SGLT2i, GLP-1A and MRA in Cardiorenal Protection

May 19, 2022

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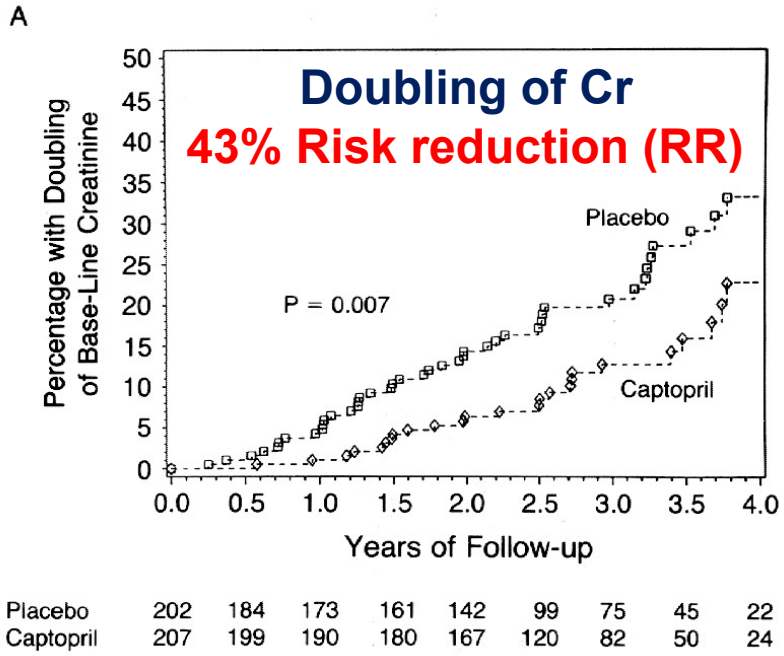
Disclosure

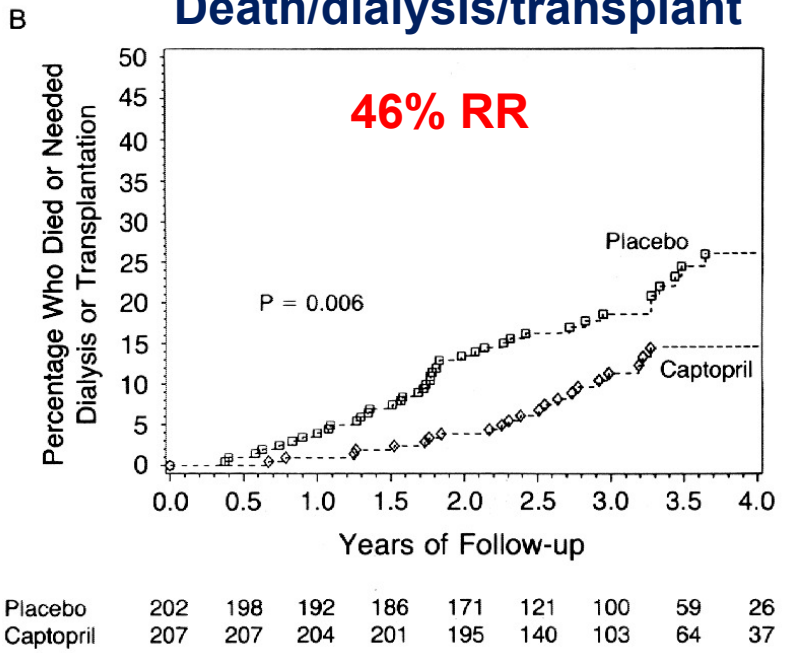
- UpToDate
- Grant funding from the VA and NIDDK

Objectives

- **SGLT2i:**
  - Glomerular and tubular effects of SGLT2i
  - Proposed mechanisms underlying benefits
  - Summary of renal outcomes *(by baseline proteinuria, eGFR)*
  - Summary of HF outcomes
- **GLP-1 receptor agonists (GLP-1RA):**
  - Proposed mechanisms underlying clinical benefits
  - Effects on CV risk factors
  - Summary of clinical CV and renal outcomes
- **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 Captopril Study





409 insulin-dependent T1DM patients:

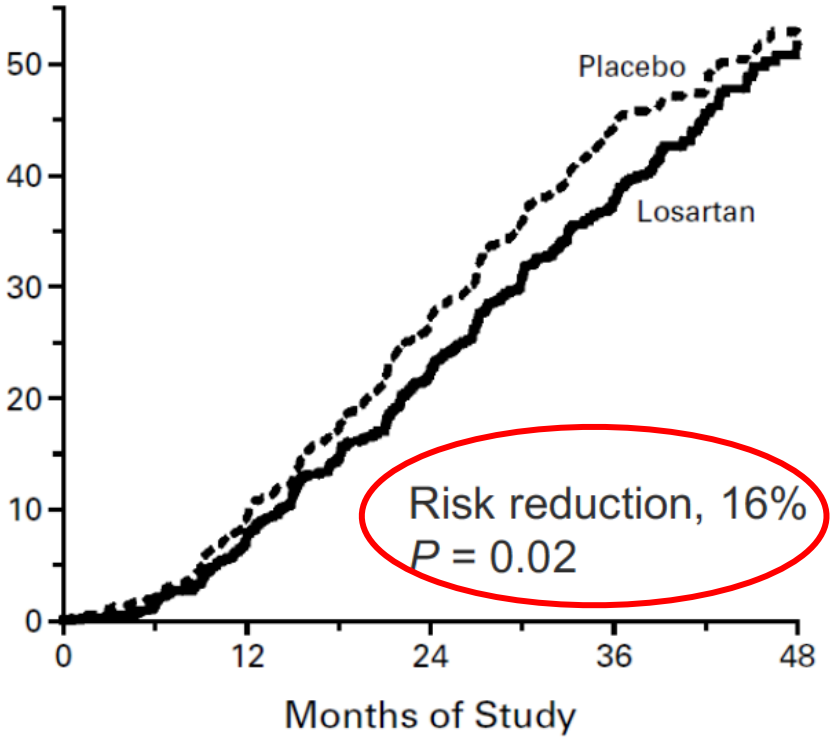
- Mean age: 35
- Duration of DM: 22 yrs
- Baseline proteinuria 2.5-3 g/g
- A1c 12%
- Mean CrCL:
  - 84 mL/min (captopril)
  - 79 mL/min (placebo)

Lewis, NEJM 1993

Renal outcomes with ARB in T2DM

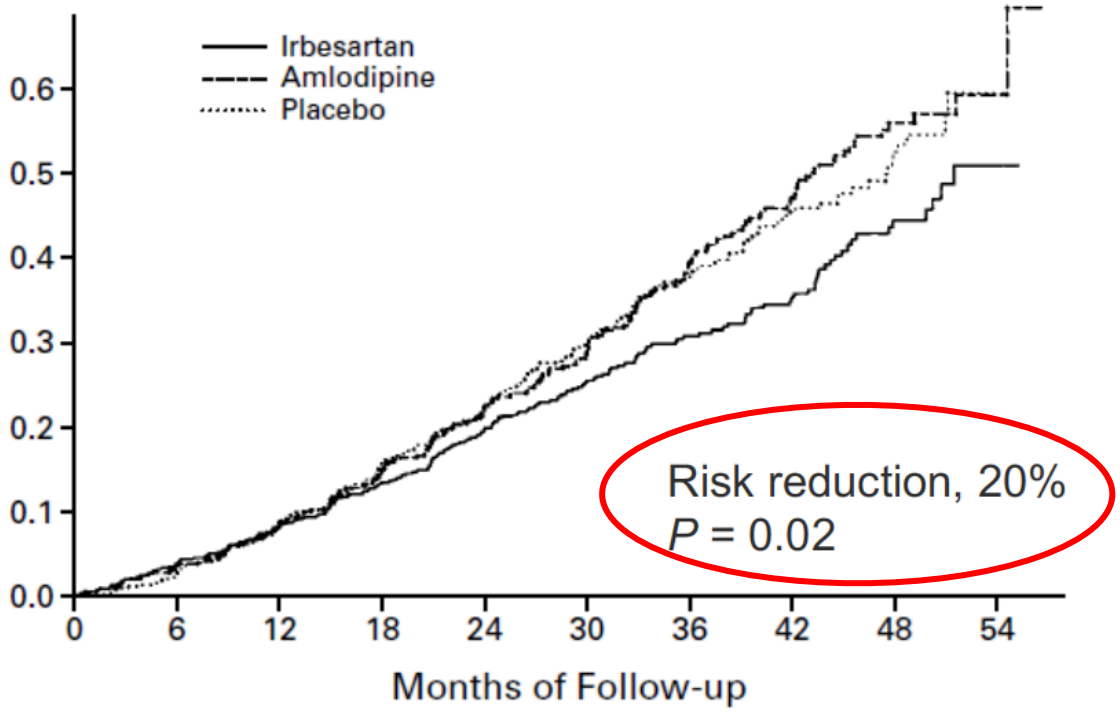
Doubling of serum creatinine, ESKD, or death

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.

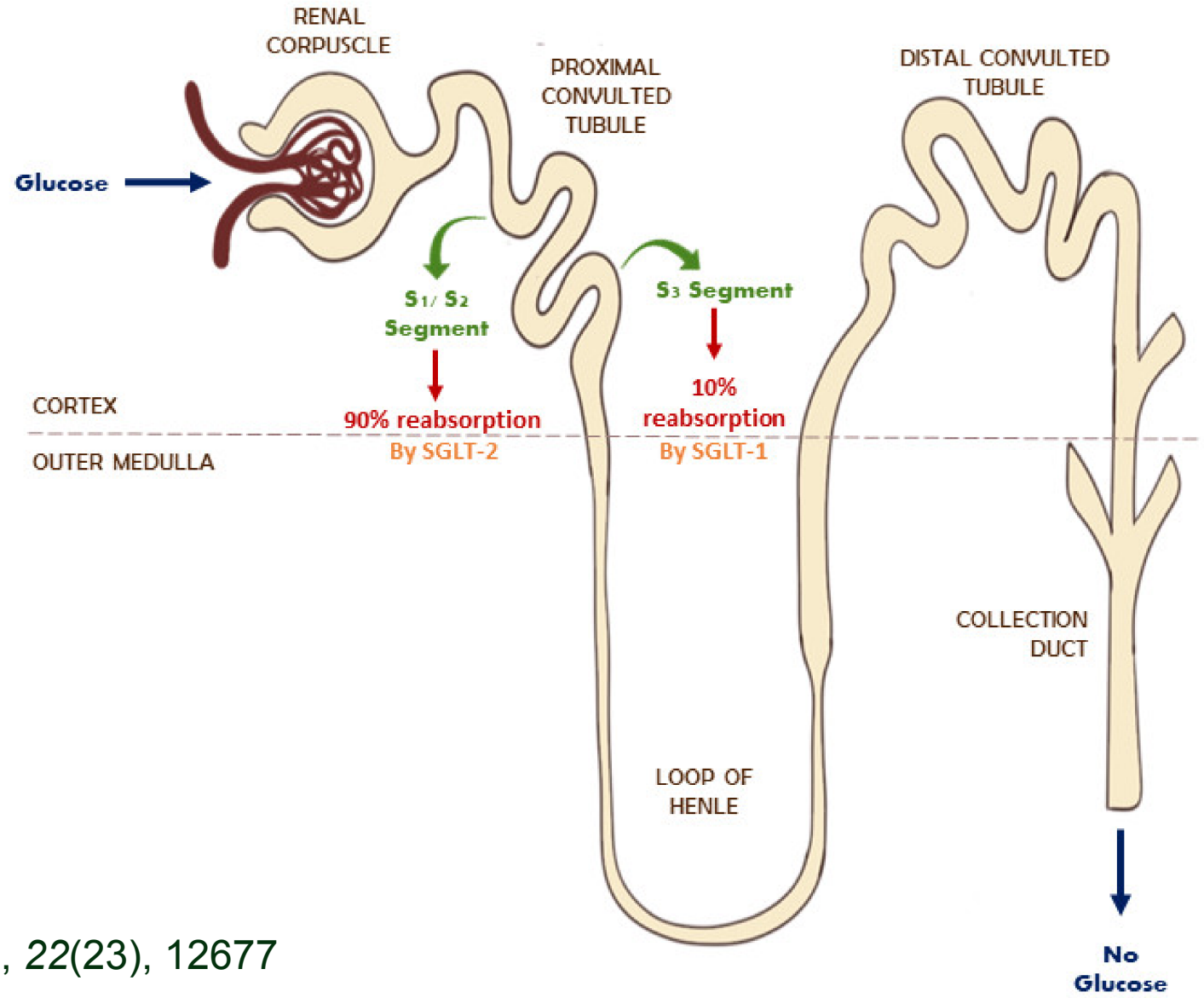
Glucose reabsorption in proximal nephron

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

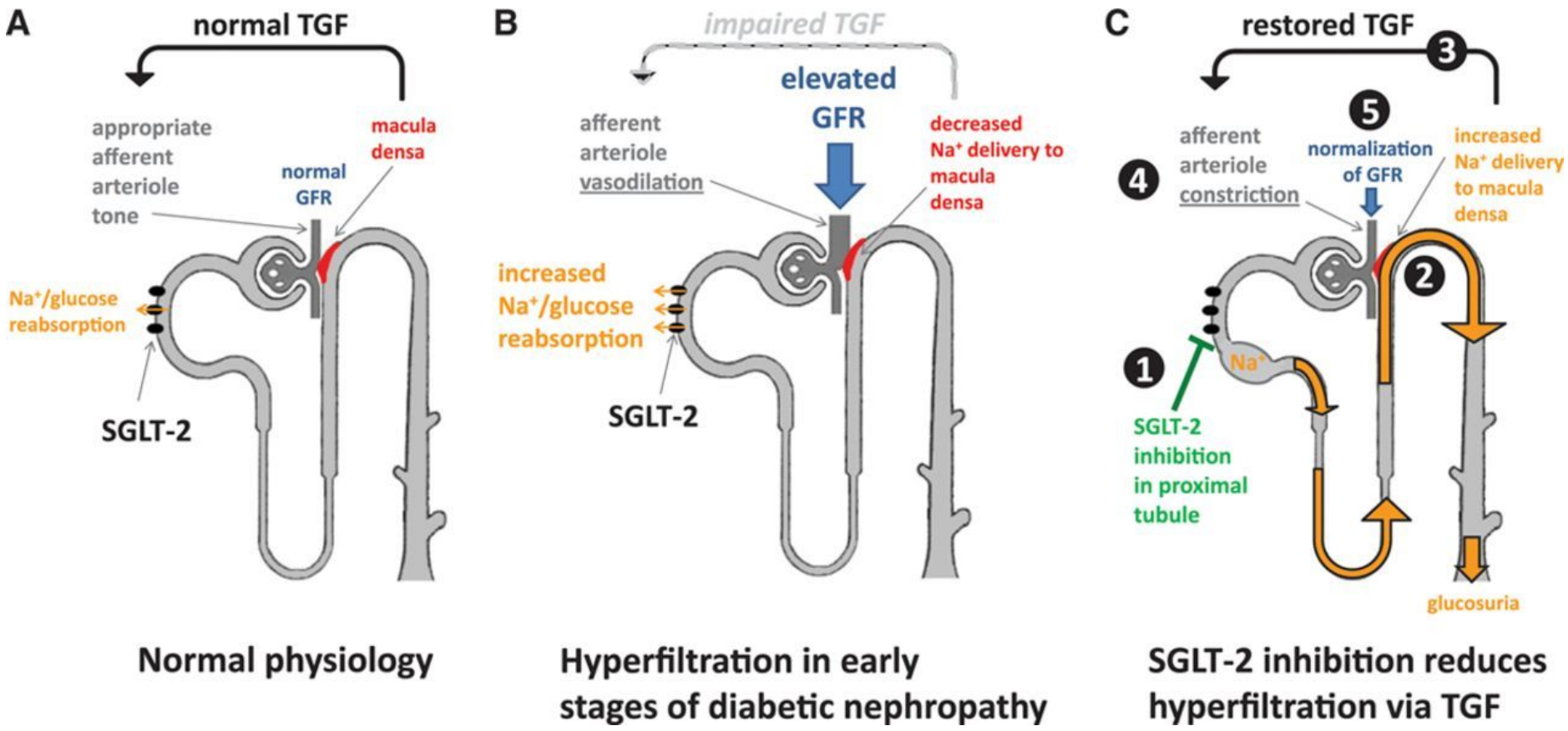
SGLT1:

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



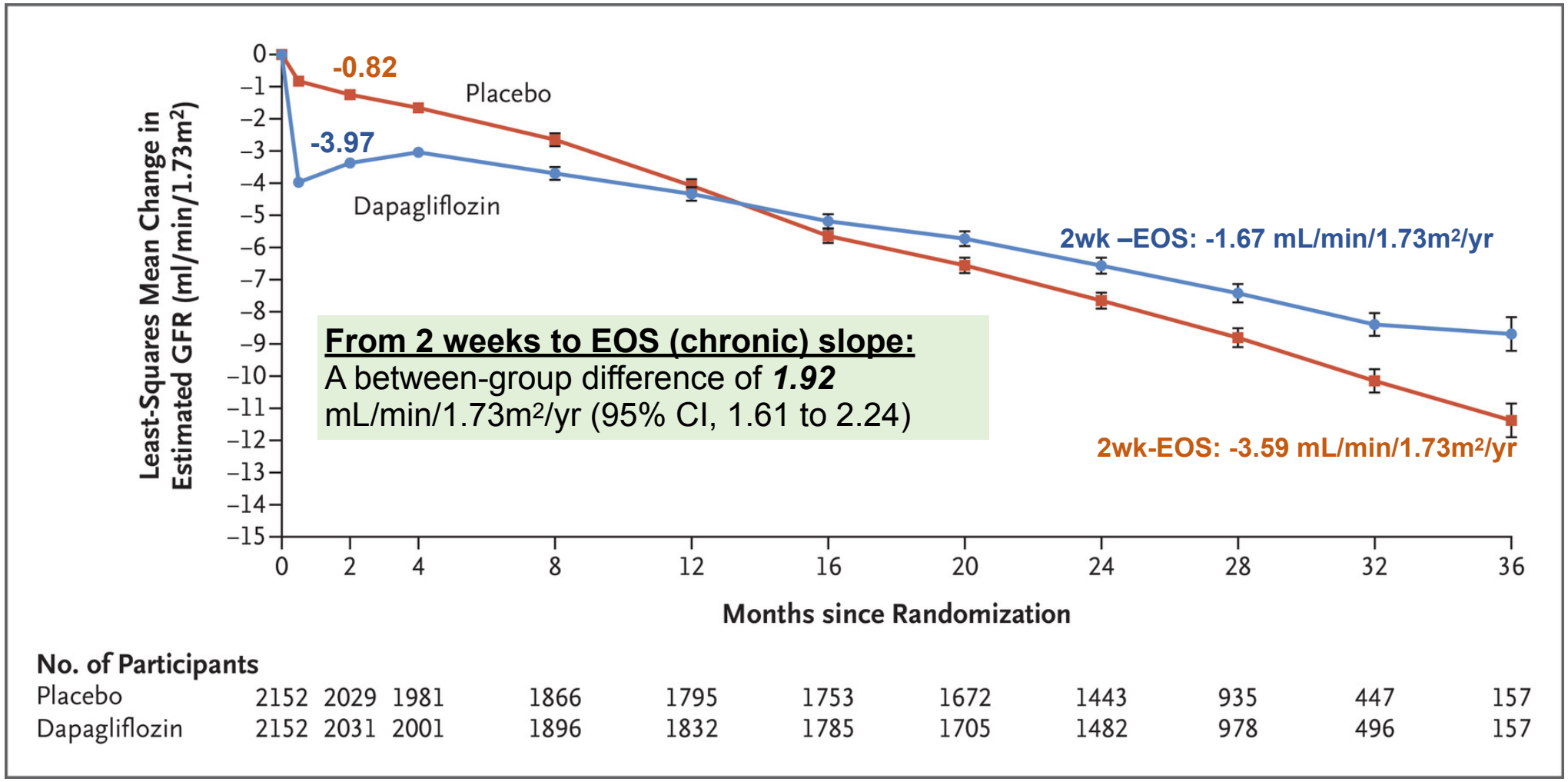
Al-Shamasi et al. Int. J. Mol. Sci. **2021**, *22*(23), 12677

The effect of proximal sodium reabsorption on tubuloglomerular feedback



Cherney et al. Circulation 2014;129:587

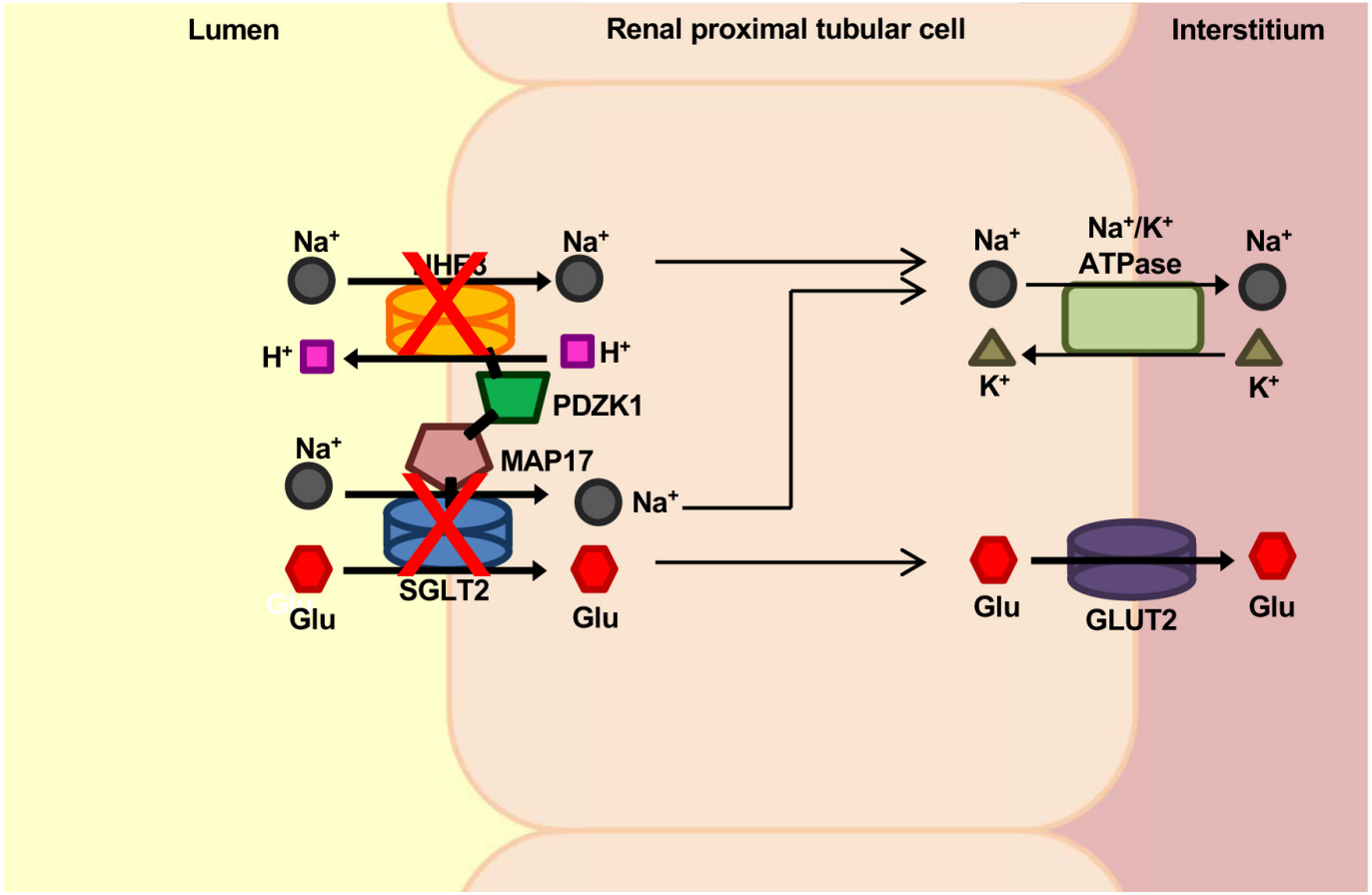
The initial fall in eGFR with SGLT2i initiation, followed by improved slope: DAPA-CKD



Heerspink et al., NEJM 2020;383:1436

SGLT2i inhibits NHE3, reducing proximal Na reabsorption

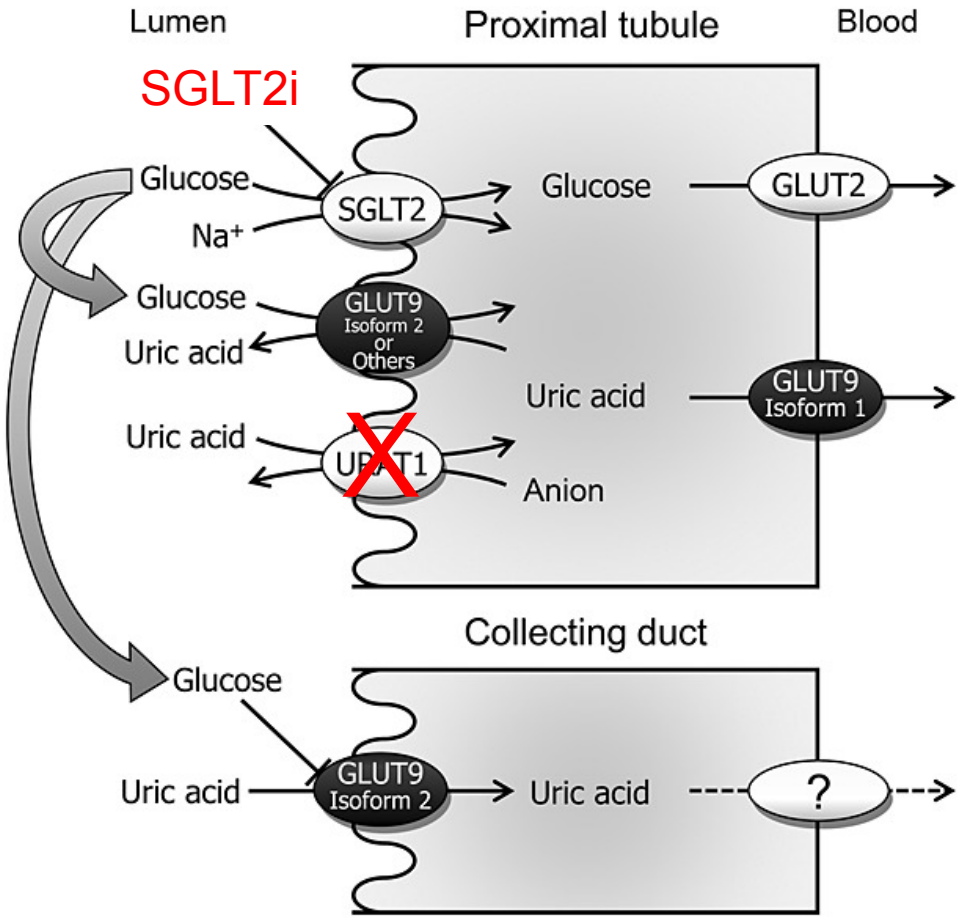
- In proximal nephron, most Na^+ is reabsorbed by ***NHE3,*** whose activity is increased by luminal glucose.
- SGLT2 and NHE3 also are interlinked by membrane associate protein 17 (MAP17) that interacts via post synaptic density protein 95/tight junction protein 1 (PDZK1).
- SGLT2 increases activity of NHE3 as well as the sodium-phosphate exchanger type IIa, the organic cation transporter, the chloride-formate exchanger, and the urate-anion exchanger.
- **These widespread effects on the proximal tubule may explain why SGLT2i maintain diuretic effect in CKD stage 3/4 despite little glycosuria.**



