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Use of Glucagon-Like Peptide-1 Receptor Agonists in Patients With Type 2 Diabetes and Cardiovascular Disease:

A Review

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Abstract

IMPORTANCE—Recent randomized clinical trials have demonstrated that glucagon-like peptide-1 receptor agonists (GLP-1RAs) reduce cardiovascular events in at-risk individuals with type 2 diabetes. Despite these findings, GLP-1RAs are underused in eligible patients, particularly by cardiologists.

OBSERVATIONS—To date, randomized clinical trials of albiglutide, dulaglutide, liraglutide, and injectable semaglutide have reported favorable cardiovascular outcomes. Most recently approved

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for clinical use, oral semaglutide has a favorable safety profile and is currently undergoing regulatory evaluation and further study for cardiovascular outcomes. Professional society guidelines now recommend GLP-1RA therapy for cardiovascular risk mitigation in patients with type 2 diabetes and established atherosclerotic cardiovascular disease (ASCVD) or multiple ASCVD risk factors, independent of glucose control or background antihyperglycemic therapy (other diabetes medications being used). Additional conditions suitable for GLP-1RA therapy include obesity and advanced chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73m^2), for which cardiovascular risk-reducing options are limited. Out-of-pocket costs and secondary advantages (eg, weight loss) may inform shared decision-making discussions regarding potential therapies. GLP-1RA therapy has a favorable safety profile. Its most common adverse effect is gastrointestinal upset, which typically wanes during the early weeks of therapy and may be mitigated by starting at the lowest dose and escalating as tolerated. Depending on baseline glycemic control, sulfonylureas and insulin may need to be decreased before GLP-1RA initiation; without concurrent use of insulin or sulfonylureas, GLP-1RAs are not associated with hypoglycemia. Multidisciplinary follow-up and collaborative care with primary care physicians and/or endocrinologists are important.

CONCLUSIONS AND RELEVANCE—Findings from this review suggest that GLP-1RAs are safe, are well tolerated, and improve cardiovascular outcomes, largely independent of their antihyperglycemic properties, but they remain underused by cardiologists. This review provides a practical resource for cardiologists for initiating GLP-1RAs and managing the therapy in patients with type 2 diabetes and established ASCVD or high risk for ASCVD.

In the US, new cases of type 2 diabetes have plateaued in recent years, but the overall public health burden of type 2 diabetes and its associated comorbidities and complications is projected to remain substantial for the foreseeable future.[1] Cardiovascular disease is a leading cause of death among patients with diabetes,[2] and individuals with established atherosclerotic cardiovascular disease (ASCVD) and diabetes are at high risk for recurrent major adverse cardiovascular events (MACE).[3] Two classes of antihyperglycemic medications, with the demonstrated advantage of reducing MACE among individuals with type 2 diabetes and established ASCVD or at high risk for ASCVD, have emerged in dedicated cardiovascular outcomes trials: glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter 2 (SGLT2) inhibitors.[4,5]

Although a parallel commentary on the role of cardiologists in prescribing SGLT2 inhibitors is equally timely and evidence based, in this review we focused on practical considerations for cardiologists when prescribing GLP-1RAs.

We searched PubMed for English-language studies published between January 1, 2005, and October 31, 2019. This search identified 7 cardiovascular outcomes trials of GLP-1RA therapy. We analyzed primary trial publications, key secondary analyses, summary meta-analyses, US Food and Drug Administration labels, and professional society guidelines. This literature search was conducted between August 1,2019, and October 31, 2019.

Observations

Among commercially available GLP-1RAs, reduction in MACE has been demonstrated in randomized clinical trials of once-daily dosed liraglutide[6] and 3 once-weekly injections of GLP-1RAs:semaglutide,[7] albiglutide,[8] and dulaglutide.[9] Studies of extended-release exenatide[10] and lixisenatide[11] have demonstrated their safety but not their superiority in reducing MACE. The US Food and Drug Administration has now approved 3 GLP-1RAs for cardiovascular risk reduction: (1) liraglutide in 2017, (2) injectable semaglutide in January 2020, and (3) dulaglutide in February 2020. Cardiovascular safety was observed with oral semaglutide,[12] which has been recently approved by the Food and Drug Administration as the first oral GLP-1RA option for type 2 diabetes; a dedicated randomized clinical trial to evaluate the cardiovascular outcomes associated with oral semaglutide use is currently being conducted.[13] Although cardiovascular benefit was shown for albiglutide,[8] the manufacturer withdrew this medication from the global market for commercial reasons. Cardiovascular outcomes associated with the use of a once-weekly injectable GLP-1RA, efpeglenatide, are currently being assessed.[14]

