Guest Editor in Chief: Barry Greenberg, MD; Guest Editor: Eileen Hsich, MD

Steroidal MRA across the spectrum of renal function: a pooled analysis of RCTs

João Pedro Ferreira, MD, PhD[1,2]; Bertram Pitt, MD[3]; John J.V. McMurray, MD[4]; Stuart J. Pocock, PhD[5]; Scott D. Solomon, MD[6]; Marc A. Pfeffer, MD[6]; Faiez Zannad, MD, PhD[2]; Patrick Rossignol, MD, PhD[2]

[1] Unic@RISE, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Porto, Portugal.

[2] Université de Lorraine, Inserm, Centre d'Investigations Cliniques - Plurithématique 14-33, and Inserm U1116, CHRU, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France.

[3] Department of Medicine, University of Michigan School of Medicine, Ann Arbor, Michigan, USA.

[4] BHF Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom.

[5] Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom.

[6] Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

Funding: None.

Disclosures: None related to the content of this work.

Acknowledgments: JPF, PR, FZ are supported by the French PIA project "Lorraine Université d'Excellence" (ANR-15-IDEX-04-LUE) programmes, and the Contrat de Plan

Etat Région Lorraine and FEDER IT2MP. X.R. has received support from the SEC-CNIC CARDIOJOVEN fellowship program.

Address for Correspondence :

Prof. Patrick Rossignol

Centre d'Investigation Clinique 1433 module Plurithématique

CHRU Nancy - Hopitaux de Brabois

Institut Lorrain du Coeur et des Vaisseaux Louis Mathieu

4 rue du Morvan, 54500 Vandoeuvre les Nancy

Tel : +33 (0) 3 83 15 73 15

Fax : +33 (0) 3 83 15 73 24

Mail: p.rossignol@chru-nancy.fr

Abstract

Background: MRAs are underused in patients with kidney dysfunction and their efficacy among patients with chronic kidney disease (CKD) is uncertain.

Objectives: To study the efficacy and safety of steroidal MRA across the spectrum of eGFR in RCTs including patients with HF or MI and advanced CKD who participated in the RALES, EMPHASIS-HF, TOPCAT-Americas, and EPHESUS trials.

Methods: Individual-patient-data meta-analysis using Cox models stratified by trial with treatment-by-eGFR interaction terms. eGFR was re-calculated using the CKD-EPI-creatinine formula.

Results: A total of 12,700 patients were included of whom 331 (2.6%) had an eGFR≤30ml/min/1.73m^2 (mean eGFR=26.8±3.2ml/min/1.73m^2). Patients with advanced CKD had higher annualized event rates for all studied outcomes: placebo event rate for the composite of cardiovascular death or HF hospitalization was ≈3-fold higher in patients with eGFR≤30 compared to those with eGFR>90ml/min/1.73m^2: 41.6 vs. 14.6 events per 100 person-years. MRA (vs. placebo) reduced the composite of cardiovascular death or HF hospitalization, but the effect was attenuated as eGFR decreased: the corresponding HRs by eGFR categories (ml/min/1.73m^2) were: >90: HR 0.62, 95%CI 0.49-0.78; 61-90: HR 0.69, 95%CI 0.61-0.77; 46-60: HR 0.84, 95%CI 0.74-0.95; 31-45: HR 0.79, 95%CI 0.68-0.91; ≤30: HR 0.96, 95%CI 0.70-1.32; treatment-by-eGFRinteractionP-trend=0.033. Investigator-reported hyperkalemia and worsening renal function were more frequent (2-3-fold) among MRA users and hyperkalemia more frequent as eGFR decreased (treatment-by-eGFRinteractionP-trend=0.002).

Conclusions: Steroidal MRAs reduced HF hospitalizations and mortality across a wide range of eGFR, although declining benefit and worsening safety may limit their use in patients with lower eGFR, particularly ≤30ml/min/1.73m^2.

Keywords: mineralocorticoid receptor antagonist- hyperkalemia- advanced chronic kidney disease- cardiorenal syndrome- heart failure

Abbreviation list

MRA, mineralocorticoid receptor antagonist

eGFR, estimated glomerular filtration rate

CKD, chronic kidney disease

HF, heart failure

MI, myocardial infarction

Introduction

Patients with heart failure (HF) or myocardial infarction (MI) complicated with systolic dysfunction have a poor prognosis which is aggravated by kidney dysfunction.[1-5]

Patients with renal impairment represent a clinical challenge because despite their poor prognosis they are often not treated with therapies that may improve their outcomes, such as angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs) and mineralocorticoid receptor antagonists (MRAs).[2] Particularly, the use of MRAs is very low in HF patients with chronic kidney disease (CKD), despite the evidence suggesting a consistent benefit of MRAs in HF and MI patients with and without CKD.[6-10]

Importantly, large outcome randomized controlled trials (RCTs) of MRAs for HF have systematically excluded patients with advanced CKD, as historically defined either by elevated serum creatinine (>2.5 mg/dL) or an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m^2, as computed with the Modification of Diet in Renal Disease (MDRD) formula. In chronic HF and MI, the creatinine-race-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula may have better accuracy for predicting GFR and outcomes than the MDRD formula.[11,12]

Using individual patient data (IPD) from the RALES,[13] EMPHASIS-HF,[14] TOPCAT,[15] and EPHESUS[16] trials comprising more than 12,500 patients we aim to study the effect of steroidal MRAs (spironolactone and eplerenone) across the spectrum of renal function, including patients with an eGFR below 30 ml/min/1.73m^2 as recalculated using the CKD-EPI formula.[12]

Methods

Study design, setting, and participants

In RALES, 1663 patients who had HF with severe symptoms and a left ventricular ejection fraction (LVEF) ≤35%, were randomly assigned to spironolactone (up to 50 mg/day) or matching placebo. Patients with a serum creatinine >2.5 mg/dL were excluded from the trial.

In EMPHASIS-HF, 2737 patients who had HF and mild symptoms and a LVEF ≤35% were randomly assigned to eplerenone (up to 50 mg/day) or matching placebo. Patients with an eGFR <30 ml/min/1.73m^2 calculated using the Modification of Diet in Renal Disease (MDRD) formula[17] were excluded from the trial.

In TOPCAT, 3445 patients with symptomatic HF and a LVEF ≥45% were randomly assigned to spironolactone (15 to 45 mg daily) or matching placebo. Patients with an eGFR <30 ml/min/1.73m^2 calculated using the MDRD formula or a serum creatinine >2.5 mg/dL were excluded from the trial. Due to the major regional variations found in the TOPCAT trial, we report only data regarding patients enrolled in "the Americas" (n =1767).[18]

In EPHESUS, 6632 patients who had an MI complicated with systolic dysfunction and HF were randomly assigned to eplerenone (up to 50 mg/day) or matching placebo. Patients with a serum creatinine >2.5 mg/dL were excluded from the trial.

Each individual randomized controlled trial was conducted in accordance with the Declaration of Helsinki and approved by the site ethics committees. All participants gave written informed consent to participate in the respective studies.

In the present analysis, all studies eGFR was recalculated using the CKD-EPI formula.

Study outcomes

For consistency across trials, in the present analysis the primary outcome was a composite of cardiovascular death or HF hospitalization. HF hospitalization and cardiovascular death alone, and all-cause death were also assessed.

The major clinical outcomes were centrally adjudicated by endpoint committees and defined by the conventional criteria (definitions have been published in the respective studies). Adverse events of worsening renal function and hyperkalemia were considered as reported by the investigators of the respective studies.

Statistical analysis

A fixed-effect model for a one-stage IPD meta-analysis was conducted.[19] Baseline clinical characteristics of patients were summarised by eGFR groups with means and standard deviation for continuous variables, with frequencies and percentages for categorical variables, hazard ratios (HRs) with their respective 95% confidence interval (95% CI) for treatment effect estimates. Univariate Cox proportional hazards' modelling was used to assess the effect of MRA treatment on the studied outcomes with an ordered treatment-by-eGFR interaction term ("interaction P-trend"), stratified by study (i.e., assuming an unique hazard ratio across strata but with a baseline hazard unique to each study).[20] To further investigate the variation of treatment effect estimates between trials, the Cochran's Q test and the Wald test of the overall treatment-by-study interaction were computed. The absence of statistically significant treatment-by-study interaction tests, suggest an absence of substantial statistical heterogeneity. Event-rates, absolute treatment effects and number needed-to-treat to benefit were also computed by eGFR subgroups. Statistical analyses were performed using STATA®, version 17 (Stata Corp, College Station, TX, USA).

Results

Kidney function categories and reclassification using the CKD-EPI formula

Patients were categorized into five eGFR stages: >90, 61-90, 46-60, 31-45, and ≤30 ml/min/1.73m^2 (compatible with the KDIGO CKD stages)[21]

Using the CKD-EPI formula instead of MDRD, resulted in a down-classification of eGFR categories with patients more having eGFR below 60, 45 and 30 ml/min/1.73m^2. For example, 152 patients more were classified as having eGFR ≤30 ml/min/1.73m^2 with the CKD-EPI formula who had been otherwise classified as having eGFR 31-45 ml/min/1.73m^2 with the MDRD formula. Such down-classification with the CKD-EPI formula almost doubled the number of patients with an eGFR ≤30 ml/min/1.73m^2: 331 patients using the CKD-EPI formula vs. 179 patients using MDRD formula. *Supplemental Table 1*.

Patients' characteristics by eGFR categories

A total of 12,700 patients were included in this study: 331 with an eGFR ≤30 (2.6%, with a mean eGFR of 26.8 ± 3.2 ml/min/1.73m^2 (median, percentile$_{25-75}$=28, 25-29 ml/min/1.73m^2), 1835 with an eGFR between 31 and 45 (14.4%), 3232 with an eGFR between 46 and 60 (25.4%), 5616 with an eGFR between 61 and 90 (44.2%), and 1686 with an eGFR >90 ml/min/1.73m^2 (13.3%). Patients with lower eGFR were older, more frequently women, with a higher prevalence of arterial hypertension, diabetes mellitus, atrial fibrillation/flutter, ischemic arterial disease (MI, stroke, peripheral artery disease), and prior HF hospitalizations, and a lower use of ACEi/ARBs, beta-blockers, and lipid-lowering drugs, and a higher use of loop diuretics (P-value for trend <0.001 for all). *Table 1*.

