SGLT2i, GLP-1A and MRA in Cardiorenal Protection: an update

May 16, 2024

Monique E. Cho, MD

Division of Nephrology and Hypertension

University of Utah

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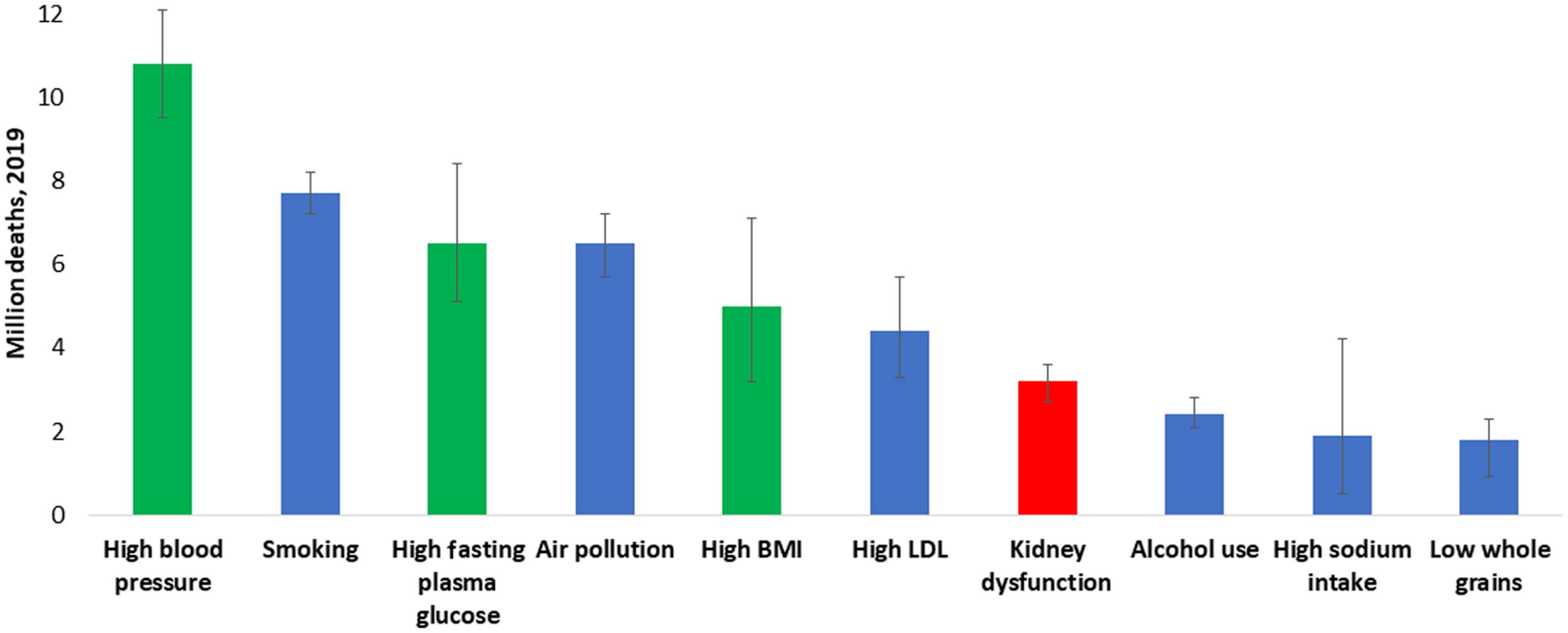
Disclosure

- UpToDate
- Grant funding from NIDDK, NIH

Objectives

- **SGLT2i:**
  - Glomerular and tubular effects of SGLT2i
  - Proposed mechanisms underlying benefits
  - Summary of the kidney outcomes ***(emphasis on the DAPA-CKD & EMPA-KIDNEY trials)***
  - Summary of CV/HF/ASCVD outcomes
- **GLP-1 receptor agonists (GLP-1RA):**
  - Proposed mechanisms underlying clinical benefits
  - Effects on CV risk factors
  - Summary of clinical CV and renal outcomes ***(Emphasis on SELECT and FLOW trials)***
- **Mineralocorticoid receptor antagonists (MRAs):**
  - Proposed mechanisms underlying clinical benefits
  - Steroidal vs non-steroidal MRAs
  - Summary of clinical CV and renal outcomes (FIDELIO & FIGARO)
- **Summary and recommendations**

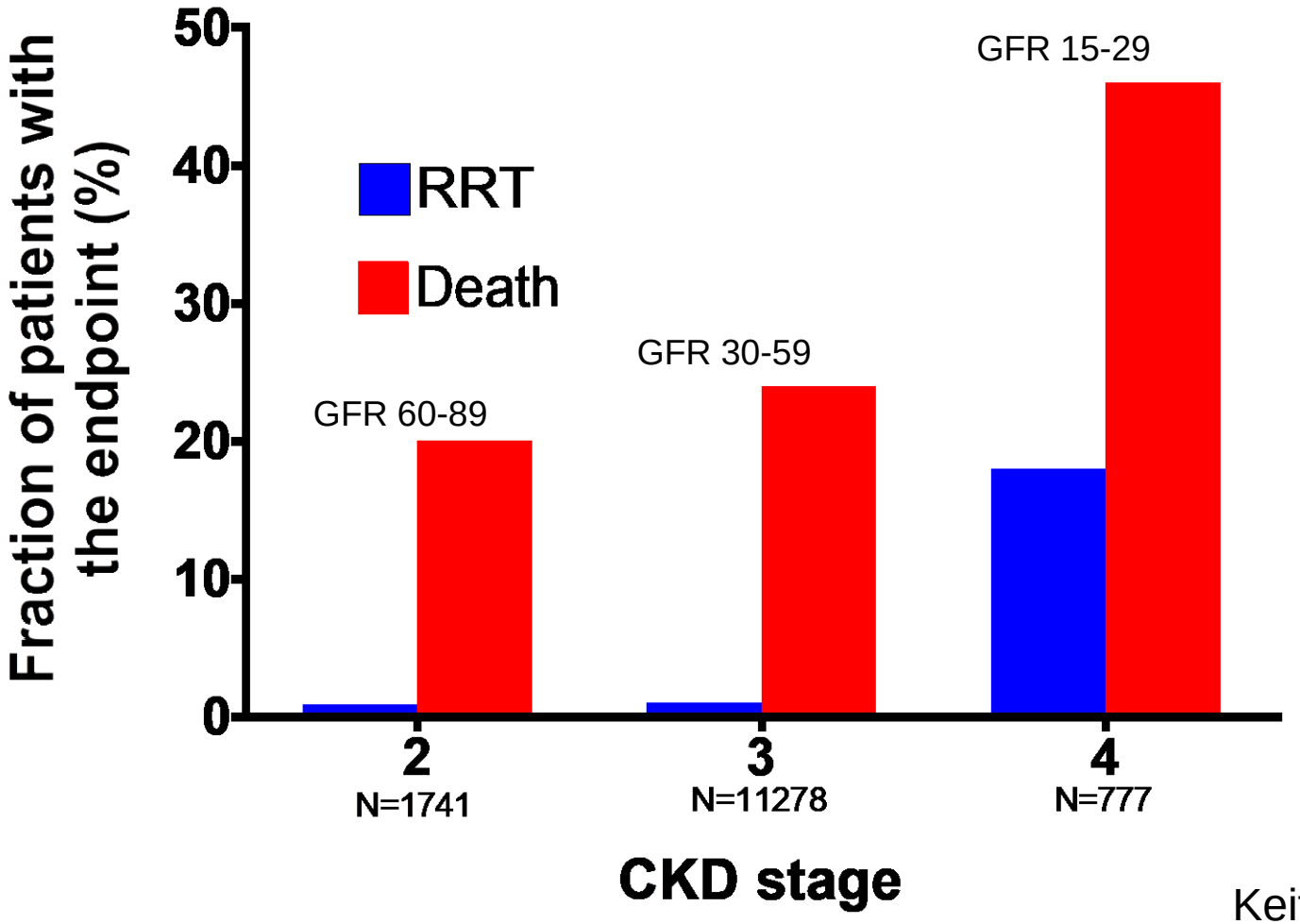
The top 10 global risk factors for death, 2019



Luyckx VA et al., Kidney Int 2024

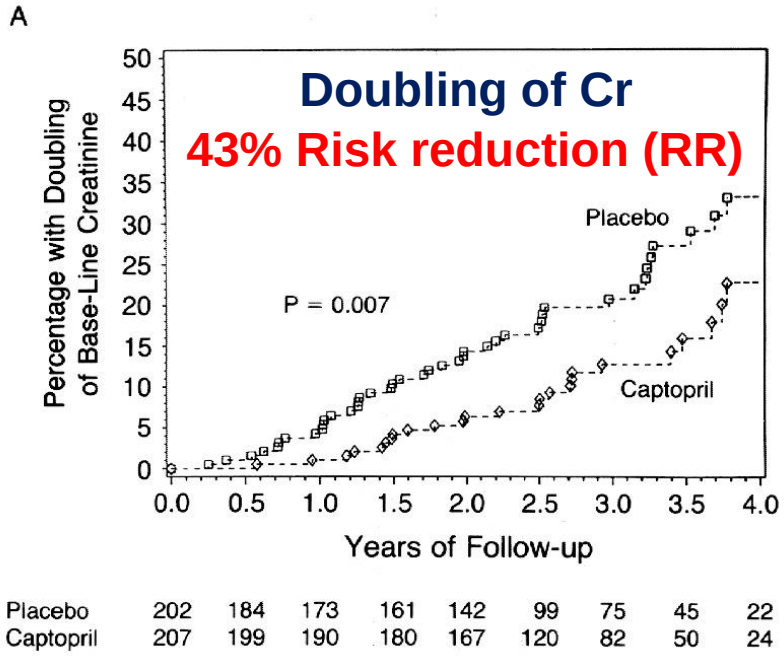
Severe mortality risk in pre-dialysis CKD

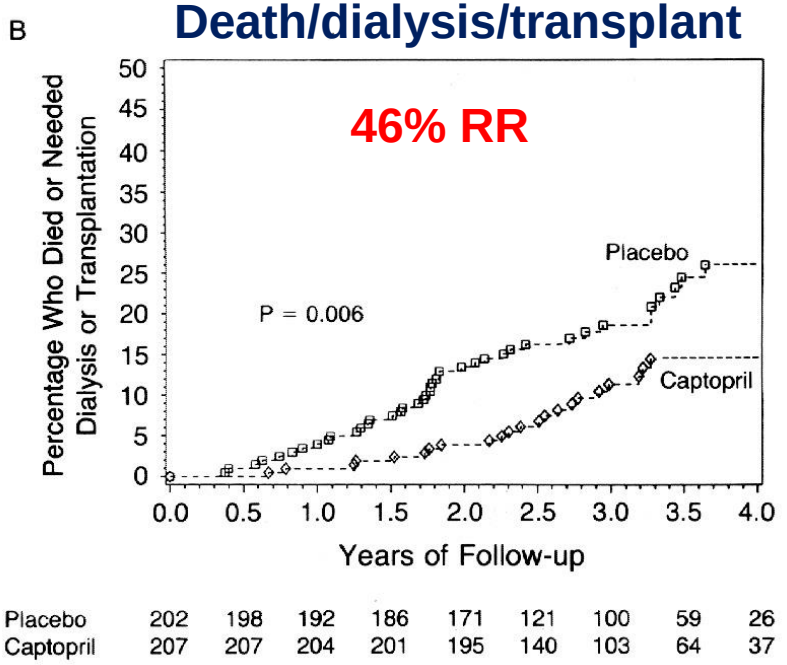
A large HMO-based observational study (N≈14,000) with 5.5-yrs follow up



Keith et al. Arch Intern Med 2004

The Captopril Study: 1993





409 insulin-dependent T1DM patients:

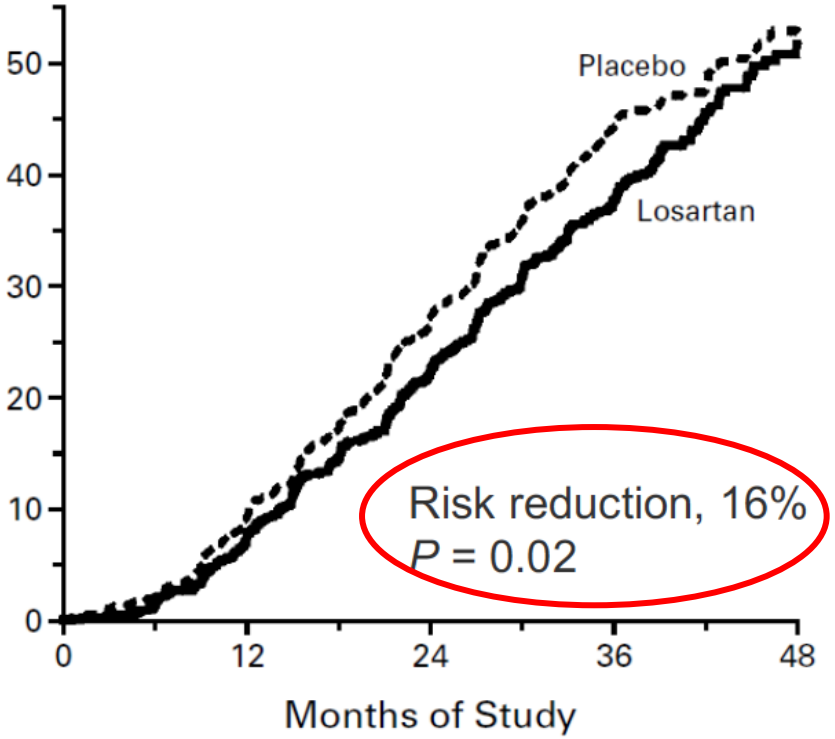
- Mean age: 35
- Duration of DM: 22 yrs
- Baseline proteinuria 2.5-3 g/g
- A1c 12%
- Mean CrCL:
  - 84 mL/min (captopril)
  - 79 mL/min (placebo)

Lewis, NEJM 1993

Kidney outcomes with ARB in T2DM: 2001

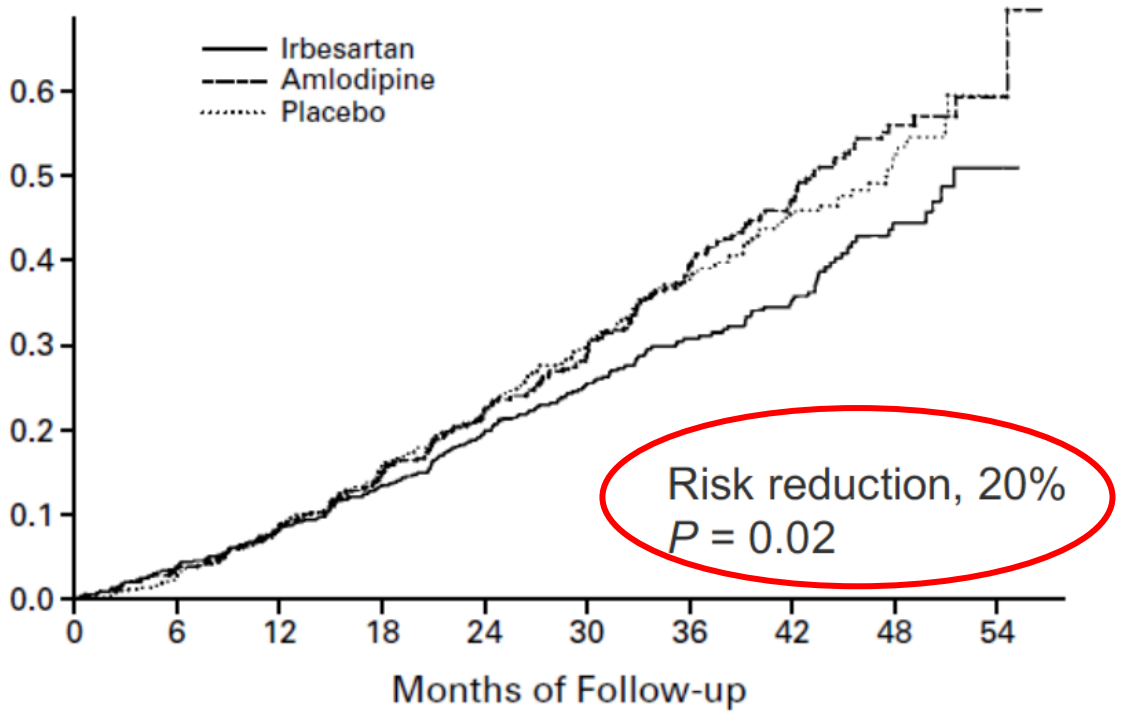
Doubling of serum creatinine, ESKD, or death

RENAAL



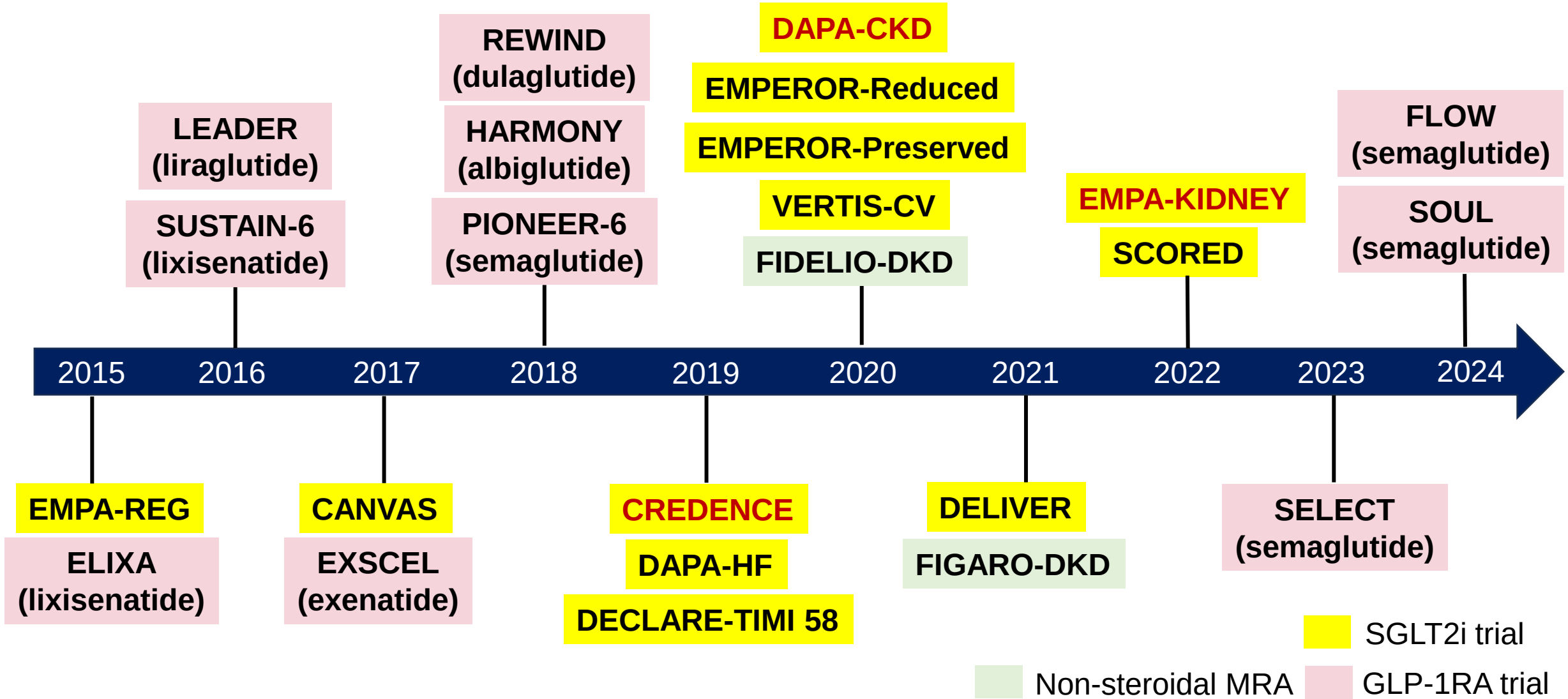
Brenner B, et al. *N Engl J Med*. 2001;345(12):861-869.

IDNT



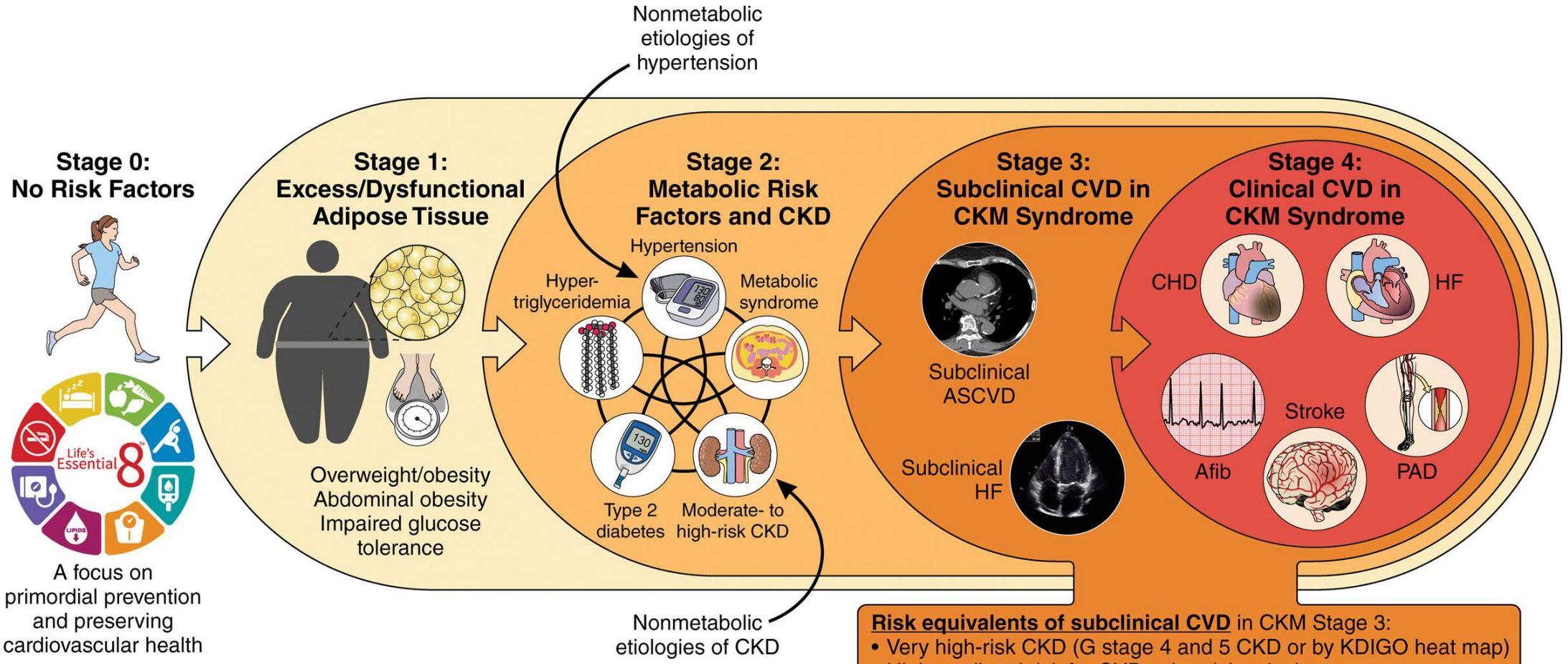
Lewis EJ, et al. *N Eng J Med*. 2001;345(12):851-860.

