Optimizing Diabetes Management in Long-Term Care

Cynthia Leung, RPh, BScPhm, PharmD, CDE

1:00 PM—4:15 PM

Lunch: 12:00 pm—1:00 pm

Break: 2:30 pm—2:45 pm

HALF DAY WORKSHOP—21-04

OPTIMIZING DIABETES MANGEMENT IN LONG-TERM CARE

CYNTHIA LEUNG, RPH, BSCPHM, PHARMD, CDE

Learning Objectives:

1. *Discuss the roles of SGLT2 inhibitors in type 2 diabetes and other conditions.*
2. *Discuss the roles of GLP-1 receptor agonists in type 2 diabetes and other conditions.*
3. *Discuss strategies on how to safely prescribe and monitor the use of SGLT2 inhibitors and GLP1 receptor agonists in LTC setting.*

Faculty/Presenter Disclosure

- **Faculty: Cynthia Leung**

- **Relationships with financial sponsors:**
  - **Speakers Bureau/Honoraria: Queen's University**

Disclosure of Financial Support

- **None**

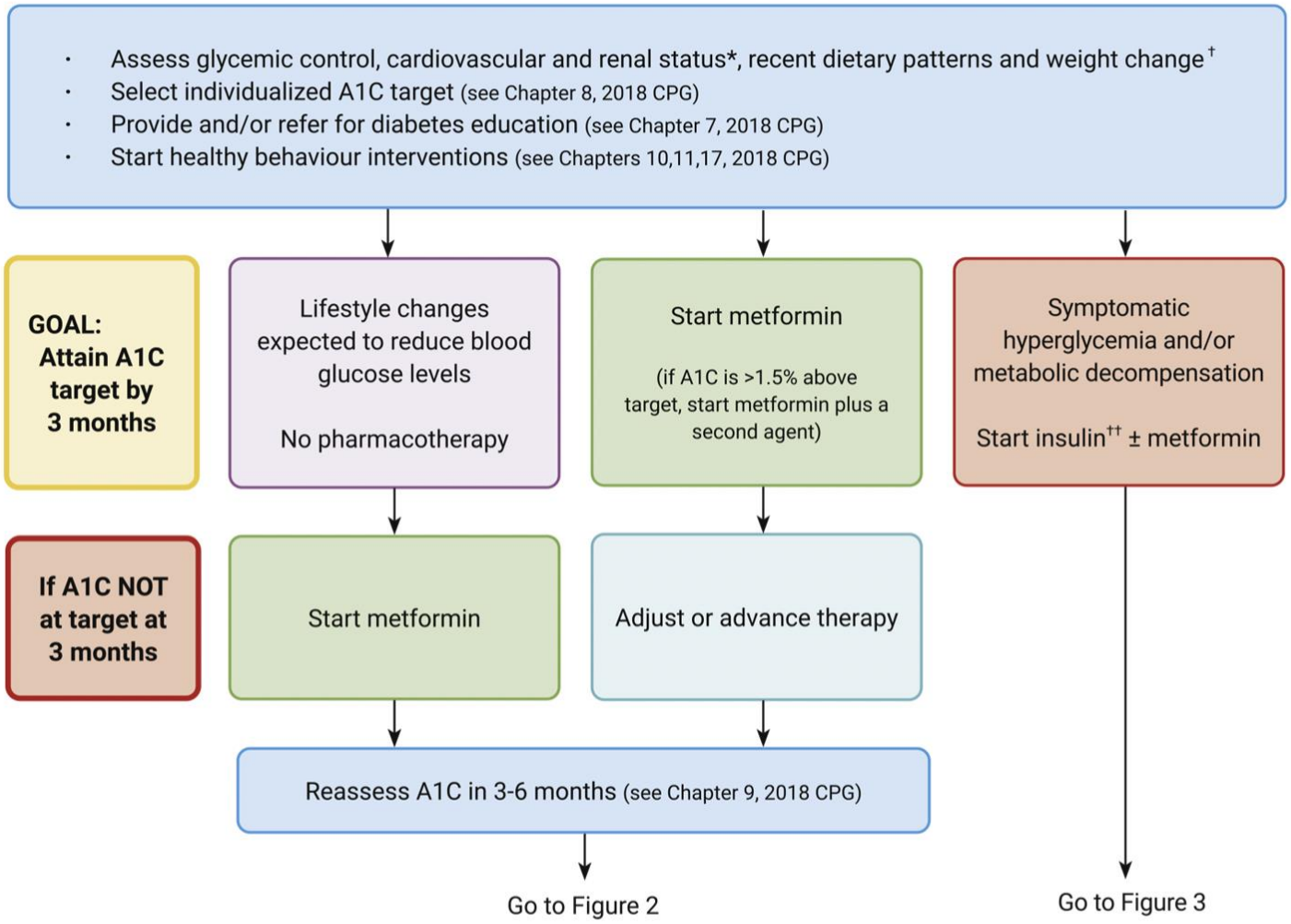
- **<u>Potential for conflict(s) of interest</u>:**
  - None

Mitigating Potential Bias

- NO BIAS IN ANY PRESENTATIONS

Diabetes Canada Guidelines

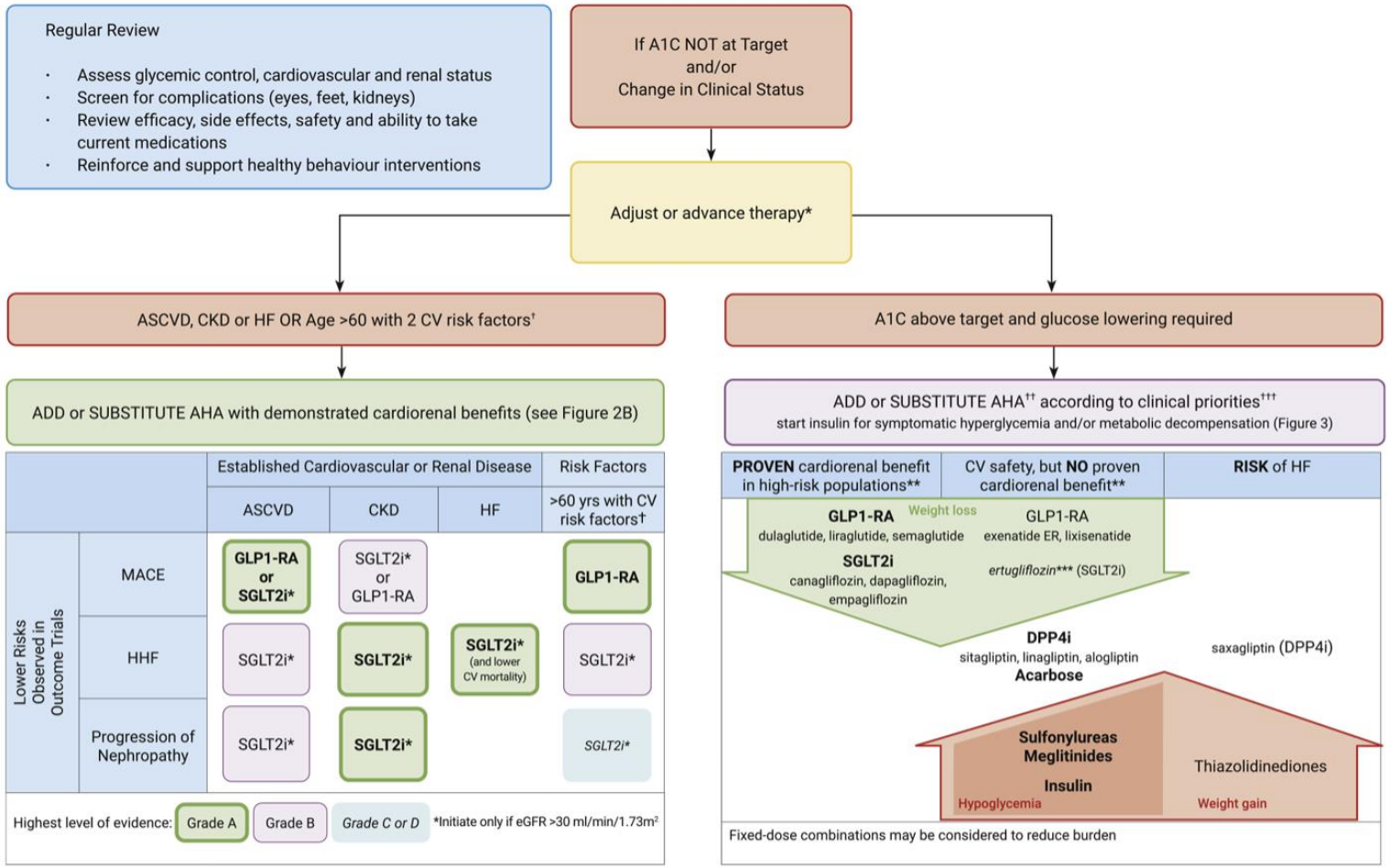
Figure 1
At diagnosis of type 2 diabetes.



