Scoring Comprehensive T2DM Management Goals

Examining the Multifaceted Effects of GLP-1 Receptor Agonists

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Getting in the Game

Treating T2DM and Beyond With GLP-1 RAs

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2022 Fast Facts on Diabetes in the United States[1]

Diabetes

- Total: 37.3 million people (11.3%) have diabetes in the United States

Diagnosed:	Undiagnosed:
28.7 million people, including 28.5 million adults	8.5 million people (23% of adults)

Prediabetes

- Total: 96 million people aged 18 years or older (38% of adults)
- 65 years or older: 26.4 million people (48.8% of older adults)

1. https://www.cdc.gov/diabetes/data/statistics-report/index.html.

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Prediabetes

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- 65 years or older: 26.4 million people (48.8% of older adults)

Currently, at least 1 out of 3 people will develop the disease in their lifetime

Projected prevalence of diabetes is 55 million individuals by 2060

1. https://www.cdc.gov/diabetes/data/statistics-report/index.html. 2. Mohebi R et al. *J Am Coll Cardiol*. 2022;80:565-578..

Recommended Screening Methods and Classification[1,2]

Glycemic Status	Fasting Glucose, mg/dL	2-h Glucose, mg/dL	A1C, %
Normal	<100	<140	<5.7
Prediabetes	100-125	140-199	5.7-6.4
Diabetes	≥126	≥200	≥6.5

- Screen if the patient is aged 35 to 70 years and has excess weight or obesity
- Screen at younger ages in patients from populations at disproportionate risk
- Repeat testing every 3 years if results are normal

1. USPSTF. *JAMA*. 2021;326:736-743. 2. ElSayed NA et al. *Diabetes Care*. 2023;46(suppl 1):S19-S40.

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Overview of T2DM-Related Macrovascular and Microvascular Complications[1]

Coronary heart disease

Prevalence: 14%-21%

Most frequently reported form of CVD and most lethal one

Risk of death from CHD is higher in women than in men; HR = 1.81 (95% CI, 1.27-2.59) vs HR = 1.48 (95% CI, 1.10-1.99)

Heart failure

Prevalence: 19%-26%

Second most common initial manifestation of CVD in T2DM

Risk of HF is up to 2-fold in men and 5-fold in women

Peripheral artery disease

Prevalence: 16%-29%

Most common initial manifestation of CVD in T2DM

Prevalence is 1.8-fold higher in women compared with men

Stroke

Prevalence: 8%-12%

Second most frequent cause of death in patients with T2DM after CHD

Prevalence is similar in men and women

Retinopathy

Prevalence: 34%

Most common microvascular complication of diabetes; responsible for 2.6% of all cases of blindness worldwide

Prevalence rates are higher in T1DM compared with T2DM (77.3% vs 25.2%)

Neuropathy

Cardiac autonomic neuropathy

Prevalence: 31%-73% in people with T2DM

No difference in prevalence between men and women

Nephropathy

Prevalence: 29%-61%

Leading cause of end-stage renal disease in the adult population worldwide

Female sex is a risk factor for nephropathy in T2DM

1. Dal Canto E et al. *Eur J Prev Cardiol*. 2019;26(suppl 2):25-32.

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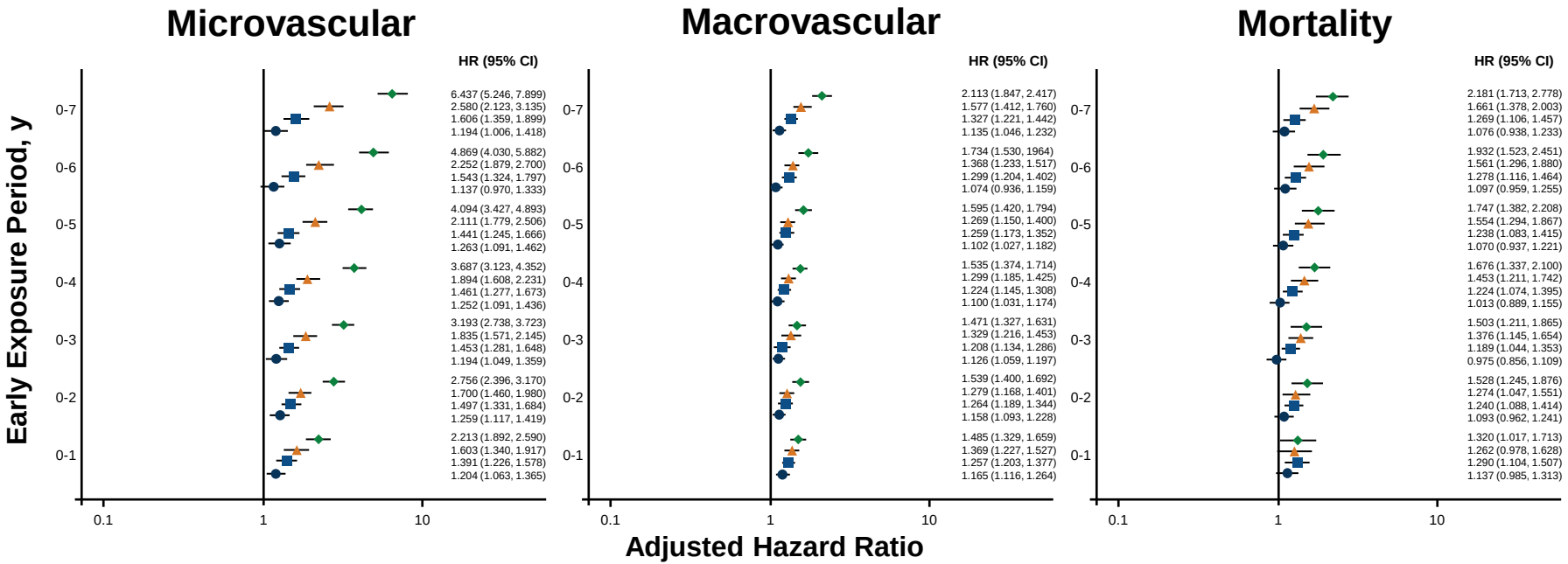
Early Glycemic Control Matters[1]



- ● A1C 6.5% to <7.0% (48 to <53 mmol/mol)
- ■ A1C 7.0% to <8.0% (53 to <64 mmol/mol)
- ▲ A1C 8.0% to <9.0% (64 to <75 mmol/mol)
- ◆ A1C 9.0% (>75 mmol/mol)

1. Laiteerapong N et al. *Diabetes Care.* 2019;42:416-426.

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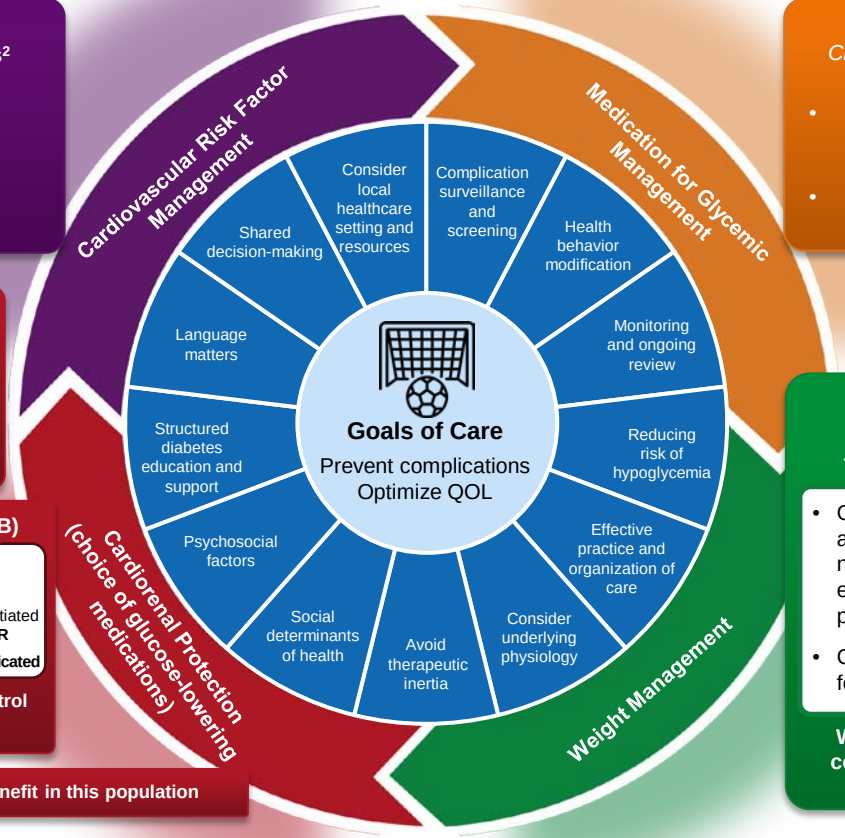
Holistic Person-Centered Approach to T2DM Management[1]



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

+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 control needed, consider combination SGLT2i/GLP-RA

+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 m^2; 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 control needed, consider combination SGLT2i/GLP-RA

+HF: SGLT2i with proven HF benefit in this population

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

1. Davies MJ et al. Diabetes Care. 2022;45:2753-2786. 2. ADA Professional Practice Committee. Diabetes Care. 2022;45:S144-S174

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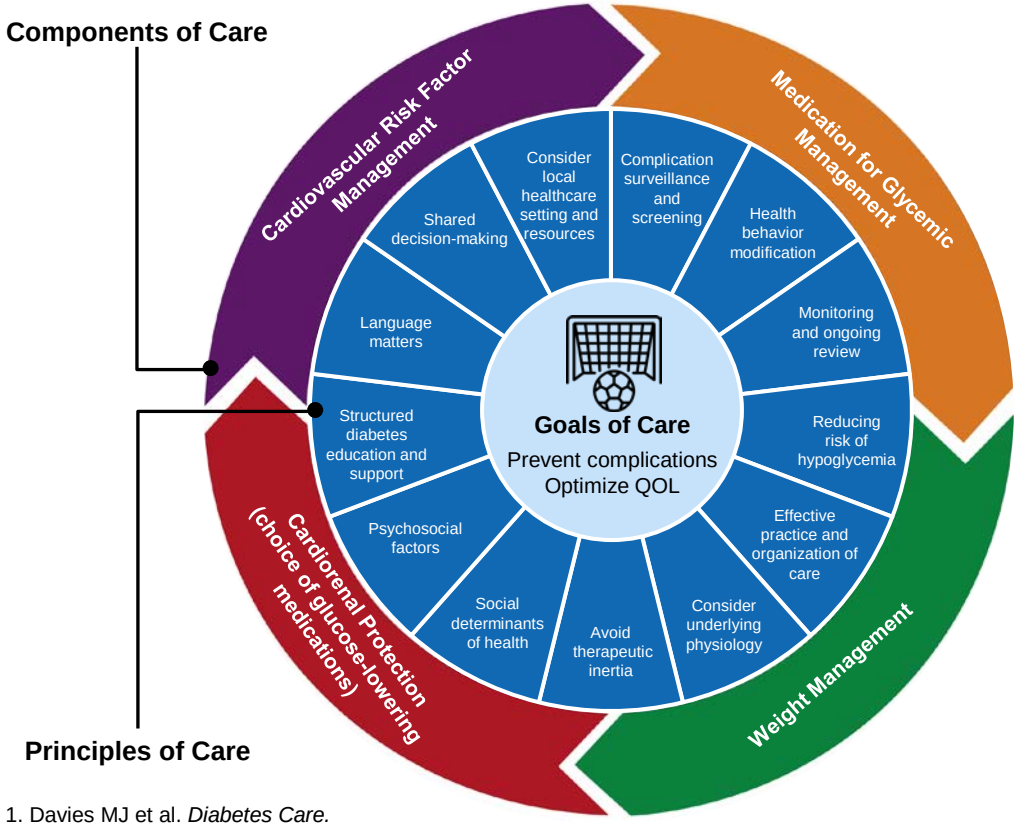
Holistic Person-Centered Approach to T2DM Management[1]



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

- CV risk factor screening and surveillance: **history, physical, and ECG NT-proBNP, BNP, or hs-cTn[3]**
- BP lowering: **target <130/80 mmHg**
- Lipid lowering: **statins**
- Antithrombotic agent: **indicated for secondary prevention**
- Smoking cessation: **for all**

1. Davies MJ et al. *Diabetes Care.* 2022;45:2753-2786. 2. ADA Professional Practice Committee. *Diabetes Care*. 2022;45:S144-S174. 3. Pop-Busui et al. *Diabetes Care*. 2022;45:1670-1690.