In addition to standard of care and largely independent of hyperglycemic outcomes, the use of GLP-1RAs has demonstrated mean relative risk reduction in MACE by 12%, cardiovascular death by 12%, all-cause mortality by 12%, stroke by 16%, myocardial infarction by 9%, and composite kidney events by 17% (driven by improvements in albuminuria).[4] Based on these accumulated data showing the cardiovascular benefit of selected GLP-1RAs, recommendations of these medications have rapidly entered multidisciplinary guidelines and consensus statements as the preferred first- or second-line therapies among patients with type 2 diabetes at high risk for ASCVD events.[15–21] In addition, GLP-1RAs have a favorable safety profile and have been associated with substantial weight loss.[4,6,7,9]

Despite these favorable data and endorsements across diabetes and cardiology society publications, uptake of GLP-1RAs in clinical practice has lagged. Although the first GLP-1RA (exenatide) was approved in 2005 for use in the US and cardiovascular superiority with liraglutide was reported in 2016, less than 8% of individuals with type 2 diabetes and ASCVD were given GLP-1RA prescriptions in 2 US-based observational studies.[22,23] Furthermore, even when GLP-1RAs were prescribed in tertiary care health centers, less than 5% of GLP-1RA prescriptions were attributable to cardiologists.[24,25] Likely reasons for the low prescribing rates by cardiologists include unfamiliarity with these agents and their use, discomfort with the possible need to adjust other antihyperglycemic therapies, the belief that drugs developed initially for diabetes are outside the cardiologist purview, the encumbrance of injection teaching, the requirement of dose escalation, competing priorities with other cardiovascular risk-mitigation approaches, and lack of care integration with primary care physicians and endocrinologists.[16]

However, encounters with cardiologists represent opportunities to initiate evidence-based, cardiovascular risk-reducing therapies for high-risk patients.[26] To that end, this review is intended to serve as a practical resource for initiating and managing GLP-1RA therapy for cardiovascular risk reduction in select patients. Because this review is targeted at

cardiologists, it focuses on marketed GLP-1RAs with Food and Drug Administration indications for cardiovascular risk reduction (ie, liraglutide, dulaglutide, and injectable semaglutide).

Candidates for GLP-1RA Therapy

Current society guidelines advise cardiologists to consider adding a GLP-1RAto the regimen of all patients with type 2 diabetes and established ASCVD or high ASCVD risk, regardless of their baseline glycemic control or background antihyperglycemic therapy (other diabetes medications already being used).[15,16,21,27] Amongthe GLP-1RA cardiovascular outcome trials to date, REWIND (Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes) enrolled the largest number of participants with cardiovascular risk factors but without established ASCVD (69% in REWIND[9] vs 0%−23% in other trials[4,6–8,10–12]) and identified identical treatment effect point estimates and CIsfor 3-component MACE in participants with and those without established ASCVD (*P* for interaction = .97). A meta-analysis of the first7GLP-1RA cardiovascular outcome trials, including REWIND, did not identify statistically significant heterogeneity of outcome between the primary and secondary ASCVD prevention populations (*P* for interaction = .22), although the authors appropriately recognized that the expected absolute risk reduction would be lower in a lower-risk primary prevention population.[4] In contemporary clinical practice, the distinction between primary and secondary ASCVD prevention may become increasingly blurred because of the availability of more sensitive biomarkers and imaging for identifying coronary and myocardial abnormalities.

Historically, metformin hydrochloride was the first-line therapy for type 2 diabetes given its ability to lower glycosylated hemoglobin (ie, hemoglobin A_{1c} [HbA_{1c}]), long-standing use in clinical practice, good safety profile, oral route of administration, global availability, and low cost. However, although metformin use was reported in 65% to 80% of patients in the completed GLP-1RA cardiovascular outcomes trials,[6–12] background metformin use was not required in any of the trials. Furthermore, in the sizable minority of patients who were not treated with metformin (20%−35%, representing thousands of participants across these trials), no evidence was found of differential cardiovascular benefit of GLP-1RAs by background metformin status.[6,7,9,28] Based on these results, the 2020 European Society of Cardiology guidelines recommend GLP-1RA (or, alternatively, SGLT2 inhibitors) as a first-line therapy in drug-naive patients with type 2 diabetes and cardiovascular disease.[21] In contrast, the 2020 update to the American Diabetes Association Standards of Medical Care in Diabetes maintains metformin as a first-line therapy but recommends that patients with established ASCVD or with indicators of high ASCVD risk preferentially receive a GLP-1RA with demonstrated cardiovascular benefit independent of glycemic control.[15]

