Diabetes and the Kidneys

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November 2020

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Disclosures

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

Research funds:
Merck, AstraZeneca, Boehringer-Ingelheim, Janssen, Novo Nordisk, Eli Lilly, Sanofi, Medtronic, Bayer, Mylan

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Objectives:

As a result of attending this session, the participants will be able to:

1) Use strategies to prevent the appearance and progression of chronic kidney disease in people with diabetes

2) Adapt antihyperglycemic therapies in patients with varying levels of CKD, including dialysis

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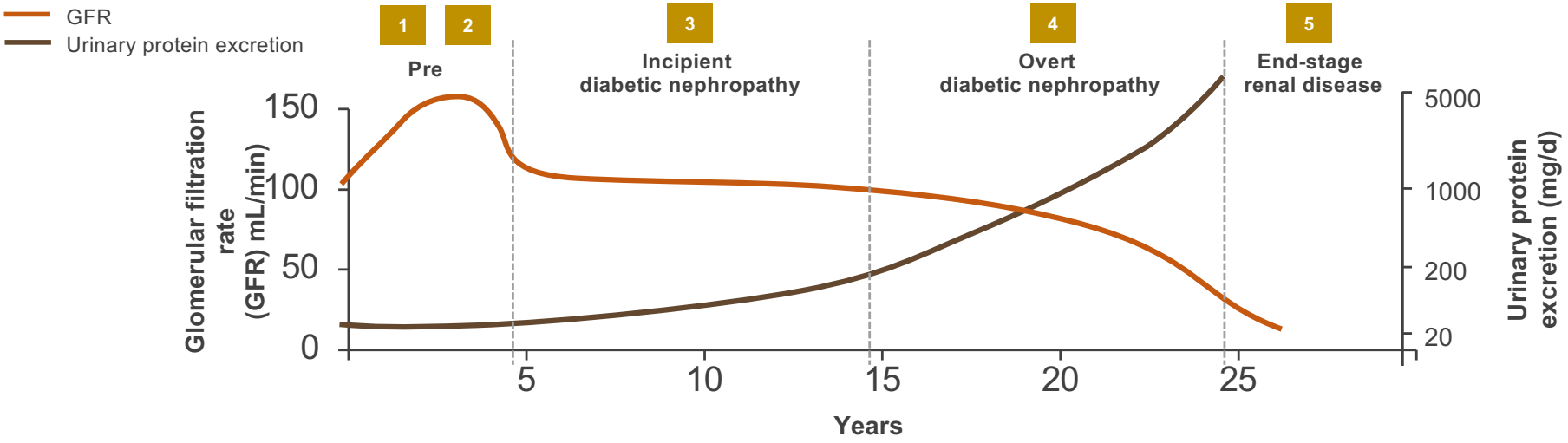
Natural History of Type 1 Diabetic Nephropathy

Glomerular hyperfiltration is one of the first steps in the development of diabetic nephropathy.



Stage	Glomerular hyperfiltration	Microalbuminuria	Macroalbuminuria	ESRD
Histology	Thickening BM Expanded mesangium	Glomerular sclerosis		
eGFR Decline	1ml/min/yr	2 ml/min/yr	5 ml/min/yr	

BM= basement membrane; eGFR: estimated Glomerular Filtration Rate
Adapted from: Rossing, Peter. Clinical pathology of nephropathy [internet]. 2015 Sep 23; Diapedia 71040851172 rev. no. 10.
Available from: https://doi.org/10.14496/dia.71040851172.10

Assessing Risk

KFRE
kidneyfailurerisk.org

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m^2) Description and range			Persistent albuminuria categories Description and range		
			A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
			<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
G1	Normal or high	≥90			
G2	Mildly decreased	60-89			
G3a	Mildly to moderately decreased	45-59			
G3b	Moderately to severely decreased	30-44			
G4	Severely decreased	15-29			
G5	Kidney failure	<15			

Am J Kidney Dis. 2015;65(2):177-205

Lady with CKD

Age and gender: **48 yo woman**

Occupation: **Nurse**

Insurance coverage: **Private**

Type 2 diabetes x **12** years A1c: **6.4%**

Cardiovascular disease ? **No** BP: **122/67** LDL-C **1.8**

Retinopathy ? **None**

Nephropathy ? **YES** eGFR **52** ACR **12**

Neuropathy ? **None**

Smoker ? **No**

BMI : **29.5**

Current Medication:

Met: **Metformin 500 mg 2 tabs BID**

SU: **Gliclazide MR 30 mg 1 tab die**

DPP-4i: **Sitagliptin 50 mg 1 tab die**

SGLT2i

GLP-1RA:

Insulin:

Statin: **Rosuvastatin 10 mg once a day**

ACEi/ARB: **Perindopril 8 mg once a day**

ASA:

Others:

Problems with past medications ?

No hypoglycemia

Other consideration:

DIABETES CANADA

www.guidelines.diabetes.ca

Can J Diabetes 44 (2020) 575–591

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

ELSEVIER

Special Article

Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update

Diabetes Canada Clinical Practice Guidelines Expert Committee

Clinical Practice Guidelines

CPG2018: Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes 42(Suppl 1): S1-325, 2018.
CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91, 2020.

Regular Review

- Assess glycemic control, cardiovascular and renal status
- Screen for complications (eyes, feet, kidneys)
- Review efficacy, side effects, safety and ability to take current medications
- 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

Weight loss

GLP1-RA
dulaglutide, liraglutide, semaglutide

GLP1-RA
exenatide ER, lixisenatide

SGLT2i
canagliflozin, dapagliflozin, empagliflozin

*ertugliflozin**** (SGLT2i)

DPP4i
sitagliptin, linagliptin, alogliptin

saxagliptin (DPP4i)

