



Diabetes Update

Kaberi Dasgupta, MD, MSc

Professor of Medicine, McGill University

Director and Scientist, Centre for Outcomes
Research and Evaluation, RI-MUHC

Co-author, Pharmacologic Glycemic
Management of Type 2 Diabetes in Adults,
Diabetes Canada

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,
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Foundations

Goals of type 2 diabetes care

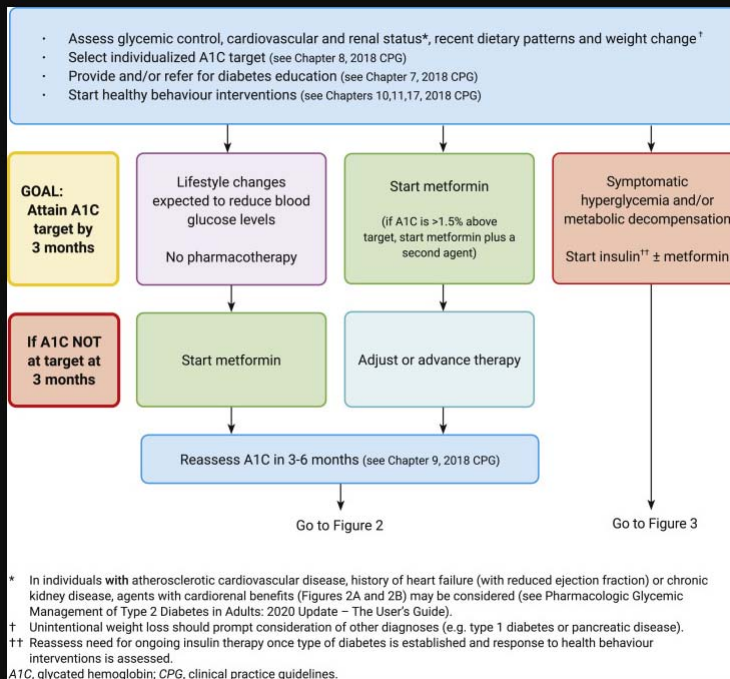
Prevent and treat hyperglycemia symptoms

- 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

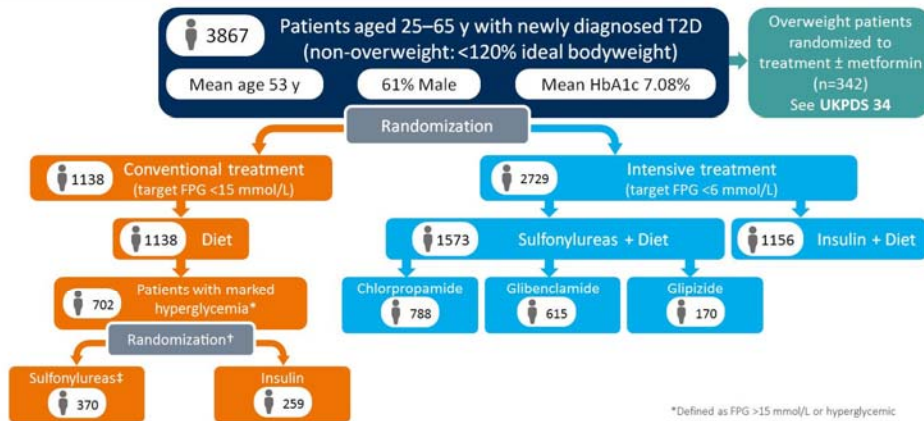
DIABETES CANADA



ERA 1: UKPDS 1998

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

UKPDS 33 trial design



Aggregate endpoints

Any diabetes-related endpoint

(sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal MI, angina, HF, stroke, renal failure, amputation, vitreous hemorrhage, retinopathy, blindness in one eye or cataract extraction)

Diabetes-related death

(death from MI, stroke, peripheral vascular disease, renal disease, hyperglycemia, hypoglycemia, or sudden death)

All-cause mortality

*Defined as FPG >15 mmol/L or hyperglycemic symptoms.