Timeline of the key current and future RCTs involving SGLT2is/GLP-1RAs/ns-MRA for CV and renal outcomes



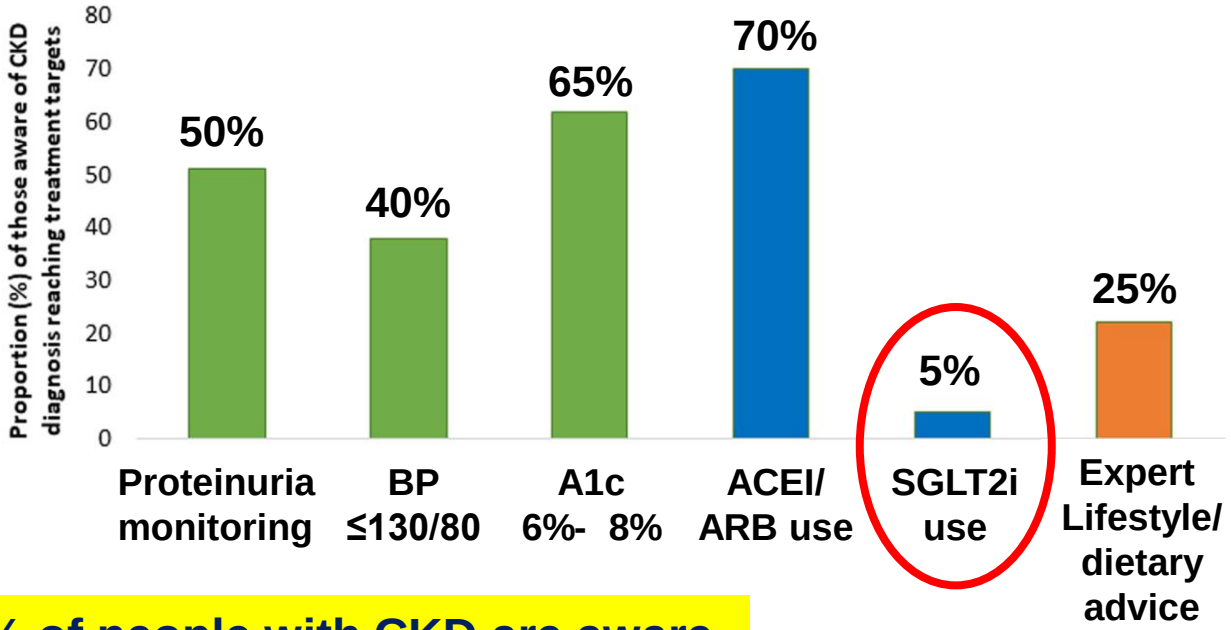
Cardiovascular-kidney-metabolic (CKM) syndrome is a systemic disorder that connects heart disease, kidney disease, diabetes, and obesity

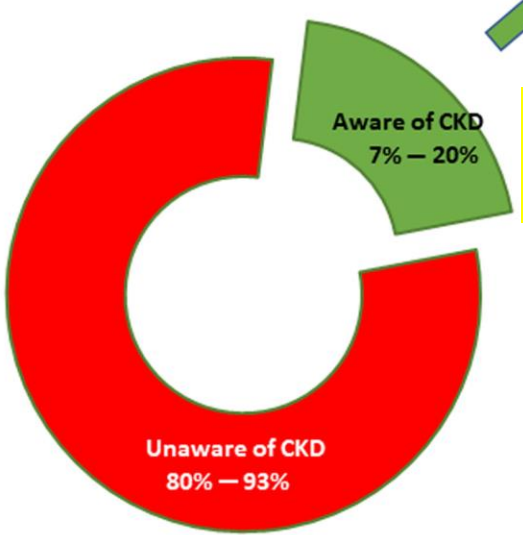
Cardiovascular-Kidney-Metabolic Health: A presidential advisory From the AHA



Ndumele CE et al., Circulation 2024

Many do not receive optimal care for CKD





7%-20% of people with CKD are aware of their diagnosis globally.

Only 5% and 6.3% of eligible patients with CKD and diabetes, respectively, continued on SGLT2i and GLP-1RA at 90 days.

Proportion of people with CKD aware of their diagnosis

Luyckx VA et al., Kidney Int 2024
Nicholas SB et al., Diabetes Obes Metab 2023

SGLT2 inhibitors: Kidney benefits

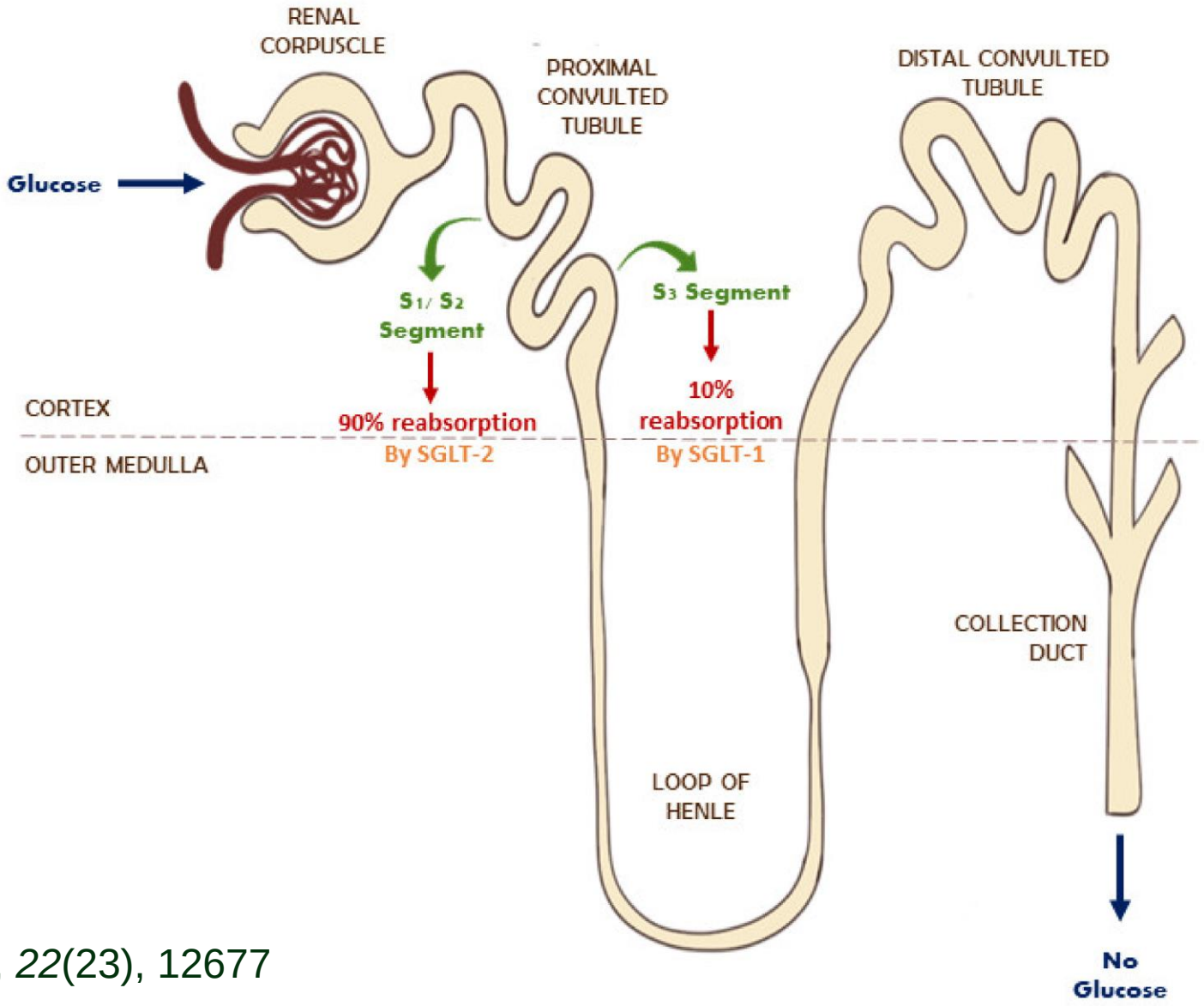
Glucose reabsorption in proximal nephron

SGLT2:

- a low affinity, high capacity luminal transporter in the S1 and S2 segments of the proximal tubule
- normally reabsorbs about 97% of filtered glucose

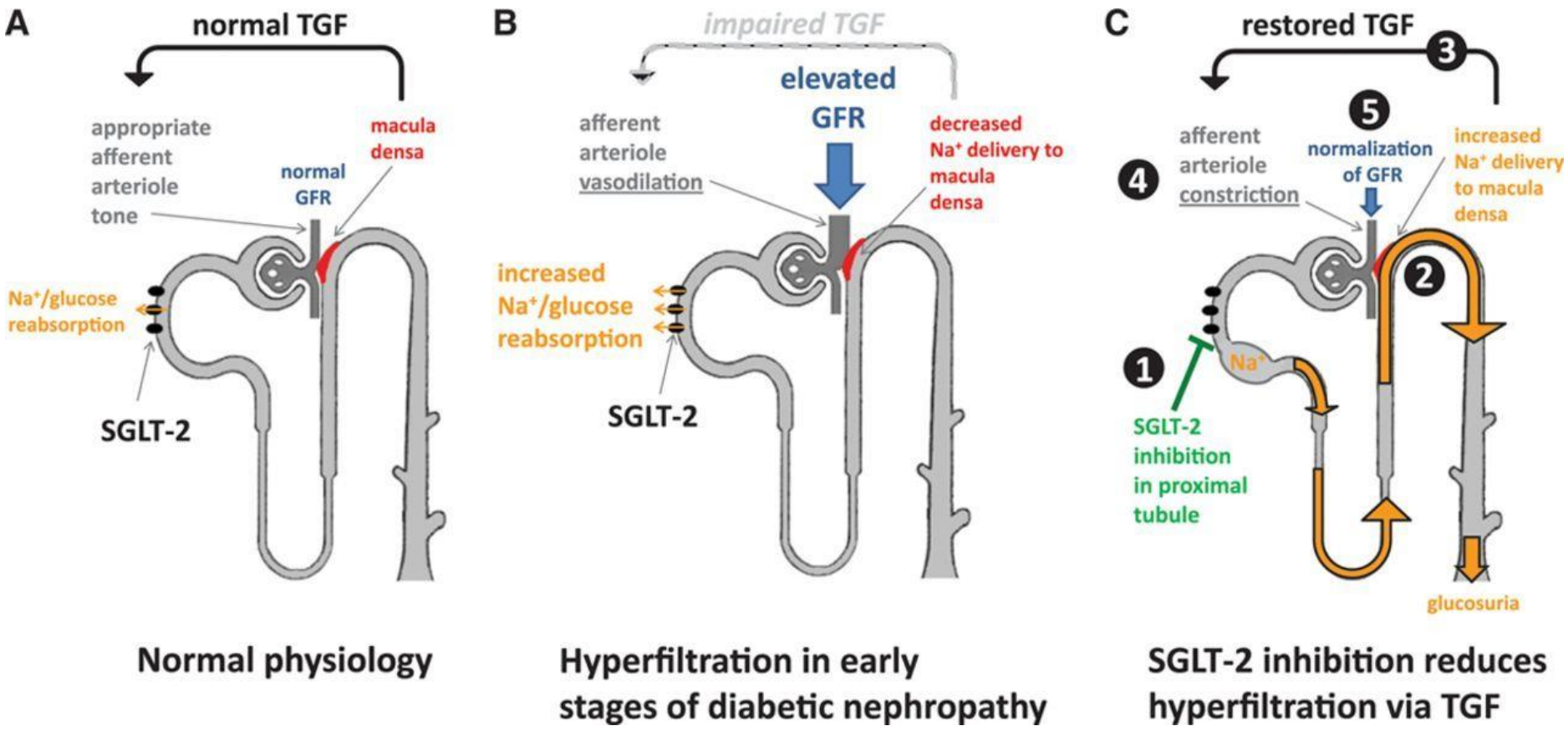
SGLT1:

- a high affinity, low capacity transporter in the S3 segment
- normally reabsorbs the remainder



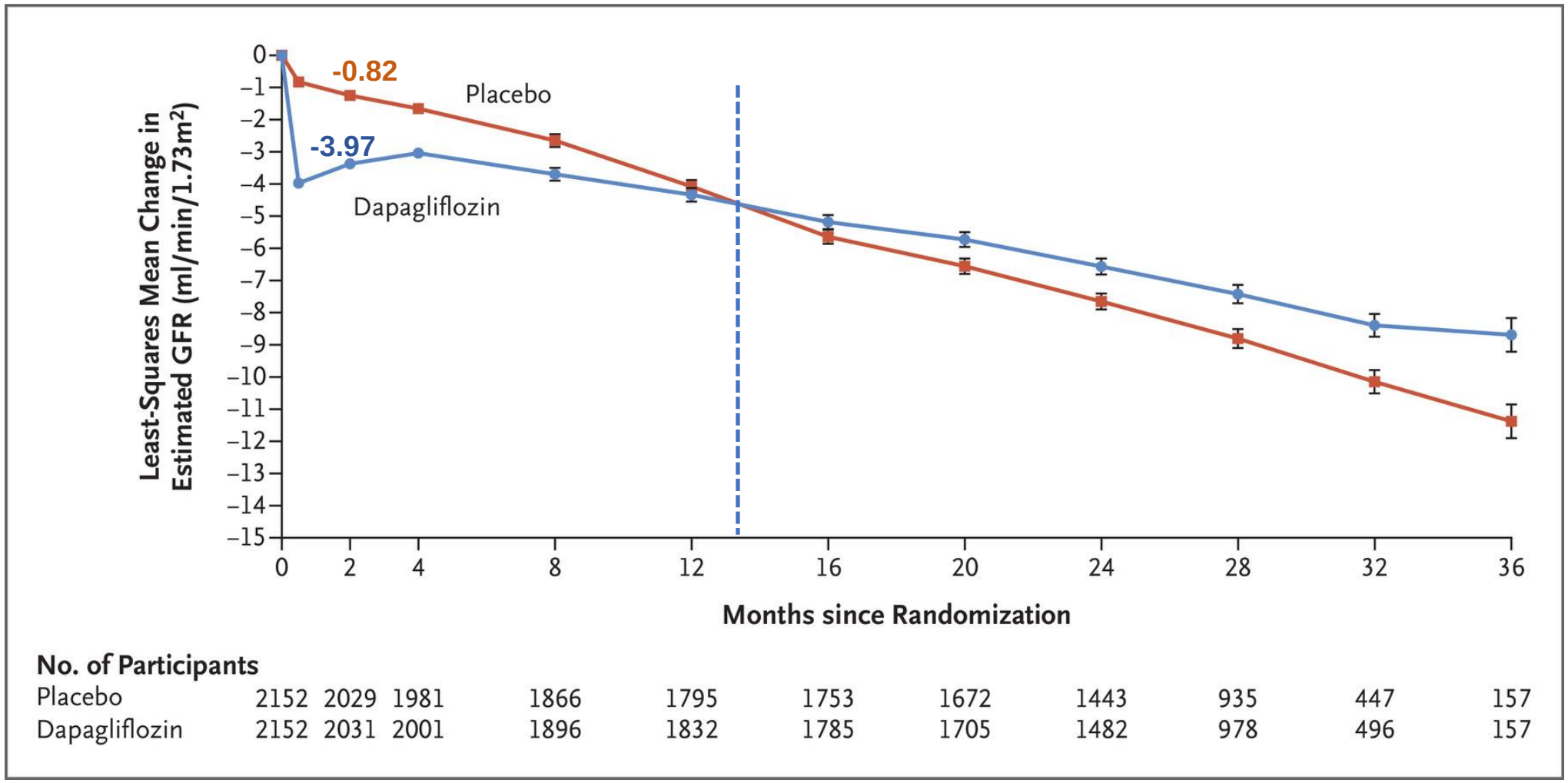
Al-Shamasi et al. Int. J. Mol. Sci. **2021**, *22*(23), 12677

The effect of proximal sodium reabsorption on tubuloglomerular feedback



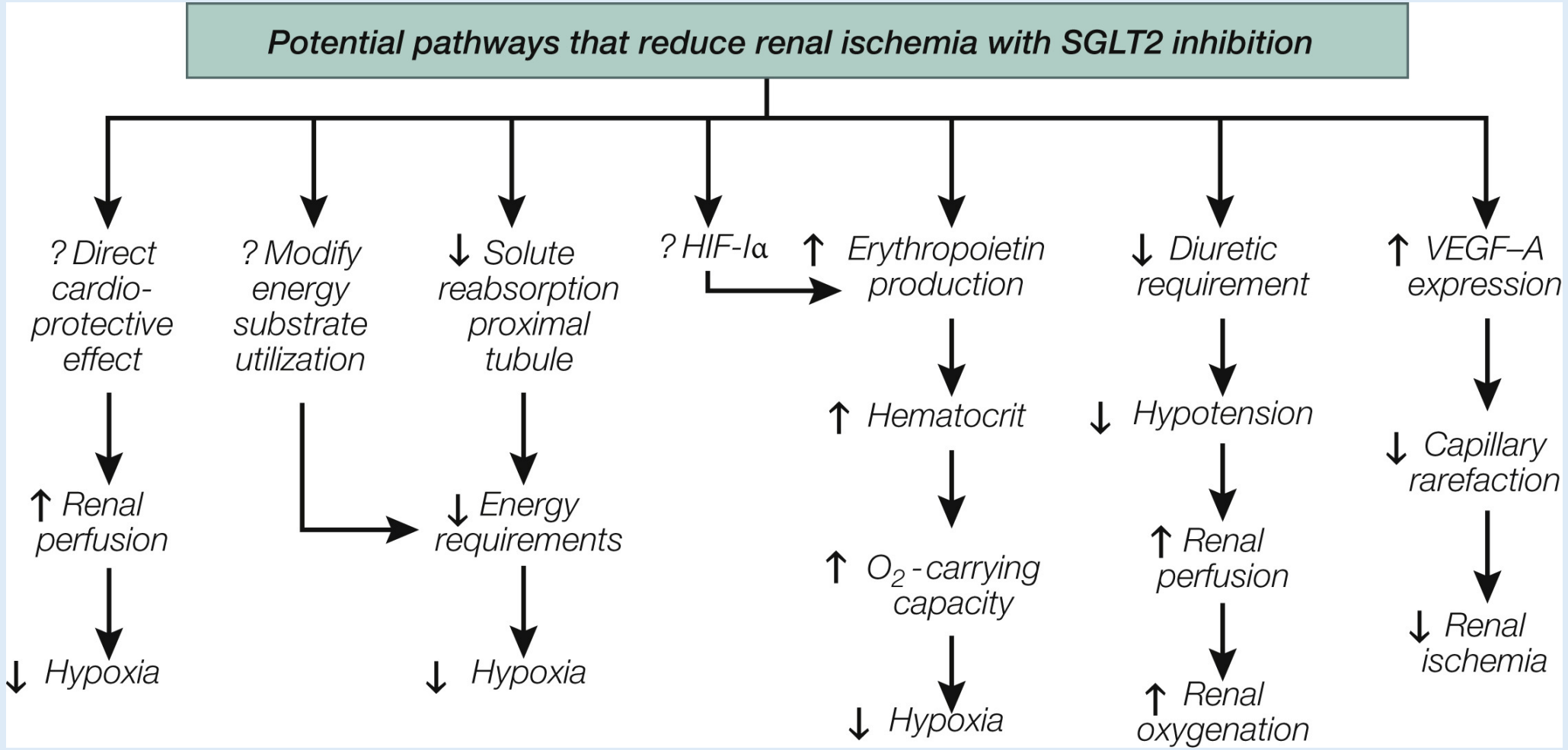
Cherney et al. Circulation 2014;129:587

DAPA-CKD: The acute drop in eGFR with SGLT2i initiation followed by slower eGFR decline