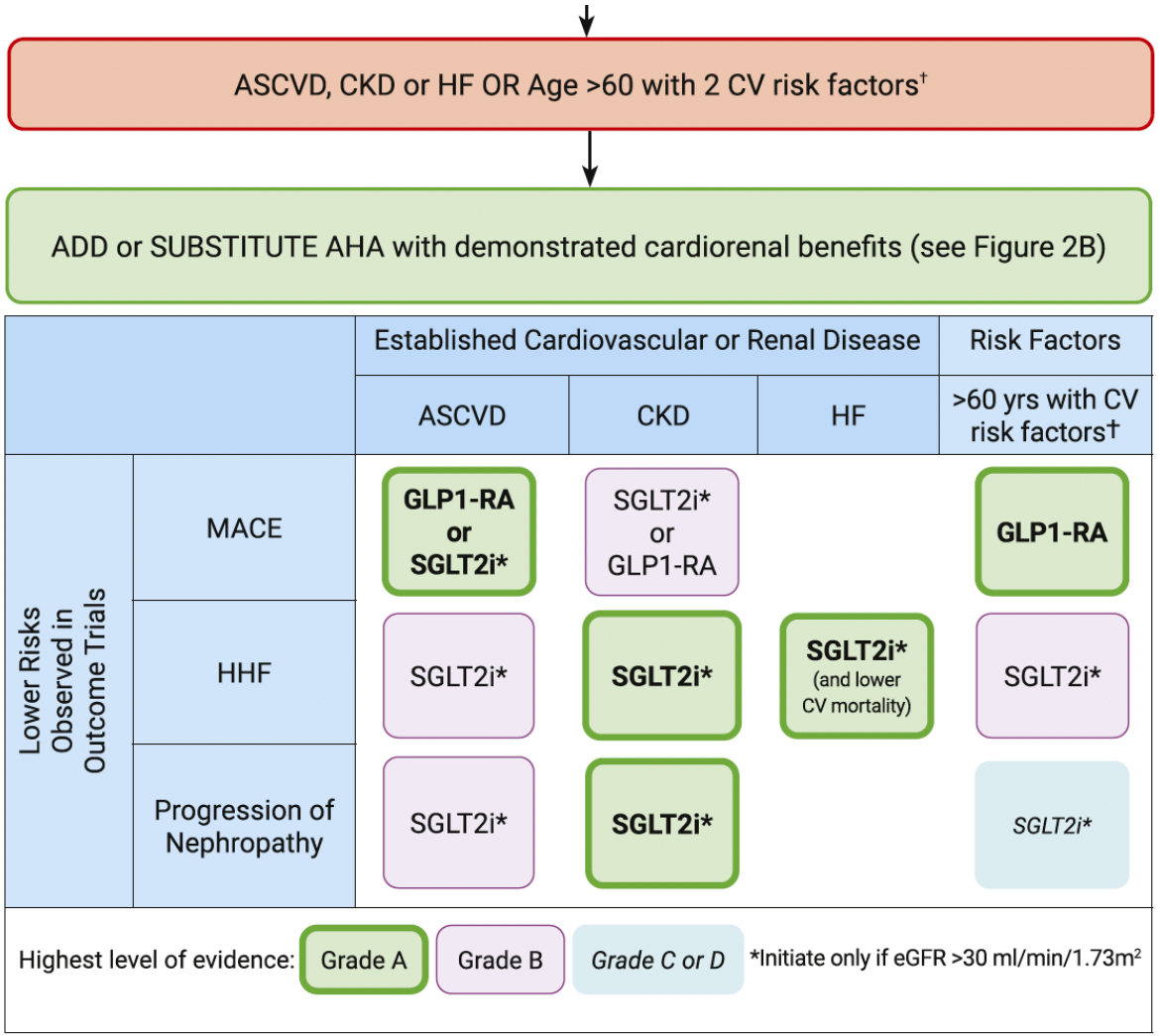
Acarbose

Sulfonylureas
Meglitinides
Insulin
Hypoglycemia

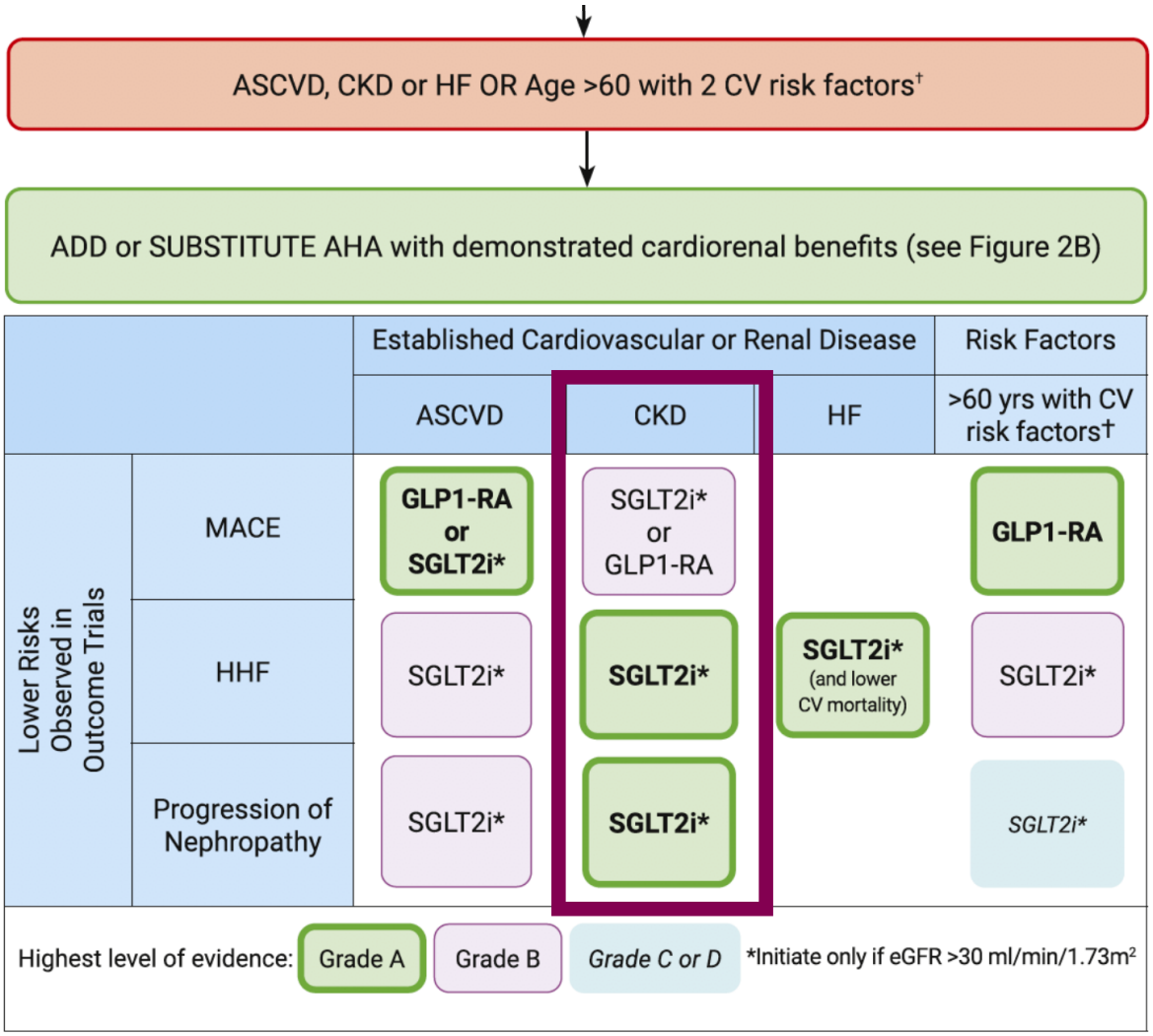
Thiazolidinediones
Weight gain

Fixed-dose combinations may be considered to reduce burden

CPG2020: Lipscombe L, et al. Canadian Journal of Diabetes 44: 575-91, 2020

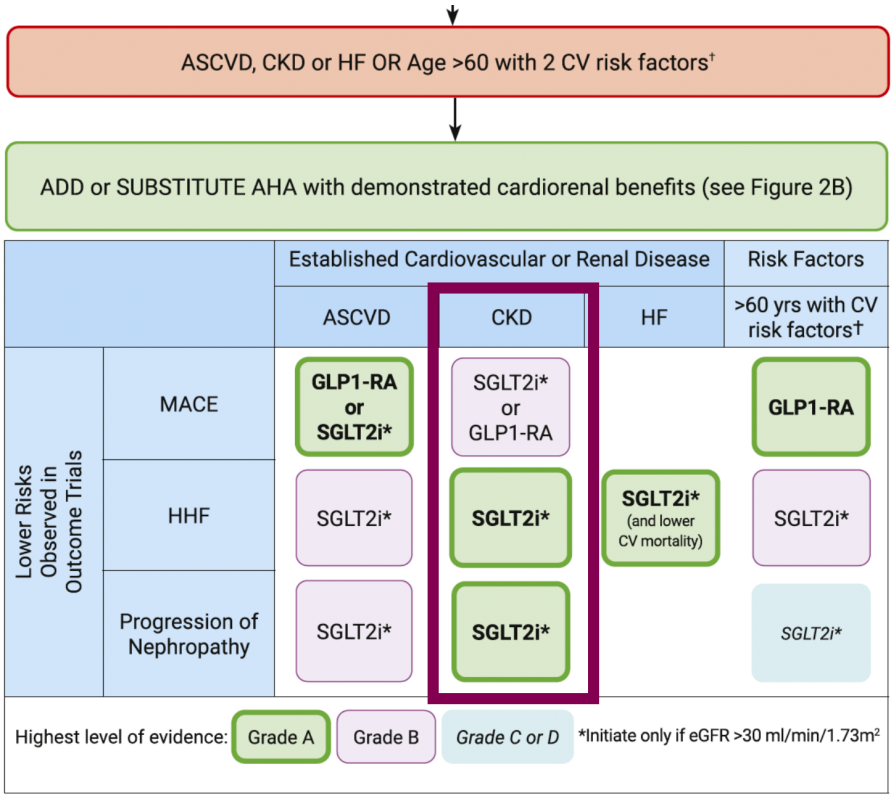


CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91, 2020.



CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91. 2020.

Chronic Kidney Disease Population



	SGLT2 Inhibitors			GLP-1 Receptor Agonists			
	Empa-gliflozin	Cana-gliflozin	Dapa-gliflozin	Lira-glutide	Semaglutide S/C	Semaglutide oral	Dulaglutide
	Jardiance	Invokana	Forxiga	Victoza	Ozempic	Rybelsus	Trulicity
Trial	EMPAREG	CREDENCE	DAPA-CKD	LEADER	SUSTAIN-6	PIONEER-6	REWIND
Population	N=7020 CVD 50%	N=4401 CVD 50%	N=4304 CVD 37%	N=9540 CVD 80%	N=3297 CVD 80%	N=3183 CVD 85%	N=9901 CVD 31%
Duration	3.2 yrs	2.6 yrs	2.4 yrs	3.8 yrs	2.0 yrs	1.3 yrs	5.4 yrs
MACE	x	↓20%	↓31% All cause mortality	↓11% < 30 ml/min	↓27% < 30 ml/min		↓27% Micro/macro-albuminuria
HHF	x	↓39%	↓29% CVD Deaths or HHF				
RENAL	x	↓30%	↓39%				

Diabetes	↓36%
No diabetes	↓50%

CPG2020: Lipscombe L et al. Canadian Journal of Diabetes 44: 575-91, 2020.
EMPAREG Outcome: Zinman B et al. NEJM 373:2117-2128, 2015. CREDENCE: Perkovic V et al. NEJM 380: 2295-2306, 2019 DAPA-CKD : Heerspink HJL et al. NEJM DOI: 10.1056/NEJMoa2024816
LEADER: Marso SP et al. NEJM 375: 211-322, 2016. SUSTAIN-6: Marso SP et al. NEJM 375: 1834-44, 2016. PIONEER-6: Husain M et al. NEJM 381: 841-51, 2019.
REWIND: Gerstein HC et al. The Lancet June 2019 DOI: 10.1016/S0 REWIND: Colhoun H et al. Poster EASD2020

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

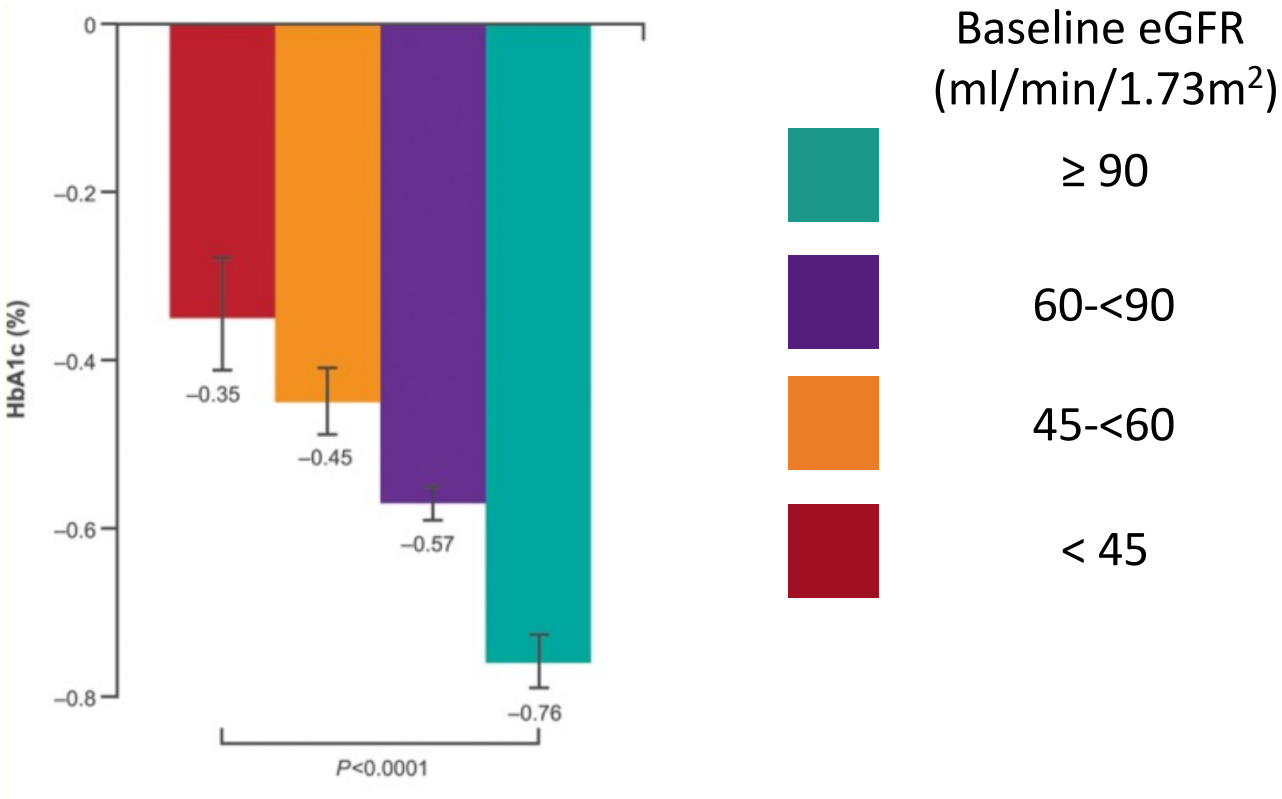
What a change!

