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Heart Failure and Cardiomyopathies

MARKERS OF EXTRACELLULAR MATRIX TURNOVER AND RISK OF DEATH IN PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION: RESULTS FROM I-PRESERVE

Poster Contributions
Poster Hall B1
Sunday, March 15, 2015, 3:45 p.m.-4:30 p.m.

Session Title: Fibrosis, Hypertrophy and Regeneration
Abstract Category: 15. Heart Failure and Cardiomyopathies: Therapy
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Background: Heart failure with preserved ejection fraction (HFpEF) is common and associated with poor long-term clinical outcomes. Little is known about the pathophysiological process; however, an increase in extracellular matrix turnover has been observed leading to myocardial fibrosis. Angiotensin II stimulates cardiac fibroblasts which may lead to changes in the balance of matrix metalloproteinase-9 (MMP-9) and their tissue inhibitors (TIMP-1).

Methods: A total of 347 patients with available plasma samples were analyzed in this substudy of the Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) trial. Concentrations of MMP-9 and TIMP-1 were measured at baseline and 6-months following randomization and patients were evaluated for all-cause mortality, primary composite endpoint (all-cause death and hospitalization), and heart failure events (death or hospitalization from heart failure) over 4134 days.

Results: In the combined cohort, mean MMP-9 was significantly reduced over 6 months (591 to 506 ng/mL, p<0.001) but not TIMP-1 (303 to 307 ng/mL, p=0.426). Neither baseline MMP-9 nor change in MMP-9 over time was associated with any of the clinical endpoints. However, the median TIMP-1 concentration was found to be highly significant in those who died versus survivors (316 vs. 282 ng/mL, p<0.001). Furthermore, risk of death was 5% higher with each 10 ng/mL increase in TIMP-1 (hazard ratio, 1.05; 95% [CI], 1.02 to 1.07; P<0.001) and remained significant after multivariable analyses. Irbesartan and placebo produced similar reductions of MMP-9 over time. TIMP-1 concentrations were increased with irbesartan at 6-months compared to placebo (14.4 vs. -5.4 ng/mL, respectively; p=0.049). However, treatment effect on outcomes was independent of these changes.

Conclusion: Elevated TIMP-1 concentrations, but not MMP-9, are independently associated with increased risk of all-cause mortality in patients with HFpEF. Treatment with irbesartan increases TIMP-1 concentrations over time but does not impact clinical outcomes. Further study is needed to determine whether MMP-9 and TIMP-1 could select for patients who may require more intensive management.