Cardio-renal Outcomes in Type 2 Diabetes

Objectives:

Disclosures

Lectures, advisory boards:
Merck, AstraZeneca, Takeda, Boehringer-Ingelheim, Janssen, Novo Nordisk, Eli Lilly, Sanofi, Abbott, Medtronic, Bayer

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Concepts that you should already have integrated in your daily practice for type 2 diabetes :

If cardiovascular disease (or if more than 60 years old…): add an SGLT2i and/or a GLP-1R agonist

We should strongly consider using an SGLT2 inhibitor if the eGFR is between 30 and 60 or in presence of micro/macro-albuminuria to protect the kidneys

The GLP-1 receptor agonists' vascular protection is conserved in presence of eGFR below 30 ml/min/1.73m^2.

The use of metformin+SGLT2 inhibitor+GLP-1 receptor agonist is particularly advantageous in many patients

If cardiovascular disease: add an SGLT2i and/or a GLP-1R agonist

CVOT

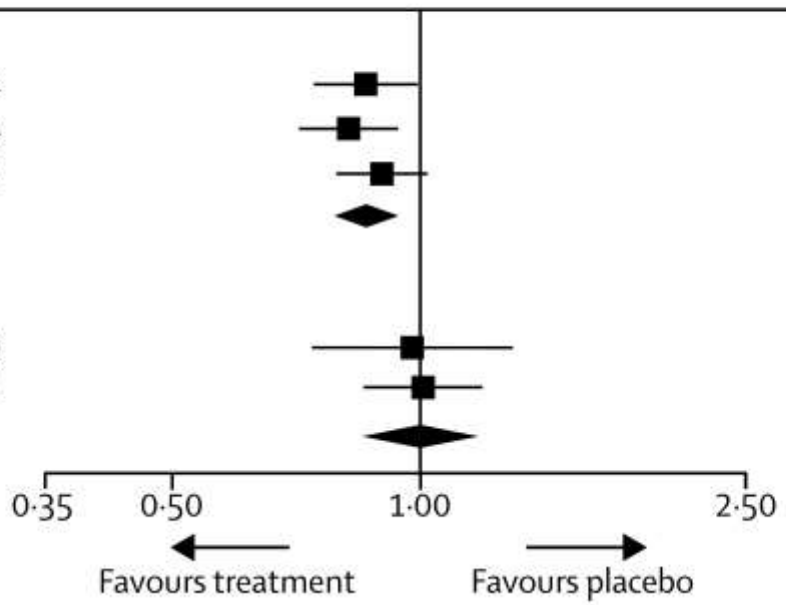
Trial	EXAMINE	SAVOR	TECOS	CARMELINA
Population	N=5380 ACS<90d	N=16492 CVD 78%	N=14671 CVD 100%	N=6980 CVD 57%
Duration	1.5 yrs	2.1 yrs	3.0 yrs	2.2 yrs
MACE	0.96 (x – 1.16) NS	1.00 (0.89-1.12) NS	0.98 (0.89-1.08) NS	1.02 (0.89-1.17) NS
CV Death or HHF				
CV Mortality	0.79 (0.60-1.04) NS	1.03 (0.87-1.22) NS	1.03 (0.89-1.19) NS	0.96 NS
Non-fatal MI	1.08 (0.88-1.33) NS	0.95 (0.80-1.12) NS	0.95 (0.81-1.11) NS	1.15 NS
Non-fatal CVA	0.91 (0.55-1.50) NS	1.11 (0.88-1.39) NS	0.97 (0.79-1.19) NS	0.88 NS
Total Mortality	0.88 (0.71-1.09) NS	1.11 (0.96-1.27) NS	1.01 (0.90-1.14) NS	
Hosp for heart failure	1.19 (0.90-1.58) NS	1.27 (1.07-1.51) P=0.007	1.00 (0.83-1.20) NS	0.90 (0.74-1.08) NS
Renal worsening		1.08 (0.96-1.22) NS		1.04 NS

Treatment of Type 2 Diabetes

Glycemic Control	Vascular Protection
Metformin	ASA
Sulfonylureas	Statins
DPP-4 Inhibitors	ACEi or ARB
SGLT2 Inhibitors	
GLP-1 Receptor Agonists	
Insulin	

SGLT2 inhibitors effect on MACE according to CV Enrollment Stratum

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687/7020	2333/7020	772	37·4	43·9	29·4	0·86 (0·74–0·99)
CANVAS Program	3756/6656	2900/6656	796	34·1	41·3	32·4	0·82 (0·72–0·95)
DECLARE-TIMI 58	3474/6974	3500/6974	1020	36·8	41·0	38·2	0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)							**0·86 (0·80–0·93)**
Patients with multiple risk factors							
CANVAS Program	2039/3486	1447/3486	215	15·8	15·5	25·9	0·98 (0·74–1·30)
DECLARE-TIMI 58	5108/10 186	5078/10 186	539	13·4	13·3	74·1	1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)							**1·00 (0·87–1·16)**