Special Considerations

Overweight or Obese Status—As a class of antihyperglycemic medications, GLP-1RAs were associated with substantial weight loss of 1.5 to 4.3 kg in trials with follow-up of 1.3 to 5.4 years,[6,7,9,29] making these agents desirable when weight loss is a priority. High-dose oral semaglutide was also associated with considerable weight loss.[30]

Overall, the greatest weight loss was observed with GLP-1RA doses that were higher than typically used for treatment of hyperglycemia or for cardiovascular risk reduction, although these higher doses have not undergone dedicated cardiovascular safety assessment, with only higher-dose liraglutide (3.0 mg daily) approved specifically for treatment of obesity. A dedicated, large cardiovascular outcome trial of injectable semaglutide in patients with obesity and ASCVD, but without type 2 diabetes, is currently being conducted (NCT03574597) using doses up to 2.4 mg weekly; such doses are greater than the approved maximum dose for cardiovascular risk reduction or glycemic control (1.0 mg weekly).[31]

Chronic Kidney Disease—Although data are limited on the use of GLP-1RAs in end-stage kidney disease (estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m^2), liraglutide, dulaglutide, and injectable semaglutide may be used in advanced chronic kidney disease (CKD) at any eGFR level and without dose adjustment (Table 1), in contrast with most other noninsulin diabetes therapies. Specifically, SGLT2 inhibitors are currently contraindicated in patients with a preinitiation eGFR less than 30 mL/min/1.73 m^2; patients with established ASCVD and an eGFR below this threshold may be good candidates for GLP-1RA therapy.

Heart Failure—A meta-analysis of large cardiovascular outcomes trials of patients with type 2 diabetes reported a nominally significant 9% reduction in heart failure (HF) hospitalization.[4] Harmony Outcomes was the only trial that demonstrated prevention of HF events in at-risk patients with type 2 diabetes; albiglutide was associated with a statistically significant reduction in HF hospitalization (hazard ratio, 0.71; 95% CI, 0.53–0.94; $P < .001$).[4,8] Few trials have separately examined the treatment outcomes of GLP-1RA among subsets of patients with prevalent HF. In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial of liraglutide, 18% of participants had New York Heart Association class I to III HF at enrollment, of whom two-thirds were New York Heart Association class II and 40% were using a maintenance loop diuretic.[32] Participants with prevalent HF experienced consistent reduction in MACE and cardiovascular and all-cause death with liraglutide compared with participants in the non-HF subgroup and showed no excess risk of HF hospitalization.[32] In the EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial, risk reduction in mortality and HF hospitalization outcomes appeared restricted to patients without prevalent HF.[33] Similarly, in a patient-level pooled analysis of SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) and PIONEER-6 (Peptide Innovation for Early Diabetes Treatment) trials, semaglutide consistently reduced MACE across subgroups, except in patients with known HF.[34]

These findings were obscured by the lack of data on HF subtype (eg, HF with preserved ejection fraction [EF] vs HF with reduced EF) among patients with prevalent and incident HF.[35] Furthermore, 2 small randomized clinical trials of liraglutide in patients with HF with reduced EF, 1 of which enrolled patients with recent HF hospitalization, suggested potential harm of liraglutide, although neither trial found statistically significant differences.[36,37] Given the pharmacological properties of GLP-1RA that increase the heart rate (which may be detrimental in HF), the safety of its use in patients with HF with reduced EF remains

uncertain. Therefore, although existing data suggest overall safety and modest HF prevention with use of GLP-1RAs among patients with type 2 diabetes, we advise caution when considering their use in patients with advanced or recently decompensated HF with reduced EF as well as close monitoring if initiating GLP-1RA therapy in patients with HF with reduced EF. Dedicated studies of GLP-1RA safety and efficacy in HF with preserved EF and HF with reduced EF are needed.

