



Beyond Obesity: *Dosing & Optimization of GLP-RAs across various pathologies*

Fall RxA PD Conference 2026

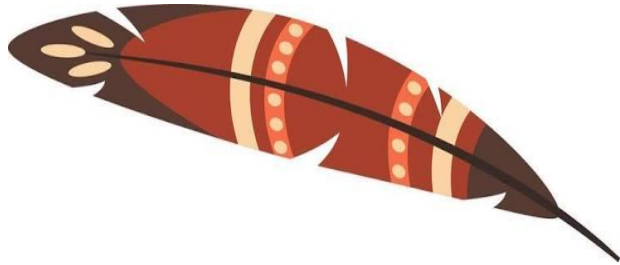
Rupam Arora, PharmD, APA, HC-CHM

Clinical Pharmacist (Nephrology)

University of Alberta Hospital (Edmonton Zone)

Rupam.Arora@albertahealthservices.ca

TREATY 6 ACKNOWLEDGEMENT



We acknowledge we are on the traditional territory of Cree, Blackfoot, Métis, Nakota Sioux, Iroquois, Dene, and Ojibway/Saulteaux/Anishinaabe nations; lands that are now known as part of Treaties 6, 7, and 8 and homeland of the Métis.



Presenter Disclosure

- Presenter: Rupam Arora, PharmD, APA, HC-CHM
- Position: Clinical Pharmacist (Nephrology), University of Alberta Hospital (Alberta Health Services)
- Disclosure statement: *I have no current or past relationships with commercial entities*
- I have received an honorarium from the Alberta Pharmacists' Association for this learning activity

Commercial Support Disclosure

- This program has received no financial or in-kind support from any commercial or other organization

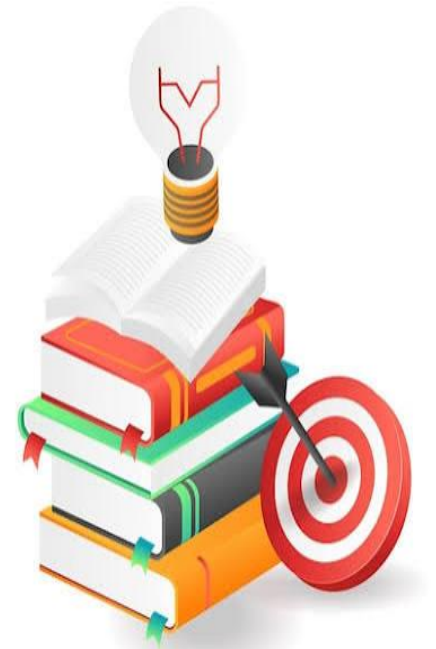
Bias Mitigation

I confirm that I have taken one or more of the following measures to ensure this learning activity/conference session is balanced and free from bias:

- ✓ Conducted a comprehensive review of the relevant literature
- ✓ Supported the content and recommendations within by best available current evidence from the literature
- ✓ Had a peer review conducted of my learning activity/conference session

Learning Objectives

- By the end of this session, participants will be able to:
 - Describe the pathophysiological mechanisms of GLP-RAs across Type 2 Diabetes, Cardiovascular disease and cardio-renal pathologies (Chronic Kidney Disease/Heart Failure)
 - Evaluate and analyze landmark clinical trial data which support the use of GLP-RAs outside of obesity.
 - Discuss indication-specific dosing strategies and challenges
 - Highlight future/emerging indications: Metabolic Dysfunction-Associated Steatohepatitis (MASH) and Obstructive Sleep Apnea (OSA)
 - Apply evidence-based medicine to a relevant patient-case scenario in practice



Over to you.....





Pathophysiological Mechanisms (Type 2 Diabetes)

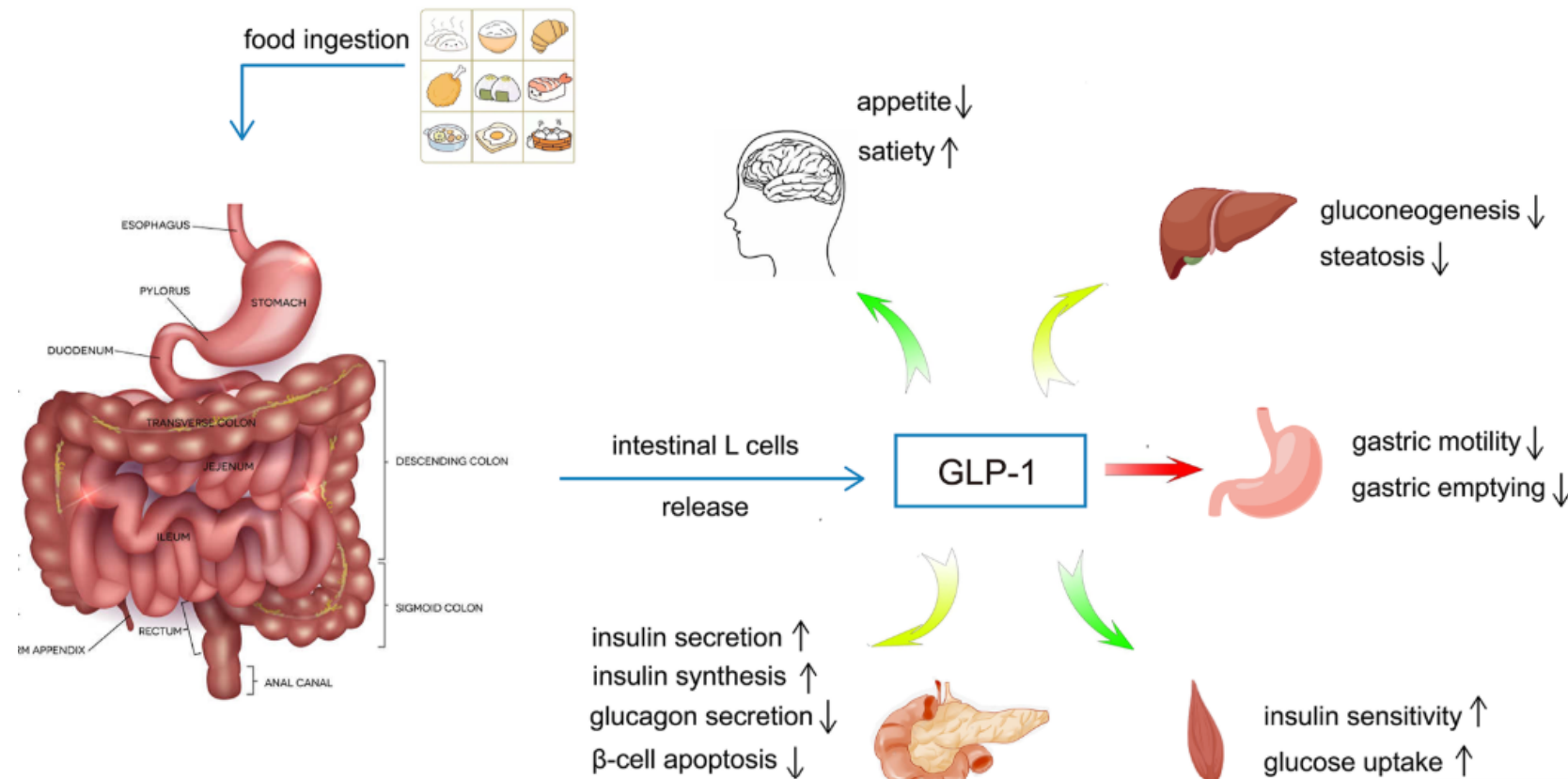


Figure 1: Frontiers in Pharmacology (2025) <https://doi.org/10.3389/fphar.2024.1483792>

Pathophysiological Mechanisms (Cardiovascular Disease)