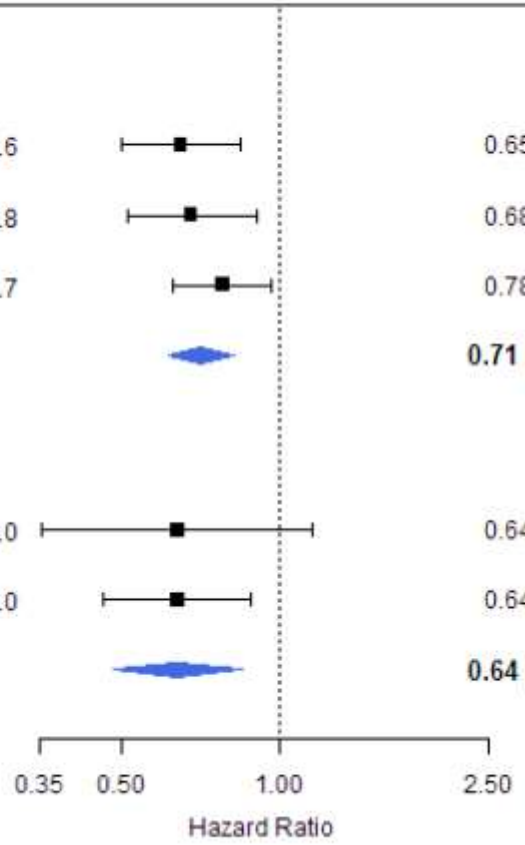


Zelniker TA et al. Lancet 2018; doi.org/10.1016/S0140-6736(18)32590-X

Effects of SGLT2 inhibitors on hospitalizations for heart failure

No heterogeneity between studies

HHF	Patients	Events	Treatment Events per 1000 pt-yrs	Placebo Events per 1000 pt-yrs	Weights (%)	HR [95% CI]
Atherosclerotic Cardiovascular Disease:						
EMPA-REG OUTCOME	7020	221	9.4	14.5	29.6	0.65 [0.50, 0.85]
CANVAS Program	6656	198	7.3	11.3	25.8	0.68 [0.51, 0.90]
DECLARE-TIMI 58	6974	343	11.1	14.1	44.7	0.78 [0.63, 0.97]
FE Model for ASCVD (P-value <0.0001)						**0.71 [0.62, 0.82]**
Multiple Risk Factor:						
CANVAS Program	3486	45	2.6	4.2	23.0	0.64 [0.35, 1.15]
DECLARE-TIMI 58	10186	155	3.0	4.6	77.0	0.64 [0.46, 0.88]
FE Model for MRF (P-value = 0.0021)						**0.64 [0.48, 0.85]**

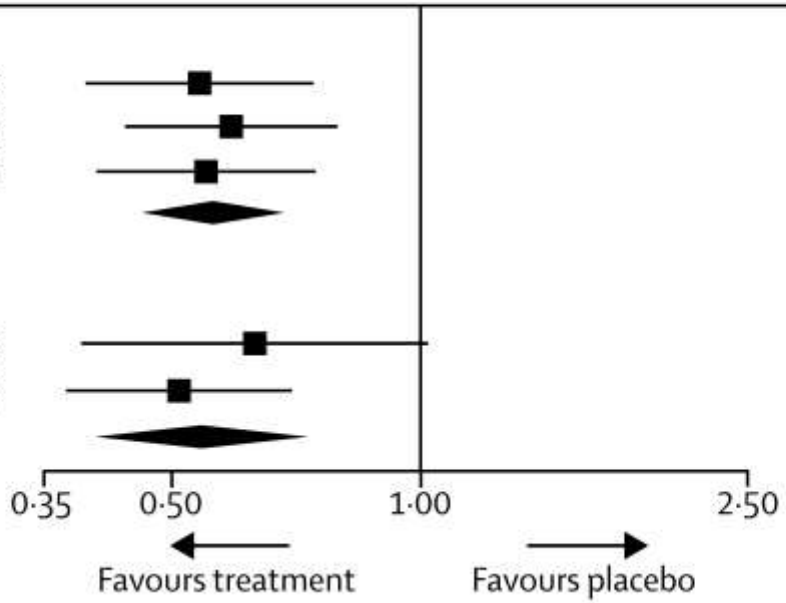


Zelniker TA et al. Lancet 2018; doi.org/10.1016/S0140-6736(18)32590-X

Effect of SGLT2 inhibitors on renal composite outcomes

No heterogeneity between studies

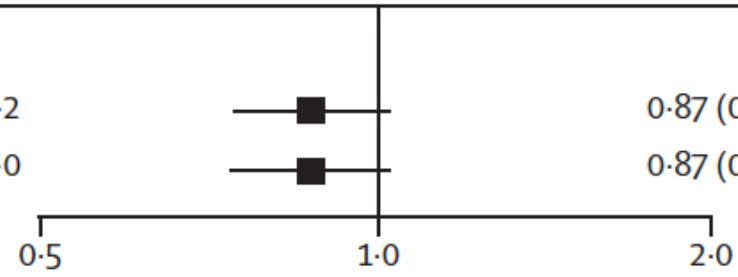
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4645/6968	2323/6968	152	6·3	11·5	31·0		0·54 (0·40–0·75)
CANVAS Program	3756/6656	2900/6656	179	6·4	10·5	35·6		0·59 (0·44–0·79)
DECLARE-TIMI 58	3474/6974	3500/6974	183	4·7	8·6	33·4		0·55 (0·41–0·75)
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								**0·56 (0·47–0·67)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	70	4·1	6·6	29·5		0·63 (0·39–1·02)
DECLARE-TIMI 58	5108/10 186	5078/10 186	182	3·0	5·9	70·5		0·51 (0·37–0·69)
Fixed effects model for multiple risk factors (p<0·0001)								**0·54 (0·42–0·71)**



