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

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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/1.73m² (mean eGFR=26.8±3.2ml/min/1.73m²). 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/1.73m²: 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/1.73m²) 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/1.73m².
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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{11,12}

Using individual patient data (IPD) from the RALES,\textsuperscript{13} EMPHASIS-HF,\textsuperscript{14} TOPCAT,\textsuperscript{15} and EPHESUS\textsuperscript{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\textsuperscript{2} as recalculated using the CKD-EPI formula.\textsuperscript{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. 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). 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/1.73m² (compatible with the KDIGO CKD stages)
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/1.73m²: 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/1.73m²) 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/1.73m². 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/1.73m² 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/1.73m². 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/1.73m² had a multifold (3 or more) higher risk of events compared to patients with eGFR >90 ml/min/1.73m². 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.\textsuperscript{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,\textsuperscript{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;\textsuperscript{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\textsuperscript{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 \leq 30 ml/min/1.73m\textsuperscript{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 \leq 30 ml/min/1.73m\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{32,33} The efficacy and safety of finerenone in patients with HFpEF with an eGFR \geq 25 ml/min/1.73m\textsuperscript{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.\textsuperscript{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,\textsuperscript{35-38} as acknowledged by recent guidelines.\textsuperscript{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.\textsuperscript{40} Sodium glucose co-transporter 2 inhibitors (SGLT2i) may reduce the incidence of hyperkalemia in HF patients, particularly those taking MRA.\textsuperscript{41-43} This strategy may be particularly attractive because both MRAs and SGLT2i improve HF outcomes.

\textbf{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”.\textsuperscript{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.\textsuperscript{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 \(\leq 30 \text{ ml/min/1.73m}^2\), 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.\textsuperscript{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