A similar pattern of patient characteristics across the eGFR spectrum was found in patients with HFrEF (RALES and EMPHASIS-HF), HFpEF (TOPCAT-Americas), and those with MI and left ventricular systolic dysfunction (EPHESUS). *Supplemental Tables 2, 3 and 4*.

Events rates and treatment effect (MRA vs. Placebo) across eGFR spectrum

Patients with advanced CKD had higher annualized event-rates (for all the studied outcomes). For example, the placebo event-rate for the composite of cardiovascular death or

HF hospitalization was ≈3-fold higher in patients with an eGFR ≤30 compared to those with an eGFR >90 ml/min/1.73m^2: 41.6 vs. 14.6 events per 100 person-years. *Table 2*.

The effect of MRA vs. placebo was demonstrated across a wide range of eGFR spectrum, but the magnitude of effect was attenuated as eGFR decreased. For example, the HRs for the composite of cardiovascular death or HF hospitalization by eGFR categories (expressed in ml/min/1.73m^2) were: >90: HR 0.62, 95%CI 0.49-0.78; 61-90: HR 0.69, 95%CI 0.61-0.77; 46-60: HR 0.84, 95%CI 0.74-0.95; 31-45: HR 0.79, 95%CI 0.68-0.91; ≤30: HR 0.96, 95%CI 0.70-1.32; treatment-by-eGFR interaction P-trend =0.033 across eGFR categories, and interaction P-trend =0.01 across eGFR as a continuous covariate. A similar pattern was observed for the individual components of the primary outcome and all-cause death. *Table 2 & Central Illustration*.

Using the MDRD formula, for the composite of cardiovascular death or HF hospitalization, provided similar results to those observed with the CKD-EPI formula, except that the number of patients with eGFR ≤30 ml/min/1.73m2 was smaller with the MDRD formula (n =179) and the 95% confidence intervals wider. *Supplemental Table 5*.

A similar pattern of treatment effects across the eGFR spectrum was found in patients with HFrEF, HFpEF, and MI with systolic dysfunction. *Supplemental Tables 6, 7 and 8*.

Adverse events by eGFR categories

Investigator-reported hyperkalemia was more frequent among patients with advanced CKD. For example, in the placebo group, patients an eGFR ≤30 had a ≈2.6-fold higher frequency of hyperkalemia compared to patients with an eGFR >90 ml/min/1.73m^2. Randomization to MRA (vs. placebo) increased the odds of developing hyperkalemia by 1.5 to 2.7-fold, with higher risk as eGFR decreased (interaction P-trend =0.002). *Table 3*.

Neither placebo group patients nor MRA-assigned patients systematically experienced more frequent investigator-reported worsening kidney function (WKF) as a function of eGFR strata. However, randomization to MRA (vs. placebo) increased stepwise the odds of developing WKF by 1.2 to 2.0-fold (in patients with advanced CKD), despite the absence of treatment-by-eGFR category heterogeneity (interaction P-trend =0.39). *Table 3*.

Discussion

The present study used individual patient data from four large RCTs of steroidal MRAs (spironolactone or eplerenone) vs. placebo including over 12,500 patients with HFrEF, HFpEF, and MI with systolic dysfunction across a wide range of eGFR, of whom 331 had an eGFR ≤30 ml/min/1.73m^2 as determined by the CKD-EPI formula. This post-hoc analysis represents a unique opportunity to study MRA efficacy and safety across a wide range of eGFR in a randomized and double-blind fashion. We observed that MRAs reduced HF hospitalizations and mortality across a wide spectrum of eGFR; however, the effect of MRAs was attenuated as eGFR decreased, becoming neutral in patients with an eGFR ≤30 ml/min/1.73m^2. Moreover, patients with lower eGFR experienced more frequent hyperkalemia and WKF episodes. Together, these findings suggest that MRA may benefit patients across a wide spectrum of eGFR, but a decreased efficacy and increased side-effects may limit the utility of steroidal MRA in patients with impaired renal function.

Renal function is a key determinant of prognosis in patients with HF and MI, with event-rates increasing progressively as eGFR decreases.[22,23] Such findings were replicated in our analysis, where patients with an eGFR ≤30 ml/min/1.73m^2 had a multifold (3 or more) higher risk of events compared to patients with eGFR >90 ml/min/1.73m^2. This graded increase in risk as eGFR decreases is clinically important *per se*; however, it may be aggravated by a lower use of therapies that modify HF prognosis, including a lower use of ACEi/ARBs.[2] The fear of causing further aggravation of kidney function and hyperkalemia may be relevant factors limiting the optimal use of these therapies in patients with renal dysfunction.[24] Despite data showing that WKF in the setting of ACEi/ARB and MRA initiation is due to a hemodynamic effect which is not associated with a loss of benefit from these therapies,[7,25-27] clinicians may perceive these laboratory results as clinically worrisome, particularly when facing complex treatment decisions in an individual patient with multiple comorbidities and impaired renal function. Hyperkalemia is another important factor that may limit the use of ACEi/ARBs and particularly MRAs. Similarly to WKF, mild hyperkalemia is not associated with poor outcomes in the setting of MRA use;[27-29] however, the fear of hyperkalemia may limit the use of MRAs in routine clinical practice. Our data confirm an increased risk of hyperkalemia and WKF with MRA use. Still, the occurrence of such adverse events should not discourage clinicians from using MRAs in patients with eGFR greater than 30 ml/min/1.73m^2 where a 20-30% relative reduction of HF hospitalizations and mortality may be expected. Notwithstanding, it is important to highlight that the MRA benefit was attenuated as eGFR decreased, particularly among patients with an eGFR ≤30 ml/min/1.73m^2, where the effect was neutral (*Central Illustration*). Moreover, the frequency of visits and trial monitoring may be difficult to achieve in clinical practice, which may render more difficult to maintain MRA therapy after the occurrence of hyperkalemia or WKF in routine practice.

To confirm these findings, larger dedicated trials of MRA in patients with advanced CKD are needed. Still, the present study is unique in presenting double-blind randomized evidence (stemming from all trials which set the stage for MRA use in HF in the international guidelines) of MRA efficacy and safety across the spectrum of eGFR. The observation of a progressive decline in MRA efficacy as eGFR decreases, suggests that the initiation or continuation of MRAs should be reconsidered in patients with impaired renal function, particularly those with an eGFR ≤30 ml/min/1.73m^2.

Data on the use of MRAs for the treatment of HF (either HFrEF or HFpEF) in patients with CKD 4-5 or dialysis are limited.[30] So far, only observational registry data were available for advanced CKD patients with a beneficial effect associated with the use of renin angiotensin aldosterone system inhibitors.[31] It should be noted that the non-steroidal MRA finerenone reduced the risk of CKD progression and cardiovascular events in patients with CKD and type 2 diabetes with a relatively small drug discontinuation related to hyperkalemia (1.2 to 2.3% in finerenone vs. 0.4 to 0.9% in placebo) in the FIDELIO-DKD and FIGARO-DKD trials.[32,33] The efficacy and safety of finerenone in patients with HFpEF with an eGFR ≥25 ml/min/1.73m^2 is currently being assessed in the FINEARTS-HF trial (ClinicalTrials.gov Identifier: NCT04435626). The ALCHEMIST (ClinicalTrials.gov Identifier: NCT01848639) and ACHIEVE (ClinicalTrials.gov Identifier: NCT03020303) trials are studying the effect of spironolactone in patients undergoing dialysis.[34]

Beyond non-steroidal MRAs, the use of novel potassium binders may enable a more persistent use of renin angiotensin aldosterone system inhibitors use including MRAs in patients with HF or MI and renal impairment,[35-38] as acknowledged by recent guidelines.[39] However, whether such approach may ultimately improve outcomes warrants dedicated outcome RCTs. Hyperkalemia mitigating-strategies (e.g., avoidance of potassium-rich foods, frequent potassium monitoring) should be adopted in all patients taking MRAs, particularly those with CKD.[40] Sodium glucose co-transporter 2 inhibitors (SGLT2i) may reduce the incidence of hyperkalemia in HF patients, particularly those taking MRA.[41-43] This strategy may be particularly attractive because both MRAs and SGLT2i improve HF outcomes.

Limitations

Some limitations should be acknowledged in this study. Our results are based on the assumption that both spironolactone and eplerenone provide similar efficacy; although spironolactone and eplerenone differ in their molecular structure, pharmacokinetics, and pharmacodynamics, it is generally accepted that the benefits of different MRAs represent a "class effect".[44] Furthermore, the doses and the treatments (spironolactone or eplerenone) could vary between trials and according to the respective dose-adjustment algorithms, but for this analysis we assumed that MRAs have a similar effect regardless of dose.[6,45] As these are selected trial populations, the rate of safety events may be lower than in unselected patients in routine clinical practice. The present study was underpowered to assess the effect of the treatment in patients with an eGFR ≤30 ml/min/1.73m^2, who represented a small minority (<3%) of the overall population. Cystatin C was not available in the data; hence, we could not determine eGFR using the new CKD-EPI-creatinine-cystatin C equations which could have led to more precise GFR estimations without using the Race variable.[46]

Conclusions

Steroidal MRAs reduced HF hospitalizations and mortality across a wide range of eGFR, although declining benefit and worsening safety may limit the use in patients with lower eGFR, particular those with eGFR below 30 ml/min/1.73m^2.

Clinical perspectives: Competency in Medical Knowledge

Clinical relevance

Steroidal mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone, reduce events among patients with heart failure (HF), but their efficacy is attenuated as estimated glomerular filtration rate (eGFR) decreases.

Translational outlook

Novel non-steroidal MRAs should be tested in patients with HF and renal dysfunction.

