ADRENERGIC RECEPTOR POLYMORPHISMS INTERACT WITH BETA-BLOCKER DOSE EFFECT ON HEART FAILURE OUTCOMES ESPECIALLY IN BLACK RACE: RESULTS FROM HF-ACTION DNA SUBSTUDY

Oral Contributions
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Background: Polymorphisms affecting Beta-1 adrenergic receptor (ADRB1) function interact with beta-blocker (BB) dose and death/hospitalizations in patients with heart failure (HF). We examined the interaction between relevant polymorphisms and BB dose with mode-specific cardiovascular (CV) outcomes by race in the HF-ACTION DNA substudy.

Methods: HF-ACTION was a randomized, multicenter trial enrolling 2331 ambulatory HF patients (NYHA class II-IV, left ventricular ejection fraction <0.35) randomized to exercise training vs. usual care, with median follow up of 2.5 years and 95% of patients on BB. A subset of patients provided plasma for genotyping. Interactions between ADRB1-389, ADRB1-49, Alpha-2C adrenergic receptor (A2C-AR) genotype and BB dose (high vs. low dose, defined as > or ≤25mg daily carvedilol equivalents) with CV modes of death (CV, sudden cardiac death, pump failure) and CV and HF hospitalizations (CVH, HFH) were tested. Analysis was also stratified by race. Results were adjusted for clinical risk factors that were found to be significantly associated with outcomes.

Results: DNA information was available for 976 patients. After adjustment, low dose BB demonstrated greater risk for CVD, CVH, and HFH in ADRB1-389 Arg homozygotes than Gly carriers (CVD: HR 2.44 vs. 0.97, Intxn P=0.062; CVD+CVH: HR 1.44 vs. 1.01, Intxn P=0.076; CVD+HFH: HR 1.74 vs. 0.78, Intxn P=0.003). The interaction signal was amplified among blacks (CVD: HR 6.50 vs. 1.04, Intxn P=0.08; CVD+CVH: 2.28 vs. 0.79, Intxn P=0.004; CVD+HFH: 4.26 vs. 0.74, Intxn P<0.001). Similar ADRB1-389 genotype-BB dose interaction trends were observed for pump failure or sudden cardiac death, but this did not reach statistical significance. ADRB1-49 and A2C-AR polymorphisms did not interact with BB dose for any mode-specific outcome.

Conclusion: Low BB dose incurs an increased risk of CVD, CVH, and HFH among ADRB1-389 Arg homozygotes but not Gly carriers. This gene/dose interaction with CV outcomes was stronger in blacks. Prospective studies incorporating ADRB1 genotyping would be useful to investigate its potential application to clinical practice.