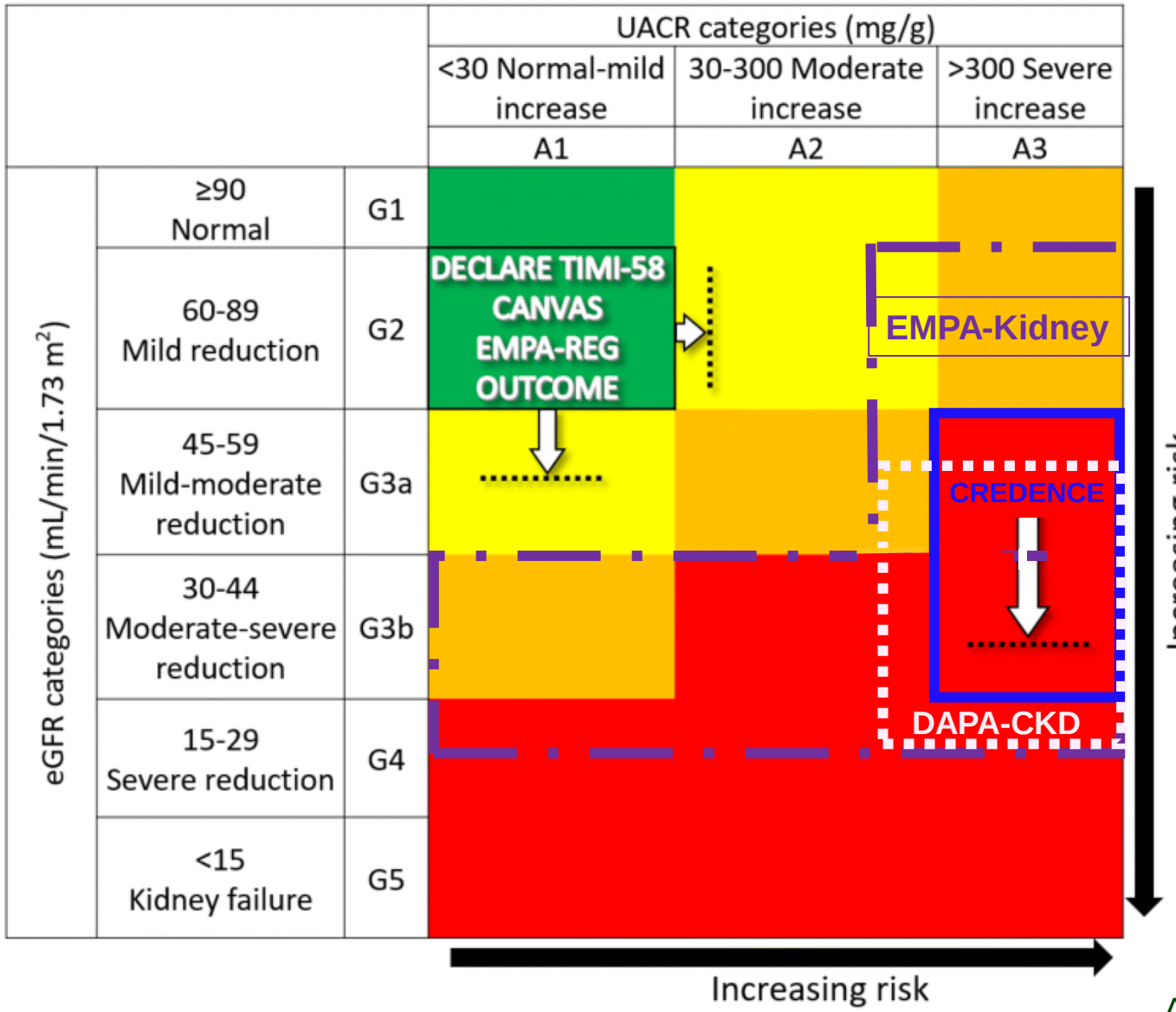
Heerspink et al., NEJM 2020;383:1436

Potential pathways involving kidney protection with SGLT2 inhibition



Van Raalte and Cherney, KI 2018 (94)459

SGLT2i trials by baseline eGFR and albuminuria



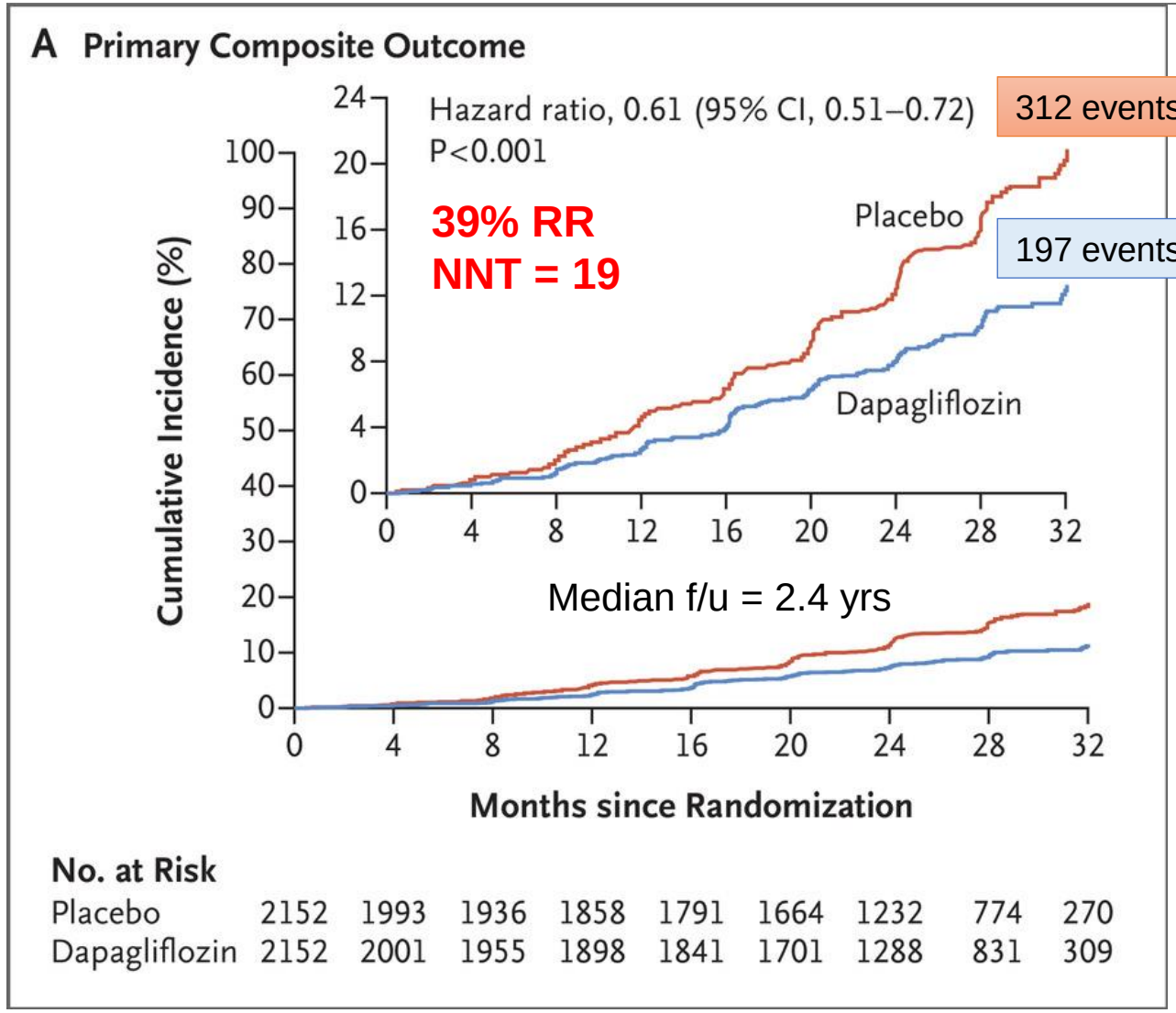
CREDENCE: N = 4401
T2DM
eGFR 30 - 89
UACR > 300 mg/g

DAPA-CKD: N = 4304
With or without T2DM
eGFR ≥ 25 - 75 *and*
UACR ≥ 200 mg/g

EMPA-KIDNEY: N = 6609
With or without T2DM
eGFR ≥ 20 - 45 *or*
eGFR ≥ 45 – 89 and UACR ≥200 mg/g

Adopted from Kluger et al., Cardiovasc Diabetology 2019

DAPA-CKD: Dapagliflozin is similarly beneficial for renal endpoints in diabetic and non-diabetic patients



Components of the primary outcome:

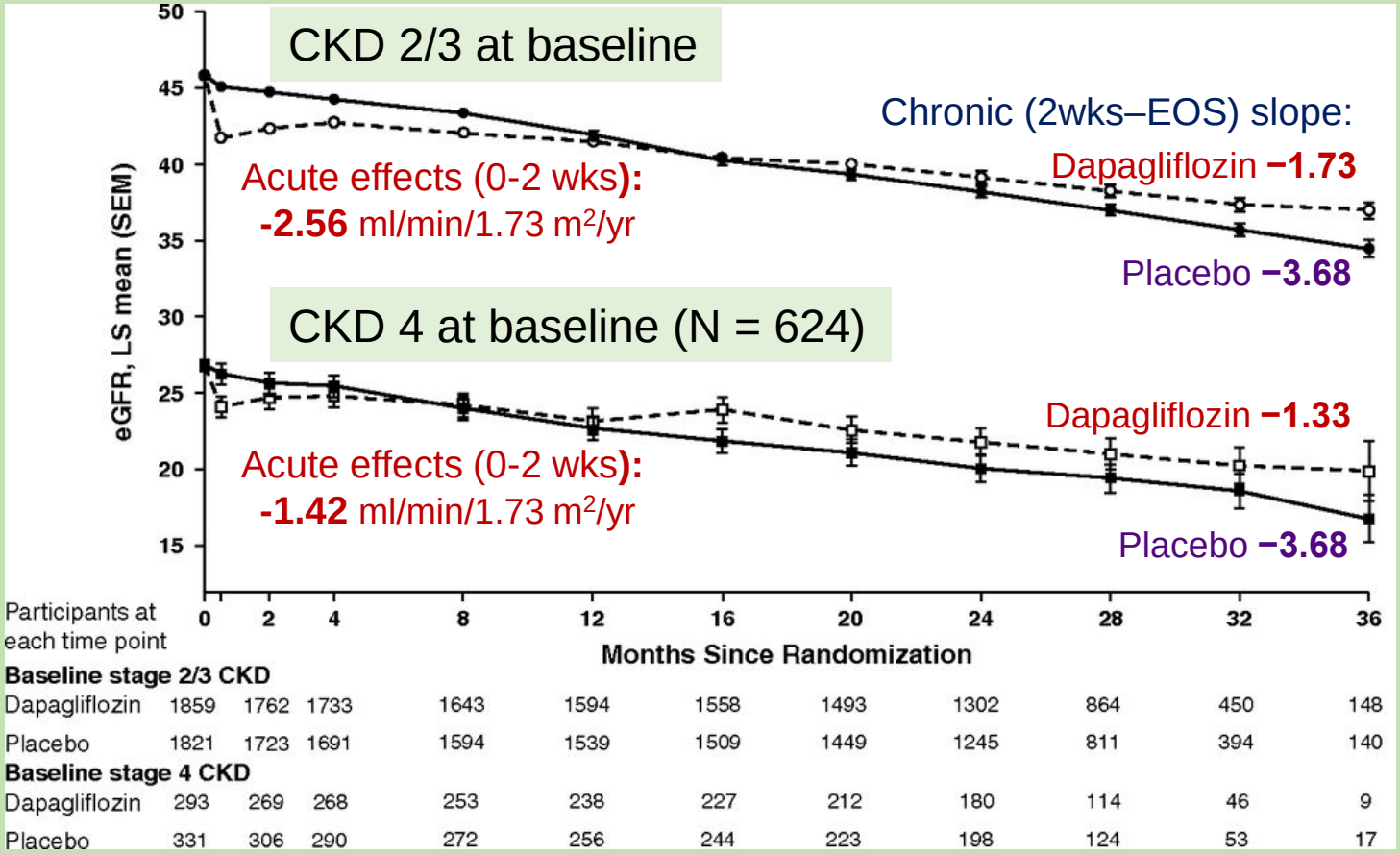
- Decline in eGFR of ≥50% 0.53 (0.42-0.67)
- ESKD 0.64 (0.50-0.82)
  - eGFR <15 0.67 (0.51-0.88)
  - Dialysis or kidney tx 0.66 (0.48-0.90)
- Death from renal/CVD 0.81 (0.58-1.12)

The HR for primary composite outcome with dapagliflozin:

- **DM : HR 0·64 (0·52–0·79)**
- **No DM: HR 0·50 (0·35–0·72)**
- $p_{interaction}$=0·24

Heerspink et al., NEJM 2020;383:1436
Wheeler DC et al., Lancet Diabetes Endocrinol 2021;9:22

Dapagliflozin is similarly effective in CKD 4 compared to CKD 2/3 in DAPA-CKD



LS mean change in eGFR over the study: Total annual slopes (week 0-EOS)

CKD 2/3:
Dapagliflozin **−2.98** ml/min/1.73 m²/yr
Placebo -3.87 ml/min/1.73 m²/yr
Δ **0.89**

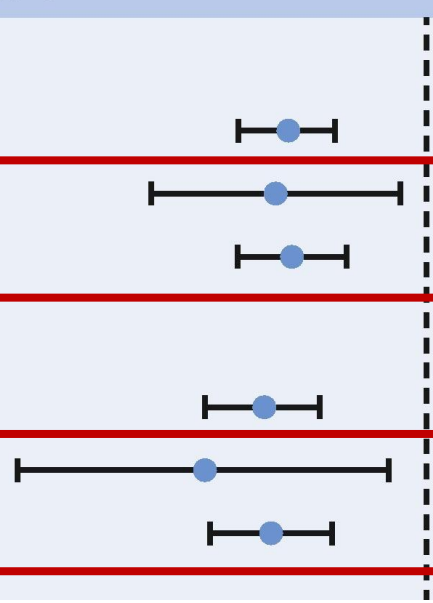
CKD 4:
Dapagliflozin **−2.15** ml/min/1.73 m²/yr
Placebo -3.38 ml/min/1.73 m²/yr
Δ **1.23**

Chertow GM et al., JASN 2021, 32 :2352

Dapagliflozin reduces the risk of renal outcomes independently of baseline HF status: *analysis from DAPA-CKD*

Effect of Dapagliflozin, Compared With Placebo, in DAPA-CKD Overall and According to Baseline Heart Failure Status

	Dapagliflozin Placebo *n/N*		Dapagliflozin Placebo *Events/100 Patient-Years*		HR (95% CI)	*P* Value for Interaction
Primary outcome: *eGFR decline ≥50%, ESKD, or kidney or CV death*						
Overall	197/2,152	312/2,152	4.6	7.5	0.61 (0.51-0.72)	
HF at baseline	31/235	51/233	6.5	11.0	0.58 (0.37-0.91)	0.59
No HF at baseline	166/1,917	261/1,919	4.4	7.0	0.62 (0.51-0.75)	
Secondary outcome: *eGFR decline ≥50%, ESKD, or kidney death*						
Overall	142/2,152	243/2,152	3.3	5.8	0.56 (0.45-0.68)	
HF at baseline	13/235	27/233	2.7	5.8	0.45 (0.23-0.87)	0.36
No HF at baseline	129/1,917	216/1,919	3.4	5.8	0.57 (0.46-0.71)	

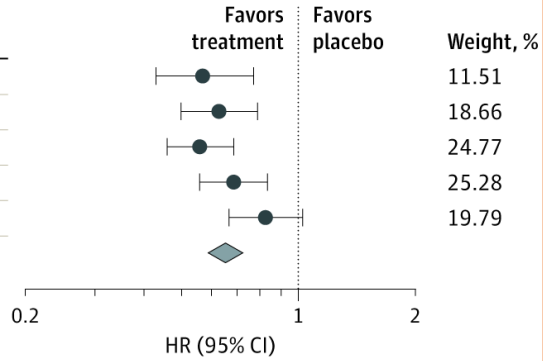


SGLT2i therapy associated with renal benefit regardless of history of ASCVD

Overall kidney outcomes

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 7.96; *df* = 4; *P* = .09; I^2 = 49.7%)					0.62 (0.56-0.70)

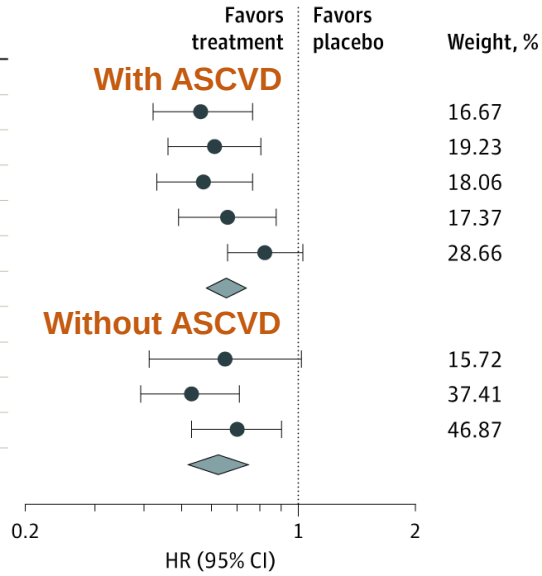
~30-40% RRR



Kidney outcomes by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 6.09; *df* = 4; *P* = .19; I^2 = 34.4%)					0.64 (0.56-0.72)
Patients without ASCVD					
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)
Fixed-effects model (Q = 1.86; *df* = 2; *P* = .40; I^2 = 0.0%)					0.60 (0.50-0.73)

~30-40% RRR



Meta-analysis of SGLT2i trials on the composite of renal worsening, ESRD, or renal death stratified by the presence of established atherosclerotic CV disease

McGuire DK et al.,
JAMA Cardiol. 2021;6:148

Design, recruitment, and baseline characteristics of the EMPA-KIDNEY trial *Started in 1/2019*

Background

STOPPED EARLY IN 4/2022

Streamlined design

RCT:
Empagliflozin 10 mg once daily
vs. matching placebo

Inclusion criteria:
eGFR ≥ 20, < 45 mL/min/1.73 m²;
or ≥ 45, < 90 and uACR ≥ 200 mg/g

Composite primary outcome:
- CV or renal death
- Maintenance dialysis or kidney transplant
- Sustained eGFR < 10 mL/min/1.73 m² or sustained ≥ 40% eGFR decline

Baseline characteristics

n = 6609

Mean age 64 (SD 14) years

♀ 33%
♂ 67%

8 countries:
Europe, N. America and Asia

eGFR, mL/min/1.73 m²:
Mean 37.5 (SD 15)
78% with eGFR < 45
34% with eGFR < 30
(DAPA-CKD - 14% with eGFR <30)

Primary renal diagnoses:
31% diabetic nephropathy
25% glomerular disease
22% ischaemic/hypertensive
12% other and 10% unknown

uACR, mg/g:
Median 412 (IQR 94–1190)
48% with uACR < 300
20% without albuminuria

Comorbidity:
46% diabetes
27% cardiovascular disease

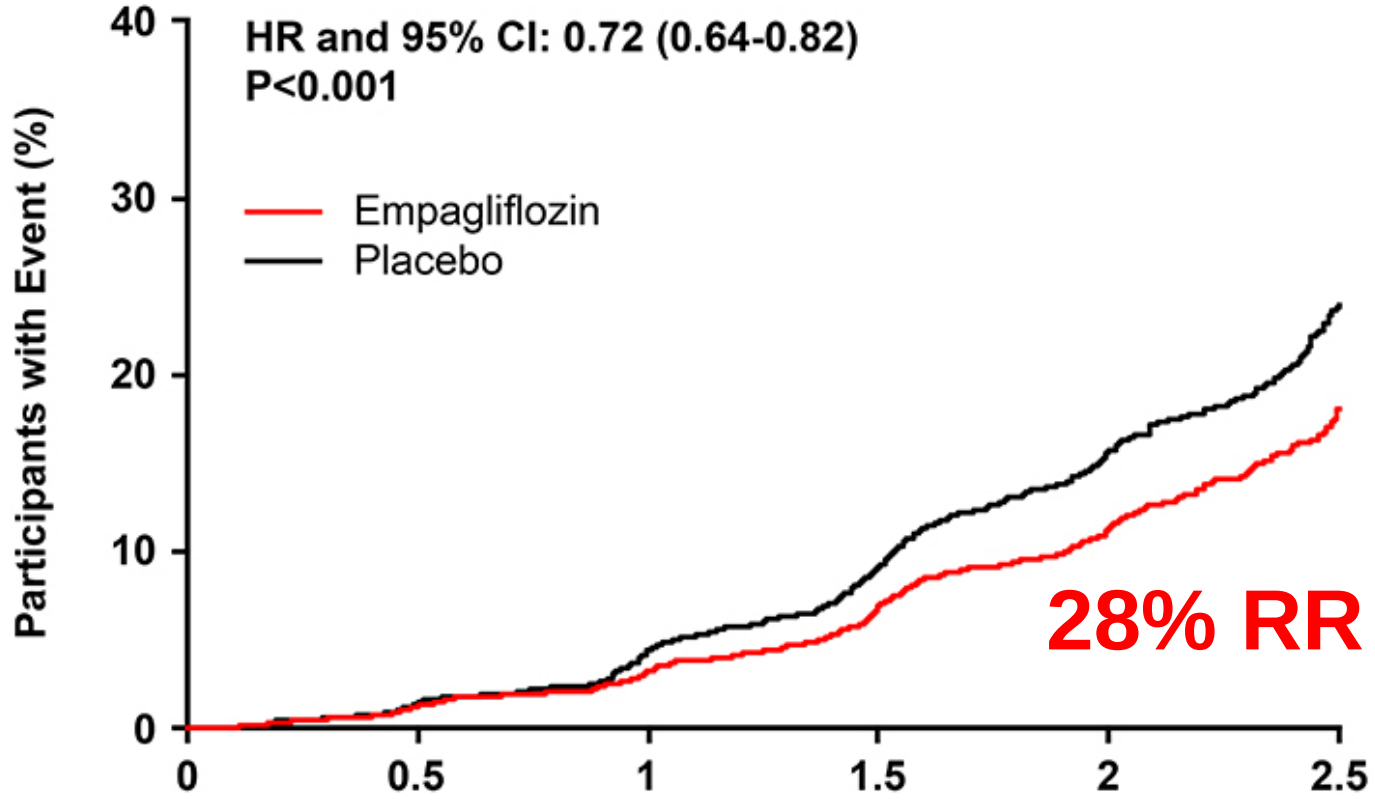
Conclusion

The EMPA-KIDNEY trial has recruited a large, widely generalizable CKD population with high proportions of the types of people without diabetes and with low eGFR or uACR who have not been included in previous trials of SGLT2i. Results are anticipated in 2022.