* In individuals **with** atherosclerotic cardiovascular disease, history of heart failure (with reduced ejection fraction) or chronic kidney disease, agents with cardiorenal benefits (Figures 2A and 2B) may be considered (see Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update – The User's Guide).
† Unintentional weight loss should prompt consideration of other diagnoses (e.g. type 1 diabetes or pancreatic disease).
†† Reassess need for ongoing insulin therapy once type of diabetes is established and response to health behaviour interventions is assessed.
A1C, glycated hemoglobin; *CPG*, clinical practice guidelines.

Diabetes Canada Guidelines

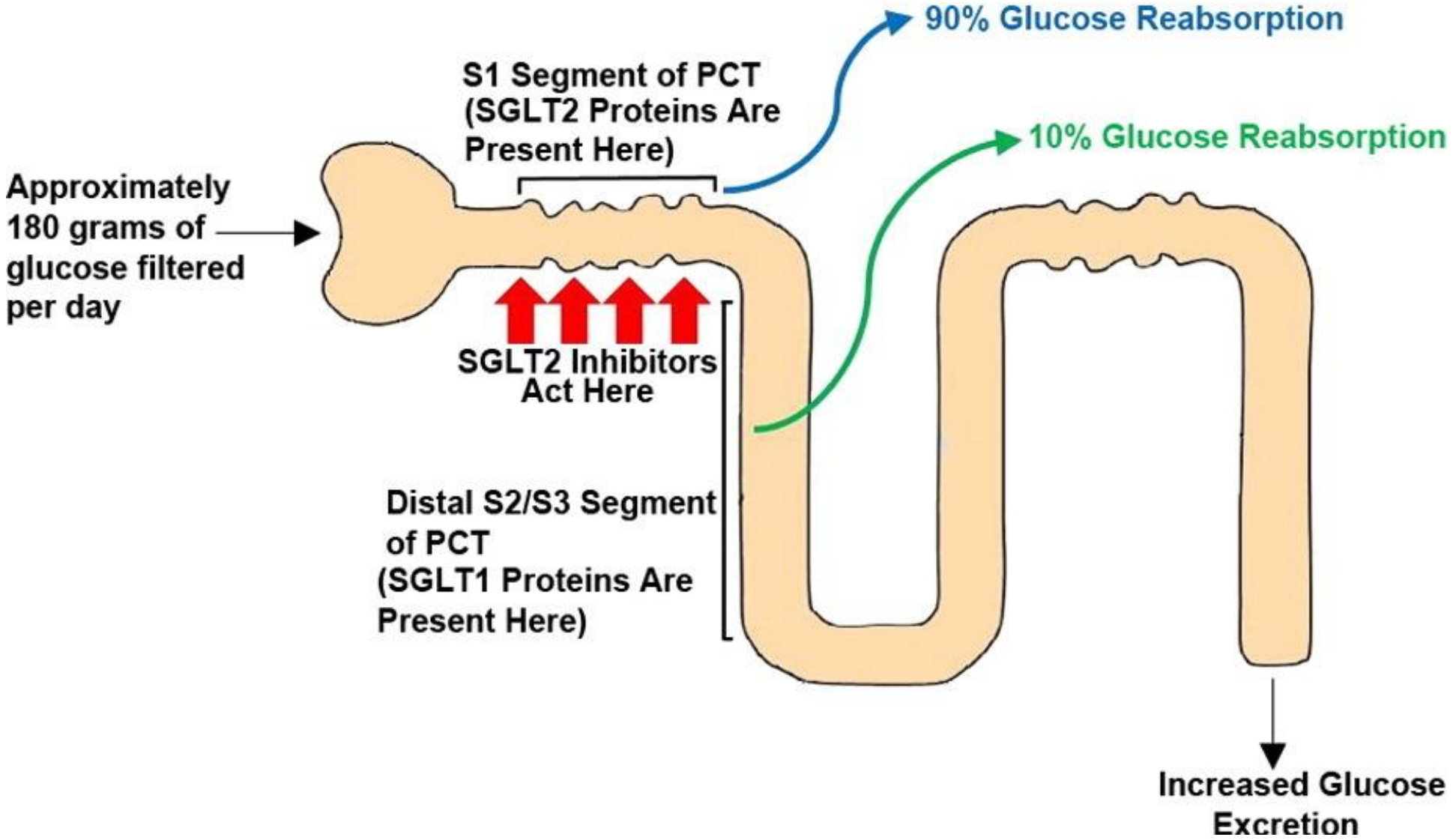
Figure 2A
Reviewing, adjusting or advancing therapy in type 2 diabetes.



* Changes in clinical status may necessitate adjustment of glycemic targets and/or deprescribing.
† Tobacco use; dyslipidemia (use of lipid-modifying therapy or a documented untreated low-density lipoprotein (LDL) ≥3.4 mmol/L, or high-density lipoprotein-cholesterol (HDL-C) <1.0 mmol/L for men and <1.3 mmol/L for women, or triglycerides ≥2.3 mmol/L); or hypertension (use of blood pressure drug or untreated systolic blood pressure [SBP] ≥140 mmHg or diastolic blood pressure [DBP] ≥95 mmHg).
†† All antihyperglycemic agents (AHAs) have Grade A evidence for effectiveness to reduce blood glucose levels.
††† Consider degree of hyperglycemia, costs and coverage, renal function, comorbidity, side effect profile and potential for pregnancy.
** In CV outcome trials performed in people with atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), heart failure (HF) or at high cardiovascular (CV) risk.
*** VERTIS (CV outcome trial for ertugliflozin) presented at American Diabetes Association (ADA) June 2020 showed noninferiority for major adverse CV events (MACE). Manuscript not published at time of writing.
A1C, glycated hemoglobin; *DPP4i*, dipeptidyl peptidase-4 inhibitors; *eGFR*, estimated glomerular filtration rate; *GLP1-RA*, glucagon-like peptide-1 receptor agonists; *exenatide ER*, exenatide extended-release; *HHF*, hospitalization for heart failure; *SGLT2i*, sodium-glucose cotransporter 2 inhibitors; *yrs*, years.

SGLT2 inhibitors

SGLT2 inhibitors: Mechanism of Action in Type 2 Diabetes



Madaan T, Akhtar M, Najmi AK. Sodium glucose CoTransporter 2 (SGLT2) inhibitors: Current status and future perspective. Eur J Pharm Sci. 2016 Oct 10;93:244-52. doi: 10.1016/j.ejps.2016.08.025. Epub 2016 Aug 12. PMID: 27531551.