Am J Physiol Cell Physiol 2020 (318)328
Wilcox CS., Hypertension. 2020;75:894

Uricosuric effect of SGLT2i

Reduction of serum uric acid by ~0.6-0.75 mg/dL

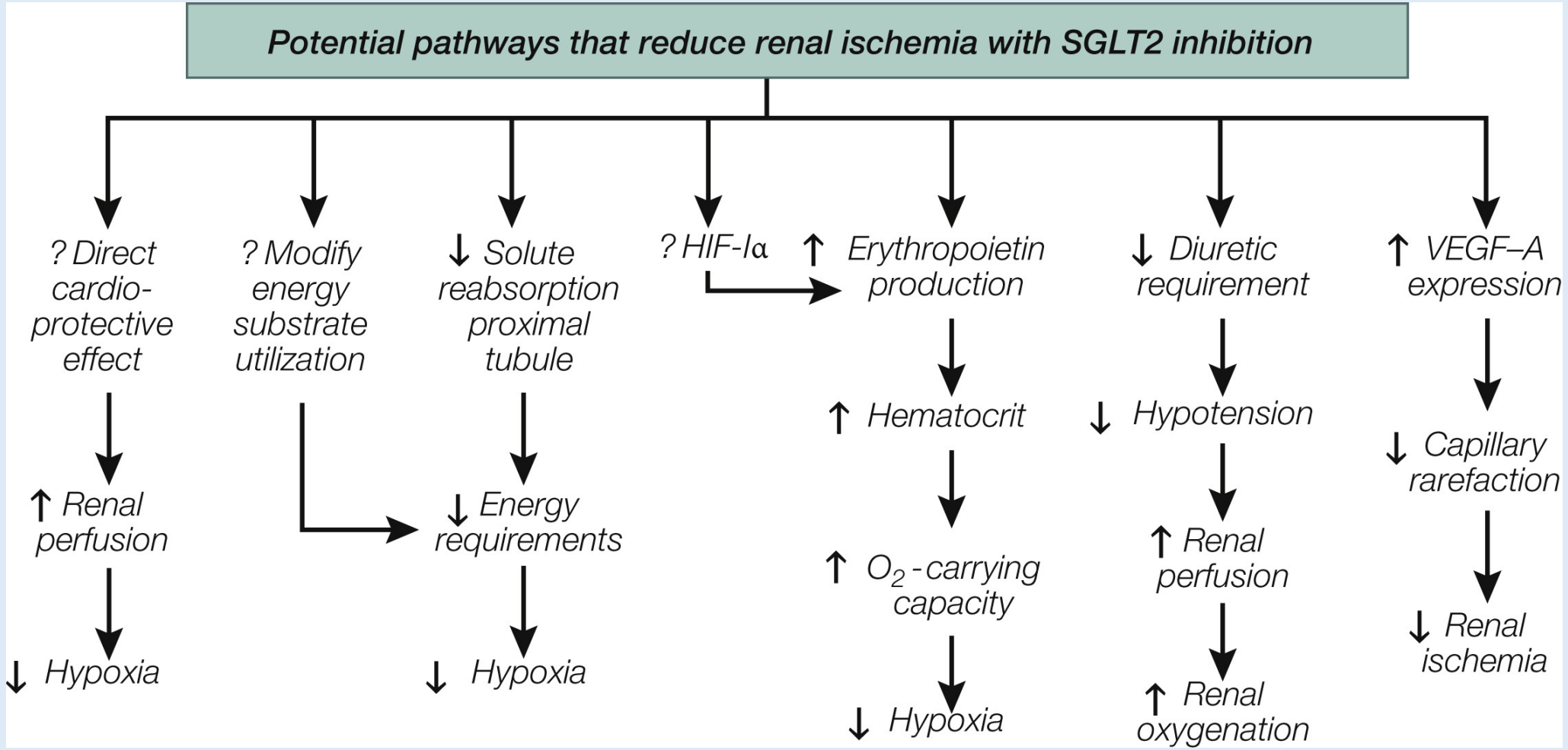


Proposed mechanisms for the uricosuric effect of SGLT2i:

- Glycosuria-induced uric acid secretion via GLUT9 isoform 2 in the proximal tubule
- Inhibition URAT1-mediated urate reabsorption in the proximal tubule
- Inhibition of uric acid uptake via GLUT9 isoform 2 at the collecting duct of renal tubule

Chino et al., Biopharm Drug Dispos. 2014;35: 391

Potential pathways that reduce renal ischemia with SGLT2 inhibition



Van Raalte and Cherney, KI 2018 (94)459

Summary of renal benefits by SGLT2i in clinical trials

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	CREDENCE	DAPA-CKD	EMPA-REG	CANVAS	DECLARE-TIMI 58	VERTIS CV	DAPA HF	EMPEROR-REDUCED	EMPEROR-PRESERVED
Drug	Cana	Dapa	Empa	Cana	Dapa	Ertugliflozin	Dapa	Empa	Empa
N	4401	4304	7020	10142	17160	8238	4744	3730	5988
Age	63	62	63	63	64	64	66	67	72
% of DM	100	67	100	100	100	100	42	50	49
eGFR	**56**	**43**	**74**	**77**	**85**	**76**	**66**	**62**	**61**
% ASCVD	50	37	100	72	41	100	-	-	-
% HF	15	11	10	14	10	24	100	100	100
Median f/u duration	2.6 yrs	2.4 yrs	3.1 yrs	2.4 yrs	4.2 yrs	3.0 yrs	18.2 mo	16 mo	26 mo
% RAASi	100	88	81	80	81	81	83	88	81
Hosp for HF	0.61		0.65	0.67	0.73	0.70	0.70	0.69	0.71
CV death	0.78	0.81	0.62	0.87	0.98	0.92	0.82	0.92	0.91
All-cause mortality	0.83	0.69	0.68	0.87	0.93	0.93	0.83	0.92	1.00
Renal endpoint	**0.66**	**0.61**	**0.54**	**0.60**	**0.53**	**0.81**	**0.71**	**0.50**	**–1.25 vs. –2.62 ml/min**
ESRD	**0.68**	**0.64**	**0.45**	-	-	-	-	-	-

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

STOPPED EARLY IN 4/2022

Background

The efficacy and safety of the sodium-glucose cotransporter-2 inhibitor (SGLT2i) empagliflozin has not been assessed in a dedicated population of people with chronic kidney disease (CKD).

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

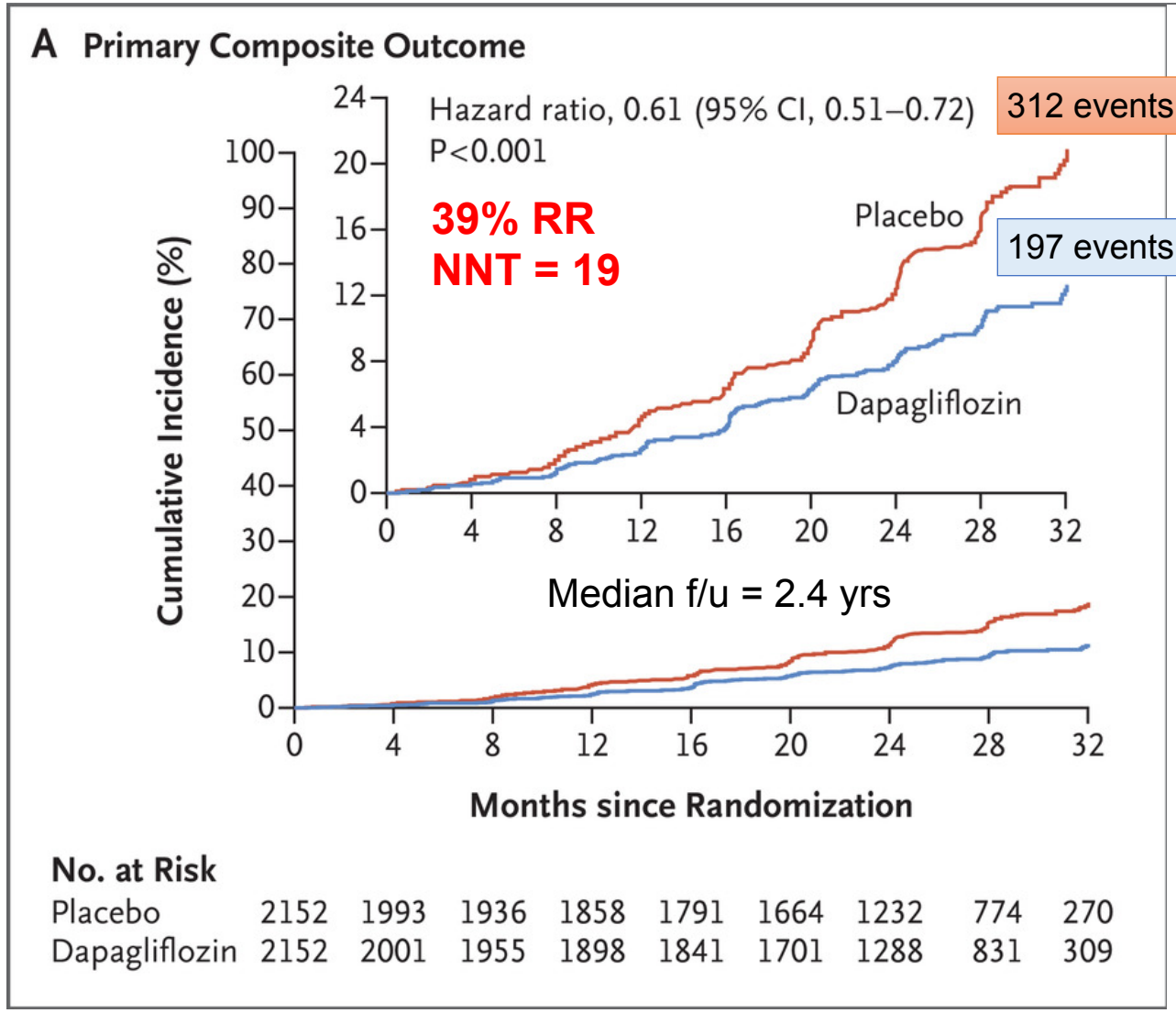
Conclusion

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

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:

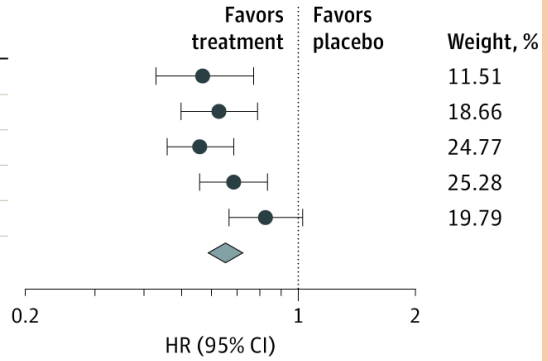
- **DM : HR 0·64 (0·52–0·79)**
- **No DM: HR 0·50 (0·35–0·72)**
- $p_{interaction}$=0·24

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

SGLT2i therapy associated with renal benefit regardless of history of ASCVD

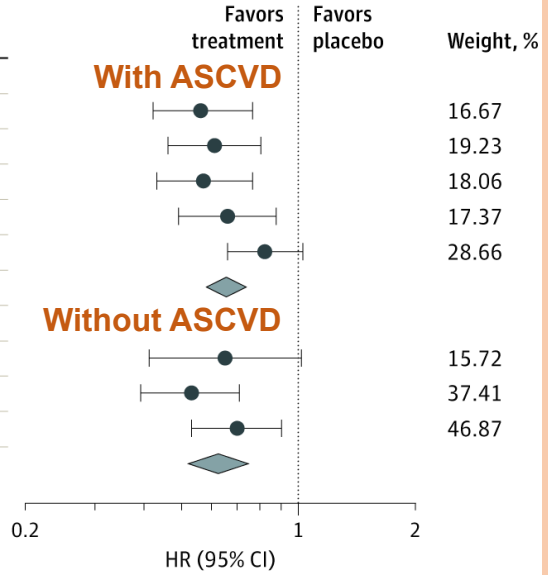
Overall kidney outcomes

	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)



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)



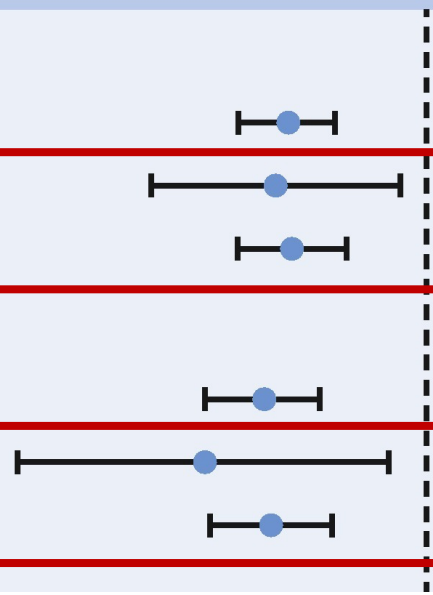
Meta-analysis of SGLT2i trials on the composite of renal worsening, ESRD, or renal death stratified by the presence of established atherosclerotic CV disease

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

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

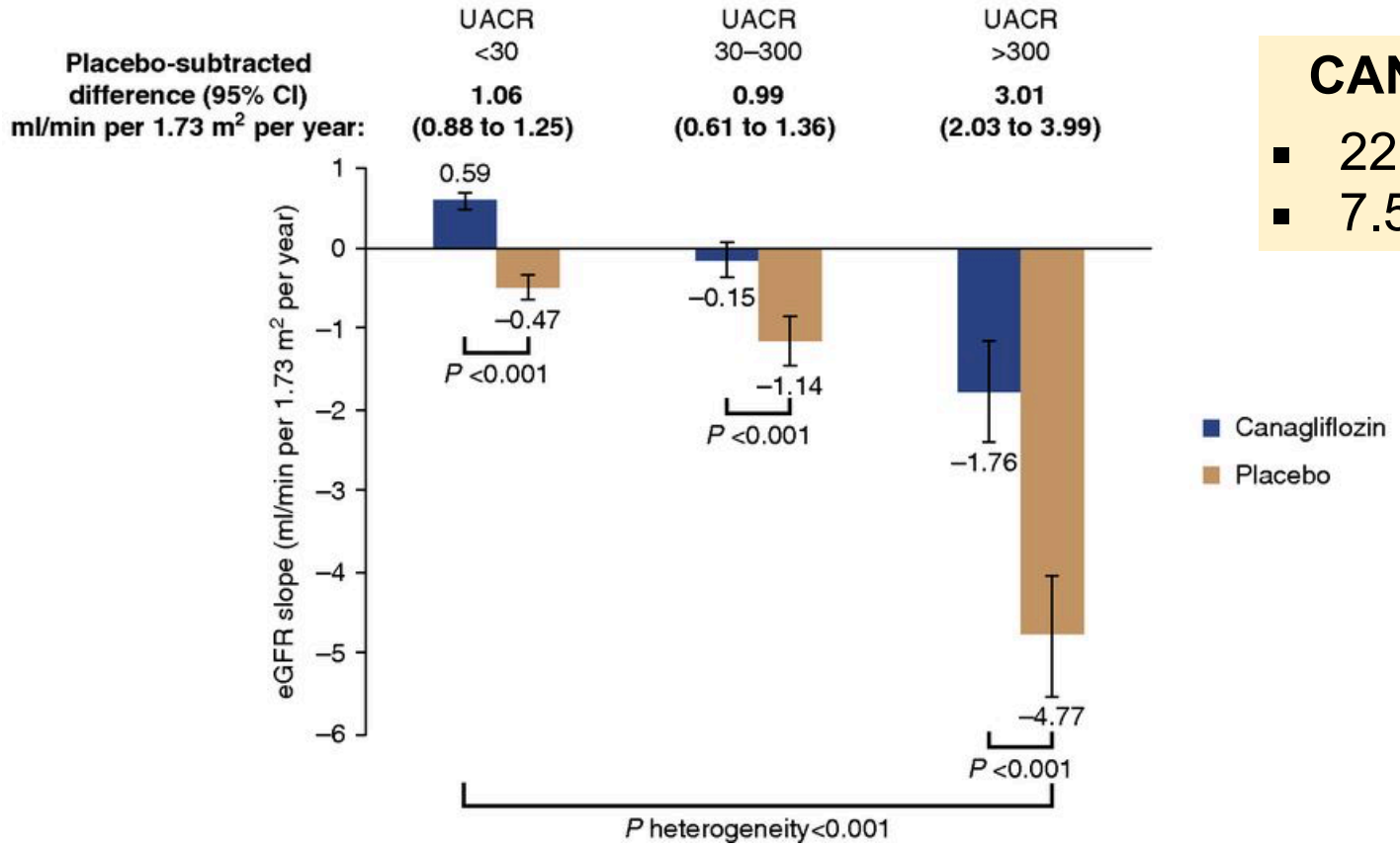
Effect of Dapagliflozin, Compared With Placebo, in DAPA-CKD Overall and According to Baseline Heart Failure Status

	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)	



The protective effect of canagliflozin on annual rate of eGFR decline consistent in all levels of albuminuria but greatest in participants with UACR >300 mg/g at baseline: CANVAS Program

Annual rate of change in eGFR from week 6 or 13 to Last available measurement

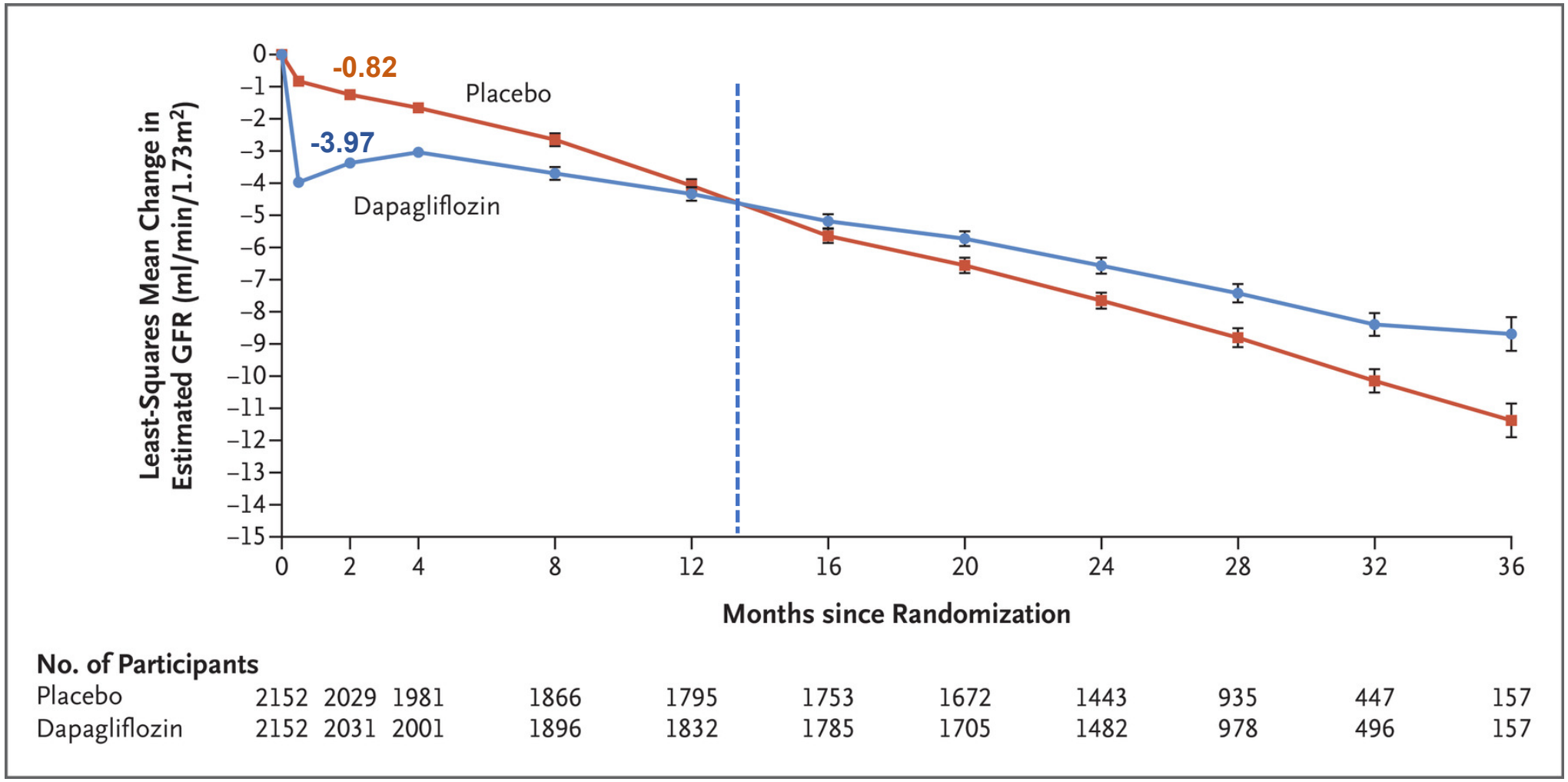


CANVAS: 10,142 patients with T2DM

- 22.3% (2,266) with UACR 30-300 mg/g
- 7.5% (760) with UACR >300 mg/g

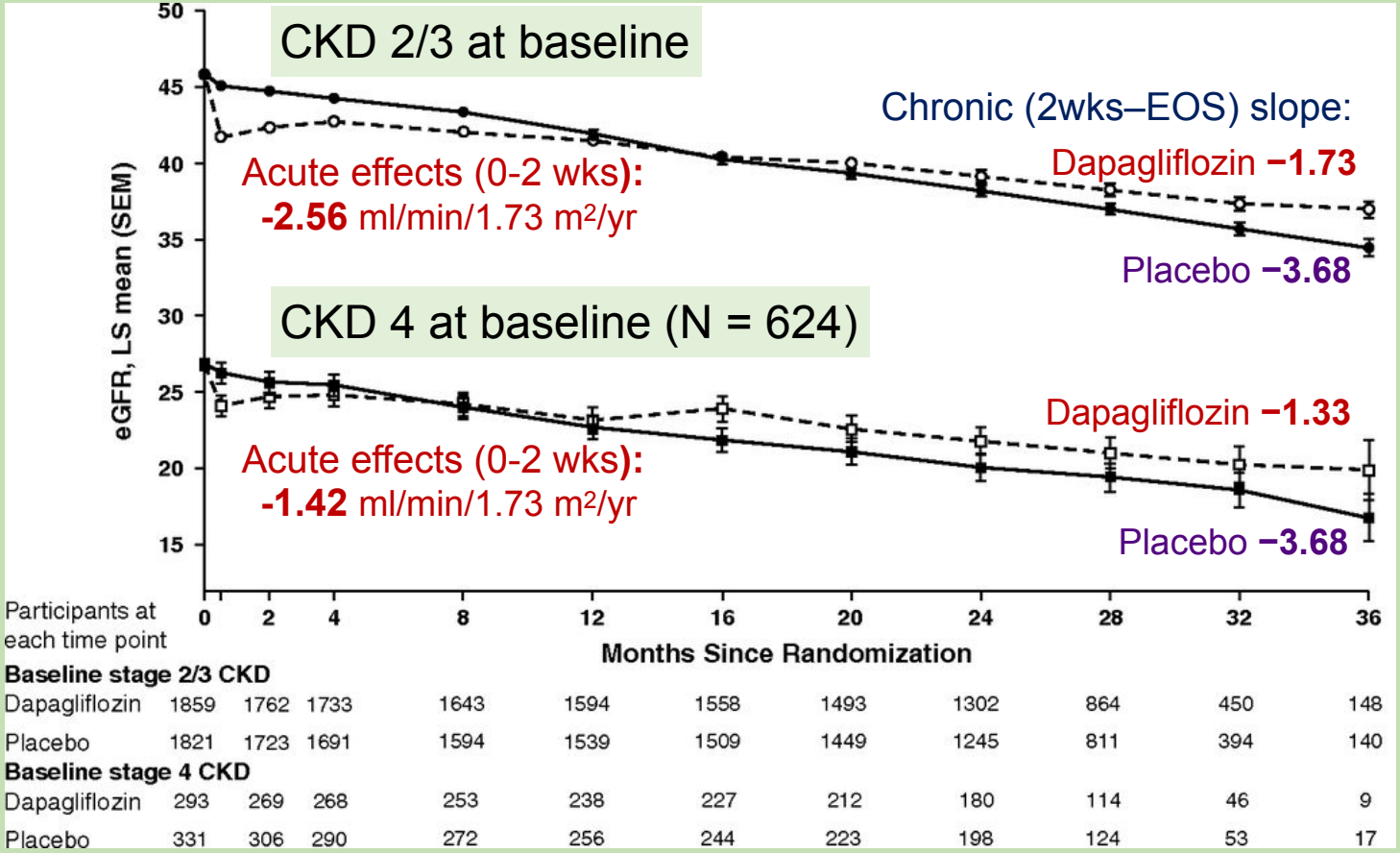
Neuen BL et al., JASN 2019;30:2229

DAPA-CKD: The drop in eGFR with SGLT2i initiation – the concern over starting SGLT2i at low eGFR (<25 mL/min)



Heerspink et al., NEJM 2020;383:1436

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



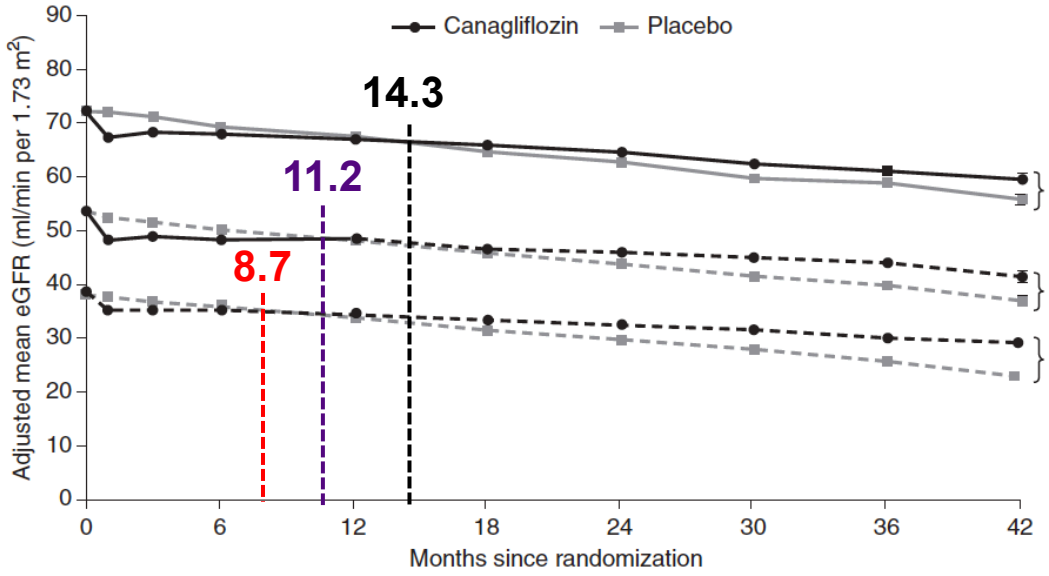
LS mean change in eGFR over the study:
Total annual slopes (week 0-EOS)

