Preventing Event by Timely Treatment in CKD Patients with DM & Hyperlipidemia

Szu-Chun Hung, MD

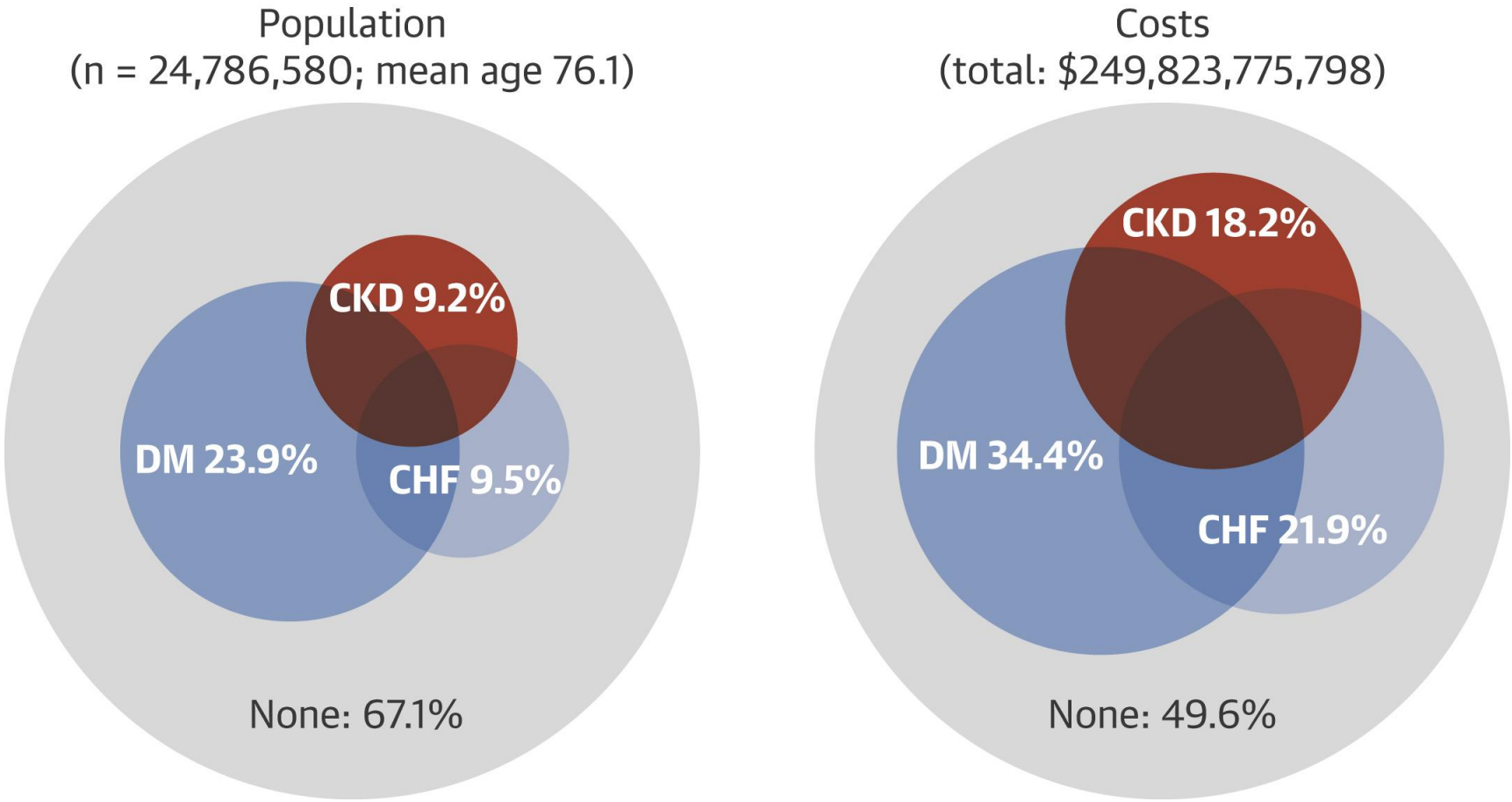
Division of Nephrology, Taipei Tzu Chi Hospital, Taiwan

Residual Risk Factors in ASCVD Patients

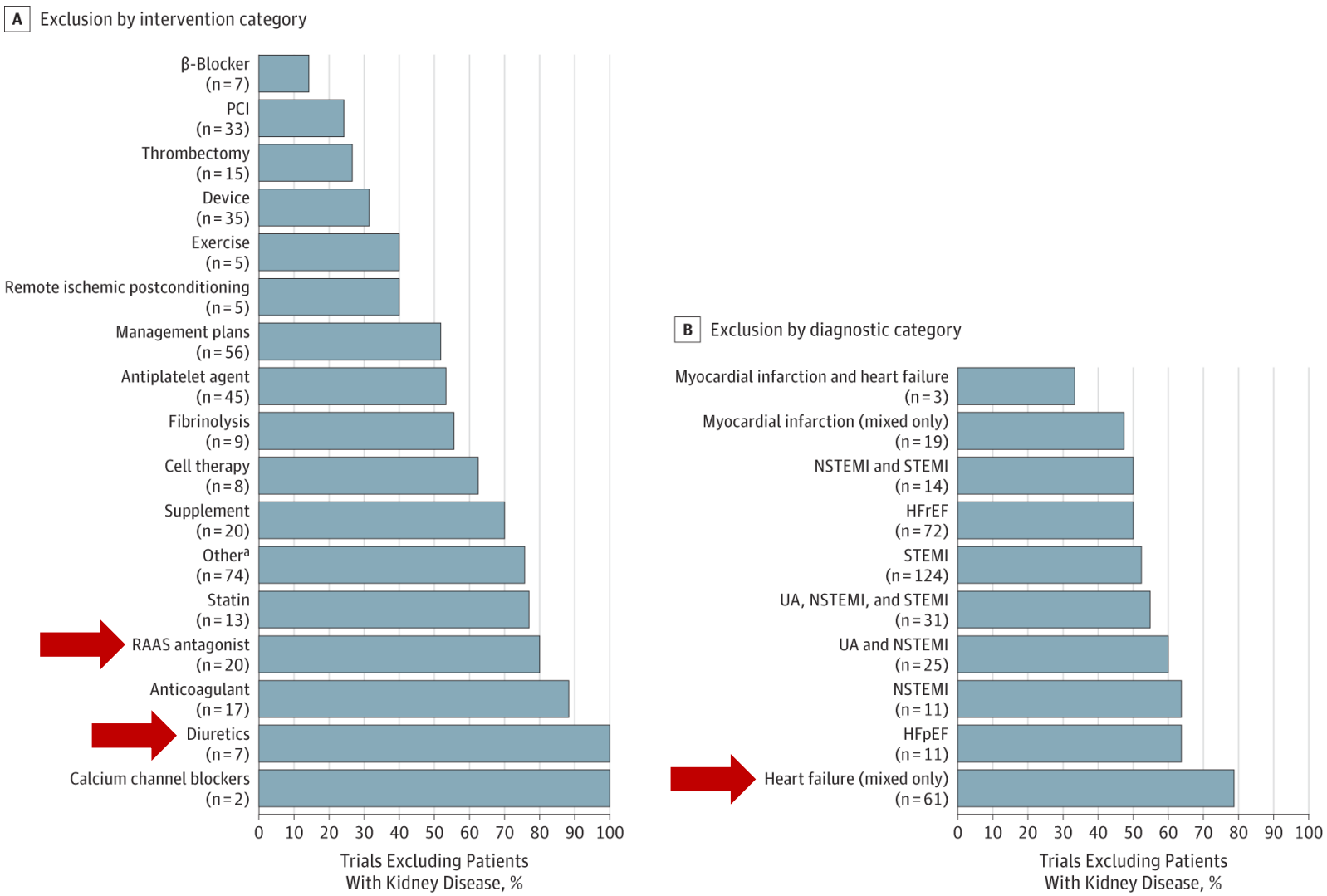
Parameter	DM patients (n = 2,117)		Non-DM patients (n = 3,366)	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age	1.02 (1.00–1.04)	0.12	1.02 (1.00–1.04)	0.07
Male (vs. female)	0.88 (0.49–1.56)	0.66	0.75 (0.44–1.27)	0.28
BMI (kg/m^2) (vs. 23 −<27.5)				
<23	1.31 (0.74–2.32)	0.35	1.53 (0.95–2.46)	0.08
≥27.5	0.99 (0.60–1.65)	0.97	0.93 (0.56–1.56)	0.79
Systolic blood pressure (mmHg)	1.01 (1.00–1.02)	0.11	1.00 (0.99–1.01)	0.66
HbA1c (%)	1.04 (0.90–1.19)	0.61	—	—
History of myocardial infarction	0.98 (0.54–1.79)	0.95	2.44 (1.27–4.69)	<0.01
History of ischemic stroke or TIA	1.03 (0.58–1.84)	0.92	1.76 (1.00–3.11)	0.05
Heart failure (NYHA class I-II)	2.23 (1.31–3.77)	<0.01	1.97 (1.17–3.31)	<0.05
Chronic kidney disease (vs. Stage 1–2)				
Stage 3	1.44 (0.85–2.47)	0.18	1.37 (0.85–2.20)	0.20
Stage 4–5	3.03 (1.49–6.16)	<0.01	3.02 (1.18–7.69)	<0.05

Lin FJ et al. Sci Rep 7:9179, 2017

Triad of Diabetes, CHF, and CKD

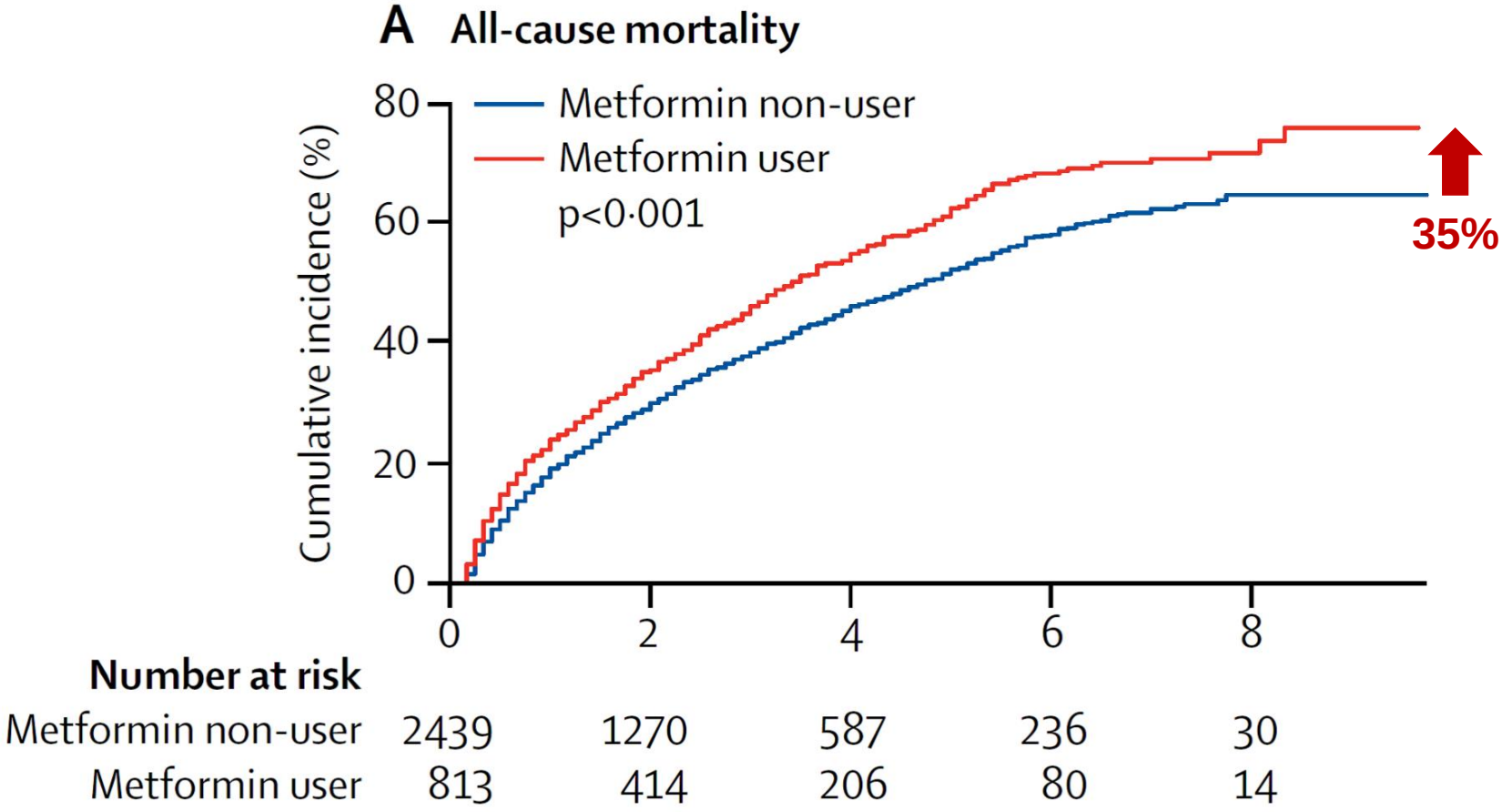


Exclusion of CKD Patients from CV Trials 2006–2014



Konstantinidis I et al. JAMA 176:121–124, 2016

Metformin Use in Advanced CKD



Hung SC et al. Lancet Diabetes Endocrinol 3:605–614, 2015

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

RESULTS

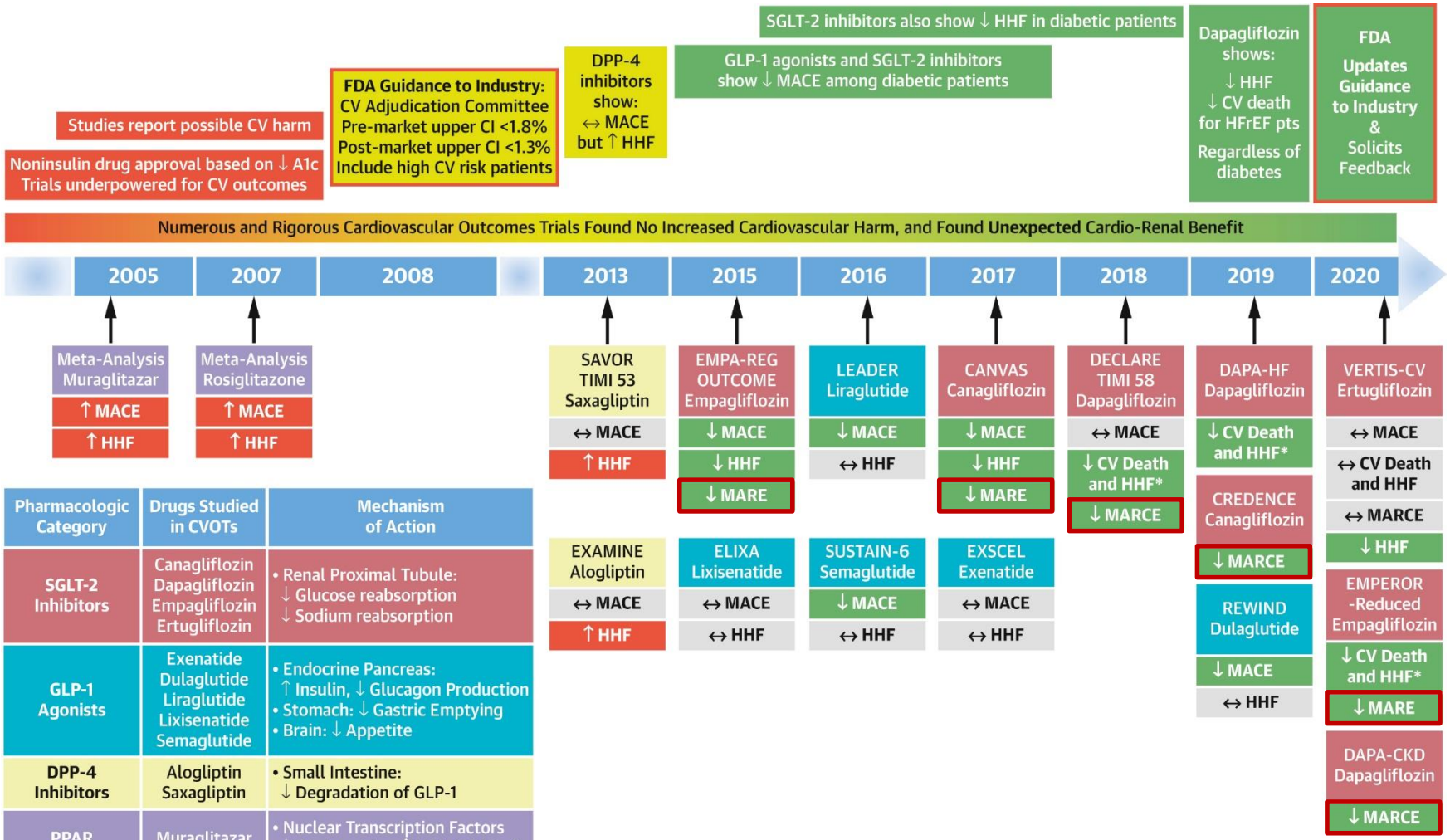
Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06).