SGLT2 inhibitors: Clinical Evidence in T2DM

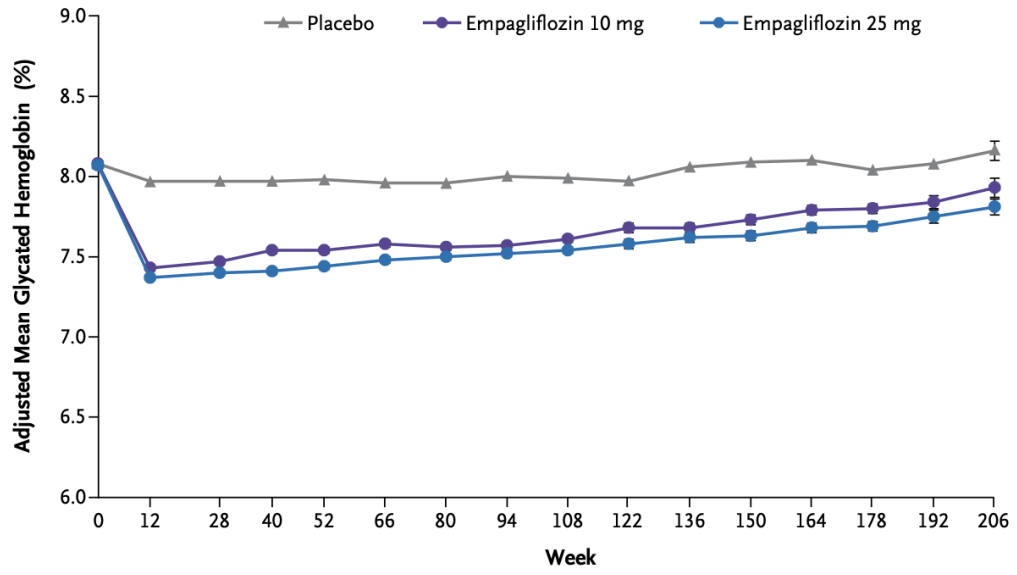
SGLT2 inhibitors	Landmark Trials	Primary Outcomes	Results
Canagliflozin	**CANVAS** N=10142/3.6 years Type 2 DM, high CV risk	Reduction in CV death Non-fatal myocardial infraction or stroke	HR 0.86, 95% CI 0.74 to 0.99
Empagliflozin	**EMPA-REG** N=7020/3.1yr Type 2 DM, established CV disease	CV death non-fatal myocardial infarction or stroke	HR 0.86, 95% CI 0.75 to 0.87
Dapagliflozin	**DECLARE-TIMI 58** N=17160/4.2yr Type 2 DM, established CV disease or multiple risk factors	CV death, non-fatal myocardial infarction or stroke	HR 0.93, 95% CI 0.84 to 1.03

Potential Mechanisms of Cardiovascular Benefits Associated with SGLT2 inhibitor therapy

Conventional Mechanisms	Novel Mechanisms
Diuresis and reduction in blood pressure	Improved myocardial energetics
Improved glycemic control	Improved myocardial ionic homeostasis
Weight loss	Autophagy
Increased in red blood cell mass and hematocrit	Altered adipokine regulation

Joshi SS, Singh T, Newby DE, Singh J. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. Heart. 2021 Feb 26;107(13):1032–8. doi: 10.1136/heartjnl-2020-318060. Epub ahead of print. Erratum in: Heart. 2021 Nov;107(22):e15. PMID: 33637556; PMCID: PMC8223636.

How well can SGLT2-inhibitors lower HbA1c?



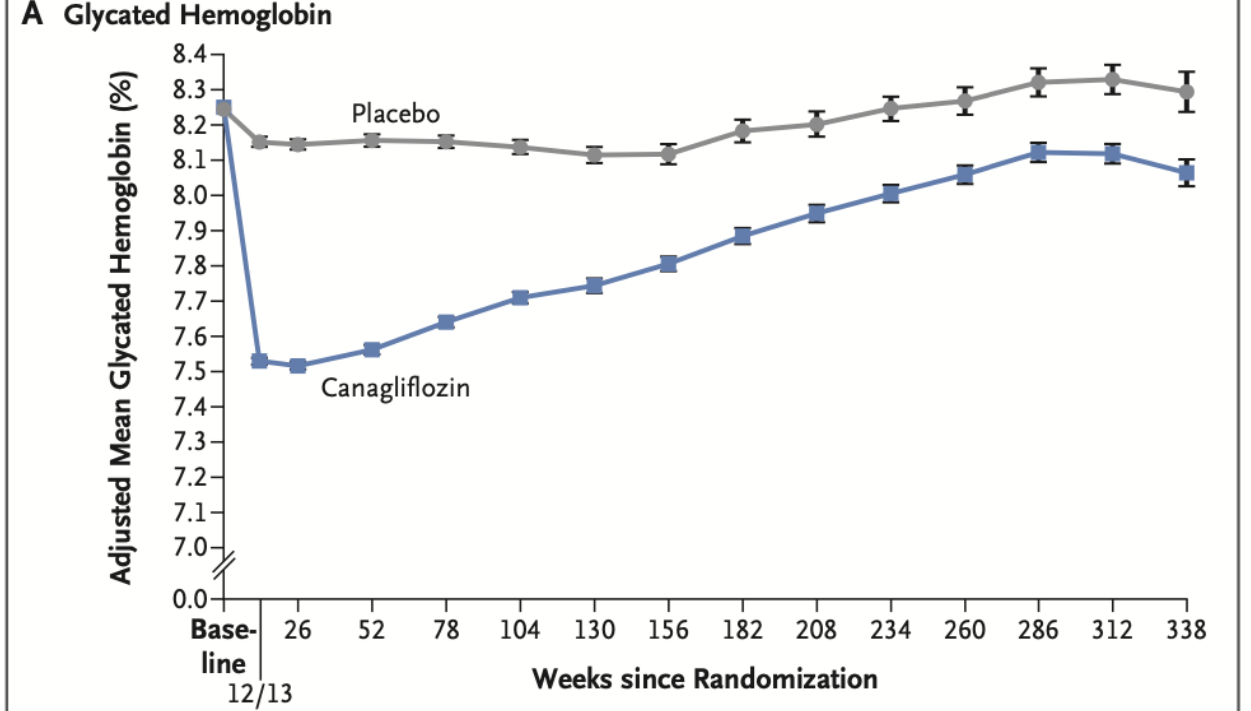
No. at Risk

Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

Figure 3. Glycated Hemoglobin Levels.

Shown are mean (±SE) glycated hemoglobin levels in the three study groups, as calculated with the use of a repeated-measures analysis as a mixed model of all data for patients who received at least one dose of a study drug and had a baseline measurement. The model included baseline glycated hemoglobin as a linear covariate, with baseline estimated glomerular filtration rate, geographic region, body-mass index, the last week a patient could have had a glycated hemoglobin measurement, study group, visit, visit according to treatment interaction, and baseline glycated hemoglobin according to visit interaction as fixed effects.

Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28. doi: 10.1056/NEJMoa1504720. Epub 2015 Sep 17. PMID: 26378978.



No. of Patients

Placebo	4231	3987	3854	3539	2891	1561	1014	878	899	783	805	726	695	245
Canagliflozin	5644	5329	5211	4864	4228	2778	2206	1965	2042	1797	1889	1690	1661	556

Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377(7):644-657. doi: 10.1056/NEJMoa1611925. Epub 2017 Jun 12. PMID: 28605608.

HbA1c Reduction ~ 0.4-0.7%

Benefits of SGLT2 inhibitors

- Improve glycemic control modestly
- Contribute to weight loss
- Low risk for hypoglycemia (as a monotherapy)
- Improve blood pressure control
- Oral route of administration

Safety Concerns with SGLT2 inhibitors

- Euglycemic Ketoacidosis
- Urinary Tract Infection / Urosepsis / Pyelonephritis
- Mycotic Yeast Infection / Genital Tract Skin Infection
- Acute Kidney Injury and Transient Hyperkalemia

- ? Limb Amputations / Fracture / Bladder Cancer

SGLT2 inhibitors: Clinical Evidence in Heart Failure

SGLT2 inhibitors	Trials	Patient Population	Outcomes & Results
Empagliflozin	**EMPA-REG**	**Patients with:** • Type 2 Diabetes Mellitus • Established CV disease • BMI≤ 45kg/m2 • GFR > 30mL/min	**Secondary Outcomes:** • HF hospitalization lower in empagliflozin group vs placebo (HR 0.65, 95% CI 0.50 to 0.85) • HF hospitalization and CV death (excluding fatal stroke) lower in empagliflozin group vs placebo (HR 0.66, 95% CI 0.55 to 0.79)
	EMPEROR-Reduced	**Patients with:** • Chronic HF, NYHA class II/III/IV • LVEF≤ 40%, HF hospitalization within 12 months • 50% patients with type 2 DM	**Primary outcomes**: • CV death or HF hospitalization for empagliflozin vs placebo (HR 0.75, 95% CI 0.65 to 0.86)
	EMPEROR-Preserved	**Patients with:** • NYHA class II/III/IV • LVEF >40%	**Primary outcomes**: • CV death or HF hospitalization for empagliflozin vs placebo (H 0.79, 95% CI 0.69 to 0.90)