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

CREDENCE: Canagliflozin led to an acute drop in eGFR which was *mildest* in those with *eGFR 30-<45 ml/min/1.73 m²* at screening, and then to *slower eGFR decline* in every screening eGFR category



No. at risk

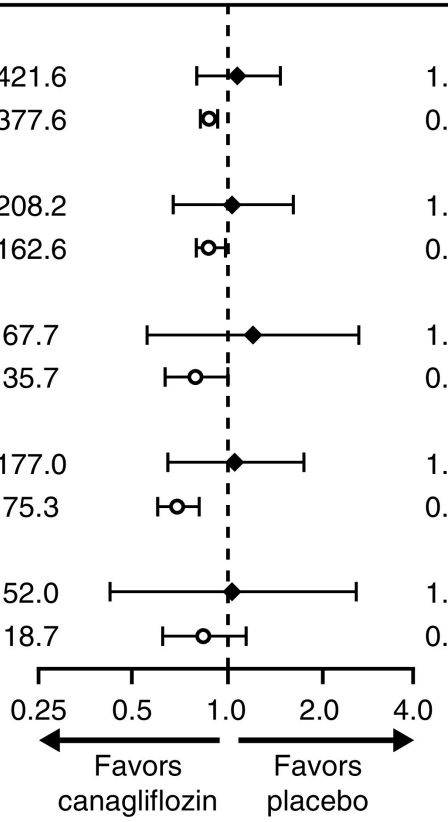
eGFR 60 to <90	Canagliflozin	899	833	803	758	710	490	288	98
	Placebo	895	829	801	755	679	471	270	100
eGFR 45 to <60	Canagliflozin	635	589	563	531	490	333	202	80
	Placebo	635	575	535	483	435	278	168	58
eGFR 30 to <45	Canagliflozin	645	583	553	493	448	293	162	63
	Placebo	648	581	546	482	422	257	145	52

Jardine MG et al., J Am Soc Nephrol.2020;31:1128

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* interaction
	Canagliflozin	Placebo	Canagliflozin	Placebo	HR (95% CI)	
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 HF outcomes with SGLT2i

The effect of empagliflozin on causes of death: EMPA-REG

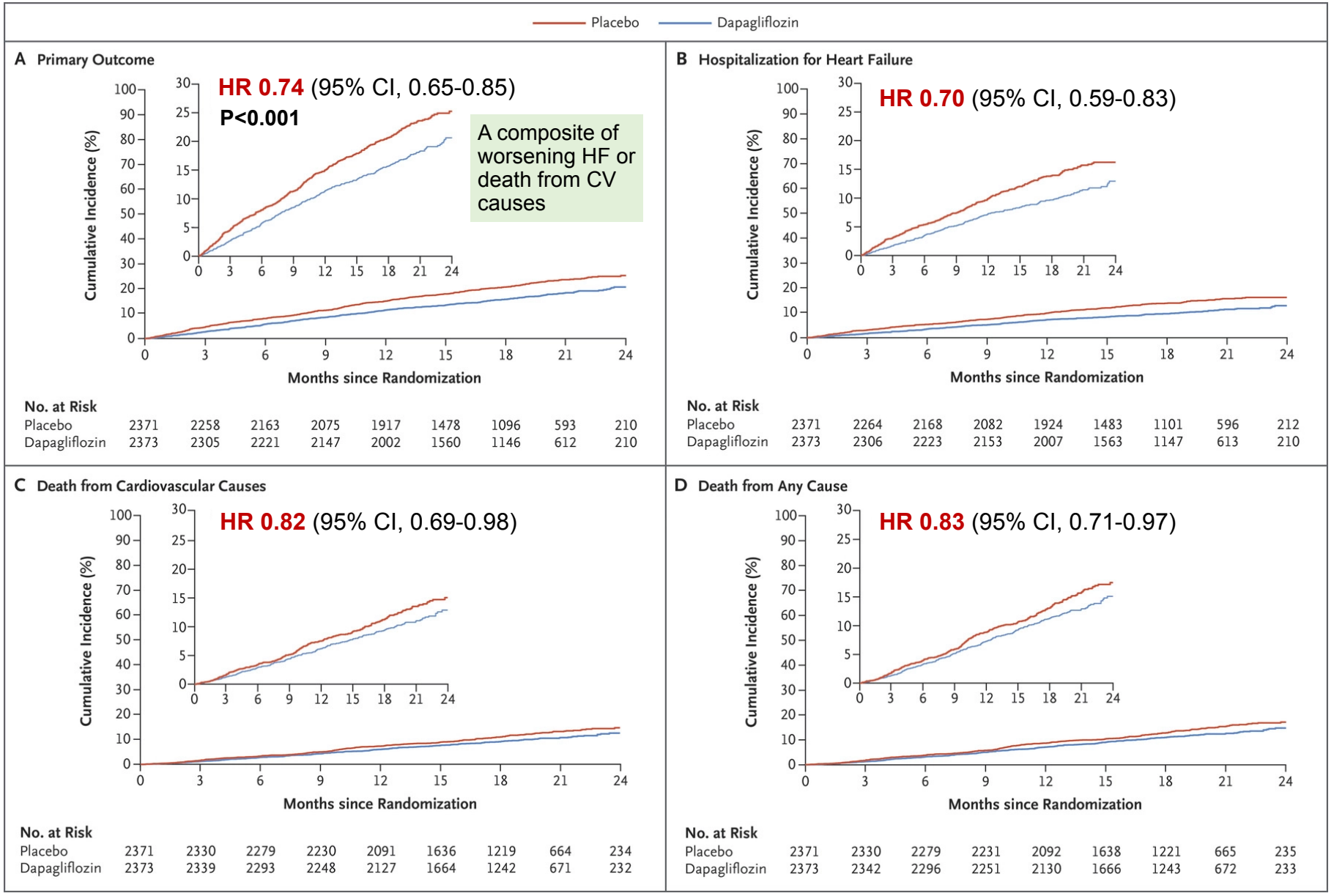
Mortality causes		Placebo (N=2333)	EMPA (N=4687)	% RRR
All-cause mortality		194 (8.3)	269 (5.7)	32
CV death		137 (5.9)	172 (3.7)	38
	Sudden death	**38 (1.6)**	**53 (1.1)**	**31**
	Worsening HF	**19 (0.8)**	**11 (0.2)**	**75**
	Acute MI	11 (0.5)	15 (0.3)	
	Stroke	11 (0.5)	16 (0.3)	
	Cardiogenic shock	3 (0.1)	3 (0.1)	
	Other	55 (2.4)	74 (1.6)	
	Not assessable	53 (2.3)	71 (1.5)	
Non-CV death		57 (2.4)	97 (2.1)	

Fitchett et al. JACC, 2016

COMORBIDITIES IN HFrEF SGLT2i RCTs

	EMPEROR-Reduced		DAPA-HF
	Empagliflozin (n=1863)	Placebo (n=1867)	Dapagliflozin (n=2373)
Age (yr)	67.2 ± 10.8	66.5 ± 11.2	66.2 ± 11.0
Women (%)	437 (23.5)	456 (24.4)	564 (23.8)
Diabetes mellitus (%)	927 (49.8)	929 (49.8)	993 (41.8)
Ischemic cardiomyopathy (%)	983 (52.8)	946 (50.7)	1316 (55.5%)
NYHA functional class II (%)	1399 (75.1)	1401 (75.0)	1606 (67.7%)
LV ejection fraction (%)	27.7 ± 6.0 (72% ≤30%)	27.2 ± 6.1 (75% ≤30%)	31.2±6.7
NT-proBNP (median, IQR), pg/mL	1887 (1077, 3429) (79% ≥1000)	1926 (1153, 3525) (80% ≥1000)	1428 (857-2655)
Hospitalization for heart failure within 12 months	577 (31.0)	574 (30.7)	647 (27.3)
Atrial fibrillation	664 (35.6)	705 (37.8)	916 (38.6)
Glomerular filtration rate (ml/min/1.73 m^2)	61.8 ± 21.7	62.2 ± 21.5	66.0 ± 19.6
Treatment for heart failure			
RAS inhibitor without neprilysin inhibitor	1314 (70.5)	1286 (68.9)	2007 (84.6)
RAS inhibitor with neprilysin inhibitor	340 (18.3)	387 (20.7)	250 (10.5)
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)	1696 (71.5)
Beta blocker	1765 (94.7)	1768 (94.7)	2278 (96.0)
Implantable cardioverter-defibrillator	578 (31.0)	593 (31.8)	622 (26.2%)
Cardiac resynchronization therapy	220 (11.8)	222 (11.9)	190 (8.0%)

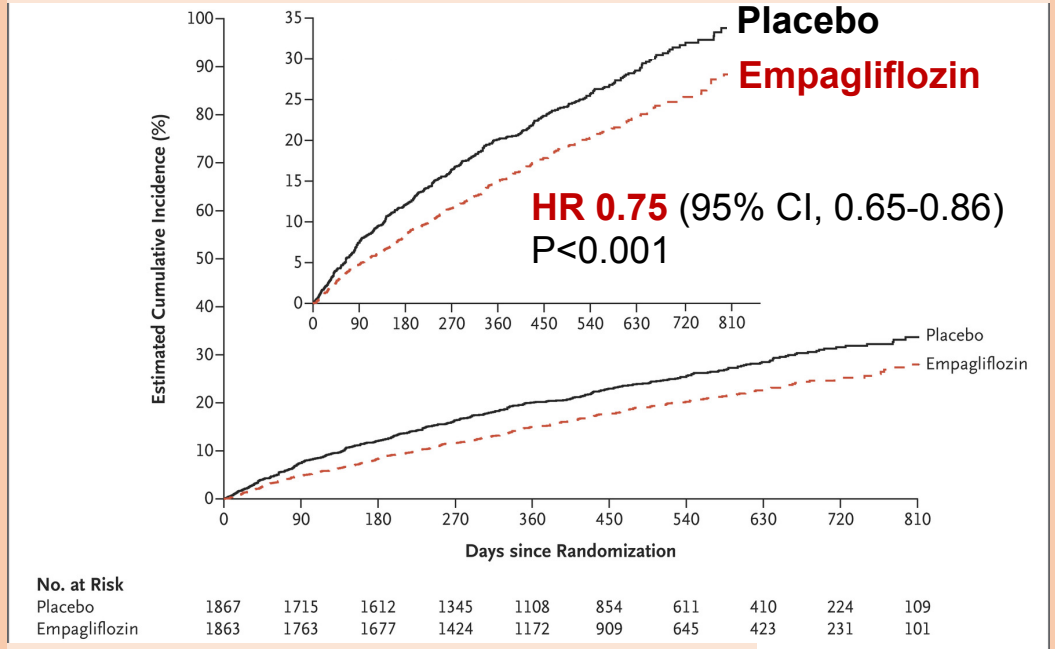
DAPA-HF McMurray et al., NEJM 2019;381:1995

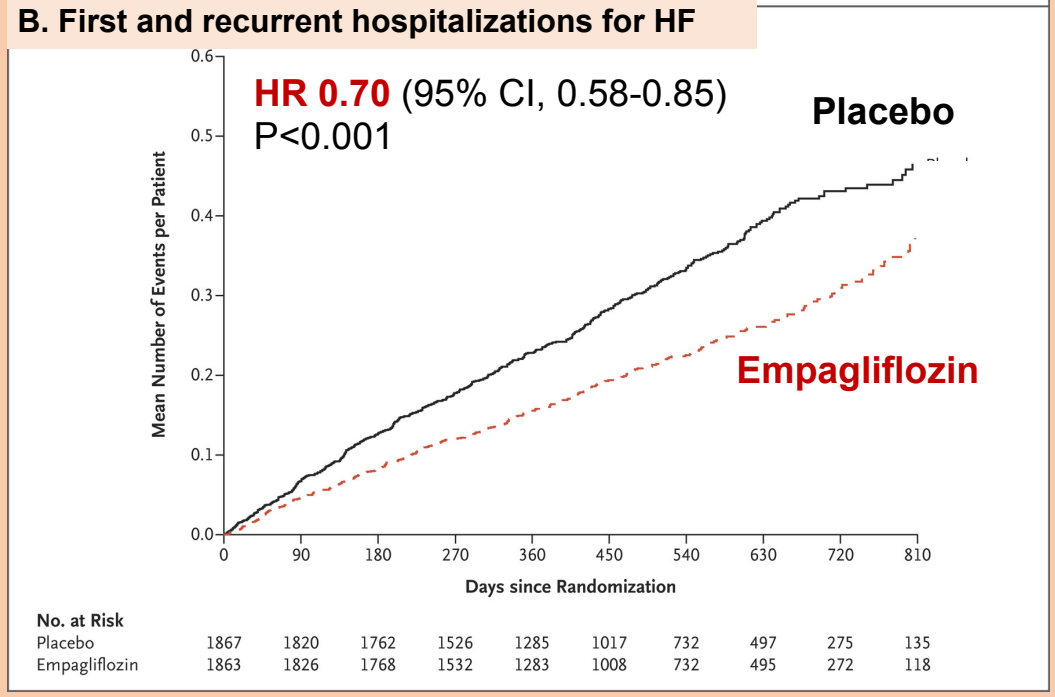


EMPEROR-REDUCED

- 3,730 participants with class II-IV HF and EF ≤40%
- In a median follow up of 16 months, the primary outcome occurred:
  - 361/1863 (19.4%) in empagliflozin
  - 462/1867 (24.7%) in placebo
- Similar efficacy in diabetic and non-diabetic participants
- The annual rate of decline in the eGFR was slower in the empagliflozin group than in the placebo group (–0.55 vs. –2.28 ml/min/1.73 m², P<0.001)

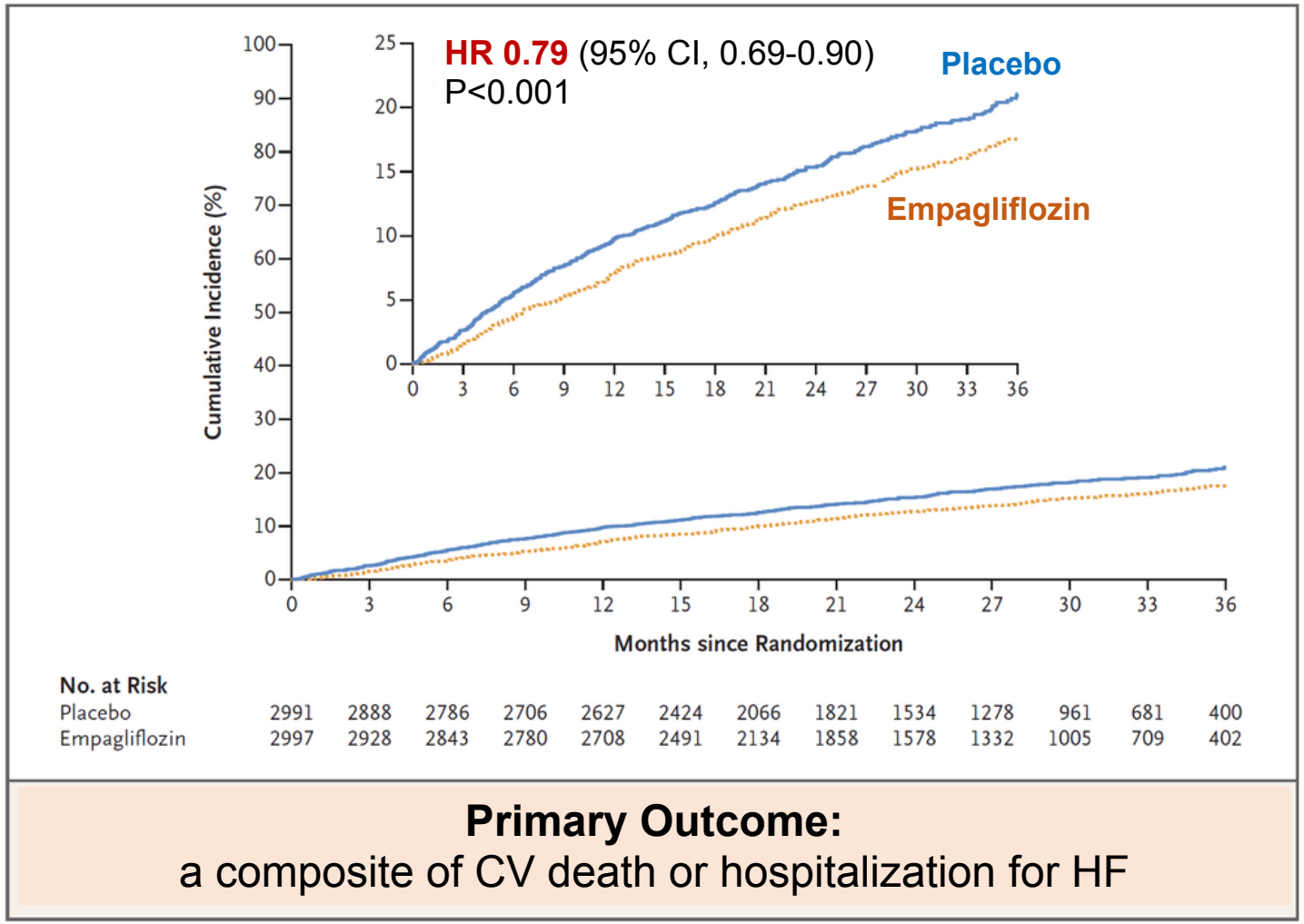
Packer M et al., NEJM 2020;383:1413





EMPEROR-PRESERVED

- A RCT of 5988 patients with class II-IV HF and EF >40%
- N-terminal proBNP >300 pg/mL or >900 pg/mL with Afib
- 49% with diabetes at baseline
- 51% with baseline Afib
- Mean baseline eGFR 61
- A median follow-up period of 26.2 months



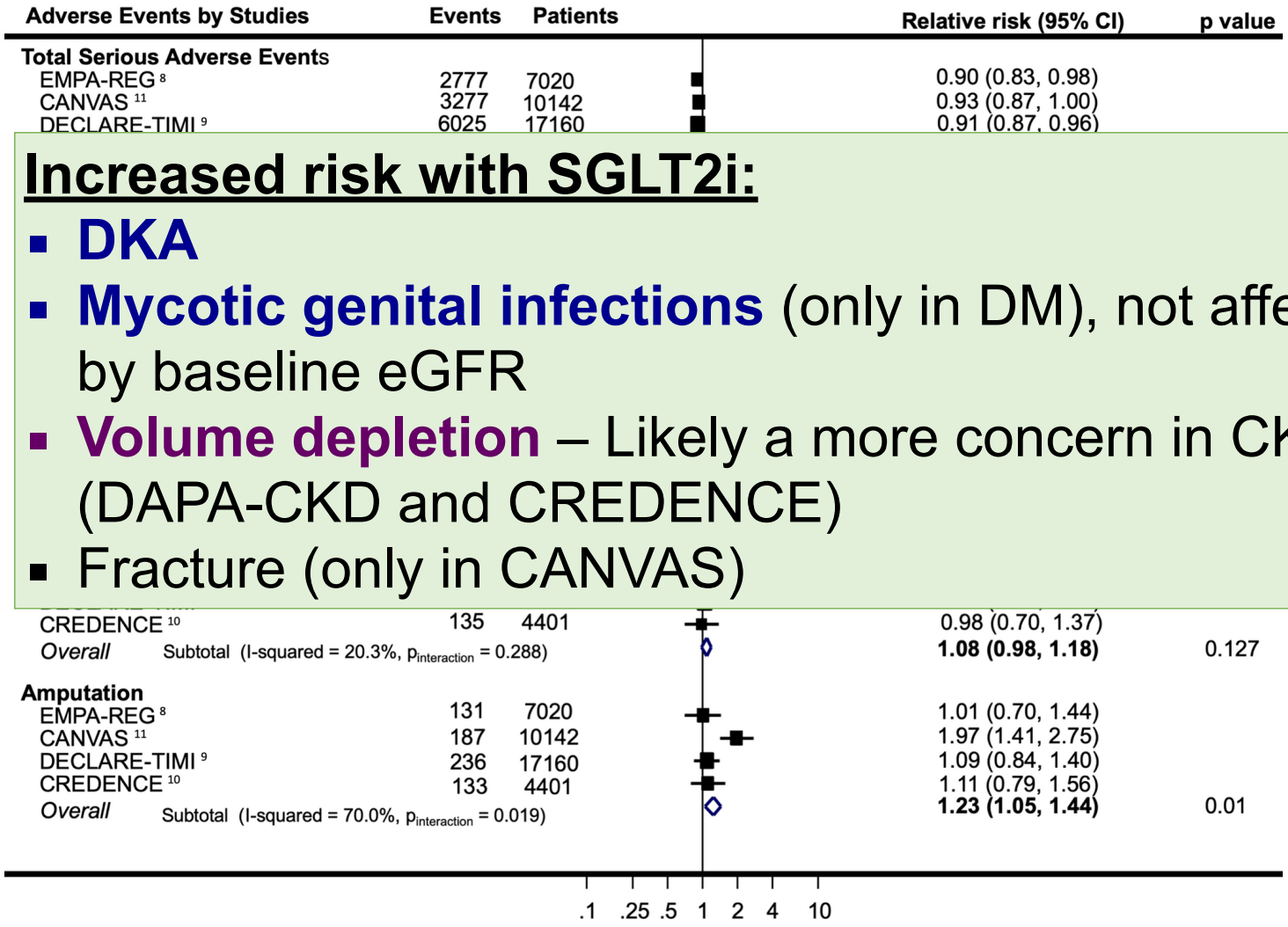
Primary Outcome:
a composite of CV death or hospitalization for HF

Anker et al., N Engl J Med 2021; 385:1451

Summary: SGLT2i

- Consistent renal and HF benefits (both HFrEF and HFpEF) across all RCTs
- Renal 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: 34-39% RRR
  - eGFR dip (up to 30% drop from baseline) in acute phase (first 4 weeks) does not alter benefit
- HF hospitalization RRR by ~30% in HF trials
- The benefits are regardless of baseline ASCVD/HF status.
- Greater renal benefit in those with greater degree of proteinuria and CKD.
- Safety similar in those with CKD 3 and 4.

Effects of SGLT2 Inhibition on SAEs



Increased risk with SGLT2i:

- **DKA**
- **Mycotic genital infections** (only in DM), 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

- Avoid initiation of antihypertensives or diuretics or upward dose titration or diuretics at the same time as starting SGLT2i.
- Monitor BP/weight
- If Cr increase ≥25%, hold the drug and repeat Cr in 1 week and rechallenge when stable.

HOLD for:

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

Who may have higher risk with SGLT2i therapy

- T2D with DKA
- frequent genital tract infection
- Patients with urinary catheterization
- dynamic volume status
- PKD + immunosuppression (until data available)
- T1DM??

