# Diabetes Update

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# Disclosures

I sit on the Diabetes Canada clinical practice guidelines committee

I will present information from this source and from other sources

My research is focused on diabetes prevention, reversal, and management using nonpharmacological strategies. My research is funded by the CIHR, Heart & Stroke Foundation, Lawson Foundation, and JR McConnell Foundations

# Goals of type 2 diabetes care

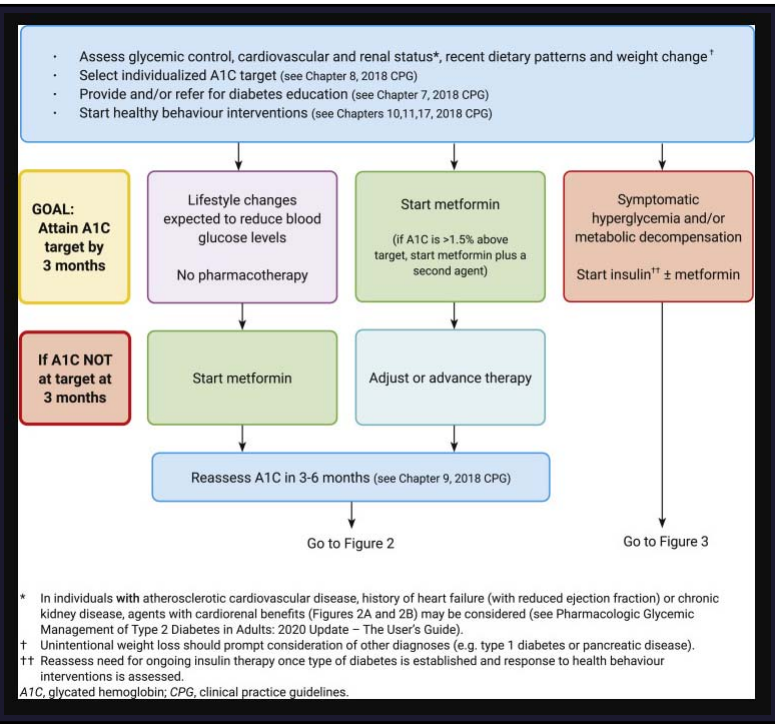
**Prevent and treat hyperglycemia symptoms**

- Dehydration, fatigue, polyuria, hyperosmolar states

**Lower risks of diabetes-related complications**

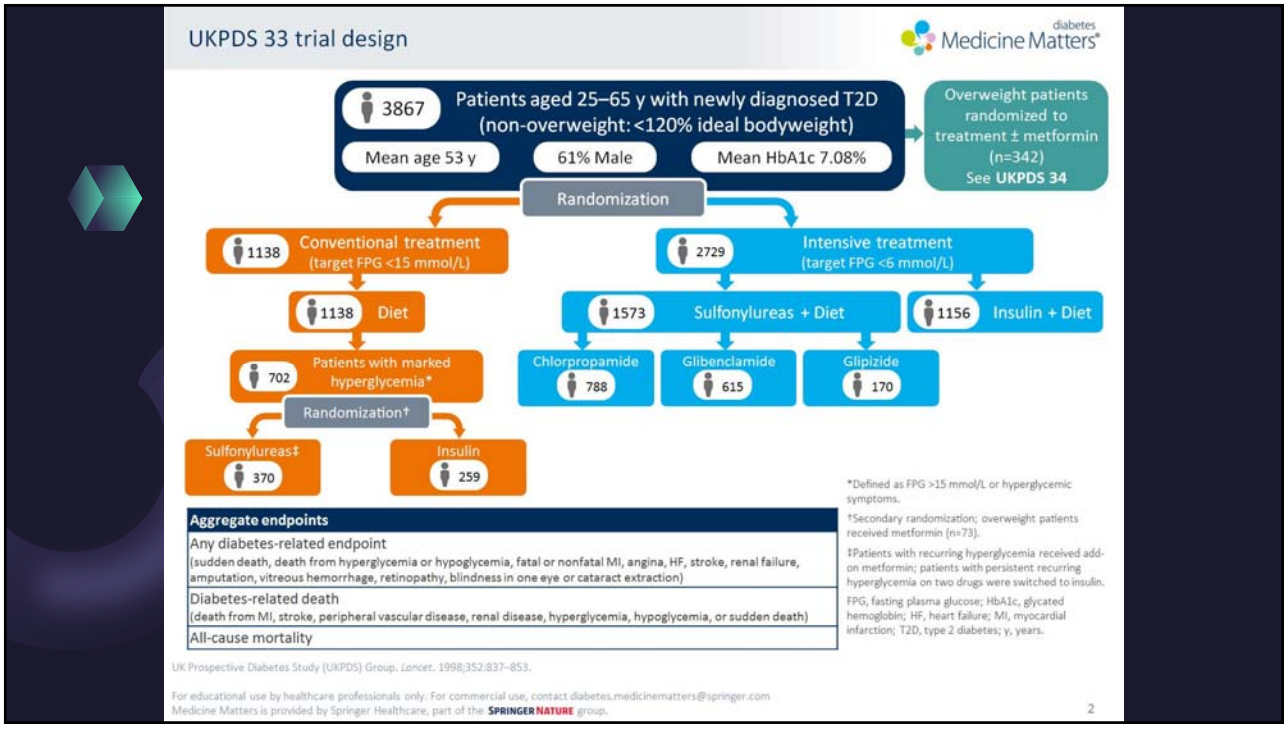
- Physical activity and exercise
- Weight control
- Dietary changes
- Medications to control blood glucose levels: **some of these medications have benefits beyond glucose lowering**
- Medications to control blood pressure
- LDL lowering medications
- Other vascular protective medications like ASA

