Considerations for Initiating Pharmacotherapy in Patients Diagnosed with Type 2 Diabetes

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Executive Summary

Select initial pharmacotherapy based on your patient's baseline A1c. Metformin should be initiated in all patients unless contraindicated and should not be discontinued until an honest effort was made to ensure tolerability. Remember to recheck the A1c in three months to assess response and adjust pharmacotherapy.

Key Takeaways

- Start and continue metformin on all patients unless contraindicated; use metformin ER 500mg tablets to improve tolerability.
- Consider an SGLT2i if initiating dual or triple therapy for CVD, HF, renal and weight benefits.
- Recheck A1c three months after initiating therapy and progress treatment if A1c goal is not achieved.

The AMG Type 2 Diabetes Treatment Algorithm recommends selecting initial treatment based on baseline A1c value.

Acronyms	
A1c	Hemoglobin A1c
BID	"Bis in die" (twice a day)
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DPP-4i	Dipeptidyl peptidase 4 inhibitor
eGFR	Estimated glomerular filtration rate
ER	Extended release
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
HF	Heart failure
PO	"Per os" (taken orally)
QAD	"Quoque alternis die" (every other day)
QAM	"Quaque die ante meridiem" (every day before noon)
SGLT2i	Sodium/glucose cotransporter 2 inhibitor

Table 1: Diabetes Treatment by Baseline A1c Value

A1c 6.5-7.5%	A1c 7.6-9.0%	A1c >9.0%
Initiate monotherapy Always metformin unless contraindicated or not tolerated	Initiate dual therapy Usually metformin + non- insulin agent *Consider an SGLT2i as first add on due to CVD, HF, Renal and weight benefits	Initiate triple therapy Usually metformin + SGLT2i and/or GLP-1 RA +/- basal insulin

Before discontinuing metformin due to intolerance, ensure the following:

- Patient is taking dose(s) with a meal
- Patient has tried metformin extended release
- Start on a low dose and slowly titrate up
    - Can start with 250mg once daily for immediate release tablets (cut 500mg tablets in half)
    - Start with 500mg once daily for extended release tablets
- Slow titration of metformin occurred:
    - 250mg PO once daily x 1 week, then
    - 500mg PO once daily x 1 week, then
    - 500mg PO BID x 1 week, then

- 1000mg PO QAM and 500mg PO QPM x 1 week, then
- 1000mg PO BID
- Do not increase dose while patient is experiencing side effects; can maintain at a lower dose until side effects diminish
- If side effects do not diminish, decrease dose to maximally-tolerated dose

Evidence for Metformin in Impaired Renal Function

Metformin is cleared through the kidneys and lactic acidosis has been associated with very high circulating levels of metformin, however the occurrence is very rare and the evidence that lactic acidosis will occur is weak. A study published in Diabetes Care in 2018 provides evidence that metformin can safely be continued in patients with moderate or severe CKD, although a stepwise decrease in dose should be employed as eGFR decreases in order to prevent excessive drug concentrations.

Table 2: Use of Metformin in Patients with Chronic Kidney Disease

Kidney function	Metformin dosing	Monitoring
eGFR ≥60 ml/min	Maximum dose 2550mg/day	Monitor eGFR at least annually
CKD stage 3a (eGFR 45-59 ml/min)	Labeling states no dosage adjustment necessary – Consider maximum dose 1500mg/day in divided doses	Monitor eGFR every 3-6 months
CKD stage 3b (eGFR 30-44 ml/min)	Maximum dose 1000mg/day in divided doses	Monitor eGFR every 3 months

In fragile patients, consider measuring lactate. Discontinue metformin if result is >5 mmol/L. If result is >2.5 mmol/L, consider repeating and discontinuing metformin if two consecutive results are >2.5 mmol/L.