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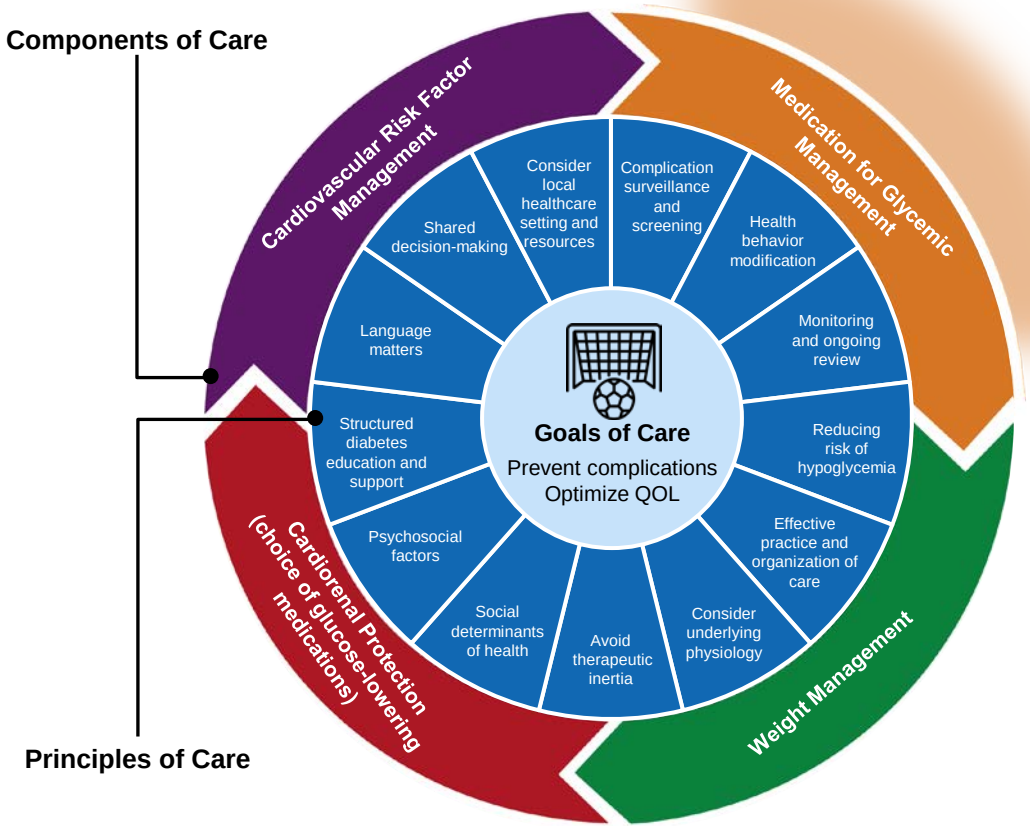

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Note that metformin monotherapy is no longer the only first-line treatment

1. Davies MJ et al. *Diabetes Care.* 2022;45:2753-2786. 2. ElSayed NA et al. *Diabetes Care.* 2023;46:S140-S157.

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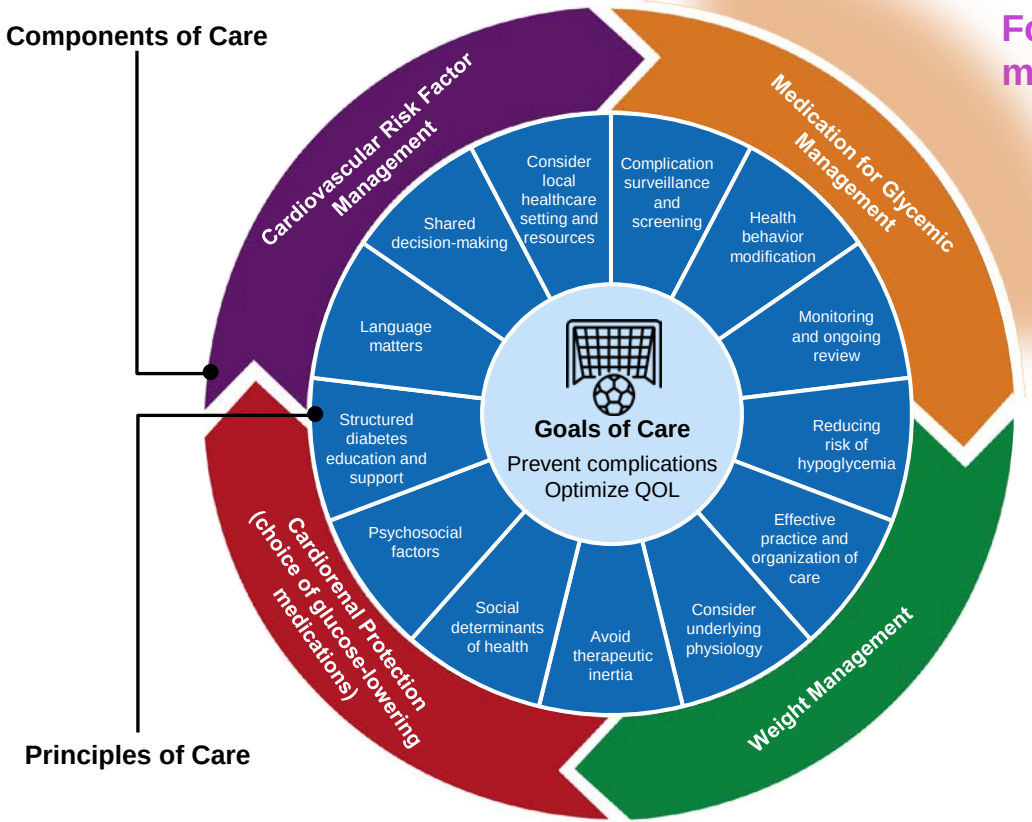

For some patients, this may include GLP-1 RAs

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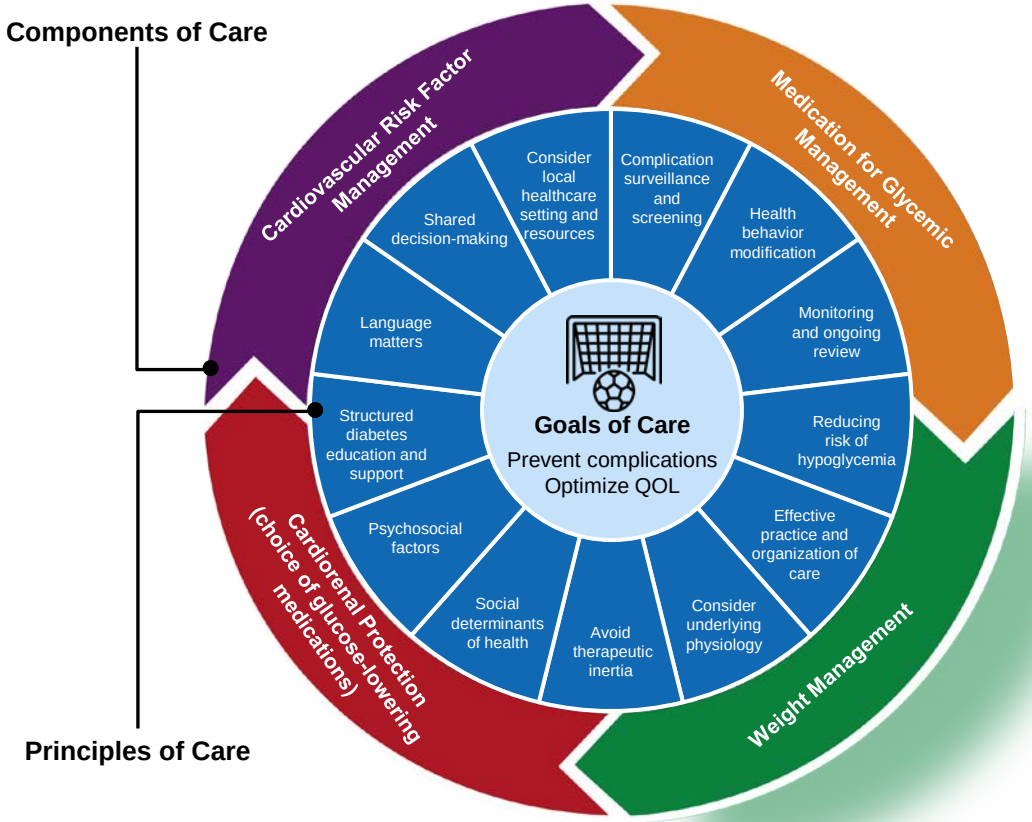

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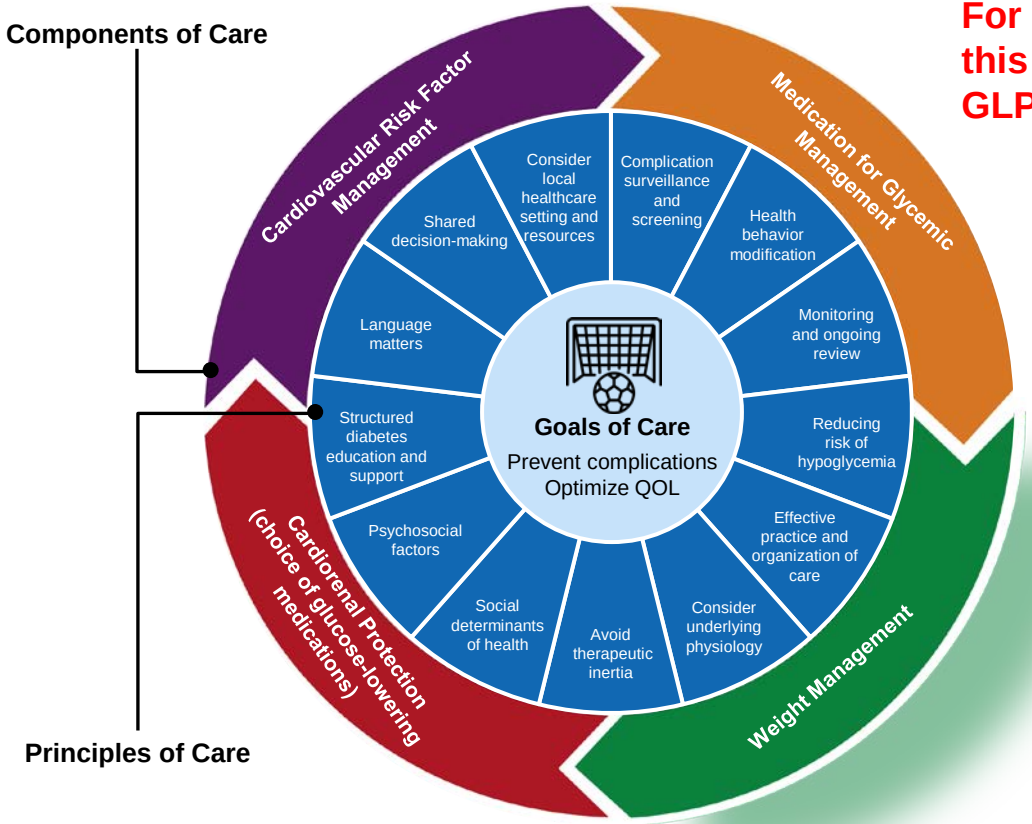