SGLT2 inhibitors: Clinical Evidence in Heart Failure

SGLT2 inhibitors	Trials	Patient Population	Outcomes & Results
Dapagliflozin	**DECLARE-TIMI 58**	**Patients with** • Type 2 diabetes mellitus • Established CV disease or multiple risk factors	**Secondary Outcomes:** • Reduction in CV death or HF hospitalization in dapagliflozin vs placebo (HR 0.83, 95% CI 0.73 to 0.95) • Reduction in HF hospitalization (HR 0.73, 95% CI 0.61 to 0.88)
	DAPA-HF	**Patients with:** • Symptomatic heart failure • LVEF ≤ 40%, • 50% patients with type 2 DM	**Primary Outcomes:** • Reduction in CV death, urgent heart failure visit or HF hospitalization in dapagliflozin group vs placebo (HR 0.74, 95% CI 0.65 to 0.85) **Secondary Outcomes:** • Fewer HF symptoms reported on KCCQ in dapagliflozin group vs placebo (HR 1.18, 95% CI 0.65 to 0.85) • Reduction in CV death and HF hospitalization (HR 0.75, 95% CI 0.65 to 0.85) • Benefits seen in both diabetics and non-diabetics
Canagliflozin	**CANVAS**	**Patients with:** • Type 2 diabetes mellitus • High CV risk	**Secondary outcome**: • Reduction in CV death and HF hospitalization greater in patients with known heart failure (HR 0.78, 95% CI 0.67 to 0.91)
	CHIEF-HF	**Patients with:** • Heart Failure (HFpEF, HFrEF) • ~29% with Type2 DM	**Primary outcome**: • The 12 week change in KCCQ TSS was 4.3 points (95% CI, 0.8-7.8; p=0.016) higher with canagliflozin than with placebo.

SGLT2-inhibitors – Mechanism of Action in Heart Failure

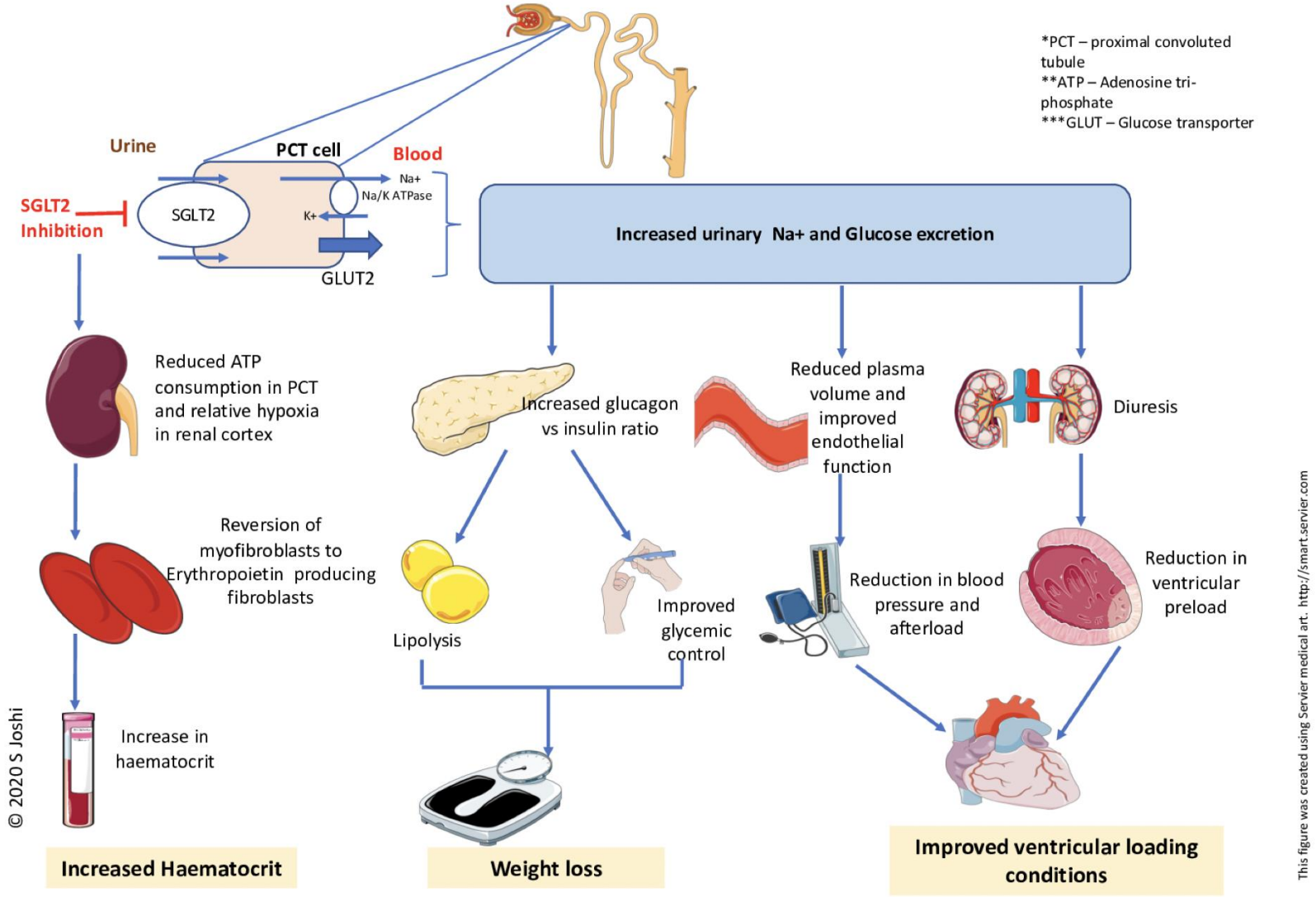


Figure 1 Schematic diagram showing conventional mechanisms of action of SGLT2 inhibitors. SGLT, sodium-glucose co-transporter.

Joshi SS, Singh T, Newby DE, Singh J. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. Heart. 2021 Feb 26;107(13):1032–8. doi: 10.1136/heartjnl-2020-318060. Epub ahead of print. Erratum in: Heart. 2021 Nov;107(22):e15. PMID: 33637556; PMCID: PMC8223636.

Role of SGLT2 inhibitors in Heart Failure

RECOMMENDATION

1. In adults with HF and LVEF $\leq$ 40%, we recommend use of SGLT2i to reduce all-cause and CV mortality, hospitalization for HF, and the composite end point of significant decline in eGFR, progression to end-stage kidney disease, or death due to kidney disease (Strong Recommendation; Moderate-Quality Evidence).

RECOMMENDATION

2. In adults with HF and LVEF $>$ 40%, we recommend use of SGLT2i to reduce hospitalization for HF (Strong Recommendation; Moderate-Quality Evidence).

- SGLT2 inhibitor is now a standard of care in heart failure
- If prescribing SGLT2 inhibitors for heart failure, suggest to reassess diuretic therapies (e.g., stop / reduce dose of furosemide)
- If the patient has Type 2 diabetes and on insulins or oral hypoglycemics, may need to assess and adjust therapies to minimize hypoglycemic risk.

Mancini GBJ, O'Meara E, Zieroth S, Bernier M, Cheng AYY, Cherney DZI, Connelly KA, Ezekowitz J, Goldenberg RM, Leiter LA, Nesrallah G, Paty BW, Piché ME, Senior P, Sharma A, Verma S, Woo V, Darras P, Grégoire J, Lonn E, Stone JA, Yale JF, Yeung C, Zimmerman D. 2022 Canadian Cardiovascular Society Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults. Can J Cardiol. 2022 Aug;38(8):1153-1167. doi: 10.1016/j.cjca.2022.04.029. PMID: 35961754.