References

1. Smith DH, Thorp ML, Gurwitz JH, McManus DD, Goldberg RJ, Allen LA, Hsu G, Sung SH, Magid DJ, Go AS. Chronic kidney disease and outcomes in heart failure with preserved versus reduced ejection fraction: the Cardiovascular Research Network PRESERVE Study. *Circ Cardiovasc Qual Outcomes*. 2013;6:333-342. doi: 10.1161/circoutcomes.113.000221
2. Patel RB, Fonarow GC, Greene SJ, Zhang S, Alhanti B, DeVore AD, Butler J, Heidenreich PA, Huang JC, Kittleson MM, et al. Kidney Function and Outcomes in Patients Hospitalized With Heart Failure. *J Am Coll Cardiol*. 2021;78:330-343. doi: 10.1016/j.jacc.2021.05.002
3. Löfman I, Szummer K, Dahlström U, Jernberg T, Lund LH. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. *Eur J Heart Fail*. 2017;19:1606-1614. doi: 10.1002/ejhf.821
4. Verma A, Anavekar NS, Meris A, Thune JJ, Arnold JM, Ghali JK, Velazquez EJ, McMurray JJ, Pfeffer MA, Solomon SD. The relationship between renal function and cardiac structure, function, and prognosis after myocardial infarction: the VALIANT Echo Study. *J Am Coll Cardiol*. 2007;50:1238-1245. doi: 10.1016/j.jacc.2007.06.018
5. Moukarbel GV, Yu ZF, Dickstein K, Hou YR, Wittes JT, McMurray JJ, Pitt B, Zannad F, Pfeffer MA, Solomon SD. The impact of kidney function on outcomes following high risk myocardial infarction: findings from 27 610 patients. *Eur J Heart Fail*. 2014;16:289-299. doi: 10.1002/ejhf.11
6. Ferreira JP, Abreu P, McMurray JJV, van Veldhuisen DJ, Swedberg K, Pocock SJ, Vincent J, Lins K, Rossignol P, Pitt B, et al. Renal function stratified dose

comparisons of eplerenone versus placebo in the EMPHASIS-HF trial. *Eur J Heart Fail*. 2019;21:345-351. doi: 10.1002/ejhf.1400

7. Vardeny O, Wu DH, Desai A, Rossignol P, Zannad F, Pitt B, Solomon SD. Influence of baseline and worsening renal function on efficacy of spironolactone in patients With severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). *J Am Coll Cardiol*. 2012;60:2082-2089. doi: 10.1016/j.jacc.2012.07.048

8. Beldhuis IE, Myhre PL, Claggett B, Damman K, Fang JC, Lewis EF, O'Meara E, Pitt B, Shah SJ, Voors AA, et al. Efficacy and Safety of Spironolactone in Patients With HFpEF and Chronic Kidney Disease. *JACC Heart Fail*. 2019;7:25-32. doi: 10.1016/j.jchf.2018.10.017

9. Mavrakanas TA, Giannetti N, Sapir-Pichhadze R, Alam A. Mineralocorticoid Receptor Antagonists and Renal Outcomes in Heart Failure Patients with and without Chronic Kidney Disease. *Cardiorenal Med*. 2020;10:32-41. doi: 10.1159/000503223

10. Cooper LB, Lippmann SJ, Greiner MA, Sharma A, Kelly JP, Fonarow GC, Yancy CW, Heidenreich PA, Hernandez AF. Use of Mineralocorticoid Receptor Antagonists in Patients With Heart Failure and Comorbid Diabetes Mellitus or Chronic Kidney Disease. *J Am Heart Assoc*. 2017;6. doi: 10.1161/jaha.117.006540

11. Ferreira JP, Girerd N, Pellicori P, Duarte K, Girerd S, Pfeffer MA, McMurray JJ, Pitt B, Dickstein K, Jacobs L, et al. Renal function estimation and Cockroft-Gault formulas for predicting cardiovascular mortality in population-based, cardiovascular risk, heart failure and post-myocardial infarction cohorts: The Heart 'OMics' in AGEing (HOMAGE) and the high-risk myocardial infarction database initiatives. *BMC Med*. 2016;14:181. doi: 10.1186/s12916-016-0731-2

12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. A new equation to estimate glomerular filtration rate. In: *Ann Intern Med*. United States; 2009:604-612.

13. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709-717. doi: 10.1056/nejm199909023411001

14. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11-21. doi: 10.1056/NEJMoa1009492

15. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383-1392. doi: 10.1056/NEJMoa1313731

16. Pitt B, Williams G, Remme W, Martinez F, Lopez-Sendon J, Zannad F, Neaton J, Roniker B, Hurley S, Burns D, et al. The EPHESUS trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. Eplerenone Post-AMI Heart Failure Efficacy and Survival Study. *Cardiovasc Drugs Ther*. 2001;15:79-87.

17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. In: *Ann Intern Med*. United States; 1999:461-470.

18. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, et al. Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone

Antagonist (TOPCAT) Trial. *Circulation*. 2015;131:34-42. doi: 10.1161/circulationaha.114.013255

19. da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. *Eur Heart J*. 2014;35:3336-3345. doi: 10.1093/eurheartj/ehu424
20. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *Bmj*. 2010;340:c221. doi: 10.1136/bmj.c221
21. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013;158:825-830. doi: 10.7326/0003-4819-158-11-201306040-00007
22. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296-1305. doi: 10.1056/NEJMoa041031
23. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. In: *N Engl J Med*. United States: 2004 Massachusetts Medical Society; 2004:1285-1295.
24. Ferreira JP, Mentz RJ, Pizard A, Pitt B, Zannad F. Tailoring mineralocorticoid receptor antagonist therapy in heart failure patients: are we moving towards a personalized approach? *Eur J Heart Fail*. 2017. doi: 10.1002/ejhf.814
25. Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. *Circ Heart Fail*. 2011;4:685-691. doi: 10.1161/circheartfailure.111.963256

26. Rossignol P, Cleland JG, Bhandari S, Tala S, Gustafsson F, Fay R, Lamiral Z, Dobre D, Pitt B, Zannad F. Determinants and consequences of renal function variations with aldosterone blocker therapy in heart failure patients after myocardial infarction: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study. *Circulation*. 2012;125:271-279. doi: 10.1161/circulationaha.111.028282

27. Rossignol P, Dobre D, McMurray JJ, Swedberg K, Krum H, van Veldhuisen DJ, Shi H, Messig M, Vincent J, Girerd N, et al. Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Circ Heart Fail*. 2014;7:51-58. doi: 10.1161/circheartfailure.113.000792

28. Vardeny O, Claggett B, Anand I, Rossignol P, Desai AS, Zannad F, Pitt B, Solomon SD. Incidence, predictors, and outcomes related to hypo- and hyperkalemia in patients with severe heart failure treated with a mineralocorticoid receptor antagonist. *Circ Heart Fail*. 2014;7:573-579. doi: 10.1161/circheartfailure.114.001104

29. Eschalier R, McMurray JJ, Swedberg K, van Veldhuisen DJ, Krum H, Pocock SJ, Shi H, Vincent J, Rossignol P, Zannad F, et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure). *J Am Coll Cardiol*. 2013;62:1585-1593. doi: 10.1016/j.jacc.2013.04.086

30. House AA, Wanner C, Sarnak MJ, Piña IL, McIntyre CW, Komenda P, Kasiske BL, Deswal A, deFilippi CR, Cleland JGF, et al. Heart failure in chronic kidney disease:

conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2019;95:1304-1317. doi: 10.1016/j.kint.2019.02.022

31. Edner M, Benson L, Dahlstrom U, Lund LH. Association between renin-angiotensin system antagonist use and mortality in heart failure with severe renal insufficiency: a prospective propensity score-matched cohort study. *Eur Heart J*. 2015;36:2318-2326. doi: 10.1093/eurheartj/ehv268

32. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, Kolkhof P, Nowack C, Schloemer P, Joseph A, et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. *N Engl J Med*. 2020;383:2219-2229. doi: 10.1056/NEJMoa2025845

33. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, Joseph A, Kolkhof P, Nowack C, Schloemer P, et al. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. *N Engl J Med*. 2021. doi: 10.1056/NEJMoa2110956

34. Rossignol P, Frimat L, Zannad F. The safety of mineralocorticoid antagonists in maintenance hemodialysis patients: two steps forward. *Kidney Int*. 2019;95:747-749. doi: 10.1016/j.kint.2018.12.006

35. Pitt B, Bakris GL, Bushinsky DA, Garza D, Mayo MR, Stasiv Y, Christ-Schmidt H, Berman L, Weir MR. Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. *Eur J Heart Fail*. 2015;17:1057-1065. doi: 10.1002/ejhf.402

36. Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, Wittes J, Christ-Schmidt H, Berman L, Pitt B. Patiromer in patients with kidney disease and

hyperkalemia receiving RAAS inhibitors. *N Engl J Med*. 2015;372:211-221. doi: 10.1056/NEJMoa1410853

37. Zannad F, Ferreira JP, Pitt B. Potassium binders for the prevention of hyperkalaemia in heart failure patients: implementation issues and future developments. *Eur Heart J Suppl*. 2019;21:A55-a60. doi: 10.1093/eurheartj/suy034

38. Zannad F, Hsu BG, Maeda Y, Shin SK, Vishneva EM, Rensfeldt M, Eklund S, Zhao J. Efficacy and safety of sodium zirconium cyclosilicate for hyperkalaemia: the randomized, placebo-controlled HARMONIZE-Global study. *ESC Heart Fail*. 2020. doi: 10.1002/ehf2.12561

39. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599-3726. doi: 10.1093/eurheartj/ehab368

40. Ferreira JP. Abnormalities of Potassium in Heart Failure. In: JACC; 2020.

41. Ferreira JP, Zannad F, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Jamal W, Steubl D, Schueler E, et al. Interplay of Mineralocorticoid Receptor Antagonists and Empagliflozin in Heart Failure: EMPEROR-Reduced. *J Am Coll Cardiol*. 2021;77:1397-1407. doi: 10.1016/j.jacc.2021.01.044

