

Workshop : Interactive Cases



Dr Jean-François Yale, MD, FRCPC
Endocrinologist

McGill University Health Centre, Montreal, Canada

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Workshop on Type 2 Diabetes: Interactive Cases

Objectives:

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

- 1) Individualize the choice of an appropriate antihyperglycemic therapy in people with type 2 diabetes
- 1) Involve and counsel the patient in the choice and use of their antihyperglycemic therapy
- 2) Minimize the social cost of newer antihyperglycemic therapies

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Case #1

Age and gender: **48 yo woman**

Occupation: **Nurse**

Insurance coverage: **Private**

Type 2 diabetes x **12** years A1c: **8.1%**

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

Retinopathy ? **None**

Nephropathy ? **None** eGFR **>60** ACR **0.3**

Neuropathy ? **None**

Smoker ? **No**

BMI : **36.5**

Current Medication:

Met: **Janumet XR 50/1000 2 tabs AM**

SU:

DPP-4i:

SGLT2i: **Jardiance 10 mg AM**

GLP-1RA:

Insulin:

Statin: **Simvastatin 5 mg HS**

ACEi/ARB:

ASA:

Others:

Problems with past medications ?

Hypos with SU

Other consideration:

Case #2

Age and gender:

Occupation:

Insurance coverage:

Type 2 diabetes x years A1c:

Cardiovascular disease ? BP: LDL-C

Retinopathy ?

Nephropathy ? eGFR ACR

Neuropathy ?

Smoker ?

BMI :

Current Medication:

Met:

SU:

DPP-4i:

SGLT2i:

GLP-1RA:

Insulin:

Statin:

ACEi/ARB:

ASA:

Others:

Problems with past medications ?

Other consideration:

Case #3

Age and gender:

Occupation:

Insurance coverage:

Type 2 diabetes x years

A1c:

Cardiovascular disease ?

BP:

LDL-C

Retinopathy ?

Nephropathy ?

eGFR

ACR

Neuropathy ?

Smoker ?

BMI :

Current Medication:

Met:

SU:

DPP-4i:

SGLT2i:

GLP-1RA:

Insulin:

Statin:

ACEi/ARB:

ASA:

Others:

Problems with past medications ?

Other consideration:

Case #4

Age and gender:

Occupation:

Insurance coverage:

Type 2 diabetes x years

A1c:

Cardiovascular disease ?

BP:

LDL-C

Retinopathy ?

Nephropathy ?

eGFR

ACR

Neuropathy ?

Smoker ?

BMI :

Current Medication:

Met:

SU:

DPP-4i:

SGLT2i:

GLP-1RA:

Insulin:

Statin:

ACEi/ARB:

ASA:

Others:

Problems with past medications ?

Other consideration:

Case #5

Age and gender:

Occupation:

Insurance coverage:

Type 2 diabetes x years

A1c:

Cardiovascular disease ?

BP:

LDL-C

Retinopathy ?

Nephropathy ?

eGFR

ACR

Neuropathy ?

Smoker ?

BMI :

Current Medication:

Met:

SU:

DPP-4i:

SGLT2i:

GLP-1RA:

Insulin:

Statin:

ACEi/ARB:

ASA:

Others:

Problems with past medications ?

Other consideration:

CVOT

	Alo-gliptin	Saxa-gliptin	Sita-gliptin	Lina-gliptin
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

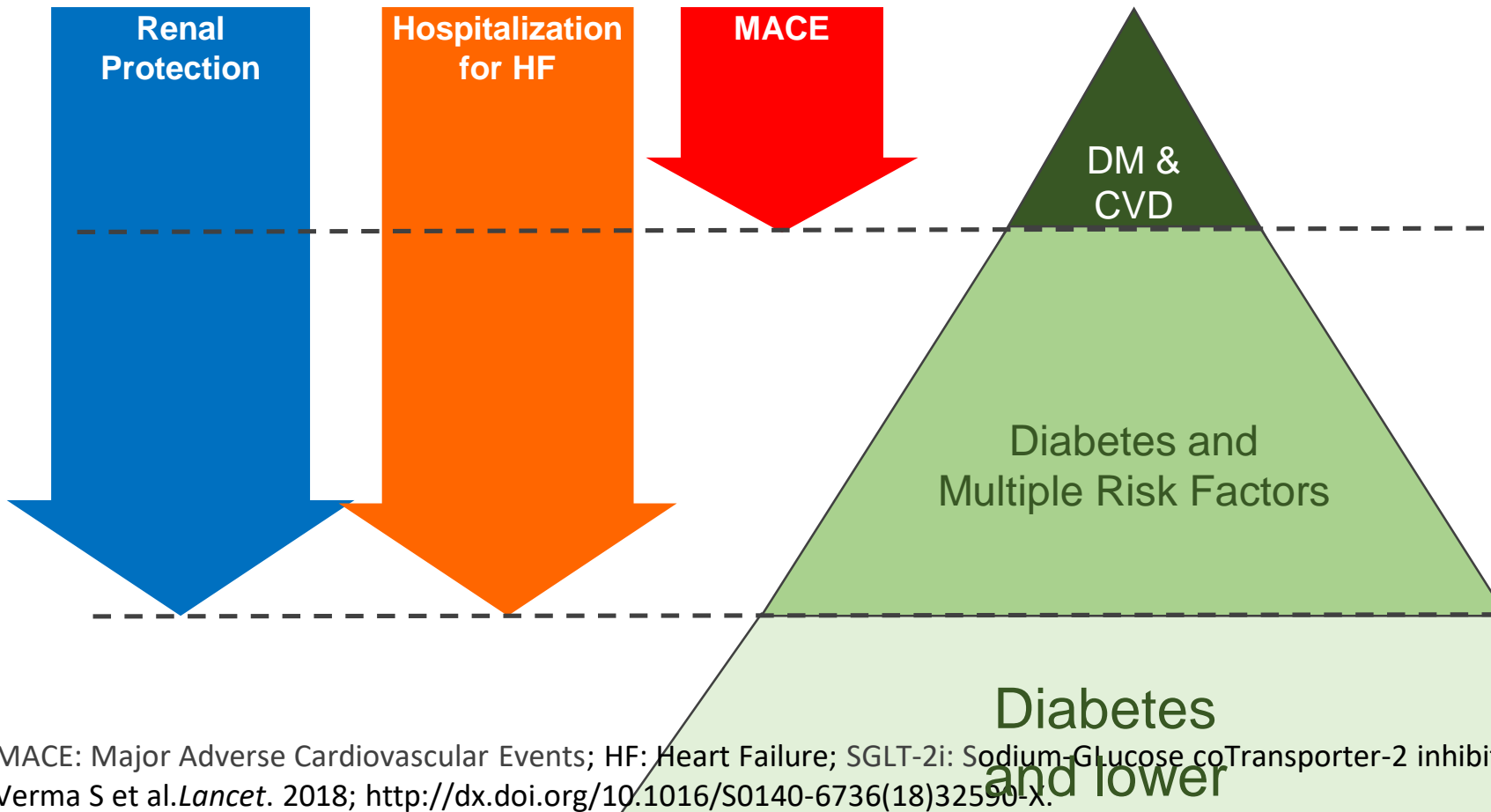
Metformin
Sulfonylureas
DPP-4 Inhibitors
SGLT2 Inhibitors
GLP-1 Receptor Agonists
Insulin

Vascular Protection

ASA
Statins
ACEi or ARB

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](http://dx.doi.org/10.1016/S0140-6736(18)32590-X).

