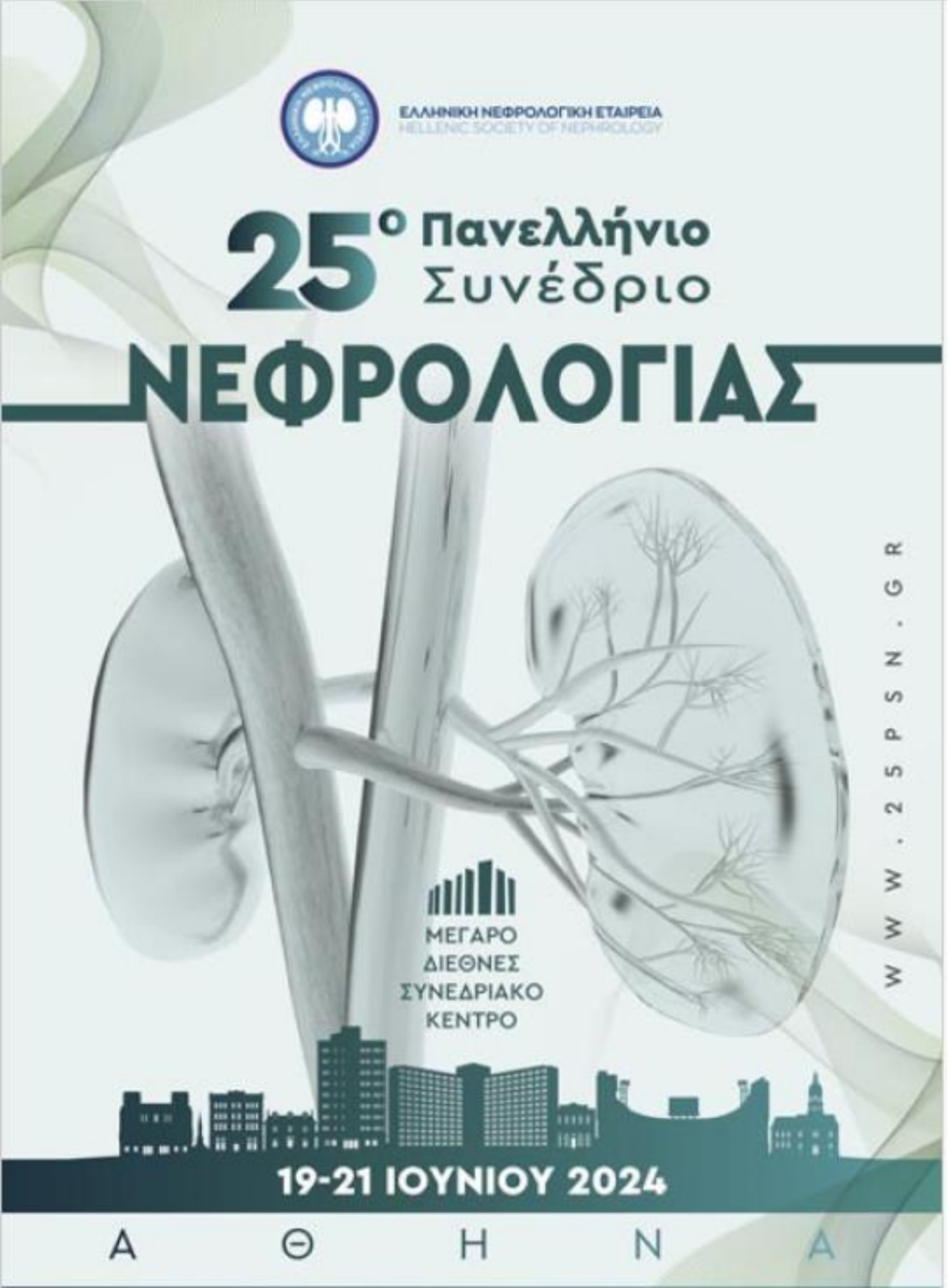

Παρασκευή, 21 Ιουνίου 2024

Αντιμετώπιση της καρδιακής ανεπάρκειας ανάλογα με το επίπεδο της νεφρικής λειτουργίας: ενδείξεις και αντενδείξεις παλιών και νέων φαρμάκων

Ανδρέας Ξανθόπουλος MD, PhD,
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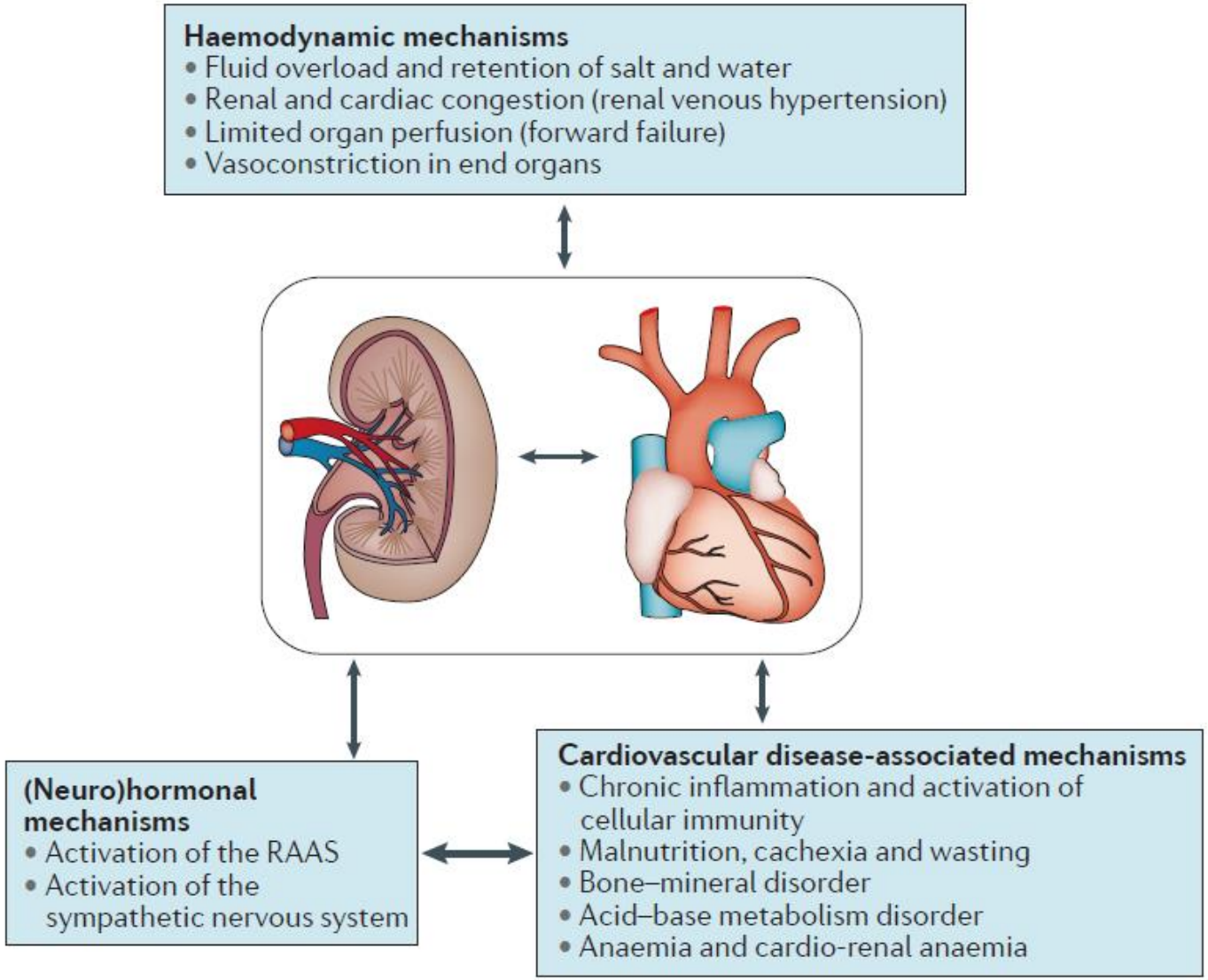
ΠΓΝ Λάρισας

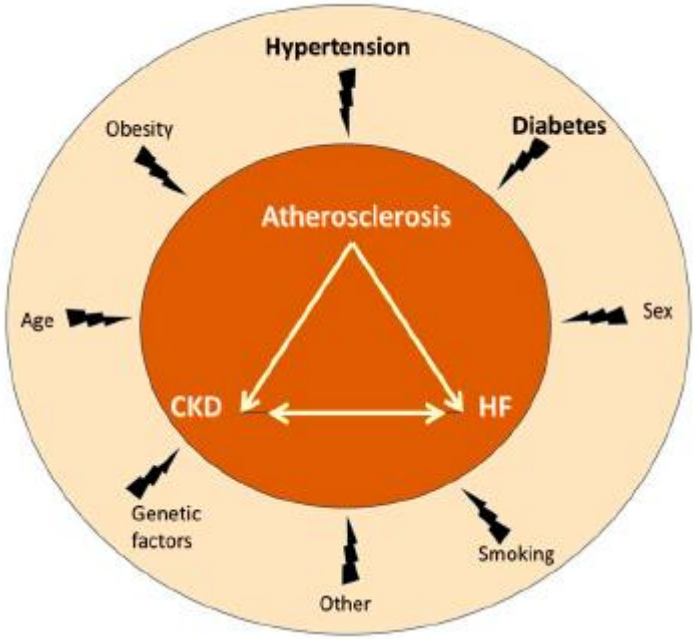
Disclosures

- Scholarship from the Hellenic Society of Cardiology, Athens, Greece
- Scholarship from the Kaufman Center of Heart Failure, Cleveland Clinic, Cleveland, USA
- Scholarship from Medtronic (Advanced Heart Failure Fellows Program), USA
- Honoraria from Novartis, Pfizer, WinMedica, Boehringer Ingelheim, AstraZeneca, Sanofi, Abbott, Merck



Schefold JC, et al. Nat Rev Nephrol. 2016;12(10):610-23

"Cardiovascular death triangle"



Xanthopoulos A, et al. J Clin Med. 2023;12(18):6105

Trajectories of Kidney Function in Heart Failure Over a 15-Year Follow-Up

Clinical Profiling and Mortality

Elisabet Zamora, MD, PhD,[a,b,c] Pau Codina, MD,[a,b] Alberto Aimo, MD, PhD,[d,e] Josep Lupón, MD, PhD,[a,b,c] Mar Domingo, MD, PhD,[a] Maribel Troya, MD, PhD,[f] Evelyn Santiago-Vacas, MD, PhD,[a,c] Germán Cediel, MD, PhD,[a,c] Andrea Borrellas, MD,[a] María Ruiz-Cueto, MD,[a] Gregorio A. Romero-González, MD,[f] Javier Santesmases, MD,[a,b] Julio Nuñez, MD, PhD,[c,g,h] Jordi Bover, MD, PhD,[f] Jordi Ara, MD, PhD,[f] Antoni Bayes-Genis, MD, PhD[a,b,c]

ABSTRACT

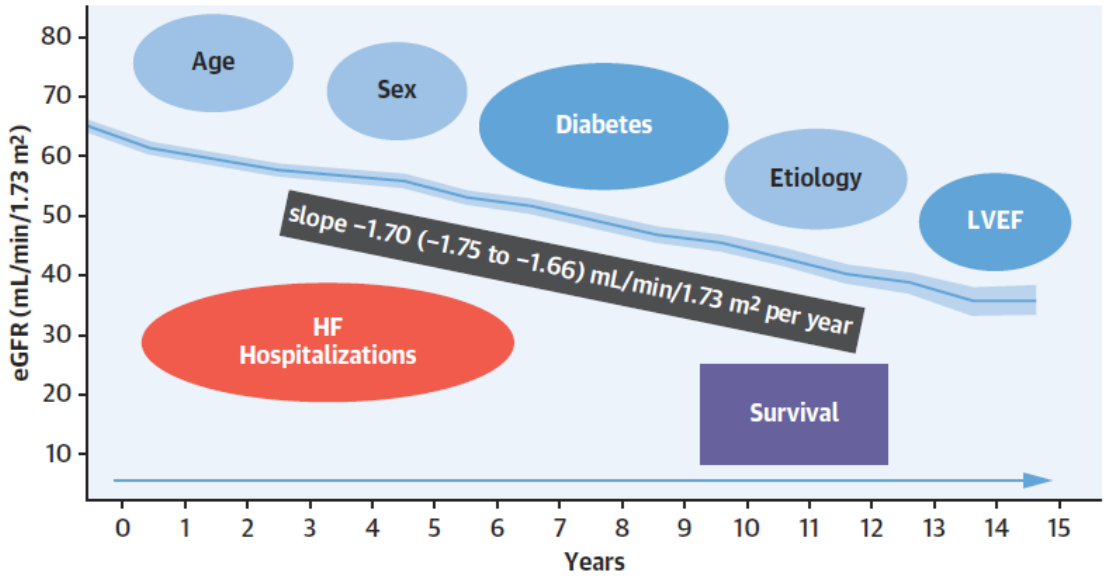
BACKGROUND Limited data are available on the long-term trajectory of estimated glomerular filtration rate (eGFR) in patients with chronic heart failure.

OBJECTIVES The authors evaluated eGFR dynamics using the 2009 Chronic Kidney Disease Epidemiology Collaboration equation and its prognostic significance in a real-world cohort over a 15-year follow-up.

METHODS A prospective observational registry of ambulatory heart failure outpatients was conducted, with regular eGFR assessments at baseline and on a 3-month schedule for ≤15 years. Urgent kidney function assessments were excluded. Locally weighted error sum of squares curves were plotted for predefined subgroups. Multivariable longitudinal Cox regression analyses were conducted to assess associations with all-cause and cardiovascular death.

RESULTS A total of 2,672 patients were enrolled consecutively between August 2001 and December 2021. The average age was 66.8 ± 12.6 years, and 69.8% were men. Among 40,970 creatinine measurements, 28,634 were used for eGFR analysis, averaging 10.7 ± 8.5 per patient. Over the study period, a significant decline in eGFR was observed in the entire cohort, with a slope of −1.70 mL/min/1.73 m^2 per year (95% CI: −1.75 to −1.66 mL/min/1.73 m^2 per year). Older patients, those with diabetes, a preserved ejection fraction, a higher baseline eGFR, elevated hospitalization rates, and those who died during follow-up experienced more pronounced decreases in the eGFR. Moreover, the decrease in kidney function correlated independently with all-cause mortality and cardiovascular death.

CONCLUSIONS These findings highlight the sustained decline in eGFR over 15 years in patients with heart failure, with variations based on clinical characteristics, and emphasize the importance of regular eGFR monitoring in this population.
(J Am Coll Cardiol HF 2024;12:849-859)



Zamora E, et al. J Am Coll Cardiol HF. 2024;12(5):849–859.

ESC European Society of Cardiology

European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3210

RESEARCH ARTICLE

Identification and outcomes of KDIGO-defined chronic kidney disease in 1.4 million U.S. Veterans with heart failure

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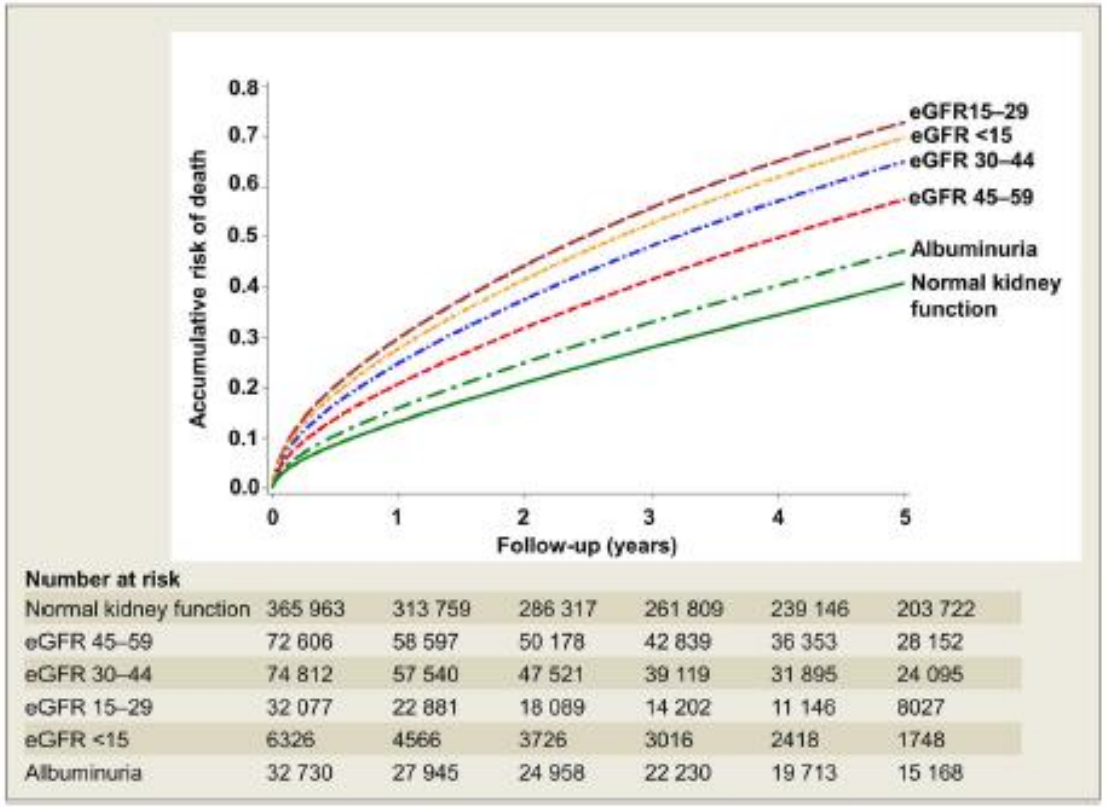
Aims According to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline, the definition of chronic kidney disease (CKD) requires the presence of abnormal kidney structure or function for >3 months with implications for health. CKD in patients with heart failure (HF) has not been defined using this definition, and less is known about the true health implications of CKD in these patients. The objective of the current study was to identify patients with HF who met KDIGO criteria for CKD and examine their outcomes.

Methods and results Of the 1 419 729 Veterans with HF not receiving kidney replacement therapy, 828 744 had data on ≥2 ambulatory serum creatinine >90 days apart. CKD was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 (n = 185 821) or urinary albumin-to-creatinine ratio (uACR) >30 mg/g (n = 32 730) present twice >3 months apart. Normal kidney function (NKF) was defined as eGFR ≥60 ml/min/1.73 m^2, present for >3 months, without any uACR >30 mg/g (n = 365 963). Patients with eGFR <60 ml/min/1.73 m^2 were categorized into four stages: 45–59 (n = 72 606), 30–44 (n = 74 812), 15–29 (n = 32 077), and <15 (n = 6326) ml/min/1.73 m^2. Five-year all-cause mortality occurred in 40.4%, 57.8%, 65.6%, 73.3%, 69.7%, and 47.5% of patients with NKF, four eGFR stages, and uACR >30 mg/g (albuminuria), respectively. Compared with NKF, hazard ratios (HR) (95% confidence intervals [CI]) for all-cause mortality associated with the four eGFR stages and albuminuria were 1.63 (1.62–1.65), 2.00 (1.98–2.02), 2.49 (2.45–2.52), 2.28 (2.21–2.35), and 1.22 (1.20–1.24), respectively. Respective age-adjusted HRs (95% CIs) were 1.13 (1.12–1.14), 1.36 (1.34–1.37), 1.87 (1.84–1.89), 2.24 (2.18–2.31) and 1.19 (1.17–1.21), and multivariable-adjusted HRs (95% CIs) were 1.11 (1.10–1.12), 1.24 (1.22–1.25), 1.46 (1.43–1.48), 1.42 (1.38–1.47), and 1.13 (1.11–1.16). Similar patterns were observed for associations with hospitalizations.

Conclusion Data needed to define CKD using KDIGO criteria were available in six out of ten patients, and CKD could be defined in seven out of ten patients with data. HF patients with KDIGO-defined CKD had higher risks for poor outcomes, most of which was not explained by abnormal kidney structure or function. Future studies need to examine whether CKD defined using a single eGFR is characteristically and prognostically different from CKD defined using KDIGO criteria.

37% CKD !!!!



Number at risk

Normal kidney function	365 963	313 759	286 317	261 809	239 146	203 722
eGFR 45–59	72 606	58 597	50 178	42 839	36 353	28 152
eGFR 30–44	74 812	57 540	47 521	39 119	31 895	24 095
eGFR 15–29	32 077	22 881	18 089	14 202	11 146	8027
eGFR <15	6326	4566	3726	3016	2418	1748
Albuminuria	32 730	27 945	24 958	22 230	19 713	15 168

Patel SS, et al. Eur J Heart Fail. 2024 May 3. Online ahead of print.

ESC HEART FAILURE
ESC Heart Failure (2024)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14892

ORIGINAL ARTICLE

Renal dysfunction is a time-varying risk predictor of sudden cardiac death in heart failure

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[1]*Department of Cardiology, Fujita Health University Bantane Hospital, Nagoya, Japan; and* [2]*Department of Cardiology, Fujita Health University School of Medicine, Toyoake, Japan*

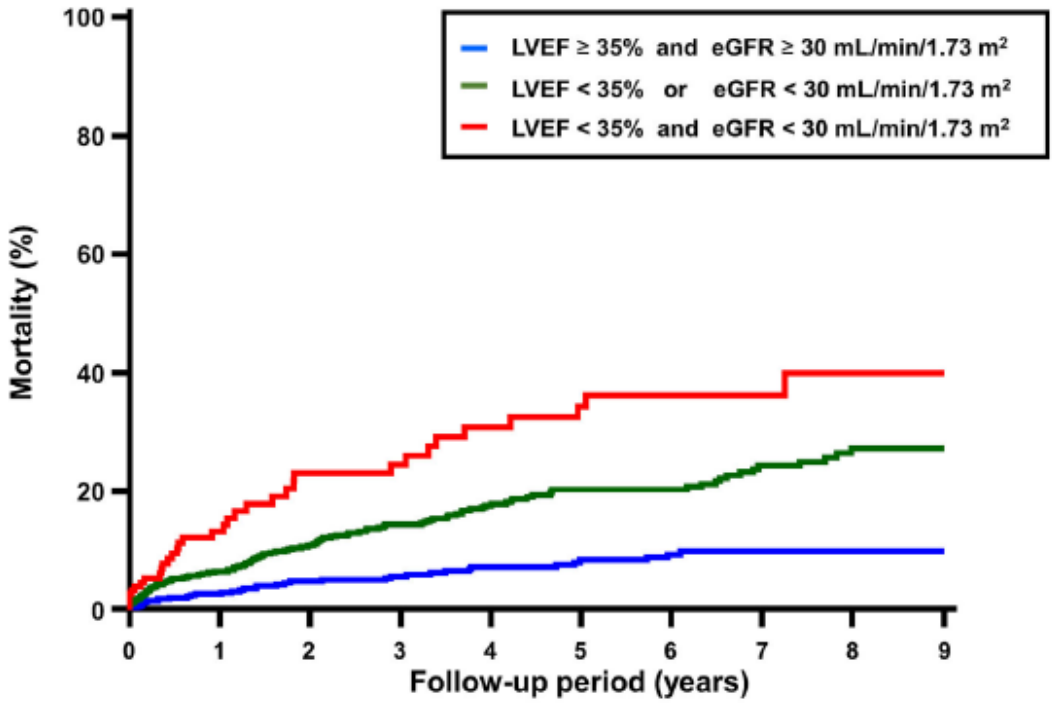
Abstract

Aims Sudden cardiac death (SCD) is a common mode of death in patients with congestive heart failure (CHF). Implantable cardioverter defibrillator (ICD) implantation is established treatment for SCD prevention, but current eligibility criteria based on left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) functional class may be due for reconsideration given the increasing effectiveness of pharmacological therapy. We sought to reconsider the risk stratification of SCD in patients with symptomatic CHF.

Methods In total, 1,676 consecutive patients (74 ± 13 years old; 56% male) with NYHA class II or III CHF between 2008 and 2015 were enrolled for this prospective study. The endpoint was SCD.

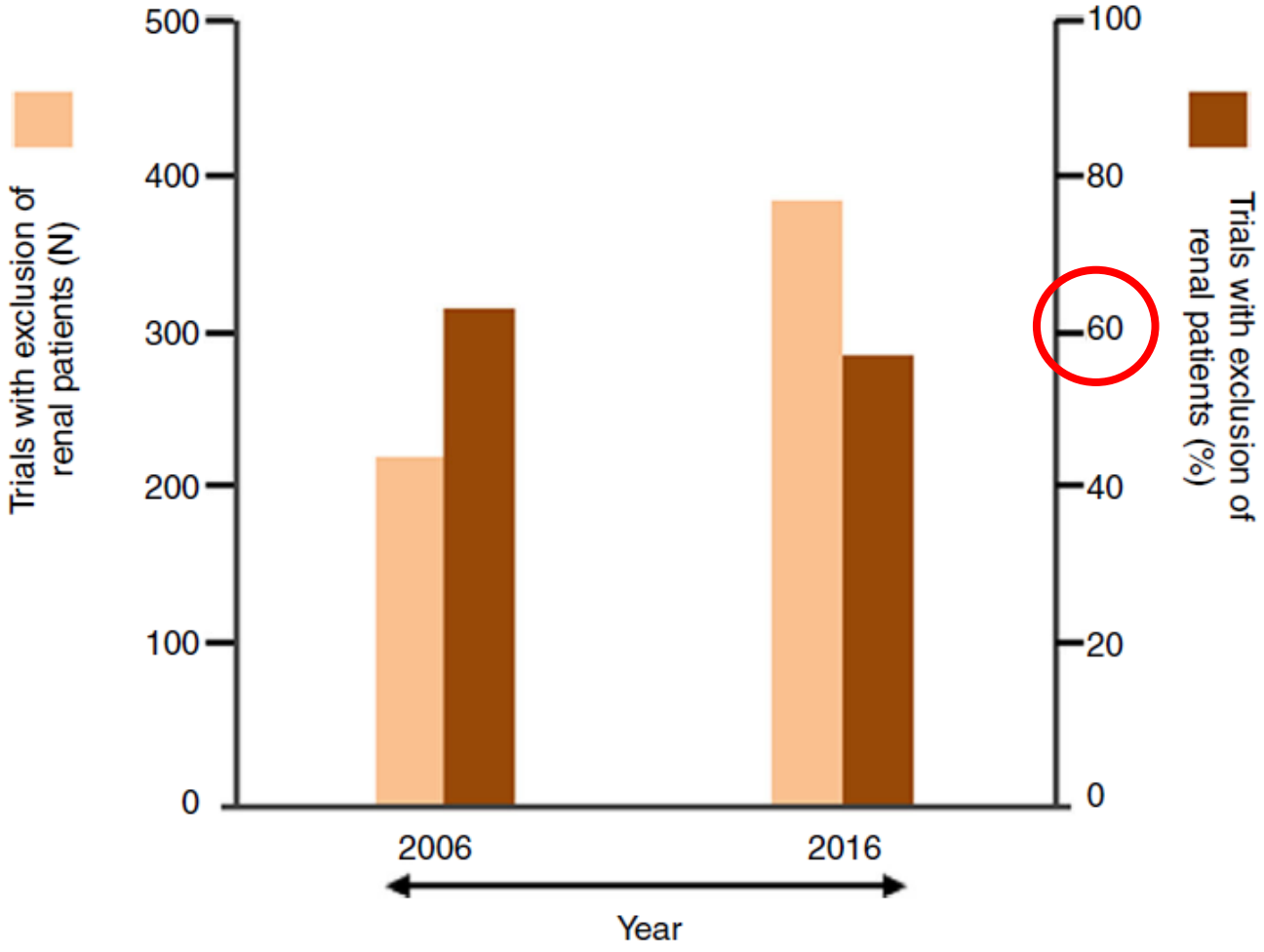
Results During a median (interquartile range) follow-up period of 25 (4–70) months, 198 (11.8%) patients suffered SCD. Of those events, 23% occurred within 3 months of discharge. In the adjusted analyses, estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2 [hazard ratio (HR) 1.73, 95% confidence interval (CI) 1.11–2.70, $P = 0.01$] and LVEF $\leq 35\%$ (HR 2.31, 95% CI 1.47–3.66, $P < 0.01$) were independent risk predictors of SCD. Addition of eGFR to LVEF significantly improved prediction of SCD in the *C*-index ($P = 0.04$), and in two metrics, net reclassification improvement ($P = 0.01$) and integrated discrimination improvement ($P = 0.03$). The predictive power of eGFR declined time-dependently over 2 years.