When choosing pharmacologic agents, a patient-centered approach should be used to guide the decision. Place considerations on the pharmacologic agent's effect on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences. Refer to the AMG Type 2 Diabetes Treatment Algorithm to help guide decision. Due to various positive clinical benefits and long term decreased overall health care costs associated with SGLT2i, this class would be preferred initial add-on to metformin.

A1c should be rechecked in three months to assess pharmacotherapy and lifestyle changes implemented by the patient. Continue to recheck A1c three months after changes in treatment. Once patient is at goal, recommend monitoring A1c every six months.

Initiating or Modifying Diabetes Treatment Regimens

- Combination of a DPP-4i and GLP-1 RA is not recommended and provides little additional clinical benefit.
- Titrate non-insulin therapies to maximum doses before adding additional agents.
  - No need to wait for A1c results to titrate metformin or SGLT2i to maximum dose → continue titrating weekly until maximum tolerated dose is reached, as renal function allows

- Cost for most GLP-1 RAs is the same regardless of dose (e.g., cost for semaglutide 0.5 mg pen is the same as semaglutide 2mg pen).
    - Titrate dulaglutide, semaglutide, and tirzepatide every four weeks up to maximum tolerated dose → even if patient has achieved their A1c goal, increasing dose to the maximum dose may result in additional weight loss.
    - Semaglutide 3mg PO and semaglutide 0.25mg SubQ are not clinically effective doses and should be titrated up to 7mg and 0.5mg respectively after four weeks.
    - Liraglutide 0.6mg SubQ is not a clinically effective dose and should be titrated up to 1.2mg after one week.
- Combination oral products can be used to decrease pill burden and decrease co-pay burden.

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Cardiorenal Risk Reduction in Type 2 Diabetes

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Executive Summary

T2DM patients at high risk for ASCVD, or that have clinical ASCVD, HF, and/or CKD should be given an SGLT2i or GLP-1 RA with demonstrated CVD benefit regardless of A1c based on proven cardiovascular benefits. Medication selection should be tailored to each individual based on comorbidities.

Key Takeaways

- The ADA Standards of Care 2023 recommends the use of a SGLT2i or GLP-1 RA regardless of baseline A1c, goal A1c or metformin use for patients who have any one of the following:
  - Established ASCVD (e.g., MI, stroke, any revascularization procedure) or indicators of high ASCVD risk (patients ≥55 years of age with two or more additional risk factors [obesity, hypertension, smoking, dyslipidemia or albuminuria])
  - CKD (eGFR <60 mL/min/1.73 m^2 or albuminuria ACR ≥30 mg/g)
  - Heart failure (current or prior symptoms of HF with documented HFrEF or HFpEF)
- The determination of which agent to use should be patient specific and based on present comorbidities.
- Drug classes with cardiovascular benefit still require a specific agent for selection in some cases.

Acronyms	
A1c	Hemoglobin A1c
ACEi	Angiotensin converting enzyme inhibitor
ARB	Angiotensin 2 receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DPP-4i	Dipeptidyl peptidase 4 inhibitor
eGFR	Estimated glomerular filtration rate
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
GIP	Glucose-dependent insulinotropic polypeptide
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
SGLT2i	Sodium/glucose cotransporter 2 inhibitor
SQ	Subcutaneous
T2DM	Type 2 diabetes mellitus

Table 1: Recommended Class Selection for Specific Comorbidities

ASCVD/Indicators of High Risk	Heart Failure	CKD
SGLT2i (with proven CVD benefit) *or* GLP-1 RA (with proven CVD benefit)	SGLT2i (with proven HF benefit)	SGLT2i* (with primary evidence of reducing CKD progression) *Or* GLP-1 RA (with proven CVD benefit if SGLT2i not tolerated or contraindicated)

*use SGLT2i in patients with an eGFR ≥20 mL/min/1.73 m^2; once initiated, continue until initiation of dialysis or transplantation