Main Inclusion Criteria



REWIND

Dulaglutide CV Outcomes Trial

Type 2 DM - Stable antihyperglycemic medication x 3 months

- on 0 -2 oral drugs +/- basal insulin or GLP-1R agonists

95.6%

A1C \leq 9.5% 92.1%

BMI \geq 23 kg/m² 95.6%

eGFR \geq 15 ml/min/1.73m² 99.5%

Age \geq 50 & vascular disease

(History of MI, CVA, revascularisation, unstable angina with ECG changes or angioplasty)

\geq 55 & sub-clinical vascular disease

(positive stress test, stenosis >50%, ABI<0.9; eGFR <60; hypertension + LVH, or albuminuria)

Age

49.7%

\geq 60 & 2 CV Risk Factors

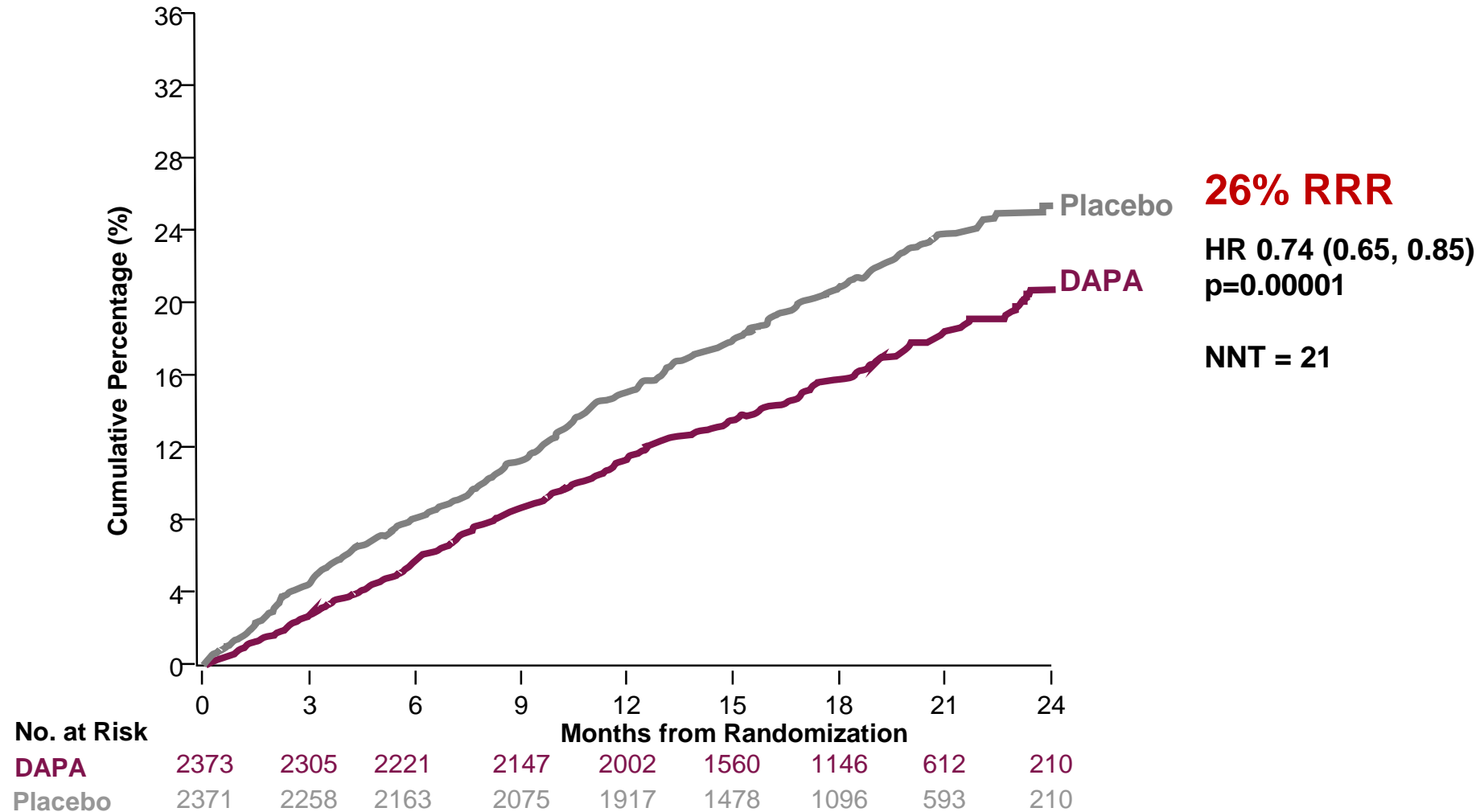
(smoking, [antilipid drug or LDL-C \geq 3.4, HDL-C < 1.0M (1.3F) or TG \geq 2.3],

\geq 1 antihypertensive or SBP \geq 140 or DBP \geq 95, elevated waist/hip ratio >1.0M (0.8F)

CV Criteria

81.8%

Primary Endpoint: CV Death or hHF or an Urgent HF Visit¹



DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat.