ERA ndt NEPHROLOGY DIALYSIS TRANSPLANTATION

The EMPA-KIDNEY Collaborative Group. NDT (2022)
@NDTSocial

EMPA-KIDNEY: Empagliflozin significantly lowers the risk for kidney disease progression or CV death in patients with CKD



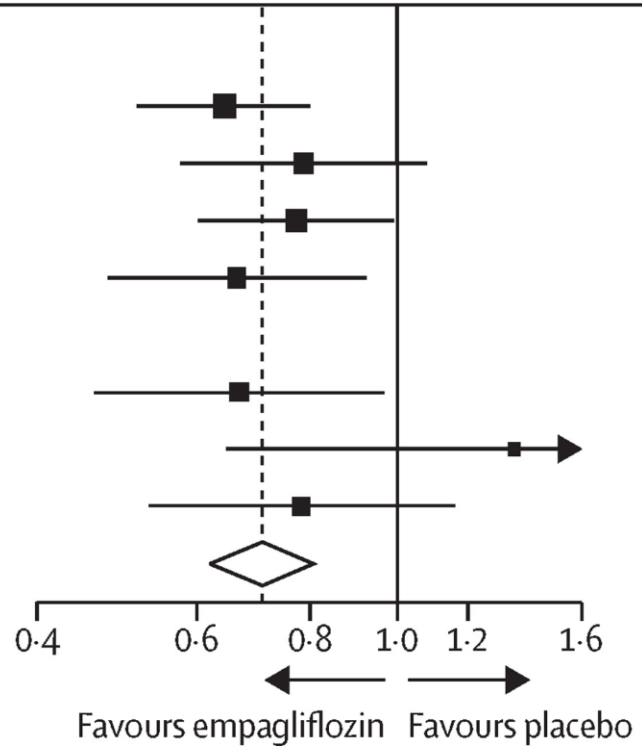
No. at Risk						
Empagliflozin	3304	3252	3163	2275	1538	624
Placebo	3305	3250	3129	2243	1496	592

<u>The primary outcome:</u>
a composite of kidney disease progression (ESKD, eGFR <10, sustained decline in eGFR of ≥40%, or a renal death) or CV death.

Herrington WG et al., NEJM 2022

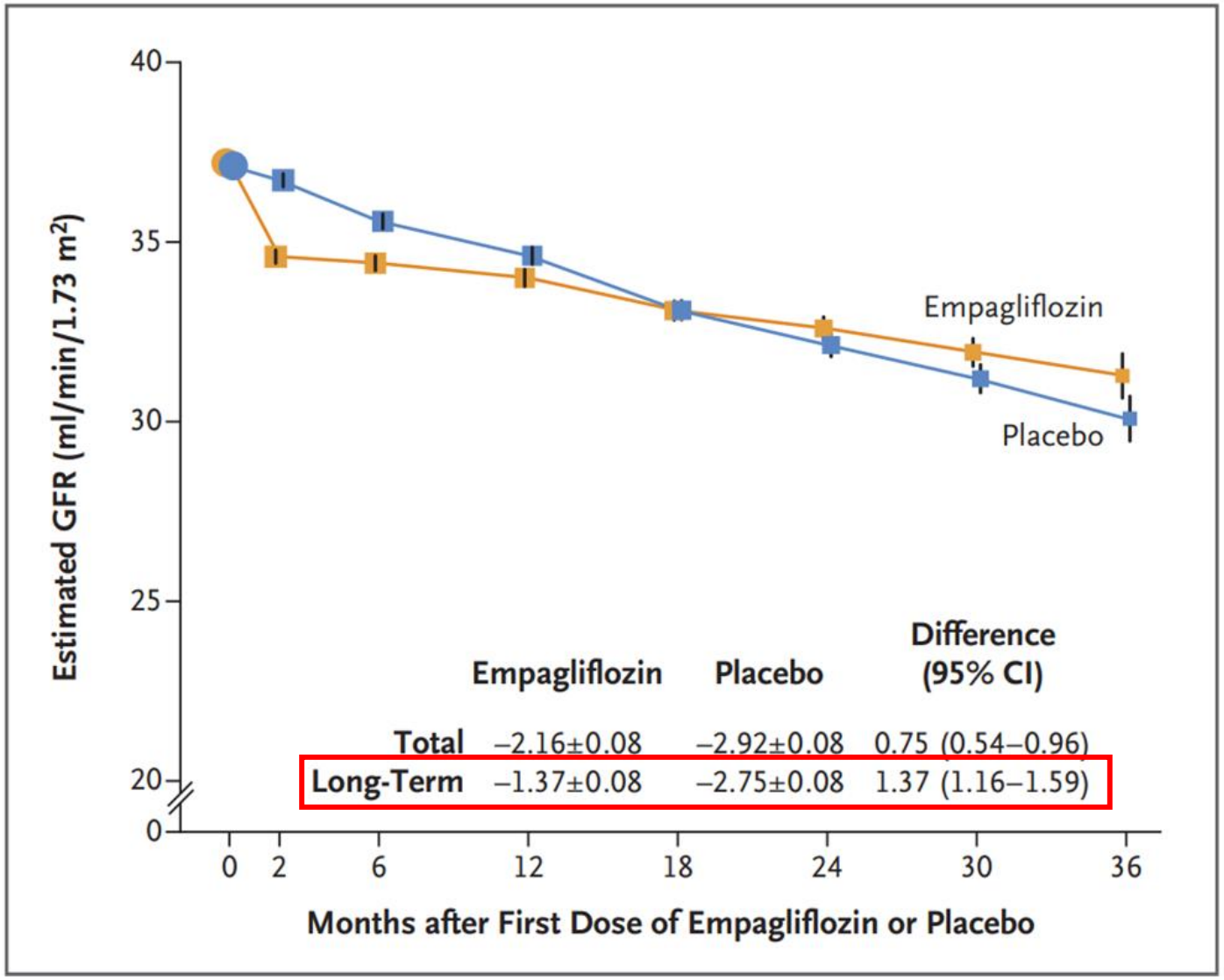
Impact of primary kidney disease on the effects of empagliflozin in patients with CKD: secondary analyses of the EMPA-KIDNEY trial

	Events/participants		Hazard ratio (95% CI)	$p_{heterogeneity}$
	Empagliflozin	Placebo		
Causes of kidney disease				0·62
Diabetic kidney disease	137/1032	189/1025	0·64 (0·52–0·80)	
Hypertensive or renovascular disease	72/706	87/739	0·79 (0·58–1·08)	
Glomerular disease	115/853	139/816	0·77 (0·60–0·99)	
Other disease or unknown	60/713	89/725	0·67 (0·48–0·92)	
Types of glomerular diseases				0·25
IgA nephropathy	51/413	67/404	0·67 (0·46–0·97)	
Focal segmental glomerulosclerosis	17/98	13/97	1·35 (0·65–2·81)	
Other glomerulonephritis	47/342	59/315	0·78 (0·53–1·16)	
All participants			**0·71 (0·62–0·81)**	



The EMPA-KIDNEY Collaborative Group, Lancet Diabetes Endocrinol. 2024;12:51

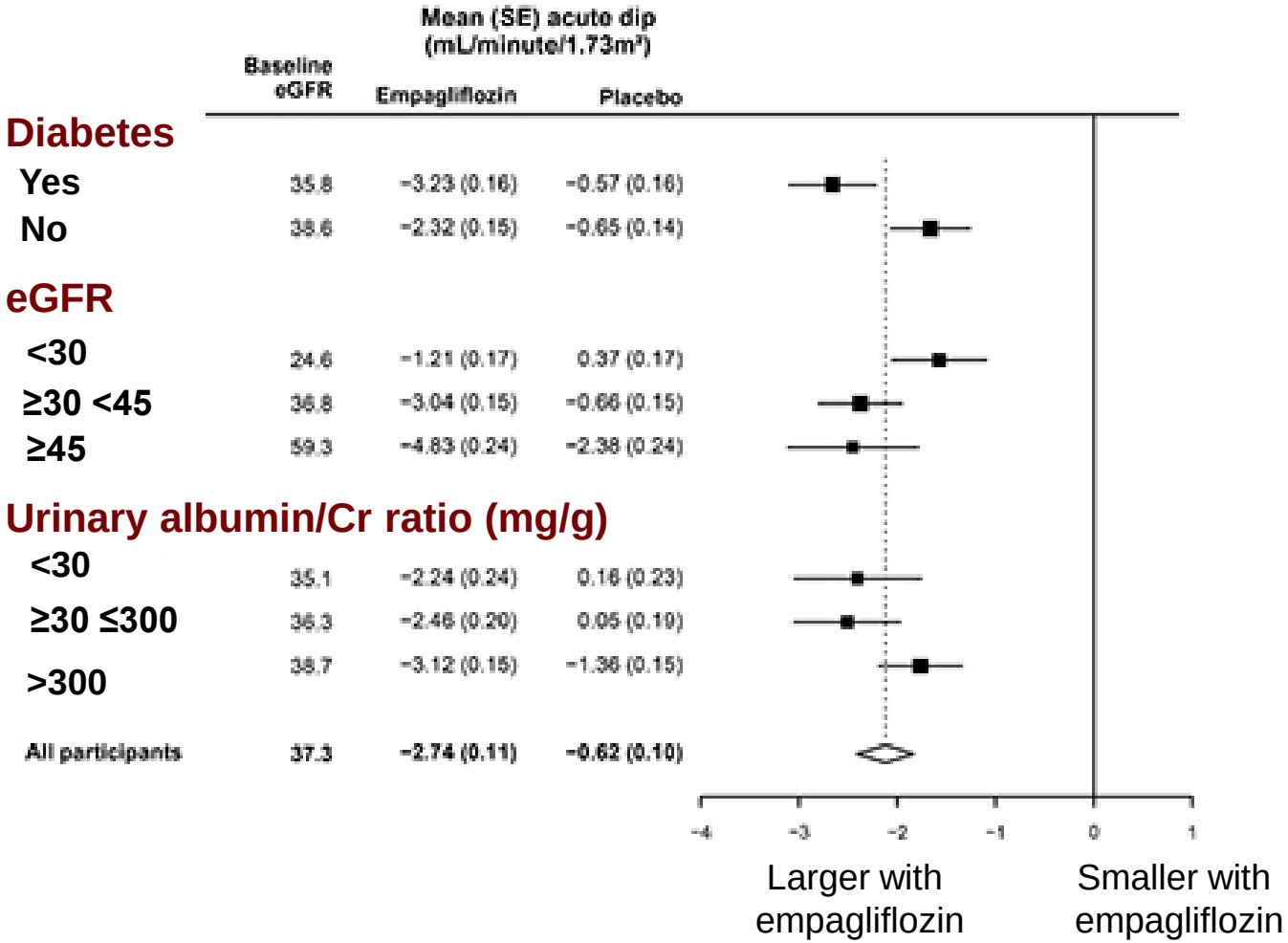
EMPA-KIDNEY: The effect of empagliflozin on eGFR



~50% reduction in chronic (2 month to final follow up) eGFR decline slope with empagliflozin

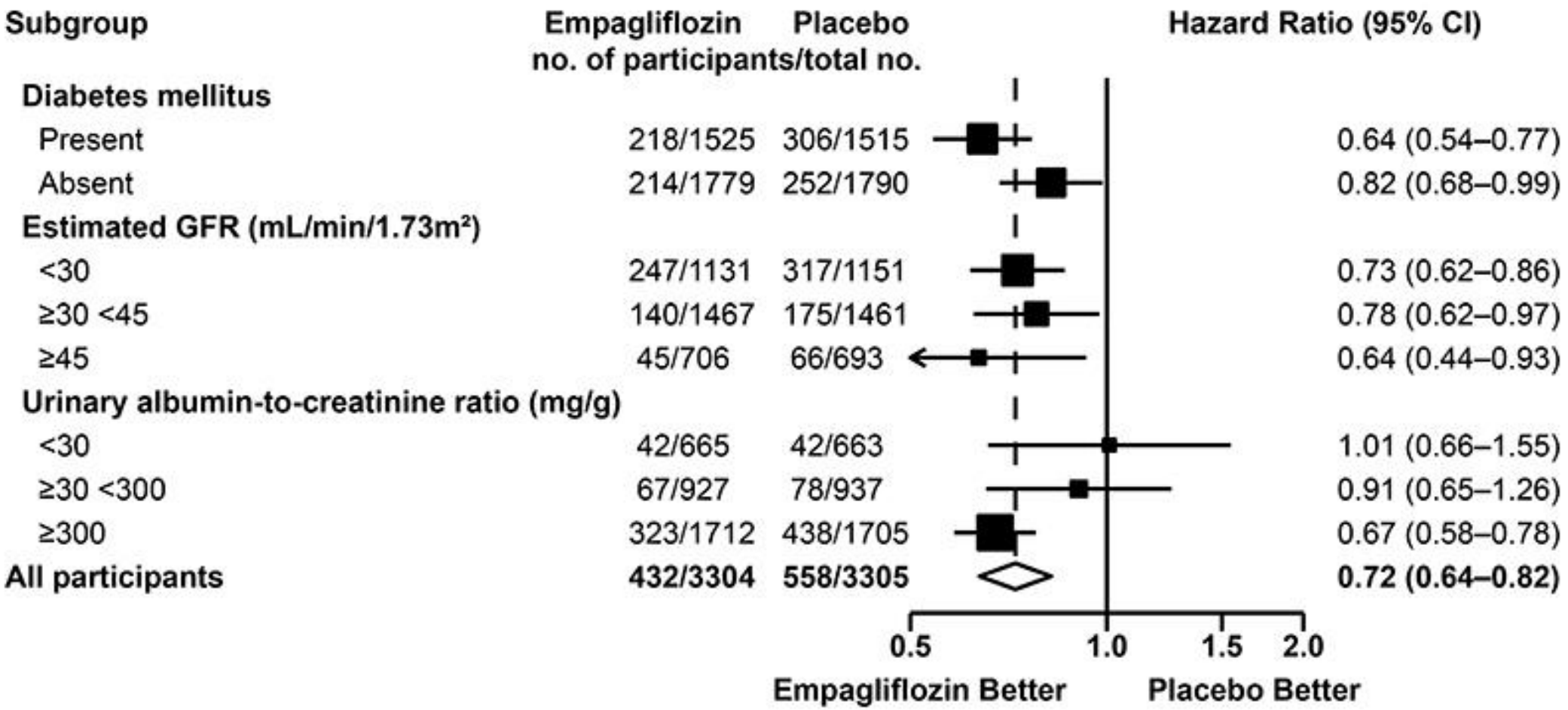
Herrington WG et al., NEJM 2022

EMPA-KIDNEY: Effect of empagliflozin on acute changes in eGFR, by key subgroups



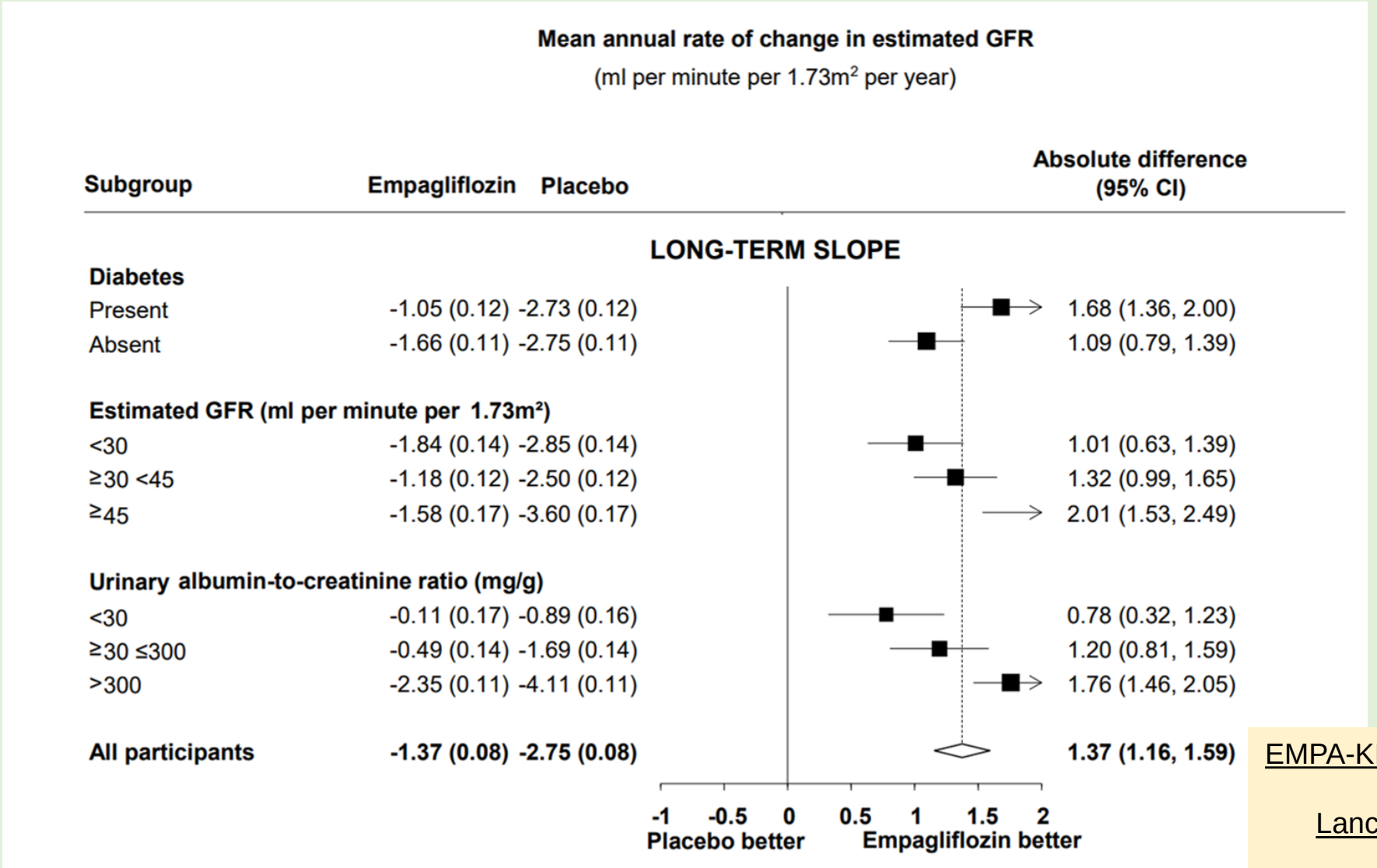
The EMPA-KIDNEY Collaborative Group, Lancet Diabetes Endocrinol. 2024;12: 39

The effect of empagliflozin on the primary outcome: *consistent across the prespecified subgroups but the proportional risk reduction may be larger in those with higher urinary ACR*



EMPA-KIDNEY, NEJM 2022

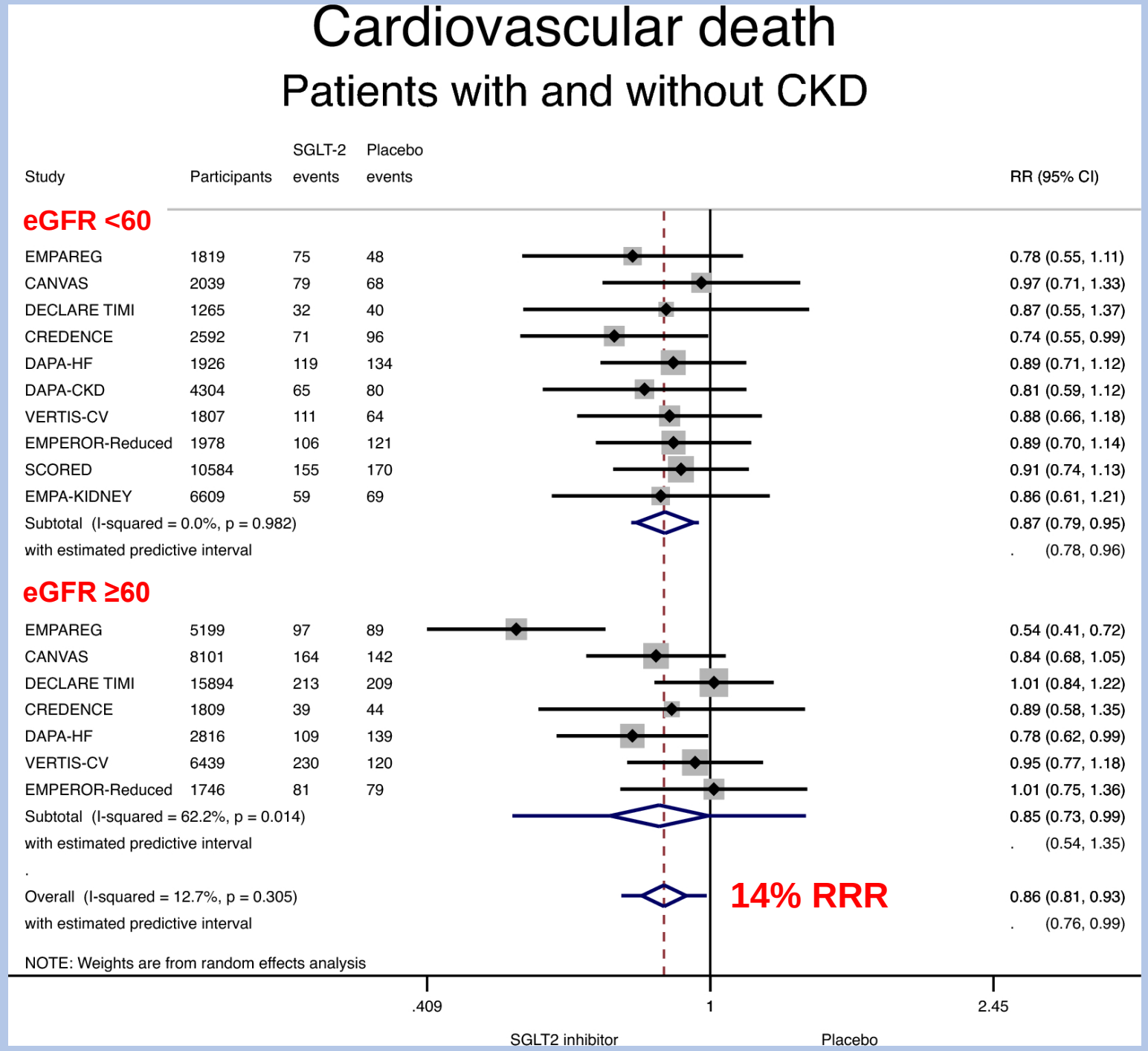
The effect of empagliflozin on chronic slope by diabetes, eGFR, and albuminuria subgroups



EMPA-KIDNEY Collaborative Group, NEJM 2022;
Lancet Diabetes Endocrinol. 2024;12: 39

