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Eplerenone prevents an increase in serum carboxy-terminal propeptide of procollagen type I after myocardial infarction complicated by left ventricular dysfunction and/or heart failure

In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), eplerenone reduced morbidity and mortality in patients who had an acute myocardial infarction (MI), complicated by systolic dysfunction, heart failure (HF) or diabetes mellitus.[1] In a prespecified secondary analysis of EPHESUS, Iraqi *et al.*[2] reported concomitant reductions in the serum concentrations of N-terminal propeptide of type I (PINP) and type III (PIIINP) collagen, which may reflect an antifibrotic effect of eplerenone; however, the carboxy-terminal propeptide of procollagen type I (PICP) was not analysed in that report. Studies of endomyocardial biopsies suggest that serum PIIINP and PICP (but not PINP fragments) reflect myocardial fibrosis.[3] Moreover, PICP originates directly from the synthesis of collagen type I in a 1:1 ratio, directly reflecting collagen type I synthesis. On the other hand, PIIINP originates from partially processed procollagen molecules on the surface of collagen type III fibres. Therefore, serum PIIINP may not accurately reflect ongoing collagen type III synthesis. Furthermore, a net release from the heart into the circulation has only been reported for PICP (and not for PIIINP).[4] Notwithstanding, for no good reason, trials of mineralocorticoid receptor antagonists (MRAs) have focused more on PIIINP than on PICP.

The type of collagen as well as the amount may be an important determinant of its effects on myocardial function. Collagen type I comprises highly cross-linked, large-diameter fibres that have a major impact on stiffness whereas collagen type III comprises mainly non-cross-linked, small-diameter, more pliable fibres.[3] Whether eplerenone also reduces serum PICP has not been reported thus far.

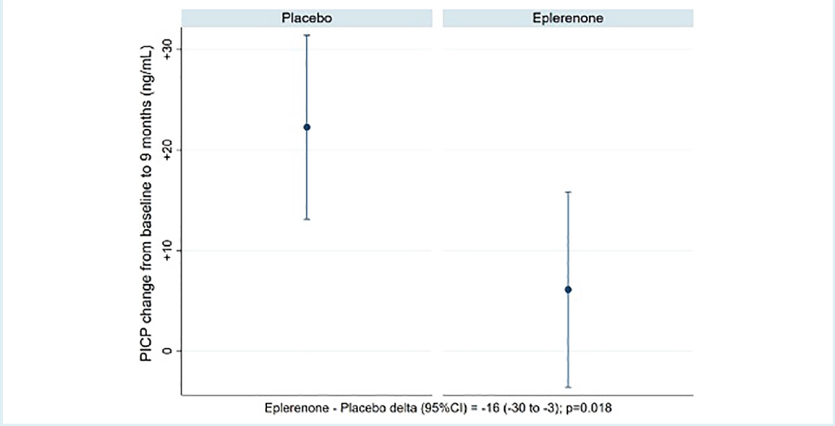

Figure 1 Carboxy-terminal propeptide of procollagen type I (PICP) change from baseline to month 9. There was a significant between-group difference for the change in PICP from baseline to month 9 where PICP increased in the placebo group compared to no change in PICP in patients treated with eplerenone. In addition to between-group differences, a significant interaction between study treatment and within-subject PICP change was also observed [F(1,225) = 4.173, $P = 0.042$, using mixed ANOVA]. CI, confidence interval.

We investigated the effect of eplerenone on serum concentrations of PICP in a substudy of EPHESUS.[1] In EPHESUS, 6632 patients were randomized to either eplerenone (up to 50 mg daily) or placebo, in addition to standard care. Compared to placebo, eplerenone reduced the occurrence of all-cause death and the combined endpoint of cardiovascular (CV) mortality and CV hospitalizations (for all-cause death: 14.4 vs. 16.7%; relative risk 0.85; $P = 0.008$; for CV mortality and CV hospitalizations: 26.7 vs. 30.0%; relative risk 0.87; $P = 0.002$).

In this biomarker substudy of EPHESUS, PICP was analysed using an ELISA assay (Quidel, San Diego, CA, USA) at baseline (3–14 days after MI diagnosis) and at 9 months in peripheral blood samples of 227 patients (27% women, 48% randomized to eplerenone). These patients had similar baseline characteristics to those of the full cohort (data not shown). A detailed account of the methods of this biomarker substudy has previously been published.[2] The number of patients included in this specific substudy was lower than the original biomarker substudy since not all patients had enough sample volume left for the measurement of PICP.

