Effects of Steroidal Mineralocorticoid Receptor Antagonists on Acute and Chronic Estimated Glomerular Filtration Rate Slopes in Patients with Chronic Heart Failure

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Structured Abstract

Aims: Steroidal mineralocorticoid receptor antagonists (MRAs) form a cornerstone of the management of heart failure (HF), but little is known about the long-term effects of MRA therapy on kidney function. We evaluated acute and chronic estimated glomerular function (eGFR) slopes in the 2 largest completed trials testing steroidal MRAs in chronic HF.

Methods and Results: We conducted parallel *post hoc* eGFR slope analyses in 2 multinational, double-blind randomized, placebo-controlled trials of steroidal MRAs in chronic HF with reduced ejection fraction (EMPHASIS-HF) and preserved ejection fraction (TOPCAT Americas region). GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation. Annual slopes of eGFR were assessed by generalized random coefficient models. Least square mean differences of eGFR slopes between steroidal MRA and placebo arms. Median follow-up was 1.8 years (EMPHASIS-HF) and 3.3 years (TOPCAT Americas). From baseline to month 4-6 ("acute eGFR slope"), compared to placebo, MRA treatment led to an acute decline in eGFR of -2.4 mL/min/1.73m^2 (95% CI -3.4 to -1.4; P <0.001) and -2.0 mL/min/1.73m^2 (95% CI -3.0 to -1.8; P <0.001) in EMPHASIS-HF and TOPCAT Americas, respectively. From month 4-6 to end of study, there was no difference in "chronic eGFR slope" between MRA and placebo arms (-0.3 mL/min/1.73m^2/year [95% CI -1.3 to 0.7; P =0.53] and 0.1 mL/min/1.73m^2/year [95% CI -1.4 to 1.7; P =0.86]) in EMPHASIS-HF and TOPCAT Americas, respectively.

Conclusions: Steroidal MRAs result in acute declines in eGFR but do not modify long-term kidney disease trajectories in chronic HF with reduced or preserved ejection fraction.

Trial Registration: EMPHASIS-HF (ClinicalTrials.gov NCT00232180) and TOPCAT (ClinicalTrials.gov NCT00094302)

Introduction

Steroidal mineralocorticoid receptor antagonists (MRAs) form a cornerstone of the management of heart failure (HF) to reduce worsening HF events and improve survival. These therapies are known to induce early increases in serum creatinine during drug titration phases, however, their cardioprotective effects appear maintained even among those who face early declines in estimated measures of kidney function (1–6). Initiation of other cardioprotective therapies, such as renin angiotensin system inhibitors (RASi) and sodium-glucose co-transporter-2 inhibitors (SGLT2i), have been shown to have distinct acute effects on estimated glomerular filtration rate (eGFR) that differ from their long-term effects on kidney function. Although MRAs are recommended to be maintained long-term, little is known about the long-term effects of MRA therapy on kidney function in patients with chronic HF. A workshop convened by the National Kidney Foundation, US Food and Drug Administration, and European Medicines Agency concluded that the rate of change in eGFR (i.e. GFR slope) is strongly associated with kidney failure and may be a viable alternative outcome for chronic kidney disease (CKD) progression in randomized trials (7). While eGFR slope has predominantly studied as a surrogate measure of kidney disease progression in those with established CKD, it may be similarly informative in the context of HF, where kidney protection represents an important ancillary treatment priority. eGFR slope analyses allow for simultaneous assessment of early effects of an intervention on kidney function (which may be due to acute hemodynamic effects) and chronic effects (as a measure of CKD progression). Furthermore, whereas traditional kidney disease endpoints (such as the need for dialysis or kidney transplantation) may be infrequent during the duration of a trial and only occur in those with fastest progression, eGFR slope analyses determines the effect of an intervention in the overall population, irrespective of their expected rate of progression. We evaluated acute, chronic, and total eGFR slopes in the 2 largest completed trials testing steroidal MRAs in chronic HF.

Methods

EMPHASIS-HF and TOPCAT Americas. We conducted parallel *post hoc* eGFR slope analyses in 2 previously published multinational, double-blind randomized, placebo-controlled trials of patients with chronic HF with reduced ejection fraction (EMPHASIS-HF [Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure]) and HF with preserved ejection

fraction (TOPCAT [Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist]). EMPHASIS-HF enrolled adults ≥55 years of age with symptomatic HF and a left ventricular ejection fraction ≤30% (or ≤35% if QRS duration was >130msec) who had experienced a recent cardiovascular hospitalization within 6 months or had elevated natriuretic peptide levels. Patients with a serum potassium level >5.0 mmol/L, eGFR<30 mL/min/1.73m^2, or who were concomitantly using a potassium sparing diuretic were excluded. Eligible participants were randomized to eplerenone or matching placebo with a starting dose of 25mg once daily (or every other day if eGFR was 30 to 49 mL/min/1.73 m^2) and uptitrated to 50mg once daily as tolerated at 4 weeks.

