AN INVESTIGATION INTO THE EFFECT OF CYTOchrome P450 (CYP) 2D6 GENOTYPE ON PHARMACOKINETICS, PHARMACODYNAMICS AND OUTCOMES DURING METOPROLOL CR/XL THERAPY IN A HEART FAILURE COHORT: A MERIT-HF SUB-STUDY

Poster Contributions
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Background: Pharmacogenetic studies of low-dose metoprolol - a selective, β1-adrenergic receptor antagonist metabolised by the highly-polymorphic CYP2D6 enzyme - have demonstrated diverse pharmacokinetic and pharmacodynamic responses. We explored the impact of CYP2D6 genotype in heart failure patients treated with high-dose metoprolol CR/XL.

Methods: In a post-hoc subgroup analysis of the Metoprolol CR/XL Randomised Intervention Trial in Chronic Heart Failure (MERIT-HF; n = 605), we assessed the CYP2D6 locus for the non-functional *4 allele (1846 G>A; rs3892097). S-metoprolol serum assay were performed at 90-days to assess pharmacokinetic effects; clinical trial data were used to assess pharmacodynamic effects and clinical outcomes.

Results: Participants were characterised as Extensive (EM, 2D6*1*1, 61.5%), Intermediate (IM, *1*4, 34.1%) or Poor Metabolisers (PM, *4*4, 4.3%), based on the presence of the common (22%) *4 allele. Pharmacokinetics: The mean dose-/weight-adjusted plasma metoprolol concentrations were 2.12-fold (p < 0.0001) and 4.47-fold (p = 0.006) greater in the IM and PM as compared to the EM group. Pharmacodynamics: In the IM/PMs vs. EMs, during titration metoprolol induced greater reductions in mean ± standard deviation heart rate (68.1 ± 8.5 vs. 71.1 ± 9.3 beats min⁻¹; p = 0.006) and diastolic blood pressure (73.5 ± 7.8 vs. 75.9 ± 8.5 mmHg, p = 0.011). This was not observed at maximal dose, suggesting a saturable effect. There were no genotypic differences in achieving target dose (200 mg day⁻¹; p = 0.248). Outcomes: A greater proportion of patients achieved a heart rate <60 beats min⁻¹ in the combined IM/PM group compared to the EM group; OR 1.51 (95% CI 1.07 - 2.76; p = 0.018). CYP2D6 genotype was associated with no difference in the observed impact on all-cause mortality and the trial combined cardiovascular endpoint.

Conclusions: The CYP2D6*4 variant modulates metoprolol pharmacokinetics/-dynamics, without adversely impacting treatment efficacy. These results support an individualised dose-titration regimen; guided by patient tolerability and heart rate response. The therapeutic target should remain once-daily 200 mg metoprolol CR/XL, or highest tolerated dose.