Table 2: Cardiovascular Benefits Associated with Each Drug Class

Drug Class	Effect on MACE	HF	Renal effects
Biguanide	Potential benefit	Neutral	Neutral
SGLT2i	**Benefit:** Canagliflozin Empagliflozin	**Benefit:** Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	**Benefit:** Canagliflozin Dapagliflozin Empagliflozin
GLP-1 RA	**Benefit**: Dulaglutide Liraglutide Semaglutide (SQ) **Neutral:** Exenatide once weekly Lixisenatide Semaglutide (oral)	Neutral	**Benefit:** Dulaglutide Liraglutide Semaglutide (SQ)
GIP/GLP-1 RA	**Under investigation** Tirzepatide (Mounjaro)	**Under investigation** Tirzepatide (Mounjaro)	**Under investigation** Tirzepatide (Mounjaro)
DPP-4i	Neutral	Neutral **Potential risk:** Saxagliptin	Neutral
Thiazolidinediones	**Potential benefit:** Pioglitazone	Increased risk	Neutral
Sulfonylureas (2nd gen)	Neutral	Neutral	Neutral

SGLT2i Renal Dose Adjustments

- Should be done for each patient individually per the clinician's judgement

Avera Health Plans Considerations for Clinical Scenarios

- If patient is on a DPP-4i and you are adding a GLP-1 RA for cardiovascular benefit, discontinue the DPP-4i.
  - Combination of a DPP-4i and GLP-1 RA is not recommended and provides little additional clinical benefit
  - Additional co-pay for patient with little clinical benefit
  - Additional cost to Avera Health Plans with little clinical benefit
- When either an SGLT2i or GLP-1 RA is indicated, consider starting with the SGLT2i.
  - Likely similar or lower copay for patient
  - Lower cost to Avera Health Plans
  - Similar glycemic efficacy and CVD benefit
  - Additional CHF benefit with SGLT2i
- For patients on basal insulin plus a GLP-1 RA, or you are considering adding on one of these agents, consider use of a combination product.
  - One copay for patient instead of two
  - Lower cost to Avera Health Plans
  - Similar glycemic efficacy
  - Xultophy (insulin degludec + liraglutide)

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        - Maximum insulin dose = 50 units/day
    - Soliqua (insulin glargine + lixisenatide)
        - Maximum insulin dose = 60 units/day
        - Does **NOT** have CVD benefit data

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Management of Chronic Kidney Disease in Type 2 Diabetes – SGLT2 Inhibitors and Finerenone

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Acronyms	
ACEi	Angiotensin converting enzyme inhibitor
ACR	Albumin to creatinine ratio
ADA	American Diabetes Association
ARB	Angiotensin receptor blocker
BP	Blood pressure
CKD	Chronic kidney disease
CrCl	Creatinine clearance
CVD	Cardiovascular disease
eGFR	Estimated flomerular filtration rate
FDA	Food and Drug Administration
KDIGO	Kidney Disease: Improving Global Outcomes
MACE	Major adverse cardiovascular events
SGLT2i	Sodium/glucose cotransporter-2 inhibitor
T2D	Type 2 diabetes

Executive Summary

Treatment options for CKD has expanded with the approval and emerging data supporting the use of SGLT2i in patients with and without diabetes, as well as the approval of finerenone, a non-steroidal mineralocorticoid receptor antagonist. SGLT2i have proven efficacy in reducing risks of CKD progression in patients with and without T2D as exhibited in several large and randomized controlled trials. In patients with T2D and CKD who cannot tolerate an SGLT2i, recommend referral to nephrology for assessment for use of finerenone.

Key Takeaways

- ACEi/ARBs remain first-line treatment options for CKD and SGLT2i; finerenone should not take their place.
- Finerenone does not replace use of SGLT2i in patients with T2D and CKD.
- In the SGLT2i class, only canagliflozin, dapagliflozin and empagliflozin have evidence supporting reduction in CKD progression in T2D (only dapagliflozin and empagliflozin have evidence supporting use in patients both with and without T2D).
- Finerenone reduces progression of CKD and has been proven to be cardioprotective in diabetic kidney disease; however, hyperkalemia and renal function can limit use and is recommended to be managed by nephrology or cardiology.

