Almost

EVERYTHING YOU WANTED TO KNOW ABOUT DIABETES MEDICATIONS

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Objectives

- Discuss the indications, contraindications & modes of action of medications used to control increased blood glucose
- Discuss briefly the Diabetes Canada 2018 guidelines pertaining specifically to the medication used in T1DM & T2DM to control blood glucose
  - Focus on recent medication releases
- Discuss briefly other medications used in patients with T1DM & T2DM
- Discuss medication cost/coverage issues as they impact patient care

Key Challenges Of T1DM

- Patient unable to produce own endogenous insulin
- Insulin is lifesaving pharmacological therapy for people with T1DM
- Insulin use increases the risk of hypoglycemia
- Risk of DKA with uncontrolled BGs
- Micro- & Macrovascular disease

Key Challenges Of T2DM

- T2 Diabetes is a progressive disease
  - Declining β-cell function
  - Deteriorating blood glucose control
  - Increased risk of CV disease
  - Difficulty controlling after meal glucose & glucose fluctuations
  - Complications & co-morbidities
- Diabetes treatments
  - Increased risk of low blood glucose with some therapies
  - Weight gain with some therapies
  - Complex treatment regimens
  - Increased requirement for self-monitoring of blood glucose

2018

ABCDES^3 Of Diabetes Care

- ✓ **A** • A1c – optimal glycemic control (usually ≤7%)
- ✓ **B** • BP – optimal blood pressure control (<130/80)
- ✓ **C** • Cholesterol – LDL <2.0 mmol/L or >50% reduction
- ✓ **D** • Drugs to protect the heart

  A – ACEi or ARB | S – Statin | A – ASA if indicated | SGLT2i/GLP-1 RA with demonstrated CV benefit if type 2 DM with CVD & A1c not at target
- ✓ **E** • Exercise / Healthy Eating
- ✓ **S** • Screening for complications
- ✓ **S** • Smoking cessation
- ✓ **S** • Self-management, stress & other barriers

2018

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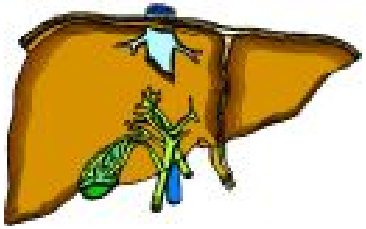
Medication Management

- Usually more than one medication is required to achieve blood glucose goals
- On average, Canadians with diabetes take 8 prescription medications daily
  - Blood sugar
  - Blood pressure
  - Kidney protection
  - Cholesterol
  - Stroke/heart attack prevention
  - Pain control

In Our Current Arsenal…

- Oral medications
  - Metformin
  - Sulfonylureas
  - Glitinides
  - α-glucosidase inhibitors
  - DPP-4 inhibitors
  - TZDs
  - SGLT-2 inhibitors
- Non-insulin injectables
  - GLP-1 analogues
    - Daily or BID
    - Weekly
- Insulin
  - Human
  - Analogues
  - Biosimilars

Sites Of Action



LIVER

↓ glucose production

- TZDs
- Metformin
- Insulin
- Incretin agents

MUSCLE/ADIPOSE

↑ peripheral glucose uptake & utilization

- TZDs
- Metformin

KIDNEY

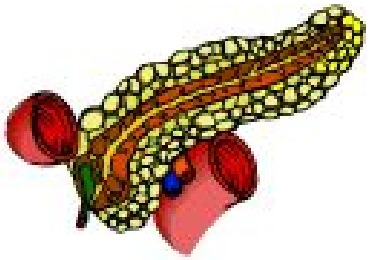
↑ excretion of glucose from kidneys

- SGLT-2 inhibitors

INTESTINE

↓ glucose absorption

- α-glucosidase inhibitors



PANCREAS

↑ secretion of insulin or replace insulin & ↓ glucagon

- Insulin
- Secretagogues
- Incretin agents

BRAIN

↑ satiety

- GLP-1 agonists

Non-Insulin Medications

Non-Insulin Medication Classes

- Sensitizers
  - Biguanides
    - Metformin
  - TZDs
    - Pioglitazone
    - Rosiglitazone
- Secretagogues
  - Sulfonylureas
    - Gliclazide
    - Glimepiride
    - Glyburide
  - Meglitinides
    - Repaglinide
- α-glucosidase inhibitors
    - Acarbose
- Incretins
  - DPP-4 inhibitors
    - Alogliptin
    - Linagliptin
    - Saxagliptin
    - Sitagliptin
  - GLP-1 analogues
    - Dulaglutide
    - Exenatide
    - Liraglutide
    - Lixisenatide
    - Semaglutide
- SGLT-2 inhibitors
    - Canagliflozin
    - Dapagliflozin
    - Empagliflozin

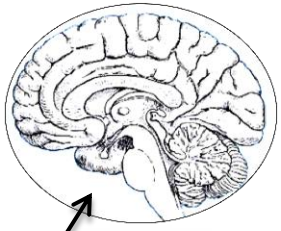
Metformin

- What it does
  - ↓ liver glucose production
  - ↑ insulin sensitivity
- A1c reduction
  - 1.0
- Hypoglycemia risk
  - Negligible as monotherapy
- Effect on CV outcomes
  - ↓ MI in overweight
- Coverage
  - ODB – 500mg
  - ↓ MI in overweight
  - NIHB – 500mg & 850mg
- Cost
  - $-$$$

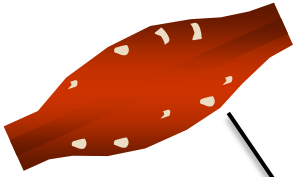
- What you should know
  - Metallic taste
  - GI side effects
  - Vitamin B_{12}/folate deficiency
  - Caution with kidney or liver problems
  - Weight neutral
  - Long-acting product may appear in stool
  - Caution with contrast media
  - Low risk of lactic acidosis

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CPS 2018; Diabetes Canada 2018 CPG; ODB 2018; NIHB Winter 2018

Role Of Incretins In Glucose Control



↑ satiety
↓ appetite

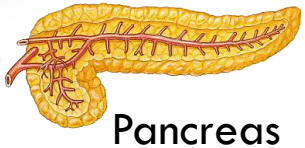


↑ glucose uptake by muscles

Release

↓ gut motility

Active GLP-1 & GIP



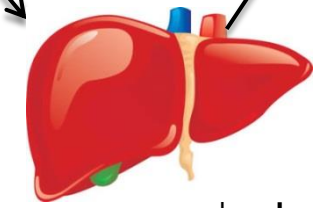
Pancreas

Decreased blood glucose

DPP-4

Inactive

- ↑ glucose-dependent insulin release, ↑ β-cell regeneration? (GLP-1 & GIP)
- ↓ glucose-dependent glucagon release from α-cells (GLP-1)



↓ glucose production

Adapted from Drucker DJ. *Cell Metab*. 2006;3(3):153-165.
Nauck MA. *Am J Med*. 2011;124(1 Suppl):S3-18.