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

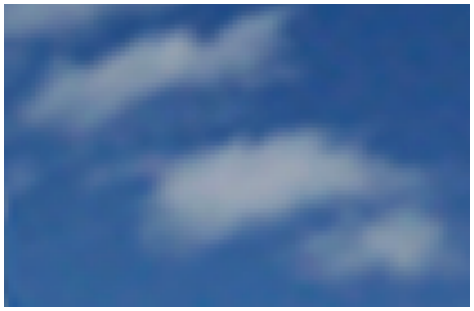
Low eGFR = Less glucosuria = Lower efficacy ?

A1c Reduction by eGFR in the CREDENCE Trial

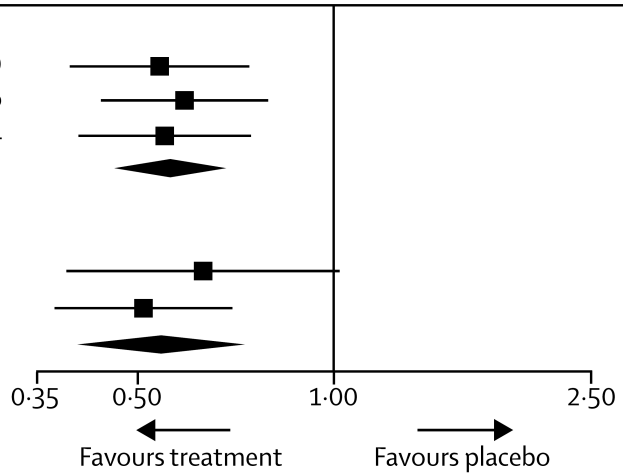


Effect of SGLT2 inhibitors on renal composite outcomes

No heterogeneity between studies

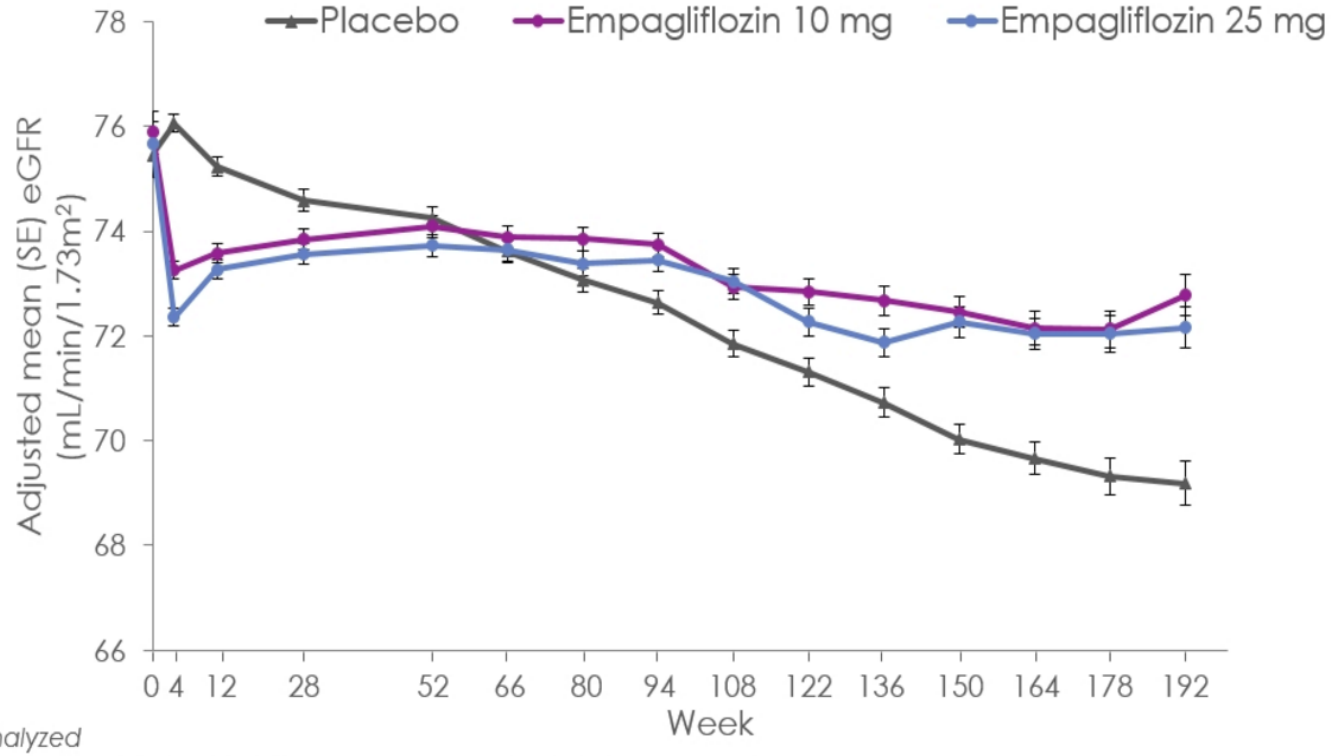


	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4645/6968	2323/6968	152	6·3	11·5	31·0	0·54 (0·40–0·75)
CANVAS Program	3756/6656	2900/6656	179	6·4	10·5	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)**



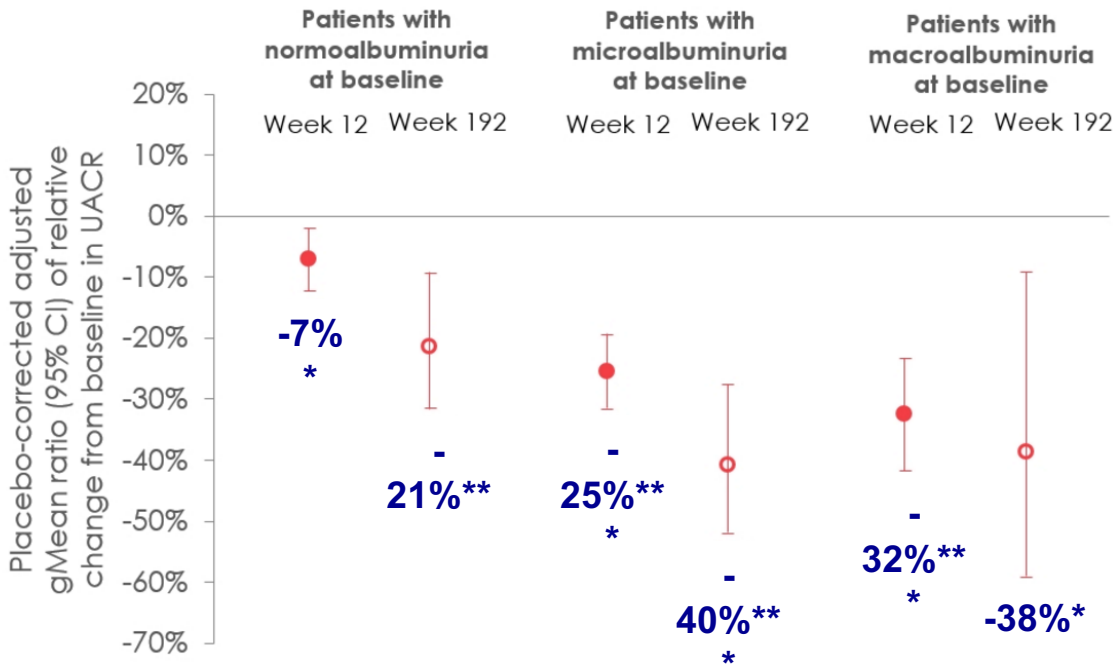
Zelniker TA et al. Lancet 2018; doi.org/10.1016/S0140-6736(18)32590-X

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®

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 m^2
- UACR 300 to 5000 mg/g (34-565 mg/mmol)
- 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

2-week placebo run-in

R

Double-blind randomization (1:1)