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

<table>
<thead>
<tr>
<th>Characteristic/eGFR cat.</th>
<th>≤30</th>
<th>31-45</th>
<th>46-60</th>
<th>61-90</th>
<th>&gt;90</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.</td>
<td>331</td>
<td>1835</td>
<td>3232</td>
<td>5616</td>
<td>1686</td>
<td></td>
</tr>
<tr>
<td><strong>Study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPHASIS</td>
<td>36  (10.9%)</td>
<td>365 (19.9%)</td>
<td>692 (21.4%)</td>
<td>1323 (23.6%)</td>
<td>287 (17.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EPHESUS</td>
<td>177 (53.5%)</td>
<td>775 (42.2%)</td>
<td>1542 (47.7%)</td>
<td>3027 (53.9%)</td>
<td>1052 (62.4%)</td>
<td></td>
</tr>
<tr>
<td>RALES</td>
<td>72  (21.8%)</td>
<td>316 (17.2%)</td>
<td>468 (14.5%)</td>
<td>615 (11.0%)</td>
<td>187 (11.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TOPCAT-Americas</td>
<td>46  (13.9%)</td>
<td>379 (20.7%)</td>
<td>530 (16.4%)</td>
<td>651 (11.6%)</td>
<td>160 (9.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>75.6 ± 8.2</td>
<td>73.1 ± 8.5</td>
<td>69.9 ± 8.7</td>
<td>64.5 ± 10.3</td>
<td>55.3 ± 9.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age &gt;75yr</td>
<td>191 (57.7%)</td>
<td>860 (46.9%)</td>
<td>1046 (32.4%)</td>
<td>935 (16.6%)</td>
<td>27 (1.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>171 (51.7%)</td>
<td>743 (40.5%)</td>
<td>1134 (35.1%)</td>
<td>1471 (26.2%)</td>
<td>322 (19.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>308 (93.1%)</td>
<td>1603 (87.4%)</td>
<td>2824 (87.4%)</td>
<td>4868 (86.7%)</td>
<td>1387 (82.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>8   (2.4%)</td>
<td>86 (4.7%)</td>
<td>126 (3.9%)</td>
<td>235 (4.2%)</td>
<td>107 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>3   (0.9%)</td>
<td>62 (3.4%)</td>
<td>97 (3.0%)</td>
<td>184 (3.3%)</td>
<td>61 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12  (3.6%)</td>
<td>84 (4.6%)</td>
<td>185 (5.7%)</td>
<td>329 (5.9%)</td>
<td>131 (7.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI, Kg/m²</strong></td>
<td>28.4 ± 5.5</td>
<td>28.8 ± 6.2</td>
<td>28.6 ± 5.9</td>
<td>28.3 ± 5.7</td>
<td>28.5 ± 5.9</td>
<td>0.026</td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
<td>80  (30.9%)</td>
<td>542 (35.7%)</td>
<td>1088 (39.4%)</td>
<td>2538 (50.8%)</td>
<td>958 (64.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>120 (38.0%)</td>
<td>576 (32.3%)</td>
<td>754 (24.0%)</td>
<td>1086 (19.9%)</td>
<td>299 (18.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IV</td>
<td>29  (9.2%)</td>
<td>112 (6.3%)</td>
<td>162 (5.2%)</td>
<td>210 (3.8%)</td>
<td>57 (3.5%)</td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>123.8 ± 20.2</td>
<td>123.1 ± 17.9</td>
<td>122.6 ± 17.2</td>
<td>121.6 ± 17.2</td>
<td>118.9 ± 16.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>71.6 ± 12.7</td>
<td>71.7 ± 11.8</td>
<td>72.9 ± 11.5</td>
<td>73.9 ± 11.2</td>