DPP-4 Inhibitors

- What they do
  - ↑ insulin secretion
  - ↓ glucagon secretion
- A1c reduction
  - 0.7
- Hypoglycemia risk
  - Negligible as monotherapy
- Effect on CV outcomes
  - Neutral
- Coverage
  - ODB – covered (including combos with metformin; alogliptin products not covered)
  - NIHB – requires prior approval (including combos with metformin; alogliptin products not covered)
- Cost
  - $$$

- What you should know
  - Weight neutral
  - Glucose-dependent action
    - No action if BG low
  - Don't impair normal glucagon response to low blood glucose
  - Rare cases of pancreatitis
    - Caution in history of pancreatitis
  - Rare cases severe joint pain
  - Caution with saxagliptin in heart failure
  - Caution in kidney problems
    - Dose reductions required for alogliptin, sitagliptin & saxagliptin
    - No dose reduction needed for linagliptin

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CPS 2018; Diabetes Canada 2018 CPG; ODB 2018; NIHB Winter 2018

GLP-1 Agonists

- What They Do
  - ↑ insulin secretion
  - ↓ glucagon secretion
  - Central satiety
- A1c reduction
  - 1.0 (less with short-acting vs long-acting)
- Hypoglycemia risk
  - Negligible as monotherapy
- Effect on CV outcomes
  - MACE & CV death with clinical CVD (liraglutide)
  - Neutral (exenatide ER; lixisenatide)
- Coverage
  - ODB – not covered
  - NIHB – not covered
- Cost
  - $$$$

- What you should know
  - SC injection
  - BID, daily or weekly
  - Weigh loss: 1.6-3kg
  - Glucose-dependent action
  - Delay gastric emptying (feel full)
  - Nausea, vomiting & diarrhea
  - Reports of pancreatitis
    - Association, not causality
  - Caution with kidney problems
  - Reduced progression of nephropathy (liraglutide)
  - Parafollicular cell hyperplasia
  - Contraindicated in history of MTC or MEN-2

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CPS 2018; Diabetes Canada 2018 CPG; ODB 2018; NIHB Winter 2018

GLP-1 Receptor Agonist Drugs

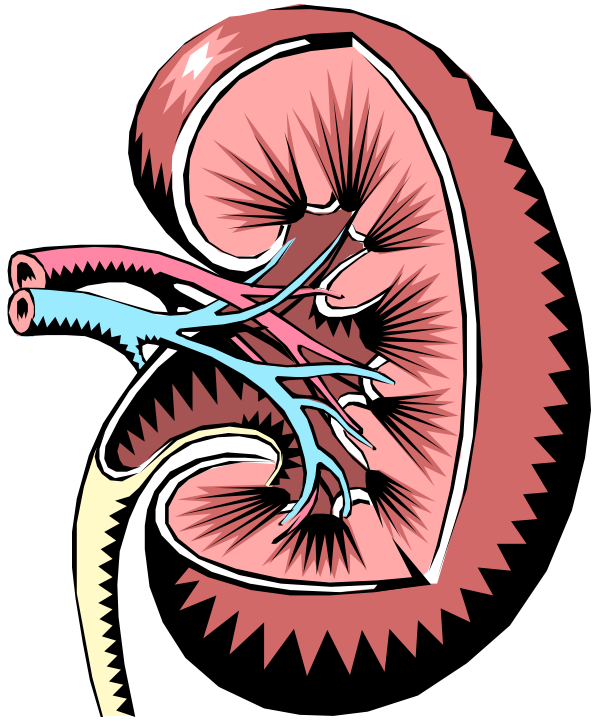
	Daily	Weekly
	Exenatide* (*Byetta*) Liraglutide (*Victoza*) Lixisenatide (*Adlyxine*)	Dulaglutide (*Trulicity*) Exenatide-LAR (*Bydureon*) Semaglutide (*Ozempic*)
Half-life	2-5h (exenatide) 12h (liraglutide)	Several days
Fasting BG	Modest reduction	Strong reduction
A1c	Modest reduction	Strong reduction
Postprandial hyperglycemia	Strong reduction	Modest reduction
Gastric emptying rate	Decrease	No effect
Blood pressure	Reduction	Reduction
Body weight reduction	1–5 kg	2–5 kg

* - BID

Meier JJ. *Nat Rev Endocrinol*. 2012;8(12):728-742.
Lund A, et al. *Eur J Intern Med*. 2014;25(5):407-414.

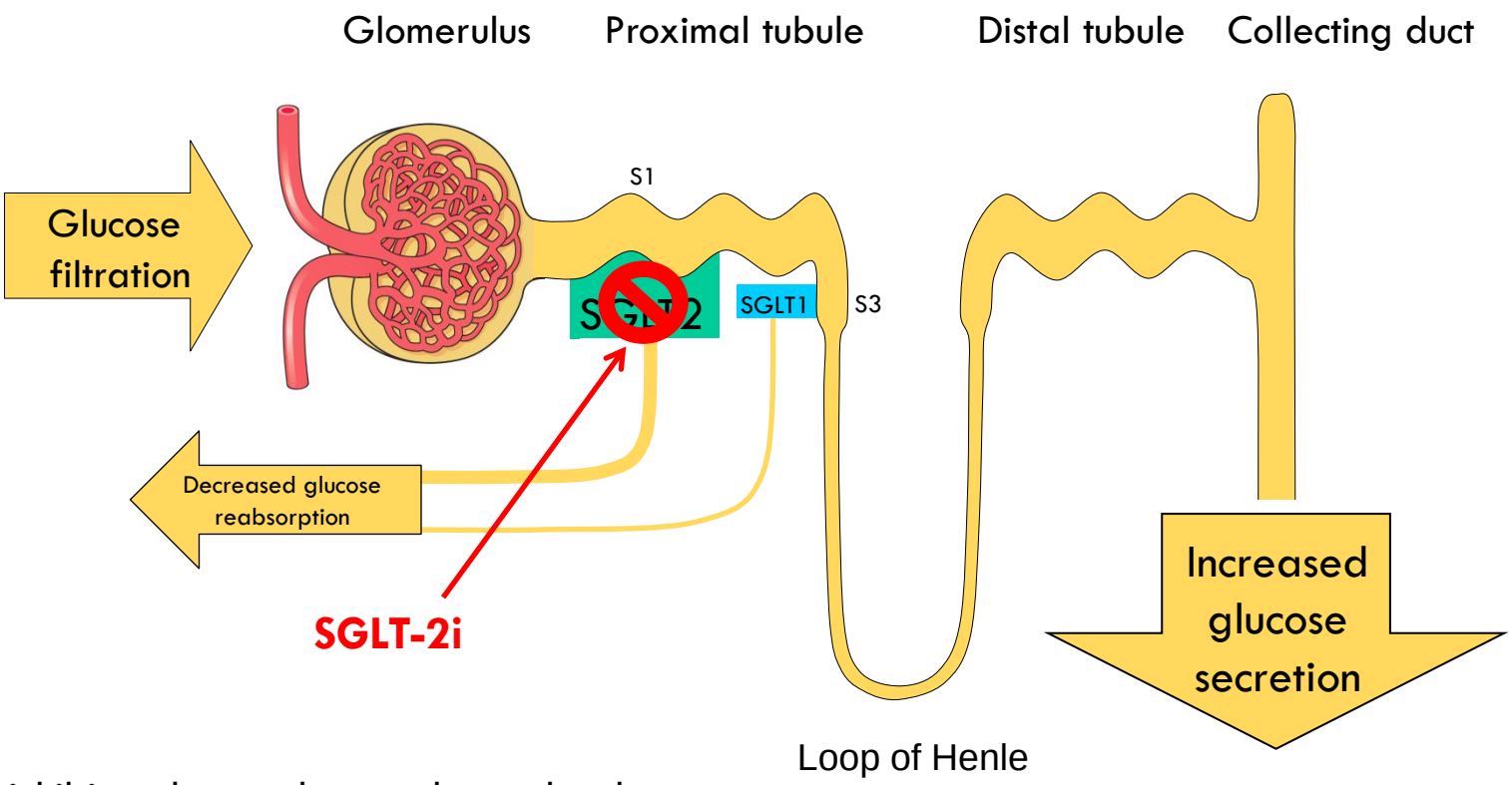
Kidney & Glucose Homeostasis

- Kidney
  - Produces glucose
  - Uses glucose
  - Filters glucose
  - Reabsorbs glucose



Adapted from: CDA CPG 2015

Mechanism Of Action



SGLT-2 inhibitors lower plasma glucose levels in patients with T2DM by inhibiting renal glucose reabsorption

Defronzo RA. Diabetes. 2009;58(4):773-795);
Rossetti et al J Clin Invest 1987:79;1510-1515);
Macdonald FR et al. Diabetes Obes Metab. 2010 Nov;12(11):1004-12)

SGLT-2 Inhibitors

- What they do
  - Block glucose reabsorption in kidney
- A1c reduction
  - 0.4-0.7
- Hypoglycemia risk
  - Low risk of hypoglycemia
- Effect on CV outcomes
  - ↓ MACE (empa; cana) & CV death (empa) with clinical CVD
- Coverage
  - ODB – covered (only *Xigduo* combo covered)
  - NIHB – requires prior approval (only *Xigduo* combo covered)
- Cost
  - $$$

- What you should know
  - ↓ BP ~6/3 mmHg
  - Weight loss: 1.6-3kg
  - Risk of UTI/genital infections
  - Rare euglycemic DKA
  - Dehydration/electrolyte imbalance (osmotic diuresis)
    - ↑ K^+
  - Acute decrease in eGFR
  - ↑ fracture risk (cana)
  - ↑ lower limb amp risk (cana); avoid if prior amp
  - Reduced progression of nephropathy & reduction in HF with CVD (empa; cana)
  - Slight increase in LDL-C
  - Caution with renal dysfunction, loop diuretics & elderly
  - Bladder/prostate/breast cancer?

