The Intersection of CKD and Heart Failure

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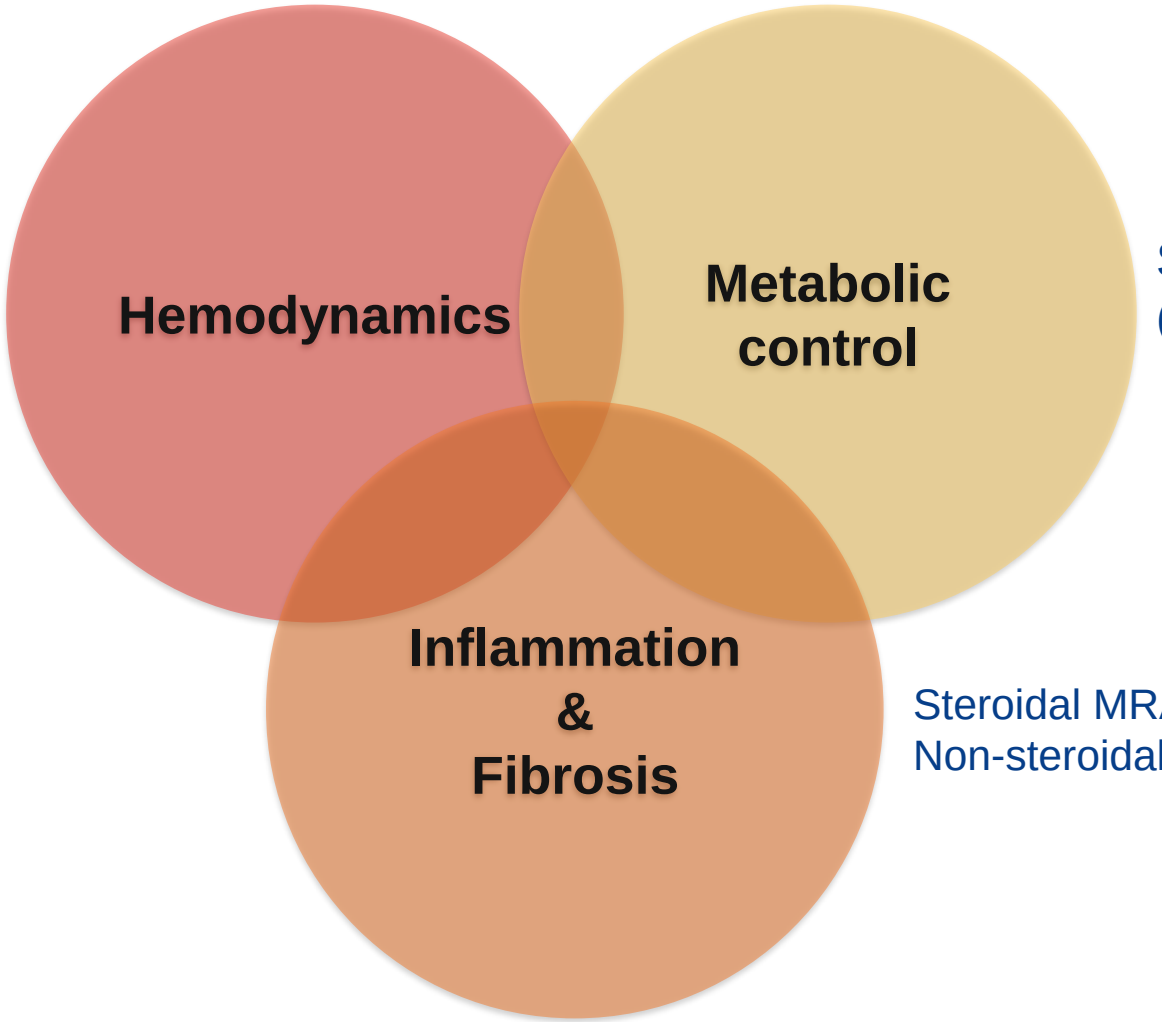
Disclosures: Amgen, AstraZeneca, Bayer AG, Boehringer Ingelheim/ Lilly, Bristol Myers Squibb, Corteria Pharmaceuticals, CSL Vifor, Cytokinetics, Merck, Novartis, PharmaIN, Pfizer, Roche Diagnostics, Sanofi, Tricog Health, and Urovant Pharmaceuticals

Intersecting Mechanistic Pathways for HF and Kidney Disease

ACE inhibitors
ARBs

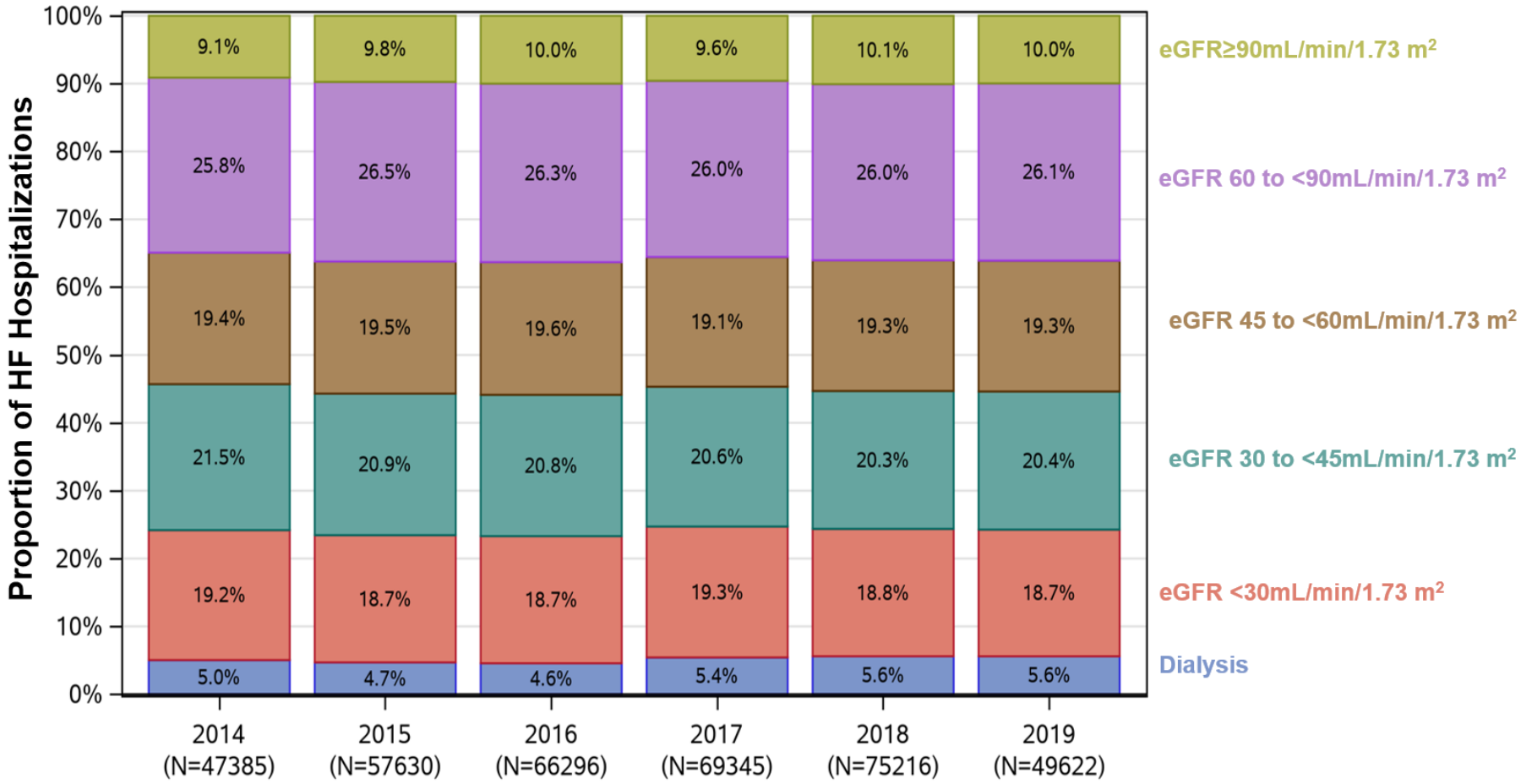


SGLT2 inhibitors
(among other mechanisms)

Steroidal MRA: spironolactone, epleronone
Non-steroidal MRA: finerenone

Kolkof P et al. *Mol Cell Endocrinol* 2012; Kolkof P et al. *J Endocrinol* 2017

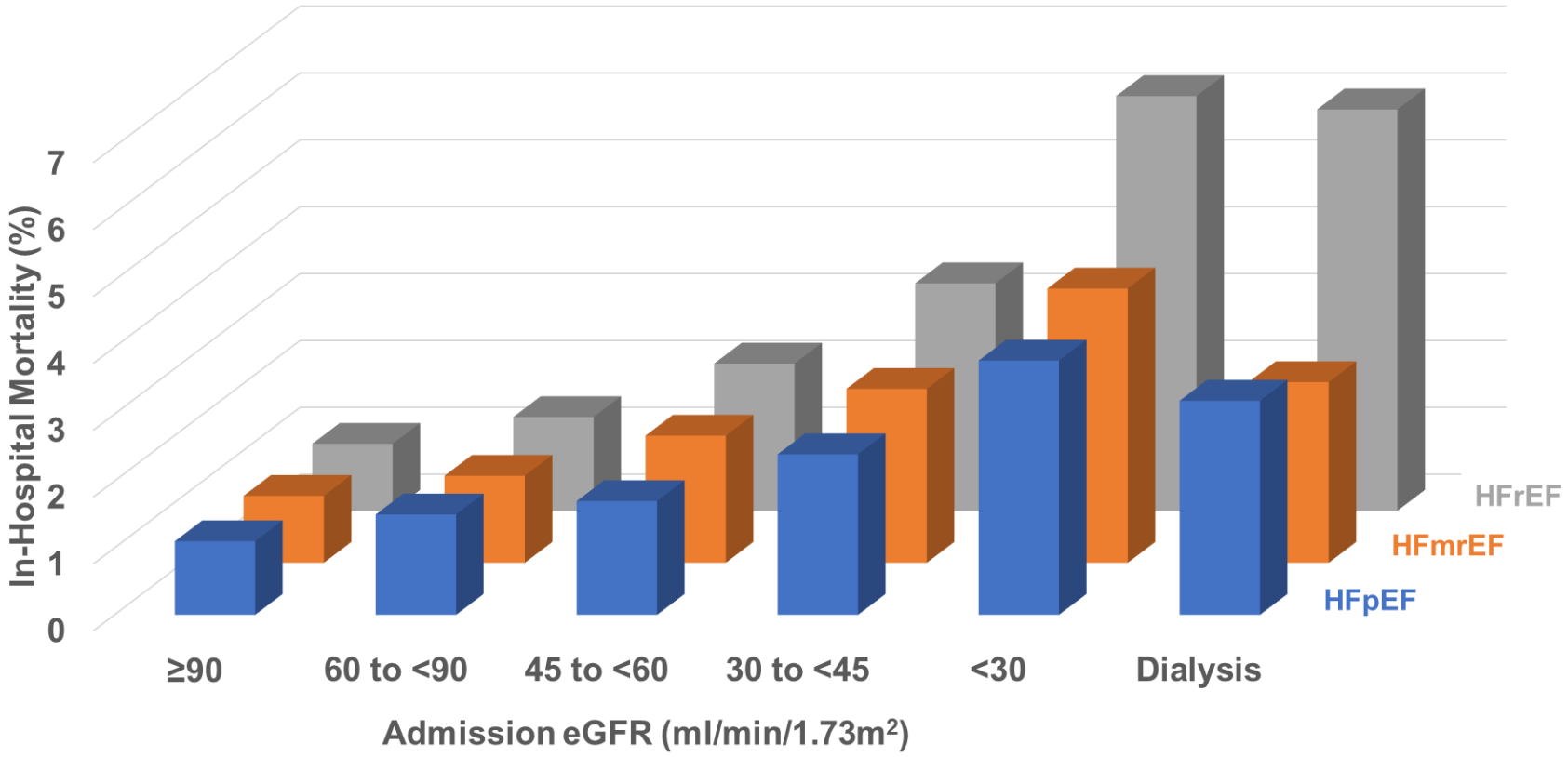
Substantial Burden of CKD Among Patients with Heart Failure