SGLT2-inhibitors – Mechanism of Action in Chronic Kidney Disease

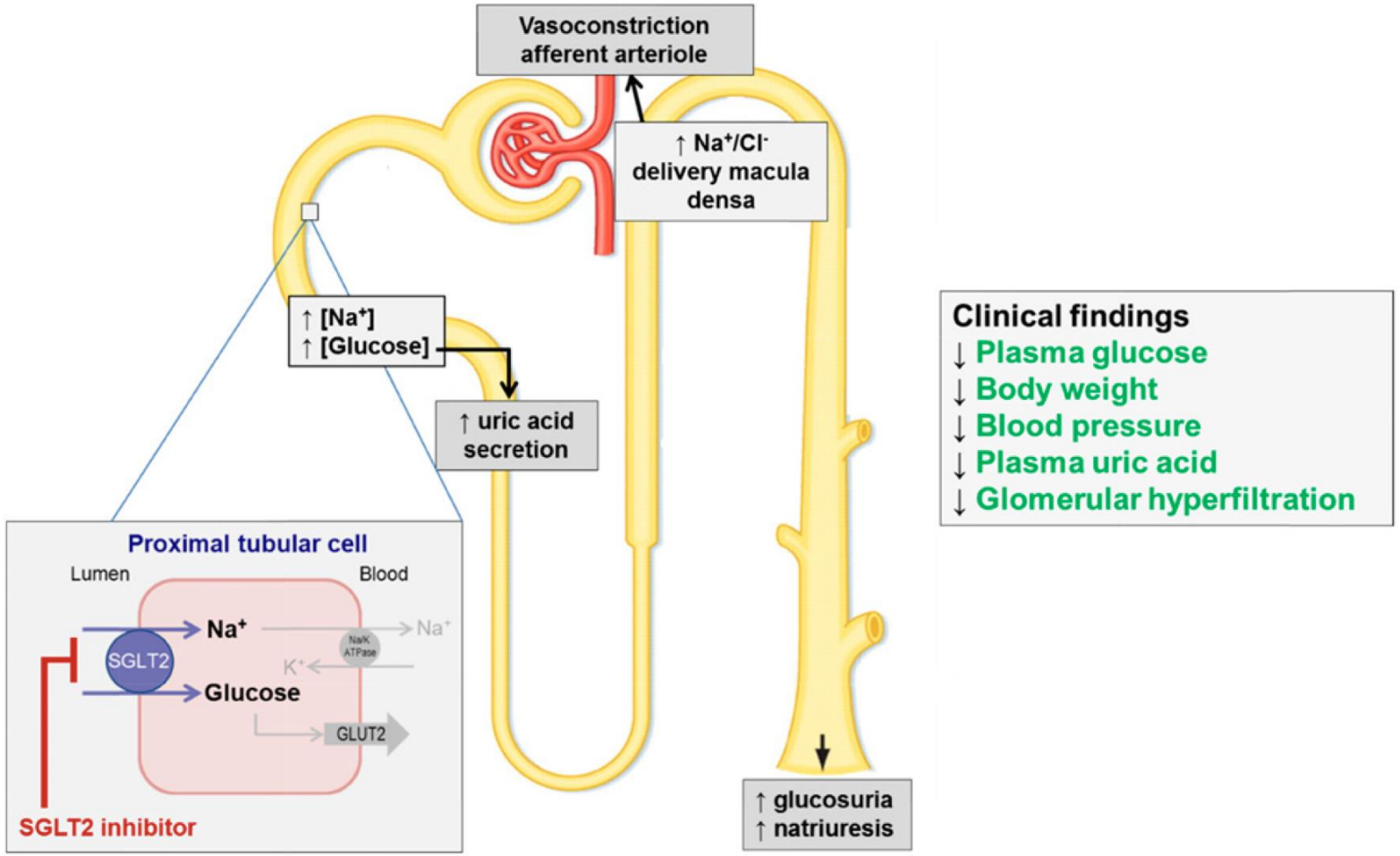
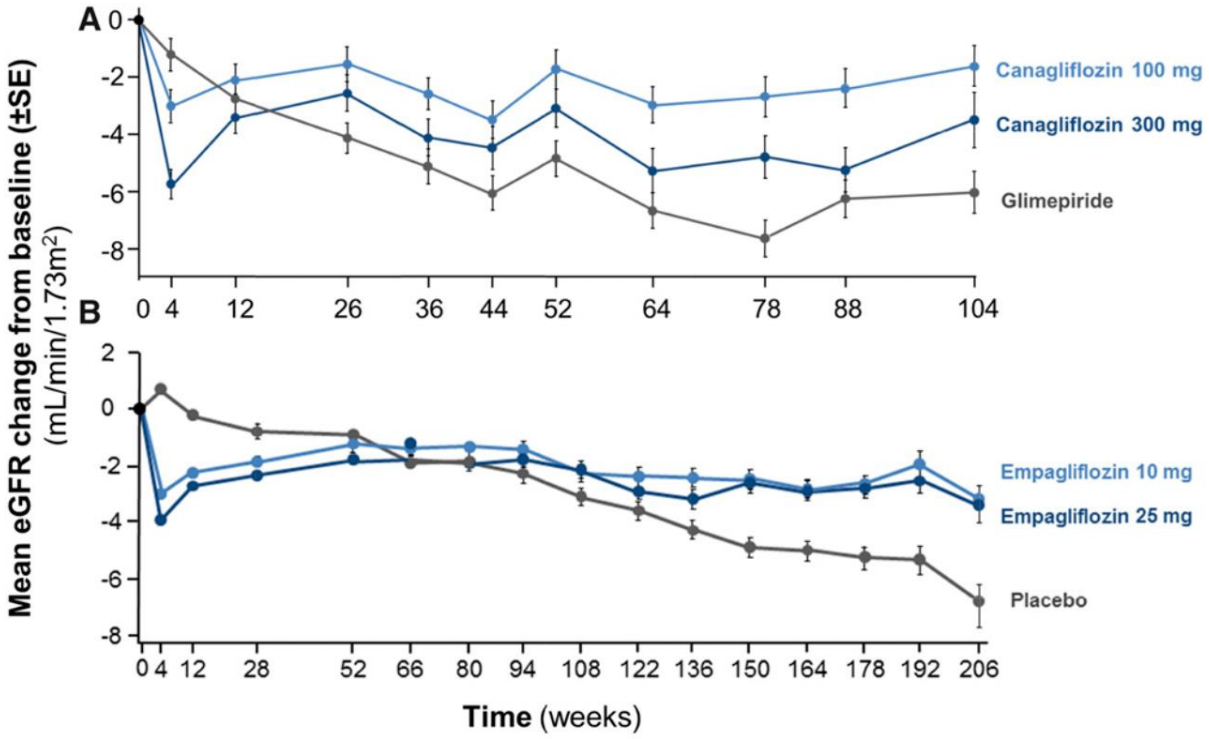


Figure 2. | **The SGLT2 inhibitors affect multiple sites in the diabetic kidney**. This figure summarizes the effect that SGLT2 inhibition has on an individual nephron, which in turn, improves different renal risk factors in type 2 diabetes. ATPase, adenosine triphosphatase; GLUT2, glucose transporter 2.

van Bommel EJ, Muskiet MH, Tonneijck L, Kramer MH, Nieuwdorp M, van Raalte DH. SGLT2 Inhibition in the Diabetic Kidney-From Mechanisms to Clinical Outcome. Clin J Am Soc Nephrol. 2017 Apr 3;12(4):700-710. doi: 10.2215/CJN.06080616. Epub 2017 Mar 2. PMID: 28254770; PMCID: PMC5383382.