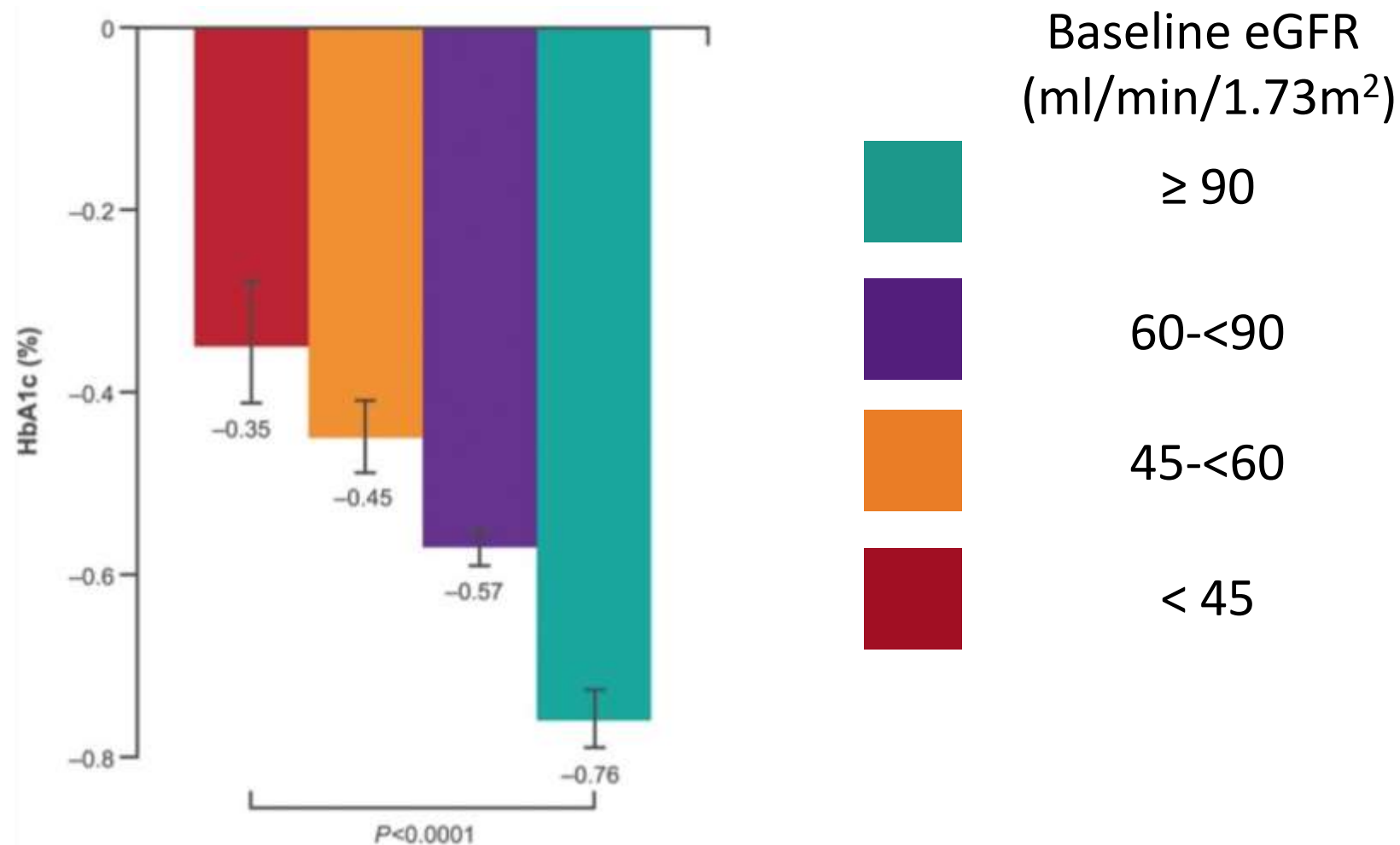
DAPA-HF Endpoints

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	

The analysis by eGFR is particularly pertinent for SGLT2i

Low eGFR = Less glucosuria = Lower efficacy ?

**A1c Reduction
by eGFR
in the CREDENCE Trial**



CREDESCENCE 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

2-week placebo run-in

R

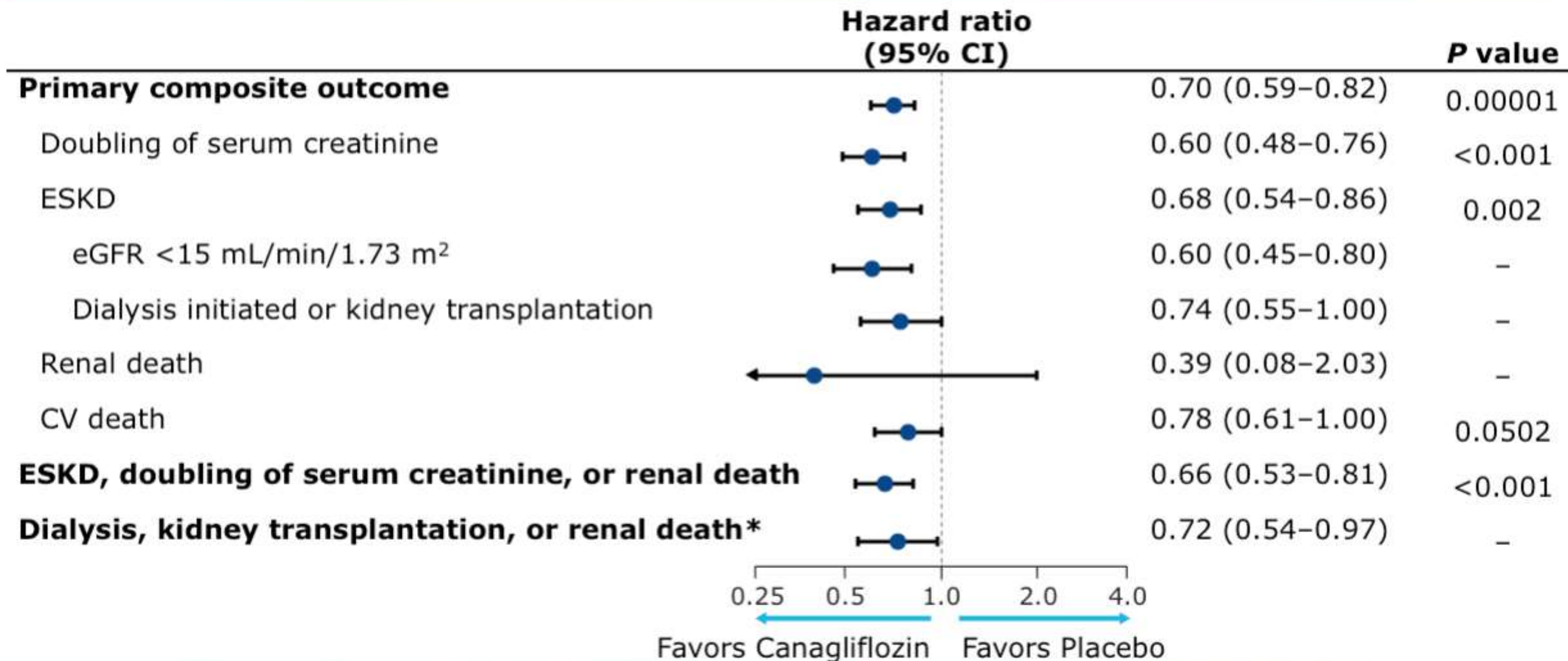
Double-blind
randomization
(1:1)

Canagliflozin 100 mg

Placebo

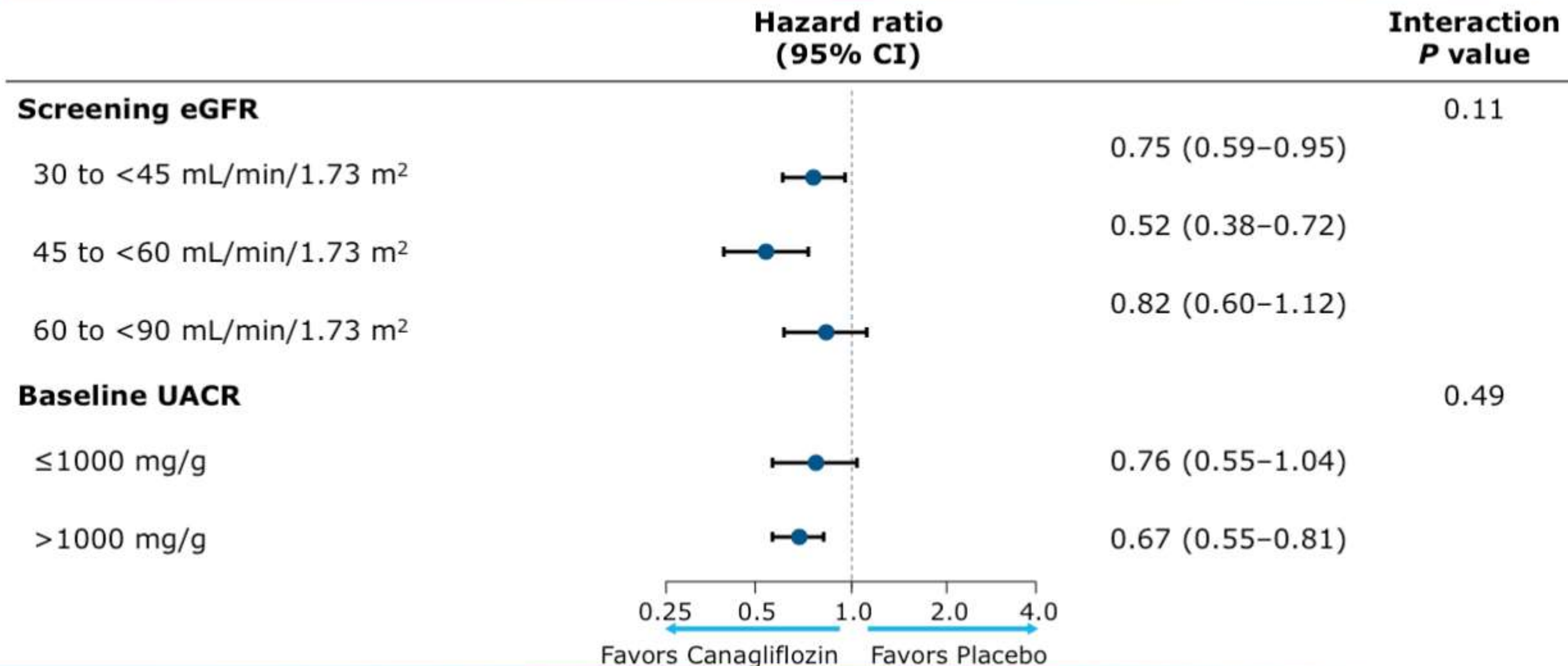
Participants continued treatment if eGFR was < 30 mL/min/1.73 m² until chronic dialysis was initiated or kidney transplant occurred.