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CPS 2018; Diabetes Canada 2018 CPG; ODB 2018; NIHB Winter 2018

Sulfonylureas

- What they do
  - Stimulate release of insulin from β-cells
- A1c reduction
  - 0.7-1.3
- Hypoglycemia risk
  - glyburide – significant
  - glimepiride – moderate
  - gliclazide/gliclazide MR – minimal/moderate
- Coverage
  - ODB – gliclazide; gliclazide MR; glyburide
  - NIHB – gliclazide; gliclazide MR; glyburide
- Cost
  - $

- What you should know
  - Relatively rapid BG lowering
  - Weight gain: 1.5-2.5kg
  - Consider other classes in patients with high risk of low blood glucose
  - Gliclazide preferred over glyburide: lower risk hypos, CV events, mortality
  - Small chance of allergic reaction if allergic to sulfa drugs
  - Caution with kidney or liver problems
  - Possible photosensitivity

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CPS 2018; Diabetes Canada 2018 CPG; ODB 2018; NIHB Winter 2018

Meglitinides

- What they do
  - Stimulate release of insulin from β-cells
- A1c reduction
  - 0.7-1.1
- Hypoglycemia risk
  - minimal/moderate
- Coverage
  - ODB – EAP
  - NIHB – full coverage
- Cost
  - $$

- What you should know
  - Rapid onset
  - Short-acting
  - Less risk of low blood glucose than SU
  - Weight gain 0.7-1.8kg
  - Safe for all stages of renal function
  - PPBG especially reduced
  - Contraindicated with clopidogrel or gemfibrozil
  - Need to be taken with every meal
    - If you skip a meal, don't take the pill for that meal

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CPS 2018; Diabetes Canada 2018 CPG; ODB 2018; NIHB Winter 2018

Thiazolidinediones (TZDs)

- What they do
  - ↑ insulin sensitivity
  - ↓ liver glucose production
- A1c reduction
  - 0.8-0.9
- Hypoglycemia risk
  - Negligible as monotherapy
- Coverage
  - ODB – EAP
  - NIHB – requires pre-approval
- Cost
  - $$$

- What you should know
  - 6-12 weeks for full effect
  - Weight gain: 2.5-5kg
  - Mild ↓ BP
  - Mild ↑ HDL-C
  - Sustained BG ↓
  - May induce edema &/or CHF
  - Contraindicated patients with or history of CHF
  - Fractures; macular edema; MI (rosi); bladder CA (pio)
  - MI risk with rosi?

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CPS 2018; Diabetes Canada 2018 CPG; ODB 2018; NIHB Winter 2018

Acarbose

- What it does
  - Delays CHO absorption
- A1c reduction
  - 0.7-0.8
- Hypoglycemia risk
  - Negligible as monotherapy
- Coverage
  - ODB – LU 175 or 176
  - NIHB – full coverage
- Cost
  - $$

- What you should know
  - GI side effects
    - Gas, bloating & flatulence
  - Treat lows with dextrose, honey or milk only
  - Weight neutral
  - Take with 1st bite of meal

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CPS 2018; Diabetes Canada 2018 CPG; ODB 2018; NIHB Winter 2018

Insulin

Insulin

- What it does
  - Replaces/supplements body's insulin supply
  - Allows body to use glucose in the blood
- A1c reduction
  - 0.9-1.2+
- Hypoglycemia risk
  - Significant
- Coverage*
  - ODB – covered (*NovoRapid* – LU: 388, 389, 390; *Fiasp, Toujeo, Tresiba, Entuzity* not covered)
  - NIHB – covered (*NovoMix 30, Basaglar, Fiasp, Toujeo, Tresiba, Entuzity* not covered)
- Cost
  - Human $
  - Analogues $$$-$$$$

- What you should know
  - Greatest ↓ A1c & no maximum dose
  - Immediate onset
  - Weight gain: 4-5kg (~0.4kg on long-acting analogue alone)
  - Can use with oral meds in T2DM
  - All common types available without a prescription (OTC)
  - May need to adjust dose with worsening kidney function
  - Absorption rate can be affected by exercise or rubbing of injection site
  - Usually requires dose adjustment to reach target blood glucose
  - Should test BGs regularly

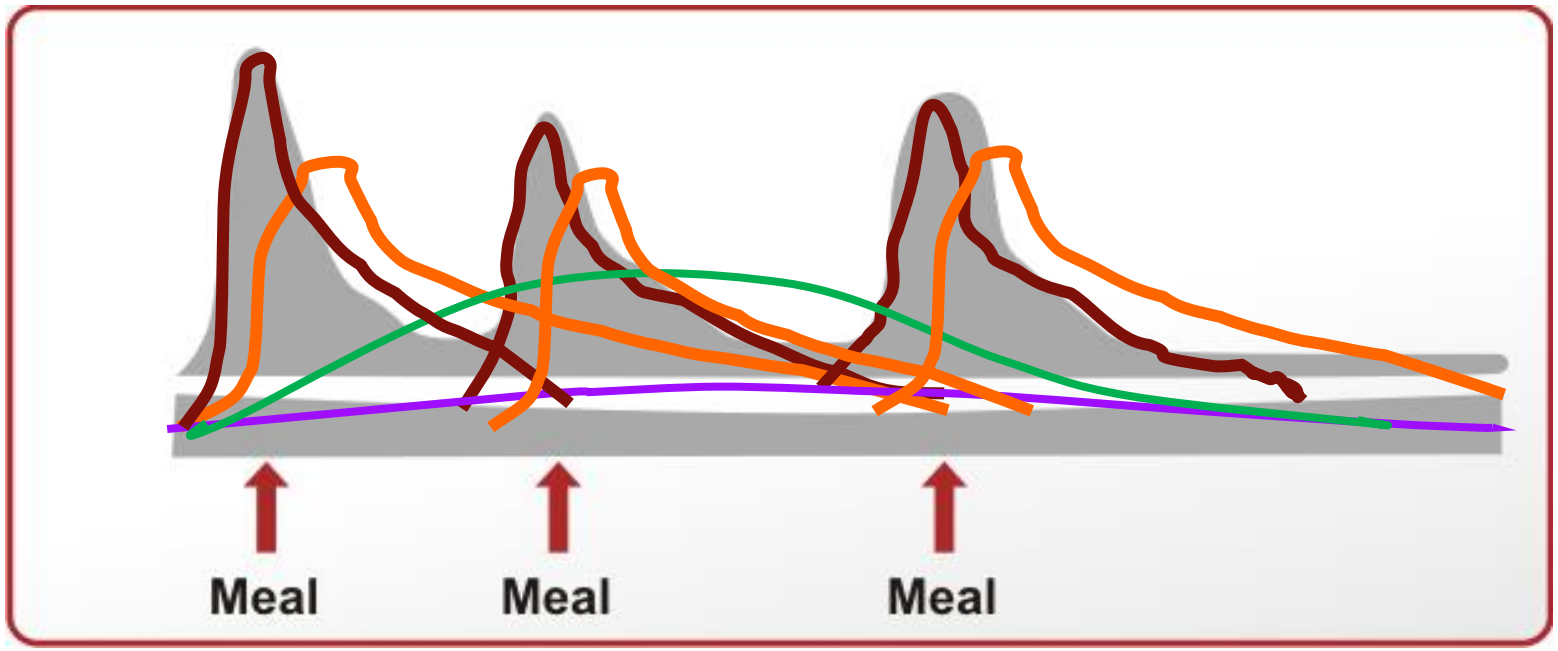
* -newer formulations awaiting coverage

Adapted from: RxFiles.ca; Therapeutic Choices 2014; CPS 2018; Diabetes Canada 2018 CPG; ODB 2018; NIHB Winter 2018

