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Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

Use of SGLT2 inhibitors and the NS-MRA with RAS Inhibitors to slow DKD progression

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Comprehensive Hypertension Center
University of Chicago Medicine

PILLARS OF THERAPY

Bakris GL

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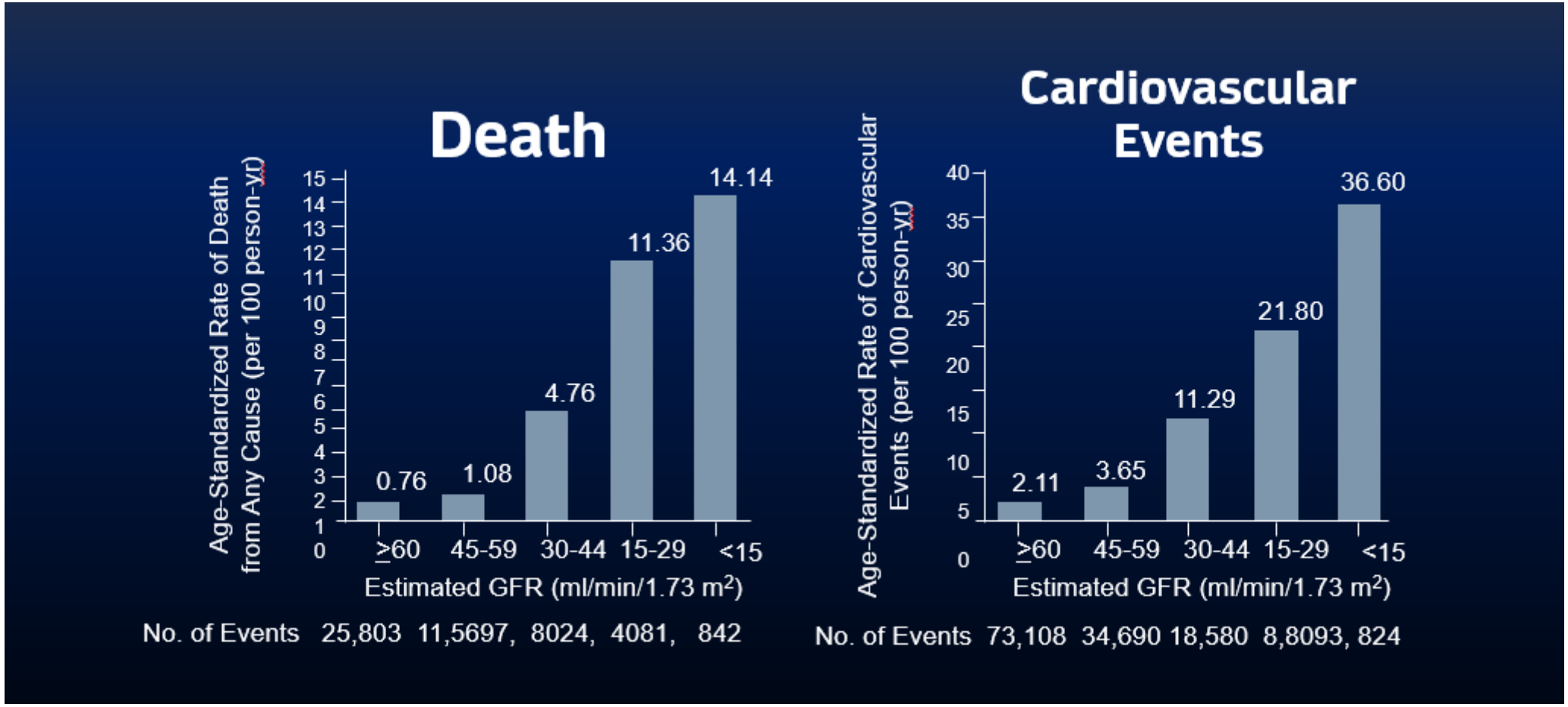
Background and Burden of CKD

Lower eGFR Is Associated With Cardiovascular Events and Death

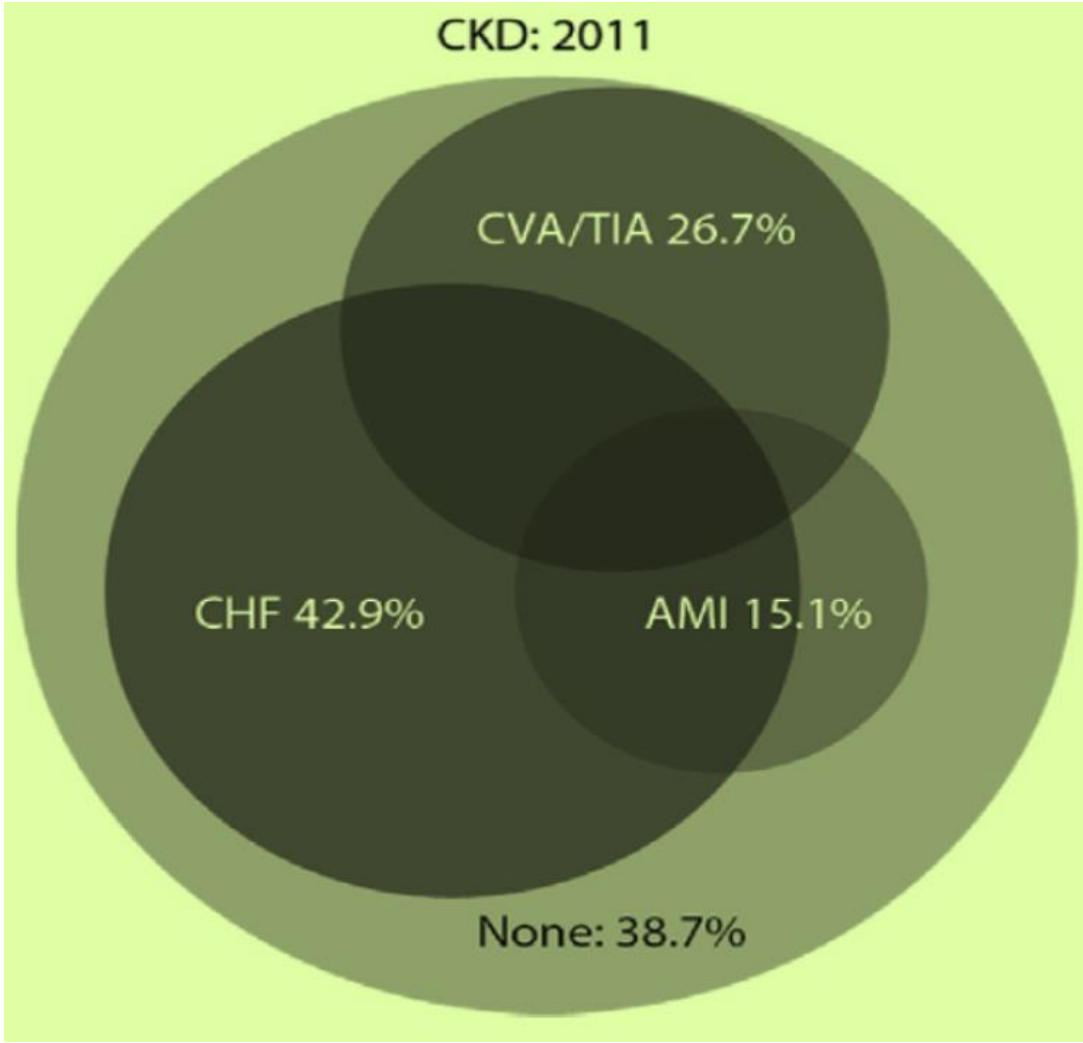


A large integrated health system including 1,120,295 patients with serum creatinine measured between 1996-2000 and median follow-up of 2.84 years.

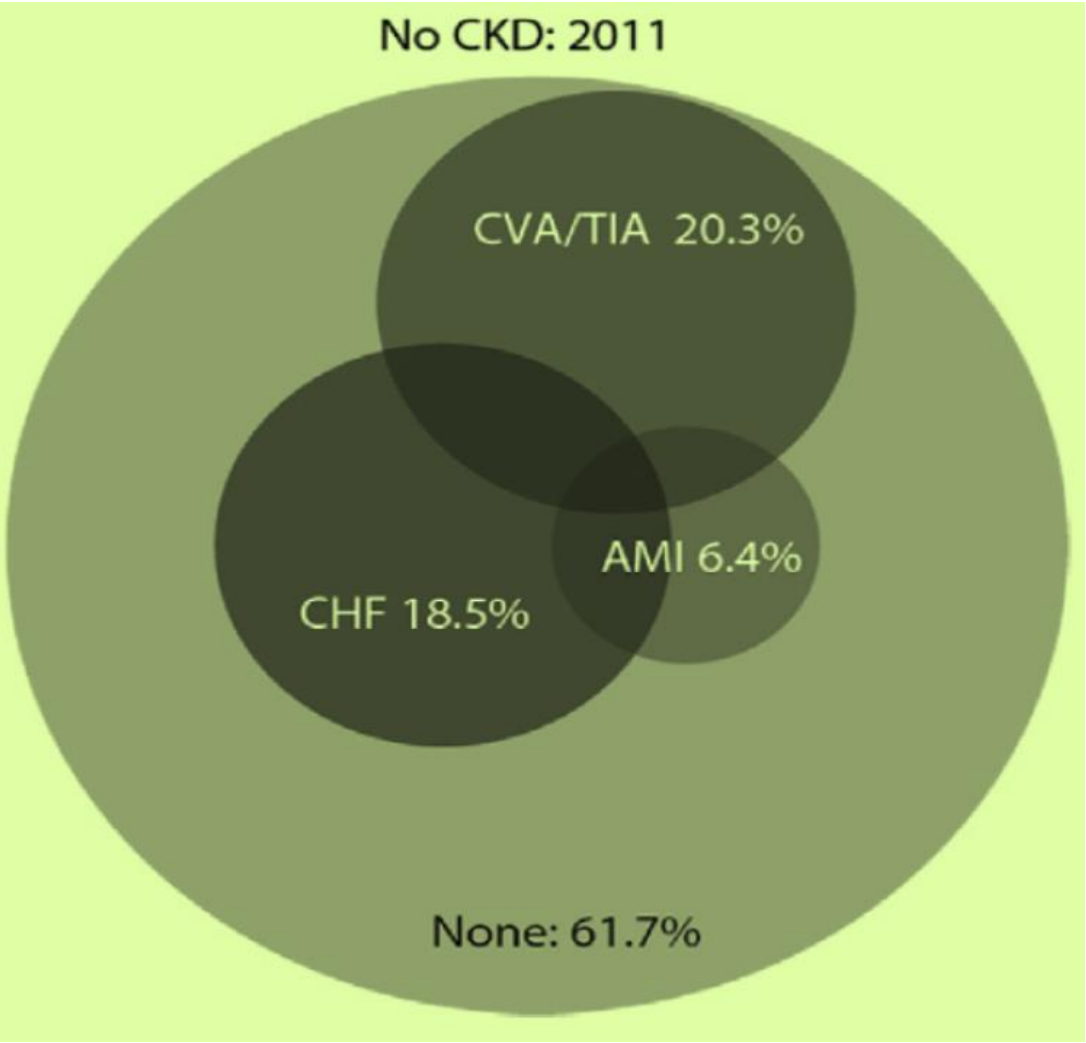
Go AS, et al. *N Engl J Med*. 2004;351:1296-1305.

Cardiovascular disease in patients with or without chronic kidney disease

WITH

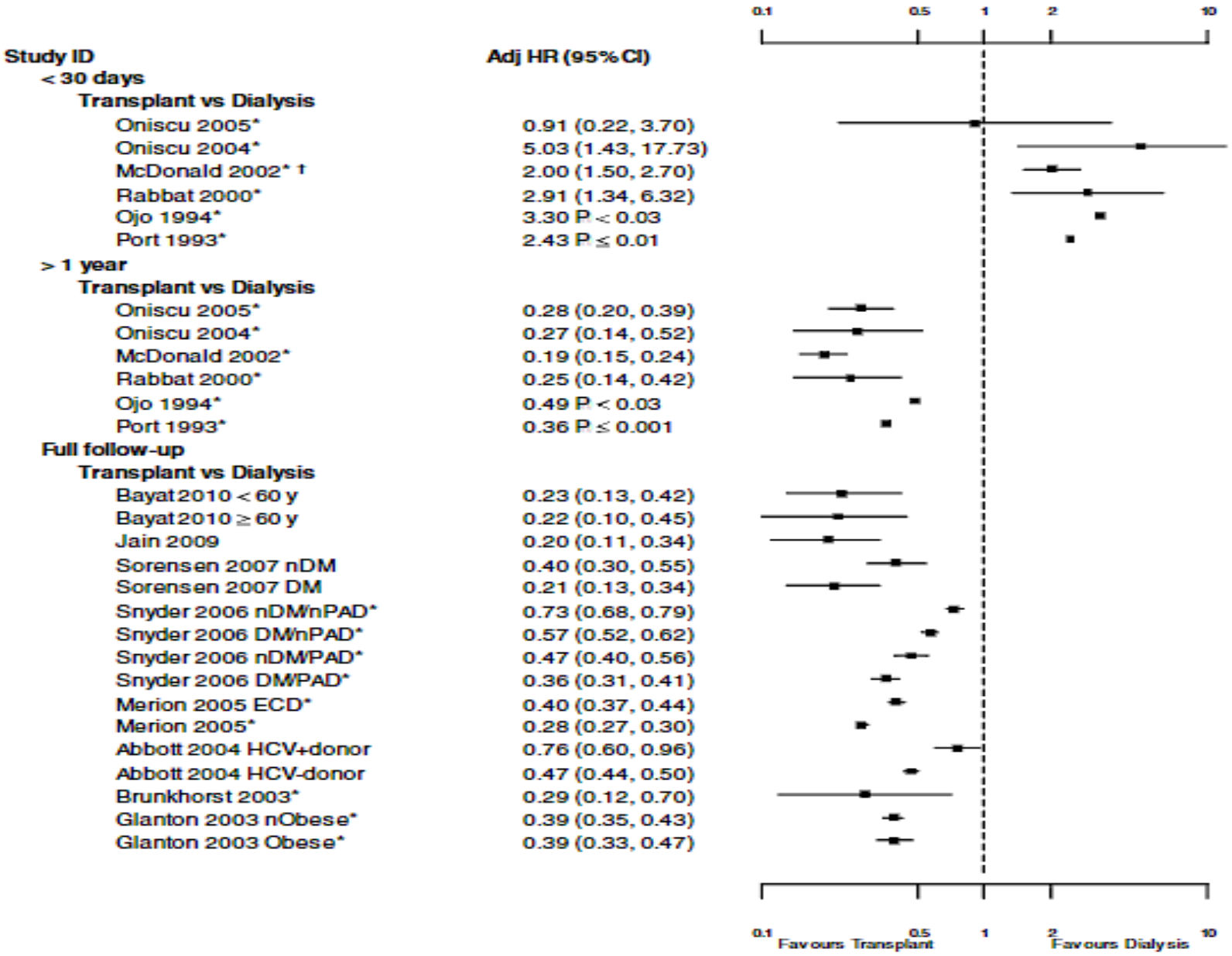


WITHOUT



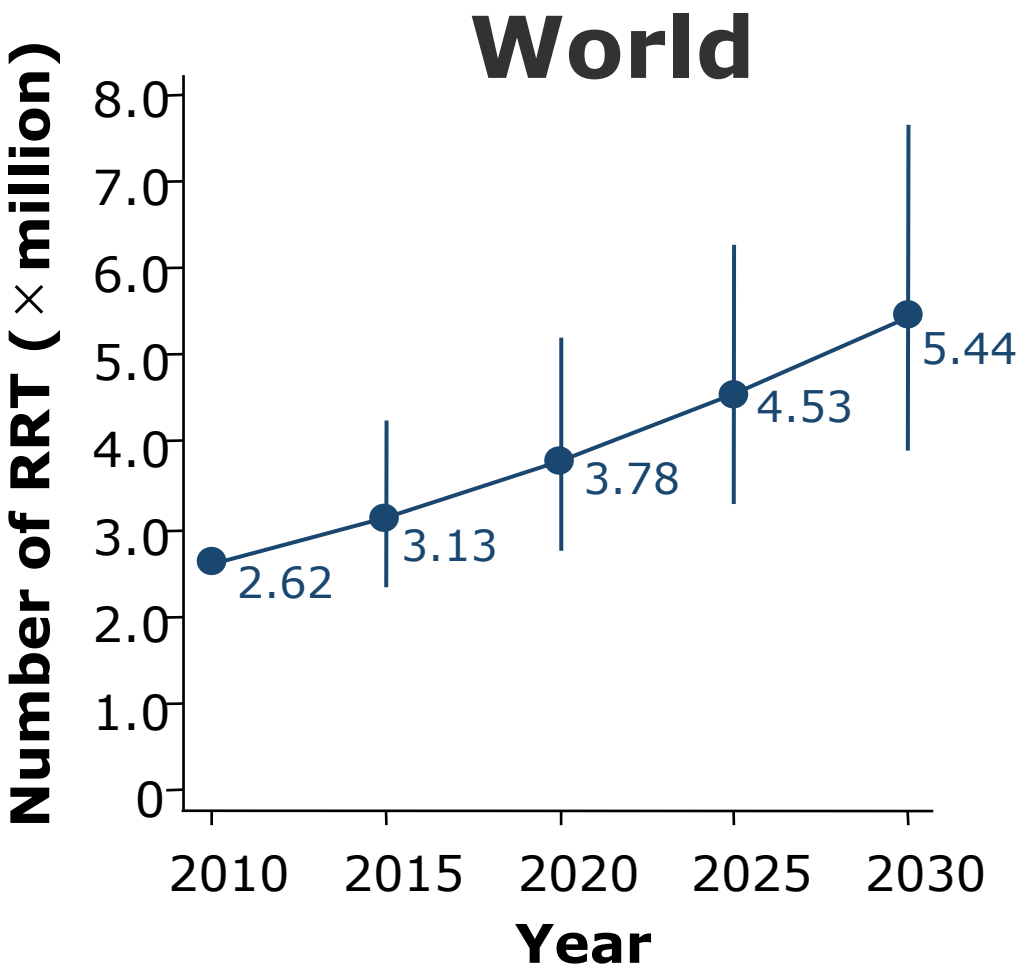
House AA Am J Kidney Dis 2018;72:284

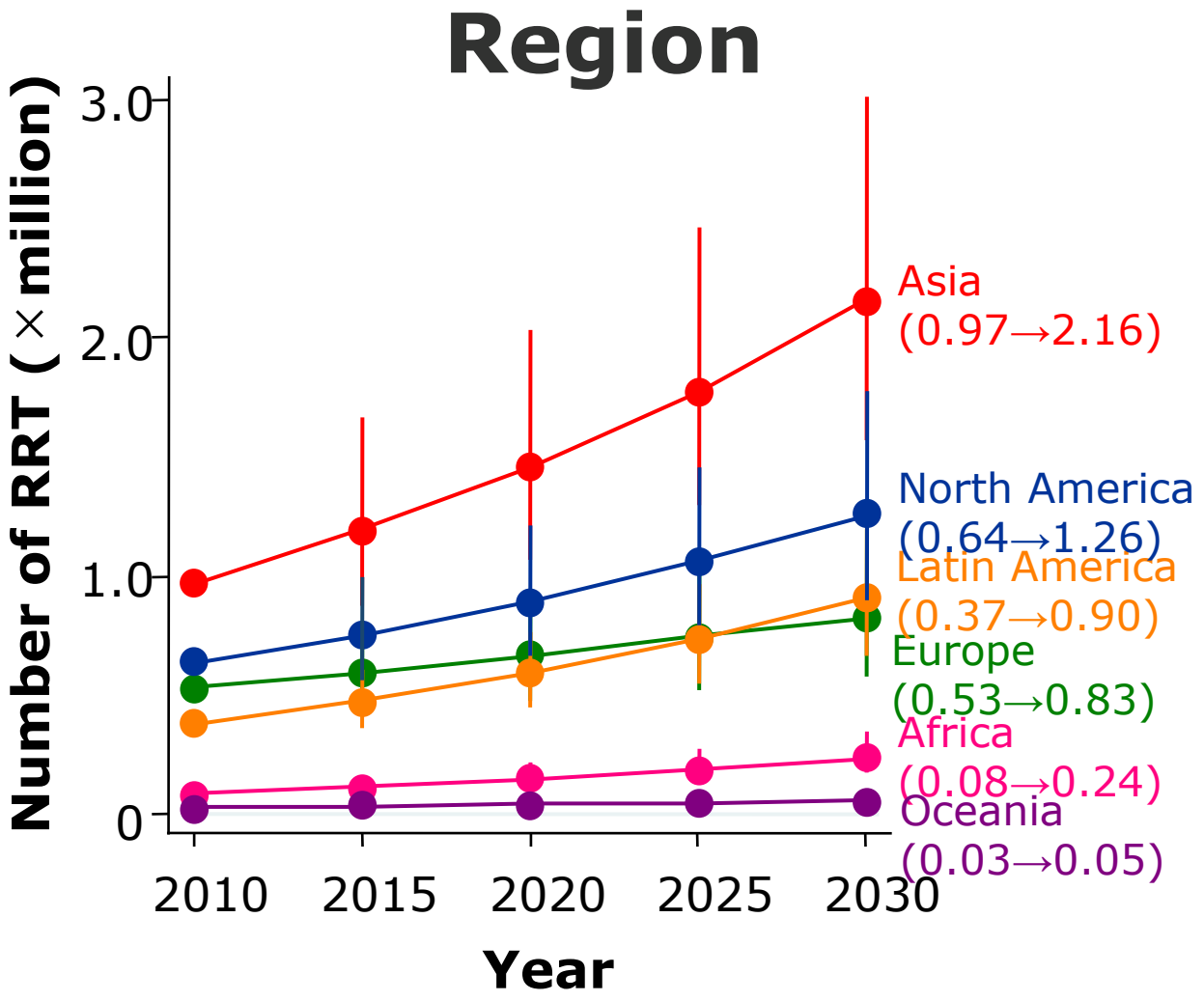
Adjusted ratio of all-cause mortality by time period



Tonelli M et.al. American Journal of Transplantation 2011; 11: 2093–2109

Number of People Receiving Renal Replacement Therapy Is Projected to Double





Liyanage T, et al. Lancet. 2015;385(9981):1975-1982.

