

Diabetes –
Which agent
should I use for
this patient?





Disclosures

- ▶ Speaker: Ting-Yu Wang, MDCM, FRCPC, Msc
- ▶ Endocrinologist:
 - ▶ St-Jean-sur-Richelieu .
 - ▶ LMC Glen
 - ▶ Hôpital Chinois de Montréal
- ▶ Disclosures:
 - ▶ Advisory board/Conferences : Amgen, Astra Zeneca, Eli Lilly/Boehringer Ingelheim, Insulet, Janssen, Merck, Novo Nordisk, Sanofi-Aventis, Valeant
 - ▶ Research: Eli lilly, novo nordisk, sanofi-aventis
- ▶ My COI is not related to the topic I will be talking about
- ▶ Despite my COI my presentation will be strictly scientific and will not be influenced by any commercial interests. Slides were created by myself.

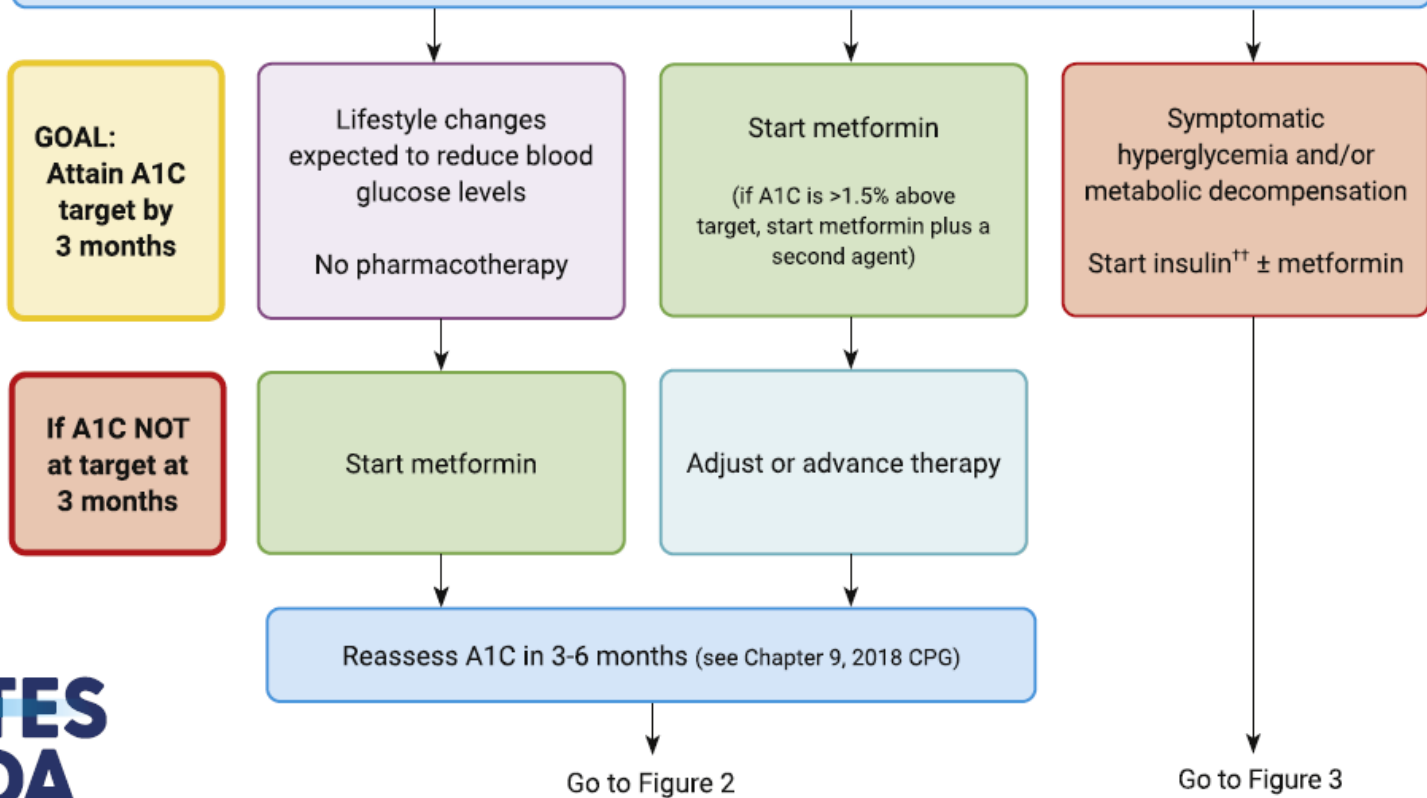


Objectives



- ▶ As a result of attending this session, participants will be able to:
 - ▶ Explore the different modalities of treatment in type 2 diabetes and help patients attain their treatment goal, with respect to the new Diabetes Canada guidelines
 - ▶ Discuss the effects of the choices of the treatment in type 2 diabetes
 - ▶ Reflect on the current practice and identify opportunities to help optimise the care to patients

- Assess glycemic control, cardiovascular and renal status*, recent dietary patterns and weight change[†]
- Select individualized A1C target (see Chapter 8, 2018 CPG)
- Provide and/or refer for diabetes education (see Chapter 7, 2018 CPG)
- Start healthy behaviour interventions (see Chapters 10,11,17, 2018 CPG)



Case 1: Mr M

- 55M DM2 x 2015
- PMH: HTN, Hypercholesterolemia
- Meds:
 - Metformin 1000mg po bid
 - Perindopril 4mg po qd
 - Atorvastatin 40mg po qd
- Physical exam:
 - BMI 29.5
 - BP 132/75
- Labs:
 - A1c 7.5%
 - Creat 70, eGFR over 60
 - LDL 1.8
 - Alb/creat 1.0



Mr M – What would you do next?

- 1. Add DPP4i
- 2. Add GLP1-RA
- 3. Add SGLT2i