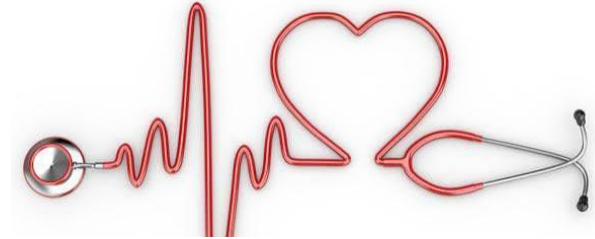
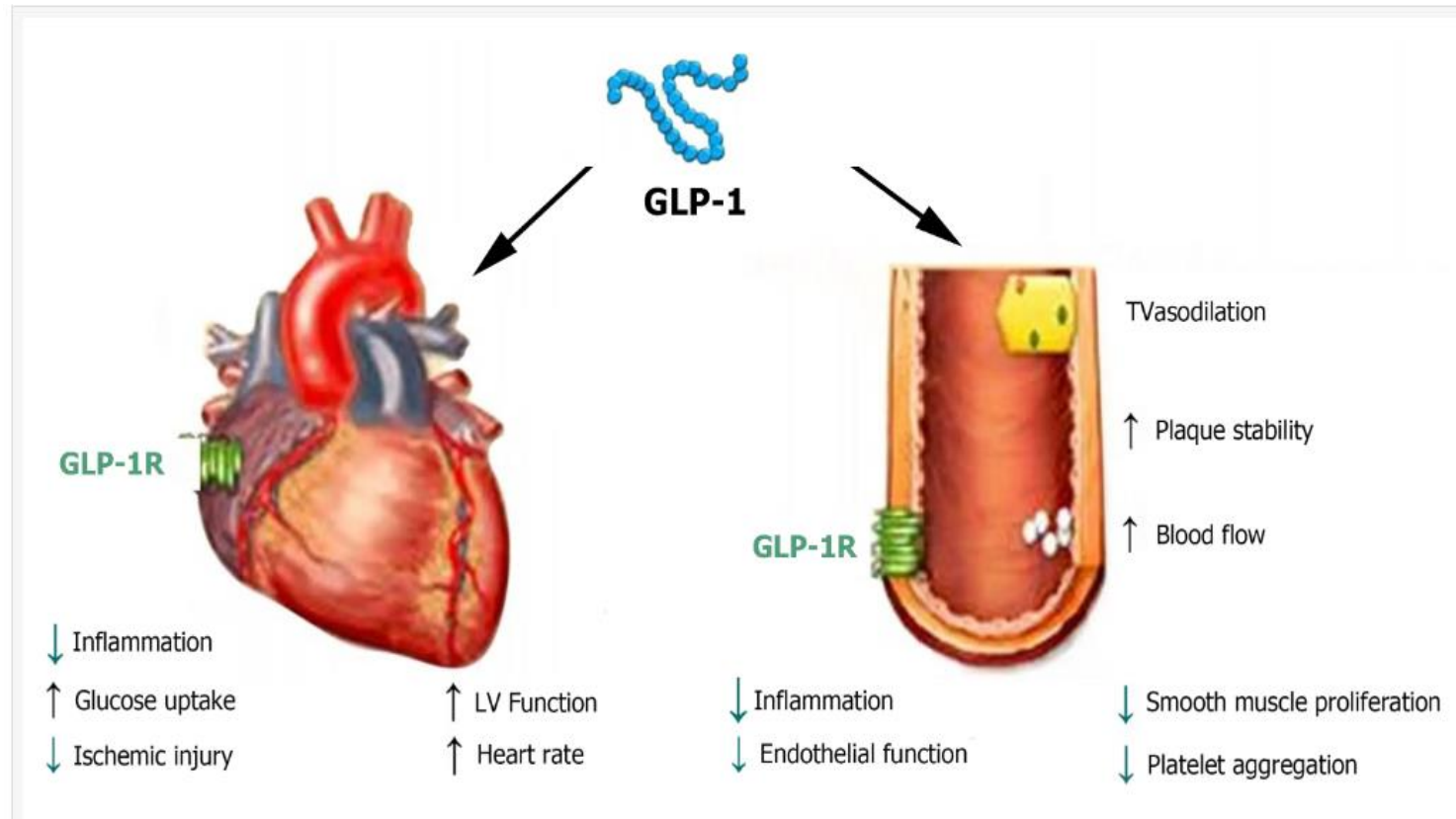
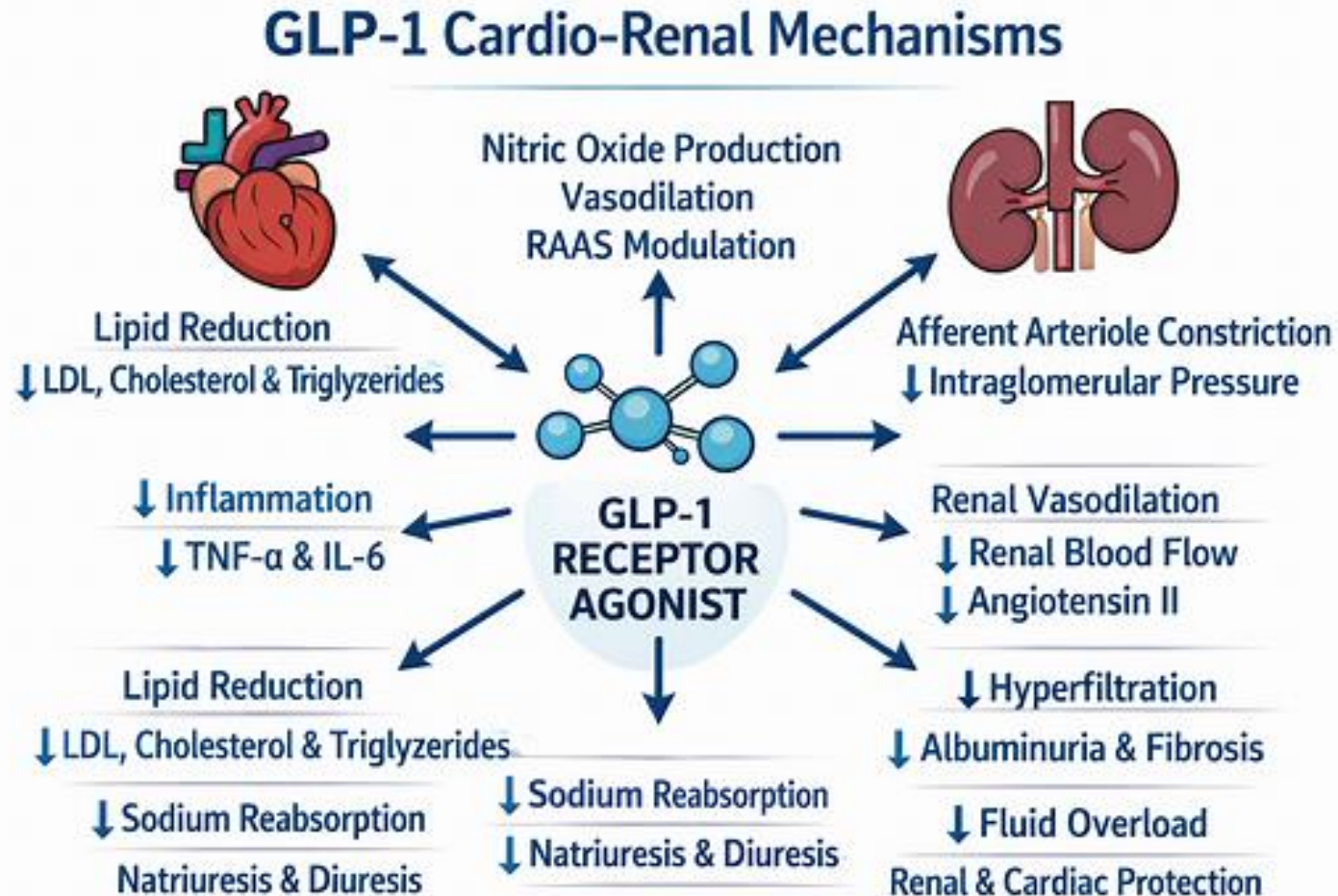


Figure 2: direct & indirect effects on the heart & blood vessels (World J Gastroenterol. Sep 28, 2024)