KDIGO Heat Map for Stages of Nephropathy

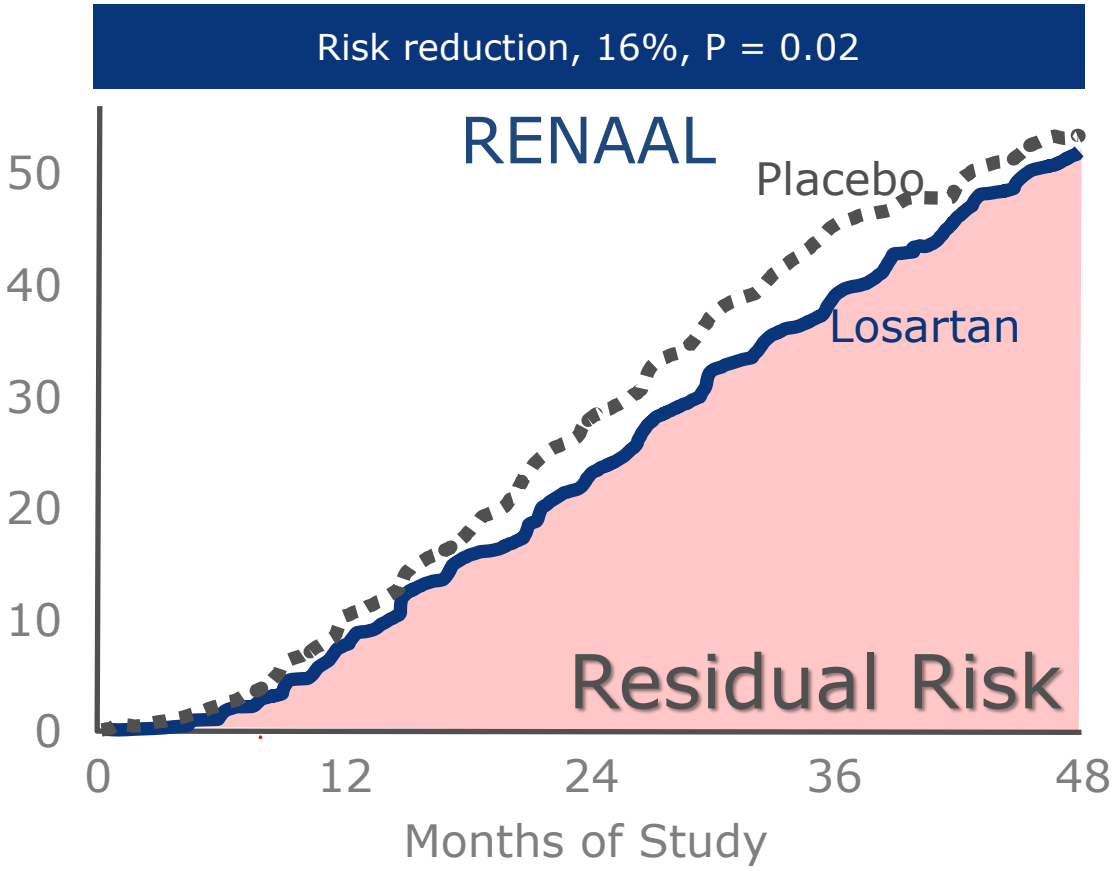
Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

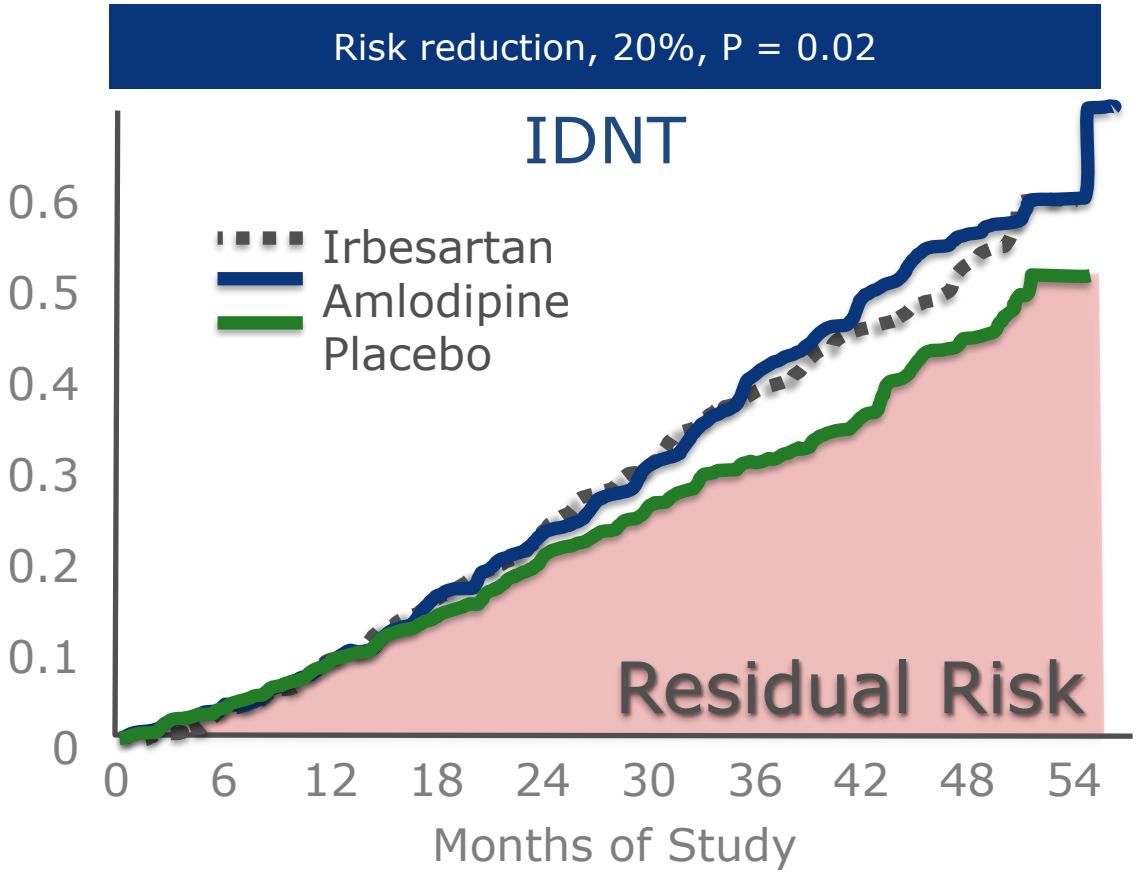
GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

KDIGO Diabetes Guidelines-Kidney Int Suppl 2020

The Only Proven Treatment for Renoprotection in T2DM: RENAAL & IDNT (2001)

Doubling of serum creatinine, ESKD, or death





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

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

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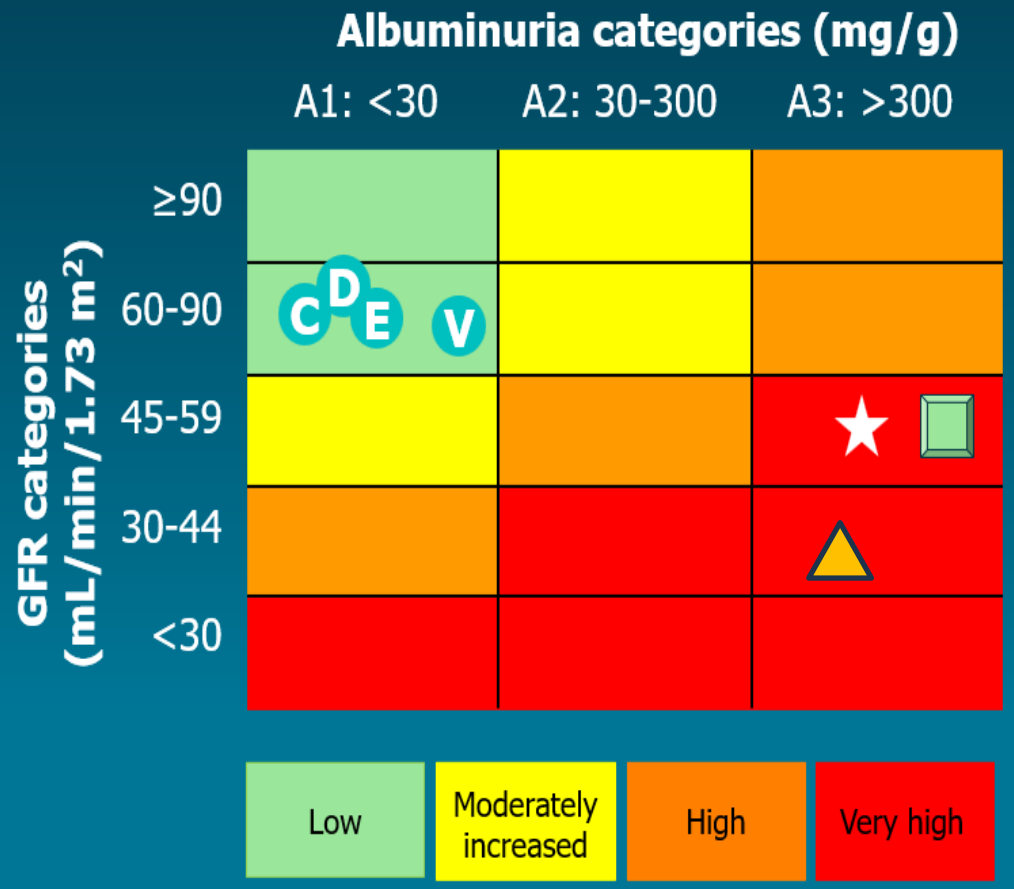
SGLT-2 Inhibitors in CKD: Rationale, Data, and Perspectives

Renal Risk in Cohorts Studied With SGLT2 Inhibitors



	Mean eGFR (mL/min/1.73 m²)	Median UACR (mg/g)
V VERTIS	76	X
D DECLARE	85	13
C CANVAS Program	76	12
E EMPA-REG OUTCOME	74	18
★ CREDENCE	56	927
▭ DAPA-CKD	43	965
▲ EMPA-KIDNEY	37	330

Sustained RRT Events

DECLARE	Not reported
CANVAS Program	18
EMPA-REG OUTCOME	11
CREDENCE	**176**
EMPA-KIDNEY	**104**

X 1.31 mg/mmol-geo mean

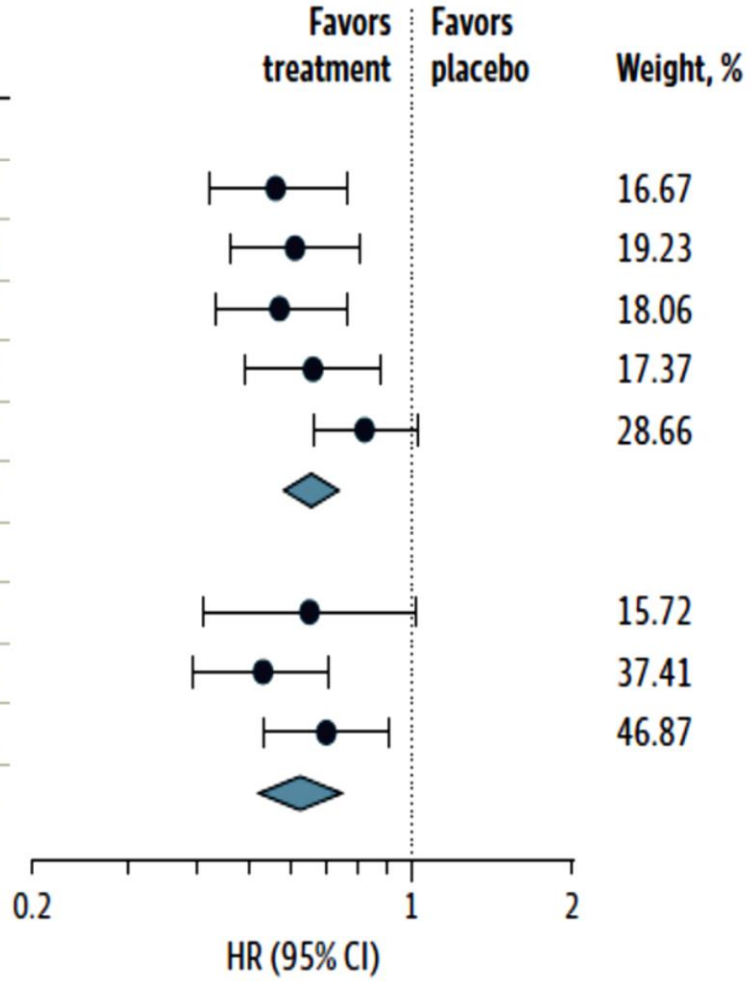
DAPA-CKD = dapagliflozin-chronic kidney disease; (e)GFR = (estimated) glomerular filtration rate; geo = geometric; RRT = renal replacement therapy; UACR = urine albumin-to-creatinine ratio.

McGuire D, et al. *JAMA Cardiol*. Published online October 7, 2020. doi:10.1001/jamacardio.2020.4511. Open Access.

Meta-analysis of SGLT2i trials on the composite of worsening of renal function, end-stage renal disease, or renal death

B Kidney outcomes by ASCVD status

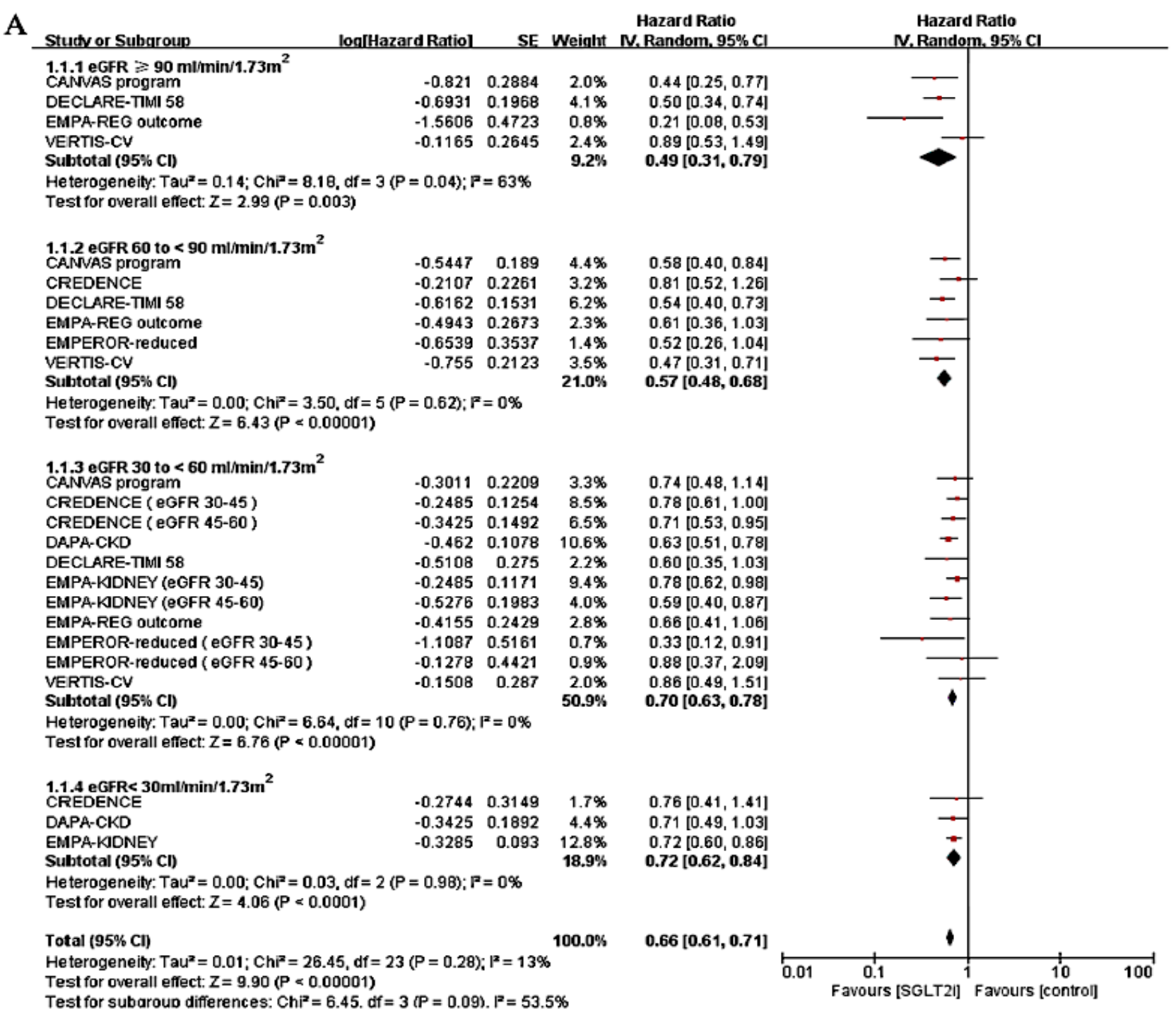
	Treatment		Placebo				
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment / Favors placebo	Weight, %
Patients with ASCVD							
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)		16.67
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)		19.23
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)		18.06
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)		17.37
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)		28.66
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)		15.72
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)		37.41
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)		46.87
Fixed-effects model ($Q = 1.86$; $df = 2$; $P = .40$; $I^2 = 0.0\%$)					0.60 (0.50-0.73)		



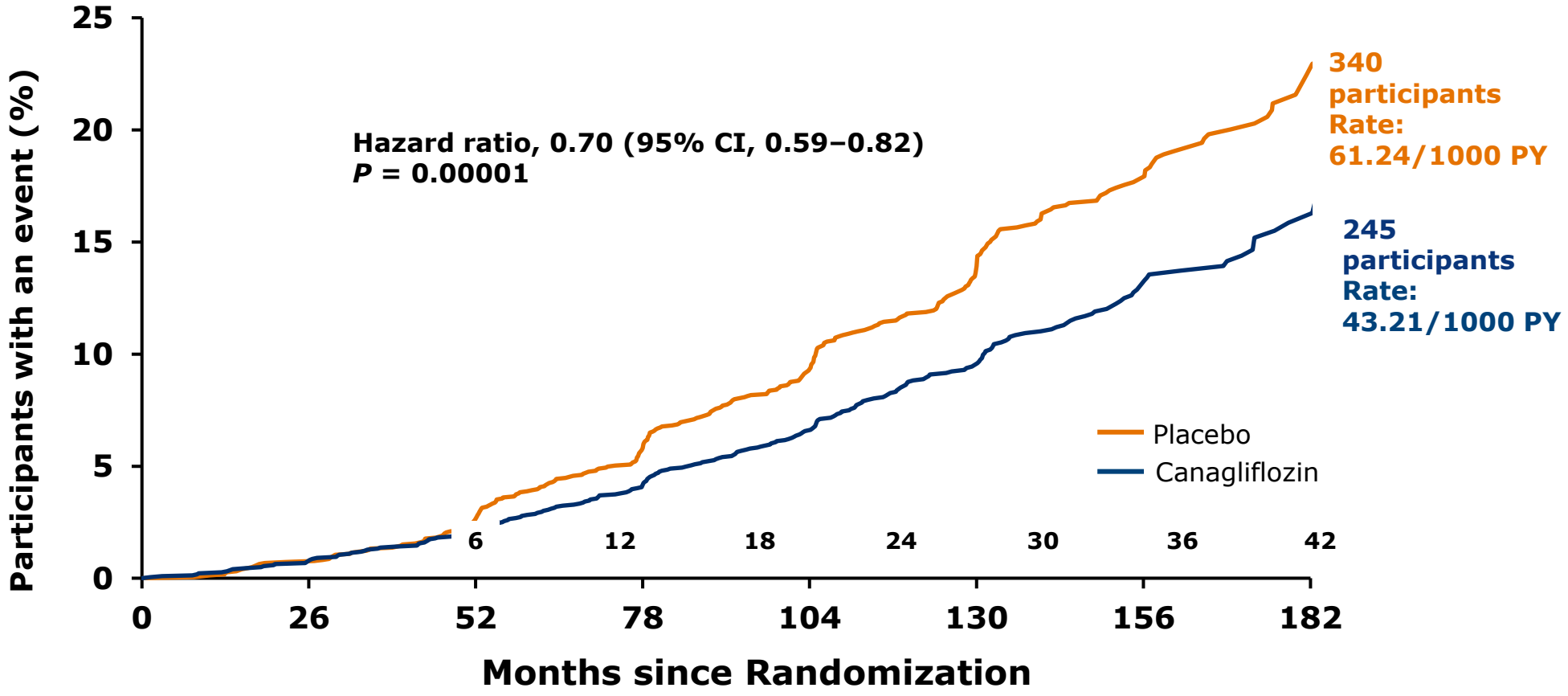
McGuire D et.al. JAMA Cardiol. 2021;6:148-158

Renal outcome in patients with SGLT2i treatment stratified by baseline eGFR

Ma,Y et.al. Acta Diabetologica (2023) 60:435–445



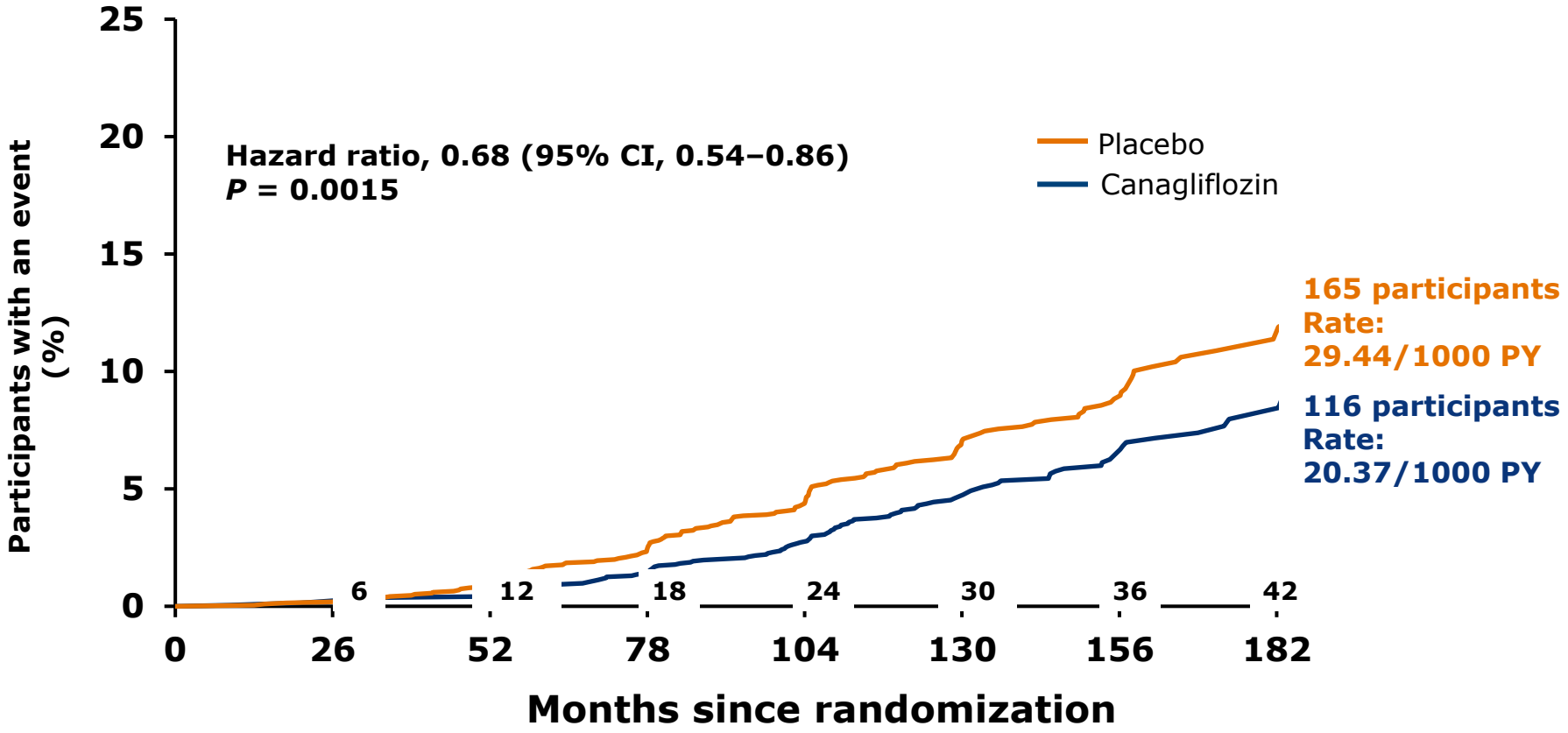
ESKD, Doubling of Serum Creatinine, or Renal or Cardiovascular Death (Primary Composite Outcome)



No. at Risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Perkovic V, et.al. N Engl J Med 2019;380:2295-306.