Among US patients hospitalized for HF, **more than 2 in 5 discharged with eGFR <45**
More than 3 in 5 discharged with eGFR <60

Patel RB, et al. *JACC 2021*

Admission eGFR and In-hospital Mortality Among Heart Failure Patients

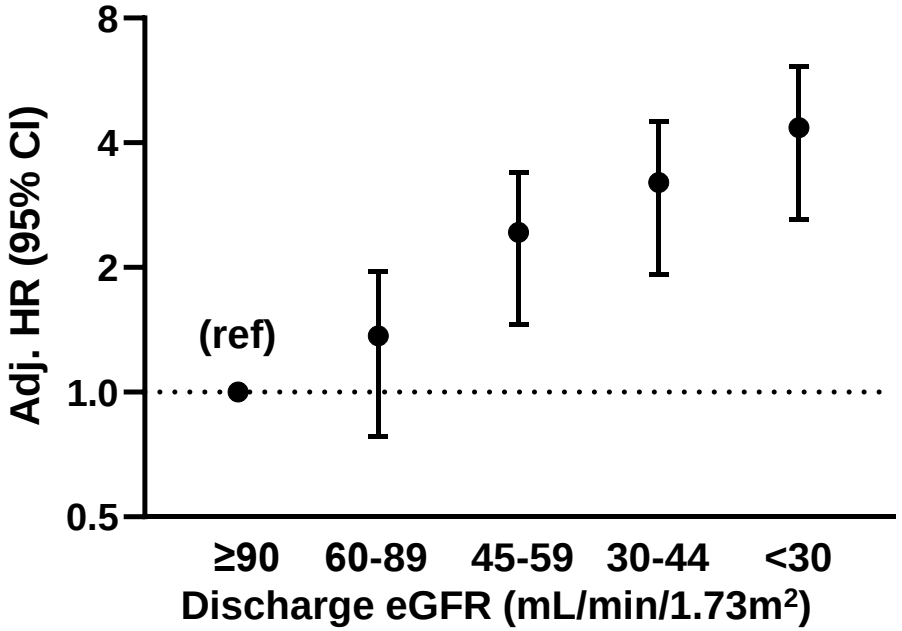


There is a graded, significant association between lower admission eGFR and higher in-hospital mortality across the LVEF spectrum

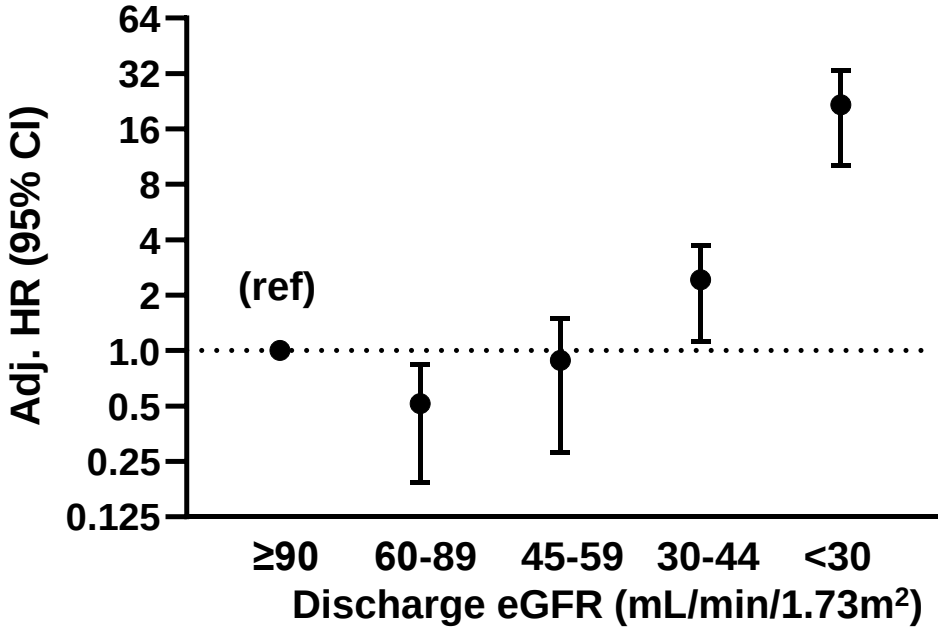
Patel RB, et al. *JACC 2021*

Significant Risk of Kidney Events After Hospitalization for HF

Post-Discharge Risks of Acute Kidney Injury over 1 Year



Post-Discharge Risks of Dialysis/ESKD over 1 Year



By 1-year, 7% of patients had been readmitted for AKI and 5% for dialysis/ESKD

Lower discharge eGFR (per 10 mL/min/1.73 m² decrease) was independently associated with increased readmission for AKI (adjusted HR 1.20[1.15-1.25]) and progression to dialysis/ESKD (adjusted HR 2.22 [1.93-2.55])

Vaduganathan M, et al. *AHA Scientific Sessions 2021*

CKD is a Powerful Predictor of HF Events, and Vice Versa

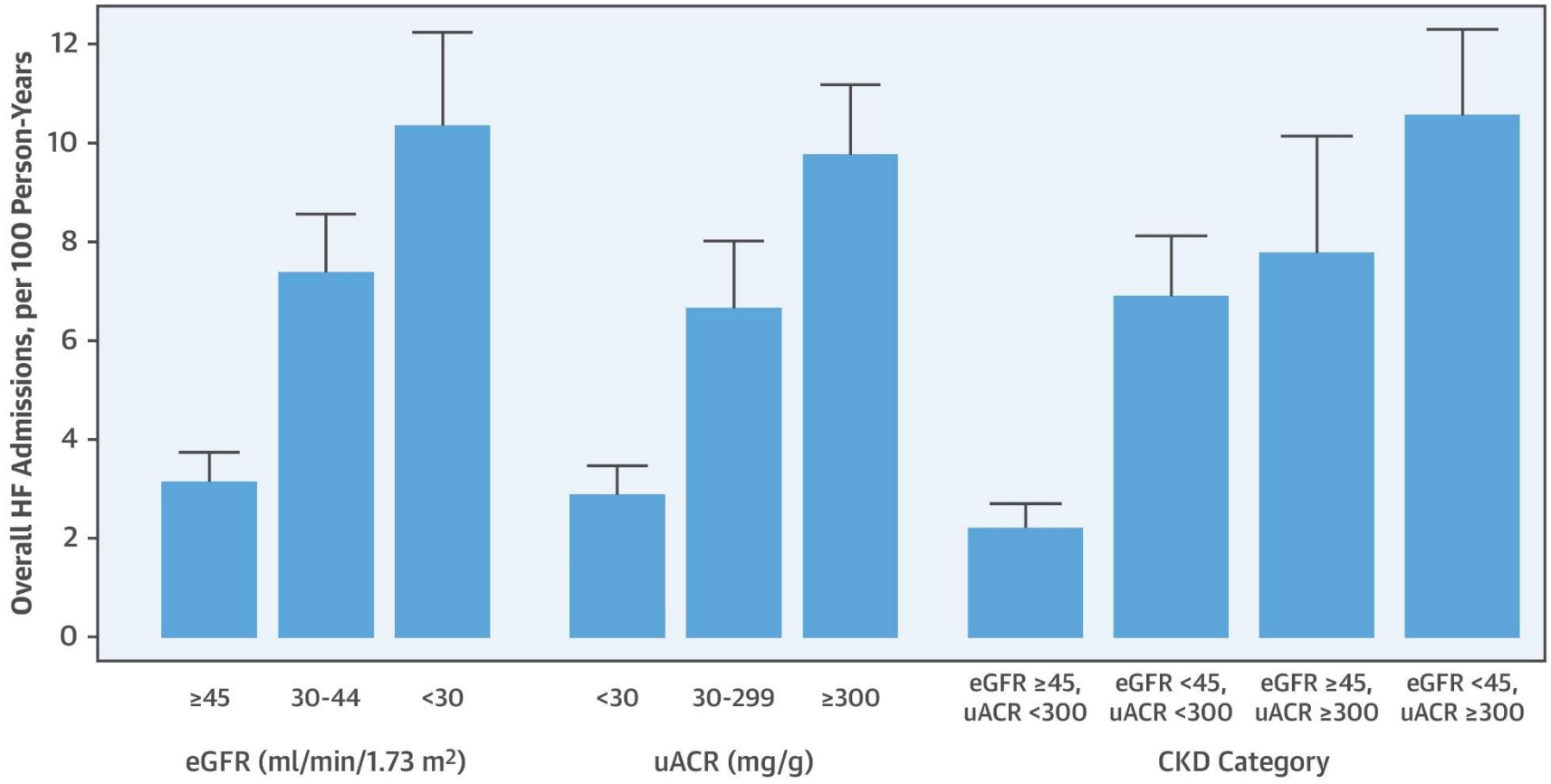
Risk Indicator	Adjusted HR (95% CI)	*P* Value	Points
Prior heart failure	4.22 (3.18–5.59)	<0.001	2
Atrial fibrillation	2.26 (1.62–3.14)	<0.001	1
Coronary artery disease	2.06 (1.45–2.93)	<0.001	1
eGFR <60 mL·min^{-1}·1.73 m^{-2}	1.85 (1.40–2.46)	<0.001	1
Urine albumin-to-creatinine ratio			
>300 mg/g	4.50 (3.18–6.36)	<0.001	2
30–300 mg/g	2.08 (1.50–2.87)	<0.001	1

