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Sodium-Glucose CoTransporter-2 Inhibitors (SGLT-2 Inhibitors) Drug Use Criteria

Created: August 2020
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Includes:

Invokana©	**Canagliflozin**
Invokamet XR©	Canagliflozin/Metformin HCl
Invokamet©	Canagliflozin/Metformin HCl
Farxiga©	**Dapagliflozin Propanediol**
XigduoXR©	Dapagliflozin/Metformin HCl
Qtern©	Dapagliflozin/Saxagliptin HCl
Jardiance©	**Empagliflozin**
Glyxambi©	Empagliflozin/Linagliptin
Synjardy XR©	Empagliflozin/Metformin HCl
Synjardy©	Empagliflozin/Metformin HCl
Steglatro©	Ertugliflozin Pidolate
Segluromet©	Ertugliflozin/Metformin
Steglujan©	Ertugliflozin/Sitagliptin

(Bolded ítems are preferred agents, consistent with the Oregon Medicaid Preferred Drug List)

GUIDELINE FOR USE:

Initial Request:

1. Is this a request for renewal of a previously approved prior authorization?
   a) Yes: Go the Renewal Criteria
   b) No: Go to #2

2. Does the patient have a diagnosis of T2DM?

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a) Yes: Go to #3
b) No: Go to #4

3. Has the patient tried and failed metformin and a sulfonylurea, have contraindications to these treatments or is the request for use of a SGLT-2 inhibitor with metformin and a sulfonylurea? (Please document clinical contraindication, if any e.g., heart failure).
a) Yes: go to question #5
b) No: pass to RPh. Deny and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

Initiating Metformin

1.	Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2.	After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
4.	The maximum effective dose can be up to 1,000 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

4. Does the patient have a diagnosis of heart failure with reduced ejection fraction (New York Heart Association Class II-IV)?
a) Has the patient tried and failed standard treatment options such as angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics? If yes, and request is for use of dapagliflozin as a secondary agent for management of a symptomatic patient with elevated N-terminal pro-B-type natriuretic peptide despite optimized therapy, approve for 6 months. Dapagliflozin is the only SGLT-2 inhibitor with a FDA approved indication for the treatment of heart failure with reduced ejection fraction.
b) If no, deny; does not meet criteria. SGLT-2 inhibitor therapy is indicated for the treatment of T2DM (and heart failure with reduced ejection fraction with dapagliflozin). Off label use of medication is not a covered benefit on the Oregon Health Plan.

Class I - No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20—100 m).Comfortable only at rest.
Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients

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5. Has the member tried and failed ONE of the thiazolidinediones such as formulary pioglitazone, (Unable to maintain or achieve goal A1c), or have a contraindication to thiazolidinedione therapy?
(Please document clinical contraindication, if any e.g., heart failure).
a) Yes: continue to #6.
b) No: do not approve. Deny and recommend trial of formulary pioglitazone.

6. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR):
- Canagliflozin and eGFR <45 mL/min/ 1.73 m2, or
- Empagliflozin and eGFR <45 mL/min/1.73 m2, or
- Dapagliflozin and eGFR <60 mL/min/1.73 m2, or
- Ertugliflozin and eGFR <60 mL/min/1.73 m2?

a) Yes: Pass to RPh. Deny; does not meet criteria
b) No: Go to #7

7. Evaluate based on HbA1c (2018 ADA and 2019 AACE Treatment Guidelines)
a) Is HbA1c ≤ 7.5%----------> If yes, do not approve.
b) Is HbA1c >7.5% and <9.0%----------> If yes, approve FFS preferred SGLT-2s x 6 months (Fall 2020: Farxiga, Invokana, and Jardiance).
c) Is HbA1c ≥ 9.0%----------> If yes, continue to #8

8. Has the provider submitted an acceptable rationale for why insulin cannot be used and/or optimized?
a) yes: approve x FFS preferred SGLT-2s x 6 months (Fall 2020: Farxiga, Invokana, and Jardiance).
b) no: deny and offer insulin.

