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Improvement in hyponatremia: insights from the acute and chronic therapeutic impact of a vasopressin antagonist in chronic heart failure

M. Gheorghiade[1], C. Zimmer[2], F. Czerwiec[2], J. Ouyang[2], C. Orlandi[2] on behalf of ACTIV in CHF Investigators

[1]*Northwestern University Medical School, Chicago, United States of America;* [2]*Otzuka Maryland Research Institute, Washington, United States of America*

Background: Hyponatremia (HYPO) is a known predictor of mortality in pts hospitalized for worsening heart failure. However, it is not known whether HYPO is only a marker of disease severity or whether improving sodium levels in hyponatremic patients would lead to improved outcomes. We studied the relationship between changes in serum sodium during hospitalization and mortality in hyponatremic patients admitted for decompensated heart failure (HF) in a post-hoc analysis of the ACTIV in CHF trial.

Methods: The ACTIV in CHF trial randomized 319 pts with systolic dysfunction hospitalized for worsening HF to receive placebo or 30, 60, or 90 mg tolvaptan, a novel vasopressin V2 receptor antagonist. Cox proportional hazards regression-analysis was used to explore the relationship between HYPO ($Na^+ < 136$ mEq/L) at baseline and improvements ≥ 2 mEq/L in serum sodium by hospital discharge, and mortality within sixty days.

Results: Mild to moderate HYPO was observed in 69 patients (21.6%), with median (IR) levels of 133 (131, 134) mEq/L at baseline. After adjustment for other covariates, HYPO was a highly statistically significant predictor of mortality at 60 days post hospital discharge ($p<0.005$). At hospital discharge, 45 out of 69 pts (65.2%) had improvements in serum sodium levels ≥ 2 mEq/L. These pts had a median (IR) baseline sodium of 133 (131, 134) mEq/L, as compared with 133 (132, 135) mEq/L in those who did not improve by hospital discharge. Pts with a serum sodium improvement at discharge had a mortality rate of 15.6% at 60 days post discharge, as compared with a 30.4% mortality rate in those showing no improvement ($p=0.0842$, log-rank). After adjustment for other covariates, change in serum sodium within the hospitalization period was a statistically significant predictor of mortality at 60 days post hospital discharge ($p<0.0269$).

Conclusions: Hyponatremia appears to be a modifiable therapeutic target and not purely a marker of disease severity. Improvements in serum sodium levels during hospitalization were associated with improved mortality at 60 days. Prospective studies are necessary in this population to assess if therapies aimed at increasing serum sodium will result in improved outcome.

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Eplerenone benefit at 30 days in high-risk subgroups in the EPHESUS trial

D.J. Van Veldhuisen[1], M. Aschermann[2], F. Zannad[3], H. Krum[4], J. Vincent[5], R. Mukherjee[5], B. Pitt[6] on behalf of EPHESUS Investigators

[1]*University Hospital Groningen, Dept. of Cardiology, Thorax-center, Groningen, Netherlands;* [2]*Interni klinika, Cardiovascular Center, Prague, Czech Republic;* [3]*Clinical Investigation Center INSERM-C, Centre d'Investigation Clinique de Nan, Dommartin-les Toul, France;* [4]*University Alfred Hospital, Prahan, Australia;* [5]*Pfizer Inc New York, New York, United States of America;* [6]*University of Michigan Medical Center, Alfred Taubman Health Care Center, Ann Arbor, MI, United States of America*

Background: The EPHESUS trial demonstrated that patients with acute myocardial infarction (AMI) complicated by heart failure (HF) and left ventricular systolic dysfunction (LVSD) experienced significant reductions in mortality and morbidity with eplerenone treatment started at a mean of 7.3 days post-AMI and used with standard therapy during a mean 16-month follow-up period. Given the adverse impact of hypertension, diabetes, and severe LVSD (LVEF$\leq$ 30%) on post-AMI outcomes, and the increased risk for mortality and morbidity during the first 30 days following an AMI in patients with HF and LVSD, the current analysis at 30 days post-randomization was performed to explore the early onset of eplerenone benefit in these high-risk subgroups.