UACR Top Predictor of HF Events in TRS-HFDM HF Risk Prediction Model

Berg DD et al. Circulation 2019

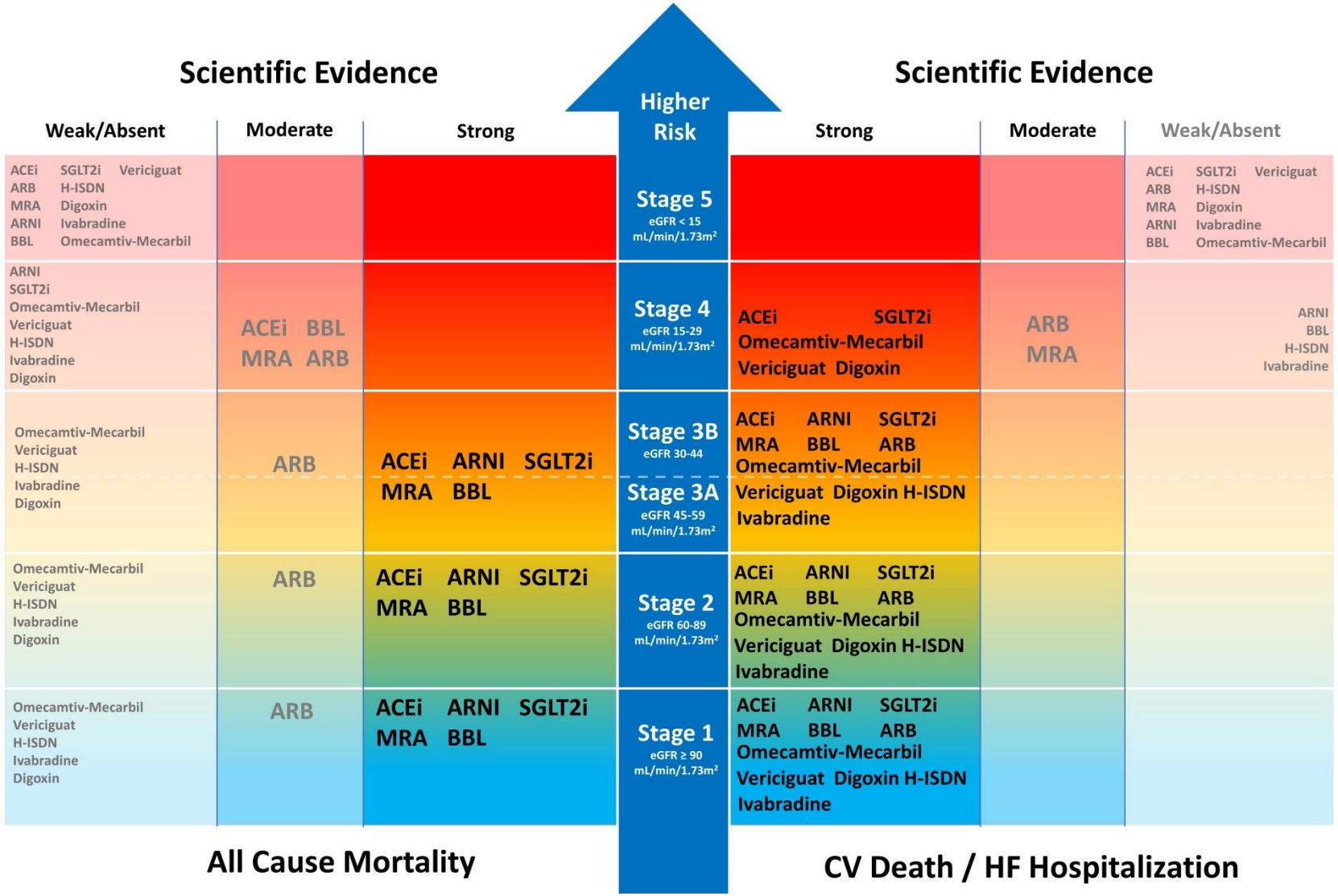
Heart Failure is a Leading Cause of Morbidity and Mortality in CKD

CENTRAL ILLUSTRATION: Heart Failure in Chronic Kidney Disease



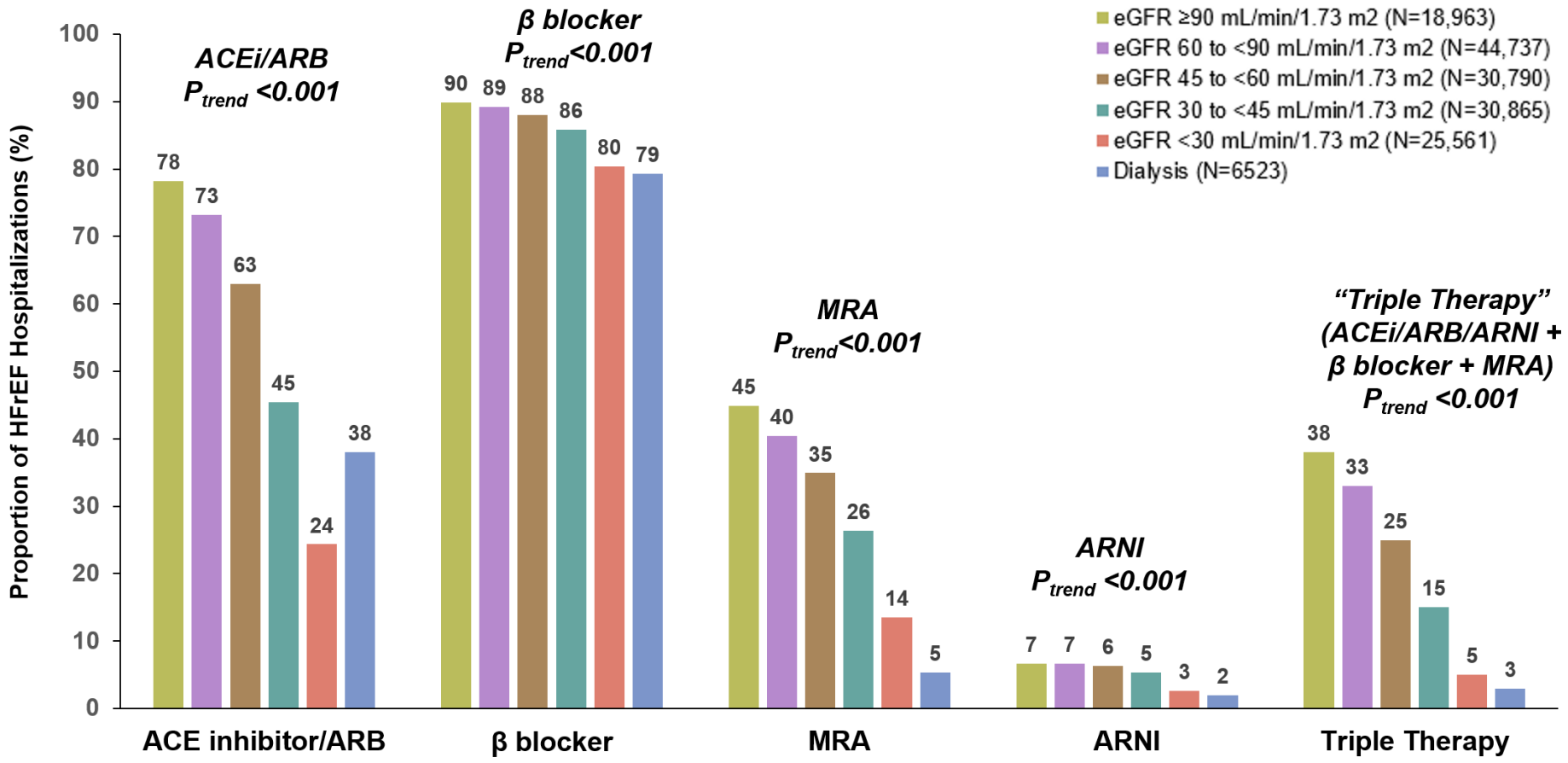
Bansal, N. et al. J Am Coll Cardiol. 2019;73(21):2691-700.

Limited Evidence-Based Strategies Available to Attenuate Risk in HF and Advanced CKD



Beldhuis I, et al. *Circulation* 2022

The Risk-Treatment Paradox in Heart Failure and CKD



Despite substantially higher clinical risk, patients with HFrEF and comorbid CKD are less likely to receive disease-modifying therapy.

Patel RB, Fonarow GC, Greene SJ, et al. *JACC 2021*

Newer Therapies for Patients with HF and CKD

Contemporary Combination Medical Therapy for CKD and HF

CKD

"Triple Therapy"

- ACEi/ARB
- *Non-Steroidal* MRA
- SGLT-2 Inhibitor

HFrEF & HFmrEF

"Quadruple Therapy"

- β-blocker
- ARNI
- *Steroidal* MRA
- SGLT-2 Inhibitor

HFpEF

"Triple Therapy"

- ARNI
- *Steroidal* MRA
- SGLT-2 Inhibitor

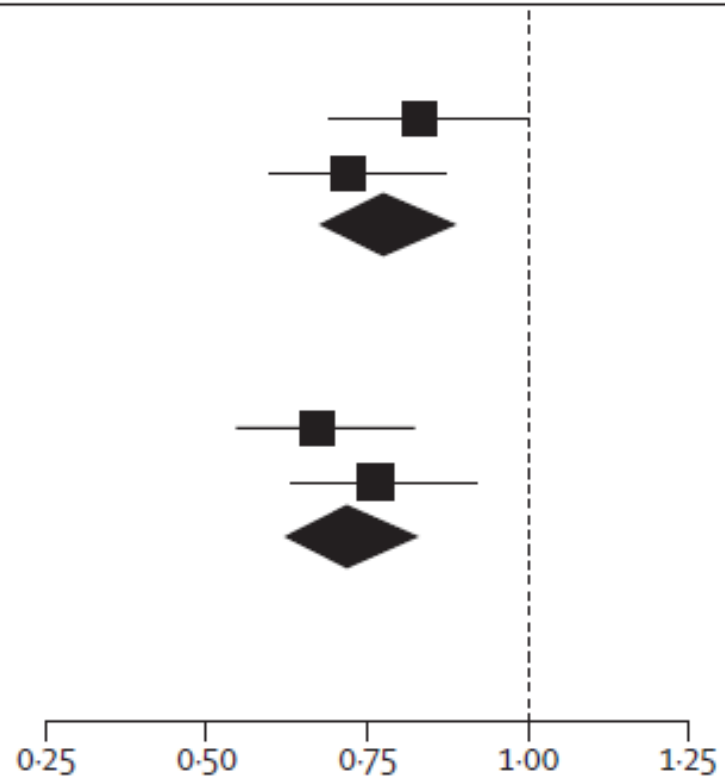
Modified from Dr. Muthiah Vaduganathan

Sodium-glucose Cotransporter 2 Inhibitors (SGLT2i)

SGLT2i in HFrEF and CKD

Cardiovascular Death or HF Hospialization

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
eGFR <60 mL/min per 1·73 m²			
EMPEROR-Reduced	202/893 (22·6)	237/906 (26·2)	0·83 (0·69–1·00)
DAPA-HF	191/962 (19·9)	254/964 (26·3)	0·72 (0·59–0·86)
Subtotal			**0·77 (0·68–0·88)**
Test for overall treatment effect p=0·0001 Test for heterogeneity of effect p=0·29			
eGFR ≥60 mL/min per 1·73 m²			
EMPEROR-Reduced	159/969 (16·4)	224/960 (23·3)	0·67 (0·55–0·83)
DAPA-HF	195/1410 (13·8)	248/1406 (17·6)	0·76 (0·63–0·92)
Subtotal			**0·72 (0·62–0·82)**
Test for overall treatment effect p<0·0001 Test for heterogeneity of effect p=0·38 Test for treatment by subgroup interaction p=0·44			