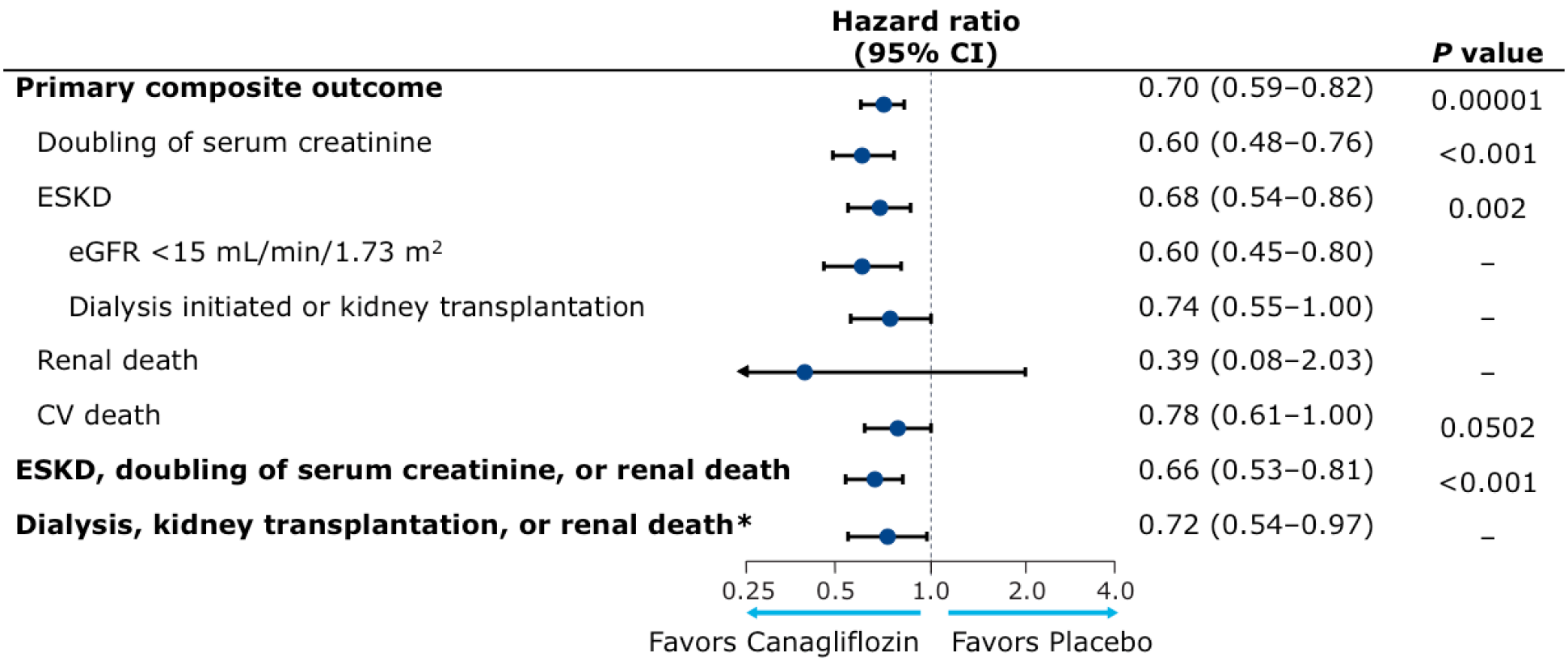
Canagliflozin 100 mg

Placebo

Participants continued treatment if eGFR was <30 mL/min/1.73 m^2 until chronic dialysis was initiated or kidney transplant occurred.

Jardine MJ, et al. *Am J Nephrol*. 2017;46(6):462-472.

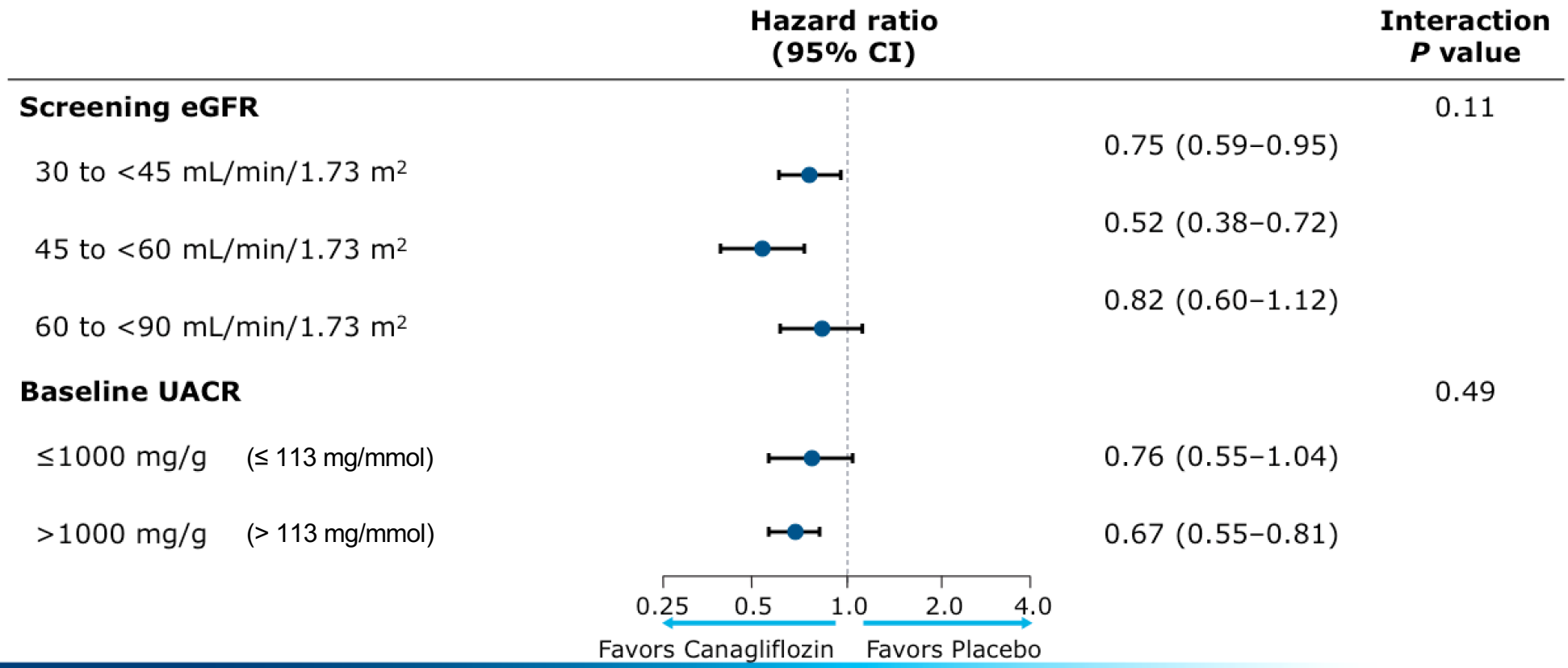
Summary of Renal Results



*Post hoc analysis.

CREDENCE

Primary Outcome by Screening eGFR and Albuminuria



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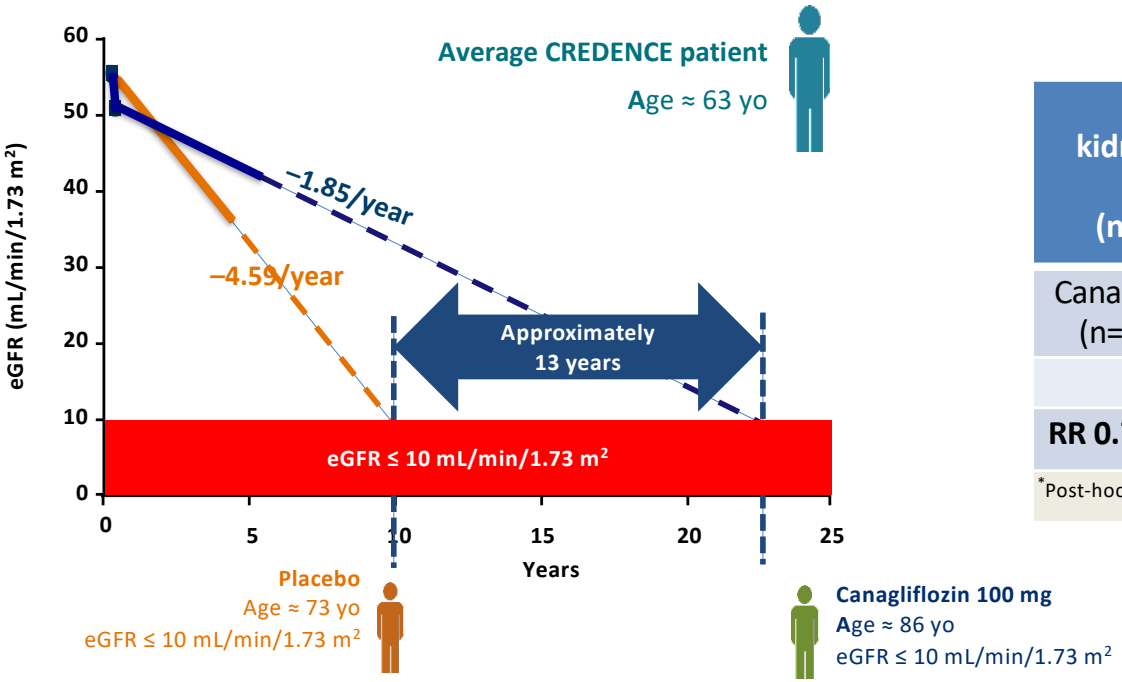
Potential Importance of SGLT2 Inhibition