Summary of Renal Results

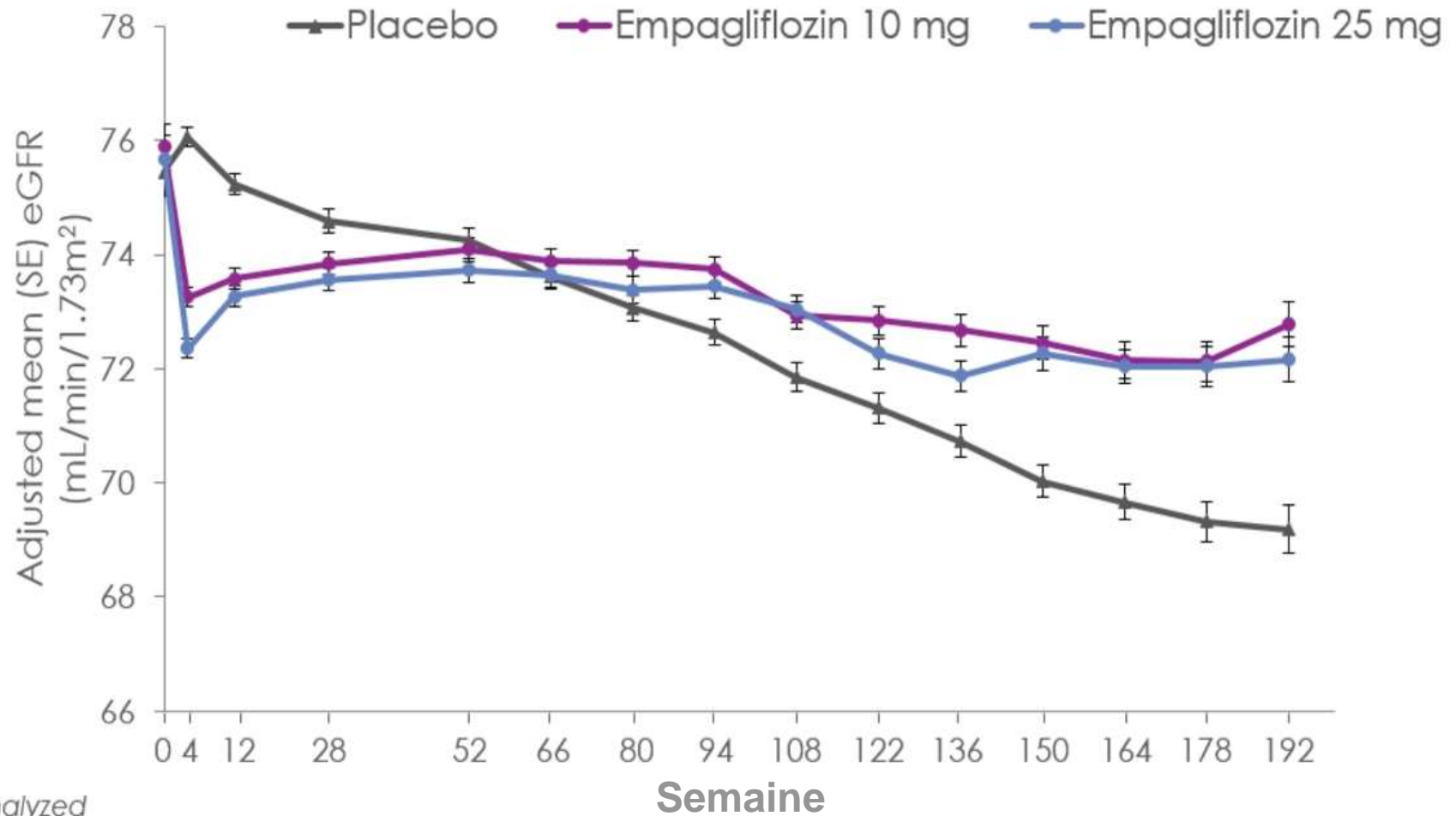


*Post hoc analysis.

Primary Outcome by Screening eGFR and Albuminuria



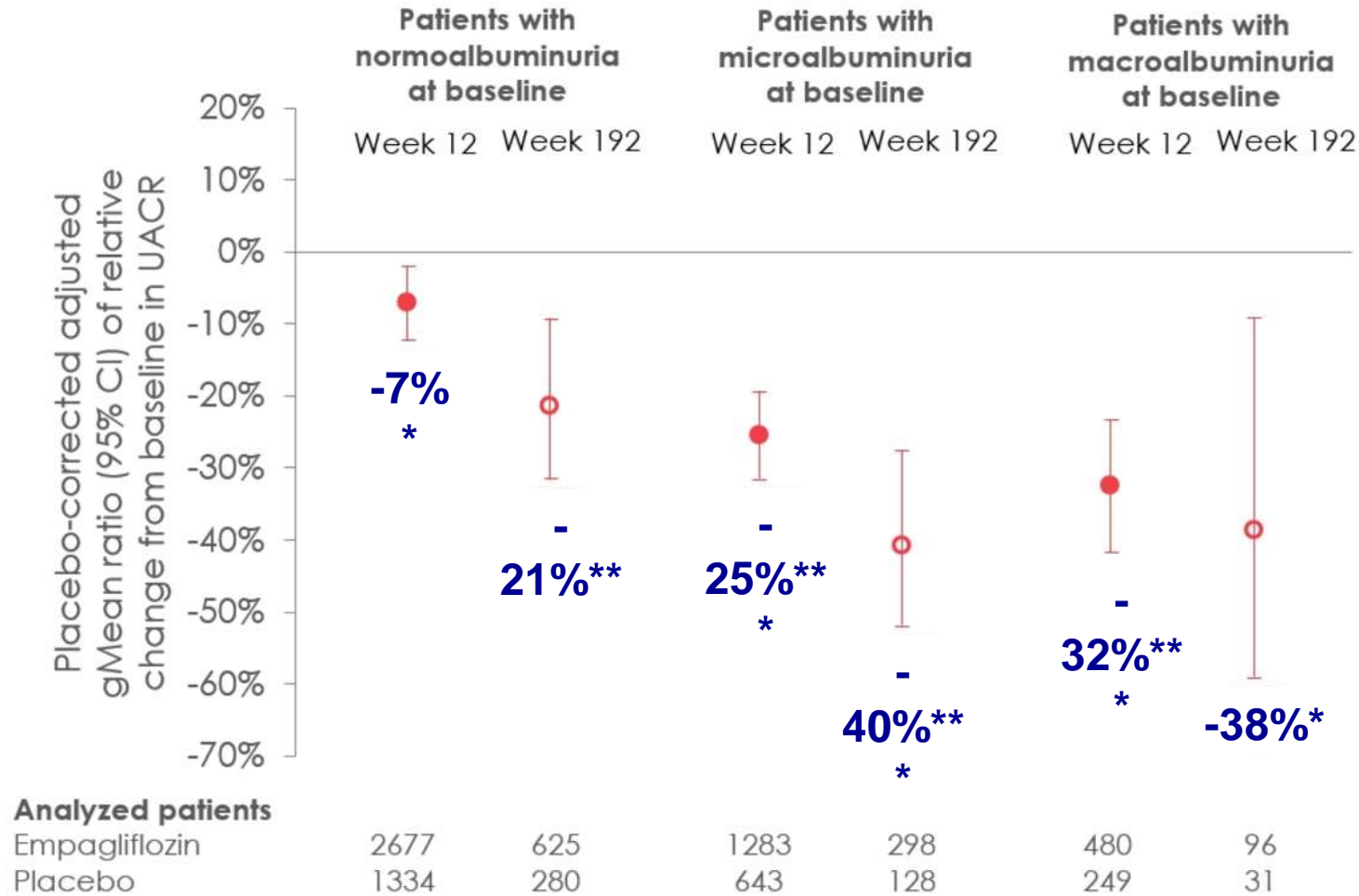
eGFR (CKD-EPI formula) over 192 weeks



No. analyzed		Semaine														
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		Semaine														
Total	7000	7000	6994	6931	6844	6745	6604	6451	6048	5114	4442	3941	3492	2797	1792	