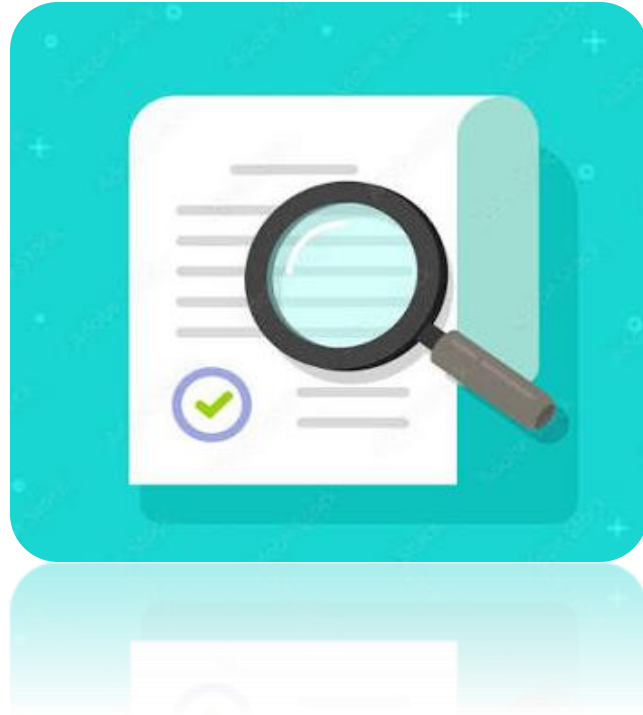


Pathophysiological Mechanisms (Cardiorenal)





Let us explore the evidence.....



Landmark Clinical Trials

LEADER (2016)

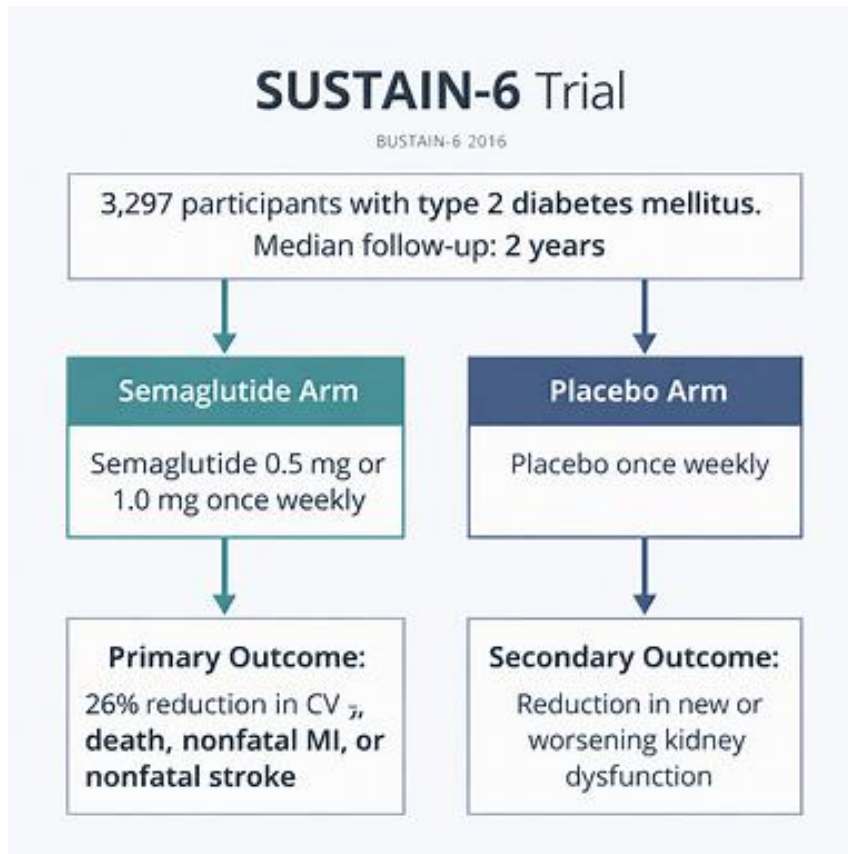
Liraglutide and cardiovascular outcomes in type 2 diabetes



- ✓ 13% reduction in major adverse cardiovascular events (MACE)
- ✓ 22% reduction in CV death
- ✓ Lower but non-statistically significant reduction in non-fatal MI, non-fatal stroke and HF hospitalization
- ✓ ~22% lower incidence of new-onset macroalbuminuria
- ✓ At 6 months, the liraglutide group experienced an absolute HbA1c reduction **1.4%**
- ✓ Over a 36-month tracking period, the liraglutide group maintained an average HbA1c **0.40% lower** than placebo

SUSTAIN-6 (2016)

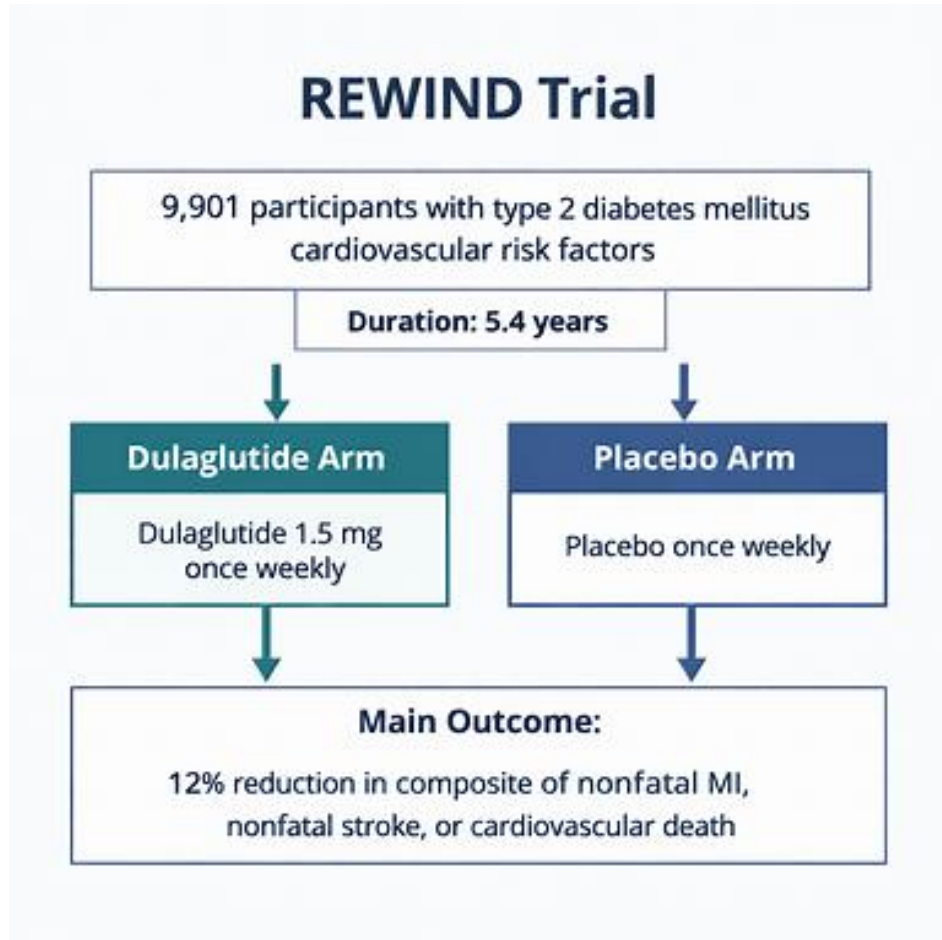
semaglutide and cardiovascular outcomes in patients with type 2 diabetes



- ✓ 26% reduction in the risk of MACE
- ✓ primary outcome reduction largely driven by a significant 39% reduction in nonfatal strokes and a 26% reduction in nonfatal heart attacks
- ✓ dose-dependent reduction in HbA1c (1.1% for 0.5 mg dose and 1.4% for 1.0 mg dose)
- ✓ reduced the composite renal endpoint by **36%**
- ✓ Reduced the risk of new onset macroalbuminuria (46%) AND progression from micro to macroalbuminuria
- ✓ slowed eGFR decline by **~0.7 mL/min/1.73 m² per year**
- ✓ **36% lower risk** of doubling of serum creatinine
- ✓ HF outcomes remain neutral