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

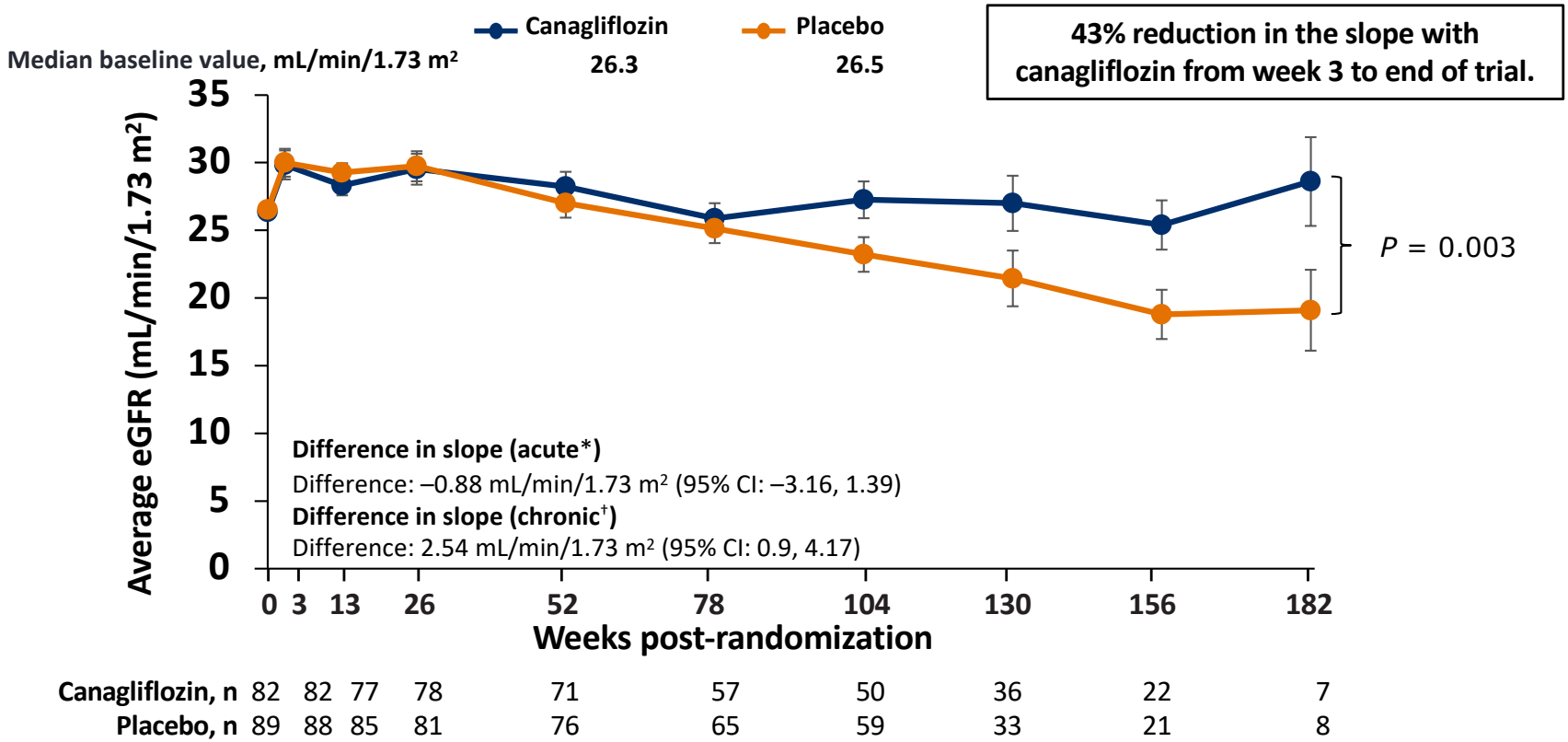
*Post-hoc analysis

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

Participants with an eGFR <30 mL/min/1.73 m^2 at randomization

		Randomization DFGe (mL/min/1.73 m^2)		
		<15	15-<30	**Total**
Screening eGFR (mL/min/1.73 m^2)	30-<45	1	160	**161**
	45-<60	0	8	**8**
	60-<90	1	4	**5**
	Total	**2**	**172**	**174**

Impact of CANA on eGFR in the <30 mL/min/1.73 m^2 at randomization cohort

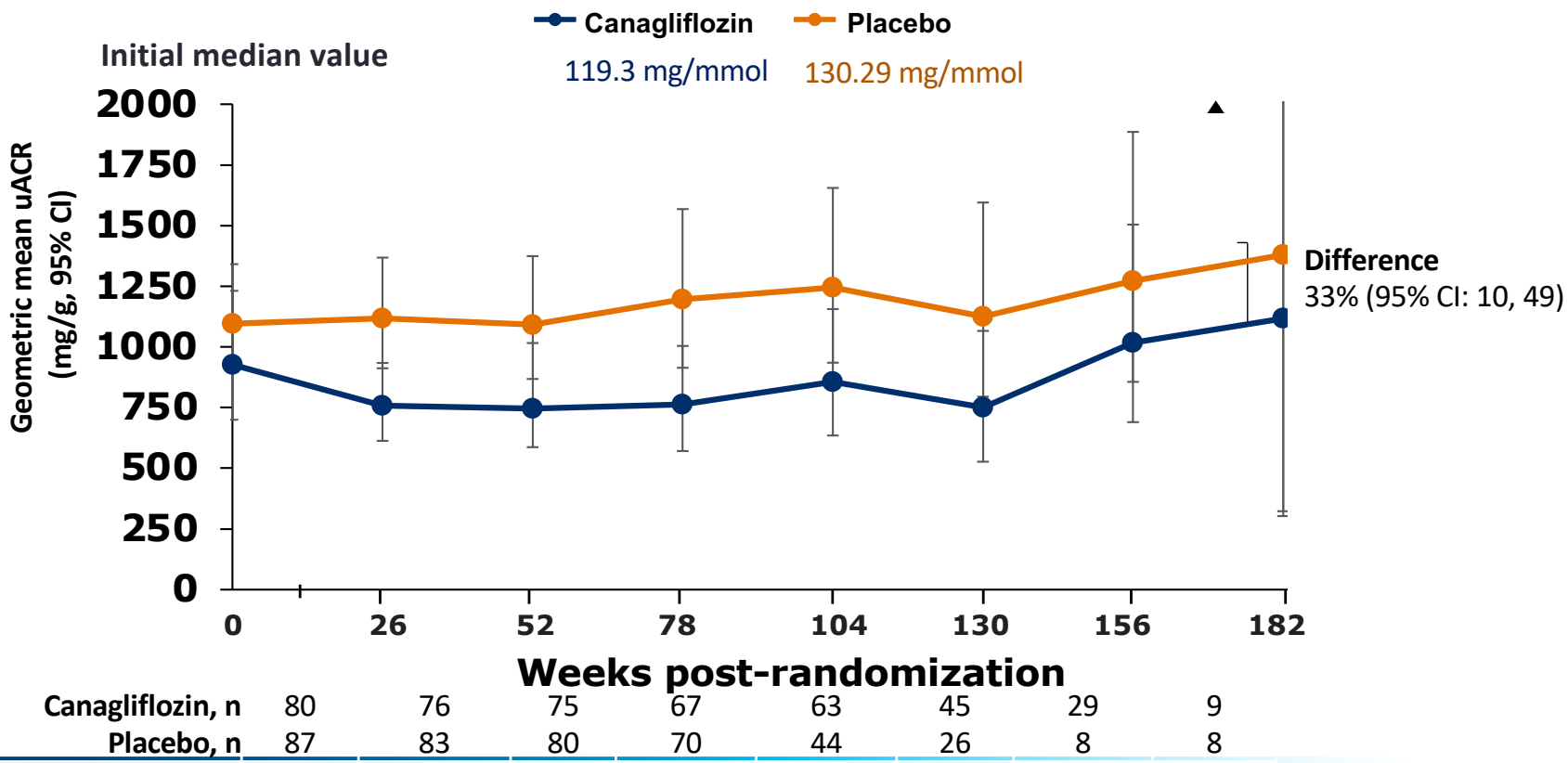


Canagliflozin, n	82	82	77	78	71	57	50	36	22	7
Placebo, n	89	88	85	81	76	65	59	33	21	8

*Measured from baseline to Week 3.
†Measured from Week 3 until the end of the study.
Presented at the American Society of Nephrology (ASN) Kidney Week 2019 Annual Meeting; November 8;

CREDENCE

Impact of CANA on uACR in the <30 mL/min/1.73 m^2 at randomization cohort



Presented at the American Society of Nephrology (ASN) Kidney Week 2019 Annual Meeting; November 8; Washington,D.C.

CREDENCE

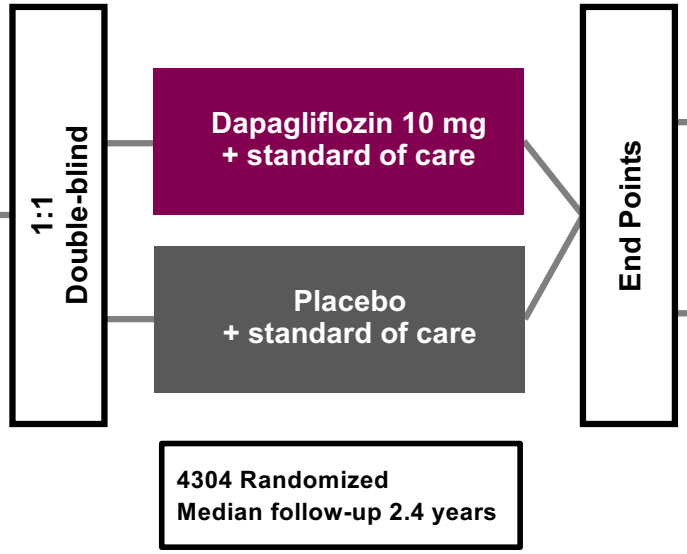
DAPA-CKD:
Dapagliflozin in Patients With Chronic Kidney Disease[1,2]

DAPACKD

Objective To assess whether treatment with dapagliflozin, compared with placebo, reduced the risk of renal and CV events in patients with CKD with or without T2D, and who were receiving standard of care including a maximum tolerated dose of an ACEi or ARB

Key Inclusion Criteria
- ≥18 years of age
- eGFR ≥25 to ≤75 mL/min/1.73m^2
- UACR ≥ 23 to ≤565 mg/mmol
- Stable max tolerated dose of ACEi/ARB for ≥4 weeks
- With and without T2D

Key Exclusion Criteria
- T1D
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy ≤6 months prior to enrollment



Primary Outcome
Composite of sustained ≥50% eGFR decline, ESKD[a], renal or CV death

Secondary Outcomes
- Composite of sustained ≥50% eGFR decline, ESKD, or renal death
- Composite of CV death or hHF
- All-cause mortality