SGLT2 inhibitors and eGFR trajectory



- eGFR may decline within the first 4 weeks.
- Overtime, SGLT2 inhibitors may prevent long term eGFR decline compared to glimepiride or placebo

Figure 3. | **SGLT2 inhibitors induce stabilization of eGFR trajectory when compared to SU or placebo**. This figure is on the basis of data from long-term follow-up of (A) the efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes Inadequately controlled with metformin (CANTATA-SU) Trial (44) and (B) the Randomized, placebo-controlled cardiovascular outcome trial of empaglifozin (EMPA-REG OUTCOME) Trial (5). A shows that the initial eGFR drop after 4 weeks of treatment, seen with both doses of canagliflozin, prevents long-term eGFR decline compared with glimepiride. The same effect is seen in B, where empagliflozin is compared with placebo. SGLT2 inhibition, thus, prevents deterioration of renal function, which often occurs in type 2 diabetes over time.

van Bommel EJ, Muskiet MH, Tonneijck L, Kramer MH, Nieuwdorp M, van Raalte DH. SGLT2 Inhibition in the Diabetic Kidney-From Mechanisms to Clinical Outcome. Clin J Am Soc Nephrol. 2017 Apr 3;12(4):700-710. doi: 10.2215/CJN.06080616. Epub 2017 Mar 2. PMID: 28254770; PMCID: PMC5383382.

SGLT2 inhibitors: Clinical Evidence in Chronic Kidney Disease

SGLT2 inhibitors	Trials	Patient Population	Main Renal Endpoints	Results
Canagliflozin	**CANVAS**	**Patients with:** • Type 2 Diabetes Mellitus • High CV risk	**Secondary**: • Albuminuria progression • Sustained 40% reduction in eGFR, need for RRT and death from renal causes	**Secondary:** • HR 0.73; 95% CI, 0.67 to 0.79 • HR 0.60; 95% CI, 0.47 to 0.77
	CREDENCE	**Patients with:** • Type 2 Diabetes • eGFR 30-90mL/min, • UACR 300-5000 mg/g • ACEi or ARB use	**Primary:** Composite renal endpoint (ERSD, doubling of SCr, renal or CV death)	**Primary:** • HR 0.70; 95% CI, 0.59 to 0.82; p=0.00001
Dapagliflozin	**DECLARE-TIMI 58**	**Patients with:** • Type 2 Diabetes • Established CV disease or multiple risk factors	**Secondary**: reduction in death due to renal or CV causes	**Secondary:** HR 0.53, 95% CI 0.43 to 0.66
	DAPA-CKD	**Patients with:** • eGFR 25-75mL/min • UACR 200 to 5000mg/g	**Primary:** Composite of sustained decline in eGFR of at least 50%, ESKD or death from renal or CV causes)	**Primary:** HR 0.61, 95% CI, 0.51 to 0.72; p< 0.001

SGLT2 inhibitors: Clinical Evidence in Chronic Kidney Disease

SGLT2 inhibitors	Trials	Patient Population	Main Renal Endpoints	Results
Empagliflozin	**EMPA-REG**	**Patients with:** • Type 2 Diabetes • Established CV disease • BMI ≤ 45 kg/m2 • GFR > 30	**Exploratory**: • New onset of macroalbuminuria • New onset or worsening of diabetic kidney disease • Doubling of serum creatinine • Initiation of RRT	**Exploratory** • HR 0.62 (0.54 to 0.72) • HR 0.61 (0.53 to 0.70) • HR 0.56 (0.39 to 0.79) • HR 0.45 (0.21 to 0.97)
	EMPA-KIDNEY	**Patients with Evidence of progressive CKD:** • eGFR ≥ 20 and < 45mL/min/1.73m2 or • eGFR ≥ 45mL and < 90mL/min/1.732 with uACR ≥ 200mg/g (or protein: creatinine ratio ≥ 300mg/g)	**Primary:** • 1st occurrence of a composite of kidney disease progression (defined as ESKD, a sustained decline in eGFR to < 10mL/min/1.73m3, renal death, or a sustained decline of ≥ 40% in eGFR from randomization or cardiovascular death	Not available; study terminated prematurely due to overwhelming positive efficacy results.

Role of SGLT2 inhibitors in Chronic Kidney Disease

RECOMMENDATION

3. In adults with CKD (UACR > 20 mg/mmol and eGFR ≥ 25 mL/min/1.73 m^2), we recommend use of SGLT2i to reduce the composite of significant decline in eGFR, progression to end stage kidney disease, or kidney death, all-cause and CV mortality, nonfatal MI, and hospitalization for HF (Strong recommendation, Moderate-Quality Evidence).

Mancini GBJ, O'Meara E, Zieroth S, Bernier M, Cheng AYY, Cherney DZI, Connelly KA, Ezekowitz J, Goldenberg RM, Leiter LA, Nesrallah G, Paty BW, Piché ME, Senior P, Sharma A, Verma S, Woo V, Darras P, Grégoire J, Lonn E, Stone JA, Yale JF, Yeung C, Zimmerman D. 2022 Canadian Cardiovascular Society Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults. Can J Cardiol. 2022 Aug;38(8):1153-1167. doi: 10.1016/j.cjca.2022.04.029. PMID: 35961754.

- SGLT2 inhibitors benefit most in individuals with overt nephropathy (UACR >20mg/mmol)
- May be added to prevent progression of chronic kidney disease or further decline in eGFR
- In the setting of LTC, the use of SGLT2 inhibitor for CKD needs to be balanced between benefits and risks.

SGLT2 inhibitors – Renal Adjustment Considerations

- **At reduced renal function:**
  - Efficacy in glycemic control goes down. However, it still exerts its cardiovascular and renal benefits.
  - The risk of side effects increases (e.g., UTI, urinary incontinence).
- **In general, avoid if eGFR ≤ 30mL/min. Usually use the lower dose.**
  - Avoid if renal function is unstable
- **In recent trials in HF and CKD, we have experience with patients taking SGLT2 inhibitors with eGFR ~ 25mL/min**

SGLT2 inhibitors: Dosing and Renal Adjustment

SGLT2	Dosing for Type 2 Diabetes	Dosing for Heart Failure*	Dosing for Chronic Kidney Disease *	Renal Adjustment	ODB coverage
Canagliflozin (Invokana)	Start: 100mg po daily Max: 300mg po daily	100mg daily	100mg daily	100mg daily	Yes
Empagliflozin (Jardiance)	Start: 10mg po daily Max: 25mg po daily	10mg daily	10mg daily	10mg daily	Yes
Dapagliflozin (Foxiga)	Start: 5mg po daily Max: 10mg po daily	10mg daily	10mg daily	5mg daily	Yes

SGLT2 inhibitors – Place in Therapy in LTC

- For Type 2 Diabetes, Heart Failure and Chronic Kidney Disease
- Caution in individuals with history of recurrent UTI, risk of dehydration and urinary incontinence
- Hold SGLT2 inhibitors (e.g., SADMANS drugs) when there is risk of dehydration (e.g., diarrhea) to prevent euglycemic ketoacidosis
- When initiating a SGLT2 inhibitor, adjust other diuretics as necessary
- For patients with Type 2 diabetes, may need to adjust insulin therapy or other oral hypoglycemics to minimize risk of hypoglycemia

