Impact of Haptoglobin Genotype and Diabetes Status on Anacetrapib-Mediated Increase in Cholesterol Efflux Capacity

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Introduction: Impaired cholesterol efflux (CEC) from macrophages to apolipoprotein A-I is linked to coronary heart disease (CHD). Haptoglobin (Hp) binds to apolipoprotein A-I, and the Hp copy number variant designated by allele “2” is linked to CEC and HDL dysfunction in diabetics. However, the direct effect of allele “2” on CEC remains unknown. Given the effects of anacetrapib (ANA) on increased HDL-C, increased CEC, and reduced CHD, we hypothesized that allele “2” would blunt the effect of ANA on CEC in diabetic patients.

Objective: To determine how Hp CNV status impacts the effect of ANA on CEC in diabetics.

Methods: This study included 332 participants with CHD and diabetes randomized to ANA 100mg vs. placebo in the DEFINE trial. BODIPY CEC from J774 macrophages to apo B-depleted plasma was measured at baseline and at 24 weeks. Hp CNV status was determined using a commercially available ELISA assay (Savyon Diagnostics, Ltd., St. Ashdod, Israel).

Results: Among the 332 participants with diabetes, 51 had the 1-1, 162 had the 2-1, and 119 had the 2-2 Hp allele (194 Men and 138 Women). In unadjusted analyses, ANA was associated with a significant increase in CEC in those with the “1” allele (18%; std beta = 0.42; p=0.0026) but not in those with the “2” allele (11%; std beta = 0.08; p=0.16; p for interaction = 0.02; Figure). These findings remained significant adjusting for baseline risk factors and serial changes in lipids including apo AI and apo B (“1” allele: std beta = 0.55; p=0.05; “2” allele: std beta = 0.19; p=0.18; p for interaction = 0.08). This effect modification by Hp genotype was consistent in both diabetic men and women but was not present in non-diabetics (p for interaction = 0.36).

Conclusion: Among diabetic patients with CHD, the effect of ANA on raising CEC was blunted in those with a Hp CNV linked to dysfunctional HDL. These findings warrant validation and suggest a strategy to identify those most likely to benefit from interventions targeting reverse cholesterol transport.

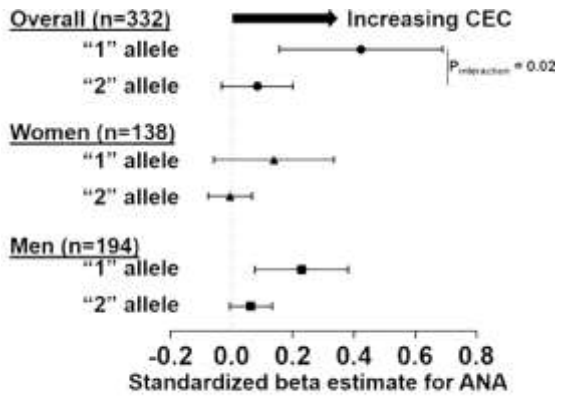

Figure: standardized beta estimates (95%CI) for ANA on follow up CEC, adjusted for baseline CEC, stratified by gender and Hp CNV genotype (allele “1” and “2”).