42. Shen L, Kristensen SL, Bengtsson O, Böhm M, de Boer RA, Docherty KF, Inzucchi SE, Katova T, Køber L, Kosiborod MN, et al. Dapagliflozin in HFrEF Patients Treated With Mineralocorticoid Receptor Antagonists: An Analysis of DAPA-HF. *JACC Heart Fail*. 2021;9:254-264. doi: 10.1016/j.jchf.2020.11.009

43. Ferreira JP, Butler J, Zannad F, Filippatos G, Schueler E, Steubl D, Zeller C, Januzzi JL, Pocock S, Packer M, et al. Mineralocorticoid Receptor Antagonists and

Empagliflozin in Patients With Heart Failure and Preserved Ejection Fraction. *J Am Coll Cardiol*. 2022;79:1129-1137. doi: 10.1016/j.jacc.2022.01.029

44. Iqbal J, Parviz Y, Pitt B, Newell-Price J, Al-Mohammad A, Zannad F. Selection of a mineralocorticoid receptor antagonist for patients with hypertension or heart failure. *Eur J Heart Fail*. 2014;16:143-150. doi: 10.1111/ejhf.31

45. Ferreira JP, Rossello X, Pocock SJ, Rossignol P, Claggett BL, Rouleau JL, Solomon SD, Pitt B, Pfeffer MA, Zannad F. Spironolactone dose in Heart Failure with Preserved Ejection Fraction: findings from TOPCAT. *Eur J Heart Fail*. 2020. doi: 10.1002/ejhf.1909

46. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, Crews DC, Doria A, Estrella MM, Froissart M, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. *N Engl J Med*. 2021. doi: 10.1056/NEJMoa2102953

Central Illustration. Treatment effect (MRA vs. Placebo) across the continuous eGFR spectrum

Legend: eGFR, estimated glomerular filtration rate categories expressed in ml/min/1.73m2; MRA, mineralocorticoid receptor antagonist; HR, hazard ratio; CI, confidence interval; Interaction P-trend, treatment-by-eGFR interaction P-value for linear trend across the spectrum of eGFR; CV, cardiovascular; HF, heart failure.

Caption: The MRA effect was attenuated as eGFR decreased.

Table 1. Patients' characteristics by eGFR categories

Characteristic/eGFR cat.	eGFR (ml/min/1.73m^2)					P-value
	≤30	31-45	46-60	61-90	>90	
N.	331	1835	3232	5616	1686	
Study						
EMPHASIS	36 (10.9%)	365 (19.9%)	692 (21.4%)	1323 (23.6%)	287 (17.0%)	<0.001
EPHESUS	177 (53.5%)	775 (42.2%)	1542 (47.7%)	3027 (53.9%)	1052 (62.4%)	
RALES	72 (21.8%)	316 (17.2%)	468 (14.5%)	615 (11.0%)	187 (11.1%)	
TOPCAT-Americas	46 (13.9%)	379 (20.7%)	530 (16.4%)	651 (11.6%)	160 (9.5%)	
Age, years	75.6 ± 8.2	73.1 ± 8.5	69.9 ± 8.7	64.5 ± 10.3	55.3 ± 9.7	<0.001
Age >75yr	191 (57.7%)	860 (46.9%)	1046 (32.4%)	935 (16.6%)	27 (1.6%)	<0.001
Women	171 (51.7%)	743 (40.5%)	1134 (35.1%)	1471 (26.2%)	322 (19.1%)	<0.001
Race						
White	308 (93.1%)	1603 (87.4%)	2824 (87.4%)	4868 (86.7%)	1387 (82.3%)	<0.001
Black	8 (2.4%)	86 (4.7%)	126 (3.9%)	235 (4.2%)	107 (6.3%)	
Asian	3 (0.9%)	62 (3.4%)	97 (3.0%)	184 (3.3%)	61 (3.6%)	
Other	12 (3.6%)	84 (4.6%)	185 (5.7%)	329 (5.9%)	131 (7.8%)	
BMI, Kg/m^2	28.4 ± 5.5	28.8 ± 6.2	28.6 ± 5.9	28.3 ± 5.7	28.5 ± 5.9	0.026
Current smoker	80 (30.9%)	542 (35.7%)	1088 (39.4%)	2538 (50.8%)	958 (64.0%)	<0.001
NYHA class						
III	120 (38.0%)	576 (32.3%)	754 (24.0%)	1086 (19.9%)	299 (18.2%)	<0.001
IV	29 (9.2%)	112 (6.3%)	162 (5.2%)	210 (3.8%)	57 (3.5%)	
SBP, mmHg	123.8 ± 20.2	123.1 ± 17.9	122.6 ± 17.2	121.6 ± 17.2	118.9 ± 16.2	<0.001
DBP, mmHg	71.6 ± 12.7	71.7 ± 11.8	72.9 ± 11.5	73.9 ± 11.2	73.9 ± 10.9	<0.001
Heart rate, bpm	75.4 ± 16.1	74.3 ± 13.7	74.4 ± 13.4	75.4 ± 13.6	77.2 ± 13.6	<0.001
LVEF, %	33.8 ± 12.7	35.2 ± 13.6	34.5 ± 12.7	33.8 ± 11.3	33.7 ± 10.5	<0.001
Hypertension	242 (73.1%)	1249 (68.1%)	2108 (65.2%)	3301 (58.8%)	860 (51.0%)	<0.001
Diabetes	128 (38.7%)	726 (39.6%)	1153 (35.7%)	1612 (28.7%)	511 (30.3%)	<0.001
Atrial Fibrillation/Flutter	83 (25.2%)	439 (24.0%)	688 (21.3%)	985 (17.6%)	173 (10.3%)	<0.001
Previous MI	138 (41.7%)	736 (40.1%)	1199 (37.1%)	1692 (30.1%)	432 (25.6%)	<0.001
Previous stroke	42 (12.7%)	211 (11.5%)	318 (9.8%)	422 (7.5%)	89 (5.3%)	<0.001
PAD	48 (16.3%)	214 (14.6%)	327 (12.9%)	391 (9.1%)	107 (7.6%)	<0.001
Prior HFH	86 (33.2%)	605 (39.8%)	826 (29.9%)	1155 (23.1%)	296 (19.7%)	<0.001
COPD	49 (14.8%)	260 (14.2%)	400 (12.4%)	630 (11.2%)	180 (10.7%)	0.002
eGFR, ml/min/1.73m2	26.8 ± 3.2	39.0 ± 4.2	53.4 ± 4.2	74.1 ± 8.5	100.4 ± 9.4	<0.001
Hemoglobin, g/dL	12.4 ± 2.0	12.8 ± 1.9	13.2 ± 1.9	13.5 ± 1.8	13.6 ± 1.9	<0.001
Potassium, mmol/L	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.4	4.3 ± 0.4	4.2 ± 0.4	<0.001
Sodium, mmol/L	138.8 ± 4.4	139.4 ± 4.0	139.7 ± 4.3	139.5 ± 4.4	139.3 ± 4.0	<0.001
ACEi/ARBs	274 (82.8%)	1584 (86.3%)	2868 (88.7%)	4957 (88.3%)	1478 (87.7%)	0.004
Beta-blockers	197 (59.5%)	1150 (62.7%)	2175 (67.3%)	4056 (72.2%)	1233 (73.1%)	<0.001
Loop diuretic	302 (91.2%)	1586 (86.4%)	2582 (79.9%)	3976 (70.8%)	986 (58.5%)	<0.001
Lipid lowering drug	132 (39.9%)	842 (45.9%)	1506 (46.6%)	2729 (48.6%)	858 (50.9%)	<0.001
Anti-thrombotics	252 (76.1%)	1352 (73.7%)	2531 (78.3%)	4549 (81.0%)	1395 (82.7%)	<0.001

Legend: BMI, body mass index; NYHA, New York Heart Association functional class; MI, myocardial infarction; PAD, peripheral artery disease: HFH, heart failure hospitalization; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists.