<td>73.9 ± 10.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>75.4 ± 16.1</td>
<td>74.3 ± 13.7</td>
<td>74.4 ± 13.4</td>
<td>75.4 ± 13.6</td>
<td>77.2 ± 13.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>33.8 ± 12.7</td>
<td>35.2 ± 13.6</td>
<td>34.5 ± 12.7</td>
<td>33.8 ± 11.3</td>
<td>33.7 ± 10.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>242 (73.1%)</td>
<td>1249 (68.1%)</td>
<td>2108 (65.2%)</td>
<td>3301 (58.8%)</td>
<td>860 (51.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>128 (38.7%)</td>
<td>726 (39.6%)</td>
<td>1153 (35.7%)</td>
<td>1612 (28.7%)</td>
<td>511 (30.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial Fibrillation/Flutter</td>
<td>83 (25.2%)</td>
<td>439 (24.0%)</td>
<td>688 (21.3%)</td>
<td>985 (17.6%)</td>
<td>173 (10.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous MI</td>
<td>138 (41.7%)</td>
<td>736 (40.1%)</td>
<td>1199 (37.1%)</td>
<td>1692 (30.1%)</td>
<td>432 (25.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>42  (12.7%)</td>
<td>211 (11.5%)</td>
<td>318 (9.8%)</td>
<td>422 (7.5%)</td>
<td>89 (5.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAD</td>
<td>48  (16.3%)</td>
<td>214 (14.6%)</td>
<td>327 (12.9%)</td>
<td>391 (9.1%)</td>
<td>107 (7.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior HFH</td>
<td>86  (33.2%)</td>
<td>605 (39.8%)</td>
<td>826 (29.9%)</td>
<td>1155 (23.1%)</td>
<td>296 (19.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>49  (14.8%)</td>
<td>260 (14.2%)</td>
<td>400 (12.4%)</td>
<td>630 (11.2%)</td>
<td>180 (10.7%)</td>
<td>0.002</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m²</td>
<td>28.8 ± 3.2</td>
<td>39.0 ± 4.2</td>
<td>53.4 ± 4.2</td>
<td>74.1 ± 8.5</td>
<td>100.4 ± 9.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.4 ± 2.0</td>
<td>12.8 ± 1.9</td>
<td>13.2 ± 1.9</td>
<td>13.5 ± 1.8</td>
<td>13.6 ± 1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.3 ± 0.5</td>
<td>4.3 ± 0.5</td>
<td>4.3 ± 0.4</td>
<td>4.3 ± 0.4</td>
<td>4.2 ± 0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>138.8 ± 4.4</td>
<td>139.4 ± 4.0</td>
<td>139.7 ± 4.3</td>
<td>139.5 ± 4.4</td>
<td>139.3 ± 4.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACEi/ARBs</td>
<td>274 (82.8%)</td>
<td>1584 (86.3%)</td>
<td>2868 (88.7%)</td>
<td>4957 (88.3%)</td>
<td>1478 (87.7%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>197 (59.5%)</td>
<td>1150 (62.7%)</td>
<td>2175 (67.3%)</td>
<td>4056 (72.2%)</td>
<td>1233 (73.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>302 (91.2%)</td>
<td>1586 (86.4%)</td>
<td>2582 (79.9%)</td>
<td>3976 (70.8%)</td>
<td>986 (58.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid lowering drug</td>
<td>132 (39.9%)</td>
<td>842 (49.9%)</td>
<td>1506 (46.6%)</td>
<td>2729 (48.6%)</td>
<td>858 (50.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-thrombotics</td>
<td>252 (76.1%)</td>
<td>1352 (73.7%)</td>
<td>2531 (78.3%)</td>
<td>4549 (81.0%)</td>
<td>1395 (82.7%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