Conclusions The addition of eGFR to current eligibility criteria may be useful for risk assessment of SCD, although its predictive power wanes over time. Roughly a quarter of the SCD occurred within 3 months after discharge in patients with CHF.



Sobue Y, et al. ESC Heart Fail. 2024 June 10. Online ahead of print.

Cardiovascular trials exclude renal patients



Zannad F, Rossignol P. Circulation. 2017;135:1769–71
Romero-González R, et al. Nefrologia. 2020;40(3):223–236

β-blocker

AJN
American Journal
of Nephrology

In-Depth Topic Review

Am J Nephrol
DOI: 10.1159/000534318

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Published online: October 3, 2023

Autonomic Nervous System Dysfunction in Peritoneal Dialysis Patients: An Underrecognized Cardiovascular Risk Factor?

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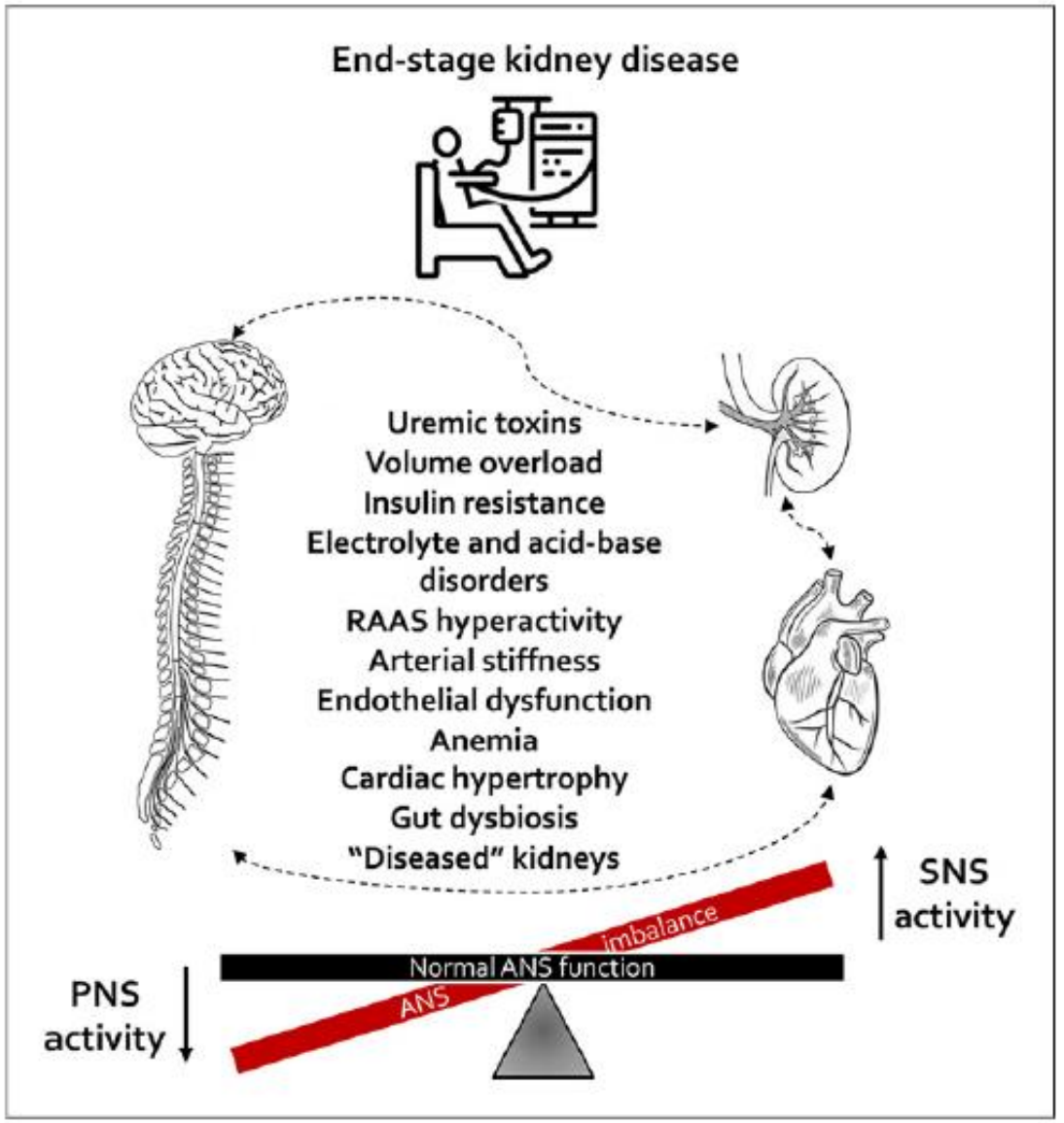
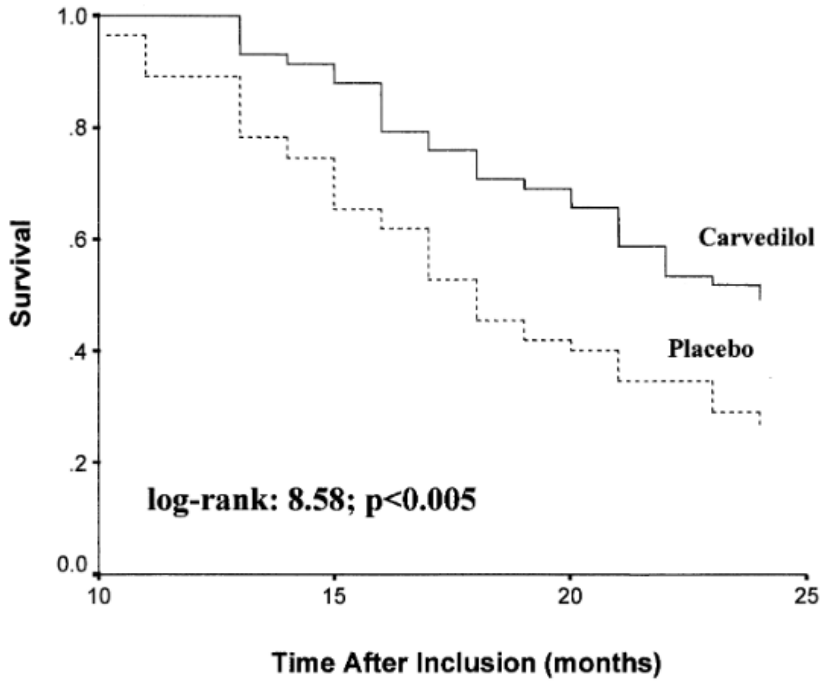


Carvedilol Increases Two-Year Survival in Dialysis Patients With Dilated Cardiomyopathy

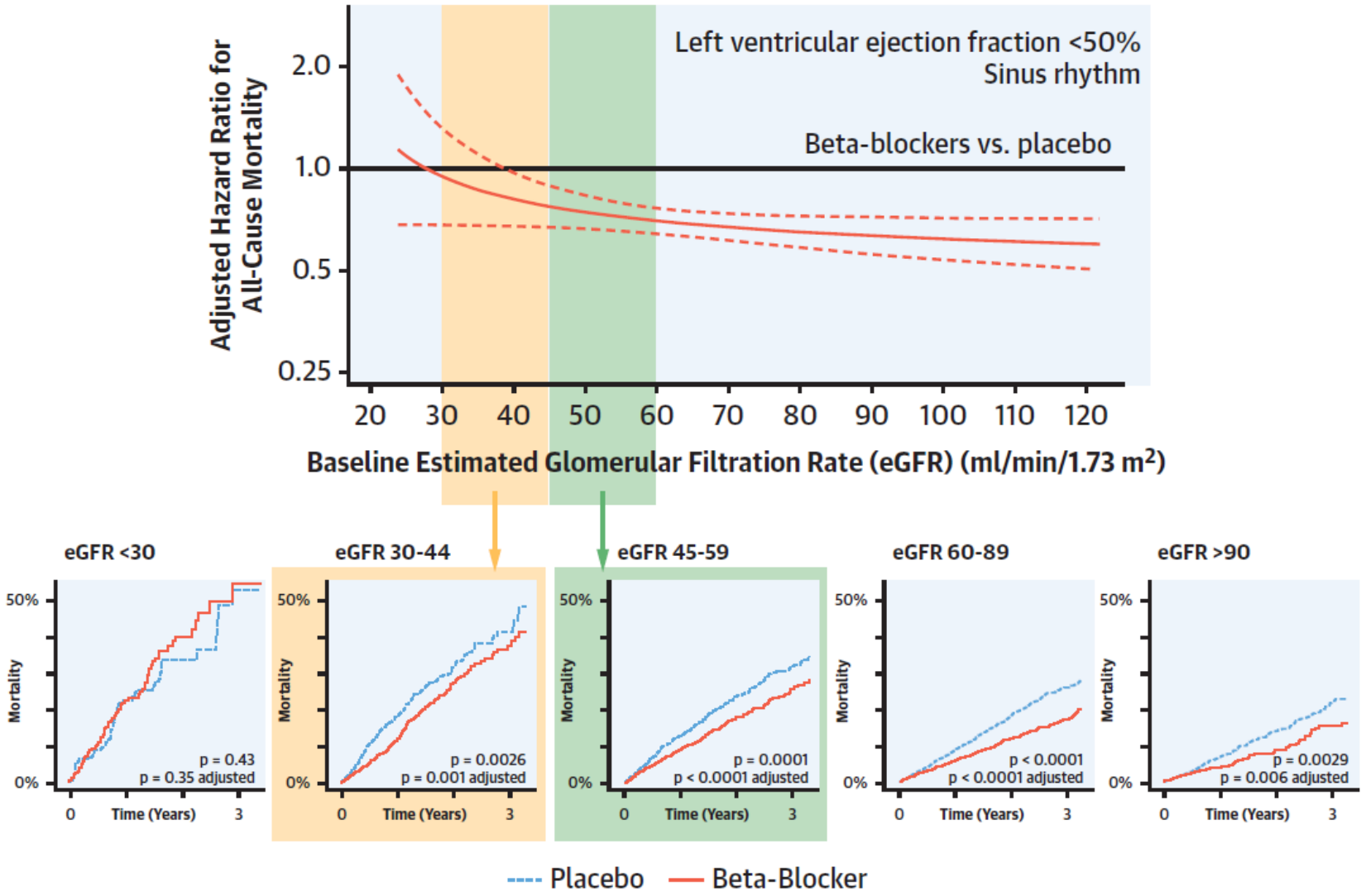
- A total of 114 dialysis patients with dilated cardiomyopathy were randomized to receive either carvedilol or placebo in addition to standard therapy.
- At two years, 51.7% of the patients died in the carvedilol group, compared with 73.2% in the placebo group ($p<0.01$). Furthermore, there were significantly fewer cardiovascular deaths (29.3%) and hospital admissions (34.5%) among patients receiving carvedilol than among those receiving a placebo (67.9% and 58.9%, respectively; $p<0.00001$).
- Carvedilol reduced morbidity and mortality in dialysis patients with dilated cardiomyopathy.



Cice G, et al. J Am Coll Cardiol. 2003;41:1438-1444

Analysis of 16,740 individual patients with left ventricular ejection fraction <50% from 10 double-blind, placebo-controlled trials was performed.

CENTRAL ILLUSTRATION Efficacy of Beta-Blockers According to Baseline Renal Function in Sinus Rhythm



Kotecha D, et al. J Am Coll Cardiol. 2019;74(23):2893-2904

Circulation: Heart Failure

ORIGINAL ARTICLE

Association Between β-Blocker Use and Mortality/Morbidity in Patients With Heart Failure With Reduced, Midrange, and Preserved Ejection Fraction and Advanced Chronic Kidney Disease

Edouard L. Fu, BSc; Alicia Uijl, PhD; Friedo W. Dekker, PhD; Lars H. Lund, MD, PhD; Gianluigi Savarese, MD, PhD; Juan J. Carrero, PharmD, PhD

BACKGROUND: It is unknown if β-blockers reduce mortality/morbidity in patients with heart failure (HF) and advanced chronic kidney disease (CKD), a population underrepresented in HF trials.

METHODS: Observational cohort of HF patients with advanced CKD (estimated glomerular filtration rate <30 mL/min per 1.73 m^2) from the Swedish Heart Failure Registry between 2001 and 2016. We first explored associations between β-blocker use, 5-year death, and the composite of cardiovascular death/HF hospitalization among 3775 patients with HF with reduced ejection fraction (HFrEF) and advanced CKD. We compared observed hazards with those from a control cohort of 15 346 patients with HFrEF and moderate CKD (estimated glomerular filtration rate <60–30 mL/min per 1.73 m^2), for whom β-blocker trials demonstrate benefit. Second, we explored outcomes associated to β-blocker among advanced CKD participants with preserved (HFpEF; N=2009) and midrange ejection fraction (HFmrEF; N=1514).

RESULTS: During a median follow-up of 1.3 years, 2012 patients had a subsequent HF hospitalization, and 2849 died in the HFrEF cohort, of which 2016 died due to cardiovascular causes. Among patients with HFrEF, β-blocker use was associated with lower risk of death (adjusted hazard ratio 0.85 [95% CI, 0.75–0.96]) and cardiovascular mortality/HF hospitalization (0.87 [0.77–0.98]) compared with nonuse. The magnitude of the associations was similar to that observed for HFrEF patients with moderate CKD. Conversely, no significant association was observed for β-blocker users in advanced CKD with HFpEF (death: 0.88 [0.77–1.02], cardiovascular mortality/HF hospitalization: 1.05 [0.90–1.23]) or HFmrEF (death: 0.95 [0.79–1.14], cardiovascular mortality/HF hospitalization: 1.09 [0.90–1.31]).

CONCLUSIONS: In HFrEF patients with advanced CKD, the use of β-blockers was associated with lower morbidity and mortality. Although inconclusive due to limited power, these benefits were not observed in similar patients with HFpEF or HFmrEF.

ORIGINAL ARTICLE

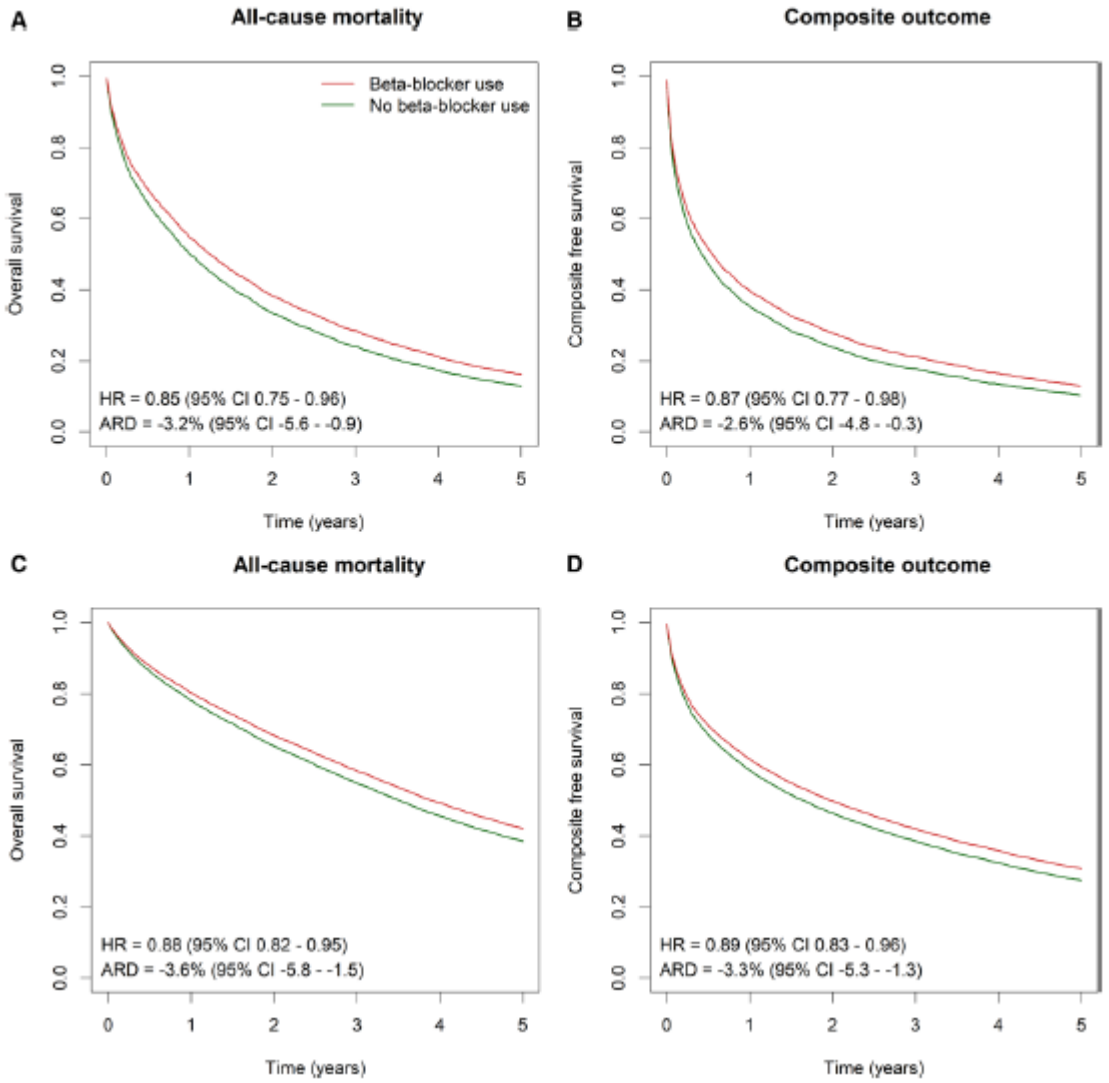
Association Between β-Blocker Use and Mortality/Morbidity in Patients With Heart Failure With Reduced, Midrange, and Preserved Ejection Fraction and Advanced Chronic Kidney Disease

Edouard L. Fu, BSc; Alicia Uijl, PhD; Friedo W. Dekker, PhD; Lars H. Lund, MD, PhD; Gianluigi Savarese, MD, PhD; Juan J. Carrero, PharmD, PhD

A and B: Patients with HF with reduced ejection fraction (HFrEF) and advanced chronic kidney disease (CKD).

C and D: Patients with HFrEF and moderate CKD (positive control analysis).
ARD=absolute risk difference at 5 y; and HR=hazard ratio

Composite outcome: cardiovascular mortality or heart failure hospitalization.



Fu EL, et al. Circ Heart Fail. 2020;13(11):e007180

Beta Blocker

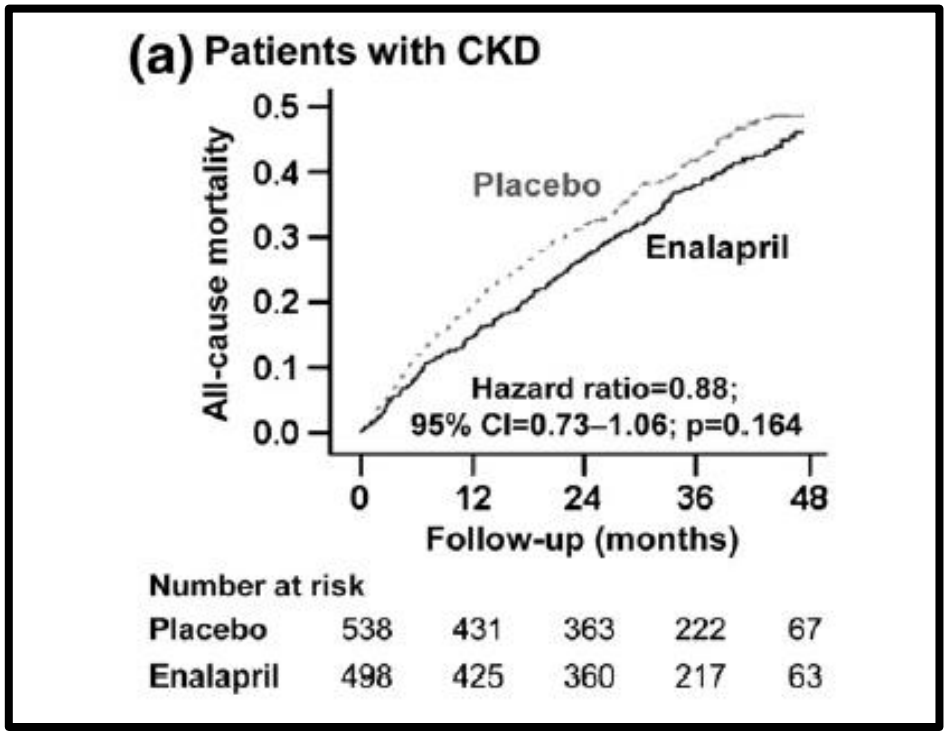
Findings in CKD Subgroups		
	All Cause Mortality	**CV Death / HF Hospitalization**
Overall	10-75 % RRR	8-24% RRR
CKD Stages (eGFR in mL/min/1.73m²)		
CKD stage 1 (> 90)	12-53% RRR[62]	7-22% RRR[63,61,64,65]
CKD stage 2 (60-89)	24-43% RRR[62]	
CKD stage 3A (45-59)	14-38% RRR[62]	19-25% RRR[63,61,64]
CKD stage 3B (30-44)	13-42% RRR[62]	
CKD stage 4 (15-29)	-91 – 13% RRR, CIs cross 1[62]	No information in HFREF
CKD stage 5 (<15/Dialysis)	**No information in HFREF**	
Effect on Renal Function		
Beta-Blockers modulate sympathetic nervous system activity and could impact GFR via this pathway, however in large studies no direct effect on renal function was observed[62]		
No acute change in eGFR after initiation [62]	Long term slope in eGFR similar with Beta-blocker and placebo[62]	In CKD stage 3-4 long term slope in eGFR steeper with Beta-blocker (possibly due to survival effect)

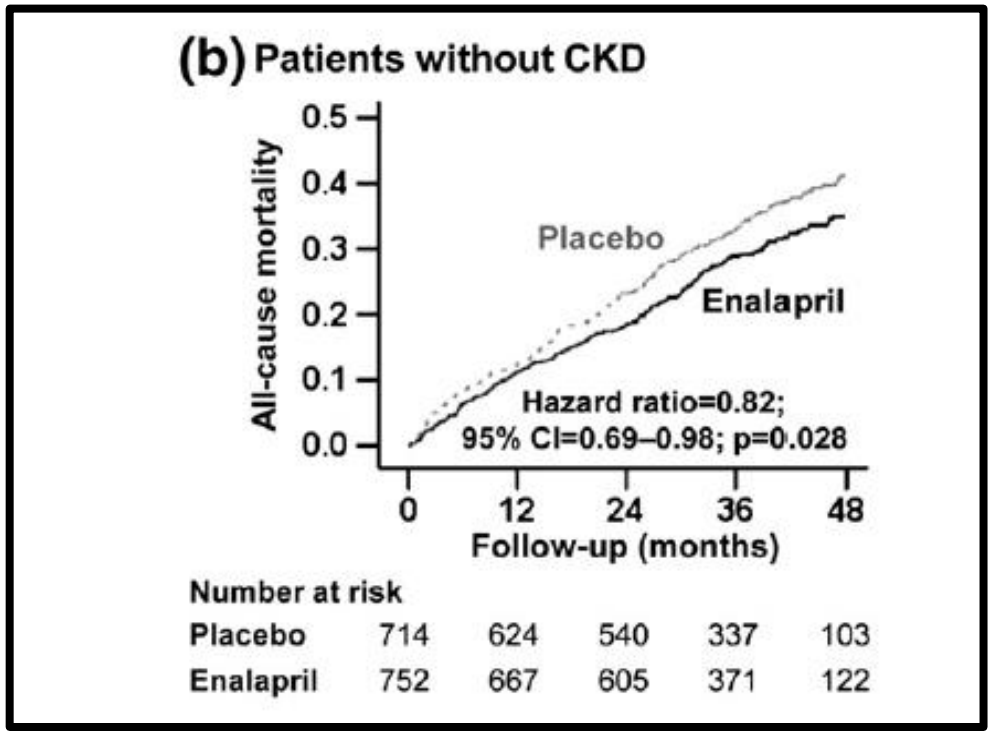
Beldhuis IE, et al. Circulation. 2022;145(9):693-712

ACE-inhibitor

Effects of enalapril in systolic heart failure patients with and without chronic kidney disease (SOLVD Treatment trial)

2569 ambulatory chronic HF patients (mainly NYHA class I-III) with LVEF ≤ 35% and serum creatinine level ≤ 2.5 mg/dl were randomized to receive either placebo (n = 1284) or enalapril (n = 1285)



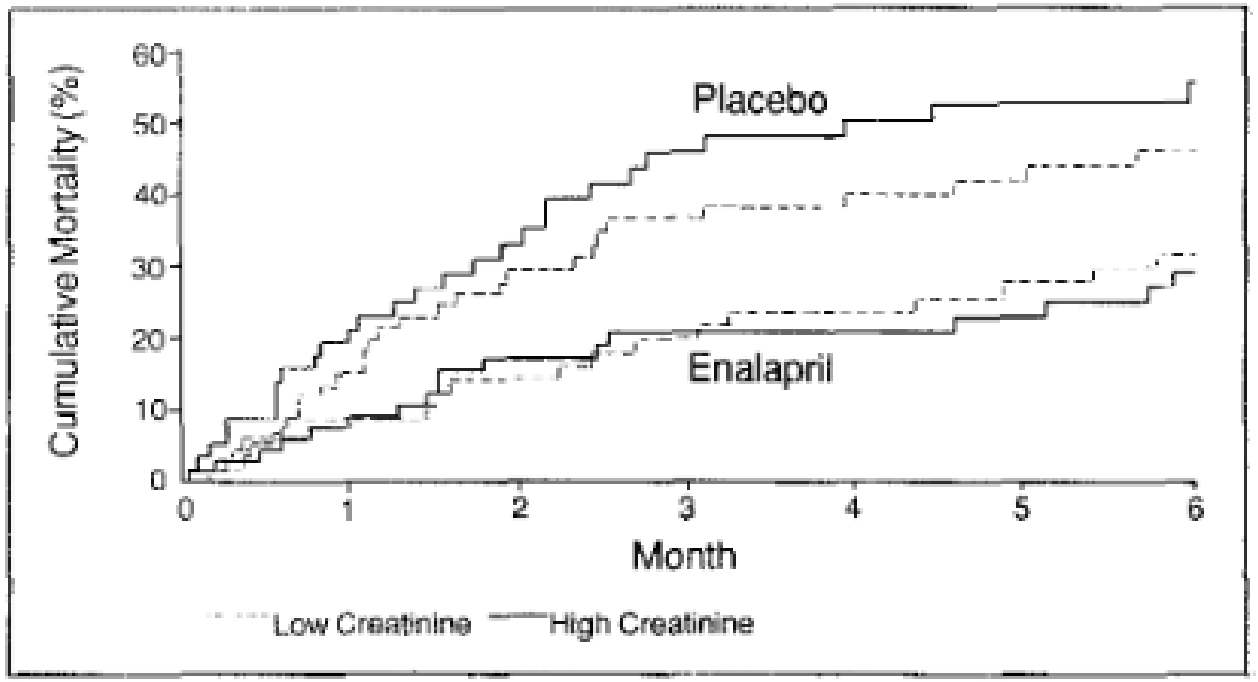


p for interaction=0.615

Enalapril reduces mortality and hospitalization in Systolic HF patients without significant heterogeneity between those with and without CKD.