Renewal Request:

1. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR):
- Canagliflozin and eGFR <45 mL/min/ 1.73 m2 , or
- Empagliflozin and eGFR <45 mL/min/1.73 m2, or
- Dapagliflozin and eGFR <60 mL/min/ 1.73 m2, or
- Ertugliflozin and eGFR <60 mL/min/ 1.73 m2?

a) Yes: Pass to RPh. Deny; does not meet criteria
b) No: Approve FFS preferred SGLT-2s for up to 6 months (Fall 2020: Farxiga, Invokana, and Jardiance).

2. Has the patient responded to therapy (For example, HgA1c reduced by 0.5%)?

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a) If yes, approve for 6 months.
b) If no, ensure dosing is optimized and recommend therapy change if no improvement.

Rationale:
To promote value within step therapy management and evidence-based standard of care for type 2 diabetes mellitus. To ensure optimization of least costly formulary alternatives including metformin and sulfonylureas prior to initiating therapy with more costly SGLT-2 inhibitors. Adherence and dose optimization will be reviewed using prescription refill history for consideration of coverage for SGLT-2 inhibitors.

FDA Approved Indication:

As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus; risk reduction of major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease; risk reduction of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with urinary albumin excretion >300 mg/day.

Mechanism of Action and dosing:

Currently, the sodium-glucose cotransporter-2 (SGLT2) inhibitor class includes canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. By inhibiting sodium-glucose cotransporter 2 (SGLT2) in the proximal renal tubules, SGLT2s reduce reabsorption of filtered glucose from the tubular lumen and lower the renal threshold for glucose (RTG). SGLT2 is the main site of filtered glucose reabsorption; reduction of filtered glucose reabsorption and lowering of RTG result in increased urinary excretion of glucose, which reduces plasma glucose concentrations. In non-diabetics, SGLT2 checks that glucose is appropriately reabsorbed, allowing for low glucose concentrations in the urine. In longstanding hyperglycemia, the renal proximal tubules try to increase the SGLT2 transport mechanism for preserving this energy source, not realizing that the blood glucose concentrations are exceeding those required for normal physiologic processes (PSAP 2019).

Please refer to the individual prescribing information on each agent for dosing information.

Contraindications/Cautions:

- Contraindications to all agents include hypersensitivity such as anaphylaxis, angioedema to or any component of the formulation
- SGLT inhibitor use in severe renal impairment is not recommended because the glucose-lowering effects do not occur at eGFRs below 30 mL/minute/1.73 m2.

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- Updated ADA recommendations recommend that clinicians consider use of a SGLT2 inhibitor in patients with type 2 diabetes and kidney disease if the eGFR is above 30 mL/minute/1.73 m2 to decrease the risk of CKD progression and/or cardiovascular events, especially if albuminuria is present.
- SGLT2 Inhibitor use is not recommended by the manufacturer(s) during the second and third trimesters of pregnancy. Breastfeeding is not recommended by the manufacturer for all SGLT2 Inhibitors currently available at the time of criteria development and approval.
- History of UTIs, acute kidney injury, DKA, chronic genitourinary conditions like benign prostatic hypertrophy or urinary incontinence, and drugs that may cause hypovolemia such as loop diuretics or nephrotoxicity such as NSAIDs (PSAP 2019).
- To decrease side effects, patients should have adequate hydration and avoid excessive hyperglycemia. Thiazide-like diuretics are generally not an issue when adding to a SGLT2 inhibitor, however, lower the loop diuretic dose by 50% when adding a SGLT2 inhibitor. To lower the acute kidney injury risk, avoid starting a thiazide-like diuretic, angiotensin- converting enzyme inhibitor, and SGLT2 inhibitor at the same time (PSAP 2019).
- Blood pressure and volume status must be sufficient prior to adding a SGLT2 inhibitor (PSAP 2019).