Table 2. Treatment effect (MRA vs. Placebo) across eGFR categories

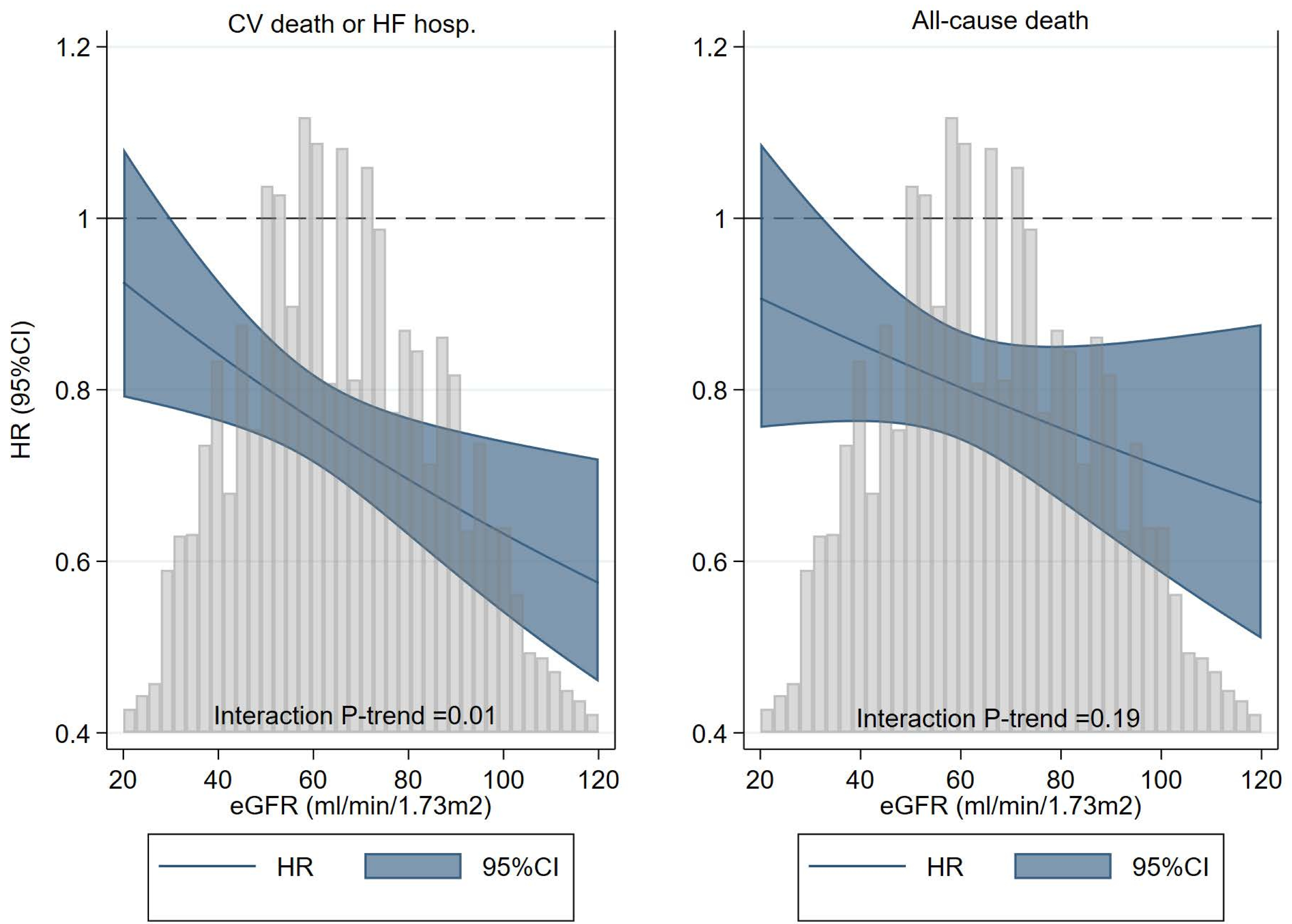
Outcome/eGFR cat.	Events PBO n/N (%)	Events MRA n/N (%)	Event-rate PBO (95%CI)	Event-rate MRA (95%CI)	HR (95%CI)	aARR	aNTT	Inter.P-trend	Study Het.
CV death or HF hosp.								0.033	0.54
>90	171/808 (21.2)	124/878 (14.1)	14.6 (12.6-17.0)	9.0 (7.5-10.7)	0.62 (0.49-0.78)	5.6	17.9		
61-90	700/2824 (24.8)	503/2792 (18.0)	16.4 (15.2-17.6)	11.0 (10.1-12.1)	0.69 (0.61-0.77)	5.4	18.5		
46-60	533/1625 (32.8)	476/1607 (29.6)	21.6 (19.8-23.5)	18.5 (16.9-20.2)	0.84 (0.74-0.95)	3.1	32.3		
31-45	409/929 (44.0)	333/906 (36.8)	31.7 (28.7-34.9)	24.9 (22.4-27.8)	0.79 (0.68-0.91)	6.8	14.7		
≤30	78/164 (47.6)	78/167 (46.7)	41.6 (33.3-51.9)	38.4 (30.7-47.9)	0.96 (0.70-1.32)	3.2	31.3		
HF hosp.								0.14	0.37
>90	102/808 (12.6)	75/878 (8.5)	8.6 (7.1-10.4)	5.3 (4.3-6.7)	0.63 (0.47-0.85)	3.3	30.3		
61-90	416/2824 (14.7)	289/2792 (10.4)	9.4 (8.6-10.4)	6.3 (5.6-7.0)	0.68 (0.58-0.79)	3.1	32.3		
46-60	339/1625 (20.9)	285/1607 (17.7)	13.3 (11.9-14.8)	10.8 (9.6-12.1)	0.80 (0.69-0.94)	2.5	40.0		
31-45	253/929 (27.2)	209/906 (23.1)	18.4 (16.3-20.9)	14.9 (13.0-17.0)	0.81 (0.68-0.98)	3.5	28.6		
≤30	40/164 (24.4)	44/167 (26.3)	18.8 (13.8-25.6)	19.4 (14.5-26.1)	1.04 (0.68-1.60)	-0.6	167		
CV death								0.19	0.94
>90	98/808 (12.1)	69/878 (7.9)	7.6 (6.3-9.3)	4.7 (3.7-5.9)	0.62 (0.46-0.85)	2.9	34.5		
61-90	400/2824 (14.2)	295/2792 (10.6)	8.4 (7.6-9.2)	6.0 (5.4-6.8)	0.73 (0.63-0.85)	2.4	41.7		
46-60	307/1625 (18.9)	279/1607 (17.4)	10.7 (9.6-12.0)	9.7 (8.6-10.9)	0.88 (0.75-1.03)	NC	NC		
31-45	258/929 (27.8)	191/906 (21.1)	16.7 (14.8-18.9)	12.2 (10.6-14.1)	0.73 (0.60-0.88)	4.5	22.2		
≤30	58/164 (35.4)	55/167 (32.9)	25.4 (19.6-32.8)	21.8 (16.7-28.4)	0.93 (0.65-1.35)	3.6	27.8		
All-cause death								0.12	0.98
>90	109/808 (13.5)	87/878 (9.9)	8.5 (7.0-10.2)	5.9 (4.8-7.3)	0.70 (0.53-0.93)	2.6	38.5		
61-90	478/2824 (16.9)	356/2792 (12.8)	10.0 (9.1-10.9)	7.3 (6.6-8.1)	0.74 (0.64-0.85)	2.7	37.0		
46-60	367/1625 (22.6)	346/1607 (21.5)	12.8 (11.6-14.2)	12.0 (10.8-13.4)	0.92 (0.79-1.06)	0.8	125		
31-45	322/929 (34.7)	248/906 (27.4)	20.9 (18.7-23.3)	15.8 (14.0-17.9)	0.76 (0.64-0.89)	5.1	19.6		
≤30	69/164 (42.1)	70/167 (41.9)	30.2 (23.8-38.2)	27.8 (22.0-35.1)	0.98 (0.70-1.36)	2.4	41.7		

Legend: eGFR, estimated glomerular filtration rate categories expressed in ml/min/1.73m^2; PBO, placebo; MRA, mineralocorticoid receptor antagonist; HR, hazard ratio; CI, confidence interval; aARR, annualized absolute risk reduction; aNNT, annualized number needed-to-treat; Inter.P-trend, treatment-by-eGFR category interaction P-value for the trend test of ordered categories; Study Het., treatment-by-study heterogeneity P-value; CV, cardiovascular; HF, heart failure; n, number of events; N, number of patients; %, percentage. Event-rate expressed as events per 100 person-years along with the respective 95% confidence intervals.

Table 3. Adverse events by eGFR categories

Outcome/eGFR cat.	Events PBO n/N (%)	Events MRA n/N (%)	OR (95%CI)	Inter.P-trend	Study Het.
Hyperkalemia				0.002	0.65
>90	52/803 (6.5)	85/865 (9.8)	1.57 (1.13-2.19)		
61-90	226/2788 (8.1)	311/2759 (11.3)	1.44 (0.88-2.35)		
46-60	167/1600 (10.4)	295/1580 (18.7)	1.97 (1.32-2.94)		
31-45	100/903 (11.1)	225/889 (25.3)	2.72 (2.02-3.67)		
≤30	27/157 (17.2)	49/162 (30.2)	2.09 (1.38-3.15)		
Worsening kidney function				0.39	0.25
>90	207/772 (26.8)	262/843 (31.1)	1.23 (0.99-1.53)		
61-90	588/2688 (21.9)	738/2668 (27.7)	1.37 (1.15-1.62)		
46-60	309/1533 (20.2)	410/1515 (27.1)	1.47 (1.28-1.68)		
31-45	180/853 (21.1)	248/851 (29.1)	1.54 (1.21-1.95)		
≤30	21/147 (14.3)	39/153 (25.5)	2.05 (1.24-3.41)		

Legend: eGFR, estimated glomerular filtration rate categories expressed in ml/min/1.73m2; PBO, placebo; MRA, mineralocorticoid receptor antagonist; OR, odds ratio; CI, confidence interval; Inter.P-trend, treatment-by-eGFR category interaction P-value for the trend test of ordered categories; Study Het., treatment-by-study heterogeneity P-value; n, number of events; N, number of patients; %, percentage.


CV death or HF hosp.
All-cause death
HR (95%CI)
1.2
1
0.8
0.6
0.4
20
40
60
80
100
120
eGFR (ml/min/1.73m2)
Interaction P-trend =0.01
Interaction P-trend =0.19
HR
95%CI

Supplemental Material

Supplemental Table 1. eGFR category comparison using the MDRD and CKD-EPI formulas

		CKD-EPI					Total
	eGFR cat.	**≤30**	**31-45**	**46-60**	**61-90**	**>90**	
MDRD	**≤30**	179 (54.1)	0	0	0	0	179
	31-45	152 (45.9)	1387 (75.6)	9 (0.3)	0	0	1548
	46-60	0	448 (24.4)	2714 (84)	72 (1.3)	0	3234
	61-90	0	0	509 (15.8)	5254 (93.6)	177 (10.6)	5940
	>90	0	0	0	290 (5.2)	1497 (89.4)	1787
	Total	331	1835	3232	5616	1674	12688

Legend: eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease formula; CKD-EPI, chronic kidney disease epidemiology collaboration formula.