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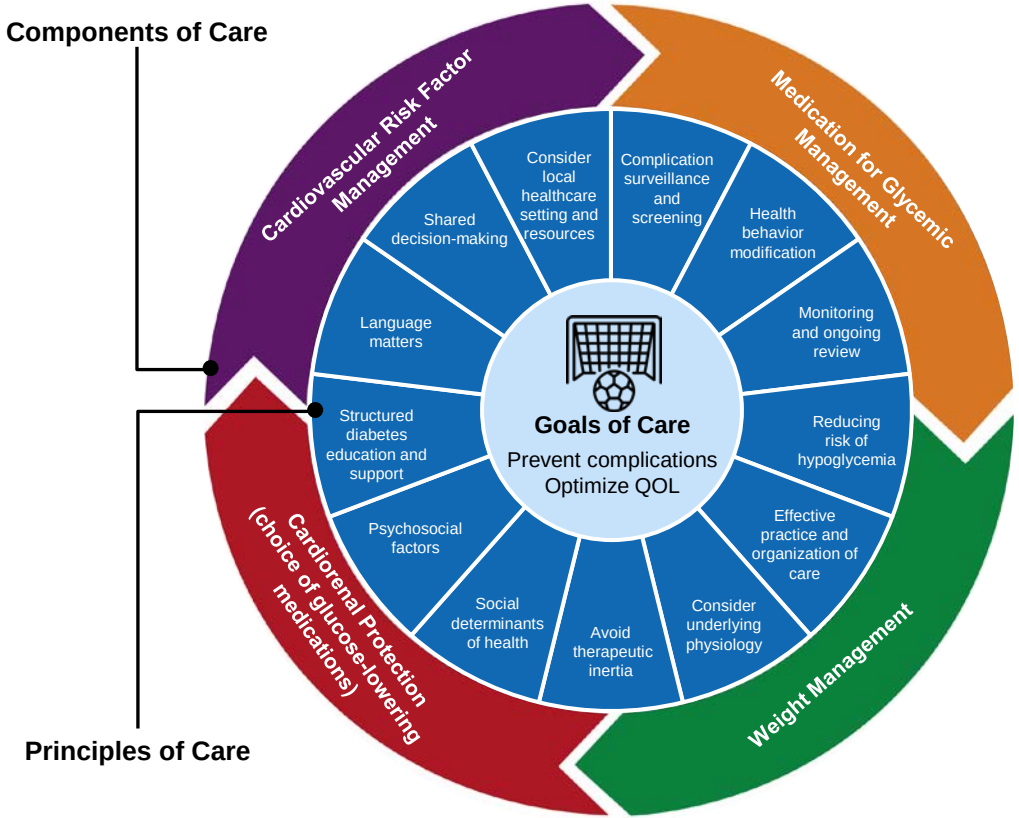

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Preferably

SGLT2i with primary evidence of reducing CKD progression

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- - - - - - OR - - - - - -

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SGLT2i with proven HF benefit in this population

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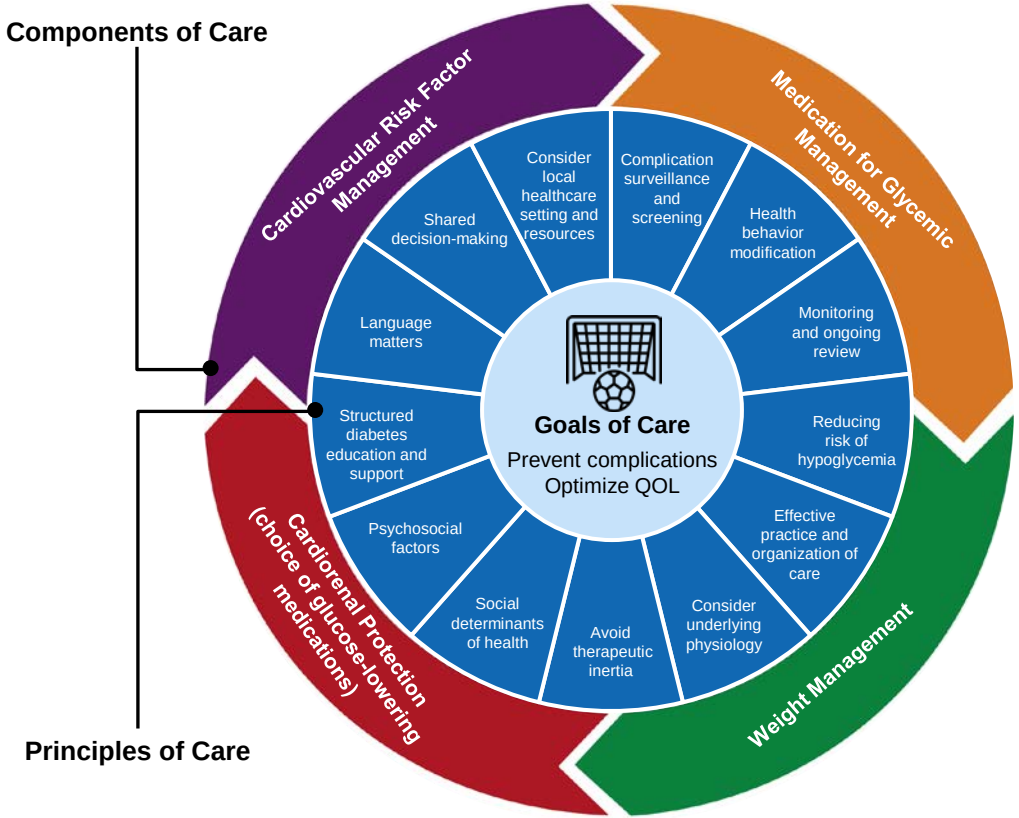

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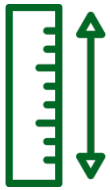
Therapeutic Benefits of GLP-1 RAs in T2DM[1,2]



High efficacy

Potential for weight loss

Reduces systolic blood pressure

Low intrinsic risk of hypoglycemia

No need for routine blood glucose monitoring

Dosing for most is independent of meals

1. Nauck M. *Diabetes Obes Metab*. 2016;18:203-216. 2. https://www.accessdata.fda.gov/scripts/cder/daf/.

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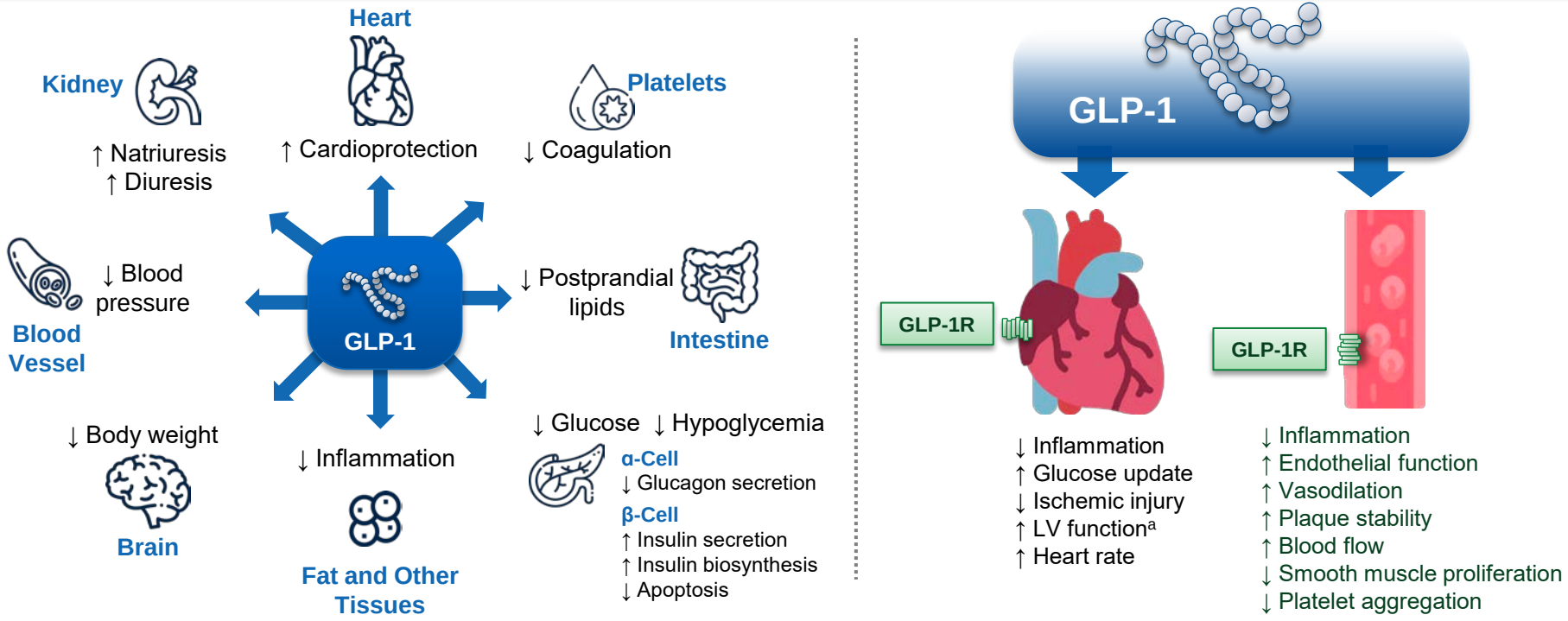
The Optimistic Octet: GLP-1 Has Broad Activity[1,2]



Beneficial effects on A1C, blood pressure, and weight only partly explain CV effects

[a] Benefits have been observed in post-MI patients, but not patients with HF.

1. Drucker DJ. *Cell Metab.* 2016;24:15-30. 2. Wong SY et al. *Cardiovasc Drugs Ther.* 2022 Jul 12. Online ahead of print.

