SGLT2 Inhibitors in the Management of Chronic Kidney Disease

Executive Summary:

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have proven efficacy in reducing risks of chronic kidney disease (CKD) progression in patients with type 2 diabetes as exhibited in several large and randomized controlled trials, in which significant reduction in risk has been demonstrated in both primary and secondary outcomes.

The DAPA-CKD trial demonstrated significant risk reduction in patients both with and without diabetes, suggesting that initiating SGLT2 inhibitors may still be beneficial in patients who are attaining their glycemic goals in addition to use in patients without type 2 diabetes.

Evidence continues to emerge on the use of SGLT2 inhibitors in CKD and the U.S. Food and Drug Administration labeling supports the usage of SGLT2i outside of routine use for type 2 diabetes management.

Abbreviation Key	
ADA	American Diabetes Association
ACR	Albumin to Creatinine Ratio
CKD	Chronic Kidney Disease
CV	Cardiovascular
CVD	Cardiovascular Disease
DAPA-CKD	Dapagliflozin in Patients with Chronic Kidney Disease
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
FDA	U.S. Food and Drug Administration
KDIGO	Kidney Disease: Improving Global Outcomes
MACE	Major Adverse Cardiovascular Events
SGLT2i	Sodium/glucose Cotransporter-2 Inhibitors
T2 Diabetes	Type 2 Diabetes

SGLT2i Pearls Recommendations

1. If SGLT2i was initiated when eGFR is ≥30 ml/min/1.73m^2, but then eGFR subsequently drops below 30 ml/min/1.73m^2	→	The SGLT2i can be continued up until the initiation of renal replacement therapy or kidney transplantation, as studied in the CREDENCE trial.
2. Recommend withholding SGLT2i during times of prolonged fasting, surgery, or critical medical illness due to the greater risk for ketosis	→	Avera's Preoperative Clinical Guideline & Algorithm recommend holding SGLT2i 3 to 4 days before surgery as well as the morning of surgery.
3. If a patient is at risk for hypovolemia:	→	Consider decreasing thiazide or loop diuretic dosages before beginning SGLT2i treatment: ▪ Educate patients on symptoms of volume depletion and low blood pressure ▪ Follow up on volume status after drug initiation
4. A reversible decrease in the eGFR with initiation of SGLT2i treatment	→	This may occur and is generally not a reason to discontinue therapy.
5. Monitor the following (in addition to monitoring blood glucose response and hypoglycemia): ☐ Renal Function – 1.) at baseline and 2.) periodically during treatment. ☐ Infections (genital mycotic and urinary tract) ☐ Volume Status (weight, BP, hematocrit, electrolytes) ☐ Signs/Symptoms of Ketoacidosis		
6. SGLT2i have not been adequately studied in kidney transplant patients who may benefit from SGLT2i, but are immunosuppressed and may be at increased risk for infections.	→	KDIGO 2020 guidelines recommend against use in this population.

SGLT2i Renal Dosing:

Canagliflozin	eGFR >60 = 100 to 300mg once daily
	eGFR 30 to <60 = 100 mg once daily
	eGFR <30 with urinary albumin >300 mg/day = 100mg once daily *urinary albumin <300 mg/day = do not initiate
Dapagliflozin	eGFR ≥45 = 5 to 10mg once daily
	eGFR 25 to <45 = no dose adjustment Note: US manufacturer does not recommend initiation for Type 2 (T2) diabetes
	eGFR <25 = do not initiate
Empagliflozin	eGFR ≥30 = 10 to 25mg once daily
	eGFR <30 = 10mg once daily

FDA Approvals:
- Dapagliflozin: approved for CKD, dosed at 10mg daily
- Canagliflozin: approved for diabetic kidney disease, dosed at 100mg daily

Practical Application of SGLT2i

Patients WITH T2 Diabetes
- Both ADA and KDIGO guidelines recommend initiating metformin and an SGLT2i as first-line treatment for patients with T2 diabetes and CKD regardless of A1c control
- Continue to utilize ACEi/ARB to slow progression of CKD
- Control co-morbidities (hypertension, hyperlipidemia)
- Implement non-pharmacologic strategies including smoking cessation, weight loss and exercise