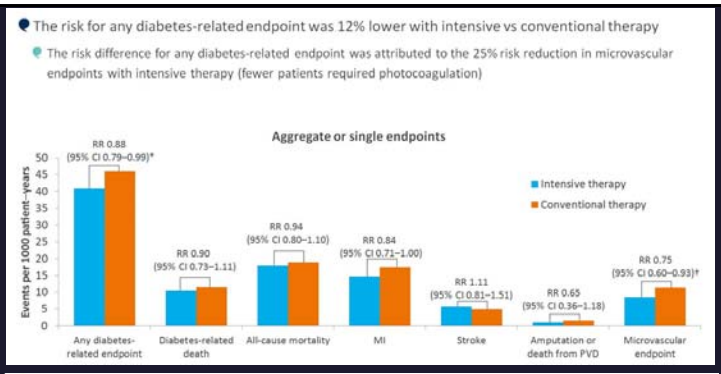
DIABETES CANADA

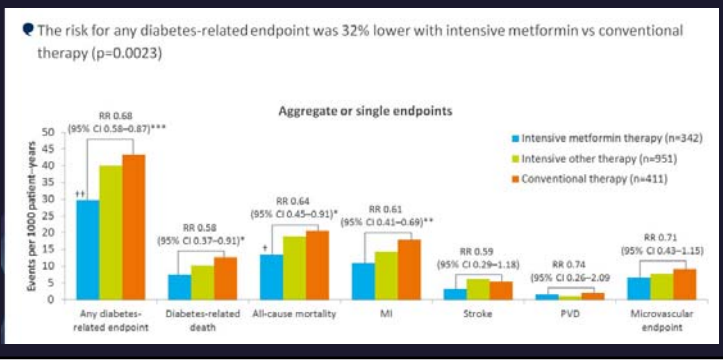


# ERA 1: UKPDS 1998

A1C 7% vs. 8%: CVD benefits with metformin, Microvascular disease benefits with SU and insulin






# ERA 2: ACCORD, ADVANCE, VADT 2008

Death with A1C with under 6% target, no benefits under 6.5%, besides metformin, SU, insulin have TZDs, acarbose, and glinides as options

# 3 trials published in 2008 looking at A1C targets and outcomes

| | Target | Number | Entry A1C on average | TZD |
|---|---|---|---|---|
| ACCORD | < 6% vs. 7 to 8% | > 10,000 | 8.3% | ~20% |
| ADVANCE | < 6.5% vs more | > 10,000 | 7.5% | 3.7% |
| VADT | 1.5% reduction vs. standard | ~ 1,700 | 9.4% | ~20% |

Mean 62 year, 38% women

9 years diabetes duration

15% smokers

1/3 prior CVD

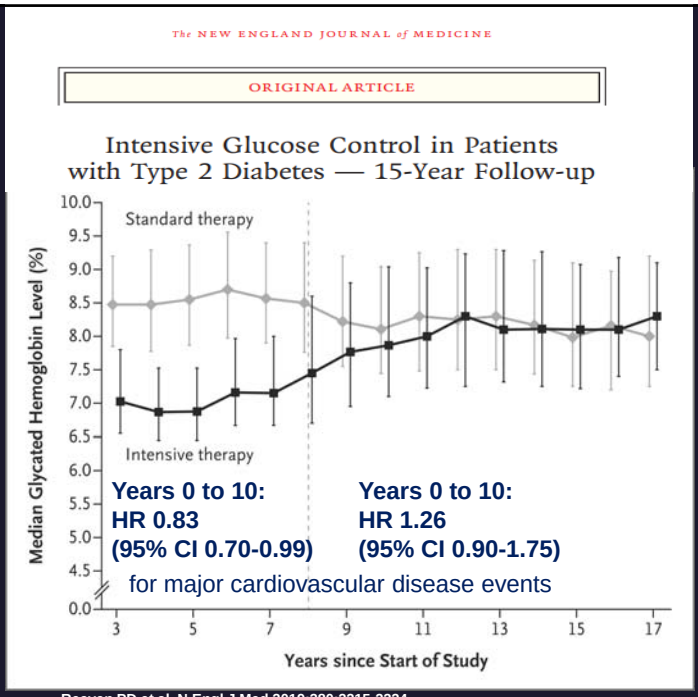
Meds available besides SU, metformin, insulin:

