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

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Disclosures

The EPHESUS trial was sponsored by Pfizer. BP, JM and FZ were members of the steering committees. BP is a consultant for Bayer, Astra Zeneca, 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 no conflicts of interest to declare.

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Abbreviations

CAD	Coronary artery disease
CV	Cardiovascular
HF	Heart failure
MRA	Mineralocorticoid receptor antagonist

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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, HF or diabetes mellitus(1). In a prespecified secondary analysis of EPHESUS, Iraqi *et al*. reported concomitant reductions in the serum concentrations of N-terminal propeptide of type-I (PINP) and type-III (PIIINP) collagen, which may reflect an anti-fibrotic effect of eplerenone (2); however, the carboxy-terminal propeptide of procollagen type I (PICP) was not analyzed 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 fibers. 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 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 fibers that have a major impact on stiffness whereas collagen type-III comprises mainly non–cross-linked, small-diameter, more pliable fibers(3). Whether eplerenone also reduces serum PICP has not been reported thus far.

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 CV mortality and CV hospitalizations (for all-cause death: 14.4 vs 16.7% (RR 0.85; p=0.008; for CV mortality and CV hospitalizations: 26.7 vs. 30.0% (RR 0.87; p=0.002).

In this biomarker substudy of EPHESUS, PICP was analyzed 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 been previously 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 (IQR 77-129) and 97 ng/mL (IQR 77-120) in patients assigned to placebo and eplerenone, respectively; and at nine 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% CI -30 to -3) in favor of eplerenone using an analysis of covariance (ANCOVA) with the treatment and baseline PICP as covariates (**Figure**). 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 nine 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 (adj. 1.24, 95% CI 0.11-13.69, p=0.86) nor with the composite endpoint of cardiovascular death and cardiovascular mortality (adj 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.

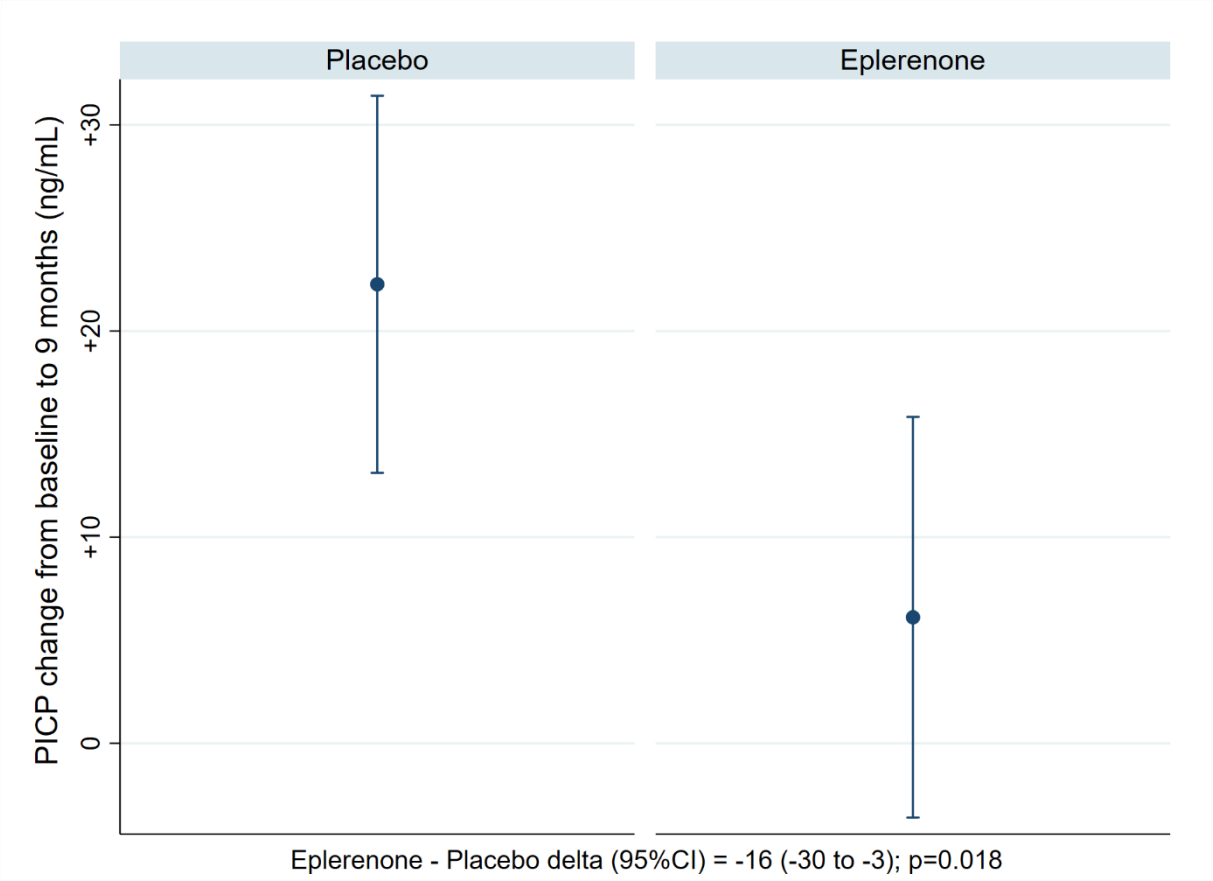
Persistent pro-fibrotic activity after an MI may contribute to a decline in cardiac function and the occurrence of arrythmias. Limiting excessive fibrosis may be a key mechanism by which eplerenone improved outcomes in the EPHESUS trial. These data suggest that eplerenone might limit the synthesis of 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 published at the HFSA meeting September 2019), suggesting that MRAs might be useful for HF prevention. In HOMAGE over 70% of the patients had a history of CAD, supporting the role of MRAs in limiting excessive fibrosis in the context of ischemia.