Patients WITHOUT T2 Diabetes
- Start with medications that have strong evidence to slow progression of CKD (ACEi/ARB)
- Control co-morbidities (hypertension, hyperlipidemia)
- Implement non-pharmacologic strategies including smoking cessation, weight loss, and exercise
- Weigh risks and cost of SGLT2i when considering the addition of an SGLT2i for CKD in patients *without* T2 diabetes

Evidence Summary – Table Overview

Large, randomized, placebo-controlled trials guiding recommendations

				The Effects On:		
Drug	Trial	Kidney-related Eligibility Criteria	Primary Outcome	Primary Outcome	Albumin-uria	GFR Loss
Canagliflozin	CANVAS Trials	eGFR ≥30 ml/min/1.73m^2	MACE	↓	↓↓	↓↓
	CREDENCE	ACR >300 mg/g and eGFR 30-90 ml/min/1.73m^2	Composite of ESRD, doubling of creatinine, or death from renal or CVD causes	↓↓	↓↓	↓↓
Dapagliflozin	DECLARE-TIMI 58	CrCl ≥60 ml/min	MACE and the composite of hospitalization for heart failure or CV death	↔/↓	↓	↓↓
	DAPA-CKD	ACR 200-5000 mg/g and eGFR 25-75 ml/min/1.73m^2 (with or without T2 diabetes)	Composite of decline of at least 50% in eGFR, onset of ESRD, or death from renal or CVD causes	↓↓ ↓↓ (Renal-specific)		↓↓
Empagliflozin	EMPA-REG OUTCOME	eGFR ≥30 ml/min/1.73m^2	MACE	↓	↓↓	↓↓
	EMPA-KIDNEY	ACR ≥200 mg/g and eGFR ≥20 to <45 ml/min/1.73m^2 (with or without T2 diabetes)	Composite of ESRD, sustained eGFR decline to <10 ml/min/1.73m^2, sustained decline of ≥40% in eGFR, and renal death	Ongoing, results expected 2022		

Abbreviation Key: ***ACR*** *= Albumin to Creatinine Ratio;* ***CVD*** *= Cardiovascular Disease;* ***eGFR*** *= Estimated Glomerular Filtration Rate;* ***ESRD*** *= End-Stage Renal Disease;* ***MACE*** *= Major Adverse Cardiovascular Events;* ***T2*** *= Type 2*

↓ - Significant reduction in risk with hazard ratio estimate >0.7 and 95% CI not overlapping 1

↓↓ - Significant reduction in risk with hazard ratio estimate ≤0.7 and 95% CI not overlapping 1

↔ - No significant difference

[ ] **Green Cells** - significant reduction in risk related to renal-specific outcomes

Last Updated: 1/3/2022
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Review Committee Member(s): Rachelle Davis, PharmD; Becky Vandekop, MD; Chad Thury, DO; Luke Merkel, PharmD

GLP-1 Receptor Agonists (GLP-1 RA) – Not All Are Created Equal

Executive Summary:

Although glucagon-like peptide-1(GLP-1) agents are all contained within the same class, differences in duration of action (e.g. short-acting vs long-acting), effects on glycemic control and weight loss, tolerability profiles and administration routes offer providers several options to choose from.

Long-acting GLP-1 receptor agonists tend to have greater A1C lowering and greater weight loss associated.

For patients struggling with gastrointestinal (GI) adverse effects, exenatide extended-release (ER) is typically associated with lower risk of adverse effects, while exenatide immediate release (IR) and semaglutide SubQ may be associated with the highest risk for adverse effects.

Pearls Recommendation for Prescribing Information on GLP-1 RAs:

Generic Name	Short/Long Acting	Initial Dose	Frequency	Route
Lixisenatide	Short	10mcg daily x 14 days; then 20mcg daily	Once daily	Sub-Q
Exenatide	Short	5mcg twice daily x 1 month; then 10mcg twice daily	Twice daily	Sub-Q
Exenatide ER	Long	2mg weekly	Once weekly	Sub-Q
Liraglutide	Long	0.6mg daily x 1 week then 1.2mg; may increase to 1.8mg	Once daily	Sub-Q
Dulaglutide	Long	0.75mg weekly x 4-8 weeks; may increase dose every 4-8 weeks to 1.5mg, then 3mg, then to max of 4.5mg	Once weekly	Sub-Q
Semaglutide	Long	0.25mg weekly x 4 weeks, then 0.5mg weekly; may increase to 1mg weekly	Once weekly	Sub-Q
Semaglutide	Long	3mg daily x 30 days, then 7mg; may increase to 14mg	Once daily	Oral