- Thiazolidinediones, acarbose, glinides

Turnbull and colleagues meta-analysis, *Diabetologia*, 2009

# Harmful or neutral for death, neutral for MACE

| HR (95% CI) | Mortality | CVD Mortality | MACE | MI | Stroke | Heart failure hospitalized or death |
|---|---|---|---|---|---|---|
| ACCORD | 1.22 (1.01-1.46) | 1.35 (1.04-1.76) | 0.90 (0.78-1.04) | 0.77 (0.64-0.93) | 1.0 (0.72-1.39) | 1.18 (0.93-1.49) |
| ADVANCE | 0.93 (0.83-1.06) | 0.88 (0.74-1.04) | 0.94 (0.84-1.06) | 0.92 (0.79-1.17) | 0.97 (0.81-1.16) | 0.95 (0.79-1.14) |
| VADT | 1.07 (0.81-1.42) | 1.32 (0.81-2.14) | 0.90 (0.70-1.16) | 0.83 (0.61-1.13) | 0.87 (0.54-1.39) | 0.92 (0.68-1.25) |

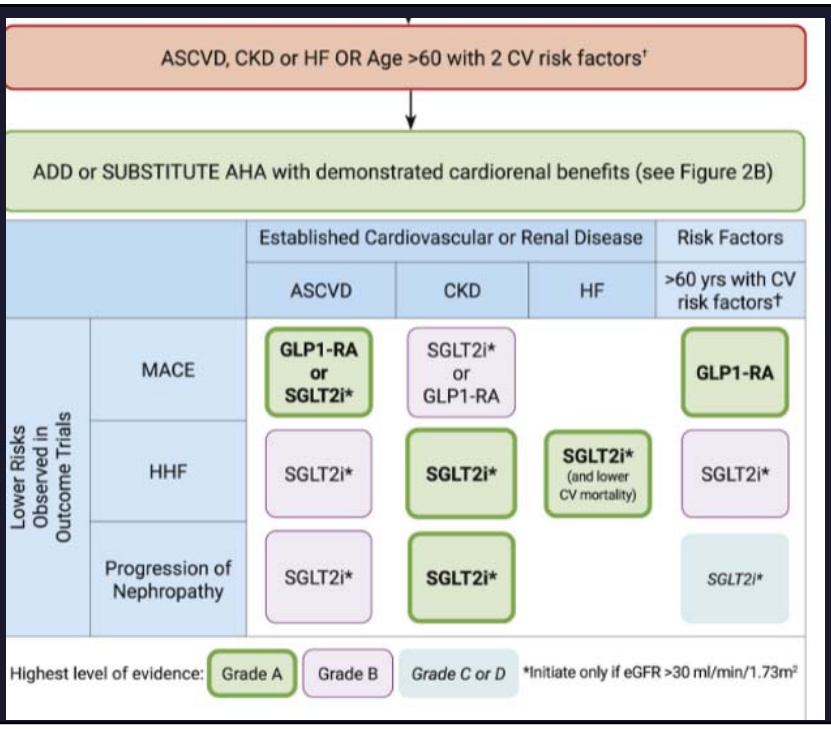



Reaven PD et al. N Engl J Med 2019;380:2215-2224

# ERA 3: SGLT-2 inhibitors and GLP-1 agonists benefits 2015 onwards

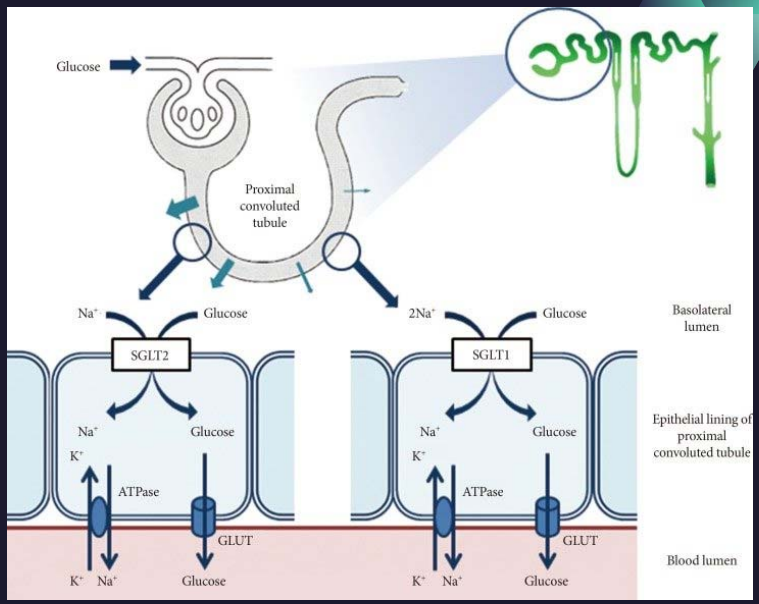
SGLT2i's reduce MACE, heart failure hospitalization, and renal disease progression in CVD, CKD with proteinuria and GFR > 30, HF, and 60 plus year olds with multiple risk factors for CVD