Zannad F, et al. Lancet 2020

DAPA-HF & EMPEROR-Reduced:
Primary Results by Kidney Function

	Dapa + SoC	Placebo + SoC	HR (95% CI)
eGFR <60	19.9%	26.4%	0.72 (0.59-0.86)
eGFR ≥60	13.9%	17.6%	0.76 (0.63-0.92)

RRR 28%

ARR 6.5%

	Empa + SoC	Placebo + SoC	HR (95% CI)
eGFR <60 or UACR >300	22.3%	27.4%	0.78 (0.65-0.93)
eGFR ≥60 & UACR ≤300	16.2%	21.6%	0.72 (0.58-0.90)

RRR 22%

ARR 5.1%

Jhund PS, et al. *Circulation* 2020; Zannad F, et al. *Circulation* 2021

EMPEROR-Preserved: Primary Results by Kidney Function

CV Death or HF Hospitalization

	Dapa + SoC	Placebo + SoC	HR (95% CI)
eGFR <60	17.5%	22.0%	0.77 (0.66-0.90)
eGFR ≥60	12.9%	14.9%	0.86 (0.71-1.04)

RRR 23%

ARR 4.5%

	Empa + SoC	Placebo + SoC	HR (95% CI)
eGFR <60	17.5%	21.6%	0.78 (0.66-0.91)
eGFR ≥60	10.2%	12.6%	0.81 (0.65-1.00)

RRR 22%

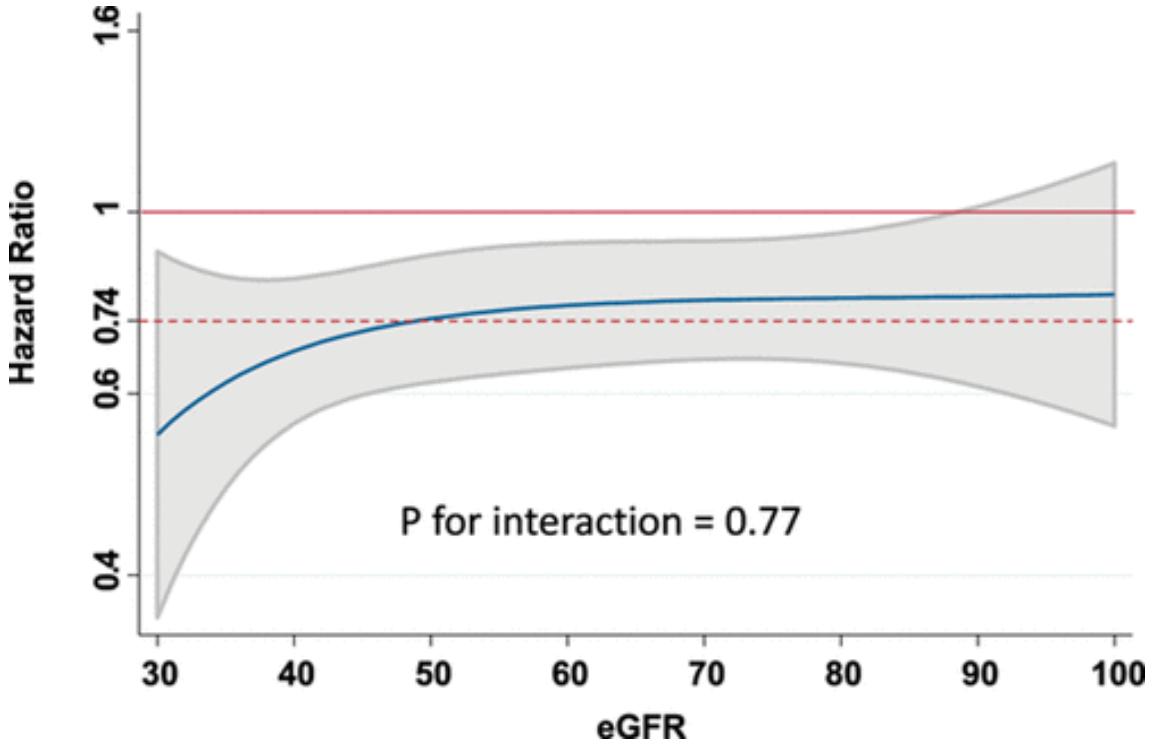
ARR 4.1%

Anker SD et al. *N Engl J Med* 2021; Vaduganathan M et al. *Lancet* 2022

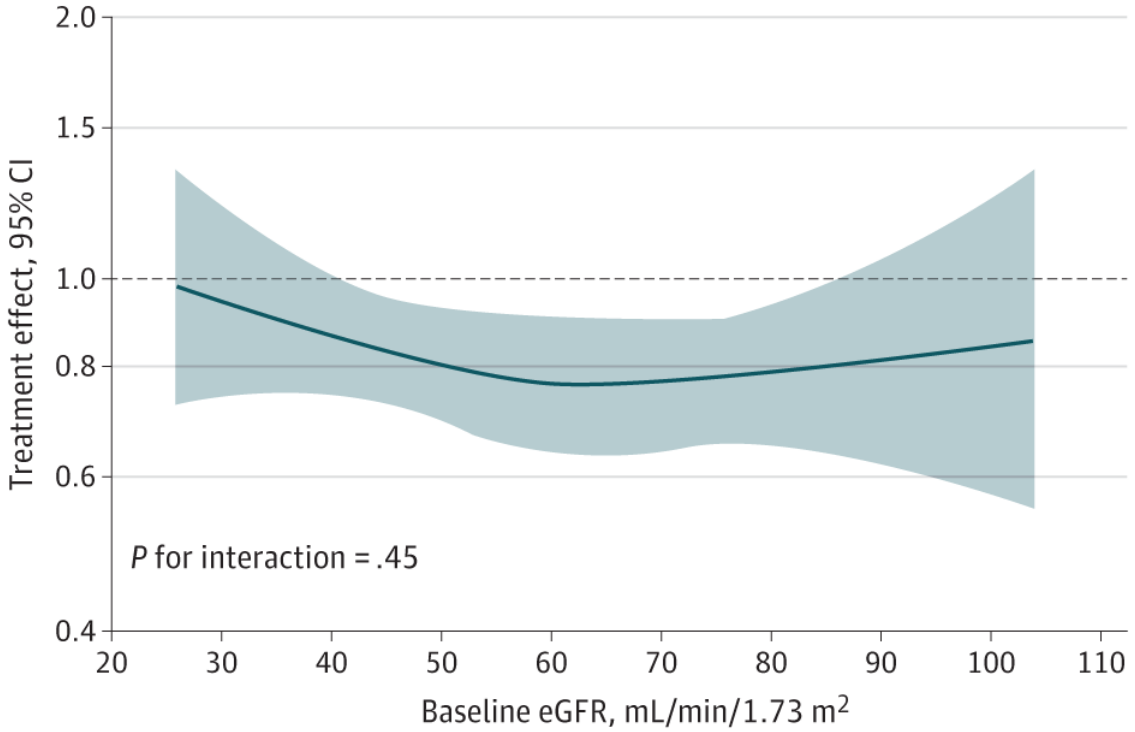
SGLT2i Improve Cardiovascular Outcomes in HFrEF and HFpEF *Across the Spectrum of Kidney Function*

Cardiovascular Death or Worsening HF

EF ≤40% *(DAPA-HF)*



EF >40% *(DELIVER)*

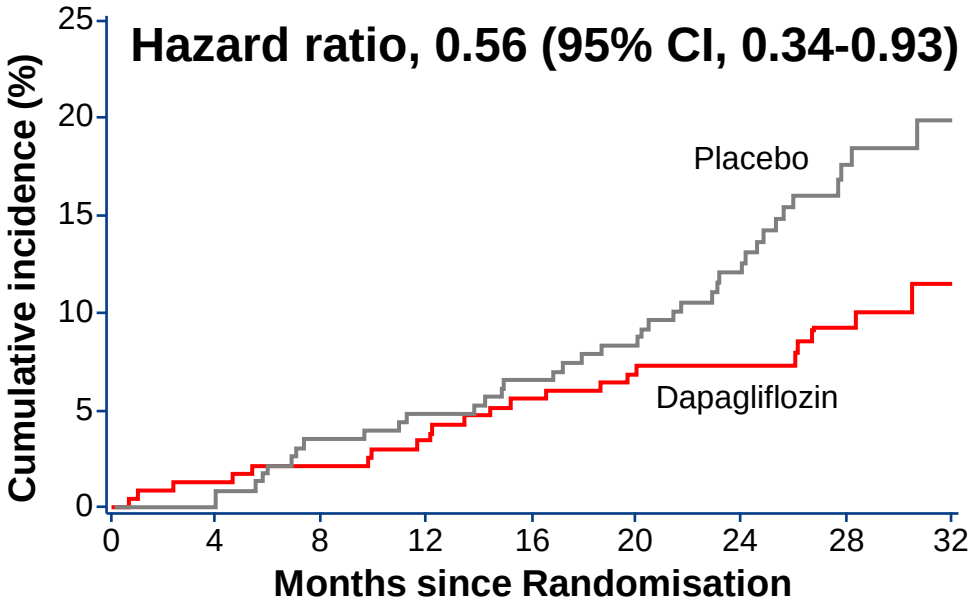


Jhund PS et al. *Circulation* 2020; McCausland FR et al. *JAMA Cardiol* 2022

DAPA-CKD: Consistent relative risk reduction, but greater absolute risk reduction, among patients with HF & CKD