GLP-1 RA Pharmacokinetics:

	Short-Acting	Long-Acting
Time Duration:	2 to 3 hour half-life	Half-life ▪ Liraglutide: 13 hours ▪ All Others: 5 to 14 days
Fluctuations in plasma drug concentration:	Large	Smaller
Peak effect on Plasma Glucose:	Exenatide: 12 weeks	Dulaglutide & Liraglutide: 2 to 4 weeks
	Lixisenatide: 2 to 4 weeks	Exenatide: 6 to 14 weeks
		Semaglutide: 12 to 16 weeks

GLP-1 RAs Average Effects on A1C and Weight:

GLP-1 RA	Average Decrease in A1C	Average Weight Loss
Short-acting		
Exenatide[1]	1%	2 kg
Lixisenatide[2]	1%	2 kg
Long-acting		
Dulaglutide[3]	1.5 to 1.8%	2.5 to 4.6 kg
Exenatide ER[4]	1.5%	1.4 to 2.5 kg
Liraglutide[5]	1.5%	2.5 kg
Semaglutide (Sub-Q)[6]	1.5%	4 kg
Semaglutide (Oral)[7]	1%	2.5 kg

Studies: Amigo[1], GetGoal[2], Award[3], Duration[4], Lead[5], Sustain[6], Pioneer[7]

Equivalent Doses of GLP-1 RAs:

Agent	Equivalent Dose†			
Exenatide XR			2 mg	
Dulaglutide		0.75 mg	1.5 mg	
Semaglutide		0.25 mg	0.5 mg	1 mg
Liraglutide	0.6 mg	1.2 mg	1.8 mg	
Lixisenatide	10 mcg	20 mcg		
Semaglutide (Oral)	3 mg	7 mg	14 mg	
Exenatide	5 mcg	10 mcg		

†Equivalent doses based on author opinion, derived from head-to-head clinical trials.
Anticipate that dulaglutide 3mg and 4.5mg would be equivalent to or more potent than semaglutide 1mg

Adverse Events (AEs):

The most common adverse events associated with GLP-1 agonists are nausea, vomiting, and diarrhea. These adverse events are typically mild to moderate in severity and diminish overtime with use of all GLP-1 RAs. Injection site reactions are also common, however greatest risk is seen with exenatide extended-release (ER).

Gastrointestinal (GI) Adverse Effects – By Risk Level		
LOW RISK	**MODERATE RISK**	**HIGH RISK**
▪ Exenatide ER	▪ Liraglutide ▪ Lixisenatide ▪ Dulaglutide ▪ Semaglutide (Oral)	▪ Exenatide ▪ Semaglutide

ASCVD/CKD Benefits:

Studies have looked at the risk reduction in patients with cardiovascular disease (CVD) using GLP-1 RAs. Those studies found that while all GLP-1 RAs show non-inferiority, liraglutide, subcutaneous semaglutide and dulaglutide have shown significant reductions in composite CV outcomes.

Currently, subcutaneous semaglutide, liraglutide and dulaglutide all have labeled indications for risk reduction of major CV events in patients with type 2 diabetes and established CVD. Dulaglutide carries an additional indication for risk reduction of major CV events in those with multiple CV risk factors.

The American Diabetes Association (ADA) recommends the use of GLP-1 RA in patients with the following comorbidities:

- Established Atherosclerotic Cardiovascular Disease (ASCVD)
- High ASCVD Risk
- Chronic Kidney Disease (CKD)

GLP-1 RAs have demonstrated a role in renal failure by preventing the onset of macroalbuminuria and slowing the decline of glomerular filtration rate. Further research is needed to understand the true impact of GLP-1 RAs on primary kidney endpoints.