GLP-1's reduce MACE in CVD




# Sodium glucose transport inhibitors-2

- Jung and Jang, *Diabetes and Metabolism*, 2014



# Empagliflozin, Canagliflozin, Dapagliflozin

## Less MACE, less heart failure hospitalization, less progression of kidney disease

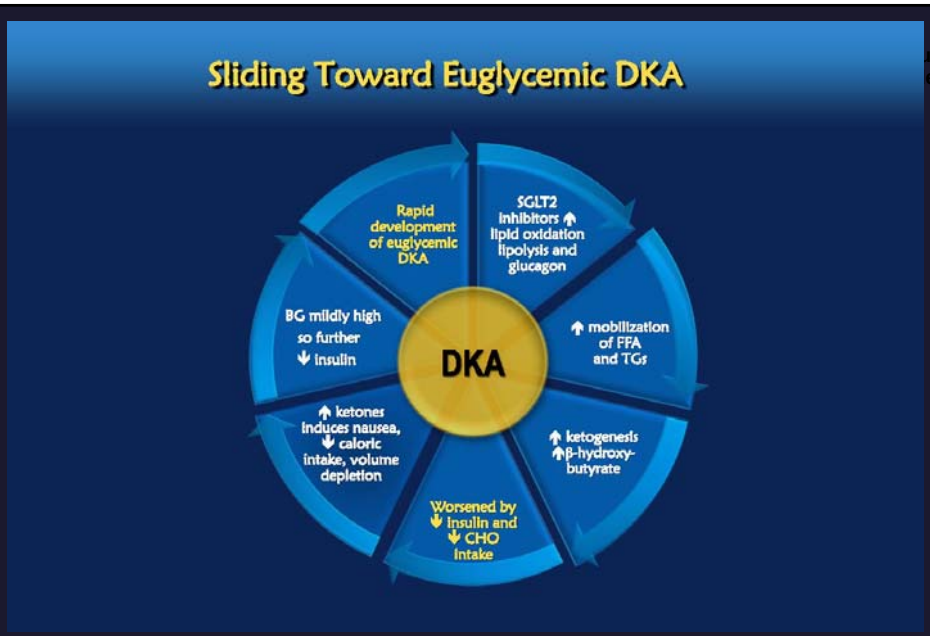
| Agent (outcome trial) | Population | Clinical outcomes (HR [95% CI] vs placebo) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | MACE | CV mortality | All-cause mortality | Fatal/ nonfatal MI | Fatal/ nonfatal stroke | Hosp HF | Progression of CKD |
| SGLT2i | | | | | | | | |
| **Empagliflozin (EMPA-REG)** | **CVD** | **0.86* (0.74-0.99)** | **0.62 (0.49-0.77)** | **0.68 (0.57-0.82)** | 0.87 (0.70–1.09) | 1.18 (0.89–1.56) | **0.65 (0.50-0.85)** | **0.61 (0.53-0.70)** |
| **Canagliflozin (CANVAS PROGRAM)** | **CVD (66%) or CV risk factors** | **0.86* (0.75-0.97)** | 0.87 (0.72-1.06) | 0.87 (0.74-1.01) | 0.89 (0.73–1.09) | 0.87 (0.69–1.09) | **0.67 (0.52-0.87)** | **0.73 (0.67-0.79)** |
| **Canagliflozin (CREDENCE)** | **CKD (eGFR 30-90 + proteinuria)** | **0.80 (0.67-0.95)** | 0.78 (0.61-1.00) | 0.83 (0.68-1.02) | – | – | **0.61 (0.47-0.80)** | **0.70*[2] (0.59-0.82)** |
| **Dapagliflozin (DECLARE-TIMI)** | **CVD (41%) or CV risk factors** | 0.93* (0.84-1.03) | 0.98 (0.82-1.17) | 0.93 (0.82-1.04) | 0.89 (0.77–1.01) | 1.01 (0.84–1.21) | **0.73 (0.61-0.88)** | **0.76 (0.67-0.87)** |
| **Dapagliflozin (DAPA-HF)** | **CHF (reduced EF) ± DM (42%)** | –[1] | **0.82 (0.69-0.98)** | **0.83 (0.71-0.97)** | – | – | **0.70 (0.59-0.83)** | 0.71 (0.44-1.16) |

# Genital infections

- Vaginitis and balanitis related to the glucose in the urine
- Mostly women and uncircumcised men
- Topical antifungals, oral fluconazole responsive
- Do not need to discontinue

# Diabetic ketoacidosis

- Nausea, vomiting, abdominal pain, confusion
- Can be euglycemic which can cause delay in diagnosis
  - SGLT2's can suppress insulin but the glycosuria may lead to euglycemia
- High anion gap and ketonemia
- Low carb diets and keto diets may increase the risk
- Avoid excess alcohol intake




Julio Rosenstock, and Ele Ferrannini Dia Care 2015;38:1638-1642



American Diabetes Association.