References:

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2. American Diabetes Association (ADA). Standards of Medical Care in Diabetes – 2019. Diabetes Care 2019;42(suppl 1):S61-S138.
3. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes algorithm – 2019 executive summary. Endocr Pract 2019;25:91-100.
4. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669-701.
5. Invokana Prescribing Information. Revised 1/2020.
6. Invokamet XR Prescribing Information. Revised 1/2020.
7. Invokamet Prescribing Information. Revised 1/2020.
8. Farxia Prescribing Information. Revised 5/2020.
9. XigduoXR Prescribing Information. Revised 1/2020.
10. Qtern Prescribing Information. Revised 1/2020.
11. Jardiance Prescribing Information. Revised 1/2020.
12. Glyxambi Prescribing Information. Revised 3/2020.
13. Synjardy XR Prescribing Information. Revised 1/2020.
14. Synjardy Prescribing Information. Revised 1/2020.

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15. Steglatro Prescribing Information. Revised 1/2020.
16. Segluromet Prescribing Information. Revised 1/2020.
17. Steglujan Prescribing Information. Revised 1/2020.
18. Sodium-glucose Cotransporter 2 (SGLT2) Inhibitors - July 31, 2018 https://www.orpdl.org/durm/PA_Docs/sgLT2inhibitors.pdf
19. https://www.orpdl.org/durm/newsletter/osdr_articles/volume10/osdr_v10_i7.pdf

Figure 6. Excerpt from Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).

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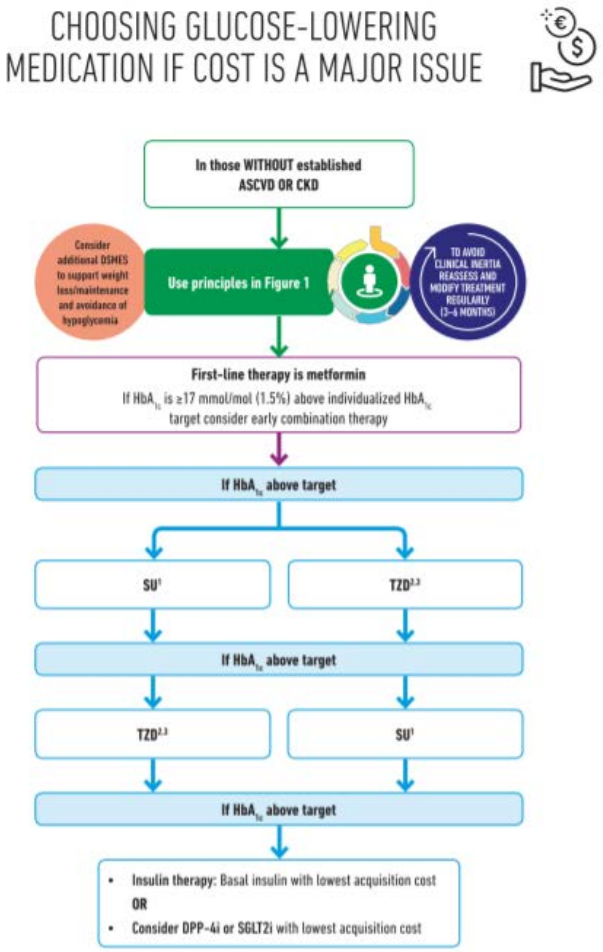

1. Choose later generation SU to minimize risk of hypoglycemia
2. Consider country- and region-specific cost of drugs. In some countries, TZD relatively more expensive and DPP-4i relatively cheaper
3. Low-dose TZDs are better tolerated

Figure 6—Choosing glucose-lowering medication if cost is a major issue. DPP-4i, dipeptidyl peptidase 4 inhibitor; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea.