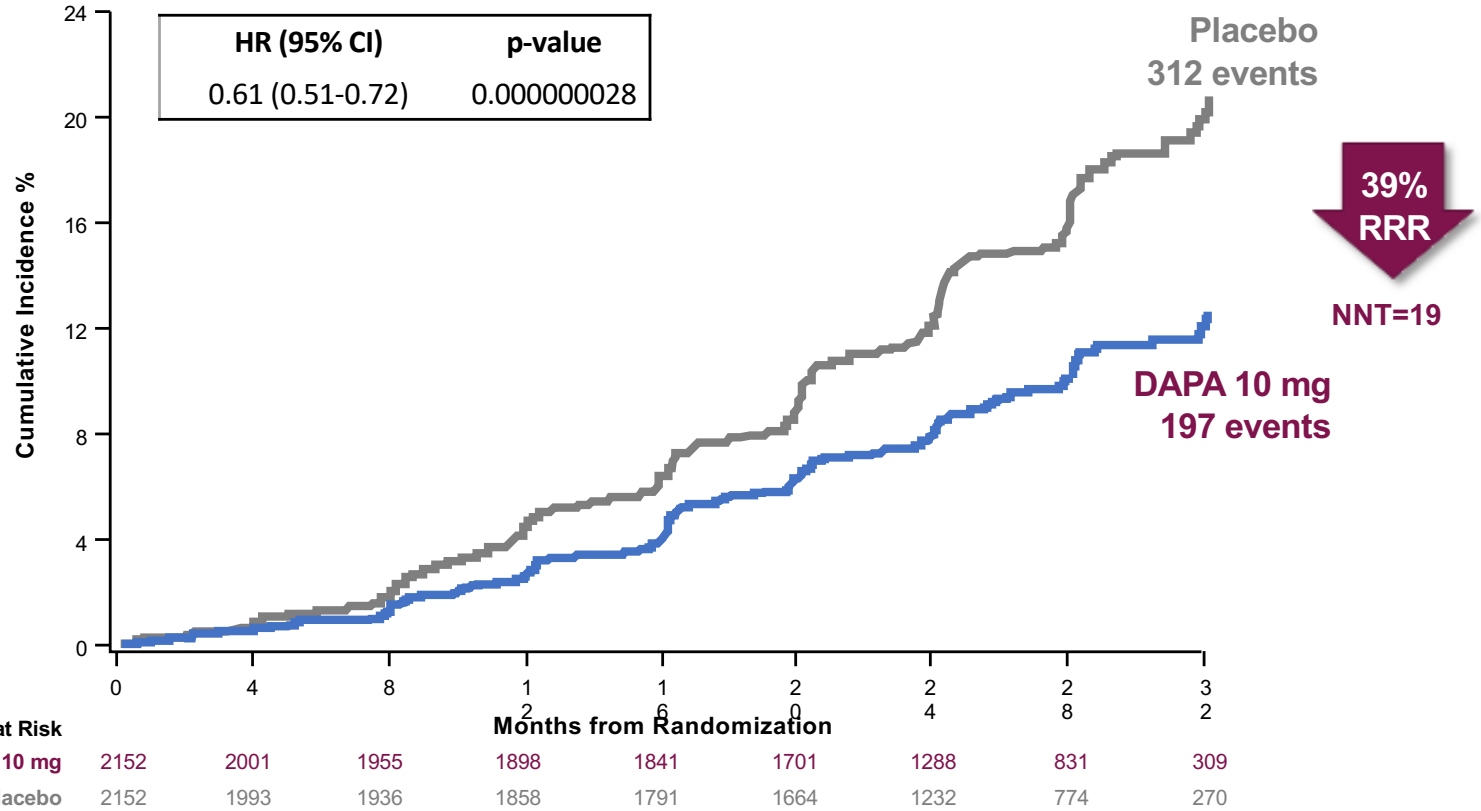
[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days.

ACEi = angiotensin-converting enzyme inhibitor; ANCA = anti-neutrophil cytoplasmic antibody; ARB = angiotensin-receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; T1D = type 1 diabetes; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

1. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282; 2. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

Primary Composite Outcome:

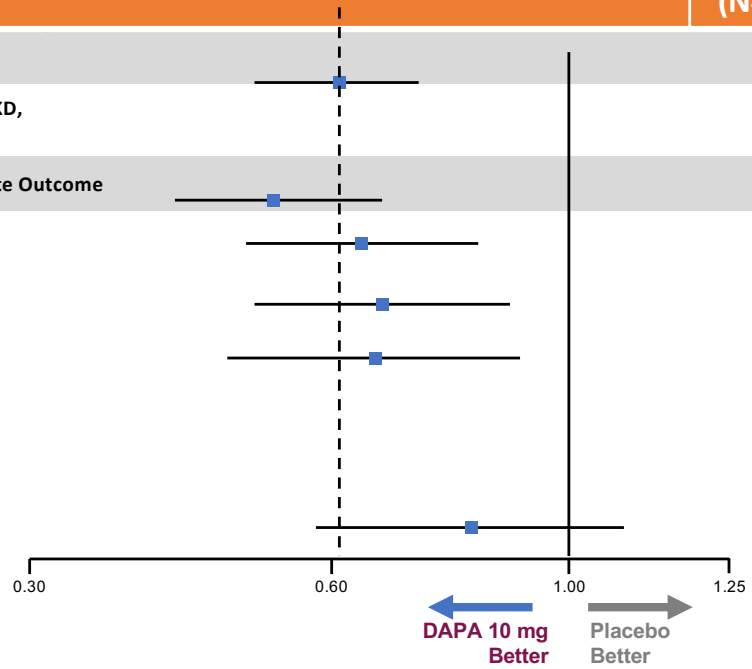
Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death[a]



[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2] CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; ; NNT = number needed to treat; RRR = relative risk reduction.

1. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020. 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

Individual Components of the Primary Composite Outcome



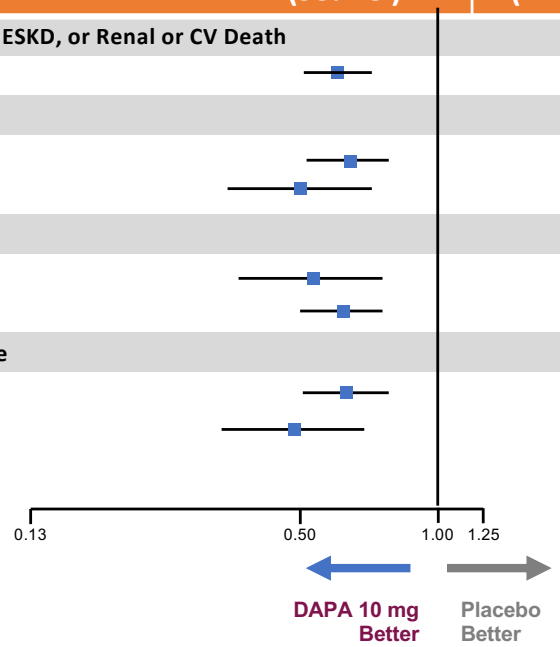
	HR (95% CI)	Number of Events: DAPA 10 mg (N=2152)	Number of Events: Placebo (N=2152)	HR	95% CI	p-value
Primary Composite Outcome						
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death		197	312	0.61	(0.51, 0.72)	0.000000028
Components of the Primary Composite Outcome						
≥50% eGFR Decline		112	201	0.53	(0.42, 0.67)	<0.0001
ESKD		109	161	0.64	(0.50, 0.82)	0.0004
eGFR <15mL/min/1.73m^2		84	120	0.67	(0.51, 0.88)	0.0045
Chronic Dialysis		68	99	0.66	(0.48, 0.90)	0.0080
Transplantation		3	8	NC		
Renal Death		2	6	NC		
CV Death		65	80	0.81	(0.58, 1.12)	0.2029

CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; NC = not calculable

Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

Primary Composite Outcome: Prespecified Subgroup Analyses

	Number of Events				
HR (95% CI)	DAPA 10 mg (N=2152)	Placebo (N=2152)	HR	95% CI	p-value Interaction
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death					
All Patients	197	312	0.61	(0.51, 0.72)	
T2D at Baseline					0.24
Yes	152	229	0.64	(0.52, 0.79)	
No	45	83	0.50	(0.35, 0.72)	
UACR (mg/mmol) at Baseline					0.52
≤ 113	44	84	0.54	(0.37, 0.77)	
> 113	153	228	0.62	(0.50, 0.76)	
eGFR (mL/min/1.73m^2) at Baseline					0.22
<45	152	217	0.63	(0.51, 0.78)	
≥45	45	95	0.49	(0.34, 0.69)	



CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.
Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

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
Urinary Tract Infection	4.0	3.7	4.83	4.51	1.5	1.6			18.0	18.1
Genital Mycotic Infection	6.9	1.75	1.26	0.61	0.9	0.1			10.0	2.6
Fournier' Gangrene					0.01	0.06				
Fracture	1.54	1.19	1.18	1.21	5.3	5.1	2.1	2.1	3.8	3.9
Amputation	0.63	0.34	1.23	1.12	0.36	0.33	0.5	0.5	0.65	0.65
Diabetic ketoacidosis	0.06	0.03	0.22	0.02	0.3	0.1	0.1	0.0	0.1	<0.1