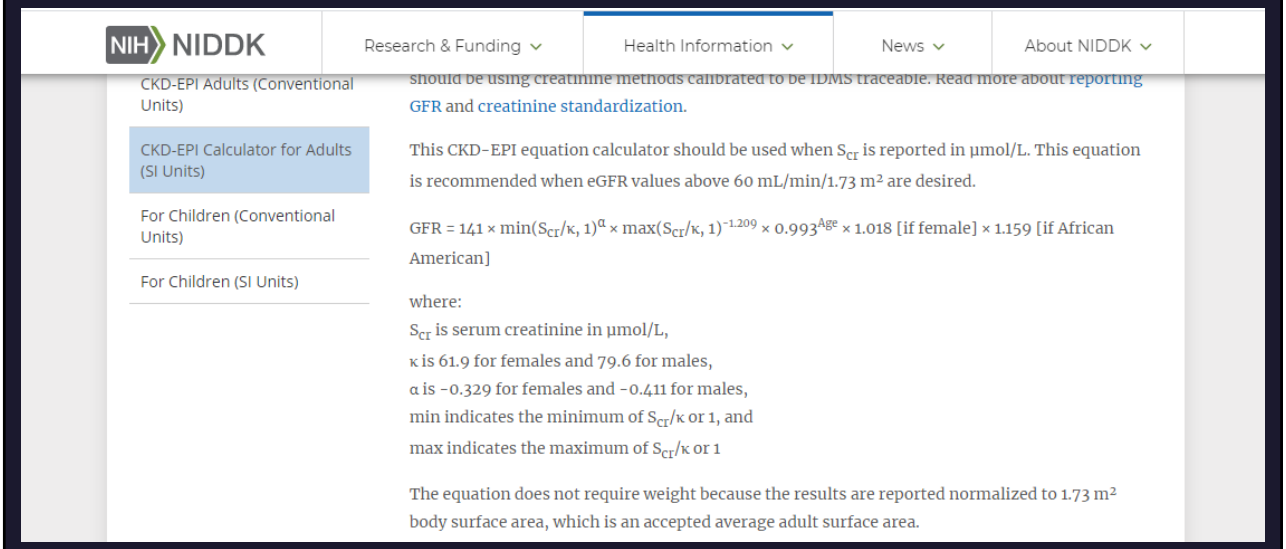
# What about the eGFR?

Renal benefits were demonstrated in people with eGFR **above** 30

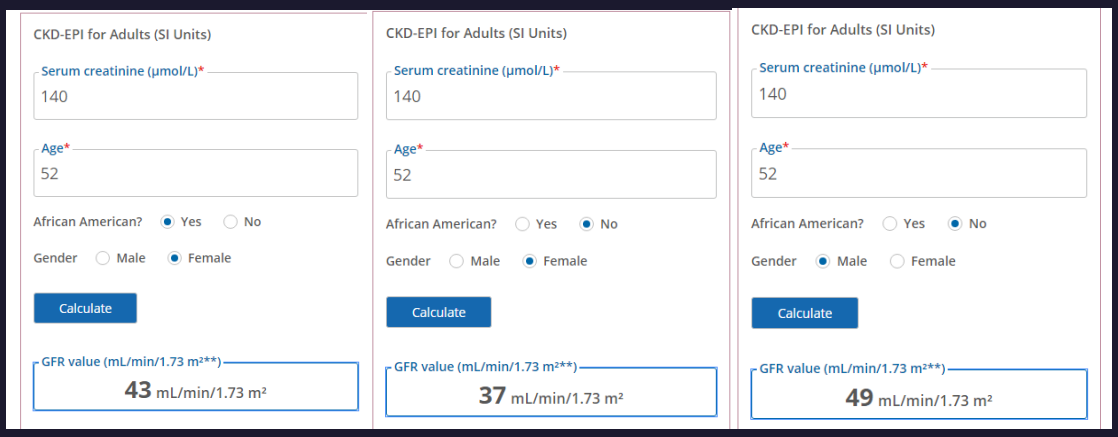
In the canagliflozin CREDENCE trial, the target population was eGFR 30 to 90 with proteinuria

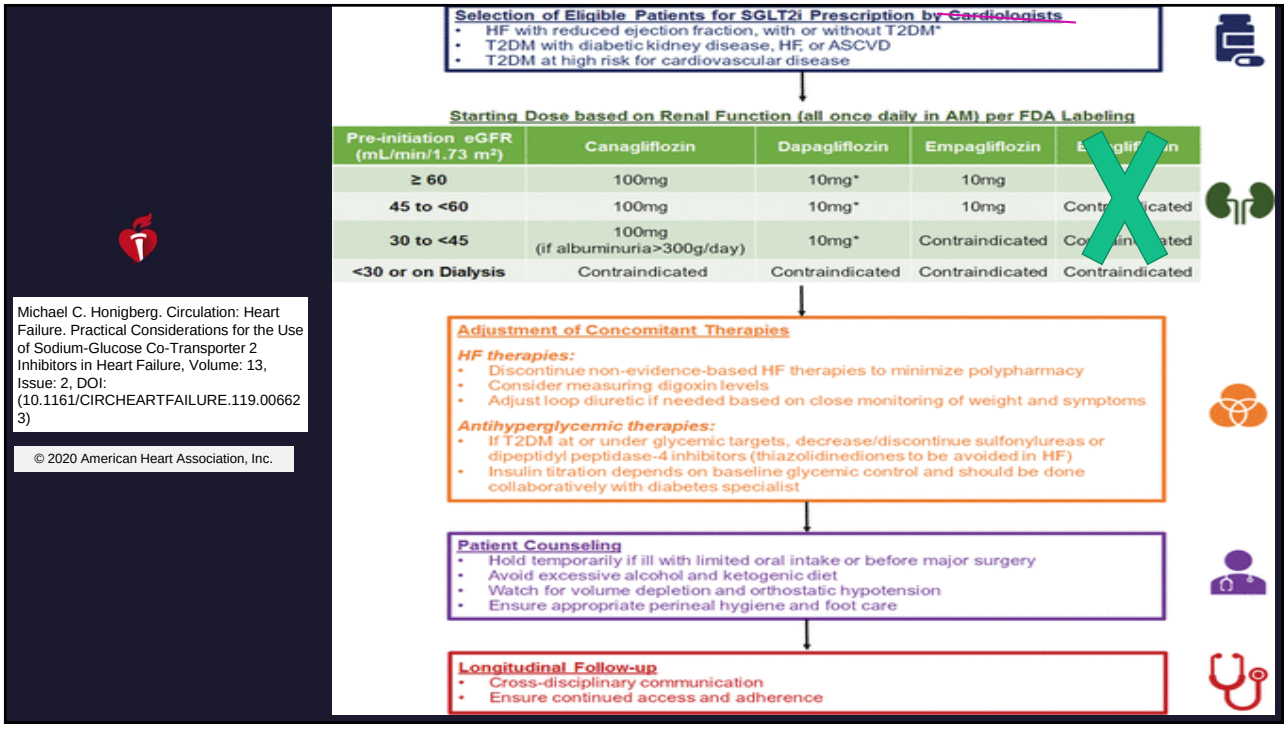
SGLT-2 inhibitors have less glucose lowering effects at eGFR under 45 *even though* they improve renal outcomes between eGFR 30 and 45