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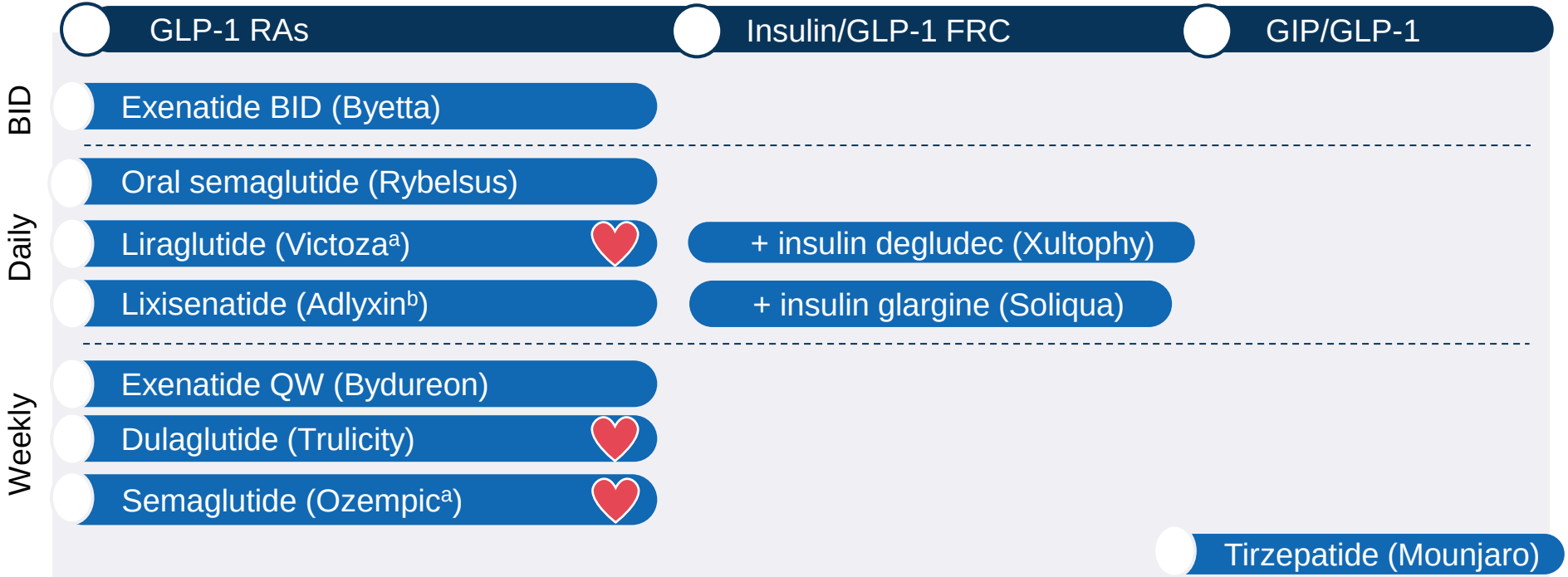
The GLP-1 Receptor Agonist Landscape[1,2]



♥ Indicated for CV risk reduction in T2DM irrespective of glycemia.

[a] At higher doses, these agents are also indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of 30 kg/m^2 or greater (obesity) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (eg, hypertension, T2DM, or dyslipidemia). [b] Discontinued as of January 2023.

1. https://www.accessdata.fda.gov/scripts/cder/daf/. 2. https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-withdrawls/drugwithdrawal_adlyxin_2023-0117.pdf.

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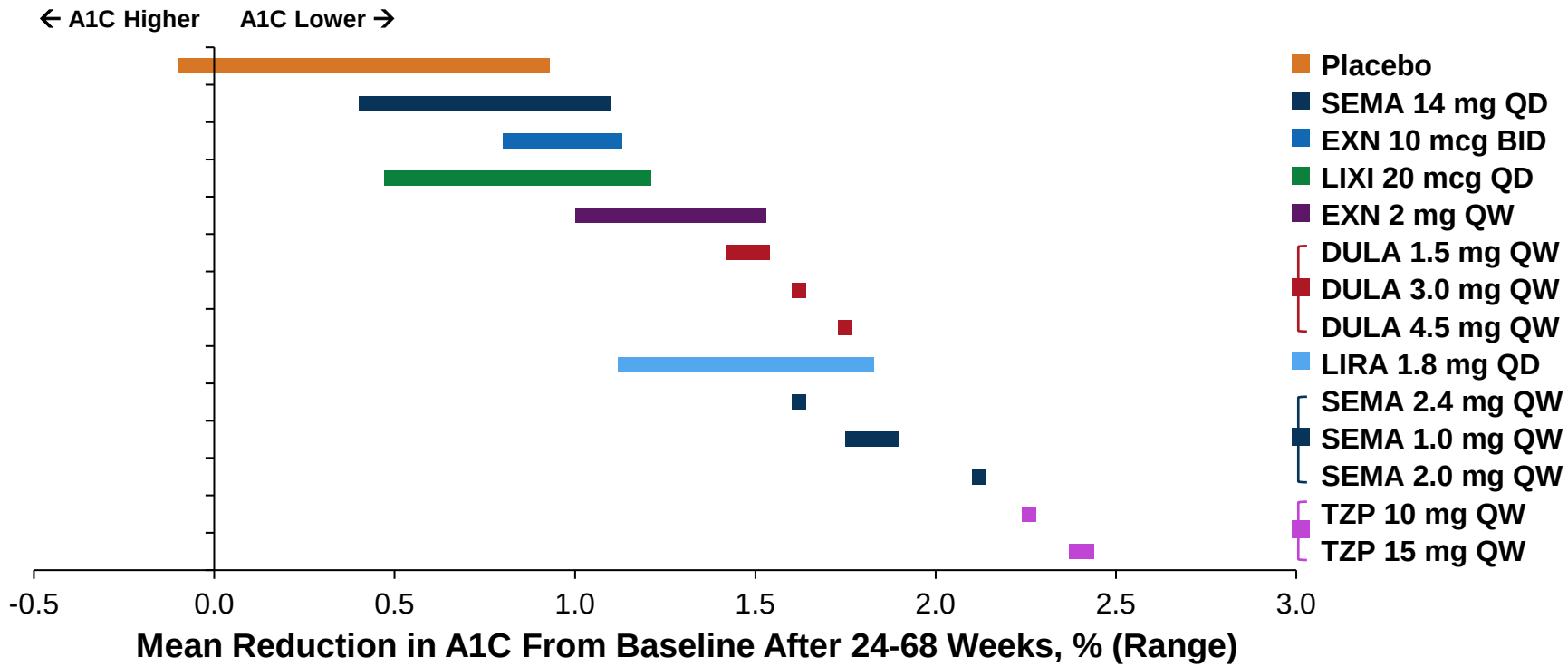
GLP-1 RAs at High Doses: A1C Reduction When Added to One or Two Oral Agents[1-7,a,b]



[a] Systematic review of 41 randomized controlled clinical trials. [b] Data for dulaglutide reported at 36 weeks; data for semaglutide 1.0-2.0 mg reported at up to 40 weeks and for semaglutide 2.4 mg at 68 weeks; data for tirzepatide reported at up to 52 weeks. Treatment policy estimands are reported.

1. Witkowski M et al. *Diabetes Ther*. 2018;9:1149-1167. 2. Morales J et al. *Postgrad Med*. 2020;132:687-696. 3. Frías JP et al. *Diabetes Care*. 2021;44:765-773. 4. Frías JP et al. *Lancet Diabetes Endocrinol*. 2021;9:563-574. 5. Frías JP et al. *N Engl J Med*. 2021;385:503-515. 6. Ludvik B et al. *Lancet*. 2021;398:583-598. 7. Davies M et al. *Lancet*. 2021;397:971-984.

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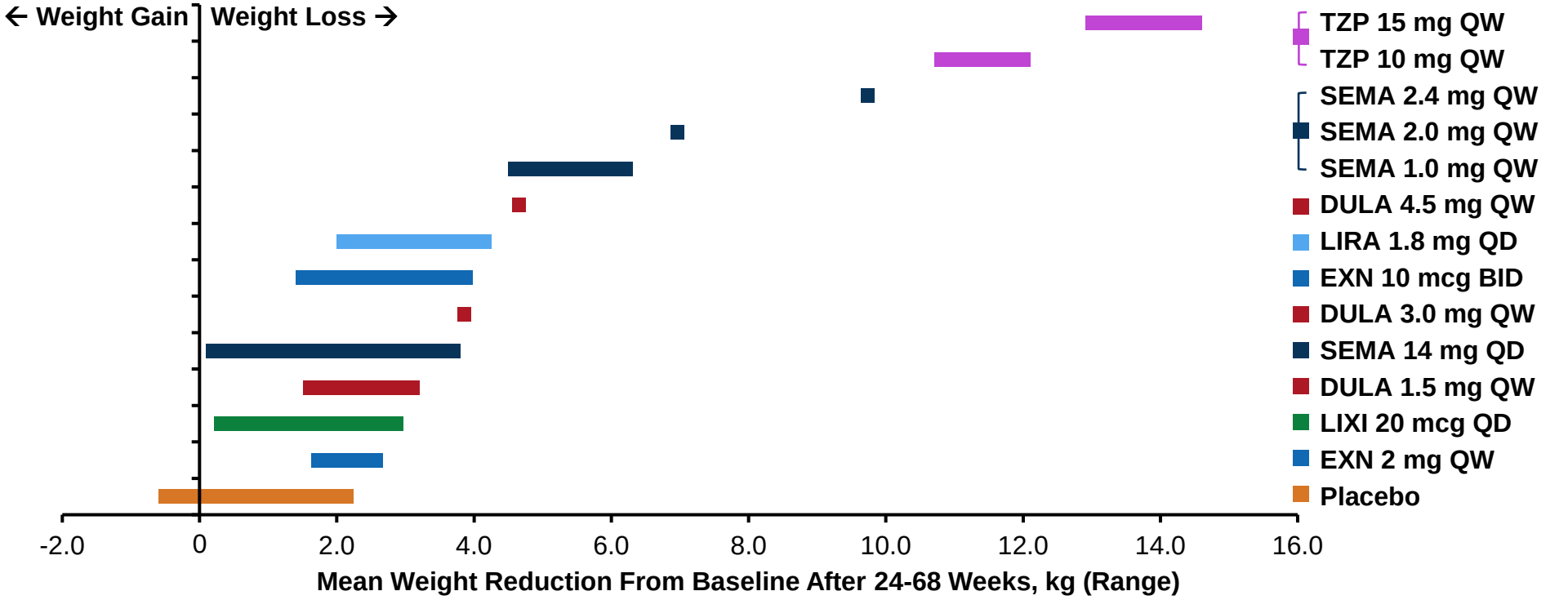
GLP-1 RAs at High Doses: Weight Effects When Added to One or Two Oral Agents[1-7,a-c]



[a] Systematic review of 41 RCTs of injectable agents; DULA 1.5 mg and SEMA 1.0 mg were the maximum doses available at the time this analysis was performed. [b] Systematic review of seven RCTs of oral SEMA. [c] Data for DULA 3.0 and 4.5 mg reported at 36 weeks; data for SEMA 2.0 mg reported at up to 40 weeks; data for TZP reported at up to 52 weeks. Treatment policy estimands are reported.

1. Witkowski M et al. *Diabetes Ther*. 2018;9:1149-1167. 2. Morales J et al. *Postgrad Med*. 2020;132:687-696. 3. Frías JP et al. *Diabetes Care*. 2021;44:765-773. 4. Frías JP et al. *Lancet Diabetes Endocrinol*. 2021;9:563-574. 5. Frías JP et al. *N Engl J Med*. 2021;385:503-515. 6. Ludvik B et al. *Lancet*. 2021;398:583-598. 7. Davies M et al. *Lancet.* 2021;397:971-984.