It must 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 degrees Celsius(5), data on long-term storage and stability of PICP is lacking. The possibility of degradation of PICP in time and/or skewness of the results can

therefore not 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 favorable 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.

Figure. 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).*



Legend: PICP, carboxy-terminal propeptide of procollagen type I

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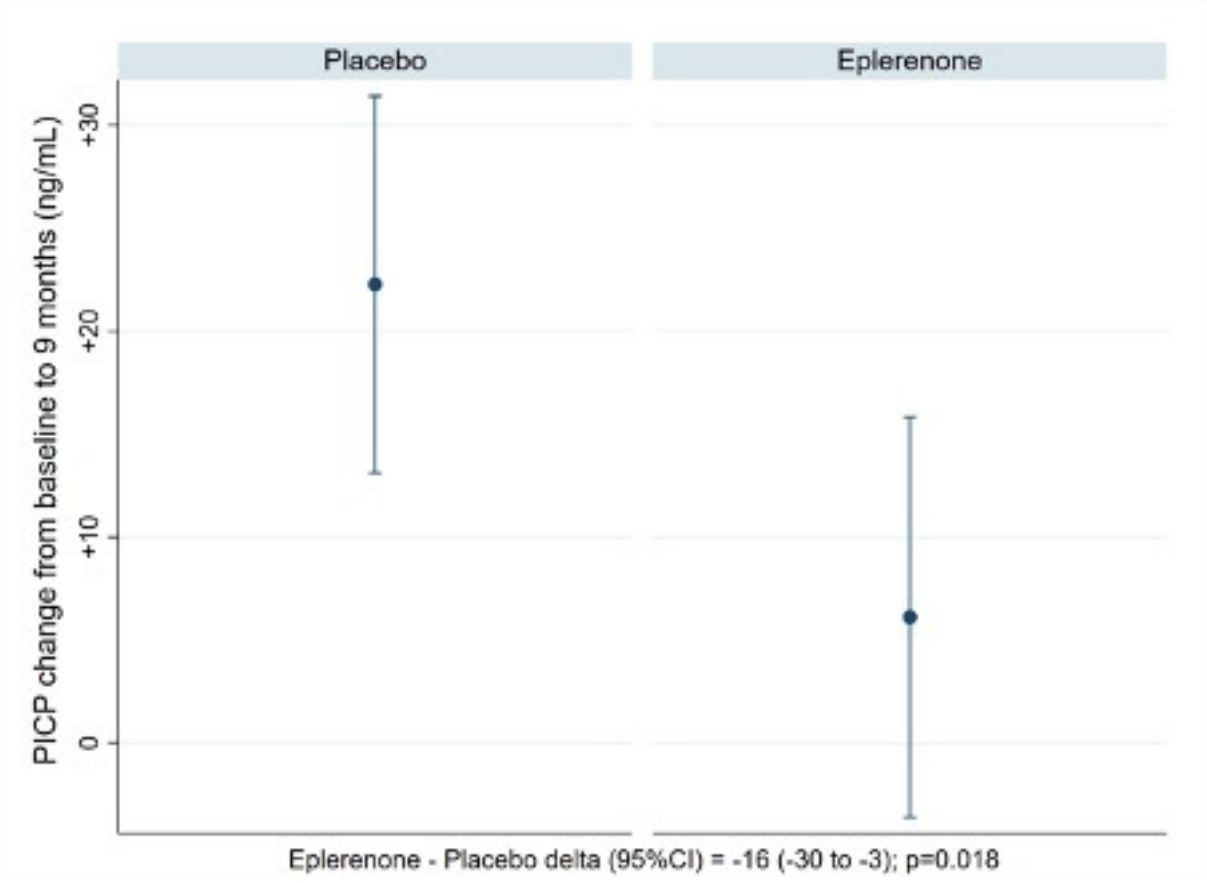

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