†Secondary randomization; overweight patients received metformin (n=73).

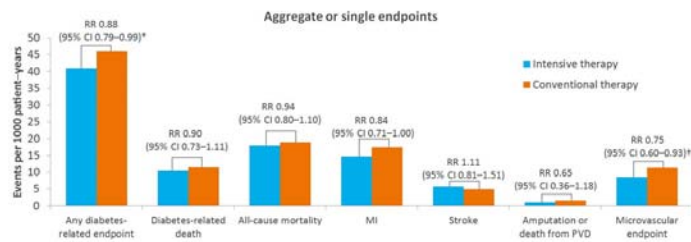
‡Patients with recurring hyperglycemia received add-on metformin; patients with persistent recurring hyperglycemia on two drugs were switched to insulin.

FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HF, heart failure; MI, myocardial infarction; T2D, type 2 diabetes; y, years.

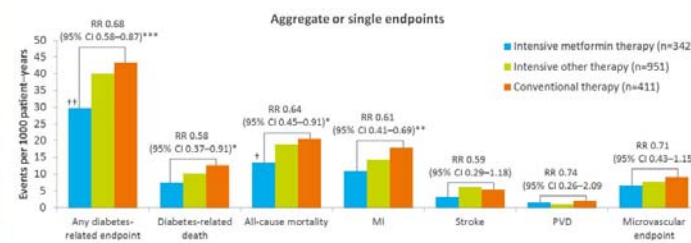
UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:837–853.

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- The risk for any diabetes-related endpoint was 12% lower with intensive vs conventional therapy
- The risk difference for any diabetes-related endpoint was attributed to the 25% risk reduction in microvascular endpoints with intensive therapy (fewer patients required photocoagulation)



- The risk for any diabetes-related endpoint was 32% lower with intensive metformin vs conventional therapy ($p=0.0023$)



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

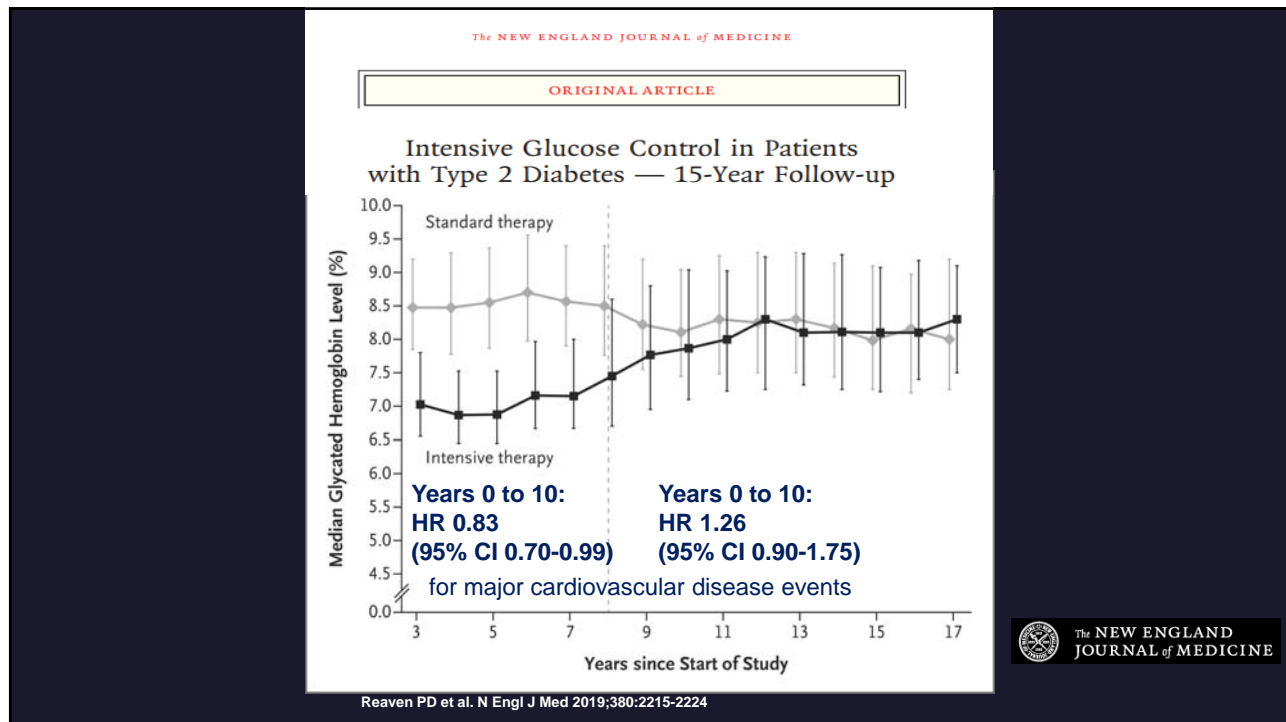
Meds available besides SU, metformin, insulin:

- Thiazolidinediones, acarbose, glinides

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

Harmful or neutral for death, neutral for MACE

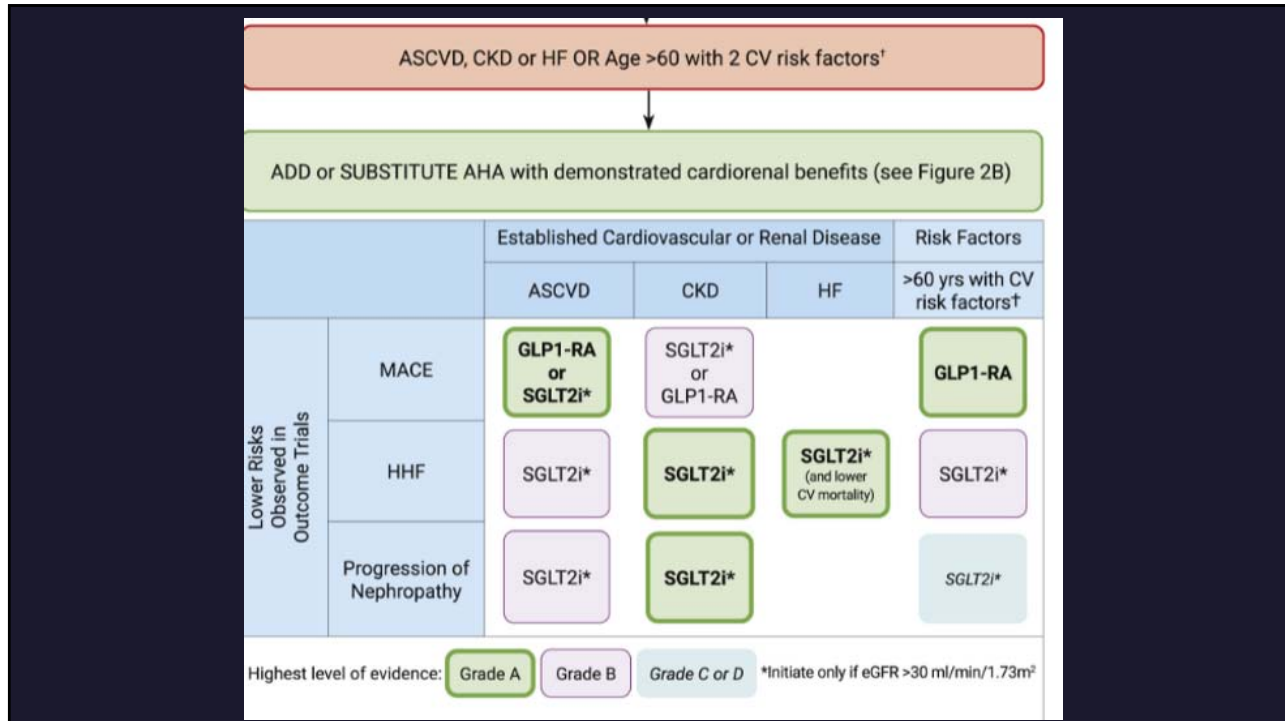
HR (95% CI)	Mortality	CVD Mortality	MACE	MI	Stroke	Heart failure hospitalized or death
ACCORD	1.22 (1.01-1.46)	1.35 (1.04-1.76)	0.90 (0.78-1.04)	0.77 (0.64-0.93)	1.0 (0.72-1.39)	1.18 (0.93-1.49)
ADVANCE	0.93 (0.83-1.06)	0.88 (0.74-1.04)	0.94 (0.84-1.06)	0.92 (0.79-1.17)	0.97 (0.81-1.16)	0.95 (0.79-1.14)
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)