GLP-1RAs, SGLT2 Inhibitors, or Both

Because both GLP-1RAs and SGLT2 inhibitors have favorable cardiovascular outcomes, cardiologists frequently care for patients for whom both classes of medications warrant consideration, independent of their glucose control. Specifically, GLP-1RAs are predominantly associated with decreased atherosclerosis-mediated events, whereas SGLT2 inhibitors are predominantly associated with HF and CKD outcomes.[38] Although head-to-head comparative effectiveness trials focused on cardiovascular outcomes are lacking, attention to contraindications, cost to the patient, route of administration, and secondary benefits may be helpful when deciding between these medication classes (Table 2).

Contraindications and Cautions

In general, GLP-1RAs are contraindicated in patients with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2 (Box), although these concerns are based exclusively on observations in rodent models with uncertain human clinical relevance, as reflected in US product labeling. Because GLP-1RAs delay gastric emptying, caution should be used in prescribing these agents to patients with gastroparesis, chronic nausea, or previous gastric surgical procedure. Complications of diabetic retinopathy were rare but more commonly seen in patients who received injectable semaglutide vs placebo (3.0% vs 1.8%) in SUSTAIN-6.[7] This findins has been attributed to the rapid reduction in blood glucose in a patient population at higher risk for retinopathy complications, which has been observed with insulin therapy when poorly controlled hyperglycemia is rapidly rectified. The early worsening of retinopathy phenomenon is reflected in product labels for all insulin medications and for injectable semaglutide as well.[7] This issue should be taken into account before semaglutide initiation among patients with proliferative diabetic retinopathy or for those with poor glucose control (eg, HbA_{1c} >10%), and a formal retinal examination should be performed before semaglutide initiation. A randomized clinical trial of the safety of injectable semaglutide in diabetic retinopathy is currently beingconducted.[39] GLP-1RA should not be used in pregnancy or breastfeeding.

Because SGLT2 inhibitors are associated with increased risk for genital mycotic infections, a history of recurrent genital mycotic infections may additionally favor GLP-1RA over SGLT2 inhibitors. Given the association of increased amputation risk with canagliflozin use reported in the CANVAS (Canagliflozin Cardiovascular Assessment Study) R trial, severe peripheral artery disease and/or active diabetic foot ulcers may favor GLP-1RA therapy over an SGLT2 inhibitor (at least over canagliflozin). However, increased amputation risk has not been seen with other SGLT2 inhibitors, nor with canagliflozin in the subsequent CREDENCE (Canagliflozin and Renal Events in Diabetes and Nephropathy Clinical

Evaluation) trial, in which such adverse events were systematically collected.[40] Therefore, the amputation risk for those with peripheral artery disease or diabetic foot disease has uncertain implications for the decision to prescribe GLP-1RAs or SGLT2 inhibitors.

Cost

Both GLP-1RAs and SGLT2 inhibitors are costly, compared with older classes of antihyperglycemic medications. In the US, the 2020 national median drug acquisition cost of GLP-1RAs ranges from $634 per month to $835 per month,[27,41] although the out-of-pocket cost borne by patients varies considerably by insurance formulary and coverage. Ascertaining projected out-of-pocket costs and patients' ability to afford copayments may help inform shared decision-making discussions of medication selection. Studies of comparative cost-effectiveness and value that account for downstream reductions in cardiovascular and kidney outcomes are needed. When both medication classes are unaffordable, metformin is a less costly, widely available alternative that has been associated with favorable cardiometabolic outcomes.[42]

Route of Administration

With the exception of oral semaglutide, which has not yet completed cardiovascular assessment, all other available GLP-1RAs are administered as a subcutaneous injection with varying dose frequencies (Table 1), including 3 once-weekly medications (dulaglutide, semaglutide, and extended-release exenatide), whereas SGLT2 inhibitors are all once-daily oral medications. The pen needles used for the GLP-1RAs are commonly 32-gauge and present minimal to no injection discomfort (vs more painful finger-stick method of blood glucose measurement). Dulaglutide pens are manufactured with a built-in needle, whereas attachable needles are included with semaglutide pens but must be prescribed separately for liraglutide (32-gauge needles). Patient preferences for daily oral medication vs daily or weekly subcutaneous injection may inform the choice of medication. Oral semaglutide is a daily medication that must betaken on an empty stomach with 4 ounces of plain water 30 minutes before food intake, which may be difficult for some patients.

