Indication Differences Among GLP-1 RAs: Prescribing Information[1]

Indications	DULA	EXN BID	EXN ER	LIRA	SEMA inj	SEMA oral	TZP
Adjunct to diet and exercise to improve glycemic control in adults with T2DM	✓	✓	✓	✓	✓	✓	✓
Adjunct to diet and exercise to improve glycemic control in patients aged ≥10 years with T2DM	✓	–	✓	✓	–	–	–
Reduce risk of MACE in adults with T2DM and established CVD	✓	–	–	✓	✓	–	–
Reduce risk of MACE in adults with T2DM and multiple CV risk factors	✓	–	–	–	–	–	–

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Practical Considerations for Selecting a GLP-1 RA

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Clinical Characteristics of GLP-1 RAs[1]

	GLP-1 RA	Delivery Format (Device)	Frequency	Starting Dose	Next Higher Dose	Next Higher Dose	Next Higher Dose	Next Higher Dose	Pen Type	Screw-On Needle	Need Separate Needle Rx
Exendin-4–Based	**Exenatide BID**	Injectable (pen)	Twice daily	5 mcg	10 mcg	—	—	—	Multidose	✓	✓
	Exenatide ER (subQ)	Injectable (autoinjector)	Weekly	2 mg	—	—	—	—	Single use	—	—
Human GLP-1–Based	**Liraglutide (subQ)**	Injectable (pen)	Daily	0.6 mg[a]	1.2 mg	1.8 mg	—	—	Multidose	✓	✓
	Dulaglutide (subQ)	Injectable (autoinjector)	Weekly	0.75 mg	1.5 mg	3 mg	4.5 mg	—	Single use	—	—
	Semaglutide (subQ)	Injectable (pen)	Weekly	0.25 mg[a]	0.5 mg	1 mg	2 mg	—	Multidose	✓	—
	Semaglutide (oral)	Oral (tablet)	Daily	3 mg[a]	7 mg	14 mg	—	—	N/A	N/A	N/A
	Tirzepatide	Injectable (autoinjector)	Weekly	2.5 mg[a]	5 mg	10.5 mg	12.5 mg	15 mg	Single use	—	—

[a]Subtherapeutic dose for treatment initiation only

Meta-Analysis of GLP-1 RA CVOTs in T2DM and at High Risk for CVD[2]

Outcome	HR (95% CI)	NNT (95% CI)	*P*	Heterogeneity
MACE-3	0.86 (0.80, 0.93)	65 (45, 130)	< .0001	Marginal
CV death	0.87 (0.80, 0.94)	163 (103, 353)	.001	No
Fatal and non-fatal MI	0.90 (0.83, 0.98)	175 (103, 878)	.02	No
Fatal and non-fatal stroke	0.83 (0.76, 0.92)	198 (140, 421)	.0002	No
All-cause mortality	0.88 (0.82, 0.94)	114 (76, 228)	.0001	No
Hospital admission for heart failure	0.89 (0.82, 0.98)	258 (158, 1,422)	.013	No
Composite kidney outcome, including macroalbuminuria	0.79 (0.73, 0.87)	47 (37, 77)	< .0001	Marginal
Worsening of kidney function	0.86 (0.72, 1.02)	241 (120, 1,694)	.089	No

Adverse Event	OR (95% CI)	*P*	Heterogeneity
Severe hypoglycemia	0.90 (0.74, 1.10)	.32	Yes
Retinopathy	1.07 (0.92, 1.25)	.39	Marginal
Pancreatitis	1.02 (0.77, 1.36)	.88	No
Pancreatic cancer	0.98 (0.56, 1.70)	.93	No

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Benefits and Risks of GLP-1–Based Agents for T2DM[3]

