% CI 0.80-0.93 for SGLT2-I) but no effect in patients with risk factors for cardiovascular disease (HR 0.94, 95% CI 0.82-1.07 for GLP-1 RA and HR 1.00, 95% CI 0.87-1.16 for SGLT2-I).¹² Metformin remains a foundational treatment strategy for T2D and long-term follow up of a small cohort of patients with overweight treated with metformin from the UKPDS demonstrate risk reduction in myocardial infarction, diabetes related mortality and all-cause mortality.⁴³ A 2020 meta-analysis of 6 cardiovascular outcomes trials demonstrated benefit from GLP-1 RA and SGLT2-I for a subgroup of metformin-naïve patients, but further studies are needed to establish the relative contribution of metformin and newer medications to cardiovascular risk reduction.⁴⁴

The ADA standards recommend either a GLP-1 RA or a GIP/GLP-1 RA combination to support weight management goals for patients with T2D and obesity. Either a high efficacy GLP-1 RA or a GIP/GLP-1 RA should be considered for patients with poor glycemic control.

The American Association of Clinical Endocrinology (AACE) Comprehensive type 2 Diabetes Algorithm 2023 Update provides complication-centric recommendations for GLP-1 RAs or SGLT2-Is as first line treatment regardless of glycemic control or other treatments including metformin. Specifically, they recommend a GLP-1 RA

Table 1. SGLT2-I, GLP1-RA, And GIP/GLP-1 RA Use in Practice for Patients with Type 2 Diabetes

Therapy and dose range	eGFR Cut-off for initiation for glycemic benefit	Additional indications for adults with type 2 diabetes	Median average wholesale price
SGLT2-Inhibitors			
Bexagliflozin (Brenzavvy), 20 mg PO once daily	30 mL/min		n/a
Canagliflozin (Invokana), 100 to 300 mg PO once daily	30 mL/min	<ul style="list-style-type: none"> Established CVD: risk reduction of MACE Diabetic nephropathy with albuminuria >300 mg/d: risk reduction of ESKD, serum creatinine doubling, CV death, and HHF 	\$684
Dapagliflozin (Farxiga), 5 to 10 mg PO once daily	45 mL/min	<ul style="list-style-type: none"> Established CVD or multiple CV risk factors: risk reduction of HHF HFrEF: risk reduction of CV death and HHF 	\$659
Empagliflozin (Jardiance), 10 to 25 mg PO once daily	30 mL/min	<ul style="list-style-type: none"> Established CVD: risk reduction CV death HFrEF and HFpEF: risk reduction CV death and HHF 	\$685
Ertugliflozin (Steglatro), 5 to 15 mg PO once daily	45 mL/min		\$390
GLP-1 receptor agonists and GIP/GLP-1 receptor agonists			
Dulaglutide (Trulicity), 0.75-4.5 mg weekly injection	n/a	<ul style="list-style-type: none"> Established CVD or multiple CV risk factors: risk reduction MACE 	\$1,064
Exenatide (Byetta), 5 to 10 mcg twice daily injection	30 mL/min		\$961
Exenatide XR (Bydureon BCise), 2 mg weekly injection	30 mL/min		\$936
Liraglutide (Victoza), 0.6-1.8 mg weekly injection	n/a	<ul style="list-style-type: none"> Established CVD: risk reduction MACE 	\$1,278
Semaglutide (Ozempic), 0.25-2 mg weekly injection	n/a	<ul style="list-style-type: none"> Established CVD: risk reduction MACE 	\$1,070
Semaglutide (Rybelsus), 7 to 14 mg PO once daily	n/a		\$1,070
GIP/GLP-1 receptor agonists			
Tirzepatide	n/a		\$1,169

Abbreviations: eGFR, estimated glomerular filtration rate (mL/min/1.73 m²); MACE, major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke); ESKD, end-stage kidney disease; HHF, hospitalization for heart failure; HFrEF, heart failure with reduced ejection fraction; CKD, chronic kidney disease; HFpEF, Heart failure with preserved ejection fraction.

