The Angiotensin II Type Receptor A1166C Polymorphism and Heart Failure Outcomes

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BACKGROUND: The effects of angiotensin II are mediated by angiotensin II type 1 receptors (AT1). A common polymorphism exists in the 3’ untranslated region of AT1 (A1166C) and the C allele has been associated with vascular stiffness and risk of hypertension. To date, few studies have evaluated the effect of this polymorphism on heart failure phenotype or outcomes. Therefore, we sought to evaluate the impact of the C allele on heart failure progression through an examination of subjects in the GRACE (Genetic Risk Assessment of Cardiac Events) database.

METHODS: 432 subjects with heart failure due to systolic dysfunction (EF<0.45) were enrolled between April 1996 and January 2001. Demographic information, New York Heart Association Class, previous cardiovascular evaluation, and medical therapy were recorded at entry, and subjects were followed prospectively to an end point of death or heart transplantation. Genomic DNA was extracted from peripheral blood and genotyped. Baseline characteristics and outcomes were analyzed in the A1166C genotype subset.

RESULTS: The mean age of the cohort was 55.6±12.0 years and the mean LVEF was 0.24±0.08. 84.3% of patients were treated with ACE inhibitors, 10.4% with angiotensin receptor blockers, and 42.5% with β-blockers. 8.6% of patients were homozygous for the C allele, 50.0% were homozygous for the A allele, and 41.4% were heterozygous (AC). There were no differences in age, sex, race, ethnicity, and therapy among the 3 subgroups. The C allele was associated with lower NYHA class (AA/AC/CC = 2.60/0.61/2.51 vs. 0.63/2.43 vs. 0.69, p=0.035). The median follow-up time for all patients was 28.43±18.19 months (range, 1 to 62 months for patients alive and transplants). However, it was not associated with poorer transplant-free survival (1 year percent survival AA/AC/CC = 79/79/79, 2-year =67/70/71, 3-year =58/59/61, p=0.38).

CONCLUSION: In our heart failure population, the AT1 C allele was associated with an enhanced response to β-blocker therapy. We examined the impact of the Ser49Gly polymorphism in vascular elasticity and hypertension, the AT1 receptor polymorphism does not appear to modulate clinical outcomes in heart failure.

The Vascular Endothelial Growth Factor +405 CC Promotor Polymorphism is Associated With an Impaired Prognosis in Patients With Chronic Heart Failure: For the MERIT-HF Study Group

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Background: Vascular endothelial growth factor (VEGF) causes angiogenesis, which may limit ischemia and may be beneficial in Chronic Heart Failure (CHF). Recent reports have shown that a common polymorphism at +405 of the VEGF gene is related to VEGF protein production, while another common polymorphism at -460 does not affect VEGF protein levels. Effects of these polymorphisms on outcome in CHF are unknown.

Methods: Using promoter polymorphisms +405 and -460 were examined by using sequence-specific primer-PCR in 609 patients enrolled in MERIT-HF. A risk ratio (RR) for each genotype was calculated using the combined endpoint of all cause mortality or hospitalisation (time to first event).

Results: The presence of the +405 CC genotype (n=84, 14%) was associated with a significant worse outcome on the combined endpoint, RR=1.68; 95% confidence intervals (CI), 1.05-2.68 (P=0.03). This remained statistically significant after adjustment for conventional risk factors and study medication (metoprolol CR/ XL or placebo). On the other hand, the -460 polymorphism was not significantly associated with an altered prognosis (p=0.84).

Conclusion: These results indicate that the VEGF +405 CC genotype, which is related to lower VEGF levels, is associated with an impaired outcome in patients with CHF. In contrast, the VEGF -460 polymorphism, which is not associated with altered VEGF protein levels, did not affect the prognosis.

The Role of a Common Adenosine Monophosphate Deaminase-1 Polymorphism in Outcome of Ischemic and Nonischemic Heart Failure

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Background: A common, nonsense variant of the adenosine monophosphate deaminase-1 gene (C34T) results in enzymatic inactivity and may increase adenosine in skeletal and cardiac muscle and confer cardioprotection through ischemic preconditioning.

Methods: We hypothetized that AMPD1 carriers with ischemic CHF in the Beta-Blocker Evaluation of Survival Trial (BEST) might have a relative survival advantage. Patient DNA samples (N=1038) of which 58% (n=605) had ischemic CHF, 42% (n=433) non-ischemic CHF and 20% (n=200) patients were Black. Patient follow-up for all-cause mortality averaged 2.0 y. DNA samples were provided by the Beta-Blocker Evaluation of Survival Trial the BEST DNA Bank co-sponsored by the National Heart, Lung, and Blood Institute.