All-cause Mortality

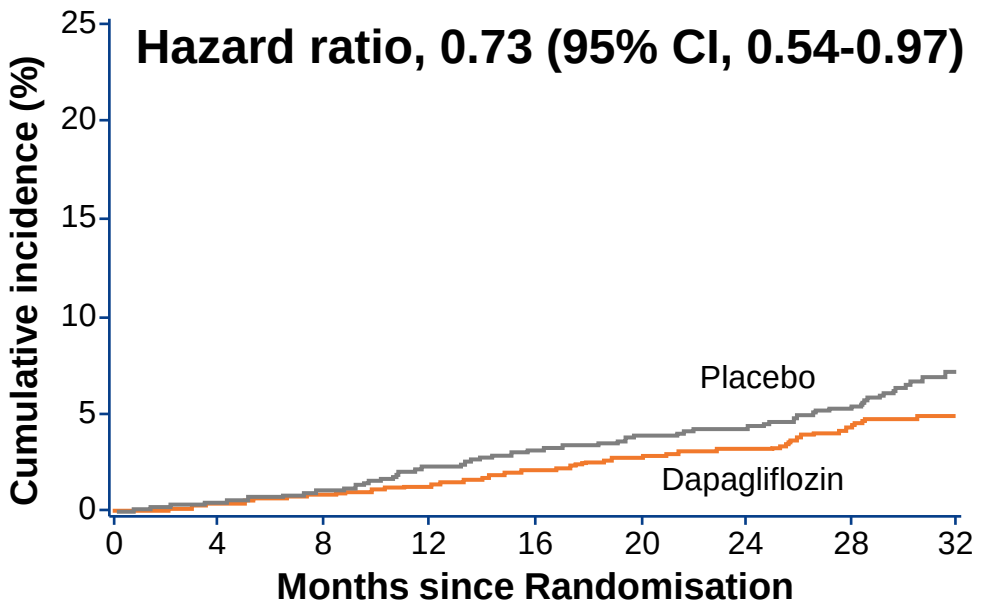
Patients with CKD and HF



RRR 44%

ARR 7.0%

Patients with CKD and no HF

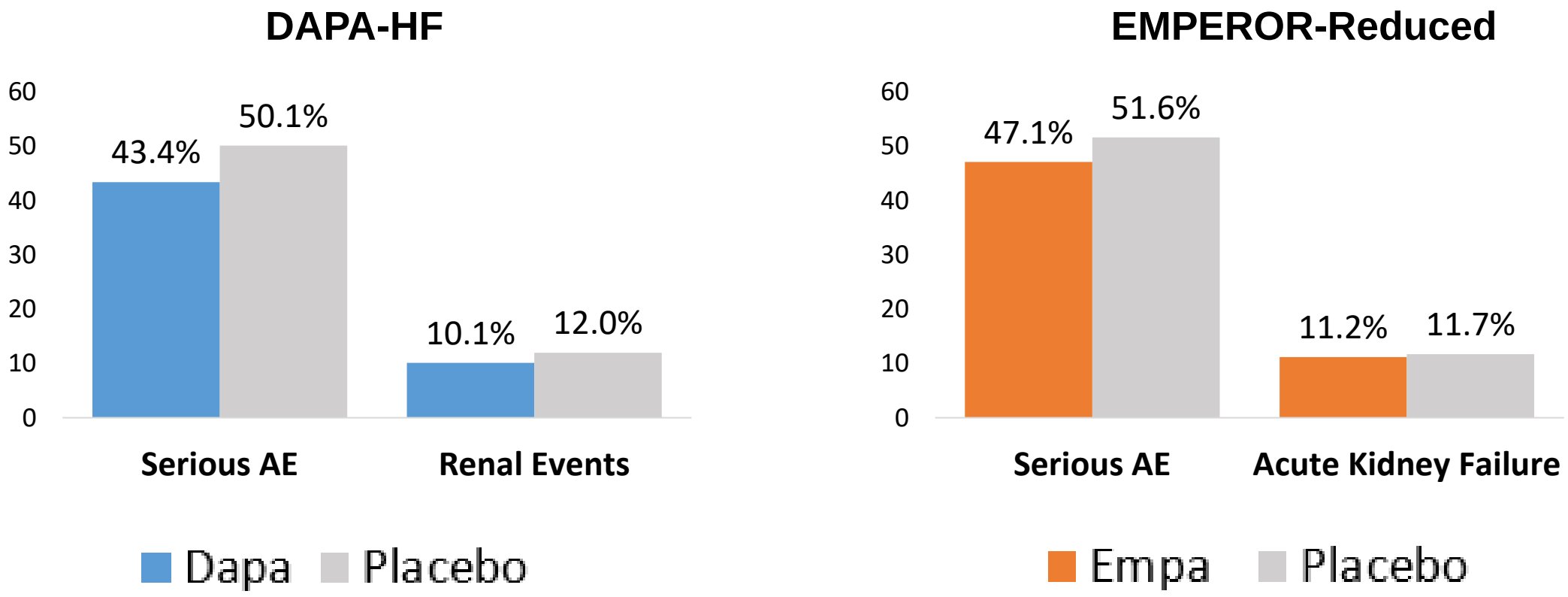


RRR 27%

ARR 1.5%

McMurray JJ, et al. *JACC Heart Fail 2021*

Safety of SGLT2i *in Patients with HFrEF and CKD*

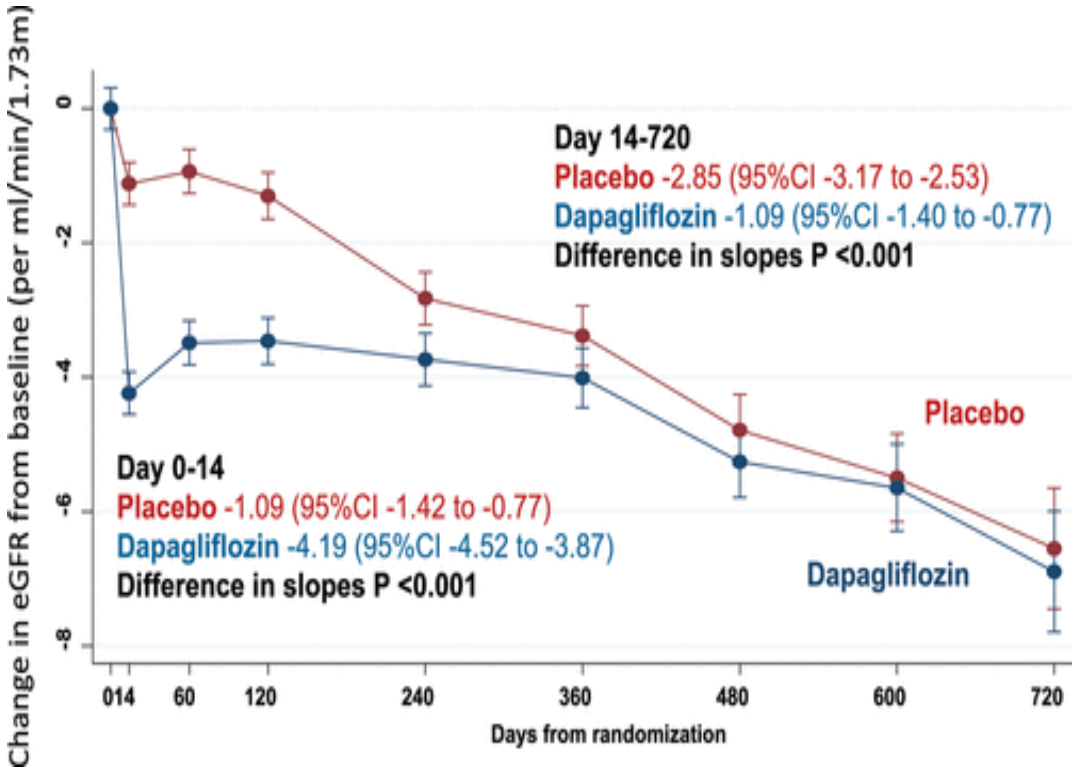


Numerically fewer adverse events with SGLT2i than placebo

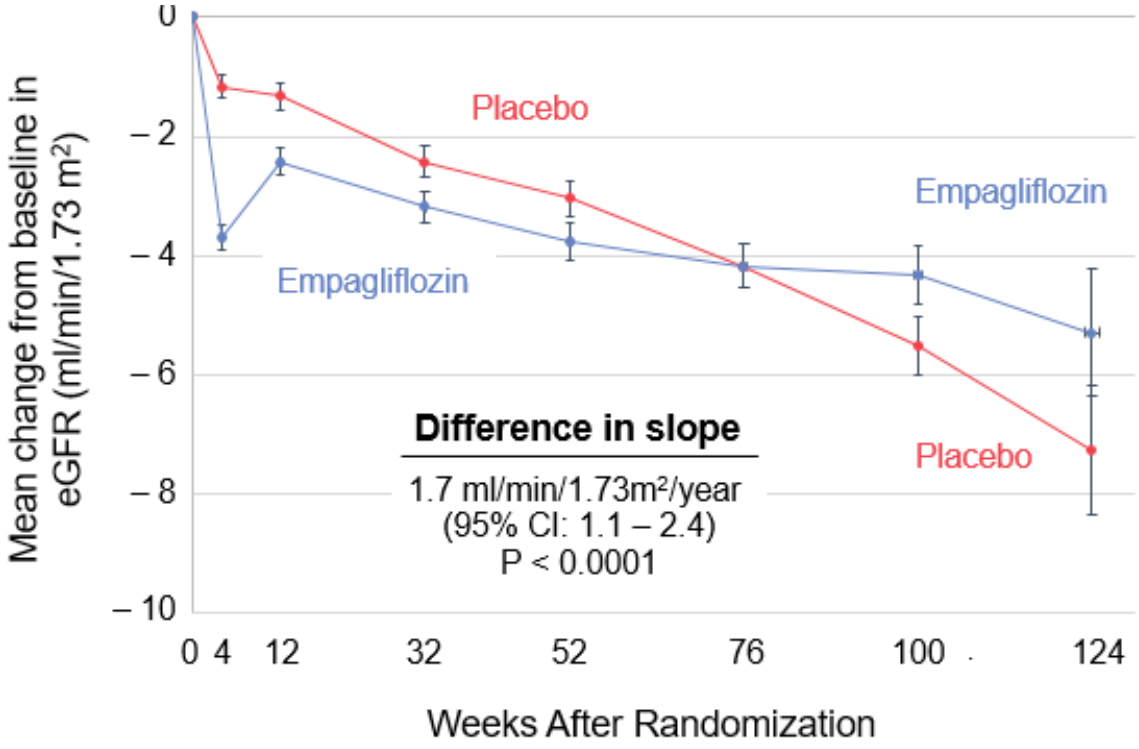
Jhund PS, et al. *Circulation* 2020; Zannad F, et al. Circulation 2021

SGLT2i Slows Progression of Kidney Disease Among Patients with HF

DAPA-HF



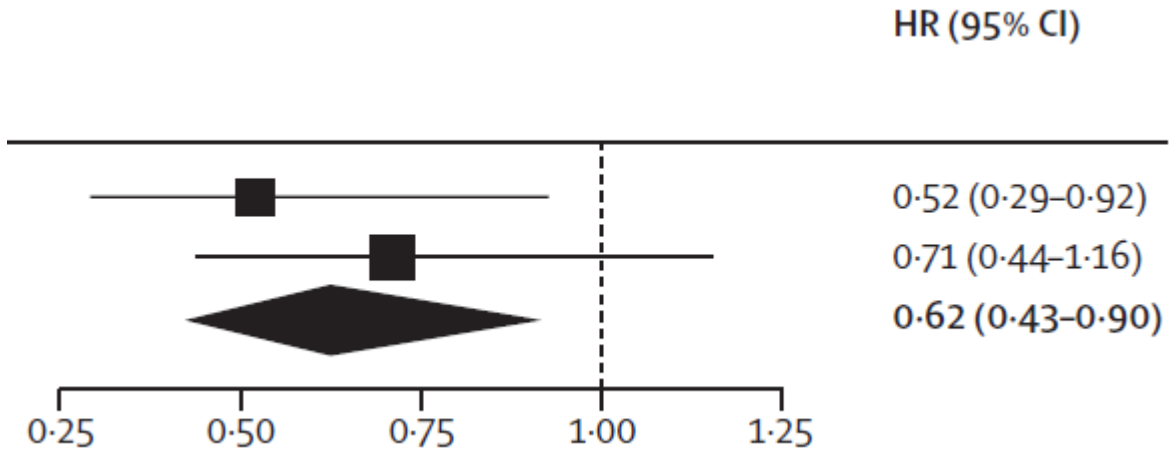
EMPEROR-Reduced



Jhund PS, et al. *Circulation* 2020; Zannad F, et al. Circulation 2021

SGLT2i Improve Kidney Outcomes Among Patients with HFrEF

Kidney Composite Outcome



↓ **38%** Kidney Events with SGLT2i

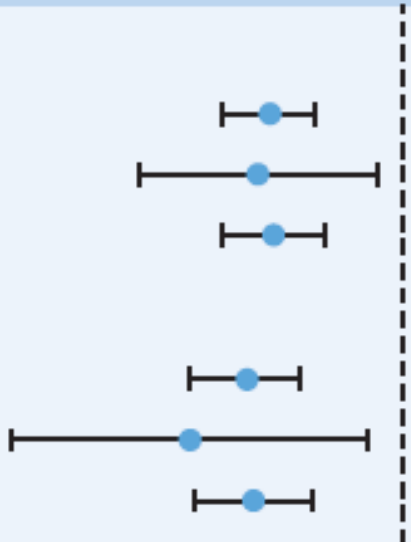
Statistically consistent treatment effect, irrespective of CKD