GLP-1 Agonists

GLP1 agonists – Mechanism of Action

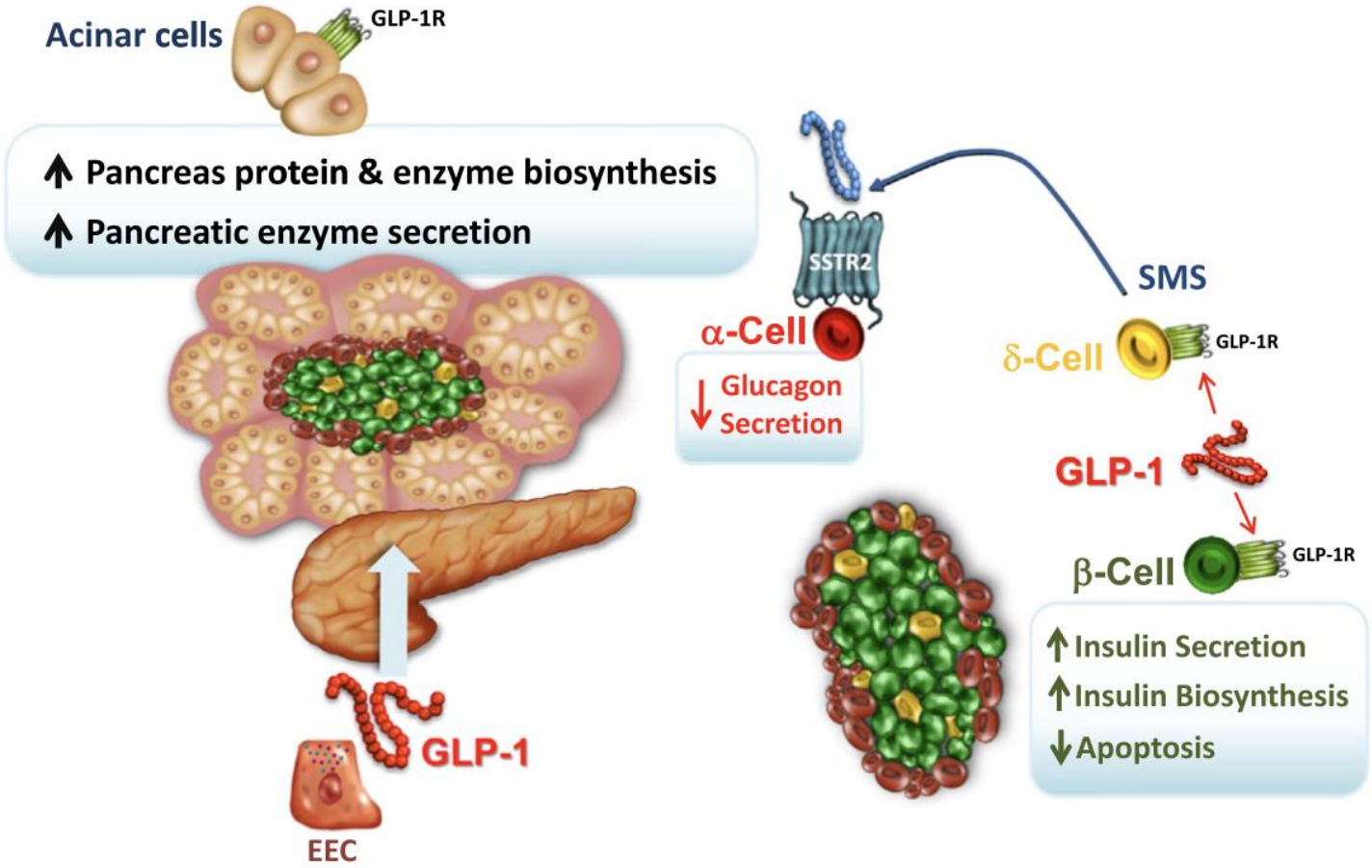


Figure 2. Pancreatic Endocrine and Exocrine Actions of GLP-1 on Islet and Acinar Cells

GLP-1 acts through the GLP-1 receptor (GLP-1R) expressed on islet β cells and δ cells to control insulin and somatostatin (SMS) secretion, respectively. SMS in turn inhibits glucagon secretion from islet α cells via the somatostatin-2 receptor (SSTR2).

Glucagon-like-Peptide-1 Actions:

1) GLP-1 increases glucose-dependence insulin synthesis and secretion in the pancreatic islets.
2) GLP-1 acts as a neurotransmitter and can act on both the CNS (satiety and loss appetite) and peripheral nervous system.
3) GLP-1 delays gastric emptying and inhibits pentagastrins and acid secretion stimulated by food ingestion.
4) GLP-1 has cardiovascular benefits on blood pressure, the vascular endothelium, atherosclerosis progression and inflammation, myocardial ischemia, heart failure.

Drucker DJ. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. Cell Metab. 2018 Apr 3;27(4):740-756. doi: 10.1016/j.cmet.2018.03.001. PMID: 29617641.

Del Olmo-Garcia MI, Merino-Torres JF. GLP-1 Receptor Agonists and Cardiovascular Disease in Patients with Type 2 Diabetes. J Diabetes Res. 2018 Apr 2;2018:4020492. doi: 10.1155/2018/4020492. PMID: 29805980; PMCID: PMC5902002.

How well can GLP1 agonist reduce HbA1c & Weight?

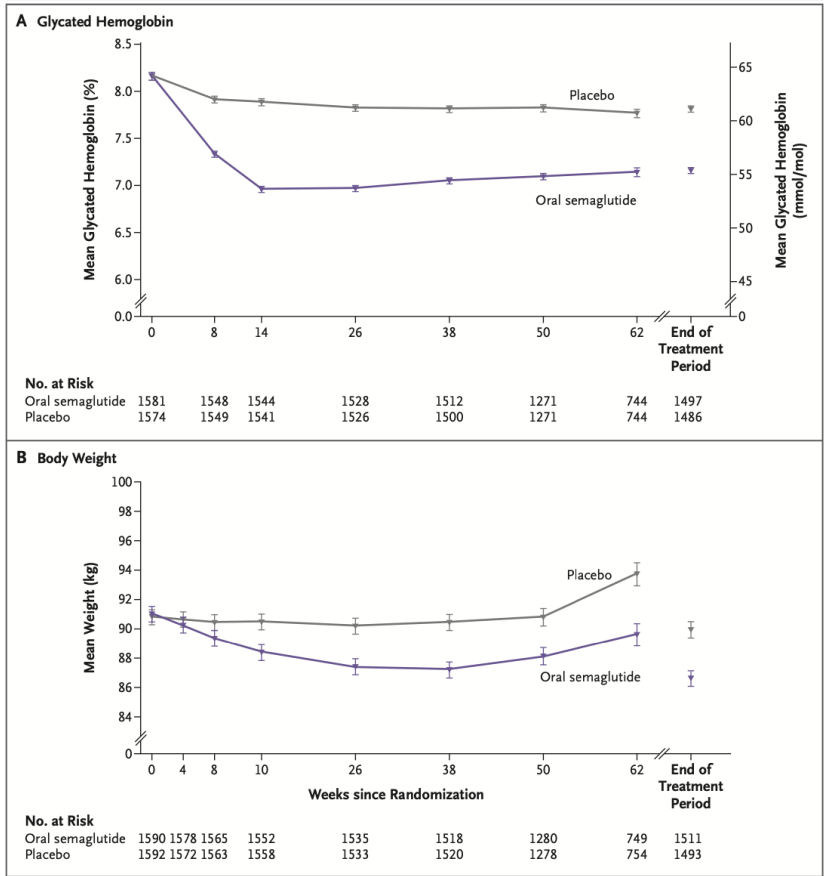


Figure 2. Efficacy Outcomes (In-Trial Observation Period).

The curves show the observed change from baseline in the glycated hemoglobin level (Panel A) and body weight (Panel B). Data are for the full analysis set during the in-trial observation period, which was from randomization to the last visit (end of treatment). The end of treatment occurred when the required number of first major adverse cardiovascular events was exceeded. The individual patients' in-trial observation period ranged from 2 to 87 weeks, with a median duration of 69 weeks. I bars indicate standard errors.

Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jul 28;375(4):311-22. doi: 10.1056/NEJMoa1603827. Epub 2016 Jun 13. PMID: 27295427; PMCID: PMC4985288.

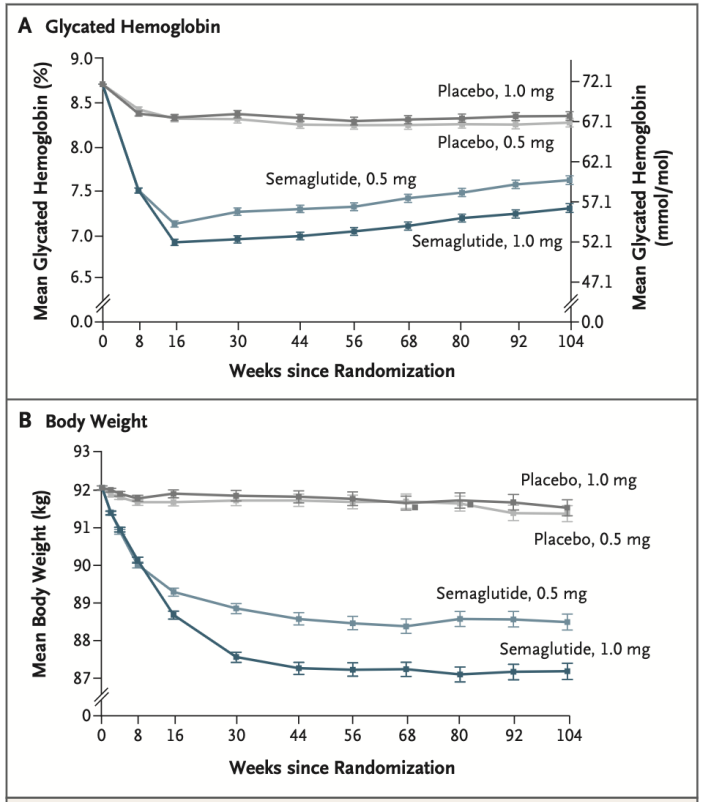


Figure 2. Glycated Hemoglobin and Body Weight.