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Overview: GLP-1 Receptor Agonists

- Excellent improvement in A1C
  - Head-to-head studies versus other classes suggest similar or greater efficacy of GLP-1 receptor agonists, even as compared to insulin
- Moderate weight loss
  - ~5-15% over 6-12 months (generally less in people with diabetes)
- Modest improvement in blood pressure
- No intrinsic increased risk of hypoglycemia
- Adverse events largely gastrointestinal
- Safety considerations (gallbladder events, renal failure, pancreatitis, medullary thyroid cancer, pancreatic cancer)

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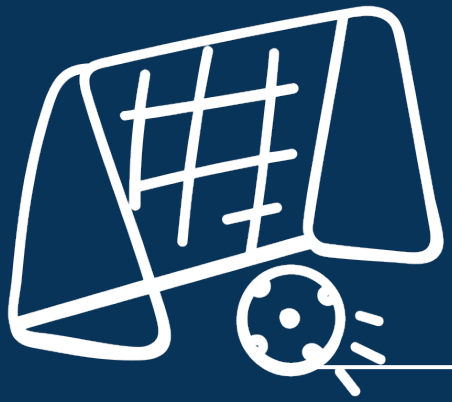

Check the Scoreboard
A Comparative Look at the GLP-1 RAs

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Joshua, a Man Aged 45 Years

Joshua

- BMI: 32.3 kg/m^2; height: 70 inches (178 cm); weight 235 lb (107 kg)
- A1C: 7.3%; BP: 142/87 mmHg; eGFR and uACR WNL
- TC: 201 mg/dL; LDL-C: 145 mg/dL; HDL-C: 40 mg/dL; TG: 80 mg/dL
- Medical history: Previously overweight, prediabetes, atrial fibrillation, DVT (10 years ago)
- Current medications
  - None

Visit Notes

- Electrician, works 60+ hours/week
- Divorced, lives alone
- Frequent fast food meals between clients
- At previous physical, 14 months ago
  - BMI was 29.5 kg/m^2
  - A1C was 6.4%
  - BP was 135/72 mmHg
  - TC was 185 mg/dL

GLP-1 RAs Are Not Exactly Alike[1,2]

Injectable Formulations						
Pharmacokinetics		Structure			Molecular Size	
Short-acting	**Long-acting**	**Exendin-4–based**	**GLP-1–based**	**GIP/GLP-1–based**	**Small**	**Large**
Exenatide BID	Exenatide QW	Exenatide BID	Liraglutide	Tirzepatide	Exenatide BID	Dulaglutide
Lixisenatide	Liraglutide	Exenatide QW	Semaglutide		Exenatide QW	
	Semaglutide	Lixisenatide	Dulaglutide		Liraglutide	
	Dulaglutide				Lixisenatide	
	Tirzepatide				Semaglutide	
					Tirzepatide	
Short-acting GLP-1 RAs retain their effect on gastric emptying (and PPG), while long-acting GLP-1 RAs seem to have more pronounced effects on FPG and A1C		Exendin-based GLP-1 RAs seem to give rise to the formation of antibodies to a higher degree than GLP-1–based; clinical implication uncertain		First GIP/GLP-1 dual agonist	Large GLP-1 RAs may not be able to penetrate into the brain to the same extent as the smaller ones, possibly affecting appetite signaling differently	

Oral Formulation		
Product	**Molecule**	**Route**
Oral semaglutide	Semaglutide	Oral with carrier molecule

1. Nauck MA et al. *Mol Metab*. 2021;46:101102. 2. Collins L, Costello RA. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/books/NBK551568/.

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

Outcome	HR (95% CI)	NNT	*P*	Heterogeneity
MACE-3	0.86 (0.80-0.93)	65 (45-30)	< .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 (158-1422)	.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

1. Sattar N et al. *Lancet Diabetes Endocrinol*. 2021;9:653-662.

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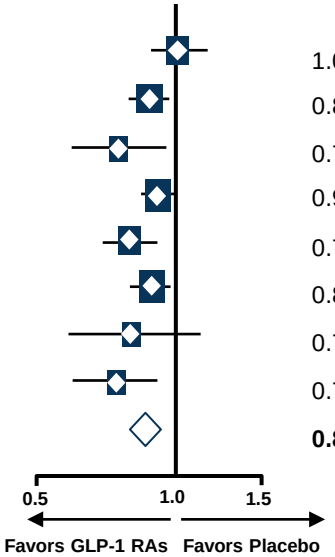
Effect of GLP-1 RAs on 3-Point MACE: Results From CVOTs[1,a]

Agent	Three-point MACE	GLP-1 RA, n/N (%)	Placebo, n/N (%)	HR (95% CI)	NNT (95% CI)	*P*
Lixisenatide	ELIXA	400/3,034 (13)	392/3,034 (13)	1.02 (0.89-1.17)		.78
Liraglutide	LEADER	608/4,668 (13)	694/4,672 (15)	0.87 (0.78-0.97)		.01
Semaglutide	SUSTAIN-6	108/1,648 (7)	146/1,649 (9)	0.74 (0.58-0.95)		.016
Exenatide	EXSCEL	839/7,356 (11)	905/7,396 (12)	0.91 (0.83-1.00)		.061
Albiglutide	Harmony Outcomes	338/4,731 (7)	428/4,732 (9)	0.78 (0.68-0.90)		.0006
Dulaglutide	REWIND	594/4,949 (12)	663/4,952 (13)	0.88 (0.79-0.99)		.026
Semaglutide PO	PIONEER 6	61/1,591 (4)	76/1,592 (5)	0.79 (0.57-1.11)		.17
Efpeglenatide	AMPLITUDE-O	189/2,717 (7)	125/1,359 (9)	0.73 (0.58-0.92)		.0069
	Subtotal (I^2 = 44.5%, *P* = .082)			**0.86 (0.80-0.93)**	**65 (45-130)**	**<.0001**



[a] Weights are from random effects analysis. In addition to primary CV outcome results papers, data were extracted from additional sources. AMPLITUDE-O data were provided by the authors. Three-point MACE consisted of CV death, MI, and stroke. NNTs were calculated over a weighted average median follow-up of 3.0 years. *P* values are for superiority. Red text denotes approved, currently marketed agents with statistically significant reductions; may not be indicated for CV risk reduction.

1. Sattar N et al. *Lancet Diabetes Endocrinol*. 2021;9:653-662.

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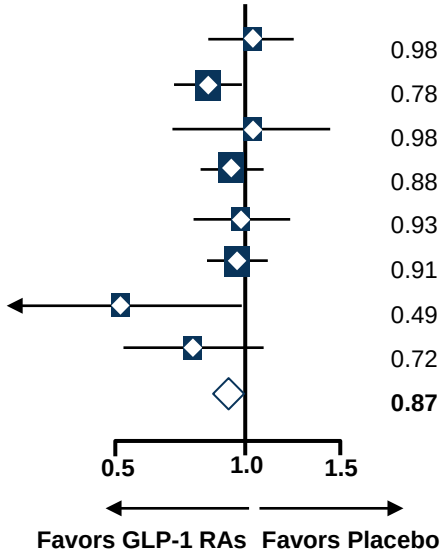
Effect of GLP-1 RAs on CV Death: Results From CVOTs[1,a]

Agent	CV death	GLP-1 RA, n/N (%)	Placebo, n/N (%)	HR (95% CI)	NNT (95% CI)	*P*
Lixisenatide	ELIXA	**156/3,034 (5)**	**158/3,034 (5)**	0.98 (0.78-1.22)		.85
Liraglutide	LEADER	219/4,668 (5)	278/4,672 (6)	0.78 (0.66-0.93)		.007
Semaglutide	SUSTAIN-6	44/1,648 (3)	46/1,649 (3)	0.98 (0.65-1.48)		.92
Exenatide	EXSCEL	340/7,356 (5)	383/7,396 (5)	0.88 (0.76-1.02)		.096
Albiglutide	Harmony Outcomes	122/4,731 (3)	130/4,732 (3)	0.93 (0.73-1.19)		.58
Dulaglutide	REWIND	317/4,949 (6)	346/4,952 (7)	0.91 (0.78-1.06)		.21
Semaglutide PO	PIONEER 6	15/1,591 (1)	30/1,592 (2)	0.49 (0.27-0.92)		.021
Efpeglenatide	AMPLITUDE-O	75/2,717 (3)	50/1,359 (4)	0.72 (0.50-1.03)		.07
	Subtotal (I^2 = 13.4%, *P* = .33)			**0.87 (0.80-0.94)**	**163 (103-353)**	**.0010**



[a] Weights are from random effects analysis. In addition to primary CV outcome results papers, data were extracted from additional sources. AMPLITUDE-O data were provided by the authors. NNTs were calculated over a weighted average median follow-up of 3.0 years. *P* values are for superiority. Red text denotes approved, currently marketed agents with statistically significant reductions; may not be indicated for CV risk reduction.

1. Sattar N et al. *Lancet Diabetes Endocrinol*. 2021;9:653-662.

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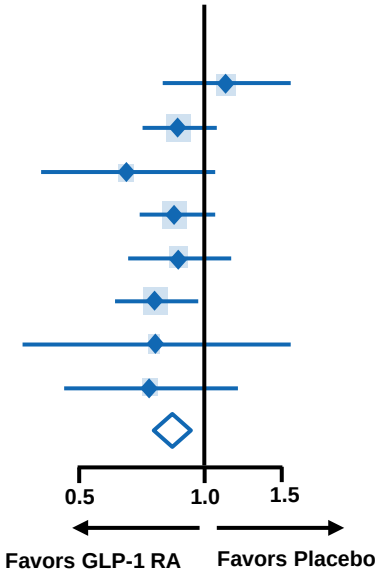
Effect of GLP-1 RAs on Stroke Outcomes: Results From CVOTs[1,2,a]

Agent		GLP-1 RA, n/N (%)	Placebo, n/N (%)	HR (95% CI)	NNT (95% CI)	*P*
	Fatal or nonfatal stroke					
Lixisenatide	ELIXA	67/3,034 (2)	60/3,034 (2)	1.12 (0.79-1.58)		.54
Liraglutide	LEADER	173/4,668 (4)	199/4,672 (4)	0.86 (0.71-1.06)		.16
Semaglutide[b]	SUSTAIN-6	30/1,648 (2)	46/1,649 (3)	0.65 (0.41-1.03)		.066
Exenatide	EXSCEL	187/7,356 (3)	218/7,396 (3)	0.85 (0.70-1.03)		.095
Albiglutide	Harmony Outcomes	94/4,731 (2)	108/4,732 (2)	0.86 (0.66-1.14)		.030
Dulaglutide	REWIND	158/4,949 (3)	205/4,952 (4)	0.76 (0.62-0.94)		.010
Semaglutide PO	PIONEER 6	13/1,591 (1)	17/1,592 (1)	0.76 (0.37-1.56)		.43
Efpeglenatide	AMPLITUDE-O	47/2,717 (2)	31/1,359 (2)	0.74 (0.47-1.17)		.19
	Subtotal (I^2 = 0.0%, *P* = .64)			**0.83 (0.76-0.92)**	**198 (140-421)**	**.0002**



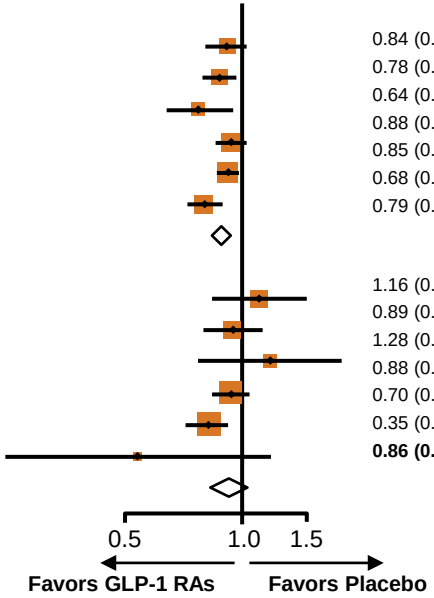
[a] Fatal or nonfatal stroke. Weights are from random effects analysis. In addition to primary cardiovascular outcome results papers, data were extracted from additional sources. AMPLITUDE-O data were provided by the authors. NNTs were calculated over a weighted average median follow-up of 3.0 years. *P* values are for superiority. Red text denotes approved, currently marketed agents with statistically significant reductions; may not be indicated for CV risk reduction. [b] The ASSET study will investigate the effect of semaglutide on clinical outcomes following an acute ischemic stroke (NCT05630586).