Interventions	OR, 95% CI								
	All Cause Death	CV Death	Nonfatal MI	Nonfatal Stroke	HHF	ESRD[a]	HRQOL Score	Severe Hypoglycemia	Drug-Specific AEs
GLP-1 RAs	0.88 (0.82 to 0.93)	0.87 (0.81 to 0.94)	0.91 (0.81 to 0.98)	0.85 (0.77 to 0.94)	0.91 (0.83 to 0.99)	0.83 (0.75 to 0.92)	0.17 (0.07 to 0.27)	0.98 (0.90 to 1.06)	Severe GI events 1.97 (1.39 to 2.80)
Tirzepatide	0.83 (0.48 to 1.44)	1.00 (0.35 to 2.85)	0.69 (0.08 to 6.10)	–	0.63 (0.16 to 2.39)	0.68 (0.09 to 4.84)	0.39 (0.13 to 0.65)	1.13 (0.42 to 3.02)	Severe GI events 4.59 (1.89 to 11.14)

High to Moderate Certainty Evidence	Low to Very Low Certainty Evidence
Among the most effective	Possibly among the most effective
Among the intermediate effective	Possibly among the intermediate effective
Not convincingly different from the standard treatment	Possibly not convincingly different from the standard treatment
Among the intermediate harmful	Possibly among the intermediate harmful
Among the most harmful	Possibly among the most harmful

Interventions	MD Δ Body Weight, kg (95% CI)
Tirzepatide	-8.57 (-9.40 to -7.75)
Semaglutide (subQ)	-4.62 (-5.22 to -4.03)
Semaglutide (oral)	-2.98 (-3.66 to -2.29)
Efpeglenatide[b]	-2.59 (-4.40 to 0.78)
Liraglutide	-2.21 (-2.58 to -1.85)
SGLT2 inhibitors	-1.98 (-2.18 to -1.78)
Exenatide BID	-1.77 (-2.47 to -1.07)
Dulaglutide	-1.40 (-1.93 to -0.88)
Exenatide ER	-1.05 (-1.67 to -0.42)
Metformin	-0.83 (-1.16 to -0.51)
α-glucosidase inhibitors	-0.38 (-0.80 to 0.04)
DPP-4 inhibitors	0.28 (0.11 to 0.46)
Bolus insulin	1.01 (0.24 to 1.79)
Meglitinides	1.26 (0.58 to 1.94)
Sufonylureas	1.78 (1.50 to 2.06)
Basal insulin	2.15 (1.74 to 2.56)
Thiazolidinediones	2.81 (2.55 to 3.07)
Basal bolus insulin	3.26 (2.10 to 4.41)
Standard treatments[c]	Reference

[a] ESRD defined as composite of long-term dialysis, kidney transplantation, sustained estimated glomerular filtration rate <15 mL per min per 1.73 m² for ≥30 days, sustained % decline in eGFR of ≥40% for ≥30 days or a doubling of SCr, or renal death; effects on ESDR rated down owing to indirectness. [b] Investigational agent not approved by the US FDA. [c] Standard of care treatments include other glucose-lowering agents from other classes and placebo with lifestyle modifications.

1. https://www.accessdata.fda.gov/scripts/cder/daf/. 2. Sattar N et al. *Lancet Diabetes Endocrinol*. 2021;9:653-662. 3. Shi Q et al. *BMJ*. 2023;381:e074068.

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ADA/EASD 2022 Consensus Guidelines for the Management of T2DM[1]

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Holistic Person-Centered Approach

+ASCVD/Indicators of High Risk

GLP-1 RA with proven CVD benefit — Either/Or — SGLT2i with proven CVD benefit

If additional cardiorenal risk reduction or glycemic management needed, consider combination SGLT2i/GLP-1 RA

+HF: SGLT2i with proven HF benefit in this population

+CKD (on maximally tolerated dose of ACEi/ARB)