Types of insulin			
Insulin type (trade name)	**Onset**	**Peak**	**Duration**
BOLUS (prandial or mealtime) insulins			
Rapid-acting insulin analogues (clear) • Insulin aspart (*NovoRapid*®) • Insulin glulisine (*Apidra*®) • Insulin lispro (*Humalog*®) U-100; U-200 • Faster-acting insulin aspart (*Fiasp*®)	 9–20min 10–15min 10–15min 4min	 1–1.5h 1–1.5h 1–2h 0.5-1.5h	 3–5h 3.5–5h 3–4.75h 3-5h
Short-acting insulins (clear) • Insulin regular (*Humulin*®*-R*, *Novolin*® *ge Toronto*) • Insulin regular U-500 (*Entuzity*® U-500)	 30min 15min	 2–3h 4-8h	 6.5h 17-24h
BASAL insulins			
Intermediate-acting (cloudy) • Insulin neutral protamine Hagedorn (*Humulin*® *N*, *Novolin*® *ge NPH*)	1–3h	5–8h	Up to 18h
Long-acting insulin (clear) • Insulin detemir (*Levemir*®) • Insulin glargine U-100 (*Lantus*®) • Insulin glargine U-300 (*Toujeo*®) • Insulin glargine biosimilar (*Basaglar*®) • Insulin degludec U-100, U-200 (*Tresiba*®)	 90min 90min Up to 6h 90min 90min	 Not applicable	 16–24h Up to 24 h >30h Up to 24 h 42h
PREMIXED insulins			
Premixed regular insulin –NPH (cloudy) • *Humulin*® *30/70* • *Novolin*® *ge 30/70, 40/60, 50/50*	A single vial or cartridge contains a fixed ratio of insulin (% of rapid-acting or short-acting insulin to % of intermediate-acting insulin)		
Premixed insulin analogues (cloudy) • Biphasic insulin aspart (*NovoMix*® *30*) • Insulin lispro/lispro protamine (*Humalog*® *Mix25 & Mix50*)			

2018 Diabetes Canada CPG

Insulin Action Profile – Basal/Bolus



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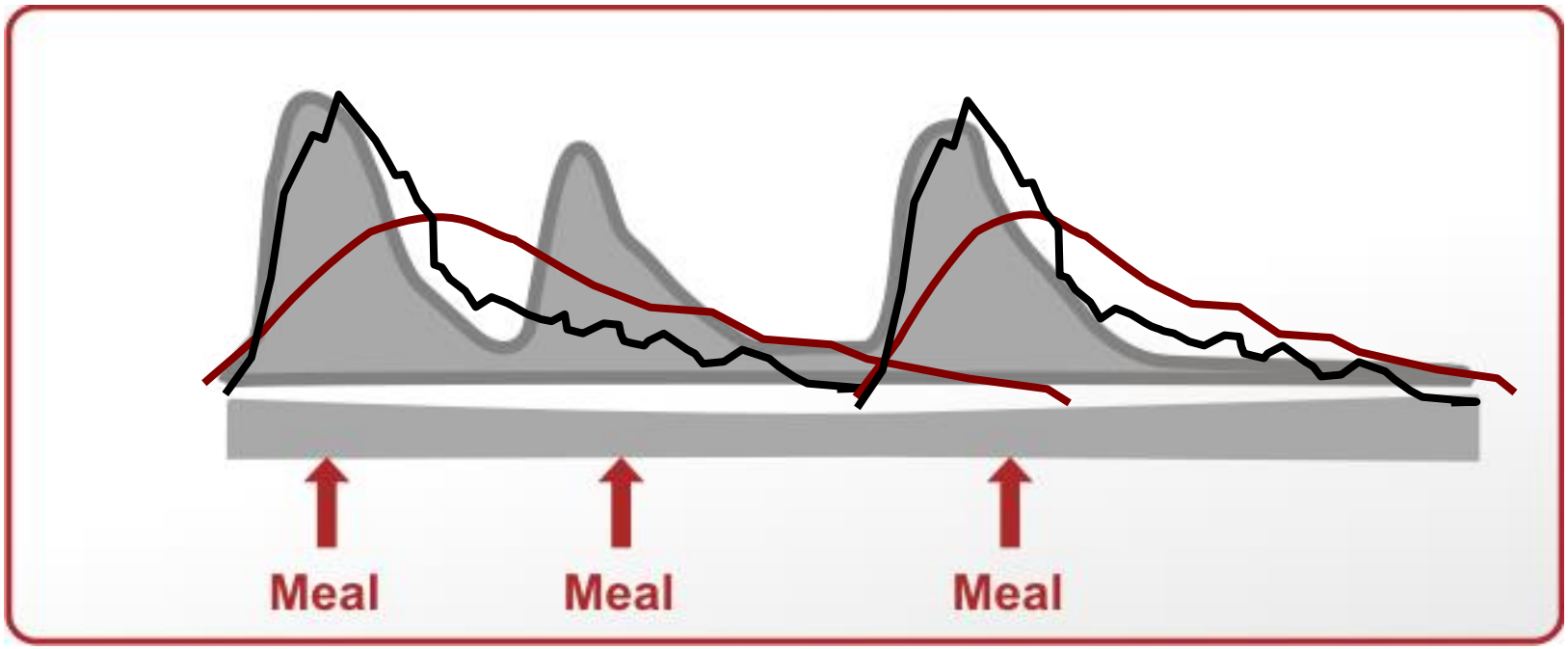
Insulin Action Profile – Premixed



— **Human Premixed**

— **Analogue Premixed**

Now What?

Consider…

- Degree of hyperglycemia
- Risk of hypoglycemia
- Overweight or obese
- Cardiovascular disease or multiple risk factors
- Comorbidities
  - Renal
  - CHF
  - Hepatic
- Preference of patient
  - Route
  - Frequency
  - “Pill burden”
- Benefit other systems?
- Access to treatment
  - Costs/coverage