1. Sattar N et al. *Lancet Diabetes Endocrinol*. 2021;9:653-662. 2. Wei J et al. *Front Endocrinol.* 2022;13:1007980.

PeerView.com

Effect of GLP-1 RAs on Kidney Outcomes: Results From CVOTs[1,a]

	GLP-1 RA, n/N (%)	Placebo, n/N (%)	HR (95% CI)	NNT (95% CI)	*P*
Composite Kidney Outcome Including Macroalbuminuria					
Lixisenatide (ELIXA)	172/2,647 (6)	203/2,639 (8)	0.84 (0.68-1.02)		.083
Liraglutide (LEADER)	268/4,668 (6)	337/4,672 (7)	0.78 (0.67-0.92)		.003
Semaglutide (SUSTAIN-6)	62/1,648 (4)	100/1,649 (6)	0.64 (0.46-0.88)		.005
Exenatide QW (EXSCEL)	366/6,256 (6)	407/6,222 (7)	0.88 (0.76-1.01)		.065
Dulaglutide (REWIND)	848/4,949 (17)	970/4,952 (20)	0.85 (0.77-0.93)		.0004
Efpeglenatide (AMPLITUDE-O)[b]	353/2,717 (13)	250/1,359 (18)	0.68 (0.57-0.79)		<.0001
Subtotal (I^2 = 47.5%, *P* = .090)			0.79 (0.73-0.87)	**47 (37 to 77)**	<.0001
Worsening kidney function					
Lixisenatide (ELIXA)	41/3,031 (1)	35/3,032 (1)	1.16 (0.74-1.83)		.513
Liraglutide (LEADER)	87/4,668 (2)	97/4,672 (2)	0.89 (0.67-1.19)		.43
Semaglutide (SUSTAIN-6)	18/1,648 (1)	14/1,649 (1)	1.28 (0.64-2.58)		.48
Exenatide QW (EXSCEL)	246/6,456 (4)	273/6,458 (4)	0.88 (0.74-1.05)		.16
Dulaglutide (REWIND)	169/4,949 (3)	237/4,952 (5)	0.70 (0.57-0.85)		.0004
Efpeglenatide (AMPLITUDE-O)[b]	7/2,717 (<1)	7/1,359 (1)	0.35 (0.10-1.27)		.11
Subtotal (I^2 = 43.0%, *P* = .12)			**0.86 (0.72-1.02)**	**241 (120 to -1,694)[c]**	**.089**



Macro-albuminuria risk reduced 21%

Worsening kidney function reduced 14%

- **Composite kidney outcome**: development of macroalbuminuria, doubling of sCr or at least 40% decline in eGFR, kidney replacement therapy, or death due to kidney disease; for ELIXA, data are for new-onset macroalbuminuria alone.
- **Worsening of kidney function**: either doubling of sCr or at least 40% decline in eGFR; for EXSCEL, the worsening of kidney function outcome included kidney replacement therapy, or death due to kidney disease

[a] GLP-1 RAs are not currently indicated for reduction of kidney risks; red text denotes agents with statistically significant reductions in kidney outcomes. [b] Not approved by US FDA. [c] Negative value indicates a number needed to harm.

1. Sattar N et al. *Lancet Diabetes Endocrinol*. 2021;9:653-662.

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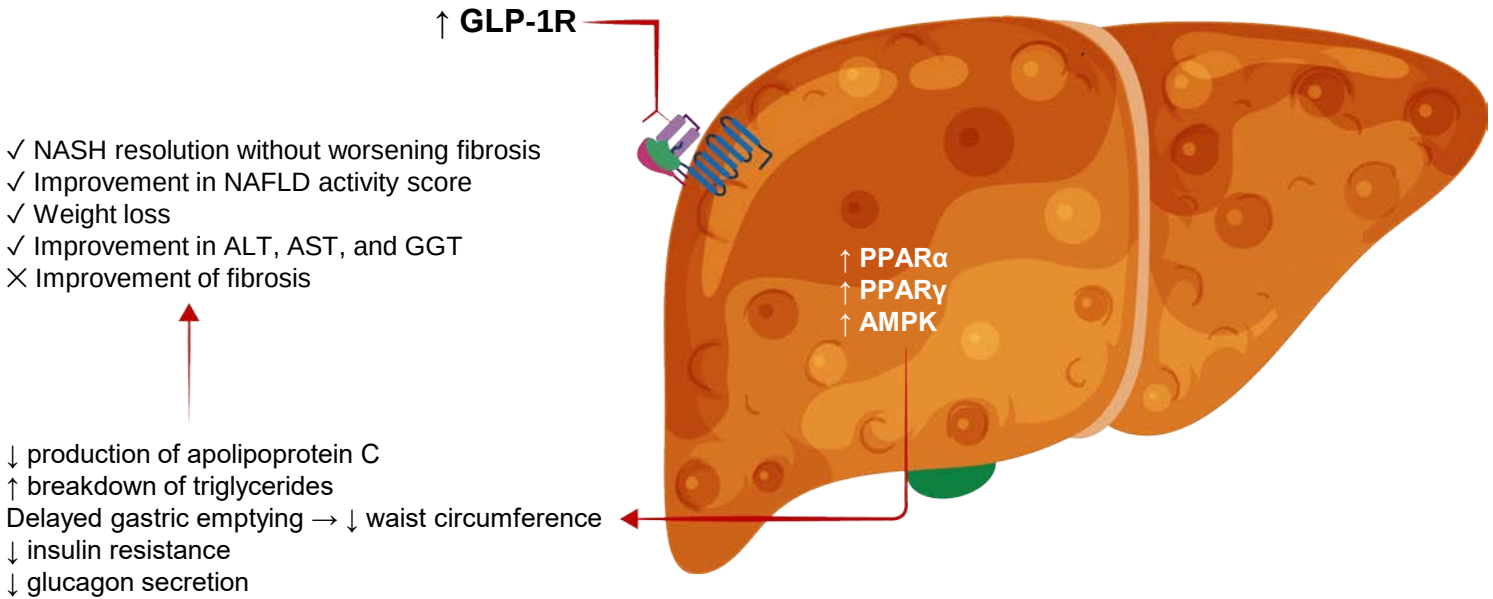
Effect of GLP-1 RAs on NAFLD and NASH[1-4]



- Dulaglutide, exenatide, liraglutide, semaglutide, and tirzepatide have been evaluated in people with NAFLD and have favorable effects on various measures of liver fat, insulin resistance, and body mass
- Currently, no GLP-1 RA is indicated for the treatment of NAFLD or NASH

1. Ahmed NR et al. *Cureus*. 2022;14:e24829. 2. Gu Y et al. *Front Pharmacol.* 2023;14:1102792. 3. Loomba R et al. *Lancet Gastroenterol Hepatol*. 2023;8:P511-522.
4. Gastaldelli A et al. *Lancet Diabetes Endocrinol*. 2022;10:393-406.

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Other Safety Findings From a Meta-Analysis of GLP-1 RA Trials in T2DM

Adverse Event	Odds Ratio (95% CI)	*P*	Heterogeneity
Severe hypoglycemia[1,a]	0.90 (0.74, 1.10)	.32	Yes
Retinopathy[1,a]	1.07 (0.92, 1.25)	.39	Marginal
Pancreatitis[1,a]	1.02 (0.77, 1.36)	.88	No
Pancreatic cancer[1,a]	0.98 (0.56, 1.70)	.93	No
Gallbladder or biliary diseases[2,b]	1.37 (1.23, 1.52)	< .05	No

[a] Data from CVOTs in patients at high CV risk. [b] Data from meta-analysis of 76 RCTs in various populations with T2DM.

1. Sattar N et al. *Lancet Diabetes Endocrinol*. 2021;9:653-662. 2. He L et al. *JAMA Intern Med*. 2022;182:513-519.

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Case Revisited: Joshua, a Man Aged 45 Years

Joshua

- BMI: 32.3 kg/m^2; height: 70 inches (178 cm); weight 235 lb (107 kg)
- A1C: 7.3%; BP: 142/87 mmHg; eGFR and uACR WNL
- TC: 201 mg/dL; LDL-C: 145 mg/dL; HDL-C: 40 mg/dL; TG: 80 mg/dL
- Medical history: Previously overweight, prediabetes, atrial fibrillation, DVT (10 years ago)
- Current medications
  - None

Visit Notes

- Electrician, works 60+ hours/week
- Divorced, lives alone
- Frequent fast food meals between clients
- At previous physical, 14 months ago
  - BMI was 29.5 kg/m^2
  - A1C was 6.4%
  - BP was 135/72 mmHg
  - TC was 185 mg/dL

ADA guidelines recommend adding metformin, a GLP-1 RA, a high-intensity statin, an ACEi or ARB, and aspirin to address glycemia and cardiovascular risks

1. ElSayed NA et al. *Diabetes Care*. 2023;46(suppl 1):S1-S291.

Knowing the Players

The Ins and Outs of Providing Comprehensive, Patient-Centered Diabetes Care With GLP-1 RAs

PeerView Live

Lynda, a Woman Aged 66 Years

Lynda

- BMI: 36.3 kg/m^2; height: 66 inches (167 cm); weight 225 lb (102 kg)
- A1C: 7.7%; BP: 128/79 mmHg
- TC: 170 mg/dL; LDL-C: 94 mg/dL; HDL-C: 46 mg/dL; TG: 150 mg/dL
- eGFR: 48 mL/min; uACR: 100 mg/g
- Medical history: Obesity, T2DM (8 years), hypertension, hyperlipidemia, atrial fibrillation, CKD, DVT (10 years ago)
- Current medications
  - Metformin, glyburide, DPP-4i, SGLT2i
  - Lisinopril/HCTZ, rosuvastatin
  - Apixaban (CHA_2DS_2-VASc score = 6)

Visit Notes

- "Has her doubts" about her T2DM medications—adherence?
- Fearful of needles
- Worried about further kidney damage

Goals and Targets: Patient Engagement[1]

- Early in the course of therapy, establish goals and targets with the patient
  - Personal and lifestyle
  - Glycemic goals (A1C, FBG)
  - Weight
  - BP
  - LDL
  - Others
- Review at least annually

1. Davies MJ et al. *Diabetes Care*. 2022;45:2753-2786.

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The Path to Successful Management of T2DM[1]

- Shared decision-making
- Provision of diabetes self-management education and support (DSMES)
- Ensure adequate assessment of the social determinants of health as well as engaging support to address them
- Continuous reassessment with a focus on adherence and persistence
- Avoid clinical inertia

1. Davies MJ et al. *Diabetes Care*. 2022;45:2753-2786.

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Personalized Diabetes Care[1,2]

- Improving lifestyle remains the essential element of all glycemic management and requires consistent personalized coaching
- The essence of personalized care is the provider's personal touch and engagement
  - Empathetic, patient-centered shared decision-making and support are critical to achieving optimal outcomes
  - Teach and do not preach!
  - Motivate and do not castigate!
  - The "everything else" of medicine is essential—eye contact, tone of voice, how you explain things