Major SGLT2i Studies Include CKD Patients

Name of the Study	EMPA-REG OUTCOME	CANVAS/ CANVAS R	DECLARE	CREDENCE	DAPA-CKD	EMPA-KIDNEY
Intervention	Empagliflozin versus placebo	Canagliflozin versus placebo	Dapagliflozin versus placebo	Canagliflozin versus placebo	Dapagliflozin versus placebo	Empagliflozin versus placebo
Patient population	CVD history	CVD risk or history	CVD risk or history	High CV risk	High CV risk	High CV risk
Kidney function inclusion criteria	eGFR ≥30	eGFR ≥30	CCr ≥60	eGFR 30-90, Macro-albuminuria	eGFR 25-75, UACR 200-5000	eGFR 20-45 or 45-90 with albuminuria
Patient number	7020	10,142	17,160	4401	4000	5000
%CKD (eGFR <60)	25.9%	20.1%	7%	60%	90%	
Prespecified renal endpoints	Progression to macroalbuminuria, doubling of SCr, RRT, renal death (MARE)	Progression of albuminuria, 40% reduction in eGFR, RRT, renal death (MARE)	Secondary: 40% decrease in eGFR to <60 (CKD-EPI) and/or ESRD and/or renal or CV death (MARCE)	Primary: Doubling of SCr, ESRD, renal or CV death (MARCE)	Primary: ≥50% reduction in eGFR or reaching ESRD or CV death or renal death (MARCE)	Primary: Composite of (eGFR <10, renal death, or ≥40% reduction in eGFR) or CV death (MARCE)

Pecoits-Filho R et al. CJASN 13:318–320, 2018

Landmark Events in Diabetes Drug Development



Pharmacologic Category	Drugs Studied in CVOTs	Mechanism of Action
SGLT-2 Inhibitors	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	• Renal Proximal Tubule: ↓ Glucose reabsorption ↓ Sodium reabsorption
GLP-1 Agonists	Exenatide Dulaglutide Liraglutide Lixisenatide Semaglutide	• Endocrine Pancreas: ↑ Insulin, ↓ Glucagon Production • Stomach: ↓ Gastric Emptying • Brain: ↓ Appetite
DPP-4 Inhibitors	Alogliptin Saxagliptin	• Small Intestine: ↓ Degradation of GLP-1
PPAR Agonists	Muraglitazar Rosiglitazone	• Nuclear Transcription Factors ↓ Triglycerides, ↑ HDL (PPAR α) ↑ Insulin Sensitivity (PPAR γ)

Ferro EG et al. J Am Coll Cardiol 76:2522–2526, 2020

CVOTs with SGLT2 Inhibitor

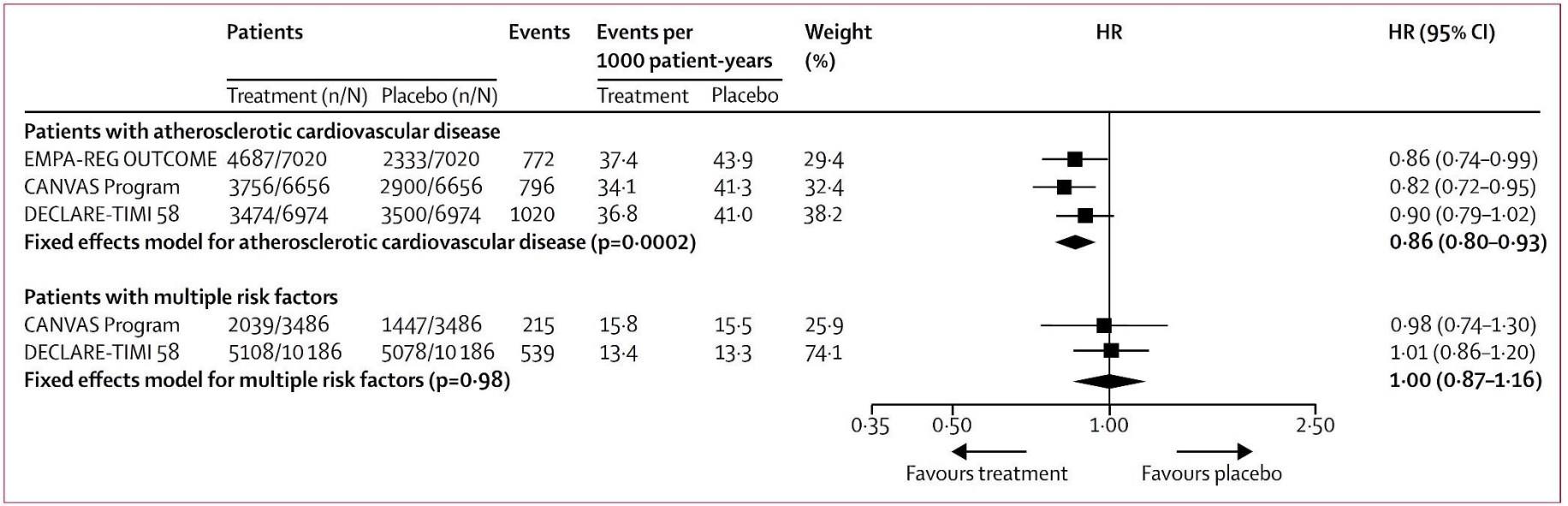
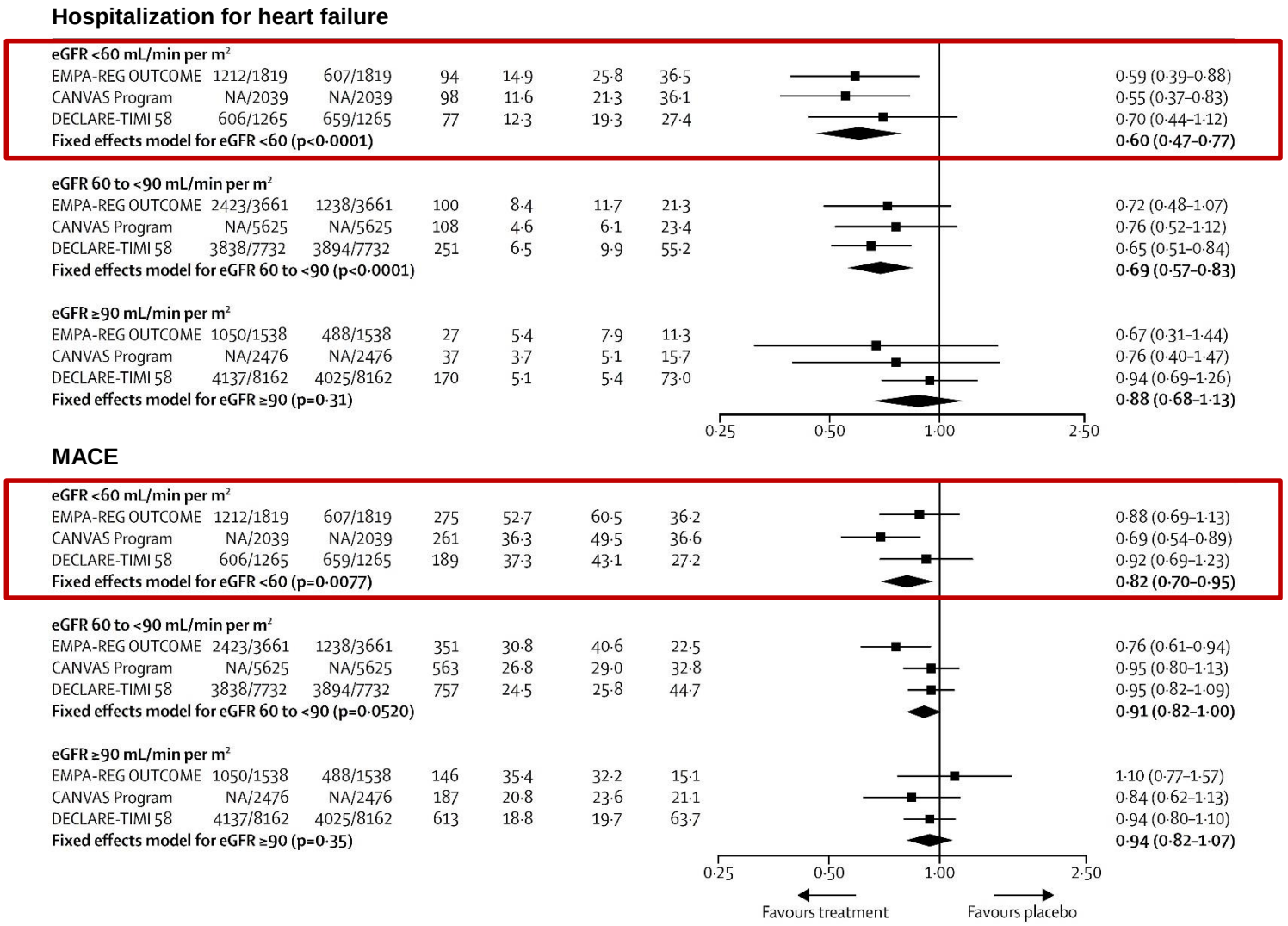


Figure 1: **Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease**

No heterogeneity was found in terms of between-study variance in the subgroups (atherosclerotic cardiovascular disease: Q statistic=0·94, p=0·63, I^2=0%; multiple risk factors: Q statistic=0·03, p=0·86, I^2=0%). Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. The p value for subgroup differences was 0·0501. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

Zelniker TA et al. Lancet 393:31–39, 2019

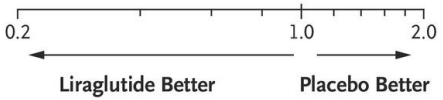
CVOTs with SGLT2 Inhibitor



Zelniker TA et al. Lancet 393:31–39, 2019

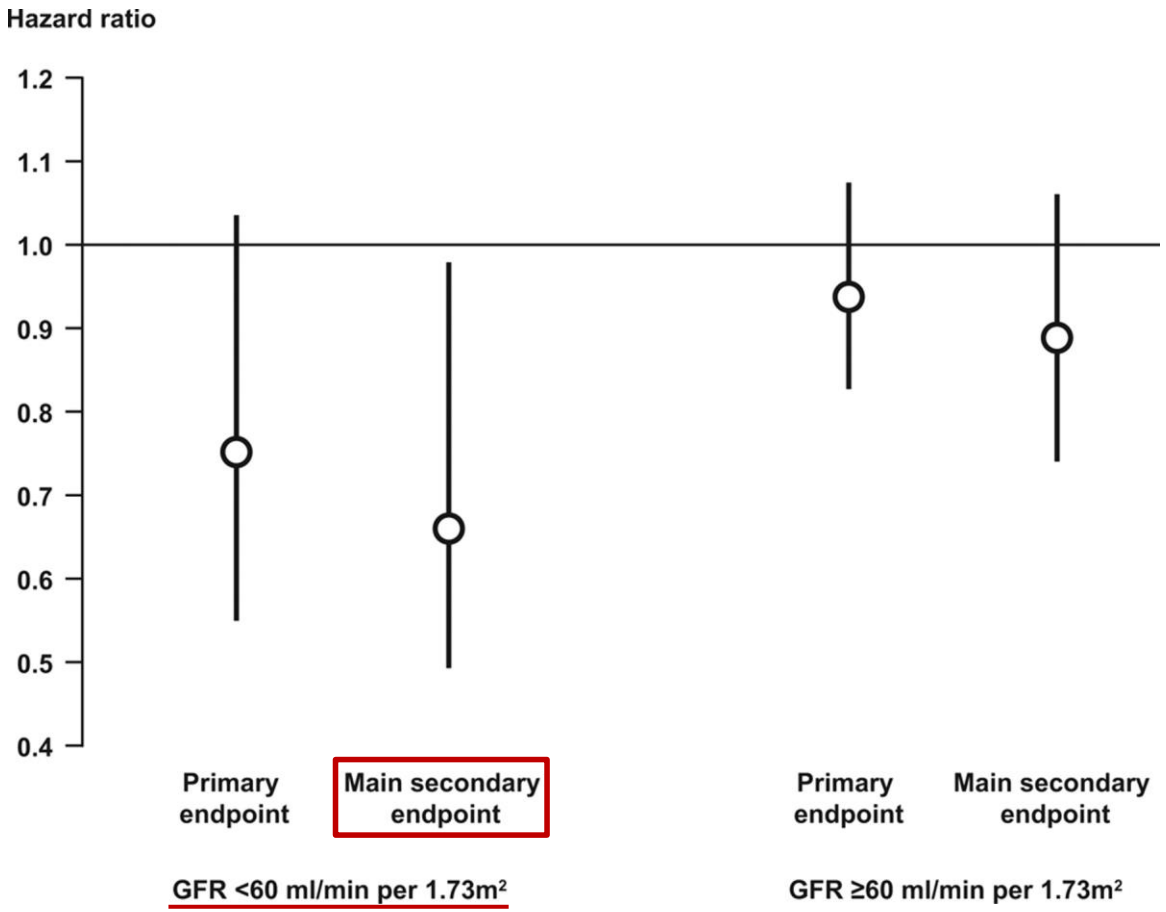
LEADER
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

Subgroup	No. of Patients	Liraglutide	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/no. of patients (%)			
Primary analysis	9340	608/4668 (13.0)	694/4672 (14.9)	0.87 (0.78–0.97)	
Sex					0.84
Female	3337	183/1657 (11.0)	209/1680 (12.4)	0.88 (0.72–1.08)	
Male	6003	425/3011 (14.1)	485/2992 (16.2)	0.86 (0.75–0.98)	
Age					0.27
<60 yr	2321	140/1197 (11.7)	166/1124 (14.8)	0.78 (0.62–0.97)	
≥60 yr	7019	468/3471 (13.5)	528/3548 (14.9)	0.90 (0.79–1.02)	
Geographic region					0.20
Europe	3296	207/1639 (12.6)	252/1657 (15.2)	0.82 (0.68–0.98)	
North America	2847	212/1401 (15.1)	216/1446 (14.9)	1.01 (0.84–1.22)	
Asia	711	24/360 (6.7)	37/351 (10.5)	0.62 (0.37–1.04)	
Rest of the world	2486	165/1268 (13.0)	189/1218 (15.5)	0.83 (0.68–1.03)	
Race					0.32
White	7238	494/3616 (13.7)	543/3622 (15.0)	0.90 (0.80–1.02)	
Black	777	47/370 (12.7)	59/407 (14.5)	0.87 (0.59–1.27)	
Asian	936	40/471 (8.5)	56/465 (12.0)	0.70 (0.46–1.04)	
Other	389	27/211 (12.8)	36/178 (20.2)	0.61 (0.37–1.00)	
Ethnic group					0.30
Hispanic	1134	68/580 (11.7)	86/554 (15.5)	0.74 (0.54–1.02)	
Non-Hispanic	8206	540/4088 (13.2)	608/4118 (14.8)	0.89 (0.79–1.00)	
Body-mass index					0.15
≤30	3574	241/1743 (13.8)	261/1831 (14.3)	0.96 (0.81–1.15)	
>30	5757	367/2920 (12.6)	431/2837 (15.2)	0.82 (0.71–0.94)	
Glycated hemoglobin					0.58
≤8.3%	4768	289/2340 (12.4)	333/2428 (13.7)	0.89 (0.76–1.05)	
>8.3%	4572	319/2328 (13.7)	361/2244 (16.1)	0.84 (0.72–0.98)	
Duration of diabetes					0.42
≤11 yr	4429	265/2216 (12.0)	316/2213 (14.3)	0.82 (0.70–0.97)	
>11 yr	4892	340/2441 (13.9)	376/2451 (15.3)	0.90 (0.78–1.04)	
Risk of CVD					0.04
≥50 yr of age and established CVD	7598	536/3831 (14.0)	629/3767 (16.7)	0.83 (0.74–0.93)	
≥60 yr of age and risk factors for CVD	1742	72/837 (8.6)	65/905 (7.2)	1.20 (0.86–1.67)	
Renal function					
Severe or moderate disease					0.01
<60 ml/min/1.73 m^2	2158	172/1116 (15.4)	223/1042 (21.4)	0.69 (0.57–0.85)	
≥60 ml/min/1.73 m^2	7182	436/3552 (12.3)	471/3630 (13.0)	0.94 (0.83–1.07)	
Severe disease					0.93
<30 ml/min/1.73 m^2	224	25/117 (21.4)	26/107 (24.3)	0.89 (0.51–1.54)	
≥30 ml/min/1.73 m^2	9116	583/4551 (12.8)	668/4565 (14.6)	0.87 (0.77–0.97)	