- 4. Add Sulfonylurea
- 5. Add Meglitinides
- 6. Add Insulin
- 7. Observe and follow up in 3-6 months

55M DM2 x 2015

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Regular Review

- Assess glycemic control, cardiovascular and renal status
- Screen for complications (eyes, feet, kidneys)
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- Reinforce and support healthy behaviour interventions

If A1C NOT at Target and/or Change in Clinical Status

Adjust or advance therapy*

ASCVD, CKD or HF OR Age >60 with 2 CV risk factors†

ADD or SUBSTITUTE AHA with demonstrated cardiorenal benefits (see Figure 2B)

		Established Cardiovascular or Renal Disease			Risk Factors
		ASCVD	CKD	HF	>60 yrs with CV risk factors†
Lower Risks Observed in Outcome Trials	MACE	GLP1-RA or SGLT2i*	SGLT2i* or GLP1-RA		GLP1-RA
	HHF	SGLT2i*	SGLT2i*	SGLT2i* (and lower CV mortality)	SGLT2i*
	Progression of Nephropathy	SGLT2i*	SGLT2i*		SGLT2i*

Highest level of evidence: Grade A Grade B Grade C or D *Initiate only if eGFR >30 ml/min/1.73m²

A1C above target and glucose lowering required

ADD or SUBSTITUTE AHA^{††} according to clinical priorities^{†††} start insulin for symptomatic hyperglycemia and/or metabolic decompensation (Figure 3)

PROVEN cardiorenal benefit in high-risk populations**	CV safety, but NO proven cardiorenal benefit**	RISK of HF
<p>GLP1-RA <i>Weight loss</i></p> <p>dulaglutide, liraglutide, semaglutide</p> <p>SGLT2i</p> <p>canagliflozin, dapagliflozin, empagliflozin</p>	<p>GLP1-RA</p> <p>exenatide ER, lixisenatide</p> <p>ertugliflozin*** (SGLT2i)</p>	
<p>DPP4i</p> <p>sitagliptin, linagliptin, alogliptin</p> <p>Acarbose</p>		<p>saxagliptin (DPP4i)</p>
<p>Sulfonylureas</p> <p>Meglitinides</p> <p>Insulin</p> <p><i>Hypoglycemia</i></p>		<p>Thiazolidinediones</p> <p><i>Weight gain</i></p>