Secondary Benefits

For patients with overweight or obesity status, GLP-1RAs may be preferred over SGLT2 inhibitors for adjunctive weight loss. These agents are associated with similar or greater weight loss compared with that observed with SGLT2 inhibitors.[29]

Given its powerful kidney protection benefits,[40,43] patients with CKD who have an eGFR of at least 30 mL/min/1.73 m^2 may favor SGLT2 inhibition over GLP-1RA therapy. However, data are limited on antihyperglycemic therapies associated with reduced risk of cardiovascular disease in individuals with more advanced CKD, and use of all SGLT2 inhibitors is currently discouraged for those with an eGFR less than 30 mL/min/1.73 m^2. Liraglutide, dulaglutide, and semaglutide may be used in patients with advanced CKD at any level of eGFR without dose adjustment.

For patients with HF with reduced EF, SGLT2 inhibitors should be prescribed preferentially over GLP-1RAs. Robust clinical benefits, including decreased mortality, were observed with

dapagliflozin in the DAPA-HF (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure) trial, regardless of type 2 diabetes status.[44]

Concurrent Use of GLP-1RAs and SGLT2 Inhibitors

Despite lifestyle modification and pharmacotherapy, patients may require further medication escalation to achieve glycemic targets. Society recommendations and guidelines support the concurrent use of GLP-1RAs and SGLT2 inhibitors when needed for adequate glycemic control, but data on whether such combinations may yield incremental cardiovascular advantages are lackingthusfar.[15,16,21] Given distinct mechanisms of action, nonoverlapping adverse effect profiles, and unique target cardiovascular effects, incremental advantages may be anticipated with concurrent use, which is reasonable in the absence of prohibitive polypharmacy or cost.

Selecting a GLP-1RA and Patient Counseling

Table 1 details the dose frequency, starting dose, and dose titration of currently available GLP-1RAs with proven favorable cardiovascular outcomes. Selection of a specific agent is likely to be affected by the drugs preferred under an individual's insurance plan and associated out-of-pocket costs. As mentioned, cardiovascular advantages have been demonstrated in trials of liraglutide, dulaglutide, and injectable semaglutide, and thus these are currently the preferred GLP-1RAs in patients with established ASCVD or at high risk for developing ASCVD.

Injection and Sharps Disposal—The injectable GLP-1RAs are manufactured as single-use pens or multiple-use pens with single-use needles (Table 1). The typical recommendation is to store pens in the refrigerator before use. They should not be frozen.

Injection teaching can be performed in 5 to 10 minutes but may be abbreviated for dulaglutide, given its built-in pen, and for patients who are already familiar with subcutaneous medications (such as insulin). The therapy can be administered in the abdomen, thighs, or upper arms. For liraglutide and semaglutide, the injection steps and technique are similar to those used in insulin injection via insulin pens. For pens requiring a pen needle (such as liraglutide and semaglutide), a new pen needle should be used with each injection. After the pen needle is attached and the appropriate dose is dialed on the pen, the needle should be inserted into the skin at an appropriate site. The dose button should be depressed and held down until the dose counter shows zero, the needle should be kept in the skin, and the individual should count slowly to 6. The needle can then be withdrawn from the skin.

For dulaglutide, proper injection consists of 3 main steps: uncap, unlock, and inject. First, with the pen locked, the gray cap is pulled off. Second, the clear base of the pen is placed firmly against the skin at an appropriate injection site, and the lock ring is turned to the unlock position. Third, the medication is injected by pressing and holding the green injection button. An initial click should be heard. The clear base should be held firmly against the skin until a second click is heard, which typically takes 5 to 10 seconds, signaling that the needle has injected, and the medication has been delivered.

For cardiologists who do not feel comfortable teaching injection technique, retail pharmacies provide injection teaching, and dedicated diabetes educators have been incorporated into endocrinology and cardiometabolic practices. Manufacturers of GLP-1RAs also provide instructional videos, including injection technique, that are available online.

Pens with attached needles and detachable needles should be discarded in a sharps container and then disposed per local municipal regulations; pharmacies can review this information with patients. Sharps containers can be purchased at local or online pharmacies or medical supply stores.