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Methods of Monitoring for Diabetes

Executive Summary:

There are currently two approaches to monitoring blood sugar levels in those living with diabetes; use of a glucometer and test strips or a continuous glucose monitor (CGM) system. CGM has proven clinical benefit with increased time in range and decreased hypoglycemia; however, the decision of which method of monitoring is best will vary based upon the patient, medications being used, and cost.

- In general, a CGM may be preferred for those with insurance coverage and on an insulin regimen whereas a glucometer and test strips may be selected in other situations.
- Read on to learn more on coverage information for Medicaid, Medicare and Avera Health Plans (*see page 2*).

Continuous Glucose Monitors (CGM) have demonstrated improved clinical outcomes when compared to finger-stick glucose readings. A recent study demonstrated at the end of an 8-month timeframe that 63% of patients using CGM to guide basal insulin adjustments had an A1C <8.0% compared to only 39% of patients using a glucometer, a relative increase of 62%.

Patients using CGM spent an average 3.8 hours more each day within goal range and 3.6 hours less each day in the very high glucose range, while also having a reduction in hypoglycemia. With improved clinical outcomes and ease of use for the patient, more patients are likely to inquire and/or benefit from CGM.

CGM constantly monitors the blood sugar level with a sensor placed just under the skin into the interstitial fluid. Both CGM and glucometer use result in knowing a glycemic level, so which is better or when is each recommended? The answer can vary depending on the patient, their diabetes medication regimen and cost.

The following table gives some suggestions of when each method may be preferred.

Glucometer	Continuous Glucose Monitor (CGM)
Patient preference toward a simple plan yielding a few data points per week	Patient desire to see more complex glycemic trends throughout the day and night
Prone to increased anxiety by having knowledge of glycemic level and trends	Motivated by data to improve self-care and overall health
Limited interest or experience with technology	Technologically savvy and/or interested by newer technologies
Use of oral and non-insulin diabetes medications	Use of insulin administered three or more times per day or via an insulin pump
More stable glycemic trends with minimal concern for significant hypoglycemia	Higher glycemic variability with a greater risk of hypoglycemia
Patients in earlier stages of type 2 diabetes	Patients with type 1 or later stages of type 2 diabetes
Patients living with others in a supportive environment	Patients living alone or with limited social support
Cash price $25-75 per month without insurance	Cash price $150-500 per month without insurance

CGMs Insurance Coverage - General

Insurance coverage for continuous glucose monitors (CGMs) is typically more restrictive than for glucometers. Most commercial payers will offer coverage for CGMs for patients with type 1 diabetes and many will cover for those with type 2 diabetes using multiple daily administrations of insulin. To further complicate coverage of CGMs, commercial plans can offer coverage under the medical benefit or as part of the pharmacy plan. To clarify coverage, the insurance company can be contacted to explain their terms of coverage or scripts can be sent to the patient's pharmacy to check coverage.

- If not covered, pharmacies will generally receive a message back from the insurance company providing their coverage criteria or indicating a need for scripts to be sent to a DME supplier to be processed as a medical benefit.

Medicaid Coverage

State Medicaid coverage for CGMs will vary with some, such as the plans in South Dakota, only covering if the CGM is prescribed by an endocrinologist or endocrinology office.

- **Minnesota:**
  MN Medicaid covers CGM for patients with insulin dependent diabetes who require frequent adjustments to insulin dosing or who have hypoglycemic unawareness. Authorization is required.
- **Iowa:**
  Medicaid covers CGM with a prior authorization if the patient is on multi-dose insulin, complies with at least 4 times a day, blood glucose testing, and has documented hypoglycemia, elevated A1c despite compliance, refractory postprandial hyperglycemia or recurring diabetic ketoacidosis.
- **Nebraska:**
  Medicaid covers CGM for patients testing at least 4 times a day, is on multi-dose insulin, requires frequent adjustments to insulin dosing, has been seen within the last 6 months by the prescribing physician and in-person office visits are planned every 6 months.

Medicare Coverage

Medicare currently covers CGMs for those meeting the following criteria:

- ☐ Have a diagnosis of diabetes mellitus; and
- ☐ Take insulin three or more times per day or use an insulin pump; and
- ☐ The insulin regimen requires frequent adjustment by the patient based on blood glucose monitoring or CGM test results; and
- ☐ Within 6 months prior to ordering the CGM, the treating practitioner has an in-person visit with the patient to evaluate their diabetes control and determined that criteria (1-3) above are met; and
- ☐ Every 6 months following the initial prescription of the CGM, the treating practitioner has an in-person visit with the patient to assess adherence to their CGM regimen and diabetes treatment plan.