TOPCAT enrolled adults ≥50 years of age with symptomatic HF and a left ventricular ejection fraction ≥45%, controlled systolic blood pressure, a serum potassium level <5.0mmol/L, and a history of HF hospitalization within 12 months or an elevated natriuretic peptide level within 60 days. Patients with eGFR<30 mL/min/1.73 m^2 or serum creatinine level ≥2.5 mg/dL were excluded. Eligible participants were randomized to either spironolactone or matching placebo at an initial dose of 15mg once daily which could be uptitrated up to 45mg once daily as tolerated through 4 months. Given marked regional variation in clinical profiles, event rates, adherence to study protocol, and treatment responses in the TOPCAT trial, this analysis focused on participants enrolled in the Americas (United States, Canada, Argentina, and Brazil) (8). All patients in both trials signed written informed consent for participation, and the trial protocols were approved by the local institutional review boards or ethics committees at each participating site.

eGFR Slope Analysis. All analyses were based on intention-to-treat principles. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation (9) based on serum creatinine measurements at each scheduled study visit. Annual slopes of eGFR were assessed by generalized random coefficient models. Each model was adjusted for timing of visit, treatment, treatment-by-visit interaction, and baseline eGFR as fixed effects, with random effects at the patient level and random slope by visit. Least square mean differences of eGFR slopes between steroidal MRA and placebo arms were separately assessed during 3 phases: 1) Acute "eGFR dip" from baseline to after drug titration at 4-6 months; 2) Chronic eGFR slope from 4-6 months to end of study; and 3) Total eGFR slope from baseline to end of study. Statistical analyses were performed using STATA version 16.1 (College Station, TX).

Results

Overall, 2,713 of 2,736 (99%) participants in EMPHASIS-HF and 1,739 of 1,767 (98%) participants in TOPCAT Americas had available baseline eGFR data. We evaluated 9,570 total eGFR measurements in EMPHASIS-HF over median follow-up of 1.8 years, and 14,312 total eGFR measurements in TOPCAT Americas over mean follow-up of 3.3 years. In EMPHASIS-HF overall, 222 (16.3%) in the eplerenone arm and 228 (16.6%) in the placebo arm discontinuing study therapy. In TOPCAT Americas, 419 (47.3%) patients in the spironolactone arm and 372 (42.2%) patients in the placebo arm had early discontinuation of the study drug. Baseline mean eGFR was 65.5±17.8 mL/min/1.73m^2 and 58.4±19.4 mL/min/1.73m^2 in EMPHASIS-HF and TOPCAT Americas, respectively; eGFR distribution was balanced at baseline between MRA and placebo arms in both trials. In EMPHASIS-HF, each participant had a median of 5 eGFR measurements (range from 1 to 14), while in TOPCAT Americas, each participant had a median of 5 measurements (range from 1 to 16). eGFR trajectories in EMPHASIS-HF and TOPCAT Americas showed an initial period of eGFR decline with MRA treatment compared with placebo. This was followed by attenuation of this decline in the MRA arm, paralleling eGFR decline patterns in placebo-treated individuals thereafter (**Figures 1 and 2**).

From baseline to month 4-6, compared to placebo, MRA treatment led to an acute decline in eGFR of -2.4 mL/min/1.73m^2 (95% CI -3.4 to -1.4; P <0.001) and -2.0 mL/min/1.73m^2 (95% CI -3.0 to -1.8; P <0.001) in EMPHASIS-HF and TOPCAT Americas, respectively. From month 4-6 to end of study, there was no difference in chronic eGFR slope between MRA and placebo arms (-0.3 mL/min/1.73m^2/year [95% CI -1.3 to 0.7; P =0.53] and 0.1 mL/min/1.73m^2/year [95% CI -1.4 to 1.7; P =0.86] in EMPHASIS-HF and TOPCAT Americas, respectively. Over the entire study periods (total eGFR slope), MRA treatment resulted in a more rapid decline in eGFR compared with placebo in EMPHASIS-HF (-1.8 [-2.5 to -1.1] mL/min/1.73m^2/year; P<0.001) and TOPCAT Americas (-2.5 [-3.4 to -1.6] mL/min/1.73m^2/year; P<0.001).

Discussion

In 2 large randomized clinical trials of chronic HF, steroidal MRAs resulted in an acute reduction in eGFR that was apparent within months of treatment initiation. After this acute eGFR decline,

participants treated with MRA experienced eGFR trajectories similar to those observed with placebo through several years of follow-up.