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

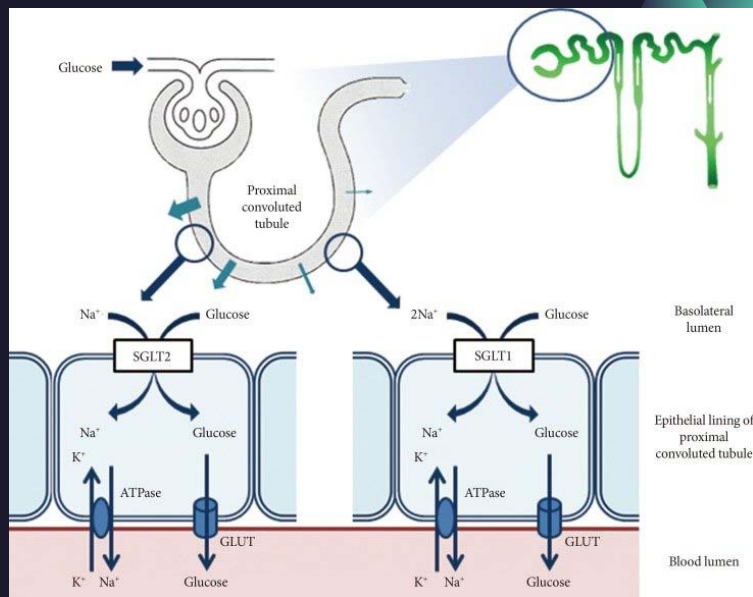
SGLT2i's reduce MACE, heart failure hospitalization, and renal disease progression in CVD, CKD with proteinuria and GFR > 30, HF, and 60 plus year olds with multiple risk factors for CVD

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 (CREDESCENCE)	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

Sliding Toward Euglycemic DKA



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

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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

NIH NIDDK

Research & Funding ▾

Health Information ▾

News ▾

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CKD-EPI Adults (Conventional Units)

CKD-EPI Calculator for Adults (SI Units)

For Children (Conventional Units)

For Children (SI Units)

should be using creatinine methods calibrated to be IDMS traceable. Read more about [reporting GFR and creatinine standardization](#).

This CKD-EPI equation calculator should be used when S_{Cr} is reported in $\mu\text{mol/L}$. This equation is recommended when eGFR values above $60 \text{ mL/min/1.73 m}^2$ are desired.

$$\text{GFR} = 141 \times \min(S_{Cr}/\kappa, 1)^\alpha \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if African American]}$$

where:

S_{Cr} is serum creatinine in $\mu\text{mol/L}$,

κ is 61.9 for females and 79.6 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of S_{Cr}/κ or 1, and

max indicates the maximum of S_{Cr}/κ or 1

The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area.

eGFR examples

CKD-EPI for Adults (SI Units)