Medicare covers CGMs under Part B as medical equipment so scripts or forms will generally need to be sent to a mail-order DME supplier to be processed and shipped to the patient. For a current list of DME suppliers, go to https://www.medicare.gov/medical-equipment-suppliers/ to access Medicare's Supplier Directory.

Avera Health Plans Coverage

Avera Health Plans offer coverage for CGMs as a pharmacy benefit with no preauthorization required. Freestyle Libre and Dexcom are covered on the preferred brand tier on the Avera formularies. These products should process without any issues at the pharmacy. Other systems available but not currently covered by Avera Health Plans include those made by Medtronic such as, "the Guardian Sensor 3" and "the Senseonics Eversense CGM" system.

- For assistance with CGMs, manufacturers offer tech support and patient assistance via phone or computer chat sessions. Diabetes educators and pharmacists may also be able to assist if needed.

Glucometers and related supplies are generally covered for all patients who need them with the challenge being to choose the formulary or preferred system for each insurance. The challenge of choosing the correct system can be minimized by sending scripts for general/universal items such as:

- Glucometer
- Test Strips
- Lancets

➔ By entering general terms rather than selecting specific, branded products, this will allow the pharmacist to work with the patient and insurance company to find the right products without seeking clarification and approval from the prescribing clinician.

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Review Committee Member(s): Rachelle Davis, PharmD; Becky Vandekop, MD; Chad Thury, DO; Luke Merkel, PharmD

Clinical Utilization of Continuous Glucose Monitoring (CGM)

Executive Summary:

When reviewing CGM reports, it is important to understand the meaning of each component and the goals associated with the metrics provided. First ensure that there is sufficient data available to interpret the data (at least 70% time that CGM is active). Assess for the differences between the Glucose Management Indicator (GMI) and the laboratory A1c value and use the GMI to better individualize goal A1c. Goal time in range is >70% and try to keep low glucose to <4%. A glucose variability (or coefficient of variation) ≤36% indicates relatively stable glucose. Use the Ambulatory Glucose Profile (AGP) to quickly identify times of day that may indicate patterns of low or high glucose.

A1c is an important measure of diabetes care and management, however when used alone it may not be sufficient to optimally guide an individualized approach to diabetes management. CGM is a powerful tool that can provide more insight into trends in hypo- and hyperglycemia, glucose variability, and the time spent in goal range.

When available, it should be used as an additional tool to optimize medication therapy and behavioral changes. To fully take advantage of this technology, it is important to understand the CGM report and the different metrics and tools available in the report.

The Ambulatory Glucose Profile (AGP) report is a standardized, one-page summary report with 3 main elements: Glucose Statistics and Targets, AGP and Daily Glucose Profiles.

Date Range and Data Sufficiency: Fourteen days of CGM data correlates well with 3 months of CGM data with regards to mean glucose, time in range, and hyperglycemia measures. Percentage of time that CGM is active of at least 70% or 10 days of CGM wear adds confidence that the data are a reliable indicator of usual patterns.

Average glucose highly correlates with A1c and measures of hyperglycemia, but if used in isolation it provides no insight into glucose patterns, glycemic variability or hypoglycemia.

Glucose Management Indicator (GMI): The CGM version of estimated A1c (eA1c). Note that the GMI does not imply that the value reported is directly linked to the laboratory A1c. Discrepancies between the two may exist for various reasons, such as measuring glucose attached to hemoglobin in red blood cells for A1c vs. measuring glucose in interstitial fluid for GMI, differences in factors that affect how glucose attaches to red blood cells or medical conditions that affect the life span of red blood cells.

The GMI may also be higher or lower than the laboratory A1c during periods of acute hyperglycemia (e.g. illness or steroid use), starting a lower carbohydrate diet, intensive exercise regimens, or in the first few weeks after starting a new glucose-lowering medication. When there are no acute or dramatic changes from the patient's usual glucose levels, the difference between the GMI and A1c can better help inform diabetes management and set more individualized A1c goals.