Zelniker TA et al. Lancet 2018; doi.org/10.1016/S0140-6736(18)32590-X

MACE in relation to CV Risk - REWIND

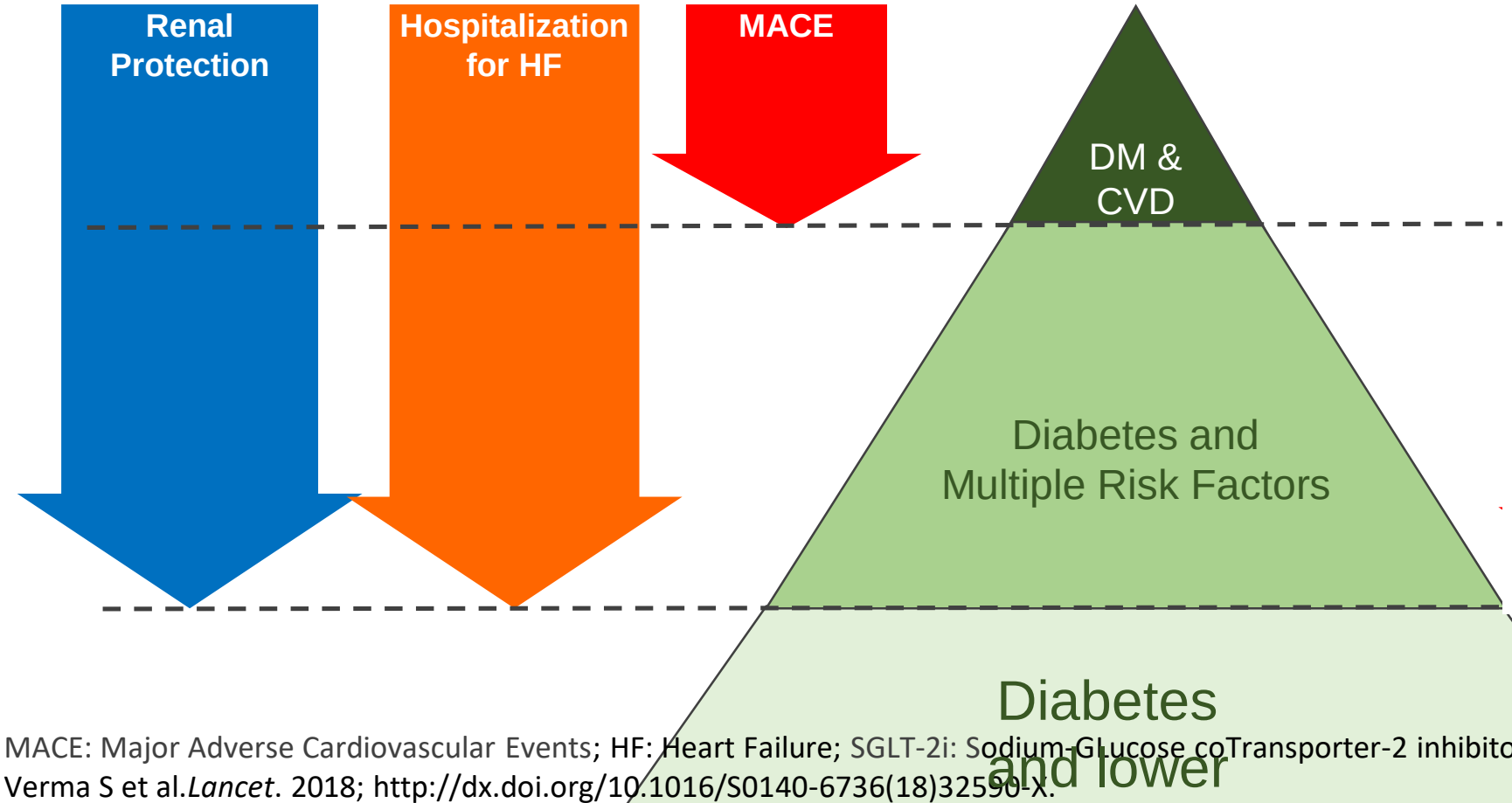
	Dulaglutide		Placebo		Hazard ratio (95% CI)	$p_{interaction}$
	Events/patients (%)	Incidence (per 100 person–years)	Events/patients (%)	Incidence (per 100 person–years)		
History of cardiovascular disease*						0·97
Yes	280/1560 (17·9%)	3·7	315/1554 (20·3%)	4·2	0·87 (0·74–1·02)	
No	277/3093 (8·9%)	1·7	317/3128 (10·1%)	2·0	0·87 (0·74–1·02)	



Total Group 0.88 (0.79-0.99)

Cardio-Renal Benefits of SGLT2 Inhibitors and GLP-1R Agonists in Various Populations with Type 2 Diabetes

Cardio-Renal Efficacy of SGLT2i



MACE: Major Adverse Cardiovascular Events; HF: Heart Failure; SGLT-2i: Sodium-Glucose coTransporter-2 inhibitors; CVD: cardiovascular disease.

Verma S et al.*Lancet*. 2018; http://dx.doi.org/10.1016/S0140-6736(18)32590-X.

DAPA-HF Endpoints

EndPoint	RR	95% CI	P	NNT
Primary	0.74	(0.65-0.85)	P=0.00001	21
Type 2 Diabetes YES	0.75	(0.63-0.90)		
Type 2 Diabetes NO	0.73	(0.60-0.88)		
Worsening HF Event	0.70	(0.59-0.83)	P=0.00003	
CV Death	0.82	(0.69-0.98)	P=0.029	
CV Death or HHF	0.75	(0.65-0.85)	P=0.00002	
All Cause Death	0.83	(0.71-0.97)	P=0.022	
Worsening Renal Function	0.71	(0.44-1.16)	P=0.17	

Renal Outcomes

We should strongly consider using an SGLT2 inhibitor if the eGFR is between 30 and 60 or in presence of micro/macro-albuminuria to protect the kidneys

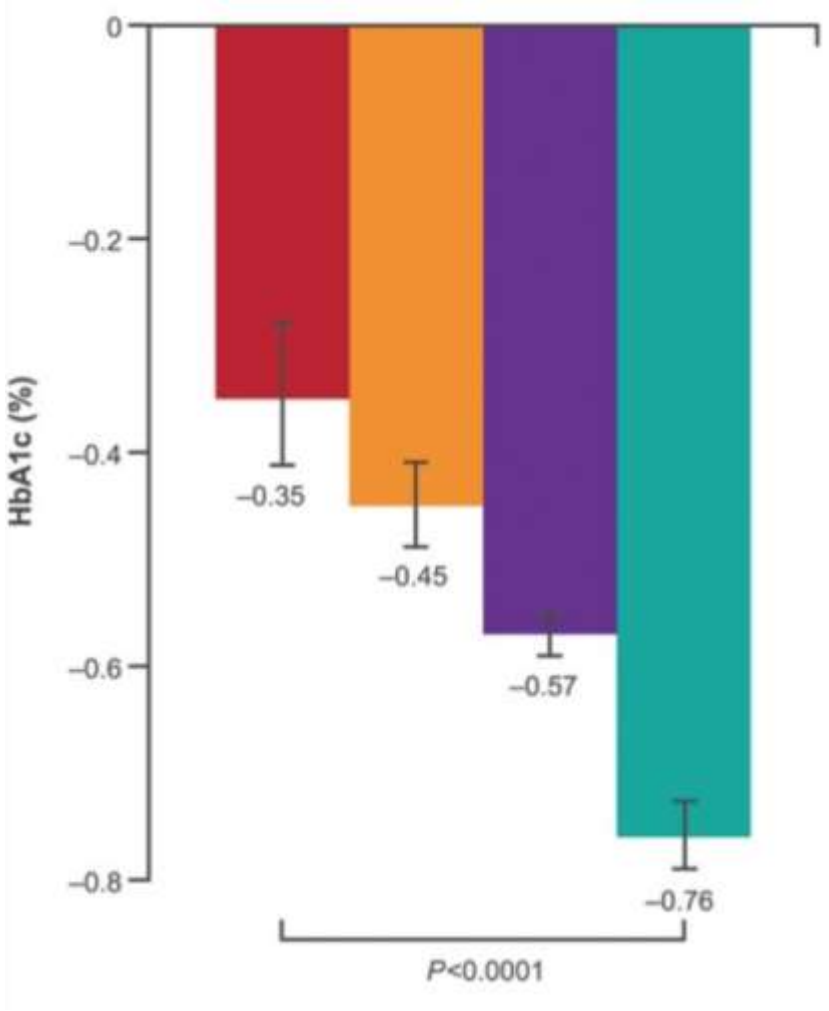
What a change!