PROactive Study

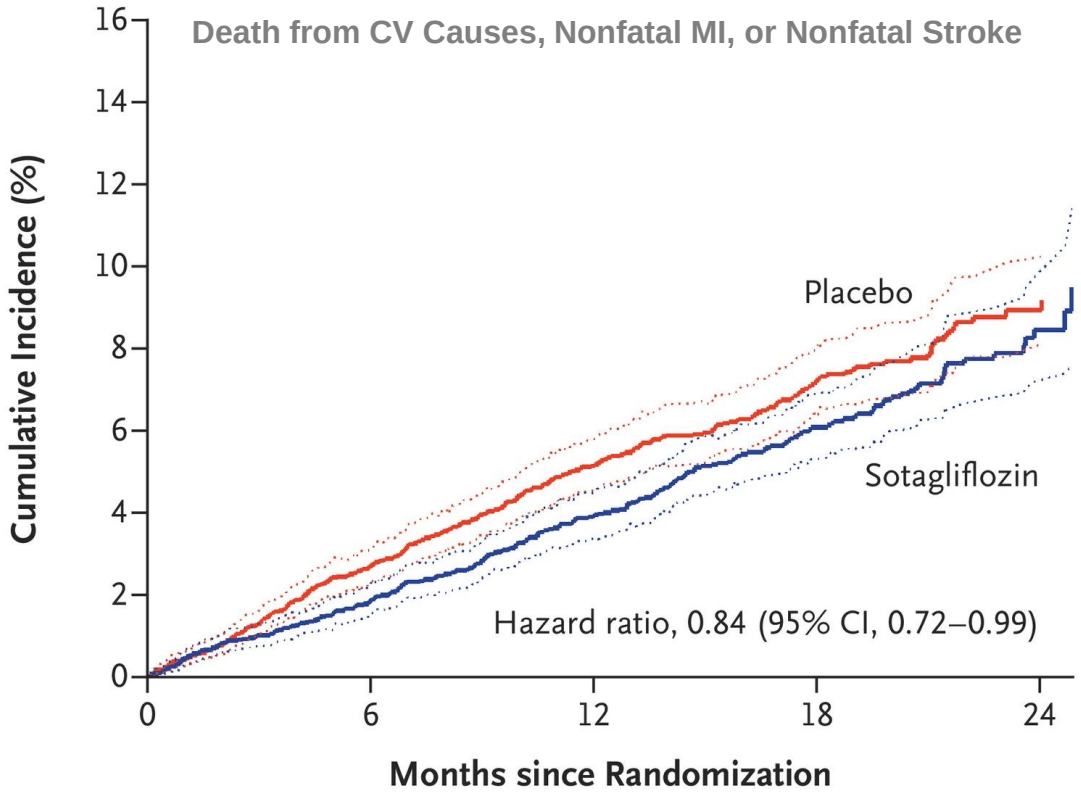
all-cause mortality, MI, and stroke



597 (11.6%) of the 5154 patients

Schneider CA et al. J Am Soc Nephrol 19:182–187, 2008

Sotagliflozin in Patients with DKD

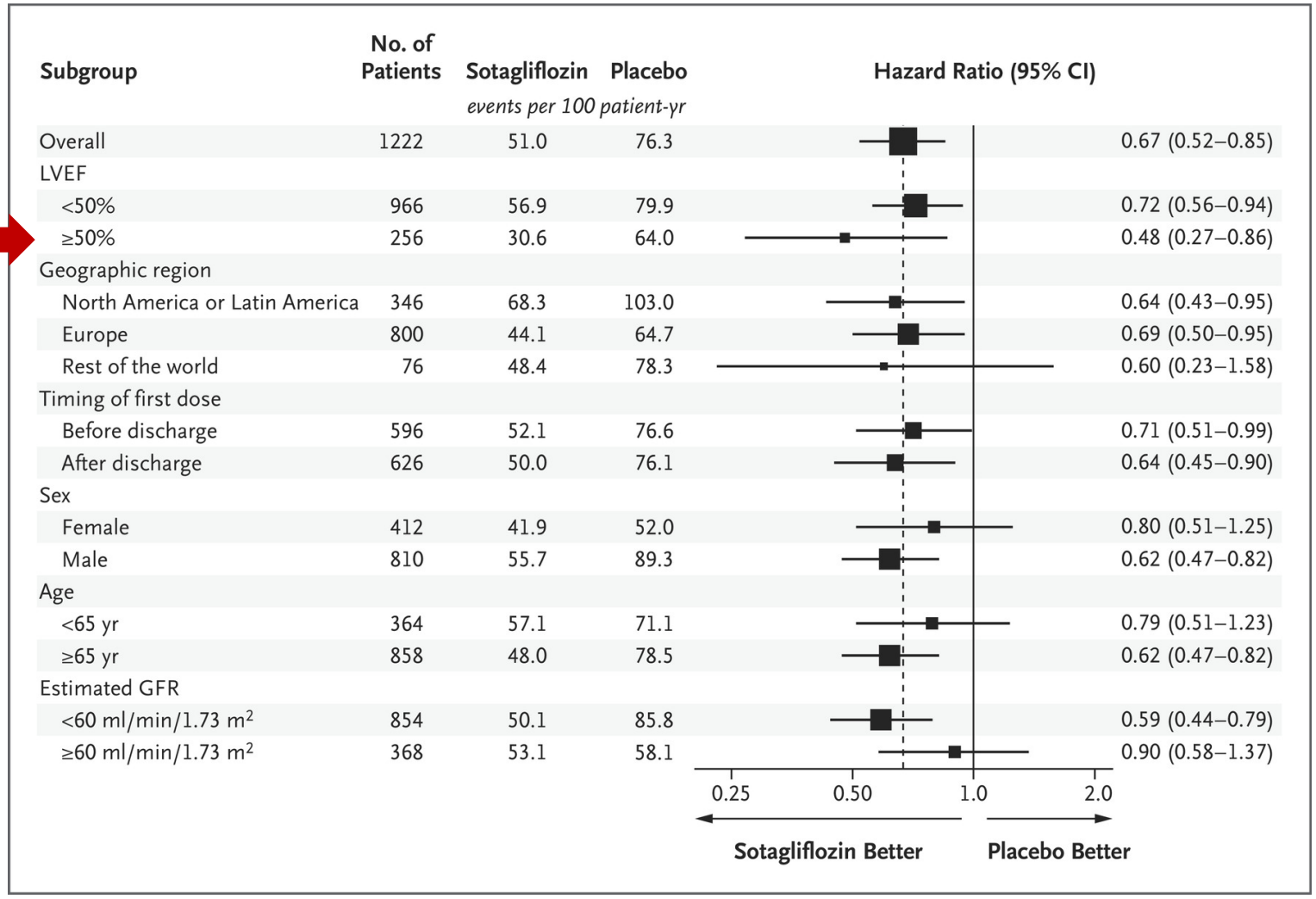


No. at Risk					
Placebo	5292	5090	3817	1985	421
Sotagliflozin	5292	5150	3892	2034	432

(median eGFR 44.4 ml/min/1.73 m^2, UACR 74)

Bhatt DL et al. N Engl J Med Nov 16, 2020

Sotagliflozin in DM and Worsening Heart Failure

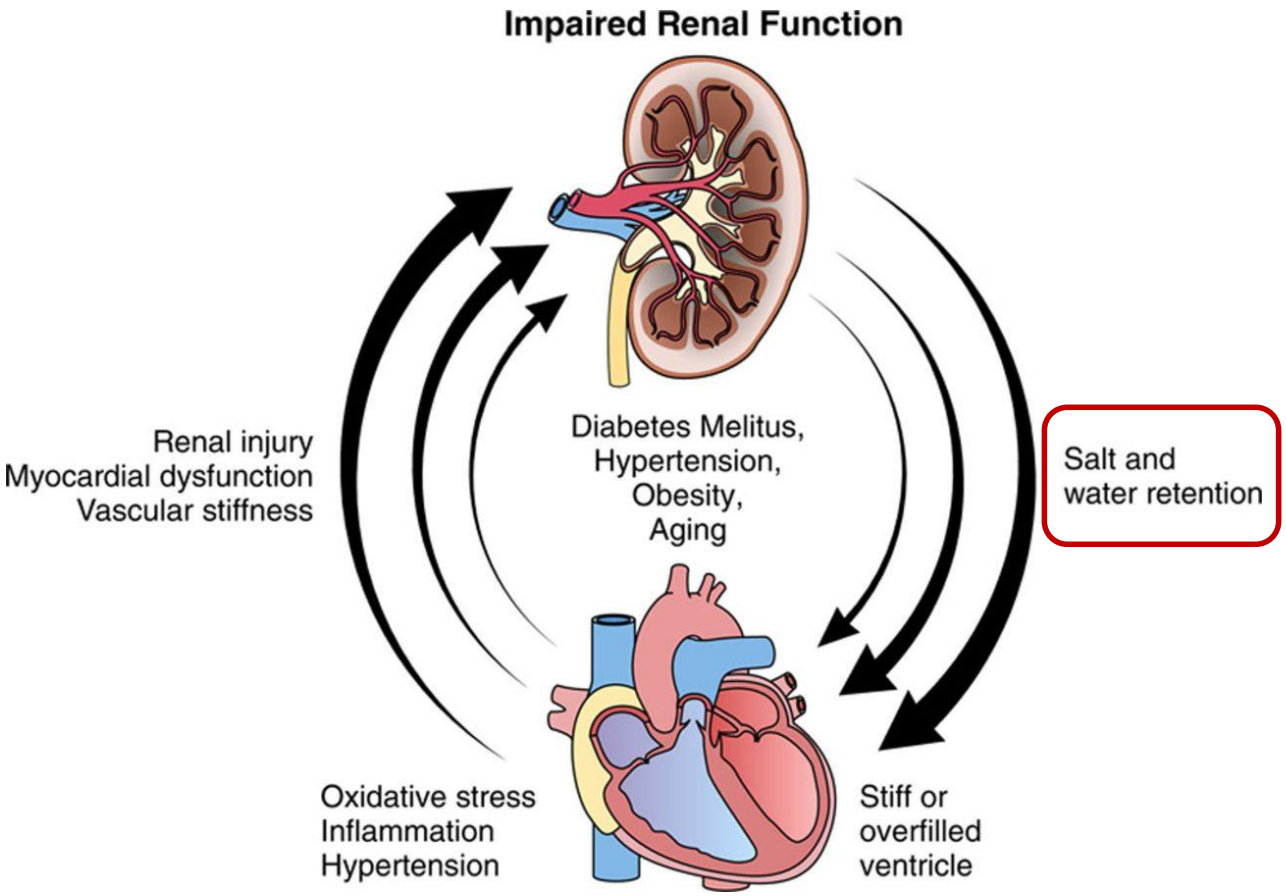


Subgroup	No. of Patients	Sotagliflozin	Placebo	Hazard Ratio (95% CI)
		events per 100 patient-yr		
Overall	1222	51.0	76.3	0.67 (0.52–0.85)
LVEF				
<50%	966	56.9	79.9	0.72 (0.56–0.94)
≥50%	256	30.6	64.0	0.48 (0.27–0.86)
Geographic region				
North America or Latin America	346	68.3	103.0	0.64 (0.43–0.95)
Europe	800	44.1	64.7	0.69 (0.50–0.95)
Rest of the world	76	48.4	78.3	0.60 (0.23–1.58)
Timing of first dose				
Before discharge	596	52.1	76.6	0.71 (0.51–0.99)
After discharge	626	50.0	76.1	0.64 (0.45–0.90)
Sex				
Female	412	41.9	52.0	0.80 (0.51–1.25)
Male	810	55.7	89.3	0.62 (0.47–0.82)
Age				
<65 yr	364	57.1	71.1	0.79 (0.51–1.23)
≥65 yr	858	48.0	78.5	0.62 (0.47–0.82)
Estimated GFR				
<60 ml/min/1.73 m^2	854	50.1	85.8	0.59 (0.44–0.79)
≥60 ml/min/1.73 m^2	368	53.1	58.1	0.90 (0.58–1.37)

Bhatt DL et al. N Engl J Med Nov 16, 2020

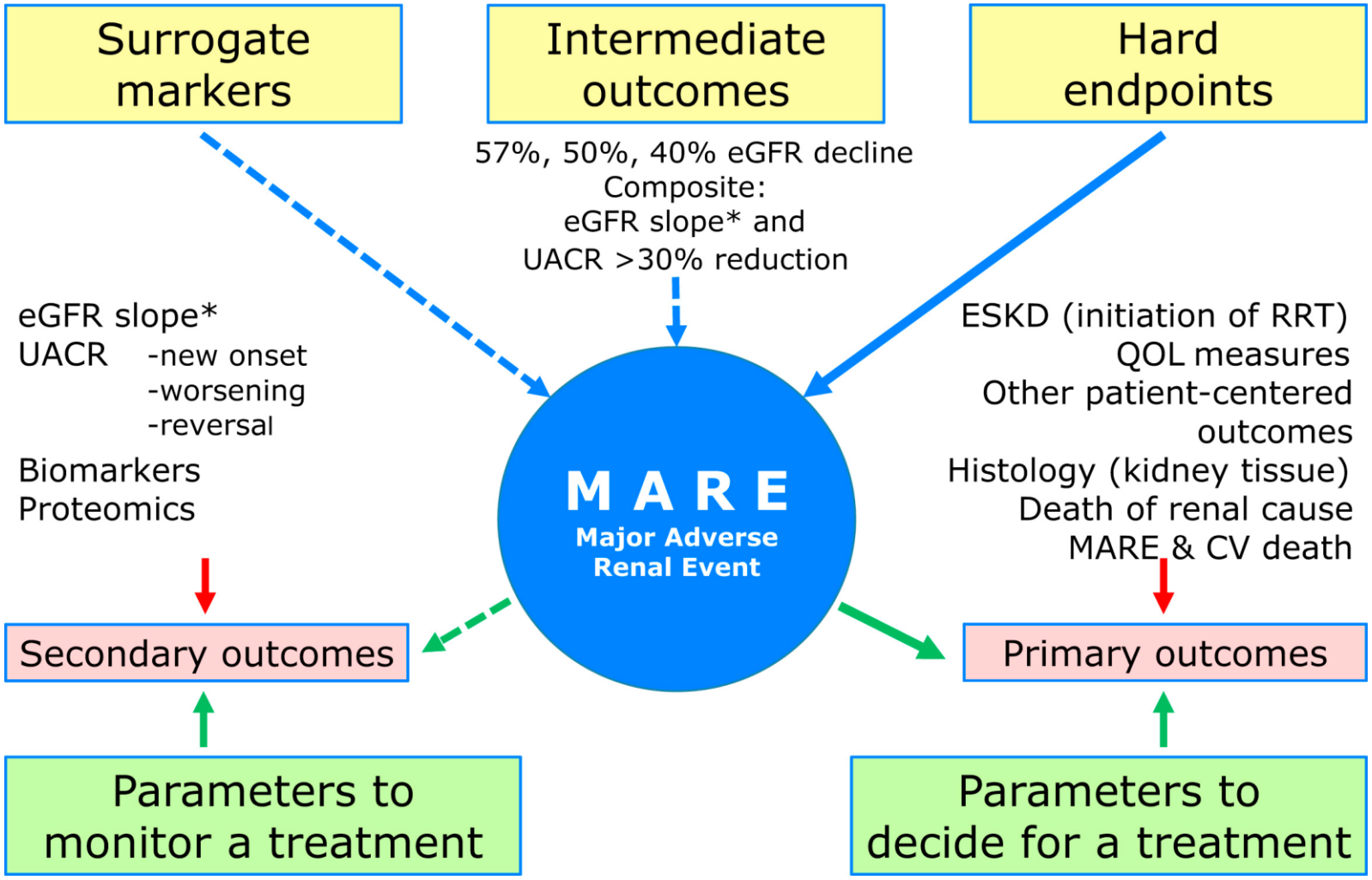
Heart Failure With Preserved Ejection Fraction

A Kidney Disorder?



Fang JC. Circulation 134:435–437, 2016

Renal Outcome Measures in DKD

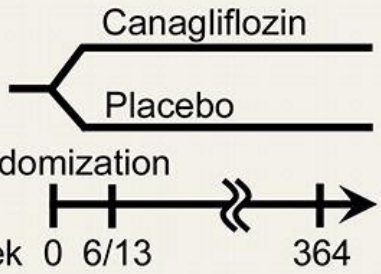


Prischl FC et al. Kidney Int Rep 3:1030–1038, 2018

Different eGFR decline thresholds and the renal effects of canagliflozin: data from the CANVAS Program

METHODS

CANVAS / CANVAS-R trial

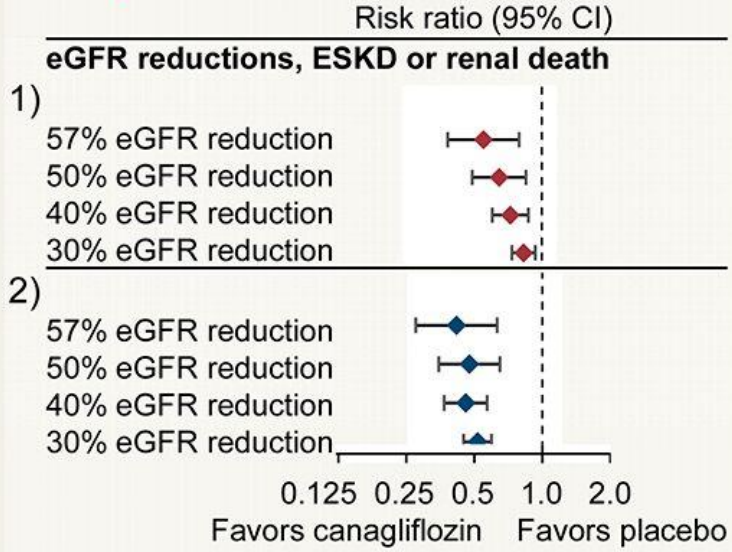


eGFR reductions were calculated

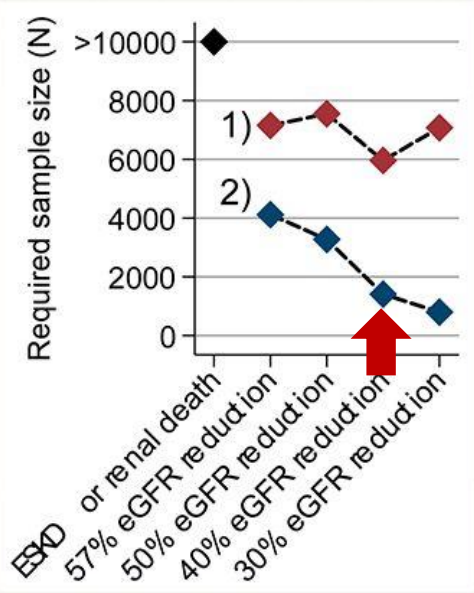
1) from **Week 0**

2) from **Week 6/13 or Week 0** in the canagliflozin or placebo group

Effects of canagliflozin on the composite renal outcomes



Required sample size



CONCLUSION

Declines in eGFR less than 57% may provide robust estimates of the effects of canagliflozin on renal outcomes, if the acute effect is controlled for.

doi: 10.1681/ASN.2019121312

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Renal Outcomes in CVOTs with SGLT2 Inhibitor