REWIND (2019)

dulaglutide and cardiovascular outcomes in type 2 diabetes



- ✓ 12% reduction in the risk of MACE
- ✓ overall MACE reduction primarily driven by a **24%** reduction in nonfatal strokes.
- ✓ Mean reduction A1c 0.6%
- ✓ reduced the composite renal endpoint by **15%**
- ✓ HF outcomes remain neutral

FLOW (2024)

effect of semaglutide vs. placebo on the progression of renal impairment in subjects with type 2 diabetes and chronic kidney disease

FLOW Trial

Duration: 3.4 years

Type 2 Diabetes with Chronic Kidney Disease

- eGFR 50–<75 mL/min with UACR >300 mg/g to <5000 mg/g
- eGFR >25–<50 mL/min with UACR >100 mg/g to <5000 mg/g

Semaglutide Arm

Semaglutide 1.0mg once weekly
+ Standard Care

Placebo Arm

Placebo once weekly
+ Standard Care

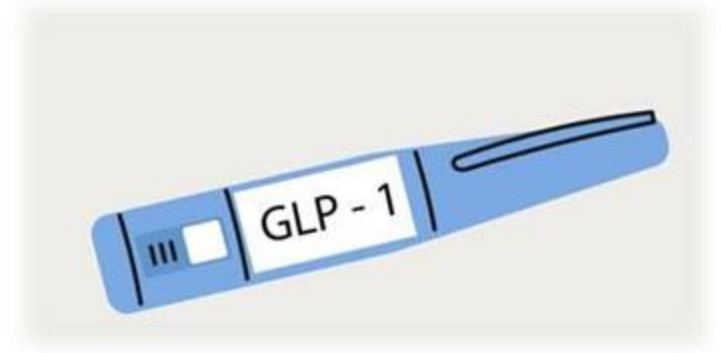
FLOW Trial — Key Outcomes and Results

Category	Measure	Semaglutide	Placebo	Effect
Primary Composite Kidney Outcome	Persistent eGFR decline $\geq 50\%$, ESKD, death from kidney or CV disease	331 events (8.8%)	410 events (10.9%)	HR 0.76 (95% CI 0.66–0.88) 24% Risk Reduction
	eGFR 55 – <65 mL/min/1.73 m ² UACR >100 mg/g to <1000 mg/g	3.7%	5.2%	
Kidney-Specific Death or ESKD	Mean annual decline	–1.16 mL/min/1.73 m ² per year		HR 0.72 (95% CI 0.58–0.89)
Albuminuria Progression	New or worsening macroalbuminuria	18%	25%	≈ 28% Relative Reduction
MACE (Major Adverse CV Events)		7.3%	9.1%	
All-Cause Mortality		6.7%	8.5%	HR 0.82 (95% CI 0.70–0.96)

Recent trials that looked into HF

STEP-HFpEF & STEP-HFpEF DM Trials

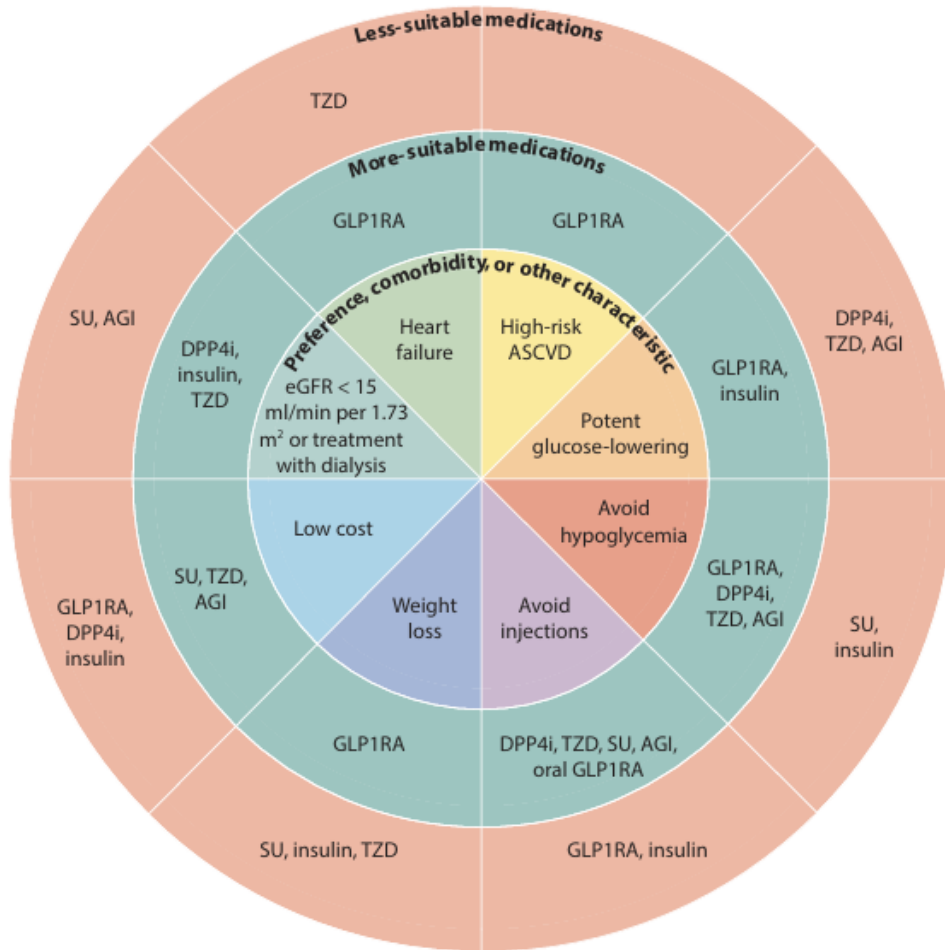
STEP-HFpEF		STEP-HFpEF DM
Publication	August 2023 (NEJM)	February 2024 (NEJM)
Study Population	529 HFpEF + Obesity (BMI $\geq$ 30) Without Diabetes	610 HFpEF + Obesity (BMI $\geq$ 30) With Type 2 Diabetes
Duration	52 Weeks	52 Weeks
Treatment	Semaglutide 2.4 mg Weekly vs. Placebo	
Primary Outcomes	$\uparrow$ KCCQ-CSS by 16.6 Points $\downarrow$ Body Weight by -13.3%	$\uparrow$ KCCQ-CSS by 13.7 Points $\downarrow$ Body Weight by -9.8%
Main HF Outcomes	Improved Symptoms & Quality of Life	Improved Symptoms & Quality of Life
	+ 21m in 6-Minute Walk	+ 20m in 6-Minute Walk