Serum creatinine (μmol/L)*
140

Age*
52

African American? Yes No

Gender Male Female

Calculate

GFR value (mL/min/1.73 m^{2.733})
43 mL/min/1.73 m²

CKD-EPI for Adults (SI Units)

Serum creatinine (μmol/L)*
140

Age*
52

African American? Yes No

Gender Male Female

Calculate

GFR value (mL/min/1.73 m^{2.733})
37 mL/min/1.73 m²

CKD-EPI for Adults (SI Units)

Serum creatinine (μmol/L)*
140

Age*
52

African American? Yes No

Gender Male Female

Calculate

GFR value (mL/min/1.73 m^{2.733})
49 mL/min/1.73 m²

Selection of Eligible Patients for SGLT2i Prescription by Cardiologists

- HF with reduced ejection fraction, with or without T2DM*
- T2DM with diabetic kidney disease, HF, or ASCVD
- T2DM at high risk for cardiovascular disease

Starting Dose based on Renal Function (all once daily in AM) per FDA Labeling

Pre-initiation eGFR (mL/min/1.73 m ²)	Canagliflozin	Dapagliflozin	Empagliflozin	Ergliflozin
≥ 60	100mg	10mg*	10mg	X
45 to <60	100mg	10mg*	10mg	Contraindicated
30 to <45	100mg (if albuminuria>300g/day)	10mg*	Contraindicated	Contraindicated
<30 or on Dialysis	Contraindicated	Contraindicated	Contraindicated	Contraindicated

Adjustment of Concomitant Therapies

HF therapies:

- Discontinue non-evidence-based HF therapies to minimize polypharmacy
- Consider measuring digoxin levels
- Adjust loop diuretic if needed based on close monitoring of weight and symptoms

Antihyperglycemic therapies:

- If T2DM at or under glycemic targets, decrease/discontinue sulfonylureas or dipeptidyl peptidase-4 inhibitors (thiazolidinediones to be avoided in HF)
- Insulin titration depends on baseline glycemic control and should be done collaboratively with diabetes specialist

Patient Counseling

- Hold temporarily if ill with limited oral intake or before major surgery
- Avoid excessive alcohol and ketogenic diet
- Watch for volume depletion and orthostatic hypotension
- Ensure appropriate perineal hygiene and foot care

Longitudinal Follow-up

- Cross-disciplinary communication
- Ensure continued access and adherence

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)

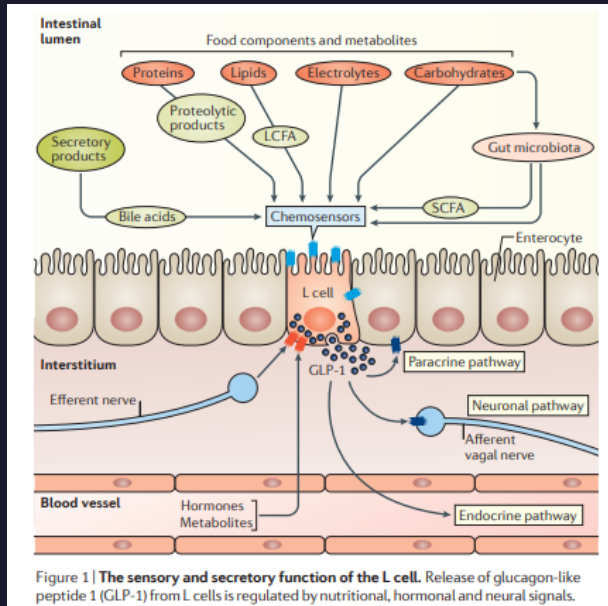
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For what indications can we prescribe these medications under the public health plan in Quebec?