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

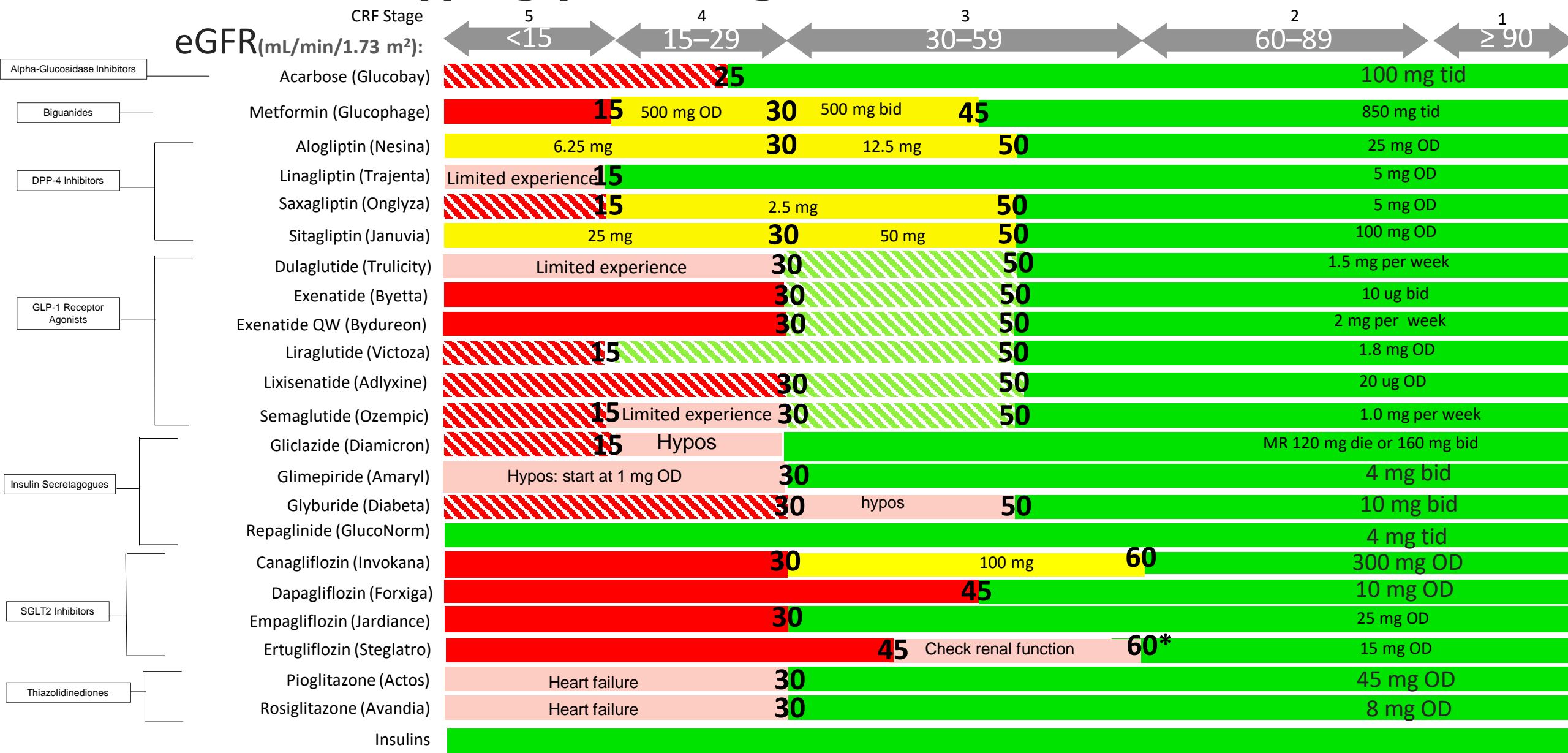


MMRM in the treated set (OC-AD). Normoalbuminuria: UACR <30 mg/g; microalbuminuria: UACR ≥30 to ≤300 mg/g; macroalbuminuria: UACR >300 mg/g.

*p<0.05; **p<0.01; ***p<0.001 for difference vs placebo.



Antihyperglycemic Agents and Renal Failure



Contraindicated

Not recommended

Dose adjustment required

Caution: reason indicated

Titrate carefully to avoid nausea

Safe

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

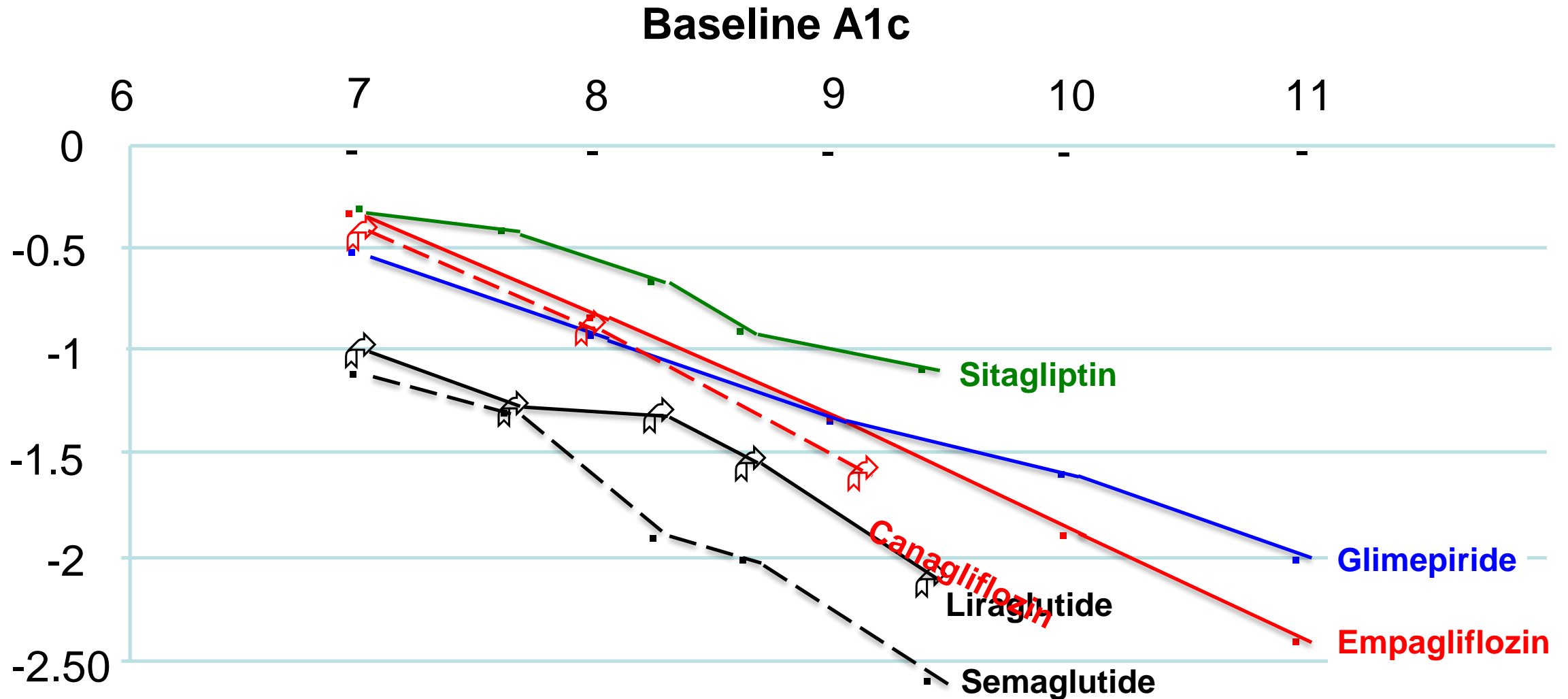
The dose indicated is the highest dose that can be used at that eGFR