Zannad F, et al. Lancet 2020

DAPA-CKD: Dapagliflozin Improves Kidney Outcomes in Patients with CKD and Heart Failure

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

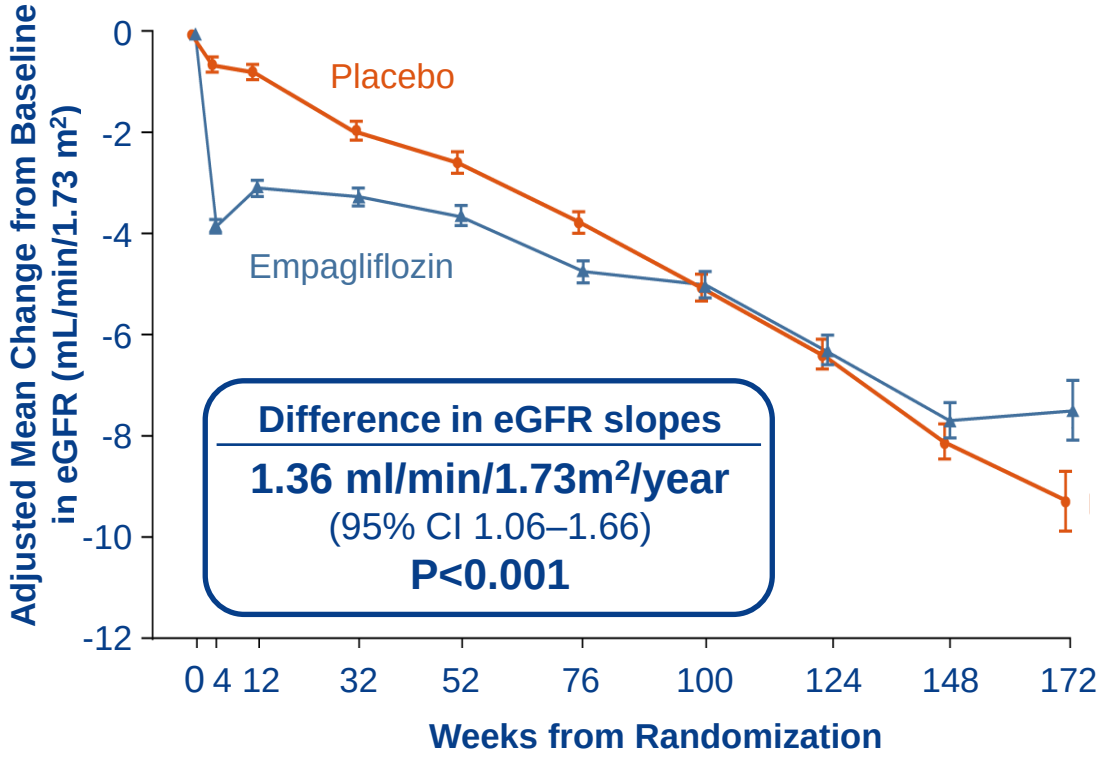
	Dapagliflozin Placebo *n/N*		Dapagliflozin Placebo *Events/100 Patient-Years*		HR (95% CI)	*P* Value for Interaction
Primary outcome: *eGFR decline ≥50%, ESKD, or kidney or CV death*						
Overall	197/2,152	312/2,152	4.6	7.5	0.61 (0.51-0.72)	
HF at baseline	31/235	51/233	6.5	11.0	0.58 (0.37-0.91)	0.59
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)	



McMurray JJV, et al. *JACC Heart Fail* 2021

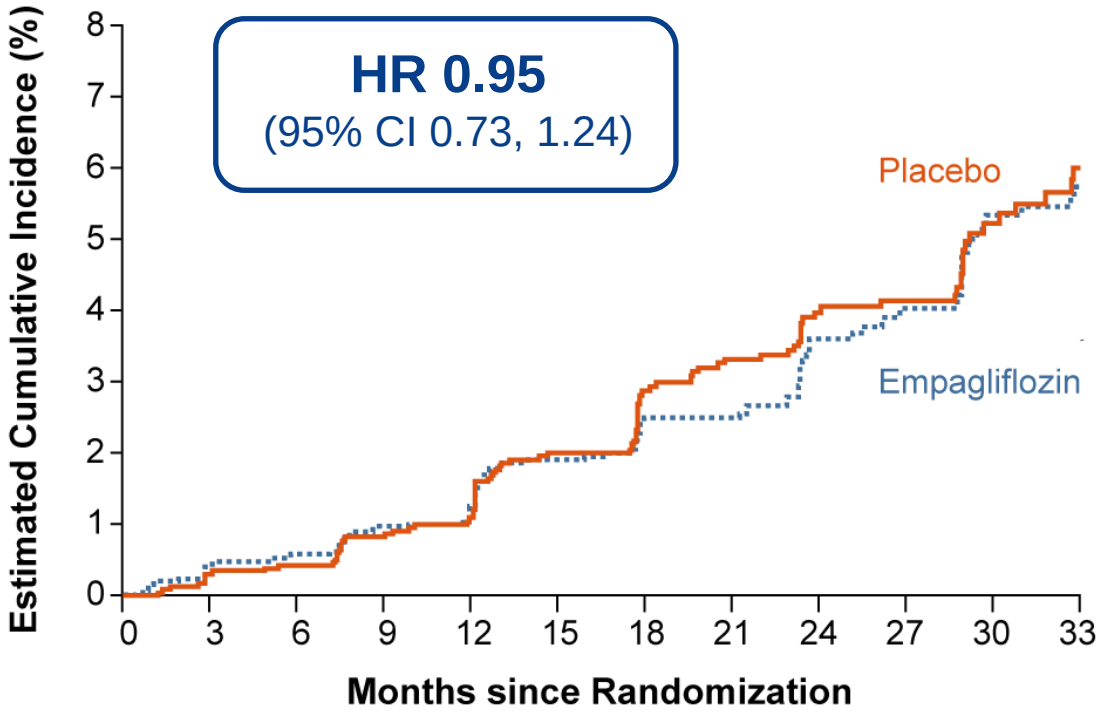
EMPEROR-Preserved: Discordance Between eGFR Slope and Renal Events

Estimated Glomerular Filtration Rate



Placebo	2911	2887	2759	2488	2333	1996	1443	1014	637	209
Empagliflozin	2925	2893	2785	2521	2343	1970	1431	1039	620	212

Major Renal Outcomes

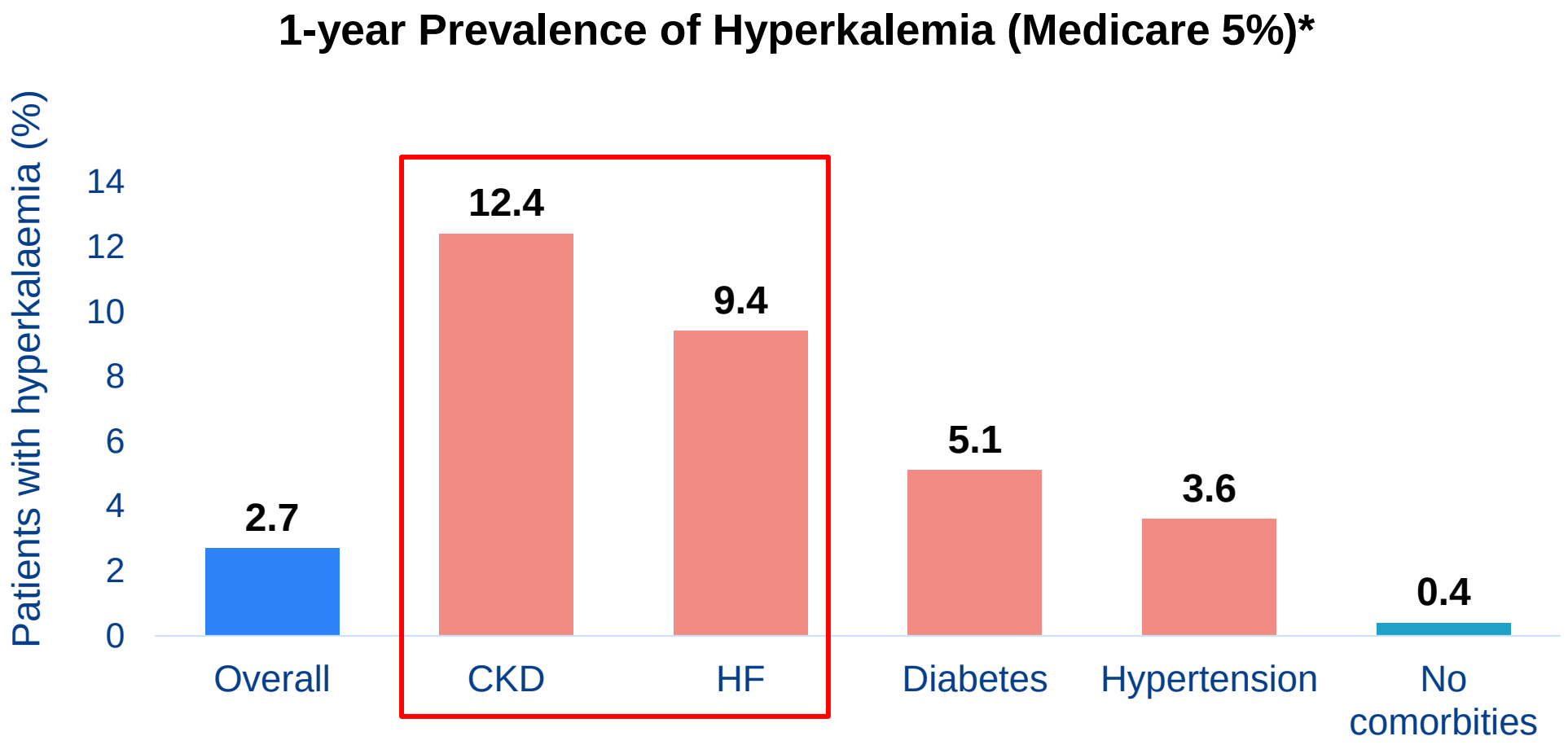


Placebo	2911	2749	2701	2558	2488	2003	1587	1442	1030	941	560	449
Empagliflozin	2997	2794	2739	2566	2502	2033	1614	1476	1062	940	544	448