Adverse Effects—Overall, GLP-1RAs have a favorable safety profile. Specifically, hypoglycemia is rare except when GLP-1RAs are coadministered with sulfonylureas or insulin. The most common adverse effect of this therapy is gastrointestinal upset, including nausea, vomiting, diarrhea, early satiety, decreased appetite, and abdominal bloating, with 15% to 40% of patients experiencing symptoms within the first 4 weeks of treatment. Package labels note case reports of acute kidney injury from dehydration associated with gastrointestinal adverse effects. However, gastrointestinal symptoms are typically transient, mild, and mitigated by starting with a low dose and up-titrating as tolerated (Table 1). Anticipatory guidance, with the expectation of early satiety and transient gastrointestinal upset soon after GLP-1RA initiation that typically improve within 4 weeks of continued use, is critical for promoting both short- and long-term patient adherence. In addition, frequent small meals and avoidance of fried or fatty foods may reduce symptoms of satiety and bloating (and may help in achieving desired weight loss goals).

As discussed, GLP-1RA initiation in individuals with poor baseline glycemic control may be a factor in worsening of diabetic retinopathy. The therapy may increase the risk of gallbladder disease, including cholelithiasis and cholecystitis[45,46]; suggestive symptoms (eg, fever, right upper-quadrant abdominal pain) should be reviewed with the patient. In addition, postmarketing reports have suggested the possibility of pancreatitis associated with GLP-1RAs, although a risk signal has not been observed in prospective randomized clinical trials.[4] Nonetheless, patients should be counseled about this small potential risk, warningsigns should be reviewed, and patients should be encouraged to report any severe or persistent abdominal pain. Injection-site reactions, including erythema, rash, and subcutaneous nodules, are commonly observed with extended-release exenatide vs other GLP-1Ras and may be prevented by rotating the injection sites.

Adjusting Other Antihyperglycemic Medications

Dipeptidyl peptidase 4 inhibitors should be discontinued before initiating GLP-1RA therapy, given the lack of anticipated additive efficacy owing to overlapping mechanisms of action. Otherwise, in general, the main antihyperglycemic medications that may require adjustment at the time of initiation of GLP-1RA are sulfonylureas and insulin, with down-titration (or discontinuation) of either if the patient has baseline glycemic control at or below target or if the patient experiences hypoglycemic events. Patients using sulfonylureas and/or insulin should monitor blood glucose closely in the weeks after GLP-1RA initiation and up-titration

to ensure safety and facilitate medication titration. Coordination and communication within the multidisciplinary care team are important, particularly when communicating the cardiovascular indication for which the cardiologist is prescribing the medication. Typically, further management of antihyperglycemic medications and monitoring of HbA_{1c} levels are the responsibility of primary care physicians, endocrinologists or diabetes specialists, and clinical pharmacists.

For patients who use sulfonylureas, consideration should be given to stopping the drug at the time of GLP-1RA initiation, especially if the baseline HbA_{1c} is 75% or lower or at any HbA_{1c} level if the patient is experiencing hypoglycemic episodes. To reduce the risk of hypoglycemia, we recommend decreasing the sulfonylurea dose initially by 50% if HbA_{1c} is 76% to 8.5%, and continuing the sulfonylurea medication at the current dose if HbA_{1c} is higher than 8.5%, with the possibility of weaning off the drug in the future as HbA_{1c} level approaches the individualized target.

For patients who use insulin, we recommend decreasing the basal insulin dose by 20% to 30% if the baseline HbA_{1c} level is at or below target before GLP-1RA initiation or if the patient is experienceing hypoglycemic episodes. In patients using higher doses of insulin or multiple daily injections of insulin, deferral of GLP-1RA initiation by the cardiologist is prudent, with referral to an endocrinologist or a diabetes specialist (if not already established) specifically to consider this therapy.

Patient Monitoring and Follow-up

In patients with type 2 diabetes and cardiovascular disease, ongoing multidisciplinary care is important, including continued reinforcement of a diabetic and heart-healthy diet, exercise, weight loss, and medication adherence. For patients receiving GLP-1RA therapy, explicit assessment of adverse effects and treatment adherence is key, given the high rates of gastrointestinal adverse effects on initiation, along with direct encouragement to continue the medication while anticipating that its adverse effects will resolve. When the initial gastrointestinal adverse effects have abated at each dose during initiation or titration, the GLP-1RA should be up-titrated to the maximum dose that has a proven favorable cardiovascular outcome, independent of glycemic targets (Table 1).