1. Davies MJ et al. *Diabetes Care*. 2022;45:2753-2786. 2. Peyrot M et al. *Diabetes Care*. 2005;28:2673-2679.

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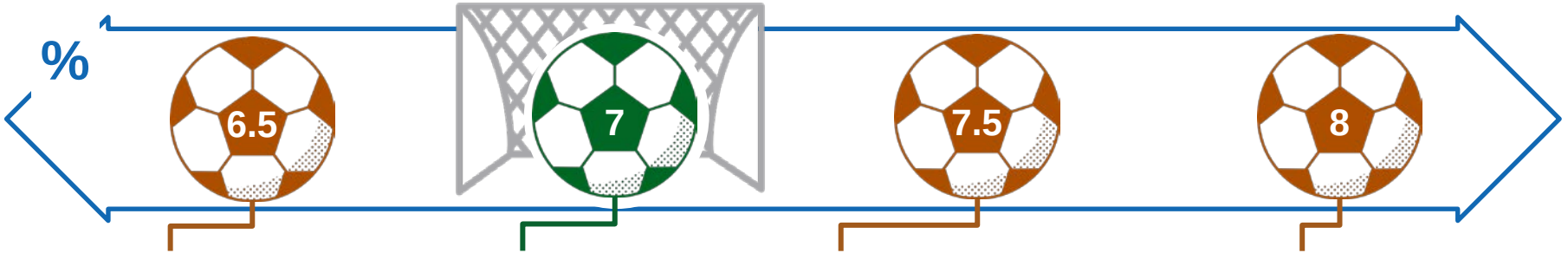
Glycemic Goals[1]



Achievement of **A1C levels lower than the goal of 7%** may be acceptable and even beneficial if it can be achieved safely without significant hypoglycemia or other AEs (based on HCP judgement and patient preference)

A goal for many nonpregnant adults of **A1C <7%** without significant hypoglycemia is appropriate

Healthy older adults with few coexisting chronic illnesses and intact cognitive function/ functional status should have **lower glycemic goals (such as A1C <7.0% to 7.5%)**

Less stringent glycemic goals (such as A1C <8.0%) should be considered in

- Older adults with multiple coexisting chronic illnesses, cognitive impairment, or functional dependence
- People with limited life expectancy or where the harms of treatment are greater than the benefits

HCPs should consider deintensification of therapy if appropriate to reduce the risk of hypoglycemia in patients with inappropriately stringent A1C targets

Glycemic goals for some older adults might reasonably be relaxed as part of individualized care, but **hyperglycemia leading to symptoms or risk of acute hyperglycemia complications should be avoided in all people with diabetes**

1. American Diabetes Association. *Diabetes Care*. 2023;46(suppl 1):S97-S110.

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Alternative Targets[1,2]

	Adiposity-Related Diabetes	Diabetes With CVD	Isolated Hyperglycemia
Major morbidity	Obesity	CVD	Hyperglycemia
Focus	Weight-centric	Cardiocentric	Glucocentric
Goal	>15% weight loss	Proven cardioprotection	A1C <7%
Primary driver	Insulin resistance	Atherosclerosis, inflammation	B-cell dysfunction
Prevalence	40%-70%	20%-40%	10%-20%
Agents to consider	ILT, weight loss drugs, surgery, GLP-1 RA, GIP/GLP-1 RA SGLT2i, metformin	GLP-1 RA with proven benefit, SGLT2i with proven benefit, TZD	Insulin, sulfonylurea, GLP-1 RA, GIP/GLP-1 RA, metformin, SGLT2i, DPP-4i
Secondary targets	Glucose, BP, lipids	Weight, glucose, BP, lipids, coagulation	N/A

1. Lingvay I et al. *Lancet.* 2022;399:394-405. 2. ElSayed NA et al. *Diabetes Care*. 2023;46(suppl 1):S1-S291.

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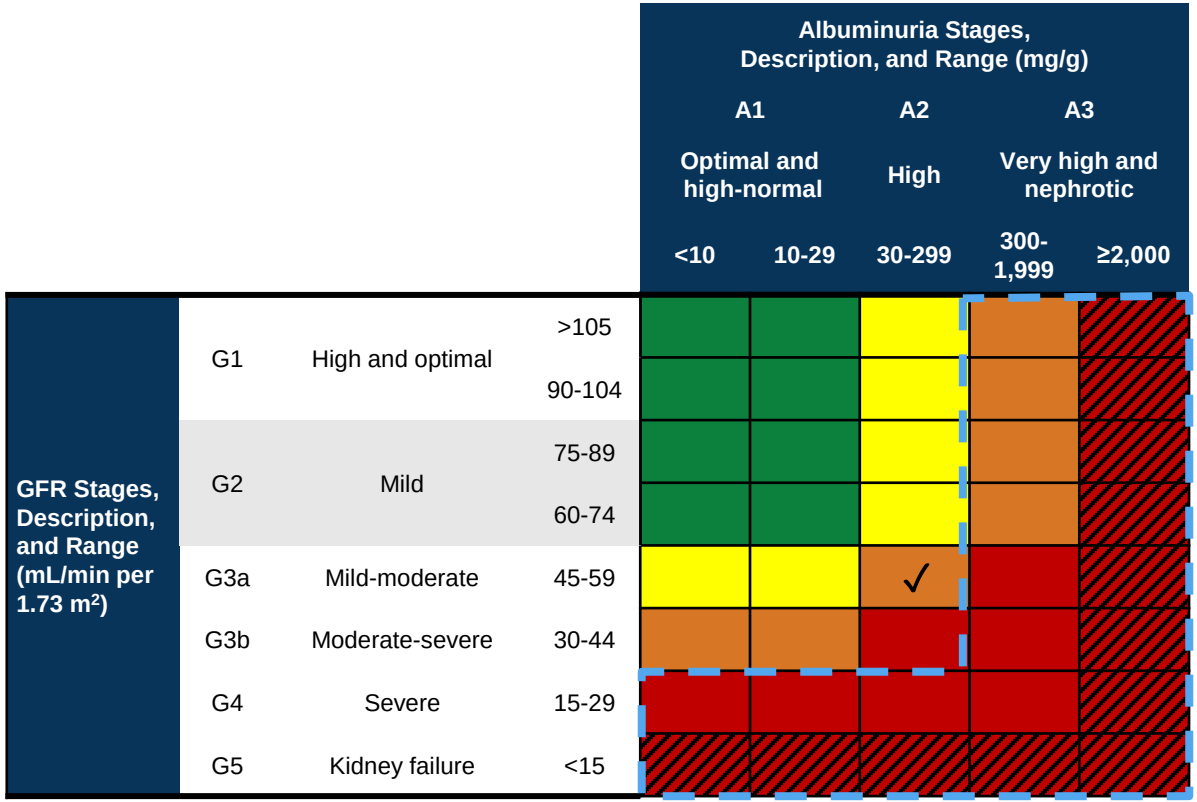
Both GFR and Albuminuria Are Needed to Assess Kidney Function[1,2]



Risk Level; Retest Frequency

- Low (no CKD); 1x/y
- Moderate; 1x/y
- High; 2x/y
- Very high; 3x/y
- Extrapolated high; 4x/y
- Refer to nephrology

1. Levey AS et al. *Kidney Int*. 2010;80:17. 2. ElSayed NA et al. *Diabetes Care*. 2023;46(suppl 1):S1-S291.

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Current Recommendations for Use of GLP-1 RAs by Renal Status[1,2]

Agent	Should Not Be Used/ Not Recommended	Use With Caution	Monitoring
Exenatide BID	CrCl <30	CrCl 30-50, renal transplant, when initiating or escalating dose in patients with renal impairment	–
Lixisenatide	eGFR <15	eGFR 60-89	Monitor renal function in patients with renal impairment reporting severe GI AEs
Liraglutide	–	When initiating or escalating dose in patients with renal impairment	–
Exenatide ER	eGFR <45	–	Monitor patients with mild renal impairment for AEs leading to hypovolemia Monitor closely for AEs leading to hypoglycemia in patients with renal transplant
Dulaglutide	–	–	Monitor renal function in patients with renal impairment reporting severe GI AEs
Semaglutide (injection[a] or oral)	–	–	
Tirzepatide	–	–	

[a] Potential kidney-protective effects of semaglutide in people with T2DM are being evaluated in FLOW.

1. https://www.accessdata.fda.gov/scripts/cder/daf/. 2. Rossing P et al. *Nephrol Dial Transplant*. 2023;38:2041-2051.

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When to Use a GLP-1 RA, When to Use an SGLT2i?[1]

Interventions	OR, 95% CI								
	All Cause Death	CV Death	Nonfatal MI	Nonfatal Stroke	HHF	ESRD[a]	HRQOL Score	Severe Hypoglycemia	Drug-Specific AEs
SGLT2is	0.88 (0.83 to 0.94)	0.86 (0.80 to 0.94)	0.90 (0.82 to 0.98)	0.99 (0.88 to 1.11)	0.66 (0.60 to 0.73)	0.61 (0.55 to 0.67)	0.30 (0.10 to 0.49)	0.90 (0.79 to 1.02)	Genital infection 3.30 (2.88 to 3.78) Amputation 1.27 (1.01 to 1.61) Ketoacidosis 2.07 (1.44 to 2.98)
GLP-1 RAs	0.88 (0.82 to 0.93)	0.87 (0.81 to 0.94)	0.91 (0.85 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 gastrointestinal events 1.97 (1.39 to 2.80)
GIP/GLP-1 RA (tirzepatide)	0.83 (0.43 to 1.44)	1.00 (0.35 to 2.85)	0.69 (0.08 to 6.10)	–	0.63 (0.16 to 0.73)	0.68 (0.09 to 4.84)	0.39 (0.13 to 0.65)	1.13 (0.42 to 3.02)	Severe gastrointestinal 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 standard treatment	Possibly not convincingly different from standard treatment
Among the intermediate harmful	Possibly among the intermediate harmful
Among the most harmful	Possibly among the most harmful

Interventions	Median Δ Bodyweight (kg, 95% CI)
Tirzepatide	-8.57 (-9.40 to -7.75)
Semaglutide (subcutaneous)	-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)
SGLT-2 inhibitors	-1.98 (-2.18 to -1.78)
Exenatide immediate release	-1.77 (-2.47 to -1.07)
Dulaglutide	-1.40 (-1.93 to -0.88)
Exenatide extended release	-1.05 (-1.67 to -0.42)
Lixisenatide	-0.83 (-1.40 to -0.26)
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)
Sulfonylureas	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 (2.10-4.41)
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 m^2 for ≥30 days, sustained % decline in eGFR of ≥40% for ≥30 days or a doubling of SCr, or renal death; effects on ESRD rated down owing to indirectness. [b] Investigational agent not currently approved by the US FDA. [c] Standard treatments include lifestyle modification and active comparators (eg, metformin, sulfonylurea) other than the drug of interest in the RCT.

1. Shi Q et al. *BMJ*. 2023;381:e074068.

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Factors Affecting the Adherence To and Persistence With GLP-1 RAs in People With T2DM[1,2]

Reasons for Treatment Discontinuation	Factors Associated With Higher Adherence and Persistence
Inadequate blood glucose control	Initiating treatment with low dose
Gastrointestinal side effects	Ease of use of injection device
Preference for oral medication over injection	Weekly dosing rather than daily or twice daily dosing
Injection-related concerns (including pain and fear)	Early (within 6 months) A1C level reduction
High cost	Early (within 6 months) weight loss
Injection site reaction	
Inadequate body weight reduction	
Inconvenience of injection schedule	

Since this study was performed, an oral GLP-1 RA has become available

1. Lee DSU, Lee H. *Diabetol Metab Syndr.* 2022;14:12. 2. Dougherty T, Heile M. *Am J Manag Care*. 2020;26(16 suppl):S325-S334.