Anker SD et al. *N Engl J Med 2021*

Approach to Hyperkalemia Among Patients with HF and CKD

Hyperkalemia is Common Among Patients with CKD and HF

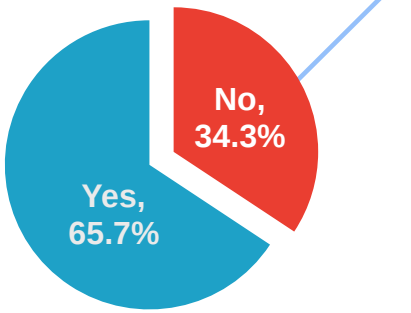


*Data reflect highest annual prevalence between 2010-2014

Mu F, et al. *Curr Med Res Opin* 2020

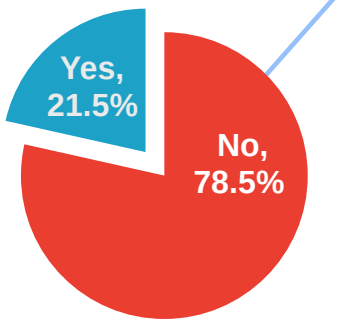
Hyperkalemia is a Common Cause of Intolerance to GDMT

ACEI



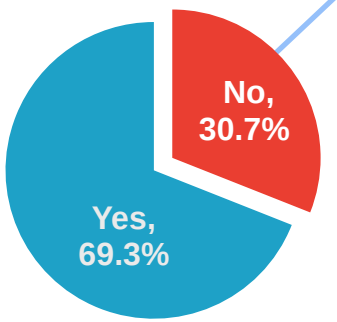
Contraindicated	**22.3%**
Not tolerated	**62.5%**
Reasons	
Cough	55.9%
Hypotension	22.5%
Worsening renal function	11.8%
Hyperkalemia	**3.9%**
Other reasons	**15.2%**

ARB



Not indicated	**79.1%**
Contraindicated	**6.6%**
Not tolerated	**6.4%**
Reasons	
Hypotension	48.1%
Worsening renal function	26.7%
Cough	7.2%
Hyperkalemia	**5.5%**
Other reasons	**7.9%**

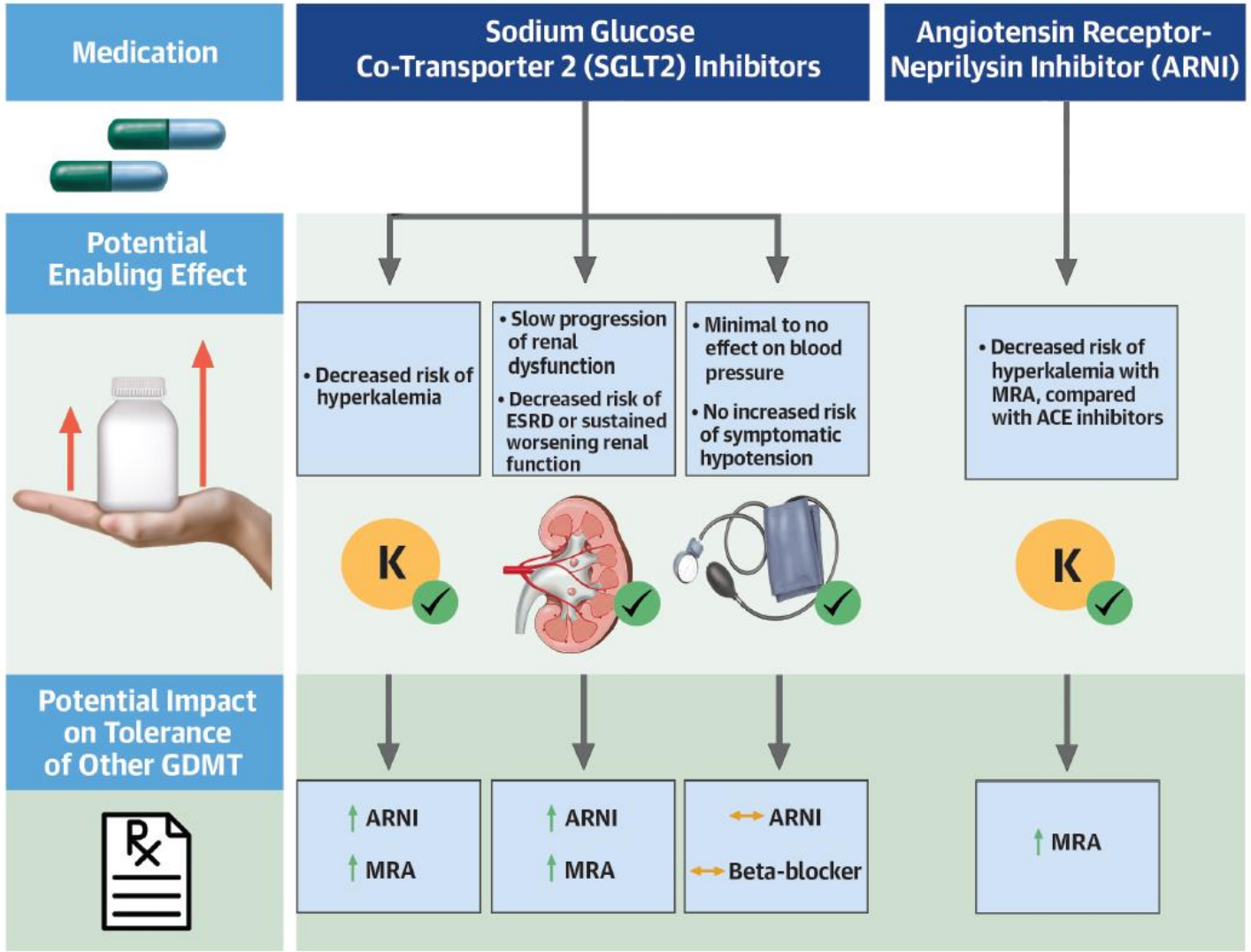
MRA



Not indicated	**61.8%**
Contraindicated	**18.9%**
Not tolerated	**14.9%**
Reasons	
Renal dysfunction	51.2%
Hyperkalemia	**31.4%**
Gynecomastia	15.3%
Other reasons	**4.5%**

Komajda M, et al. *Eur J Heart Fail* 2016

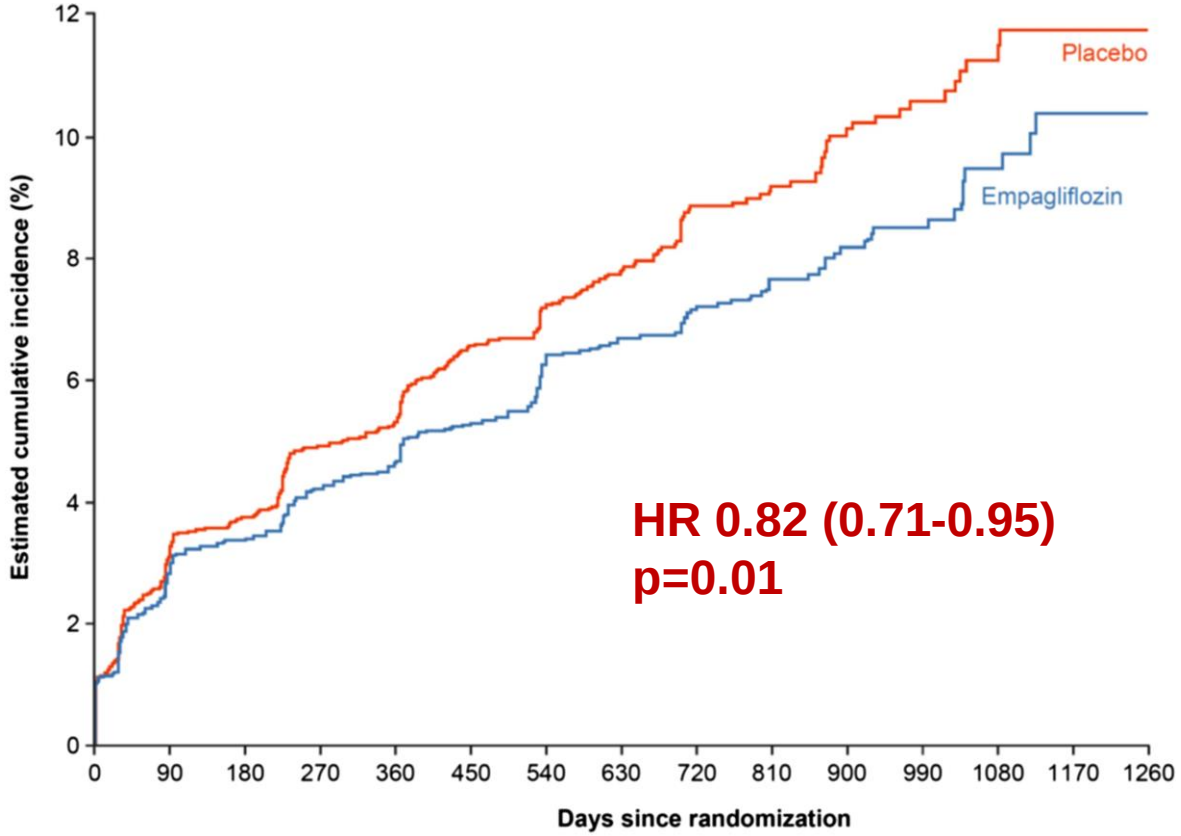
SGLT2i & ARNI as Tools to Prevent Hyperkalemia