with proven benefit for people with established or high risk for ASCVD to reduce risk of myocardial infarction, stroke, or cardiovascular (CV) death. Alternatively, they recommend an SGLT2-I with proven benefit for people with established ASCVD for reduction in heart failure hospitalization risk, major CV events, and CV death, and for people with high risk for ASCVD to reduce heart failure hospitalization. For people with T2D and heart failure, an SGLT2-I is recommended to improve HF symptoms, reduce HF hospitalization risk and CV death. Finally, an SGLT2-I with proven benefit is recommended for people with T2D and CKD when eGFR is ≥ 25 without HF or ≥ 20 with HF to reduce the progression of CKD and the risk of ASCVD. Alternatively, a GLP-1 RA with proven benefit is recommended for people with T2D and DKD

and eGFR ≥ 15 for reduction in proteinuria progression and the risk of ACVD.³⁶

2022 American Heart Association/American College of Cardiology/Heart Failure Society of America Guideline makes separate recommendations for use of SGLT2-Is in patients who do not have diabetes.⁴⁵ Kidney Disease: Improving Global Outcomes (KDIGO) guidelines are under revision with anticipated finalization in late 2023. The FDA indicates 2 SGLT2-Is for use in patients without type 2 diabetes: dapagliflozin to reduce the risk of CV death and HHF in adults with heart failure with reduced ejection fraction⁴⁶ and empagliflozin to reduce the risk of CV death and HHF in adults with HF (preserved and reduced ejection fraction).⁴⁷

A criticism of these guidelines has been the variable definition of cardiovascular disease in different cardiovascular outcomes trials (CVOTs), making it difficult to apply these findings into practice. Most commonly, CVOT inclusion criteria included patients with a prior myocardial infarction, stroke, or transient ischemic attack, >50% stenosis of the coronary, carotid, or peripheral artery, or a coronary, carotid, or peripheral artery revascularization procedure, a history of asymptomatic cardiac ischemia, a history of symptomatic coronary heart disease, or New York Heart Association (NYHA) class II or III heart failure. Most commonly, patients age 55 and older with 2 risk factors for cardiovascular disease were included in the CVOTs; risk factors include obesity, hypertension, tobacco use, dyslipidemia, and proteinuria.⁹ Contextualizing these recommendations into primary care practice, clinicians should use clinical judgment in continuing to use metformin as first-line therapy for patients without established cardiovascular disease given the cost and lack of strong evidence for patients with risk factors for cardiovascular disease. Clinicians can use the interactive MATCH-IT tool to explore the benefit of these medications for patients with different cardiovascular risk profiles.⁴⁸ Given the possible additional benefit of metformin, clinicians should consider combining metformin with SGLT2-Is and GLP-1 RAs for glycemic and cardiovascular benefit.

Combining GLP-1 RAs and SGLT2-Is

The ADA Standards suggest a combination of GLP-1 RAs and SGLT2-Is when appropriate.⁹ In a meta-analysis, combination therapy led to improvements in glycemic control, body weight, BMI, systolic blood pressure, and LDL-C in comparison to monotherapy.⁴⁹ Hypoglycemia and adverse effects including vomiting and diarrhea were higher in combination therapy. This study did not demonstrate additional benefit for cardiovascular and renal outcome improvement beyond monotherapy, and further real-world studies are needed to evaluate whether the combination of therapies provides additional benefit outside of glycemic control.

Medication Adjustment

When initiating a GLP-1 RA, GIP/GLP-1 RA, or SGLT2-I, clinicians may need to adjust other glucose-lowering medications to avoid iatrogenic hypoglycemia. When initiating agents with very

high glucose-lowering efficacy (subcutaneous semaglutide, dulaglutide, tirzepatide), clinicians should individualize insulin reductions based on glycemic control. One recommended approach is to reduce basal insulin by 20% and bolus insulin by 50% for A1C <7%; basal insulin by 10 to 20% and bolus insulin by 25% for A1C 7 to 8%, and basal insulin by 10% and bolus insulin by 25% for A1C >8% if high risk for hypoglycemia.⁵⁰ Patients with higher A1C levels >8% may not require any adjustment.⁵¹ For patients with A1C <7% who are prescribed <10 units of insulin per meal or prescribed sulfonylureas, clinicians can consider discontinuing bolus insulin and sulfonylureas and allowing permissive hyperglycemia while titrating agents with very high glucose-lowering efficacy, with further adjustments as needed. For high efficacy agents, smaller reductions in insulin and sulfonylureas may be sufficient.⁵¹