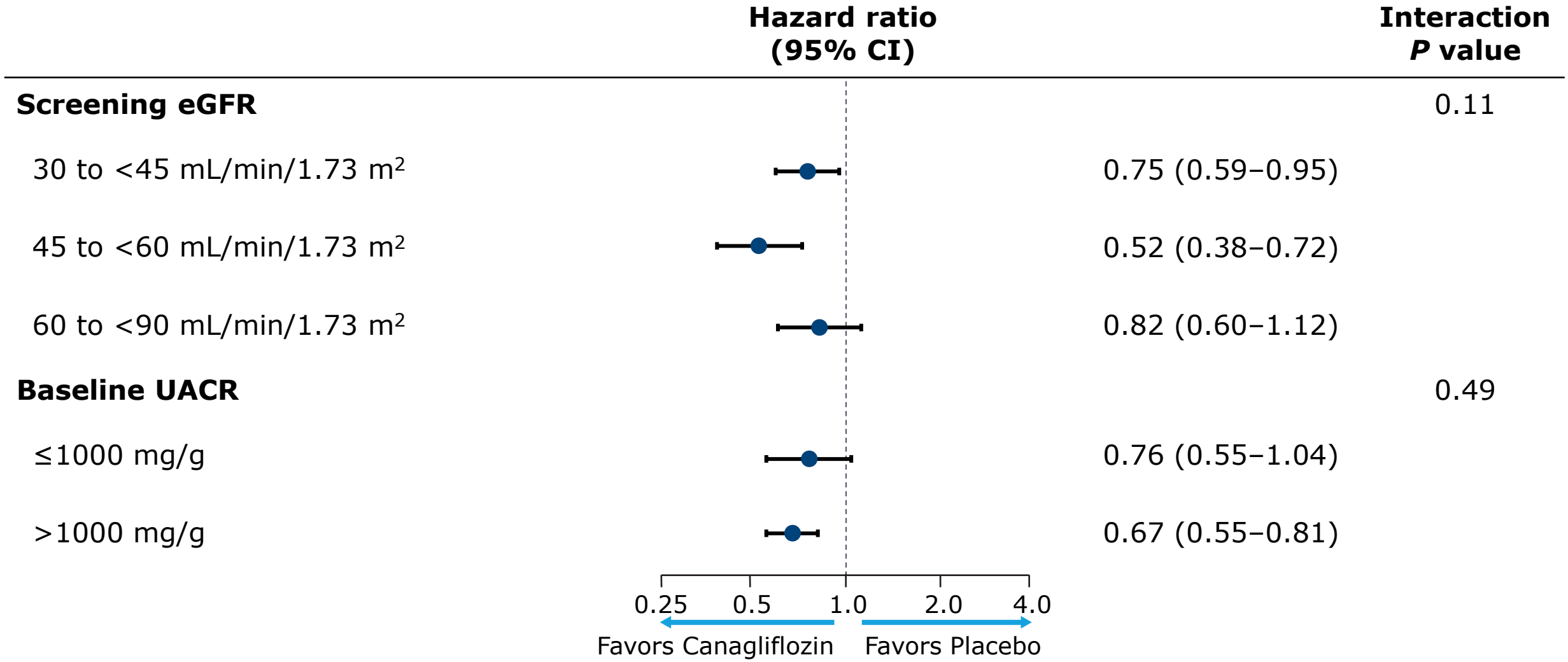
End-stage Kidney Disease (ESKD)



No. at Risk								
Placebo	2199	2182	2141	2063	1752	1152	641	178
Canagliflozin	2202	2182	2146	2091	1798	1217	654	199

Perkovic V, et.al. N Engl J Med 2019;380:2295-306.

Primary Outcome by Screening eGFR and Albuminuria



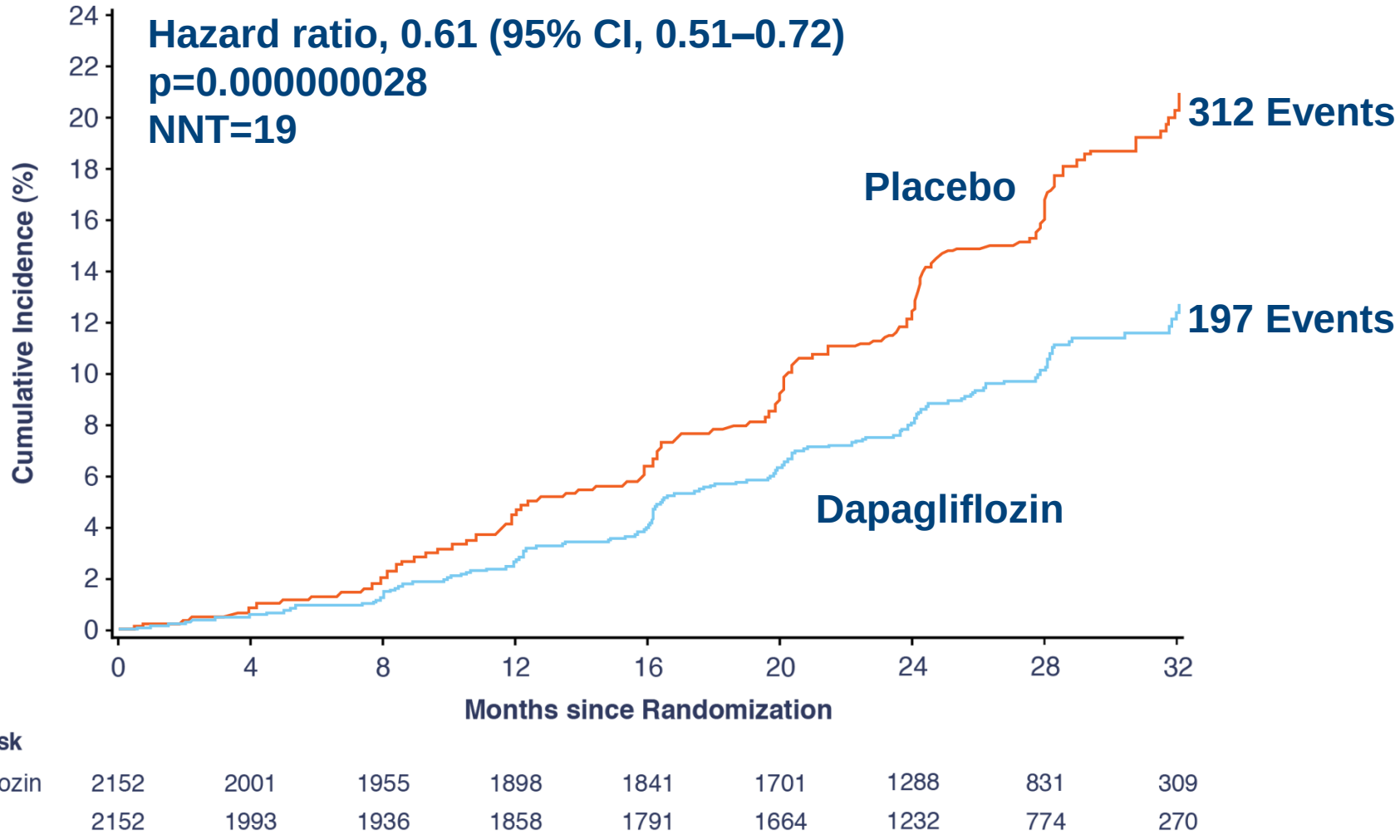
Perkovic V, et.al. N Engl J Med 2019;380:2295-306.

DAPA-CKD-Primary outcome: Sustained ≥50% eGFR decline, ESKD, renal or CV death

4299 (99.9%) vital status known;

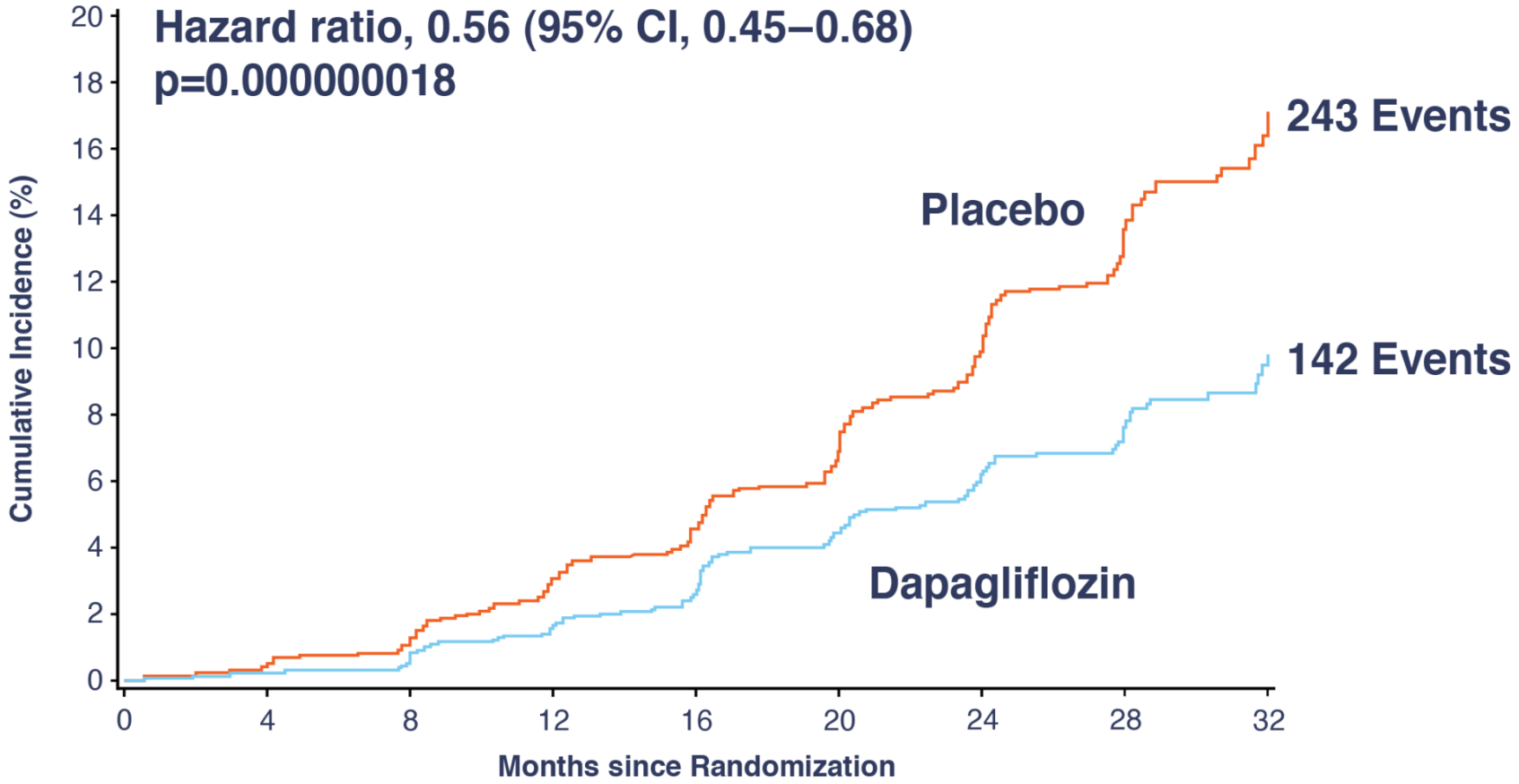
4289 (99.7%) completed study

33%had *nondiabetic kidney disease*



Heerspink HJL. et.al. N Engl J Med. 2020 Oct 8;383(15):1436-1446

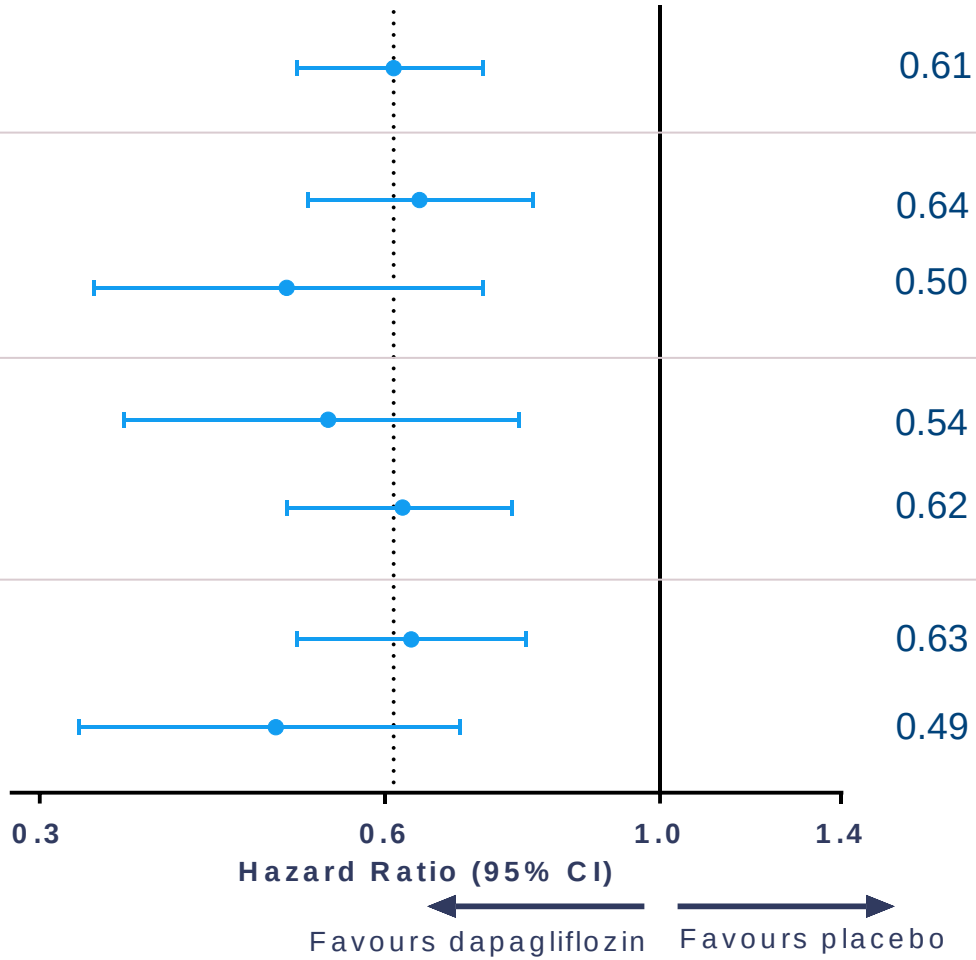
Secondary outcome: DAPA CKD
Sustained ≥50% eGFR decline, ESKD, renal death



Heerspink HJL. et.al. N Engl J Med. 2020 Oct 8;383(15):1436-1446.

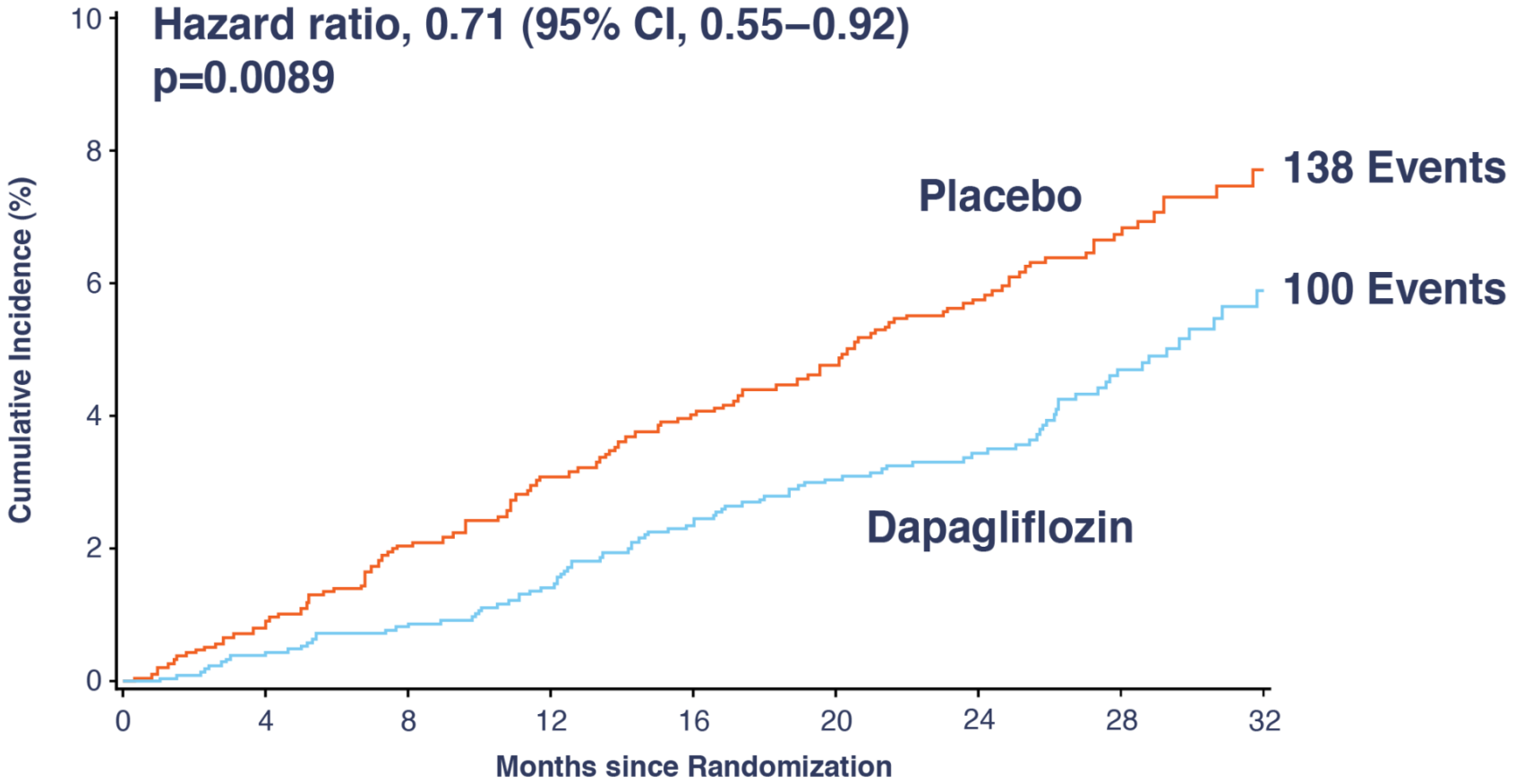
Primary outcome – pre-specified subgroup analysis

	Dapagliflozin events	Placebo events	Hazard Ratio (95% CI)	p-value interaction
All patients	197	312	0.61 (0.51, 0.72)	
With type 2 diabetes	152	229	0.64 (0.52, 0.79)	
Without type 2 diabetes	45	83	0.50 (0.35, 0.72)	0.24
UACR ≤1000 mg/g	44	84	0.54 (0.37, 0.77)	
UACR >1000 mg/g	153	228	0.62 (0.50, 0.76)	0.52
eGFR <45 mL/min/1.73m²	152	217	0.63 (0.51, 0.78)	
eGFR ≥45 mL/min/1.73m²	45	95	0.49 (0.34, 0.69)	0.22



Heerspink HJL. et.al. Presented at ESC 2020.

Secondary outcome:
CV death or heart failure hospitalization



Heerspink HJL. et.al. N Engl J Med. 2020 Oct 8;383(15):1436-1446.