Fixed-dose combinations may be considered to reduce burden

Mr M

➤ 55M DM2 x 2015

➤ BMI 29.5

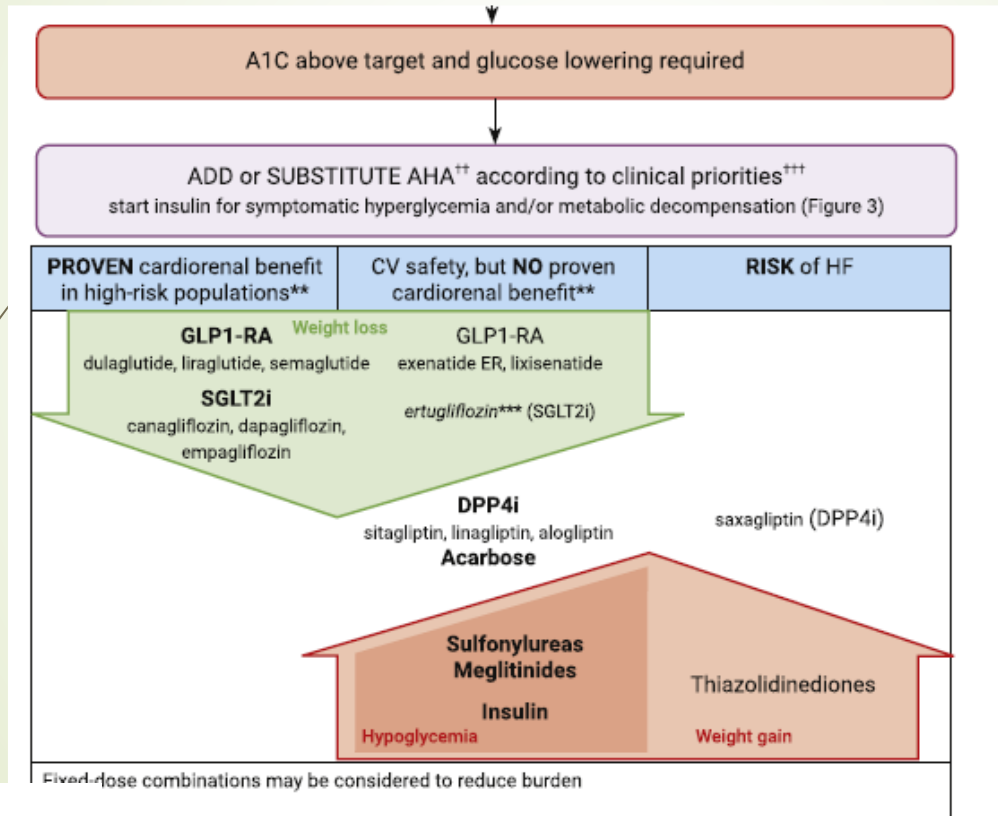
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Class	Effect on CVD Outcomes	Hypo-glycemia	BW	Relative A1C Lowering when added to metformin	Other therapeutic considerations	Cost
GLP-1RA	Lira: Superiority Sema OW: Superiority* Dula: Superiority Exenatide LAR & Lixi: Neutral	Rare	↓↓	↓↓ to ↓↓↓	GI side-effects, Gallstone disease. Contraindicated with personal / family history of medullary thyroid cancer or MEN 2. Requires subcutaneous injection.	\$\$\$\$
SGLT2i	Empa: Superiority Cana: Superiority	Rare	↓↓	↓↓ to ↓↓↓	Genital infections, UTI, hypotension. Rare diabetic ketoacidosis (may occur with no hyperglycemia). Canagliflozin showed increased risk of amputations in one study.	\$\$\$
DPP-4i	Neutral	Rare	Neutral	↓↓	Caution with saxagliptin in heart failure Rare joint pain.	\$\$\$
Insulin	IGlar: Neutral Degludec: Neutral	Yes	↑↑	↓↓↓↓	No dose ceiling, flexible regimens. Requires subcutaneous injection.	\$- \$\$\$\$
SUs		Yes	↑	↓↓	More rapid BG-lowering response. Reduced postprandial glycemia with meglitinides but usually requires 3 to 4 times daily dosing. Gliclazide and glimepiride associated with less hypoglycemia than glyburide. Poor durability	\$