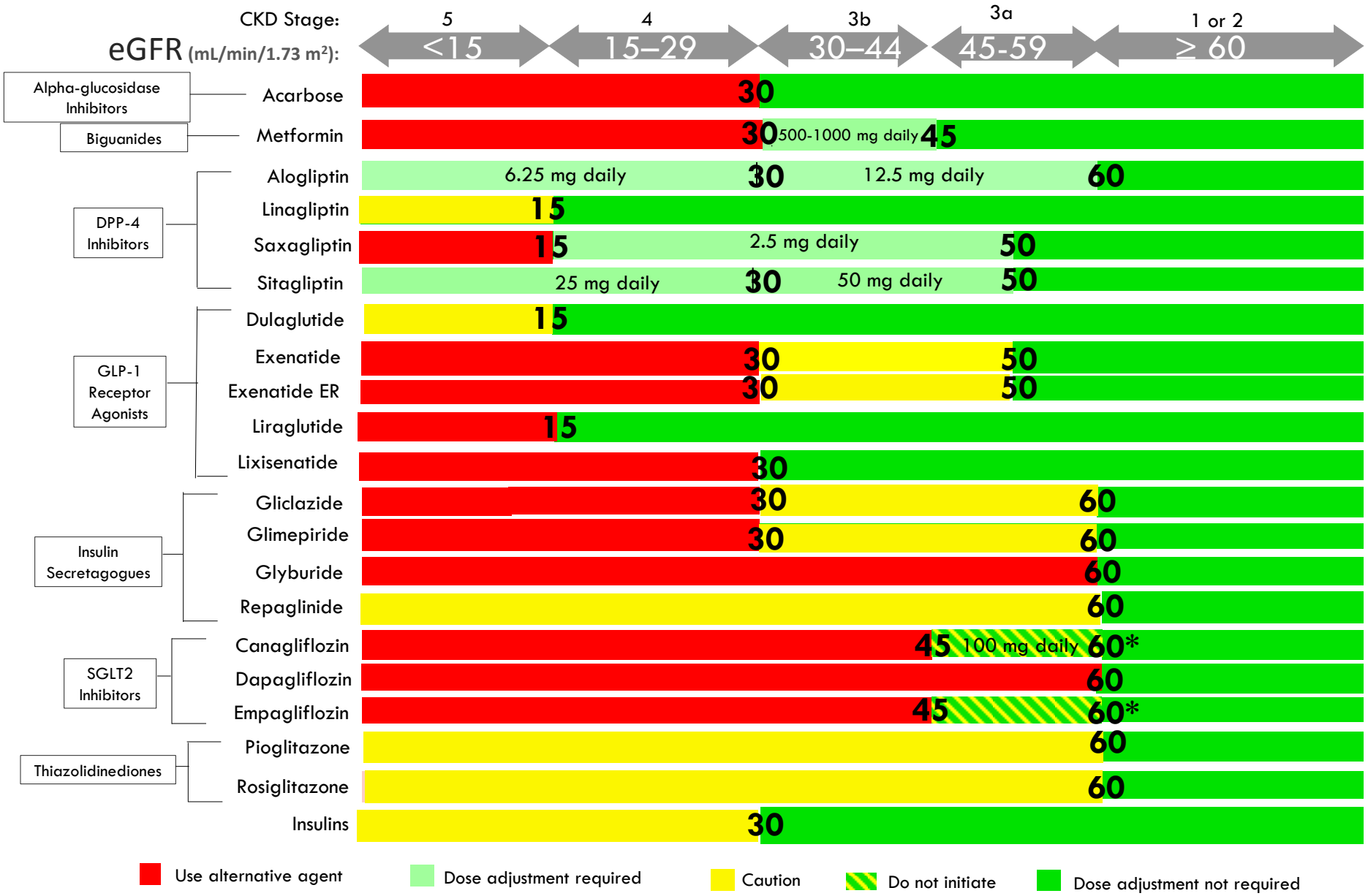
Individualizing A1c Target

2018

≤6.5	Adults with type 2 diabetes to reduce the risk of CKD & retinopathy **if at low risk of hypoglycemia**
≤7.0	**MOST ADULTS WITH TYPE 1 OR TYPE 2 DIABETES**
7.1 ↓ **8.5**	**7.1-8.0%**: Functionally dependent* **7.1-8.5%**: • Recurrent severe hypoglycemia &/or hypoglycemia unawareness • Limited life expectancy • Frail elderly &/or with dementia
Avoid higher A1c to minimize risk of symptomatic hyperglycemia as well as acute & chronic complications	
End of life	A1c measurement not recommended. Avoid symptomatic hyperglycemia & any hypoglycemia

* Based on class of antihyperglycemic medication(s) utilized & person's characteristics

Antihyperglycemic Agents & Renal Function



**May be considered when indicated for CV & renal protection with eGFR< 60 but >30 ml/min/1.73²*

2018 Diabetes Canada CPG

T1 Diabetes

Medications In T1DM

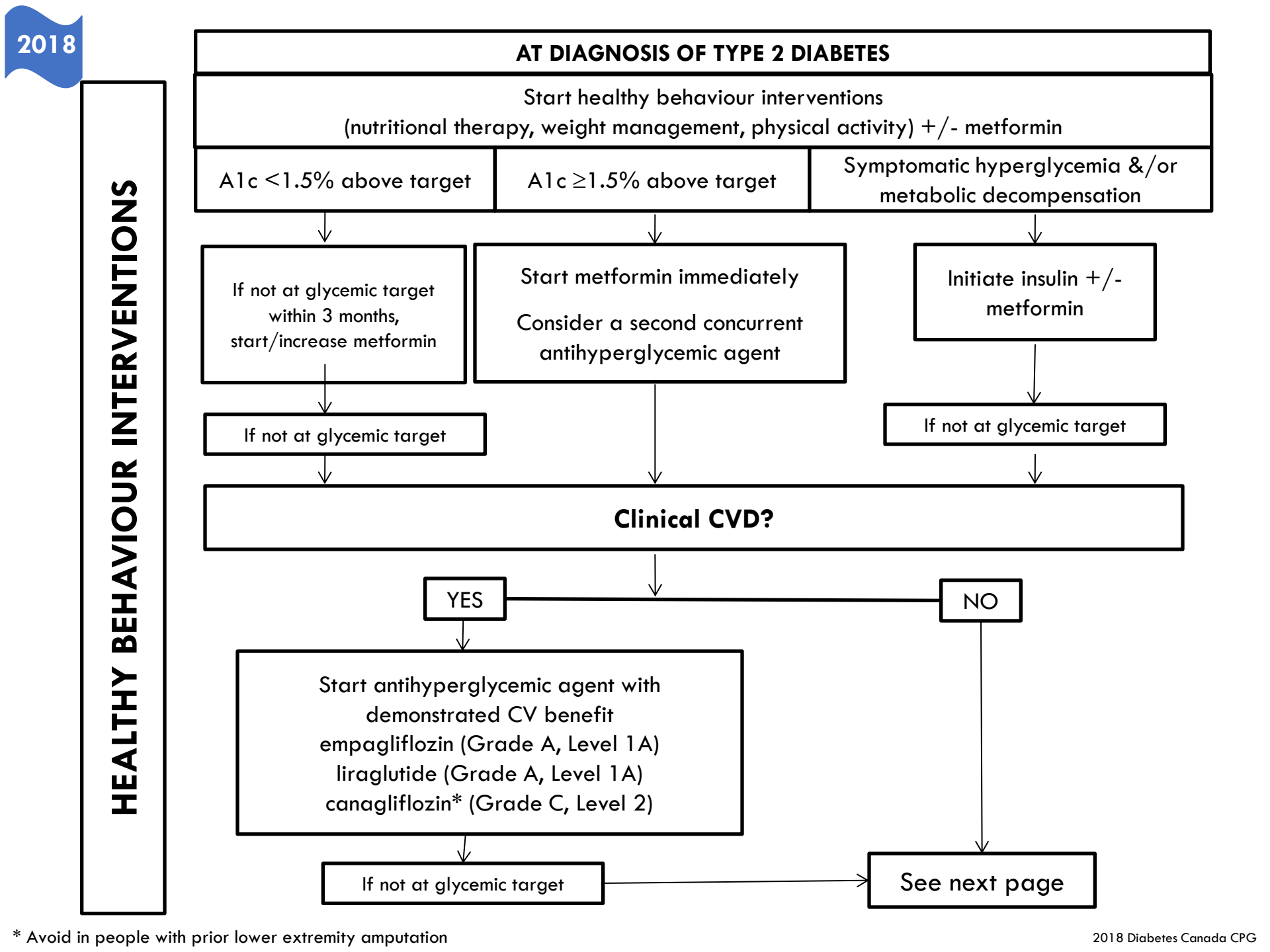
- Insulin
  - Basal/bolus or MDI
    - Long-acting analogue/rapid-acting analogue
  - Continuous subcutaneous insulin infusion (CSII)
    - Insulin pump
    - Rapid-acting analogue
- Individualize regimen
  - Treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status & ability for self-management
- Hypoglycemia
  - Counsel about the risk, prevention & treatment of low blood glucose
  - Hypoglycemia unawareness
    - Increased frequency of blood glucose monitoring, including occasional overnight testing; use of CGM
    - Less strict blood glucose targets

Adjunctive Therapy In T1DM

- Non-insulin medications have been studied
  - Metformin did not provide sustained metabolic or CV benefits
  - SGLT2 inhibitors showed some metabolic benefits but risk of DKA needs to be better understood
  - Liraglutide showed some metabolic benefits but there are no current indications for use in type 1 diabetes

- **No CURRENT recommendation for adjunctive therapy, but…**

T2 Diabetes


2018
HEALTHY BEHAVIOUR INTERVENTIONS
AT DIAGNOSIS OF TYPE 2 DIABETES
Start healthy behaviour interventions
(nutritional therapy, weight management, physical activity) +/- metformin
A1c <1.5% above target
A1c ≥1.5% above target
Symptomatic hyperglycemia &/or metabolic decompensation
If not at glycemic target within 3 months, start/increase metformin
Start metformin immediately
Consider a second concurrent antihyperglycemic agent
Initiate insulin +/- metformin
If not at glycemic target
If not at glycemic target
Clinical CVD?
YES
NO
Start antihyperglycemic agent with demonstrated CV benefit
empagliflozin (Grade A, Level 1A)
liraglutide (Grade A, Level 1A)
canagliflozin* (Grade C, Level 2)
If not at glycemic target
See next page
* Avoid in people with prior lower extremity amputation
2018 Diabetes Canada CPG

