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# Heart Failure and Cardiomyopathies

## ALPHA-2C ADRENERGIC RECEPTOR POLYMORPHISM INTERACTS WITH BETA-BLOCKER DOSE EFFECT ON HEART FAILURE OUTCOMES DIFFERENTLY IN BLACK RACE: RESULTS FROM THE HF-ACTION DNA SUBSTUDY

Poster Contributions
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**Background:** Adrenergic activation is a key determinant of heart failure (HF) outcomes. The Alpha-2C adrenergic receptor (A2C-AR) Del 322-325 polymorphism is a loss of function variant. We examined the interaction between A2C-AR Del 322-325 and beta-blocker (BB) dose with cardiovascular (CV) outcomes 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. A subset of patients provided plasma for genotyping A2C-AR as wild type or Del carriers (≥1 Del 322-325 allele). Interaction between A2C-AR polymorphism and BB doses (high vs. low dose, defined as > or ≤25mg daily carvedilol equivalents) with CV outcomes was tested using Cox proportional hazards regression and by race.

**Results:** Genotype data was available for 965 patients (94% on BB). Del carrier prevalence was 28.3% (60% in blacks, 12.7% in whites). Table 1 displays gene-dose interaction with outcomes.

**Conclusion:** Although no interaction between A2C-AR genotype and BB dose was found in the overall population, BB dose appeared to influence outcomes when the analysis was stratified by race. Low BB dose conferred less risk in the presence of A2C-AR polymorphism among blacks, but increased risk among whites. This gene polymorphism/BB dose interaction and differential response by race group should be examined in a large, prospective study.

Table 1: Interaction between Alpha-2C-AR and Beta-Blocker Dose (Low vs. High) with Cardiovascular Outcomes

| Outcome | All Patients | | Whites | | Blacks | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | Intxn P-Value | HR (95% CI) | Intxn P-Value | HR (95% CI) | Intxn P-Value |
| ACD | | | | | | |
| Wild Type | 1.39 (0.92 - 2.11) | 0.975 | 1.17 (0.73 - 1.87) | 0.261 | 3.56 (1.29 - 9.80) | 0.092 |
| Deletion Carriers | 1.41 (0.74 - 2.67) | | 2.34 (0.77 - 7.16) | | 1.16 (0.51 - 2.65) | |
| ACD+ACH | | | | | | |
| Wild Type | 1.32 (1.09 - 1.60) | 0.826 | 1.40 (1.12 - 1.74) | 0.100 | 1.32 (0.84 - 2.07) | 0.638 |
| Deletion Carriers | 1.37 (1.02 - 1.84) | | 2.31 (1.32 - 4.02) | | 1.15 (0.80 - 1.64) | |
| CVD | | | | | | |
| Wild Type | 1.51 (0.92 - 2.46) | 0.867 | 1.27 (0.72 - 2.24) | 0.614 | 3.43 (1.12 - 10.5) | 0.227 |
| Deletion Carriers | 1.39 (0.65 - 2.98) | | 1.92 (0.43 - 8.58) | | 1.41 (0.57 - 3.51) | |
| CVD+CVH | | | | | | |
| Wild Type | 1.20 (0.97 - 1.48) | 0.716 | 1.23 (0.97 - 1.57) | 0.387 | 1.44 (0.88 - 2.34) | 0.575 |
| Deletion Carriers | 1.29 (0.94 - 1.77) | | 1.64 (0.90 - 3.00) | | 1.20 (0.82 - 1.76) | |
| CVD+HFH | | | | | | |
| Wild Type | 1.09 (0.81 - 1.46) | 0.242 | 1.00 (0.71 - 1.41) | 0.143 | 2.06 (1.09 - 3.90) | 0.424 |
| Deletion Carriers | 1.47 (0.98 - 2.21) | | 1.96 (0.86 - 4.46) | | 1.49 (0.92 - 2.40) | |

Intxn: Interaction P-value; ACD: All-cause death; ACH: All-cause hospitalizations; CVD: Cardiovascular death; CVH: Cardiovascular hospitalizations; HFH: Heart failure hospitalizations