THE TRP719ARG VARIANT OF KIF6 AND CARDIOVASCULAR OUTCOMES IN STATIN-TREATED, CORONARY STABLE PATIENTS OF THE TNT AND IDEAL PROSPECTIVE STUDIES

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Background: Carriers of the KIF6 Trp719Arg genetic variant are at increased risk for cardiovascular disease (CVD). It has been suggested that CVD risk in carriers of the KIF6 variant can be significantly reduced by statin therapy. We hypothesized that carriers of the KIF6 variant obtain more benefit from high-dose statin therapy than do noncarriers in two large randomized clinical trials (RCT) of stable coronary patients.

Methods: We used a Cox proportional hazard model that adjusted for age, sex, and smoking to assess the hazard ratio (HR) for the reduction of major cardiovascular events (MCVE) by 80 mg/day atorvastatin over 10 mg/day atorvastatin in 4,599 patients of the Treating to New Targets (TNT) study and by 80 mg/day atorvastatin over 20-40 mg/day simvastatin in 6,541 patients of the Incremental Decrease in End Points Through Aggressive Lipid-Lowering (IDEAL) study. Major cardiovascular event (MCVE) was defined as coronary death, nonfatal myocardial infarction, resuscitation after cardiac arrest and fatal or nonfatal stroke.

Results: A total 381 and 648 patients experienced a major cardiovascular event (MCVE) during follow-up in TNT and IDEAL, respectively. In TNT, for noncarriers of the Trp719Arg allele (n=1883), the hazard ratio (HR) was 0.81 (95% CI, 0.59-1.11). In carriers of one or two risk alleles (n=2716), the HR was 0.85 (0.66-1.11) and carriers of two copies of the risk allele (n=580) obtained a significant risk reduction (HR: 0.44, 95% CI, 0.23-0.84). In IDEAL, for noncarriers of the Trp719Arg allele (n=2676), the HR was 0.85 (0.67-1.10). In carriers of one or two risk alleles (n=3865), the HR was 0.88 (0.62-1.07) and in carriers of two copies of the risk allele (n=834), the HR was 0.91 (95% CI, 0.58-1.43). The p-value for treatment by 3-level genotype was 0.063 for TNT and 0.699 in IDEAL and the p-value for treatment by Trp719Arg carrier status was 0.810 for TNT and 0.421 in IDEAL.

Conclusions: In these two large RCTs, carriers of the KIF6 Trp719Arg allele did not obtain greater cardiovascular benefit upon high-dose statin therapy than noncarriers. Carriers of two copies of this variant had a significant risk reduction in TNT, but genotype did not affect treatment benefit in IDEAL.