Bowling CB, et al. Int J Cardiol 2013;167:151–6

Effects of enalapril on prognosis in severe congestive heart failure (CONSENSUS Trial)

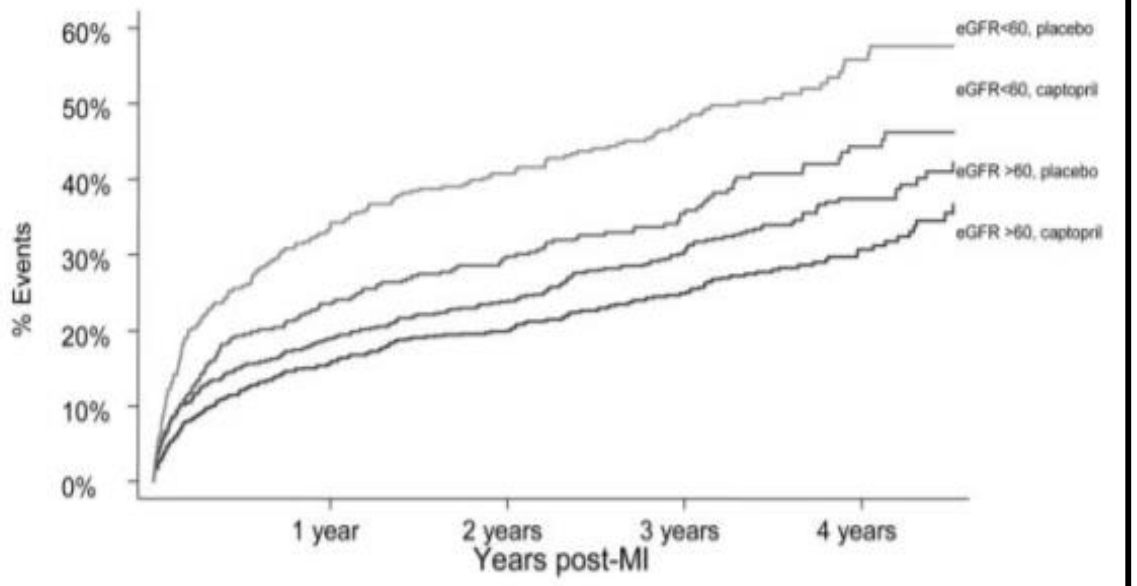


- This study enrolled 253 patients with severe heart failure (NYHA IV) from 35 centers in Scandinavia, randomly assigned to treatment with placebo or enalapril in addition to their usual treatment for heart failure
- Patients with high creatinine levels had significantly higher mortality, and their prognoses were significantly improved by enalapril

Exclusion: Creatinine > 3.3 mg/dl

Swedberg K, et al. Am J Cardiol 1990;66:Suppl D:40–5
Ljungman S, et al. Am J Cardiol. 1992;70(4):479-87.

Chronic Kidney Disease, Cardiovascular Risk, and Response to Angiotensin-Converting Enzyme Inhibition After Myocardial Infarction (SAVE Study)



Variable	Events/Patients, n/n (%) Placebo	Captopril	Risk Reduction	Power	Test for Interaction
Total mortality					
eGFR ≥60	142/730 (19.5)	127/734 (17.3)	13 (−11 to 31)	0.473	*P*=0.30
eGFR <60	127/360 (35.3)	96/359 (26.7)	28 (6–45)	0.502	
CV mortality/morbidity					
eGFR ≥60	248/730 (34.0)	209/734 (28.5)	20 (4–33)	0.791	*P*=0.29
eGFR <60	186/360 (51.7)	141/359 (39.3)	31 (14–45)	0.773	

- SAVE randomized post-MI subjects (3 to 16 days after MI) with LVEF≤ 40% and serum creatinine 2.5 mg/dL to captopril or placebo.
- CKD was associated with a heightened risk for all major CV events after MI, particularly among subjects with an estimated glomerular filtration rate <45 mL /min /1.73 m^2
- Randomization to captopril resulted in a reduction of CV events irrespective of baseline kidney function

Tokmakova MP, et al. Circulation. 2004;110:3667-3673

Exclusion: Creatinine > 2.5 mg/dl

ACE Inhibitors (ACEi)

	All Cause Mortality	CV Death / HF Hospitalization
Overall	16-27% RRR	24-28% RRR
CKD Stages (eGFR in mL/min/1.73m²)		
CKD stage 1 (> 90) CKD stage 2 (60-89)	13-16% RRR[20,25]	20-26% RRR[25]
CKD stage 3A (45-59) CKD stage 3B (30-44)	7-28% RRR[20,25]	4-13% RRR[25]
CKD stage 4 (15-29)	Limited data, large CIs No evidence of harm	Limited data, large CIs Lower number of events with ACEi +21% - 53% RRR
CKD stage 5 (<15/Dialysis)	**No information in HFREF**	

Effect on Renal Function

ACE inhibitors cause efferent glomerular vasodilation, decreasing Filtration Fraction, preserving RBF and leading to a (reversible) decline in GFR [34]

Early decline in eGFR after initiation (up to 5-10 mL/min/1.73m²)[26,27]	Long term slope ~ - 0.5-1.0 mL/min/1.73m²/year (not different from placebo in SOLVD)[26]	WRF during uptitration of ACEi-inhibition not associated with worse outcomes[39]

Management of substantial increase in serum creatinine/drop in eGFR during initiation/uptitration

In the context of uptitration of ACE inhibitors some increase in serum creatinine / drop in eGFR is expected and acceptable. The survival benefit seen with this class of drugs far outweigh the risks associated with this perceived worsening of renal function (WRF)

Δ serum creatinine (%)	Max serum creatinine (mg/dL)	Min eGFR mL/min/1.73m²	Max serum potassium (mmol/L)	Action advised
< 50	3 mg/dL	25	5.0	None, uptitrate and evaluate renal function and electrolytes
50-100	3.5 mg/dL	20	5.5	Evaluate clinical status and other causes of WRF. Consider halving ACEi and re-evaluate
> 100	> 3.5 mg/dL	< 20	> 5.5	Evaluate clinical status and other causes of WRF. Consider stopping ACEi and re-evaluate

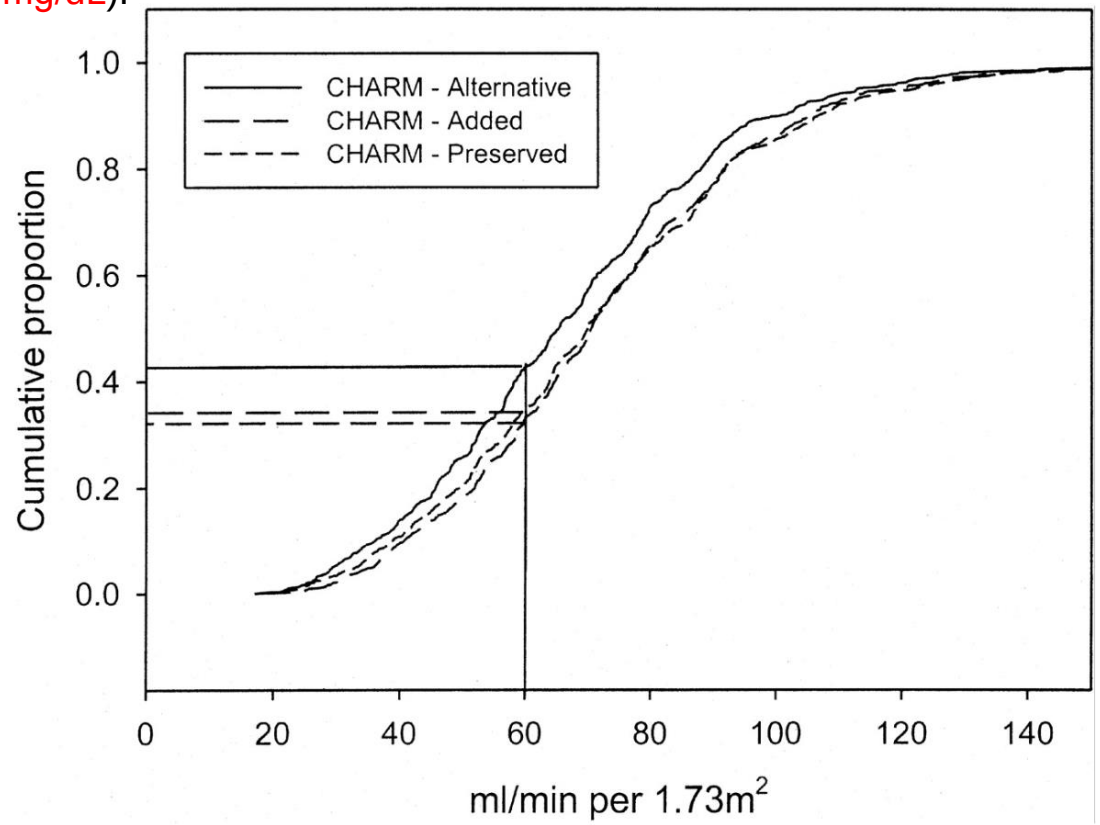
Rechallenge after 2-4 weeks (if possible at lower dose) when dosing reduced or stopped all together if renal function has improved

Beldhuis IE, et al. Circulation. 2022;145(9):693-712

Angiotensin Receptor Blocker

Effects of candesartan in heart failure patients with and without renal dysfunction

7601 patients were randomly assigned candesartan (n=3803, titrated to 32 mg once daily) or matching placebo (n=3796), and followed up for at least 2 years. A key exclusion criterion was a serum creatinine ≥ 3 mg/dL).



- The proportion of patients with eGFR <60 mL/min per 1.73 m^2 was 36.0%; 42.6% for CHARM-Alternative, 33.0% for CHARM-Added, and 34.7% for CHARM-Preserved.
- The risk for cardiovascular death or hospitalization for worsening CHF as well as the risk for all-cause mortality increased significantly below an eGFR of 60 mL/min per 1.73 m^2 (adjusted HR, 1.54 for 45 to 60 mL/min per 1.73 m^2 and 1.86 for <45 mL/min per 1.73 m^2 for cardiovascular death or hospitalization for heart failure, both P<0.001, and HR of 1.50, P=0.006, and 1.91, P=0.001, respectively, for all-cause mortality).
- There was no interaction between creatinine and the effect of candesartan (Wald test for interaction term, P=0.84).

Pfeffer MA, et al. Lancet 2003;362:759–66

Angiotensin II Receptor Blockers (ARB)

Findings in CKD Subgroups		
	All Cause Mortality	**CV Death / HF Hospitalization**
Overall	-2 – 13% RRR, CIs cross 1	13-23% RRR
CKD Stages (eGFR in mL/min/1.73m^2)		
CKD stage 1 (> 90) CKD stage 2 (60-89)	7-14% RRR CIs cross 1[31-33]	8-24% RRR[30,31,33]
CKD stage 3A (45-59) CKD stage 3B (30-44)	3-22% RRR CIs cross 1[32]	6-24% RRR CIs cross 1[31-33]
CKD stage 4 (15-29)	Limited data 4-52% RRR, CIs cross 1 No evidence of harm[32]	Limited data 14-35% RRR, CIs cross 1 No evidence of harm[32]
CKD stage 5 (<15/Dialysis)	**No information in HFREF**	

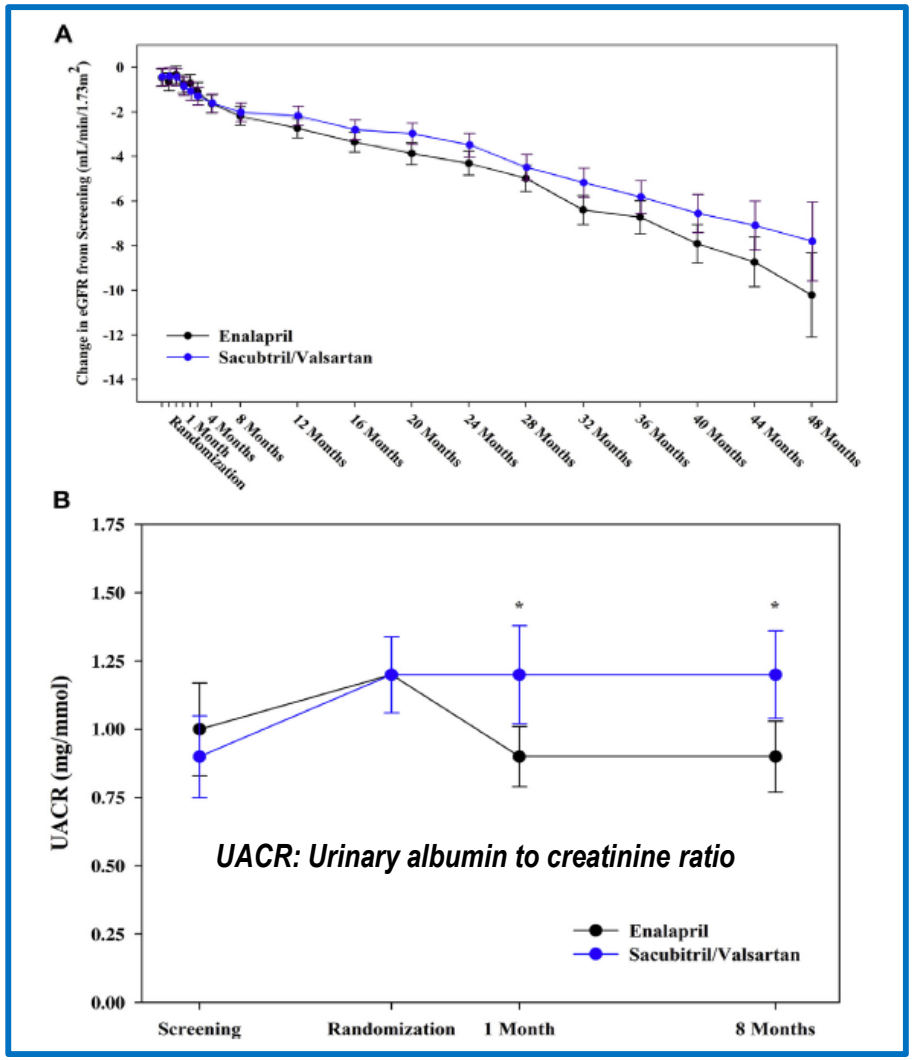
Effect on Renal Function		
ARBs cause efferent glomerular vasodilation by blocking response to angiotensin II, decreasing Filtration Fraction, preserving RBF and leading to a (reversible) decline in GFR		
Early decline in eGFR after initiation (up to 6.4 ml/min/1.73m^2)[32]	Long term slope not different from placebo in CHARM HFREF subgroup and ValHeFt[32,33]	WRF during uptitration of ARB-inhibition not associated with worse outcomes[39,43]

Management of substantial increase in serum creatinine/drop in eGFR during initiation/uptitration				
In the context of uptitration of ARBs some increase in serum creatinine / drop in eGFR is expected and acceptable. The survival benefit seen with this class of drugs far outweigh the risks associated with this perceived worsening of renal function (WRF)				
Δ serum creatinine (%)	**Max serum creatinine** (mg/dL)	**Min eGFR** mL/min/1.73m^2	**Max serum potassium** (mmol/L)	**Action advised**
< 50	**3 mg/dL**	**25**	**5.0**	None, uptitrate and evaluate renal function and electrolytes
50-100	**3.5 mg/dL**	**20**	**5.5**	Evaluate clinical status and other causes of WRF. Consider halving ARB and re-evaluate
> 100	**> 3.5 mg/dL**	**< 20**	**> 5.5**	Evaluate clinical status and other causes of WRF. Consider stopping ARB and re-evaluate
Rechallenge after 2-4 weeks (if possible at lower dose) when dosing reduced or stopped all together if renal function has improved				

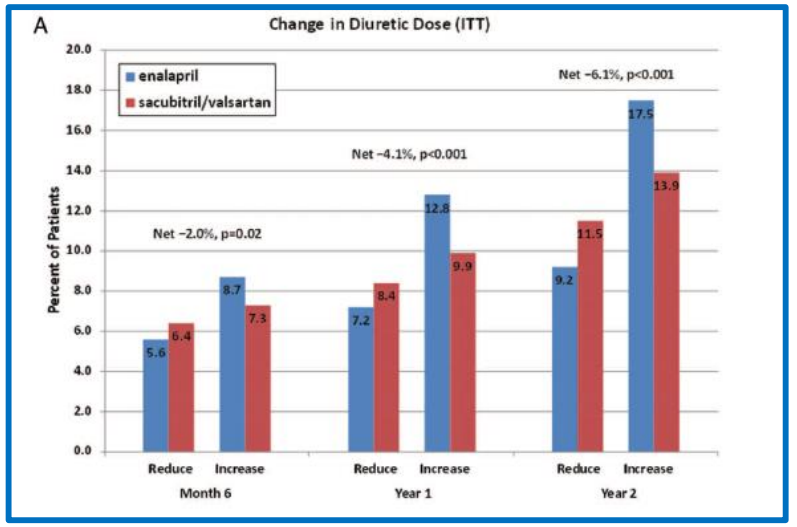
Beldhuis IE, et al. Circulation. 2022;145(9):693-712

Sacubitril-Valsartan

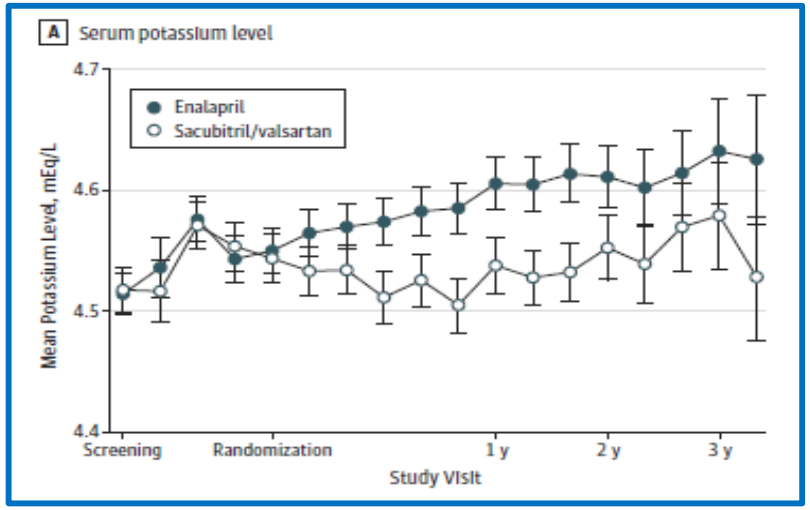
Renal Effects and Associated Outcomes (PARADIGM-HF)



Reduced loop diuretic use in patients taking sac/valsartan compared with enalapril (PARADIGM-HF)

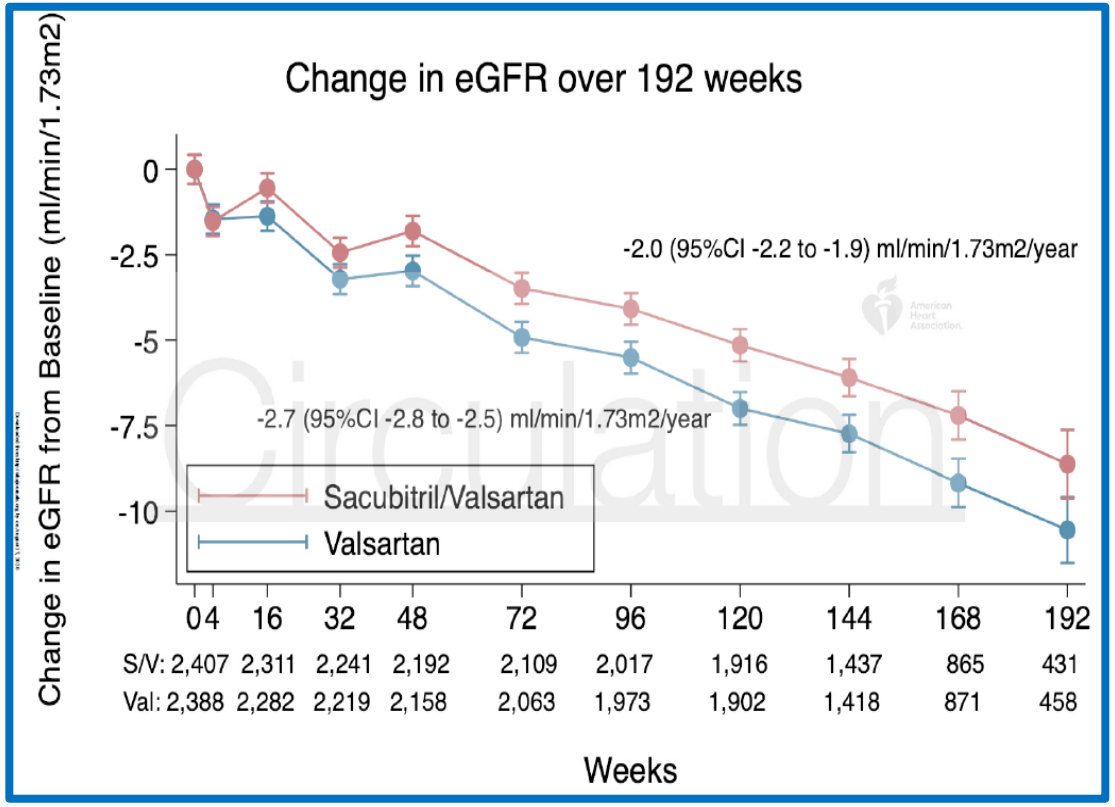


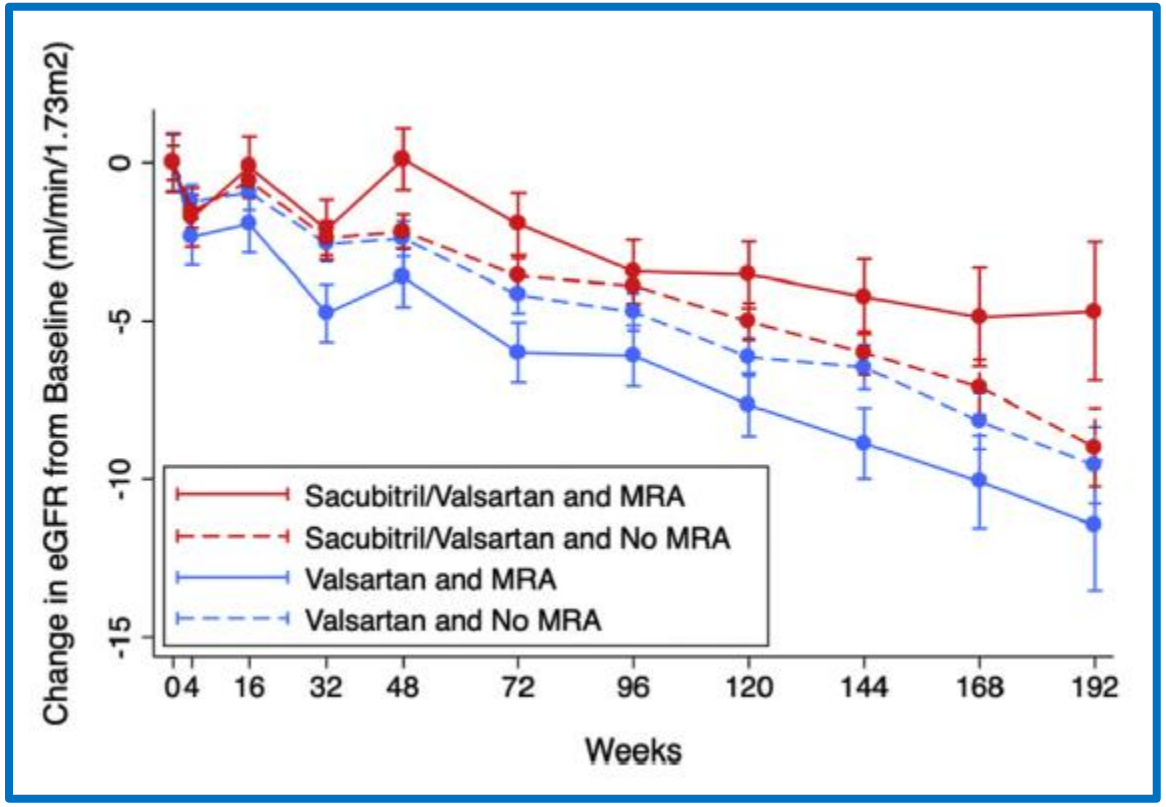
Reduced Risk of Hyperkalemia During Treatment of Heart Failure With MRAs by Use of Sac/Valsartan Compared With Enalapril (PARADIGM-HF)



Damman K, et al. JACC Heart Fail. 2018;6(6):489-498
Varrdeny O, et al. Eur J Heart Fail. 2019;21:337–341
Desai AS, et al. JAMA Cardiol. 2017;2(1):79-85

Renal effects of sacubitril-valsartan in patients with heart failure and preserved ejection fraction





Causland FR Mc, et al. Circulation. 2020;142(13):1236-1245

Jering KS, et al. JACC Heart Fail. 2020;S2213-1779(20)30556-4

ORIGINAL RESEARCH

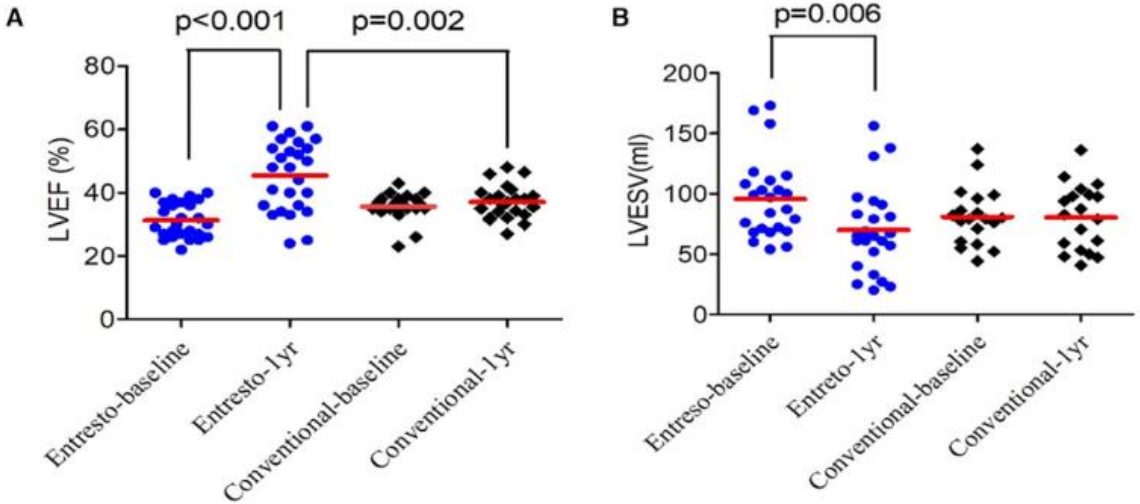
Sacubitril/Valsartan in Patients With Heart Failure and Concomitant End-Stage Kidney Disease

Chih-Yuan Niu, MD; Shang-Feng Yang, MD, PhD; Shuo-Ming Ou, MD, PhD; Cheng-Hsueh Wu, MD; Po-Hsun Huang, MD, PhD; Chung-Lieh Hung, MD, PhD; Chih-Ching Lin, MD, PhD; Szu-Yuan Li, MD, PhD

BACKGROUND: Heart failure with reduced ejection fraction (HFrEF) is a chronic disease with substantial mortality. Management of HFrEF has seen significant breakthrough after the launch of neprilysin inhibitor. The PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impacton Global Mortality and Morbidity in Heart Failure) trial showed that sacubitril/valsartan significantly reduces HFrEF mortality and the heart failure hospitalization rate. However, in patients with advanced kidney disease, who have the highest prevalence of heart failure, the efficacy and safety of sacubitril/valsartan remains uncertain. We aim to study the efficiency of sacubitril/valsartan in patients with end-stage kidney disease.