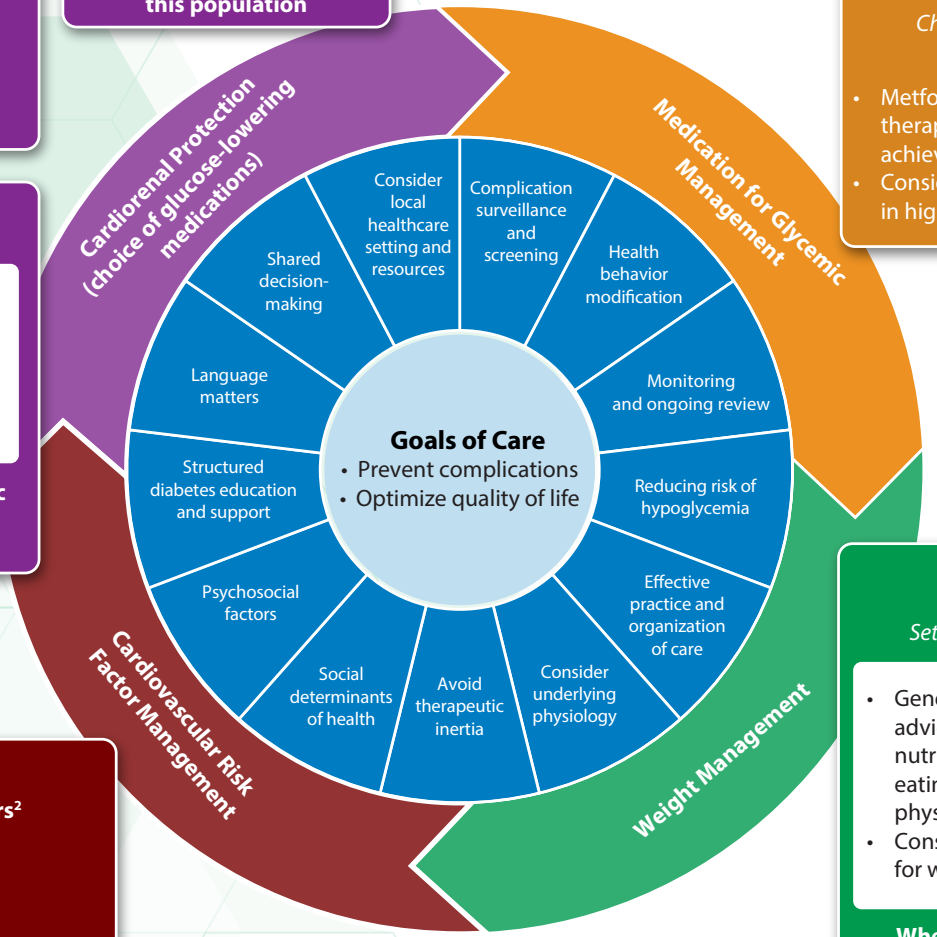
Preferably

SGLT2i with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation, **OR**

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If additional cardiorenal risk reduction or glycemic management needed, consider combination SGLT2i/GLP-1 RA



Glycemic Management

Choose Approaches That Provide the Efficacy to Achieve Goals

- Metformin or agent(s) including combination therapy that provide adequate efficacy to achieve and maintain treatment goals
- Consider avoidance of hypoglycemia a priority in high-risk individuals

Achievement and Maintenance of Weight Management Goals

Set Individualized Weight Management Goals

- General lifestyle advice: medical nutrition therapy, eating patterns, physical activity
- Consider medication for weight loss
- Intensive, evidence-based, structured weight management program
- Consider metabolic surgery

When choosing glucose-lowering therapies, consider regimen with high-to-very-high dual glucose and weight efficacy

Ensure Strategies Are in Place to Detect and Optimize Management of CV Risk Factors[2]

- CV risk factor screening and surveillance
- BP lowering
- Lipid lowering
- Antithrombotic agent
- Smoking cessation

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Impact of Physical Behaviors on Cardiometabolic Health

Sitting/Breaking Up Prolonged Sitting

- Limit sitting
- Break up sitting (every 30 min) with short, regular bouts of slow walking/simple resistance exercises to improve glucose metabolism

Stepping

- An increase of only 500 steps per day is associated with 2% to 9% decreased risk of CV morbidity and all-cause mortality
- A 5 to 6 min brisk-intensity walk per day equates to ~4 y greater life expectancy