**DIABETES
CANADA**

*Test for superiority not a pre-specified endpoint. BG, blood glucose; BW, body weight; CVD, cardiovascular disease; GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist; LAR, long-acting release; MEN 2, multiple endocrine neoplasia type 2; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; UTI, urinary tract infection. Lipscombe L et al. *Can J Diabetes* 2008;42:S88-103.

What if Mr M had a history of MI?

- ▶ 55M DM2 x 2015
- ▶ PMH: HTN, Hypercholesterolemia
- ▶ Hx of MI 3 years ago, stent x 1
- ▶ Meds:
 - ▶ Metformin 1000mg po bid
 - ▶ Perindopril 4mg po qd
 - ▶ Atorvastatin 40mg po qd
 - ▶ ASA 80mg po qd
 - ▶ Bisoprolol 5mg
- ▶ Physical exam:
 - ▶ BMI 29.5
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55M DM2 x 2015

Hx of MI x 2018

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	Progression of Nephropathy	SGLT2i*	SGLT2i*		SGLT2i*

Highest level of evidence: Grade A Grade B Grade C or D *Initiate only if eGFR >30 ml/min/1.73m²

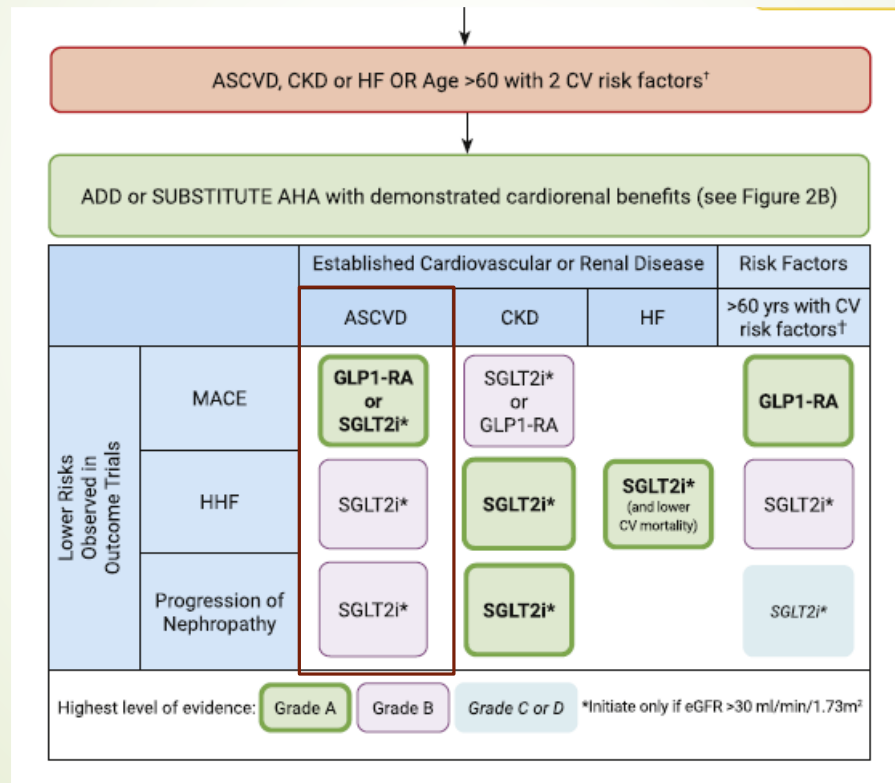
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Fixed-dose combinations may be considered to reduce burden


Mr M – hx of MI 3 years ago



Summary of outcome trials of drugs with cardiorenal benefits							
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
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)†	-
Albiglutide (HARMONY) (withdrawn from market)	CVD or PVD	0.78* (0.68-0.90)	0.93 (0.73-1.19)	0.95 (0.79-1.16)	0.96 (0.79-1.15)	0.76 (0.62-0.94)	-
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)
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)
Canagliflozin (CRENDENCE)	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)
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)
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)

What if Mr M has CKD?