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit **EITHER/ OR** SGLT2i§ with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

— — — — — OR — — — — —

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1 RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

If A1C above target

Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/ renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

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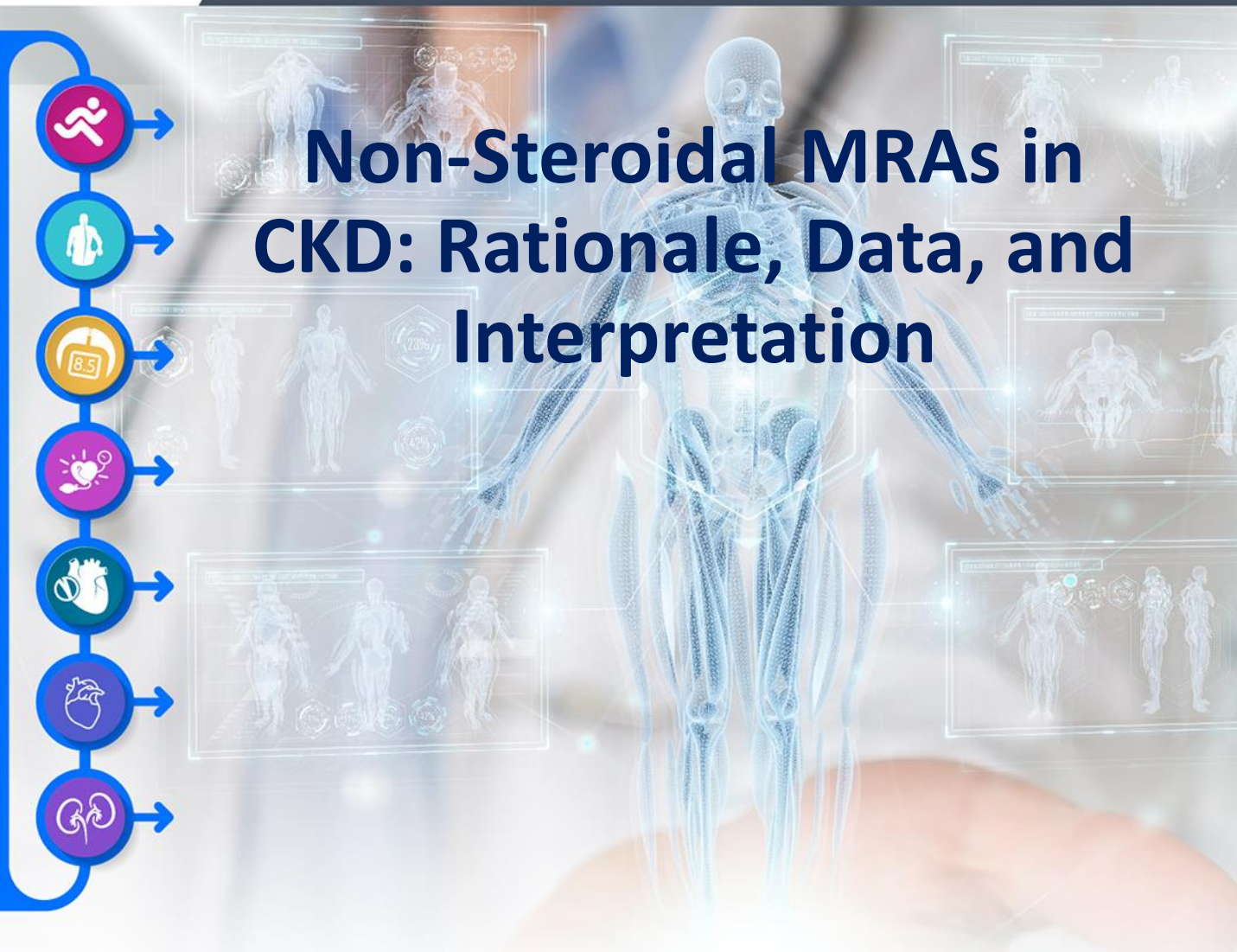
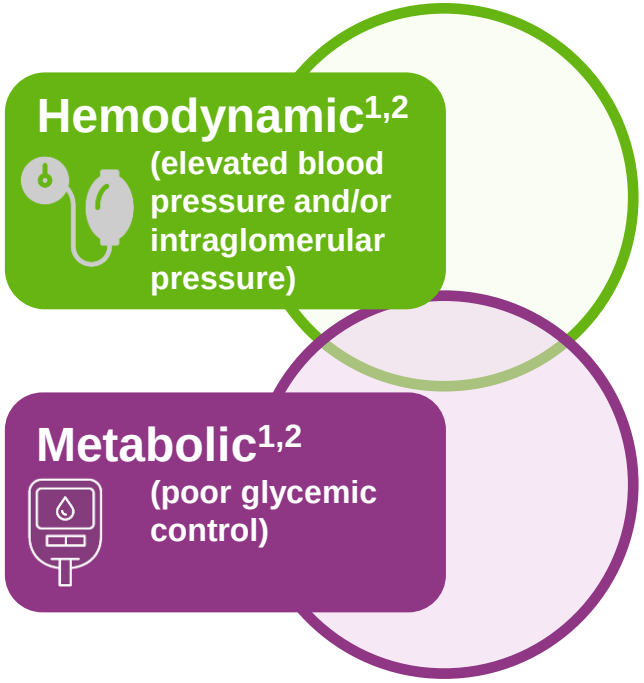


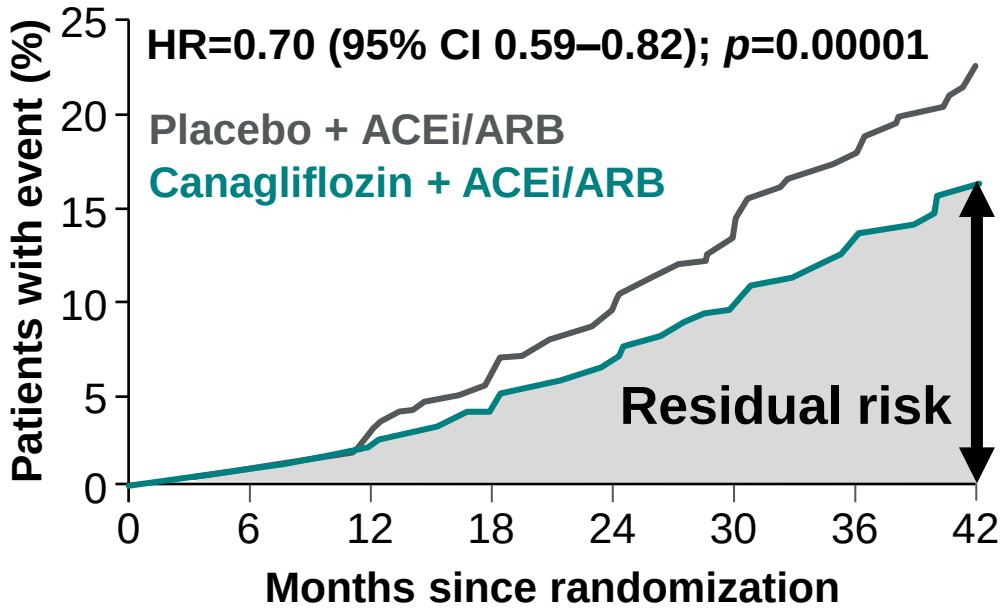
Non-Steroidal MRAs in CKD: Rationale, Data, and Interpretation

FIDELIO-DKD RATIONALE

High Residual Risk Of CKD Progression With Current Therapies



CREDENCE[3]
Cardiorenal composite endpoint*



1. Alicic RZ, et al. Clin J Am Soc Nephrol 2017;12:2032; 2. Mora-Fernández C, et al. J Physiol 2014;18:3997;
3. Perkovic V, et al. N Engl J Med 2019;380:2295

MR overactivation is a major driver of kidney damage

Mineralocorticoid receptors
regulate gene expression through co-factor recruitment[1]

In renal disease, multiple factors overactivate the MR
including aldosterone, Rac1, cortisol and others[2,3]

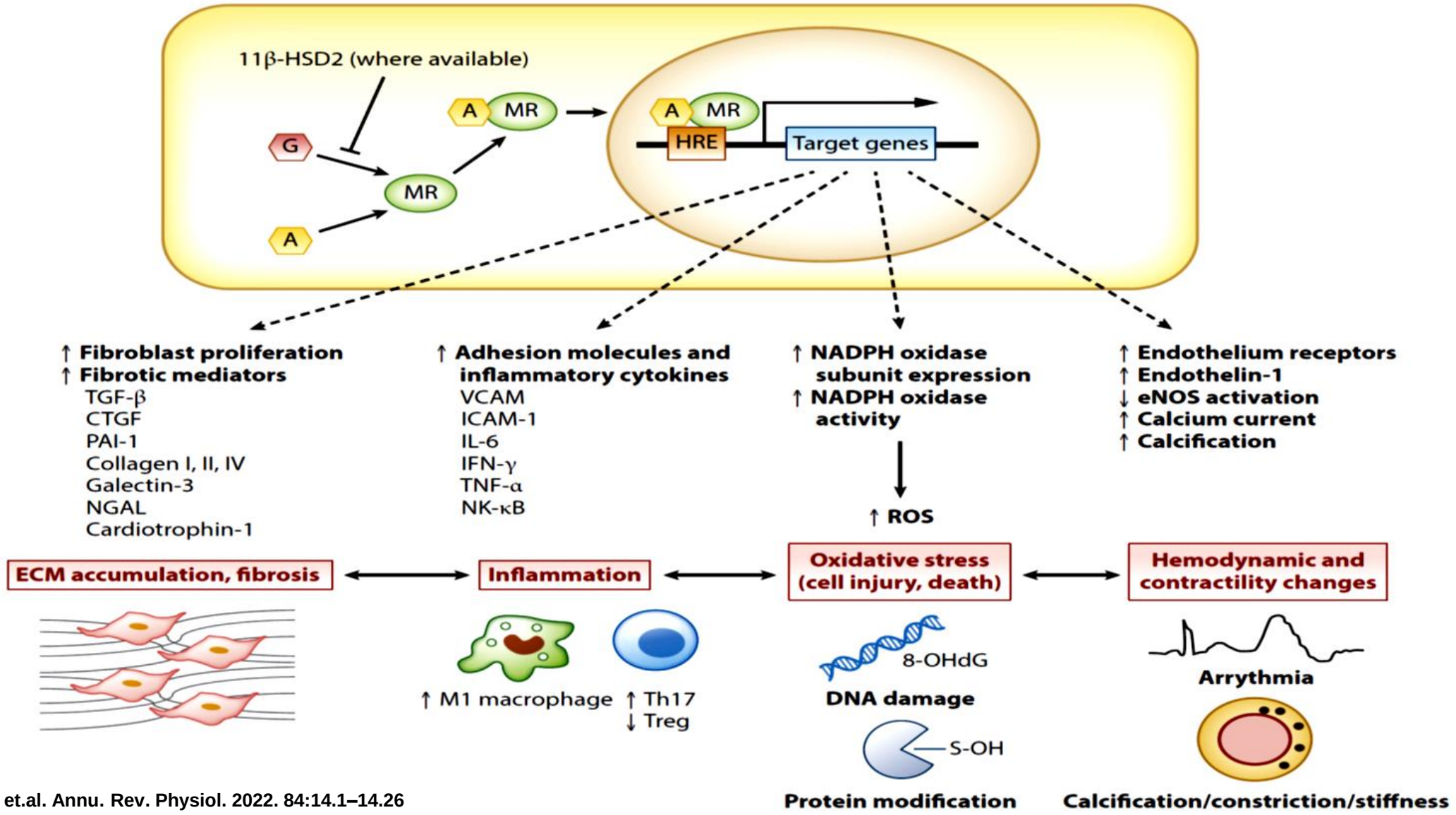
Overactivation of the MR signalling pathway drives inflammation and fibrosis
via pro-inflammatory cytokines and fibrotic proteins,
e.g. TNF-α, IL-1b and IL-6[1,2]

MR overactivation results in deleterious effects on the heart and kidney, promoting cardiac remodelling and progression of both renal and cardiovascular disease[2]

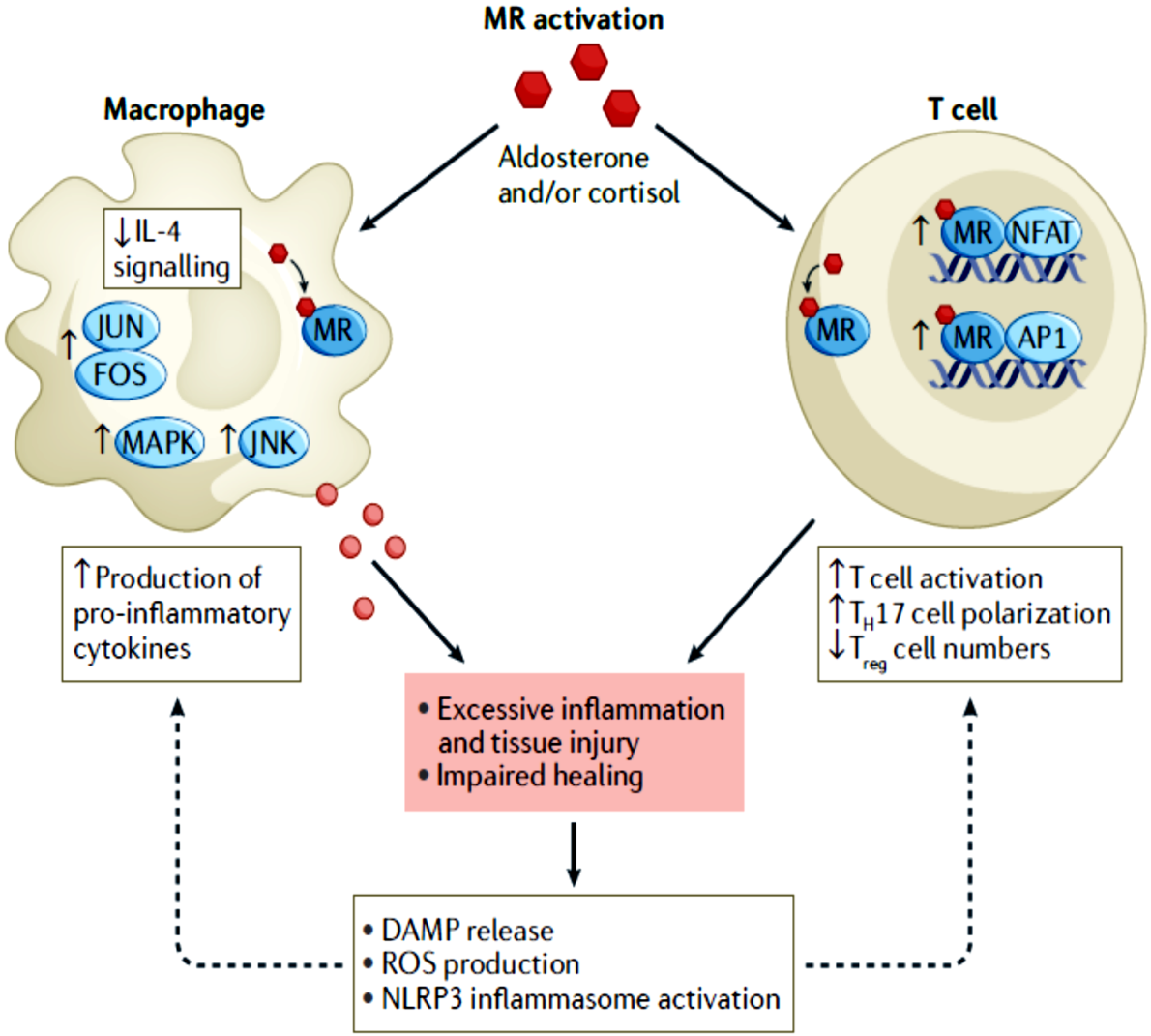
MR, mineralocorticoid receptor; IL-1b, interleukin-1b; IL-6, interleukin-6; TNF-α, tumour necrosis factor alpha; Rac1, Ras-related C3 botulinum toxin substrate 1

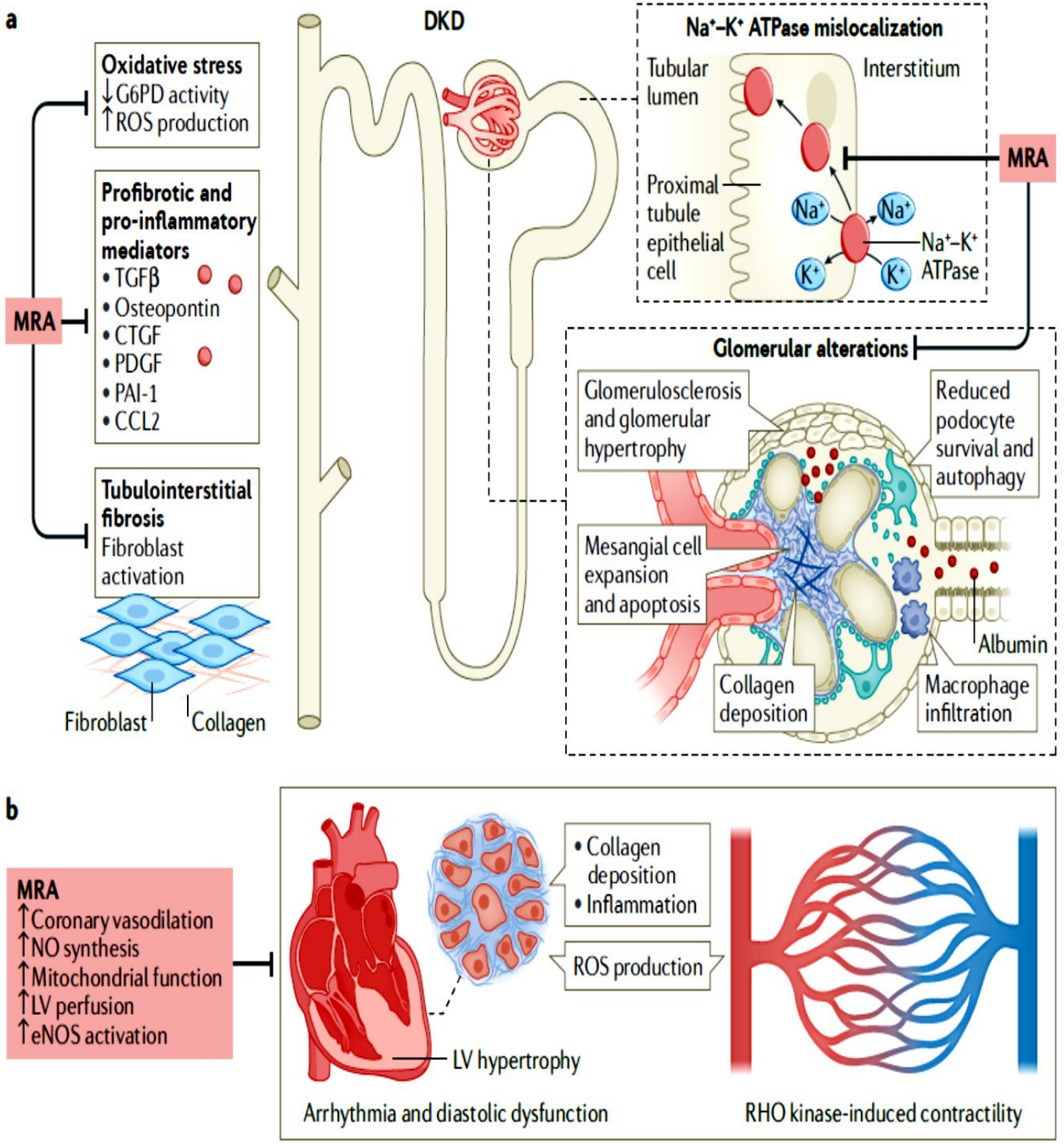
1. Ong GS & Young MJ. J Mol Endocrinol 2017;58:33–57; 2. Bauersachs J, et al. Hypertension 2015;65:257–263; 3. Bertocchio JP, et al. Kidney Int 2011;79:1051–1060

Summary of the pathological mechanisms elicited by MR activation. MR activation by aldosterone (A) or glucocorticoids (G) induces the expression of several genes

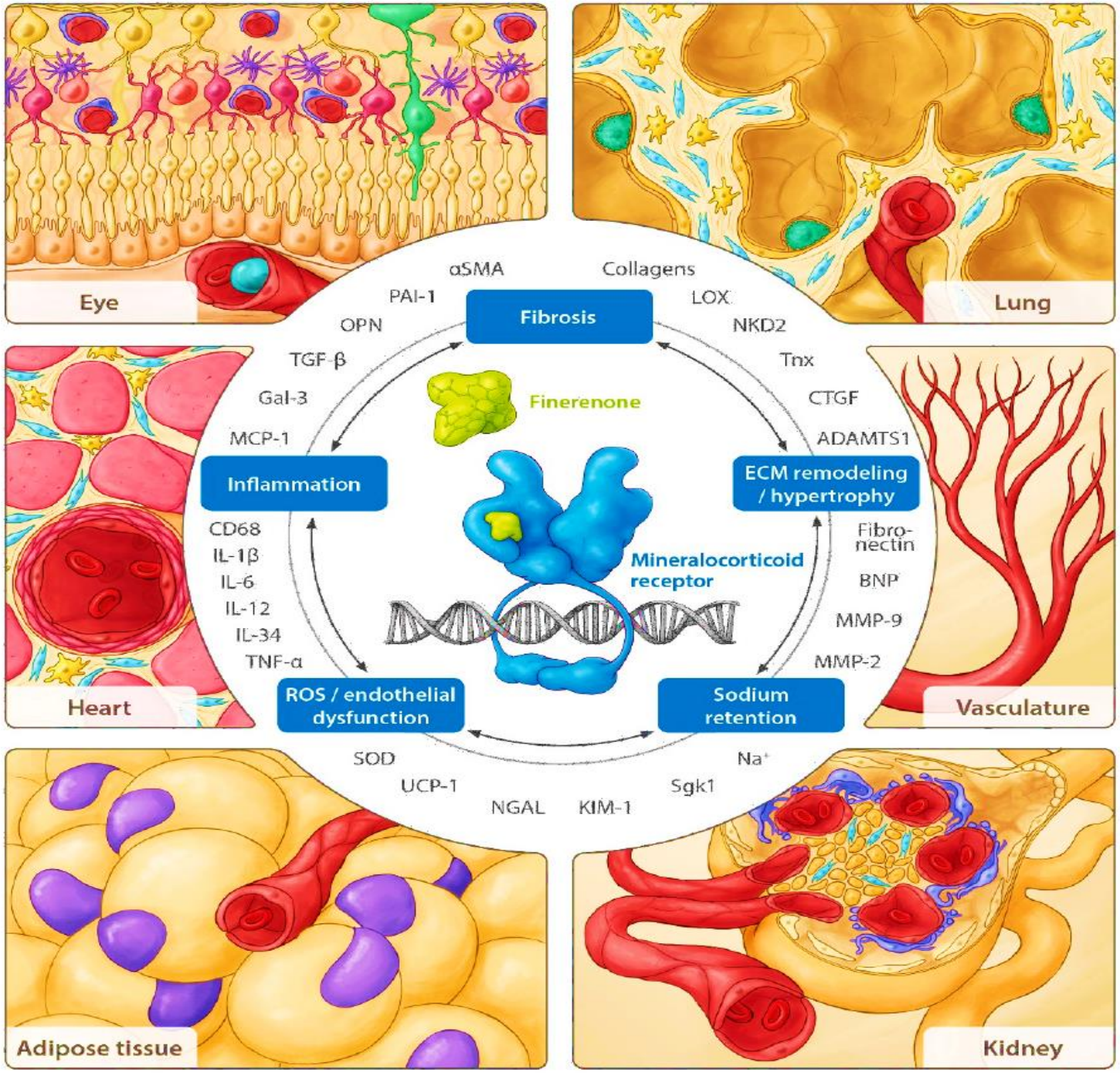


Barrera-Chimel et.al. Annu. Rev. Physiol. 2022. 84:14.1–14.26





Barrera-Chimal J, Lima-Posada I, Bakris GL, Jaisser F. Nat Rev Nephrol 2021.