Dosing Strategies/some practice pearls



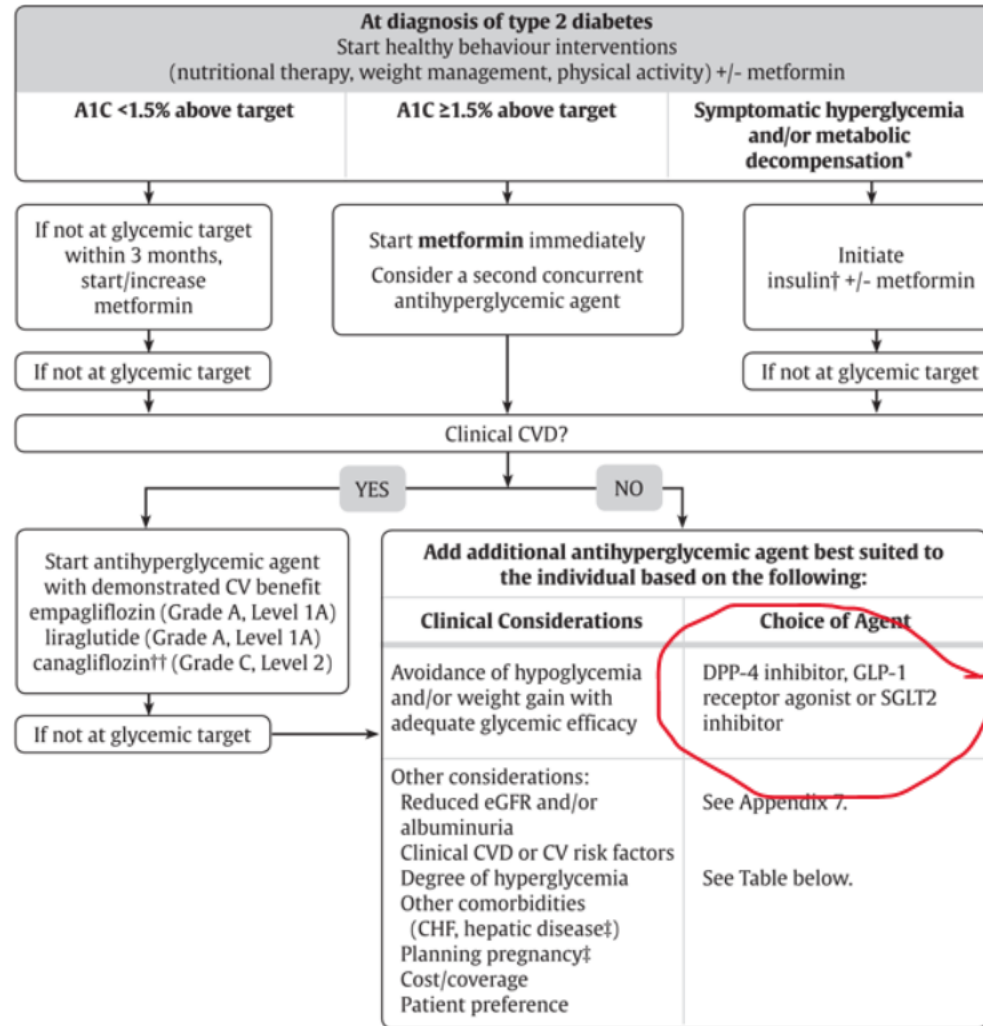
GLP-1 RA: General Considerations



- ✓ Initiate in patients with T2DM & CKD, if unable to achieve individualized glycemic targets despite combination of metformin + SGLT2i OR if unable to use either of these medications OR if financially feasible
- ✓ May preferentially in T2DM patients with hx CKD OR Obesity OR atherosclerotic CVD
- ✓ Evidence of ++ glucose lowering potency in comparison to SGLT2i in this patient population
- ✓ **1.0% A1c lowering up to 2.4%** (vs. 0.5-0.7% in DPP4-inhibitors and 0.4-0.7% in SGLT2i)
- ✓ Albuminuria reduction benefit
- ✓ Low hypoglycemic risk alone (but caution in addition with sulfonylureas or insulin concurrently)
- ✓ Retinopathy assessment

Figure 25 (KDIGO 2022)

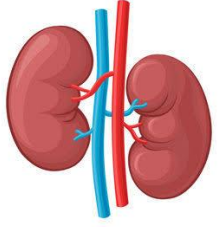
GLP-1 RA: Type 2 Diabetes



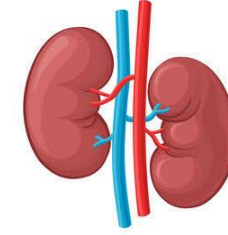
YES....BUT WHAT ABOUT THE GLYCEMIC BENEFITS OUTSIDE OF WEIGHT LOSS IF ONLY TYPE 2 DIABETES WITHOUT ANY COMPLICATIONS (ie. CKD, CVD, HF) ???



Figure: Management of hyperglycemia in type 2 diabetes (Diab Canada guidelines Chapter 13 (2018)).



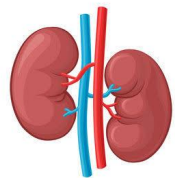
GLP1-RA: CKD Considerations



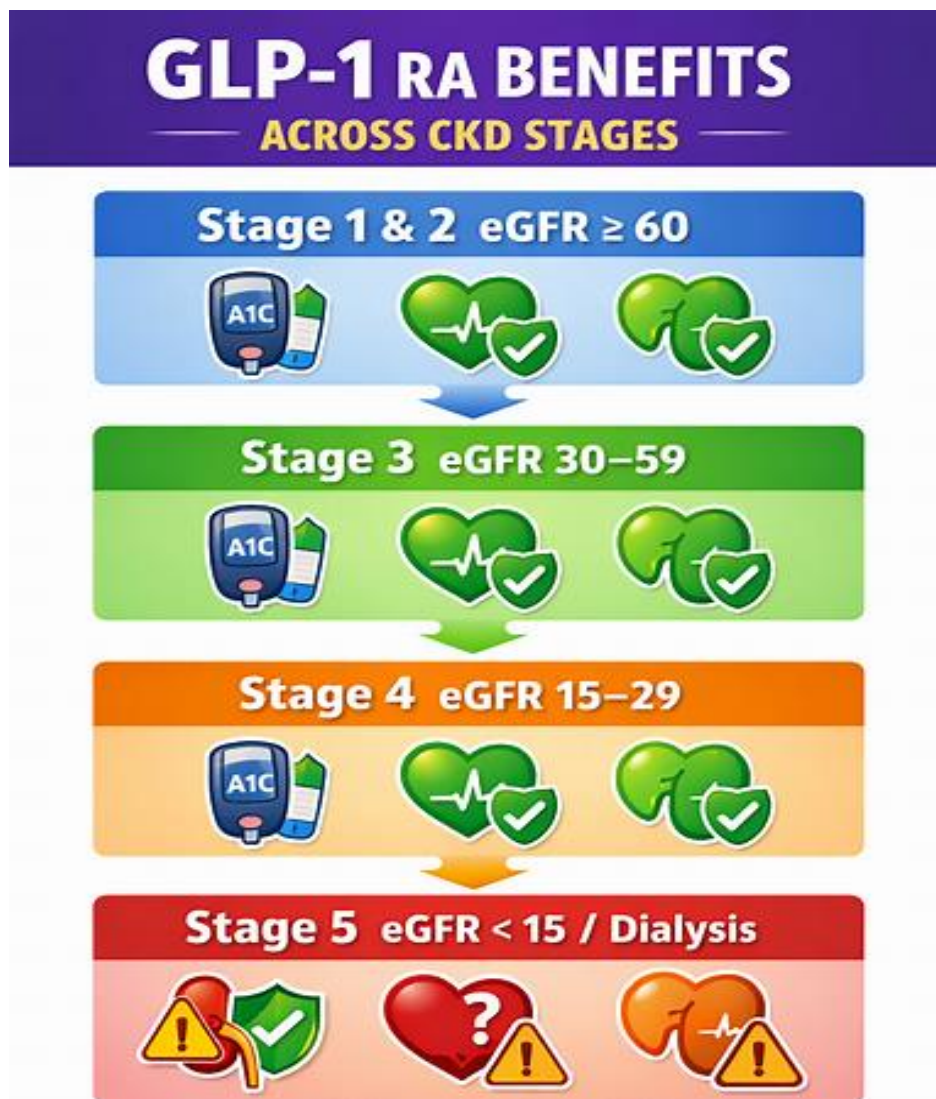
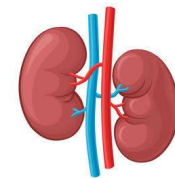
In adults with T2DM and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2 inhibitor treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA (KDIGO Recommendations 3.9.1. 2024)

- Prioritize agents with documented cardiovascular benefits
- Risk of CKD progression is proportional to residual albuminuria
- Reduction of albuminuria and slowing the rate of eGFR decline
- Optimal choice if T2DM + CKD + atherosclerotic CVD
- UACR $\geq 100\text{mg/g}$





Benefits across CKD Stages



Renal dosing in CKD patients (non-dialysis)

	Dulaglutide (SC)	Semaglutide (SC/ORAL)	Liraglutide (SC)
Normal Renal Function	0.75 -4.5 mg/wk	SC: 0.5-2 mg/wk PO: 3-14 mg/day	0.6-1.8 mg/day
CKD Stage 1 and 2 (eGFR > 60)	No adjustment	No adjustment	No adjustment
CKD Stage 3a (eGFR 45-59)	No adjustment	No adjustment	No adjustment
CKD Stage 3b (eGFR 30-44)	No adjustment	No adjustment	No adjustment
CKD Stage 4 (eGFR 15-29)	No adjustment	Limited Data	Limited Data
CKD Stage 5 (eGFR <15)	AVOID	Limited Data	Limited Data