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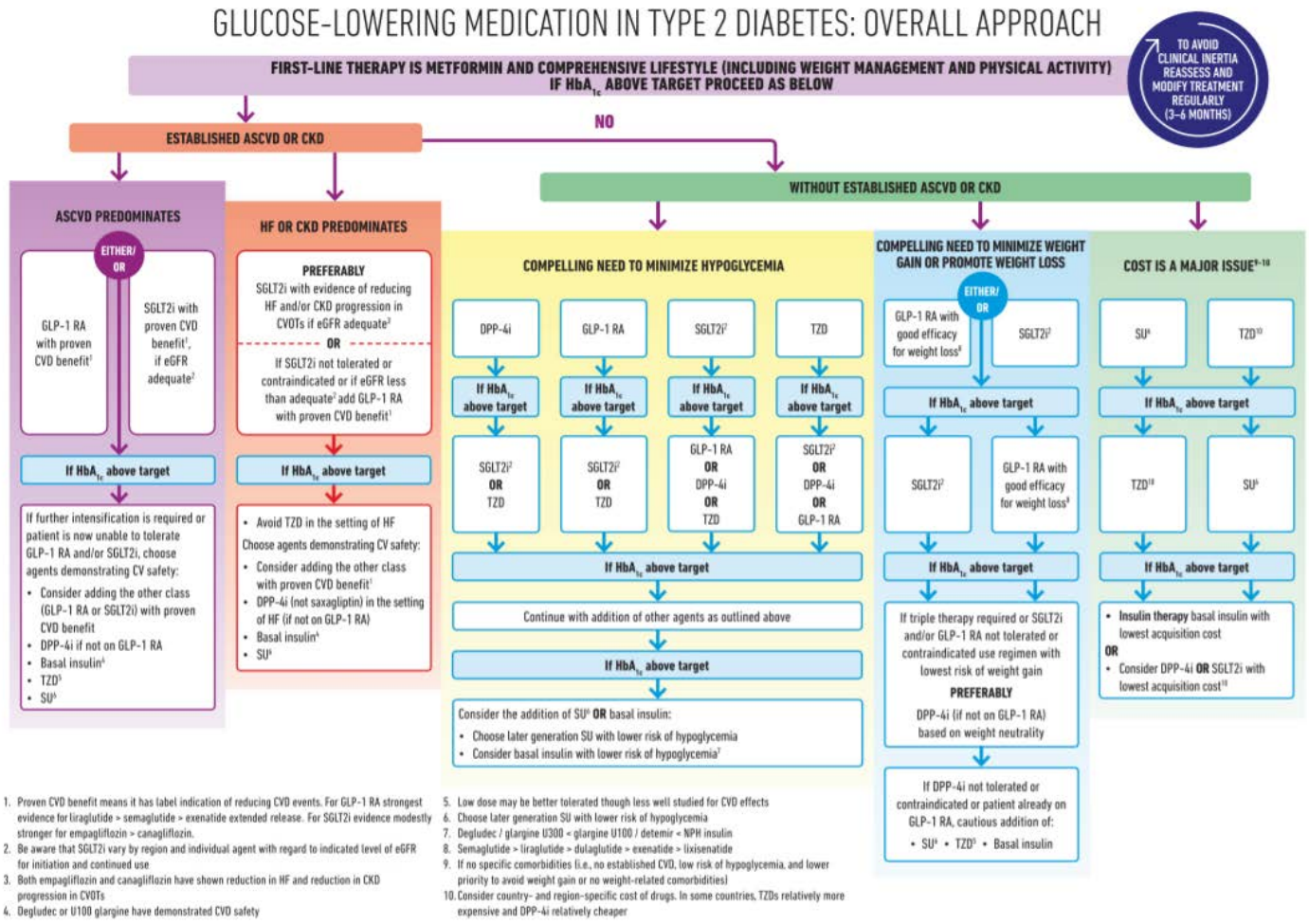
Figure 2. Excerpt from Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).