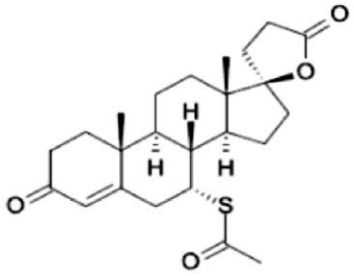


Components of pathophysiological MR overactivation that are counteracted by finerenone in different organs and cell types, including relevant biomarkers

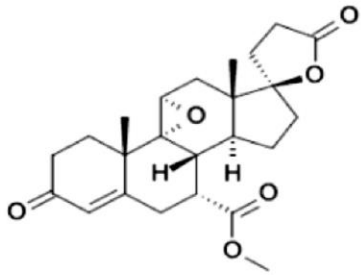
Kolkhof P, et.al. and Bakris GL Int. J. Mol. Sci. 2022, 23, 9243

TWO DIFFERENT CLASSES OF AGENTS THAT INHIBIT THE MR

Steroidal MRAs
(Aldosterone Antagonists)

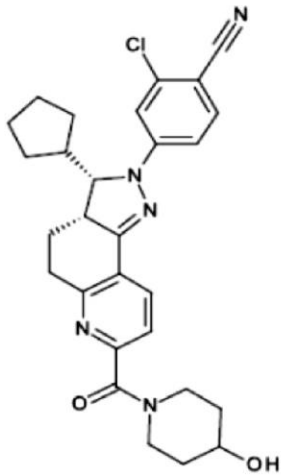


Spironolactone

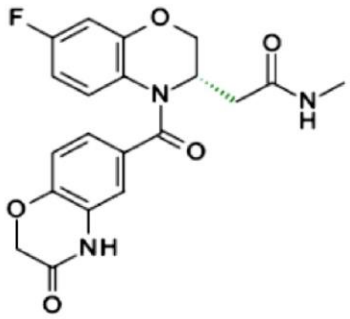


Eplerenone

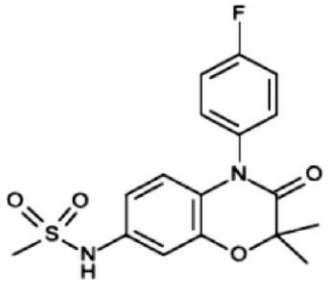
Nonsteroidal MRAs



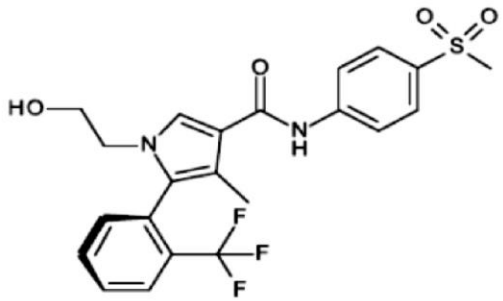
KBP-5074
(Phase II)



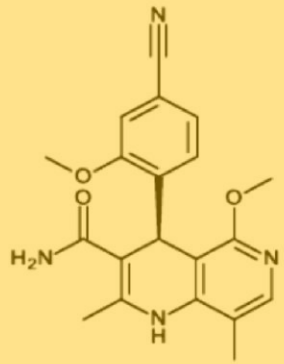
AZD9977
(Phase II)



Apararenone
MT-3995
(Phase II)



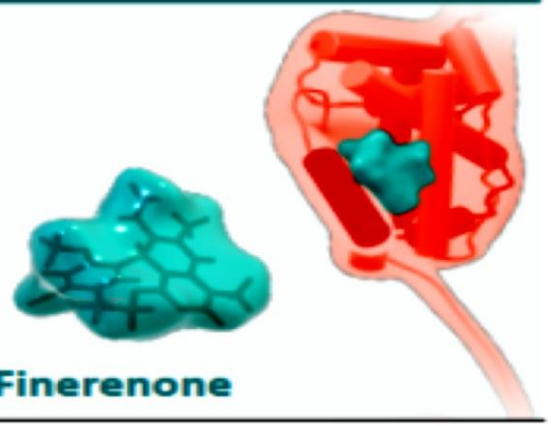
Esaxerenone
CS-3150
(launched in Japan)



Finerenone
BAY 94-8862
(launched in the U.S.)

Kintscher U, Bakris GL, and Kolkhof P. Br J Pharmacol 2022;179:3220-3234

Comparison of MRA inhibitors: Steroidal and Non-steriodal

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

Kintscher U, Bakris GL, and Kolkhof P. Br J Pharmacol 2022;179:3220-3234

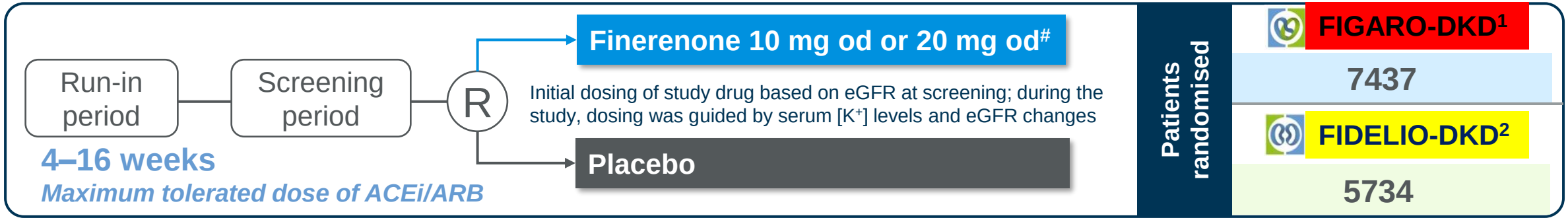
The Finerenone Program

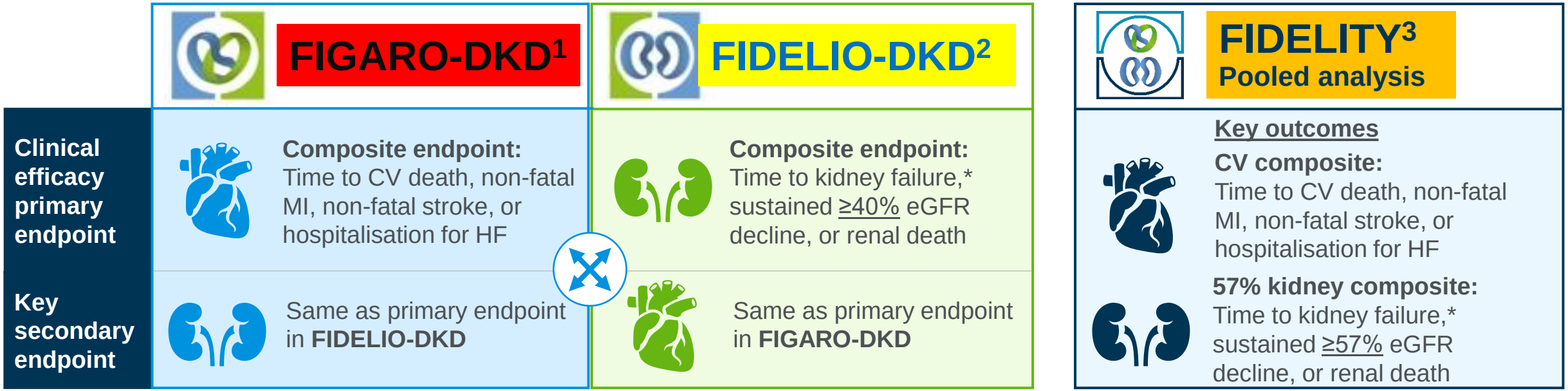
FIDELIO-DKD

FIGARO-DKD

FIDELITY-DKD

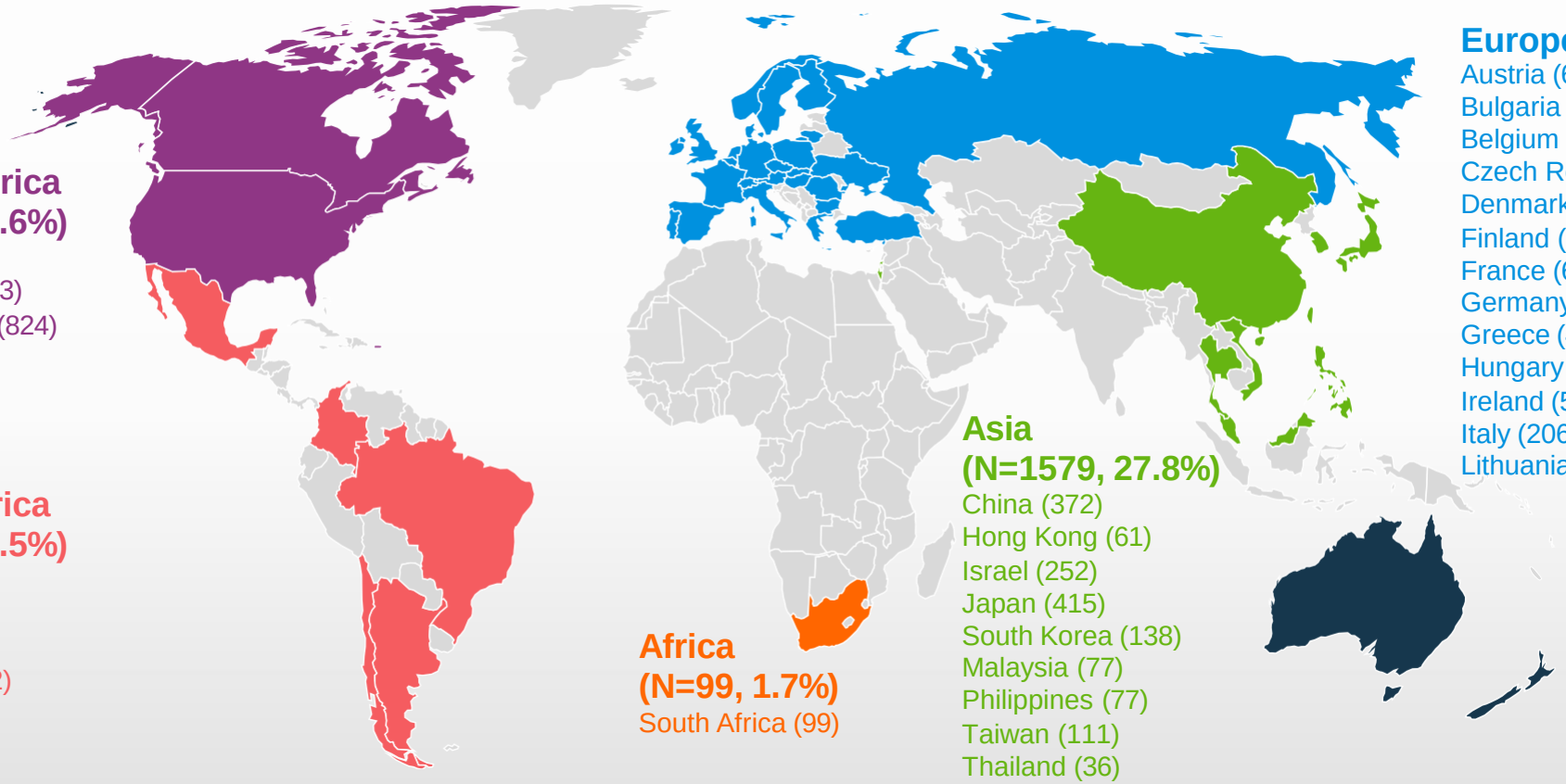
FIDELITY: FIGARO-DKD and FIDELIO-DKD investigated the effects of finerenone on kidney and CV outcomes in over 13,000 patients with CKD and T2D[1,2]





Ruilope LM, *et al. Am J Nephrol* 2019;50:345–356; Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; *Agarwal R , Filipattos G, et.al….and Bakris GL, Eur Heart J 2022;43:474-484*

Patients were randomized from 48 countries worldwide



North America (N=944; 16.6%)
Canada (107)
Puerto Rico (13)
United States (824)

Latin America (N=593; 10.5%)
Argentina (84)
Brazil (176)
Chile (31)
Colombia (182)
Mexico (120)

Africa (N=99, 1.7%)
South Africa (99)

Asia (N=1579, 27.8%)
China (372)
Hong Kong (61)
Israel (252)
Japan (415)
South Korea (138)
Malaysia (77)
Philippines (77)
Taiwan (111)
Thailand (36)
Vietnam (56)

Europe (N=2358; 41.6%)
Austria (62)
Bulgaria (225)
Belgium (54)
Czech Republic (99)
Denmark (111)
Finland (62)
France (64)
Germany (88)
Greece (48)
Hungary (140)
Ireland (5)
Italy (206)
Lithuania (9)
Netherlands (72)
Norway (26)
Poland (112)
Portugal (130)
Romania (59)
Russia (263)
Slovakia (7)
Spain (260)
Sweden (34)
Switzerland (10)
Turkey (72)
United Kingdom (67)
Ukraine (73)

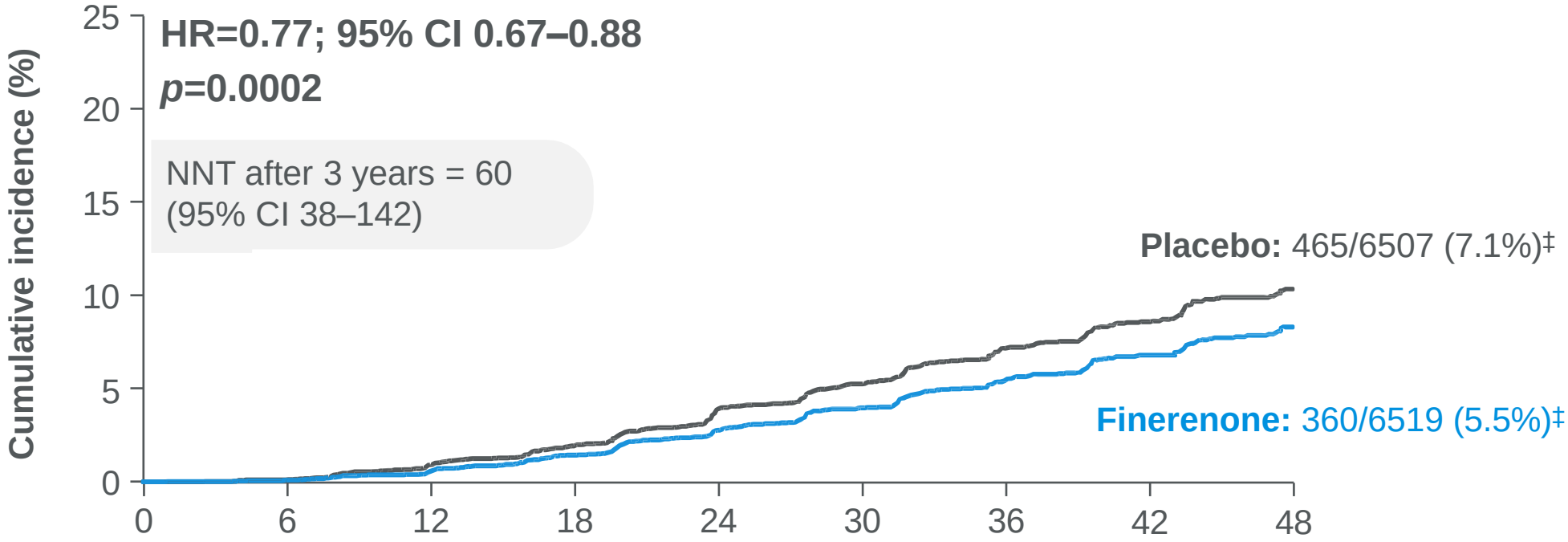
Oceania (N=101, 1.7%)
Australia (63)
New Zealand (38)

5734 patients randomized – 5674 patients in FAS – 99.7% completed the study

Bakris GL et.al. Am J Nephrol 2019 ;50:333-344

FIDELITY pooled analysis: Effect of finerenone on the ≥57% eGFR kidney composite outcome

Time to kidney failure,* sustained ≥57% decrease in eGFR from baseline, or renal death#

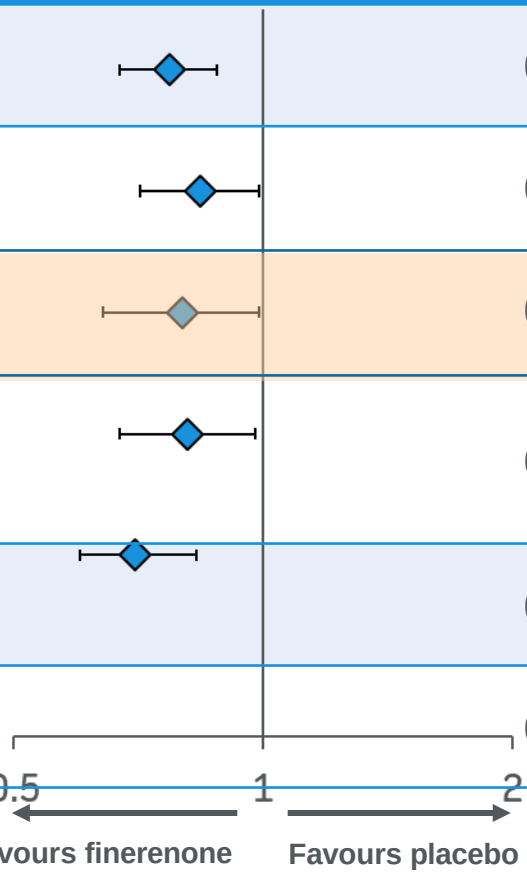


No. at risk									
Finerenone	6519	6291	6107	5848	5027	3973	2815	2024	959
Placebo	6507	6292	6071	5815	4949	3932	2798	1988	962

Agarwal R , Filipattos G, et.al….and Bakris GL, Eur Heart J 2022 ;43:474-484

FIDELITY pooled analysis: Effects of finerenone on the components of the ≥57% eGFR kidney composite outcome

Outcome	Finerenone (n=6519)		Placebo (n=6507)		HR (95% CI)	*p*-value
	n (%)	n per 100 PY	n (%)	n per 100 PY		
≥57% eGFR kidney	**360 (5.5)**	**1.96**	**465 (7.1)**	**255**	**0.77 (0.67–0.88)**	**0.0002**
Kidney failure*	254 (3.9)	1.38	297 (4.6)	1.62	0.84 (0.71–0.99)	0.039
End-stage kidney disease	151 (2.3)	0.76	188 (2.9)	0.96	0.80 (0.64–0.99)	0.040‡
Sustained# decrease in eGFR to <15 ml/min/1.73 m^2	195 (3.0)	1.06	237 (3.6)	1.29	0.81 (0.67–0.98)	0.026‡
Sustained# ≥57% decrease in	257 (3.9)	1.40	361 (5.5)	4.03	0.70 (0.60–0.83)	<0.0001
Renal death	2 (<0.1)	0.01	4 (<0.1)	0.02	0.53 (0.10–2.91)	0.459

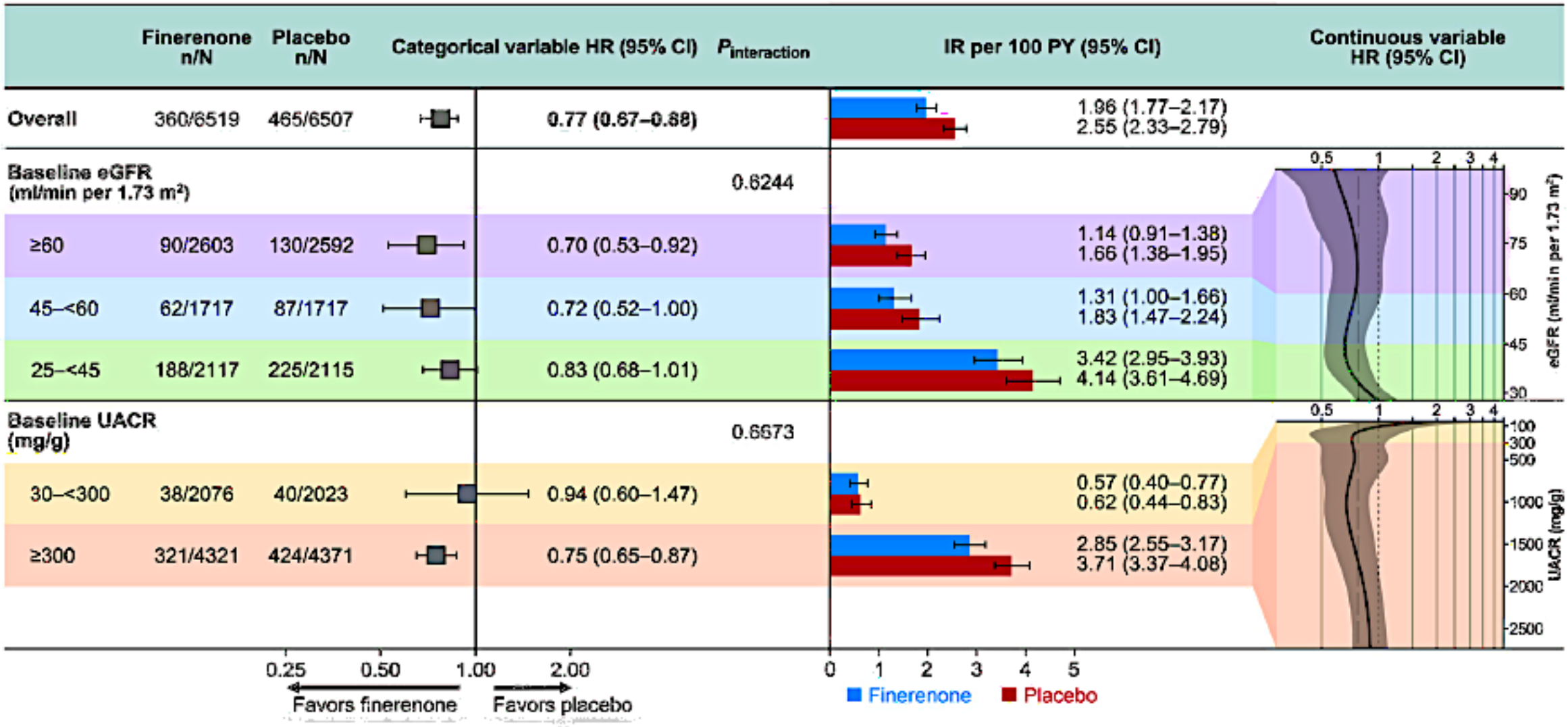


*Kidney failure defined as either ESKD (initiation of chronic dialysis for ≥90 days or kidney transplant) or sustained decrease in eGFR <15 ml/min/1.73 m^2; #confirmed by two eGFR measurements ≥4 weeks apart; ‡Analyses for p-values not prespecified

CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; PY, patient-years.