Table 1: SGLT2i Recommendations

1. Implement renal dosing of SGLT2i (differs based on indication: T2D vs. CKD/DKD vs. heart failure); if eGFR subsequently drops (while on SGLT2i) below the cutoff for initiation of treatment:	The SGLT2i can be continued up until the initiation of renal replacement therapy or kidney transplantation, as studied in the CREDENCE trial. • Canagliflozin → eGFR <25 – 30 = do not initiate • Dapagliflozin → eGFR <25 = do not initiate • Empagliflozin → eGFR <20 = do not initiate
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 three to four 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. May see 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 (avoid use in Type 1 diabetes due to euglycemic diabetic 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 2022 guidelines recommend against use in this population.

Table 2: Practical Application of SGLT2i

Patients with T2D

- Both ADA and KDIGO guidelines recommend initiating metformin and an SGLT2i as first-line treatment for patients with T2D and CKD, regardless of A1c control.
- Continue to utilize ACEi/ARB to slow progression of CKD.
- Control comorbidities (hypertension, hyperlipidemia).
- Implement non-pharmalogic strategies including smoking cessation, weight loss and exercise.

Patients without T2D

- Start with medications that have strong evidence to slow progression of CKD (ACEi/ARB).
- Control comorbidities (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 patients **without** T2D.

FDA Approvals

- Dapagliflozin: approved for CKD without T2D, dosed at 10mg daily
- Canagliflozin: approved for diabetic kidney disease, dosed at 100mg daily
- *Empagliflozin indication for CKD not approved at time of publishing, expected before end of 2023.*

Table 3: Finerenone Applications

- **Mechanism of action**: Selectively blocks mineralocorticoid receptor-mediated sodium reabsorption in the collecting duct of nephrons, reducing inflammation and fibrosis.
- Research has shown that the addition of finerenone **significantly reduces the progression of CKD** in patients with persistent albuminuria/proteinuria, despite treatment with ACEi/ARBs.
- In addition to renoprotective properties, has proven to be **cardioprotective in diabetic kidney disease** patients.
- **KDIGO 2022 Guidelines** recommend adding finerenone in patients with T2D, eGFR ≥25 ml/min per 1.73 m^2, normal serum potassium, and **albuminuria ≥30 mg/g** despite maximum tolerated dose of RAS inhibitor.

Concerns

- Lack of definitive data regarding adding finerenone to SGLT2i
- Hyperkalemia, maintenance dose guided by potassium levels
- Not recommended if eGFR <25 ml/min/1.73 m^2
- Costly, comparable to cost of SGLT2i