Implementation of GLP-1RA Prescribing in a Cardiology Practice

Optimizing cardiometabolic health through lifestyle modification and pharmacotherapy is central to preventing adverse outcomes and promoting good quality of life in patients with type 2 diabetes who have or are at high risk for cardiovascular disease. Cardiologists may initially feel hesitant to take ownership of relatively new and evolving classes of medications, such as GLP-1RAs, even when their safety and cardiovascular benefit have been demonstrated.

Cardiologists frequently encounter patients with type 2 diabetes and ASCVD after cardiovascular procedures or events in the inpatient setting, allowing an opportunity to start GLP-1RA therapy with counseling and injection teaching before hospital discharge as well as leveraging the multidisciplinary expertise of nursing, diabetes educators, pharmacists, and

diabetes services. Creating multidisciplinary care teams either within a cardiology practice (eg, involving diabetes educators and clinical pharmacists who can assist with injection teaching) or across clinical practices (eg, joint visits with endocrinologists or formation of dedicated cardiometabolic centers) represents a potential strategy to facilitate prescribing GLP-1RAs to patients shown to gain the most cardiovascular advantages and to ensure optimal, patient-centered cardiometabolic care for this high-risk population.

Conclusions

GLP-1RAs appear to be a safe, well-tolerated therapy that can improve cardiovascular outcomes, largely independent of their antihyperglycemic properties. This review provides a practical guide for cardiologists in facilitating GLP-1RA initiation and managing GLP-1RA therapy for the purpose of cardiovascular risk reduction and events in patients with type 2 diabetes and established ASCVD or high risk for ASCVD.

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Box.

Approach to Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA) Prescribing by Cardiologists

Ideal Candidates for GLP-1RA Therapy

- Patients with type 2 diabetes and established atherosclerotic cardiovascular disease (ASCVD) or high ASCVD risk
- Patients with overweight or obese status
- Patients with advanced diabetic kidney disease

Safety Screen Before Starting GLP-1RA Therapy

Contraindications

- GLP-1RA hypersensitivity
- Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2
- Pregnancy or breastfeeding

Extra vigilance

- Gastroparesis or previous gastric surgical procedure
- History of pancreatitis
- Proliferative diabetic retinopathy

Patient Counseling

Adverse effects

- Gastrointestinal (common): nausea and/or vomiting, diarrhea, bloating
  - Usually transient in the early weeks after initiation
  - Mitigated by starting low dose and escalating to target
  - Frequent small meals helpful
- Injection site reaction
- Hypoglycemia (uncommon unless used with insulin and/or sulfonylureas)
  - Adjust other agents
- Gallbladder disease
- Pancreatitis (rare, <1%)[4]
- Report severe abdominal pain

Adjusting Other Antihyperglycemic Therapies at Initiation

Sulfonylureas

- If hemoglobin A_{1c} (HbA_{1c}) ≤7.5% or hypoglycemic episodes, stop sulfonylurea medication
- If HbA_{1c} 7.6%−8.5%, decrease sulfonylurea medication by 50%
- If HbA_{1c} >8.5%, continue sulfonylurea medication with possibility of future weaning

Insulin

- If HbA_{1c} is at or below individualized target or hypoglycemic episodes, decrease basal insulin by 20%−30%
- Coordination with primary care physician and/or endocrinologist strongly encouraged

Dipeptidyl peptidase-4 inhibitors

- Discontinue after starting GLP-1RA

Other agents do not require adjustment

Monitoring and Follow-up

- Monitor adverse effects and medication adherence
- Titrate dose to evidence-based dose for cardiovascular risk reduction, independent of glycemic control
- Communicate closely with primary care physicians and endocrinologists

Table 1.

Prescribing and Dose of Glucagon-Like Peptide-1 Receptor Agonist With Demonstrated Cardiovascular Benefit

Medication/ administration	FDA approved for cardiovascular risk reduction?	Initial dose	Dose titration/ target dose[a]	How medication is supplied	Need to prescribe pen needles separately?	Kidney adjustment
Once-daily administration						
Liraglutide	Yes	0.6 mg Once daily (can be taken anytime)	Can increase weekly. After 1 wk, increase to 1.2 mg daily. Then increase to 1.8 mg daily if further glycemic control is needed.	1 Pen with 3 different programmable doses (0.6 mg, 1.2 mg, and 1.8 mg). Multiple-use pen is to be used with single-use needles.	Yes	None (limited data in ESKD)
Weekly administration						
Semaglutide	Yes	0.25 mg Weekly (can be taken anytime)	Can increase dose every 4 wk. After 4 wk, increase to 0.5 mg weekly. Then increase to 1.0 mg weekly if further glycemic control is needed.	2 Different pens available, each with 2 programmable doses: 1 pen allows 0.25 mg and 0.5 mg doses, and 1 pen allows 1.0 mg doses. Multiple-use pen is to be used with single-use needles.	No (pen needles come in box with pens)	None (limited data in ESKD)
Dulaglutide	Yes	0.75 mg Weekly	Can increase dose to 1.5 mg weekly if further glycemic control is needed.	2 Different pens, each with a different dose (0.75 mg and 1.5 mg). Single-use pen.	No (needle is built into pen)	None (limited data in ESKD)