Agarwal R , Filipattos G, et.al….and Bakris GL, Eur Heart J 2022 ;43:474-484

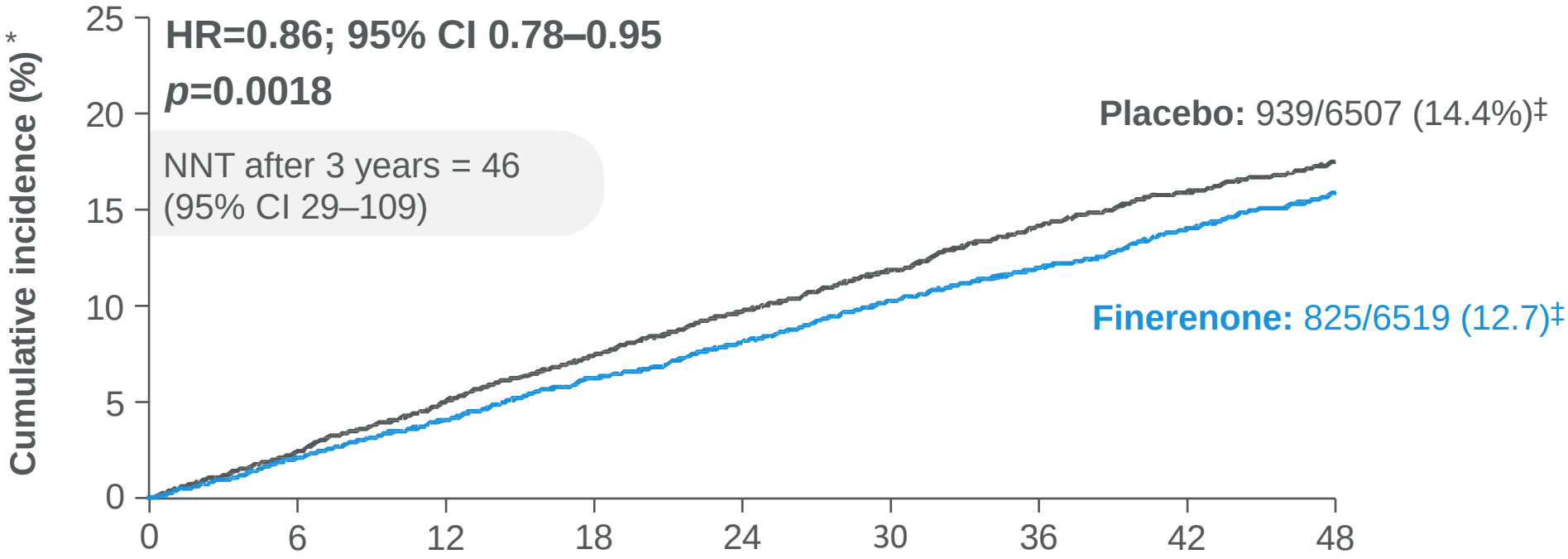
Composite kidney outcome, including a >57% eGFR decrease component by baseline UACR and eGFR categories.



Bakris GL et.al. Kidney Int 2022

FIDELITY pooled analysis: Finerenone significantly reduced the risk of the CV composite outcome by 14%

Time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for HF

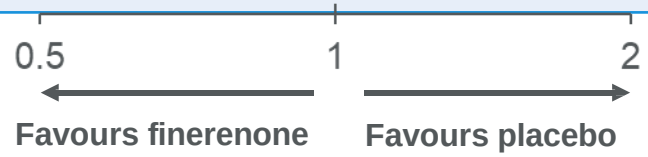


No. at risk#									
Finerenone	6519	6360	6202	6009	5273	4207	3065	2187	1087
Placebo	6507	6330	6125	5938	5184	4147	2969	2135	1082

Agarwal R , Filipattos G, et.al….and Bakris GL, Eur Heart J 2022 ;43:474-484

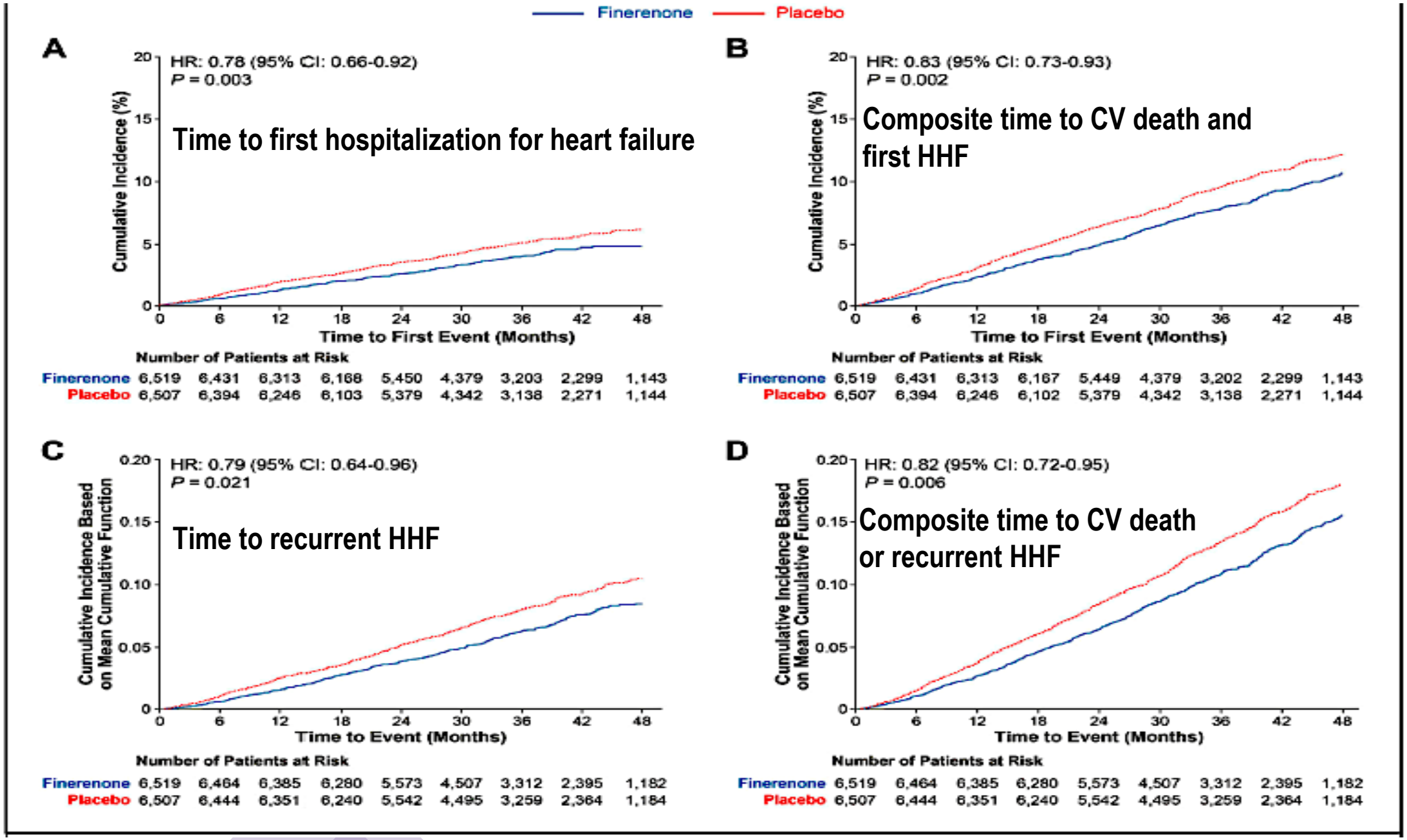
FIDELITY pooled analysis: Finerenone had consistent effects on CV death and hospitalisation for HF

Outcome	Finerenone (n=6519)		Placebo (n=6507)		Hazard ratio (95% CI)	*p*-value
	n (%)	n per 100 PY	n (%)	n per 100 PY		
Composite CV outcome*	**825 (12.7)**	**4.34**	**939 (14.4)**	**5.01**	**0.86 (0.76–0.95)**	**0.0018**
CV death	322 (4.9)	1.61	364 (5.6)	1.84	0.88 (0.76–1.02)	0.0922
Non-fatal MI	173 (2.7)	0.88	189 (2.9)	0.97	0.91 (0.74–1.12)	0.3601
Non-fatal stroke	198 (3.0)	1.01	198 (3.0)	1.02	0.99 (0.82–1.21)	0.9460
Hospitalisation for HF	256 (3.9)	1.31	325 (5.0)	1.68	0.78 (0.66–0.92)	0.0030



*Composite of time to first onset of CV death, non-fatal MI, non-fatal stroke, or hospitalisation for HF
CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction

Agarwal R , Filipattos G, et.al….and Bakris GL, Eur Heart J 2022 ;43:474-484

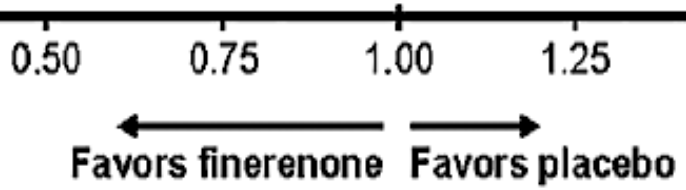


Finerenone and Heart Failure Outcomes: FIDELITY ANALYSIS

Filippatos G et.al. J Am Coll Cardiol HF 2022;10:860–870

Risk of all-cause mortality and CV mortality (primary intention-to-treat analysis and on-treatment analysis)

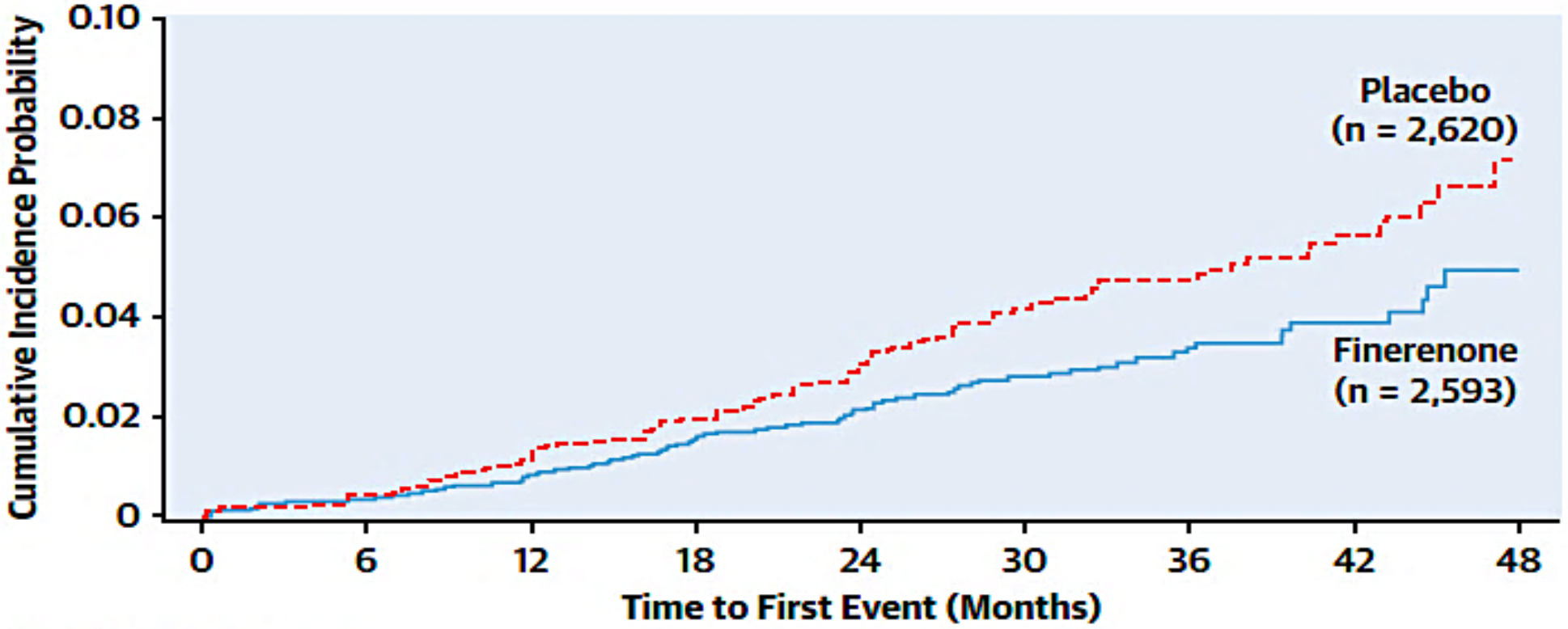
Endpoint	Finerenone (n=6519)		Placebo (n=6507)		Hazard ratio (95% CI)	*P*-value
	n (%)	n/100 PY	n (%)	n/100 PY		
Primary analysis						
All-cause mortality	552 (8.5)	2.76	614 (9.4)	3.10	0.89 (0.79–1.00)	0.051
CV mortality	322 (4.9)	1.61	364 (5.6)	1.84	0.88 (0.76–1.02)	0.092
On-treatment analysis[a]						
All-cause mortality	280 (4.3)	1.62	344 (5.3)	1.98	0.82 (0.70–0.96)	0.014
CV mortality	189 (2.9)	1.09	233 (3.6)	1.34	0.82 (0.67–0.99)	0.040



Filippatos G et.al. Eur Heart J 2023; 9:183–191

FIGURE 1 Time to New-Onset of AFF in Patients Without a History of AFF

Finerenone = 82/2,593 (3.2%; incidence: 1.20 per 100 PY; 95% CI: 0.96–1 .48)
Placebo = 117/2,620 (4.5%; incidence: 1.72 per 100 PY; 95% CI: 1.42–2.04)
HR: 0.71 (95% CI: 0.53–0.94); p = 0.0164



Number of patients at risk									
Finerenone	2,593	2,563	2,524	2,459	1,939	1,444	961	539	109
Placebo	2,620	2,580	2,532	2,463	1,914	1,446	945	552	112

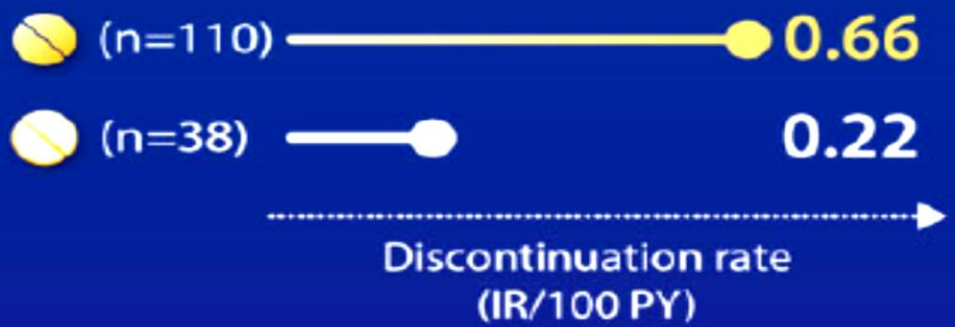
Filippatos G et.al. JACC 2021;78:142-152

CONCLUSION

Results

	HR (95% CI)	p-value	Risk ↓
Endpoint CV composite	0.86 (0.78 – 0.95)	0.0018	14%
Kidney composite	0.77 (0.67 – 0.88)	0.0002	23%
HHF	0.78 (0.66 – 0.92)	0.0030	22%
Dialysis	0.80 (0.64 – 0.99)	0.040	20%

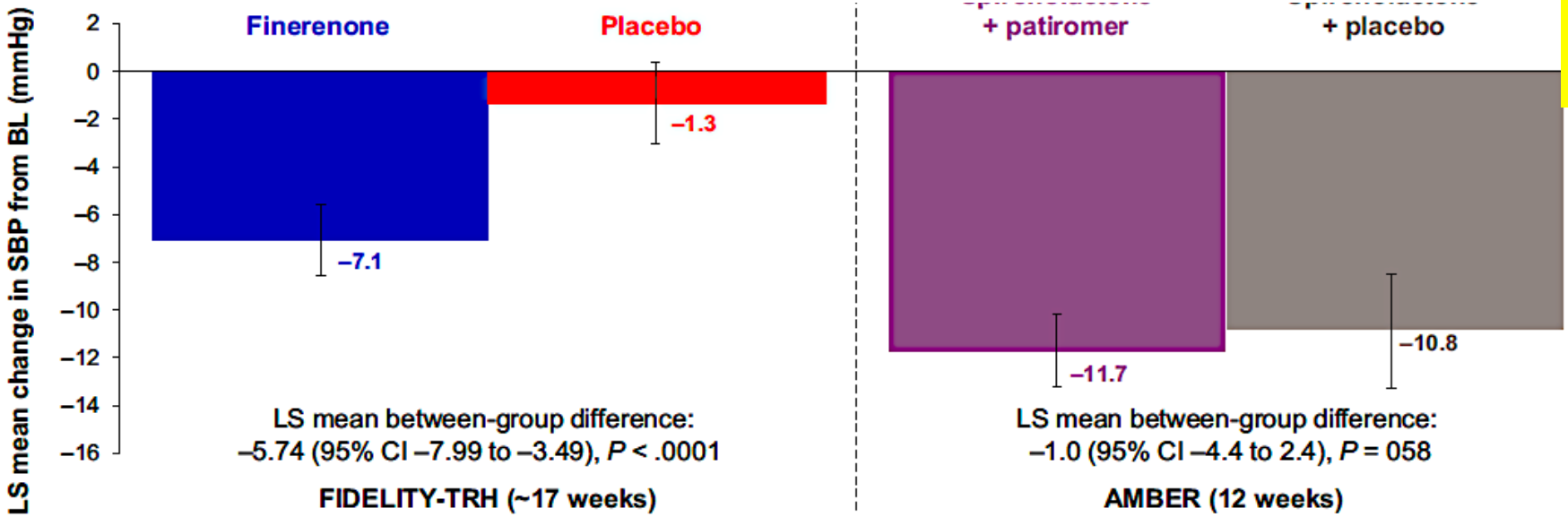
Few hyperkalemia-related discontinuations occurred



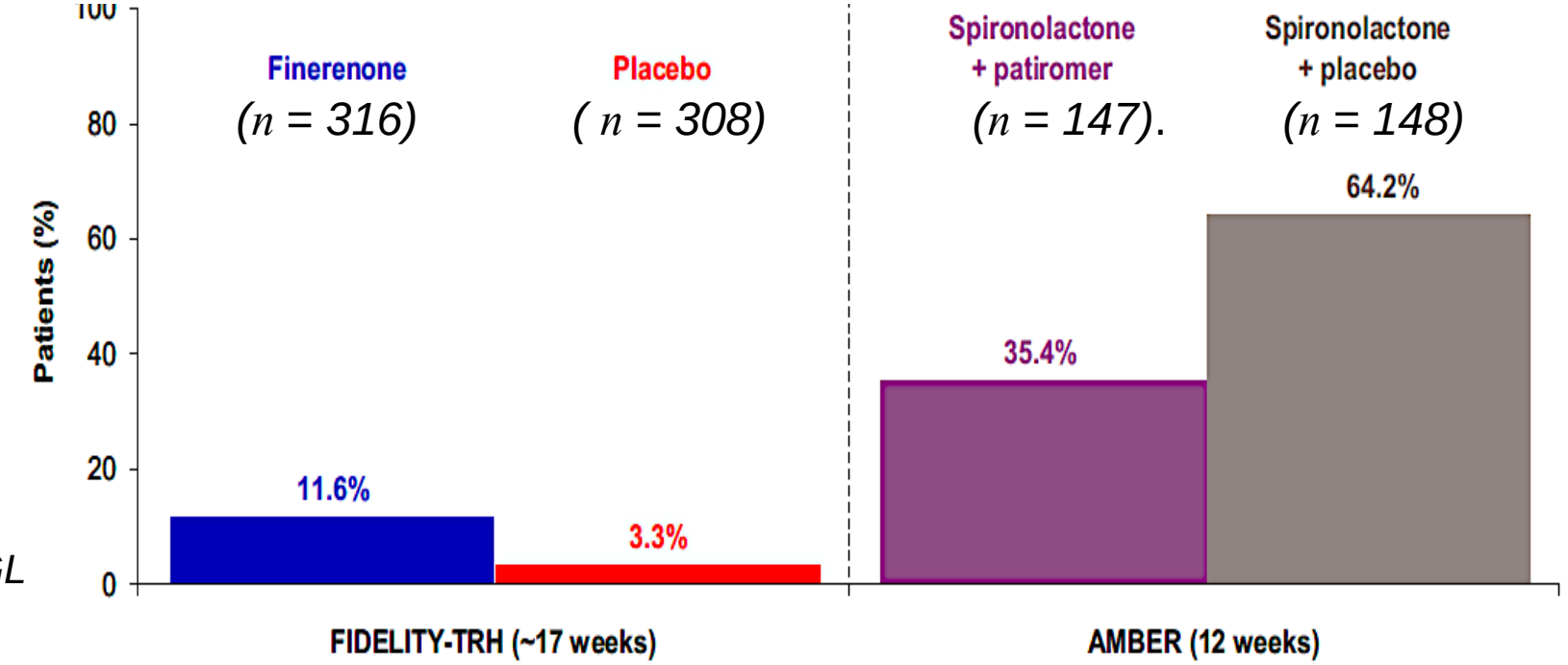
Agarwal R, Filippatos G, Pitt B, et.al…. Bakris GL Eur Heart J 2022 ;43:474-484

Comparison of Spiro to Finerenone in a Subset of TRH patients with comparable eGFRs

BL SBP 146 (7) 146 (7) 143 (7) 145 (7.0



eGFR- 37 (8) 36 (7) 35 (7) 36 (8)



Agarwal R, Pitt B, Palmer B et.al.. and BakrisGL Clinical Kidney Journal, 2023;16:293–302