METHODS AND RESULTS: Heart function was screened by echocardiogram among all patients with end-stage kidney disease in 2 hospitals. Patients with HFrEF received either sacubitril/valsartan or conventional treatment. Fifteen echocardiographic parameters were compared before and after treatment. After 1-year sacubitril/valsartan treatment, parameters of systolic (left ventricular ejection fraction 31.3% to 45.1%, $P<0.0001$; left ventricular end-systolic volume 95.7 to 70.1 mL, $P=0.006$; left ventricular internal diameter at end-systole phase 47.2 to 40.1 mm, $P=0.005$), and diastolic (E/A ratio 1.3 to 0.8, $P=0.009$; E/Med e' ratio 25.3 to 18.8, $P=0.010$) function improved in patients with HFrEF and end-stage kidney disease. These parameters were unchanged in the conventional treatment group. Serum potassium did not increase in the sacubitril/valsartan group.

CONCLUSIONS: Sacubitril/valsartan improves left ventricular systolic and diastolic function in patients with HFrEF and end-stage kidney disease.



Adverse events	Sacubitril/valsartan (n=26)	Conventional (n=23)	*P* value
New-onset intradialytic hypotension*	2/26 (7.7%)	1/23 (4.3%)	1.000
Hyperkalemia (>5.5 mEq/L)	3/26 (11.5%)	4/23 (17.4%)	0.692
Cough	0/26 (0%)	0/23 (0%)	1.000
Angio-edema	0/26 (0%)	0/23 (0%)	1.000
Abnormal AST/ALT (>40 U/L)	1/26 (3.8%)	0/23 (0%)	1.000
Hospitalization of all causes	13/26 (50%)	13/23 (56.5%)	0.776
Hospitalization because of cardiovascular diseases	6/26 (23.1%)	7/23 (30.4%)	0.747

ALT indicates alanine aminotransferase; and AST, aspartate aminotransferase.

*Intradialytic hypotension defined as decrease in systolic blood pressure ≥20 mm Hg or mean blood pressure ≥10 mm Hg during dialysis treatment with associated symptoms (cramping, headache, lightheadedness, vomiting, or chest pain) or need for intervention (reduction in ultrafiltration, administration of fluids or blood pump flow reduction).

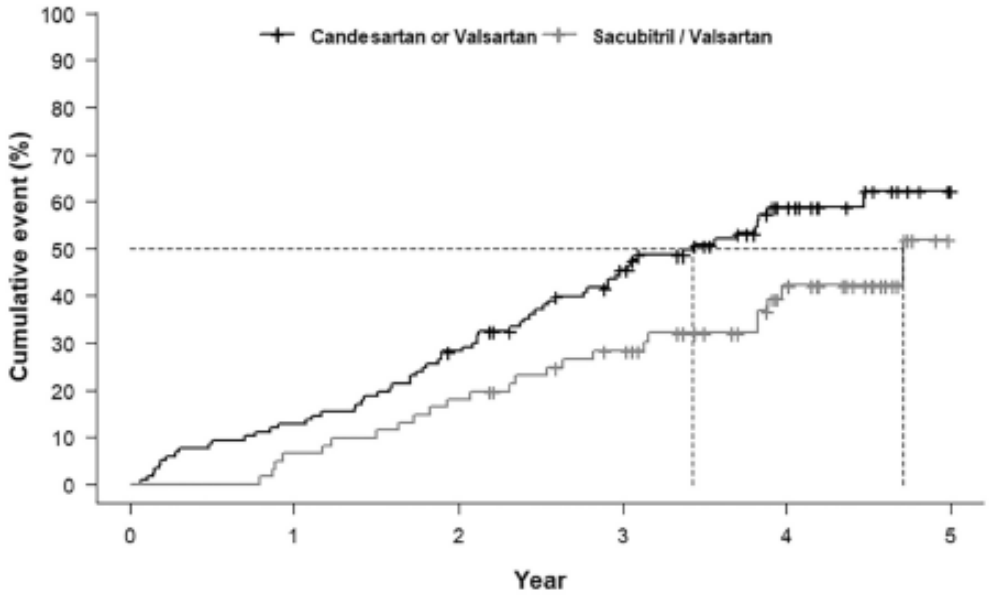
Niu et al. J Am Heart Assoc. 2022;11:e026407

ARTICLE

Long-Term Outcomes of Sacubitril/Valsartan in Heart Failure with Reduced Ejection Fraction and Coexisting End-Stage Renal Disease

Wan-Ying Lin[1,†], Yu-Hsuan Joni Shao[2,3,4,†], Andy F. Chiang[1], Chih-Chieh Huang[5], Kim F. Chiang[6], Chao-Shun Chan[7,8,9], Chun-Yao Huang[7,8,9] and Bu-Yuan Hsiao[7,8,9,*]

Sacubitril/valsartan (Entresto) has proven therapeutic effects in heart failure (HF) patients, but its impact on those with advanced chronic kidney disease (CKD) remains unclear, particularly in HF patients with coexisting end-stage renal disease (ESRD). This study aims to assess the long-term survival of patients with heart failure with reduced ejection fraction (HFrEF) and coexisting ESRD treated with sacubitril/valsartan. A retrospective cohort study included 2,860 HFrEF and ESRD patients between January 2008 and December 2020. After propensity score matching, data from a sacubitril/valsartan group ($n=61$) and a candesartan or valsartan group ($n=117$) were analyzed. Patients on sacubitril/valsartan for at least 9 months had significantly lower 5-year all-cause mortality (39.3%) compared with the non-sacubitril/valsartan group (54.7%) (HR 0.46; 95% CI, 0.25–0.82; $P=0.0094$). Left ventricular ejection fraction (LVEF) improvement after 3 years in the sacubitril/valsartan group (14.51 ± 18.98) was significantly greater than the non-sacubitril/valsartan group (6.91 ± 18.44) ($P=0.0408$). Average hospitalizations in sacubitril/valsartan and non-sacubitril/valsartan groups were 1.39 and 0.97, respectively (incidence rate ratio, 1.59; 95% CI, 0.90–2.82; $P=0.1106$). Sacubitril/valsartan treatment demonstrated significantly lower 5-year mortality rates and greater LVEF improvement in HFrEF patients with coexisting ESRD compared with candesartan or valsartan. These findings suggest that sacubitril/valsartan is a beneficial treatment option for this patient population.



Lin W-Y, et al. Clin Pharmacol Ther. 2024 June 16. Online ahead of print.

RENAL FAILURE
2024, VOL. 46, NO. 1, 2349135
https://doi.org/10.1080/0886022X.2024.2349135

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CHRONIC KIDNEY DISEASE AND PROGRESSION

OPEN ACCESS Check for updates

The role of sacubitril/valsartan in abnormal renal function patients combined with heart failure: a meta-analysis and systematic analysis

Xinyue Yang†, Jingjing Jin†, Meijuan Cheng, Jinsheng Xu and Yaling Bai

Department of Nephrology, Hebei Key Laboratory of Vascular Calcification in Kidney Disease, Hebei Clinical Research Center for Chronic Kidney Disease, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China

ABSTRACT

Aims: This study aimed to investigate the efficacy and safety of sacubitril/valsartan in abnormal renal function (eGFR < 60 ml/min/1.73m²) patients combined with heart failure based on randomized controlled trials (RCTs) and observational studies.

Methods: The Embase, PubMed and the Cochrane Library were searched for relevant studies from inception to December 2023. Dichotomous variables were described as event counts with the odds ratio (OR) and 95% confidence interval (CI) values. Continuous variables were expressed as mean standard deviation (SD) with 95% CIs.

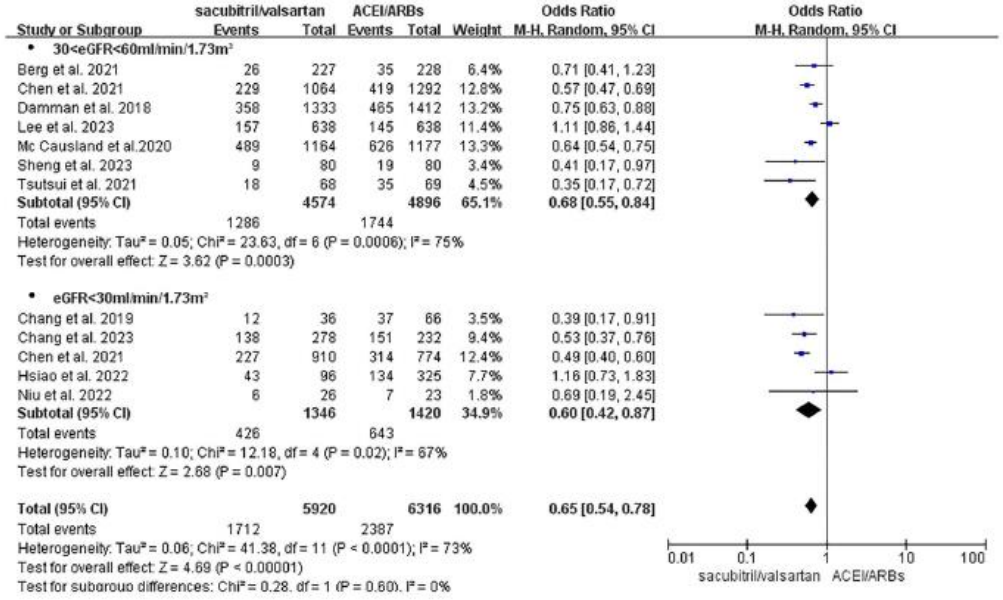
Results: A total of 6 RCTs and 8 observational studies were included, involving 17335 eGFR below 60 ml/min/1.73m² patients combined with heart failure. In terms of efficacy, we analyzed the incidence of cardiovascular events and found that sacubitril/valsartan significantly reduced the risk of cardiovascular death or heart failure hospitalization in chronic kidney disease (CKD) stages 3–5 patients with heart failure (OR: 0.65, 95%CI: 0.54–0.78). Moreover, sacubitril/valsartan prevented the serum creatinine elevation (OR: 0.81, 95%CI: 0.68–0.95), the eGFR decline (OR: 0.83, 95% CI: 0.73–0.95) and the development of end-stage renal disease in this population (OR:0.73, 95%CI:0.60–0.89). As for safety outcomes, we did not find that the rate of hyperkalemia (OR:1.31, 95%CI:0.79–2.17) and hypotension (OR:1.57, 95%CI:0.94–2.62) were increased in sacubitril/valsartan group among CKD stages 3–5 patients with heart failure.

Conclusions: Our meta-analysis proves that sacubitril/valsartan has a favorable effect on cardiac function without obvious risk of adverse events in abnormal renal function patients combined with heart failure, indicating that sacubitril/valsartan has the potential to become perspective treatment for these patients.

ARTICLE HISTORY
Received 5 December 2023
Revised 25 March 2024
Accepted 2 April 2024

KEYWORDS
Sacubitril/valsartan; chronic kidney disease; heart failure; meta-analysis; randomized controlled trials; observational studies

A Cardiovascular events



Yang X, et al. Renal Failure. 2024; 46(1): 2349135

Angiotensin Receptor blocker Neprilysin Inhibitor (ARNI)

Findings in CKD Subgroups		
	All Cause Mortality	CV Death / HF Hospitalization
Overall	16 % RRR	20% RRR
CKD Stages (eGFR in mL/min/1.73m²)		
CKD stage 1 (> 90)	23% RRR[80]	23% RRR[80]
CKD stage 2 (60-89)	7% RRR[80]	17% RRR[80]
CKD stage 3A (45-59)	29% RRR[80]	27% RRR[80]
CKD stage 3B (30-44)	7% RRR[80]	10% RRR[80]
CKD stage 4 (15-29)	No information in HFREF	
CKD stage 5 (<15/Dialysis)	No information in HFREF	

Effect on Renal Function		
The effect of ARNI on renal function is not entirely clear, but is attributed to higher circulating natriuretic peptide levels, the improved clinical status, an effect on renal podocyte function and the need for less loop diuretics.		
Early decline in eGFR after initiation (0.5-1.0 mL/min/1.73m²)[80]	Long term slope in eGFR less with ARNI vs ACEi: -1.61 vs. -2.04 mL/min/1.73m²/year)[80]	Change in serum creatinine/eGFR similar between ARNI/ACEi in PARADIGM-HF and PIONEER[80,81]

Management of substantial increase in serum creatinine/drop in eGFR during initiation/uptitration

In the context of uptitration of ARNI some increase in serum creatinine / drop in eGFR is expected and acceptable. The survival benefit seen with this class of drugs far outweigh the risks associated with this perceived worsening of renal function (WRF)

Δ serum creatinine (%)	Max serum creatinine (mg/dL)	Min eGFR mL/min/1.73m²	Max serum potassium (mmol/L)	Action advised
< 50	2.5 mg/dL	30	5.0	None, uptitrate and evaluate renal function and electrolytes
50-100	3.5 mg/dL	20	5.5	Evaluate clinical status and other causes of WRF. Consider halving ARNI and re-evaluate
> 100	> 3.5 mg/dL	< 20	> 5.5	Evaluate clinical status and other causes of WRF. Consider stopping ARNI and re-evaluate

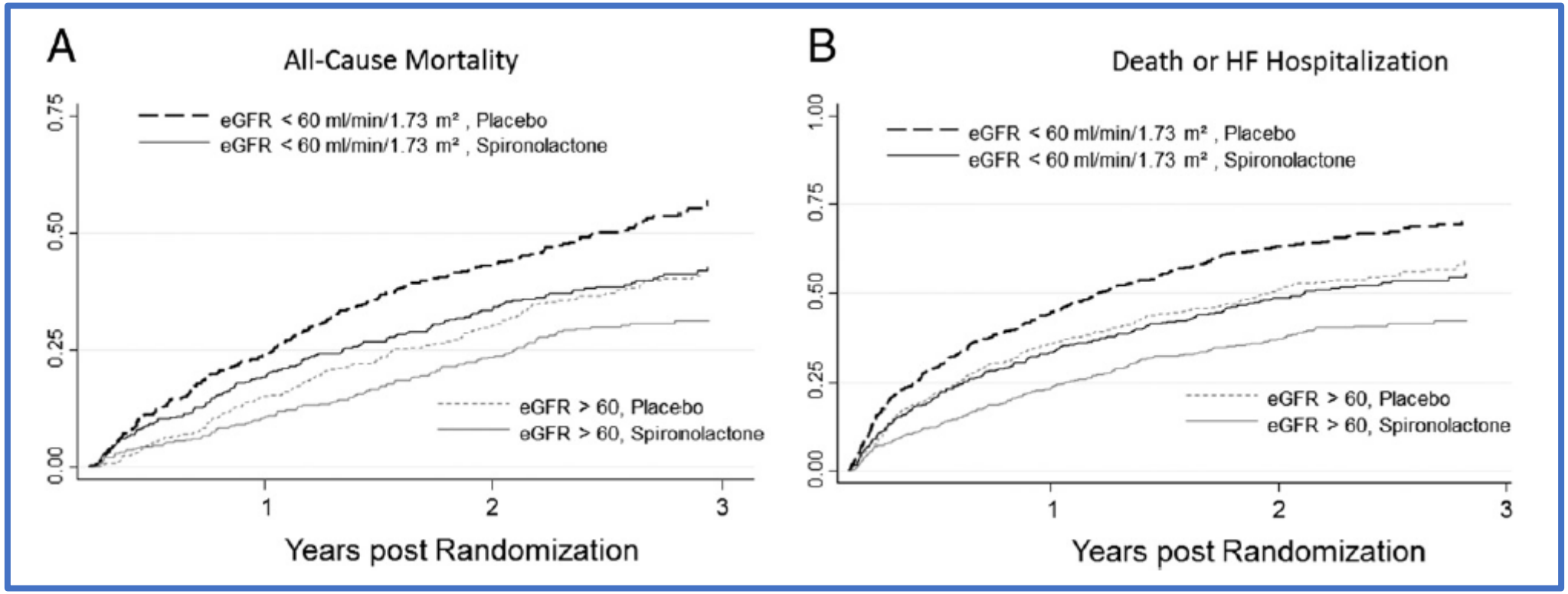
Rechallenge after 2-4 weeks (if possible at lower dose) when dosing reduced or stopped all together if renal function has improved

Beldhuis IE, et al. Circulation. 2022;145(9):693-712

Mineralocorticoid Antagonist

Influence of Baseline and Worsening Renal Function on Efficacy of Spironolactone in Patients With Severe Heart Failure (RALES)

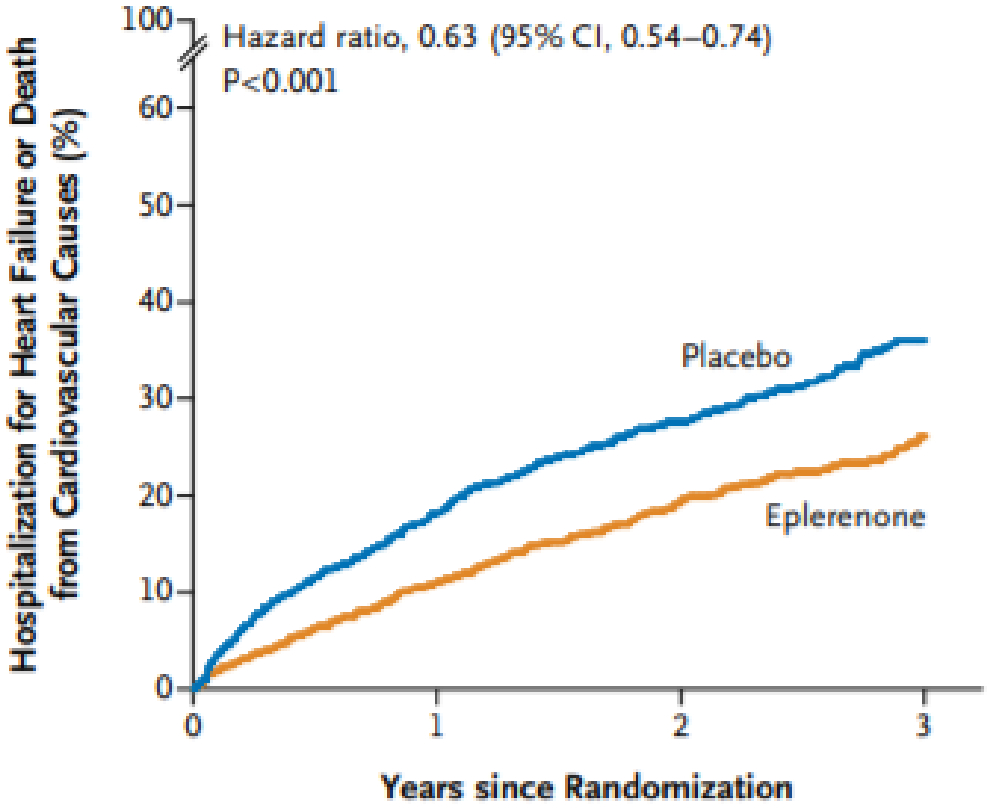
Individuals with reduced baseline eGFR (NYHA class III or IV, LVEF≤ 35%) exhibited similar relative risk reductions in all-cause death and the combined endpoint of death or hospital stays for HF as those with a baseline eGFR>60 ml/min/1.73 m^2 and greater absolute risk reduction compared with those with a higher baseline eGFR (10.3% vs. 6.4%).



Patients with serum creatinine level ≥ 2.5 mg/dl or serum potassium level > 5.0 mEq/l were excluded.

Vardeny O, et al. J Am Coll Cardiol. 2012;60(20):2082-9

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (EPHASIS-HF)



No. at Risk				
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

Subgroup	No. of Patients	Hazard Ratio (95% CI)	P Value for Interaction
Overall	2737		
Sex			0.36
Female	610		
Male	2127		
Age			0.37
<65 yr	883		
≥65 yr	1854		
Age			1.00
<75 yr	2080		
≥75 yr	657		
Region			0.46
Asia, Middle East, or Africa	380		
Eastern Europe	911		
North or South America	346		
Western Europe or Australia	1100		
Systolic blood pressure			0.65
Below median	1352		
At or above median	1384		
Pulse pressure			0.75
Below median	1272		
At or above median	1464		
Heart rate			0.79
Below median	1340		
At or above median	1383		
Estimated GFR			0.50
<60 ml/min/1.73 m^2	912		
≥60 ml/min/1.73 m^2	1821		

Zannad F, et al. N Engl J Med. 2011;364(1):11-21

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 83, NO. 24, 2024

PUBLISHED BY ELSEVIER

Mineralocorticoid Receptor Antagonists in Patients With Heart Failure and Impaired Renal Function

Shingo Matsumoto, MD, PhD,[a] Alasdair D. Henderson, PhD,[a] Li Shen, MD, PhD,[a] Mingming Yang, MD, PhD,[a] Karl Swedberg, MD, PhD,[b] Muthiah Vaduganathan, MD, MPH,[c] Dirk J. van Veldhuisen, MD, PhD,[d] Scott D. Solomon, MD,[c] Bertram Pitt, MD,[e] Faiez Zannad, MD, PhD,[f] Pardeep S. Jhund, MBChB, MSc, PhD,[a] John J.V. McMurray, MD[a]

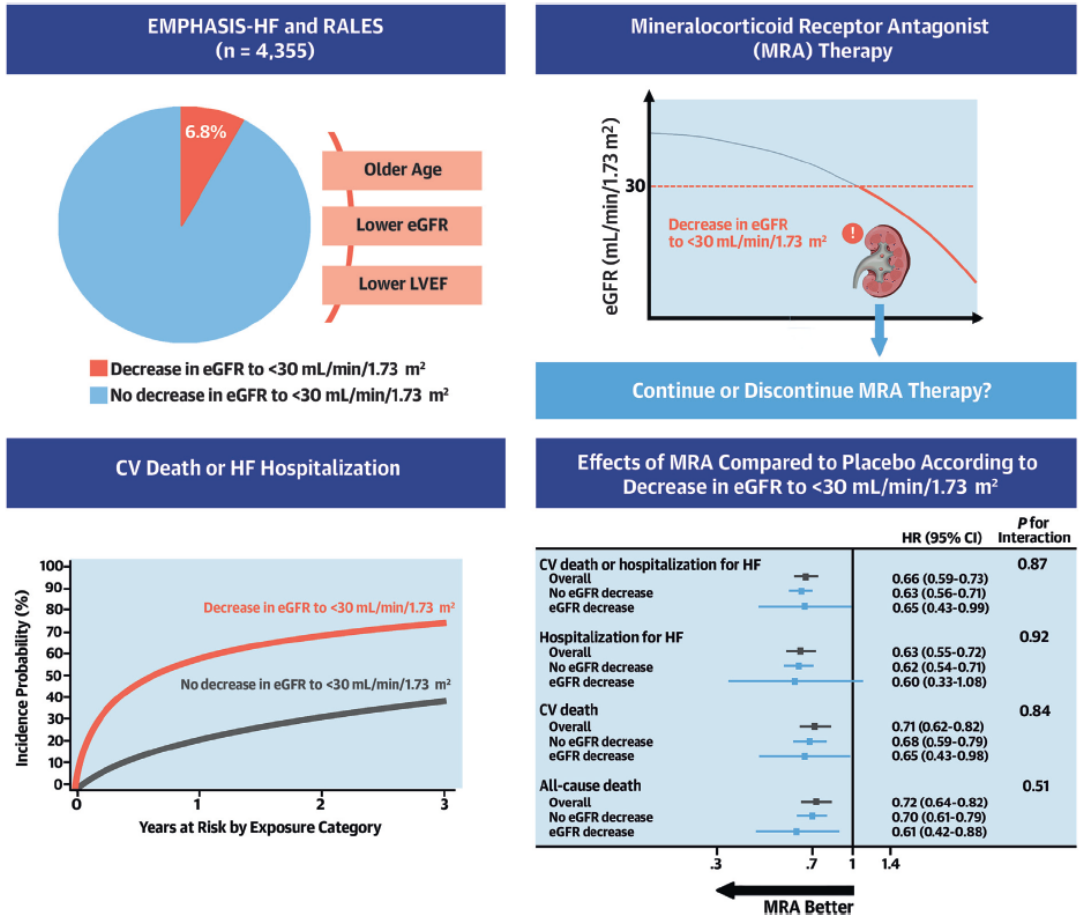
BACKGROUND Kidney dysfunction often leads to reluctance to start or continue life-saving heart failure (HF) therapy.

OBJECTIVES This study sought to examine the efficacy and safety of mineralocorticoid receptor antagonists (MRAs) in patients with HF with reduced ejection fraction experiencing significant kidney dysfunction.

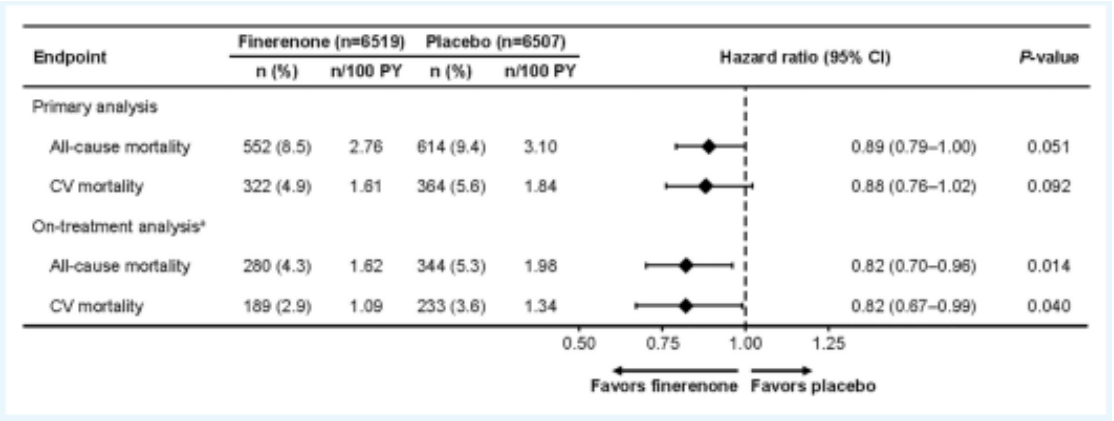
METHODS We pooled individual patient data from the RALES (Randomized Aldactone Evaluation Study) and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trials. The association between MRA treatment and outcomes was assessed according to whether the estimated glomerular filtration rate (eGFR) declined to <30 mL/min/1.73 m^2 or not. The primary outcome was cardiovascular death or HF hospitalization.