# eGFR



# eGFR examples




Michael C. Honigberg. Circulation: Heart Failure. Practical Considerations for the Use of Sodium-Glucose Co-Transporter 2 Inhibitors in Heart Failure, Volume: 13, Issue: 2, DOI: (10.1161/CIRCHEARTFAILURE.119.006623)

## For what indications can we prescribe these medications under the public health plan in Quebec?

- **EN 179**: Only empagliflozin has a code for a cardiovascular disease indication with the requirements that the A1C is above 7% *and* other antihyperglycemic agents are prescribed
- **EN148**: All 3 have a code for use in combo with metformin if a sulfonuylurea is not tolerated, contraindicated, or not effective (A1C high)
- **EN149**: Similarly all 3 have a code for use in combo with sulfonylurea if metformin is not tolerated, contraindicated, or not effective
- **EN167**: Canagliflozin and dapagliflozin have a code for use if neither sulfonylurea nor metformin are tolerated or if they are both contraindicated

If my patient has atherosclerotic heart disease, reduced ejection fraction heart failure, or renal disease or a combination of these, SGLT-2 inhibitors are a good choice… when prescription is financially possible

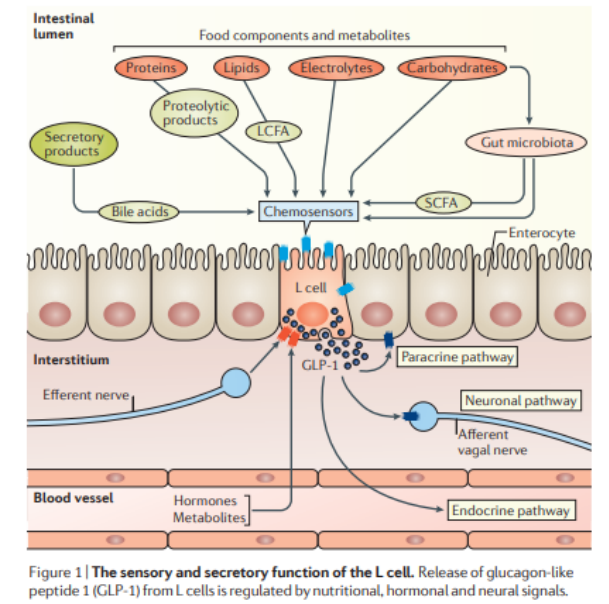



Figure 1 | **The sensory and secretory function of the L cell.** Release of glucagon-like peptide 1 (GLP-1) from L cells is regulated by nutritional, hormonal and neural signals.

Muskiet and colleagues, *Nature Reviews*, 2017

# Glucagon-like peptide-1 (GLP1)

- Hormone made in the gut epithelial cells ('enteroendocrine cells') and neurotransmitters within enteric nervous system
- Triggered within minutes of meal ingestion
- Stimulate glucose-dependent insulin release from pancreas
- Many other effects