2018

From previous page

Add additional antihyperglycemic agent best suited to the individual based on the following

CLINICAL CONSIDERATIONS	CHOICE OF AGENT
Avoidance of hypoglycemia &/or weight gain with adequate glycemic efficacy	DPP-4 inhibitor, GLP-1 receptor agonist or SGLT-2 inhibitor
Other considerations: Reduced eGFR &/or albuminuria Clinical CVD or CV risk factors Degree of hyperglycemia Other comorbidities (CHF, hepatic disease) Planning pregnancy Cost/coverage Patient preference	see Renal Impairment Appendix See Table Below

2018

Add additional antihyperglycemic agent best suited to the individual by prioritizing patient characteristics (*agents listed in alphabetical order by CV outcome data*):						
Class	**Effect on CVD Outcomes**	**Hypo-glycemia**	**Weight**	**Relative A1C Lowering when added to metformin**	**Other therapeutic considerations**	**Cost**
GLP-1R agonists	lira: Superiority in T2DM with clinical CVD exenatide LAR & lixi: Neutral	Rare	↓↓	↓↓ to ↓↓↓	GI side-effects, Gallstone disease Contraindicated with personal / family history of medullary thyroid cancer or MEN 2 Requires subcutaneous injection	$$$$
SGLT2 inhibitors	Cana & empa: Superiority in T2DM patients with clinical CVD	Rare	↓↓	↓↓ to ↓↓↓	Genital infections, UTI, hypotension, dose-related changes in LDL-C. Caution with renal dysfunction, loop diuretics, in the elderly. Dapagliflozin not to be used if bladder cancer. Rare diabetic ketoacidosis (may occur with no hyperglycemia). Increased risk of fractures and amputations with canagliflozin. Reduced progression of nephropathy & CHF hospitalizations with empagliflozin and canagliflozin in those with clinical CVD	$$$
DPP-4 Inhibitors	alo, saxa, sita: Neutral	Rare	Neutral	↓↓	Caution with saxagliptin in heart failure Rare joint pain	$$$
Insulin	glar: Neutral degludec: noninferior to glar	Yes	↑↑	↓↓↓↓	No dose ceiling, flexible regimens Requires subcutaneous injection	$-$$$$
Thiazolidinediones	Neutral	Rare	↑↑	↓↓	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks for maximal effect	$$
α-glucosidase inhibitor (acarbose)		Rare	Neutral	↓	GI side-effects common Requires 3 times daily dosing	$$
Insulin secretagogue: **Meglitinide**		Yes	↑	↓↓	More rapid BG-lowering response Reduced postprandial glycemia with meglitinides but usually requires 3 to 4 times daily dosing.	$$
Sulfonylurea		Yes	↑	↓↓	Gliclazide and glimepiride associated with less hypoglycemia than glyburide. Poor durability	$
Weight loss agent (orlistat)		None	↓	↓	GI side effects Requires 3 times daily dosing	$$$

If not at glycemic targets

Add another antihyperglycemic agent from a different class &/or add/intensify insulin regimen
Make timely adjustments to attain target A1c within 3-6 months

Add additional antihyperglycemic agent best suited to the individual by prioritizing patient characteristics (***agents listed in alphabetical order by CV outcome data***):

Class	Effect on CVD Outcomes	Hypo-glycemia	Weight	Relative A1c Lowering when added to metformin	Other therapeutic considerations	Cost
GLP-1R agonists	lira: Superiority in T2DM with clinical CVD exenatide LAR & lixi: Neutral	Rare	↓↓	↓↓ to ↓↓↓	GI side-effects, Gallstone disease Contraindicated with personal / family history of medullary thyroid cancer or MEN 2 Requires subcutaneous injection	$$$$
SGLT2 inhibitors	Cana & empa: Superiority in T2DM patients with clinical CVD	Rare	↓↓	↓↓ to ↓↓↓	Genital infections, UTI, hypotension, dose-related changes in LDL-C. Caution with renal dysfunction, loop diuretics, in the elderly. Dapagliflozin not to be used if bladder cancer. Rare diabetic ketoacidosis (may occur with no hyperglycemia). Increased risk of fractures & amputations with canagliflozin. Reduced progression of nephropathy & CHF hospitalizations with empagliflozin & canagliflozin in those with clinical CVD	$$$
DPP-4 Inhibitors	alo, saxa, sita: Neutral	Rare	Neutral	↓↓	Caution with saxagliptin in heart failure Rare joint pain	$$$
Insulin	glar: Neutral degludec: noninferior to glar	Yes	↑↑	↓↓↓↓	No dose ceiling, flexible regimens Requires subcutaneous injection	$- $$$$
Thiazolidinediones	Neutral	Rare	↑↑	↓↓	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks for maximal effect	$$
α-glucosidase inhibitor (acarbose)		Rare	Neutral	↓	GI side-effects common Requires 3 times daily dosing	$$
Insulin secretagogue: **Meglitinide** **Sulfonylurea**		Yes Yes	↑ ↑	↓↓ ↓↓	More rapid BG-lowering response Reduced postpriandal glycemia with meglitinides but usually requires 3 to 4 times daily dosing. Gliclazide & glimepiride associated with less hypoglycemia than glyburide. Poor durability	$$ $
Weight loss agent (orlistat)		None	↓	↓	GI side effects Requires 3 times daily dosing	$$$

Special Populations

Elderly

Pregnancy

Elderly

- Assess for level of functional dependency (frailty)
- Glycemic targets based "frailty" (A1c ≤ 8.5% for frail elderly)
  - If otherwise healthy, use the same targets as younger people
- Avoid hypoglycemia
  - Especially in cognitive impairment
- Choose antihyperglycemic therapy carefully
  - Caution with
    - Sulfonylureas - hypoglycemia
    - Thiazolidinediones - fractures; heart failure
  - Caution with renal dysfunction
  - Basal analogues instead of NPH or human 30/70 insulin
  - Premixed analogue insulins & prefilled pens
- Regular diets instead of "diabetic diets" or nutritional formulas in nursing homes

Pregnancy

- Preconception care
  - Aim for A1c ≤ 7%
  - Stop ACEi, ARB & statins
  - Switch from OADs to insulin
- May use rapid acting analogues
  - No difference in baby outcomes
- May use glyburide or metformin during pregnancy for T2DM women who are non-adherent to or who refuse insulin
  - Likely safe BUT no long-term data
  - Need risk/benefit discussion with patient

Other Medications

Other Meds To Consider In T2DM

- Blood Pressure/Vascular Protection
  - ACEIs ("-prils")
  - ARBs ("-sartans")
  - Thiazides
  - Calcium channel blockers
  - Beta blockers ("-ololS")
- Cholesterol/lipids
  - HMG-CoA reductase inhibitors ("-statins")
  - Fibrates
  - Cholesterol absorption inhibitor
  - PCSK9 inhibitors (injectable)
- Weight Loss Agents
  - Orlistat (*Xenical*)
  - Liraglutide (*Saxenda*)
- Cardiovascular
  - ECASA
  - Clopidogrel
  - Other anti-platelets
- Neuropathic Pain
  - Anticonvulsants
  - Antidepressants
  - Opioid analgesics
  - Local anesthetics

2018

ABCDES^3 Of Diabetes Care

- ✓ **A** • A1c – optimal glycemic control (usually ≤7%)
- ✓ **B** • BP – optimal blood pressure control (<130/80)
- ✓ **C** • Cholesterol – LDL <2.0 mmol/L or >50% reduction
- ✓ **D** • Drugs to protect the heart