Supplemental Table 2. HFrEF (RALES + EMPHASIS) patients' characteristics by eGFR categories

Characteristic/eGFR cat.	≤30	31-45	46-60	61-90	>90	P-value
N	108	681	1160	1938	474	
Study						
EMPHASIS	36 (33.3%)	365 (53.6%)	692 (59.7%)	1323 (68.3%)	287 (60.5%)	<0.001
RALES	72 (66.7%)	316 (46.4%)	468 (40.3%)	615 (31.7%)	187 (39.5%)	
Age, years	74.6 ± 7.6	72.1 ± 8.4	69.7 ± 8.2	66.2 ± 8.7	57.5 ± 10.3	<0.001
Age >75yr	56 (51.9%)	283 (41.6%)	346 (29.8%)	306 (15.8%)	7 (1.5%)	<0.001
Women	47 (43.5%)	192 (28.2%)	314 (27.1%)	413 (21.3%)	83 (17.5%)	<0.001
Race						<0.001
White	101 (93.5%)	592 (86.9%)	1009 (87.0%)	1628 (84.0%)	348 (73.4%)	
Black	2 (1.9%)	16 (2.3%)	36 (3.1%)	80 (4.1%)	53 (11.2%)	
Asian	2 (1.9%)	55 (8.1%)	77 (6.6%)	158 (8.2%)	47 (9.9%)	
Other	3 (2.8%)	18 (2.6%)	38 (3.3%)	72 (3.7%)	26 (5.5%)	
BMI, Kg/m2	27.4 ± 3.5	27.2 ± 4.7	27.6 ± 4.8	27.6 ± 4.9	27.7 ± 5.3	0.71
Current smoker	13 (36.1%)	156 (42.7%)	328 (47.4%)	589 (44.5%)	121 (42.2%)	<0.001
NYHA class						<0.001
III	50 (46.3%)	221 (32.5%)	333 (28.7%)	432 (22.3%)	136 (28.8%)	
IV	22 (20.4%)	94 (13.8%)	135 (11.6%)	181 (9.3%)	50 (10.6%)	
SBP, mmHg	126.2 ± 24.1	122.3 ± 19.3	122.8 ± 18.1	124.4 ± 17.8	122.4 ± 16.7	0.006
DBP, mmHg	73.1 ± 12.2	73.0 ± 11.0	73.7 ± 10.9	75.6 ± 10.4	75.8 ± 10.5	<0.001
Heart rate, bpm	74.8 ± 15.3	74.9 ± 13.4	75.1 ± 13.9	75.4 ± 14.2	76.6 ± 13.9	0.28
LVEF, %	25.7 ± 6.2	25.8 ± 5.7	25.7 ± 5.7	25.9 ± 5.4	25.9 ± 5.7	0.82
Hypertension	54 (50.0%)	357 (52.4%)	591 (50.9%)	998 (51.5%)	192 (40.5%)	<0.001
Diabetes	32 (29.6%)	206 (30.2%)	353 (30.4%)	512 (26.4%)	111 (23.4%)	0.014
Atrial Fibrillation/Flutter	25 (23.1%)	185 (27.2%)	296 (25.5%)	480 (24.8%)	67 (14.1%)	<0.001
Previous MI	56 (51.9%)	312 (45.8%)	521 (44.9%)	778 (40.1%)	174 (36.7%)	<0.001
Previous stroke	11 (10.2%)	71 (10.4%)	97 (8.4%)	142 (7.3%)	21 (4.4%)	0.003
PAD	5 (6.9%)	19 (6.0%)	21 (4.5%)	22 (3.6%)	0 (0.0%)	0.010
Prior HFH	15 (41.7%)	228 (62.5%)	380 (54.9%)	654 (49.4%)	146 (50.9%)	<0.001
COPD	14 (13.0%)	103 (15.1%)	151 (13.0%)	278 (14.3%)	65 (13.7%)	0.74
eGFR, ml/min/1.73m2	26.9 ± 3.1	39.3 ± 4.1	53.3 ± 4.3	73.6 ± 8.5	99.5 ± 9.5	<0.001
Hemoglobin, g/dL	13.4 ± 1.5	13.3 ± 1.6	13.6 ± 1.6	14.0 ± 1.5	14.1 ± 1.7	<0.001
Potassium, mmol/L	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	0.002
Sodium, mmol/L	138.7 ± 4.4	139.1 ± 4.1	139.7 ± 3.8	139.8 ± 4.0	139.3 ± 4.2	<0.001
ACE/ARBs	97 (89.8%)	619 (90.9%)	1092 (94.1%)	1829 (94.4%)	438 (92.4%)	0.007
Beta-blockers	42 (38.9%)	329 (48.3%)	656 (56.6%)	1231 (63.5%)	259 (54.6%)	<0.001
Loop diuretic	105 (97.2%)	644 (94.6%)	1083 (93.4%)	1697 (87.6%)	395 (83.3%)	<0.001
Lipid lowering drug	33 (30.6%)	266 (39.1%)	478 (41.2%)	846 (43.7%)	175 (36.9%)	0.005
Anti-thrombotics	63 (58.3%)	451 (66.2%)	806 (69.5%)	1362 (70.3%)	300 (63.3%)	0.003
MRA	55 (50.9%)	327 (48.0%)	584 (50.3%)	957 (49.4%)	248 (52.3%)	0.66

Legend: HFrEF, heart failure with reduced ejection fraction; BMI, body mass index; NYHA, New York Heart Association functional class; MI, myocardial infarction; PAD, peripheral artery disease: HFH, heart failure hospitalization; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists.

Supplemental Table 3. HFpEF (TOPCAT) patients' characteristics by eGFR categories

Characteristic/eGFR cat.	≤30	31-45	46-60	61-90	>90	P-value
N	46	379	530	651	160	
Study						
TOPCAT-Americas	46 (100.0%)	379 (100.0%)	530 (100.0%)	651 (100.0%)	160 (100.0%)	
Age, years	78.3 ± 8.7	74.9 ± 9.1	72.5 ± 8.9	70.8 ± 9.5	61.2 ± 6.4	<0.001
Age >75yr	32 (69.6%)	215 (56.7%)	238 (44.9%)	256 (39.3%)	6 (3.8%)	<0.001
Women	26 (56.5%)	212 (55.9%)	245 (46.2%)	327 (50.2%)	72 (45.0%)	0.029
Race						0.10
White	38 (82.6%)	292 (77.0%)	430 (81.1%)	508 (78.0%)	115 (71.9%)	
Black	6 (13.0%)	63 (16.6%)	76 (14.3%)	118 (18.1%)	39 (24.4%)	
Other	2 (4.3%)	24 (6.3%)	24 (4.5%)	25 (3.8%)	6 (3.8%)	
BMI, Kg/m2	33.7 ± 7.3	33.3 ± 8.0	33.7 ± 7.9	33.8 ± 8.4	35.8 ± 8.5	0.021
NYHA class III	21 (45.7%)	154 (40.7%)	183 (34.5%)	217 (33.4%)	45 (28.3%)	0.021
SBP, mmHg	123.2 ± 15.4	126.7 ± 16.0	127.0 ± 15.2	128.5 ± 16.1	128.4 ± 16.7	0.085
DBP, mmHg	64.9 ± 11.1	69.3 ± 11.1	70.3 ± 11.2	72.7 ± 11.4	75.9 ± 11.5	<0.001
Heart rate, bpm	67.3 ± 17.6	68.9 ± 11.2	67.8 ± 10.7	69.5 ± 11.5	71.7 ± 12.6	0.002
LVEF, %	59.4 ± 8.1	58.0 ± 7.8	58.2 ± 7.6	58.3 ± 7.7	57.6 ± 8.5	0.62
Hypertension	45 (97.8%)	343 (90.5%)	482 (90.9%)	575 (88.5%)	143 (89.4%)	0.24
Diabetes	23 (50.0%)	204 (53.8%)	249 (47.0%)	243 (37.4%)	69 (43.1%)	<0.001
Atrial Fibrillation/Flutter	9 (20.0%)	96 (25.8%)	138 (26.2%)	180 (28.1%)	23 (14.6%)	0.011
Previous MI	13 (28.3%)	143 (37.7%)	194 (36.6%)	172 (26.5%)	45 (28.1%)	<0.001
Previous stroke	4 (8.7%)	32 (8.4%)	51 (9.6%)	49 (7.5%)	14 (8.8%)	0.79
PAD	7 (15.2%)	60 (15.8%)	69 (13.0%)	55 (8.5%)	16 (10.0%)	0.005
Prior HFH	32 (69.6%)	250 (66.0%)	308 (58.1%)	339 (52.2%)	111 (69.4%)	<0.001
COPD	7 (15.2%)	56 (14.8%)	94 (17.7%)	108 (16.6%)	26 (16.3%)	0.83
eGFR, ml/min/1.73m2	28.5 ± 1.7	38.6 ± 4.3	52.8 ± 4.2	73.1 ± 8.3	98.7 ± 7.5	<0.001
Hemoglobin, g/dL	12.0 ± 1.7	12.3 ± 2.2	12.6 ± 2.5	12.9 ± 2.7	13.0 ± 3.2	0.002
Potassium, mmol/L	4.3 ± 0.5	4.2 ± 0.5	4.2 ± 0.4	4.1 ± 0.5	4.2 ± 0.4	0.007
Sodium, mmol/L	139.3 ± 4.2	139.7 ± 3.0	139.7 ± 3.2	139.5 ± 6.3	139.7 ± 3.1	0.88
ACE/ARBs	30 (65.2%)	291 (76.8%)	420 (79.2%)	508 (78.0%)	136 (85.0%)	0.046
Beta-blockers	41 (89.1%)	299 (78.9%)	416 (78.5%)	503 (77.3%)	120 (75.0%)	0.33
Loop diuretic	44 (95.7%)	347 (91.6%)	468 (88.3%)	566 (86.9%)	138 (86.3%)	0.086
Lipid lowering drug	35 (76.1%)	260 (68.6%)	356 (67.2%)	389 (59.8%)	102 (63.7%)	0.009
Anti-thrombotics	31 (67.4%)	223 (58.8%)	316 (59.6%)	353 (54.2%)	96 (60.0%)	0.17
Spironolactone	26 (56.5%)	191 (50.4%)	259 (48.9%)	322 (49.5%)	88 (55.0%)	0.60

Legend: HFpEF, heart failure with preserved ejection fraction; BMI, body mass index; NYHA, New York Heart Association functional class; MI, myocardial infarction; PAD, peripheral artery disease: HFH, heart failure hospitalization; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists.