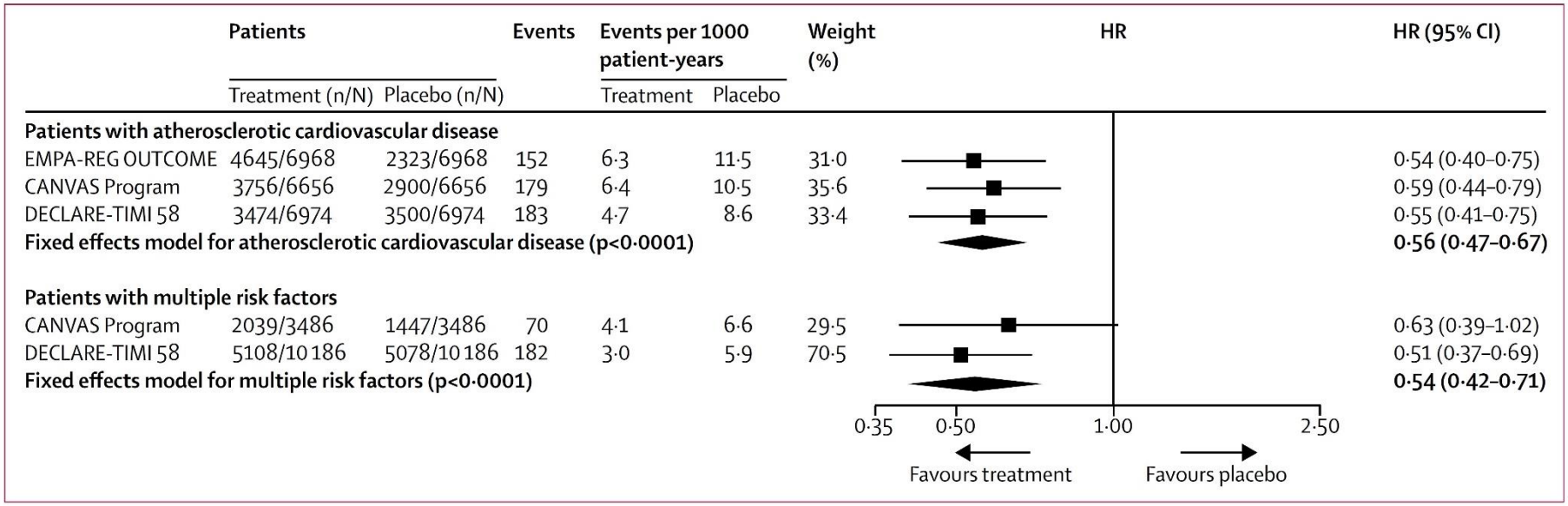
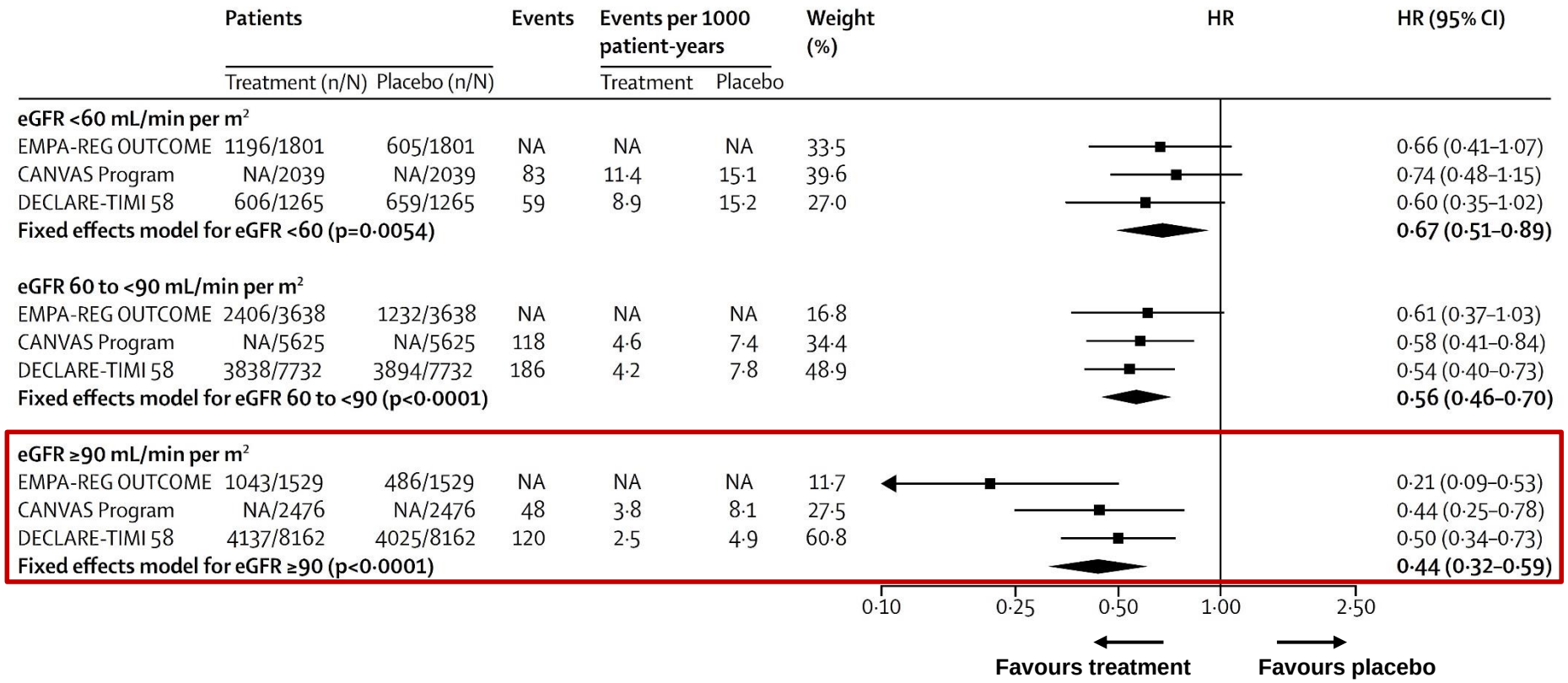


Figure 4: **Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death stratified by the presence of established atherosclerotic cardiovascular disease**

Atherosclerotic cardiovascular disease: Q statistic=0·19, p=0·91, I^2=0%; multiple risk factors: Q statistic=0·52, p=0·47, I^2=0% The p value for subgroup differences was 0·71. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

Zelniker TA et al. Lancet 393:31–39, 2019

Renal Outcomes in CVOTs with SGLT2 Inhibitor



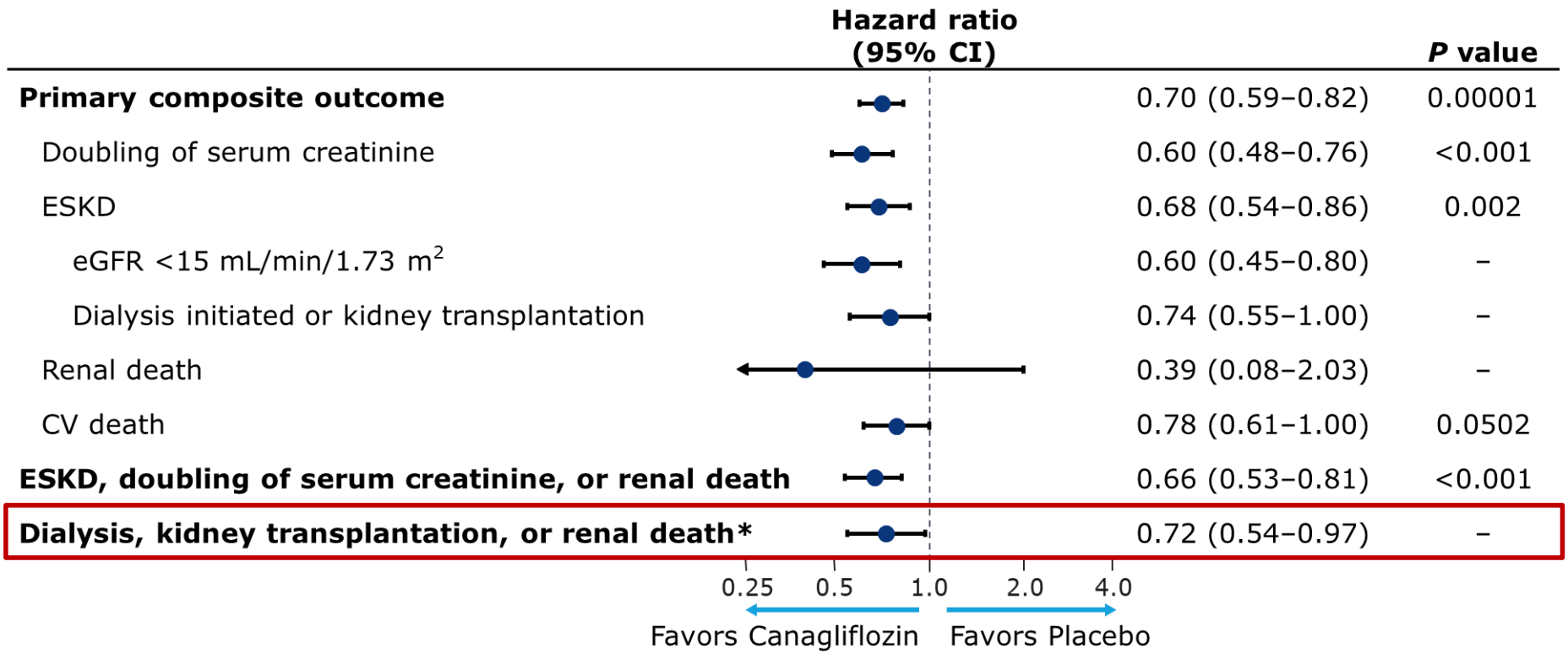
Zelniker TA et al. Lancet 393:31–39, 2019

Prognosis of CKD by GFR and Albuminuria

	eGFR	UACR	RRT
DECLARE	85	13	NA
CANVAS	76	12	18
EMPA-REG	74	18	11

GFR, mL min^{-1} 1.73 m^{-2} Description and range			Persistent albuminuria categories Description and range		
			A1	A2	A3
			<30 mg/g	30–300 mg/g	>300 mg/g
	G1	≥90	Low risk	Moderate risk	High risk
	G2	60–89	DECLARE CANVAS EMPA-REG		
	G3a	45–59			CREDENCE
	G3b	30–44		SCORED	DAPA-CKD
	G4	15–29	Very high risk		
	G5	<15			

CREDENCE

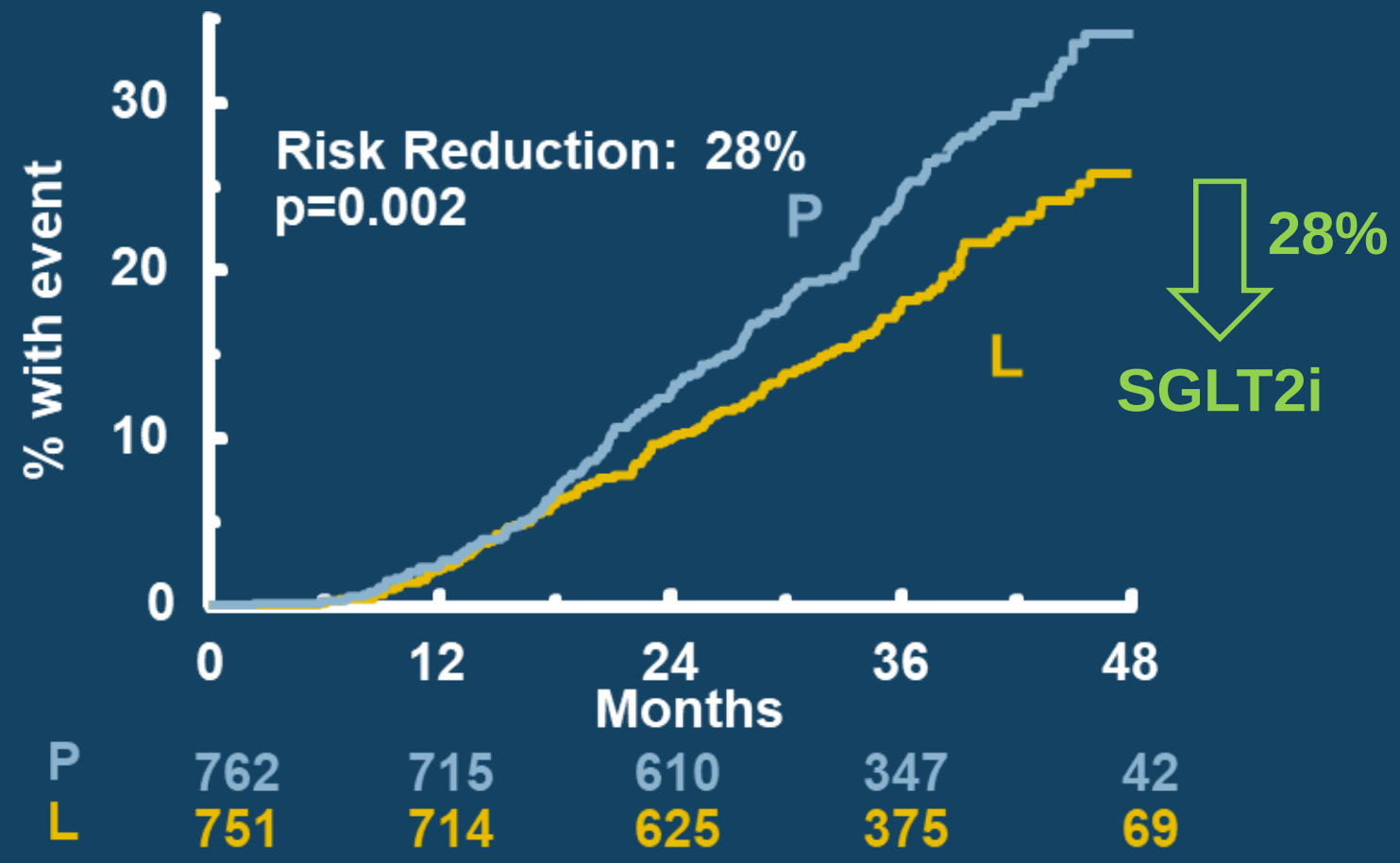


*Post hoc analysis (n=183)