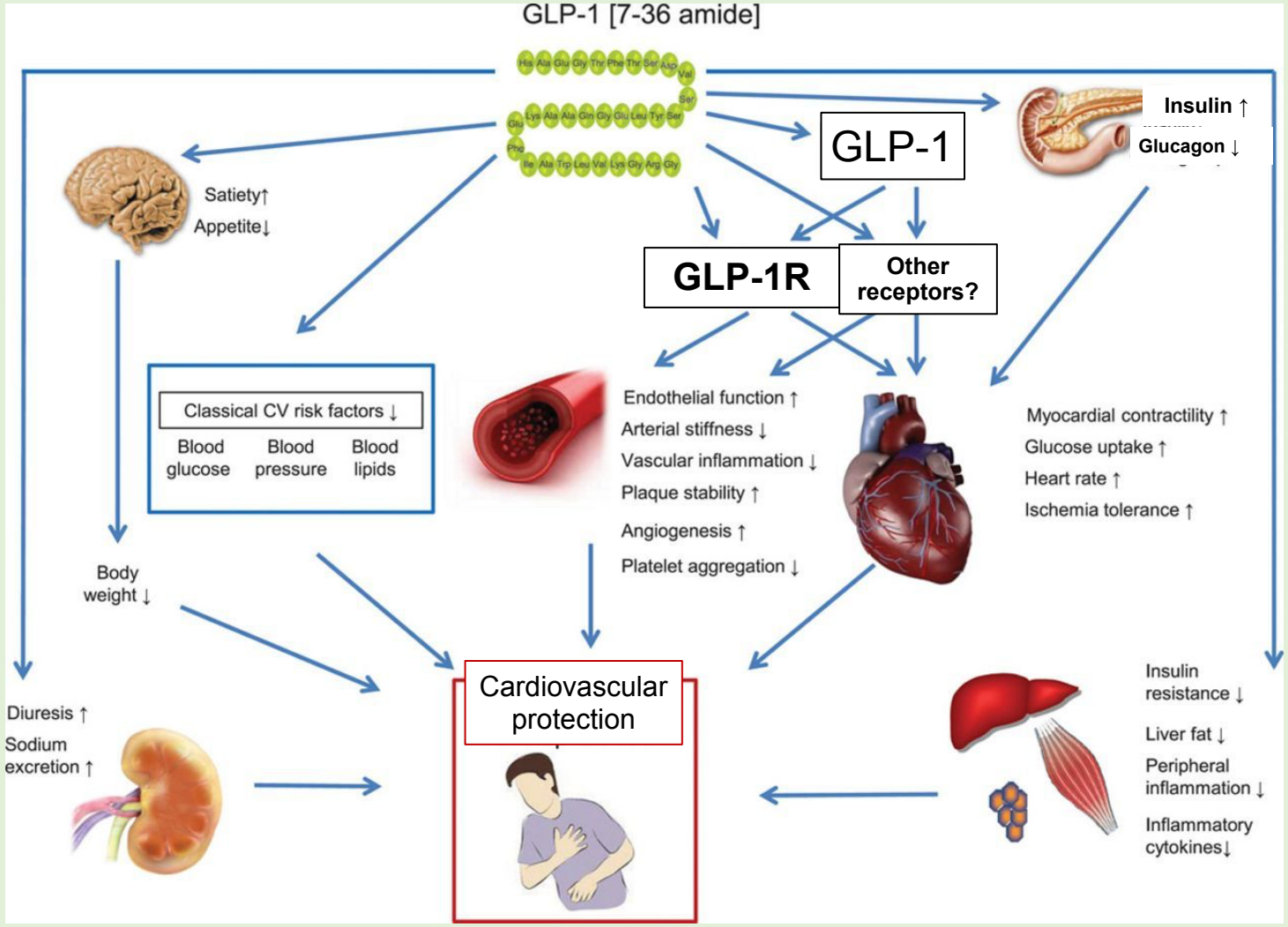
Cardiorenal effects of glucagon-like peptide-1 receptor agonists (GLP-1RA)

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

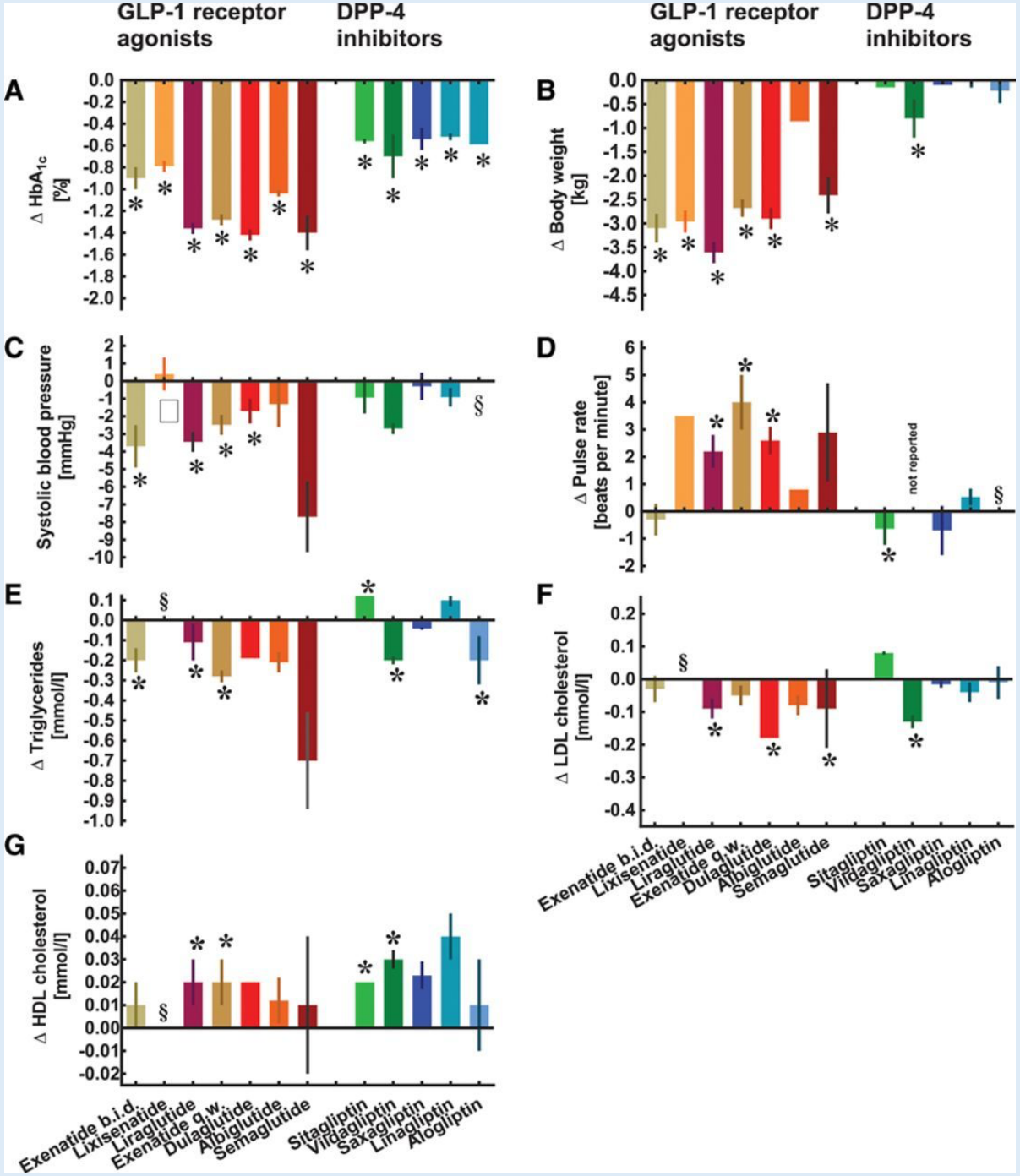


Adopted from Nauck et al., Circulation 2017, 136: 849

GLP-1 Receptor Agonists

	Short-Acting	Long-Acting
FDA-approved drugs	Exenatide (Byetta) Lixisenatide (Adlyxin)	Liraglutide (Victoza) Exenatide-LAR (Bydureon) Albiglutide (Tanzeum) Dulaglutide (Trulicity)
Half-life	2–5 h	12 h–several days
Fasting BG	Modest reduction	Strong reduction
A1C	Modest reduction	Strong reduction
Postprandial hyperglycemia	Strong reduction	Modest reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Weight reduction	1–5 kg	2–5 kg
Nausea	20%– 50%; slowly attenuates (weeks/months)	20%–40%; quickly attenuates (≅4 –8 weeks)
Heart rate	No/small increase (0-2 bpm)	Moderate increase (2-5 bpm)

Meier JJ. *Nat Rev Endocrinol*. 2012;8(12):728-742.
Lund A, et al. *Eur J Intern Med*. 2014;25(5):407-414.



Effects of treatment with GLP-1R agonists and DPP-4 inhibitors on CV risk factors as described in RCT

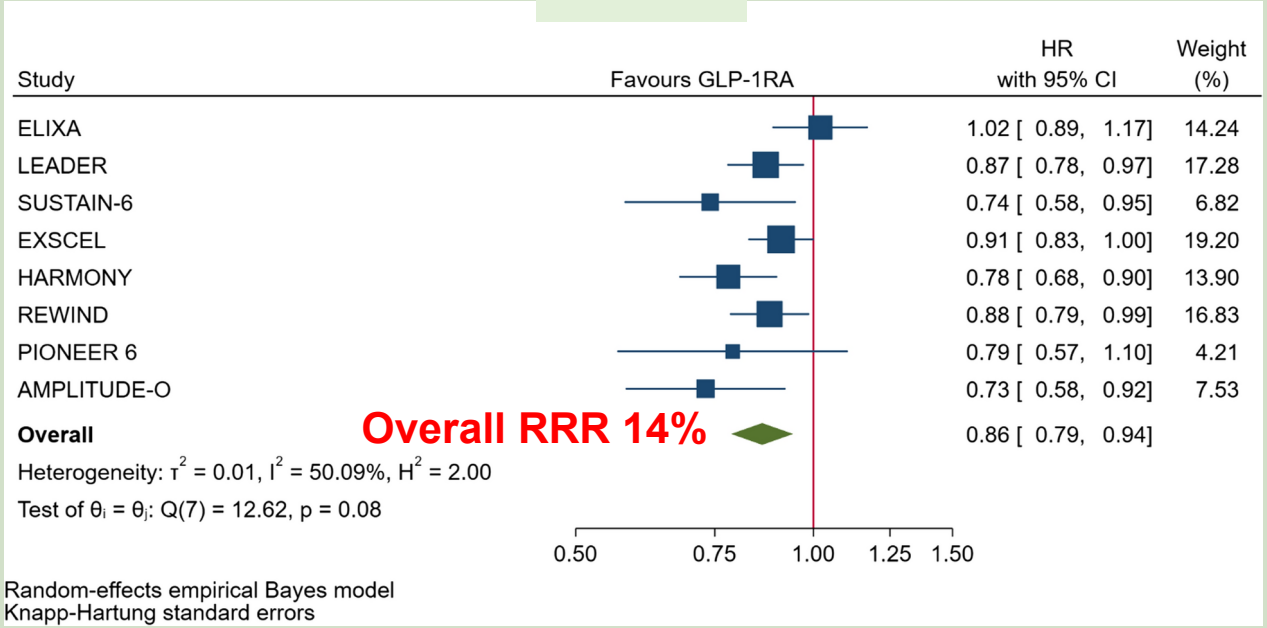
Nauck et al.,
Circulation. 2017;136:849

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

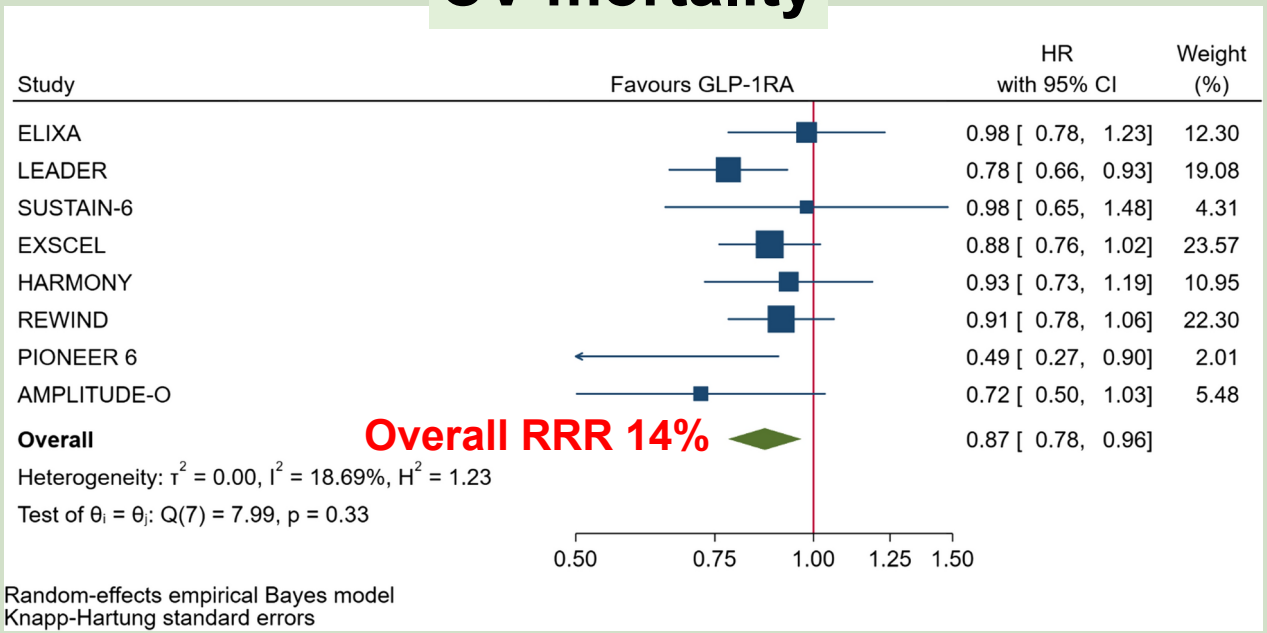
Primary outcome:

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

MACE

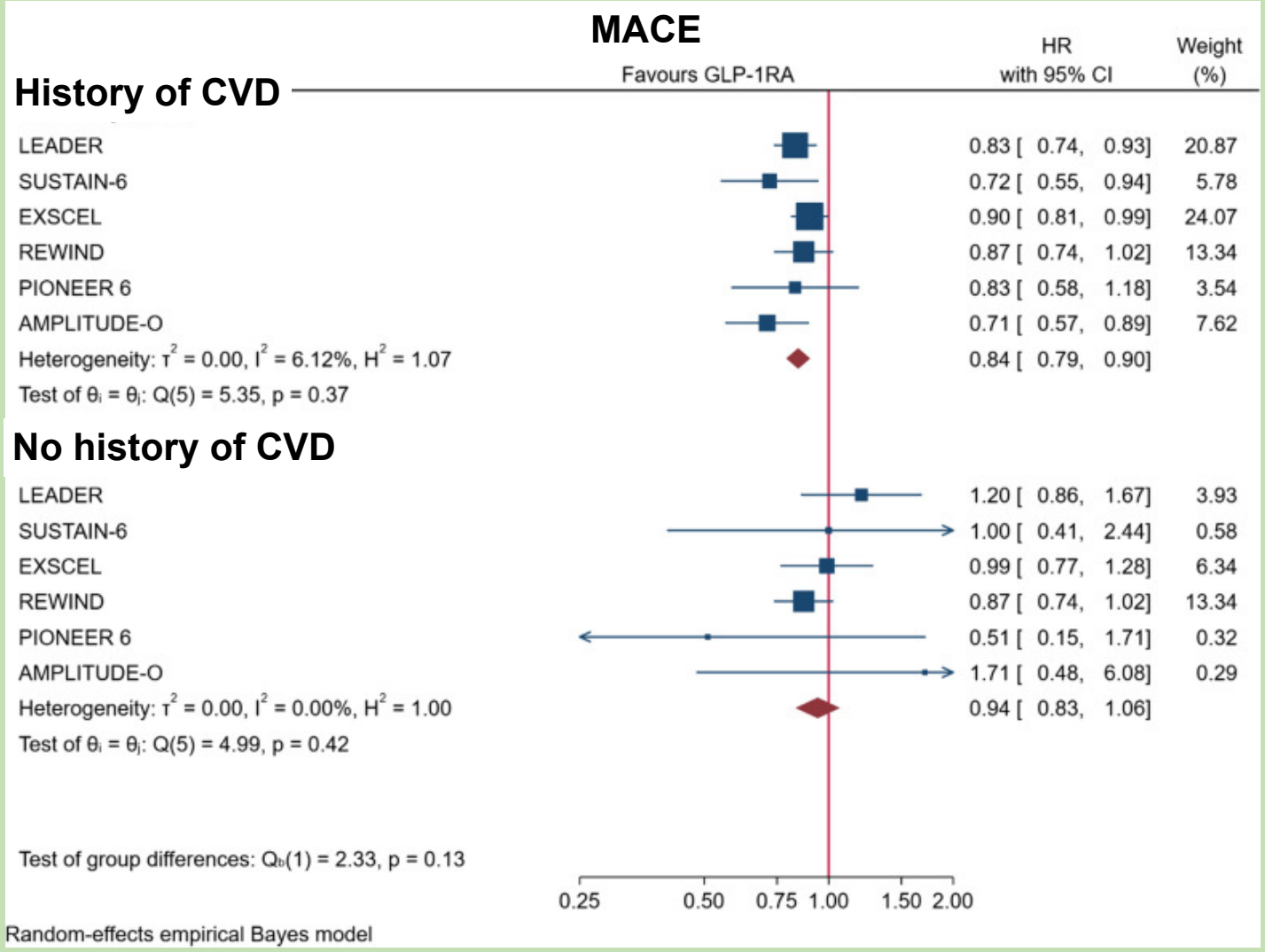


CV mortality



Giugliano D et al., Cardiovasc Diabetol. 2021;20:189

The benefit of GLP-1RA on MACE limited to those with history of CVD



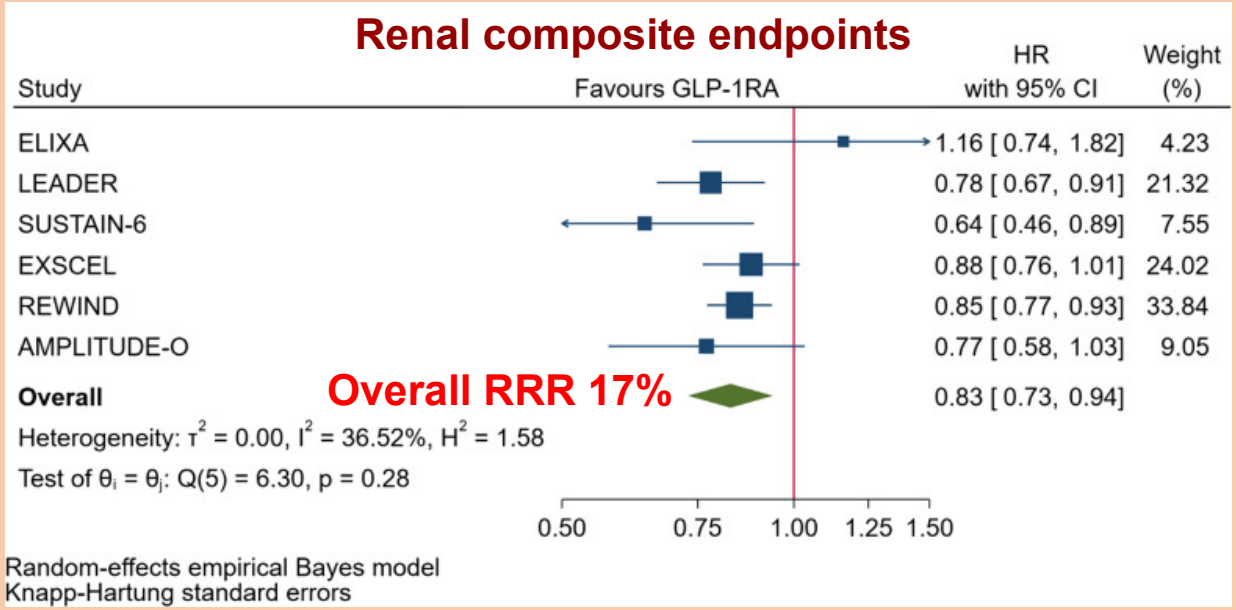
Giugliano D et al., Cardiovasc Diabetol. 2021;20:189

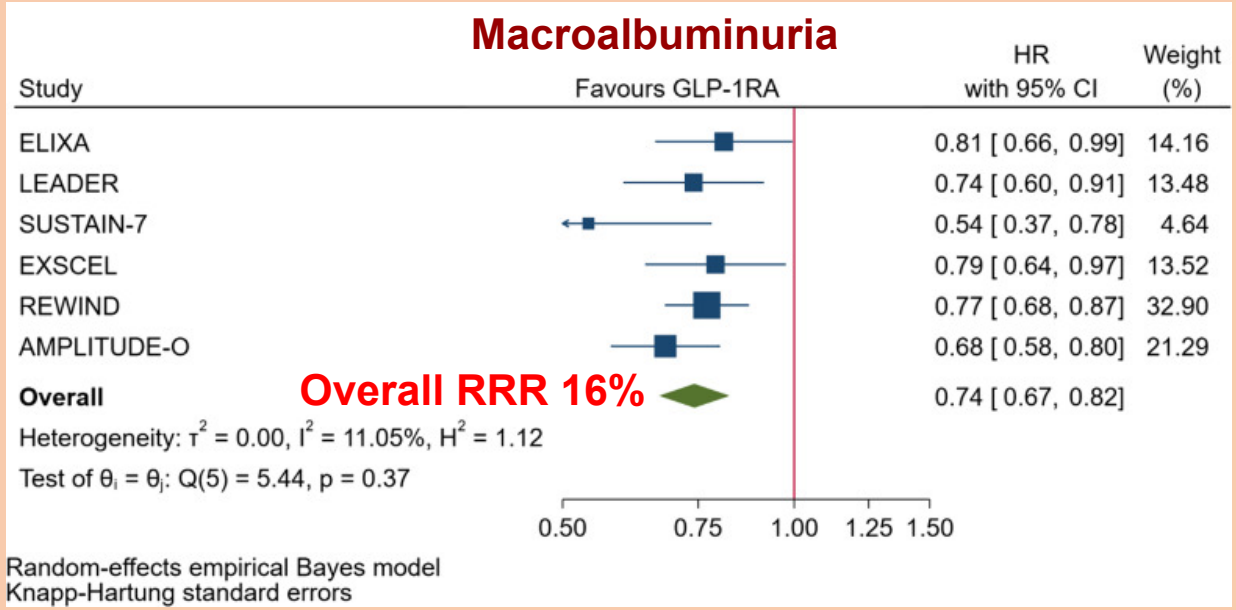
GLP-1RA: Renal outcomes

Renal composite endpoint:

- time to new-onset macroalbuminuria
- sustained decline in eGFR of ≥30% from baseline
- doubling of serum creatinine
- ESRD/chronic renal replacement therapy and/or renal death

In 6 CVOTs, GLP1-RA reduced the risk of the broad composite kidney outcome by 17% (HR = 0.83), which was driven by a reduction in macroalbuminuria only (HR = 0.74)





Giugliano D et al., Cardiovasc Diabetol. 2021;20:189

Use of GLP-1 RA in CKD

- There is limited experience with most GLP-1 receptor agonists in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2).

LONG-ACTING AGENTS

- **Liraglutide (Victoza), dulaglutide (Trulicity), and semaglutide (Ozembic):**
  - 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.
  - 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.

KDIGO 2020 guideline: KI (2020) 98:S1

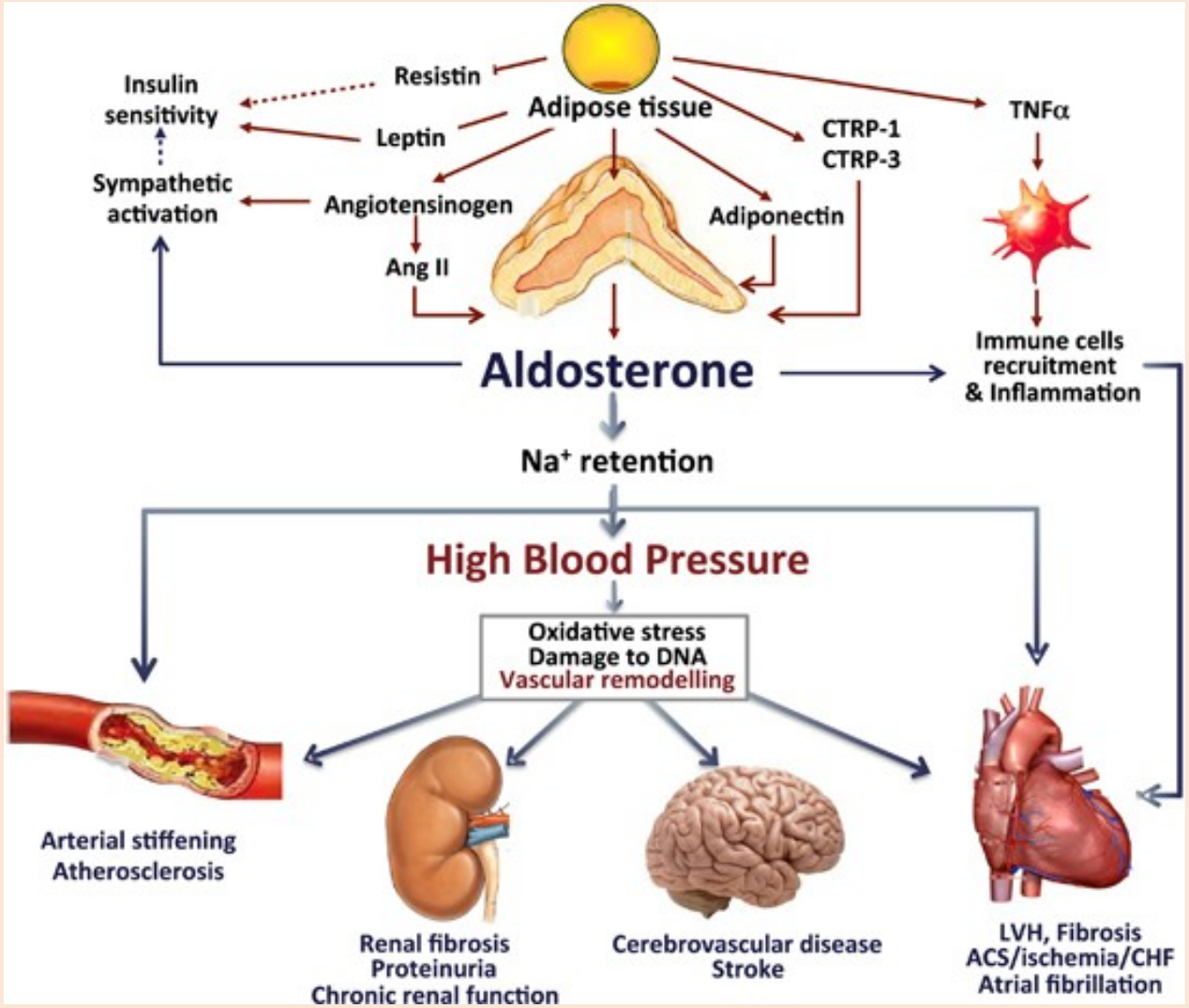
Drug	Trial	Kidney-related eligibility criteria	Primary outcome	Effect on primary outcome	Albuminuria	GFR loss	Adverse effects
SGLT2 inhibitors					**SGLT2 inhibitors**		
Empagliflozin	EMPA-REG OUTCOME	eGFR ≥30 ml/min per 1.73 m^2	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA
Canagliflozin	CANVAS trials	eGFR ≥30 ml/min per 1.73 m^2	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA, amputation
	CREDENCE	ACR >300 mg/g [30 mg/mmol] and eGFR 30–90 ml/min per 1.73 m^2	Progression of CKD[b]	↓↓	↓↓	↓↓	Genital mycotic infections, DKA
Dapagliflozin	DECLARE-TIMI 58	CrCl ≥60 ml/min	Dual primary outcomes: MACE and the composite of hospitalization for heart failure or CV death[c]	↔/↓	↓	↓↓	Genital mycotic infections, DKA
GLP-1 receptor agonists					**GLP-1 receptor agonists**		
Lixisenatide	ELIXA	eGFR ≥30 ml/min per 1.73 m^2	MACE	↔	↓	↔	None notable
Liraglutide	LEADER	eGFR ≥15 ml/min per 1.73 m^2	MACE	↓	↓	↔	GI
Semaglutide	SUSTAIN-6	Patients treated with dialysis excluded	MACE	↓	↓↓	NA	GI
	PIONEER 6	eGFR ≥30 ml/min per 1.73 m^2	MACE	↔	NA	NA	GI
Exenatide	EXSCEL	eGFR ≥30 ml/min per 1.73 m^2	MACE	↔	↔	↔	None notable
Albiglutide	HARMONY	eGFR ≥30 ml/min per 1.73 m^2	MACE	↓	↔	NA	Injection site reactions
Dulaglutide	REWIND	eGFR ≥15 ml/min per 1.73 m^2	MACE	↓	↓	↓	GI
DPP-4 inhibitors					**DPP4 inhibitors**		
Saxagliptin	SAVOR-TIMI 53	eGFR ≥15 ml/min per 1.73 m^2	MACE	↔	↓	↔	**↑HF, hypoglycemic events**
Alogliptin	EXAMINE	Patients treated with dialysis excluded	MACE	↔	NA	NA	None notable
Sitagliptin	TECOS	eGFR ≥30 ml/min per 1.73 m^2	MACE	↔	NA	NA	None notable
Linagliptin	CARMELINA	eGFR ≥15 ml/min per 1.73 m^2	Progression of CKD[b]	↔	↓	↔	None notable

Long-acting GLP-1 RAs

MACE ~12% RRR

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:

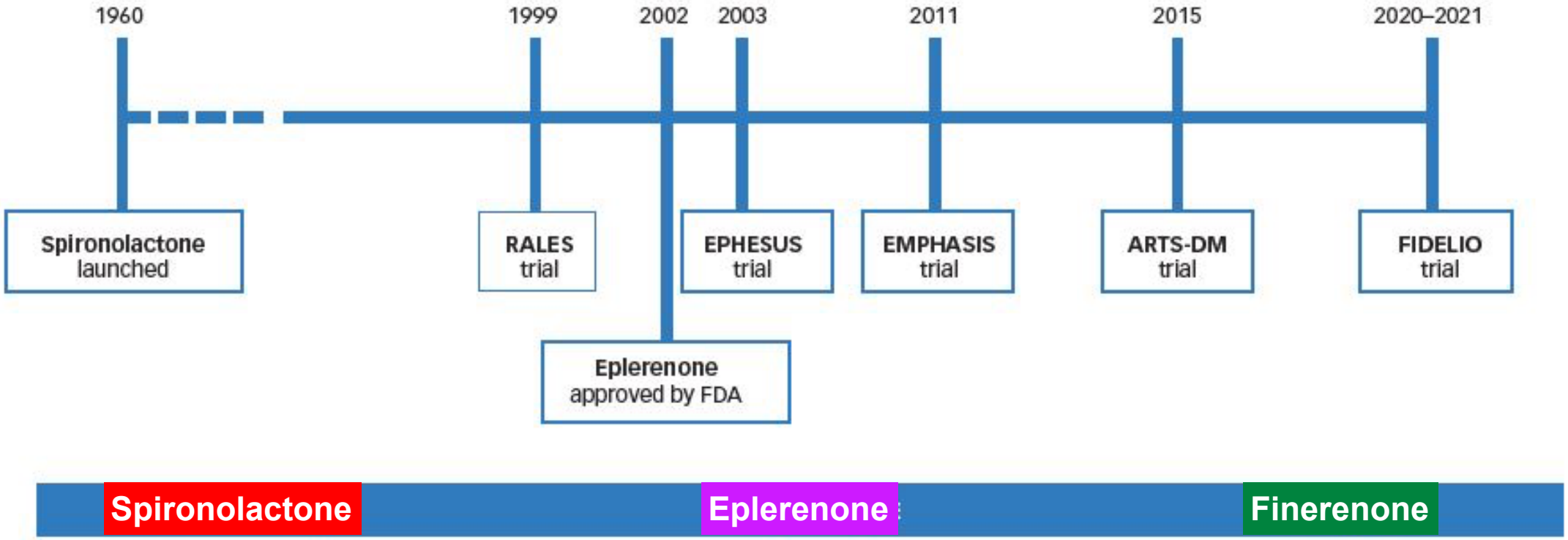
- myocardial hypertrophy
- ventricular remodeling
- proarrhythmogenic effects
- myocardial ischemia
- reduced coronary blood flow
- myocardial injury

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

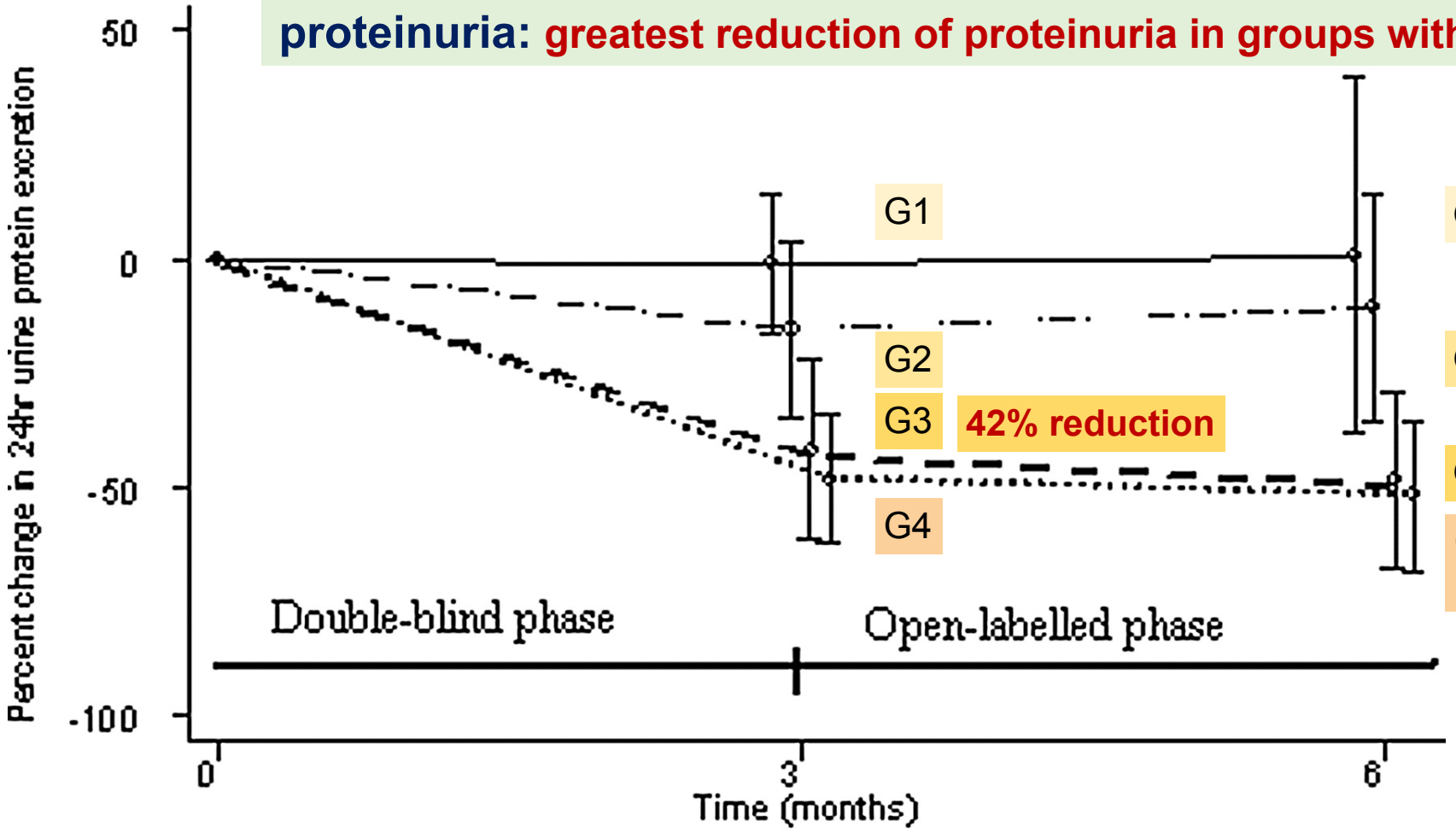
Milestones in the development of MRA for treatment of HF and diabetic kidney disease



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

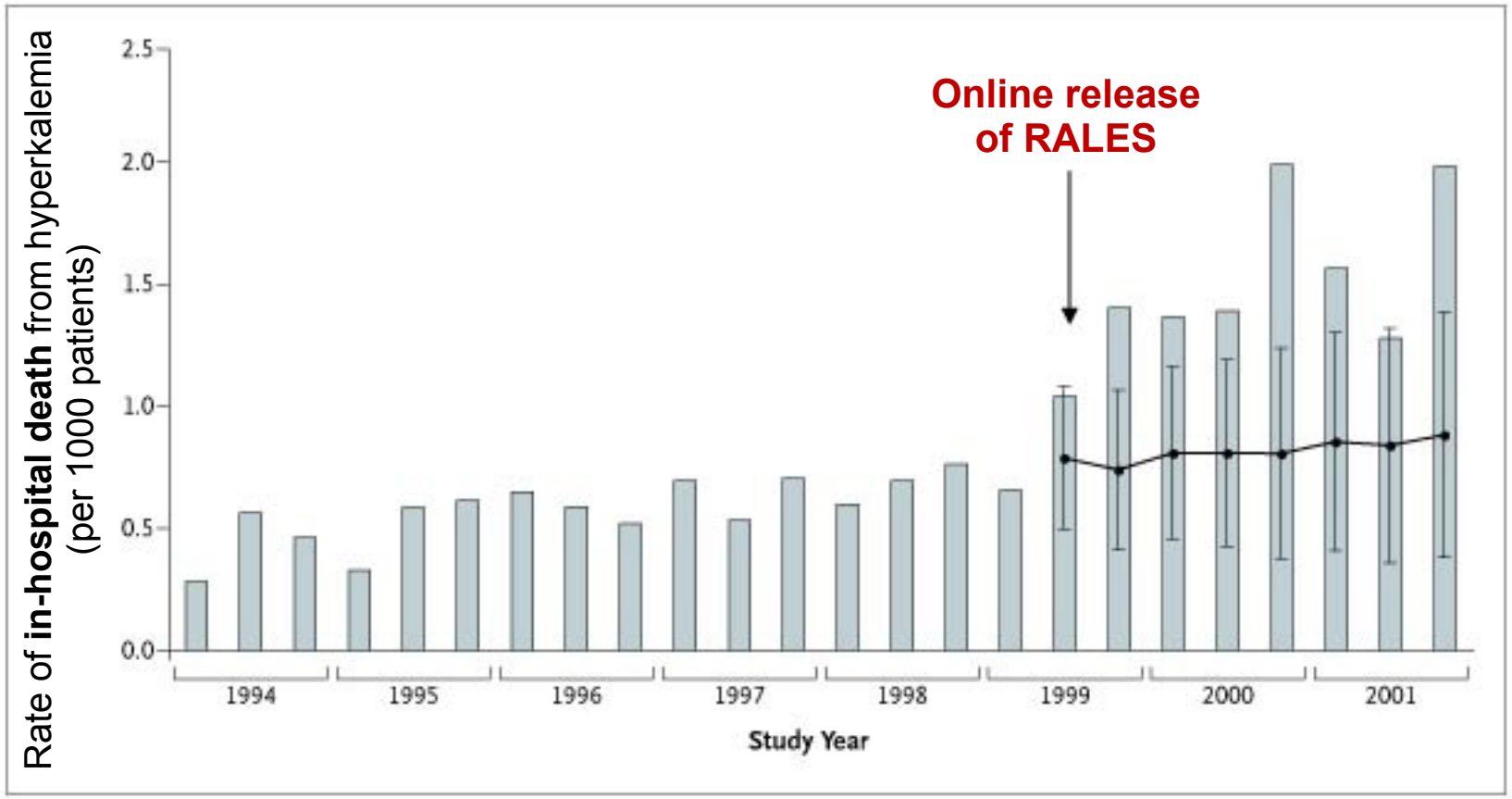
G4. Ramipril + irbesartan + spironolactone

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

CV outcomes in clinical trials with MRA

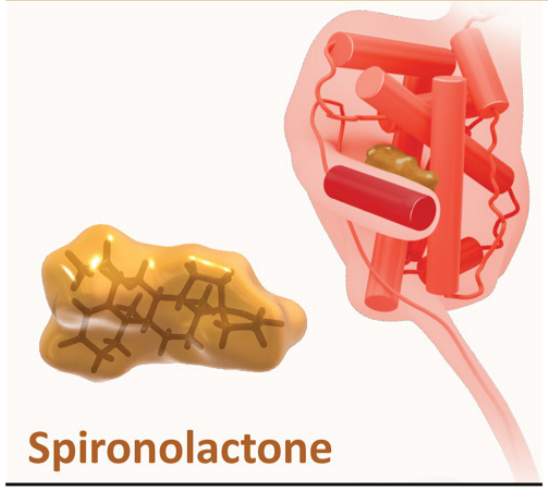
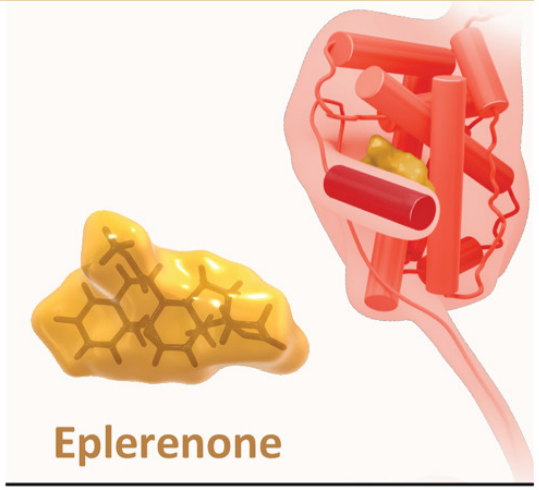
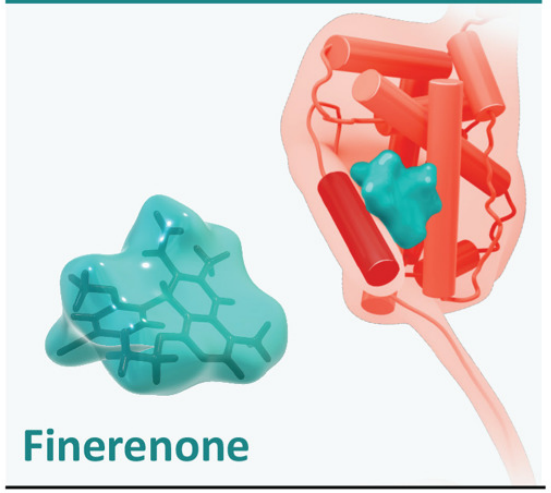
Trial	Patient group	N	MRA	Outcomes	
RALES	Severe HF, EF ≤35%, Cr ≤ 2.5, on ACEI/diuretics	822	Spironolactone	1. All-cause mortality	↓ 30% RRR
				2. HF hospitalization	↓ 35% RRR
EPHESUS	EF <40% and HF following MI on optimal medical therapy	6632	Eplerenone	1. All-cause mortality	↓ 15% RRR
				2. Death 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



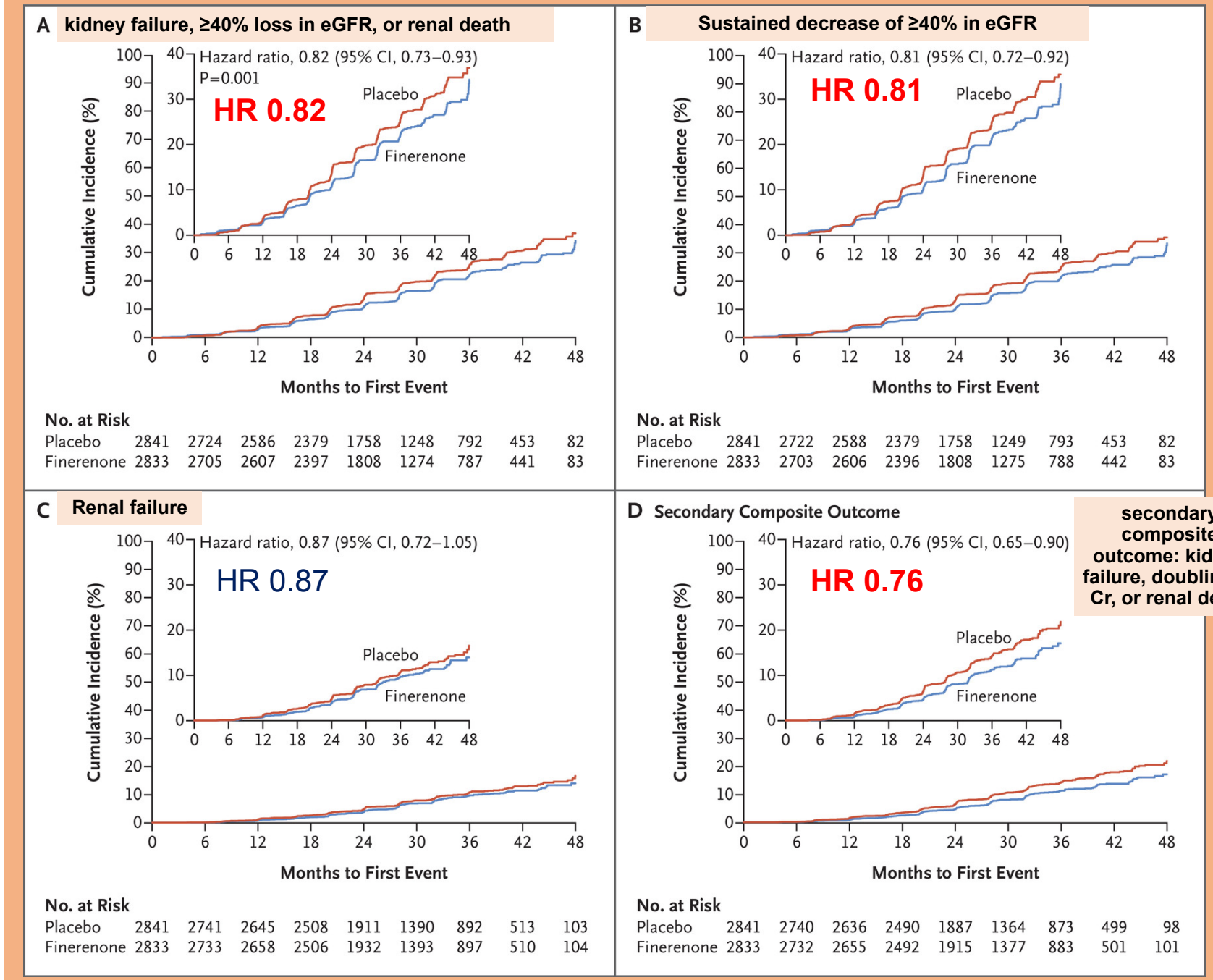
Juurlink DN et al., NEJM 2004; 351:543

Kintscher U et al.,
2021 British J Pharm

	Steroidal MRAs		Finerenone
	 Spironolactone	 Eplerenone	 Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (non-steroidal)
Potency to MR	+++	+	+++
Selectivity to MR	+	++	+++
CNS penetration	+	+	–
Sexual side effects	++	(+)	–
Half-life	>20 h**	4–6 h**	2–3 h*
Active metabolites	++	–	–
Effect on BP	+++	++	+

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

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

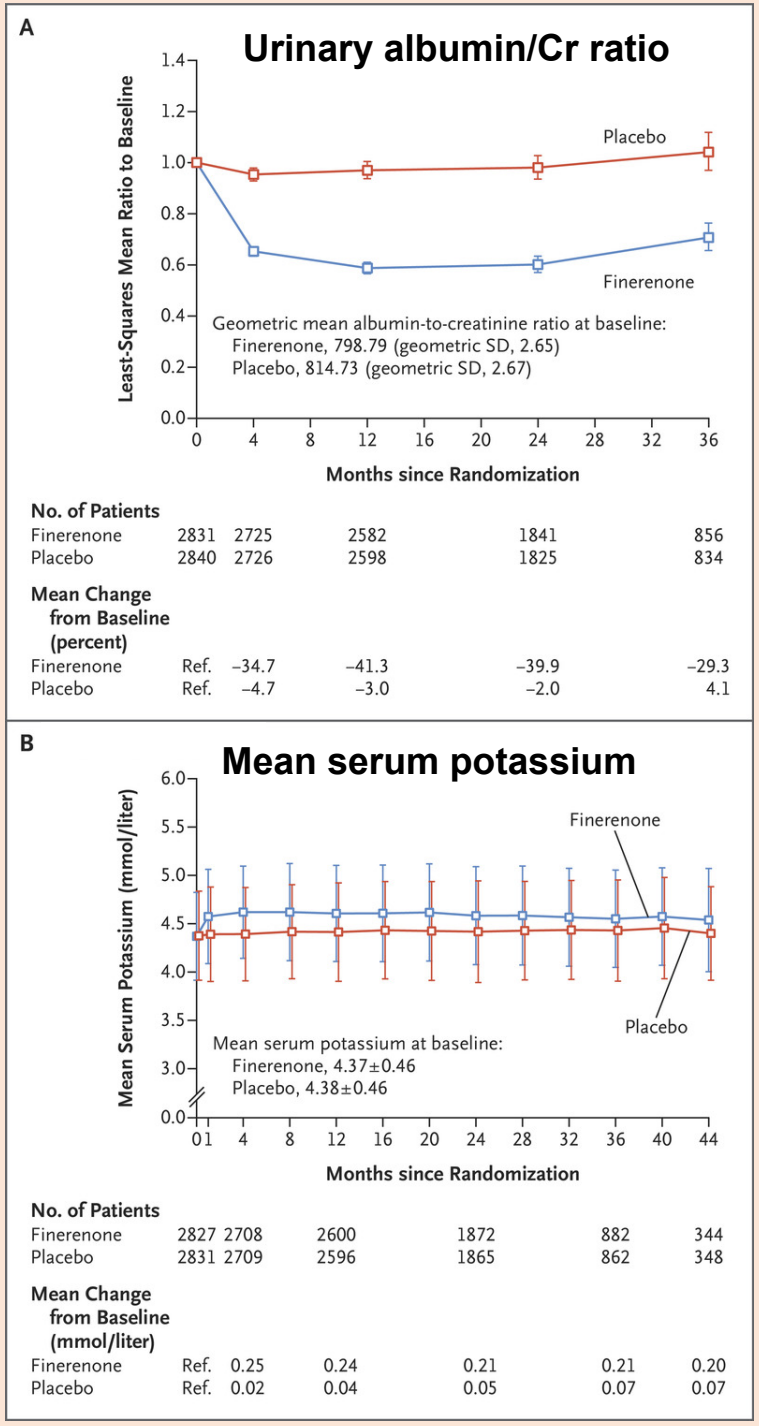


secondary composite outcome: kidney failure, doubling of Cr, or renal death

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

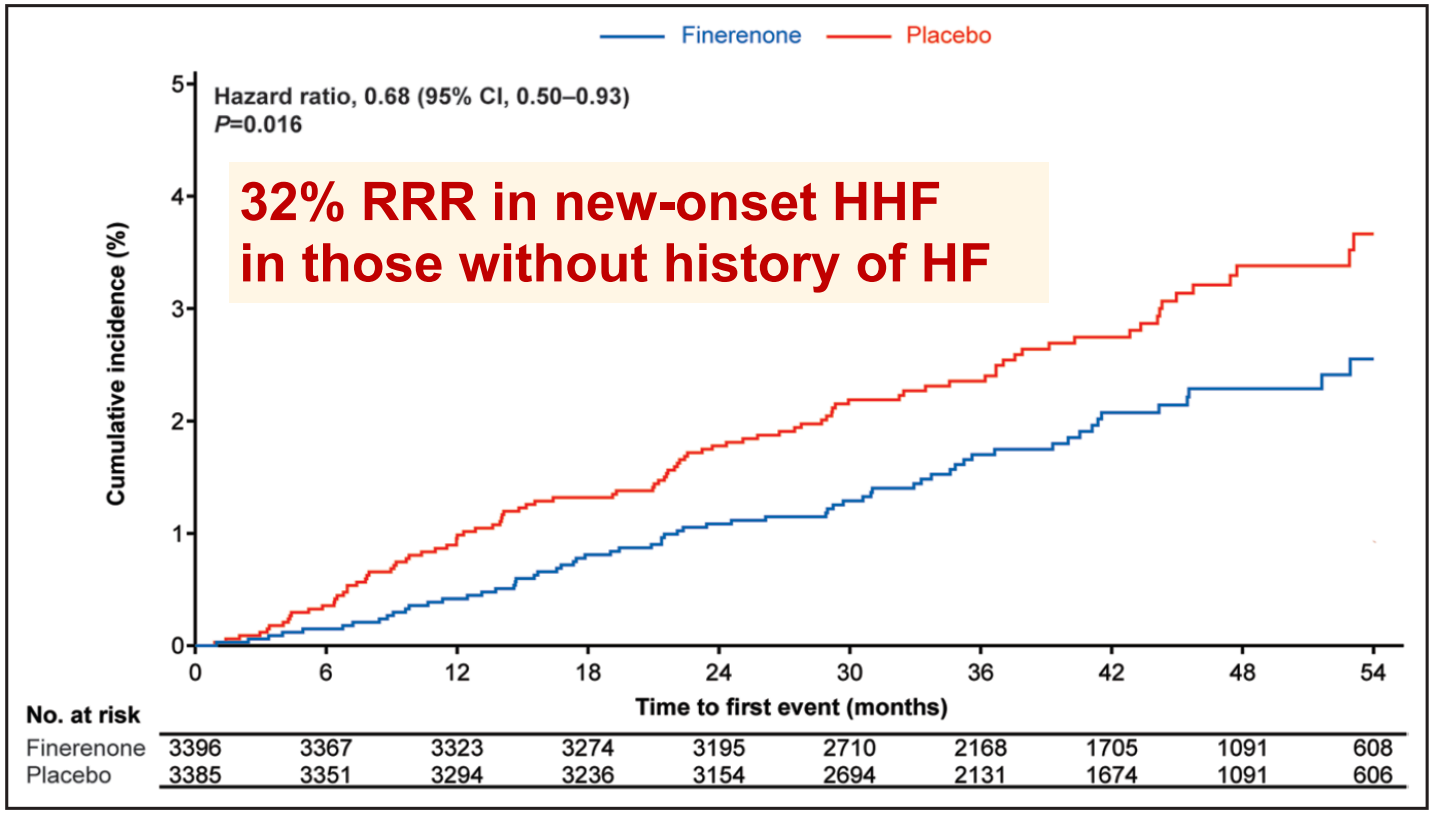


Effect of finerenone on proteinuria and hyperkalemia in diabetic CKD treated with ACEI/ARB

- 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



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

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

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.