Supplemental Table 4. MI (EPHESUS) patients' characteristics by eGFR categories

Characteristics/eGFR cat.	≤30	31-45	46-60	61-90	>90	P-value
N	177	775	1542	3027	1052	
Study						
EPHESUS	177 (100.0%)	775 (100.0%)	1542 (100.0%)	3027 (100.0%)	1052 (100.0%)	
Age, years	75.5 ± 8.3	73.0 ± 8.2	69.2 ± 8.9	62.0 ± 10.5	53.3 ± 9.2	<0.001
Age >75yr	103 (58.2%)	362 (46.7%)	462 (30.0%)	373 (12.3%)	14 (1.3%)	<0.001
Women	98 (55.4%)	339 (43.7%)	575 (37.3%)	731 (24.1%)	167 (15.9%)	<0.001
Race						0.038
White	169 (95.5%)	719 (92.8%)	1385 (89.8%)	2732 (90.3%)	924 (87.8%)	
Black	0 (0.0%)	7 (0.9%)	14 (0.9%)	37 (1.2%)	15 (1.4%)	
Asian	1 (0.6%)	7 (0.9%)	20 (1.3%)	26 (0.9%)	14 (1.3%)	
Other	7 (4.0%)	42 (5.4%)	123 (8.0%)	232 (7.7%)	99 (9.4%)	
BMI, Kg/m2	27.2 ± 4.4	27.3 ± 4.5	27.3 ± 4.4	27.4 ± 4.5	27.6 ± 4.7	0.66
Current smoker	67 (37.9%)	386 (49.8%)	760 (49.4%)	1949 (64.4%)	837 (79.6%)	<0.001
Killip class						<0.001
III	49 (30.2%)	201 (27.8%)	238 (16.4%)	437 (15.2%)	118 (11.7%)	
IV	7 (4.3%)	18 (2.5%)	27 (1.9%)	29 (1.0%)	7 (0.7%)	
SBP, mmHg	122.5 ± 18.5	122.1 ± 17.3	120.9 ± 16.8	118.3 ± 16.2	115.9 ± 15.1	<0.001
DBP, mmHg	72.4 ± 12.9	71.6 ± 12.7	73.1 ± 12.0	73.1 ± 11.5	72.8 ± 10.8	0.024
Heart rate, bpm	78.0 ± 15.5	76.4 ± 14.3	76.2 ± 13.3	76.7 ± 13.2	78.3 ± 13.4	<0.001
LVEF, %	32.0 ± 6.8	32.0 ± 6.2	32.8 ± 6.2	33.4 ± 5.9	33.5 ± 6.0	<0.001
Hypertension	143 (80.8%)	549 (70.8%)	1035 (67.1%)	1728 (57.1%)	525 (49.9%)	<0.001
Diabetes	73 (41.2%)	316 (40.8%)	551 (35.7%)	857 (28.3%)	331 (31.5%)	<0.001
Atrial Fibrillation/Flutter	49 (27.7%)	158 (20.4%)	254 (16.5%)	325 (10.7%)	83 (7.9%)	<0.001
Previous MI	69 (39.0%)	281 (36.3%)	484 (31.4%)	742 (24.5%)	213 (20.2%)	<0.001
Previous stroke	27 (15.3%)	108 (13.9%)	170 (11.0%)	231 (7.6%)	54 (5.1%)	<0.001
PAD	36 (20.3%)	135 (17.4%)	237 (15.4%)	314 (10.4%)	91 (8.7%)	<0.001
Prior HFH	39 (22.0%)	127 (16.4%)	138 (8.9%)	162 (5.4%)	39 (3.7%)	<0.001
COPD	28 (15.8%)	101 (13.0%)	155 (10.1%)	244 (8.1%)	89 (8.5%)	<0.001
eGFR, ml/min/1.73m2	26.4 ± 3.4	38.9 ± 4.1	53.6 ± 4.2	74.6 ± 8.5	101.0 ± 9.5	<0.001
Hemoglobin, g/dL	12.4 ± 2.0	12.9 ± 1.7	13.2 ± 1.7	13.4 ± 1.7	13.5 ± 1.7	<0.001
Potassium, mmol/L	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.4	4.2 ± 0.4	<0.001
Sodium, mmol/L	138.7 ± 4.4	139.5 ± 4.3	139.7 ± 5.0	139.4 ± 4.1	139.3 ± 4.0	0.018
ACE/ARBs	147 (83.1%)	674 (87.0%)	1356 (87.9%)	2620 (86.6%)	904 (85.9%)	0.32
Beta-blockers	114 (64.4%)	522 (67.4%)	1103 (71.5%)	2322 (76.7%)	854 (81.2%)	<0.001
Loop diuretic	153 (86.4%)	595 (76.8%)	1031 (66.9%)	1713 (56.6%)	453 (43.1%)	<0.001
Lipid lowering drug	64 (36.2%)	316 (40.8%)	672 (43.6%)	1494 (49.4%)	581 (55.2%)	<0.001
Anti-thrombotics	158 (89.3%)	678 (87.5%)	1409 (91.4%)	2834 (93.6%)	999 (95.0%)	<0.001
Eplerenone	86 (48.6%)	388 (50.1%)	764 (49.5%)	1513 (50.0%)	542 (51.5%)	0.88

Legend: MI, myocardial infarction; BMI, body mass index; PAD, peripheral artery disease: HFH, heart failure hospitalization; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists.

Supplemental Table 5. Treatment effect (MRA vs. Placebo) across eGFR categories using the MDRD formula

Outcome/eGFR cat.	Events PBO n/N (%)	Events MRA n/N (%)	Event-rate PBO (95%CI)	Event-rate MRA (95%CI)	HR (95%CI)	Inter.P-trend	Study Het.
CV death or HF hosp.						0.0.68	0.64
>90	193/847 (22.8)	143/940 (15.2)	15.5 (13.5-17.9)	9.5 (8.1-11.2)	0.63 (0.50-0.78)		
61-90	732/2987 (24.5)	561/2953 (19.0)	16.1 (14.9-17.3)	11.6 (10.7-12.6)	0.73 (0.66-0.82)		
46-60	567/1641 (34.6)	478/1593 (34.6)	23.1 (21.3-25.1)	19.2 (17.5-21.0)	0.81 (0.72-0.92)		
31-45	354/776 (45.6)	285/772 (36.9)	34.2 (30.9-38.0)	25.2 (22.4-28.3)	0.76 (0.65-0.89)		
≤30	42/90 (46.7)	46/89 (51.7)	45.7 (33.8-61.9)	50.4 (37.8-67.3)	1.05 (0.69-1.60)		

Legend: eGFR, estimated glomerular filtration rate categories expressed in ml/min/1.73m^2; PBO, placebo; MRA, mineralocorticoid receptor antagonist; HR, hazard ratio; CI, confidence interval; aARR, annualized absolute risk reduction; aNNT, annualized number needed-to-treat; Inter.P-trend, treatment-by-eGFR category interaction P-value for the trend test of ordered categories; Study Het., treatment-by-study heterogeneity P-value; CV, cardiovascular; HF, heart failure; n, number of events; N, number of patients; %, percentage. Event-rate expressed as events per 100 person-years along with the respective 95% confidence intervals.

Supplemental Table 6. HFrEF (RALES + EMPHASIS) treatment effect (MRA vs. Placebo) across eGFR categories

Outcome/eGFR cat. (ml/min/1.73m2)	Events PBO	Event-rate PBO	Events MRA	Event-rate MRA	HR (95%CI)	Inter.P-trend	Study Het.
CV death or HF hosp.						0.70	0.23
>90	67/226 (29.6)	19.5 (15.4-24.8)	43/248 (17.3)	10.5 (7.8-14.2)	0.53 (0.36-0.77)		
61-90	323/981 (32.9)	20.4 (18.3-22.8)	218/957 (22.8)	12.7 (11.1-14.5)	0.64 (0.54-0.76)		
46-60	241/576 (41.8)	29.2 (25.7-33.1)	192/584 (32.9)	19.8 (17.2-22.9)	0.67 (0.55-0.81)		
31-45	176/354 (49.7)	37.3 (32.2-43-3)	124/327 (37.9)	26.0 (21.8-31.0)	0.69 (0.55-0.87)		
≤30	31/53 (58.5)	50.0 (35.1-71.0)	27/55 (49.1)	40.6 (27.8-59.2)	0.86 (0.52-1.45)		
HF hosp.						0.99	0.11
>90	41/226 (18.1)	11.2 (8.2-15.2)	28/248 (11.3)	6.5 (4.5-9.4)	0.58 (0.36-0.94)		
61-90	207/981 (21.1)	12.1 (10.6-13.9)	136/957 (14.2)	7.6 (6.4-9.0)	0.64 (0.52-0.80)		
46-60	162/576 (28.1)	17.8 (15.3-20.8)	120/584 (20.5)	11.5 (9.6-13.8)	0.65 (0.51-0.82)		
31-45	117/354 (33.1)	21.1 (17.6-25.3)	76/327 (23.2)	13.9 (11.1-17.4)	0.65 (0.49-0.87)		
≤30	17/53 (32.1)	19.4 (12.0-31.1)	14/55 (25.5)	15.6 (9.2-26.3)	0.81 (0.40-1.64)		
CV death						0.47	0.85
>90	43/226 (19.0)	11.1 (8.2-14.9)	27/248 (10.9)	6.2 (4.2-9.0)	0.54 (0.33-0.87)		
61-90	188/981 (19.2)	10.4 (9.0-12.0)	135/957 (14.1)	7.2 (6.1-8.5)	0.71 (0.57-0.89)		
46-60	147/576 (25.5)	14.7 (12.5-17.2)	123/584 (21.1)	11.3 (9.5-13.5)	0.75 (0.59-0.96)		
31-45	116/354 (32.8)	20.4 (17.0-24.4)	80/327 (24.5)	14.4 (11.6-18.0)	0.70 (0.53-0.93)		
≤30	23/53 (43.4)	28.9 (19.2-43.5)	23/55 (41.8)	30.3 (20.2-45.7)	1.08 (0.61-1.93)		
All-cause death						0.63	0.81
>90	48/226 (21.2)	12.3 (9.3-16.4)	35/248 (14.1)	8.0 (5.7-11.1)	0.63 (0.41-0.97)		
61-90	211/981 (21.5)	11.6 (10.2-13.3)	151/957 (15.8)	8.1 (6.9-9.5)	0.71 (0.58-0.88)		
46-60	163/576 (28.3)	16.3 (13.9-19.0)	139/584 (23.8)	12.8 (10.8-15.1)	0.77 (0.61-0.96)		
31-45	142/354 (40.1)	24.9 (21.1-29.4)	95/327 (29.1)	17.1 (14.0-21.0)	0.68 (0.52-0.88)		
≤30	29/53 (54.7)	36.4 (25.3-52.4)	29/55 (52.7)	38.3 (26.6-55.1)	1.08 (0.65-1.81)		