Abbreviations: ESKD, end-stage kidney disease; FDA, US Food and Drug Administration.

[a]If patients experience gastrointestinal adverse effects, wait until symptoms resolve before escalating the dose. If symptoms do not resolve with higher dose, reduce dose to highest tolerated dose. For liraglutide and semaglutide, the lowest doses (0.6mg and 0.25mg, respectively) are starting doses intended to reduce gastrointestinal symptoms during initial titration and are not intended for glycemic control.

Table 2.

Considerations for Selecting Between Glucagon-Like Peptide-1 Receptor Agonist and Sodium-Glucose Cotransporter 2 Inhibitor

Considerations	GLP-lRAs may be a better choice[a]	SGLT2 inhibitors may be a better choice[a]	Rationale
Cardiorenal	Established atherosclerotic cardiovascular and/or cerebrovascular disease; eGFR <30 mL/min/1.73 m^2	HF or CKD predominates	GLP-lRAs primarily reduce atherosclerotic events, including myocardial infarction and stroke. SGLT2 inhibitors have shown benefits in preventing and managing HF. GLP-lRAs (semaglutide, liraglutide, and dulaglutide) can be used in eGFR <30 mL/min/1.73 m^2; no SGLT2 inhibitor is currently FDA approved for use in eGFR <30 mL/min/1.73 m^2.
Glycemic control and DKA	More HbA_{lc} reduction needed; history of DKA		GLP-lRAs are associated with greater HbA_{lc} reduction than SGLT2 inhibitors. SGLT2 inhibitors are associated with a rare risk of DKA.
Comorbidities	Obesity; frequent genital mycotic infections; osteoporosis or history of fractures; lower-limb ulcers or amputations	Active gallbladder disease; pancreatitis; gastroparesis or delayed gastric emptying; personal or family history of MTC or MEN-2; history of proliferative retinopathy	GLP-lRAs are associated with a greater degree of weight loss compared with SGLT2 inhibitors, which are associated with genital mycotic infections (eg, balanitis and vulvovaginal candidiasis). Fournier gangrene has also been reported. CANVAS reported an increased risk of fractures and amputations with canagliflozin, although this was not seen in the CREDENCE trial and has not been seen with other SGLT2 inhibitors. GLP-lRAs are associated with a higher risk of gallbladder disease. Cases of acute and chronic pancreatitis have been reported with GLP-1RA, although this risk has not been borne out in cardiovascular outcome trials or other large studies. GLP-lRAs can slow gastric emptying and can thus exacerbate symptoms in individuals with gastroparesis or delayed gastric emptying. GLP-lRAs have been associated with an increased risk of thyroid C-cell tumors in rodents, and thus a personal or family history of MTC or MEN-2 is a contraindication for GLP-1RA. A small but substantial increase in worsening diabetic retinopathy was observed with injectable semaglutide and has been attributed to rapid lowering of blood glucose.
Other	Patient preference	Patient preference	NA

Abbreviations: CANVAS, Canagliflozin Cardiovascular Assessment Study; CKD, chronic kidney disease; CREDENCE, Canagliflozin and Renal Events in Diabetes and Nephropathy Clinical Evaluation; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; GLP-1RA,g lucagon-like peptide-1 receptora gonist; HbA_{1C}, hemoglobin A_{1C}; HF, heart failure; MEN-2, multiple endocrine neoplasia type 2; MTC, medullary thyroid cancer; NA, not applicable; SGLT2, sodium-glucose cotransporter 2.

[a]Many patients are reasonable candidates for either a GLP-1RA or an SGLT2 inhibitor. Concurrent use should be considered among eligible patients in the absence of prohibitive polypharmacy or cost.