Serum PICP at baseline was 99 ng/mL [interquartile range (IQR) 77–129] and 97 ng/mL (IQR 77–120) in patients assigned to placebo and eplerenone, respectively; and at 9 months 124 ng/mL (IQR 93–152) and 105 ng/mL (IQR 84–134) for placebo and eplerenone, respectively. The between-group difference for the change in PICP was −16 ng/mL [95% confidence interval (CI) −30 to −3] in favour of eplerenone using an analysis of covariance (ANCOVA) with the treatment and baseline PICP as covariates (*Figure 1*). Baseline levels of PICP were only modestly correlated with PIIINP and PINP (Spearman rho of 0.29 and 0.34, respectively). Change in PICP from baseline to 9 months was also only modestly correlated with change in PIIINP and PINP (Spearman rho of 0.36 and 0.44, respectively).

After adjustment for eplerenone treatment and baseline PICP levels, a PICP decrease from baseline to month 9 was not significantly associated with all-cause mortality [adjusted hazard ratio (HR) 1.24, 95% CI 0.11–13.69; $P = 0.86$) nor with the composite endpoint of CV death and CV mortality (adjusted HR 1.18, 95% CI 0.49–2.83; $P = 0.71$). However, event rates in this substudy were very low [5 (2%) and 31 (14%) patients experienced all-cause mortality and CV death/CV hospitalization, respectively], precluding any definitive conclusions regarding PICP changes and outcome associations. Larger studies need to further assess the prognostic value of changes in PICP and outcome in MI patients.

Persistent pro-fibrotic activity after an MI may contribute to a decline in cardiac function and the occurrence of arrhythmias. Limiting excessive fibrosis may be a key mechanism by which eplerenone improved outcomes in the EPHESUS trial. These data suggest that eplerenone might limit the synthesis of collagen type 1 and retard or prevent excessive and potentially deleterious myocardial fibrosis. These beneficial effects may not be limited to patients with MI and/or HF since spironolactone (another MRA) also reduced PICP levels in patients at risk of developing HF in the HOMAGE trial (NCT02556450, results presented at the HFSA meeting in September 2019), suggesting that MRAs might be useful for HF prevention. In HOMAGE, over 70% of the patients had a history of coronary artery disease, supporting the role of MRAs in limiting excessive fibrosis in the context of ischaemia.

It should be noted that for this substudy, PICP measurements were performed in samples that were stored for more than 15 years. Although PINP was stable over a duration of 12 months at −80°C,[5] data on long-term storage and stability of PICP are lacking. The possibility of degradation of PICP in time and/or skewness of the results cannot therefore be excluded. Moreover, a detailed cardiac function characterization (e.g. chamber volumes, diastolic function parameters) was not available; in consequence we cannot ascertain whether the change in PICP levels correlates (or not) with changes in cardiac structure and function.

In conclusion, this is the first analysis to suggest a favourable effect of eplerenone on collagen type 1 synthesis, which might contribute to its beneficial effects observed in patients after an MI, complicated with systolic dysfunction, HF, or diabetes mellitus.

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Conflict of interest: B.P. is a consultant for Bayer, AstraZeneca, Sanofi, KBP Biosciences*, Sarfez*, Relypsa/Vifor*, Tricida*, Stealth Peptides. *=Stock options. He holds a patent for site-specific delivery of eplerenone to the myocardium (US patent # 9931412). All other authors have nothing to disclose.

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Fibroblast growth factor 23 mediates the association between iron deficiency and mortality in worsening heart failure