GLP-1RA: CVD Considerations



- If Type 2 DM + (ASCVD OR with additional risk factors for ASCVD),
irrespective of baseline A1c, CKD, or HF
 - ✓ reduce the risk of all-cause or CV mortality or MACE
 - ✓ MACE reduction independent of glucose lowering effect
 - ✓ MACE reduction is not fully dependent on BP reduction (given they modestly reduce BP)
 - ✓ reduce the risk of nonfatal stroke
 - ✓ benefits are INDEPENDENT of whether patient is concurrent therapy (ie. SLGT2i)

GLP-1 RA: Cardiorenal considerations

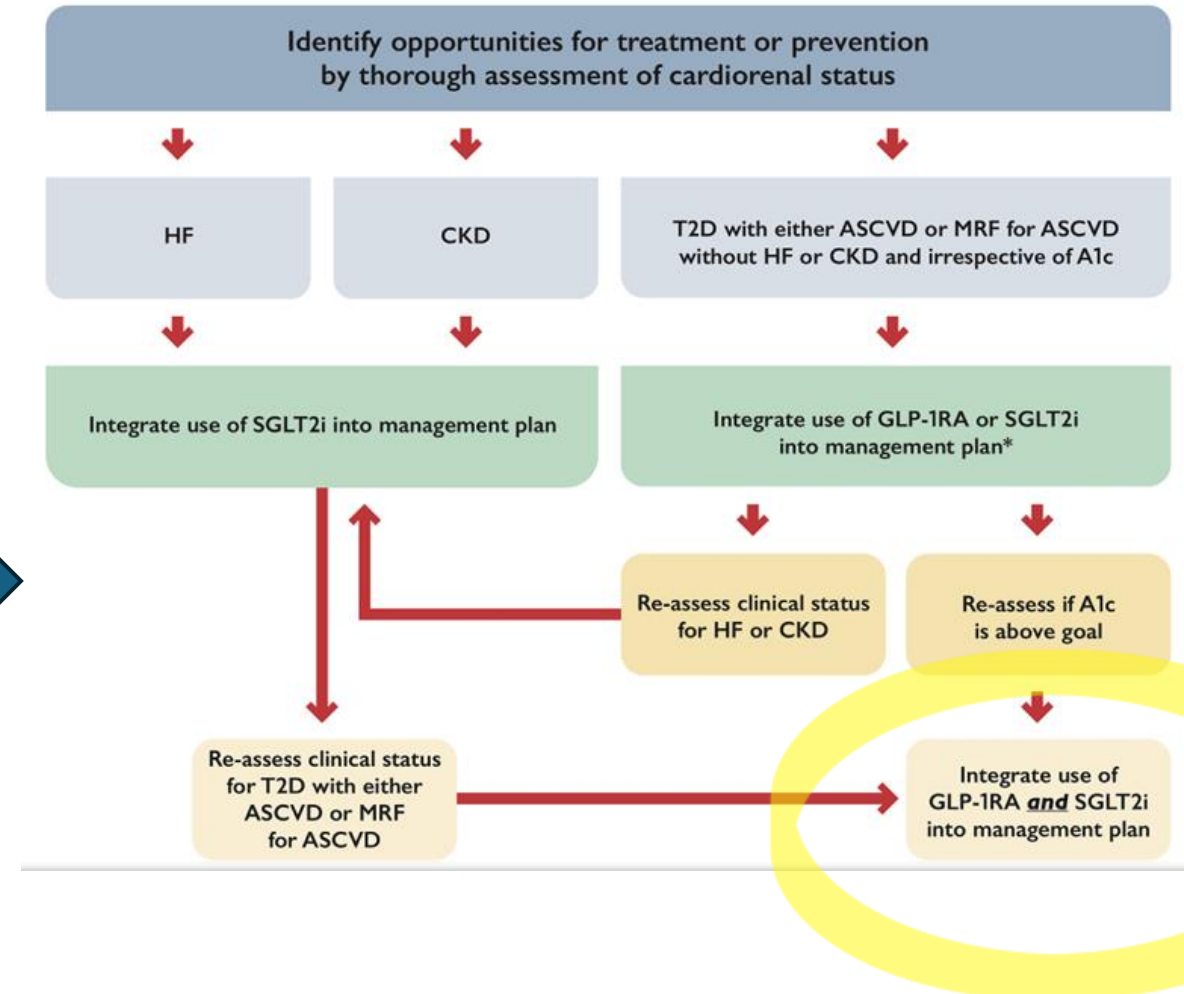
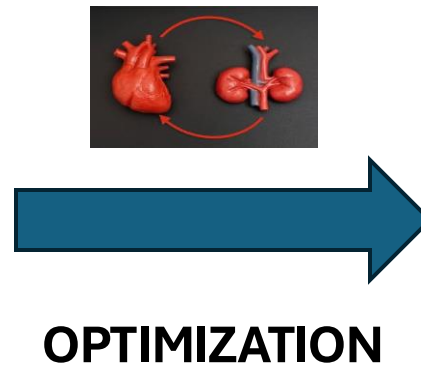
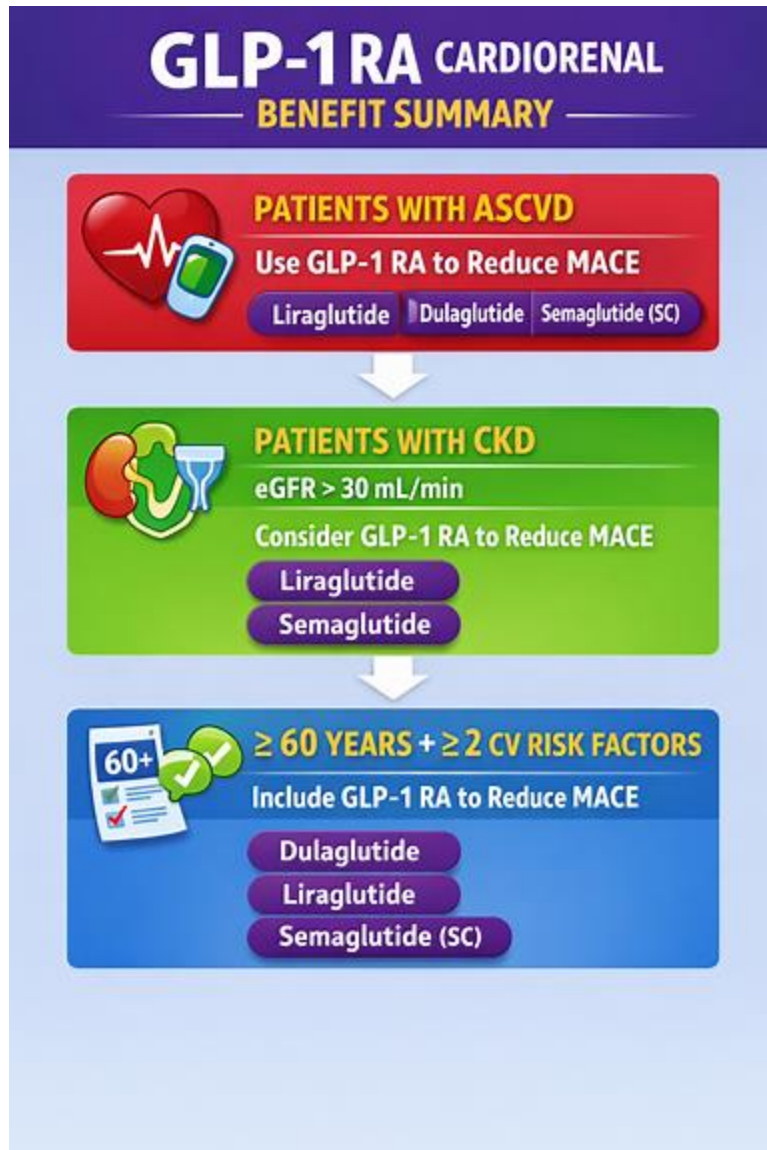


Figure: Canadian Journal of Cardiology Volume 38 (2022)



GLP-1 RA: HF Considerations



- **HFrEF** : unclear mortality benefits, not recommended specifically for this indication (unless where indicated ie. ASCVD + T2DM)
- **HFmrEF**: can be considered for symptom and functional capacity improvement. It has shown efficacy for people with symptomatic HF, LVEF $\geq 45\%$, and body mass index $\geq 30 \text{ kg/m}^2$ to reduce the risk of HF hospitalization and to improve quality of life



Ready to initiate GLP-1 RA?.....