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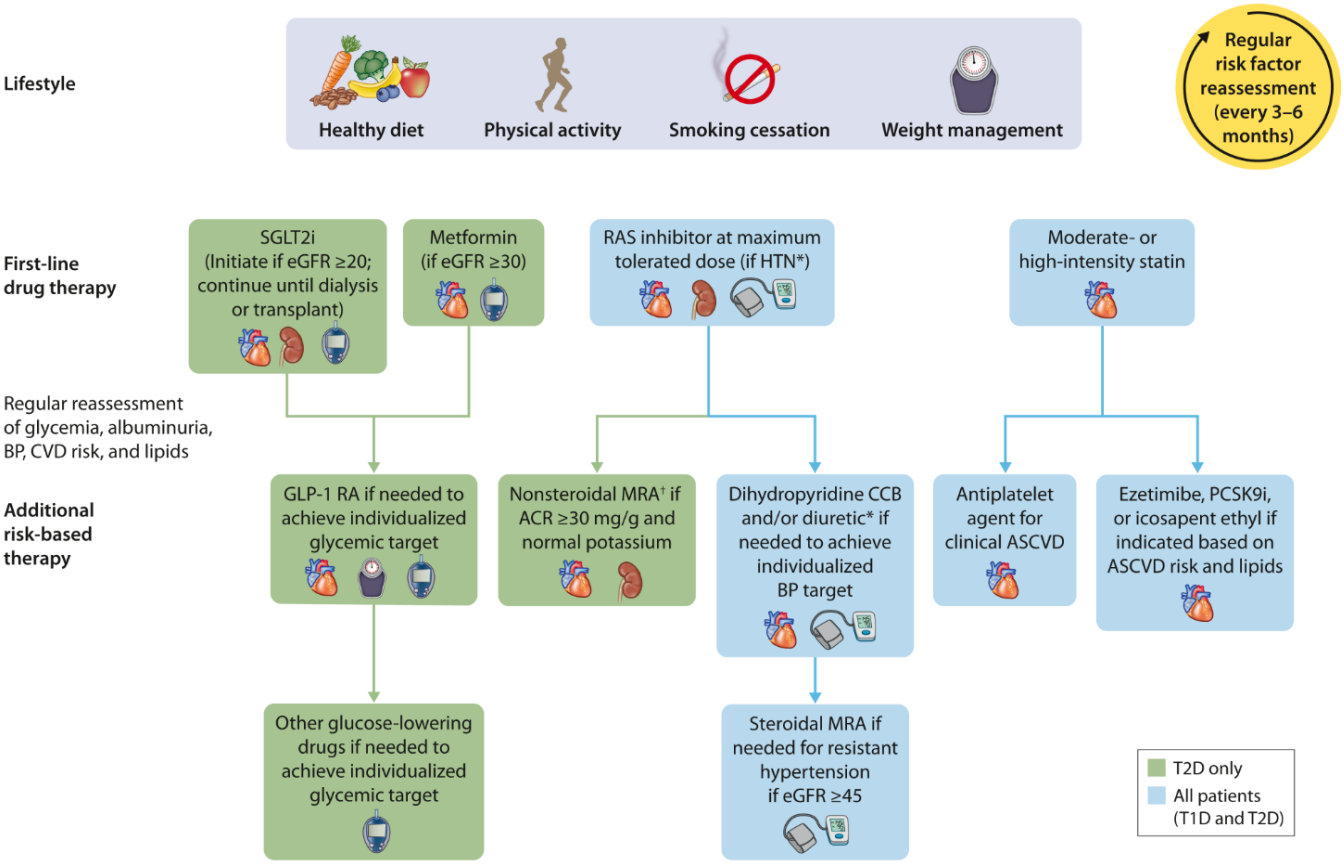

*ACEi or ARB (at maximal tolerated doses) should be first-line therapy for hypertension when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker or diuretic can also be considered; all three classes are often needed to attain BP targets.
†Finerenone is currently the only ns-MRA with proven clinical kidney and cardiovascular benefits.

Figure 1: Consensus Report by ADA and KDIGO

Table 3: Evidence Summary Overview: Large, Randomized, Placebo-controlled Trials Guiding Recommendations

				The Effects on:		
Drug	Trial	Kidney-related Eligibility Criteria	Primary Outcome	Primary Outcome	Albuminuria	GFR Loss
Canagliflozin	CANVAS	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 T2D)	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	eGFR ≥20 to <45 ml/min/1.73m^2 *or* ACR ≥200 mg/g and eGFR ≥45 to <90 ml/min/1.73m^2	Progression of renal disease (ESRD, sustained eGFR decline to <10 ml/min/1.73m^2, sustained decline of ≥40% in eGFR, and renal death); or death from CVD causes	↓	Progression of renal disease ↓	
Finerenone	FIDELIO-DKD	ACR 30 to <300 mg/g and eGFR 25-60 ml/min/1.73 m^2; *or* ACR 300-5000 mg/g and eGFR 25-75 ml/min/1.73 m^2	Composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline over at least a 4-week period, or death from renal causes	↓		↓
	FIGARO-DKD	ACR 30 to <300 mg/g and eGFR 25-90 ml/min/1.73 m^2; *or* ACR 300-5000 mg/g and eGFR at least 60 ml/min/1.73 m^2	Composite of death from CV causes, nonfatal MI, nonfatal stroke or hospitalization for heart failure	↓		