Not so long ago, we were requiring an eGFR above 60 to initiate any SGLT2 inhibitor…

The analysis by eGFR is particularly pertinent for SGLT2i

Low eGFR = Less glucosuria = Lower efficacy ?

A1c Reduction by eGFR in the CREDENCE Trial



Baseline eGFR (ml/min/1.73m^2)

- ≥ 90
- 60-<90
- 45-<60
- < 45

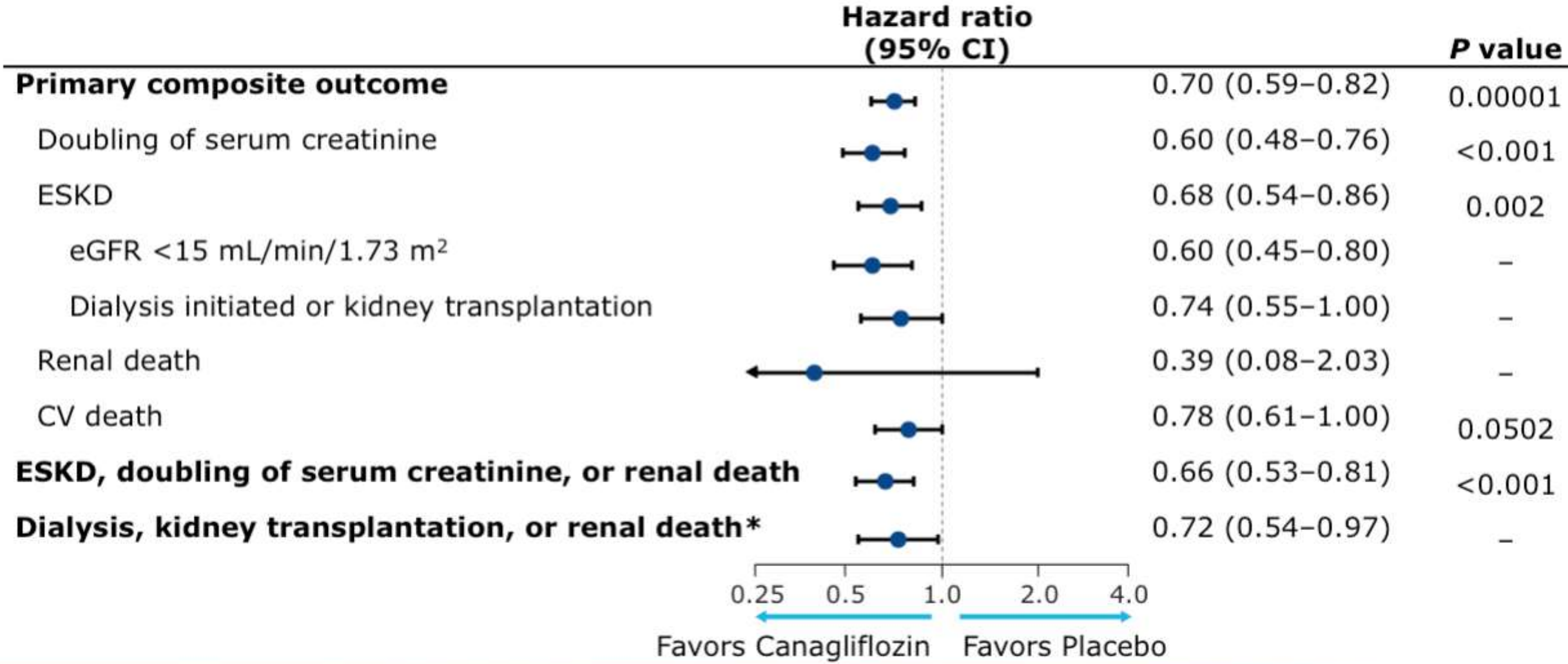
CREDENCE Study Design

Key inclusion criteria
- ≥30 years of age
- T2DM and HbA1c 6.5% to 12.0%
- eGFR 30 to 90 mL/min/1.73 m²
- UACR 300 to 5000 mg/g
- Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks

Key exclusion criteria
- Other kidney diseases, dialysis, or kidney transplant
- Dual ACEi and ARB; direct renin inhibitor; MRA
- Serum K^+ >5.5 mmol/L
- CV events within 12 weeks of screening
- NYHA class IV heart failure
- Diabetic ketoacidosis or T1DM

Participants continued treatment if eGFR was <30 mL/min/1.73 m² until chronic dialysis was initiated or kidney transplant occurred.