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

Legend: 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 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

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

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

<table>
<thead>
<tr>
<th>MDRD</th>
<th>eGFR cat.</th>
<th>≤30</th>
<th>31-45</th>
<th>46-60</th>
<th>61-90</th>
<th>&gt;90</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤30</td>
<td>179 (54.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>179</td>
</tr>
<tr>
<td>31-45</td>
<td>152 (45.9)</td>
<td>1387 (75.6)</td>
<td>9 (0.3)</td>
<td>0</td>
<td>0</td>
<td>1548</td>
<td></td>
</tr>
<tr>
<td>46-60</td>
<td>0</td>
<td>448 (24.4)</td>
<td>2714 (84)</td>
<td>72 (1.3)</td>
<td>0</td>
<td>3234</td>
<td></td>
</tr>
<tr>
<td>61-90</td>
<td>0</td>
<td>0</td>
<td>509 (15.8)</td>
<td>5254 (93.6)</td>
<td>177 (10.6)</td>
<td>5940</td>
<td></td>
</tr>
<tr>
<td>&gt;90</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>290 (5.2)</td>
<td>1497 (89.4)</td>
<td>1787</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>331</td>
<td>1835</td>
<td>3232</td>
<td>5616</td>
<td>1674</td>
<td>12688</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Characteristic/eGFR cat.</th>
<th>≤30</th>
<th>31-45</th>
<th>46-60</th>
<th>61-90</th>
<th>&gt;90</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>108</td>
<td>681</td>
<td>1160</td>
<td>1938</td>
<td>474</td>
<td></td>
</tr>
<tr>
<td><strong>Study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPHASIS</td>
<td>36</td>
<td>365</td>
<td>692</td>
<td>1323</td>
<td>287</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RALES</td>
<td>72</td>
<td>316</td>
<td>468</td>
<td>615</td>
<td>187</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>74.6</td>
<td>72.1</td>
<td>69.7</td>
<td>66.2</td>
<td>57.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Age &gt;75yr</strong></td>
<td>56</td>
<td>283</td>
<td>346</td>
<td>306</td>
<td>7</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>47</td>
<td>192</td>
<td>314</td>
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<td>27.6</td>
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<td>432</td>
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<td>IV</td>
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<td>135</td>
<td>181</td>
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<tr>
<td>SBP, mmHg</td>
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<td>24.1</td>
<td>122.3</td>
<td>122.8</td>
<td>124.4</td>
<td>0.006</td>
</tr>
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<tr>
<td>Heart rate, bpm</td>
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<td>74.9</td>
<td>75.1</td>
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<td>LVEF, %</td>
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<td>25.8</td>
<td>25.7</td>
<td>25.9</td>
<td>0.82</td>
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<td>998</td>
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<td>206</td>
<td>353</td>
<td>512</td>
<td>111</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial Fibrillation/Flutter</td>
<td>25</td>
<td>185</td>
<td>296</td>
<td>480</td>
<td>67</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous MI</td>
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<td>521</td>
<td>778</td>
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<td>97</td>
<td>142</td>
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<td>PAD</td>
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<td>19</td>
<td>21</td>
<td>22</td>
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<tr>
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<td>228</td>
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<td>654</td>
<td>146</td>
<td>&lt;0.001</td>
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<td>COPD</td>
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<td>103</td>
<td>151</td>
<td>278</td>
<td>65</td>
<td>0.74</td>
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<tr>
<td>eGFR, ml/min/1.73m2</td>
<td>26.9</td>
<td>3.1</td>
<td>39.3</td>
<td>53.3</td>
<td>73.6</td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>13.4</td>
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<td>13.3</td>
<td>13.6</td>
<td>14.0</td>
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</tr>
<tr>
<td>Potassium, mmol/L</td>
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<td>4.3</td>
<td>4.3</td>
<td>4.3</td>
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</tr>
<tr>
<td>Sodium, mmol/L</td>
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<td>4.4</td>
<td>139.1</td>
<td>139.7</td>
<td>139.8</td>
<td>0.001</td>
</tr>
<tr>
<td>ACE/ARBs</td>
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<td>619</td>
<td>1092</td>
<td>1829</td>
<td>438</td>
<td>0.007</td>
</tr>
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<td>Beta-blockers</td>
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<td>656</td>
<td>1231</td>
<td>259</td>
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</tr>
<tr>
<td>Loop diuretic</td>
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<td>644</td>
<td>1083</td>
<td>1697</td>
<td>395</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid lowering drug</td>
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<td>266</td>
<td>478</td>
<td>846</td>
<td>175</td>
<td>0.005</td>
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<tr>
<td>Anti-thrombotics</td>
<td>63</td>