RESULTS Among 4,355 patients included, 295 (6.8%) experienced a deterioration of eGFR after randomization to <30 mL/min/1.73 m^2. These patients had more impaired baseline cardiac and kidney function (eGFR 47.3 ± 13.4 mL/min/1.73 m^2 vs 70.5 ± 21.8 mL/min/1.73 m^2) and had a higher risk of the primary outcome than patients without eGFR deterioration (HR: 2.49; 95% CI: 2.01-3.08; $P < 0.001$). However, the risk reduction in the primary outcome with MRA therapy was similar in those who experienced a decrease in eGFR to <30 mL/min/1.73 m^2 (HR: 0.65; 95% CI: 0.43-0.99) compared with those who did not (HR: 0.63; 95% CI: 0.56-0.71) ($P_{interaction} = 0.87$). In patients with a decrease in eGFR to <30 mL/min/1.73 m^2, 21 fewer individuals (per 100 person-years) experienced the primary outcome with MRA treatment, vs placebo, compared with an excess of 3 more patients with severe hyperkalemia (>6.0 mmol/L).

CONCLUSIONS Because patients experiencing a decrease in eGFR to <30 mL/min/1.73 m^2 are at very high risk, the absolute risk reduction with an MRA in these patients is large and this decline in eGFR should not automatically lead to treatment discontinuation. (J Am Coll Cardiol 2024;83:2426-2436) © 2024 by the American College of Cardiology Foundation.



Matsumoto S, et al. J Am Coll Cardiol 2024;83:2426-2436



ESC European Society of Cardiology
European Heart Journal - Cardiovascular Pharmacotherapy (2023) 9, 183–191
https://doi.org/10.1093/ehjcvp/pvad001

ORIGINAL ARTICLE

Finerenone and effects on mortality in chronic kidney disease and type 2 diabetes: a FIDELITY analysis

Gerasimos Filippatos[1,*], Stefan D. Anker[2], Phyllis August[3,4], Andrew J.S. Coats[5], James L. Januzzi[6], Boris Mankovsky[7], Peter Rossing[8,9], Luis M. Ruilope[10,11,12], Bertram Pitt[13], Pantelis Sarafidis[14], John R. Teerlink[15], Chris J. Kapelios[1,16], Martin Gebel[17], Meike Brinker[18], Amer Joseph[19], Andrea Lage[20], George Bakris[21] and Rajiv Agarwal[22]; on behalf of the FIDELIO-DKD and FIGARO-DKD investigators

Does finerenone work in people with stage 4 CKD? A subgroup analysis of FIGARO and FIDELIO.

CJASN
Clinical Journal of the American Society of Nephrology

FIDELITY is a combined analysis of FIGARO-DKD and FIDELIO-DKD

- Type 2 DM
- eGFR <30 (Ave 26.9)
- Albuminuria 720 mg/g

	CV Composite	Kidney Composite	Hyperkalemia
Finerenone 10-20 mg N=490	17%	21%	26%
Matching placebo N=450	20%	20%	13%

3 years follow-up

HR 0.78; 95% CI 0.57–1.07

Nonsignificant

Conclusions: Finerenone offered cardiovascular benefits in people with stage 4 CKD. Finerenone also reduced albuminuria in CKD 4 but did not reduce the kidney composite outcome in people with CKD stage 4.

Pantelis Sarafidis, Rajiv Agarwal, Bertram Pitt, et al. ***Outcomes with Finerenone in Patients with Stage 4 CKD and Type 2 Diabetes***. CJASN doi: 10.2215/CJN.0000000000000149. **Visual Abstract by Joel Topf, MD, FACP**

ESC European Society of Cardiology

European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3253

STUDY DESIGN

Finerenone in patients with heart failure with mildly reduced or preserved ejection fraction: Rationale and design of the FINEARTS-HF trial

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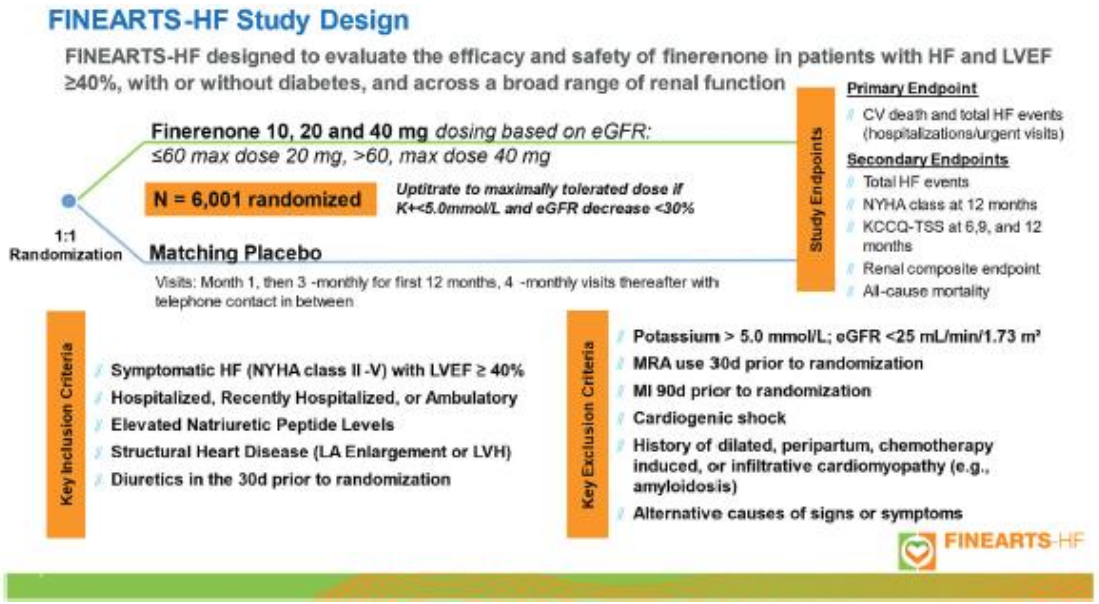


Vaduganathan M, et al. Eur J Heart Fail. 2024 May 14. Online ahead of print.

Mineralocorticoid Receptor Antagonists (MRA)

Findings in CKD Subgroups		
	All Cause Mortality	**CV Death / HF Hospitalization**
Overall	15 – 30% RRR	13-37% RRR
CKD Stages (eGFR in mL/min/1.73m²)		
CKD stage 1 (> 90) CKD stage 2 (60-89)	34% RRR[50]	8-24% RRR[48,50,51]
CKD stage 3A (45-59) CKD stage 3B (30-44)	32% RRR[50]	34-38 % RRR[48,50,51]
CKD stage 4 (15-29)	Limited data No evidence of harm	Limited data No evidence of harm
CKD stage 5 (<15/Dialysis)	No information in HFREF	

Effect on Renal Function		
The precise pathophysiology of the effect of MRA on renal function is unclear		
Early decline in eGFR after initiation (2.3 to 6.7 mL/min/1.73m²)[48]	Long term slope in eGFR slightly steeper with eplerenone vs placebo (-0.3 vs -0.1 mL/min/1.73m²/year)[48,51]	WRF during uptitration of MRA-inhibition not associated with worse outcome [39,43]

Management of substantial increase in serum creatinine/drop in eGFR during initiation/uptitration

In the context of uptitration of MRAs some increase in serum creatinine / drop in eGFR is expected and acceptable. The survival benefit seen with this class of drugs far outweigh the risks associated with this perceived worsening of renal function (WRF)

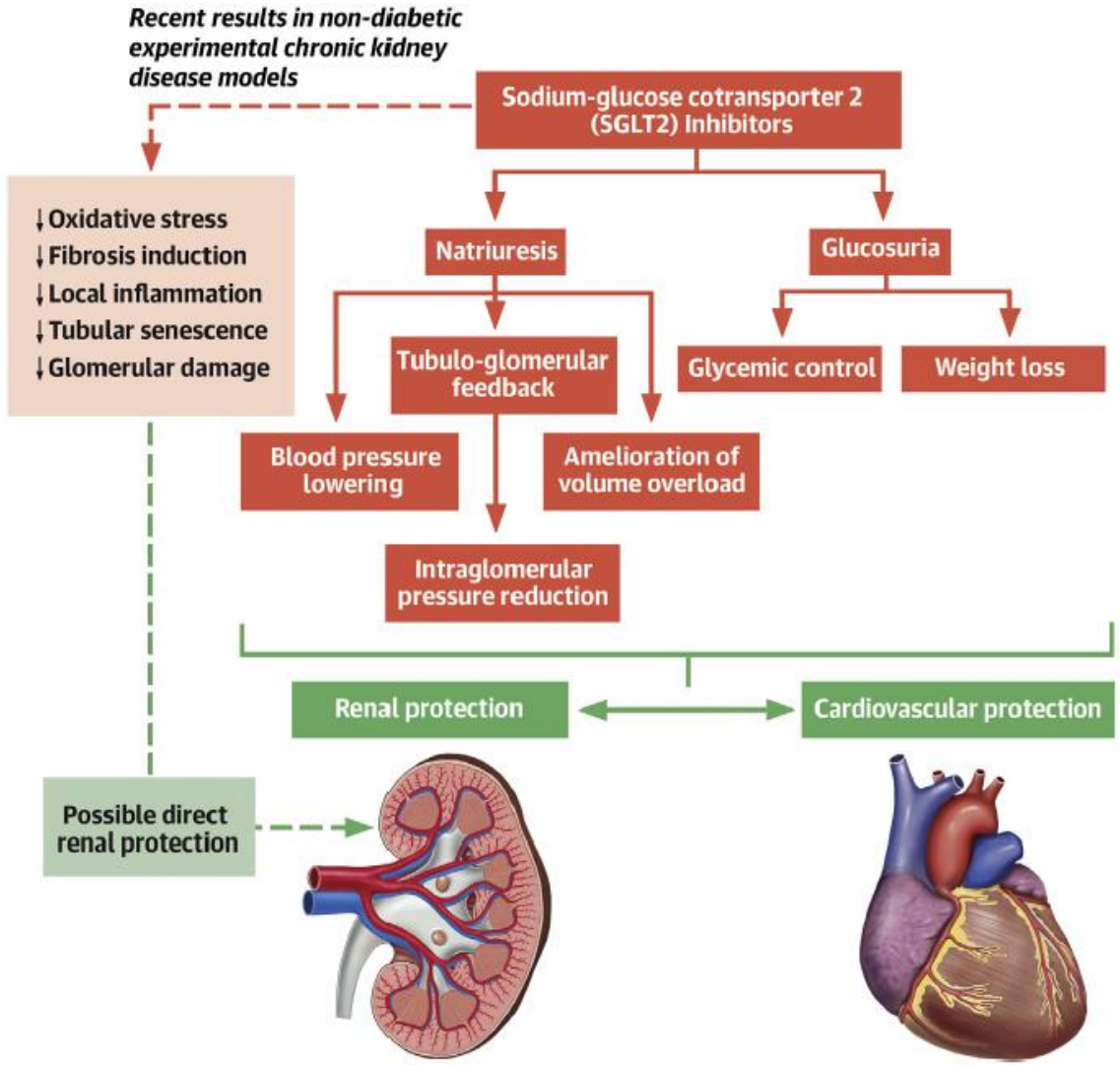
Δ serum creatinine (%)	Max serum creatinine (mg/dL)	Min eGFR mL/min/1.73m²	Max serum potassium (mmol/L)	Action advised
< 50	2.5 mg/dL	30	5.0	None, uptitrate and evaluate renal function and electrolytes
50-100	3.5 mg/dL	20	5.5	Evaluate clinical status and other causes of WRF. Consider halving MRA and re-evaluate
> 100	> 3.5 mg/dL	< 20	> 6.0	Evaluate clinical status and other causes of WRF. Consider stopping MRA and re-evaluate

Rechallenge after 2-4 weeks (if possible at lower dose) when dosing reduced or stopped all together if renal function and/or potassium has improved

Beldhuis IE, et al. Circulation. 2022;145(9):693-712

SGLT-2 inhibitor

Sodium-Glucose Cotransporter 2 Inhibitor



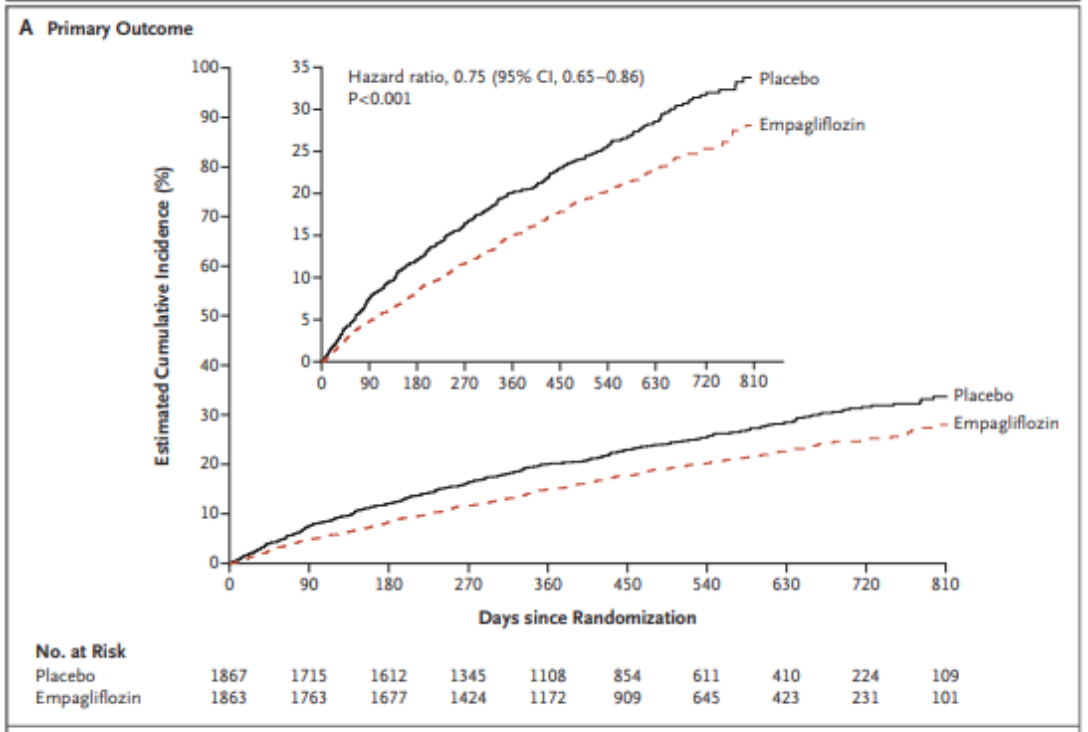
Zelniker, T.A. et al. J Am Coll Cardiol. 2020;75(4):422-34.

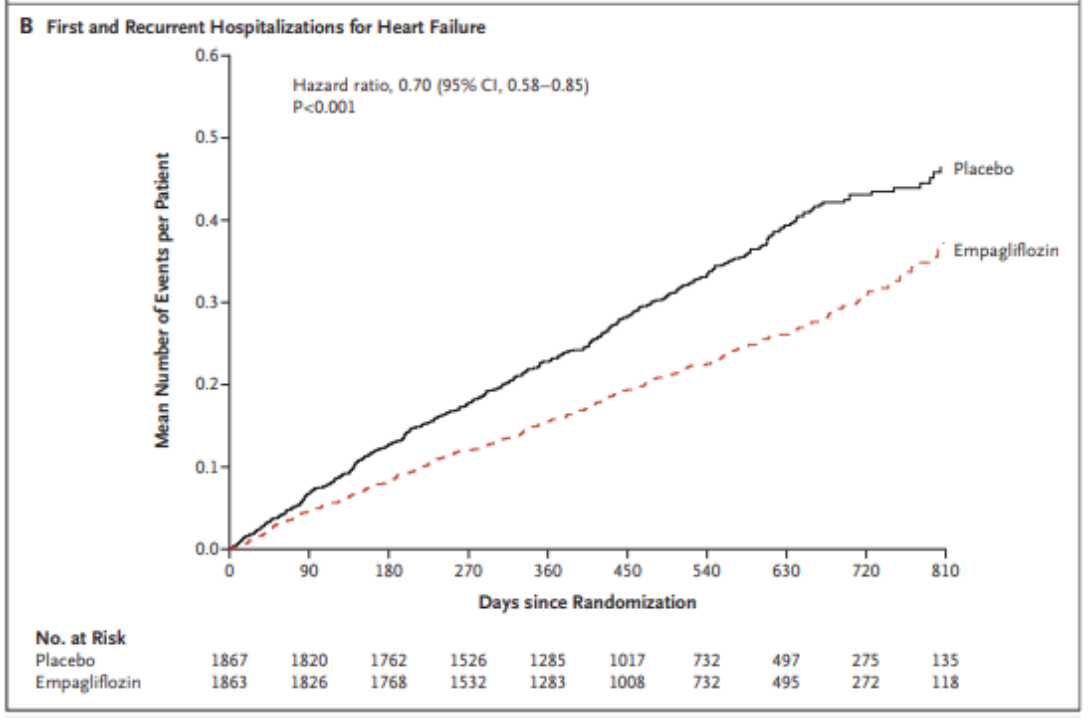
EMPEROR Reduced

In this double-blind trial, we randomly assigned 3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure.

Exclusion: Impaired renal function, defined as eGFR < 20 mL/min/1.73 m^2 or requiring dialysis

Packer M, et al. N Engl J Med. 2020;383(15):1413-1424



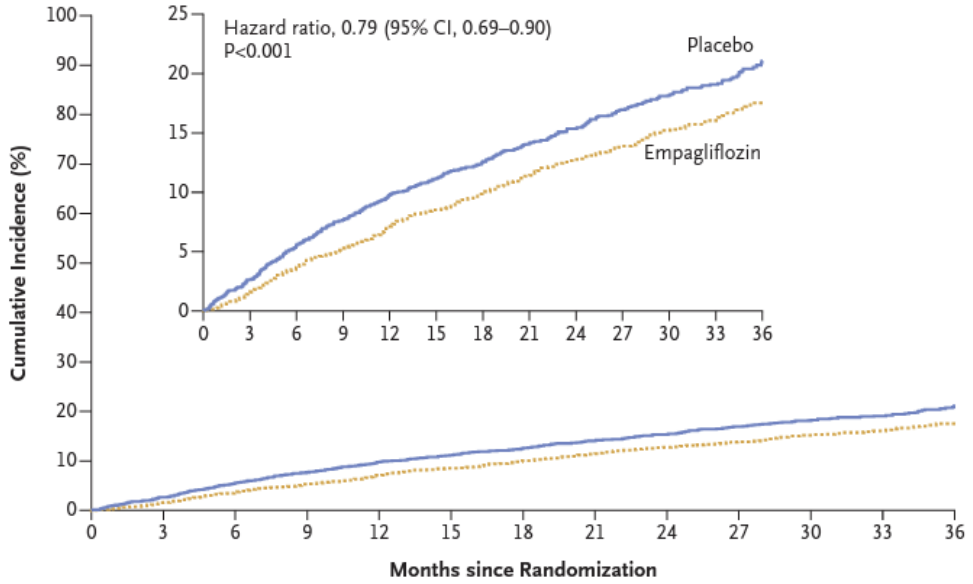


EMPEROR Preserved

In this double-blind trial, we randomly assigned 5988 patients with class II–IV heart failure and an ejection fraction of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

Exclusion: Impaired renal function, defined as eGFR < 20 mL/min/1.73 m^2 or requiring dialysis

Primary Outcome



No. at Risk													
Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

Anker SD, et al. N Engl J Med. 2021;385(16):1451-1461

Efficacy of Empagliflozin in Patients With Heart Failure Across Kidney Risk Categories

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ABSTRACT

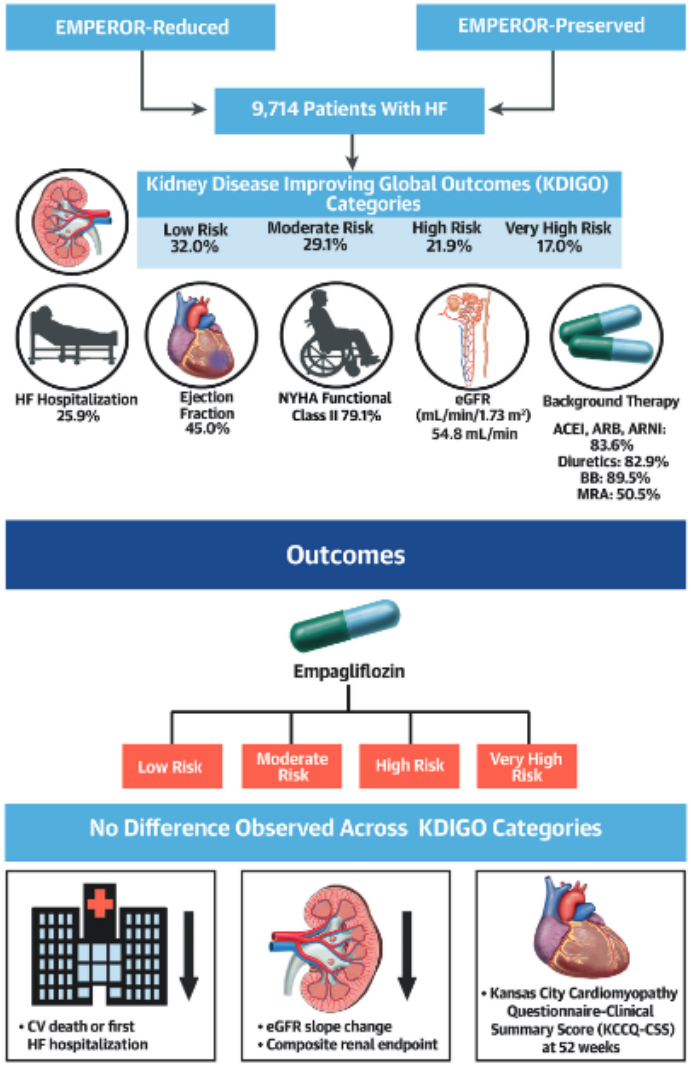
BACKGROUND Empagliflozin reduces the risk of major heart failure outcomes in heart failure with reduced or preserved ejection fraction.

OBJECTIVES The goal of this study was to evaluate the effect of empagliflozin across the spectrum of chronic kidney disease in a pooled analysis of EMPEROR-Reduced and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced or Preserved Ejection Fraction, respectively).

METHODS A total of 9,718 patients were grouped into Kidney Disease Improving Global Outcomes (KDIGO) categories based on estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio into low-, moderate-, high-, and very-high-risk categories, comprising 32.0%, 29.1%, 21.9%, and 17.0% of the participants, respectively.

RESULTS In the placebo arm, when compared with lower risk categories, patients at higher risk experienced a slower rate of decline in eGFR, but a higher risk of a composite kidney event. Empagliflozin reduced the risk of cardiovascular death or heart failure hospitalizations similarly in all KDIGO categories (HR: 0.81; 95% CI: 0.66-1.01 for low-; HR: 0.63; 95% CI: 0.52-0.76 for moderate-; HR: 0.82; 95% CI: 0.68-0.98 for high-; and HR: 0.84; 95% CI: 0.71-1.01 for very-high-risk groups; *P* trend = 0.30). Empagliflozin reduced the rate of decline in eGFR whether it was estimated by chronic slope, total slope, or unconfounded slope. When compared with the unconfounded slope, the magnitude of the effect on chronic slope was larger, and the effect on total slope was smaller. In EMPEROR-Reduced, patients at lowest risk experienced the largest effect of empagliflozin on eGFR slope; this pattern was not observed in EMPEROR-Preserved.

CONCLUSIONS The benefit of empagliflozin on major heart failure events was not influenced by KDIGO categories. The magnitude of the renal effects of the drug depended on the approach used to calculate eGFR slopes.



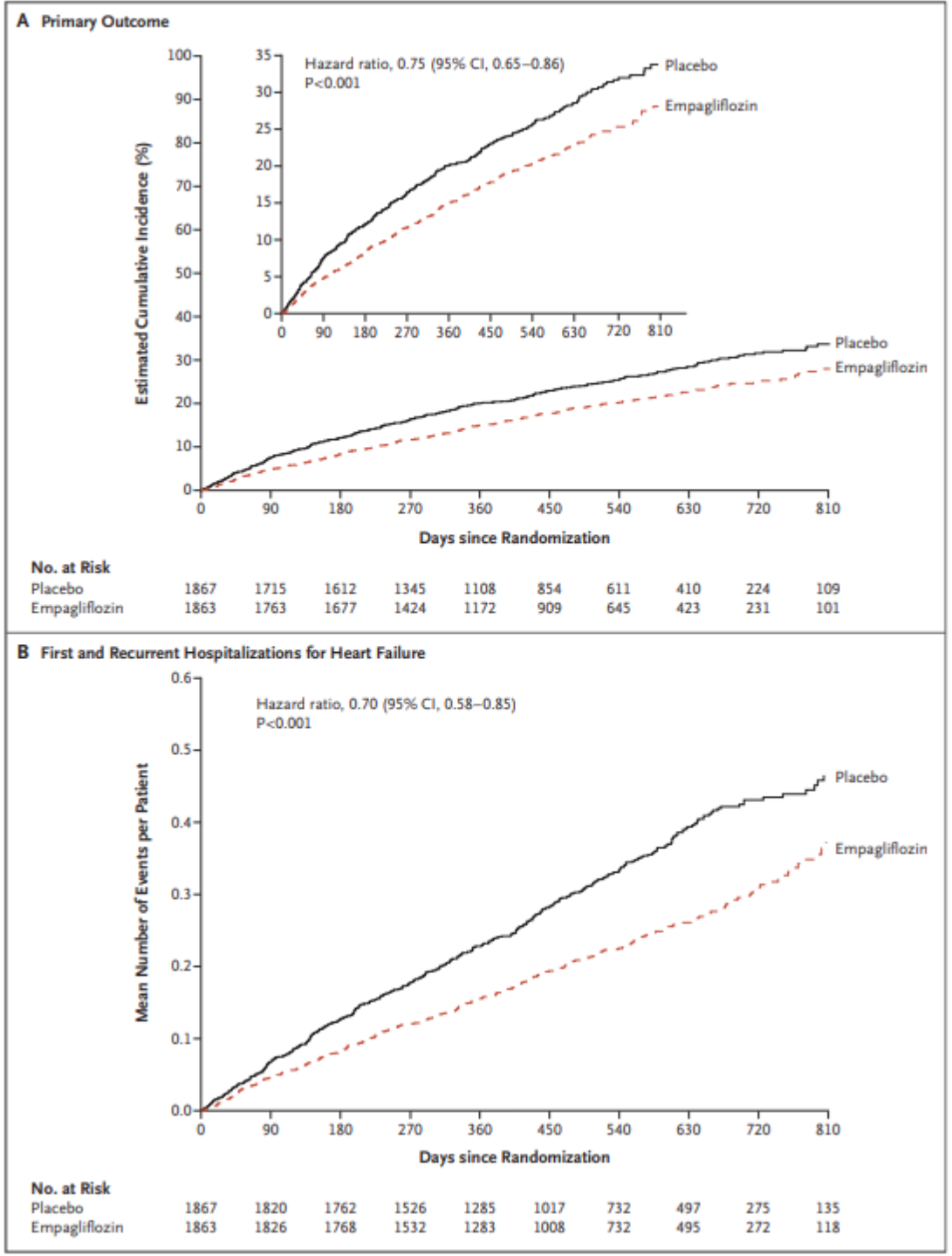
Butler J, et al. J Am Coll Cardiol. 2023;81(19):1902–1914

DAPA-HF

In this phase 3, placebo-controlled trial, we randomly assigned 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

Exclusion: Severe (eGFR <30 mL/min/1.73 m^2), unstable or rapidly progressing renal disease at the time of randomization

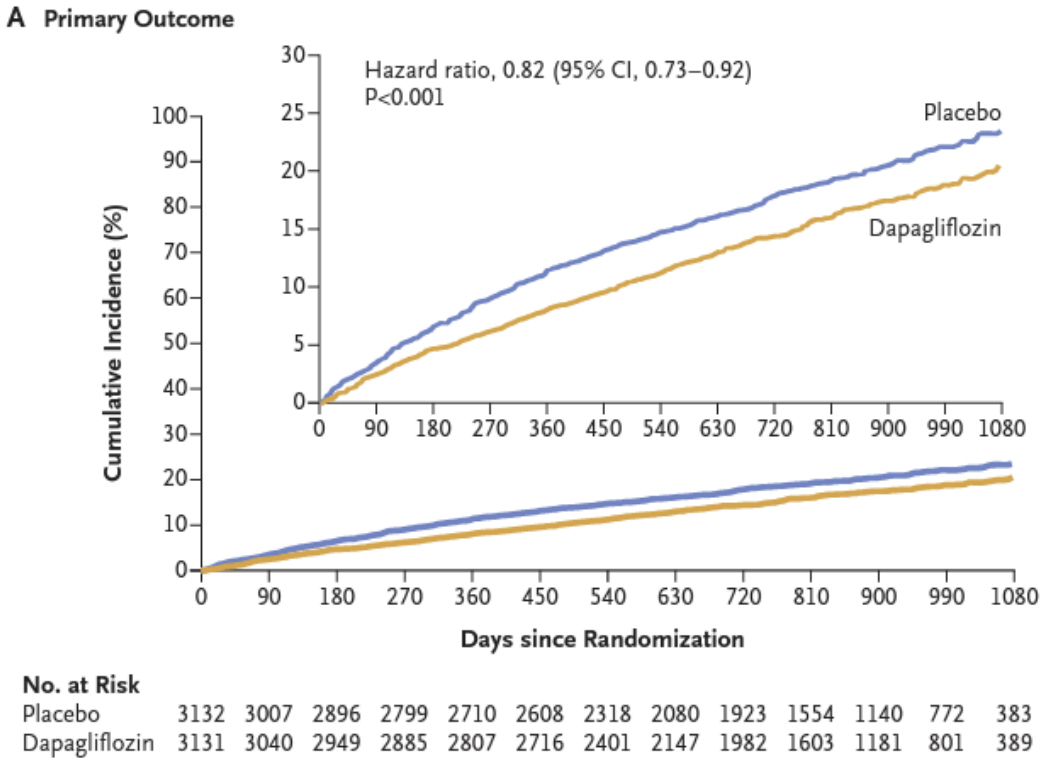
McMurray J, et al. N Engl J Med. 2019;381(21):1995-2008



DELIVER

We randomly assigned 6263 patients with heart failure and a left ventricular ejection fraction of more than 40% to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo, in addition to usual therapy. The primary outcome was a composite of worsening heart failure (which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death, as assessed in a time-to-event analysis.