- **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 sulfonylurea 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





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

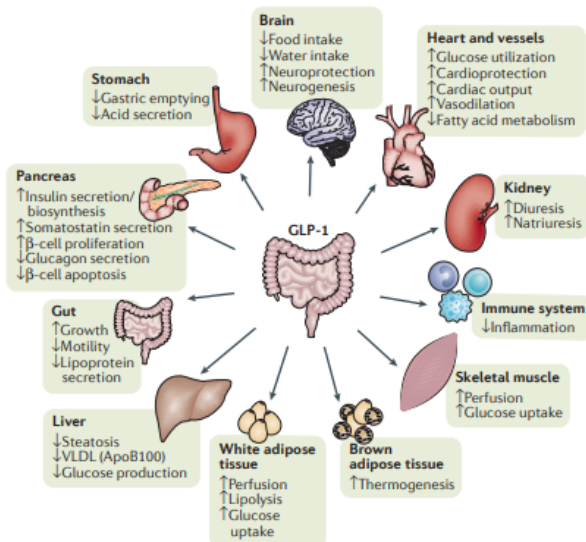


Figure 3 | Putative actions of glucagon-like peptide 1 (GLP-1). The best elucidated physiological roles of GLP-1 are those related to pancreatic islet cell function. However, GLP-1 and GLP-1 receptor agonists also have pleiotropic effects on various other tissues and organs, with various potential physiological,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

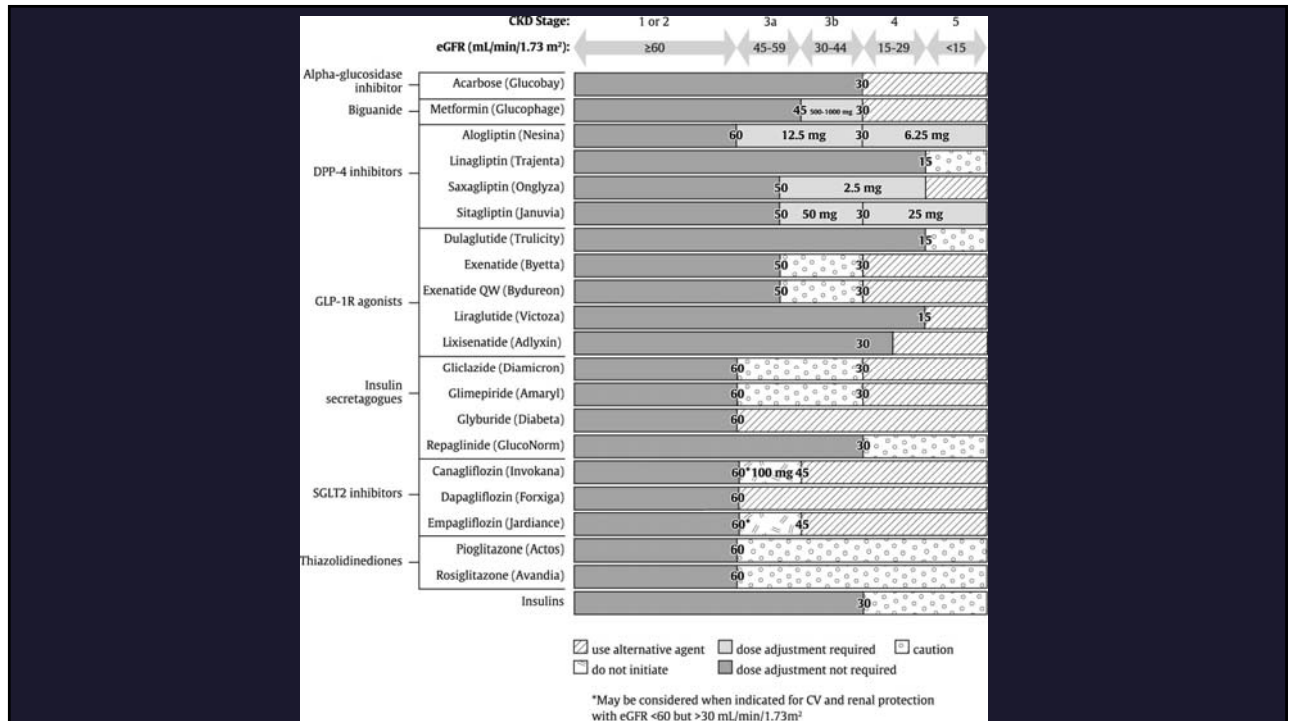
Muskiet and colleagues, *Nature Reviews*, 2017