Cardiovascular death

Patients with and without CKD

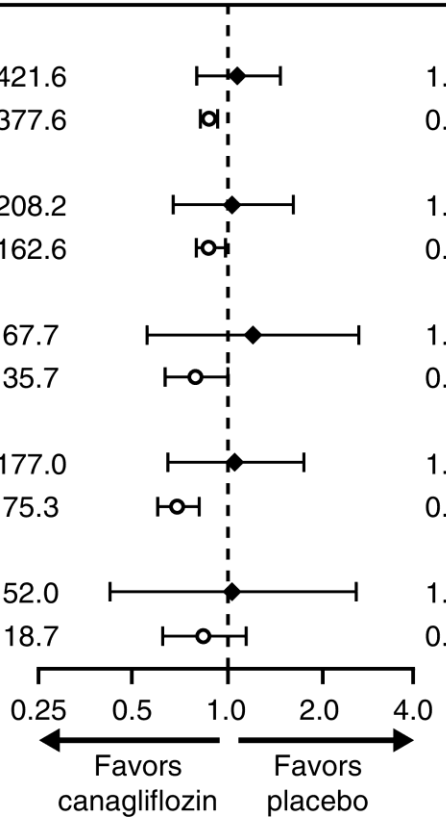


Mavrakanas TA et al., 2023

No difference in adverse events between those with eGFR <30 ml/min/1.73 m² and >30 ml/min/1.73 m²

(a subgroup analysis of CREDENCE)

	Number of participants with an event		Participants with an event per 1000 patient-years			*P*
	Canagliflozin	Placebo	Canagliflozin	Placebo	HR (95% CI)	interaction
Any AE						
eGFR <30 ml/min per 1.73 m²	77	81	435.0	421.6	1.08 (0.79, 1.47)	0.17
eGFR ≥30 ml/min per 1.73 m²	1706	1779	348.3	377.6	0.87 (0.82, 0.93)	
Any serious AE						
eGFR <30 ml/min per 1.73 m²	37	40	209.0	208.2	1.03 (0.66, 1.61)	0.50
eGFR ≥30 ml/min per 1.73 m²	700	766	142.9	162.6	0.87 (0.79, 0.97)	
Hyperkalemia						
eGFR <30 ml/min per 1.73 m²	13	13	73.4	67.7	1.20 (0.55, 2.63)	0.43
eGFR ≥30 ml/min per 1.73 m²	138	168	28.2	35.7	0.79 (0.63, 0.99)	
Any kidney-related AE						
eGFR <30 ml/min per 1.73 m²	29	33	175.1	177.0	1.06 (0.64, 1.75)	0.12
eGFR ≥30 ml/min per 1.73 m²	261	355	53.3	75.3	0.69 (0.59, 0.81)	
AKI						
eGFR <30 ml/min per 1.73 m²	9	10	50.8	52.0	1.04 (0.42, 2.55)	0.70
eGFR ≥30 ml/min per 1.73 m²	77	88	15.7	18.7	0.84 (0.62, 1.14)	



Bakris et al., Clin J Am Soc Nephrol. 2020; 15: 1705

Summary of CV outcomes with SGLT2i

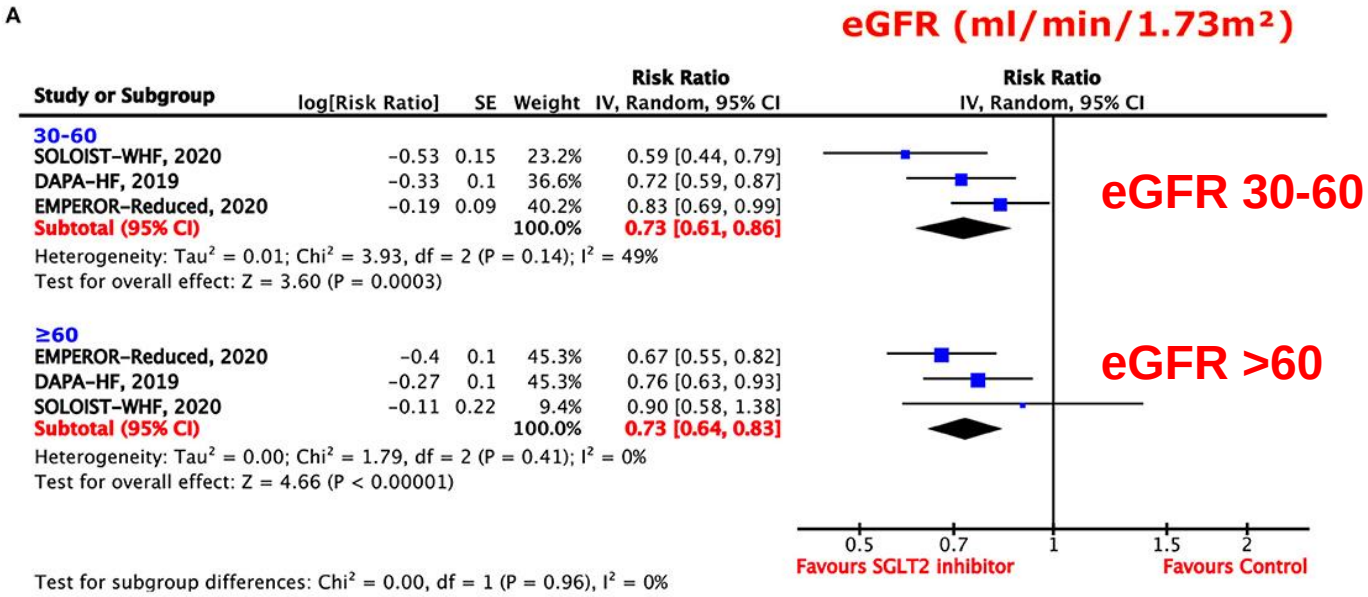
Summary of CV outcome, HF and renal trials published on SGLT2i drugs (shown as HR)

Renal endpoint: 50% decline in eGFR, ESKD, renal or CV death

	CKD outcome trial		CV Outcome trials				HF outcome trials		
Trial	EMPA-KIDNEY	DAPA-CKD	EMPA-REG	CANVAS	DECLARE-TIMI 58	VERTIS CV	DAPA HF	EMPEROR-REDUCED	EMPEROR-PRESERVED
Drug	Empa	Dapa	Empa	Cana	Dapa	Ertugliflozin	Dapa	Empa	Empa
N	6609	4304	7020	10142	17160	8238	4744	3730	5988
Age	64	62	63	63	64	64	66	67	72
% of DM	46	67	100	100	100	100	42	50	49
eGFR	**37**	**43**	**74**	**77**	**85**	**76**	**66**	**62**	**61**
% CVD	27	37	100	72	41	100	-	-	-
% HF	-	11	10	14	10	24	100	100	100
Median f/u duration	2.0 yrs	2.4 yrs	3.1 yrs	2.4 yrs	4.2 yrs	3.0 yrs	18.2 mo	16 mo	26 mo
% RAASi	85	88	81	80	81	81	83	88	81
Hosp for HF	-	-	**0.65**	**0.67**	**0.73**	**0.70**	**0.70**	**0.69**	**0.71**
CV death	0.84	0.81	0.62	0.87	0.98	0.92	0.82	0.92	0.91
All-cause mortality	0.87	0.69	0.68	0.87	0.93	0.93	0.83	0.92	1.00
Renal endpoint	**0.71**	**0.61**	**0.54**	**0.60**	**0.53**	**0.81**	**0.71**	**0.50**	**–1.25 vs. –2.62 ml/min**
ESRD	**0.73**	**0.64**	**0.45**	-	-	-	-	-	-

Subgroup analyes: HHF + CV-MORTALITY

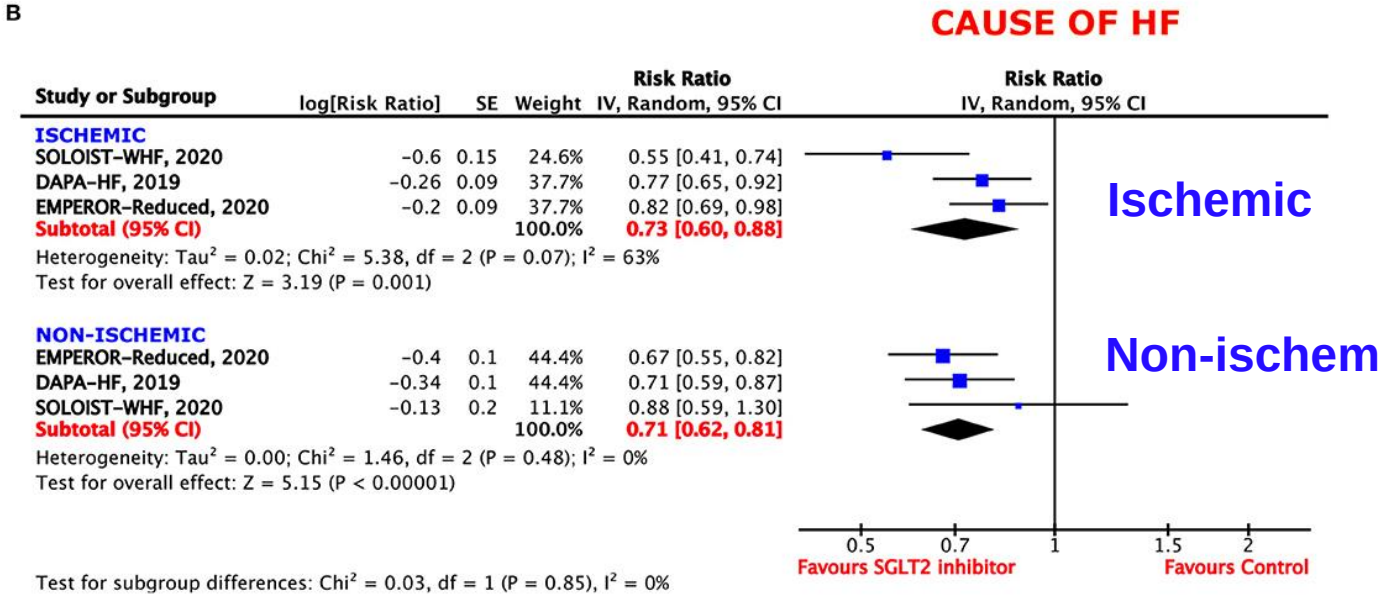
A



eGFR 30-60

eGFR >60

B



Ischemic

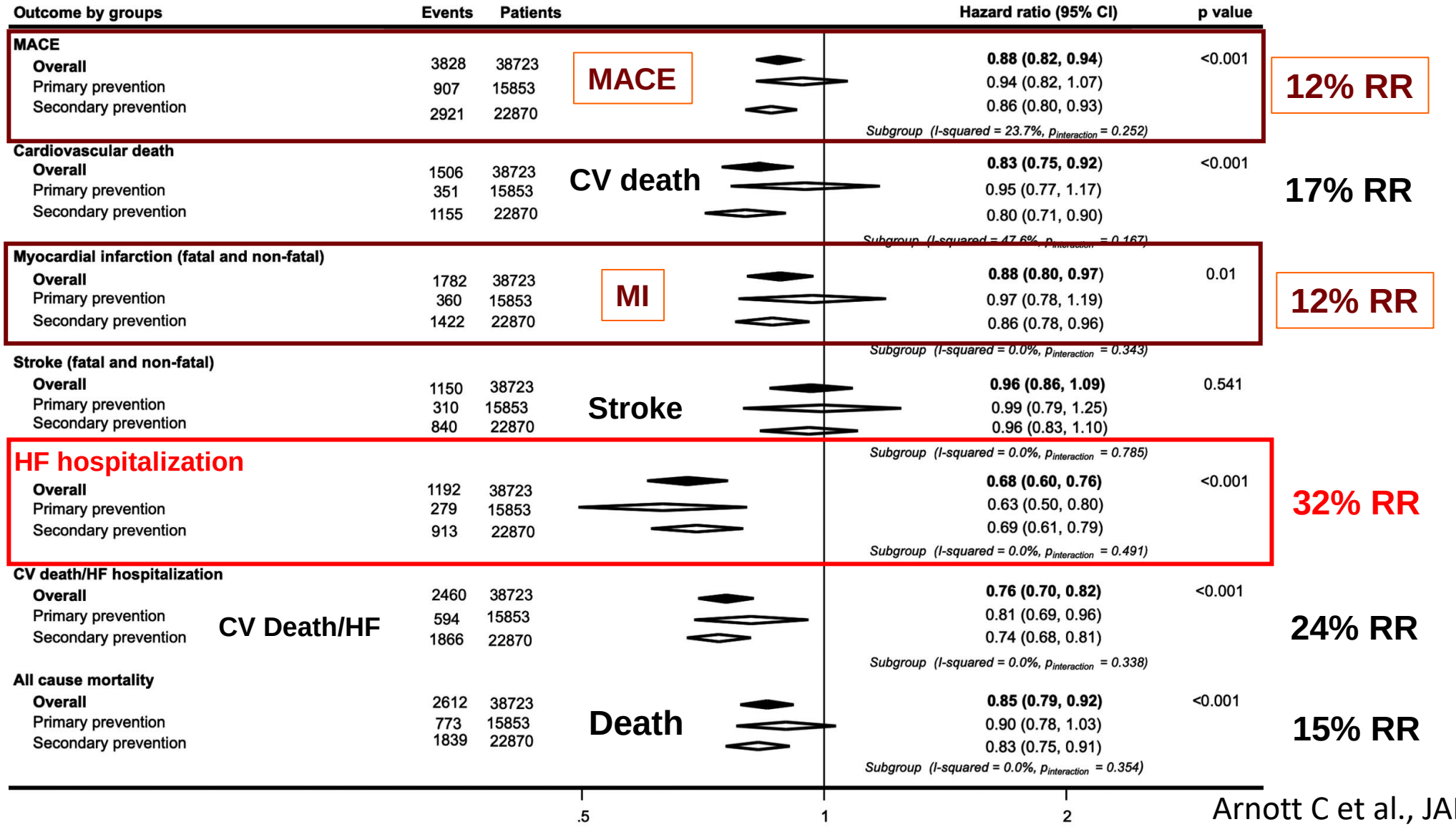
Non-ischemic

CV Outcome in Patients Treated With SGLT2 Inhibitors for Heart Failure: A Meta-Analysis

SGLT2i provides **a consistent ~30% reduction in HF hospitalization** regardless of baseline eGFR or the cause of HF.

Gager GM et al., Front. Cardiovasc. Med., 2021

Effects of SGLT2 inhibition on death and cause-specific CV events for patients with and without CV disease at baseline



Arnott C et al., JAHA, 2020

Effect of SGLT-2 inhibitors on arrhythmia events: insight from a secondary analysis of > 88,000 patients

Effect of SGLT2i on Arrhythmias?

- To date no RCTs
- Studies reported inconsistent results

Baseline characteristics:

- Included studies: 33 RCTs
- Sample size: 88098
- Age: 64.9±9.4 yrs
- Male: 63.0%
- LVEF: 39.2±14.6%
- eGFR: 67.3±23.6 ml/min/1.73m²

Strengths of our study:

- Large sample size
- Subgroup/regression/sensitivity analyses, TSA
- Statistical power

Pooled analysis

14% RRR in AF

Atrial arrhythmias

AF: RR: 0.88(0.78,1.00)

AFL: RR: 0.78(0.60,1.03)

AF/AFL: RR: 0.86(0.77,0.96)

Ventricular arrhythmias

VF: RR: 1.05(0.70,1.59)

VT: RR: 0.99(0.80,1.22)

VES: RR: 1.36(0.67,2.76)

Sudden cardiac death

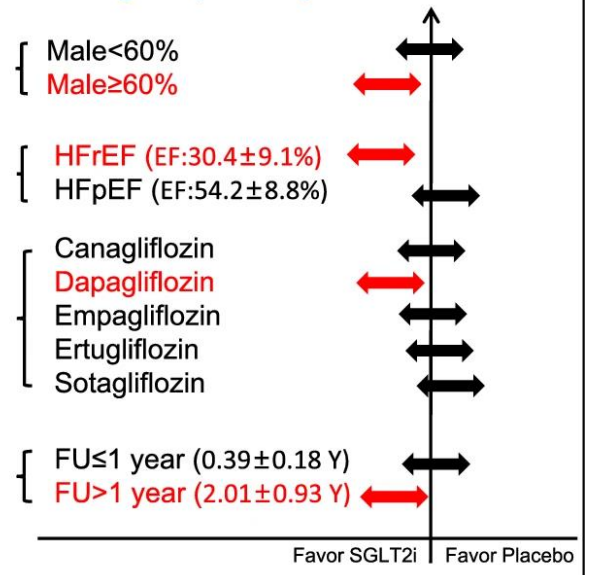
33% RRR in HF

SCD: RR: 0.85(0.63,1.14)

SCD in HF only: RR: 0.67(0.44-1.01)

Favor SGLT2i | Favor Placebo

Subgroup analyses for AF

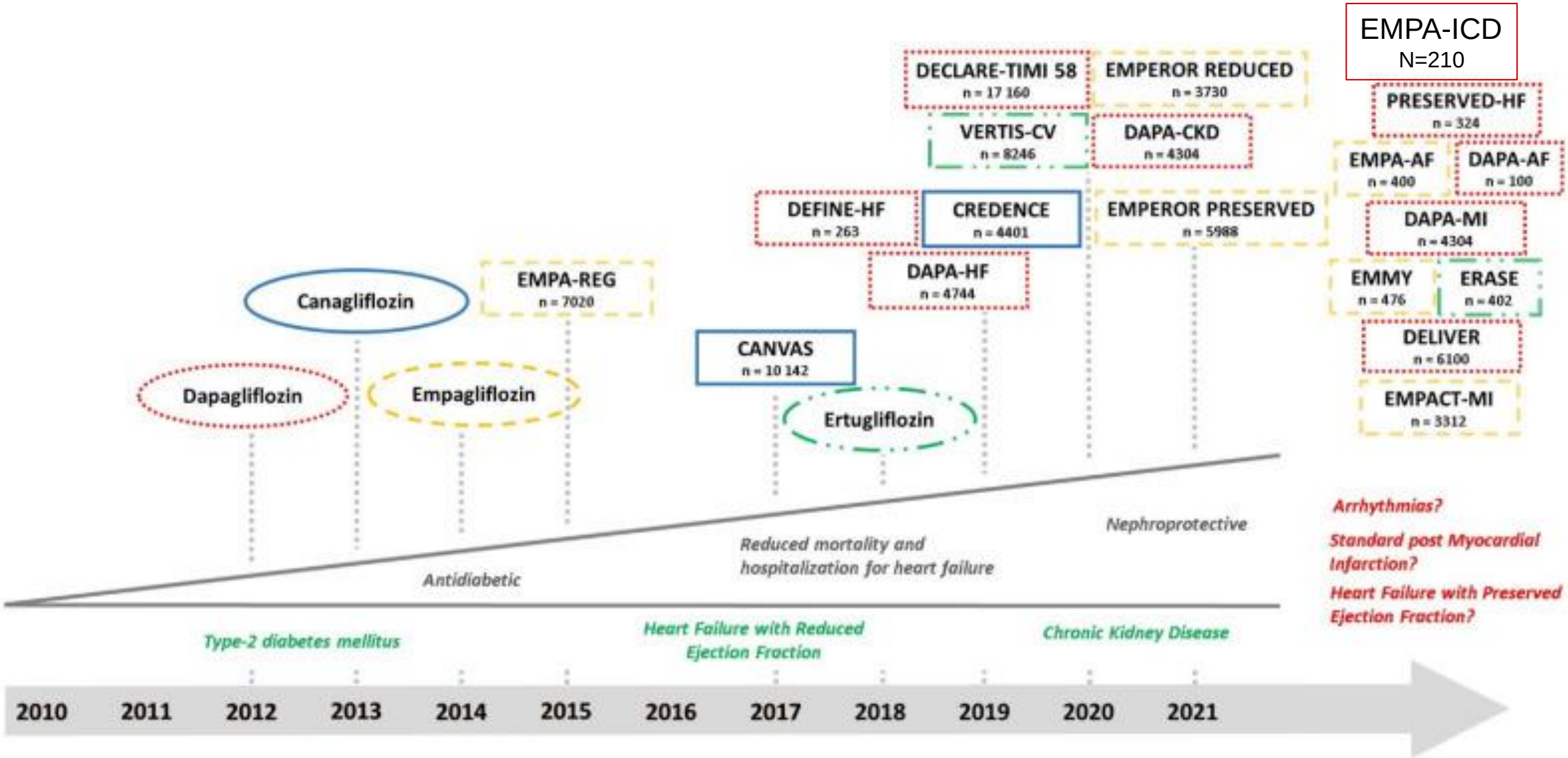


Meta-regression for AF: Gender & LVEF

Variables	Effect of SGLT2i on AF			
	Coef.	Z value	P value	Log RR 95%CI
Male, %	-0.021	-2.34	0.019	-0.039 to -0.0035
LVEF, %	0.024	2.62	0.009	0.006 to 0.04

Liao J et al., Cardiovasc Diabetology 2024

History, completed, and ongoing clinical trials of the SGLT2is

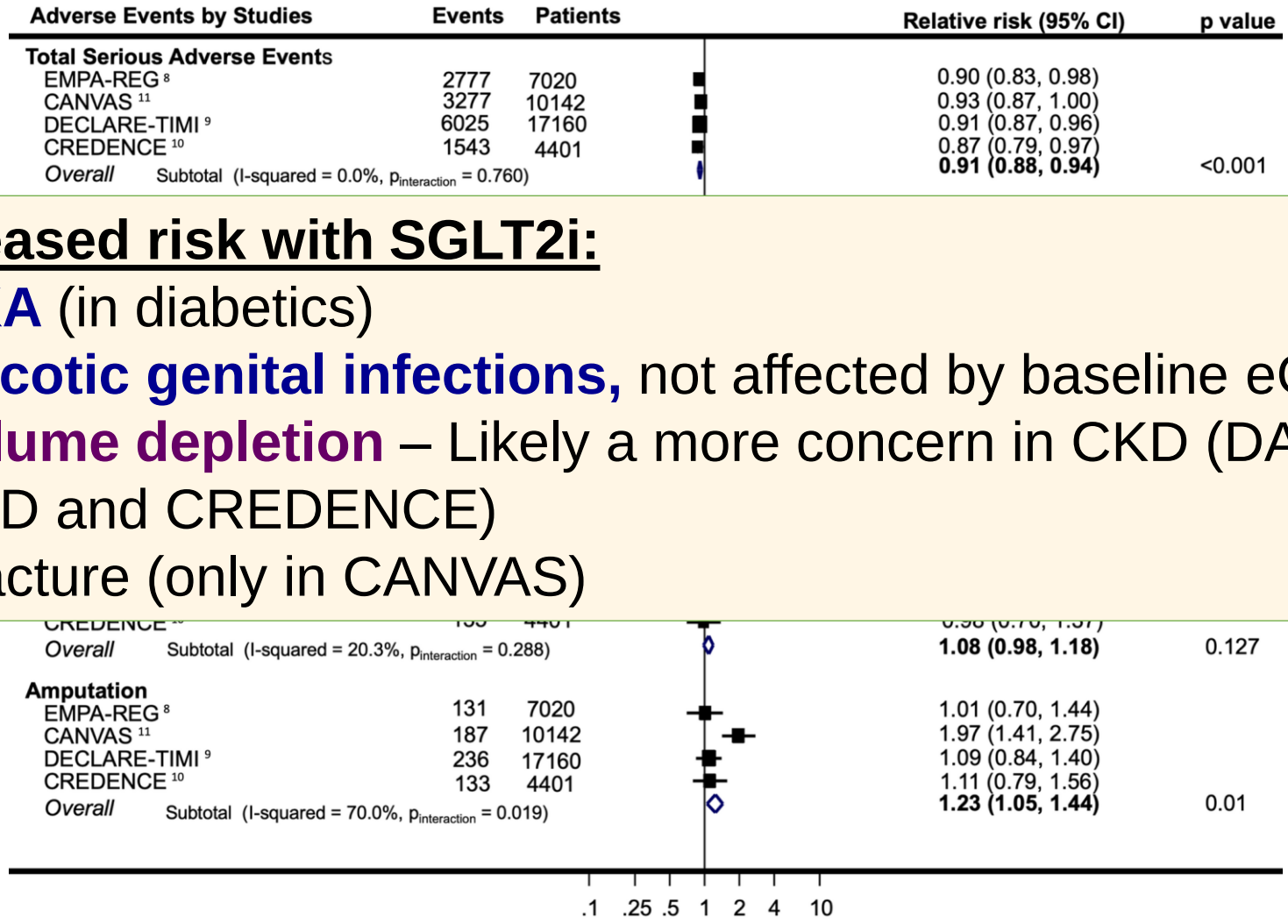


Kolesnik E et al., Int J Mol Sci. 2022 Feb; 23(3): 1678

Summary: SGLT2i

- Consistent kidney and HF benefits (both HFrEF and HFpEF) across all RCTs
- Kidney benefit (eGFR slope decline rate) takes ~12 months to become evident, where as the HF benefit is seen almost immediately (1-3 months).
- Renal composite endpoint: 29-39% RRR
  - eGFR dip (up to 30% drop from baseline) in acute phase (first 4-8 weeks) does not alter benefit
  - **Lack of proteinuria should NOT preclude SGLT2i therapy.**
- Greater renal benefit in those with greater degree of proteinuria and CKD.
- HF hospitalization RRR by ~30% in HF trials
- SGLT2is confer 12% reduction in ASCVD/MACE and reduce sudden death.
- The benefits are regardless of baseline ASCVD/HF status.