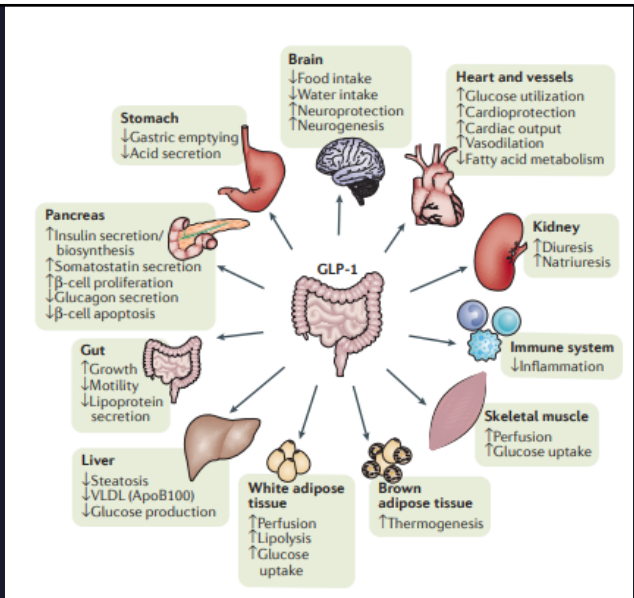



Figure 3 | **Putative actions of glucagon-like peptide 1 (GLP-1).** The best elucidated physiological roles of GLP-1 are those related to pancreatic islet cell function. However, GLP-1 and GLP-1 receptor agonists also have pleiotropic effects on various other tissues and organs, with various potential physiological, pathophysiological and pharmacological implications. VLDL, very low density lipoprotein.

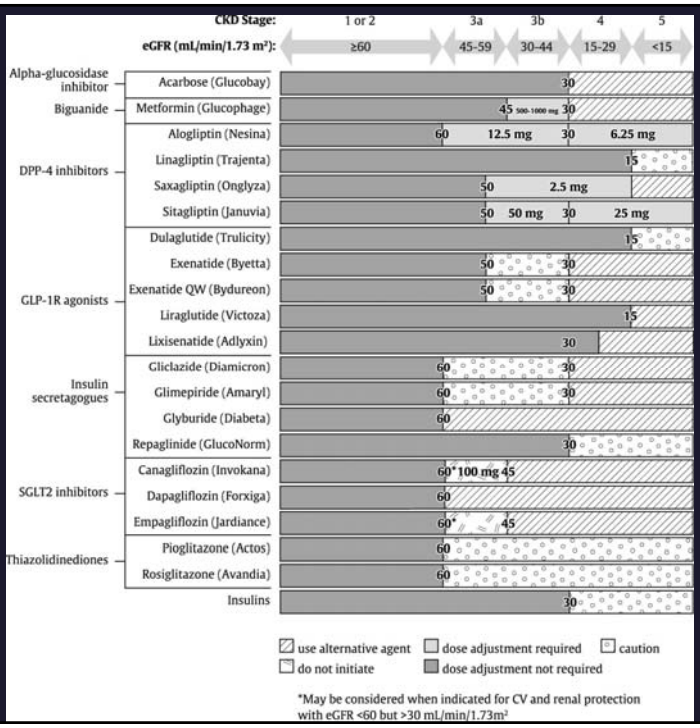
Muskiet and colleagues, *Nature Reviews*, 2017

Most common side effects are nausea and vomiting

Titrate dose to limit this

# Exenatide, Liraglutide, Semaglutide, Dulaglutide
## Less MACE, Less stroke

| Agent (outcome trial) | Population | Clinical outcomes (HR [95% CI] vs placebo) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | MACE | CV mortality | All-cause mortality | Fatal/ nonfatal MI | Fatal/ nonfatal stroke | Hosp HF | Progression of CKD |
| GLP1-RA | | | | | | | | |
| **Exenatide (EXSCEL)** | **CVD (73%) or CV risk factors** | 0.91* (0.83-1.00) | 0.88 (0.76–1.02) | **0.86 (0.77-0.97)** | 0.97 (0.85–1.10) | 0.85 (0.70–1.03) | – | – |
| **Liraglutide (LEADER)** | **CVD (72%) or CV risk factors** | **0.87* (0.78-0.97)** | **0.78 (0.66–0.93)** | **0.85 (0.74-0.97)** | 0.86 (0.73–1.00) | 0.86 (0.71–1.06) | – | – |
| **Semaglutide SC (SUSTAIN 6)** | **CVD (59%) or CV risk factors** | **0.74* (0.58-0.95)** | 0.98 (0.65–1.48) | 1.05 (0.74-1.50) | 0.74 (0.51-1.08)† | **0.61 (0.38-0.99)†** | – | – |
| **Semaglutide Oral (PIONEER 6)** | **CVD (85%) or CV risk factors** | 0.79* (0.57-1.11) | **0.49 (0.27–0.92)** | **0.50 (0.31-0.84)** | 1.18 (0.73-1.90)† | 0.74 (0.35-1.57)† | – | – |
| **Dulaglutide (REWIND)** | **CVD (31.5%) or CV risk factors** | **0.88* (0.79-0.99)** | 0.91 (0.78–1.06) | 0.90 (0.80-1.01) | 0.96 (0.79-1.16)† | **0.76 (0.61-0.95)†** | – | – |



# GLP-1 agonists available in Quebec

Medicaments d'exception at RAMQ. **No codes-complete form**

**Liraglutide (Victoza)**

- With metformin if T2DM, inadequate control, BMI > 30, and DPP-4 not tolerated
- Authorized Q12months and lowering by 0.5% has to be proven
- Daily injections

**Semaglutide (Ozempic)**

- In T2DM with metformin if SU not tolerated or not effective
- Weekly injections or oral daily tablets

