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Emphasis on abdominal obesity as a modifier of eplerenone effect in heart failure: Hypothesis-generating signals from EMPHASIS-HF

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Heart failure (HF) has interesting relationships with some of its risk factors. For example, both high blood pressure and smoking are risk factors for incident HF, but for patients with HF, these risk factors seem to have paradoxical beneficial associations with outcomes.[1–5] Obesity also has a paradoxical association with HF. It is associated with a higher risk of incident HF, but in patients with HF it is associated with a lower risk of death.[6,7] Obesity and HF are also related neurohormonally, as serum aldosterone concentrations are elevated in both conditions. However, it is unknown if patients with both HF and obesity have higher concentrations of serum aldosterone than do patients with either condition. In particular, little is known about the role of abdominal obesity in patients with HF and reduced ejection fraction (HFrEF).

Patients with HFrEF have higher serum aldosterone concentrations than do those without HF, and patients with cardiac cachexia have higher serum aldosterone than do those without cachexia.[8] However, it is unknown if serum aldosterone concentrations vary with adiposity in patients with mild to moderate HFrEF without cardiac cachexia. Importantly, it is unknown if serum aldosterone concentrations vary with the magnitude and topographical location of excess adiposity. Finally, it is unknown whether the effect of mineralocorticoid-receptor antagonists (MRAs) on outcomes in patients with mild to moderate HFrEF without cardiac cachexia is modified by the magnitude and location of excess adiposity.

Elevated serum aldosterone concentrations have been shown to be associated with excess visceral fat, a high body mass index (BMI), and an increased waist circumference.[9–11] Serum aldosterone may contribute to the high risk of cardiovascular disease associated with obesity including hypertension and left ventricular hypertrophy.[12] Similarly, abdominal

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obesity has been associated with increased release of adipocytokines, sub-clinical inflammation and a significant increased risk for cardiovascular events. Aldosterone antagonists have been shown to improve blood pressure and diastolic function in patients with hypertension.[13,14]

Serum aldosterone is also elevated in patients with HFrEF and may play a central role in its pathophysiology by stimulating collagen synthesis and ventricular remodeling.[15] However, it remains unclear whether serum aldosterone plays any role in the pathogenesis of obesity-associated higher risk of incident HFrEF. Therapy with spironolactone and eplerenone, both MRAs, has been shown to be associated with improved outcomes in patients with HFrEF.[16,17] However, to our knowledge, there are no prior reports describing whether the effects of MRAs in HFrEF vary by magnitude of excess adiposity, or its regional distribution.

Although patients with both abdominal obesity and HFrEF exhibit increased concentrations of serum aldosterone, it is unknown whether obese patients with HFrEF have higher serum aldosterone concentrations than do their non-obese counterparts and if so, whether obesity modifies the effects of MRAs in HFrEF. Both aging and HFrEF are associated with increased sympathetic stimulation and down-regulation of beta-adrenoceptors; however, there is no evidence that the effect of beta-blockers is more pronounced in older HFrEF patients than in their younger counterparts.[18] Further, there is little evidence from laboratory animals to support the hypothesis that obesity modifies the effect of MRAs in HFrEF. In one laboratory study involving spontaneously hypertensive rats without HF, chronic eplerenone treatment had no significant effect on myocardial mineralocorticoid receptor gene expression and did not significantly alter the hemodynamic and vascular parameters studied.[19] In that study, eplerenone was associated with improved metabolic parameters and preservation of systolic and diastolic function mostly in obese rats, whereas it delayed cardiac remodeling and development of HF in both obese and non-obese rats.[19]

In the randomized, controlled Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial, 2737 patients with mild to moderate HFrEF (EF <35%) were randomized to receive eplerenone or placebo up to 50 mg daily. After 21 months of median follow-up, there was a significant reduction in the risk of the primary composite end points of HF hospitalization or cardiovascular death (HR, 0.63; 95% CI, 0.54–0.74) as well as all-cause mortality (HR, 0.76; 95% CI, 0.62–0.93). In the current issue of the Journal, Oliver and colleagues analyzed the EMPHASIS-HF data to examine if, during the same 21 months of median follow-up as in the original EMPHASIS-HF trial, the clinical benefit of eplerenone varied with the magnitude and location of excess adiposity, and observed that eplerenone improved outcomes in HFrEF patients regardless of the amount or distribution of excess fat, although the benefit appeared to be more pronounced among those with abdominal obesity.[20]