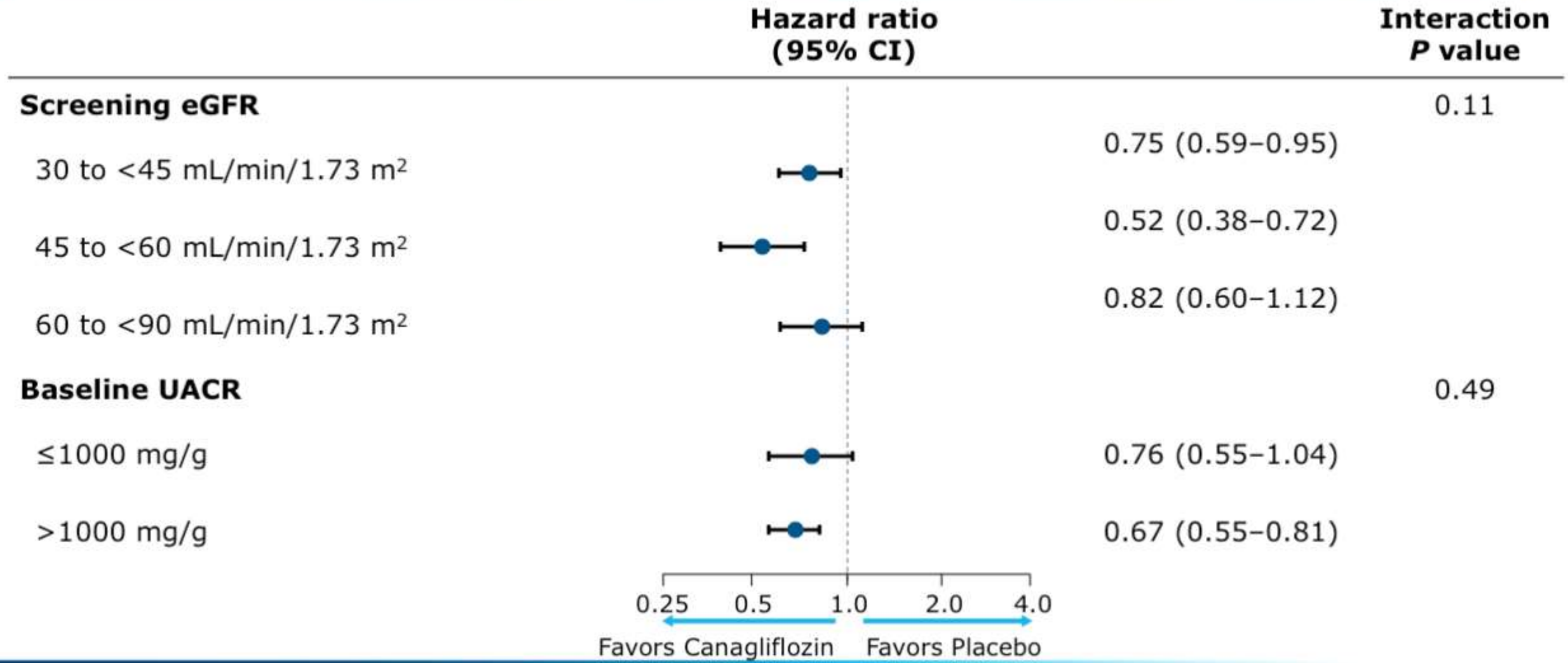
Summary of Renal Results



*Post hoc analysis.

CREDENCE

Primary Outcome by Screening eGFR and Albuminuria



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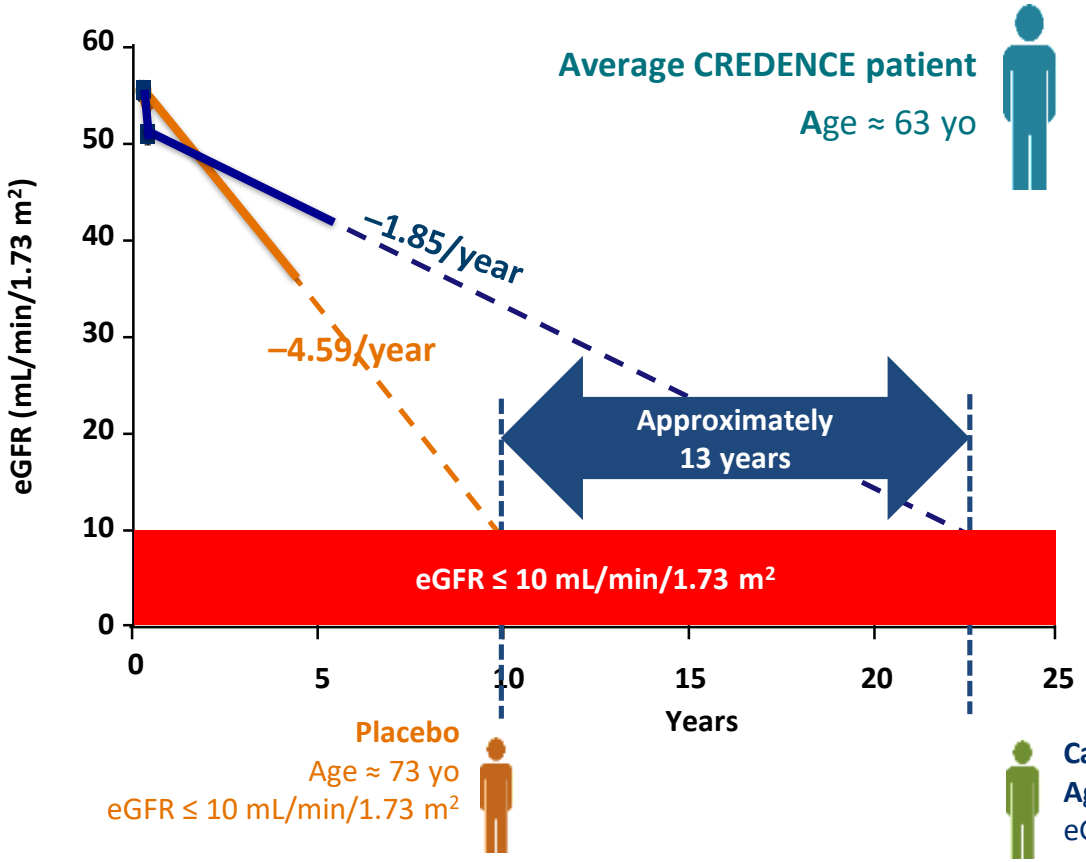
Potential Importance of SGLT2 Inhibition