Iron deficiency (ID) is prevalent in heart failure (HF) and associated with a poor prognosis.[1,2] The pathophysiological mechanisms of ID are not fully understood. While a strong link between ID and anaemia exists, ID is associated with increased mortality in non-anaemic patients as well.[3] Additionally, intravenous iron administration is also beneficial in non-anaemic patients. This implies other, non-haematopoietic effects of ID on outcome. ID has been linked to increased levels of fibroblast growth factor 23 (FGF23), which is a phosphaturic osteocyte-derived hormone. FGF23 inhibits renal phosphate reabsorption and regulates $1,25(OH)_2$ vitamin D. The association between iron status and FGF23 originates from studies in FGF23-related autosomal dominant hypophosphataemic rickets, which has an iron-dependent onset.[4] Previously, we have shown that in HF patients, FGF23 is independently associated with congestion, unsuccessful angiotensin-converting enzyme inhibitor and angiotensin receptor blocker up-titration, and poor prognosis.[5] Moreover, FGF23 has been linked to incident HF and mortality in community-based studies and development of left ventricular hypertrophy and mortality in chronic kidney disease patients.[6,7] Recent preclinical data suggest an association between FGF23 and cardiac renin–angiotensin–aldosterone system activation, thereby leading to cardiac fibrosis and hypertrophy.[8] Finally, correction of ID seems related to significant reductions in FGF23 levels in HF patients, a finding which further links iron status and FGF23 together.[9] The association between iron status, FGF23 and outcome in HF is currently unclear. This study therefore focused on the interplay between iron and FGF23, and whether FGF23 mediates the association between iron status and outcome in HF.

This study is a post-hoc analysis of the 'systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure' (BIOSTAT-CHF), which has been described previously.[5] In short, BIOSTAT-CHF prospectively enrolled 2516 patients with worsening signs and/or symptoms of HF and a left ventricular ejection fraction ≤40% or brain natriuretic peptide levels >400 pg/mL or N-terminal prohormone of brain natriuretic peptide >2000 pg/mL. BIOSTAT-CHF was approved by local medical ethics committees at each participating centre. We measured the following biomarkers in 2279 stored samples, drawn at the time of presentation at the emergency department or hospital admission: iron, transferrin saturation (TSAT), ferritin, hepcidin, soluble transferrin receptor (sTfR) and FGF23 [using a c-terminal ELISA (Immutopics, Inc., San Clemente, CA, USA), measuring both intact and c-terminal FGF23 cumulatively].[5] Univariable and multivariable linear regression analyses were performed using log-transformed FGF23 levels as dependent variables and log-transformed TSAT, sTfR, ferritin and hepcidin as independent variables. The multivariable models were adjusted for predictors that have previously been associated with FGF23.[5] Univariable and FGF23-adjusted restricted cubic splines based on Cox proportional hazard regression were constructed to assess the association between iron parameters and all-cause mortality. Mediation analyses were performed according to the methods described by Baron and Kenny.[7]

Baseline characteristics of all patients are depicted in *Table 1*. Mean (± standard deviation) age of the patients was 69 ± 12 years, 26.1% were female and median (interquartile range) left ventricular ejection fraction was 30% (25–36%). Patients with higher FGF23 levels were more frequently female, had lower ferritin, TSAT, and hepcidin levels and higher levels of inflammatory markers (P for trend <0.001). FGF23 levels were strongly correlated to TSAT (Spearman's $\rho = -0.42$), sTfR ($\rho = 0.43$), ferritin ($\rho = -0.31$) and hepcidin ($\rho = -0.37$; all $P < 0.0001$). Individual levels of TSAT, sTfR, ferritin and hepcidin were the strongest predictors of FGF23 levels compared to previously established determinants of FGF23 levels (all $P < 0.001$).[5] During a median follow-up of 21 months (interquartile range 16–27 months), 596 patients (26%) died. Continuous iron parameter levels were strongly associated with prognosis in univariable analyses (all $P < 0.001$) (*Figure 1*). When adjusting for FGF23, all iron parameters lost their predictive value. There was a significant interaction between TSAT and FGF23 on outcome ($P = 0.012$). Moreover, we identified a highly significant interaction between a history of renal disease and FGF23 in the association between iron parameters and all-cause mortality ($P < 0.01$). Finally, we evaluated whether the association between iron parameters and all-cause mortality was mediated by FGF23. FGF23 levels significantly mediated the association between TSAT, ferritin, sTfR, and hepcidin and all-cause mortality [P for indirect effect (FGF23-mediated) <0.0001]. The direct effect (non-FGF23-mediated) was not significant for all iron parameters in these models (*Table 1*). As a sensitivity analysis, we also evaluated whether inflammation alters the association between iron status and outcome. Adjustment for C-reactive protein and interleukin-6 did not affect the prognostic consequences of iron parameters.

In this study, we found that in a large, multinational cohort of worsening HF patients, iron parameters are independently related