Legend: HFrEF, heart failure with reduced ejection fraction; eGFR, estimated glomerular filtration rate categories expressed in ml/min/1.73m2; PBO, placebo; MRA, mineralocorticoid receptor antagonist; HR, hazard ratio; CI, confidence interval; aARR, annualized absolute risk reduction; aNNT, annualized number needed-to-treat; Inter.P-trend, treatment-by-eGFR category interaction P-value trend; Study Het., treatment-by-study heterogeneity P-value; CV, cardiovascular; HF, heart failure. Event-rate expressed as events per 100 person-years.

Supplemental Table 7. HFpEF (TOPCAT) treatment effect (MRA vs. Placebo) across eGFR categories

Outcome/eGFR cat. (ml/min/1.73m2)	Events PBO	Event-rate PBO	Events MRA	Event-rate MRA	HR (95%CI)	Inter.P
CV death or HF hosp.						0.25
>90	18/72 (25.0)	10.5 (6.6-16.7)	14/88 (15.9)	5.6 (3.3-9.4)	0.54 (0.27-1.09)	
61-90	93/329 (28.3)	11.2 (9.1-13.7)	67/322 (20.8)	7.6 (6.0-9.7)	0.69 (0.50-0.94)	
46-60	79/271 (29.2)	10.4 (8.3-12.9)	76/259 (29.3)	10.4 (8.3-13.0)	0.99 (0.73-1.36)	
31-45	81/188 (43.1)	19.0 (15.3-23.6)	70/191 (36.6)	15.8 (12.5-19.9)	0.83 (0.60-1.15)	
≤30	9/20 (45.0)	22.2 (11.6-42.7)	15/26 (57.7)	29.9 (18.0-49.6)	1.34 (0.59-3.07)	
HF hosp.						0.7
>90	13/72 (18.1)	7.6 (4.4-13.1)	10/88 (11.4)	4.0 (2.2-7.4)	0.54 (0.24-1.24)	
61-90	68/329 (20.7)	8.1 (6.4-10.3)	54/322 (16.8)	6.2 (4.7-8.0)	0.77 (0.54-1.10)	
46-60	63/271 (23.2)	8.3 (6.5-10.6)	52/259 (20.1)	7.1 (5.4-9.3)	0.86 (0.59-1.24)	
31-45	64/188 (34.0)	15.0 (11.8-19.2)	55/191 (28.8)	12.4 (9.5-16.2)	0.83 (0.58-1.19)	
≤30	8/20 (40.0)	19.8 (9.9-39.6)	13/26 (50.0)	25.9 (15.1-44.7)	1.30 (0.54-3-14)	
CV death						0.57
>90	9/72 (12.5)	4.7 (2.4-9.0)	6/88 (6.8)	2.2 (1.0-5.0)	0.47 (0.17-1.33)	
61-90	37/329 (11.2)	3.8 (2.7-5.2)	22/322 (6.8)	2.3 (1.5-3.5)	0.61 (0.36-1.03)	
46-60	35/271 (12.9)	4.1 (2.9-5.6)	33/259 (12.7)	4.1 (2.9-5.7)	1.00 (0.62-1.60)	
31-45	42/188 (22.3)	8.1 (6.0-11.0)	30/191 (15.7)	5.6 (3.9-8.0)	0.67 (0.42-1.08)	
≤30	4/20 (20.0)	7.6 (2.8-20.2)	5/26 (19.2)	6.3 (2.6-15.1)	0.79 (0.21-2.94)	
All-cause death						0.92
>90	10/72 (13.9)	5.2 (2.8-9.7)	10/88 (11.4)	3.7 (2.0-6.9)	0.70 (0.29-1.68)	
61-90	59/329 (17.9)	6.0 (4.7-7.8)	46/322 (14.3)	4.8 (3.6-6.4)	0.79 (0.54-1.17)	
46-60	64/271 (23.6)	7.4 (5.8-9.5)	59/259 (22.8)	7.3 (5.6-9.4)	0.98 (0.69-1.39)	
31-45	66/188 (35.1)	12.7 (10.0-16.2)	58/191 (30.4)	10.8 (8.3-13.9)	0.83 (0.59-1.19)	
≤30	6/20 (30.0)	11.4 (5.1-25.3)	9/26 (34.6)	11.3 (5.9-21.7)	0.94 (0.33-2.65)	

Legend: HFpEF, heart failure with preserved ejection fraction; eGFR, estimated glomerular filtration rate categories expressed in ml/min/1.73m2; PBO, placebo; MRA, mineralocorticoid receptor antagonist; HR, hazard ratio; CI, confidence interval; aARR, annualized absolute risk reduction; aNNT, annualized number needed-to-treat; Inter.P, treatment-by-eGFR category interaction P-value; CV, cardiovascular; HF, heart failure. Event-rate expressed as events per 100 person-years.

Supplemental Table 8. MI (EPHESUS) treatment effect (MRA vs. Placebo) across eGFR categories

Outcome/eGFR cat. (ml/min/1.73m2)	Events PBO	Event-rate PBO	Events MRA	Event-rate MRA	HR (95%CI)	Inter.P
CV death or HF hosp.						0.19
>90	86/510 (16.9)	13.2 (10.7-16.3)	67/542 (12.4)	9.2 (7.3-11.7)	0.71 (0.52-0.98)	
61-90	284/1514 (18.8)	15.3 (13.6-17.2)	218/1513 (14.4)	11.2 (9.8-12.7)	0.74 (0.62-0.89)	
46-60	213/778 (27.4)	24.1 (21.1-27.5)	208/764 (27.2)	23.9 (20.8-27.3)	0.99 (0.82-1.20)	
31-45	152/387 (39.3)	38.6 (33.0-45.3)	139/388 (35.8)	33.6 (28.4-39.7)	0.88 (0.70-1.10)	
≤30	38/91 (41.8)	44.6 (32.5-61.3)	36/86 (41.9)	41.6 (30.0-57.7)	0.93 (0.59-1.46)	
HF hosp.						0.12
>90	48/510 (9.4)	7.4 (5.6-9.8)	37/542 (6.8)	5.1 (3.7-7.0)	0.70 (0.46-1.08)	
61-90	141/1514 (9.3)	7.6 (6.4-9.0)	99/1513 (6.5)	5.1 (4.2-6.2)	0.68 (0.53-0.88)	
46-60	114/778 (14.7)	12.9 (10.8-15.5)	113/764 (14.8)	13.0 (10.8-15.6)	1.01 (0.78-1.31)	
31-45	72/387 (18.6)	18.3 (14.6-23.1)	78/388 (20.1)	18.9 (15.1-23.6)	1.04 (0.75-1.43)	
≤30	15/91 (16.5)	17.7 (10.7-29.3)	17/86 (19.8)	19.7 (12.2-31.7)	1.11 (0.55-2.21)	
CV death						0.53
>90	46/510 (9.0)	6.5 (4.9-8.7)	36/542 (6.6)	4.7 (3.4-6.6)	0.72 (0.47-1.12)	
61-90	175/1514 (11.6)	8.8 (7.6-10.2)	138/1513 (9.1)	6.7 (5.7-7.9)	0.77 (0.62-0.97)	
46-60	125/778 (16.1)	12.6 (10.5-15.0)	123/764 (16.1)	12.6 (10.6-15.1)	1.00 (0.78-1.29)	
31-45	100/387 (25.8)	22.0 (18.1-26.7)	81/388 (20.9)	17.1 (13.8-21.3)	0.78 (0.58-1.05)	
≤30	31/91 (34.1)	32.3 (22.7-45.9)	27/86 (31.4)	27.9 (19.1-40.7)	0.87 (0.52-1.45)	
All-cause death						0.19
>90	51/510 (10.0)	7.2 (5.5-9.5)	42/542 (7.7)	5.5 (4.1-7.5)	0.76 (0.51-1.15)	
61-90	208/1514 (13.7)	10.4 (9.1-11.9)	159/1513 (10.5)	7.8 (6.6-9.1)	0.75 (0.61-0.92)	
46-60	140/778 (18.0)	14.1 (11.9-16.6)	148/764 (19.4)	15.2 (13.0-17.9)	1.08 (0.86-1.36)	
31-45	114/387 (29.5)	25.1 (20.9-30.1)	95/388 (24.5)	20.1 (16.4-24.6)	0.80 (0.61-1.06)	
≤30	34/91 (37.4)	35.4 (25.3-49.5)	32/86 (37.2)	33.1 (23.4-46.8)	0.94 (0.58-1.52)	

Legend: MI, myocardial infarction; eGFR, estimated glomerular filtration rate categories expressed in ml/min/1.73m2; PBO, placebo; MRA, mineralocorticoid receptor antagonist; HR, hazard ratio; CI, confidence interval; aARR, annualized absolute risk reduction; aNNT, annualized number needed-to-treat; Inter.P, treatment-by-eGFR category interaction P-value; CV, cardiovascular; HF, heart failure. Event-rate expressed as events per 100 person-years.