- ▶ 55M DM2 x 2015
- ▶ PMH: HTN, Hypercholesterolemia
- ▶ Meds:
 - ▶ Metformin 1000mg po bid
 - ▶ Perindopril 4mg po qd
 - ▶ Atorvastatin 40mg po qd
- ▶ Physical exam:
 - ▶ BMI 29.5
 - ▶ BP 132/75
- ▶ Labs:
 - ▶ A1c 7.5%
 - ▶ Creat 120, eGFR 50
 - ▶ LDL 1.8
 - ▶ Alb/creat 3.5



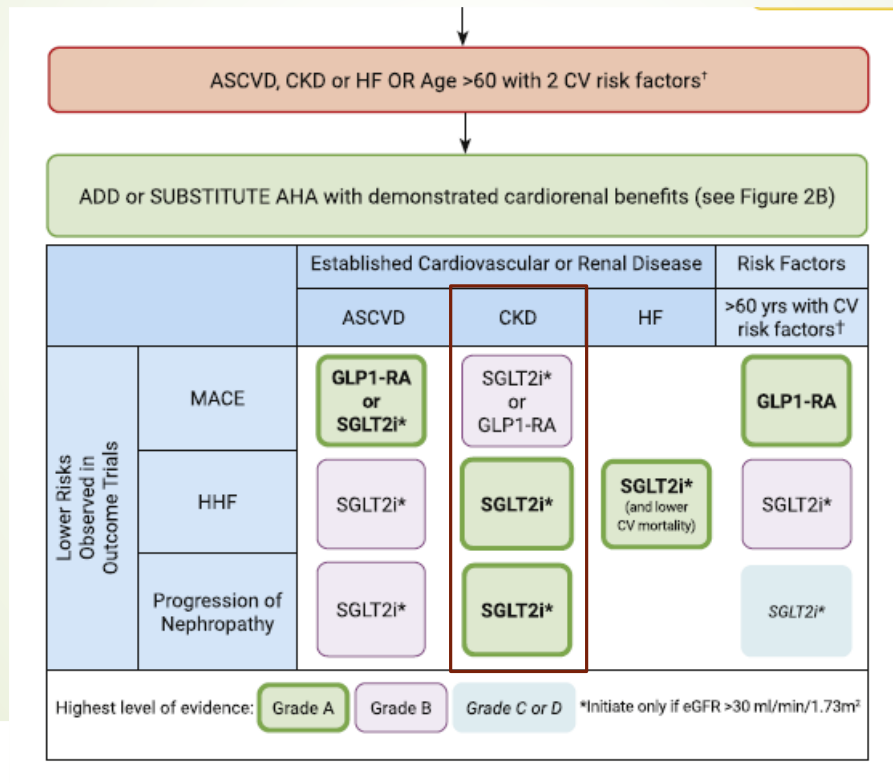
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- 1. Add DPP4i
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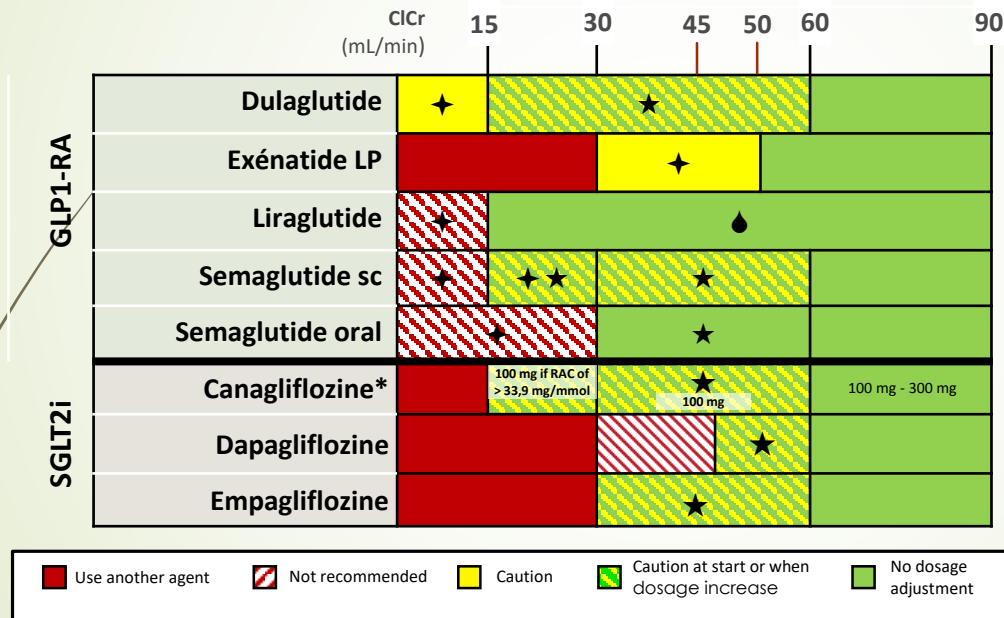
Mr M – eGFR 50, alb/cr 3.5