We previously reported that in EMPHASIS-HF, eplerenone increased the risk of >30% reduction of eGFR compared with placebo (16% vs. 12%) (6). Prior data from RALES (Randomized Aldactone Evaluation Study) similarly identified higher rates of >30% reduction in eGFR with spironolactone compared with placebo (17% vs. 7%) during drug titration (through 12 weeks) among patients with severe HF with reduced ejection fraction (2); however, missingness in eGFR measurements thereafter was high. In EPHESUS, eplerenone resulted in a modest, but significant decline in eGFR as early as a month after initiation (-1.3±0.4 mL/min/1.73m^2) that persisted over time in patients with HF and left ventricular systolic dysfunction after an acute myocardial infarction (5). Finally, in TOPCAT Americas, spironolactone increased early risks of doubling of serum creatinine (corresponding to an eGFR decline of 57%) by 4 months compared with placebo (18% vs. 12%) (1). Despite this excess risk of kidney events, steroidal MRAs consistently reduced cardiovascular events in these chronic HF and post-myocardial infarction trial populations (1–6).

Like many other cardioprotective agents such as RASi and SGLT2 inhibitors, MRAs appear to have early effects on kidney function that differ from their long-term effects. The acute decline in eGFR with MRA treatment may reflect a reduction in intraglomerular pressure, hydraulic conductivity, or surface of the glomerular basement membrane, however whether this effect is purely hemodynamic and reversible is uncertain as eGFR data after trial completion were not available, nor were urinary markers of tubular injury.

Study limitations include variable missingness of eGFR data in follow-up; similar to prior calculations of eGFR slope, all available measurements were considered without imputation. More frequent eGFR measurement, especially early during drug initiation and titration, may have allowed for accurate and robust estimation of acute eGFR slopes. As EMPHASIS-HF and TOPCAT were conducted during different time periods, estimates of eGFR slopes may differ on more contemporary background medical therapies. We were also unable to incorporate MRA dosing changes, drug discontinuation, or therapeutic adherence into our estimation of eGFR slopes, however prior studies have suggested that dosing may not substantially influence expected cardiovascular benefits with MRAs in HF (10,11). Similarly, while early drug discontinuation was relatively frequent in both trials, this appeared relatively balanced between

study arms. Traditional kidney disease outcomes (i.e. doubling of serum creatinine or kidney failure) were not systematically collected in these trials and could not be reliably estimated due to missingness and lack of consistency in measurements. As such, assessment of acute and chronic eGFR slopes may provide a robust and validated approach to understanding the therapeutic effects of MRAs on kidney function over time, an approach which is being employed in several ongoing kidney outcome trials evaluating effects on kidney disease progression. However, larger, cross-trial analyses are required to confirm that eGFR slope represents a valid surrogate of kidney disease progression in HF (as has been demonstrated in CKD).

These data indicate that steroidal MRAs cause acute declines in eGFR but do not modify long-term kidney disease trajectories in HF during average follow-up of ~2-3 years. While small trials in people with proteinuric CKD collectively suggest that steroidal MRAs reduce proteinuria and therefore might protect the kidney (12), we observed no long-term renoprotective effect as measured by chronic eGFR slope in people across the spectrum of HF. These observations appear qualitatively similar to eGFR trajectories with RASi in HF (13,14). It is noteworthy that the placebo group of both trials experienced an eGFR decline that was ~1 mL/min which is similar to the rate of decline that would be expected with aging alone. This may in part explain why steroidal MRAs in these trials failed to show significant effects on chronic slope as this population appeared to have a very low rate of CKD progression overall. It is plausible that MRAs may have different long-term effects on kidney function trajectory among selected cohorts of HF who experience faster CKD progression (such as those with albuminuria). Recently, a selective, non-steroidal MRA, finerenone was demonstrated to slow chronic eGFR decline and reduce the risk of kidney disease outcomes in patients with type 2 diabetes and proteinuric CKD (15,16). Ongoing trials will evaluate whether finerenone with its more balanced cardiac and kidney tissue effects will slow kidney disease progression in HF with preserved ejection fraction (NCT04435626) and in non-diabetic CKD (NCT05047263).

Disclosures

Dr. Vaduganathan has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Pharmacosmos, Relypsa, Roche Diagnostics,

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Dr. Rossignol reports (outside this manuscript) consulting for Bayer, Cincor, G3P, Idorsia, and KBP; honoraria from Ablative Solutions, AstraZeneca, Bayer, Boehringer-Ingelheim, Corvidia, CVRx, Fresenius, Grunenthal, Novartis, Novo Nordisk, Relypsa Inc., a Vifor Pharma Group Company, Sanofi, Sequana Medical, Servier, Stealth Peptides, and Vifor Fresenius Medical Care Renal Pharma; Cofounder: CardioRenal.