CMHC
Cardiometabolic Health Congress

www.cardiometabolichealth.org

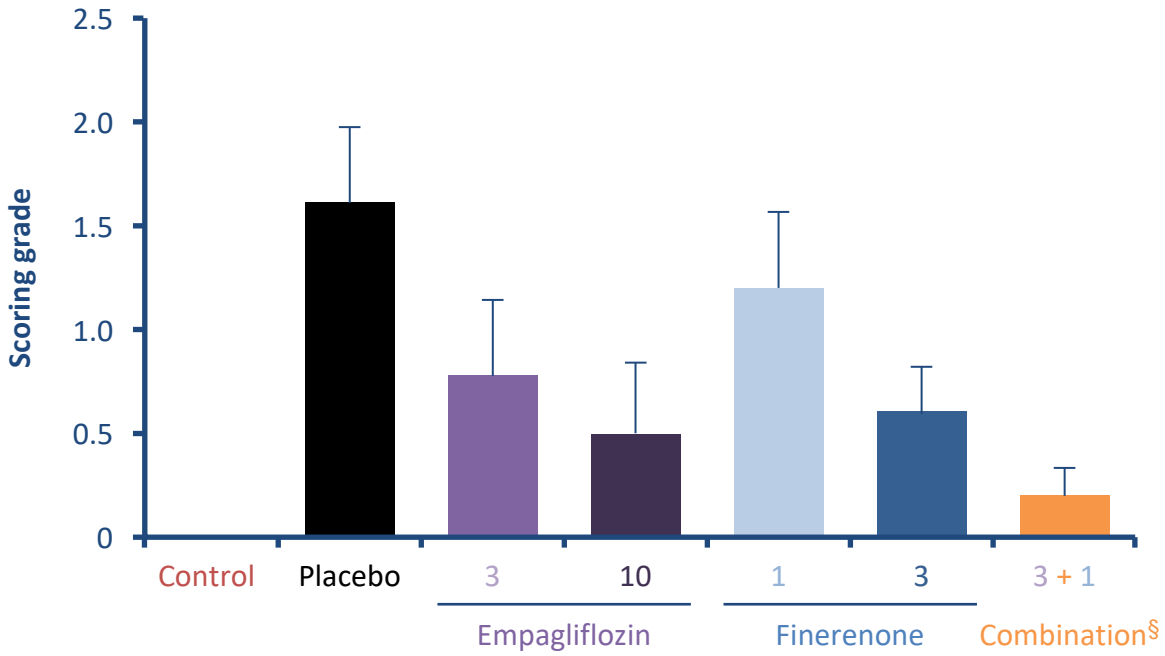
Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

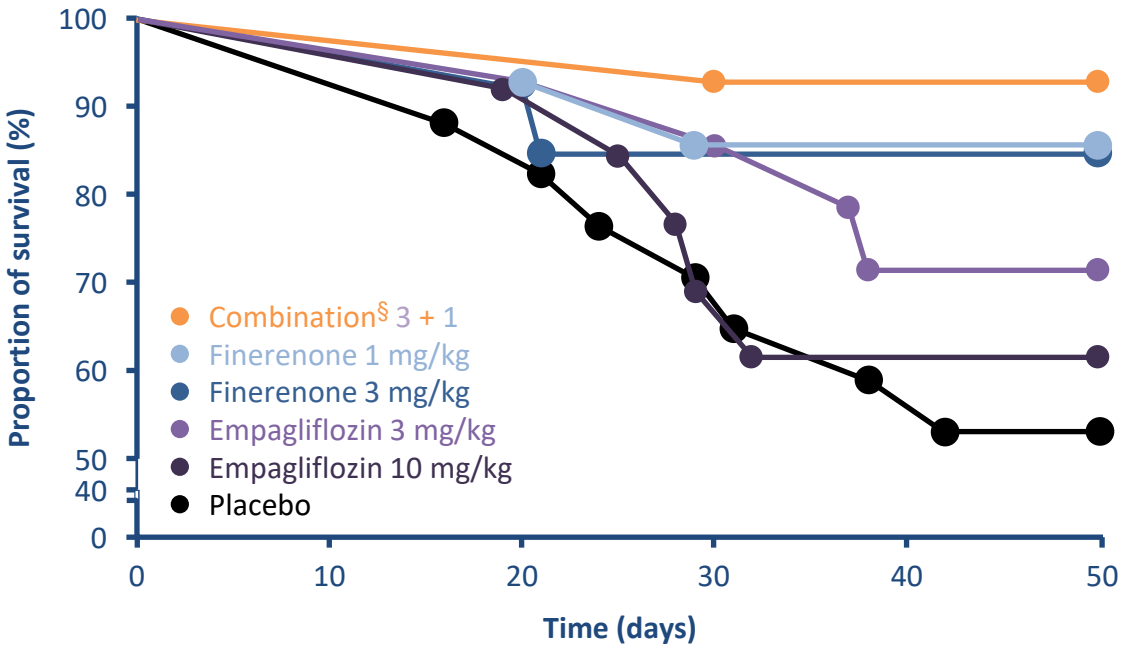
What About The Combination of an SGLT2 inhibitor and Finerenone on Outcomes

Preclinical data show that combination therapy with finerenone and an SGLT-2i has benefits over monotherapy*

Cardiac fibrosis#



Survival‡



Low-dose combination tended to have more anti-fibrotic effects than each low dose monotherapy

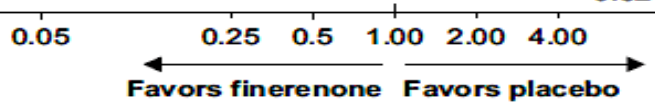
Greatest survival benefit observed with combined treatment of finerenone and empagliflozin

*CV morbidity and mortality studied in hypertensive, N(ω)-nitro-L-arginine methyl ester-treated, renin-transgenic (mRen2)27 rats; #cardiac fibrosis determined by Sirius Red/Fast Green staining; ‡proportion of survival defined as the absence of mortality and severe morbidity per group over the course of the study; §combination therapy of finerenone (1 mg/kg) and empagliflozin (3 mg/kg)
Data are mean±SEM. SEM, standard error of the mean
CV, cardiovascular; SEM, standard error of the mean; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

Kolkhof P et al. *Am J Nephrol*. 2021; 52(8):642-652

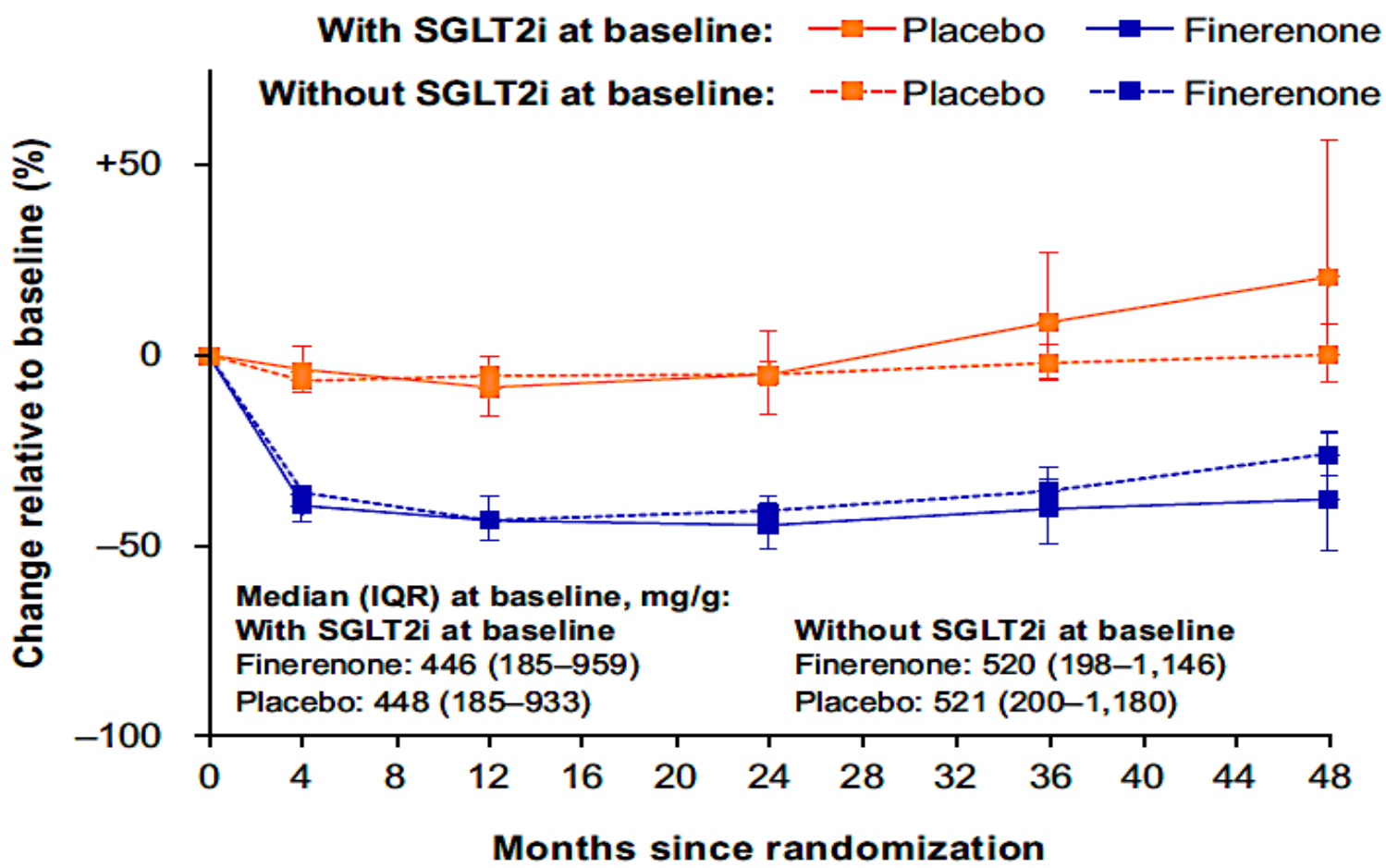
Analysis of kidney and CV composite outcomes in those receiving an SGLT2i at baseline and receiving an SGLT2i at any time during the on-treatment period

	Finerenone	Placebo	Finerenone	Placebo	HR (95% CI)	$P_{interaction}$
	n/*N* (%)		*n* per 100 PY			
Analysis for outcomes in patients receiving/not receiving an SGLT2i at baseline						
Cardiovascular composite						
SGLT2i at baseline	39/438 (8.9)	52/439 (11.8)	2.95	4.08	0.67 (0.42–1.07)*	0.46†
No SGLT2i at baseline	786/6,081 (12.9)	887/6,068 (14.6)	4.44	5.08	0.87 (0.79–0.96)*	
Kidney composite						
SGLT2i at baseline	9/438 (2.1)	17/439 (3.9)	0.70	1.37	0.42 (0.16–1.08)*	0.29†
No SGLT2i at baseline	351/6,081 (5.8)	448/6,068 (7.4)	2.06	2.64	0.80 (0.69–0.92)*	
Hospitalization for heart failure						
SGLT2i at baseline	10/438 (2.3)	22/439 (5.0)	0.74	1.68	0.44 (0.19–0.99)*	0.18†
No SGLT2i at baseline	246/6,081 (4.0)	303/6,068 (5.0)	1.35	1.68	0.80 (0.68–0.95)*	
All-cause death						
SGLT2i at baseline	20/438 (4.6)	30/439 (6.8)	1.46	2.23	0.58 (0.30–1.10)*	0.24†
No SGLT2i at baseline	532/6,081 (8.7)	584/6,068 (9.6)	2.86	3.16	0.90 (0.80–1.02)*	
On-treatment period – Time-varying analyses for outcomes in patients receiving/not receiving an SGLT2i at any time‡						
	n		*n* per 100 PY			
Cardiovascular composite						
SGLT2i use	41	58	2.40	3.20	0.77 (0.51–1.15)§	0.77§
No SGLT2i use	579	700	3.83	4.69	0.82 (0.73–0.91)§	
Kidney composite						
SGLT2i use	11	13	0.63	0.70	0.92 (0.41–2.08)§	0.50§
No SGLT2i use	213	312	1.40	2.06	0.69 (0.58–0.83)§	
Hospitalization for heart failure						
SGLT2i use	4	23	0.23	1.24	0.18 (0.06–0.53)§	0.015§
No SGLT2i use	175	248	1.14	1.62	0.71 (0.58–0.86)§	
All-cause death						
SGLT2i use	14	15	0.79	0.80	0.98 (0.47–2.03)§	0.64§
No SGLT2i use	266	329	1.71	2.12	0.82 (0.70–0.96)§	



Rossing P, Anker S et.al… and Agarwal R Diabetes Care 2022;45:2991–2998

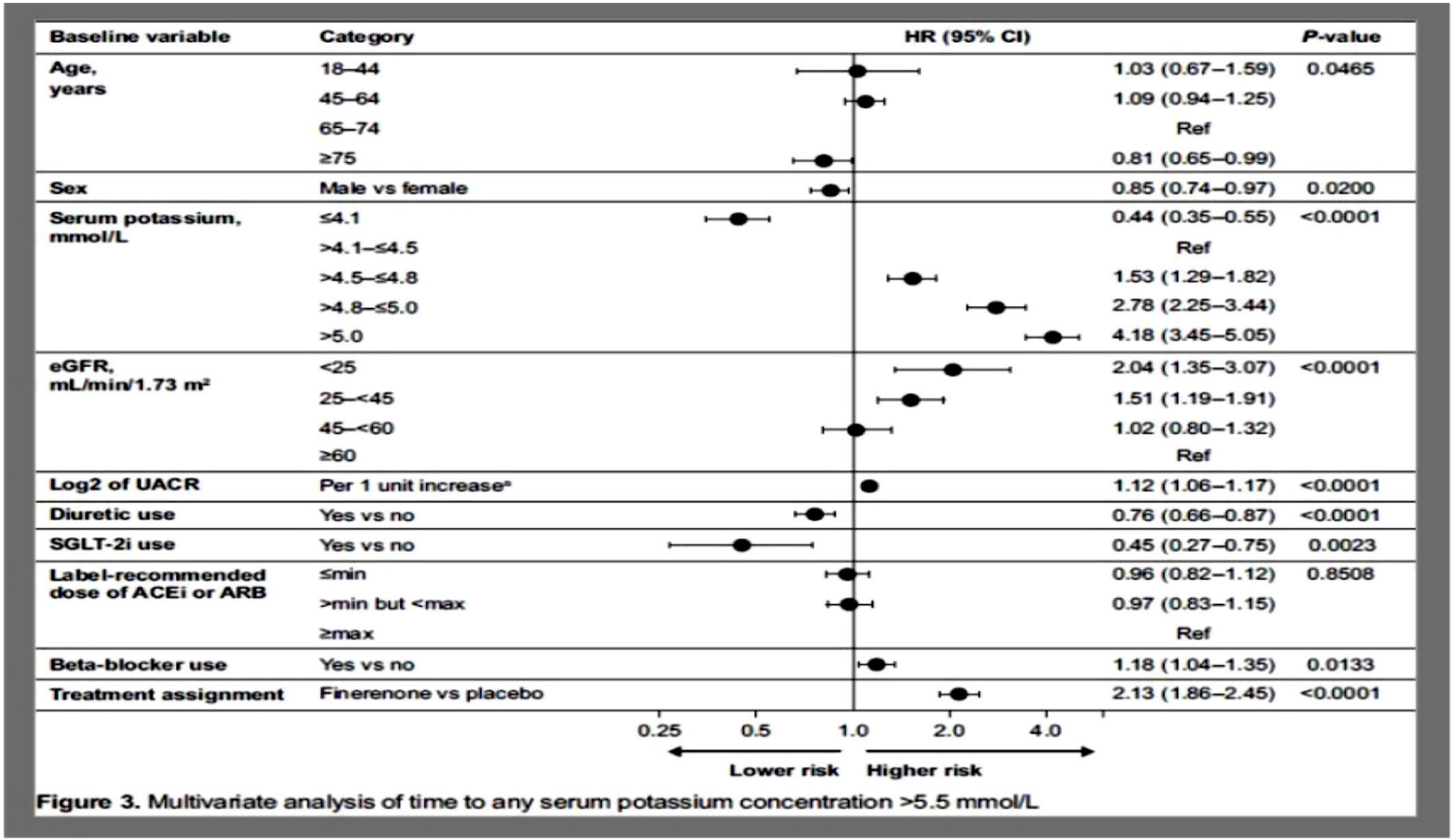
Change in UACR over time in patients receiving or not receiving an SGLT2i at baseline



No. of patients					
With SGLT2i at baseline					
Finerenone	424	413	336	191	64
Placebo	417	404	336	178	61
Without SGLT2i at baseline					
Finerenone	5,849	5,575	4,531	2,554	835
Placebo	5,822	5,569	4,493	2,528	811

Rossing P, Anker S et.al… and Agarwal R Diabetes Care 2022;45:2991–2998

Multivariate analysis-time to any serum [K+] >5.5 mmol/L; FIDELIO trial

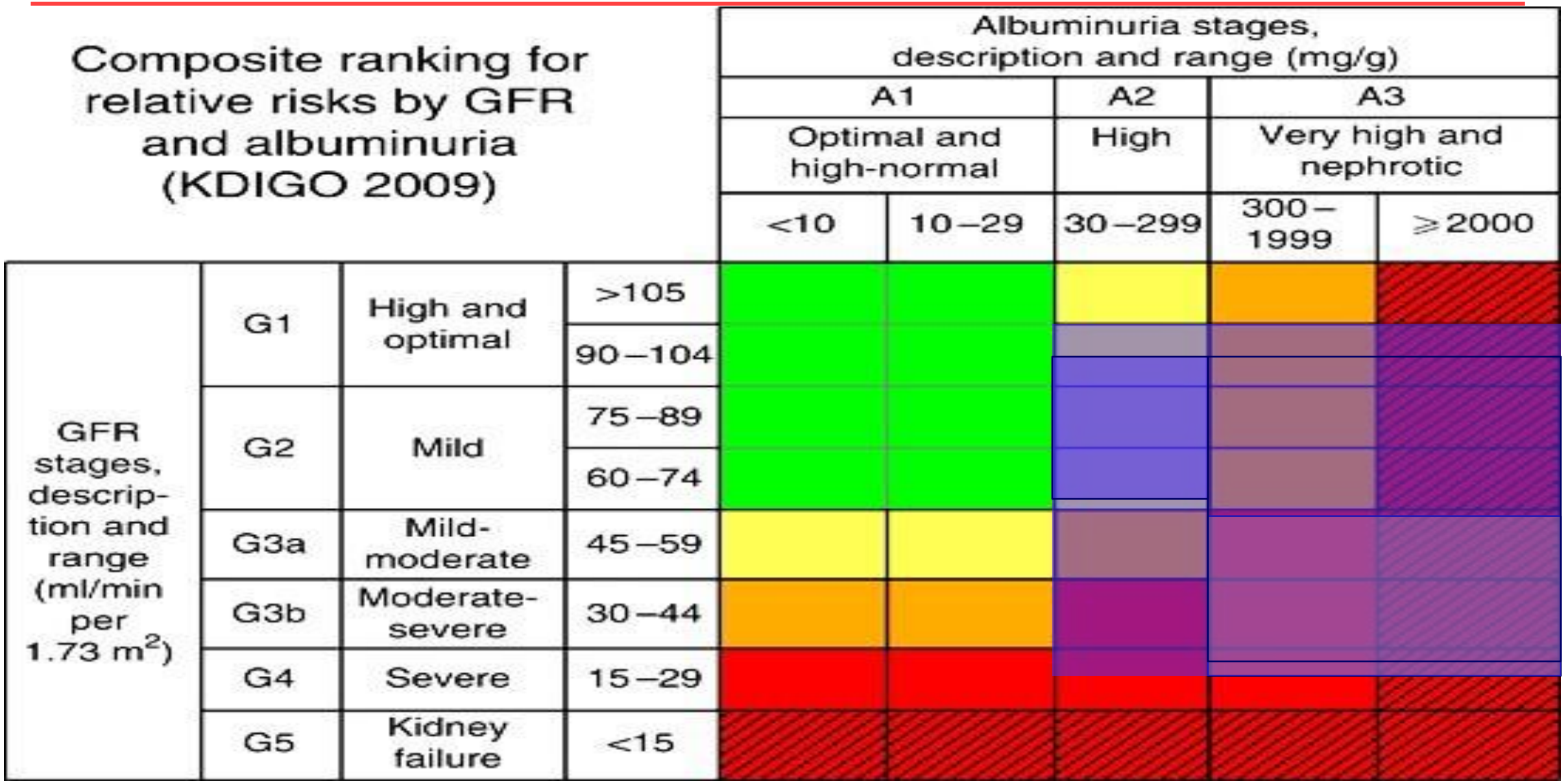


Baseline variable	Category	HR (95% CI)	*P*-value
Age, years	18–44	1.03 (0.67–1.59)	0.0465
	45–64	1.09 (0.94–1.25)	
	65–74	Ref	
	≥75	0.81 (0.65–0.99)	
Sex	Male vs female	0.85 (0.74–0.97)	0.0200
Serum potassium, mmol/L	≤4.1	0.44 (0.35–0.55)	<0.0001
	>4.1–≤4.5	Ref	
	>4.5–≤4.8	1.53 (1.29–1.82)	
	>4.8–≤5.0	2.78 (2.25–3.44)	
	>5.0	4.18 (3.45–5.05)	
eGFR, mL/min/1.73 m²	<25	2.04 (1.35–3.07)	<0.0001
	25–<45	1.51 (1.19–1.91)	
	45–<60	1.02 (0.80–1.32)	
	≥60	Ref	
Log2 of UACR	Per 1 unit increase[a]	1.12 (1.06–1.17)	<0.0001
Diuretic use	Yes vs no	0.76 (0.66–0.87)	<0.0001
SGLT-2i use	Yes vs no	0.45 (0.27–0.75)	0.0023
Label-recommended dose of ACEi or ARB	≤min	0.96 (0.82–1.12)	0.8508
	>min but <max	0.97 (0.83–1.15)	
	≥max	Ref	
Beta-blocker use	Yes vs no	1.18 (1.04–1.35)	0.0133
Treatment assignment	Finerenone vs placebo	2.13 (1.86–2.45)	<0.0001

Figure 3. Multivariate analysis of time to any serum potassium concentration >5.5 mmol/L

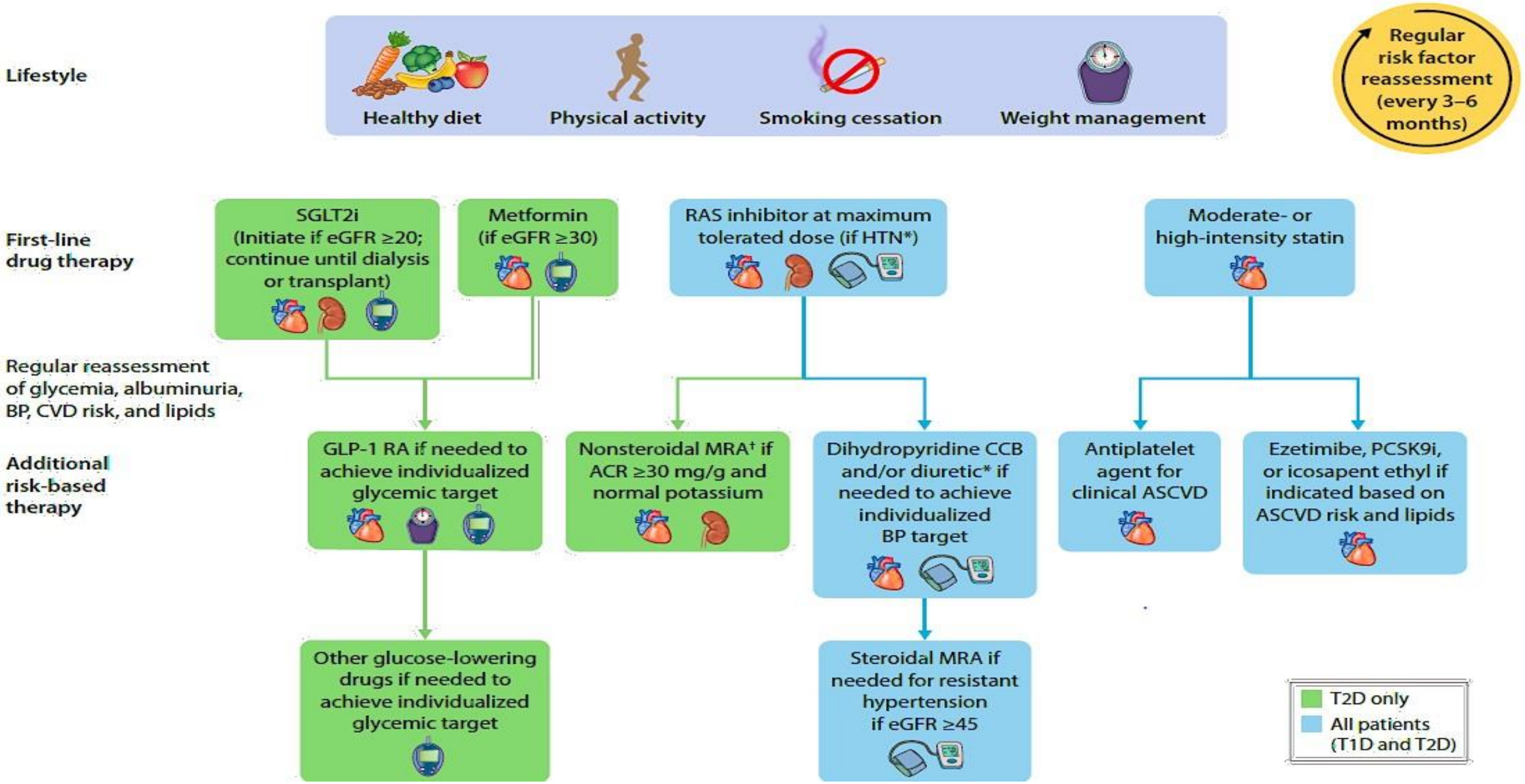
Agarwal R, Joseph A, et. al.,…and Bakris GL J Am Soc Nephrol. 2022;33(1):225-37.