In that study, Oliver et al reported that the eplerenone-associated lower risk of the primary composite end point of HF hospitalization or cardiovascular death was significantly more pronounced in patients with, versus without, abdominal obesity, as defined using sex-specific waist circumference (multivariable-adjusted HR, 0.48; 95% CI, 0.37– 0.63 versus HR, 0.77; 95% CI, 0.61–0.98; p for interaction, p, 0.01). However, when obesity was defined

using BMI, the adjusted association of eplerenone with the primary composite endpoint was not significantly different (interaction p, 0.11) between obese (HR, 0.49; 95% CI, 0.35–0.71) and non-obese (HR, 0.69; 95% CI, 0.57–0.83) patients. Taken together, these findings suggest a significantly greater benefit in those with abdominal obesity, and a potentially greater benefit of eplerenone in patients with general obesity.

Of note, the evidence of internal consistency was weaker for the individual components of the primary composite endpoints. For example, the adjusted association of eplerenone with cardiovascular mortality was significantly different (interaction p, 0.09) between patients with abdominal obesity (HR, 0.58; 95% CI, 0.40–0.83) and those without (HR, 0.87; 95% CI, 0.64–1.18). In contrast, this association was not significantly different between those with general obesity (HR, 0.71; 95% CI, 0.43–1.18) and those without (HR, 0.73; 95% CI, 0.57–0.94; interaction p, 0.93). Eplerenone was associated with significantly lower risk of HF hospitalization regardless of obesity type. Despite these limitations, these data provide novel insights into the potential role of abdominal obesity in patients with HFrEF receiving eplerenone therapy.

Post hoc subgroup analyses without a priori hypothesis are often interpreted with caution. For example, a post hoc analysis of the MERIT-HF data suggested that the efficacy of metoprolol succinate extended release was observed only among patients enrolled from Europe and not from the USA (interaction p, 0.003), which was considered a chance finding.[21] While it is tempting to suggest that patients with HFrEF with abdominal obesity may derive greater benefit from therapy with eplerenone, findings from the current study should be considered as hypothesis generating and should not be used to guide therapy unless these data are replicated in other larger contemporary real-world HF patient populations.

Oliver et al also examined the impact of abdominal obesity and general obesity on outcomes in patients in the placebo and eplerenone groups. Abdominal obesity exhibited no adjusted association with the primary end point in the placebo group (HR 0.96, 95% CI, 0.76–1.20), but did in the eplerenone group (HR 0.60, 95% CI, 0.45–0.80; interaction p, 0.01). Similarly, there was no significant independent association of general obesity with the primary end point in the placebo group (HR 0.95, 95% CI, 0.74–1.23) whereas there was in the eplerenone group (HR 0.69, 95% CI, 0.50–0.94; interaction p, 0.11). These findings in the placebo group suggest lack of a paradoxical beneficial association of either obesity type with the primary end point. The beneficial paradoxical association observed in the eplerenone group is intriguing as patients in the placebo group exhibited higher baseline event rates and would have been more amenable to a paradoxical beneficial association. Thus, these findings are unlikely to explain the paradoxical association of obesity in patients with HFrEF.

Findings from the EMPHASIS-HF trial demonstrated that eplerenone reduced the risk of poor outcomes in patients with HFrEF, and findings from the current subgroup analyses confirm that the clinical benefits of eplerenone are unaffected by obesity of either type, and that obesity should not be used to determine eligibility for MRA use in patients with HFrEF. Nevertheless, this study provides provocative observations on the possible role of abdominal obesity in patients with mild to moderate HFrEF. Further studies are needed to confirm and extend these observations in larger populations of younger and older HFrEF patients that

include women, and patients from diverse racial and ethnic backgrounds. Additionally, it would be important to assess whether excess adiposity plays a role in the treatment response in patients with HFpEF, who exhibit significant activation of the renin-angiotensin-aldosterone system, but in whom a clinical benefit from the use of MRAs as not been shown, to date.[20]

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