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Figure 1. Mean eGFR Over Time in EMPHASIS-HF (**Panel A**) and TOPCAT Americas (**Panel B**). In EMPHASIS-HF, eplerenone could be titrated to 50mg once daily as tolerated at 4 weeks, while in the TOPCAT trial, spironolactone could titrated up to 45mg once daily as tolerated through 4 months.

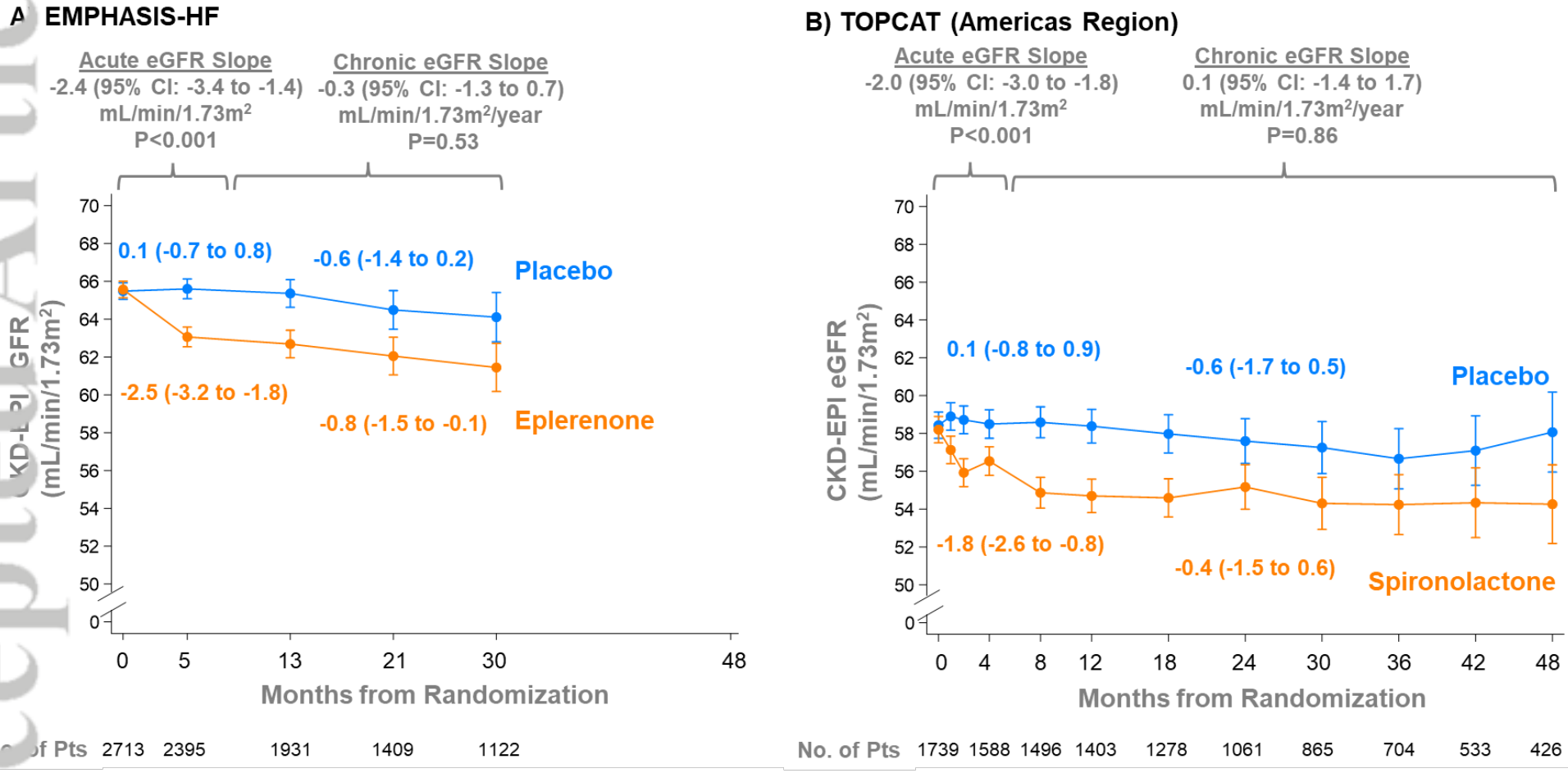

Figure 2. Change in eGFR from Baseline in EMPHASIS-HF (**Panel A**) and TOPCAT Americas (**Panel B**).