Effects of SGLT2 Inhibition on SAEs



Increased risk with SGLT2i:

- **DKA** (in diabetics)
- **Mycotic genital infections,** not affected by baseline eGFR
- **Volume depletion** – Likely a more concern in CKD (DAPA-CKD and CREDENCE)
- Fracture (only in CANVAS)

Fixed effect models with inverse variance weighting. P values have not been adjusted for multiple comparisons.

Arnott et al. JAHA 2020

General strategy for prescribing SGLT2i

- **Strongly consider initiation in anyone with:**
  - CKD (eGFR <60), particularly if albuminuria >30 mg/g
  - History of HF or risk for HF regardless of proteinuria amount (both HFrEF or HFpEF),
  - Diabetics with or without proteinuria
  - Prediabetics with any proteinuria
- **Avoid initiation of antihypertensives or diuretics or upward dose titration or diuretics at the same time as starting SGLT2i.**
- **If Cr increase ≥25%, hold the drug and repeat Cr in 1 week and rechallenge when stable.**
- **<u>HOLD</u> for:**

  Pregnancy
  DKA – follow serum ketone levels
  Fournier's gangrene
  Acute illness/perioperative period

Who may have higher risk with SGLT2i therapy

- T2D with history of DKA
- Frequent genital tract infection
- Patients with history of Fournier’s gangrene
- Patients with obstructive urinary physiology
- Polycystic kidney disease
- T1DM

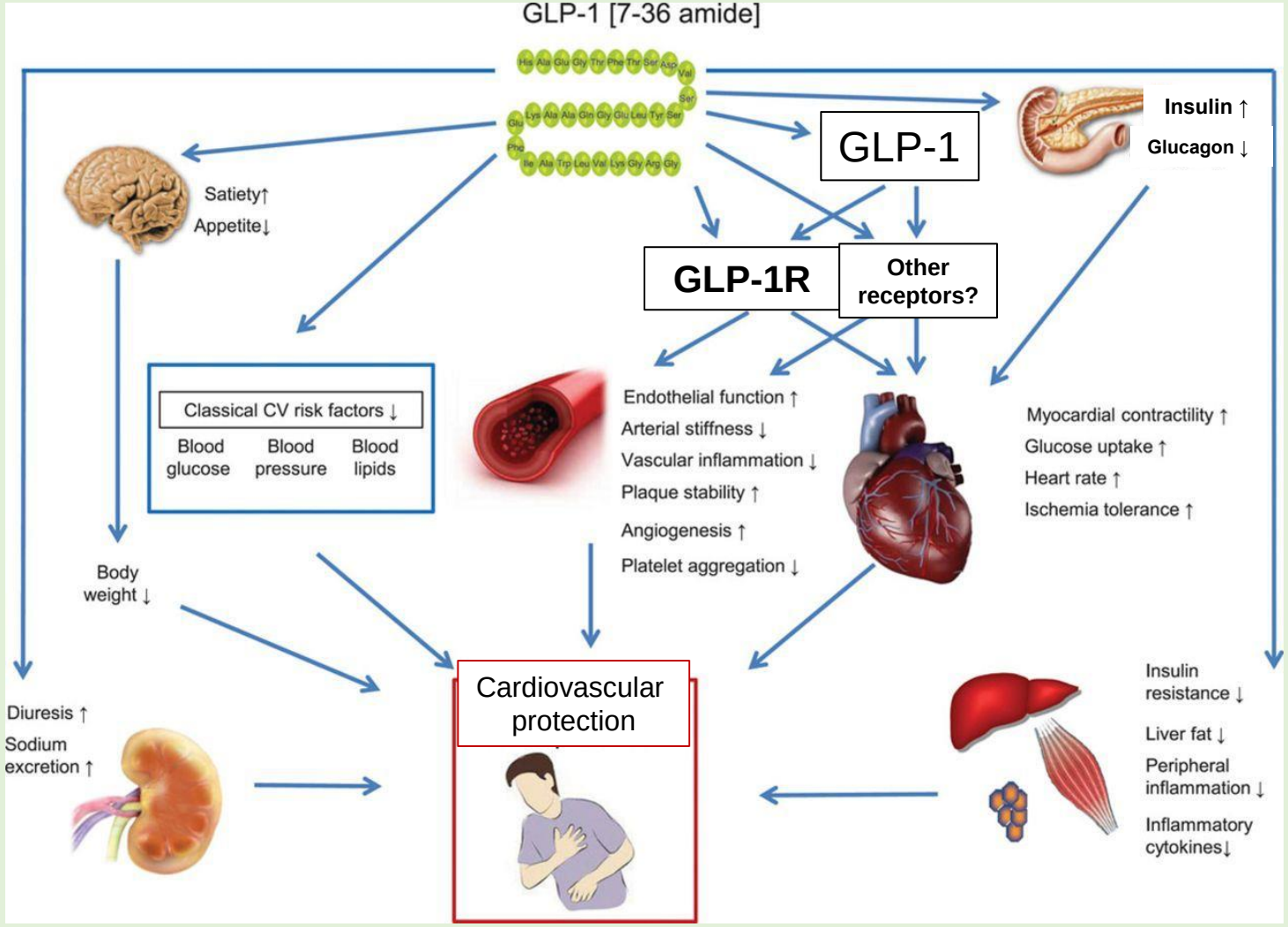
CV and kidney effects of glucagon-like peptide-1 receptor agonists (GLP-1RA)

Pleiotropic effects of GLP-1 or GLP-1R agonists

Glucagon-like peptide-1 (GLP-1):

- A peptide hormone produced in the intestine in response to meal intake.
- Enhances insulin secretion and reduces glucagon secretion, thus limiting hepatic glucose output.
- GLP-1 receptor (GLP-1R) is widely expressed in a variety of tissues (gut, pancreas, hypothalamus, CV system, kidney).
- Rapidly degraded by dipeptidyl peptidase IV (DPP-IV).
- GLP-1 receptor agonists prolong the effects of GLP-1.

Potential mechanisms underlying benefits of GLP-1

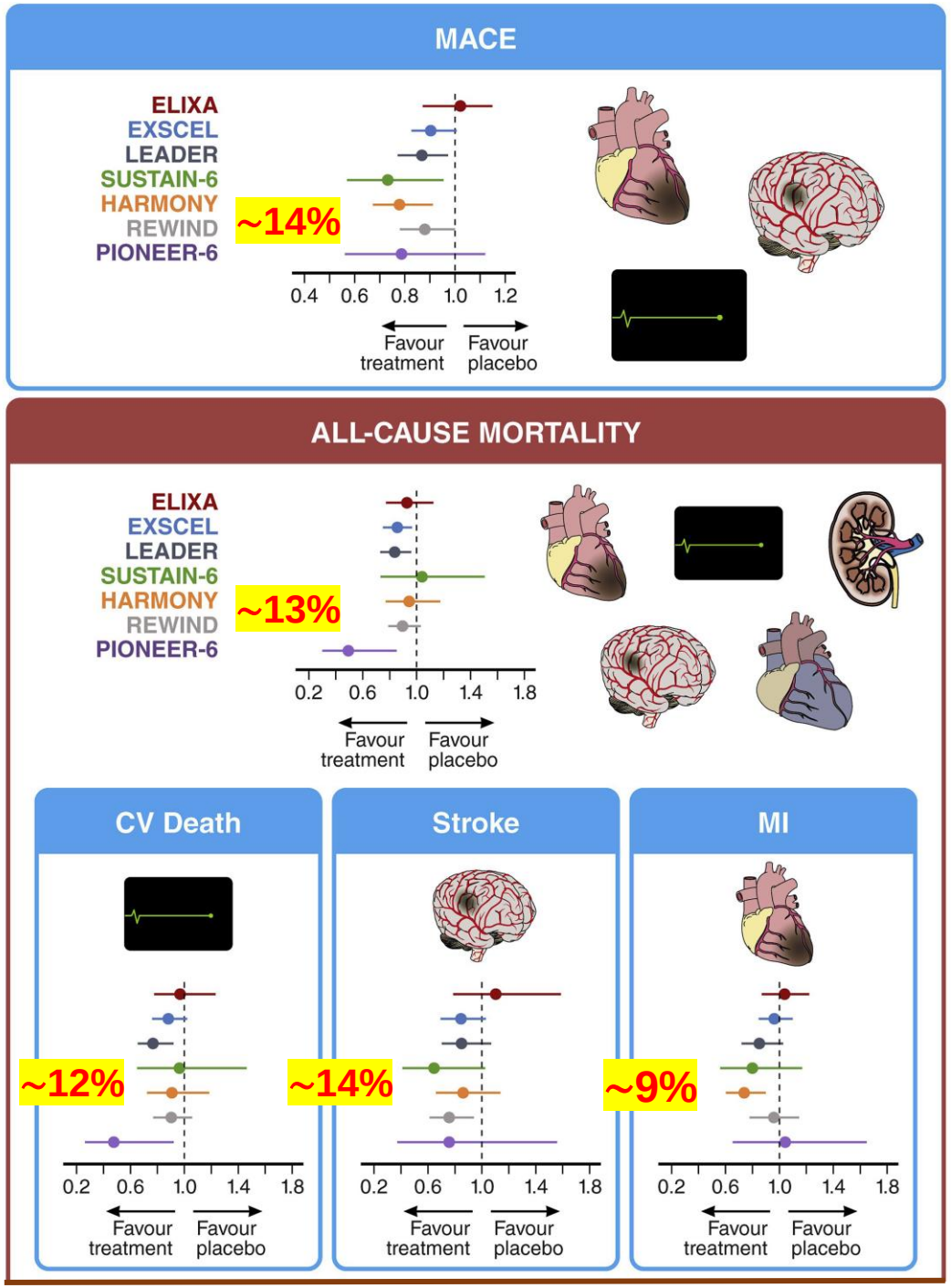


Adopted from Nauck et al., Circulation 2017, 136: 849

Summary of head-to-head trial data for GLP-1 receptor agonists

Drug	Peptide base	Within class comparability of A1c lowering efficacy	Within class comparability on weight	Within class comparability of GI adverse effects
Short-acting				
Exenatide	*Exendin-4*	*Low*	*Low*	*Highest*
Lixisenatide	*Exendin-4*	*Low*	*Low*	*Intermediate*
Long-acting				
Exenatide XR	*Exendin-4*	*Intermediate*	*Low*	*Low*
Liraglutide	Human GLP-1	High	High	Intermediate
Dulaglutide	Human GLP-1	High	Intermediate	Intermediate/high
Semaglutide (injection)	Human GLP-1	Highest	Highest	High
Semaglutide (oral)	Human GLP-1	High/Highest	Highest	Intermediate/high

Trujillo JM et al., Ther Adv Endocrinol Metab. 2021



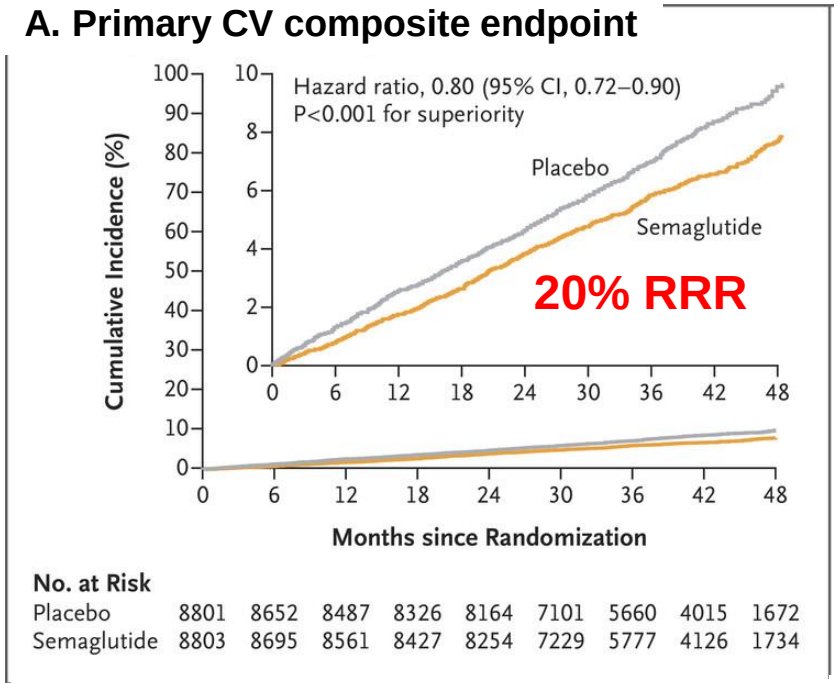
GLP-1RA have moderate benefits on MACE and CV mortality in T2DM

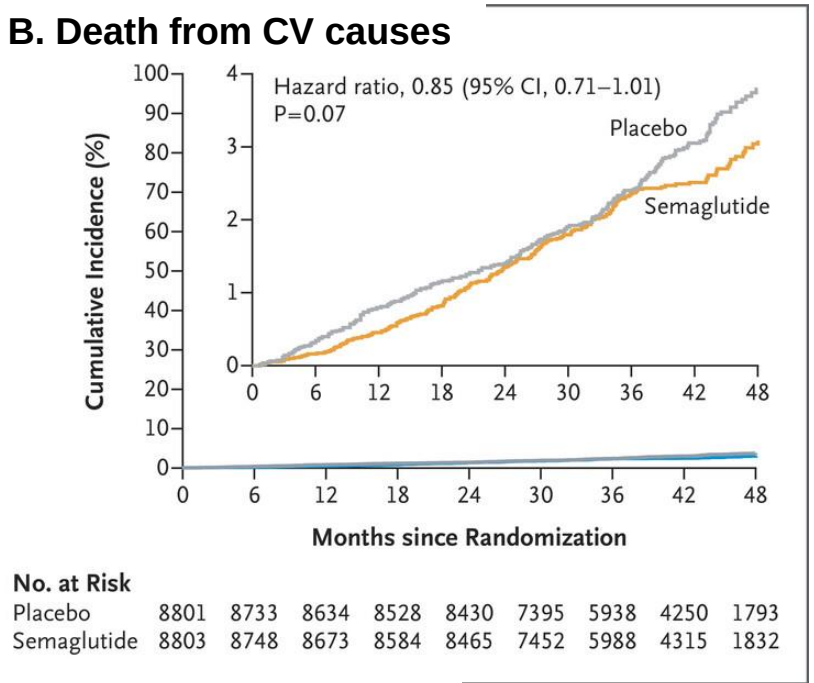
Primary outcome:

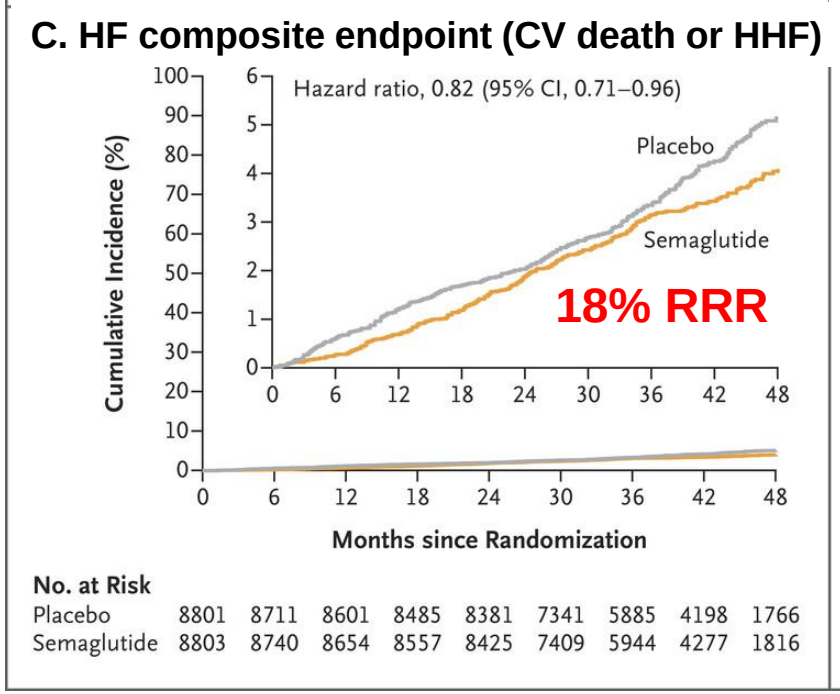
- **3-point MACE -** CV death, nonfatal MI and nonfatal stroke
- **4-point MACE** also included hospitalization for unstable angina for the ELIXA trial only

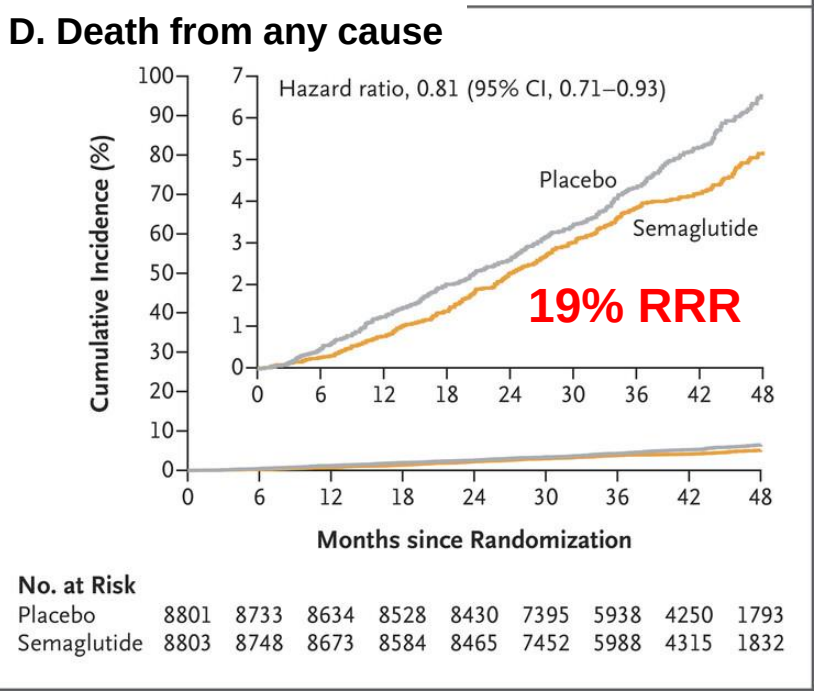
Varin EM et al., Can J Diabetes 2019, 44:68

GLP-1RA for CV protection in non-diabetic patients?