Perkovic V et al. N Engl J Med 380:2295–2306, 2019

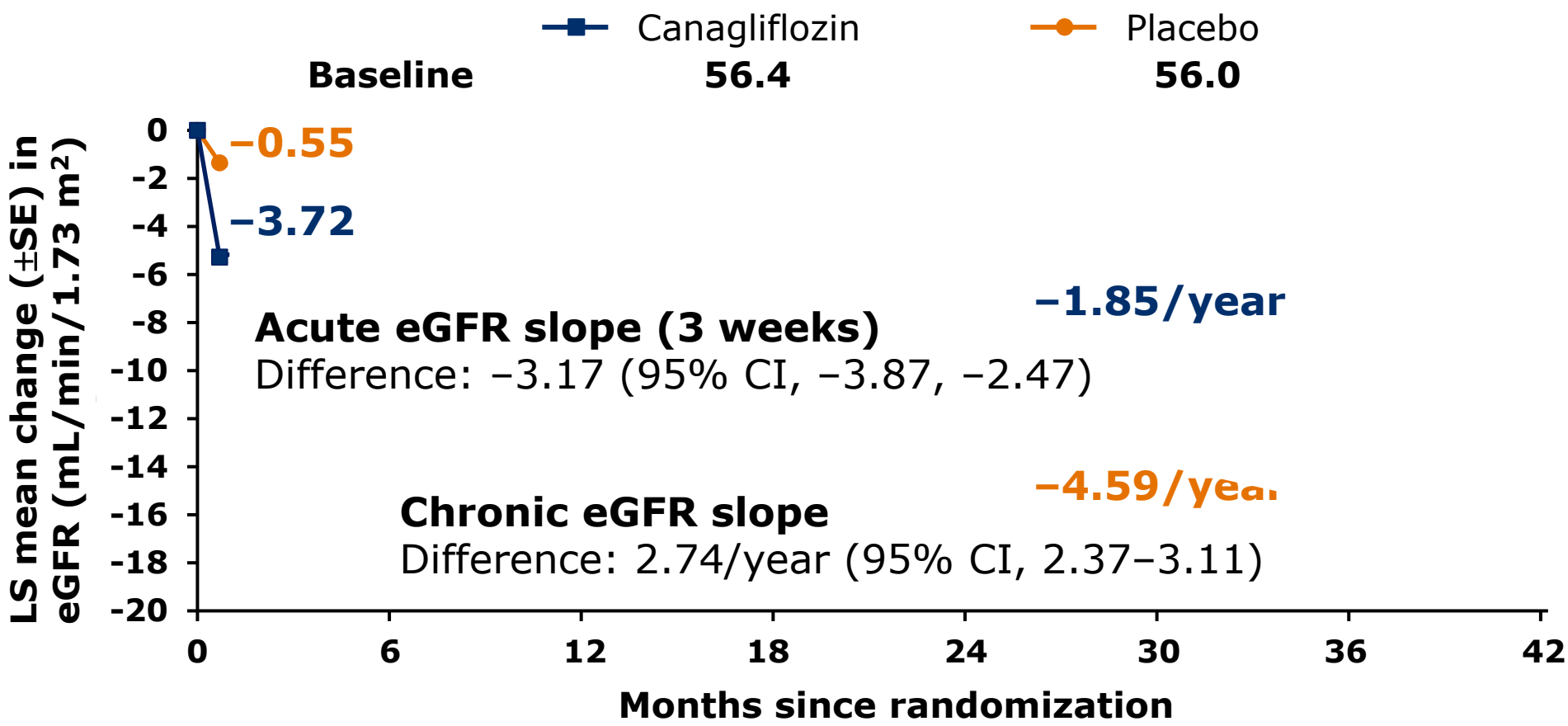
RENAAL

ESKD



Brenner BM et al. New Engl J Med 345:861–869, 2001

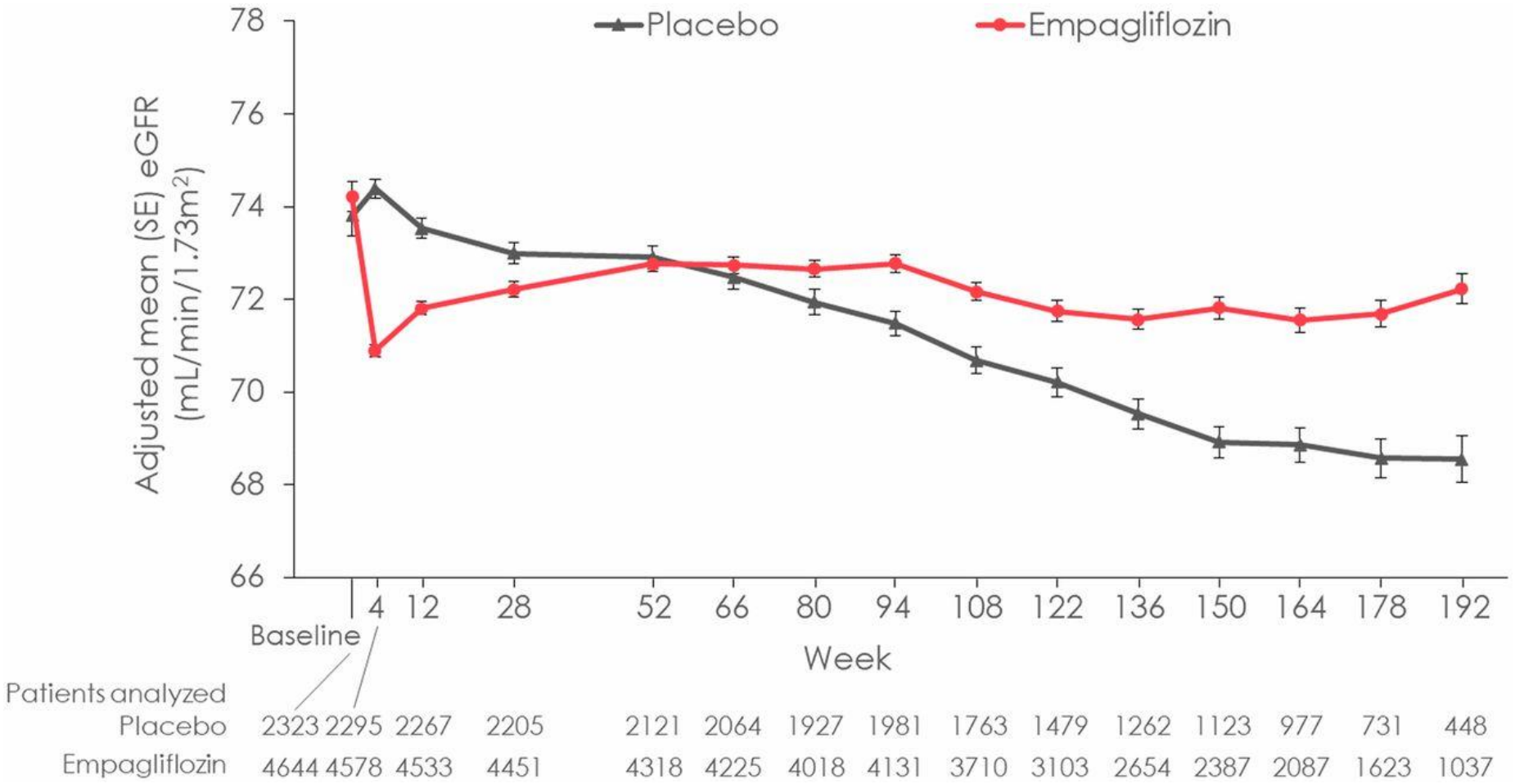
CREDENCE



No. of Participants									
Placebo	2178	2084	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2074	2005	1919	1782	1648	1116	652	241

Perkovic V et al. N Engl J Med 380:2295–2306, 2019

EMPA-REG OUTCOME eGFR Slope Analysis



Wanner C et al. JASN 29:2755–2769, 2018

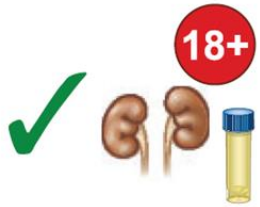
DAPA-CKD

RCT Protocol

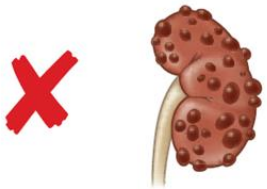
Dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD)

Rationale and trial protocol

Multicentre ~ 400
Target n = 4300
Patients with and without type 2 diabetes



≥ 18 years
25–75 ml/min/1.73 m^2
uACR ≥ 200 mg/g



Polycystic kidney disease
Lupus nephritis
ANCA vasculitis
Type I diabetes

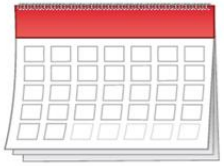
Interventions

Dapagliflozin 10 mg

1:1

Placebo

Follow-up

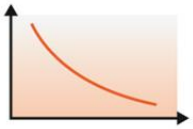


~ 45 months

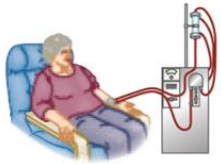
Event-driven (681 events)

Primary outcome

Composite renal endpoint



≥ 50% decline in eGFR



End-stage kidney disease

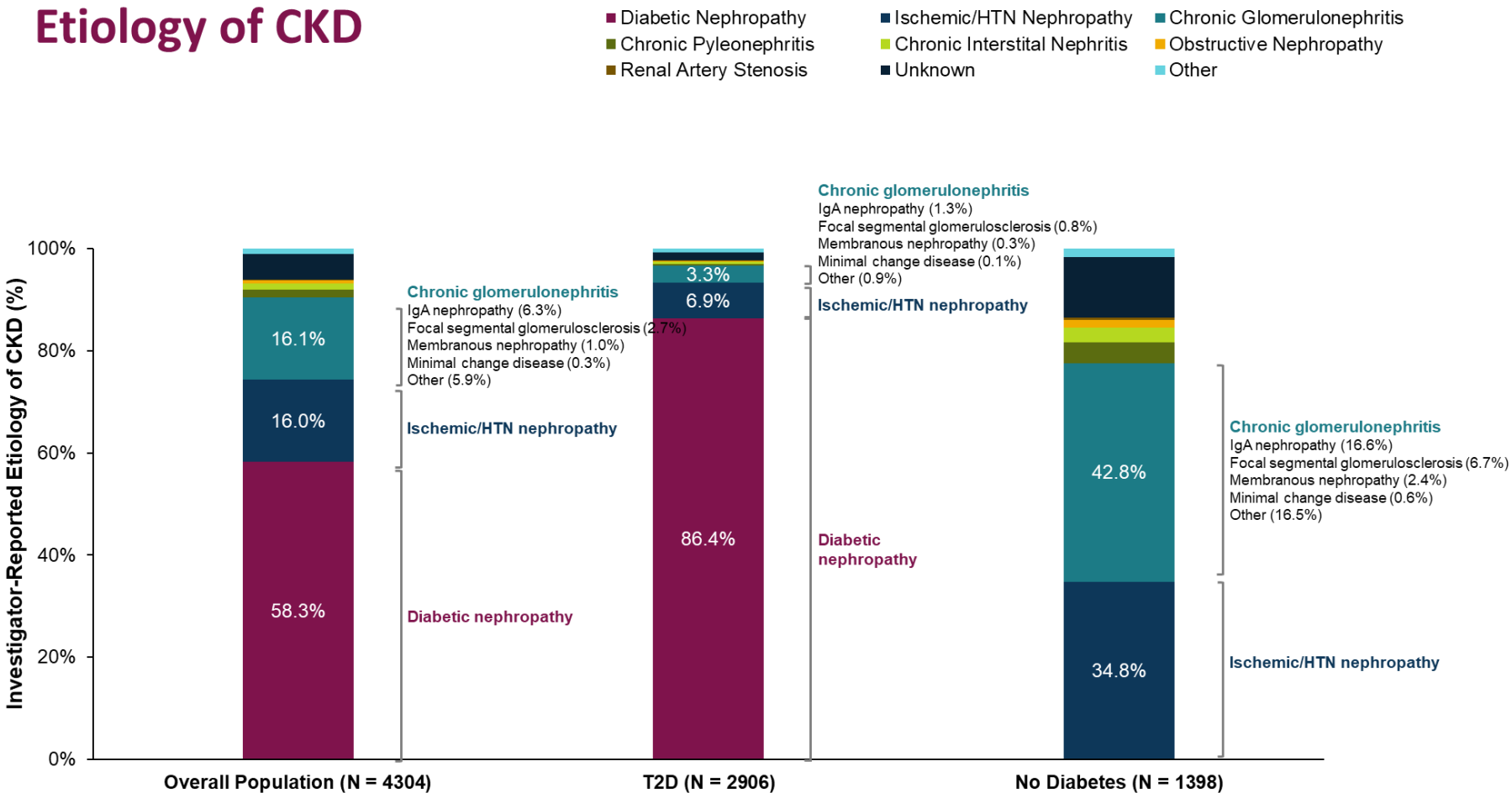
Renal or cardiovascular death

ndt NEPHROLOGY DIALYSIS TRANSPLANTATION

Heerspink HJL et al. NDT (2019)
@NDTSocial

DAPA-CKD

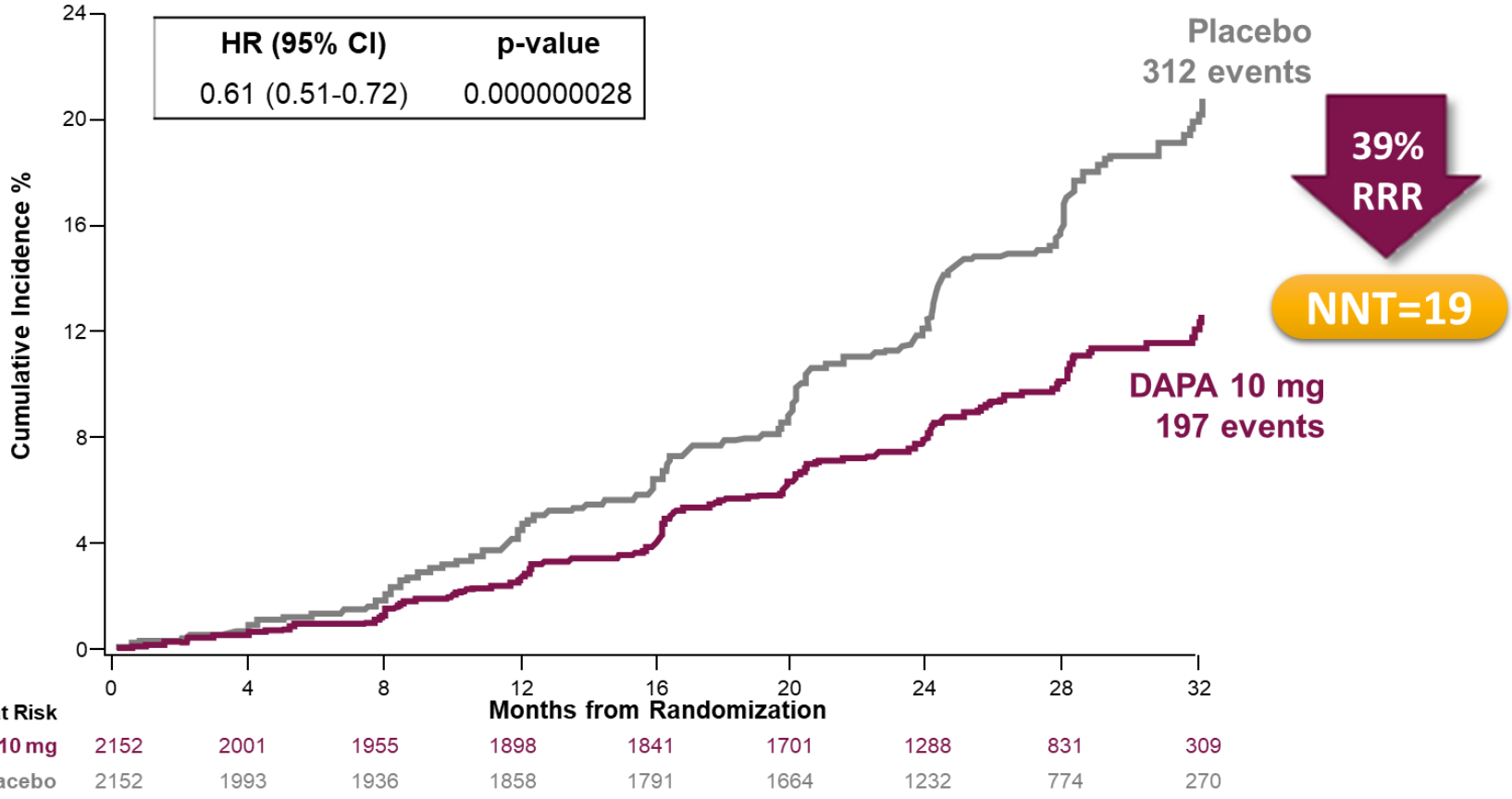
Etiology of CKD



Heerspink HJL et al. N Engl J Med 383:1436–1446, 2020

DAPA-CKD

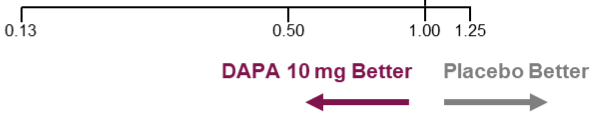
≥50% eGFR Decline, ESKD, Renal or CV Death



Heerspink HJL et al. N Engl J Med 383:1436–1446, 2020

DAPA-CKD

	Number of Events				
HR (95% CI)	DAPA 10 mg (N=2152)	Placebo (N=2152)	HR	95% CI	p-value Interaction
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death					
All Patients	197	312	**0.61**	(0.51, 0.72)	
T2D at Baseline					**0.24**
Yes	152	229	**0.64**	(0.52, 0.79)	
No	45	83	**0.50**	(0.35, 0.72)	
UACR (mg/g) at Baseline					**0.52**
≤1000	44	84	**0.54**	(0.37, 0.77)	
>1000	153	228	**0.62**	(0.50, 0.76)	
eGFR (mL/min/1.73m^2) at Baseline					**0.22**
<45	152	217	**0.63**	(0.51, 0.78)	
≥45	45	95	**0.49**	(0.34, 0.69)	



36% RRR in patients *with* T2D
HR, 0.64 (0.52-0.79)

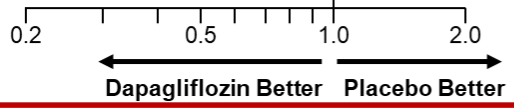
50% RRR in patients *without* T2D
HR, 0.50 (0.35-0.72)

P for interaction=0.24 (NS)

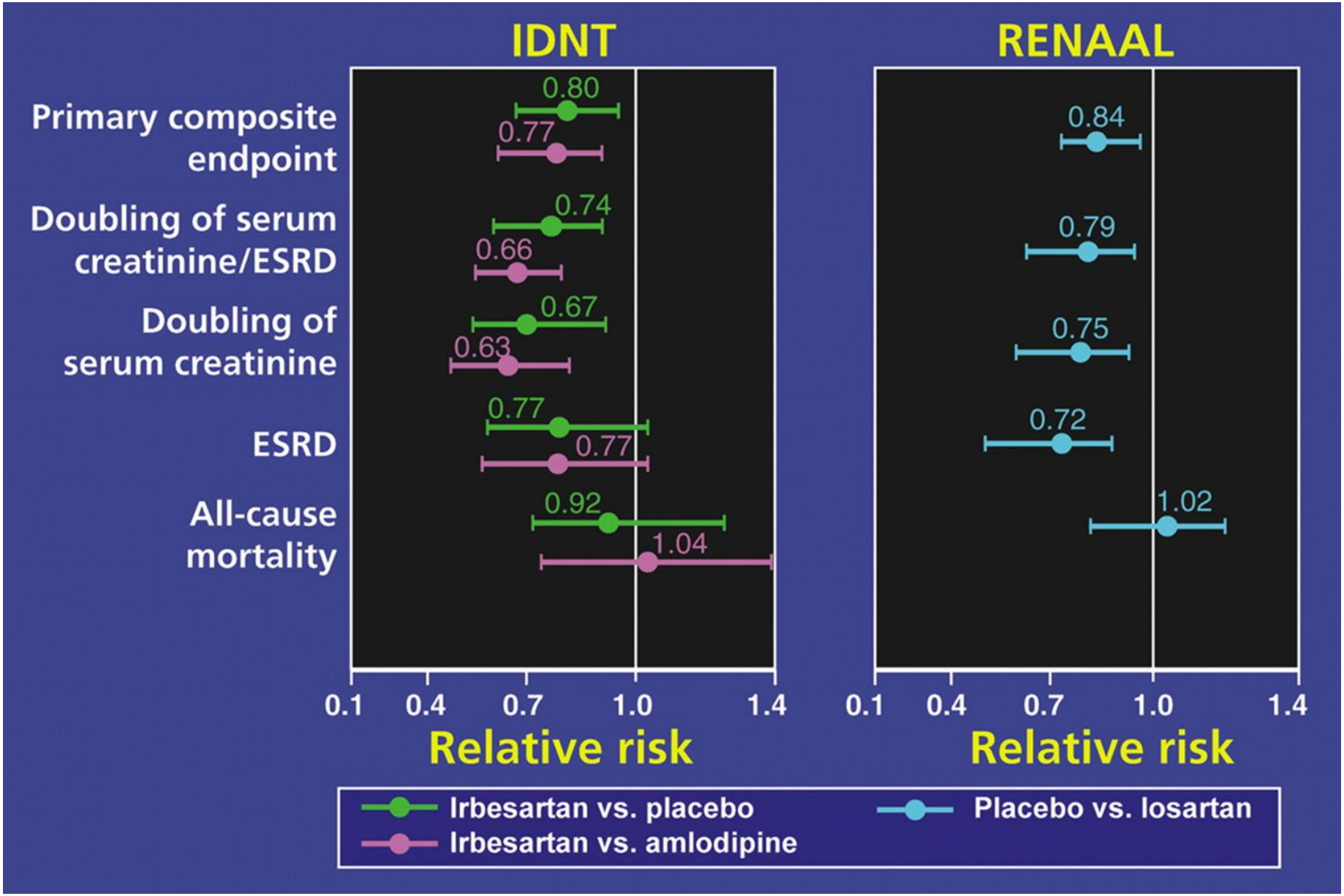
Heerspink HJL et al. N Engl J Med 383:1436–1446, 2020