Network Meta-analysis (26 weeks)

Add-on to metformin when A1c above target

	A1c	Weight	Hypos
No addition to MET	-0.08	+0.89	2.15%
Sulfonylurea	-0.81	+2.28	12.7%
DPP-4 inhibitors	-0.64	+ 0.23	3.11%
SGLT2 inhibitors	-0.69	-1.91	2.44%
GLP-1R agonists	-0.87	-1.39	3.28%
TZD	-0.80	+ 2.46	1.02%
Basal insulin	-1.24	+5.44	10.6%

Impact of Baseline A1c on Efficacy



1. Pratley et al. Int J Clin Pract. 65:397, 2011

2. Rosenstock J et al. Diabetes Care 38:376,2015

3. Matthews et al. ADA Poster 1096-P, 2014

4. De Fronzo et al. ADA Poster 1276-P, 2015

5. Ahrens B et al. Lancet Diabetes Endocrinology 5:341, 2017

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



The use of these newer therapies can be less expensive than conventional therapies

One Barrier:

Cost



Antihyperglycemic Coverage by RAMQ

Class	Medication	\$/day at max dose	MONO if SU and MET NT or CI	+ MET if SU CI,NT or INEFF	+ SU if Met CI, NT or INEFF	IF CVD + A1c>7	+ MET if DPP4i INEFF, NT or CI and BMI > 30 and high A1c	If other SU  NT or INEFF
Biguanides	Metformin (Glucophage)	0.18						
α-Glucosidase Inhibitors	Acarbose (Glucobay)	1.03						
DPP-4 Inhibitors	Alogliptin (Nesina)	2.10	EN167	EN148 (EN150 Kazano)	EN149			
	Linagliptin (Trajenta)	2.25	EN167	EN148 (EN150 Jentaduetto)				
	Saxagliptin (Onglyza)	2.30		EN148 (EN150 Komboglyze)	EN149			
	Sitagliptin (Januvia)	2.62	EN167	EN148 (EN150 Janumet et XR)				
SGLT2 Inhibitors	Canagliflozin (Invokana)	2.62	EN167	EN148	EN149			
	Dapagliflozin (Forxiga)	2.45		EN148 (EN150 Xigduo)	EN149			
	Empagliflozin (Jardiance)	2.62	EN167	EN148 (EN219 Synjardy)		EN179		
GLP-1R Agonists	Liraglutide (Victoza)	6.85					Form	
	Exenatide (Byetta)	2.49						
	Exenatide QW (Bydureon)	6.85						
	Dulaglutide (Trulicity)	6.85					Form	
	Semaglutide (Ozempic)	6.85					Form	
Thiazolidinediones	Pioglitazone (Actos)	1.05	EN121	EN118	EN119			
	Rosiglitazone (Avandia)	2.87	EN121	EN118  (EN81 Avandamet)	EN119			
Insulin Secretagogues	Gliclazide (Diamicon)	0.50						
	Glimepiride (Amaryl)	0.77						EN23
	Glyburide (Diabeta)	0.23						
	Repaglinide (GlucoNorm)	0.84						

Code EN179
Empagliflozin:
 if CVD and A1c > 7%

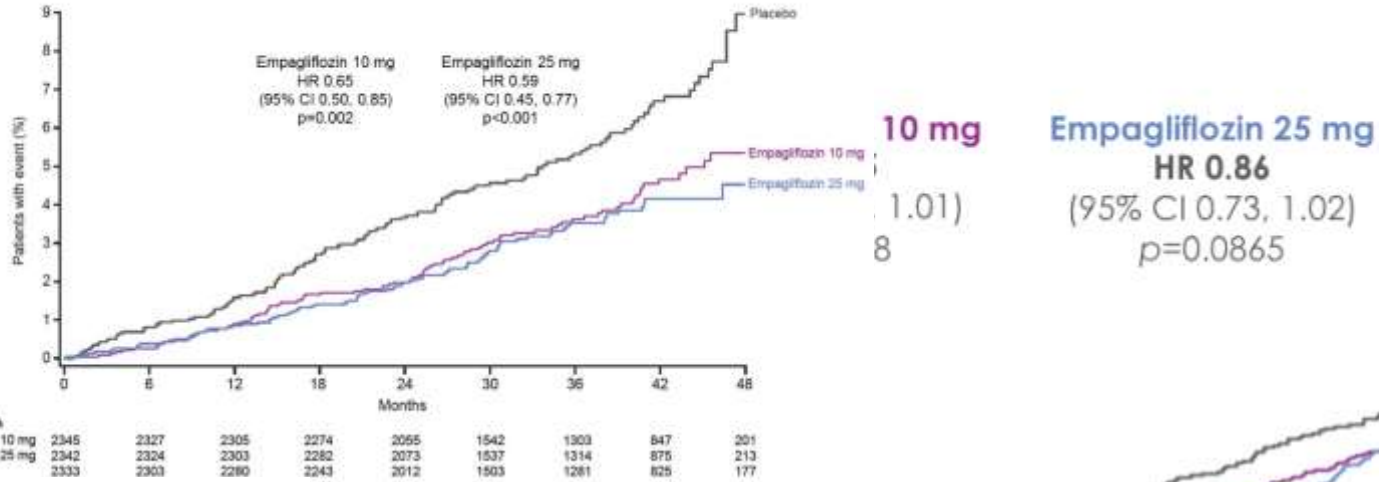
Form:
Liraglutide
Dulaglutide:
 + metformin
 BMI > 30
 A1c > 6.5%
 despite DPP-4i
 Annual renewal.