<td>451</td>
<td>806</td>
<td>1362</td>
<td>300</td>
<td>0.003</td>
</tr>
<tr>
<td>MRA</td>
<td>55</td>
<td>327</td>
<td>584</td>
<td>957</td>
<td>248</td>
<td>0.66</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Characteristic/eGFR cat.</th>
<th>≤30</th>
<th>31-45</th>
<th>46-60</th>
<th>61-90</th>
<th>&gt;90</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOPCAT-Americas</td>
<td>46 (100.0%)</td>
<td>379 (100.0%)</td>
<td>530 (100.0%)</td>
<td>651 (100.0%)</td>
<td>160 (100.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years</td>
<td>78.3 ± 8.7</td>
<td>74.9 ± 9.1</td>
<td>72.5 ± 8.9</td>
<td>70.8 ± 9.5</td>
<td>61.2 ± 6.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age &gt;75yr</td>
<td>32 (69.6%)</td>
<td>215 (56.7%)</td>
<td>238 (44.9%)</td>
<td>256 (39.3%)</td>
<td>6 (3.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>26 (56.5%)</td>
<td>212 (55.9%)</td>
<td>245 (46.2%)</td>
<td>327 (50.2%)</td>
<td>72 (45.0%)</td>
<td>0.029</td>
</tr>
<tr>
<td>Race</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>White</td>
<td>38 (82.6%)</td>
<td>292 (77.0%)</td>
<td>430 (81.1%)</td>
<td>508 (78.0%)</td>
<td>115 (71.9%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>6 (13.0%)</td>
<td>63 (16.6%)</td>
<td>76 (14.3%)</td>
<td>118 (18.1%)</td>
<td>39 (24.4%)</td>
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</tr>
<tr>
<td>Other</td>
<td>2 (4.3%)</td>
<td>24 (6.3%)</td>
<td>24 (4.5%)</td>
<td>25 (3.8%)</td>
<td>6 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>BMI, Kg/m2</td>
<td>33.7 ± 7.3</td>
<td>33.3 ± 8.0</td>
<td>33.7 ± 7.9</td>
<td>33.8 ± 8.4</td>
<td>35.8 ± 8.5</td>
<td>0.021</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>21 (45.7%)</td>
<td>154 (40.7%)</td>
<td>183 (34.5%)</td>
<td>217 (33.4%)</td>
<td>45 (28.3%)</td>
<td>0.021</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>123.2 ± 15.4</td>
<td>126.7 ± 16.0</td>
<td>127.0 ± 15.2</td>
<td>128.5 ± 16.1</td>
<td>128.4 ± 16.7</td>
<td>0.085</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>64.9 ± 11.1</td>
<td>69.3 ± 11.1</td>
<td>70.3 ± 11.2</td>
<td>72.7 ± 11.4</td>
<td>75.9 ± 11.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>67.3 ± 17.6</td>
<td>68.9 ± 11.2</td>
<td>67.8 ± 10.7</td>
<td>72.7 ± 11.4</td>
<td>71.7 ± 12.6</td>
<td>0.002</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>59.4 ± 8.1</td>
<td>58.0 ± 7.8</td>
<td>58.2 ± 7.6</td>
<td>58.3 ± 7.7</td>
<td>57.6 ± 8.5</td>
<td>0.62</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45 (97.8%)</td>
<td>343 (90.5%)</td>
<td>482 (90.9%)</td>
<td>575 (88.5%)</td>
<td>143 (89.4%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23 (50.0%)</td>
<td>204 (53.8%)</td>
<td>249 (47.0%)</td>
<td>243 (37.4%)</td>
<td>69 (43.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial Fibrillation/Flutter</td>
<td>9 (20.0%)</td>
<td>96 (25.8%)</td>
<td>138 (26.2%)</td>
<td>180 (28.1%)</td>
<td>23 (14.6%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Previous MI</td>
<td>13 (28.3%)</td>
<td>143 (37.7%)</td>
<td>194 (36.6%)</td>
<td>172 (26.5%)</td>
<td>45 (28.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>4 (8.7%)</td>
<td>32 (8.4%)</td>
<td>51 (9.6%)</td>
<td>49 (7.5%)</td>
<td>14 (8.8%)</td>
<td>0.79</td>
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<tr>
<td>PAD</td>
<td>7 (15.2%)</td>
<td>60 (15.8%)</td>
<td>69 (13.0%)</td>
<td>55 (8.5%)</td>
<td>16 (10.0%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Prior HFH</td>
<td>32 (69.6%)</td>
<td>250 (66.0%)</td>
<td>308 (58.1%)</td>
<td>339 (52.2%)</td>
<td>111 (69.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>7 (15.2%)</td>
<td>56 (14.8%)</td>
<td>94 (17.7%)</td>
<td>108 (16.6%)</td>
<td>26 (16.3%)</td>
<td>0.83</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m2</td>
<td>28.5 ± 1.7</td>
<td>38.6 ± 4.3</td>
<td>52.8 ± 4.2</td>
<td>73.1 ± 8.3</td>
<td>98.7 ± 7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.0 ± 1.7</td>
<td>12.3 ± 2.2</td>
<td>12.6 ± 2.5</td>
<td>12.9 ± 2.7</td>
<td>13.0 ± 3.2</td>
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</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.3 ± 0.5</td>
<td>4.2 ± 0.5</td>
<td>4.2 ± 0.4</td>
<td>4.1 ± 0.5</td>
<td>4.2 ± 0.4</td>
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</tr>
<tr>
<td>Sodium, mmol/L</td>
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<td>139.7 ± 3.0</td>
<td>139.7 ± 3.2</td>
<td>139.5 ± 6.3</td>
<td>139.7 ± 3.1</td>
<td>0.88</td>
</tr>
<tr>
<td>ACE/ARBs</td>
<td>30 (65.2%)</td>
<td>291 (76.8%)</td>
<td>420 (79.2%)</td>
<td>508 (78.0%)</td>
<td>136 (85.0%)</td>
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<tr>
<td>Beta-blockers</td>
<td>41 (89.1%)</td>
<td>299 (78.9%)</td>
<td>416 (78.5%)</td>
<td>503 (77.3%)</td>
<td>120 (75.0%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>44 (95.7%)</td>
<td>347 (91.6%)</td>
<td>468 (88.3%)</td>
<td>566 (86.9%)</td>
<td>138 (86.3%)</td>
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<td>Lipid lowering drug</td>
<td>35 (76.1%)</td>
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<tr>
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<td>31 (67.4%)</td>
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<td>96 (60.0%)</td>
<td>0.17</td>
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<tr>
<td>Spironolactone</td>
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<td>191 (50.4%)</td>
<td>259 (48.9%)</td>
<td>322 (49.5%)</td>
<td>88 (55.0%)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