Summary of outcome trials of drugs with cardiorenal benefits

Agent (outcome trial)	Population	Progression of CKD
GLP1-RA		
Exenatide (EXSCEL)	CVD (73%) or CV risk factors	–
Liraglutide (LEADER)	CVD (72%) or CV risk factors	–
Semaglutide SC (SUSTAIN 6)	CVD (59%) or CV risk factors	–
Semaglutide Oral (PIONEER 6)	CVD (85%) or CV risk factors	–
Dulaglutide (REWIND)	CVD (31.5%) or CV risk factors	–
Albiglutide (HARMONY) (withdrawn from market)	CVD or PVD	–
SGLT2i		
Empagliflozin (EMPA-REG)	CVD	0.61 (0.53–0.70)
Canagliflozin (CANVAS PROGRAM)	CVD (66%) or CV risk factors	0.73 (0.67–0.79)
Canagliflozin (CREDENCE)	CKD (eGFR 30–90 + proteinuria)	0.70*2 (0.59–0.82)
Dapagliflozin (DECLARE-TIMI)	CVD (41%) or CV risk factors	0.76 (0.67–0.87)
Dapagliflozin (DAPA-HF)	CHF (reduced EF) ± DM (42%)	0.71 (0.44–1.16)

Adjustment of the dosage in renal failure



Legend :	
★	Limited clinical experience
★	Follow renal funtion, esp if GI symptoms
●	Caution in patients with dehydration


Warning:

- **Canagliflozine** : insufficient data to start when eGFR < 30 mL/min/1,73 m²
- **Empagliflozine** : stop treatment if eGFR drops < 30 mL/min/1,73 m²
- **Dapagliflozine** : not recommended if eGFR < 45 mL/min/1,73 m²

* Peut être utilisé pour les bienfaits cardiovasculaires chez les patients présentant une MCV clinique, un taux d'HbA_{1c} supérieur à la cible et un DFGe > 30 mL/min/1,73 m² (1 f.p.j.), une fois par semaine; CICr, clairance de la créatinine; DFG, débit de filtration glomérulaire; iDPP-4, inhibiteur de la dipeptidyl peptidase-4; iSGLT2, inhibiteur de cotransporteur sodium-glucose de type 2; LP, libération prolongée; RAC, ratio albumine/créatinine. Monographie de la canagliflozine, Janssen Inc., 2020; monographie de la dapagliflozine, AstraZeneca Canada Inc., 2020; comité d'experts des Lignes directrices de pratique clinique de Diabète Canada. Can J Diabetes. 2018;42 Suppl 1:S88-103; monographie de la dulaglutide, Eli Lilly Canada Inc., 2019; monographie de l'empagliflozine, Boehringer Ingelheim (Canada) Ltd., 2019; monographie de l'exénatide LP, AstraZeneca Canada Inc., 2019; monographie du liraglutide, Novo Nordisk Canada Inc., 2020; monographie du semaglutide oral, Novo Nordisk Canada Inc., 2020; monographie du semaglutide 1 f.p.s., Novo Nordisk Canada Inc., 2018. Comité d'experts des Lignes directrices de pratique clinique de Diabète Canada. Can J Diabetes. 2018;42 Suppl 1:S47-53.