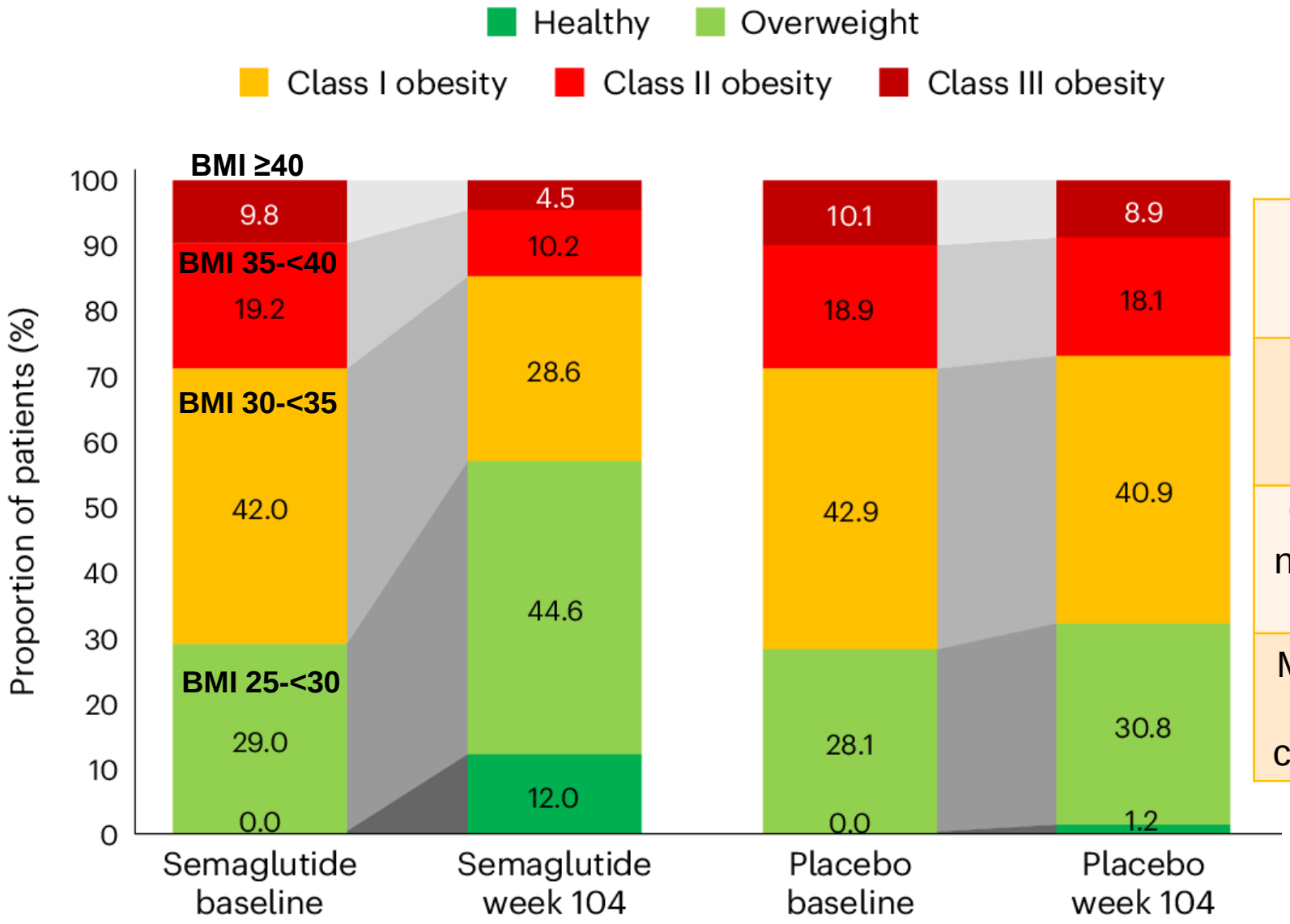
SELECT Trial

- A RCT of 17,604 **non-diabetic pts**
- ≥45 years of age
- preexisting CV disease
- BMI ≥27
- randomly assigned in a 1:1 ratio to receive once-weekly SQ semaglutide (2.4 mg) or placebo.
- A mean f/u pf 40 months
- 17% of semaglutide group discontinued the drug vs 8% in placebo

- **The primary outcome:** a composite of CV death, nonfatal MI, or nonfatal stroke.

Lincoff AM et al., NEJM 2023;389:2221

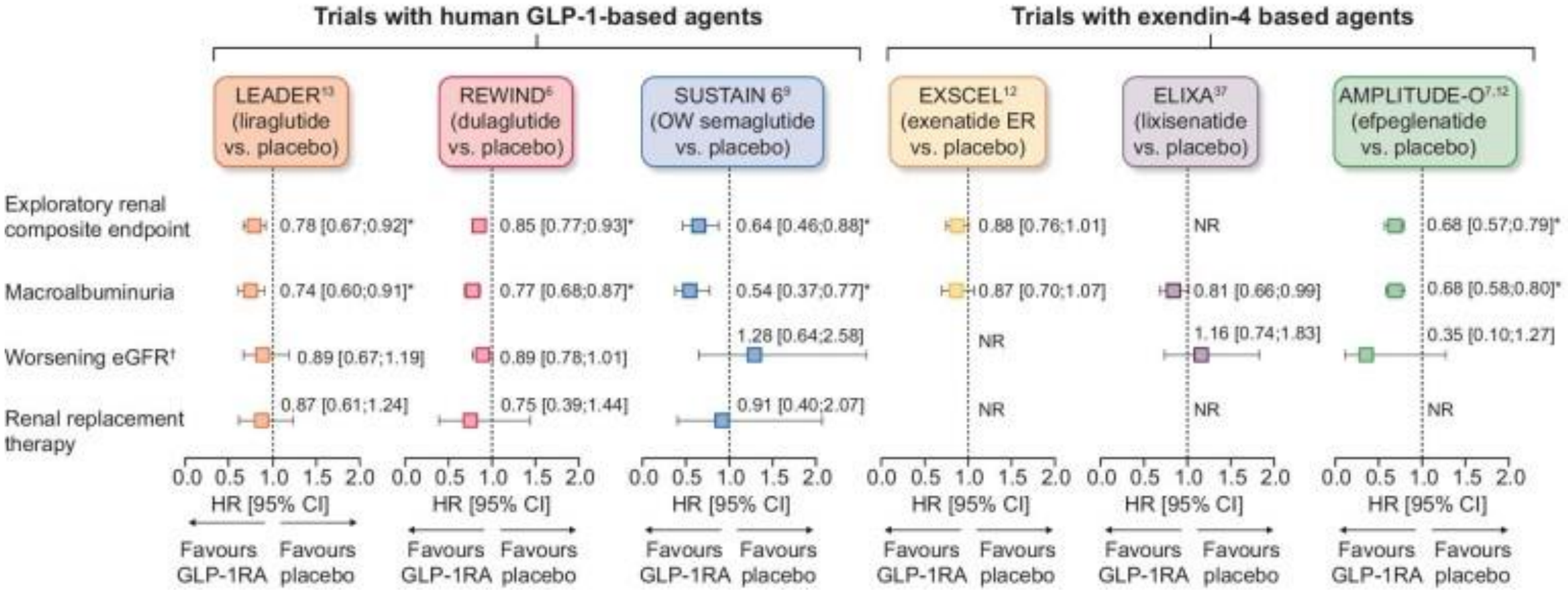
SELECT trial: Change in BMI category between baseline and week 104



	Semaglutide	placebo
Mean body weight change (%)	**-9.4**	+0.9
% achieving normal weight status	**12**	1.2
Mean change in waist circumference	**-7.7 cm**	-1.3 cm

Ryan DH et al., Nature Medicine 2024

The rationale for FLOW trial I: Exploratory kidney analyses from GLP-1RA CV outcomes trials: *kidney benefit driven by reduction of albuminuria*



Rossing P et al., NDT 2023

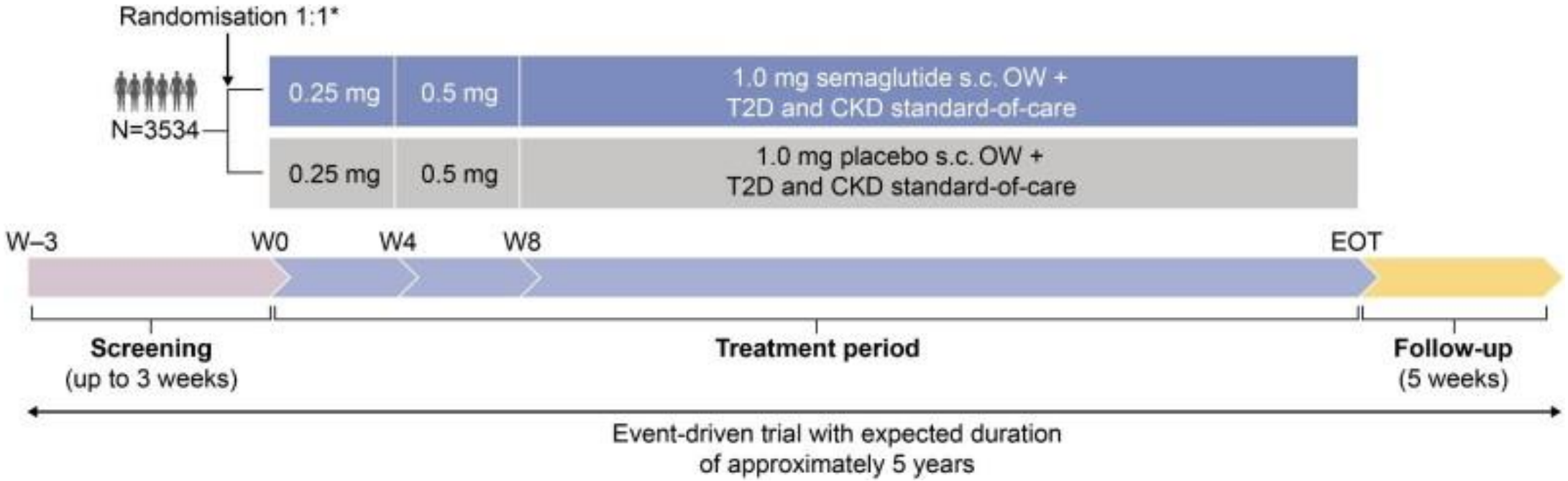
FLOW trial rationale I

- Evidence has emerged of the potential kidney-protective effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in people with type 2 diabetes (T2D).
- Data mostly derived from CV outcome or glycemic control trials, NOT CKD outcome trials.
- Reduction of CKD progression by GLP-1RAs is yet to be confirmed and requires dedicated trials of kidney outcomes with GLP-1RAs.
- **FLOW (NCT03819153) is a dedicated kidney outcomes** trial to assess semaglutide, a once-weekly GLP-1RA, in ***diabetic patients with CKD*** **at high risk of kidney disease progression.**

FLOW trial design

- Participants recruited from 28 countries with T2DM, A1c ≤10%, & CKD
- CKD defined by: eGFR ≥50-≤75 AND UACR >300 -<5000 **OR** eGFR ≥25 and <50 with UACR >100-<5000 mg/g
- **Primary outcome:** time to a composite endtpoint of kidney failure (dialysis/tx or eGFR <15), renal/CV death, ≥50% reduction in eGFR

24% RRR of primary endpoint with semaglutide vs placebo



Rossing P et al., NDT 2023

Use of GLP-1 RA in CKD

- Growing evidence suggest that GLP-1 receptor agonists can be safe in advanced CKD, including ESKD.

LONG-ACTING AGENTS

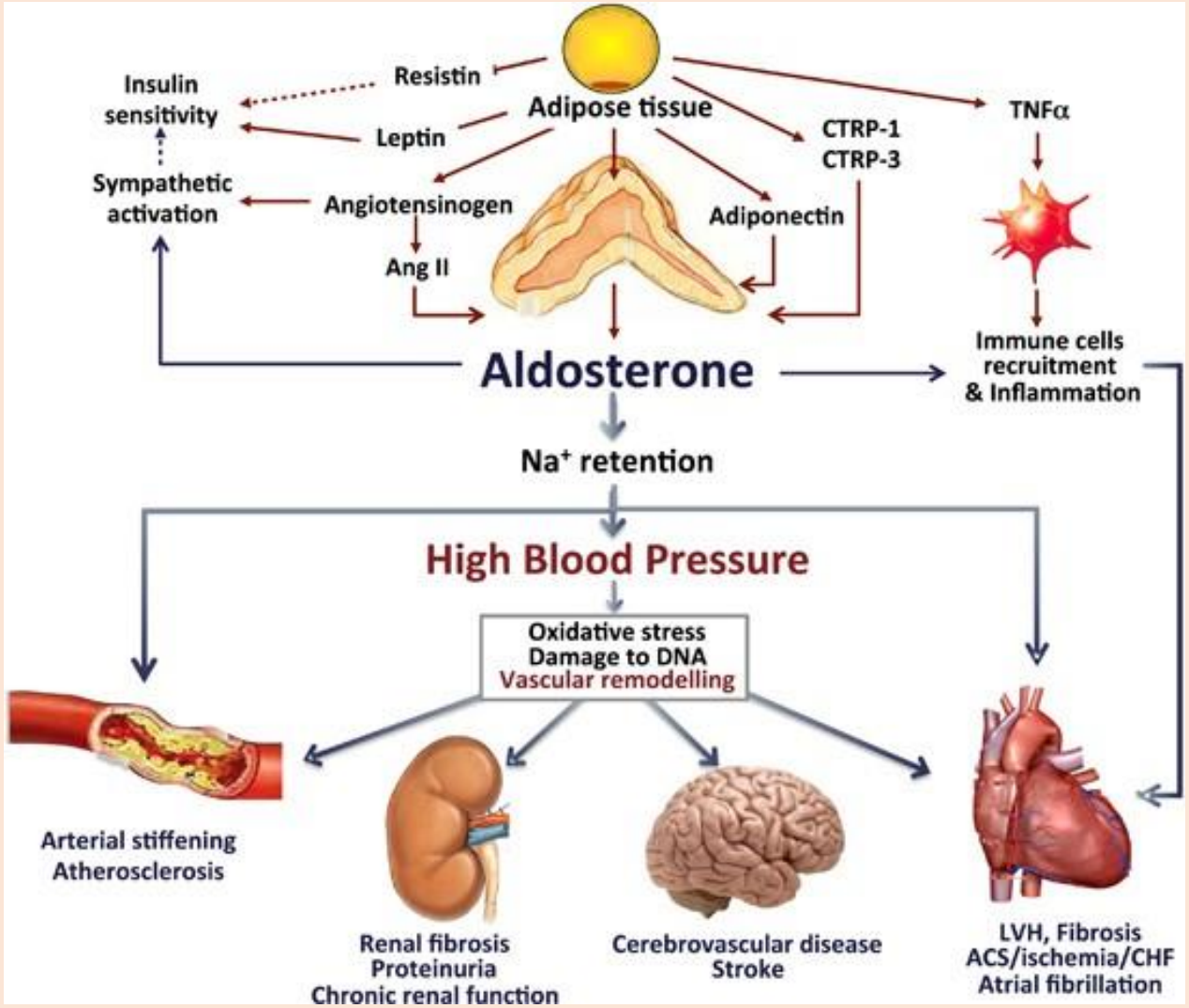
- **Liraglutide (Victoza), dulaglutide (Trulicity), and semaglutide (Ozempic):**
  - Kidney and CV protective benefits as well as *documented safety* in patients with CKD 4 (eGFR 15-29 mL/min/1.73 m^2) and thus preferred agents for CKD 4.
  - **Limited safety data in dialysis patients**
  - Use in CKD 4 → need to monitor for signs and symptoms of dehydration due to nausea or satiety to reduce the risk of pre-renal AKI
  - Not excreted by the kidneys → dose reductions not necessary in CKD
- **Exenatide once weekly** – AVOID in patients with eGFR <45 mL/min/1.73 m^2.

SHORT-ACTING AGENTS – avoid in eGFR <30

- **Lixisenatide:**
  - The clinical outcomes are not affected by mild (eGFR 60 to 89 mL/min/1.73 m^2) or moderate (eGFR 30 to 59 mL/min/1.73 m^2) CKD.
  - Paucity of data in patients with eGFR 15 to 29 mL/min/1.73 m^2.
  - Lixisenatide is presumed to be eliminated by the kidneys with increased exposure in CKD.
  - Need to monitor closely for gastrointestinal adverse effects, which may increase risk of AKI.

Cardiorenal effects of mineralocorticoid receptor antagonists (MRA)

The deleterious effects of aldosterone/MR activation in heart and kidneys



Rossi and Seccia, 2013

Direct deleterious effects of aldosterone in the heart include development of:

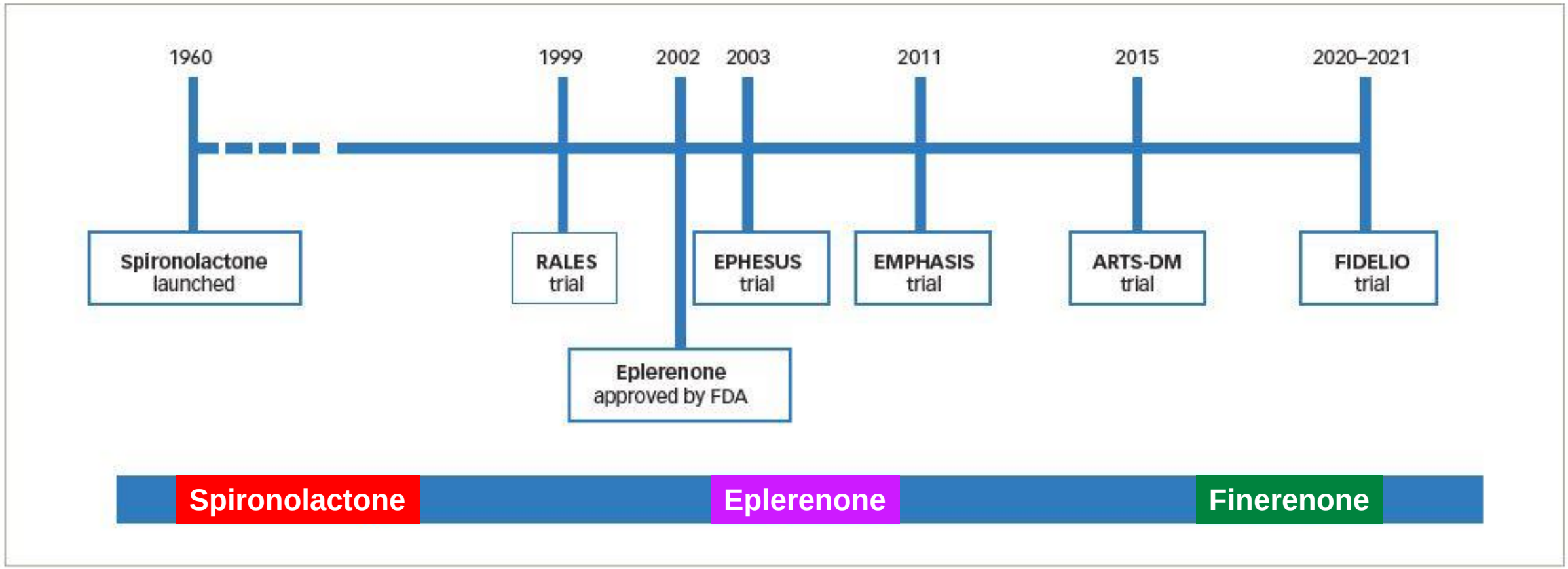
- myocardial hypertrophy
- ventricular remodeling
- proarrhythmogenic effects
- myocardial ischemia
- reduced coronary blood flow
- myocardial injury

The effects of aldosterone on the kidneys include:

- glomerular hypertrophy
- glomerulosclerosis
- proteinuria
- reduced renal blood flow
- renal injury

Bauersachs J et al., Hypertension 2015;65:257

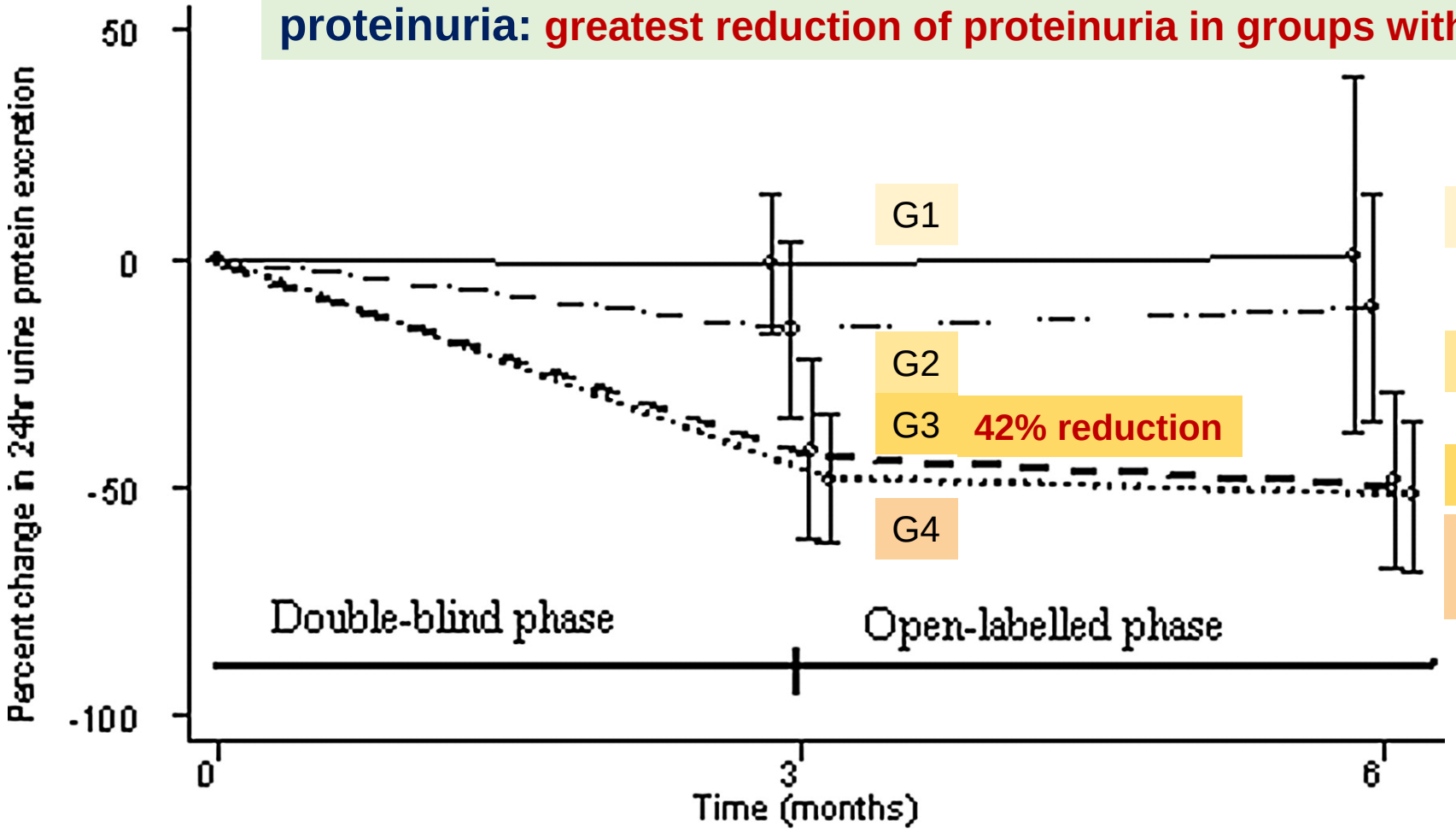
Milestones in the development of MRA for treatment of HF and diabetic kidney disease