Form:
Semaglutide:
 + metformin
 + SU CI, NT or INEFF
No annual renewal

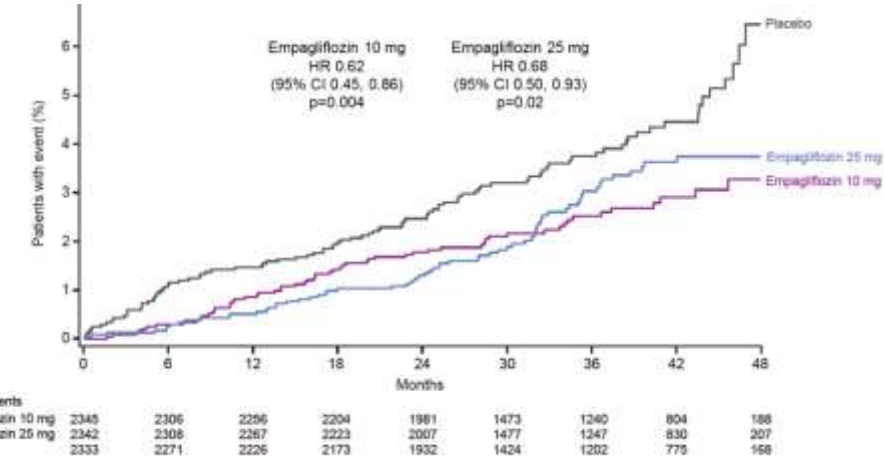
Green = on general list: no code or form required Orange = Médicament d'exception: code or form required
 NT=Not tolerated INEFF=Inefficacious CI=Contraindicated SU=Sulfonylurea MET=Metformin Mono=Monotherapy Form=Médicament d'exception form required
 JF Yale April 2019

Impact of Empagliflozin Dose

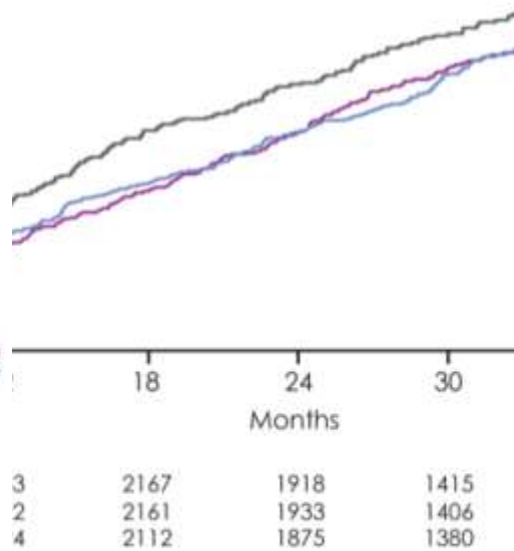
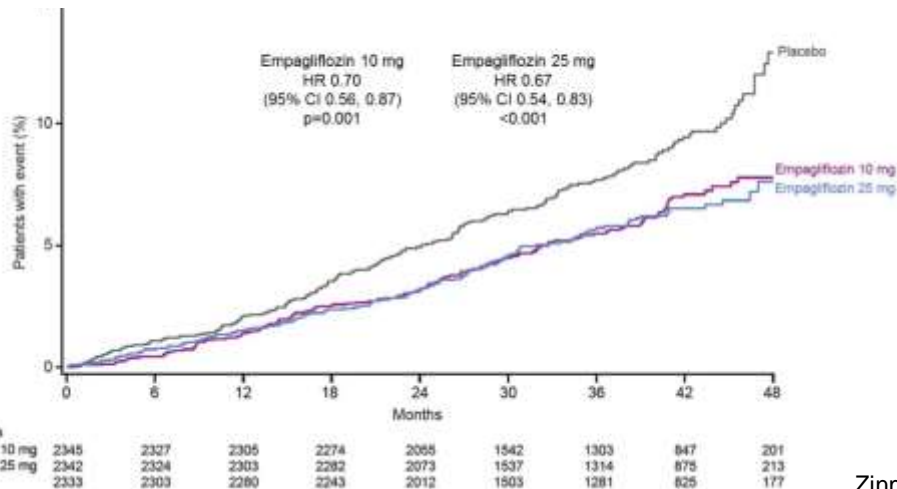
Cardiovascular Deaths