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**

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

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

<table>
<thead>
<tr>
<th>Outcome/eGFR cat.</th>
<th>Events PBO n/N (%)</th>
<th>Events MRA n/N (%)</th>
<th>Event-rate PBO (95%CI)</th>
<th>Event-rate MRA (95%CI)</th>
<th>HR (95%CI)</th>
<th>Inter.P-trend</th>
<th>Study Het.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or HF hosp.</td>
<td>193/847 (22.8) 143/940 (15.2)</td>
<td>15.5 (13.5-17.9) 9.5 (8.1-11.2)</td>
<td>0.63 (0.50-0.78)</td>
<td>0.0.68</td>
<td>0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;90</td>
<td>732/2987 (24.5) 561/2953 (19.0)</td>
<td>16.1 (14.9-17.3) 11.6 (10.7-12.6)</td>
<td>0.73 (0.66-0.82)</td>
<td>0.73</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>61-90</td>
<td>567/1641 (34.6) 478/1593 (34.6)</td>
<td>23.1 (21.3-25.1) 19.2 (17.5-21.0)</td>
<td>0.81 (0.72-0.92)</td>
<td>0.81</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46-60</td>
<td>354/776 (45.6) 285/772 (36.9)</td>
<td>34.2 (30.9-38.0) 25.2 (22.4-28.3)</td>
<td>0.76 (0.65-0.89)</td>
<td>0.76</td>
<td>0.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-45</td>
<td>42/90 (46.7) 46/89 (51.7)</td>
<td>45.7 (33.8-61.9) 50.4 (37.8-67.3)</td>
<td>1.05 (0.69-1.60)</td>
<td>1.05</td>
<td>0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>732/2987 (24.5) 561/2953 (19.0)</td>
<td>16.1 (14.9-17.3) 11.6 (10.7-12.6)</td>
<td>0.73 (0.66-0.82)</td>
<td>0.73</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend: 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 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>
<thead>
<tr>
<th>Outcome/eGFR cat. (ml/min/1.73m²)</th>
<th>Events PBO</th>
<th>Event-rate PBO</th>
<th>Events MRA</th>
<th>Event-rate MRA</th>
<th>HR (95%CI)</th>
<th>Inter.P-trend</th>
<th>Study Het.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or HF hosp. &gt;90</td>
<td>67/226 (29.6)</td>
<td>19.5 (15.4-24.8)</td>
<td>43/248 (17.3)</td>
<td>10.5 (7.8-14.2)</td>
<td>0.53 (0.36-0.77)</td>
<td>0.70</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>61-90</td>
<td>323/981 (32.9)</td>
<td>20.4 (18.3-22.8)</td>
<td>218/957 (22.8)</td>
<td>12.7 (11.1-14.5)</td>
<td>0.64 (0.54-0.76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>46-60</td>
<td>241/576 (41.8)</td>
<td>29.2 (25.7-33.1)</td>
<td>192/584 (32.9)</td>
<td>19.8 (17.2-22.9)</td>
<td>0.67 (0.55-0.81)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>31-45</td>
<td>176/354 (49.7)</td>
<td>37.3 (32.2-43.3)</td>
<td>124/327 (37.9)</td>
<td>26.0 (21.8-31.0)</td>
<td>0.69 (0.55-0.87)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>31-45</td>
<td>31/53 (58.5)</td>
<td>50.0 (35.1-71.0)</td>
<td>27/55 (49.1)</td>
<td>40.6 (27.8-59.2)</td>
<td>0.86 (0.52-1.45)</td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>41/226 (18.1)</td>
<td>11.2 (8.2-15.2)</td>
<td>28/248 (11.3)</td>
<td>6.5 (4.5-9.4)</td>
<td>0.58 (0.36-0.94)</td>
<td>0.99</td>
<td>0.11</td>
</tr>
<tr>
<td>HF hosp. &gt;90</td>
<td>207/981 (21.1)</td>
<td>12.1 (10.6-13.9)</td>
<td>136/957 (14.2)</td>
<td>7.6 (6.4-9.0)</td>
<td>0.64 (0.52-0.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>162/576 (28.1)</td>
<td>17.8 (15.3-20.8)</td>
<td>120/584 (20.5)</td>
<td>11.5 (9.6-13.8)</td>
<td>0.65 (0.51-0.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>117/354 (33.1)</td>
<td>21.1 (17.6-25.3)</td>
<td>76/327 (23.2)</td>
<td>13.9 (11.1-17.4)</td>
<td>0.65 (0.49-0.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>17/53 (32.1)</td>
<td>19.4 (12.0-31.1)</td>
<td>14/55 (25.5)</td>
<td>15.6 (9.2-26.3)</td>
<td>0.81 (0.40-1.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death &gt;90</td>
<td>43/226 (19.0)</td>
<td>11.1 (8.2-14.9)</td>
<td>27/248 (10.9)</td>
<td>6.2 (4.2-9.0)</td>
<td>0.54 (0.33-0.87)</td>
<td>0.47</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>188/981 (19.2)</td>
<td>10.4 (9.0-12.0)</td>
<td>135/957 (14.1)</td>
<td>7.2 (6.1-8.5)</td>
<td>0.71 (0.57-0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>147/576 (25.5)</td>
<td>14.7 (12.5-17.2)</td>
<td>123/584 (21.1)</td>
<td>11.3 (9.5-13.5)</td>
<td>0.75 (0.59-0.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>116/354 (32.8)</td>
<td>20.4 (17.0-24.4)</td>
<td>80/327 (24.5)</td>
<td>14.4 (11.6-18.0)</td>
<td>0.70 (0.53-0.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>23/53 (43.4)</td>
<td>28.9 (19.2-43.5)</td>
<td>23/55 (41.8)</td>
<td>30.3 (20.2-45.7)</td>
<td>1.08 (0.61-1.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause death &gt;90</td>
<td>48/226 (21.2)</td>
<td>12.3 (9.3-16.4)</td>
<td>35/248 (14.1)</td>
<td>8.0 (5.7-11.1)</td>
<td>0.63 (0.41-0.97)</td>
<td>0.63</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>211/981 (21.5)</td>
<td>11.6 (10.2-13.3)</td>
<td>195/957 (15.8)</td>
<td>8.1 (6.9-9.5)</td>
<td>0.71 (0.58-0.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>163/576 (28.3)</td>
<td>16.3 (13.9-19.0)</td>
<td>139/584 (23.8)</td>
<td>12.8 (10.8-15.1)</td>
<td>0.77 (0.61-0.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>142/354 (40.1)</td>
<td>24.9 (21.1-29.4)</td>
<td>95/327 (29.1)</td>
<td>17.1 (14.0-21.0)</td>
<td>0.68 (0.52-0.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>29/53 (54.7)</td>
<td>36.4 (25.3-52.4)</td>
<td>29/55 (52.7)</td>
<td>38.3 (26.6-55.1)</td>
<td>1.08 (0.65-1.81)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