Shown are the mean values for glycated hemoglobin (Panel A) and body weight (Panel B) during the trial period. The I bars represent standard errors. Data were estimated on the basis of scheduled visits in the full analysis set with the use of a mixed model for repeated measures with treatment group (semaglutide doses of 0.5 mg and 1.0 mg and corresponding placebo doses) and all possible combinations of stratification factors used for randomization as fixed factors.

Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016 Nov 10;375(19):1834-1844. doi: 10.1056/NEJMoa1607141. Epub 2016 Sep 15. PMID: 27633186.

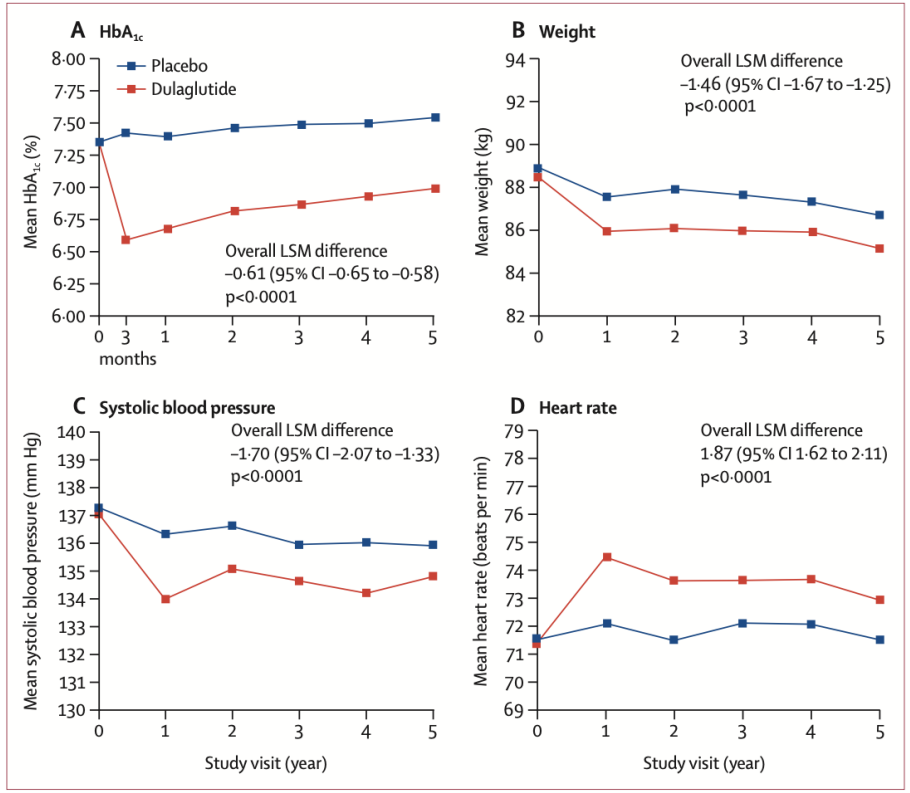


***Figure 4:* Continuous measures during follow-up**

LSM=least-square means. HbA_{1c}=glycated haemoglobin A_{1c}.

Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Riesmeyer JS, Riddle MC, Rydén L, Xavier D, Atisso CM, Dyal L, Hall S, Rao-Melacini P, Wong G, Avezum A, Basile J, Chung N, Conget I, Cushman WC, Franek E, Hancu N, Hanefeld M, Holt S, Jansky P, Keltai M, Lanas F, Leiter LA, Lopez-Jaramillo P, Cardona Munoz EG, Pirags V, Pogosova N, Raubenheimer PJ, Shaw JE, Sheu WH, Temelkova-Kurktschiev T; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019 Jul 13;394(10193):121-130. doi: 10.1016/S0140-6736(19)31149-3. Epub 2019 Jun 9. PMID: 31189511.

HbA1c Reduction ~ 1.0-1.5%; Weight Reduction ~ 1-3 kg

GLP1 agonists – Benefits

- Improve glycemic controls (up to 1-1.5% drop in HgA1c)
- Contribute to Weight loss
- Minimal hypoglycemia as a monotherapy*
- Minimally affected by Chronic Kidney Disease
- Once weekly injection with semaglutide may improve adherence

GLP1 agonists – Safety and Tolerance

- Gastrointestinal Side Effects during initiation and titration
- Affect appetite and intake
- Injection site irritation
- Risk of Hypoglycemia with insulin or other oral hypoglycemic agents
- Risk of Pancreatitis
- ? Thyroid Cancer/Thyroid C-cell tumours
- ? Gallbladder disease (liraglutide)

GLP1 agonists: Clinical Evidence in T2DM

GLP1 agonist	Landmark Trials	Primary Outcomes	Results
Liraglutide	**LEADER** N=9340 patients (3.8 years)	First occurrence of death from cardiovascular causes, non-fatal myocardial infarction and nonfatal stroke	HR 0.87; 95% CI, 0.78 to 0.97; p< 0.001 for non-inferiority
Semaglutide	**SUSTAIN-6** N=3297 patients (2.1 years)	First occurrence of death from cardiovascular causes, nonfatal myocardial infarction and nonfatal stroke	HR 0.74, 95% CI, 0.58 to 0.95; p < 0.001 for non-inferiority
Dulaglutide	**REWIND** N=9901 patients (N=5.4 years)	First occurrence of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes (including unknown causes)	HR 0.88, 95% CI 0.79 to 0.99; p=0.026

GLP-1 agonists – Available Options

GLP-1 agonists	Diabetes Dosing	Cardiorenal Benefits	ODB coverage
Exenatide (Byetta)	5mg subcut BID (max 10mg subcut BID)	No	No
Liraglutide (Victoza)	0.6mg subcut daily for 1 week, 1.2mg subcut daily for 1 week, 1.8mg subcut daily thereafter	Yes (LEADER)	No
Dulaglutide (Trulicity)	0.75mg subcut weekly (max 1.5mg subcut weekly)	Yes (SUSTAIN-6)	No
Semaglutide (Ozempic)	0.25mg subcut weekly for 4 weeks, then 0.5mg subcut weekly thereafter (Max 1mg/week but recent evidence with 2mg/week from SUSTAIN FORTE)	Yes (REWIND)	Yes
Semaglutide (Rebelsys)	3mg po daily x 30 days, then 7mg po daily x 30 days, then 14mg po daily thereafter	No	No
Lixisenatide (Adlyxine)	10mg subcut daily for 2 weeks, then 20mg subcut daily thereafter	No	Yes

GLP1 agonist – Clinical Considerations

- **Improve glycemic control with ~ 1-1.5% reduction in HbA1C. Agents proven with CV benefits include: liraglutide, semaglutide and dulaglutide. An alternative to rapid-acting insulin**

- **Gastrointestinal side effects are very common**; Start low and titrate slowly and monitor tolerance before further increasing the dose

- **Stop DPP4 inhibitors**. If individual is on a DPP4 inhibitor (e.g., linagliptin, sitagliptin), these agents should be discontinued as they work along the same pathway/mechanism of action

- **Monitor glucose closely and adjust insulins or oral hypoglycemic agents as needed.** If individual is on insulins or other oral hypoglycemic agents, may need to monitor closely or reduce dose pre-emptively.

- **Avoid in frail individuals or individuals with difficulty maintaining current weight**

- **In LTC setting, should have a policy in place how to give weekly injection across the institution (e.g., every Tuesday)**

Questions?