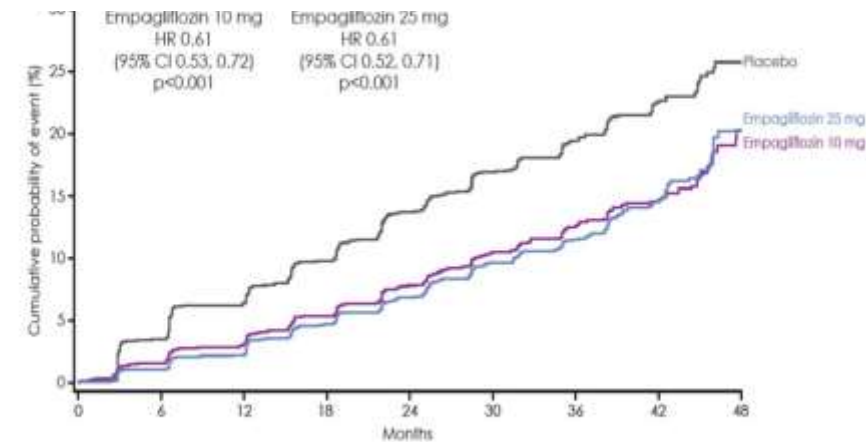
Hospitalizations for HF



Total Mortality

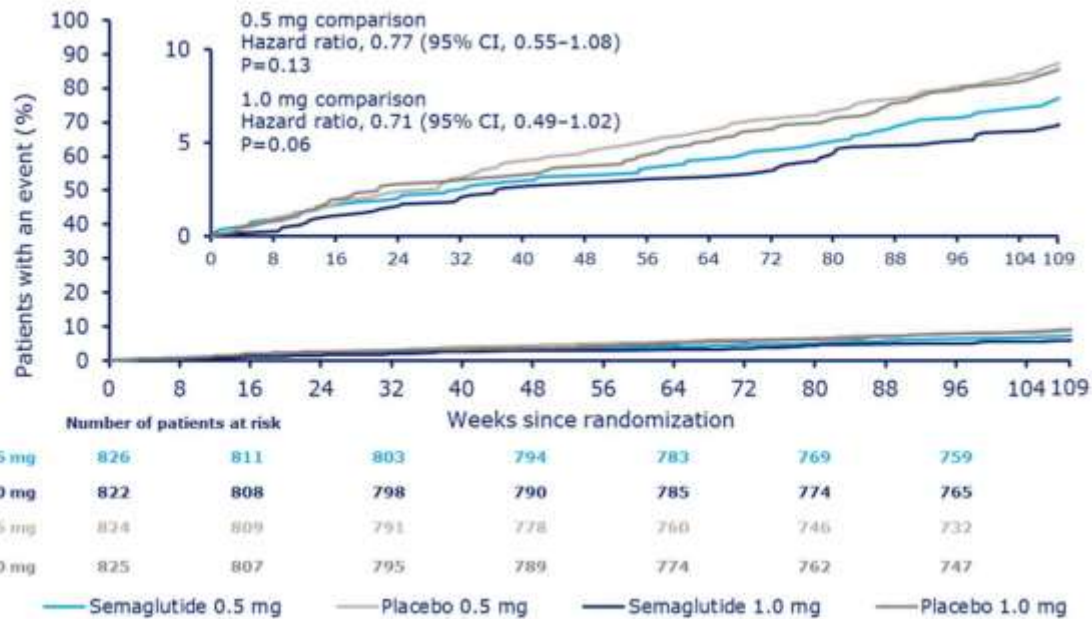


Worsening of nephropathy

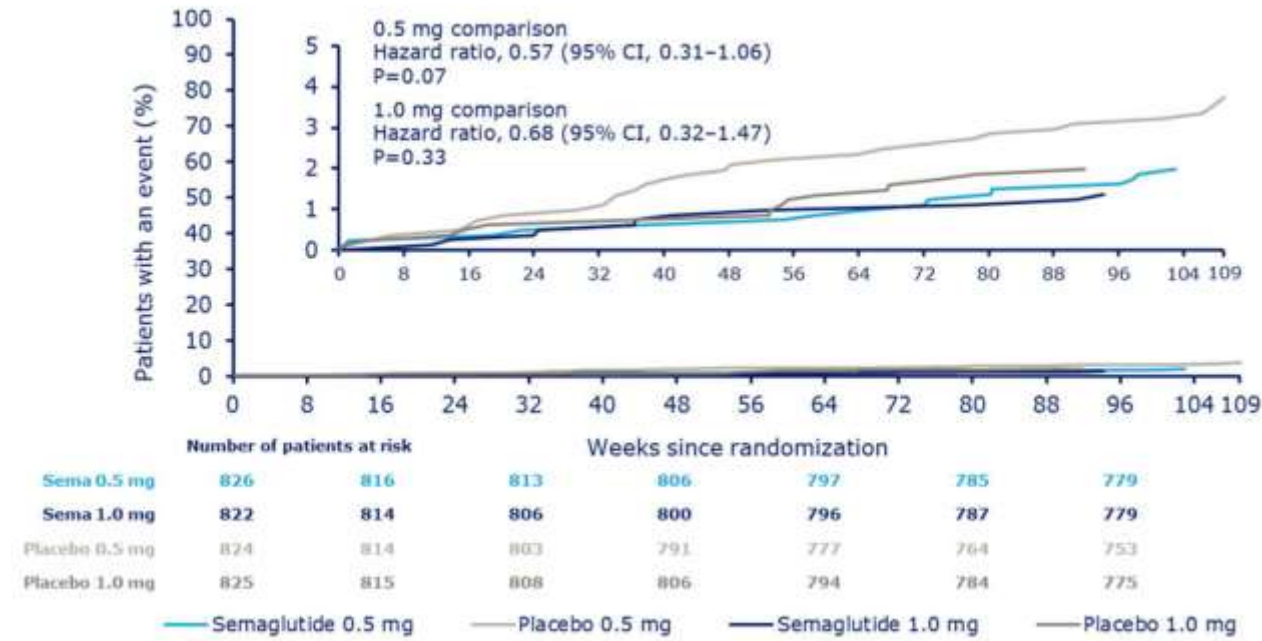


Impact of semaglutide dose on cardio-renal benefits

Primary Outcome



Non fatal Stroke



Decreasing SGLT2i Cost

Canagliflozin 100 mg

2.62/day



Canagliflozin 300 mg

2.62/day



Empagliflozin 10 mg

2.62/day



Empagliflozin 25 mg

2.62/day



Dapagliflozin 5 mg

2.45/day



Dapagliflozin 10 mg

2.45/day



Reducing the Cost of a GLP-1R Agonist

Pen 0.25/0.5 mg



0.5 mg per week = \$ 6.25 per day
One 2 mg pen = \$ 175,00

Pen 1.0 mg



1.0 mg per week = \$ 6.25 per day
One 4 mg pen = 175,00\$

Using this pen to give 0.5 mg per week reduces
the cost to \$ 3.12 per day.

But they must count the clicks... 36 clicks

How to decrease the cost of new medications

Classical Approach

Agent	Cost \$/d	A1c drop
Metformin 850 BID	0.06	-1.1
Gliclazide MR 120 die	0.12	-0.8
Sitagliptin 100 die	2.62	-0.7
1 strip / day	0.70	
Total Cost	3.50	

\$4.43 x 365 = Savings of \$1600 / year

New Approach

Agent	Cost \$/d	A1c drop
Metformin 850 BID	0.06	-1.1
Empagliflozin 10 die	2.62	-0.7
Semaglutide 0.5/week	6.25	-1.3
0 strip / day	0	
Total Cost	8.93	

The End



Jean-Francois.Yale@Mcgill.ca
www.dryale.ca

CVOT

	Alo- gliptin	Saxa- gliptin	Sita- gliptin	Lina- gliptin	Empa- gliclozin	Canag- gliclozin	Dapa- gliclozin	Canag- gliclozin	Lixi- senatide	Lira- glutide	Sema- glutide	Exenatide QW	Dula- glutide
Trial	EXAMINE	SAVOR	TECOS	CARMELINA	EMPAREG	CANVAS	DECLARE	CREDENCE	ELIXA	LEADER	SUSTAIN-6	EXSCEL	REWIND
Population	N=5380 ACS<90d	N=16492 CVD 78%	N=14671 CVD 100%	N=6980 CVD 57%	N=7020 CVD 100%	N=10142 CVD 65%	N=17160 CVD 41%	N=4401 CVD 50.4%	N=6068 ACS 180d	N=9540 CVD 80%	N=3297 CVD 80%	N=14752 CVD 73%	N=9901 CVD 31%
Duration	1.5 yrs	2.1 yrs	3.0 yrs	2.2 yrs	3.2 yrs	2.4 yrs	4.2 yrs	2.6 yrs	2.1 yrs	3.8 yrs	2.0 yrs	3.3 yrs	5.4 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	0.86 (0.74-0.99) P=0.0382	0.86 (0.75-0.97) P=0.0158	0.93 (0.84-1.03) NS	0.80 (0.67-0.95) P=0.01	1.02 (0.89-1.17) NS	0.87 (0.78-0.97) P=0.01	0.74 (0.58-0.95) P=0.02	0.91 (0.83-1.00) NS	0.88 (0.79-0.99) P=0.026
CV Death or HHF					0.66 (0.55-0.79) P<0.001	0.78 (0.67-0.91)	0.83 (0.73-0.95)	0.69 (0.57-0.83)					
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	0.62 (0.49-0.77) P<0.0001	0.87 (0.72-1.06) NS	0.98 (0.82-1.17) NS	0.78 (0.61-1.00)	0.98 (0.78-1.22) NS	0.78 (0.66-0.93) P=0.007	0.98 (0.65-1.48) NS	0.88 (0.76-1.02) NS	0.91 (0.78-1.06) NS
	1.08 (0.88-1.33) NS	0.95 (0.80-1.12) NS	0.95 (0.81-1.11) NS	1.15 NS	0.87 (0.70-1.09) NS	0.85 (0.69-1.05) NS	0.89 (0.77-1.01) NS		1.03 (0.87-1.22) NS	0.88 (0.75-1.03) NS	0.74 (0.51-1.08) NS	0.95 (0.84-1.09) NS	0.96 (0.79-1.16) 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	1.24 (0.92-1.67) NS	0.90 (0.71-1.15) NS	1.01 (0.84-1.21) NS		1.12 (0.79-1.58) NS	0.89 (0.72-1.11) NS	0.61 (0.38-0.99) P=0.04	0.86 (0.70-1.07) NS	0.76 (0.61-0.95) P=0.017
Total Mortality	0.88 (0.71-1.09) NS	1.11 (0.96-1.27) NS	1.01 (0.90-1.14) NS		0.68 (0.57-0.82) P<0.0001	0.87 (0.74-1.01) NS		0.83 (0.68-1.02)	0.94 (0.78-1.23) NS	0.85 (0.74-0.97) P=0.02	1.05 (0.74-1.50) NS	0.86 (0.77-0.97) P=0.016	0.90 (0.80-1.01) 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	0.65 (0.50-0.85) P=0.0017	0.67 (0.52-0.87)	0.73 (0.61-0.88)	0.61 (0.47-0.80) P<0.001	0.96 (0.75-1.23) NS	0.87 (0.73-1.05) NS	1.11 (0.77-1.61) NS	0.94 (0.78-1.13) NS	0.93 (0.77-1.12) NS
Renal worsening		1.08 (0.96-1.22) NS		1.04 NS	0.61 (0.53-0.70) P<0.001	0.60 (0.47-0.77)	0.53 (0.43-0.66)	0.70 (0.59-0.82) P=0.00001		0.78 (0.67-0.92) P=0.003	0.64 (0.46-0.88) P=0.005		0.85 (0.77-0.93) P=0.004