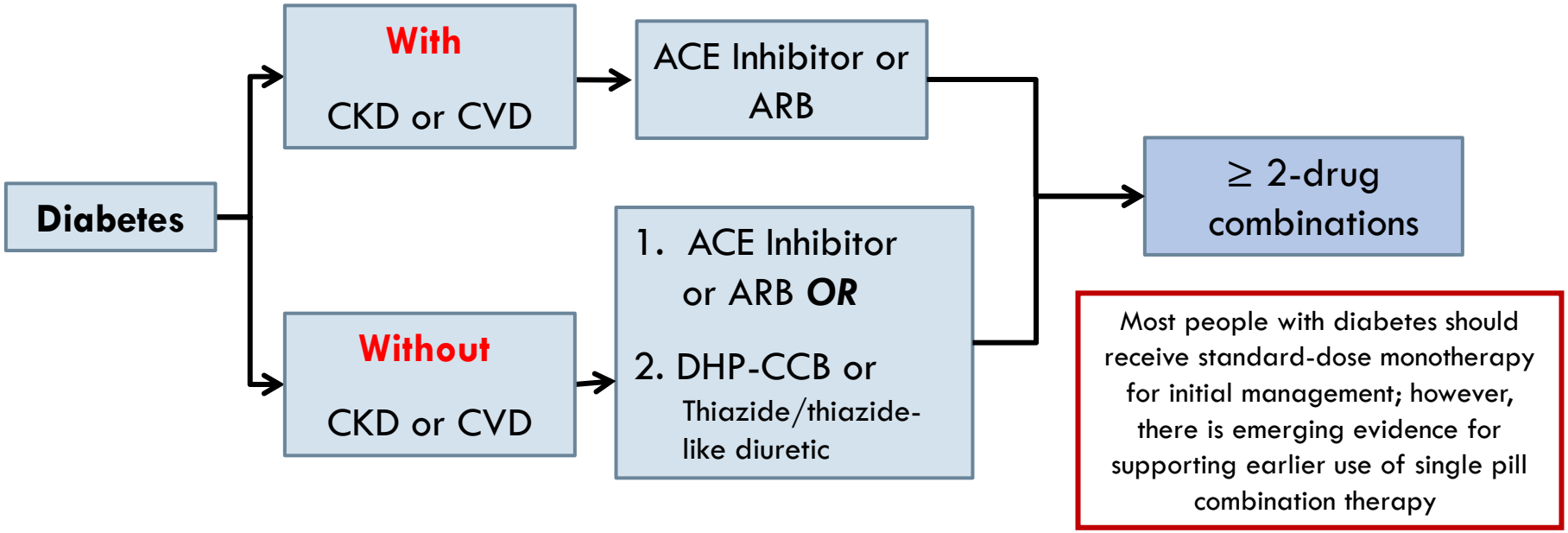
  A – ACEi or ARB | S – Statin | A – ASA if indicated | SGLT2i/GLP-1 RA with demonstrated CV benefit if type 2 DM with CVD & A1c not at target
- ✓ **E** • Exercise / Healthy Eating
- ✓ **S** • Screening for complications
- ✓ **S** • Smoking cessation
- ✓ **S** • Self-management, stress & other barriers

Hypertension Checklist

- Assess for hypertension (≥ 130/80 mmHg)
- Treat to target < 130/80 mmHg
- Use multiple antihypertensive medications often needed to achieve target
- Consider initial combination therapy

HTN Therapy In Patients With Diabetes

Threshold ≥130/80 mmHg & Target <130/80 mmHg



Check serum **potassium** & **creatinine** at **baseline** & **within 1 to 2 weeks** of initiation of an **ACEI or ARB**

Combinations of agents that block the **RAAS** (ACEi, ARB, DRI) **should not be used**

More than 3 drugs may be needed to reach target values for people with diabetes

Hypertension CANADA

CKD, chronic kidney disease; CVD, cardiovascular disease; DHP-CCB, dihydropyridine calcium channel blocker; DRI, direct renin inhibitor

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Who Should Receive Statins?

- Clinical CVD ***OR***
- Age ≥40 yrs ***OR***
- Microvascular complications ***OR***
- Diabetes >15 yrs duration & age >30 yr ***OR***
- Warrants therapy based on the *2016 Canadian Cardiovascular Society Guidelines for the Diagnosis & Treatment of Dyslipidemia*
- Regardless of baseline LDL-C

Among women with childbearing potential, statins should only be used in the presence of proper preconception counselling & reliable contraception. Stop statins prior to conception.

Dyslipidemia Checklist

- Lipid profile at diagnosis then yearly or every 3-6 months when on treatment
- Statins as first-line therapy
- Second line agent only when LDL-C is not at target despite statin therapy
- Fibrate when TG >10.0 mmol/L

2nd Line Lipid Medications

Drug class Generic name	Principal effects	Other considerations
Bile acid sequestrants (BAS) • Cholestyramine resin • Colesevelam • Colestipol HCl	• Lowers LDL-C	• GI intolerability, which worsens with increasing doses • May elevate TG • Colesevelam has A1c lowering effect
Cholesterol absorption inhibitor • Ezetimibe	• Lowers LDL-C	• Less effective than statins as monotherapy • Effective when used in combination with a statin to further lower LDL-C
Fibrates • Bezafibrate • Fenofibrate • Gemfibrozil	• Lowers TG • Variable effect on LDL-C • Highly variable effect on HDL-C (more effective at raising HDL-C when baseline TG is high)	• May increase creatinine & homocysteine levels; however, favorable effects on renal function have been noted with long-term fenofibrate treatment; possible benefit of fenofibrate on retinopathy • Do not use gemfibrozil in combination with a statin due to increased risk of myopathy & rhabdomyolysis
Nicotinic acid • Extended-release niacin • Immediate-release niacin) • Long-acting (e.g. "no-flush") **not recommended**	• Raises HDL-C • Lowers TG • Lowers LDL-C • Lowers Lp(a)	• To be used selectively & cautiously but not to be used prior to trials of ezetimibe or BAS • Can cause dose-related deterioration of glycemic control • Long-acting niacin should **not** be used due to increased hepatotoxicity & decreased efficacy
PCSK9 Inhibitor • Alirocumab • Evolocumab	• Lowers LDL-C • Lowers Lp(a)	• Injection site reactions •CV risk reduction shown in one randomized clinical trial of secondary prevention, including in a subset with type 2 diabetes

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CV Protective Medications

- Statins
- ACE-inhibitors or Angiotensin receptor blockers (ARB)
- Certain antihyperglycemic agents
- ASA selective use

Who Should Receive Statins?

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- Microvascular complications ***OR***
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- Warrants therapy based on the *2016 Canadian Cardiovascular Society Guidelines for the Diagnosis & Treatment of Dyslipidemia*
- Regardless of baseline LDL-C

Among women with childbearing potential, statins should only be used in the presence of proper preconception counselling & reliable contraception. Stop statins prior to conception.

What If LDL-C <2.0 mmol/L?

- Irrespective of initial LDL-C
  - Patients obtain similar benefit
- If a person with diabetes qualifies for statins
  - <2.0 mmol/L
  - Target reduction of ≥50% in LDL-C

Cardiovascular Protective medications

- Statins
- ACE-inhibitors or Angiotensin receptor blockers (ARB)
- Certain antihyperglycemic agents
- ASA selective use

Who Should Receive An ACEi or ARB?