Exclusion: eGFR <25 mL/min/1.73 m^2 at Visit 1.



McMurray J, et al. N Engl J Med. 2019;381(21):1995-2008

Dapagliflozin in Patients With Heart Failure and Deterioration in Renal Function

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ABSTRACT

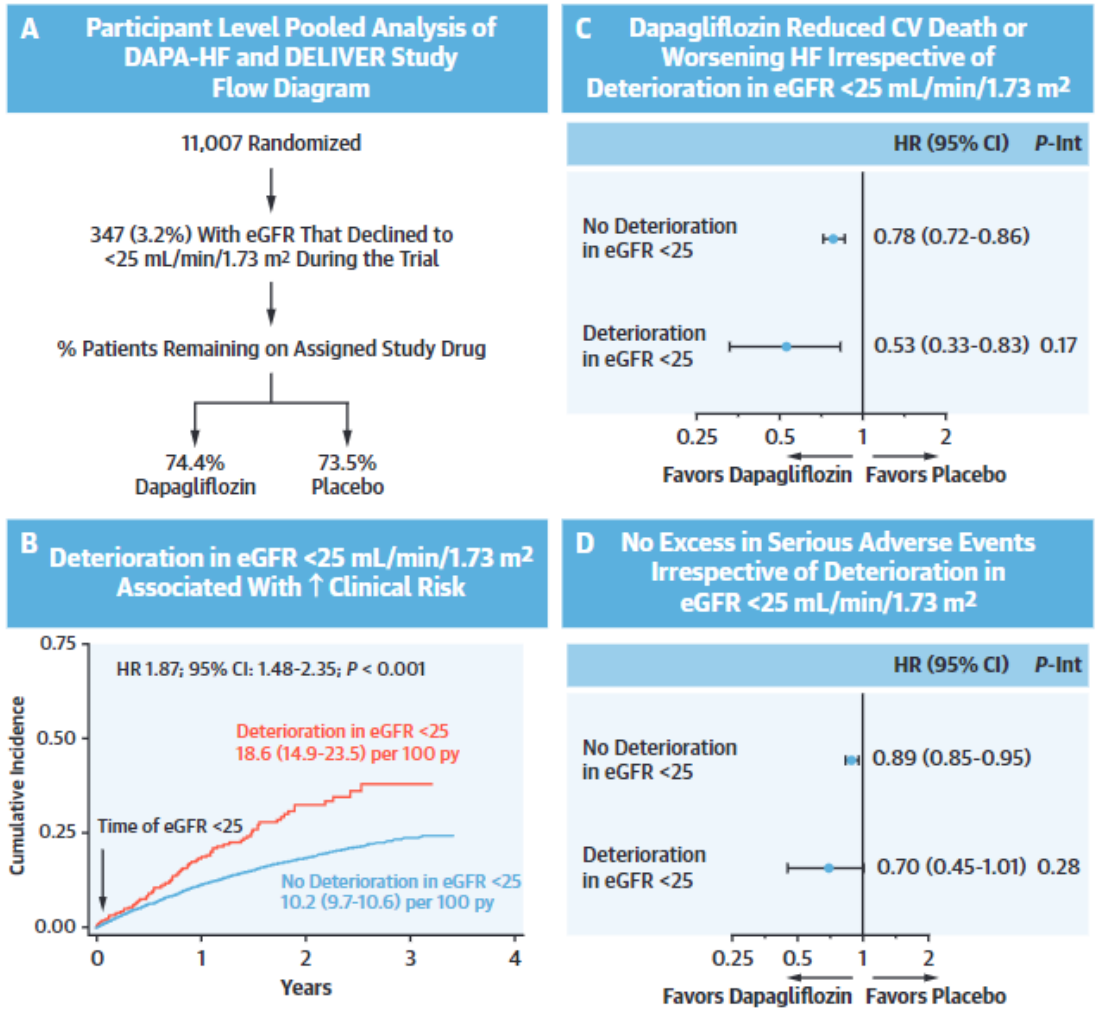
BACKGROUND Sodium-glucose cotransporter-2 (SGLT2) inhibitors are guideline recommended in the management of heart failure (HF). Although these therapies can be initiated even in patients with comorbid chronic kidney disease, some patients may face deterioration of kidney function over time.

OBJECTIVES In this study, the authors sought to examine the safety and efficacy of continuing SGLT2 inhibitors in HF when the estimated glomerular filtration rate (eGFR) falls below thresholds for initiation.

METHODS Associations between a deterioration of eGFR to <25 mL/min/1.73 m^2, efficacy, and safety outcomes and treatment with dapagliflozin were evaluated in time-updated Cox proportional hazard models in a participant-level pooled analysis of the DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) trials.

RESULTS Among 11,007 patients, 347 (3.2%) experienced a deterioration of eGFR to <25 mL/min/1.73 m^2 at least once in follow-up. These patients had a higher risk of the primary composite outcome (HR: 1.87; 95% CI: 1.48-2.35; $P < 0.001$). The risk of the primary outcome was lower with dapagliflozin compared with placebo among patients who did (HR: 0.53; 95% CI: 0.33-0.83) as well as did not (HR: 0.78; 95% CI: 0.72-0.86) experience deterioration of eGFR to <25 mL/min/1.73 m^2 ($P_{interaction} = 0.17$). The risk of safety outcomes, including drug discontinuation, was higher among patients with deterioration of eGFR to <25 mL/min/1.73 m^2; however, rates remained similar between treatment groups including among those who remained on study drug.

CONCLUSIONS Patients with deterioration of eGFR to <25 mL/min/1.73 m^2 had elevated risks of cardiovascular outcomes yet appeared to benefit from continuation of dapagliflozin with no excess in safety outcomes between treatment groups. The benefit-to-risk ratio may favor continuation of dapagliflozin treatment in patients with HF experiencing deterioration of kidney function. Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure [DAPA-HF]; NCT03036124; and Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure [DELIVER]; NCT03619213)
(J Am Coll Cardiol 2023;82:1854-1863)



Chatur S, et al. J Am Coll Cardiol. 2023;82(19):1854–1863

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2024) **0**, 1–13
https://doi.org/10.1093/ehjcvp/pvae003

REVIEW
Heart failure/cardiomyopathy

Effects of sodium-glucose co-transporter 2 inhibitors on heart failure events in chronic kidney disease: a systematic review and meta-analysis

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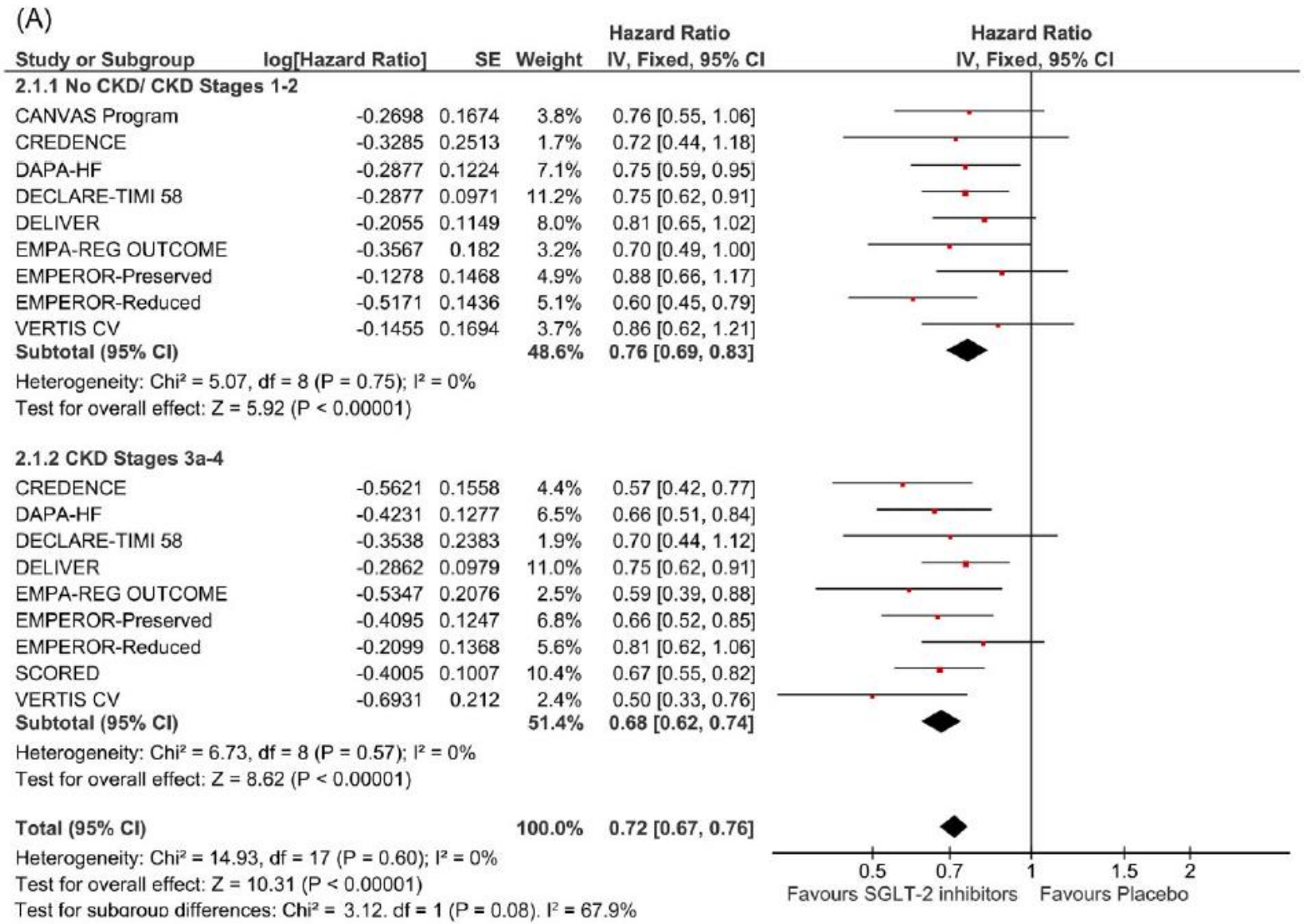
Aims Sodium-glucose co-transporter 2 (SGLT-2) inhibitors significantly reduce the risk for hospitalizations for heart failure (HF) in patients with diabetes, and HF; findings in patients with chronic kidney disease (CKD) are not uniform. We aimed to perform a meta-analysis exploring the effect of SGLT-2 inhibitors on HF events in patients with CKD and across subgroups defined by baseline kidney function.

Methods and results A systematic search in major electronic databases was performed. Randomized controlled trials (RCTs) providing data on the effect of SGLT-2 inhibitors on the primary outcome, time to hospitalization or urgent visit for worsening HF in patients with prevalent CKD at baseline or across subgroups stratified by baseline estimated glomerular-filtration-rate (eGFR) were included. Twelve studies (n = 89,191 participants) were included in the meta-analysis. In patients with CKD, treatment with SGLT-2 inhibitors reduced the risk for HF events by 32% compared to placebo [hazard ratio (HR) 0.68; 95% confidence interval (CI) 0.63–0.73]. Reduction in HF events with SGLT-2 inhibitors was more prominent in patients with eGFR <60 ml/min/1.73 m^2 (HR 0.68; 95% CI 0.62–0.74) than in those with eGFR ≥60 ml/min/1.73 m^2 (HR 0.76; 95% CI 0.69–0.83). Subgroup analysis according to type of SGLT-2 inhibitor showed a consistent treatment effect across all studied agents (p-subgroup-analysis = 0.44). Sensitivity analysis including data from studies including only diabetic patients showed an even more pronounced effect in eGFR subgroup <60 ml/min/1.73 m^2 (HR 0.62; 95% CI 0.54–0.70).

Conclusion Treatment with SGLT-2 inhibitors led to a significant reduction in HF events in patients with CKD. Such findings may change the landscape of prevention of HF events in patients with advanced CKD.
PROSPERO Registration number CRD42022382857.

Keywords SGLT-2 inhibitors • Chronic kidney disease • Heart failure • Hospitalization for heart failure

Theodorakopoulou M…Sarafidis P. Eur Heart J-CV Pharm. 2024; 0: 1-13



Theodorakopoulou M…Sarafidis P.
Eur Heart J-CV Pharm. 2024; 0: 1-13

NEJM Journal Watch

SUMMARY AND COMMENT | GENERAL MEDICINE, AMBULATORY MEDICINE, HOSPITAL MEDICINE

INFORMING PRACTICE

May 9, 2024

SGLT-2 Inhibitors in Patients with Stage 5 CKD?

Daniel D. Dressler, MD, MSc, MHM, FACP, reviewing Yen F-S et al. Ann Intern Med 2024 Apr 30

In a retrospective study, patients with severe chronic kidney disease who received SGLT-2 inhibitors had better outcomes than patients who didn't.

Randomized clinical trials have shown that sodium–glucose cotransporter-2 (SGLT-2) inhibitors slow progression of chronic kidney disease (CKD) and need for dialysis (e.g., NEJM JW Gen Med Dec 1 2022 and *N Engl J Med* 2023; 388:117). Although various guidelines suggest initiating SGLT-2 inhibitors in patients with estimated glomerular filtration rates (eGFR) of ≥20 mL/minute/1.73 m^2, SGLT-2 inhibitors have not been evaluated in patients with stage 5 CKD (CKD 5; eGFR, ≤15 mL/minute/1.73 m^2). Investigators in Taiwan retrospectively assessed 5 years of outcome data for nearly 48,000 patients with type 2 diabetes and CKD 5 — half of patients had newly initiated SGLT-2 inhibitors, and half were not taking these drugs.

Compared with SGLT-2 inhibitor nonusers, users had significantly lower risk for dialysis (adjusted hazard ratio, 0.34) and fewer hospitalizations for heart failure, acute myocardial infarction, diabetic ketoacidosis, and acute kidney injury (aHRs, 0.6–0.8). All-cause mortality was similar in the two groups.

COMMENT

This study was retrospective, with inherent risks for residual confounding, so the authors stop short of recommending that patients with CKD 5 routinely be prescribed SGLT-2 inhibitors. Nevertheless, this first analysis in patients with severe renal disease shows that SGLT-2 inhibitors probably are associated with outcome improvements — including less progression to dialysis. It might pave the way for considering these medications in a broader group of patients with CKD.

CITATIONS

Yen F-S et al. Sodium–glucose cotransporter-2 inhibitors and the risk for dialysis and cardiovascular disease in patients with stage 5 chronic kidney disease. *Ann Intern Med* 2024 Apr 30; [e-pub]. (https://doi.org/10.7326/M23-1874)

Sodium Glucose Co-Transporter 2 inhibitor (SGLT2i)

Findings in CKD Subgroups

	All Cause Mortality	CV Death / HF Hospitalization
Overall	8-18 % RRR	25-29% RRR
CKD Stages (eGFR in mL/min/1.73m²)		
CKD stage 1 (> 90)	3 -19% RRR[85,86]	10 – 27% RRR[86,85]
CKD stage 2 (60-89)		
CKD stage 3A (45-59)	9 - 15% RRR[85,86]	9 – 15% RRR[85]
CKD stage 3B (30-44)		8 – 41% RRR[85,86]
CKD stage 4 (15-29)	No information in HFREF	32% RRR [85]
CKD stage 5 (<15/Dialysis)	**No information in HFREF**	

Effect on Renal Function

It is hypothesized that SGLT2i cause afferent arteriolar vasoconstriction (and possibly some efferent vasodilation) due to activated tubuloglomerular feedback caused by more distal sodium delivery to macula densa.

Early decline in eGFR after initiation (0.3-4.0 mL/min/1.73m²)[85,86]	Long term slope in eGFR less with SGLT2i vs Placebo: -0.6 to 1.09 vs. -2.3 to 2.9 mL/min/1.73m²/year[85,86]	Drop in eGFR with SGLT2i no reason to discontinue

Management of substantial increase in serum creatinine/drop in eGFR during initiation/uptitration

In the context of initiation of SGLT2i some increase in serum creatinine / drop in eGFR is expected and acceptable.

Δ serum creatinine (%)	**Max serum creatinine** (mg/dL)	**Min eGFR** mL/min/1.73m²	**Action advised**
< 50	**2.5 mg/dL**	**30**	None, continue SGLT2i and reevaluate renal function regularly
50-100	**3.5 mg/dL**	**20**	Continue SGLT2i if eGFR/or serum creatinine are acceptable. Evaluate other causes in parallel. SGLT2i do not cause hyperkalemia. Evaluate potassium if creatinine rises steeply
> 100	**> 3.5 mg/dL**	**< 20**	Such large increases in serum creatinine are unexpected with SGLT2i and should prompt further evaluation. . SGLT2i do not cause hyperkalemia. Evaluate potassium if creatinine rises steeply. If deemed clinically appropriate, continue SGLT2i with close monitoring; if no other option, stop SGLT2i.

Rechallenge after 2-4 weeks (if possible at lower dose) when dosing reduced or stopped all together if renal function has improved

Beldhuis IE, et al. Circulation. 2022;145(9):693-712

The NEW ENGLAND JOURNAL of MEDICINE

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Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. Van der Meer, D. von Lewinski, D. Wolf, and M.C Petrie, for the STEP-HFpEF Trial Committees and Investigators*

We randomly assigned 529 patients who had HFpEF and a BMI of 30 or higher to receive once-weekly **semaglutide (2.4 mg)** or **placebo** for 52 weeks.

The dual primary end points were the change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations) and the change in body weight.

Table 1. Baseline Demographic and Clinical Characteristics of the Participants.*

Characteristic	Semaglutide (N = 263)	Placebo (N = 266)	Total (N = 529)
Female sex — no. (%)	149 (56.7)	148 (55.6)	297 (56.1)
Median age (IQR) — yr	70 (62–75)	69 (62–75)	69 (62–75)
Ethnic group — no. (%)†			
Hispanic or Latino	15 (5.7)	21 (7.9)	36 (6.8)
Not Hispanic or Latino	248 (94.3)	245 (92.1)	493 (93.2)
Race — no. (%)†			
Black	8 (3.0)	13 (4.9)	21 (4.0)
White	255 (97.0)	252 (94.7)	507 (95.8)
Other	0	1 (0.4)	1 (0.2)
Median body weight (IQR) — kg	104.7 (92.4–120.1)	105.3 (92.4–122.0)	105.1 (92.4–120.8)
Median BMI (IQR)	37.2 (33.9–41.1)	36.9 (33.3–41.6)	37.0 (33.7–41.4)
BMI stratum — no. (%)			
30 to <35	89 (33.8)	91 (34.2)	180 (34.0)
≥35	174 (66.2)	175 (65.8)	349 (66.0)
Median waist circumference (IQR) — cm	119.0 (110.5–127.1)	120.0 (110.5–129.0)	119.4 (110.5–128.0)
Median systolic blood pressure (IQR) — mm Hg	133 (122–145)	132 (120–142)	133 (121–144)
Median NT-proBNP level (IQR) — pg/ml	414.4 (229.2–1014.0)	499.8 (204.7–1025.0)	450.8 (218.2–1015.0)
Median CRP level (IQR) — mg/liter	3.8 (1.9–7.0)	3.9 (2.0–8.4)	3.8 (1.9–7.7)
Median LVEF (IQR) — %	57.0 (50.0–60.0)	57.0 (50.0–60.0)	57.0 (50.0–60.0)
LVEF stratum — no. (%)			
45 to <50%‡	37 (14.1)	48 (18.0)	85 (16.1)
50 to 59%	113 (43.0)	102 (38.3)	215 (40.6)
≥60%	113 (43.0)	116 (43.6)	229 (43.3)
Median KCCQ-CSS (IQR) — points§	59.4 (42.7–72.9)	58.3 (40.5–72.9)	58.9 (41.7–72.9)
Median 6-minute walk distance (IQR) — m	316.0 (251.0–386.0)	325.8 (232.4–392.0)	320.0 (240.0–389.0)
Hospitalization for heart failure within 1 year — no. (%)	42 (16.0)	39 (14.7)	81 (15.3)
Coexisting conditions at screening — no. (%)			
Atrial fibrillation	135 (51.3)	140 (52.6)	275 (52.0)
Hypertension	216 (82.1)	217 (81.6)	433 (81.9)
Coronary artery disease	53 (20.2)	45 (16.9)	98 (18.5)
NYHA functional class — no. (%)			
II	183 (69.6)	167 (62.8)	350 (66.2)
III or IV	80 (30.4)	99 (37.2)	179 (33.8)
Concomitant medication — no. (%)			
Diuretic	207 (78.7)	220 (82.7)	427 (80.7)
Loop diuretic	158 (60.1)	171 (64.3)	329 (62.2)
Thiazide	40 (15.2)	50 (18.8)	90 (17.0)
MRA	89 (33.8)	95 (35.7)	184 (34.8)
ACEI, ARB, or ARNI	210 (79.8)	214 (80.5)	424 (80.2)
Beta-blocker	201 (76.4)	217 (81.6)	418 (79.0)
SGLT2 inhibitor	8 (3.0)	11 (4.1)	19 (3.6)

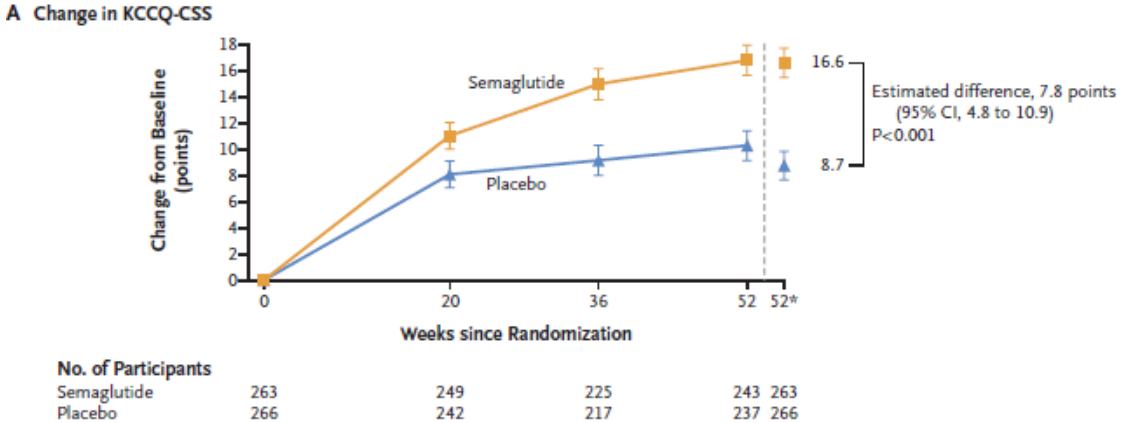
Kosiborod MN, et al. N Engl J Med. 2023;389(12):1069-1084

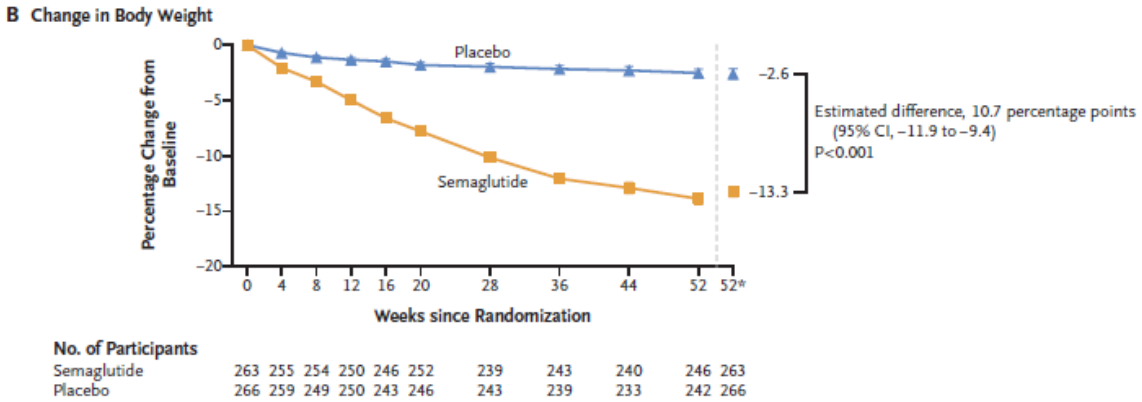
The NEW ENGLAND JOURNAL of MEDICINE

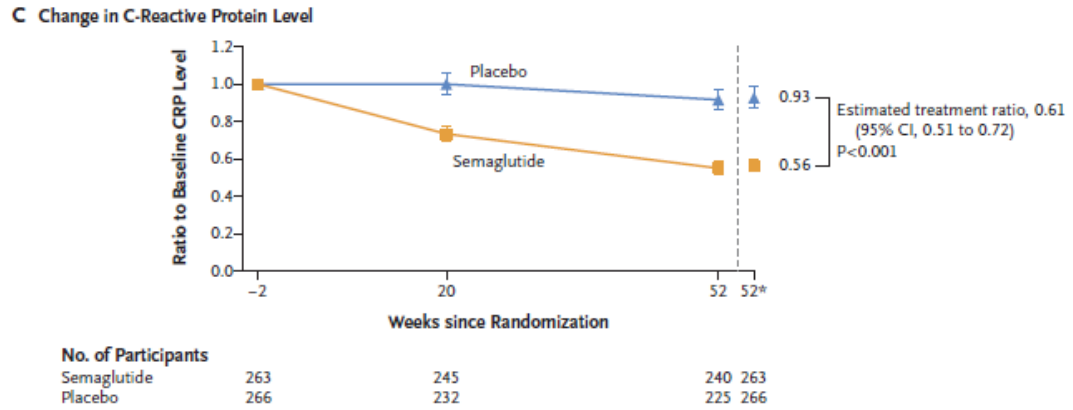
ESTABLISHED IN 1812 SEPTEMBER 21, 2023 VOL. 389 NO. 12

Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. Van der Meer, D. von Lewinski, D. Wolf, and M.C Petrie, for the STEP-HFpEF Trial Committees and Investigators*



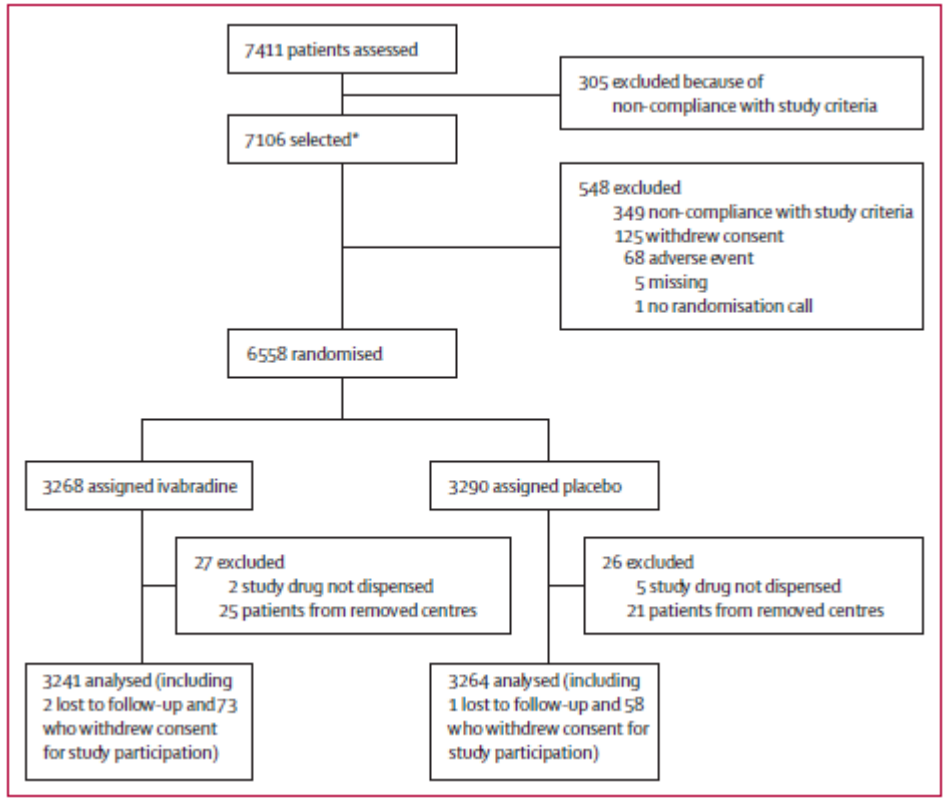




Kosiborod MN, et al. N Engl J Med. 2023;389(12):1069-1084

Other HF treatments

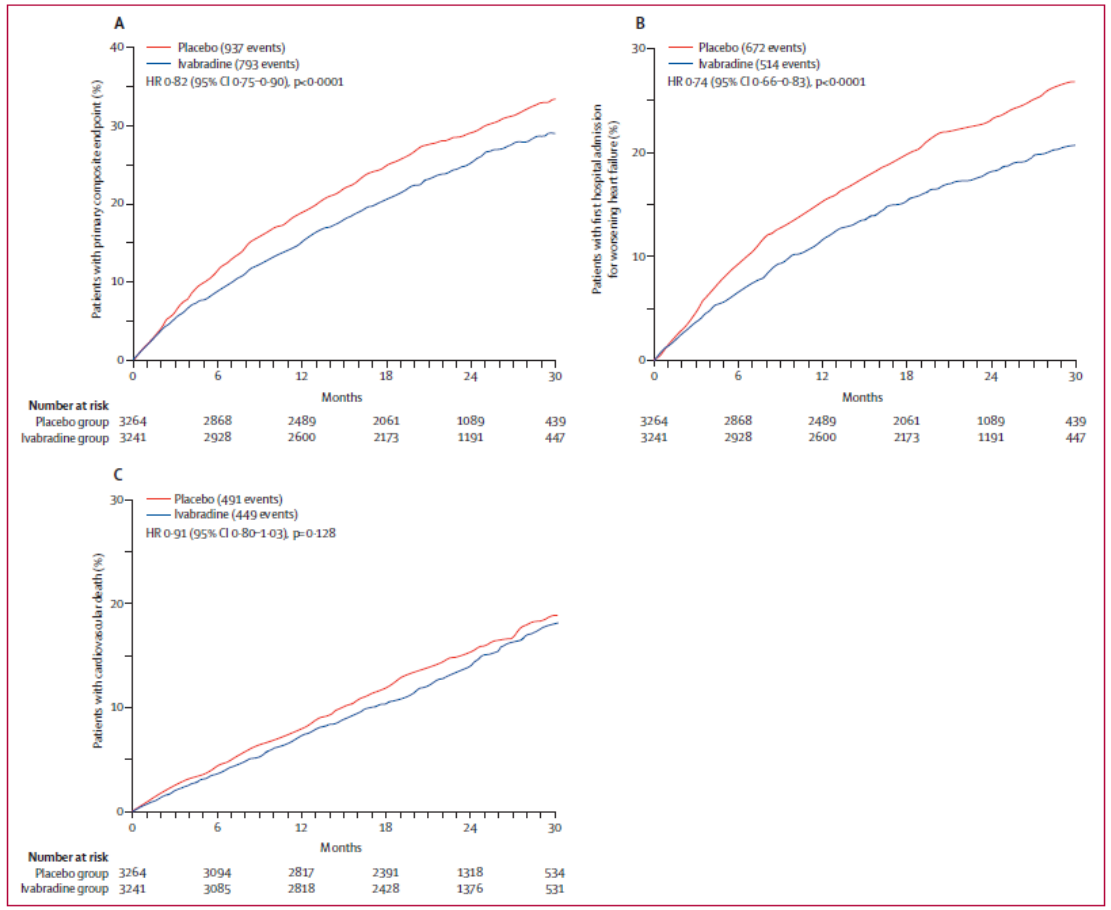
Systolic Heart Failure Treatment With the *IF* Inhibitor Ivabradine Trial *(SHIFT)*



- 6,558 patients were randomly assigned to treatment groups (3,268 ivabradine, 3,290 placebo)
- Median follow-up 22.9 (IQR 18–28) months
- NYHA II-III
- LVEF ≤35%
- SR, HR ≥70 bmp

Swedberg K, et al. Lancet. 2010;376(9744):875-85

Outcomes



Kaplan-Meier cumulative event curves for (A) the primary composite endpoint of cardiovascular death or hospital admission for worsening heart failure, (B) hospital admission for worsening heart failure, and (C) cardiovascular death.

There was no formal renal function cutoff as exclusion criteria besides “severe renal disease.” The beneficial effect of ivabradine on the combined end point was similar in patients with eGFR higher and lower than 60 mL/min/1.73 m^2. As expected from the mechanism of action, ivabradine had no effect on eGFR or serum creatinine over time.

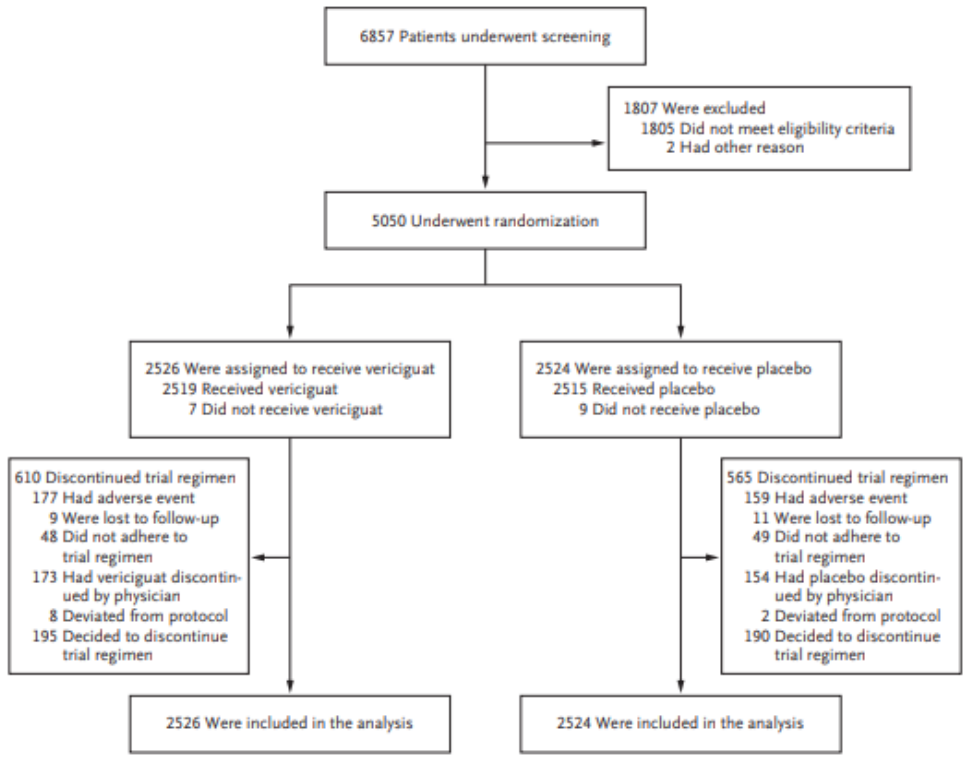
Swedberg K, et al. Lancet. 2010;376(9744):875-85

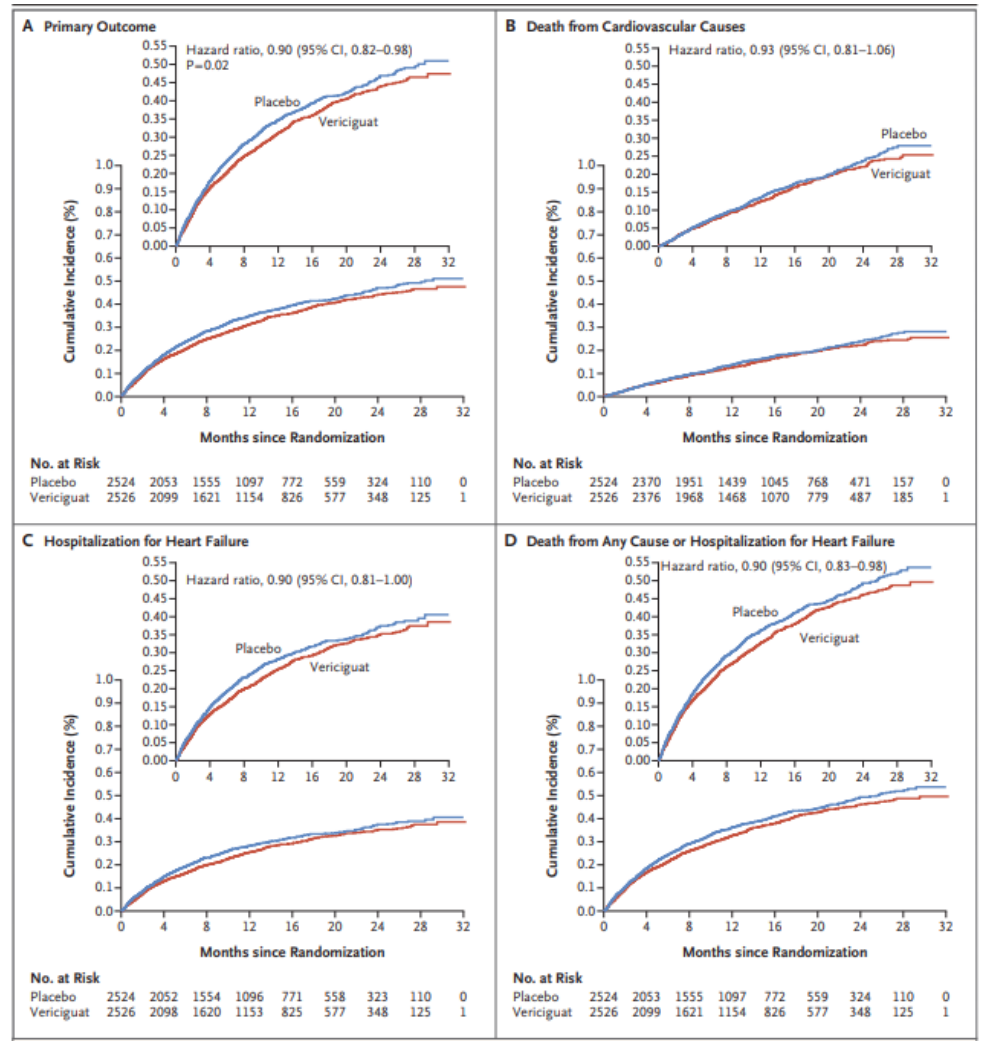
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 14, 2020 VOL. 382 NO. 20

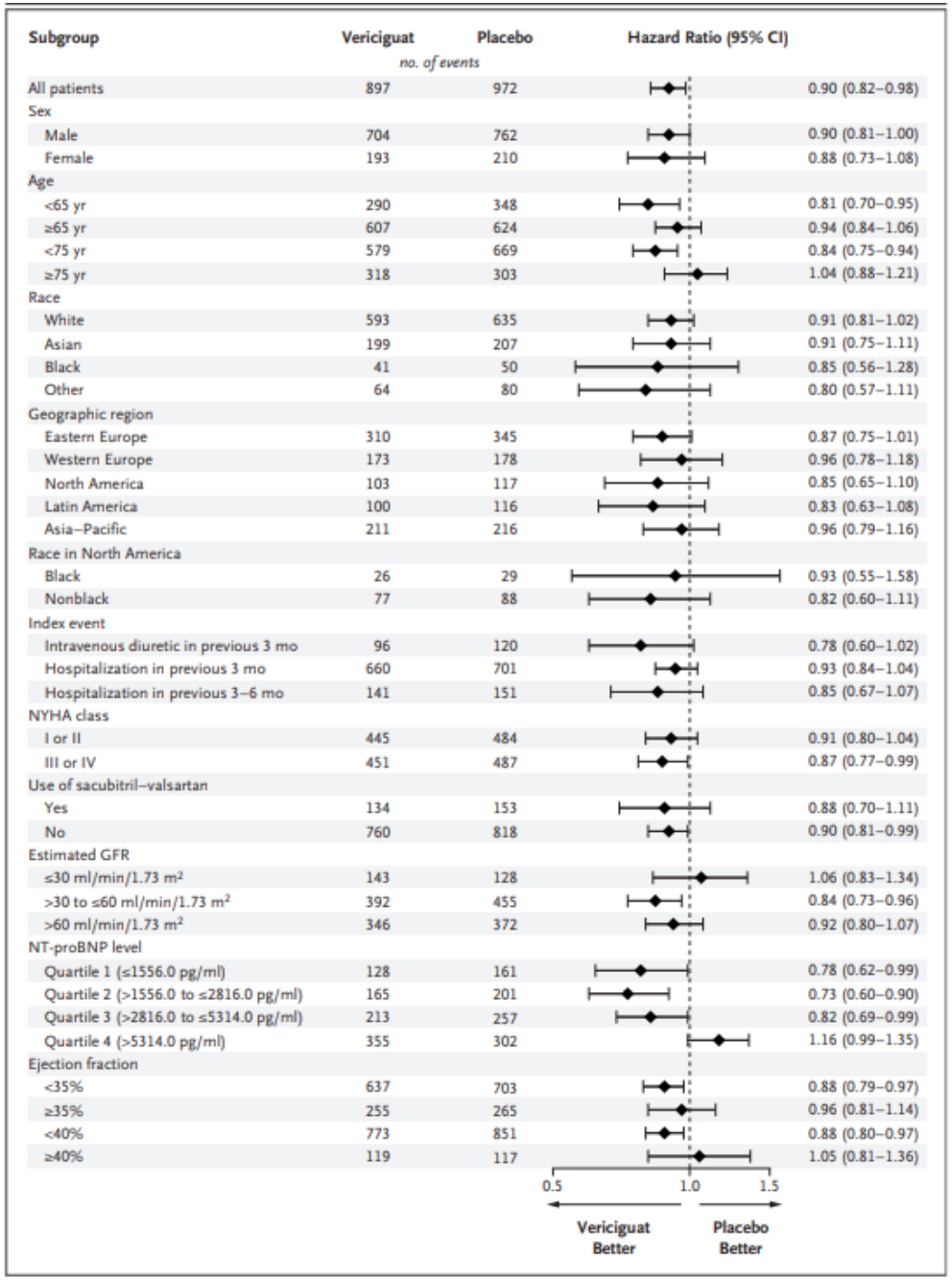
Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

Paul W. Armstrong, M.D., Burkert Pieske, M.D., Kevin J. Anstrom, Ph.D., Justin Ezekowitz, M.B., B.Ch., Adrian F. Hernandez, M.D., M.H.S., Javed Butler, M.D., M.P.H., M.B.A., Carolyn S.P. Lam, M.B., B.S., Ph.D., Piotr Ponikowski, M.D., Adriaan A. Voors, M.D., Ph.D., Gang Jia, Ph.D., Steven E. McNulty, M.S., Mahesh J. Patel, M.D., Lothar Roessig, M.D., Joerg Koglin, M.D., Ph.D., and Christopher M. O'Connor, M.D., for the VICTORIA Study Group*





Armstrong PW, et al. N Engl J Med. 2020;382(20):1883-1893



	PARADIGM-HF	DAPA-HF	VICTORIA
NYHA III-IV	25%	32%	41%
Median NT-proBNP	1608	1437	2816

Symptomatic hypotension occurred in 9.1% of the patients in the vericiguat group and in 7.9% of the patients in the placebo group (P=0.12), and syncope occurred in 4.0% of the patients in the vericiguat group and in 3.5% of the patients in the placebo group (P=0.30)

In this study, the lower limit of eGFR allowed by protocol was 15 mL/min/1.73 m^2, and it was intended that 15% of patients should have an eGFR between 15 and 30 mL/min/1.73 m^2

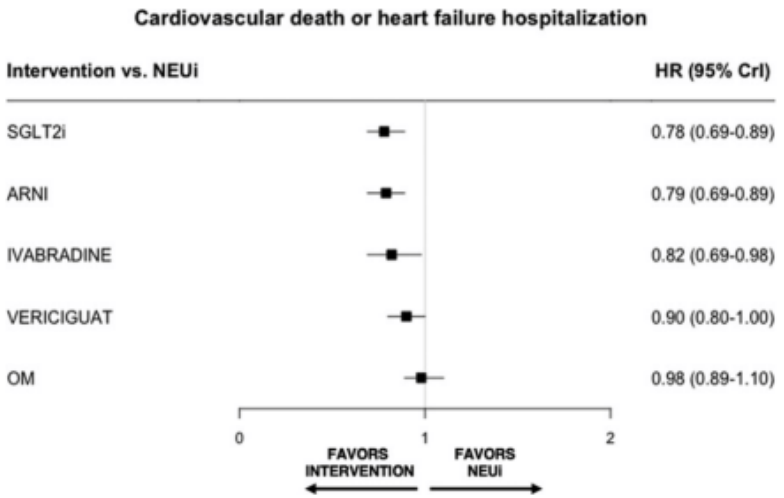
During 48 weeks of treatment, the trajectories in eGFR and creatinine with vericiguat were similar to placebo (P = 0.50 and 0.18). The beneficial effects of vericiguat on the primary outcome were not influenced by baseline eGFR (interaction P = 0.48)

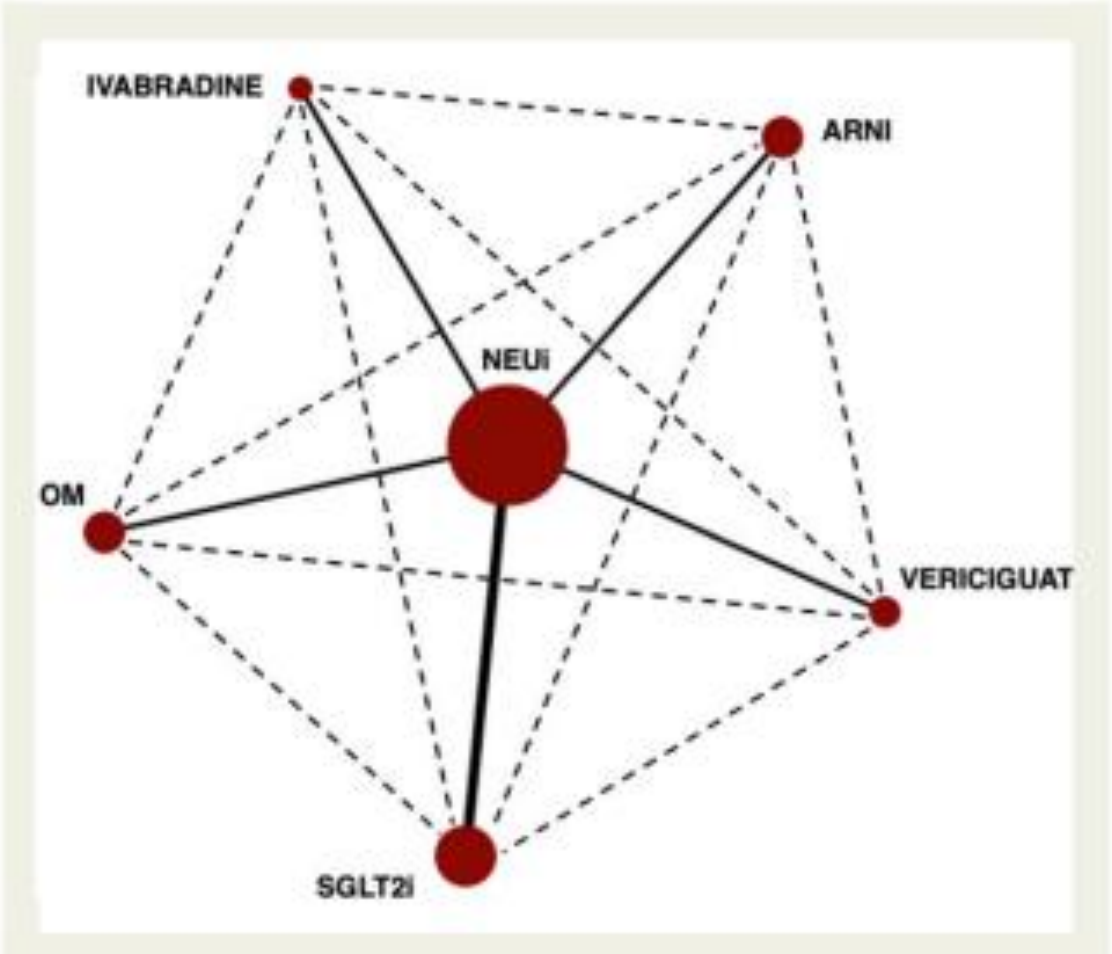
Armstrong PW, et al. N Engl J Med. 2020;382(20):1883-1893
Voors AL, et al. Eur J Heart Fail. 2021;23(8):1313-1321

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Pharmacotherapy (2022) **8**, 768–776
https://doi.org/10.1093/ehjcvp/pvab088
ORIGINAL ARTICLE
Heart failure/cardiomyopathy

Efficacy of new medical therapies in patients with heart failure, reduced ejection fraction, and chronic kidney disease already receiving neurohormonal inhibitors: a network meta-analysis

Pietro Ameri[1,2,*,†], Vincenzo De Marzo[1,2,†], Giuseppe Biondi Zoccai[3,4], Lucia Tricarico[5,6], Michele Correale[5], Natale Daniele Brunetti[5,6], Marco Canepa[1,2], Gaetano Maria De Ferrari[7,8], Davide Castagno[7,8] and Italo Porto[1,2]





NEUi: neurohormonal inhibition
OM: Omecamtiv Mecarbil

The New England
Journal of Medicine

VOLUME 336 FEBRUARY 20, 1997 NUMBER 8

THE EFFECT OF DIGOXIN ON MORTALITY AND MORBIDITY IN PATIENTS WITH HEART FAILURE

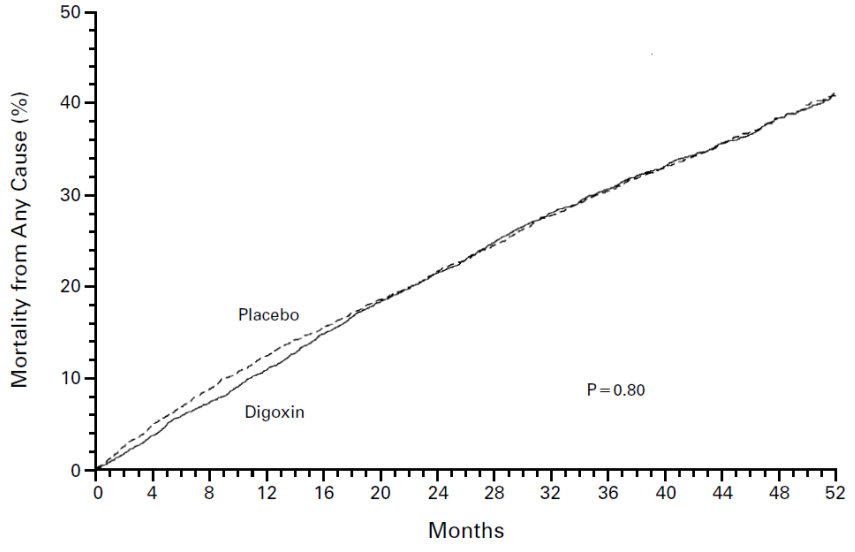
THE DIGITALIS INVESTIGATION GROUP*

In the main trial, patients with left ventricular ejection fractions of 0.45 or less were randomly assigned to digoxin (3397 patients) or placebo (3403 patients) in addition to diuretics and angiotensin-converting–enzyme inhibitors (median dose of digoxin, 0.25 mg per day; average follow-up, 37 months). In an ancillary trial of patients with ejection fractions greater than 0.45, 492 patients were randomly assigned to digoxin and 496 to placebo.

In the DIG study (Digitalis Investigation Group) with digoxin, patients were included up to a serum creatinine level of 3.0 mg/dL, which roughly corresponds to an eGFR of around 20 mL/min/1.73 m^2.