Clinicians should perform a risk assessment for hypoglycemia, educate patients about symptoms and management of hypoglycemia, frequent blood glucose monitoring with a glucometer or continuous glucose monitor, and when to call and reduce medications if hypoglycemia occurs. Generally, patients can be instructed to reduce totally daily insulin by 10 to 20% for mild hypoglycemia (glucose 54 – 69 mg/dL) and 20 to 40% for severe hypoglycemia (glucose <40 mg/dL).⁵¹ Clinicians should educate all patients on the use of glucose to treat hypoglycemia and prescribe glucagon for people using insulin or at high risk of hypoglycemia.⁵²

Cost and Coverage of GLP-1 RAs and SGLT2-Is

GLP-1 RAs and SGLT2-Is are more expensive than other classes of glucose-lowering medications; out-of-pocket copayments and cost-sharing are variable among patients with different insurance coverage. Despite the robust data supporting effectiveness at reducing cardiovascular and renal complications, a recent study suggested that prices for these medications would need to fall by 70% to 90% be cost-effective.⁵³ A generic version of liraglutide may be available as soon as 2024 and a generic version of dapagliflozin may also soon be available.^{54,55} In 2023, bexagliflozin became the first lower cost SGLT2-I available via an online pharmacy.⁵⁶ In contrast, metformin, sulfonylureas, and some formulations of insulin are available inexpensively under most insurance plans and for patients with no insurance coverage.

Clinicians may use online tools such as Fingertip Formulary or Coverage Search to assist patients in identifying medications covered by their insurance, and programs like Cover My Meds to facilitate prior authorization. Patient assistance programs (PAP) and coupon copay assistance programs can be beneficial for patients with commercial and Medicare insurance to obtain financial assistance with drug costs. Fewer coupon programs are available for patients with Medicare and these programs are not available for patients with Medicaid; online tools are available aggregating this information.^{57,58} The Inflation Reduction Act of 2023 currently limits the cost-sharing for insulin for Medicare Part B and D plans and is projected to lower prices for Jardiance (empagliflozin) and Farxiga (dapagliflozin) and other diabetes medications in the future.⁵⁹ Putting cost-effectiveness data into context, clinicians can promote glycemic control and weight management by helping patients adopt lifestyle management strategies and obtain inexpensive medications and consider GLP-1 RAs and SGLT2-Is for patients with established cardiovascular disease and the highest risk for renal complications who are most likely to benefit.

The Federal Food, Drug and Cosmetic Act listed Ozempic (semaglutide) on the Drug Shortages List, allowing compounding pharmacies to respond by producing compounded semaglutide.⁶⁰ Because compounded formulations are not regulated by the Food and Drug Administration (FDA), clinicians should take caution in recommending these options to patients; an analysis of compounded semaglutide performed by Novo Nordisk, manufacturer of Ozempic, found impurities, unsafe peptides, and inaccurate doses.⁵⁹ Alternative strategies include prescribing an equivalent dose of an available injectable or oral GLP-1 RA.

Coordination of Care

GLP-1 RAs and SGLT2-Is may be initiated for patients in other settings. For example, patients with heart failure exacerbation may be started on a SGLT2-I before hospital discharge or by a nephrology or cardiology consultant. GLP-1 RAs may be initiated by a cardiology or obesity medicine consultant. They may be stopped due to side effects or cost burden by another clinician in an ambulatory or hospital setting. The primary care clinician has an important role to play in assessing patient adherence, cost burden, adjusting medications, and

communicating and coordinating care with specialty clinicians.

Conclusions

Outside of glucose lowering, GLP-1 RAs and SGLT2-Is are important medications that family physicians need to be prescribing to reduce the risk of cardiovascular disease and diabetic kidney disease in patients with type 2 diabetes. Using shared decision making with patients, clinicians should choose GLP-1 RAs and SGLT2-Is on an individualized approach based on patient preference, tolerability, comorbidities, cost, and accessibility. Additional FDA-label indications for GLP-1 RAs and SGLT2-Is may change as new trial data supports their benefits.

To see this article online, please go to: <http://jabfm.org/content/37/3/372.full>.

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Appendix

Practice Recommendations Using Strength of Recommendation Taxonomy:

1. GLP-1 RAs and SGLT2-Is are first line options for many people with type 2 diabetes (A).
2. Use of SGLT2-Is is recommended for people with diabetic kidney disease or heart failure (A).
3. Use of GLP-1 RAs is recommended for people with obesity (A).
4. Use of shared decision making is recommended to help decide between GLP-1 RA versus SGLT2-I therapy in patients with ASCVD or high risk for cardiovascular disease based on patient preference, tolerability, comorbidities, cost, and availability (A).