Methods: In EPHESUS, patients with post-AMI HF and LVSD (ejection fraction $\leq$40%) on standard therapies were randomized 3-14 days after the index AMI to eplerenone (25 mg titrated to 50 mg QD at 1 month; n=3319) or placebo (n=3313). The assessment of the treatment effects at 30 days post-randomization was performed on the intention-to-treat patients in high-risk subgroups using a Cox proportional hazards regression model with treatment group as the only factor, stratified by geographic region. The estimated 95% confidence intervals were based on the Wald test statistic.

Reductions in risk with eplerenone relat

End Point	History of hypertension subgroup (N=4007)		Diabetic subgroup (N=2142)		LVEF $\leq$ 30% subgroup (N=2106)	
	Risk Ratio (95% CI)	P value	Risk Ratio (95% CI)	P value	Risk Ratio (95% CI)	P value
All-cause Mortality	0.68 (0.50, 0.93)	0.017	0.70 (0.47, 1.02)	0.066	0.57 (0.40, 0.82)	0.002
CV Mortality	0.67 (0.48, 0.92)	0.015	0.68 (0.45, 1.01)	0.057	0.56 (0.39, 0.82)	0.002
CV Mortality/ CV Morbidity	0.86 (0.71, 1.05)	0.138	0.79 (0.62, 1.01)	0.062	0.71 (0.56, 0.91)	0.006
Fatal/Nonfatal HF Hospitalization	0.84 (0.62, 1.14)	0.257	0.61 (0.42, 0.90)	0.013	0.69 (0.47, 1.02)	0.059
Sudden Cardiac Death	0.63 (0.35, 1.16)	0.139	0.57 (0.27, 1.19)	0.136	0.43 (0.22, 0.82)	0.01

Conclusions: In EPHESUS, eplerenone reduced all-cause mortality by 32%, 30%, and 43% in the hypertensive, diabetic and LVEF $\leq$30% subgroups, respectively, within 30 days of initiation. Eplerenone also notably reduced the other end points, including CV mortality and sudden cardiac death, during this period of increased risk. These data demonstrate the early benefits of eplerenone in high-risk patients with HF post-AMI and suggest the need for early initiation and maintenance of eplerenone treatment in these patients.

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Internal thoracic impedance monitoring: a new tool for the early diagnosis and treatment of acute heart failure

M. Shochat[1], M. Kazatsker[1], G. Xarax[2], A. Frimerman[1], P. Rabinovich[2], A. Shotan[1], S. Maisel[1] on behalf of The Technion, Haifa, Israel

[1]*Hillel Yaffe Medical Center, ICCU, Hadera, Israel;* [2]*Sackler Faculty of Medicine, Ichilov, Internal Medicine C, Tel Aviv, Israel*

Current therapy of acute heart failure (AHF) is initiated only after the appearance of clinical signs that characterized the alveolar stage of pulmonary edema. No clinical signs are present during the interstitial stage of AHF.

We utilized a monitor based on the novel principal of Internal Thoracic Impedance (ITI) measurement that allows recognition of small fluid changes in the lung.Device was applied in AMI patients for the diagnosis of the interstitial stage of AHF and to examine whether early initiation of treatment can prevent the alveolar stage of AHF. Patients without evidence of AHF on admission were monitored for 72 hours. ITI, respiratory rate, heart rate, lung rales and blood saturation were measured every 30 minutes.

Study included 399 patients (mean age 63.1$\pm$12.8) with AMI. Of these,315 remained without AHF (group 1),63 patients developed AHF throughout monitoring (group 2), and 21 received early treatment(group 3).Lung rales was the first clinical sign to appear of all variables. ITI decrease in group 1 was 4.5$\pm$3.3% (NS) from initial value (range, 0-11.5%). All group 2 patients developed mild AHF, 80% progressed to