Key: ↓ - 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

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Cost-Effectiveness of GLP-1 Receptor Agonists and SGLT2 Inhibitors

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Executive Summary

Clinical efficacy in T2DM glycemic outcomes and non-glycemic related outcomes has placed GLP-1 RA and SGLT2i use at the forefront of diabetes management. These medications come with a significant cost however, which may affect both the patient and the health system. The goal of medication stewardship is to ensure optimal outcomes are achieved by the patient, while also ensuring appropriate financial stewardship and appropriate use of high-cost medications. This article focuses on the cost considerations with GLP-1 RA and SGLT2i use. Previous Pharmacy Pearls for Prescribers articles have addressed GLP-1 RA and SGLT2i place in therapy.

- Cardiovascular Risk Reduction in Type 2 Diabetes
- Reducing Total Cost of Care through Optimal Pharmacologic Treatment

Acronyms	
ACO	Accountable care organization
ASCVD	Atherosclerotic cardiovascular disease
DPP-4i	Dipeptidyl peptidase 4 inhibitor
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
ICD-10	International Classification of Diseases, tenth revision
ICER	Incremental cost effectiveness ratio
QALY	Quality adjusted life year
SGLT2i	Sodium/glucose cotransporter 2 inhibitor
T2DM	Type 2 diabetes mellitus

Key Takeaways

- It is important to take economic impact into consideration when initiating a new medication. The retrospective cost-effectiveness data that is currently available favors use of SGLT2i over GLP-1 RA, primarily due to a decrease in total medication costs.
- When considering use of an SGLT2i versus a GLP-1 RA, weight the benefit of SGLT2i for use in heart failure and CKD versus the high cost and weight loss potential with a GLP-1 RA.
- SGLT2i is preferred over DPP-4i; SGLT2i affords significantly more benefit compared to DPP-4i at relatively the same cost.
- ACO initiatives are in progress to ensure clinical outcomes are met and to reduce medication cost when appropriate in regard to GLP-1 RA use.
- Contraindications exist for each class and should be reviewed prior to initiating therapy; risk of euglycemic DKA with SGLT2i is higher with elevated baseline A1c, consider withholding SGLT2i when baseline A1c is greater than 9%.

Cost-Effectiveness Data

There have been multiple retrospective studies comparing the cost-effectiveness of GLP-1 RA and SGLT2i. The three studies summarized below reach a similar conclusion that while both GLP-1 RA and SGLT2i may decrease health care utilization and costs, the higher pharmacy costs associated with GLP-1 RA may outweigh this benefit. It is important to note that the below data was obtained between the years 2015 to 2018, before semaglutide (Ozempic) was widely used. Additionally, patients were followed for approximately one year in each study.

Given the limited follow-up time of these retrospective studies, it is also worthwhile to analyze long term cost-effectiveness projections available in simulation studies. While these studies focus on use of SGLT2i and GLP-1 RA in different prescribing scenarios, the data may be useful to better understand economic impact.

Retrospective Studies

Study 1 (Newman, 2021)

- This study looked at health care utilization and costs for patients that were switched from a DPP-4i to a SGLT2i or GLP-1 RA. Both groups had lower rates of inpatient hospitalizations. SGLT2i group did not have significant differences in medical or pharmacy costs compared to DPP-4i, whereas the GLP-1 RA group had significantly higher total pharmacy costs. Authors concluded that these higher pharmacy costs may outweigh the savings of decreased health care utilization costs.