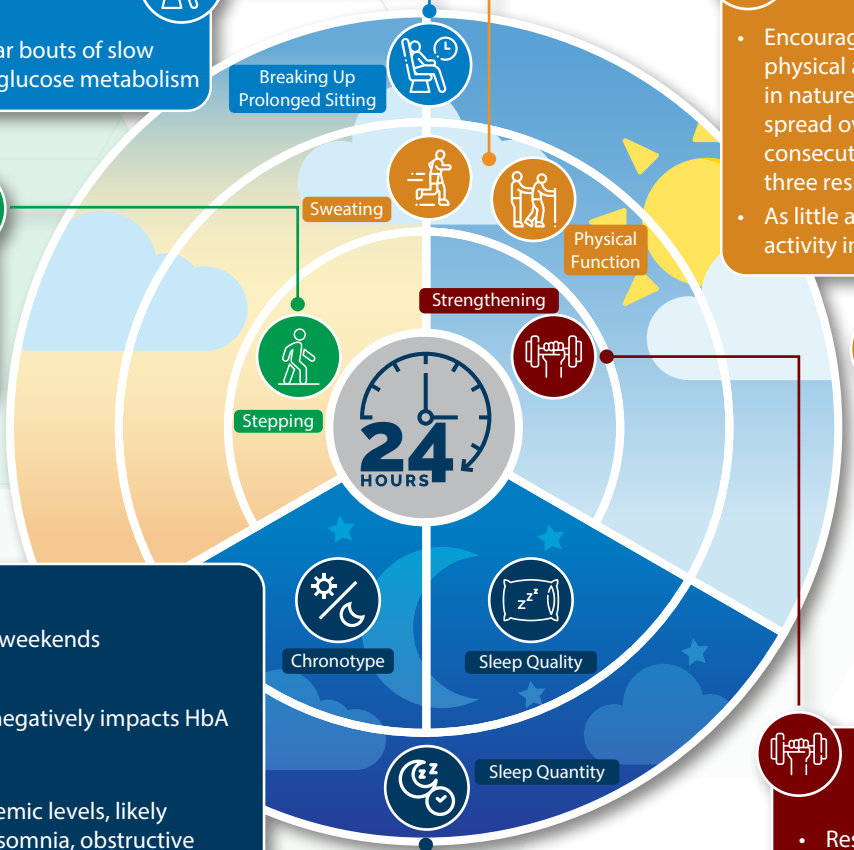
Sleep

Aim for consistent, uninterrupted sleep, even on weekends

Quantity: long (>8 h) and short (<6 h) sleep negatively impacts HbA

Quality: irregular sleep results in poorer glycemic levels, likely influenced by the increased prevalence of insomnia, obstructive sleep apnea, and restless leg syndrome in people with T2DM

Chronotype: evening chronotypes (ie, night owl: go to bed/get up late) may be more susceptible to inactivity and poorer glycemic levels vs morning chronotypes (ie, early bird: go to bed/get up early)



Sweating (Moderate-to-Vigorous Activity)

- Encourage ≥150 min per week of moderate-intensity physical activity (ie, uses large muscle groups, rhythmic in nature) OR ≥75 min per week vigorous-intensity activity spread over ≥3 days per week, with no more than two consecutive days of inactivity. Supplement with two to three resistance, flexibility, and/or balance sessions
- As little as 30 min per week of moderate-intensity physical activity improves metabolic profiles

Physical Function/ Frailty/Sarcopenia

- The frailty phenotype in T2DM is unique, often encompassing obesity alongside physical frailty, at an earlier age. The ability of people with T2DM to undertake simple functional exercises in middle-age is similar to that in those over a decade older

Strengthening

- Resistance exercise (ie, uses the person's own body weight or works against a resistance) also improves insulin sensitivity and glucose levels; activities like tai chi and yoga also encompass elements of flexibility and balance

1. Davies MJ et al. *Diabetes Care*. 2022;45:2753-2786. 2. ADA Professional Practice Committee. *Diabetes Care*. 2023;46:S1-S291.

PRACTICE AID

Applying the "3Es" to Manage GI Adverse Events of GLP-1 RAs[1]

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The First Es: Education/Explanation and Escalation

Education and Explanation

Patient consultation and counseling

- Counsel patients on
  - The potential for GI AEs and their typically mild-to-moderate, temporary nature
  - Dietary modifications: recommend reducing meal size, being mindful to stop eating once full, avoiding eating when not hungry, avoiding high-fat or spicy food, and moderating alcohol intake
- Discuss any current GI symptoms, treat if needed, and counsel the patient on how to manage any potential worsening symptoms after GLP-1 RA initiation

Escalation to an Appropriate Dose

Initiation with gradual dose escalation

- Follow the gradual dose escalation strategy recommended in the GLP-1 RA prescribing information
- Consider slower dose escalation for patients reporting challenges with GI symptoms in the first few weeks of treatment

