EFFECTS OF BETA ADRENERGIC RECEPTOR GENE POLYMORPHISMS ON MORTALITY AND THEIR PHARMACOGENETIC INTERACTION IN THE SECONDARY PREVENTION SETTINGS OF ACUTE MYOCARDIAL INFARCTION

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Background: Although beta adrenergic receptor (ADRB) gene polymorphisms have been shown to influence the regulation of cardiovascular function, their impact on mortality is still unclear.

Methods: We determined the genotypes of ADRB1, ADRB2, and ADRB3 genes (ADRB1: Arg389Gly, Ser49Gly, ADRB2: Arg16Gly, Gln27Glu, Arg-19Cys, and ADRB3: Arg64Arg) in 3091 AMI survivors registered in the Osaka Acute Coronary Insufficiency Study between 1998 and 2008. To evaluate the effects of ADRB gene polymorphisms on mortality and their pharmacogenetic interaction in the secondary prevention settings of acute myocardial infarction (AMI), the mortality effects of these polymorphisms and their combination, which was identified by principle components analysis (PCA), were examined with multivariate Cox regression analysis. Further, their pharmacogenetic interactions with β-blockers, renin angiotensin system (RAS) inhibitors and statins were examined.

Results: There were 192 deaths during the median follow-up period of 1584 days. There was a significant association between ADRB2 Arg16Gly polymorphism and an increase in all-cause mortality (Arg/Arg or Arg/Gly vs Gly/Gly: HR 1.99; 95%CI: 1.17-3.36, p=0.0094), whereas the other polymorphisms not. In addition, the combination of ADRB1 389Arg/Arg, ADRB1 49Ser/Gly, ADRB2 27Gln/Gln and ADRB2 -19Arg/Cys was significantly associated with all-cause mortality (HR 2.09; 95%CI: 1.28-3.42, p=0.0028). Although significant pharmacogenetic interaction was observed for Arg389Gly with RAS inhibitors in terms of mortality (p for interaction =0.0252), other drug-gene interactions for any polymorphism or combination were observed with none of β-blockers, RAS inhibitors and statins.

Conclusions: Polymorphisms in the ADRB genes seem to affect all-cause mortality in the secondary prevention after AMI. Although pharmacogenetic interaction of ADRB1 Arg389Gly with RAS inhibitors was observed, cardiovascular secondary prevention medication might not modify the risk of ADRB polymorphisms enough in other situations. Further researches are required to better treat patients with AMI and increased risk of ADRB polymorphisms.