DAPA-CKD

	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	P-value for Interaction
	No. of participants/total no.			
Primary outcome				
Overall	197/2152	312/2152	0.61 (0.51, 0.72)	
With type 2 diabetes	152/1455	229/1451	0.64 (0.52, 0.79)	
Without type 2 diabetes	45/697	83/701	0.50 (0.35, 0.72)	0.24
Renal-specific outcome				
Overall	142/2152	243/2152	0.56 (0.45, 0.68)	
With type 2 diabetes	103/1455	173/1451	0.57 (0.45, 0.73)	
Without type 2 diabetes	39/697	70/701	0.51 (0.34, 0.75)	0.57
CV death or heart failure				
Overall	100/2152	138/2152	0.71 (0.55, 0.92)	
With type 2 diabetes	85/1455	119/1451	0.70 (0.53, 0.92)	
Without type 2 diabetes	15/697	19/701	0.79 (0.40, 1.55)	0.78
All-cause mortality				
Overall	101/2152	146/2152	0.69 (0.53, 0.88)	
With type 2 diabetes	84/1455	113/1451	0.74 (0.56, 0.98)	
Without type 2 diabetes	17/697	33/701	0.52 (0.29, 0.93)	0.25



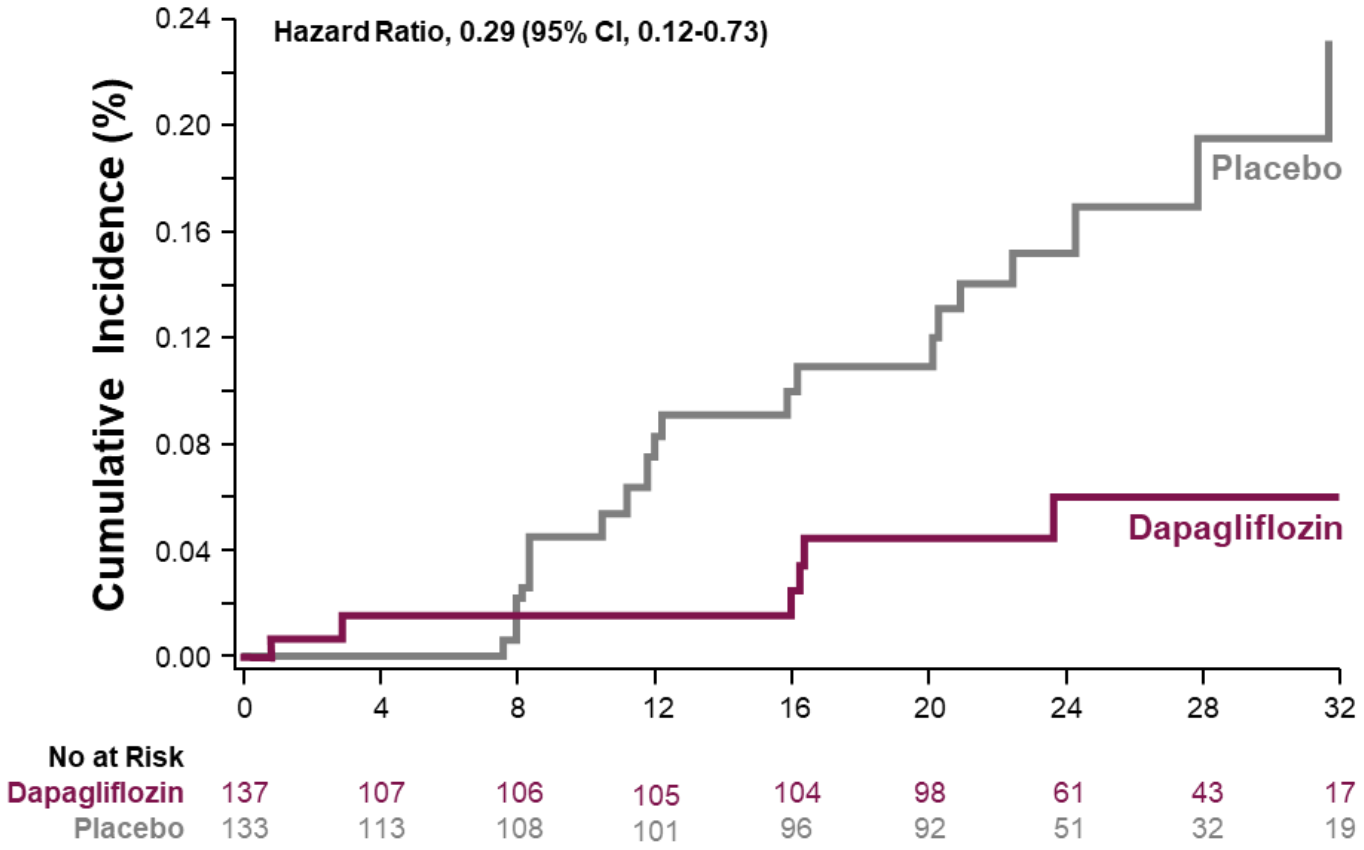
Heerspink HJL et al. N Engl J Med 383:1436–1446, 2020



Parving HH et al. N Engl J Med 345:870–878, 2001
Brenner BM et al. N Engl J Med 345:861–869, 2001

DAPA-CKD

Primary outcome in participants with IgA nephropathy

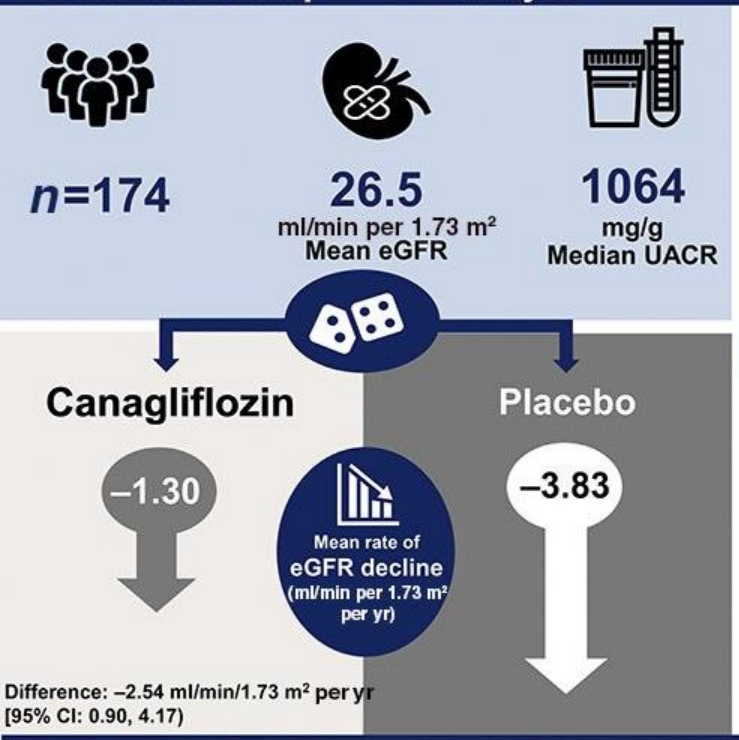


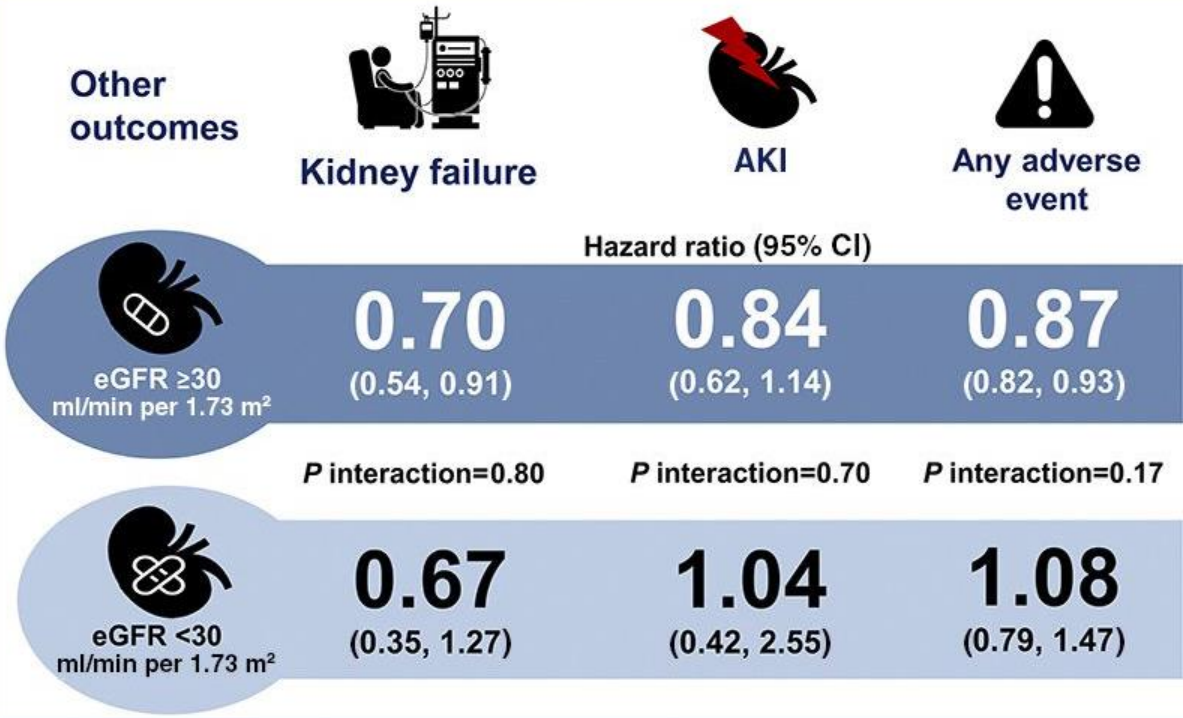
Heerspink HJL et al. N Engl J Med 383:1436–1446, 2020

What are the effects of canagliflozin in patients with type 2 diabetes and baseline eGFR <30 ml/min per 1.73 m² per yr?

CJASN
Clinical Journal of the American Society of Nephrology

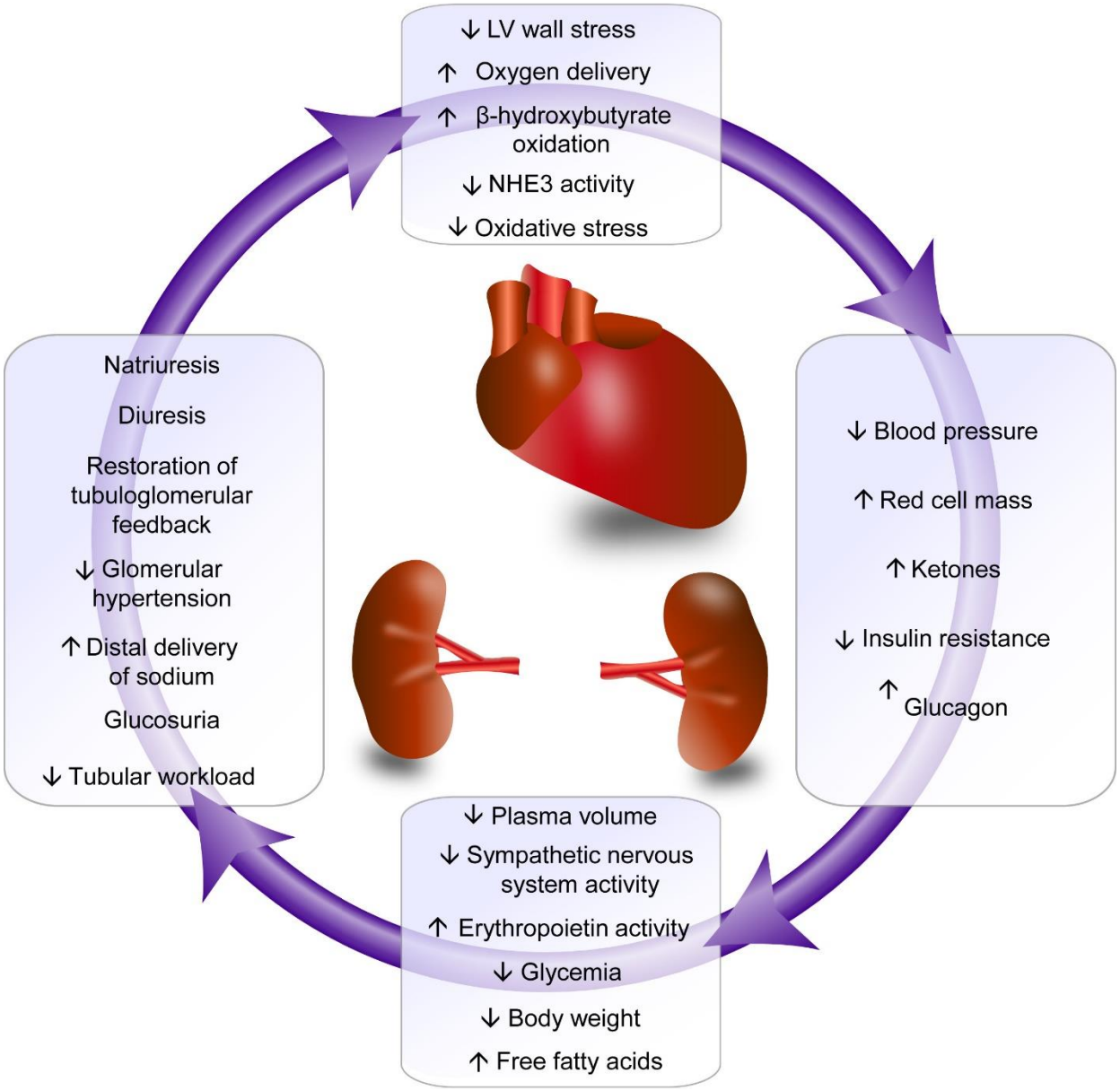
CREDENCE trial *post hoc* analysis





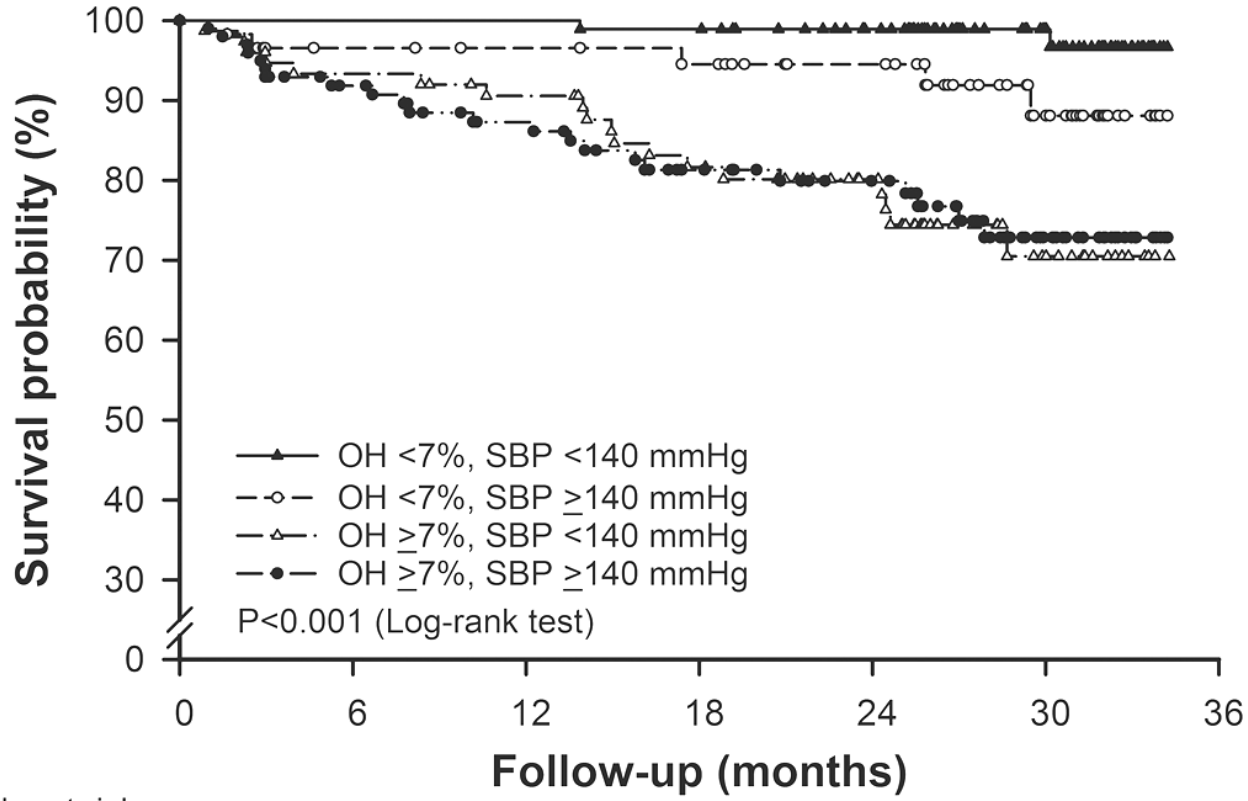
Conclusions: Canagliflozin slowed progression of kidney disease, without increasing acute kidney injury, even in patients with diabetes and eGFR <30 ml/min per 1.73 m²