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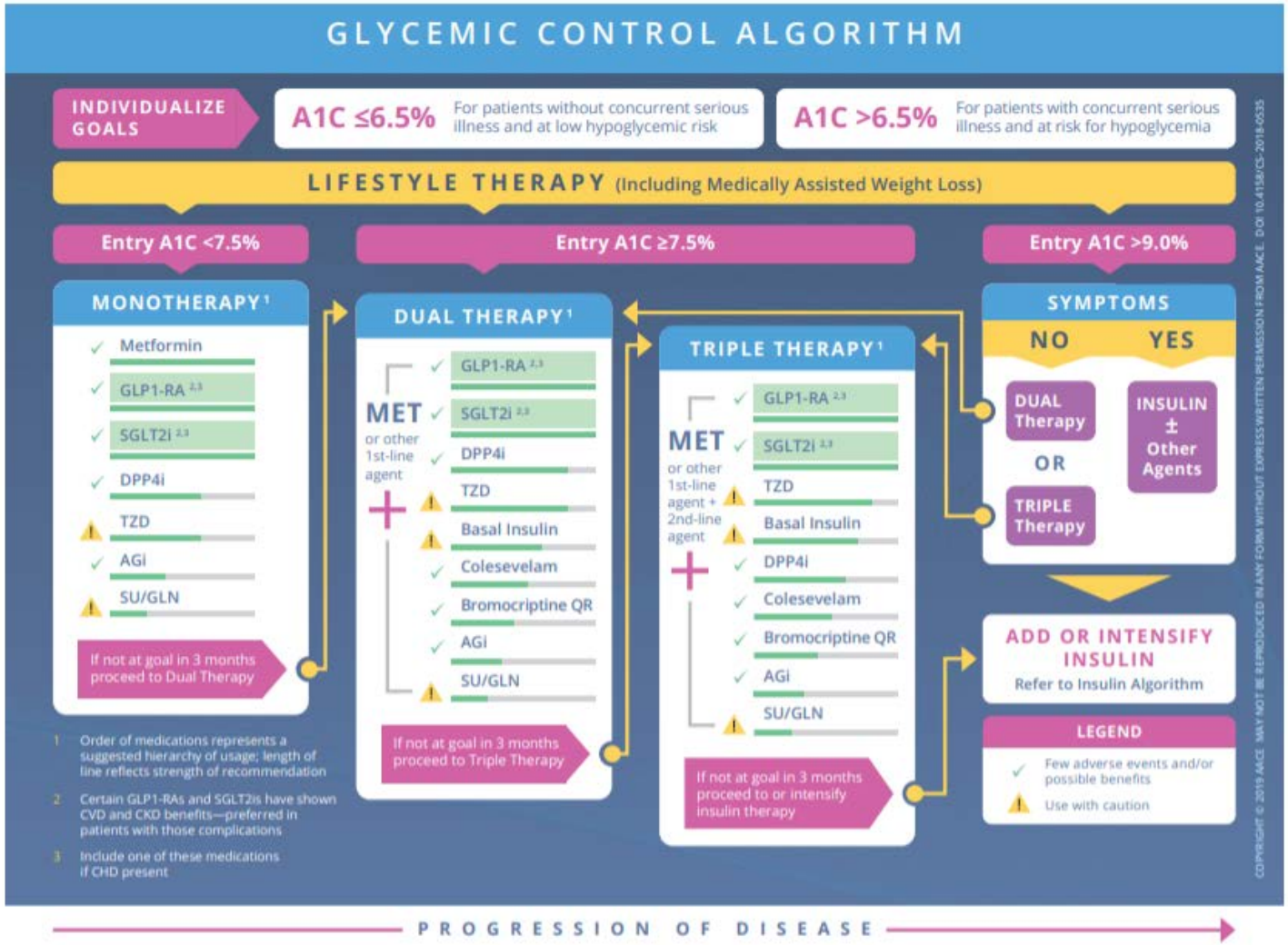
Excerpt of Glycemic Control Algorithm: Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes algorithm – 2019 executive summary.



Approved by Advanced Health Pharmacy and Therapeutics Committee 9-30-2020, 10-21-20