Study 2 (Poonawalla, 2021)

- Authors compared patients newly started on an SGLT2i or GLP-1 RA regarding CV outcomes, treatment persistence and health care utilization and costs. No differences were found in number of cardiovascular events (MI, stroke, all cause death) between groups regardless of ASCVD status. Occurrence of heart failure was significantly lower in the SGLT2i group. Other findings—including better adherence, decreased health care utilization costs and decreased pharmacy costs—favored SGLT2i use.

Study 3 (Wilke, 2022)

- This study was completed in Germany and compared cost for patients who were newly started on a DPP-4i, GLP-1 RA or empagliflozin. Results showed no significant cost difference in hospital expenditures in the first year between patients who were started on empagliflozin versus a GLP-1 RA; however, pharmacy costs were significantly higher in the GLP-1 RA group. It is notable that groups were not matched on baseline glycemic control.

Simulation Studies

Study 4 (Choi, 2022)

- This study funded by the ADA looked to evaluate whether SGLT2i and GLP-1 RA would be cost effective when used first line compared to metformin. While both agents were projected to improve life expectancy by a few months, neither agent would be cost effective according to an assumed willingness to pay threshold of less than $150,000 per QALY gained. The ICER of SGLT2i was $478,000 per QALY gained, ICER of injectable GLP-1 RA was inferior to metformin and the ICER of oral GLP-1 RA was $823,000 per QALY gained.

Study 5 (Morton, 2023)

- This was a simulation study published in Diabetologia this year looked at cost-effectiveness of SGLT2i and GLP-1 RA regarding cardiovascular and kidney benefits only if widespread use was implemented. Outcomes were QALYs, total costs and ICER. Authors concluded that at current

prices (Australian dollars), SGLT2i would be cost effective for their cardiovascular and kidney benefits only. GLP-1 RA were not found to be cost effective with current pricing. Authors were using this data to reinforce that SGLT2i use should not be limited to those with T2DM.

ACO Considerations

Avera and Wellmark have identified cost optimization opportunities within diabetes management to transition patients from a GLP-1 RA to a similarly effective but lower cost medication (SGLT2i). The goal of this initiative is to ensure optimal outcomes for patients while ensuring appropriate financial stewardship.

Wellmark will identify patients deemed appropriate for transitioning to alternative therapy. The following patients will be excluded from consideration for switching to an alternative therapy:

- On an SGLT2i or have recently trialed an SGLT2i
- On insulin
- History of ASCVD, chronic kidney disease stage 4 or 5, hypoglycemia or urinary tract infection
- Note – need to have a paid claim in prior two years with corresponding ICD-10 diagnosis code

Review of patients will assess how well patients are meeting clinical outcomes of GLP-1 RA use (such as A1c lowering and weight loss of 5% or more) as well as appropriate dosing of medications.

SGLT2i

- Elevated baseline A1c may be a risk factor for development of euglycemic DKA. Literature states an A1c greater than 10%[1] is associated with an increased risk. In clinical practice, it maybe reasonable to hold if baseline A1c is greater than 9%. It is important to take into account recent glycemic trends and other medications the patient is taking, such as insulin.
- Do not start in patients who have risk factors for lower limb amputations, such as severe neuropathy, foot deformity, vascular disease, or history of previous foot ulcer.
- Cardiovascular, heart failure, and renal benefit
- Weight loss benefit (intermediate)
- Glucose lowering efficacy (intermediate to high)
- Potential reduction in blood pressure

GLP-1 RA

- Avoid in patients with a history of pancreatitis. If pancreatitis is confirmed during therapy, medication should be stopped.
- Avoid use in patients with personal or family history (first-degree) of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B. If history is in second degree relative, some providers may consider starting after additional thyroid workup is complete.
- Cardiovascular benefit
- Weight loss benefit (intermediate to very high - following discontinuation of GLP-1, patients regain two-thirds of prior weight loss)
- Glucose lowering efficacy (high to very high)

Figure 1: Clinical considerations when initiating either SGLT2i or GLP-1RA therapy

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