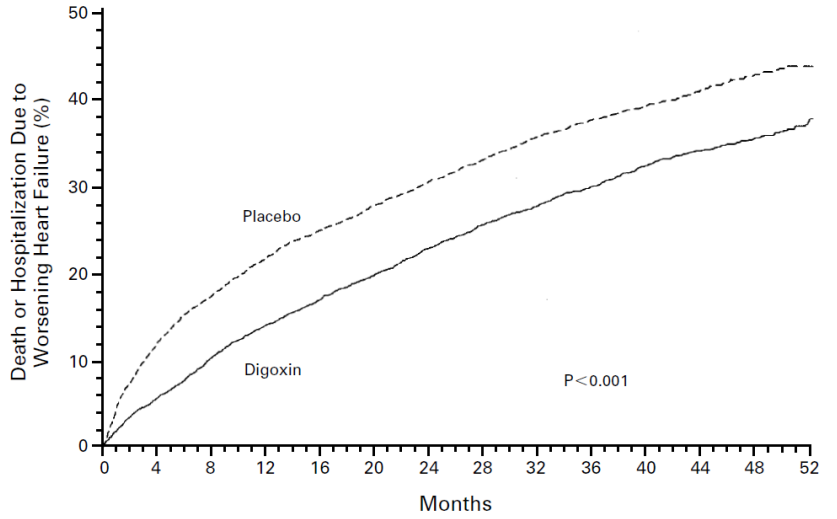
The effect of digoxin on HF-related death and HF rehospitalization was similar in all CKD stages

Digitalis Investigation Group. N Engl J Med. 1997;336(8):525-33.



NO. OF PATIENTS AT RISK

Placebo	3403	3239	3105	2976	2868	2758	2652	2551	2205	1881	1506	1168	734	339
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335



NO. OF PATIENTS AT RISK

Placebo	3403	2915	2674	2473	2328	2197	2071	1954	1659	1397	1111	859	546	250
Digoxin	3397	3120	2888	2696	2544	2392	2241	2115	1825	1521	1188	916	578	255

ESC European Society of Cardiology

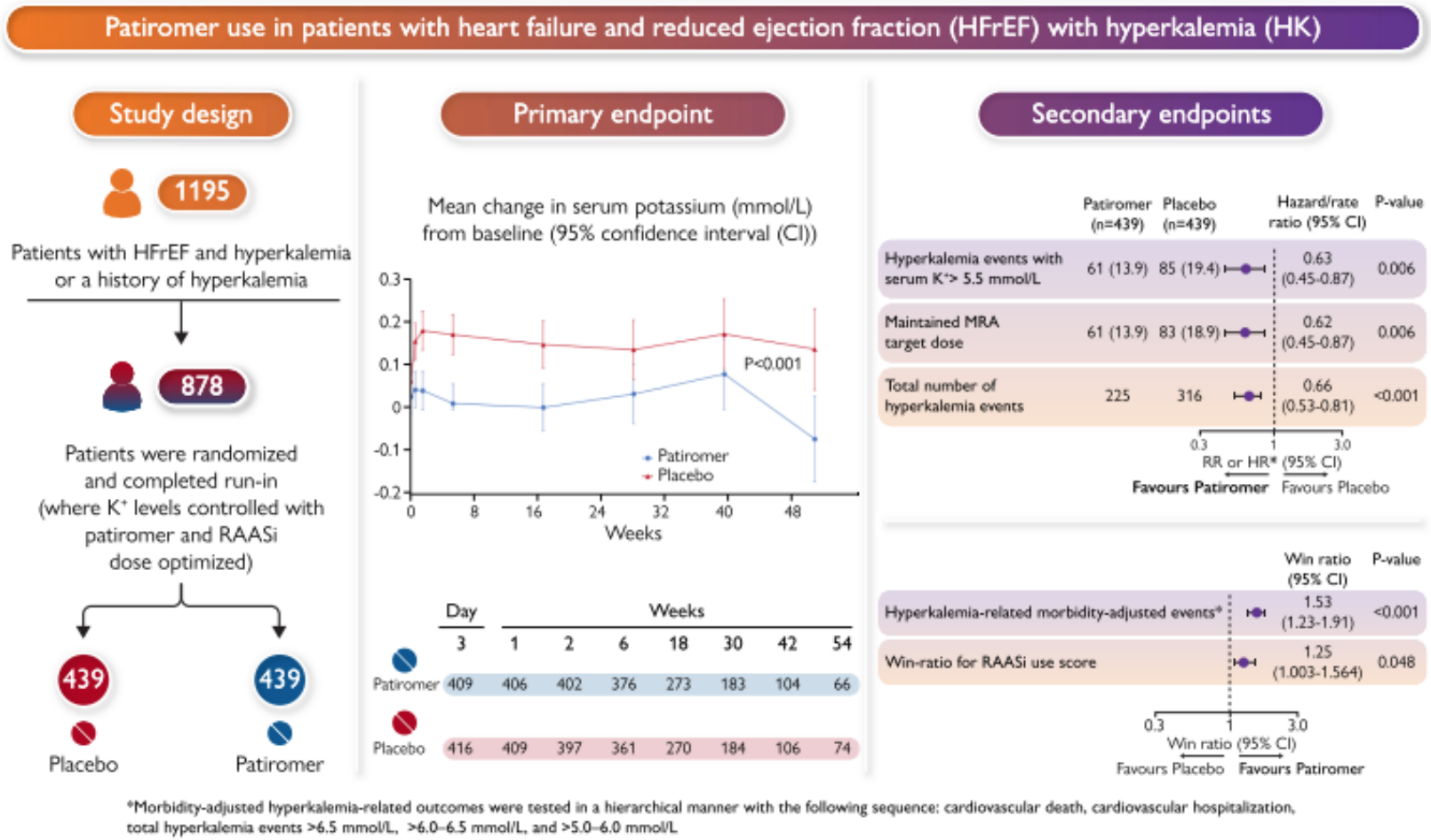
European Journal of Heart Failure (2019) 21, 676–684
doi:10.1002/ejhf.1452

STUDY DESIGN

Rationale and design of the DIGIT-HF trial (DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure): a randomized, double-blind, placebo-controlled study

- Patients with chronic HF, NYHA functional class III–IV and LVEF ≤40%, or patients in NYHA functional class II and LVEF ≤30% are randomized 1:1 in a double-blind fashion to treatment with digitoxin (target serum concentration 8–18 ng/mL) or matching placebo.
- A total of 2190 eligible patients will be included in this clinical trial (1095 per group).
- The primary outcome is a composite of all-cause mortality or hospital admission for worsening HF (whatever occurs first).
- Key secondary endpoints are all-cause mortality, hospital admission for worsening HF, and recurrent hospital admission for worsening HF.

Bavendiek U, et al. Eur J Heart Fail. 2019;21(5):676-684



*Morbidity-adjusted hyperkalemia-related outcomes were tested in a hierarchical manner with the following sequence: cardiovascular death, cardiovascular hospitalization, total hyperkalemia events >6.5 mmol/L, >6.0–6.5 mmol/L, and >5.0–6.0 mmol/L

Patients with eGFR <30 ml/min/1.73 m2 were excluded!!!

Butler J, et al. Eur Heart J. 2022; 43:4362–4373

- Diuretic Resistance

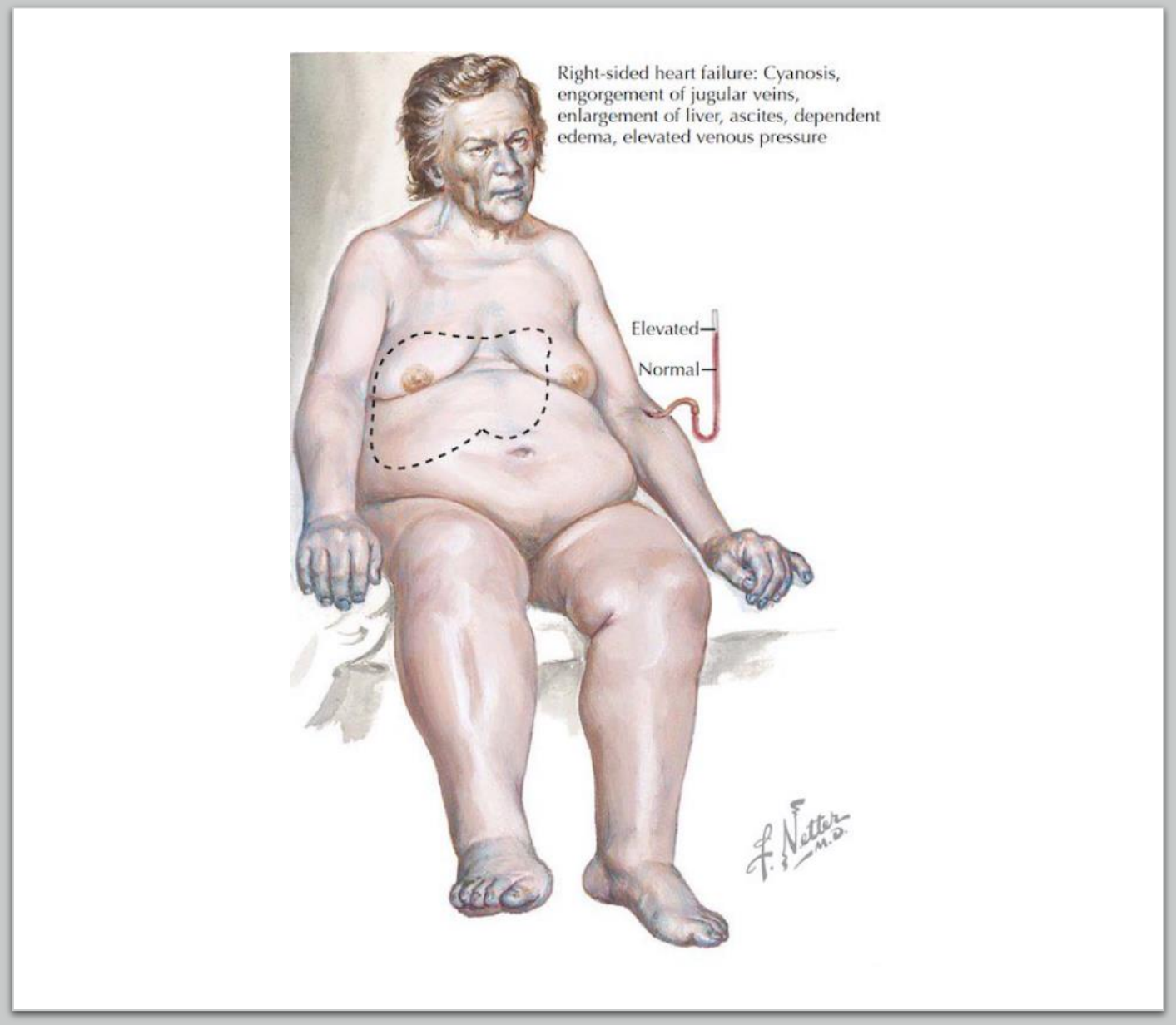


Table 1. Causes of Diuretic Resistance.

- Inadequate dose of diuretic
- Nonadherence
  - Not taking drug
  - High sodium intake
- Pharmacokinetic factors
  - Slow absorption of diuretic because of gut edema
  - Impaired secretion of diuretic into the tubule lumen
    - Chronic kidney disease
    - Aging
    - Drugs
      - Nonsteroidal antiinflammatory drugs*
      - Probenecid
- Hypoproteinemia
- Hypotension
- Nephrotic syndrome
- Antinatriuretic drugs
  - Nonsteroidal antiinflammatory drugs*
  - Antihypertensive agents
- Low renal blood flow
- Nephron remodeling
- Neurohormonal activation

Ellison DH, Felker GM.
N Engl J Med 2017; 377:1964-75

Practical Approach to Diuretic Resistance

- Assessment of compliance with salt restriction and medicine intake (if necessary measure salt and diuretic in the urine).
- Discontinue NSAIDs.
- Adjust the dose of the diuretic in patients with renal impairment.
- Switch from furosemide to tor(a)semide or bumetanide
- Switch to IV administration to overcome problems associated with oral absorption.
- Combine loop diuretics with other diuretics, preferably a thiazide diuretic.
- Consider tolvaptan, dopamine (HFrEF) or hypertonic saline when other options have failed (?).

De Bruyne LK. Postgrad Med J 2003; 79:268-71
Bowman BN, et al. Cardiology in Review 2016; 24: 256–260
Wan SH, et al. Circ Heart Fail. 2016;9:e002593

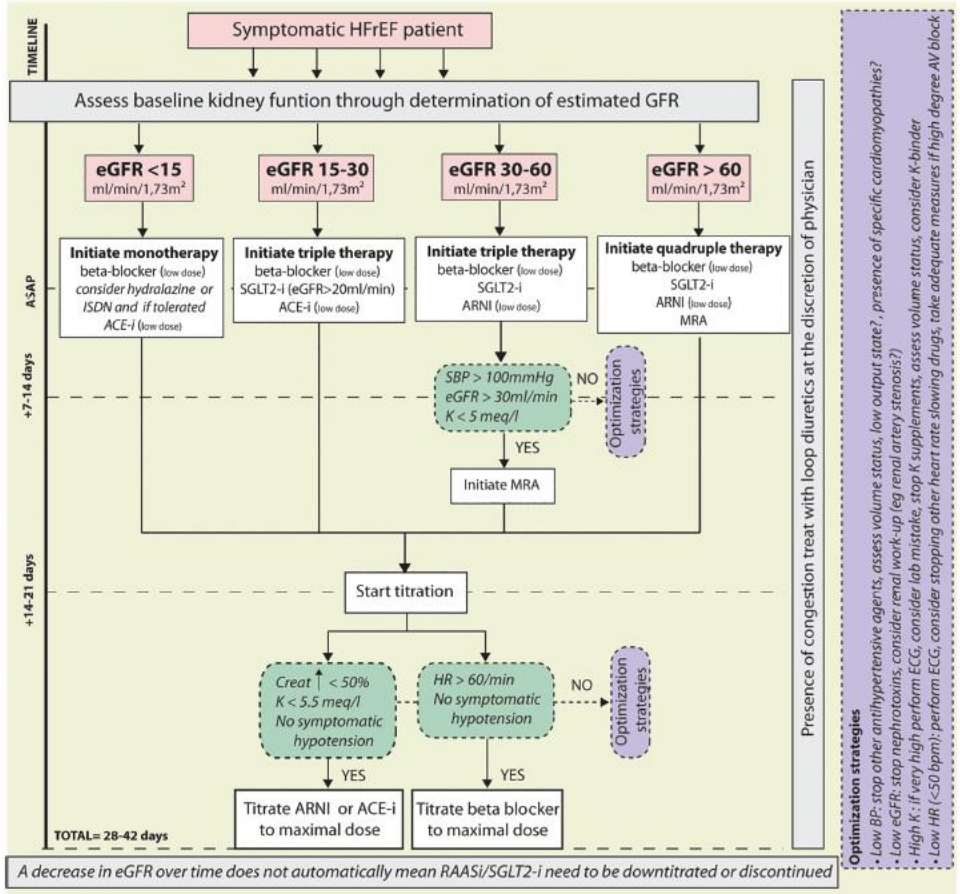
ESC European Society of Cardiology

European Journal of Heart Failure (2022) **24**, 603–619
doi:10.1002/ejhf.2471

POSITION PAPER

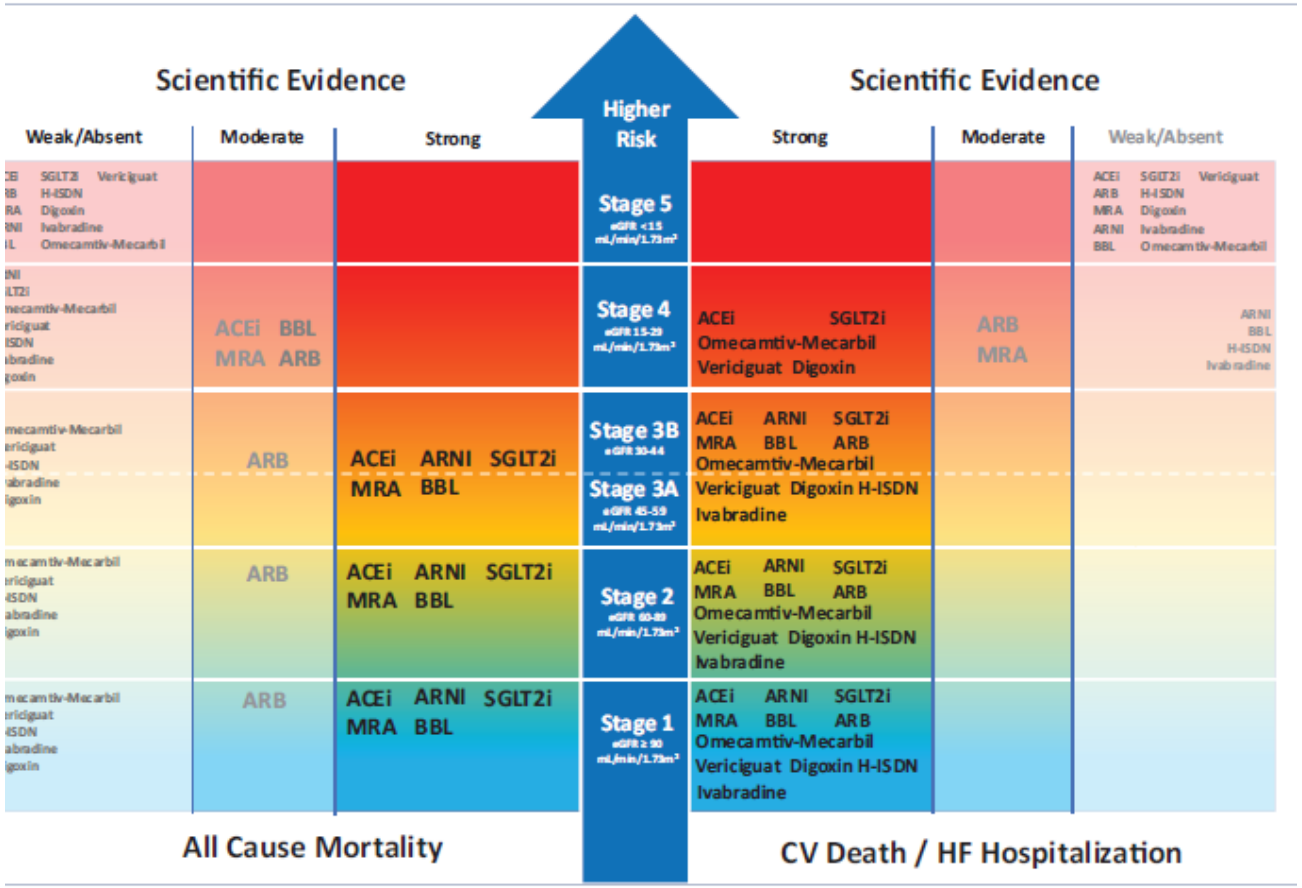
Renal effects of guideline-directed medical therapies in heart failure: a consensus document from the Heart Failure Association of the European Society of Cardiology

Wilfried Mullens[1]*, Pieter Martens[1,2], Jeffrey M. Testani[3], W.H. Wilson Tang[2], Hadi Skouri[4], Frederik H. Verbrugge[5,6,7], Marat Fudim[8,9], Massimo Iacoviello[10], Jennifer Franke[11], Andreas J. Flammer[12], Alberto Palazzuoli[13,14], Paola Morejon Barragan[15], Thomas Thum[16,17], Marta Cobo Marcos[18], Òscar Miró[19], Patrick Rossignol[20], Marco Metra[21], Johan Lassus[22], Francesco Orso[23], Ewa A. Jankowska[24], Ovidiu Chioncel[25], Davor Milicic[26], Loreena Hill[27], Petar Seferovic[28], Giuseppe Rosano[29], Andrew Coats[30], and Kevin Damman[31]



Mullens W, et al. Eur J Heart Fail. 2022;24(4):603-619

Conceptual overview of evidence-based treatments in HFrEF according to baseline CKD status



- With more severe CKD stages, prognosis worsens, and scientific evidence becomes scarce.
- There is more evidence for CKD stage 1 to 4 for preventing cardiovascular death/HF hospitalization with evidence-based treatments compared with preventing all-cause mortality.
- Among treatments, there is some evidence for efficacy of SGLT2i, omecamtiv-mecarbil, ACEi, Sac/Valsartan, digoxin, and vericiguat in CKD stage 4.
- Overall, the renal safety profile in all classes of CKD with essentially all treatments is good if the clinical status is considered and renal function and potassium are checked regularly.
- Loop diuretics are not depicted in the absence of large randomized, placebo-controlled trials

Beldhuis IE, et al. Circulation. 2022;145(9):693-712

Journal of
Clinical Medicine

MDPI

Review

Heart Failure in Patients with Chronic Kidney Disease

Andrew Xanthopoulos [1], Adamantia Papamichail [2], Alexandros Briasoulis [2], Konstantinos Loritis [2], Angeliki Bourazana [1], Dimitrios E. Magouliotis [3], Pantelis Sarafidis [4], Ioannis Stefanidis [5], John Skoularigis [1] and Filippos Triposkiadis [6,*]

1 Department of Cardiology, University Hospital of Larissa, 41110 Larissa, Greece
2 Amyloidosis Center, Department of Clinical Therapeutics, Faculty of Medicine, Alexandra Hospital, National and Kapodistrian University of Athens, 15772 Athens, Greece
3 Unit of Quality Improvement, Department of Cardiothoracic Surgery, University of Thessaly, 41110 Larissa, Greece
4 Department of Nephrology, Hippokration Hospital, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece
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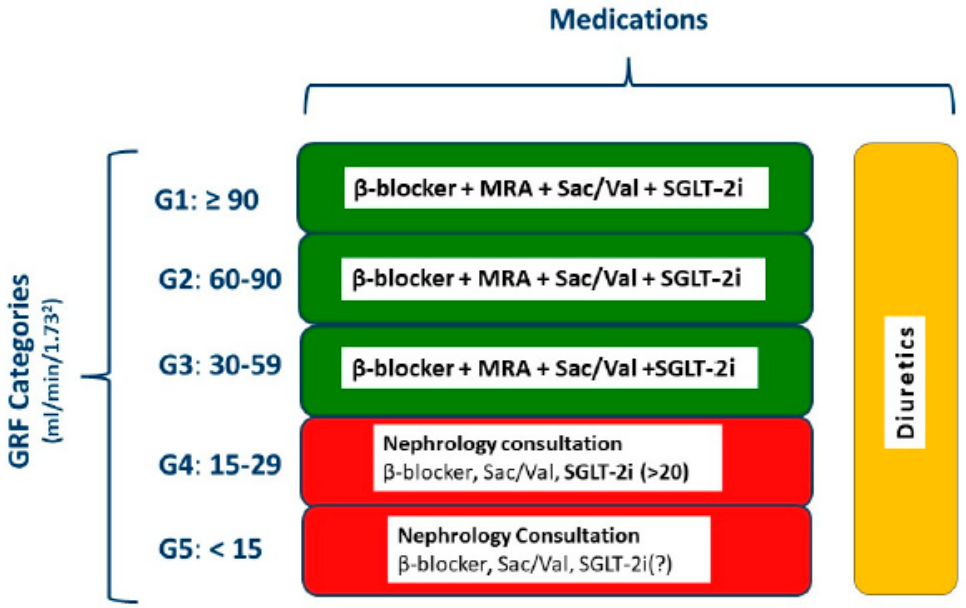
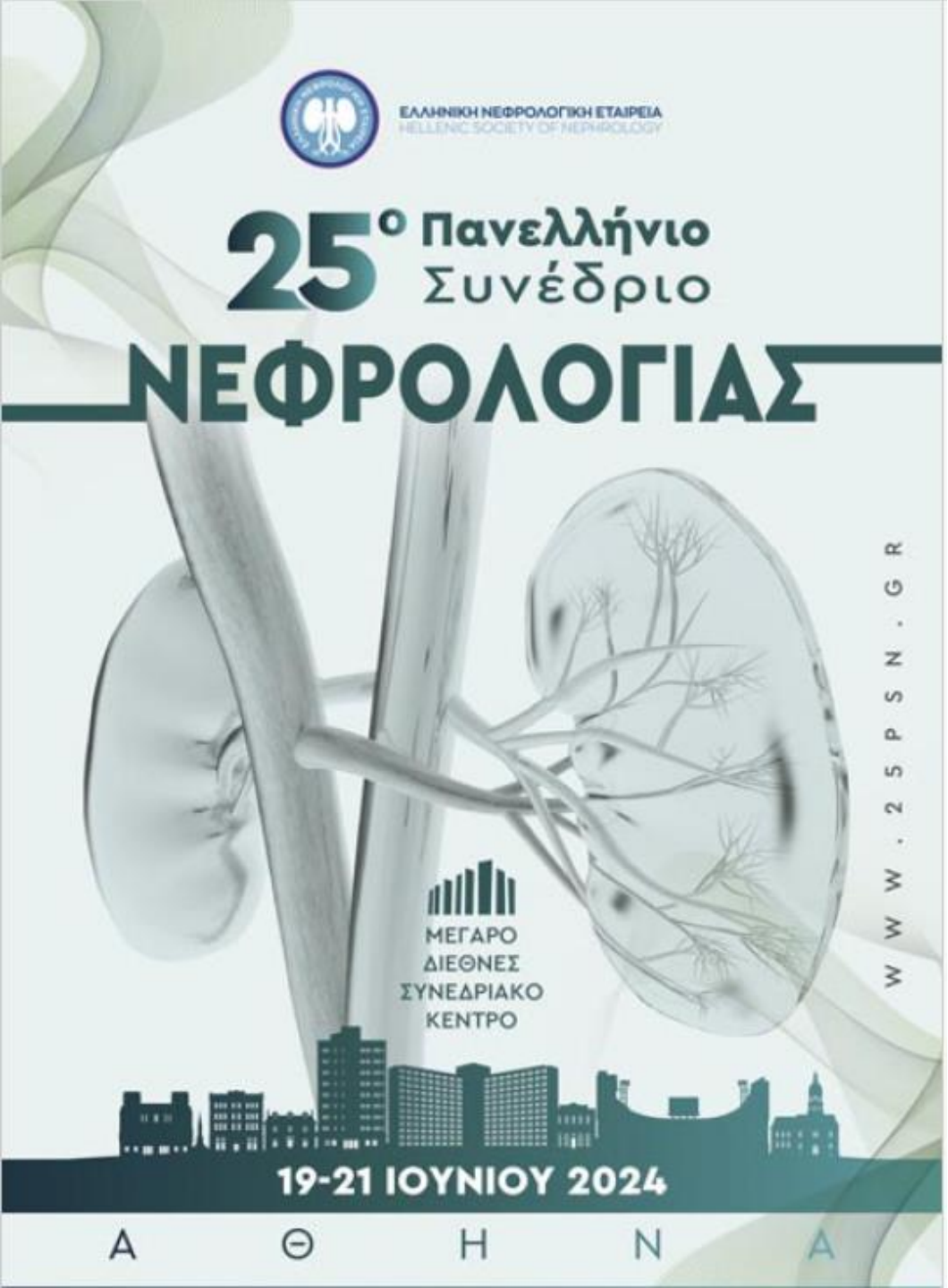
6 School of Medicine, European University Cyprus, 2404 Nicosia, Cyprus
* Correspondence: ftriposkiadis@gmail.com

Management of heart failure according to the stage of chronic kidney disease



J Clin Med. 2023 Sep; 12(18): 6105



Παρασκευή, 21 Ιουνίου 2024

Αντιμετώπιση της καρδιακής ανεπάρκειας ανάλογα με το επίπεδο της νεφρικής λειτουργίας: ενδείξεις και αντενδείξεις παλιών και νέων φαρμάκων

Ανδρέας Ξανθόπουλος MD, PhD,
FESC, FACC, FHFA, FHFSA
Καρδιολογική Κλινική
ΠΓΝ Λάρισας