Let us discuss some dosing strategies/pearls.....



General conservative recommendation: Consider decreasing basal insulin (if appropriate) by 20% when initiating therapy to help mitigate hypoglycemia

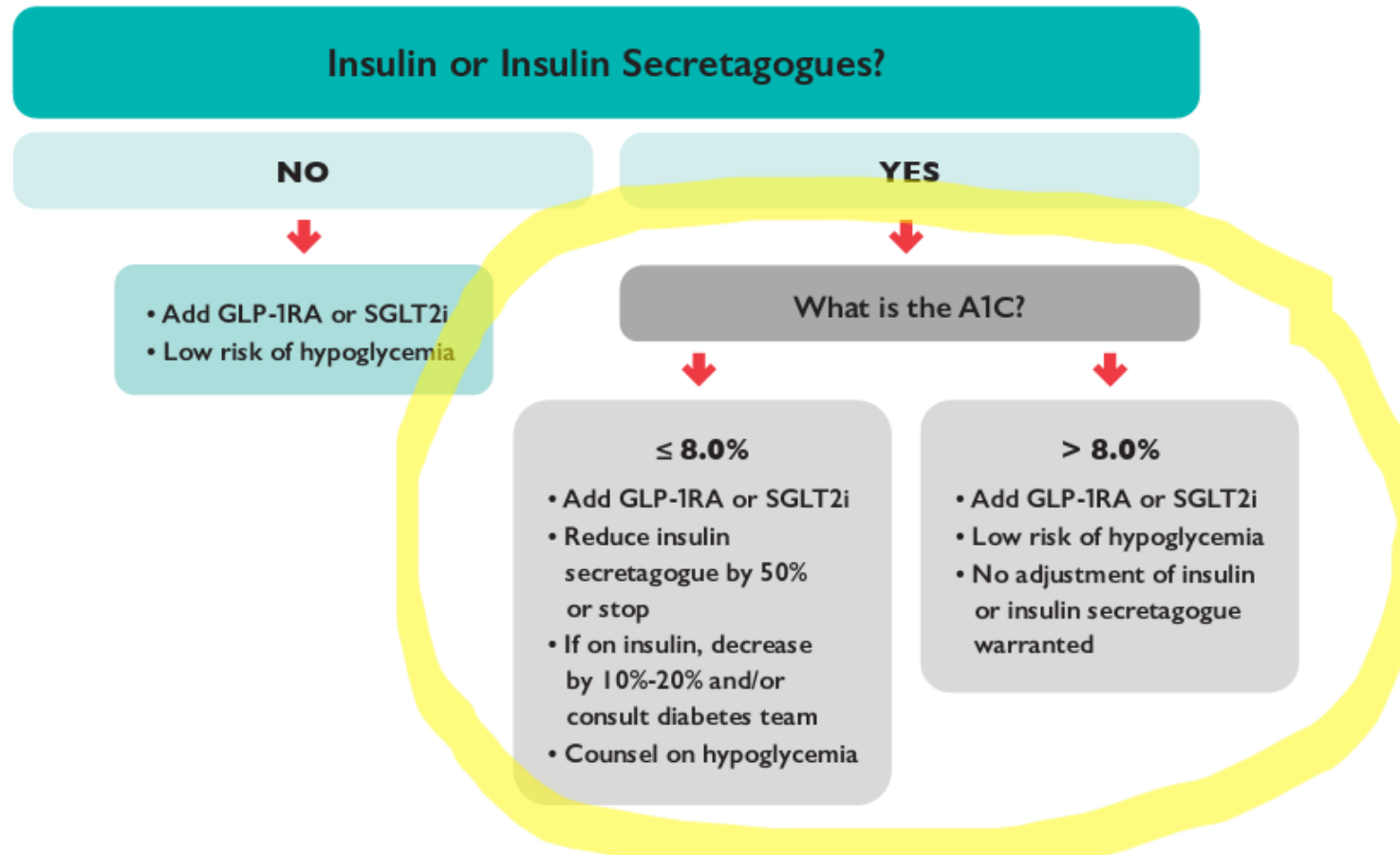


Figure: Cardiorenal risk reduction adults (CCS 2022) Integration of SGLT2i and GLP-1RA in patients with type 2 diabetes already being treated with other antihyperglycemic agents

General Strategies to mitigate gastrointestinal adverse effects

Slow titration of dose

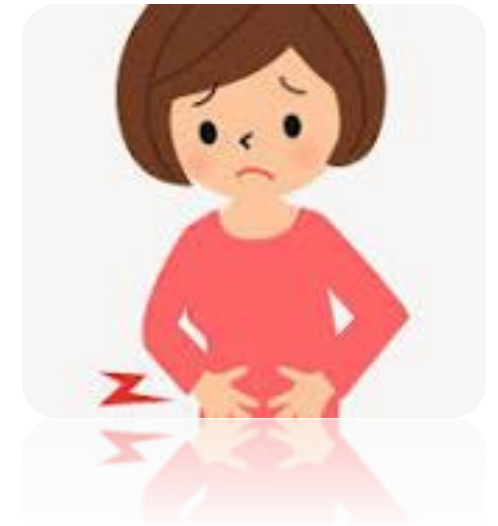
Smaller, more frequent meals

Stop eating when no longer hungry

Avoid spicy or fatty foods

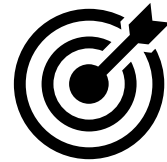
Maintain adequate hydration

Use antiemetics if required (under medical guidance)



SEVERE / PERSISTENT SYMPTOMS

- No drinks during meals; hydrate 30–60 min before/after



Symptom-specific mitigation strategies



NAUSEA	VOMITING	DIARRHEA	CONSTIPATION (less common)
• Eat crackers, apples, mint, ginger drinks 30 min post-dose • Avoid strong smells	• Generous hydration • Smaller, more frequent meals	• Hydration with bicarbonate water • Avoid high-fiber, fatty, spicy foods • Choose rice or cooked vegetables	• Adequate fibre intake • Increase physical activity • Maintain hydration

Semaglutide (Injectable)

1

General titration: 0.25 mg SC weekly x 4 weeks,
then 0.5 mg SC weekly x 4 weeks, then 1 mg SC weekly

Biggest
jump in
glycemic
efficacy

DOSE	Average A1c REDUCTION from trials
0.5 mg	1-1.5%
1.0 mg	1.4-1.8%
2.0 mg	1.8-2.0%

Fasting ↓ (mmol/L)	Post-Prandial ↓ (mmol/L)
2.0–2.5	3–4
2.5–3.5	4–6
3.5–4.0	5–7

2

RENAL

- Albuminuria reduction most at **1 mg**
- Slows egfr decline **most clear at 1 mg**
- Slow CKD progression **consistent 0.5-2 mg**
- most renoprotective benefits consistent across 0.5-1 mg (then plateau)

3

CVD

- Trials show prominent cardioprotective benefits between **0.5-1 mg doses**
- **Cardiorenal protection at 0.5 mg**
- Unclear cardiovascular outcomes/protection above 2 mg

4

HF



Semaglutide (Oral)

1

General titration: 3 mg daily x 30 days, then 7 mg daily x 30 days, then increase to 14 mg daily if required

DOSE	Average A1c REDUCTION from trials
3 mg	Minimal
7 mg	1%
14 mg	1.2-1.5%

Fasting Glucose Reduction	Post-Prandial Glucose Reduction
~0.5–1.0 mmol/L	~1–2 mmol/L
~1.5–2.0 mmol/L	~2–3 mmol/L
~2.0–2.5 mmol/L	~3–4 mmol/L

2

RENAL

- 3 mg: minimal changes in albuminuria or egfr decline
- 7 mg: modest reduction in albuminuria and some slowing egfr decline
- 14 mg: studies found more prominent albuminuria reduction and egfr decline but need more clear evidence