Greene SJ, Khan MS. *JACC* 2021

SGLT2i Decrease Risk of Hyperkalemia

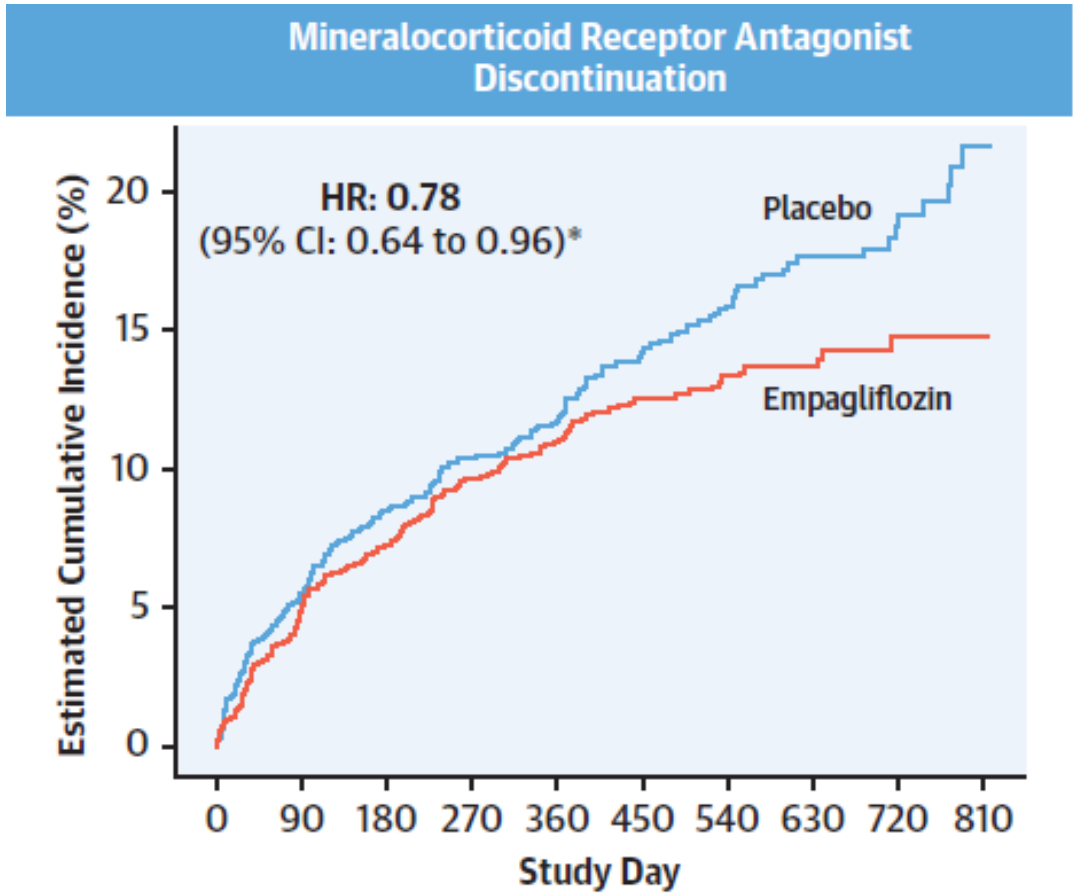
Investigator-reported hyperK or initiation of potassium binders



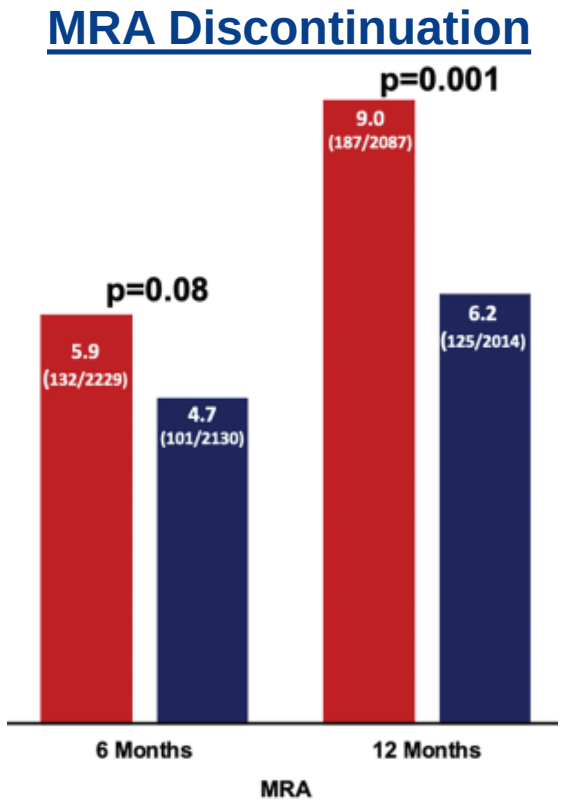
Patients on MRA – Risk of Moderate/Severe Hyperkalemia	
	K >6.0 mmol/L
DAPA-HF (dapagliflozin)	**0.50 (0.29 – 0.85)** **[61 events]**
EMPEROR-R (empagliflozin)	**0.64 (0.38 – 1.05)** **[64 events]**

Ferreira JP et al. *Eur Heart J* 2022; Shen L et al. *JACC HF* 2021; Ferreira JP et al. *JACC* 2021

Initiating SGLT2i or Switching to ARNI Reduces MRA Discontinuation



Ferreira JP et al. *JACC* 2021



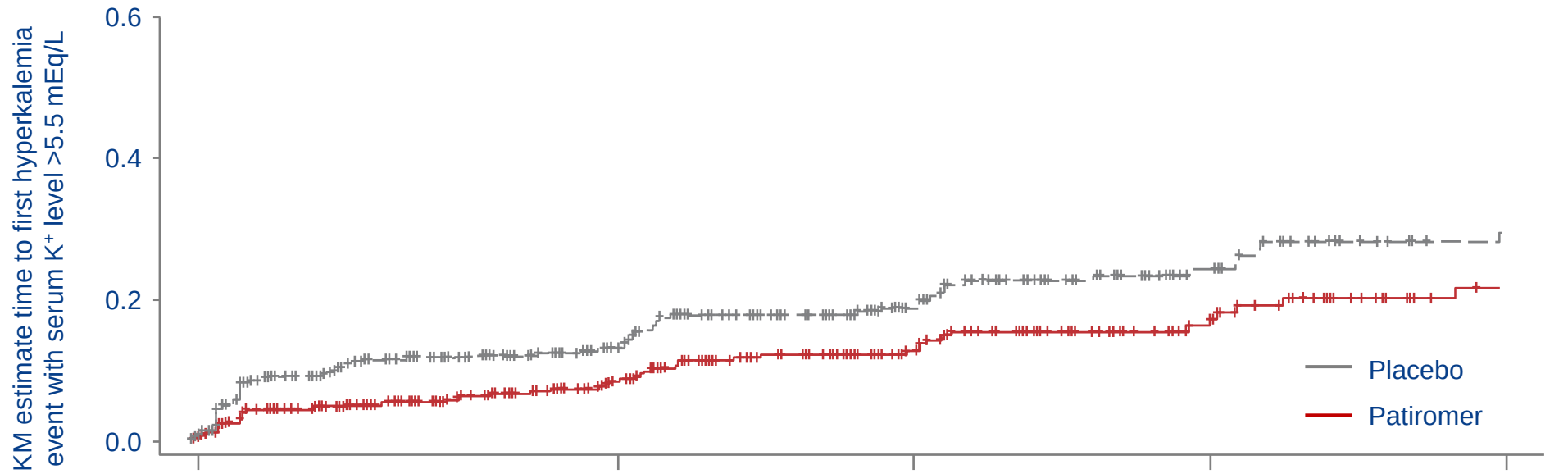
Bhatt AS et al. *Eur J Heart Fail* 2021

Delaying initiation of SGLT2i or delaying switch from ACEI to ARNI needlessly exposes patients to excess risk of hyperkalemia and MRA discontinuation

Potassium Binders

DIAMOND Trial:
Patiromer decreases risk of hyperkalemia >5.5 mEq/L

Patiromer (N=439) n (%)	Placebo (N=439) n (%)	HR (95% CI)	P value
61 (13.9)	85 (19.4)	0.63 (0.45, 0.87)	0.006



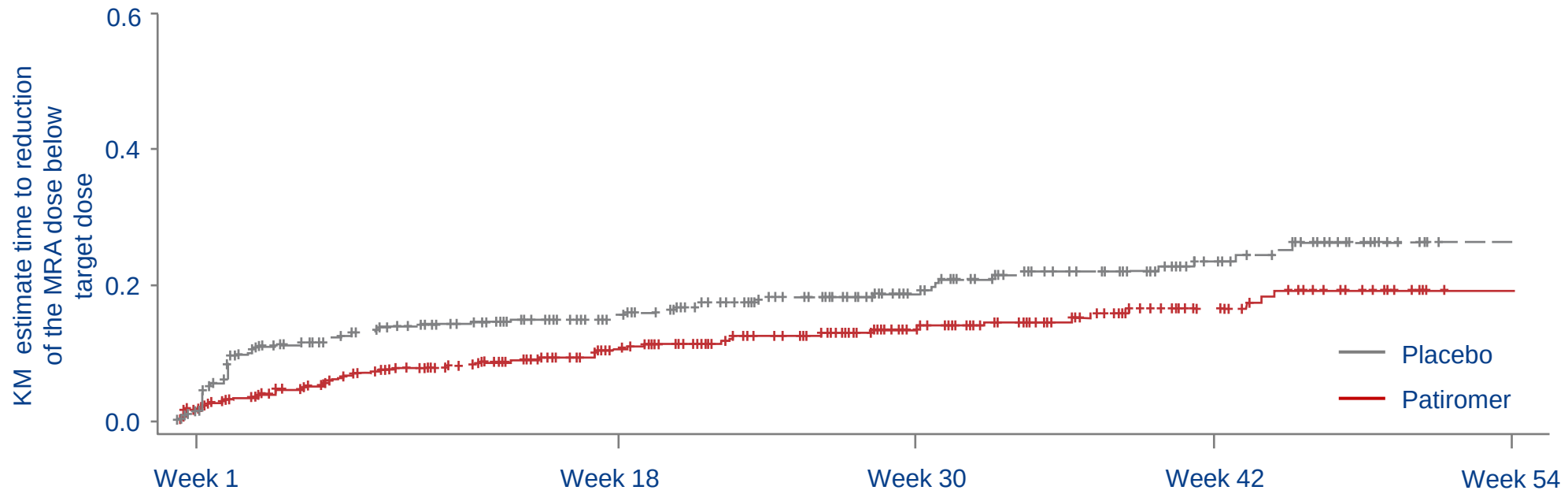
Number at Risk (Events)

Patiromer	414 (9)	249 (32)	156 (44)	89 (49)	52 (53)
Placebo	406 (18)	233 (55)	146 (69)	83 (76)	53 (81)

Butler J et al. *ACC Scientific Sessions 2022*

DIAMOND Trial:
Patiromer improves persistence of MRA target dosing

Patiromer (N=439) n (%)	Placebo (N=439) n (%)	HR (95% CI)	P value
61 (13.9)	83 (18.9)	0.62 (0.45, 0.87)	0.006



Number at Risk (Events)

Patiromer	417 (8)	256 (40)	169 (48)	98 (52)	62 (55)
Placebo	399 (18)	238 (61)	156 (70)	89 (77)	56 (80)

Target defined as 50 mg of spironolactone or eplerenone. Participants not on MRA target dose at baseline are censored on Day 1.

Butler J et al. *ACC Scientific Sessions 2022*

Summary – Intersection of CKD and HF

- HF and CKD share common mechanistic pathways and are highly overlapping in clinical practice.
- Worsening disease status of one condition forecasts heightened risk of exacerbating the other.
- Patients with both conditions face particularly high risk of death and adverse CV/kidney outcomes.
- Despite high risk, patients with HF and CKD are paradoxically less likely to be treated with traditional disease-modifying therapies.
- Common therapies have been shown to efficacious and safe in the management of HF and CKD.
  - ➢ Newer therapies include SGLT2i and novel potassium binders.