2018 Diabetes Canada CPG – Chapter 29. Chronic Kidney Disease in Diabetes

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

Insulin or secretagogues

- Consider ↓ dose if glycemia close to normal

Anti-hypertensives

- Consider ↓ dose if BP normal

Genital mycotic infections

- Counselling, optional anti-fungal prescription

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

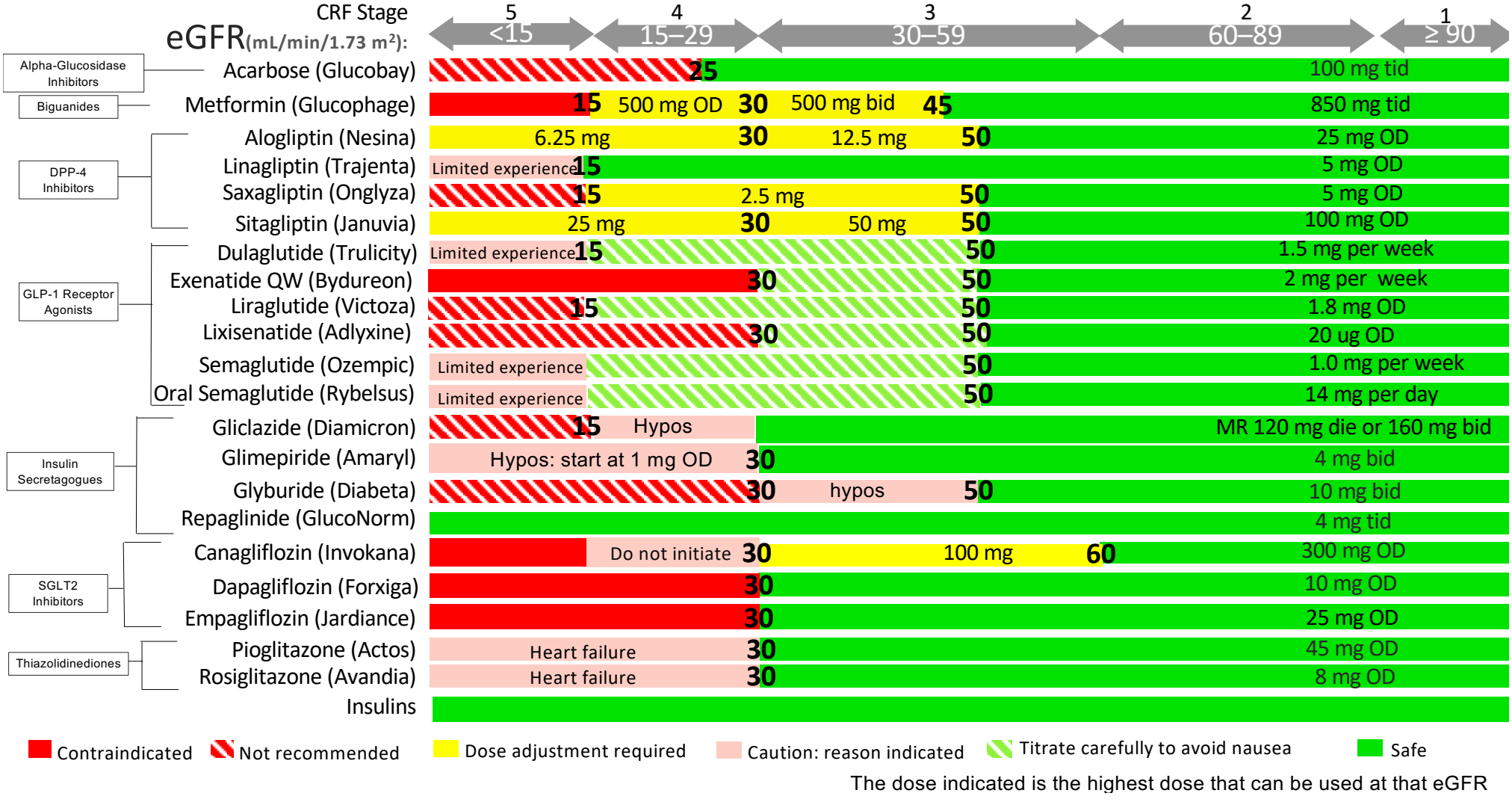
H: Nystatin cream, tube of 15g
F: Fluconazole 150 mg 1tab po stat

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.

Antihyperglycemic Agents and Renal Failure

Yale JF, version November2020
www.dryale.ca



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

Antihyperglycemic Agents and Renal Failure

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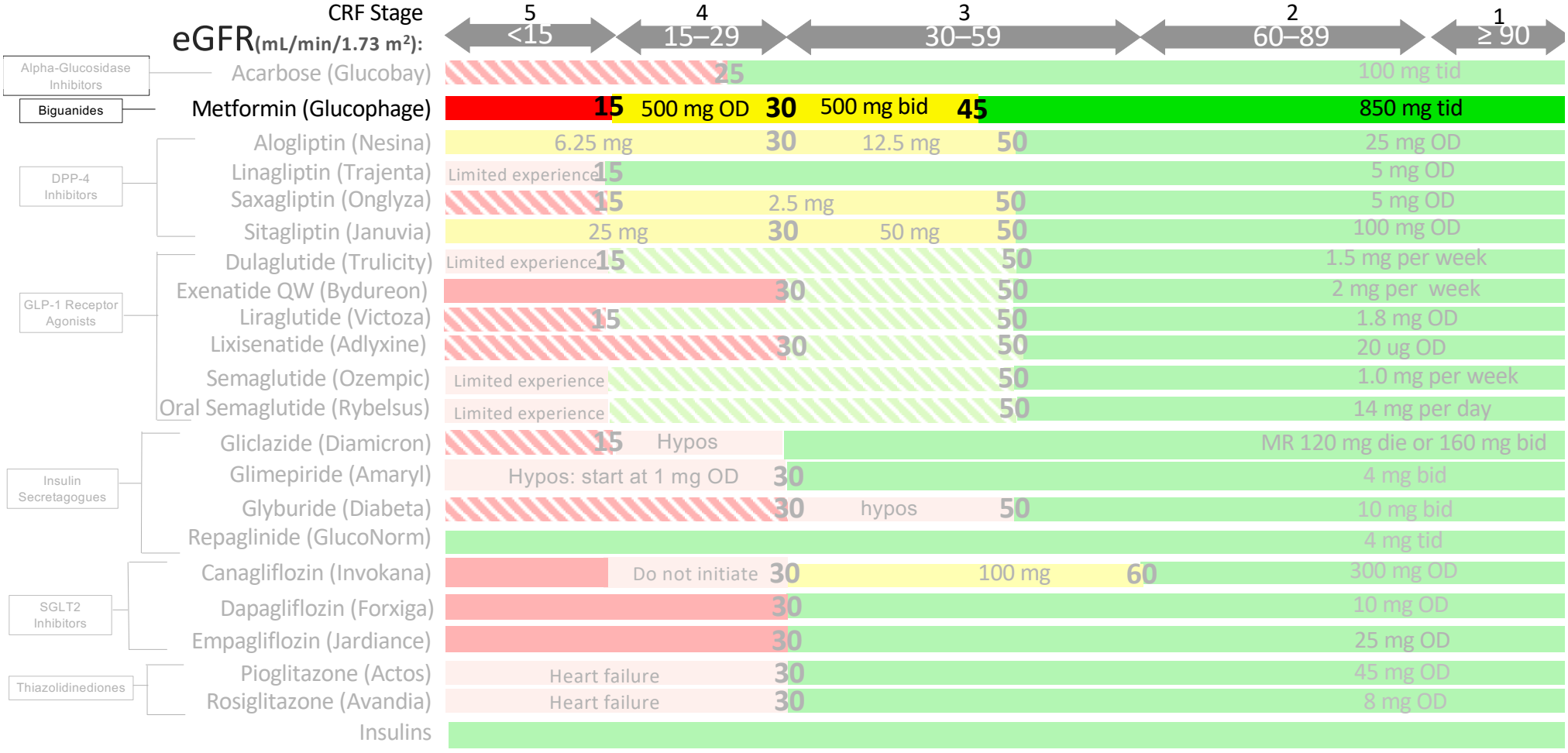

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	CRF Stage 5	CRF Stage 4	CRF Stage 3	CRF Stage 2	CRF Stage 1
eGFR (mL/min/1.73 m²):	<15	15–29	30–59	60–89	≥ 90
Alpha-Glucosidase Inhibitors					
Acarbose (Glucobay)	25				100 mg tid
Biguanides					
Metformin (Glucophage)	15	500 mg OD 30	500 mg bid 45		850 mg tid
DPP-4 Inhibitors					
Alogliptin (Nesina)	6.25 mg	30	12.5 mg 50		25 mg OD
Linagliptin (Trajenta)	Limited experience 15				5 mg OD
Saxagliptin (Onglyza)	15	2.5 mg	50		5 mg OD
Sitagliptin (Januvia)	25 mg	30	50 mg 50		100 mg OD
GLP-1 Receptor Agonists					
Dulaglutide (Trulicity)	Limited experience 15		50		1.5 mg per week
Exenatide QW (Bydureon)		30	50		2 mg per week
Liraglutide (Victoza)	15		50		1.8 mg OD
Lixisenatide (Adlyxine)		30	50		20 ug OD
Semaglutide (Ozempic)	Limited experience		50		1.0 mg per week
Oral Semaglutide (Rybelsus)	Limited experience		50		14 mg per day
Insulin Secretagogues					
Gliclazide (Diamicron)	15	Hypos			MR 120 mg die or 160 mg bid
Glimepiride (Amaryl)	Hypos: start at 1 mg OD	30			4 mg bid
Glyburide (Diabeta)		30	hypos 50		10 mg bid
Repaglinide (GlucoNorm)					4 mg tid
SGLT2 Inhibitors					
Canagliflozin (Invokana)		Do not initiate 30	100 mg	60	300 mg OD
Dapagliflozin (Forxiga)		30			10 mg OD
Empagliflozin (Jardiance)		30			25 mg OD
Thiazolidinediones					
Pioglitazone (Actos)	Heart failure	30			45 mg OD
Rosiglitazone (Avandia)	Heart failure	30			8 mg OD
Insulins					

Contraindicated | Not recommended | Dose adjustment required | Caution: reason indicated | Titrate carefully to avoid nausea | Safe