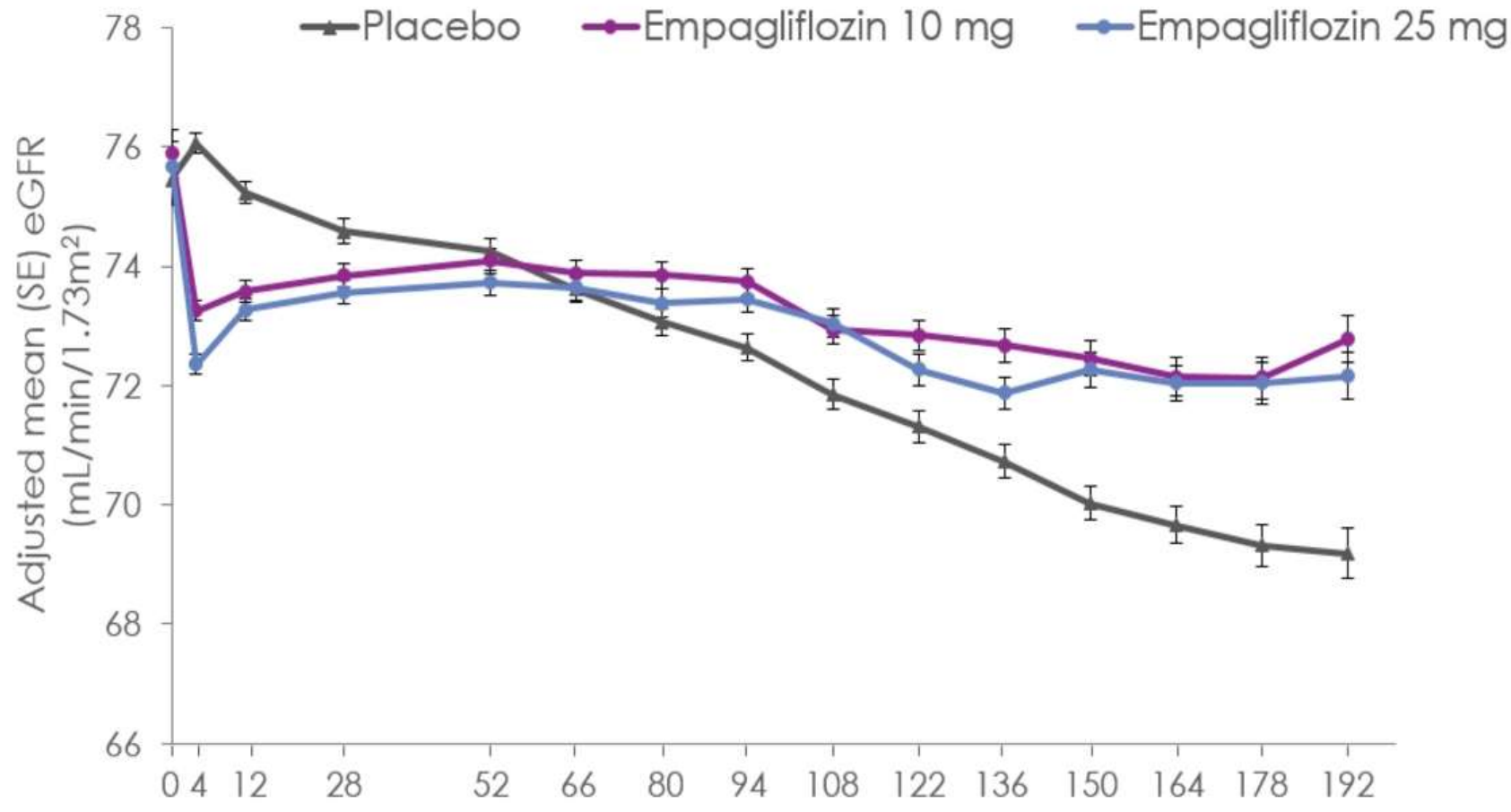


Dialysis, kidney transplantation or drenal death (number of events)*	
Canagliflozin (n=2202)	Placebo (n=2199)
78	105
RR 0.72 (95% CI 0.54–0.97)	

*Post-hoc analysis

Adapté de: Perkovic et al., *N Engl J Med* 2019, DOI: 10.1056/NEJMoa1811744.
Rivara & Mehrotra, *Semin Nephrol*. 2017; 37(2): 181–193.

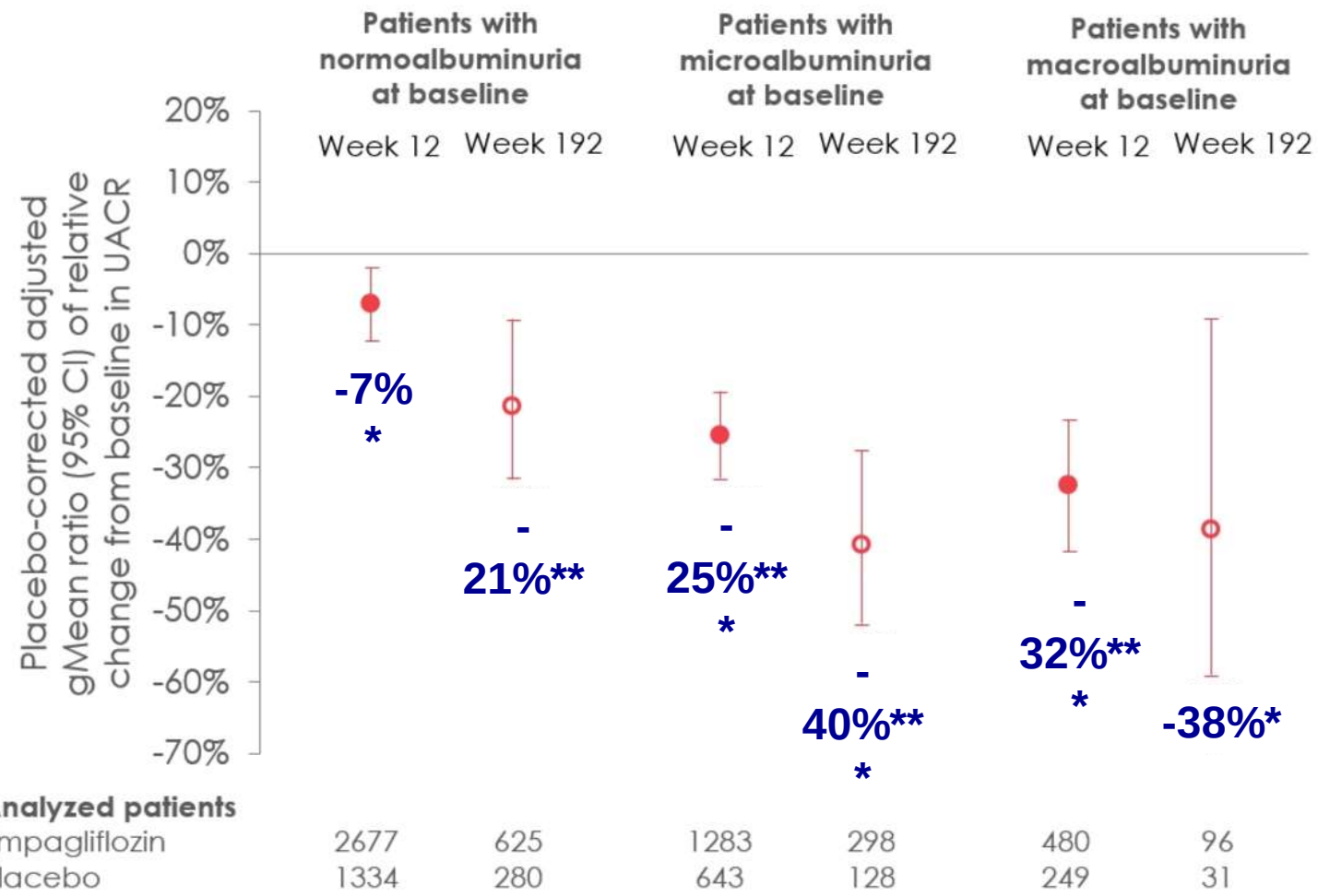
eGFR (CKD-EPI formula) over 192 weeks



No. analyzed														
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524

