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Evening levels and circadian changes of salivary cortisol predict adverse events in heart failure patients with comorbid depression - a MOOD-HF substudy

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Background: Depression is frequent in heart failure (HF) and associated with adverse clinical outcomes. The randomized MOOD-HF trial showed that in depressed patients with systolic heart failure (HF) the selective serotonin reuptake inhibitor escitalopram (E) improved neither survival nor depression compared to placebo (P). The hypothalamic-pituitary-adrenocortical axis is known to be altered in depression or HF. This MOOD-HF substudy aimed to clarify whether circadian salivary cortisol levels (SCL) were predictive of adverse events in depressed MOOD-HF participants and whether outcomes differed according to treatment with E.

Methods: MOOD-HF participants (all suffering from symptomatic systolic HF with left ventricular ejection fraction (LVEF) <45% and current major depression) were eligible for the present analysis if providing samples for SCL determination (luminescence immunoassay) at baseline visit (BL) and if not on oral glucocorticosteroid therapy. Depression severity was determined with the Montgomery–Åsberg Depression Rating Scale (MADRS) and LVEF measured by echocardiography.

Results: In the total study cohort (146 patients on E, 147 on P) median morning SCL at BL was 0.210 μg/dL (IQR 0.141–0.338 μg/dL) and median evening (pm) SCL 0.067 μg/dL (0.036–0.128 μg/dL, p<0.001). Median circadian change was 0.124 μg/dL (0.044–0.239 μg/dL). In patients with BL pm-SCL above the median MADRS-score was 21.7±9.1 and LVEF 33.7±8.4% respectively, in patients with pm-SCL below the median these values were 19.6±9.1 and 36.5±7.8% (p=0.048; p=0.004).

During 12 months follow-up the composite endpoint (all-cause death or rehospitalization) occurred least in E-treated patients with low pm-SCL and most often in E-treated patients with high pm-SCL (HR 2.02, 95% CI 1.12–3.65, p=0.010); patients on P had comparable event rates irrespective of BL pm-SCL (Figure A). Thus, numerically patients on E with low BL pm-SCL had lower event rates compared with corresponding P-treated patients (HR 0.76 (0.41–1.40, p=0.796)), while patients with high BL pm-SCL had higher event rates (HR 1.29 (0.74–2.24, p=0.799)) than corresponding P-treated patients. Patients with circadian SCL changes above the median receiving P experienced the composite primary endpoint least, while both subgroups with circadian SCL changes below the median and also patients with circadian SCL changes above the median on E had higher event rates (HR 0.66 (0.45–0.97, p=0.039), Figure B).

Conclusion: In depressed patients with systolic HF high pm-SCL are associated with more severe disease (depression and cardiac dysfunction). Extending primary MOOD-HF results indicating unfavourable outcomes related to E, the current findings suggest a SCL x treatment interaction with higher event rates in (sicker) patients with high pm-SCL and lower event rates in (less sick) patients with low pm-SCL when treated with the antidepressant. Low circadian changes of SCL were always associated with higher event rates.