D'Marco L et al., 2021

A double-blind RCT on the Effect of Spironolactone in DM and non-DM patients with persistent proteinuria

41 participants with Cr <2.26 mg/dL and ~ mean of 2.5 g/d of proteinuria: greatest reduction of proteinuria in groups with spironolactone



G1. Ramipril only

G2. Ramipril + irbesartan

G3. Ramipril + spironolactone

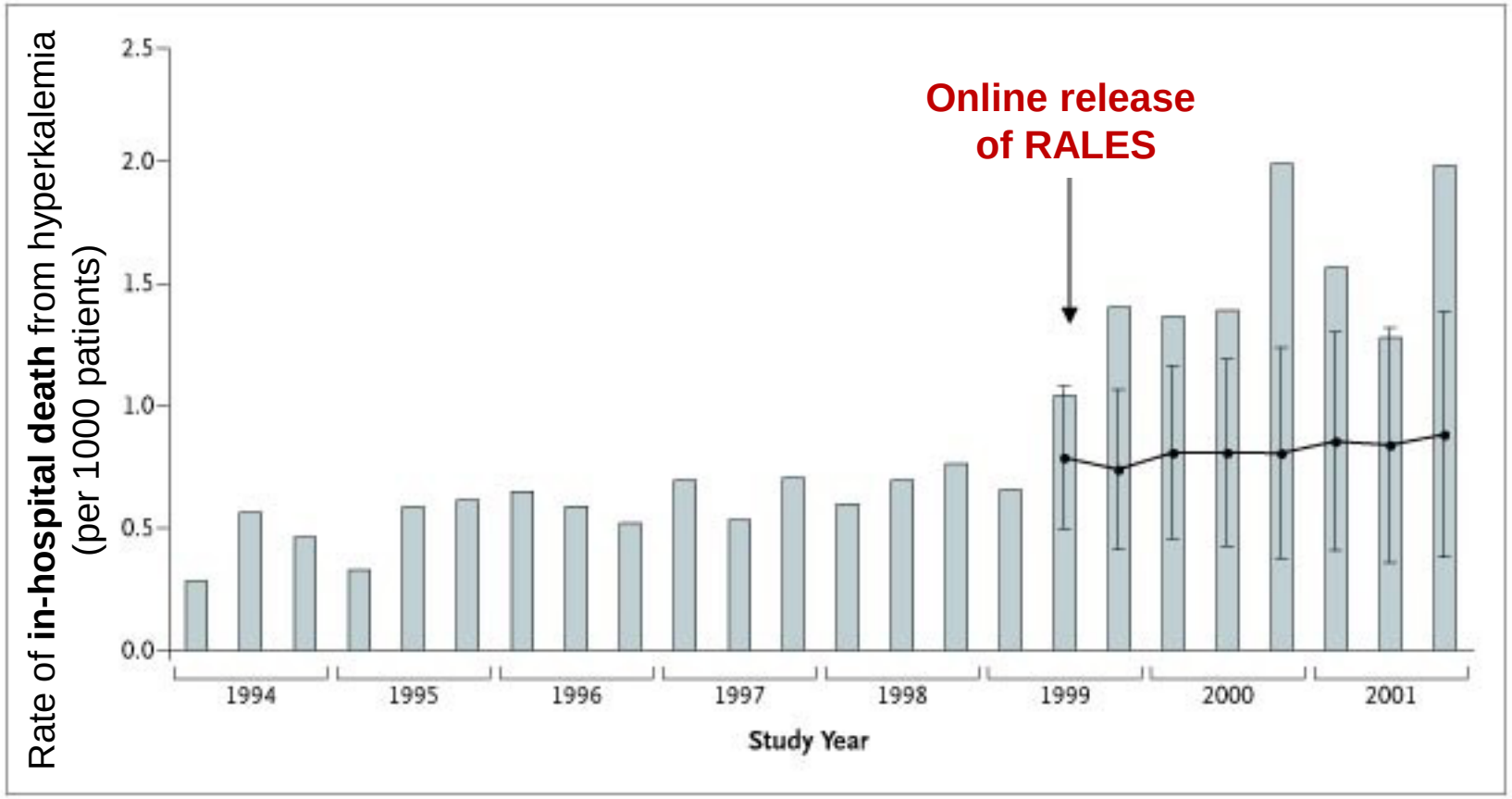
G4. Ramipril + irbesartan + spironolactone

Chrysostomou A et al., CJASN 2006, 1:256

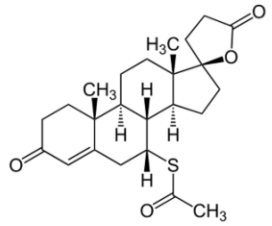
CV outcomes in clinical trials with MRA

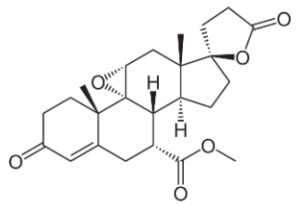
Trial	Patient group	N	MRA	Outcomes	
RALES	Severe HF, EF ≤35%, Cr ≤ 2.5, on ACEI/diuretics	822	Spironolactone	1. All-cause mortality	↓ 30% RRR
				2. HF hospitalization	↓ 35% RRR
EPHESUS	EF <40% and HF following MI on optimal medical therapy	6632	Eplerenone	1. All-cause mortality	↓ 15% RRR
				2. Death from CV cause or CV hospitalization	↓ 13% RRR
EMPHASIS -HF	Mild HF (NYHA II) and EF ≤35%	2737	Eplerenone	Composite of death from CV causes and HF hospitalization	↓ 37% RRR
TOPCAT	Symptomatic HF and EF ≥45%	3445	Spironolactone	Composite of death from CV causes, aborted cardiac arrest, and hospitalization for HF	↓ 11% RRR (P=0.14)

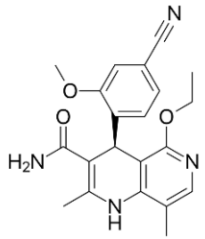
The publication of RALES associated with abrupt increases in the rate of prescriptions for spironolactone and in hyperkalemia-associated morbidity and mortality



Juurlink DN et al., NEJM 2004; 351:543





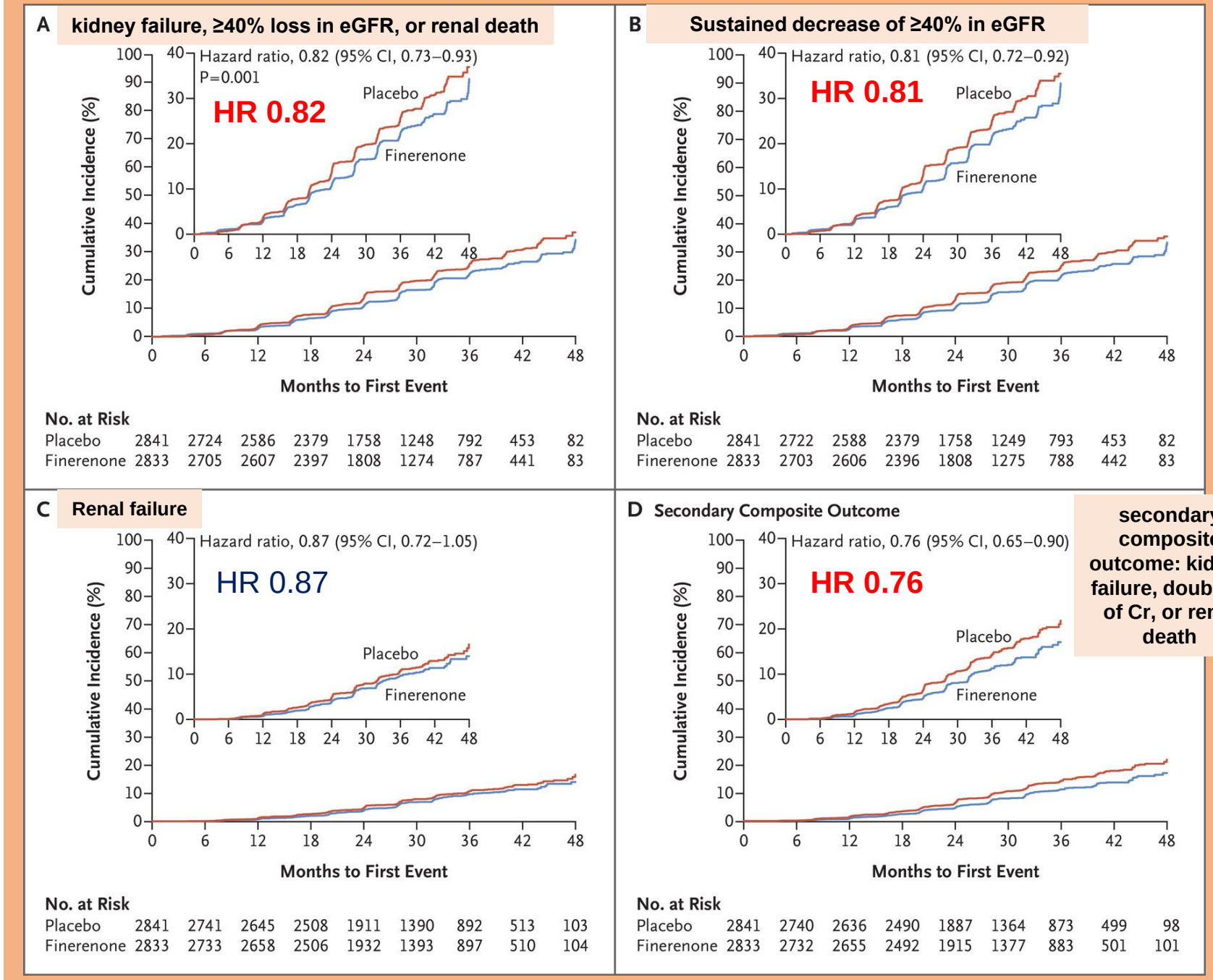


Characteristics	Spironolactone	Eplerenone	Finerenone
MR antagonist class	Steroidal		Non-steroidal
Structural prop.s	Flat	Flat	Bulky
Potency			
Selectivity			
MR IC^{50} (nM)	24	990	17.8
GR IC^{50} (nM)	2,410	≥ 21,980	≥ 10,000
AR rec. IC^{50} (nM)	77	≥ 21,240	≥ 10,000
PR EC^{50} (nM)	740	≥ 31,210	≥ 10,000
OR α & β IC^{50} (nM)	5,970 & 4,940	≥ 30,000 & ≥ 30,000	≥ 10,000 & ≥ 10,000
Metabolites	Multiple, active	No active	No active
Half-life	>20:0H	4-6:0H	2-3:0H
Tissue distribution in rodents	1 >6	1 ~3	1 1
CNS penetration	+	+	–
Effect on BP	+++	++	+
Excretion (unchanged)	<1%	<3%	<1%

>500-fold more selective for the MR than steroid receptors within the same superfamily (glucocorticoid, androgen, progesterone)

Di Lullo L et al.,
J Clin Med 2023;12:3992

Addition of finerenone, a non-steroidal selective MRA, further improves renal outcomes: FIDELIO-DKD

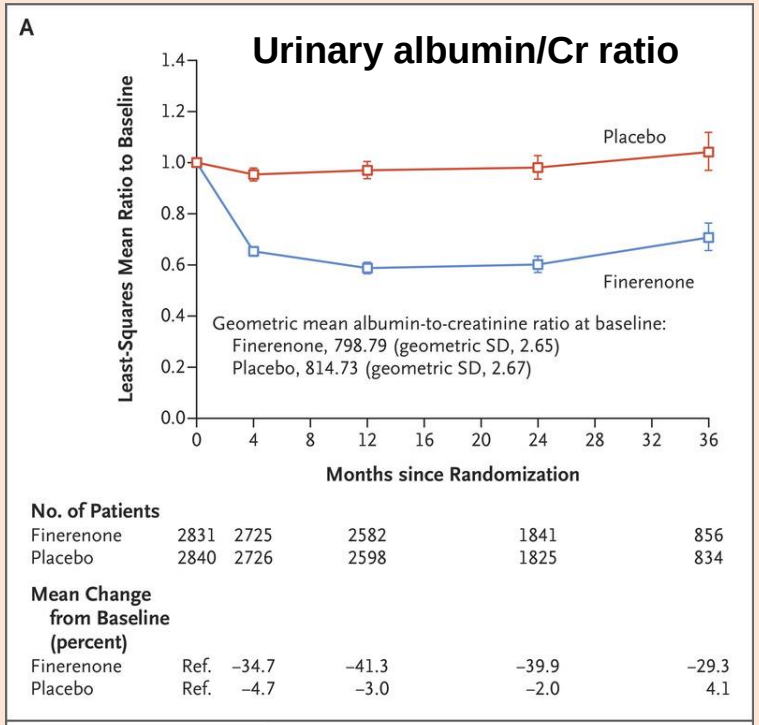


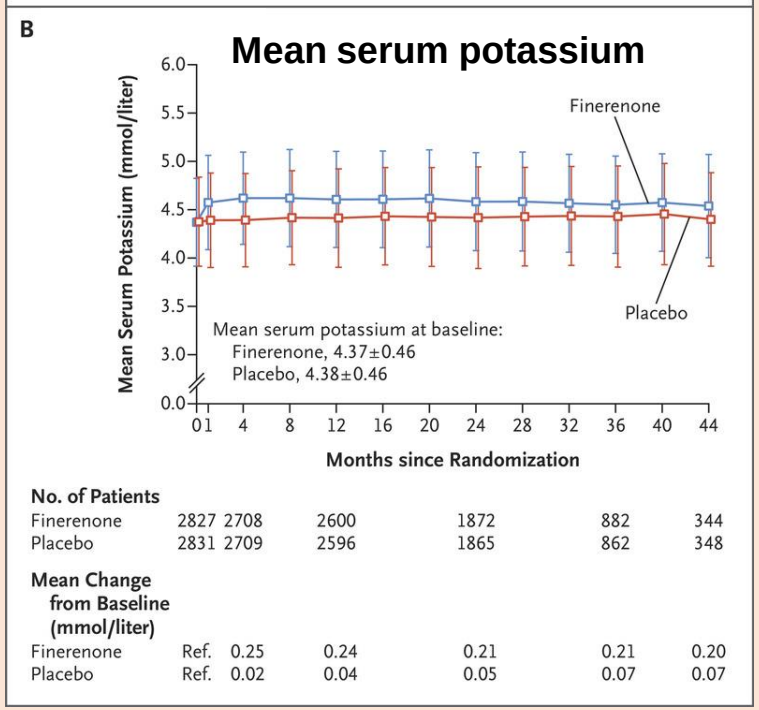
secondary composite outcome: kidney failure, doubling of Cr, or renal death

FIDELIO-DKD (N=5674):

- T2DM with CKD on ACEI/ARB,
- mean eGFR 44 (25 - <75),
- median albuminuria = 852 mg/g (300-5000)
- Mean f/u 2.6 yrs

Bakris GL et al., NEJM 2020;383:2219



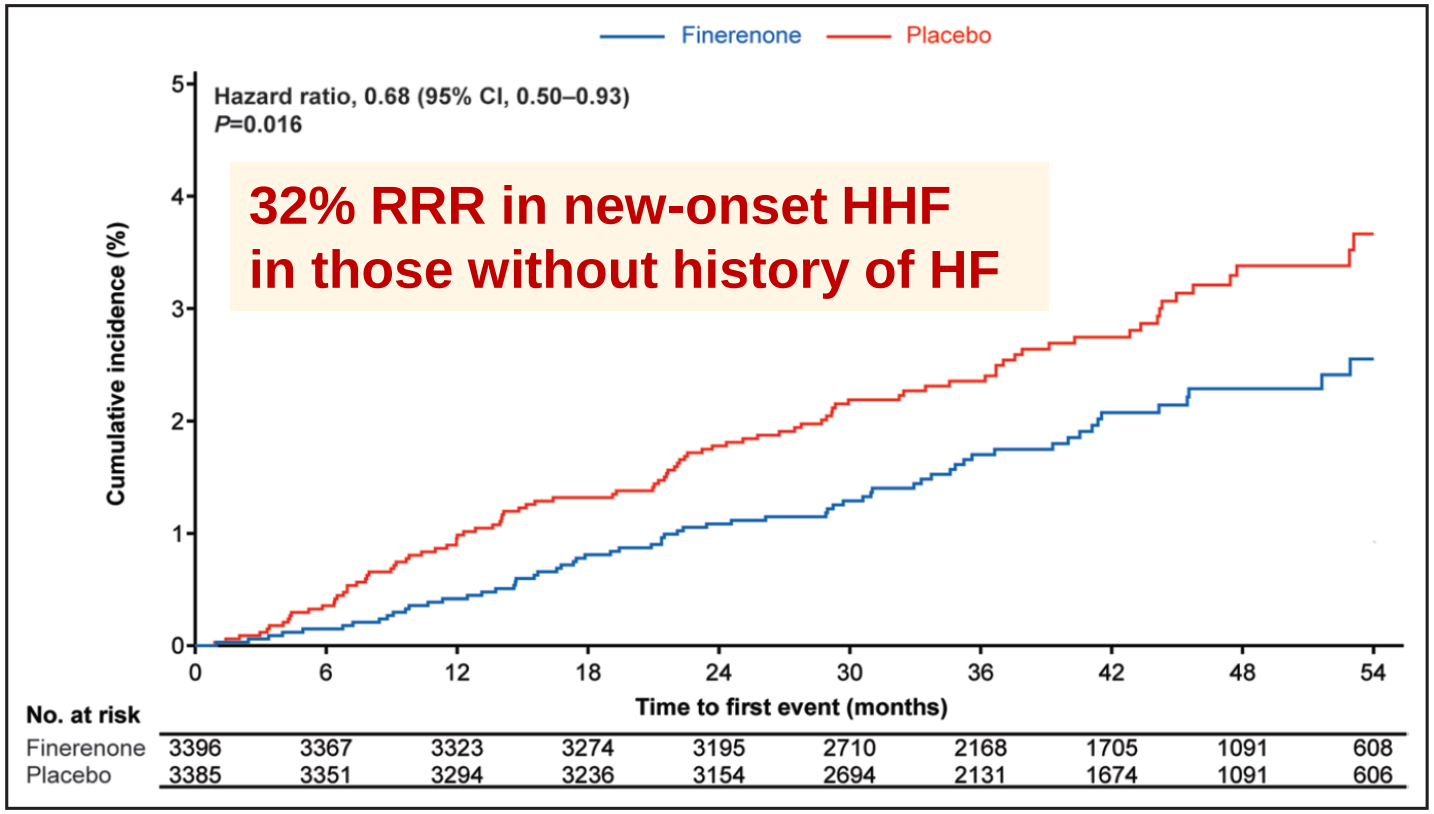


Effect of finerenone on proteinuria and hyperkalemia in diabetic CKD treated with ACEI/ARB

- Overall hyperkalemia-related adverse events were twice as frequent with finerenone as with placebo (18.3% and 9.0%, respectively)
- a maximal K level difference of 0.23 mmol per liter was observed at month 4.
- The incidences of serum K levels of more than 5.5 mmol/L and more than 6.0 mmol/L:
  - Finerenone: 21.7% and 4.5%
  - Placebo: 9.8% and 1.4%
- Discontinuation of the trial regimen due to hyperkalemia was infrequent in finerenone group **(2.3%)** and **markedly lower** than in trials of dual RAS blockade *(**8% with spironolactone in RALES**, **4.8%** with combination therapy with a direct renin inhibitor and an ACE inhibitor or ARB and **9.2%** with dual ACE inhibitor + ARB therapy).*
- Changes in mean SBP from baseline to month 1 and 12 were −3.0 and −2.1 mm Hg.

Bakris GL et al., NEJM 2020;383:2219

Finerenone reduces risk of incident HF in patients with CKD and T2DM: the FIGARO-DKD Trial



Filippatos G et all, Circulation. 2022, 145: 437

FIGARO-DKD (N=7437):

- T2DM with albuminuria treated with ACEI/ARB
- 571/7437 (8%) with hx of HF
- Mean eGFR ∽67
- mean albuminuria ∽300 mg/g

FIGARO-DKD is the first study to show that a MRA, specifically the selective, nonsteroidal MRA finerenone, may prevent the development of HF in patients with CKD and T2DM

Summary: MRAs

- Steroidal MRAs (spironolactone, eplerenone) have less selectivity to mineralocorticoid receptor and also have more renal distribution and are thus associated with greater risk for side effects (i.e. gynecomastia, amenorrhea, hyperkalemia).
- Non-steroidal MRA (finerenone) is >500 times more selective for MR, also have equal distribution in heart and kidney, with less risk for hyperkalemia.
- Finerenone has much less BP-lowering effect (2-3 mm Hg vs 10-20 mm Hg by spironolactone)
- Finerenone significantly lowers composite renal endpoint by 18% compared to standard therapy and prevents incident HF.

Overall summary

- **SGLT2i – "most potent overall protection for CKD and HF in DM and non-DM"**
  - ~ 12% risk reduction in MACE
  - ~ 30% risk reduction in HF hospitalization (within 1-3 months)
  - 30-40% risk reduction in composite renal endpoints
  - The renal benefits of SGLT2i are greatest in those with lower eGFR and greater proteinuria, regardless of DM status, ***BUT SGLT2i slows eGFR decline rate even in those without proteinuria***.
- **GLP-1RA (Long-acting formulations) – "weight and MACE reduction in T2DM"**
  - Significant weight reduction
  - Modest benefit on reduction of MACE, CV mortality, and proteinuria. GLP-1RA have not shown significant benefit on HF hospitalization or hard renal endpoints (i.e. progression to ESRD or doubling of Cr).
  - Liraglutide, semaglutide, and dulaglutide may be cautiously used in CKD 4/CKD 5.
  - Semaglutide lowers MACE in non-diabetic patients by 20% (the SELECT trial) and renal events by 24% in T2DM .
- **Finerenone: "prevent ESRD and HF with smaller effects on SBP"**
  - Highly selective MRA, equal distribution in the kidney/heart, decreased hypotensive effect (↓ SBP by 2-3 mm Hg)
  - Significantly ***prevents incident HF*** in T2DM patients without symptomatic HF
  - Reduce composite renal endpoints by 18% on top of ACEI/ARB

Decision algorithm for prescribing SGLT2i, GLP-1 RA, and MRA to optimize kidney and heart protection in patients at risk