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.
<table>
<thead>
<tr>
<th>Outcome/eGFR cat. (ml/min/1.73m²)</th>
<th>Events PBO</th>
<th>Event-rate PBO</th>
<th>Events MRA</th>
<th>Event-rate MRA</th>
<th>HR (95%CI)</th>
<th>Inter.P</th>
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<td>86/510 (16.9)</td>
<td>13.2 (10.7-16.3)</td>
<td>67/542 (12.4)</td>
<td>9.2 (7.3-11.7)</td>
<td>0.71 (0.52-0.98)</td>
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<td>61-90</td>
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<td>15.3 (13.6-17.2)</td>
<td>218/1513 (14.4)</td>
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<td>46-60</td>
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<td>24.1 (21.1-27.5)</td>
<td>208/764 (27.2)</td>
<td>23.9 (20.8-27.3)</td>
<td>0.99 (0.82-1.20)</td>
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<td>31-45</td>
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<td>38.6 (33.0-45.3)</td>
<td>139/388 (35.8)</td>
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<td>38/91 (41.8)</td>
<td>44.6 (32.5-61.3)</td>
<td>36/86 (41.9)</td>
<td>41.6 (30.0-57.7)</td>
<td>0.93 (0.59-1.46)</td>
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<td>7.4 (5.6-9.8)</td>
<td>37/542 (6.8)</td>
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<td>99/1513 (6.5)</td>
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<td>31-45</td>
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<td>19.7 (12.2-31.7)</td>
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<tr>
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<td>46/510 (9.0)</td>
<td>6.5 (4.9-8.7)</td>
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<td>4.7 (3.4-6.6)</td>
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<td>8.8 (7.6-10.2)</td>
<td>138/1513 (9.1)</td>
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<td>123/764 (16.1)</td>
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<tr>
<td>≤30</td>
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<td>27/86 (31.4)</td>
<td>27.9 (19.1-40.7)</td>
<td>0.87 (0.52-1.45)</td>
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<tr>
<td>All-cause death</td>
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<td>0.19</td>
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<td>&gt;90</td>
<td>51/510 (10.0)</td>
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<td>33.1 (23.4-46.8)</td>
<td>0.94 (0.58-1.52)</td>
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</tr>
</tbody>
</table>

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.