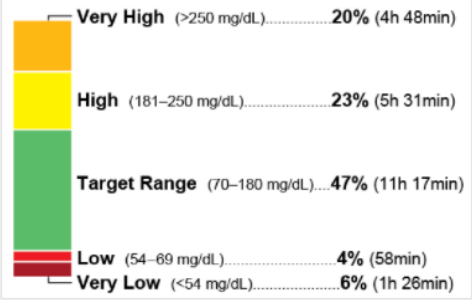
Time In Range (TIR): The percentage of time a patient's glucose is between 70 and 180 mg/dL (this range is recommended for individuals with type 1 and type 2 diabetes; ranges may be adjusted on an individual basis such as during pregnancy or for individuals on hybrid closed-loop insulin pump therapy). TIR is further broken down to time-above-range (TAR) and time-below-range (TBR). *See table 1.1 and figure 1.2 below.*

Table 1.1 - Time in Range (TIR)

Metric	Measure	Goal
TAR level 2	% of readings and time >250 mg/dL	<5%
TAR level 1	% of readings and time 181-250 mg/dL	<25%*
TIR	% of readings and time 70-180 mg/dL	>70%
TBR level 1	% of readings and time 54-69 mg/dL	<4%**
TBR level 2	% of readings and time <54 mg/dL	<1%

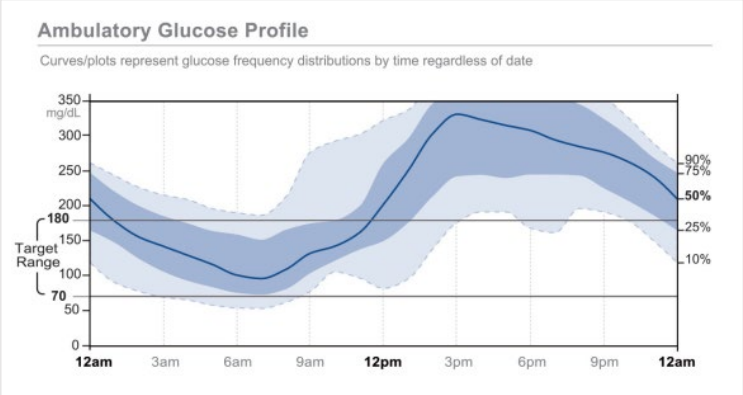
**includes % of values >250 mg/dL*
*** includes % of values <54 mg/dL*

Figure 1.2 – Time in Range (TIR) Example Report



Glucose Variability (coefficient of variation): Refers to how much the glucose reading varies from the mean or median glucose. Less than or equal to 36% indicates low variability and relatively stable glucose.

AGP: The AGP represents 14 daily glucose profiles combined into a single visual display. The solid line represents the median. The curves shaded in dark blue are the 25th and 75th percentile curves represent the 50% of all values and is a good visual indicator of the degree of glucose variability. The dashed outer lines are the 10th to 90th percentile curves, indicating that only 10% of readings were above or below those values. The AGP offers a quick view to determine the times of day that pose low or high patterns that might require immediate attention. The goal of overall management is to keep the curve as narrow and flat as possible within the target range.



Tips for Effective Review of the AGP to Guide Clinical Decision Making:

1. Ensure there is adequate data to make a clinical decision (data sufficiency)
2. Ask your patient to describe/explain what he/she sees on the report and why
3. Look for patterns of low glucose
    a. From the example above, 10% or more of readings from 3am to 9am are below 70 mg/dL and immediate action should be taken
    b. Use the daily glucose profiles to identify patterns of low glucose (e.g. weekends vs weekdays)
4. Look for patterns of high glucose
    a. Assess for adherence to medications
    b. Discuss with the patient whether high values are before or after typical mealtimes
    c. Assess for differences between weekdays and weekends
5. Assess glucose variability and discuss lifestyle modifications that could be implemented to try and reduce the variability (e.g. adjust time/amount of food intake, carbohydrate counting, timing of medications, exercise, and stress)
6. Compare the current AGP report to the report from the last visit and discuss progress, what worked, and what didn't work
7. Care plan adjustments – always treat hypoglycemia first

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