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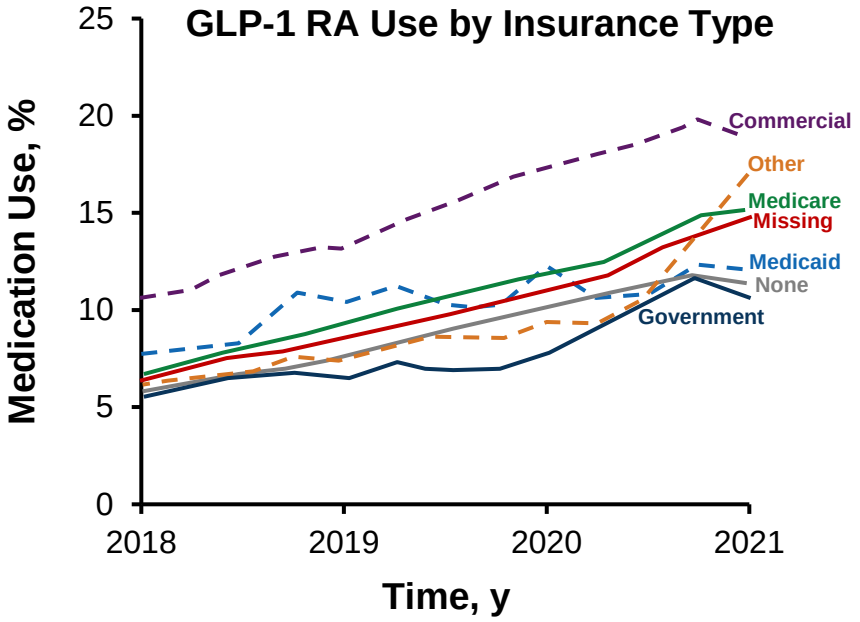
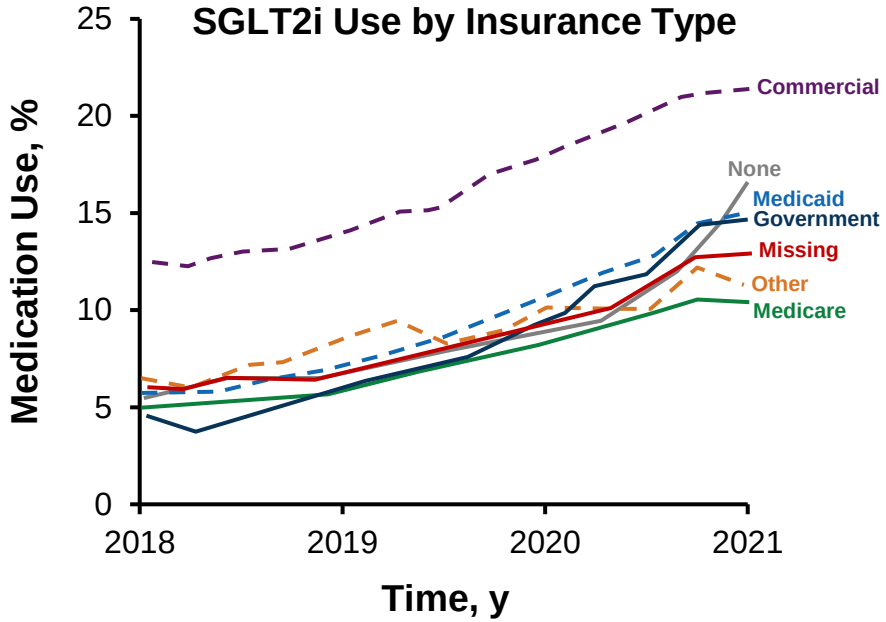
GLP-1 RA (and SGLT2i) Use Is Suboptimal, but Slowly Increasing in PwT2D and ASCVD[1,a]





[a] Government insurance represents coverage through publicly funded policies other than Medicare or Medicaid.

1. Nanna MG et al. *JAMA Cardiol*. 2023;8:89-95.

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Resources for Reducing Medication Acquisition Costs

Examples of Readily Available Formulary Lookup Tools[1-4,a]

Clarivate™ | DRG Fingertip Formulary - formulary lookup

PrescriberPoint®

VA Health

VA Formulary Advisor

Retail Pharmacies and Pricing[5,6]

GoodRx

MARK CUBAN CostPlus DRUG COMPANY

Medication Access Programs[7,8]

Prescription Hope
Unmatched Rx Savings

Commercial insurance coverage for GLP-1 RAs has improved, but varies by region, plan, and agent

[a] Free registration may be required.

1. https://prescriberpoint.com/coverage-restrictions. 2. https://lookup.decisionresourcesgroup.com/. 3. https://mobile.va.gov/app/ask-a-pharmacist.
4. https://www.va.gov/formularyadvisor/. 5. https://www.goodrx.com/. 6. https://costplusdrugs.com/medications/categories/diabetes/.
7. https://prescriptionhope.com/about/. 8. https://www.aace.com/prescription-help.

Case Revisited: Lynda, a Woman Aged 66 Years

Lynda

- BMI: 36.3 kg/m^2; height: 66 inches (167 cm); weight 225 lb (102 kg)
- A1C: 7.7%; BP: 128/79 mmHg
- TC: 170 mg/dL; LDL-C: 94 mg/dL; HDL-C: 46 mg/dL; TG: 150 mg/dL
- eGFR: 48 mL/min; uACR: 100 mg/g
- Medical history: Obesity, T2DM (8 years), hypertension, hyperlipidemia, atrial fibrillation, CKD, DVT (10 years ago)
- Current medications
  - Metformin, glyburide, DPP-4i, SGLT2i
  - Lisinopril/HCTZ, rosuvastatin
  - Apixaban (CHA_2DS_2-VASc score = 6)

Visit Notes

- "Has her doubts" about her T2DM medications—adherence?
- Fearful of needles
- Worried about further kidney damage

ADA guidelines recommend replacing the DPP-4i with a GLP-1 RA and adding finerenone to address glycemia and cardiorenal risks

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Essential Patient Counseling When Prescribing a GLP-1 RA[1,2]

- **Small servings, eat slowly, stop eating when no longer hungry**
- **Caution with alcohol, high fat, spicy foods**
- **Adverse effects of weight loss, independent of therapy: loss of muscle mass, fluid and electrolyte deficits, cold intolerance, constipation, gallbladder events[1]**
  - >1 g/kg/d of high-quality protein intake, drink plenty of water, consider higher sodium intake (tomato juice, soups), eat vegetables and other sources of fiber
  - Exercise, preferably at least 5 days per week, and do not forget strength training
  - Take a jacket with you everywhere
- **Sense of well-being and the enjoyment of food improves once rapid weight loss slows**
- **Communicate common AEs associated with GLP-1 RAs and share when patients should notify their HCP**

1. Pi-Sunyer FX. *Ann Int Med*. 1993;119:722-726. 2. Wharton S et al. *Postgrad Med*. 2022;134:14-19.

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The Future of Incretin-Based Therapies: Who Are the Up and Coming Players?

- **Oral GLP-1 RAs**
  - Semaglutide at 25 mg and 50 mg: obesity[1]
  - Danuglipron, orforglipron, GSBR-1290 (nonpeptide agonists) fewer eating restrictions, can be coformulated with other agents (eg, SGLT2is): obesity, T2DM[2-5]
- **Combination therapies**
  - Survodutide (GLP-1/glucagon analogue): obesity, NAFLD[6]
  - Cagrilintide/semaglutide (GLP-1/amylin analogue): T2DM, obesity[7]
  - AMG-133 (GLP-1/GIP mAb) administered once monthly: obesity[8,9]
  - Retatrutide (GLP-1/GIP/glucagon [GGG]): obesity[10]

1. Knop FK et al. *Lancet*. 2023;402:705-719. 2. Saxena AR et al. *Diabetes Obes Metab*. 2023;25:2805-2814. 3. Wharton S et al. *N Engl J Med*. 2023;389:877-888.
4. Frías JP et al. *Lancet*. 2023;402:472-483. 5. Coll B et al. *Diabetes*. 2023;72(suppl 1):754-P. 6. Le Roux C et al. *Diabetes*. 2023;72(suppl 1):51-OR.
7. Frías JP et al. *Lancet*. 2023;402:720-730. 8. Bailey CJ et al. *Peptides*. 2023;161:170939. 9. https://www.pharmaceutical-technology.com/comment/amg-133-obesity-therapies/. 10. Rosenstock J et al. *Lancet.* 2023;402:529-544.

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Summary

- **Screening and early intervention for T2DM appear to improve outcomes**
- **Selected GLP-1 RAs (and SGLT2is) have compelling indications for use in those at high risk of CVD, HF, and CKD (independent of A1C or background therapy)**
  - GLP-1 RAs are especially compelling if ASCVD or stroke risk is elevated, if A1C goals cannot be reached with oral medications, or if >10% weight loss is needed
  - Not all GLP-1 RAs are the same: dulaglutide, liraglutide, and semaglutide are the only ones with CV indications
- **The path to successful management involves empathetic, personalized shared decision-making and support**
  - Arrange assistance of using community resources for diabetes self-management education and support and to address social determinants of health
  - Continuously reassess goals with a focus on adherence and persistence

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Audience Q&A

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Please remember to complete the Program Evaluation.

PeerView.com/T2DM-Survey-ZKJ

Thank you and have a good day.

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Abbreviations

- ACEi: angiotensin-converting enzyme inhibitors
- ADA: American Diabetes Association
- ARB: angiotensin receptor blockers
- ASCVD: atherosclerotic cardiovascular disease
- BMI: body mass index
- BNP: brain natriuretic peptide
- CHA2DS2-VASc: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female)
- CHD: coronary heart disease
- CKD: chronic kidney disease
- CVD: cardiovascular disease
- CVOT: cardiovascular outcome trial
- DPP-4i: dipeptidyl peptidase 4 inhibitor
- DSMES: diabetes self-management education and support
- DULA: dulaglutide
- ECG: echocardiogram
- eGFR: estimated glomerular filtration rate
- EXN: exenatide
- FBG: fasting blood glucose
- FRC: fixed-ratio combination
- GIP: gastric inhibitory peptide
- GLP-1 RA: glucagon-like peptide 1 receptor agonist
- GLP-1: glucagon-like peptide 1
- HCTZ: hydrochlorothiazide
- HDL: high-density lipoprotein
- HF: heart failure
- LDL: low-density lipoprotein
- LIRA: liraglutide
- LIXI: lixisenatide
- MACE: major adverse cardiovascular events

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Abbreviations

- MI: myocardial infarction
- NAFLD: nonalcoholic fatty liver disease
- NASH: nonalcoholic steatohepatitis
- NNT: number needed to treat
- NT-proBNP: N-terminal pro-brain natriuretic peptide
- PA: prior authorization
- PwT2D: people with type 2 diabetes
- QL: quantity limit
- QOL: quality of life
- RCT: randomized controlled trial
- SBP: systolic blood pressure
- SEMA: semaglutide
- SGLT2i: sodium-glucose cotransporter 2 inhibitors
- ST: step therapy
- T2DM: type 2 diabetes mellitus
- TC: total cholesterol
- TG: triglyceride
- TZP: Tirzepatide
- uACR: urine albumin-creatinine ratio
- WNL: within normal limit

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