**Dulaglutide (Trulicity)**

- Same as liraglutide

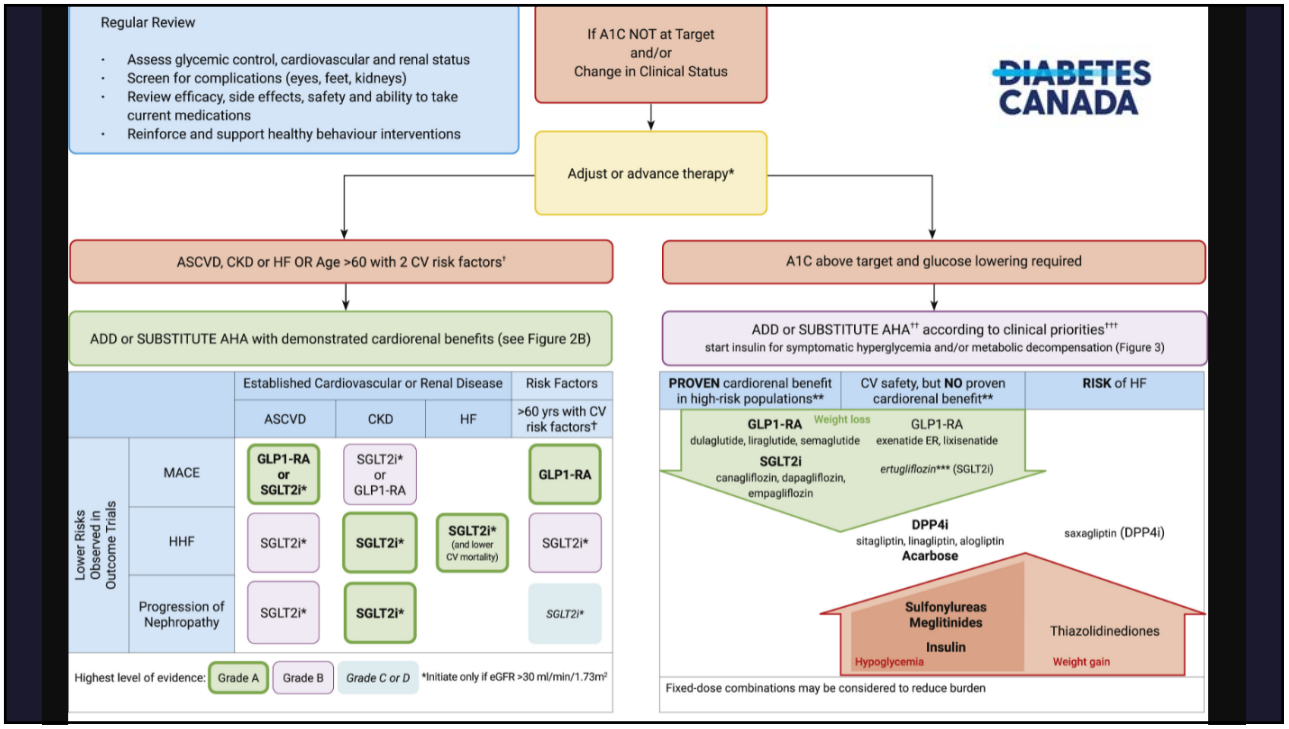
# STEP trials AND semaglutide

NOTE: approvals are for diabetes, not obesity

| | 2021 | Overweight or obese | Drugs | Features | Weight loss |
|---|---|---|---|---|---|
| STEP 1 | *NEJM* | No diabetes | 2.4 mg vs. placebo | 68 weeks; monthly dietitian visit both arms | 2.4 vs. 15% |
| STEP 2 | *Lancet* | Type 2 diabetes | 2.4 mg vs. 1 mg vs. placebo | 68 weeks; monthly dietitian visit both arms | 9.6 vs. 6.9 vs. 3.4% Similar 1.5% A1C lowering |
| STEP 3 | *JAMA* | No diabetes | 2.4 mg vs. placebo | 68 weeks, intensive behaviour therapy both arms (low calorie diets with meal replacement 8 weeks) | 5.7 vs. 16%; 75% lost 10% or more of weight |
| STEP 4 | *JAMA* | No diabetes | 2.4 mg vs. placebo | 20 wks semaglutide everyone then randomized for 28 weeks | 17.4% weight loss with semaglutide throughout; 6.9% regain with placebo for net 5% |

# From Diabetes Educators Calgary website

| | Monthly cost |
|---|---|
| Metformin | $4 |
| Gliclazide MR | $3 to $14 |
| Repaglinide | $7 |
| Sitagliptin | $92 |
| Empagliflozin | $81 |
| Canaglifozin | $84 |
| Dapagliflozin | $82 |
| Liraglutide | $91 to $272 |
| Semaglutide | $195 |



# (My) summary points

- A1C lowering itself provides some degree of reduction in diabetes complications but pharmacologic lowering below 6.5% may not be helpful and below 6% may be harmful
- Metformin is the first line for pharmacotherapy
- With CVD, SGLT2i's and GLPi's have important added benefits, beyond those attributable to A1C lowering
- SGLTi's slow renal disease at GFR above 30 and also reduce hospitalization for heart failure
- GLPi's at higher doses have weight loss benefits but are not yet approved or covered for this indication