No. in follow-up for adverse/outcome events

Placebo-corrected change in UACR from baseline at week 12 and week 192



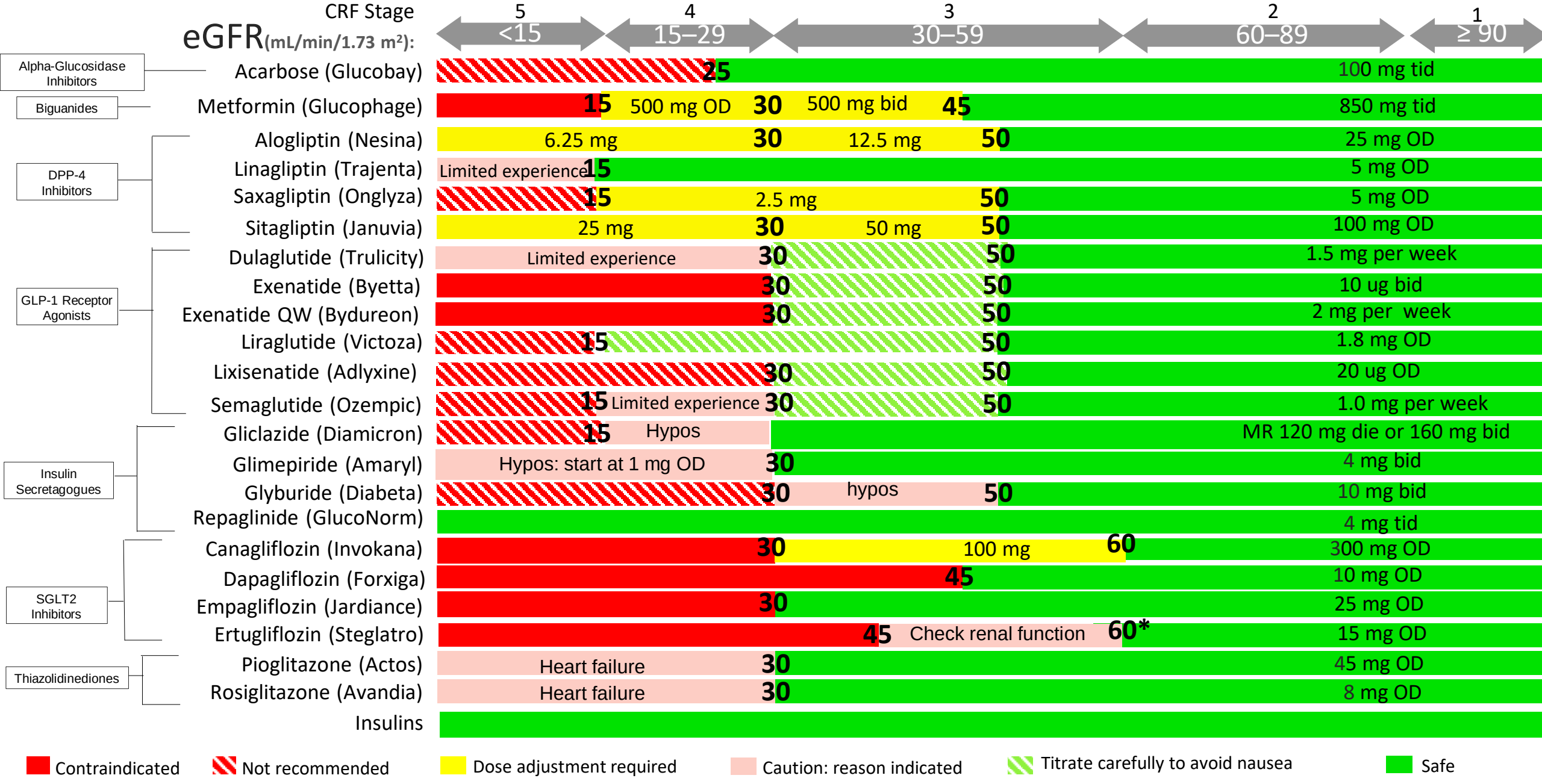
Analyzed patients						
Empagliflozin	2677	625	1283	298	480	96
Placebo	1334	280	643	128	249	31

MMRM in the treated set (OC-AD). Normoalbuminuria: UACR <30 mg/g; microalbuminuria: UACR ≥30 to ≤300 mg/g; macroalbuminuria: UACR >300 mg/g.
*p<0.05; **p<0.01; ***p<0.001 for difference vs placebo.

EMPA-REG OUTCOME®

Antihyperglycemic Agents and Renal Failure

Yale JF, version October 2019
www.dryale.ca



*=Do not initiate if eGFR is < 60 ml/min

The dose indicated is the highest dose that can be used at that eGFR

Evidence for the use of SGLT2i and GLP-1Ra by sub-populations

Clinical Cardiovascular Disease

	SGLT2 inhibitors	GLP-1 receptor agonists
MACE	CANA DAPA **EMPA**	**DULA LIRA SEMA**
Heart Failure	**CANA DAPA EMPA**	
Renal deterioration	**CANA** DAPA EMPA	DULA LIRA SEMA

High Risk for Cardiovascular Disease

	SGLT2 inhibitors	GLP-1 receptor agonists
MACE	~~CANA DAPA~~	**DULA** ~~LIRA SEMA~~
Heart Failure	CANA **DAPA**	
Renal deterioration	**CANA** DAPA	DULA LIRA SEMA

Pre-existing Renal Disease

	SGLT2 inhibitors	GLP-1 receptor agonists
MACE		
Heart Failure	**CANA** DAPA EMPA	
Renal deterioration	**CANA** DAPA EMPA	

YES, but…

Adverse Events in SGLT2i CVOTs

	CANVAS		CREDENCE		DECLARE		DAPA-HF		EMPAREG	
	Cana	Placebo	Cana	Placebo	Dapa	Placebo	Dapa	Placebo	Empa	Placebo
Volume Depletion	2.6	1.85	2.84	2.35	2.5	2.4	7.5	6.8	5.1	4.9
Acute Kidney Injury	3.0	4.1	1.69	2.00	1.5	2.0	6.5	7.2	5.2	6.6