If patient presents with GI adverse events … (continued next page)

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Applying the "3Es" to Manage GI Adverse Events of GLP-1 RAs[1]

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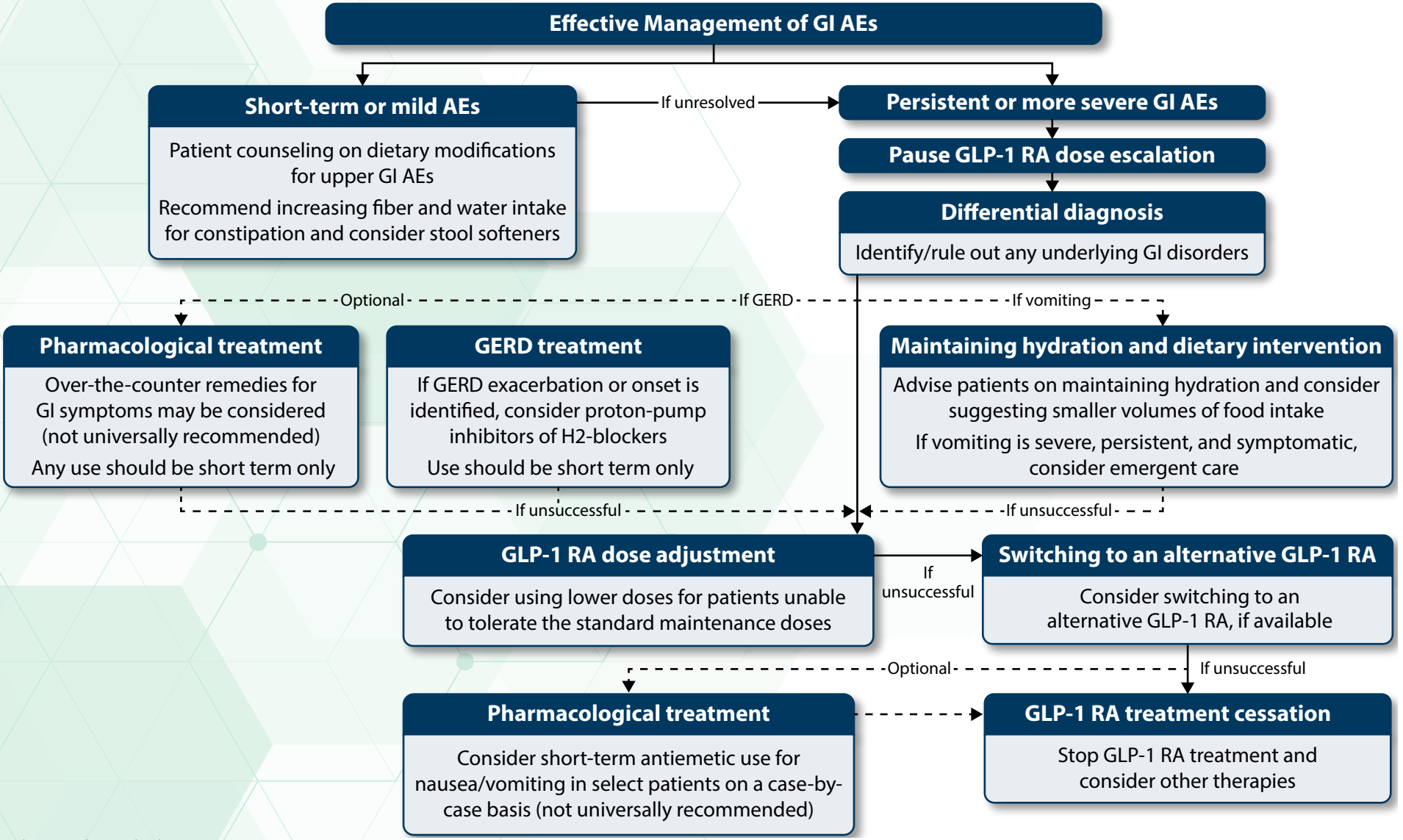
The Final E: Effective Management



1. Wharton S et al. *Postgrad Med*. 2022;134:1,14-19.