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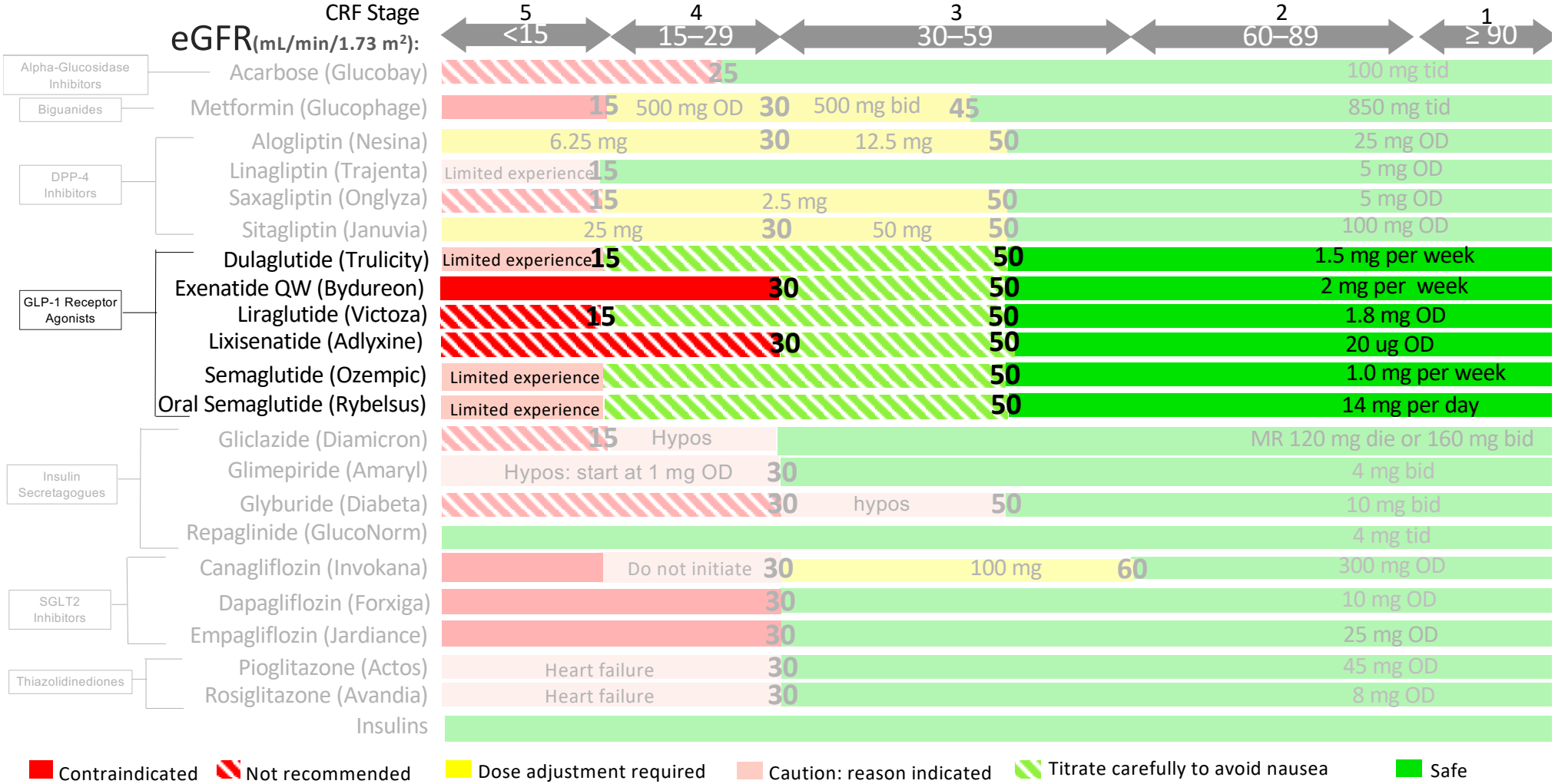

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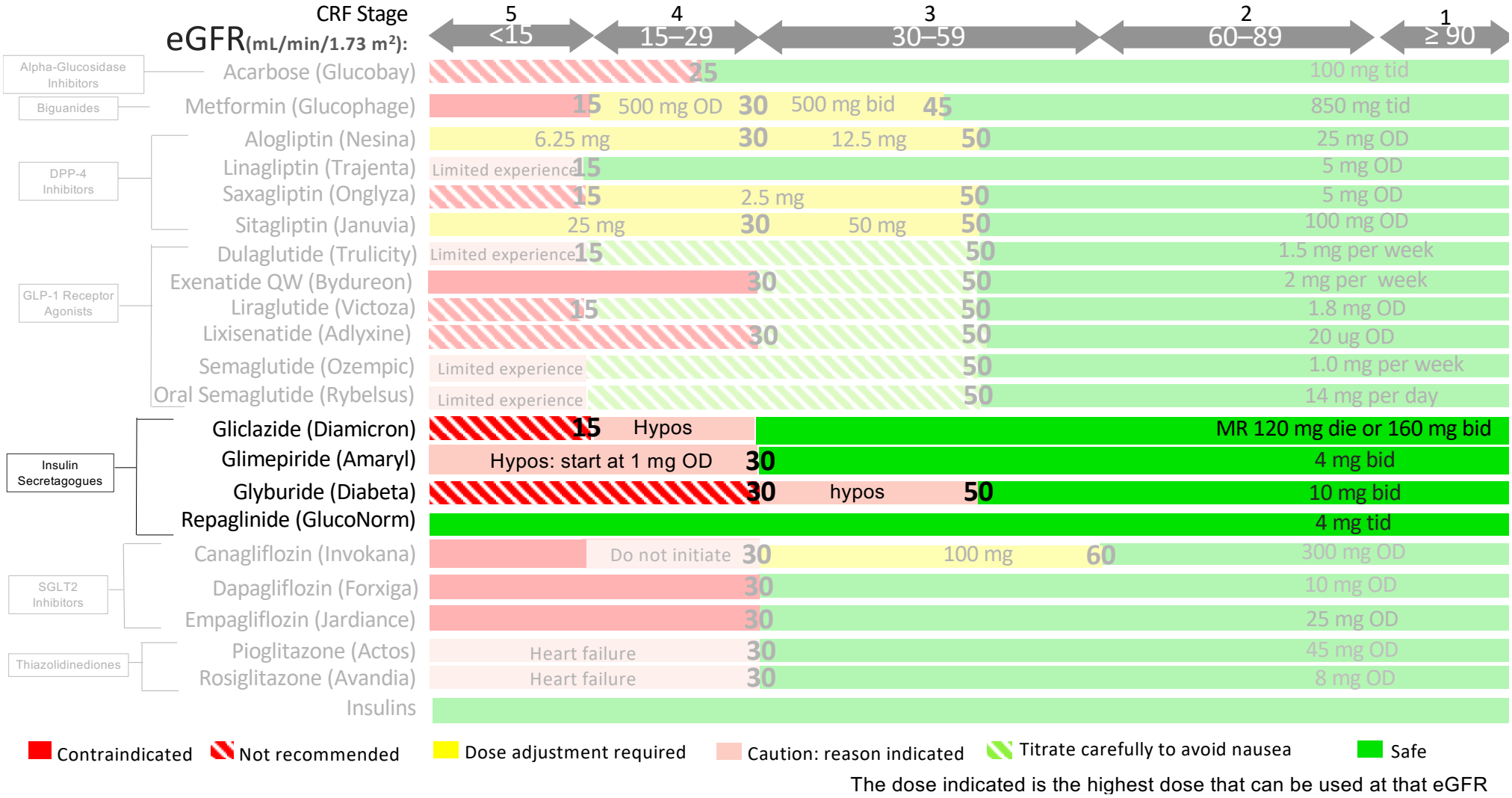

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GLP-1 Receptor Agonists — Dulaglutide (Trulicity)	Limited experience 15		50		1.5 mg per week
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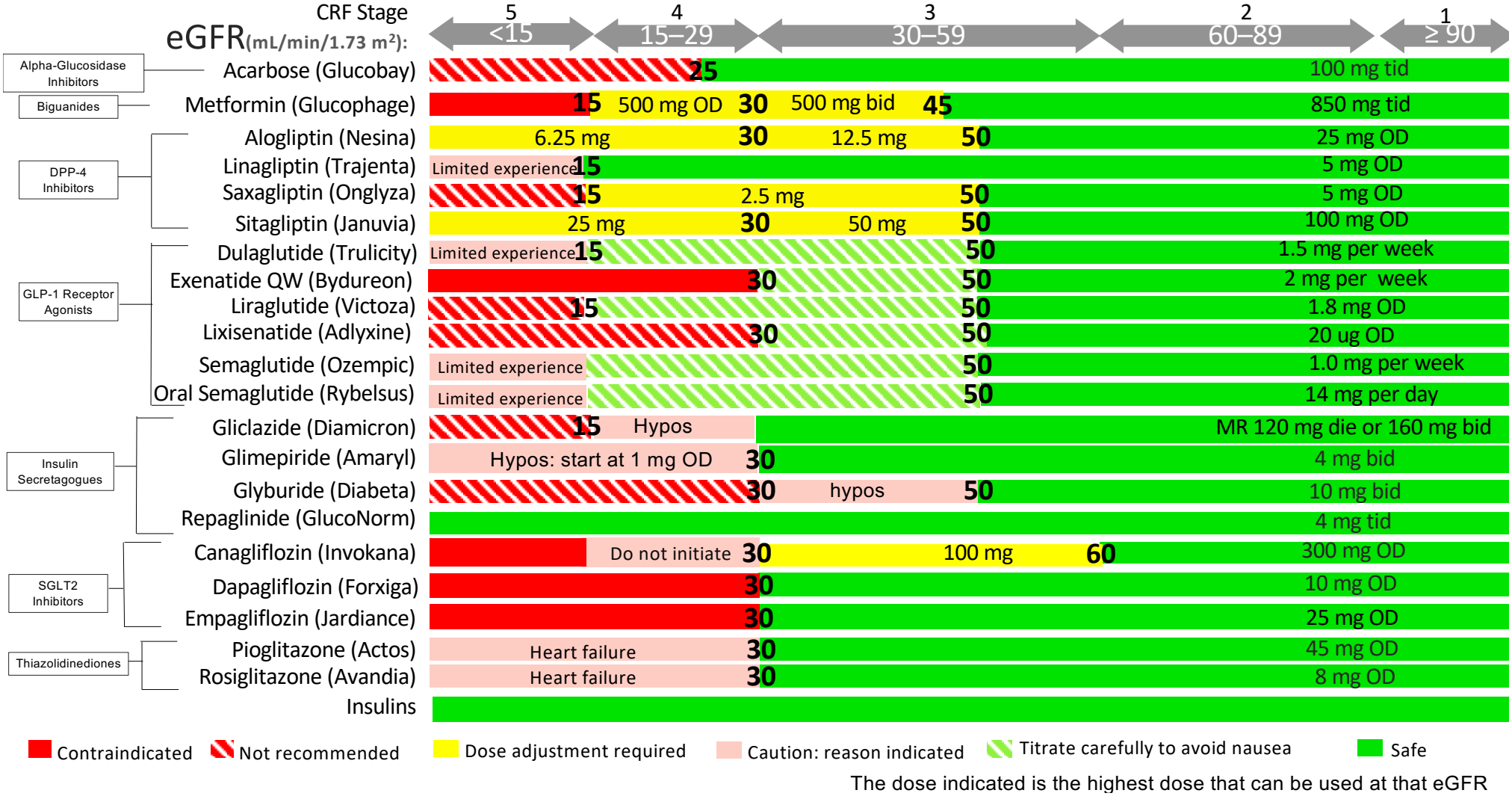

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The End
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