George Bakris, Megumi Oshima, Kenneth W. Mahaffey, et al. ***Effects of Canagliflozin in Patients with Baseline eGFR <30 ml/min per 1.73 m²: Subgroup Analysis of the Randomized CREDENCE Trial***. CJASN doi: 10.2215/CJN.10140620. **Visual Abstract by Divya Bajpai, MD, PhD**



Scheen AJ et al. Circ Res 122:1439–1459, 2018

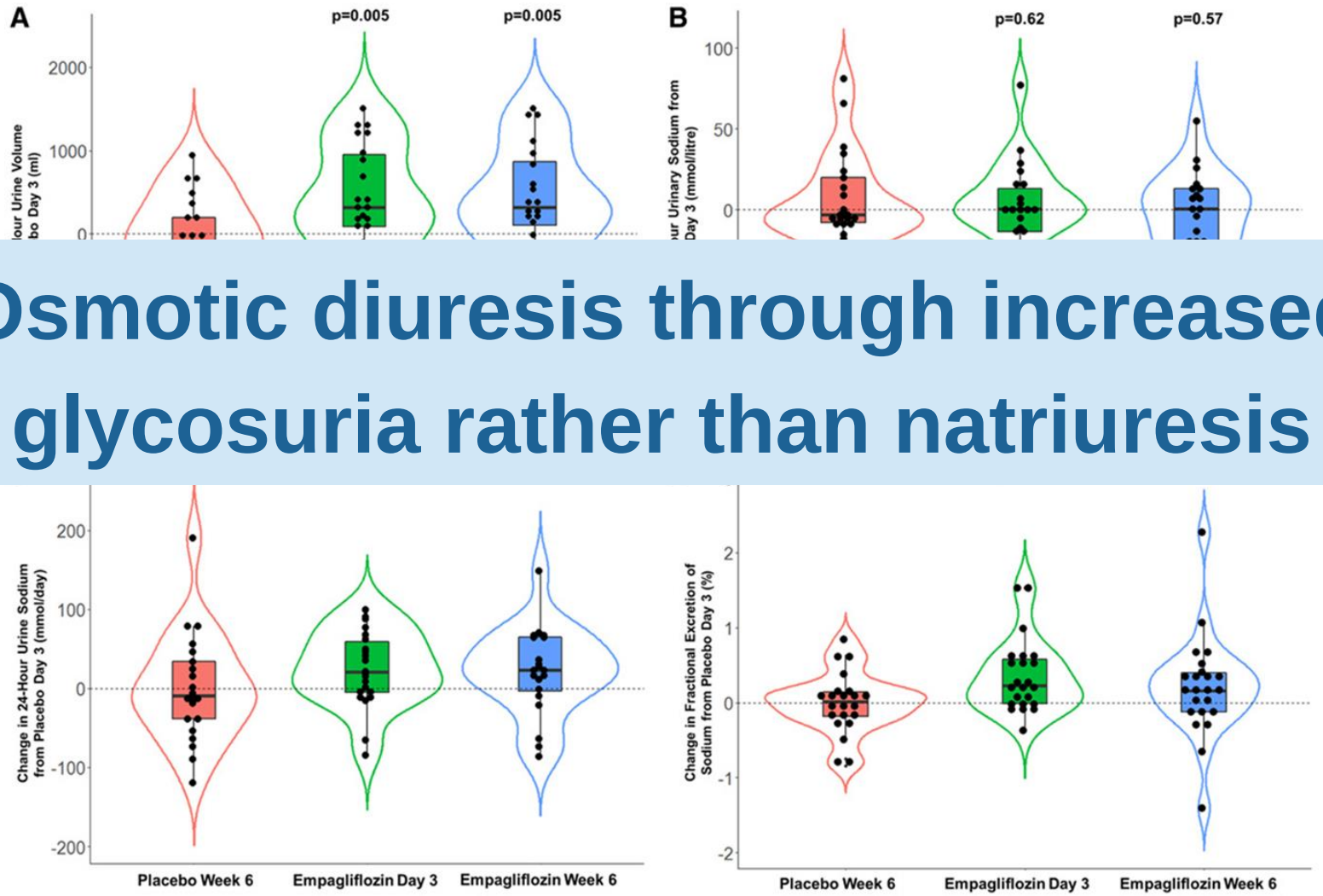
Volume Overload and CV Outcomes in CKD



No. at risk						
OH <7%, SBP <140 mmHg:	105	103	96	92	80	45
OH <7%, SBP ≥140 mmHg:	58	51	49	47	41	22
OH ≥7%, SBP <140 mmHg:	76	69	63	55	43	16
OH ≥7%, SBP ≥140 mmHg:	99	83	74	63	53	24

Hung SC et al. J Am Heart Assoc 4:e001918, 2015

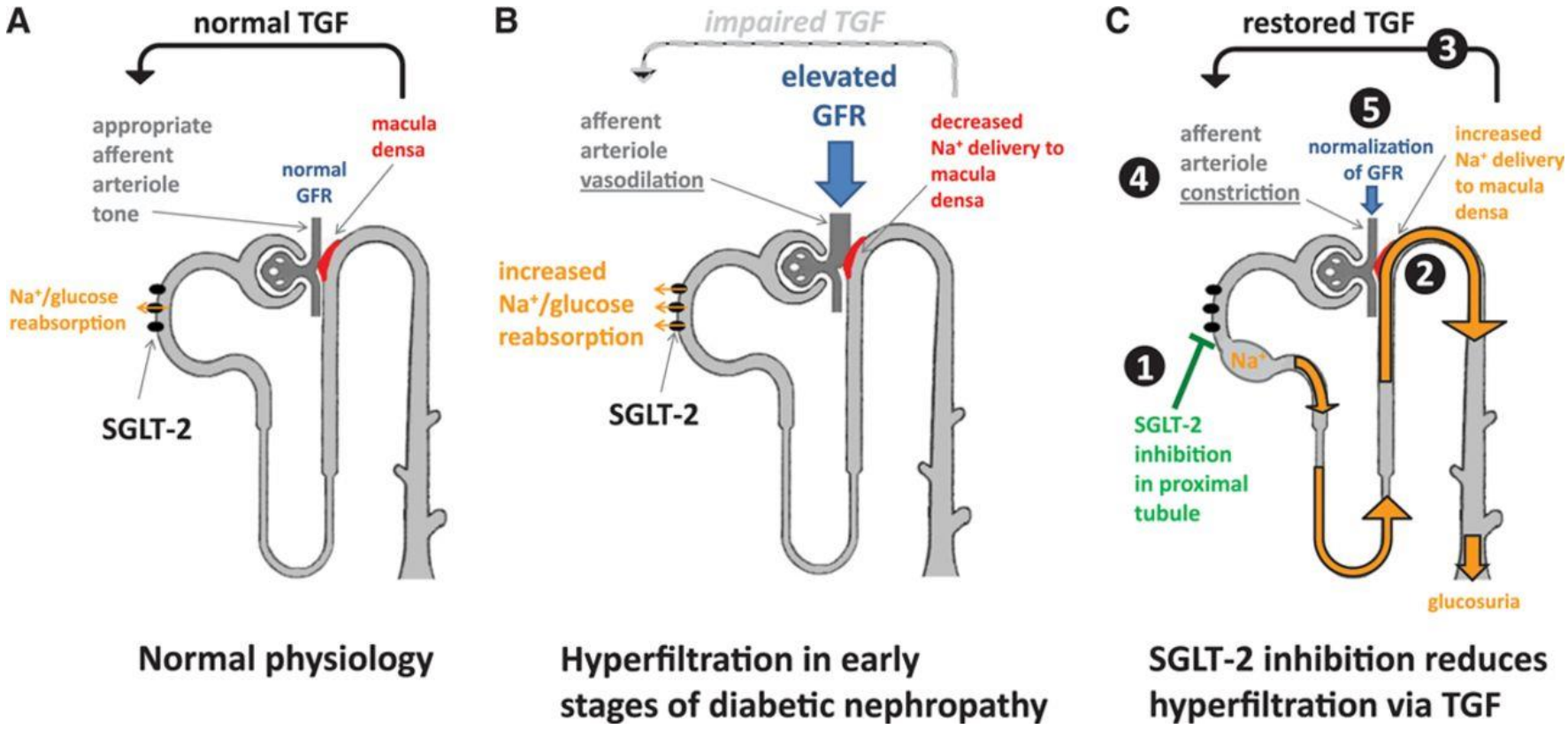
SGLT2 Inhibition in Combination With Loop Diuretics in Patients With Type 2 Diabetes and Chronic Heart Failure



Osmotic diuresis through increased glycosuria rather than natriuresis

Mordi NA et al. Circulation 142:1713–1724, 2020

Tubuloglomerular Feedback

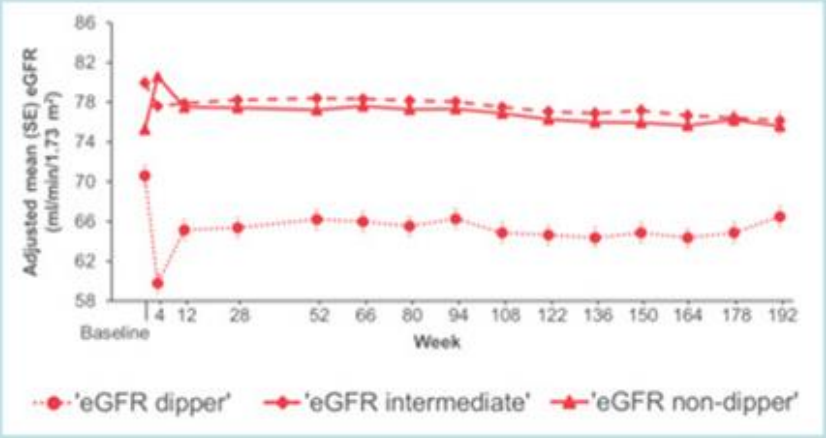


Cherney DZI et al. Circulation 129:587–597, 2014

EMPA-REG OUTCOME *post hoc* analysis

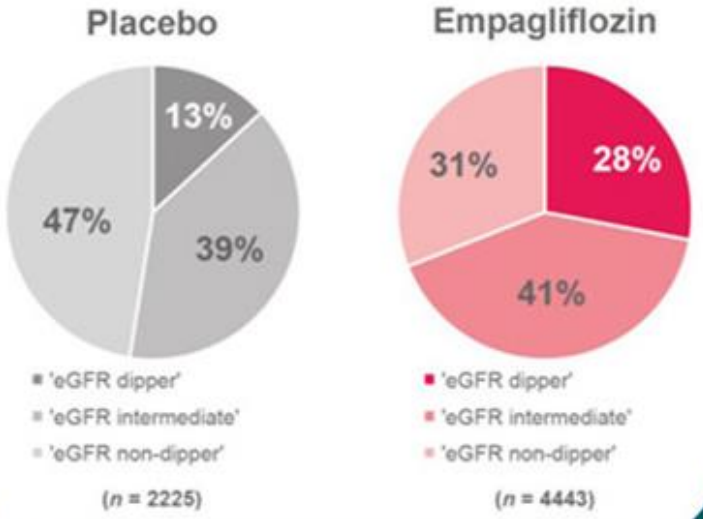
- **6668 participants with type 2 diabetes (T2D) and cardiovascular (CV) disease**
- Categorized by percent eGFR change from baseline at Week 4 into:
  - 'eGFR dipper' (>10% decline)
  - 'eGFR intermediate' (>0% to ≤10% decline)
  - 'eGFR non-dipper' (no decline)

eGFR over time per dipping category with empagliflozin



Higher **KDIGO risk category** and **diuretic treatment at baseline** were independently predictive for 'eGFR dip' >10% with empagliflozin versus placebo

28% empagliflozin-treated participants experienced an 'eGFR dip' >10%



Kraus BJ et al. Kidney Int November 09, 2020

Early changes in albuminuria with canagliflozin predict kidney and cardiovascular outcomes

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

Post-hoc analysis of the CREDENCE trial
N=3836

eGFR 30-<90 ml/min

UACR 300-5000 mg/g

Effect of canagliflozin vs placebo

↓

Early change in UACR (week 26)

↓

Kidney and CV outcomes

OUTCOME

Effect of canagliflozin at week 26:

31% reduction in albuminuria
(95% CI 27-36)

Regression in albuminuria stage
OR 1.85 (95% CI 1.55-2.22)

Each 30% reduction in albuminuria associated with:

Kidney outcome
HR 0.71
(95% CI 0.67-0.76)

MACE
HR 0.92
(95% CI 0.88-0.96)

HF or CV death
HR 0.86
(95% CI 0.81-0.90)

Conclusion
In type 2 diabetes and CKD, canagliflozin results in early and sustained reductions in albuminuria, which are independently associated with long-term kidney and cardiovascular outcomes.

doi: 10.1681/ASN.2020050723

Lifestyle therapy

Physical activity
Nutrition
Weight loss

First-line therapy

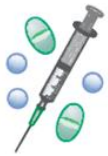
Metformin

eGFR < 45	eGFR < 30	Dialysis
Reduce dose	Discontinue	Discontinue

+

SGLT2 inhibitor

eGFR < 30	Dialysis
Do not initiate	Discontinue



Additional drug therapy as needed for glycemic control

GLP-1 receptor agonist (preferred)

DPP-4 inhibitor | **Insulin**

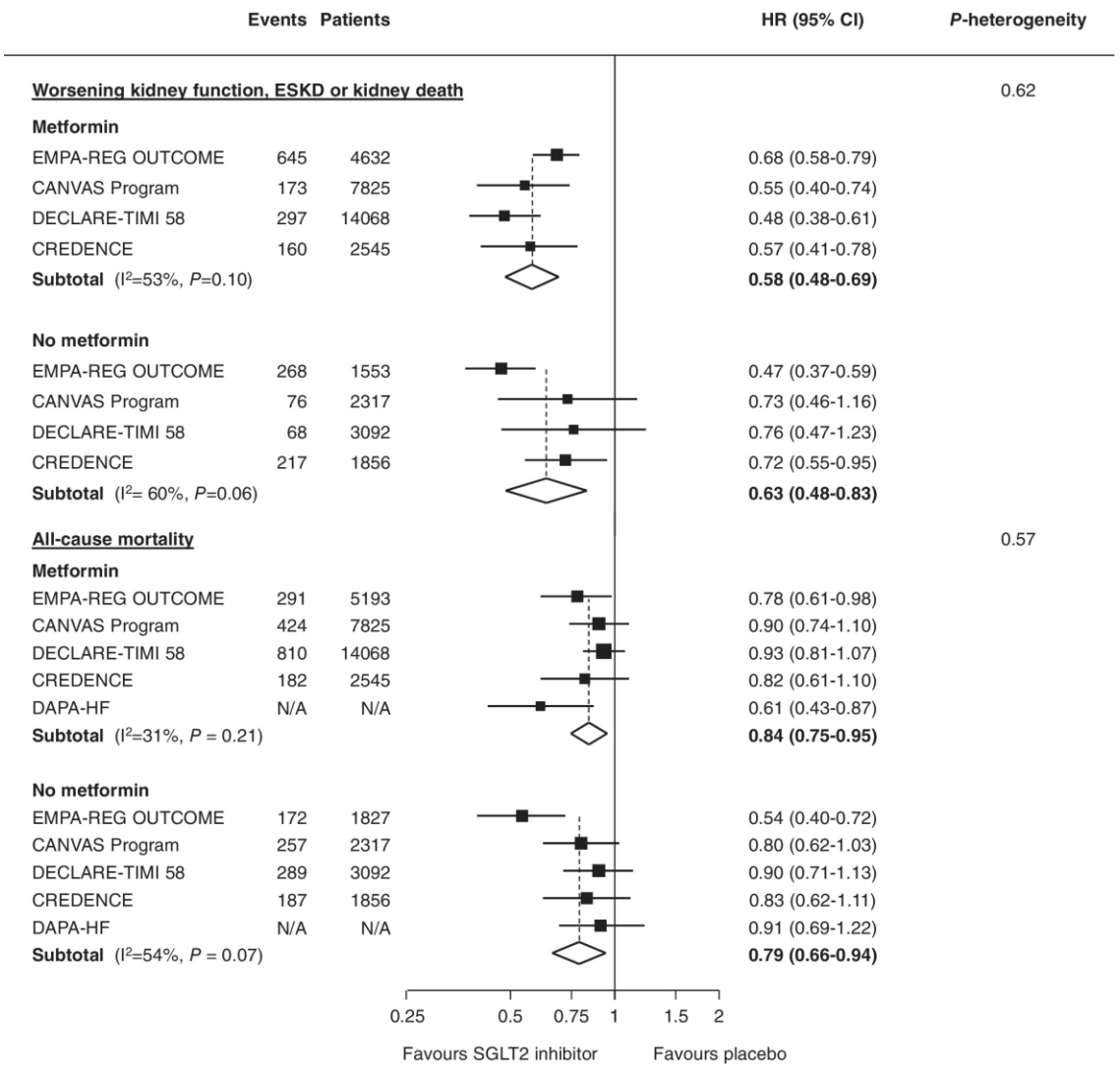
Sulfonylurea | **TZD**

Alpha-glucosidase inhibitor

- Guided by patient preferences, comorbidities, eGFR, and cost
- Includes patients with eGFR < 30 ml/min per 1.73 m^2 or treated with dialysis
- See Figure 20