What if Mr M is 65 year old

- ▶ **65M** DM2 x 2015
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- ▶ Meds:
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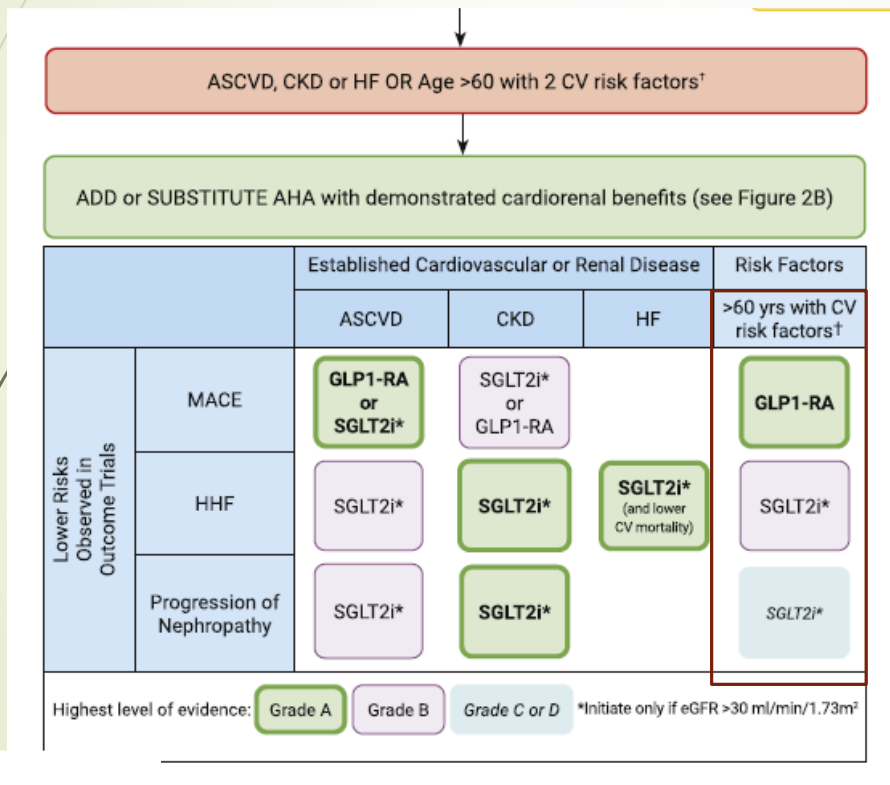
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Mr M – 65 year old



CV Risk factors:

- Smoking (tobacco use)
- Hypertension
 - Untreated BP ≥140/90, or
 - Current antihypertensive therapy
- Dyslipidemia
 - Untreated LDL >3.4 mmol/L OR HDL-C <1.0 mmol/L (men) <1.3 mmol/L (women) OR triglyceride >2.3 mmol/L, or
 - Current lipid-lowering therapy
- Central obesity

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	HHF	SGLT2i*	SGLT2i*	SGLT2i* (and lower CV mortality)	SGLT2i*
	Progression of Nephropathy	SGLT2i*	SGLT2i*		SGLT2i*

Highest level of evidence: Grade A Grade B Grade C or D *Initiate only if eGFR >30 ml/min/1.73m²

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<p>Sulfonylureas</p> <p>Meglitinides</p> <p>Insulin</p> <p><i>Hypoglycemia</i></p>		<p>Thiazolidinediones</p> <p><i>Weight gain</i></p>

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Questions?