3

CVD

- 3 or 7 mg: ???
- 14 mg: statistically significant reduction in
- MACE

Liraglutide (SC)

1

General titration: 0.6 mg SC daily x 1 week, then increase to 1.2 mg daily x 1 week, then 1.8 mg daily

DOSE	Average A1c REDUCTION from trials
0.6 mg	Minimal
1.2 mg	1-1.3%
1.8 mg	1.3-1.6%

Fasting Glucose ↓ (mmol/L)	Post-Prandial Glucose ↓ (mmol/L)
~0.5–1.0	~1–2
~1.5–2.0	~2–3
~2.0–2.5	~3–4

2

RENAL

- 0.6 mg: not clinically meaningful
- 1.2 mg: meaningful reduction in albuminuria + slowing of egfr decline
- 1.8 mg: **most robust** albuminuria reduction + slowing of egfr decline

3

CVD

- 0.6 mg: ---
- 1.2 mg: ?some benefit
- 1.8 mg: **optimal cardioprotection** (MACE reduction)

Dulaglutide (SC)

1

General titration: 0.75 mg weekly, may increase to
1.5 mg weekly in 4-8 wks if required
3 mg weekly in at least 4 wks -> if required (then 4.5 mg if required)

Dose (weekly)	A1c Reduction	Fasting Plasma Glucose ↓ (mmol/L)	Post-Prandial Glucose ↓ (mmol/L)
0.75 mg	~0.7–0.9%	~1.0–1.5	~1–2
1.5 mg	~1.1–1.3%	~1.5–2.0	~2–3
3.0 mg	~1.4–1.6%	~2.0–2.5	~3–4
4.5 mg	~1.6–1.8%	~2.5–3.0	~4–5

2

RENAL

- 0.75 mg: not clinically meaningful
- 1.5 mg: meaningful reduction in albuminuria + slowing of egfr decline
- 3 mg: **strong** albuminuria reduction + slowing of egfr decline
- 4.5 mg: **most pronounced** albuminuria reduction + strongest slowing of egfr decline

3

CVD

- 0.75 mg: ?data
- 1.5 mg: **MACE reduction** (cardioprotection)



What are the Challenges

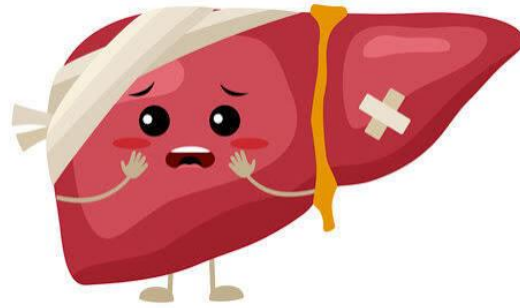


- Financial (due to cost/drug coverage policies)
- Generics (ONLY semaglutide)
- Supply shortages
- Injections
- Often therapy interruption during hospitalizations due to number of reasons

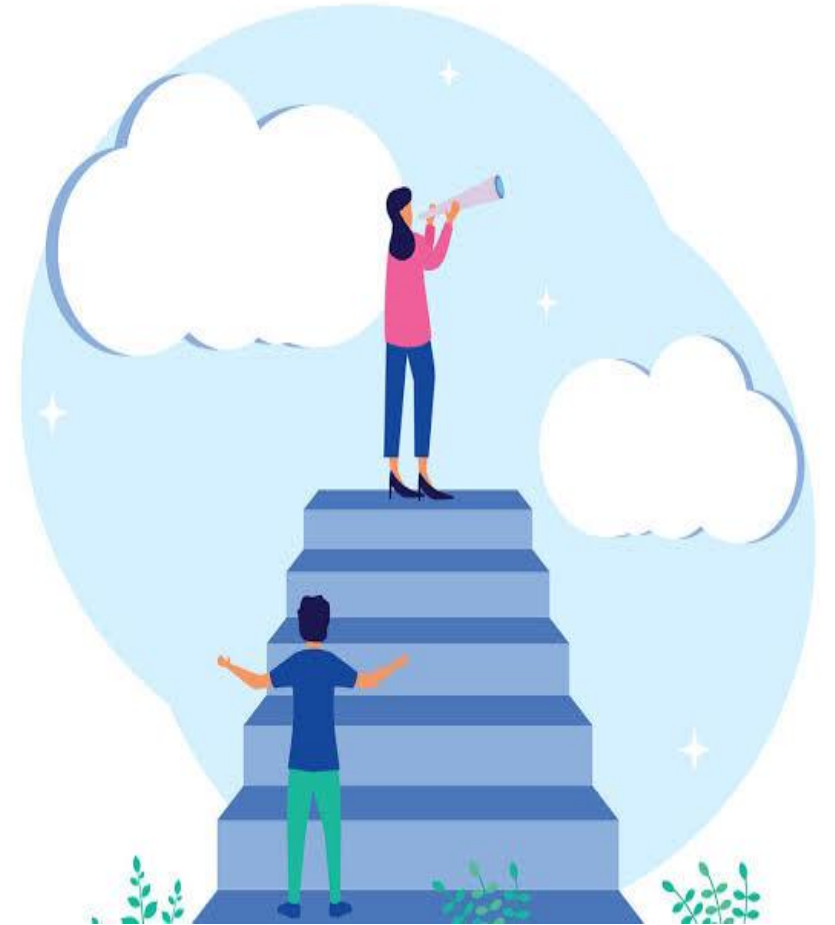


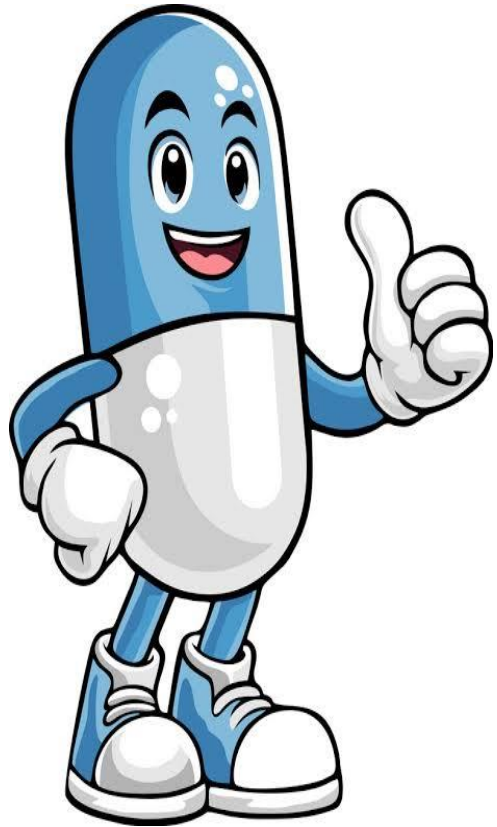
Future/emerging indications

- MASH



- OSA





Role of the pharmacist



- ✓ Identifying/screening patients who would benefit from therapy
- ✓ Ensuring optimized, yet safe dose titration
- ✓ Adverse effect management and mitigation strategies
- ✓ Device training/safe use
- ✓ Therapeutic monitoring for efficacy and safety
- ✓ Compliance monitoring/strategies for compliance
- ✓ PATIENT EDUCATION !!



Patient Case Scenario



Meet J.J (55 year old male) in the CKD clinic....

Medical History	- Type 2 Diabetes Mellitus (10+ years) - CKD Stage 3 (baseline SCr low 120s) - Hypertension - Dyslipidemia
Recent Labs	- Serum Creatinine: 130 $\mu\text{mol/L}$ - eGFR: 40 mL/min/1.73 m² - Electrolytes: Normal - HbA1c: 8.0% (1 month ago) - Previous HbA1c: 7.5% (6 months ago)
Vitals	- BP: 120/83 mmHg (near baseline)
Current Medications	- Ramipril 5 mg BID - Atorvastatin 40 mg qhs - Empagliflozin 10 mg daily



Dr. wants to prescribe linagliptin 5 mg po daily. What do you recommend and why?

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16. Images: Courtesy of google images

Thank you for listening!.....



Questions ??