Counsel all Patients About

Sick Day Medication List

Visit guidelines.diabetes.ca for patient handout

Instructions for Healthcare Professionals:
If patients become ill and are unable to maintain adequate fluid intake, or have an acute decline in renal function (e.g. due to gastrointestinal upset or dehydration), they should be instructed to hold medications which will:

A) Increase risk for a decline in kidney function:
- Angiotensin-converting enzyme inhibitor
- Angiotensin receptor blockers
- Direct renin inhibitors
- Non-steroidal anti-inflammatory drugs
- Diuretics
- SGLT2 inhibitors

B) Have reduced clearance and increase risk for adverse effects:
- Metformin
- Sulfonylureas (gliclazide, glimepiride, glyburide)

S sulfonylureas
A ACE-inhibitors
D diuretics, direct renin inhibitors

M metformin
A angiotensin receptor blockers
N non-steroidal anti-inflammatory
S SGLT2 inhibitors

Please complete the following card and give it to your patient.

Patients should be instructed that increased frequency of self blood glucose monitoring will be required and adjustments to their doses of insulin or oral antihyperglycemic agents may be necessary.

Instructions for Patients
When you are ill, particularly if you become dehydrated (e.g. vomiting or diarrhea), some medicines could cause your kidney function to worsen or result in side effects.

If you become sick and are unable to drink enough fluid to keep hydrated, you should **STOP** the following medications:

- Blood pressure pills
- Water pills
- Metformin
- Diabetes pills
- Pain medications
- Non-steroidal anti-inflammatory drugs (see below)

_____

_____

_____

_____

_____

Please be careful not to take non-steroidal anti-inflammatory drugs (which are commonly found in pain medications (e.g. Advil) and cold remedies).

Please check with your pharmacist before using over-the-counter medications and discuss all changes in medication with your healthcare professional.

Please increase the number of times you check your blood glucose levels. If they run too high or too low, contact your healthcare professional.

If you have any problems, you can call:

_____

DIABETES CANADA

Practical Aspects to Consider

SGLT-2i

- Start with the lowest dose
- eGFR > 45 dapagliflozin
  eGFR > 30 canagliflozin*/empagliflozin

Insulin or secretagogues

- Consider ↓ dose if glycemia close to normal

GLP-1 RA

Canagliflozin (Invokana)	100 mg
Dapagliflozin (Forxiga)	5 mg
Empagliflozin (Jardiance)	10 mg

Dulaglutide (Trulicity)	0.75 mg then 1.5 mg per week
Liraglutide (Victoza)	0.6 then 1.2 then 1.8 mg per day
Semaglutide (Ozempic)	0.25 then 0.5 then1.0 mg per week

DFGe : débit de filtration glomérulaire estimé; prn: au besoin; TA: tension artérielle.
*Chez les adultes avec diabète de type 2 et MCV clinique chez qui les cibles glycémiques ne sont pas atteintes avec la médication antihyperglycémique actuelle
Reid T. *Clinical Diabetes* 2013;31:148-57.
Bettge K et coll. *Diab Obes Metab* 2017;19:336-47.

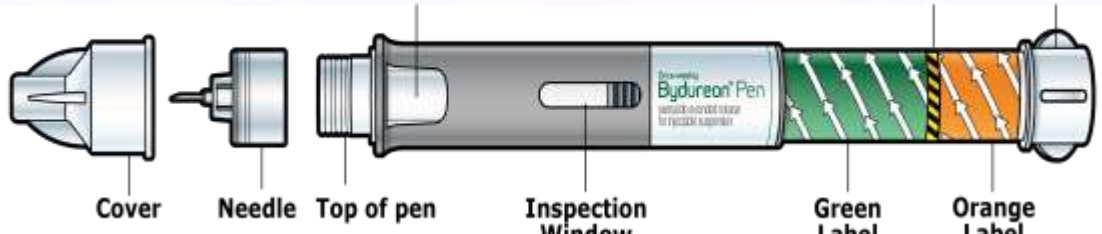
GLP-1R Agonist Pens

Liraglutide
Once a day
0.6,1.2 or 1.8 mg
Adjustable by clicks
32g needle

Dulaglutide
Once a week
0.75 or 1.5 mg
Non-Adjustable
29g needle

Semaglutide
Once a week
0.25, 0.5 or 1.0 mg
Adjustable by clicks
32g needle

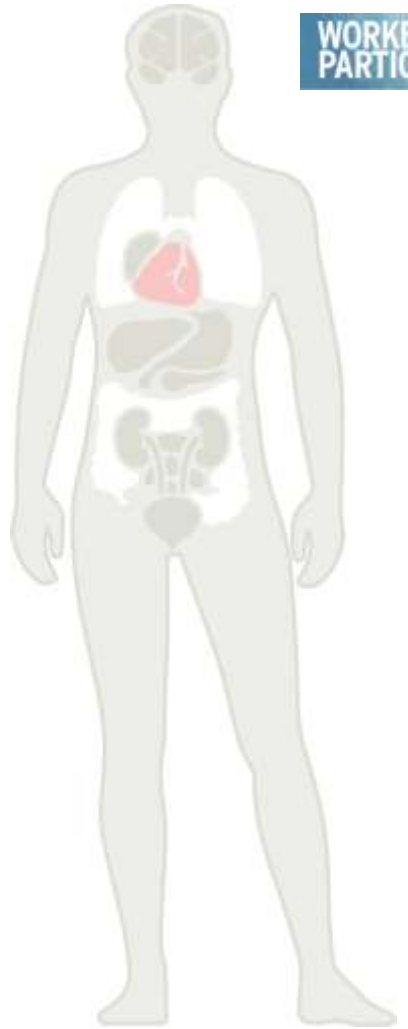
Exenatide QW
Once a week
2.0 mg
Non-Adjustables
23g needle



Discussion With Patient: Choice of Treatment to Add to Metformin

WORKBOOK PARTICIPANT

	A1C (%)	Weight	Hypoglycemia	HEART	KIDNEYS	Other adverse effects	RAMQ
TABLETS							
Sulfonylureas							
SGLT-2i							
DPP-4i							
INJECTIONS							
GLP-1RA							
INSULIN							



EX: exception

Lipscombe L et al. *Can J Diabetes* 2018;42;S88–S103.


The End
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