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

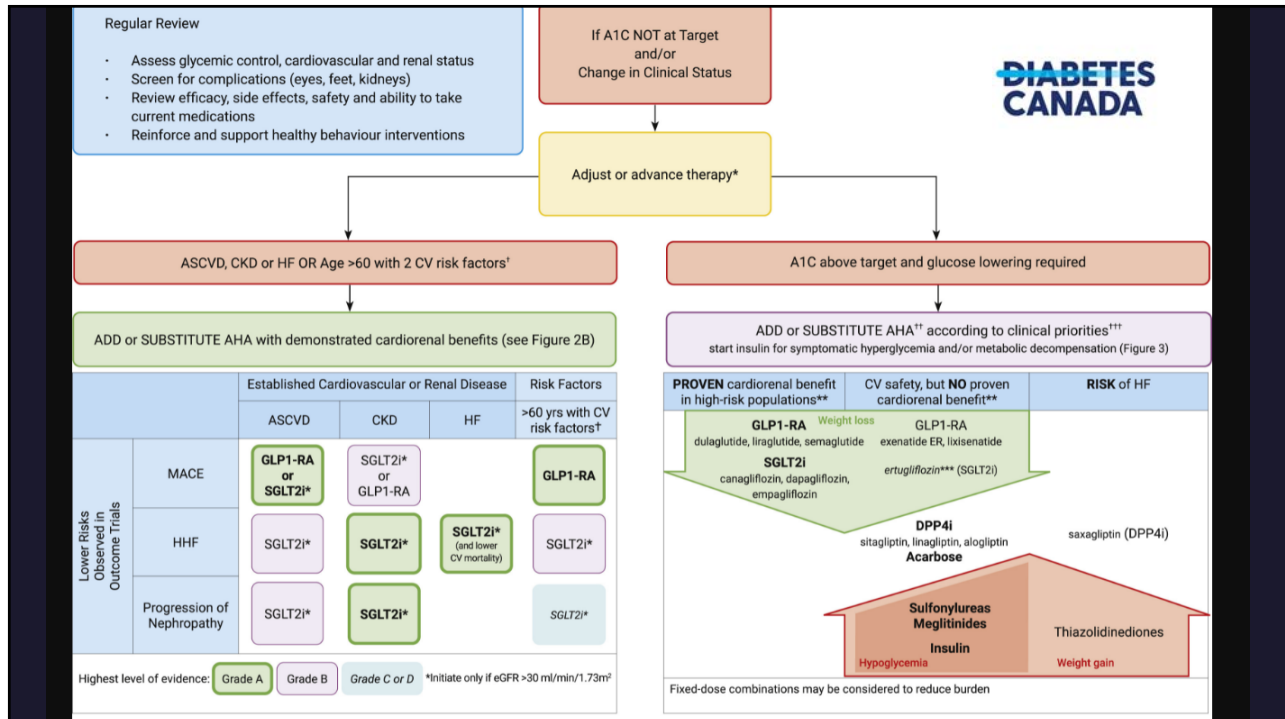
STEP trials AND semaglutide

NOTE: approvals are for diabetes, not obesity

	2021	Overweight or obese	Drugs	Features	Weight loss
STEP 1	<i>NEJM</i>	No diabetes	2.4 mg vs. placebo	68 weeks; monthly dietitian visit both arms	2.4 vs. 15%
STEP 2	<i>Lancet</i>	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	<i>JAMA</i>	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	<i>JAMA</i>	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
Canagliflozin	\$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