**RENIN-ANGIOTENSIN SYSTEM GENE POLYMORPHISMS AND THE RISK OF STROKE IN PATIENTS WITH ATRIAL FIBRILLATION:**

**A PROSPECTIVE OBSERVATION STUDY**

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Little evidence is available for the impact of genetic polymorphisms on the risk of stroke in patients with AF. Angiotensin II plays a pathophysiological role in prothrombotic endocardial remodeling. We planned to investigate the effect of polymorphisms of renin-angiotensin system genes on the incidence of stroke in a prospective cohort of patients with atrial fibrillation (AF). We assessed 311 AF patients and longitudinally followed up for 7.3+/-1.8 years. +/-G-217A, G-152A, A-20C, G-6A, M235T and T174M polymorphisms of angiotensinogen (AGT) gene, I/D polymorphism of ACE gene, and A1166C polymorphism of AT1R were genotyped. Incident physician-diagnosed ischemic stroke was the outcome measure. At the end of follow-up, thirty-one patients developed stroke. G-6A polymorphism of AGT gene was associated with the risk of stroke. Patients carrying G-6 allele were more likely to develop stroke than non-carriers (log-rank P=0.012). In Cox analysis, subjects carrying G-6 had increased risk of stroke (HR 2.74, 95% CI 1.23-6.11; P=0.014) after adjustment for non-genetic covariates. In AGT gene haplotype analysis, haplotypes consisting of -217G/-6G were associated with risk of AF (P=0.011). G-217/G-6 haplotype carriers were more likely to develop stroke than non-carriers (log-rank p=0.003). For pharmacogenetic analysis, the risk of stroke in subjects carrying G-6 was comparable to non-carriers, if they took ACEI or ARB during follow-up. In conclusions, AGT gene polymorphisms may be considered a genetic marker predisposing to an increase in risk of stroke in subjects with AF. From a pharmacogenetic view, ACEI or ARB may prevent stroke in patients with high risk AGT gene variants.