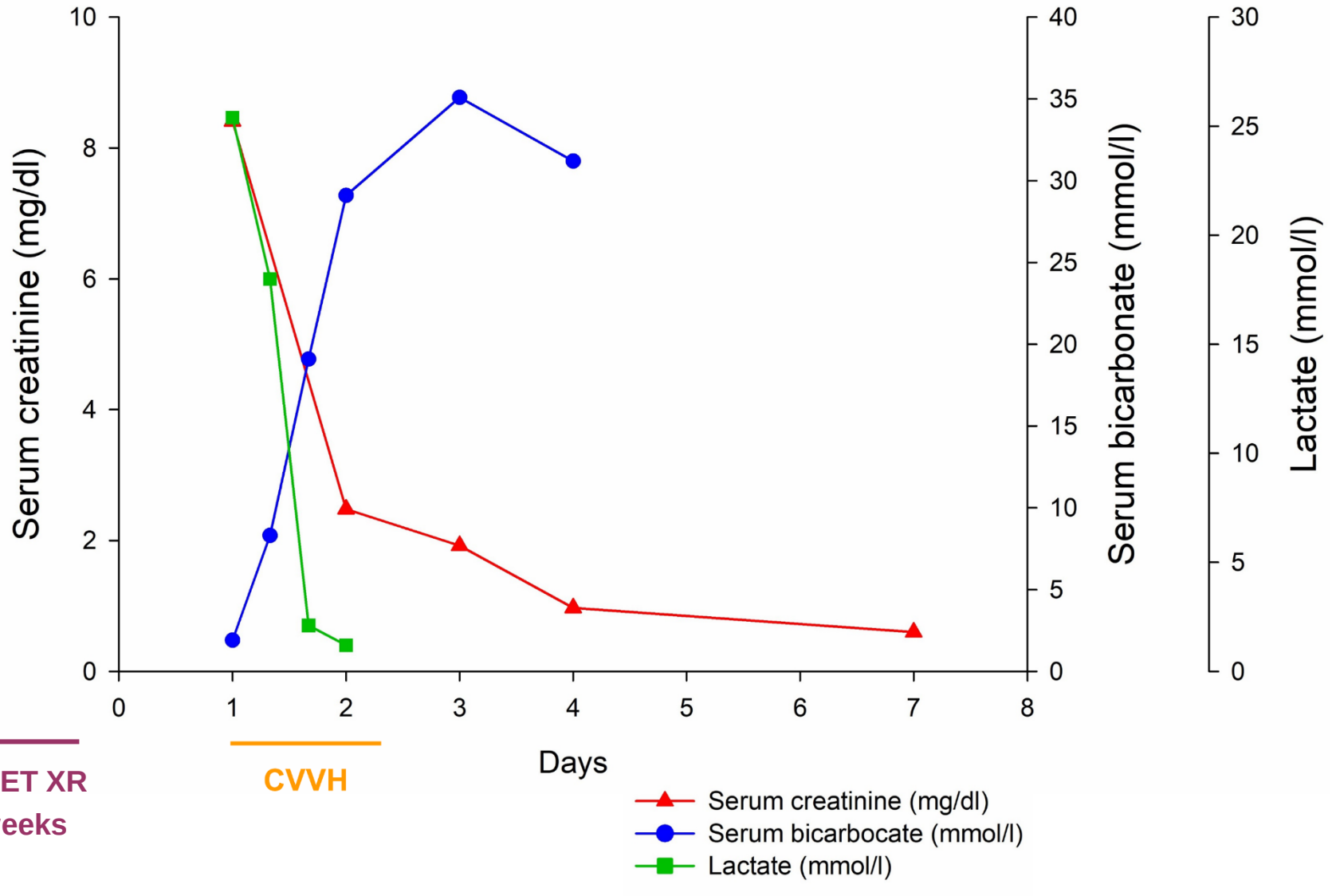
KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES · KDIGO

SGLT2i With and Without Metformin: Meta-analysis



Neuen SD et al. Diabetes Obes Metab Oct 11, 2020

AKI and Severe Lactic Acidosis



DECLARE: Key Safety Events

Table 2. Safety Events.*

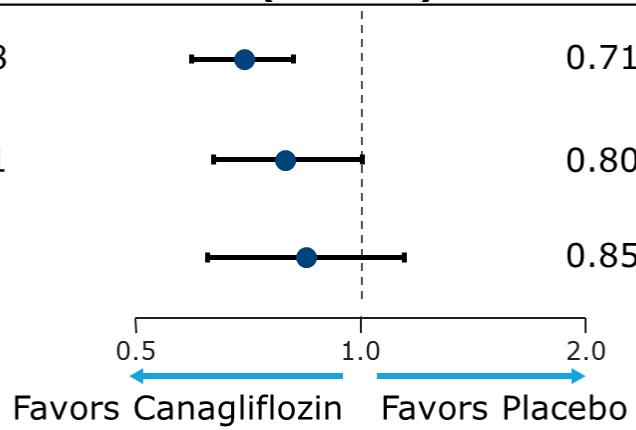
Event	Dapagliflozin (N=8574)	Placebo (N=8569)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Serious adverse event	2925 (34.1)	3100 (36.2)	0.91 (0.87–0.96)	<0.001
Adverse event leading to discontinuation of trial regimen	693 (8.1)	592 (6.9)	1.15 (1.03–1.28)	0.01
Major hypoglycemic event	58 (0.7)	83 (1.0)	0.68 (0.49–0.95)	0.02
Diabetic ketoacidosis	27 (0.3)	12 (0.1)	2.18 (1.10–4.30)	0.02
Amputation	123 (1.4)	113 (1.3)	1.09 (0.84–1.40)	0.53
Fracture	457 (5.3)	440 (5.1)	1.04 (0.91–1.18)	0.59
Symptoms of volume depletion	213 (2.5)	207 (2.4)	1.00 (0.83–1.21)	0.99
Acute kidney injury	125 (1.5)	175 (2.0)	0.69 (0.55–0.87)	0.002
Genital infection	76 (0.9)	9 (0.1)	8.36 (4.19–16.68)	<0.001
Urinary tract infection	127 (1.5)	133 (1.6)	0.93 (0.73–1.18)	0.54
Cancer	481 (5.6)	486 (5.7)	0.99 (0.87–1.12)	0.83
Bladder cancer	26 (0.3)	45 (0.5)	0.57 (0.35–0.93)	0.02
Breast cancer	36 (0.4)	35 (0.4)	1.02 (0.64–1.63)	0.92
Hypersensitivity	32 (0.4)	36 (0.4)	0.87 (0.54–1.40)	0.57
Hepatic event	82 (1.0)	87 (1.0)	0.92 (0.68–1.25)	0.60

Wiviott SD et al. N Engl J Med 380:347–357, 2019

CREDENCE

Renal Safety

	Number of participants with an event, n		Hazard ratio (95% CI)
	Canagliflozin (N = 2200)	Placebo (N = 2197)	
All renal-related AEs	290	388	0.71 (0.61–0.82)
Hyperkalemia	151	181	0.80 (0.65–1.00)
Acute kidney injury	86	98	0.85 (0.64–1.13)



Perkovic V et al. N Engl J Med 380:2295–2306, 2019

DAPA-CKD

Safety outcomes, %	With T2D		Without T2D	
	Dapagliflozin (n=1453)	Placebo (n=1450)	Dapagliflozin (n=696)	Placebo (n=699)
Discontinuation due to AE	5.6	6.5	5.2	4.1
Any serious AE	33.2	38.8	21.6	23.9
AE of interest				
Amputation	2.4	2.6	0	0.1
Diabetic ketoacidosis	0	0.1	0	0
Fracture	4.5	3.5	2.9	2.6
Renal related adverse event	8.3	10.2	4.9	5.7
Major hypoglycemia	1.0	1.9	0	0
Volume depletion	**6.3**	**4.9**	**5.0**	**2.7**

Heerspink HJL et al. N Engl J Med 383:1436–1446, 2020

AKI With SGLT2 Inhibitors Versus Other Glucose-Lowering Drugs

Study Design

Retrospective Cohort

Manitoba, Canada

Patients with type 2 diabetes mellitus

SGLT inhibitors
versus
Other glucose-lowering drugs (oGLD)

Analysis: Survival analysis and logistic regression
Adjustment using propensity score matching

SGLT2i users	oGLD users
N = 4,778	N = 4,778

Results

117 AKI events total
- **47 with SGLT2i use**
- **70 with oGLD use**

Incident AKI	**HR 0.64** (95% CI 0.40 -1.03)
AKI at 30 days	**OR 0.70** (95% CI 0.27 - 1.84)
AKI at 90 days	**OR 0.36** (95% CI 0.36 - 1.16)

CONCLUSION: SGLT2 inhibitor use was not significantly associated with higher risk of AKI compared to other glucose-lowering drugs.

Christie Rampersad, Eyal Kraut, Reid H. Whitlock, et al (2020)
@AJKDonline | DOI: 10.1053/j.ajkd.2020.03.019

AJKD
AMERICAN JOURNAL OF KIDNEY DISEASES

FDA

Search Menu

FDA Drug Safety Communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR)

[06-14-2016]

Safety Announcement

The U.S. Food and Drug Administration (FDA) has strengthened the existing warning about the risk of acute kidney injury for the type 2 diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). Based on recent reports, we have revised the warnings in the drug labels to include information about acute kidney injury and added recommendations to minimize this risk.

OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

kidney INTERNATIONAL supplements

Treat all CKD patients ≥50 y/o regardless of LDL levels

IMPROVING GLOBAL OUTCOMES

KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease

VOLUME 3 | ISSUE 3 | NOVEMBER 2013

http://www.kidney-international.org

DAPA-CKD

Baseline characteristics

- Mean **61.8** years old
- **33%** of female
- **34%** of Asian
- eGFR of **43** mL/min/1.73m^2
- UACR of **949** mg/g

32% without T2DM

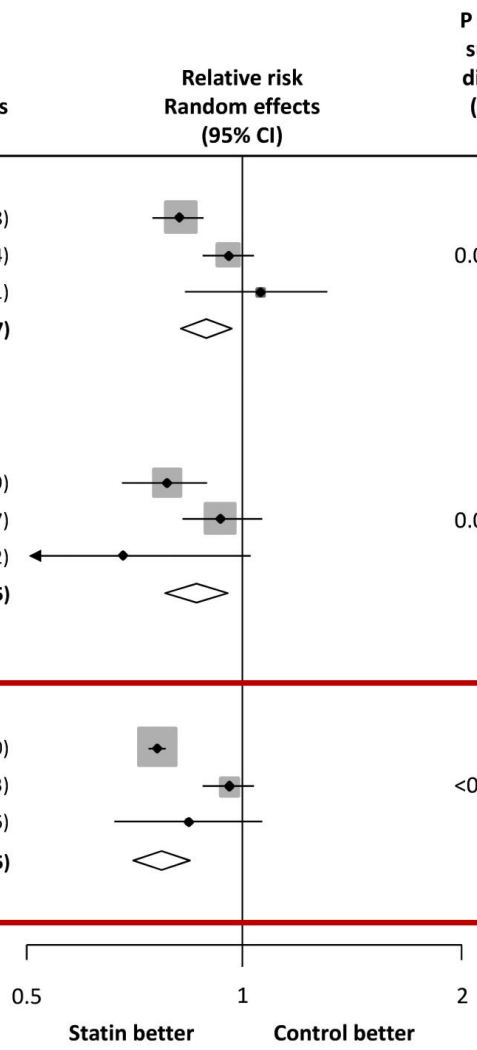
Medication

ACEi/ARB	97%
Statin	65%
Antidiabetic	63%
CCB	51%
Antithrombotic	47%
Diuretic	44%

Heerspink HJL et al. N Engl J Med 383:1436–1446, 2020

Statin for CKD: Meta-analysis

Category	No. of trials or subsets*	Statin n	Statin N	Control n	Control N	Relative risk Random effects (95% CI)	P value for subgroup difference (stage of CKD)	Variance explained by stage of kidney disease
All cause mortality								
CKD not on dialysis	11	1005	14 063	1281	14 213	0.81 (0.74 to 0.88)		
Dialysis	13	938	2352	988	2353	0.96 (0.88 to 1.04)	0.009	89%
Transplant	6	152	1382	144	1378	1.05 (0.84 to 1.31)		
All trials	**32**	**3280**	**22 517**	**3575**	**22 637**	**0.89 (0.82 to 0.97)**		
Heterogeneity across all trials: χ^2=43.412 P=0.07, I^2=29%								
Cardiovascular mortality								
CKD not on dialysis	8	439	9480	574	9579	0.78 (0.68 to 0.89)		
Dialysis	13	446	2311	1512	2312	0.94 (0.82 to 1.07)	0.08	100%
Transplant	4	38	1161	56	1161	0.68 (0.45 to 1.02)		
All trials	**27**	**1307**	**17 672**	**1512**	**17 745**	**0.86 (0.78 to 0.95)**		
Heterogeneity across all trials: χ^2=18.33, P=0.86, I^2=0%								
Major cardiovascular events								
CKD not on dialysis	14	2525	17 912	3361	18 121	0.76 (0.73 to 0.80)		
Dialysis	4	852	3557	899	3527	0.95 (0.87 to 1.03)	<0.0001	99%
Transplant	1	112	1050	134	1052	0.84 (0.66 to 1.06)		
All trials	**20**	**3495**	**22 589**	**4404**	**22 773**	**0.78 (0.72 to 0.85)**		
Heterogeneity across all trials: χ^2=41.28 P=0.002, I^2=54%								



Palmer SC et al. Ann Intern Med 157:263–275, 2012

Predictor	PAD	MACE	Mortality
Indoxyl sulfate (10 μg/mL increase)	1.19 (1.05–1.35)[a]	1.00 (0.90–1.12)	0.98 (0.90–1.07)
BMI (kg/m^2)	1.04 (0.94–1.14)	1.05 (0.97–1.14)	0.96 (0.90–1.02)
Systolic BP (10 mmHg increase)	1.08 (0.90–1.29)	1.17 (1.00–1.36)	1.04 (0.93–1.17)
TC (10 mg/dL increase)	1.04 (0.96–1.13)	1.03 (0.96–1.11)	1.01 (0.95–1.07)
HDL-C (10 mg/dL increase)	0.94 (0.75–1.17)	0.91 (0.76–1.11)	0.92 (0.79–1.07)
LDL-C (10 mg/dL increase)	1.08 (0.98–1.19)	**1.10 (1.00–1.21)[b]**	1.03 (0.96–1.11)
Triglycerides (10 mg/dL increase)	1.00 (0.97–1.03)	1.00 (0.97–1.02)	1.01 (0.99–1.03)
TC:HDL-C	1.05 (0.93–1.18)	1.01 (0.90–1.13)	0.99 (0.90–1.10)
Calcium (mg/dL)	1.04 (0.68–1.61)	1.61 (1.15–2.27)[a]	1.46 (1.12–1.89)[a]
Phosphate (mg/dL)	1.06 (0.86–1.31)	0.99 (0.81–1.22)	0.93 (0.78–1.10)
Ln CRP (mg/L)	0.91 (0.67–1.24)	1.06 (0.82–1.37)	1.31 (1.10–1.56)[a]

JUPITER

	eGFR <60 ml/min/1.73 m²						eGFR ≥60 ml/min/1.73 m²					
	Rosuvastatin		Placebo				Rosuvastatin		Placebo			
	n	Rate	n	Rate	**HR (95% CI)**	p Value	n	Rate	n	Rate	**HR (95% CI)**	p Value
Primary end point	40	1.08	71	1.95	**0.55 (0.38–0.82)**	0.002	102	0.69	180	1.21	**0.57 (0.45–0.72)**	<0.001
Myocardial infarction	8	0.21	20	0.54	**0.40 (0.17–0.90)**	0.02	23	0.15	48	0.32	**0.48 (0.29–0.79)**	0.003
Stroke	10	0.27	14	0.38	**0.71 (0.31–1.59)**	0.40	23	0.15	50	0.33	**0.46 (0.28–0.76)**	0.002
Arterial revascularization	19	0.51	39	1.07	**0.48 (0.28–0.83)**	0.006	52	0.35	92	0.62	**0.57 (0.40–0.80)**	0.001
Myocardial infarction, stroke, or confirmed cardiovascular death	24	0.64	40	1.09	**0.59 (0.36–0.99)**	0.04	59	0.40	117	0.78	**0.50 (0.37–0.69)**	<0.001
Venous thromboembolism	6	0.16	17	0.46	**0.34 (0.14–0.88)**	0.02	28	0.19	43	0.29	**0.65 (0.41–1.05)**	0.08
All-cause mortality	34	0.85	61	1.53	**0.56 (0.37–0.85)**	0.005	164	1.04	186	1.17	**0.88 (0.72–1.09)**	0.25
Primary end point plus any death	64	1.72	114	3.13	**0.55 (0.41–0.75)**	0.0001	231	1.56	327	2.20	**0.71 (0.60–0.84)**	<0.001
Primary end point plus VTE plus any death	69	1.86	127	3.51	**0.53 (0.40–0.71)**	<0.0001	251	1.69	356	2.41	**0.70 (0.60–0.83)**	<0.001

Ridker PM et al. J Am Coll Cardiol 55:1266–1273, 2010

Second Revolution in Cardiovascular Prevention

	Prevention		Treatment	
	Statins	SGLT2i	Statins	SGLT2i
Coronary heart disease	V	X	V	V
Myocardial infarction	V	X	V	V
Stroke	V	X	V	V
Peripheral artery disease	V	X	V	V
Chronic kidney disease (1–4)	X	V	V	V
End-stage kidney disease	X	V	X	X
Heart failure	X	V	X	V

Chiang CE et al. J Chin Med Assoc 83:327–336, 2020

Summary and Take-home Messages

- The 2008 FDA mandate significantly changed how patients with CKD are treated.
- SGLT2i can prevent/treat HF and prevent CKD/ESKD.
- CV and renal protection of SGLT2i is not through anti-atherosclerotic effect.
- SGLT2i is complementary to statin in the management of multiple risk factors in CKD.
- Earlier treatment is better for preventing event in CKD patients with DM and hyperlipidemia.