- **Clinical CVD**
- **Age ≥55 years with an additional CV risk factor or end organ damage** (albuminuria, retinopathy, left ventricular hypertrophy)
- **Microvascular complications**

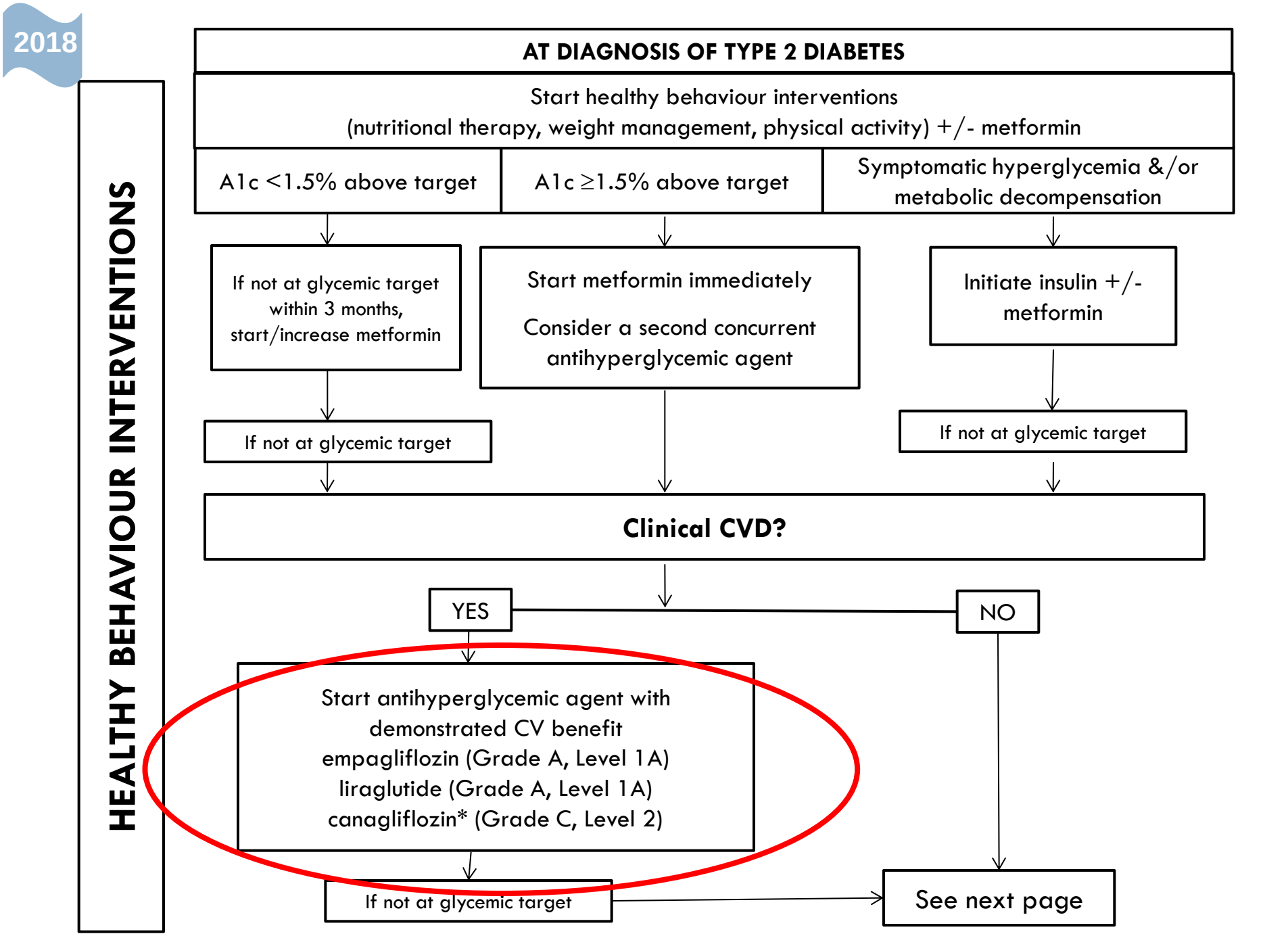
At doses that have shown vascular protection [perindopril 8 mg daily (EUROPA), ramipril 10 mg daily (HOPE), telmisartan 80 mg daily (ONTARGET)]

Among women with childbearing potential, ACEi or ARB should only be used in the presence of proper preconception counselling & reliable contraception. Stop ACEi or ARB either prior to conception or immediately upon detection of pregnancy.

EUROPA Investigators, Lancet 2003;362(9386):782-788.
HOPE study investigators. Lancet. 2000;355:253-59.
ONTARGET study investigators. NEJM. 2008:358:1547-59

Cardiovascular Protective Medications

- Statins
- ACE-inhibitors or Angiotensin receptor blockers (ARB)
- Certain antihyperglycemic agents
- ASA selective use



* Avoid in people with prior lower extremity amputation

Cardiovascular Protective medications

- Statins
- ACE-inhibitors or Angiotensin receptor blockers (ARB)
- Certain antihyperglycemic agents
- ASA selective use

Who Should Receive ASA?

- In people with established CVD, low-dose ASA therapy (81-162 mg) should be used to prevent CV events
- ASA should not be used routinely for the primary prevention of CVD in people with diabetes
  - Insufficient evidence to support use of ASA for primary prevention
  - Risk of bleeding may be more serious than CV risk
- ASA may be used in the presence of additional CV risk factors

Other Considerations

Weight Loss

- Goal is to prevent weight gain, promote weight loss & prevent weight re-gain
- Weight loss of only 5-10% improves:
  - Insulin sensitivity
  - Glycemic control
  - Blood pressure
  - Lipid levels

Adapted from: CDA CPG - 2013

Weight Loss Strategies

- Lifestyle
- Medications
  - Orlistat (*Xenical*)
    - PO
    - Loose stools, GI upset
    - Relative weight loss - ↓
    - Cost: $$$
  - Liraglutide (*Saxenda*)
    - SC injection
    - Nausea, GI upset
    - Relative weight loss - ↓↓
    - Cost: $$$$
- Bariatric surgery
- Consider weight effect of current medications

Diabetes Canada CPG 2018

Reducing Progression Of Diabetic Nephropathy

- Optimal glycemic control in T1 & T2DM shown to reduce the development & progression of nephropathy
- Optimal blood pressure control
- ACE inhibitor or ARB
- SGLT-2 inhibitor with proven renal benefit (empagliflozin)
  - eGFR >30 mL/min/1.73 m^2

Neuropathic Pain

- Prevent with good blood sugar control
- Doctor will inspect feet at every visit & test with monofilament or tuning fork
- Treated with anticonvulsants or antidepressants
  - Start at low doses & increase slowly to decrease risk of drowsiness or side effects
- Few patients will receive complete relief from pain
  - 30-50% reduction in pain considered a good result

	Class	Common Medications
1st Line	Anticonvulsants	Gabapentin (*Neurontin*) Pregabalin (*Lyrica*) Valproate
	Antidepressants	Amitriptyline (*Elavil*) Desipramine (*Norpramin*) Nortriptyline (*Aventyl*) Duloxetine (*Cymbalta*) Venlafaxine (*Effexor*)
2nd Line	Opiods	Dextromethorphan Morphine ER Oxycodone ER (*OxyNEO*) Tapentadol ER (*Nucynta*) Tramadol ER
Others	Topical nitrates Cannabinoids Capsaicin Electrical nerve stimulation	

2018 Diabetes Canada CPG

Erectile Dysfunction

- All adult men with diabetes should be regularly screened
- 1st line treatments are PDE-5 inhibitors
- Investigate for hypogonadism if men with ED do not respond to PDE-5 inhibitor therapy

	Once daily	As needed
Sildenafil (*Viagra*)		√
Tadalafil (*Cialis*)	√	√
Vardenafil (*Levitra*)		√

- Contraindications: grapefruit & nitroglycerin products
- Side effects include flushing, dizziness, headache

Natural Health Products

- Vitamins & minerals, herbal remedies, homeopathic medicines, traditional medicines, such as traditional Chinese medicines, probiotics & other products like amino acids & essential fatty acids
- Regulated under the Natural Health Products Regulations
- Insufficient evidence to make a recommendation regarding efficacy & safety of complementary or alternative medicine for individuals with diabetes

Common Medications That Can Lower Blood Glucose

- Alcohol
- Aspirin
- Some blood pressure medications
- Some antibiotics
- Some seizure medications
- Quinine
- Beta-blockers (atenolol, bisoprolol, metoprolol) can mask low blood sugar

Common Medications That Can Raise Blood Glucose

- Corticosteroids (prednisone; dexamethasone)
- Atypical antipsychotics
- Anti-viral medications
- Diuretic/water pills
- Birth control pills/estrogen/progesterone
- Epinephrine
- Pseudoephedrine (*Sudafed*)
- Niacin
- Caffeine (in large amounts)

Formulating A Management Plan: Collaboration

- People are the experts in their own lives
- Health professionals are the experts in clinical aspects of diabetes
- 99% of diabetes care is self care
- Behavior change takes place as health professionals help people make informed decisions about their self care
- Not all patients will be primary decision makers in their own care

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Questions…

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