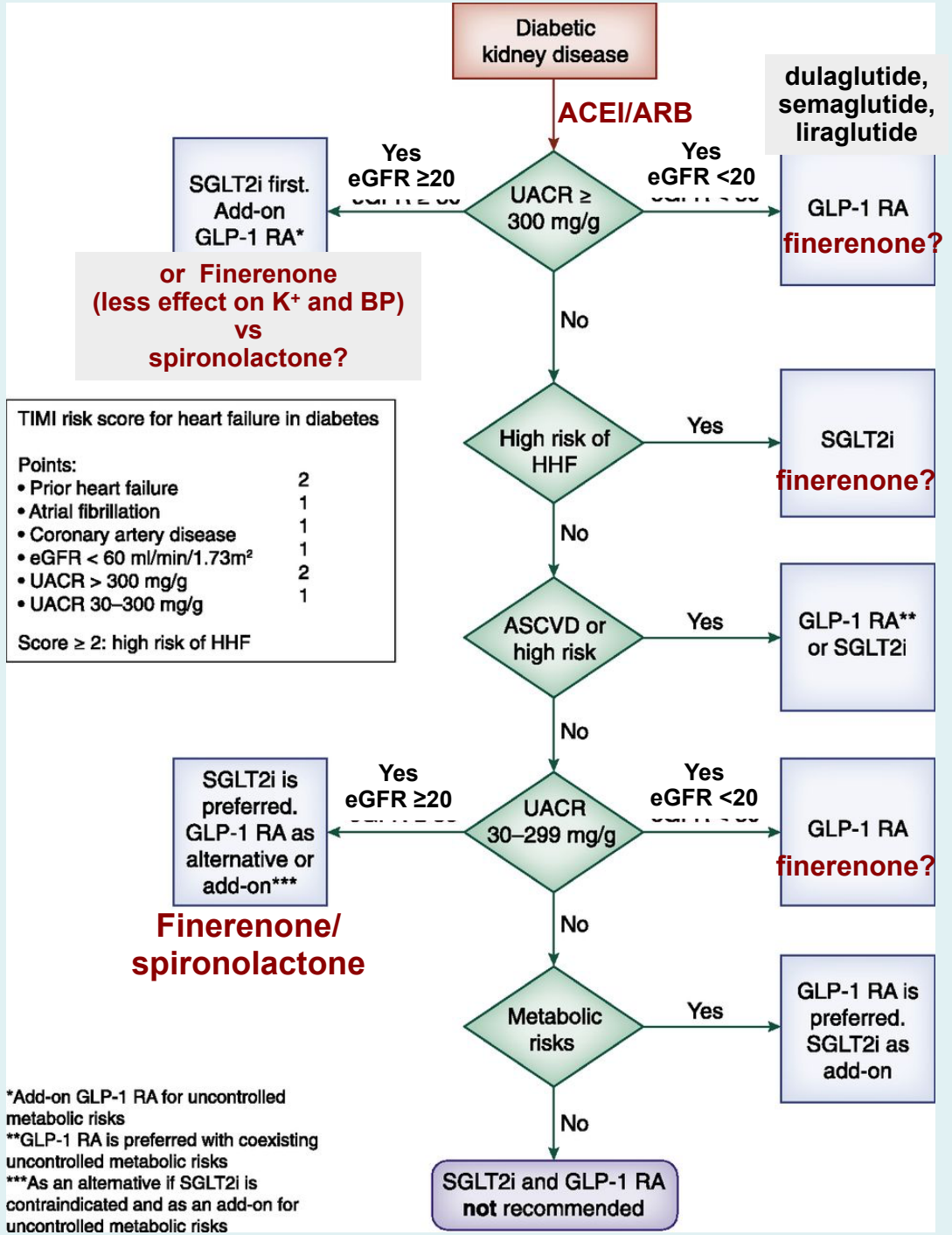
Overall summary

- **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.
- **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.
  - Not been studied in non-DM populations for CV or renal outcomes.
- **Finerenone: "prevent ESRD and HF with smaller effects on SBP and potassium"**
  - lower risk of severe hyperkalemia, decreased hypotensive effect (↓ SBP by 2-3 mm Hg)
  - significantly ***prevent incident HF*** in T2DM patients without symptomatic HF
  - Reduce composite renal endpoints by 18% on top of ACEI/ARB

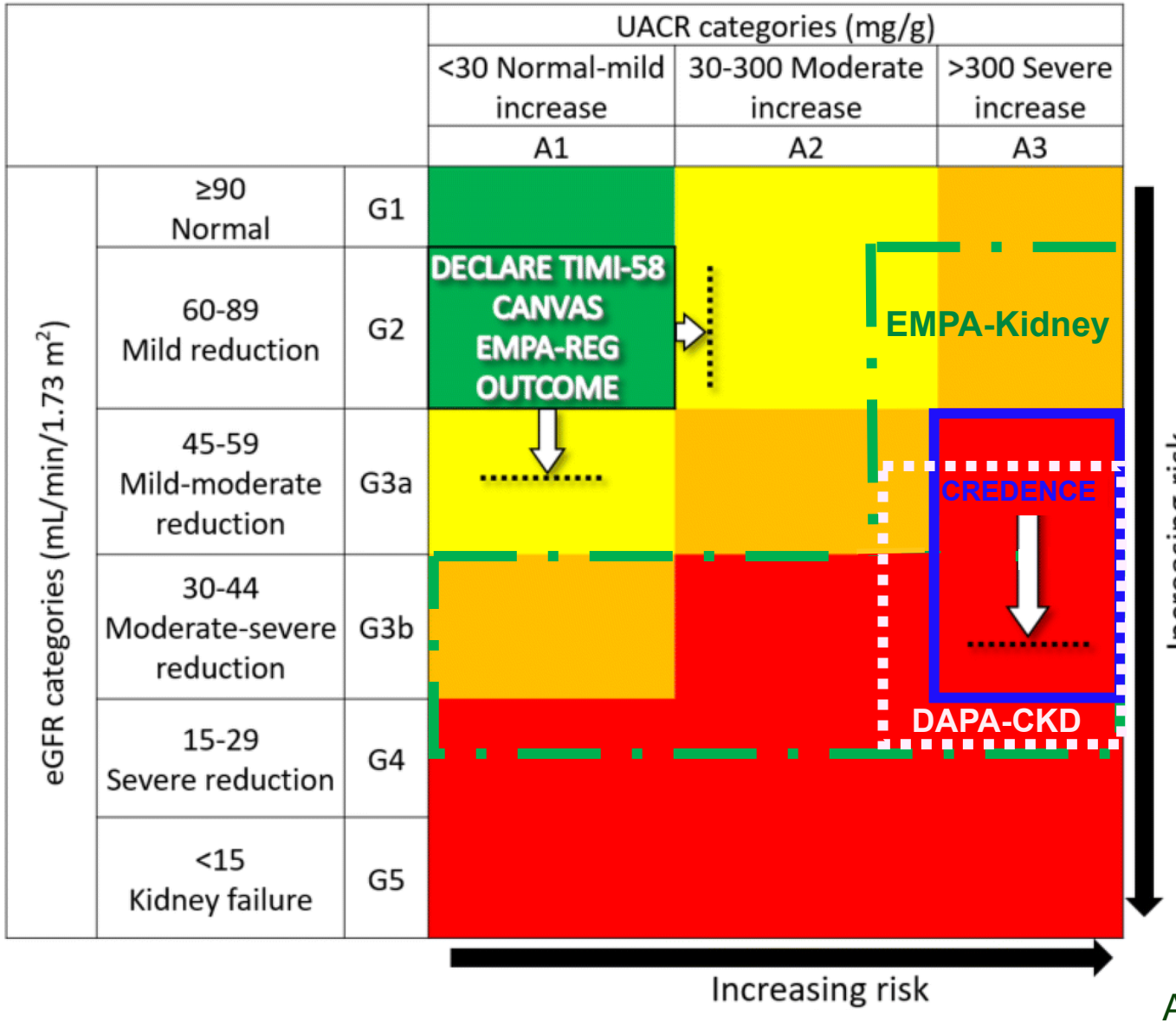
Decision algorithm for prescribing SGLT2i and GLP-1 RA to optimize cardiorenal protection in diabetic CKD

- Both SGLT2i and GLP-1 RA prevent progression to macroalbuminuria (by 20-30%) and reduce albuminuria (30-40%) in those with albuminuria ≥300 mg/g.
- Addition of finerenone to ACEI/ARB provides further 31% reduction of proteinuria and renal survival benefit.
- Currently, there is no head-to-head study comparing kidney failure protection between SGLT2i and GLP-1 RA. The recommendation is on the basis of the overall strength of the placebo-controlled trials of SGLT2i and GLP-1 RA.
- No data on the efficacy of GLP-1 RA or finerenone in non-diabetic CKD

Li et al., CJASN 2020 (15) 1678



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

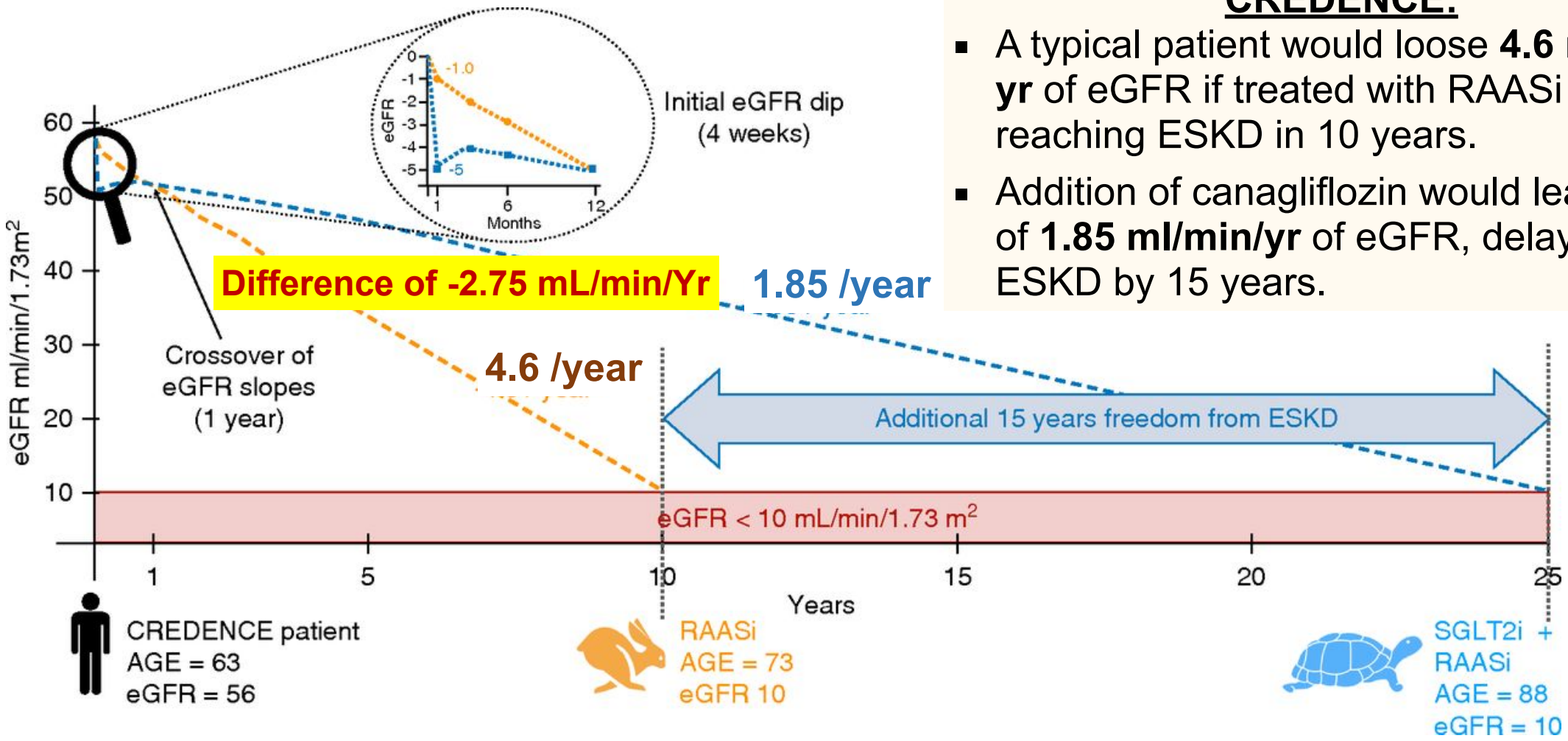
EMPA-KIDNEY: N = 6609
With or without T2DM
eGFR ≥ 20 - 45 *or*
eGFR ≥ 45 – 89 and UACR ≥200 mg/g

Adopted from Kluger et al., Cardiovasc Diabetology 2019

Studies on SGLT2 inhibitors and LV function

Author	Drug	Cohort	Imaging	Outcomes
Verma et al. 2016	Empa	10 pts with T2DM and CVD	TTE before and 3 months after	• Improved LV diastolic fx • Reduced LV mass index
Matsutani et al.	Cana	37 with T2DM with CVD or RFs	TTE before and 3 months after	• Improved LV diastolic fx • Reduced LV mass index
Soga et al.	Dapa	53 with T2DM & HFrEF or HFpEF	TTE before and 6 months after	• Improved LV diastolic fx • Reduced LV mass index, LA volume index • Improved LVEF
Sakai et al.	Empa/ Luseo/Tofo	59/63/62 T2DM with HFpEF	TTE before and 3 months after	• Improved LV diastolic fx according to the E/A and E/e′ ratios
Verma et al.	Empa vs. placebo	97 T2DM and CVD/48 placebo	Cardiac MRI before and 6 months after	• Improved LV mass index • No difference in LV EF and LV end-systolic vol
Cohen et al.	Empa vs. placebo	25 T2DM (8/25 placebo)	Cardiac MRI before and 6 months after	• Reduced LV end-diastolic volume • No difference in LV mass, LV EF, atrial volumes, and markers of cardiac fibrosis

SGLT2is may delay ESKD by 15 years

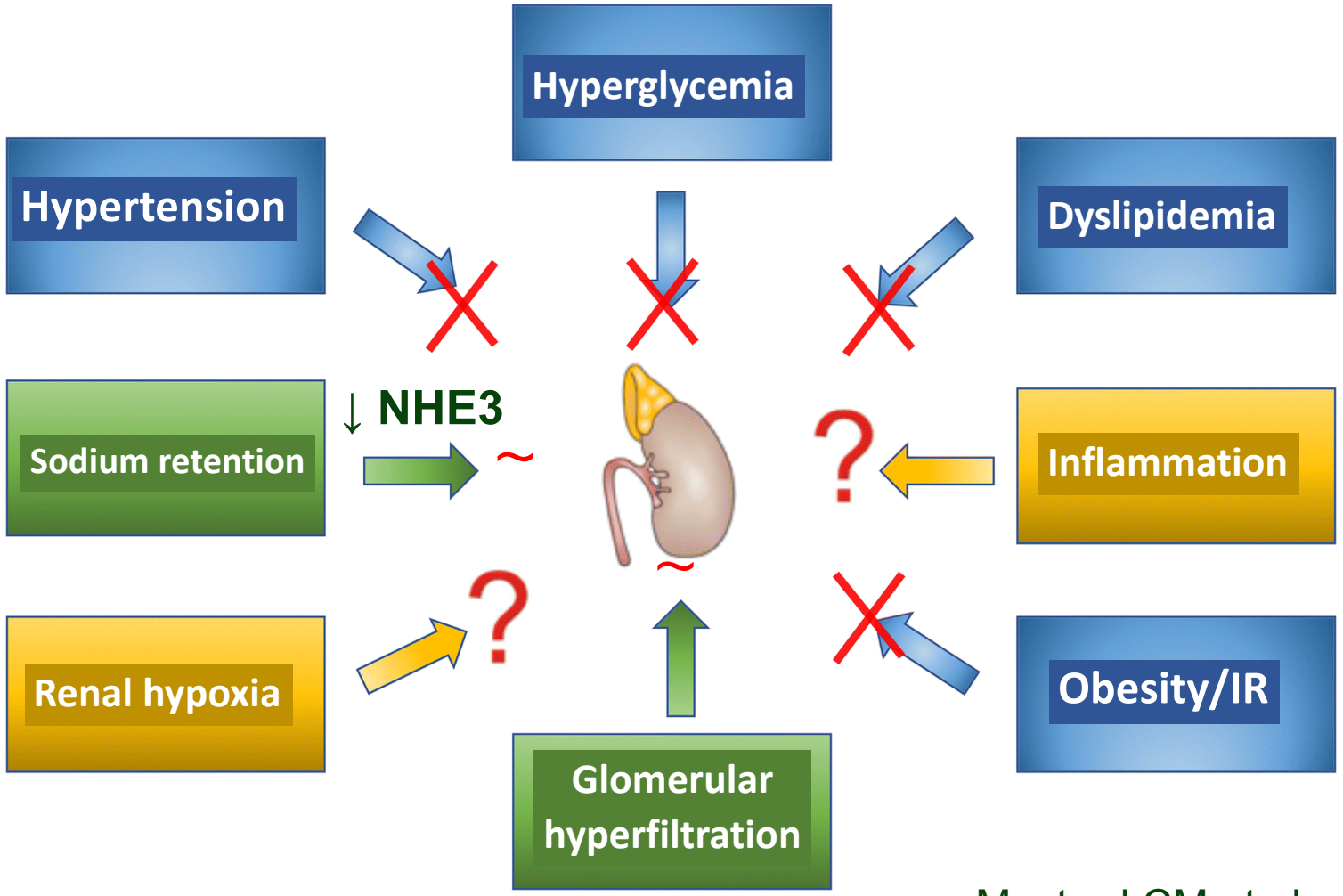


CREDENCE:

- A typical patient would loose **4.6 ml/min/yr** of eGFR if treated with RAASi only, reaching ESKD in 10 years.
- Addition of canagliflozin would lead to loss of **1.85 ml/min/yr** of eGFR, delaying ESKD by 15 years.

Meraz-Munoz et al., Kidney360:2021, 2 (6) 1042

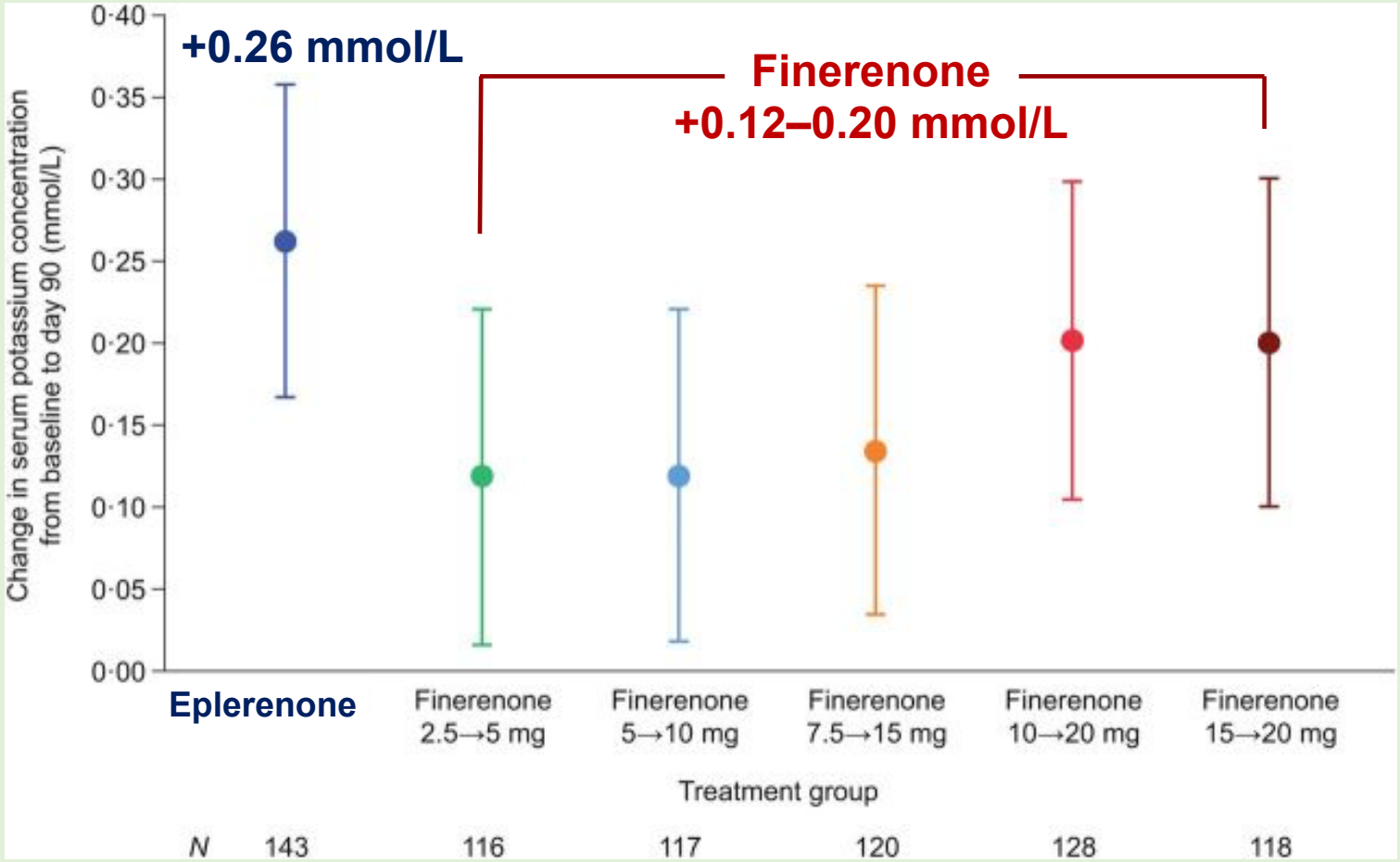
Nephroprotective effects of GLP-1 receptor agonists



Mosterd CM et al., J Nephrol 2020, 33:965

Finerenone associated with less increase in serum K^+ compared to steroidal MRA eplerenone: ARTS-HF study

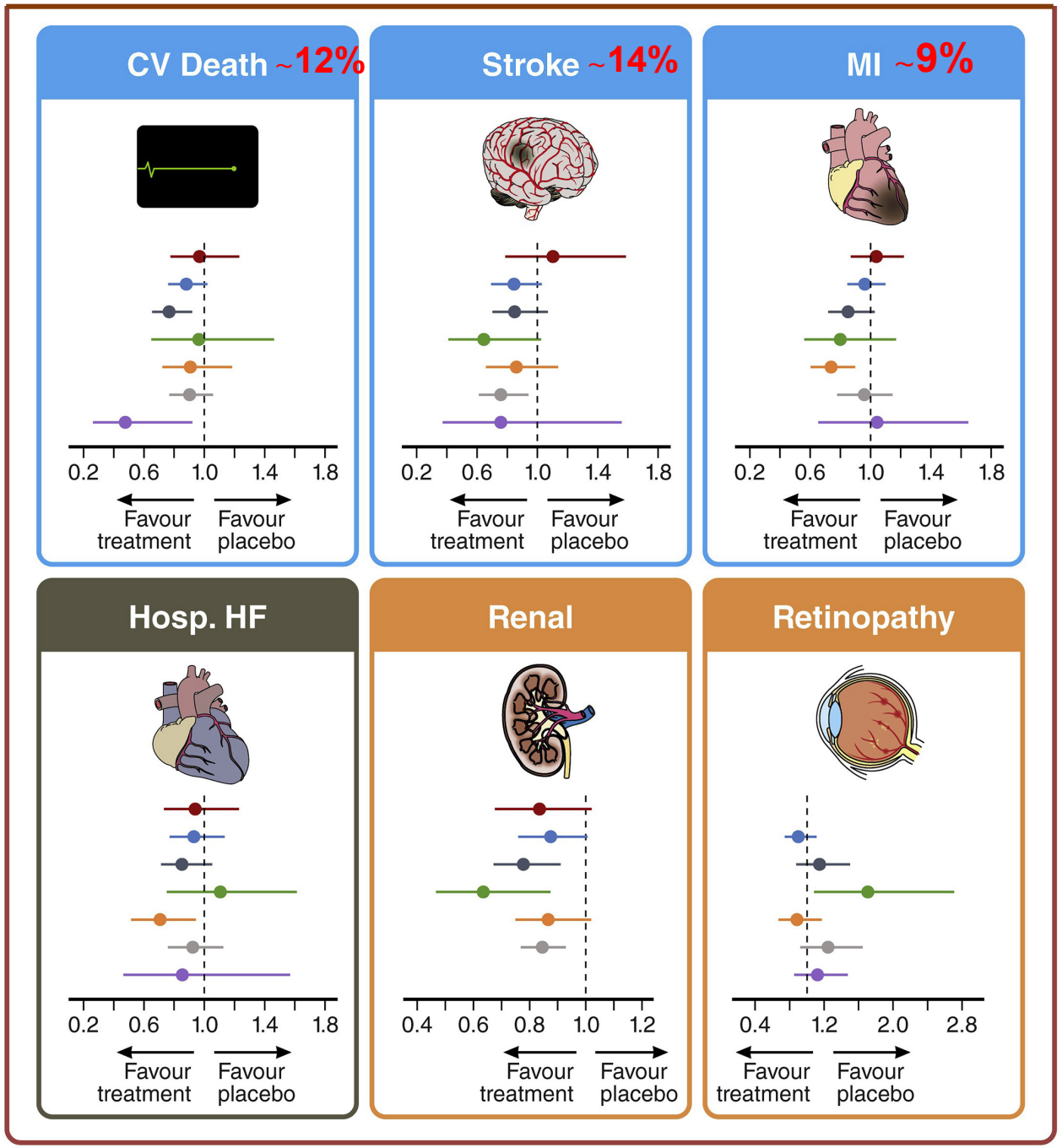
Mean change in serum [K^+] from baseline to Day 90 in patients with worsening chronic HFrEF



- A phase 2b, RCT of 1066 patients with worsening HFrEF (EF ≤ 40%) requiring hospitalization with IV diuretics
- T2DM with eGFR >30 or no DM with eGFR 30-60
- Mean change from baseline to Day 90 in serum potassium concentration was greater in the eplerenone group **(+0.26 mmol/L)** than in each of the finerenone dose groups **(+0.12–0.20 mmol/L)**

Eur Heart J. 2016 Jul 14; 37(27): 2105

GLP-1 RA in T2DM: Review of CV Outcome Trials



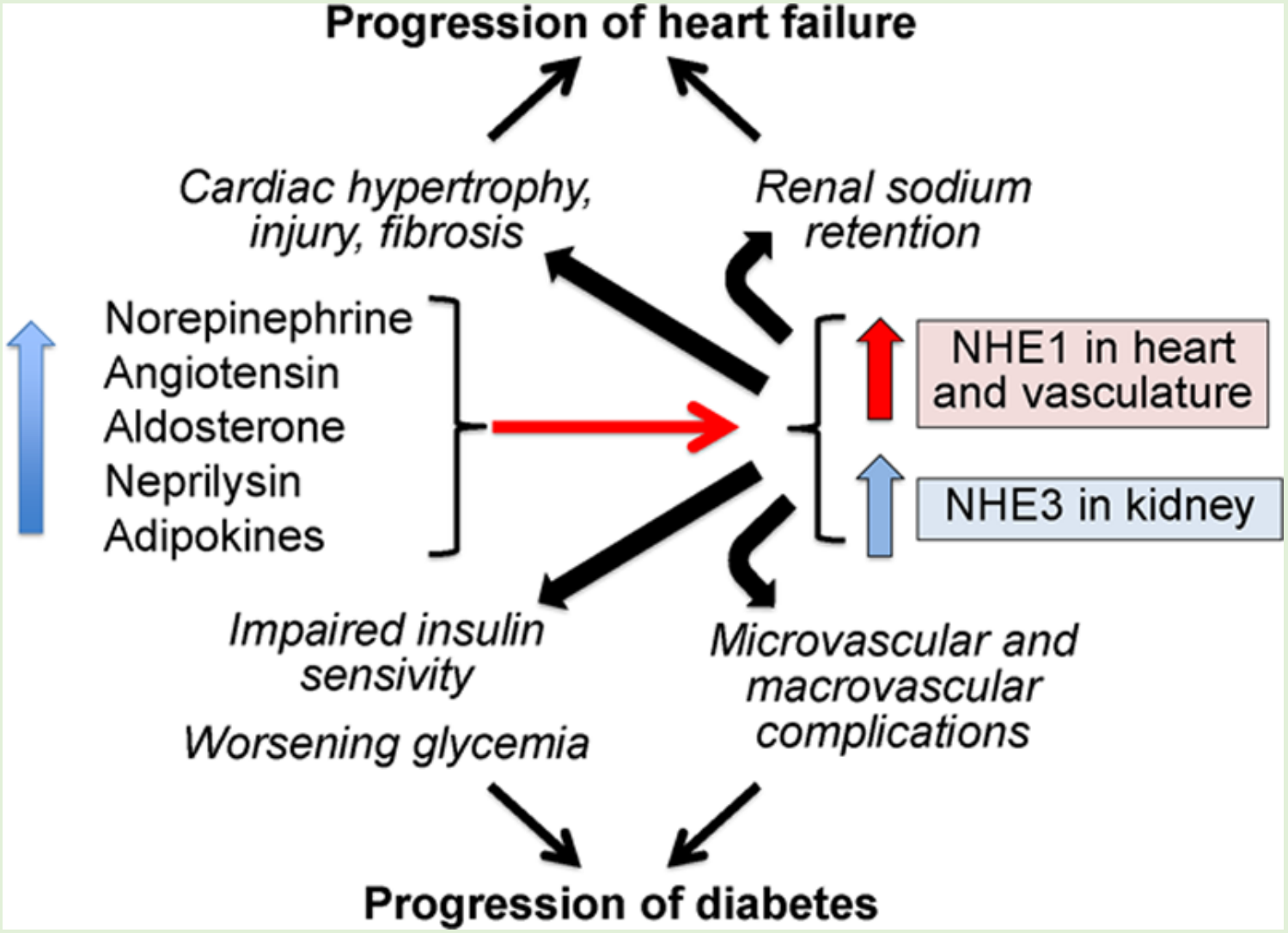
Renal composite endpoint:

typically composed of the following:

- **time to new-onset macroalbuminuria**
- **sustained decline in eGFR of ≥30% from baseline**
- **doubling of serum creatinine**
- **ESRD/chronic renal replacement therapy and/or renal death**

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

NHE-dependent pathways that may underlie the interplay of the pathogenesis of HF and diabetes

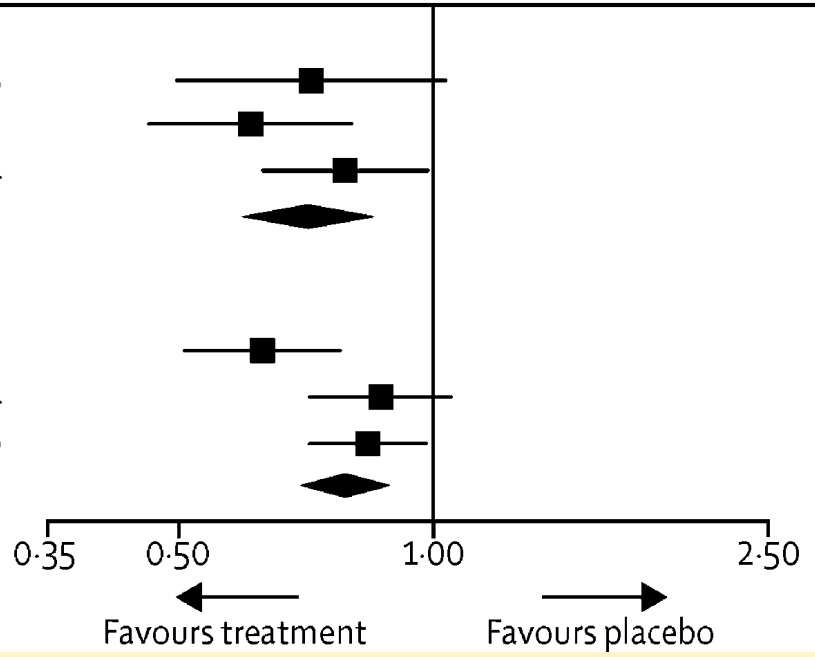


Packer,
Circulation 2017

Meta-analysis of SGLT2i trials on HF hospitalization and CV death stratified by history of HF

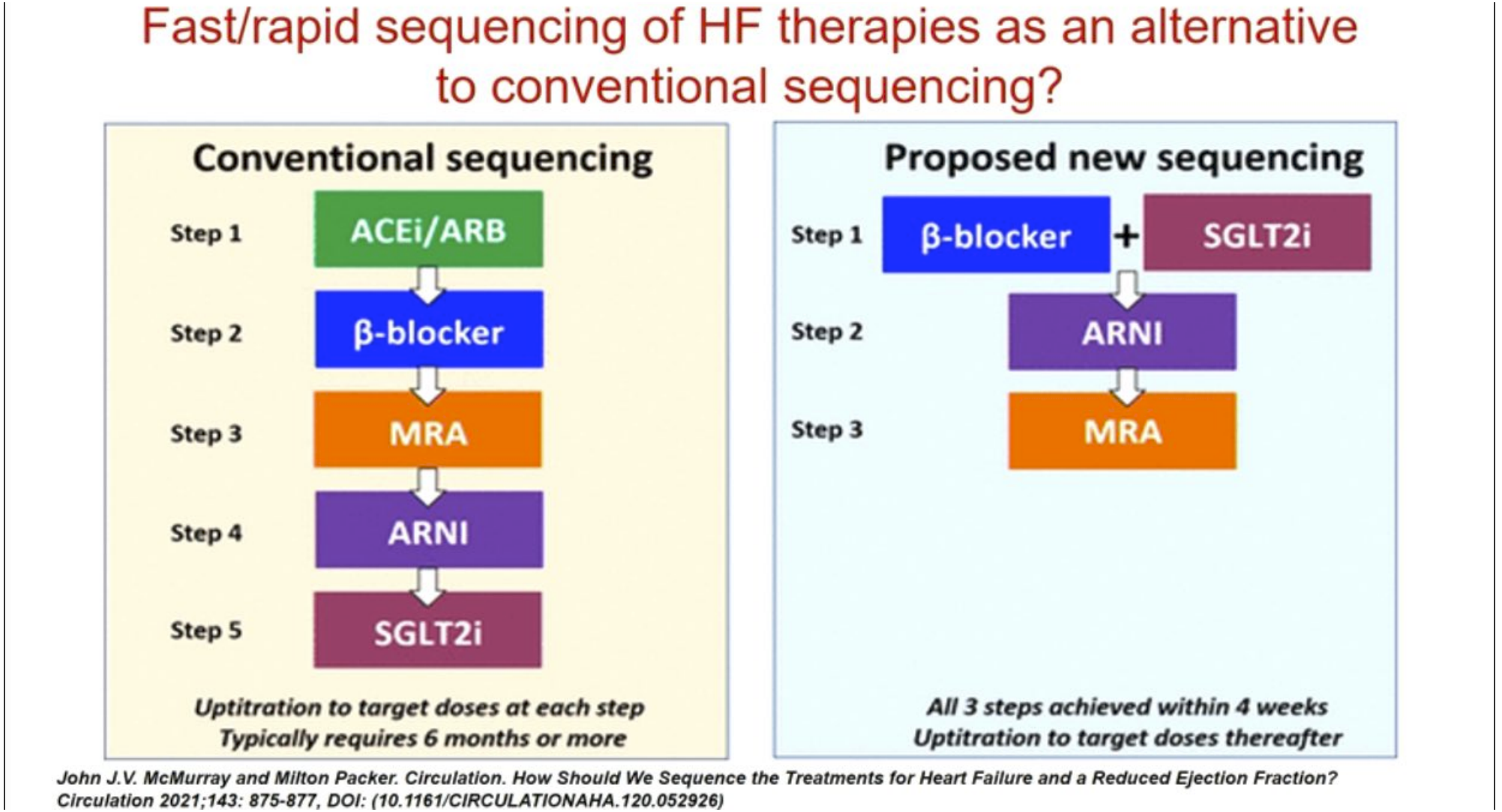
The reduction in the composite of CV death or hospitalization for HF was not statistically different in patients with (HR 0·71 [95% CI 0·61–0·84]) or without (0·79 [0·71–0·88]) a history of HF at baseline.

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with history of heart failure								
EMPA-REG OUTCOME	462	244	124	63·6	85·5	23·6		0·72 (0·50–1·04)
CANVAS Program	803	658	203	35·4	56·8	34·1		0·61 (0·46–0·80)
DECLARE-TIMI 58	852	872	314	45·1	55·5	42·4		0·79 (0·63–0·99)
Fixed effects model for history of heart failure (p<0·0001)								**0·71 (0·61–0·84)**
Patients with no history of heart failure								
EMPA-REG OUTCOME	4225	2089	339	15·5	24·9	30·0		0·63 (0·51–0·78)
CANVAS Program	4992	3689	449	13·6	15·2	32·4		0·87 (0·72–1·06)
DECLARE-TIMI 58	7730	7706	599	8·9	10·5	37·6		0·84 (0·72–0·99)
Fixed effects model for no history of heart failure (p<0·0001)								**0·79 (0·71–0·88)**



Zelniker et al. Lancet 2019 (393):31=39

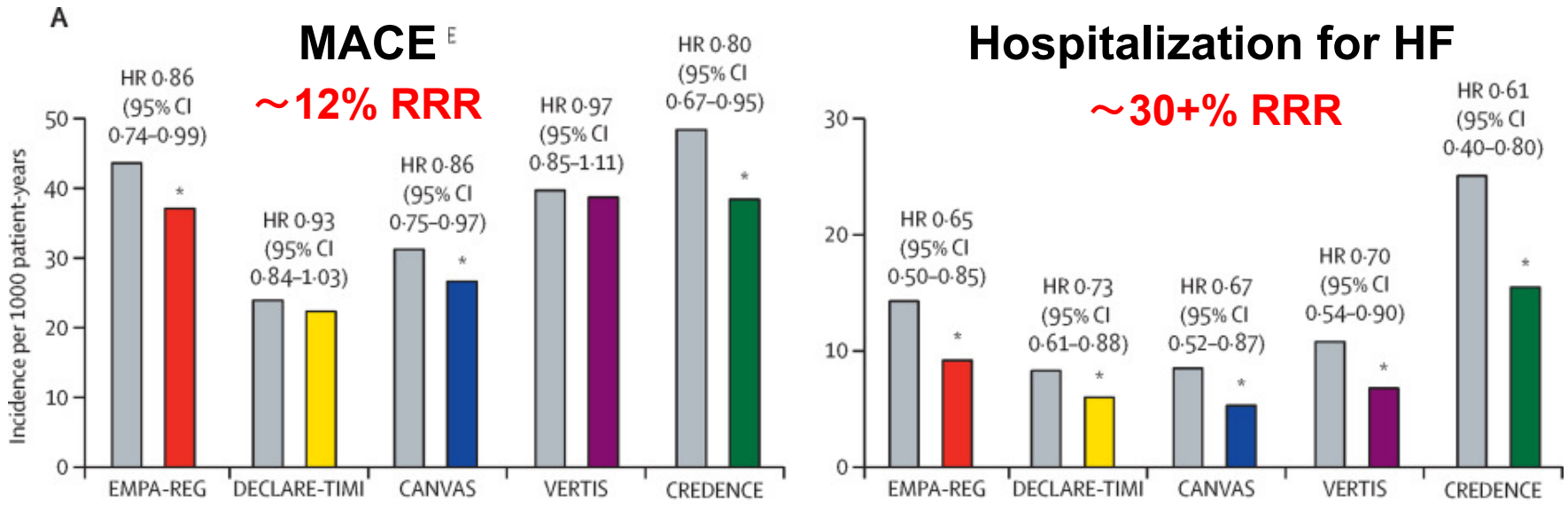
HF THERAPEUTICS RE-ORGANIZED



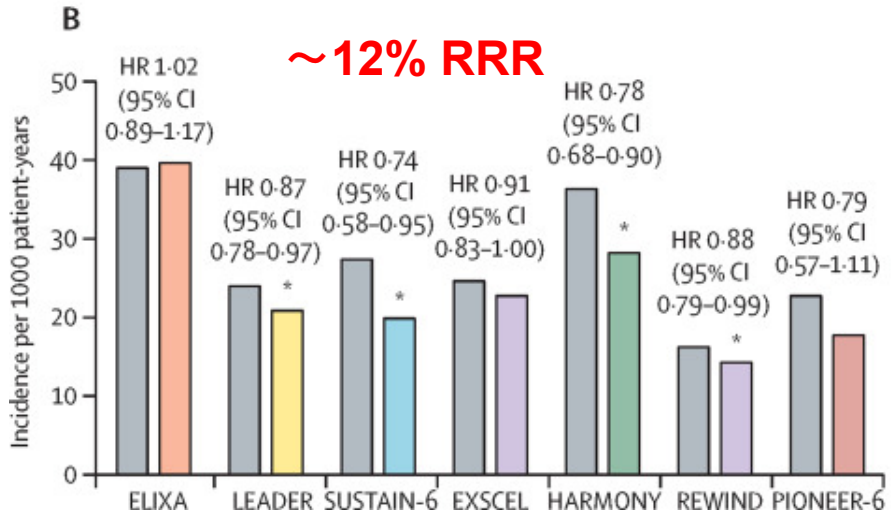
John J.V. McMurray and Milton Packer. Circulation. How Should We Sequence the Treatments for Heart Failure and a Reduced Ejection Fraction? Circulation 2021;143: 875-877, DOI: (10.1161/CIRCULATIONAHA.120.052926)

Cardiovascular outcomes from the key CV outcome trials with SGLT2i and GLP-1R agonists versus placebo

SGLT2i

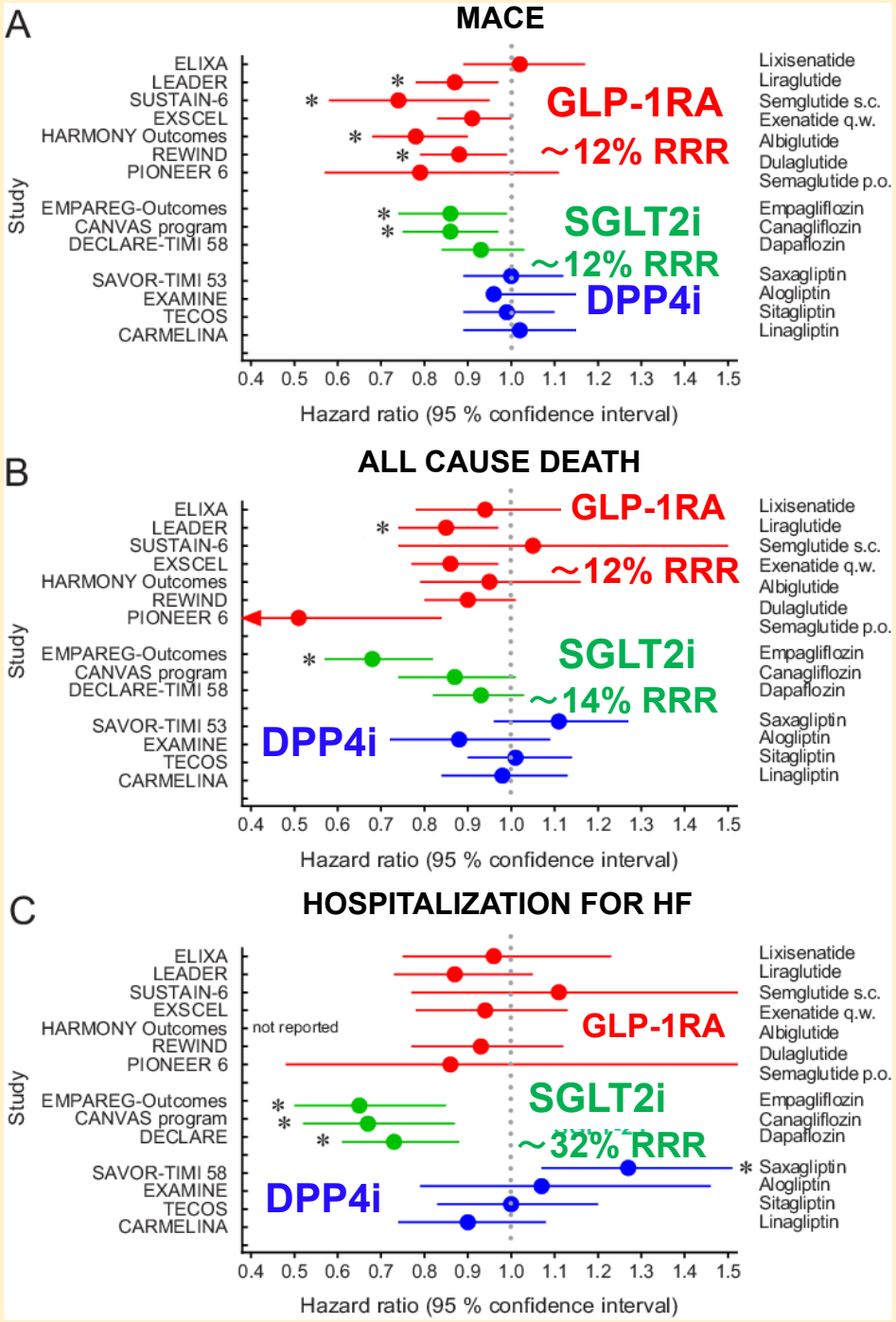


GLP-1R agonists



Placebo:

Brown et al., Lancet 2021, 398:262

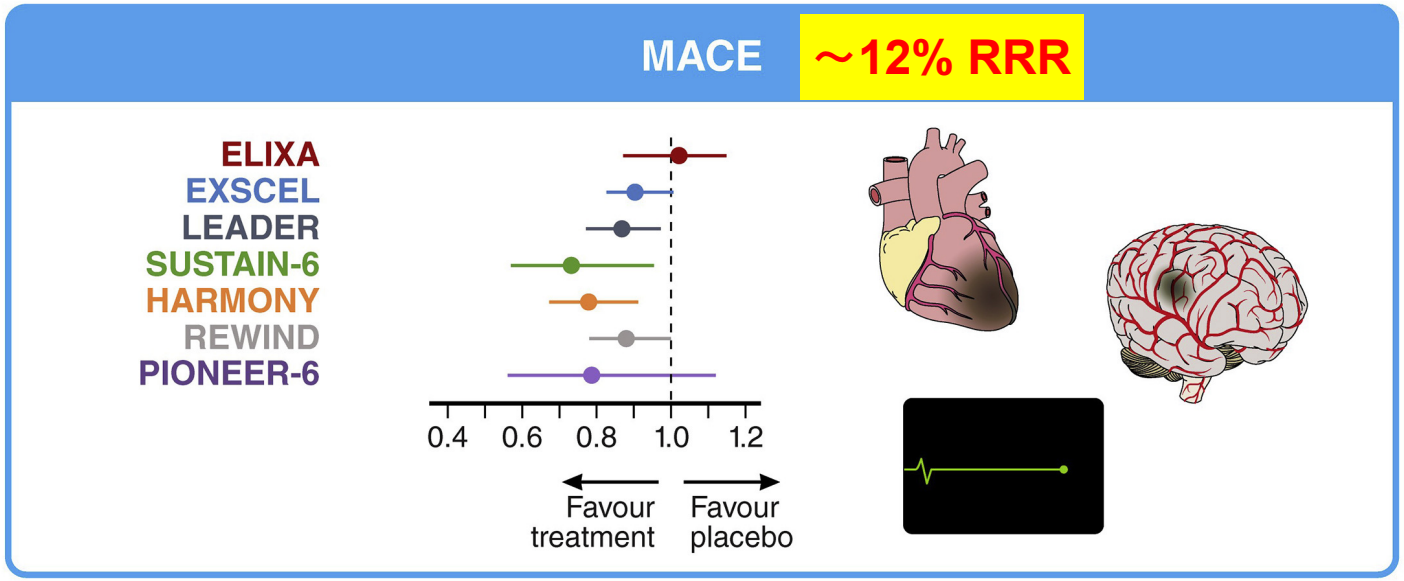


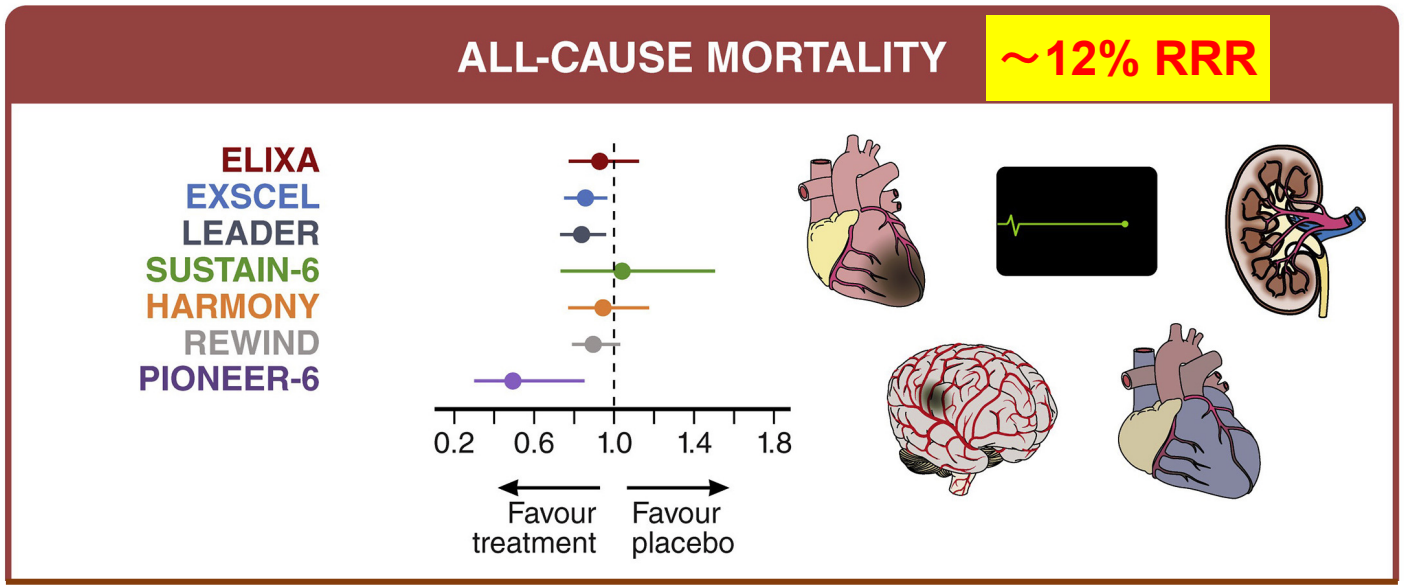
CV outcomes trials of GLP-1RA, SGLT2i, and DPP4i

Nauck and Meier, Eur J Endocrinol (2019) 181:R21

Brown et al., Lancet 2021, 398:262

GLP-1 RA in T2DM: Review of CV Outcome Trials



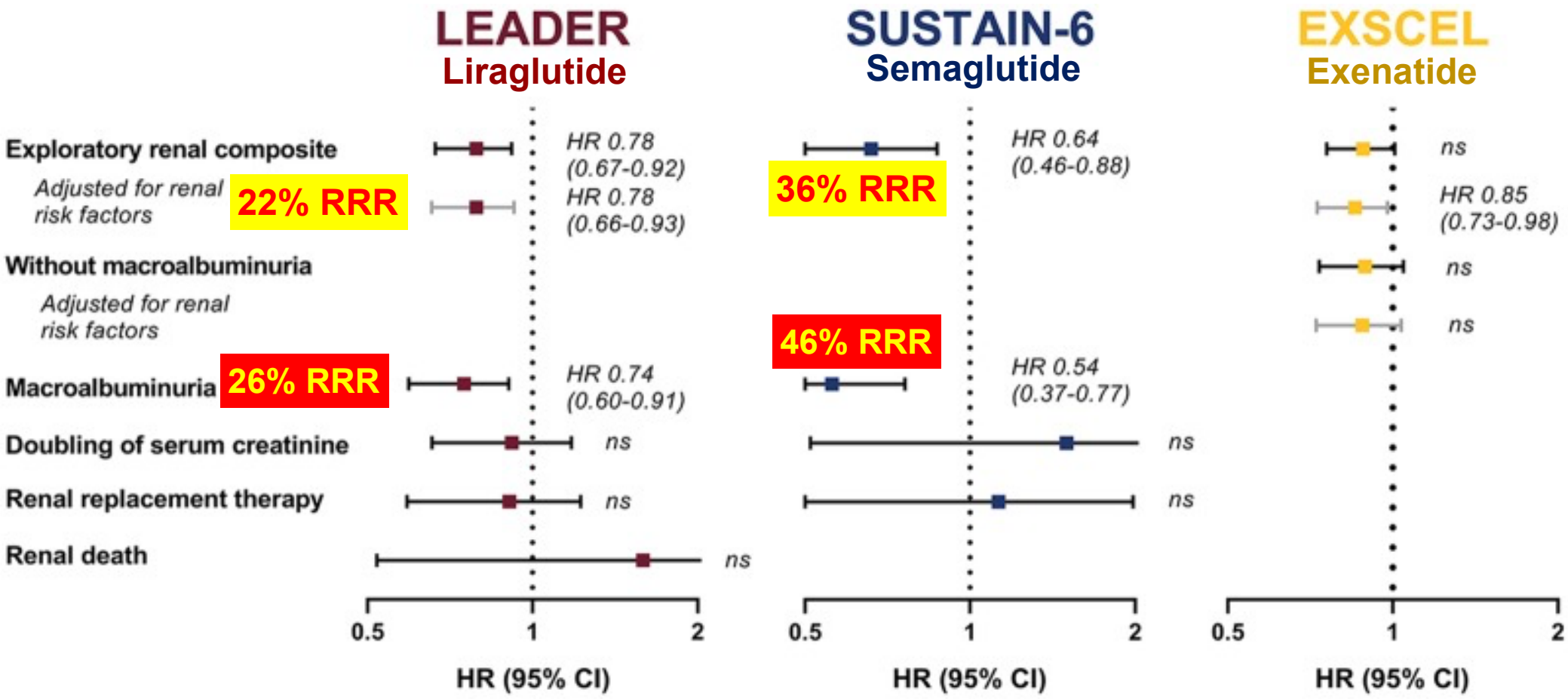


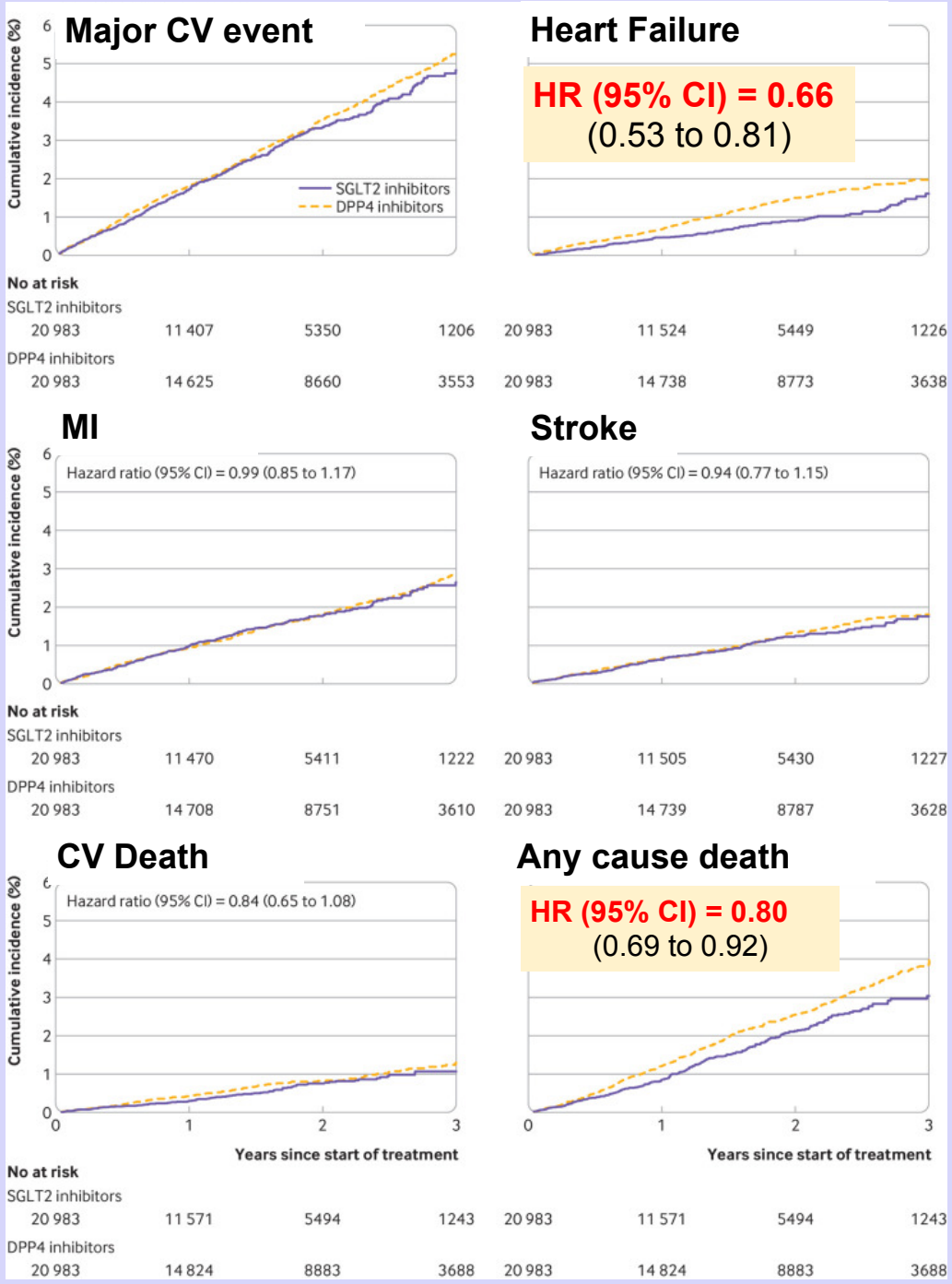
Primary outcome:

- **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

Exploratory renal outcomes and their individual components in GLP-1RA trials





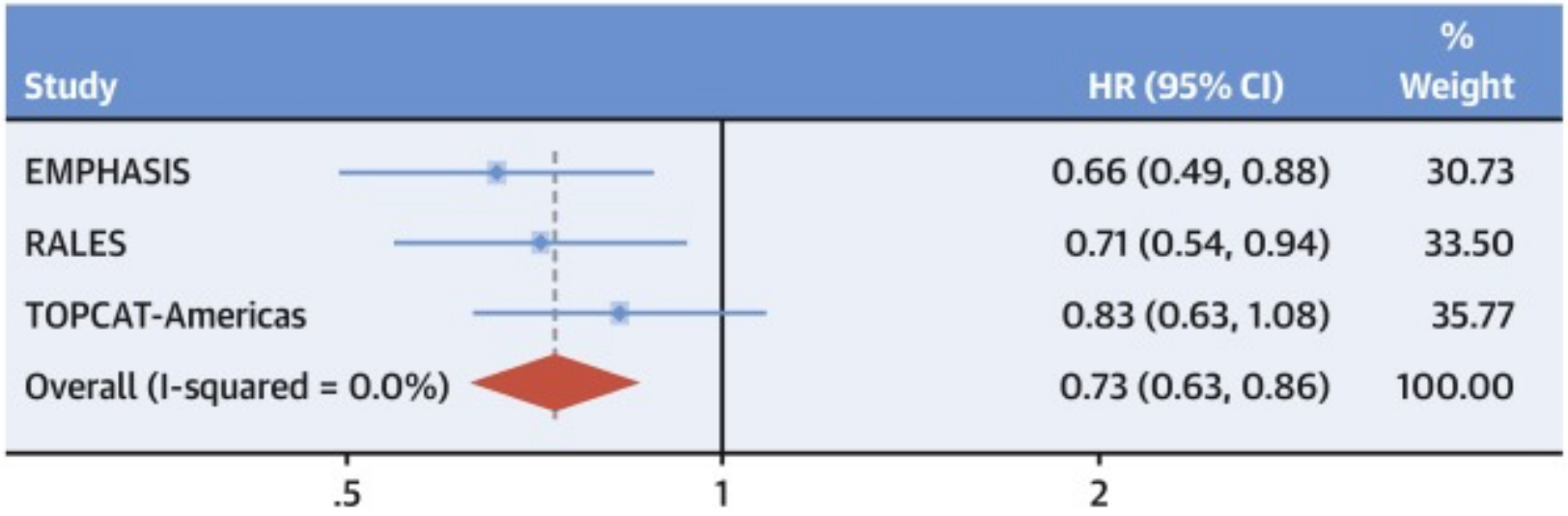
Cumulative incidence of CV events associated with SGLT2i compared with DPP4i

- A Scandinavian cohort study from 2013 to 2016.
- 20,983 new users of SGLT2i and 20,983 new users of dipeptidyl peptidase 4 (DPP4) inhibitors.
- 19% with prior CVD, 6% with prior HF, ***5% with prior CKD***
- Ages 35-84, matched by age, sex, history of major CVD and propensity score.
- SGLT2i arm:
  - 83% - dapagliflozin,
  - 16% - empagliflozin,
  - 1% - canagliflozin.
- SGLT2i, compared to DPP4i, associated with a ***34% reduced risk of HF*** and a ***20% reduced risk of*** the secondary outcome ***any cause death.***

BMJ. 2019; 366: l4772

CV outcomes in clinical trials with MRA

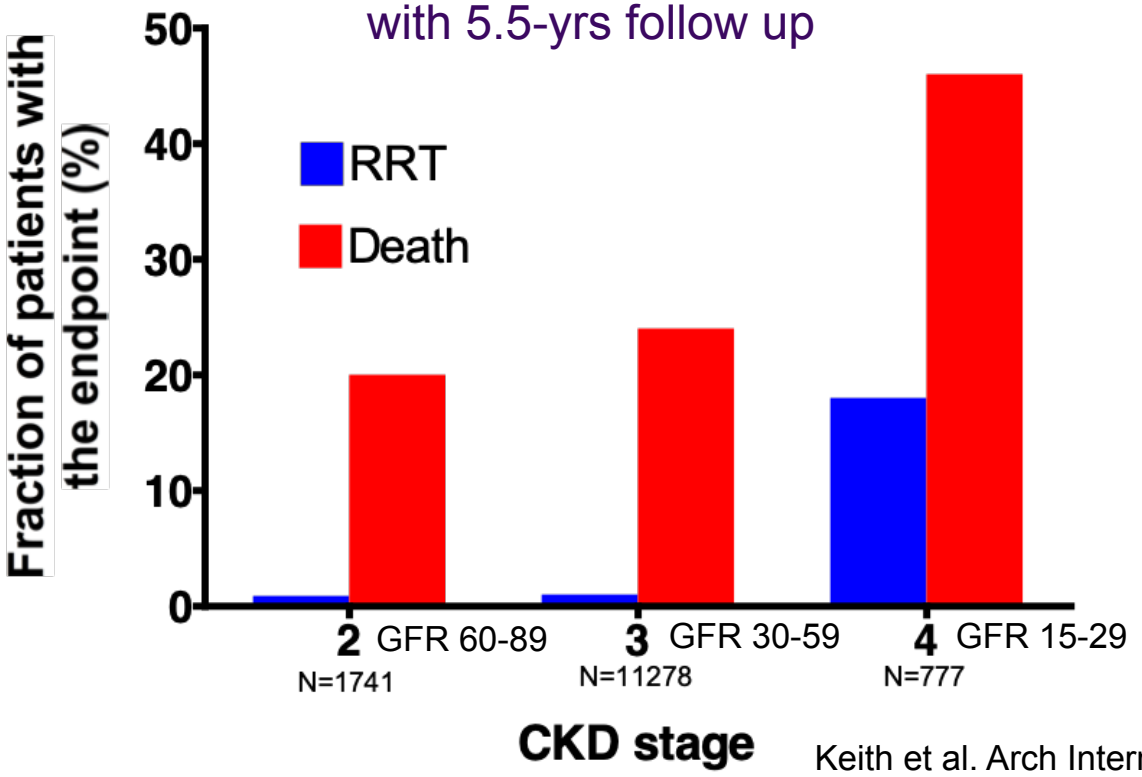
CENTRAL ILLUSTRATION: MRA Treatment Effect on the Overall HF Population ≥75 Years of Age (Primary Outcome of CV Death or HF Hospitalization)



Ferreira, J.P. et al. J Am Coll Cardiol HF. 2019;7(12):1012-21.

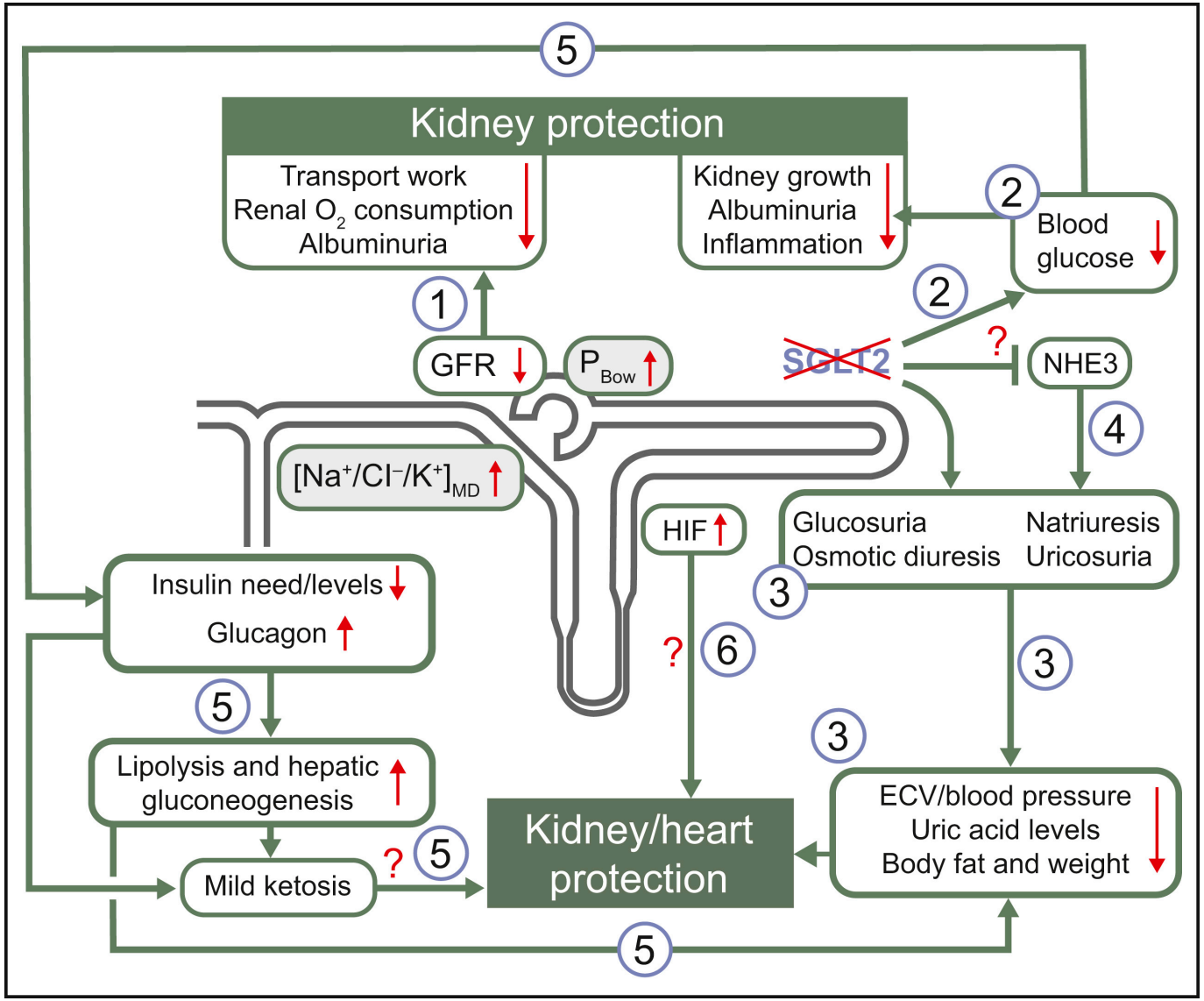
Severe mortality risk in pre-dialysis CKD

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



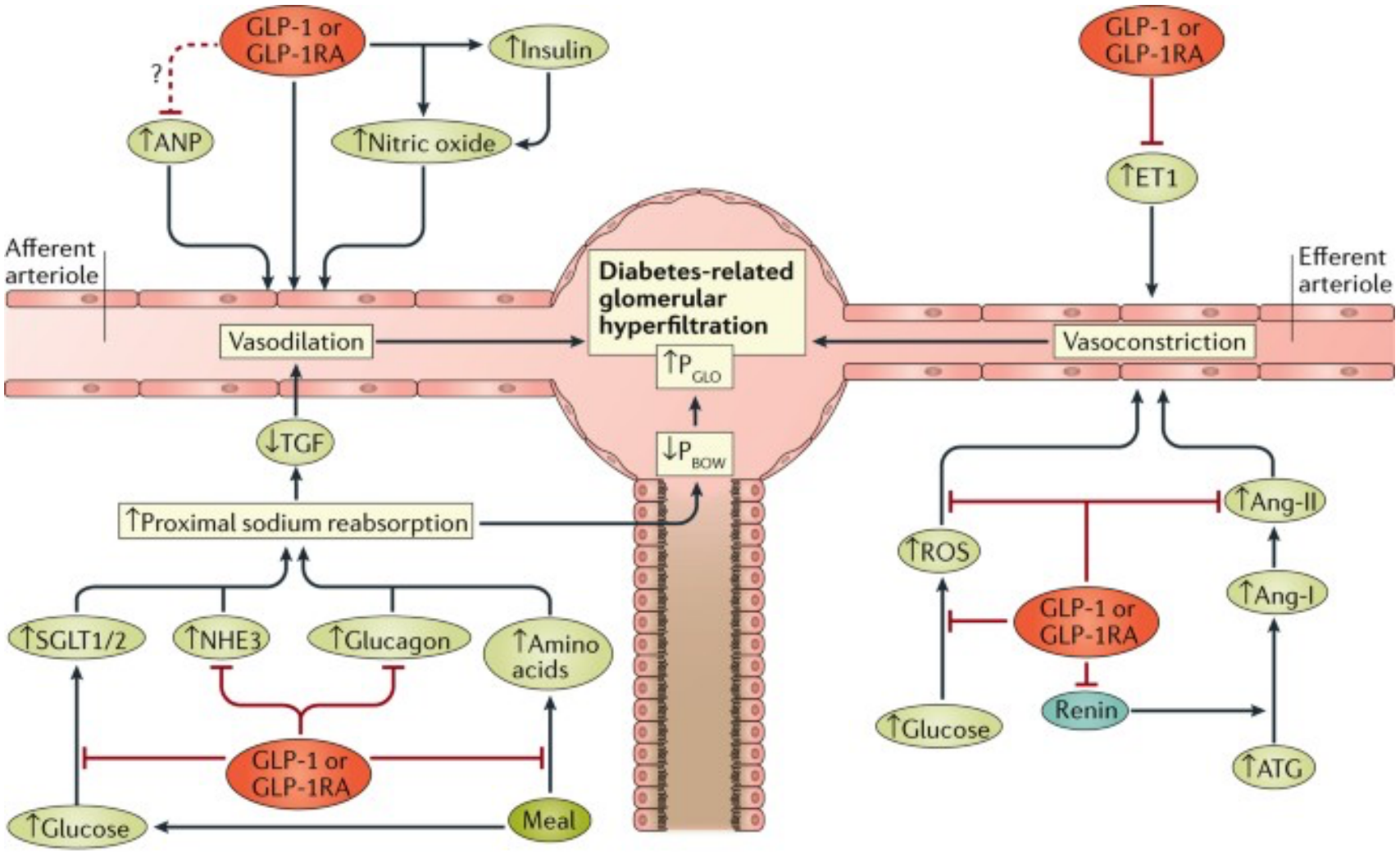
Keith et al. Arch Intern Med 2004

A summary of possible mechanisms of cardiorenal protection associated with SGLT2i



Diabetologia. 2017; 60:215-225

Renal effects of GLP-1



Muskiet MH et al., Nature Reviews Nephrol 2017, 13:605

Nature Reviews | Nephrology

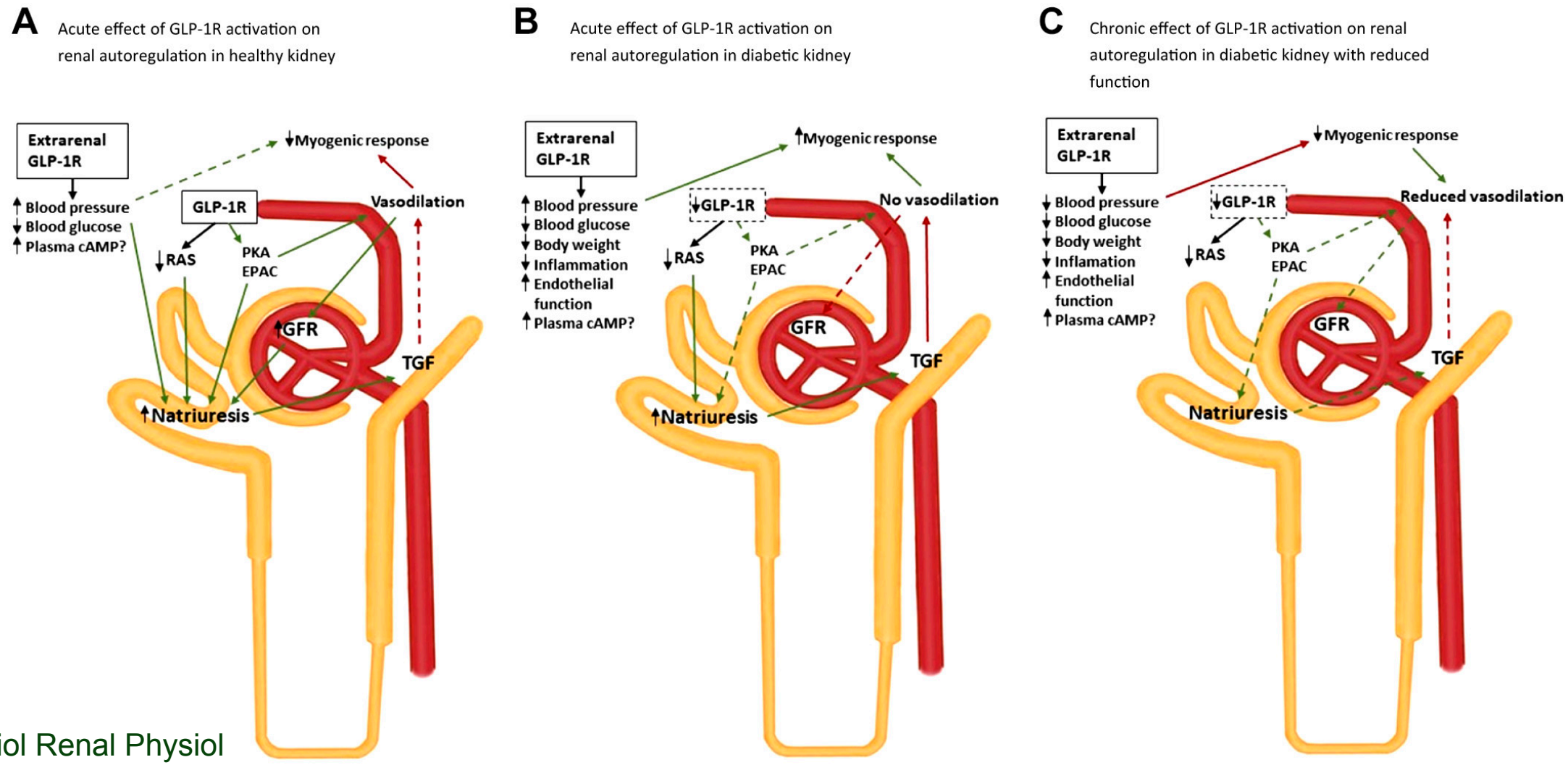
Table 2 | **Glucose-independent effects of incretin-based therapies on renal risk factors in type 2 diabetes mellitus**

Renal risk factor	GLP-1RA	DPP-4 inhibitor	Putative GLP-1-mediated mechanisms	Putative GLP-1-independent mechanisms of DPP-4 inhibitors
Obesity	Decrease	Neutral effect	↓Appetite (direct effect on CNS or via vagal afferents, ↓GEE* and ↑nausea) ↑Energy expenditure[35]? ↑Natriuresis and/or diuresis?	Effect possibly counteracted by ↑PYY (1–36) and ↓PYY (3–36)[257,258‡]
Blood pressure	Decrease	Decrease or neutral effect	↓Body weight ↑Endothelial independent vasodilation[259,260]? ↑Natriuresis[261§] ↓Intestinal sodium reabsorption[98]? ↓Sodium intake (direct effect on CNS)? ↓RAAS activity[87,127]? ↑ANP[130]?	↑Natriuresis (↑SDF1α[119], ↓DPP-4/NHE3 complex[262]?, ↑BNP[263]) ↑Vasodilation (↑BNP[263], ↑bradykinin) Effects possibly counteracted by ↑substance P (↑SNS activity) and ↑NPY (potentiates SNS activity) during concomitant ACE inhibition[127‖]
Dyslipidaemia	Decrease	Neutral effect	↓Body weight ↓Intestinal lipid uptake (partly by ↓GEE*) ↓Hepatic lipoprotein synthesis and secretion ↑Insulin sensitivity (partly by ↓body weight) ↑Insulin and ↓glucagon ↑Triglyceride uptake in white adipose tissue ↑Brown adipose tissue activation[169]	Effects possibly counteracted by factors related to steroid metabolism[264]
Inflammation and fibrosis	Decrease	Decrease	↓Renal ROS production (cAMP and PKA)[102,179] ↓AGE–RAGE-mediated renal ROS production (cAMP)[181,265,266] ↓Angiotensin II-induced renal ROS production (PKC)[182,183] ↑Adiponectin (reduces podocyte inflammation; PKA in adipocytes)[267]	↑SDF1α[119,268,269] ↓Profibrotic endothelial-to-mesenchymal transition[185,186¶]
Glomerular hyperfiltration	Decrease or neutral effect	Neutral effect	↑Tubuloglomerular feedback (by ↓NHE3 activity) ↓Postprandial glucagon (particularly short-acting GLP-1RA)[70,71,90]? ↓Body weight[90]? ↓GEE* (postprandial hyperfiltration)[90]? ↓RAAS activity[87,127]?	↑SDF1α[119]?

ACE, angiotensin-converting enzyme; AGE, advanced glycation end products; BNP, brain natriuretic peptide; CNS, central nervous system; DPP-4, dipeptidyl peptidase 4; GEE, gastric emptying rate; GLP-1, glucagon-like peptide 1; GLP-1RA, GLP-1 receptor agonist; NHE3, sodium–hydrogen exchanger isoform 3; PKA, protein kinase A; PKC, protein kinase C; PYY, peptide YY; RAAS, renin–angiotensin–aldosterone system; RAGE, receptor for AGE; ROS, reactive oxygen species, SDF1α, stromal cell-derived factor 1α. *GEE reduction is subject to tachyphylaxis after prolonged treatment with long-acting GLP-1RA; however, loss of body weight continues[35,270]. ‡DPP-4 inhibition could blunt GLP-1-mediated effects on central regulation of satiation by concomitantly increasing levels of PYY (1–36), which increase appetite, and decreasing level of PYY (3–36), which decrease appetite. § Natriuresis seems to only be sustained with short-acting GLP-1RAs[116,117]; initial natriuresis with long-acting GLP-1RA may result in a new steady state with lower extracellular volume and/or lower sodium stores in the glycocalyx. ‖An ongoing trial is investigating this hypothesis in detail[223]. ¶This effect could be drug-specific as linagliptin, but not sitagliptin, reduces endothelial-to-mesenchymal transition[271].

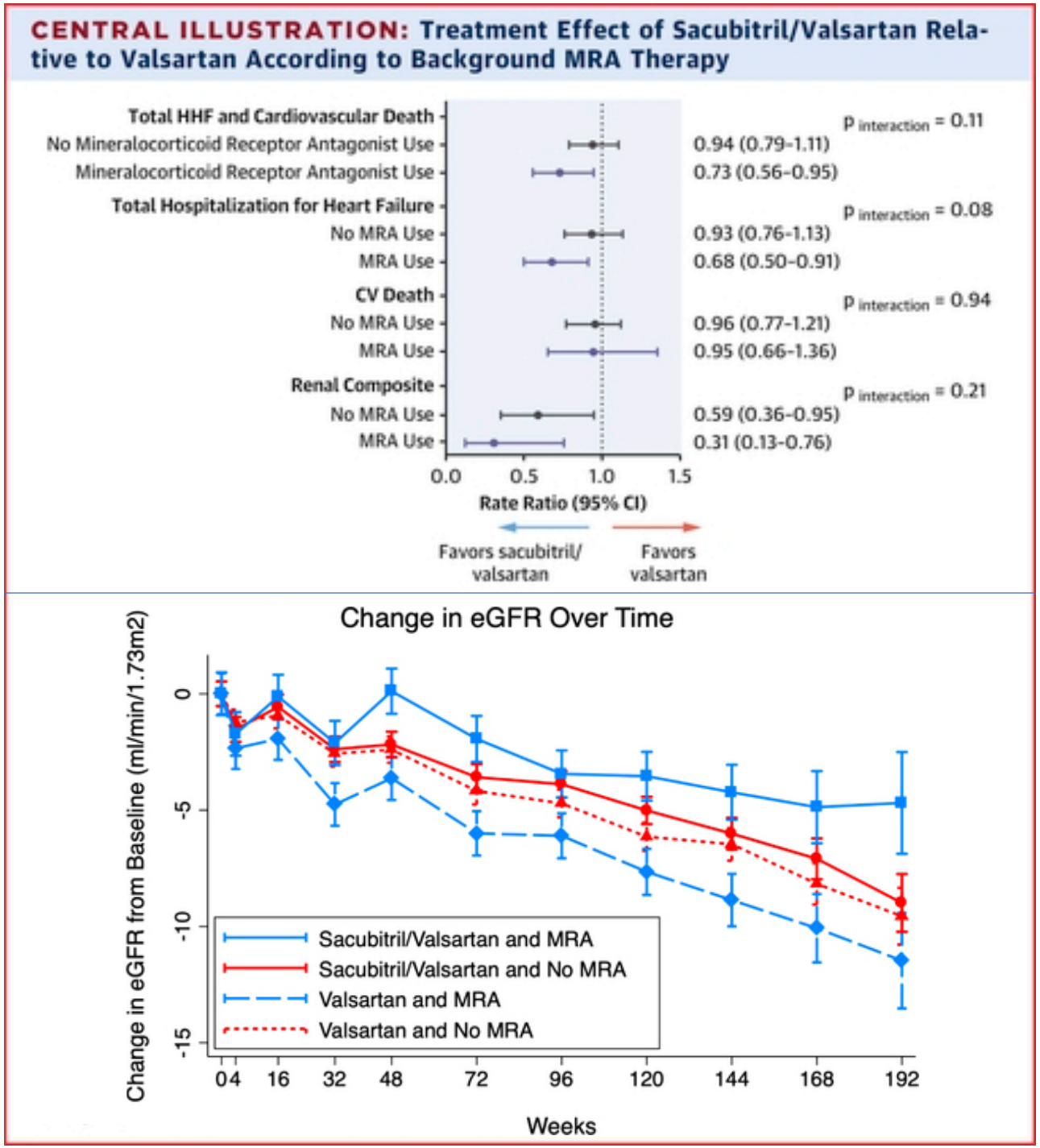
Muskiet MH et al., Nature Reviews Nephrol 2017, 13:605

Glucagon-like peptide-1 receptor (GLP-1R) activation and renal autoregulatory pathways in the healthy and diabetic kidney



AM J Physiol Renal Physiol
2020, 318:F443

CV and Renal Outcomes of MRA Use in PARAGON-HF



Jering KS et al., J Am Coll Cardiol HF. 2021 Jan, 9 (1) 13–24