Composite Ranking for Relative Risks by glomerular filtration rate (GFR) and Albuminuria (Kidney Disease: Improving Global Outcomes (KDIGO) 2009



Levey AS et.al. Eur Heart J. 2020; 41: 4592–4598.

ADA/KDIGO: HOLISTIC APPROACH



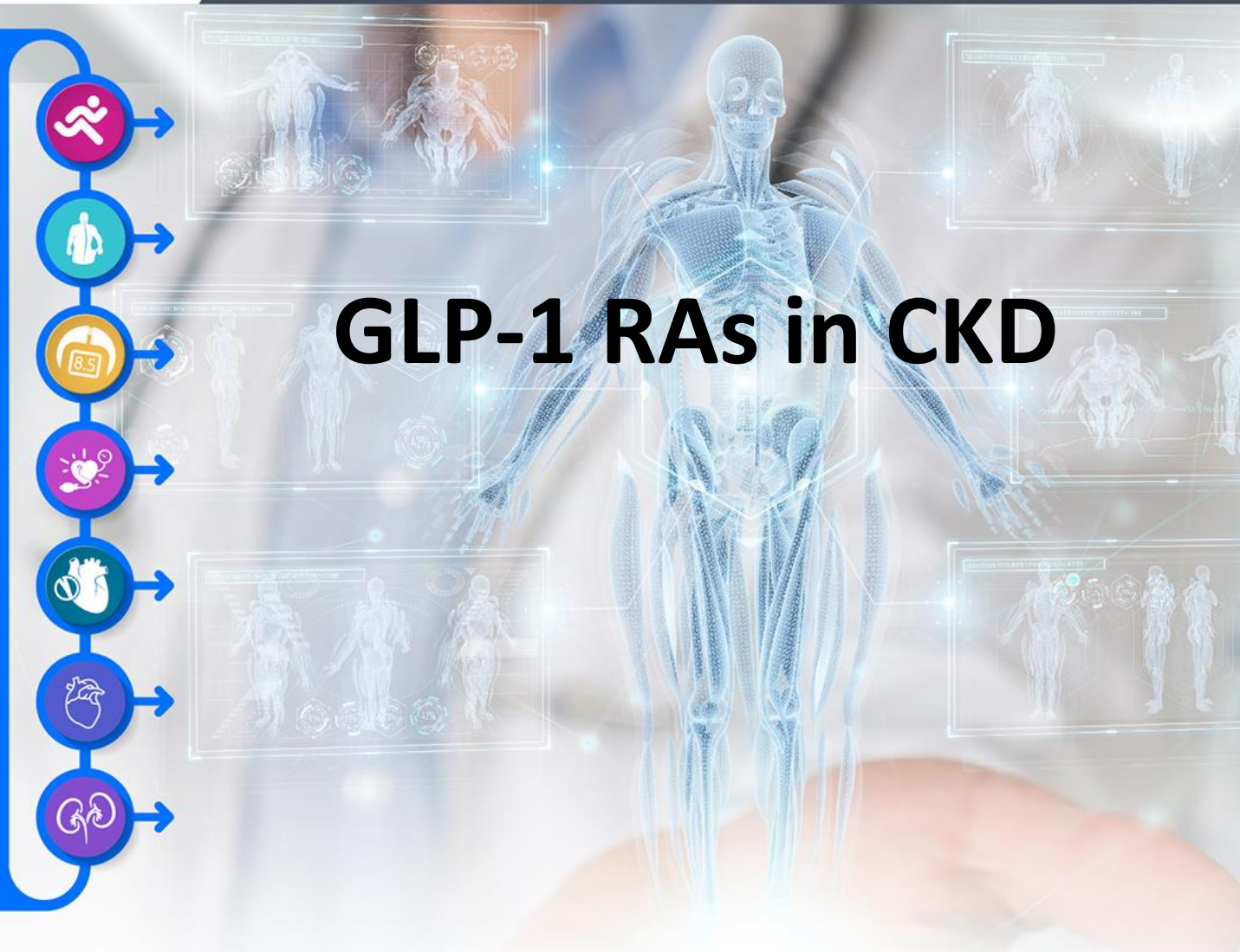
de Boer IH.... and Bakris GL. Diabetes Care 2022. https://doi.org/10.2337/dci22-0027

CMHC
Cardiometabolic Health Congress

www.cardiometabolichealth.org

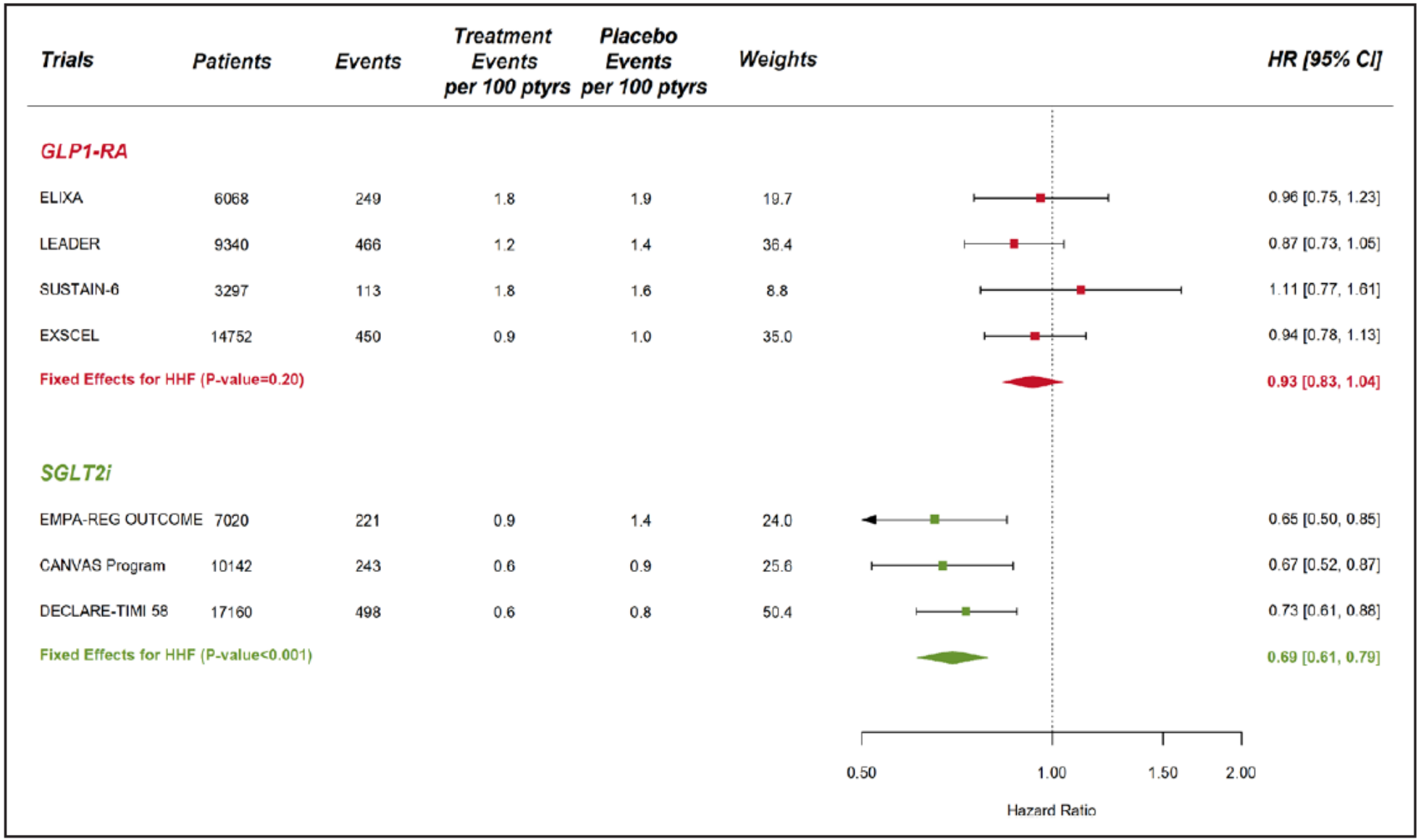
Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)



GLP-1 RAs in CKD

Meta-analysis of GLP1-RA and SGLT2i trials on hospitalization for heart failure (HHF) stratified by drug class

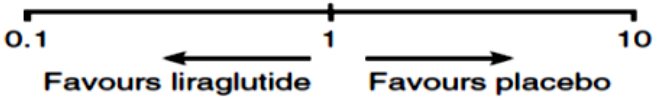


Zelniker T et.al. Circulation. 2019;139:2022–2031

Cardiorenal outcomes by baseline blood pressure (BP) category, adjusted for baseline variables related to cardiorenal risk, in the LEADER (A) and SUSTAIN 6 trials (B).

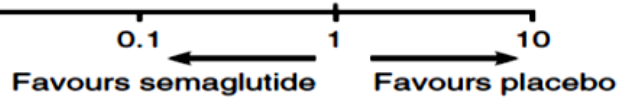
(A)

	N with event (%) Liraglutide	N with event (%) Placebo	HR (95% CI)	*P*-interaction	(*P*-interaction Gail-Simon)
Primary MACE†					
LEADER overall[7]	608 (13.0)	694 (14.9)	0.87 (0.78–0.97)		
BP normal	98 (14.2)	100 (14.2)	1.00 (0.75–1.32)		
BP elevated	80 (12.1)	64 (9.9)	1.21 (0.87–1.68)	0.06	0.39
BP stage 1 hypertension	156 (11.2)	208 (14.8)	0.73 (0.60–0.90)		
BP stage 2 hypertension	274 (14.3)	322 (16.9)	0.84 (0.72–0.99		
Nephropathy‡					
LEADER overall[7]	268 (5.7)	337 (7.2)	0.78 (0.67–0.92)		
BP normal	26 (3.8)	31 (4.4)	0.81 (0.48–1.36)		
BP elevated	33 (5.0)	28 (4.3)	1.12 (0.68–1.86)	0.14	0.70
BP stage 1 hypertension	61 (4.4)	102 (7.2)	0.58 (0.42–0.79)		
BP stage 2 hypertension	148 (7.7)	176 (9.2)	0.80 (0.65–1.00)		

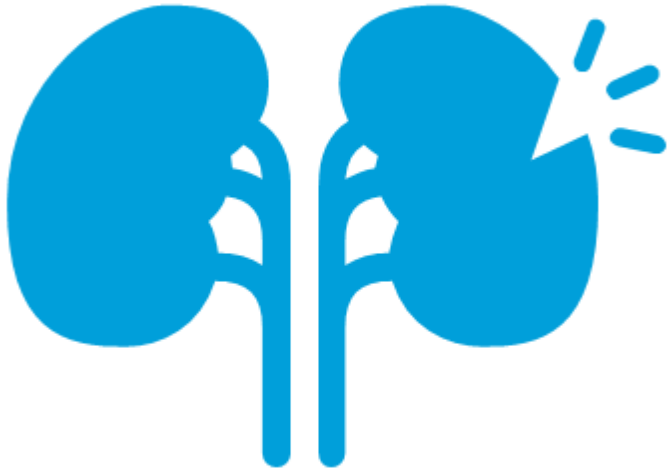


(B)

	N with event (%) Semaglutide	N with event (%) Placebo	HR (95% CI)	*P*-interaction	(*P*-interaction Gail-Simon)
Primary MACE†					
SUSTAIN 6 overall[8]	108 (6.6)	146 (8.9)	0.74 (0.58–0.95)		
BP normal	15 (6.9)	19 (8.7)	0.79 (0.40–1.56)		
BP elevated	9 (4.1)	22 (10.0)	0.43 (0.20–0.95)	0.40	0.88
BP stage 1 hypertension	24 (4.8)	37 (7.2)	0.62 (0.37–1.03)		
BP stage 2 hypertension	60 (8.4)	68 (9.8)	0.85 (0.60–1.21)		
Nephropathy†§					
SUSTAIN 6 overall[8]	62 (3.8)	100 (6.1)	0.64 (0.46–0.88)		
BP normal	4 (1.8)	12 (5.5)	0.34 (0.11–1.05)		
BP elevated	3 (1.4)	14 (6.3)	0.24 (0.07–0.84)	0.27	0.88
BP stage 1 hypertension	19 (3.8)	25 (4.8)	0.69 (0.38–1.26)		
BP stage 2 hypertension	36 (5.1)	49 (7.1)	0.72 (0.47–1.11)		



Leiter L et.al. Diabetes Obes Metab. 2020;22:1690–1695.



The FLOW trial: Effect of semaglutide versus placebo on the progression of renal impairment in subjects with type 2 diabetes and chronic kidney disease

FLOW
semaglutide | renal outcomes trial

The FLOW trial

Objectives

Primary

To demonstrate that semaglutide delays the progression of renal impairment, and lowers the risk of renal and CV mortality in subjects with T2D and CKD

Secondary

To compare the effect of semaglutide versus placebo in subjects with T2D and CKD with regards to Cardiovascular morbidity, peripheral artery disease, glycaemic control, body weight, blood pressure, and safety.

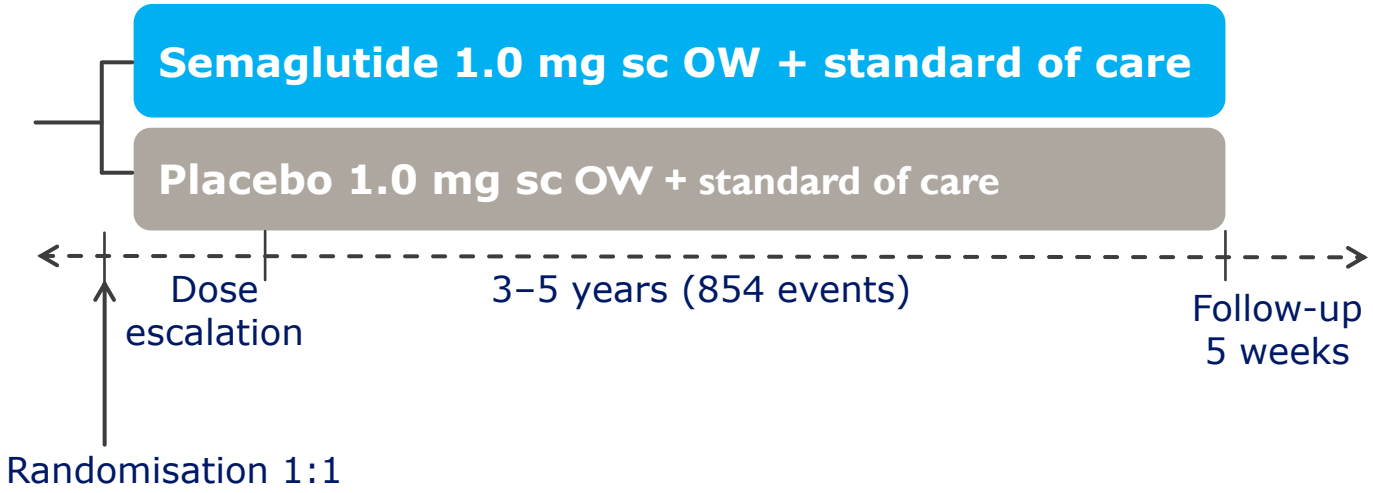
FLOW
semaglutide | renal outcomes trial

TRIAL DESIGN

FLOW trial

N=3160

- T2D, HbA_{1c} ≤10%
- RAAS blocker
- eGFR ≤75 and ≥50* and UACR >300 mg/g
  Or
  eGFR <50 and ≥25* and UACR >100 mg/g
- Upper UACR level (5000 mg/g)
- (20% cap of patients having eGFR ≥60*)



Key endpoints

Primary:
- Persistent 50% reduction in eGFR
- Onset of persistent eGFR <15*
- Initiation of chronic renal replacement therapy
- Renal death
- CV death

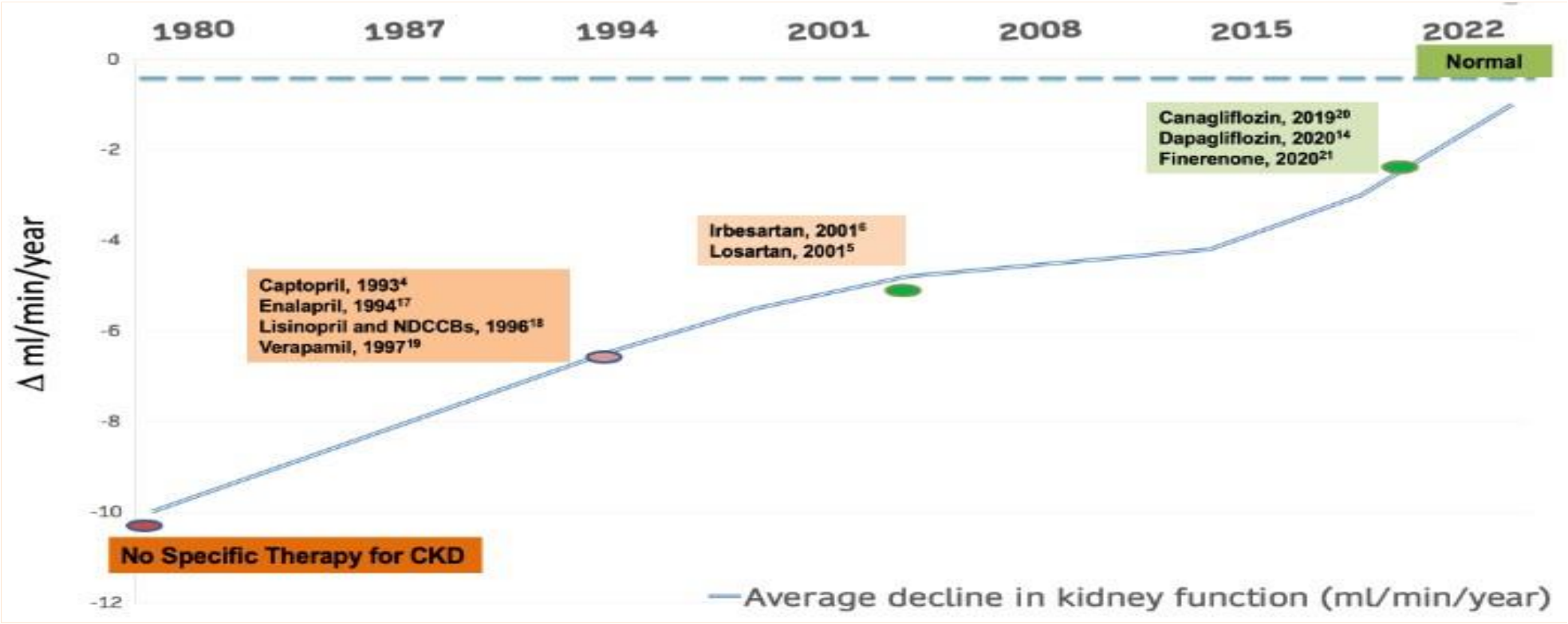
Secondary confirmatory:
- Change in eGFR (eGFR slope)
- MACE
- All-cause mortality

Trial information
- Event driven
- Stratified by SGLT-2i use at baseline

FPFV in July 2019

*(mL/min/1.73 m^2)
CV, cardiovascular; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular events; RAAS, renin–angiotensin aldosterone system (maximum labelled or tolerated dose); UACR, urinary albumin-creatinine ratio
sc, subcutaneous; SGLT-2i, sodium glucose transporter-2 inhibitor, T2D, type 2 diabetes
NCT03819153. ClinicalTrials.gov. Last accessed March 2019

History of Successful Intervention to Slow GFR Decline



Naaman SC, Bakris GL. Chronic Kidney Disease and Type 2 Diabetes. Arlington (VA), 2021:28-32.

PILLARS OF THERAPY

Bakris GL

Key point summary

- Reduction of CKD progression and subsequent CVD risk, primarily heart failure hospitalizations, now have 2 additional agents to supplement RAS blocking use.
- Maximizing newer approaches to CKD risk reduction (with maximally tolerated background therapy) demonstrate additional slowing of DKD progression to a little less than 2.5-3 ml/min/year- Normal decline is 0.8 ml/min/year
- Additional trial data will be forthcoming over the next two years with GLP1-RAs to further extend these findings in advanced CKD.