OR-9
A-ADDUCIN GLY460TRP POLYMORPHISM AND THE CARDIOVASCULAR RISK ASSOCIATED WITH SYSTOLIC PRESSURE — A PROSPECTIVE POPULATION STUDY

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Preliminary evidence suggested that in hypertensive patients the α-adducin 460Trp allele might be associated with a twofold higher risk of coronary heart disease. In a prospective population study, we investigated whether the α-adducin Gly460Trp polymorphism, alone or in combination with other risk factors, predicted outcome. From August 1985 until July 2003, we randomly recruited 2235 Belgian residents. We obtained information on vital status (until July 1, 2004) and the incidence of events via registries and repeat (median, 3) examinations. For the main analyses, we used multiple Cox regression. After adjustment for other risk factors, we found strong interaction between systolic blood pressure at baseline, analyzed as a continuous variable, and the α-adducin polymorphism in relation to total (P=0.01) and cardiovascular mortality (P=0.008), all cardiovascular (P=0.003) complications, and cardiac (P=0.0009) and coronary events (P=0.03). The hazard ratios for total mortality associated with the Trp allele relative to Gly homoyzogosity were 2.30 (95% confidence interval, 1.09 to 4.83) in patients with stage-2 systolic hypertension (≥160 mm Hg) and 0.88 (0.62 to 1.25) in the other participants. For all cardiovascular complications, these estimates were 2.94 (1.24 to 6.95) and 0.83 (0.58 to 1.19), respectively. For all cardiovascular events in stage-2 systolic hypertension, the positive predictive value and the attributable risk associated with the Trp allele were 76.9 percent and 44.3 percent, respectively. In combination with systolic blood pressure, the α-adducin Gly460Trp polymorphism is a strong predictor of cardiovascular mortality and morbidity.

Key Words: Cardiovascular Risk, Genetics, Hypertension

OR-10
ABSENCE OF AN INTERACTION BETWEEN THE ACE INSERTION-DELETION POLYMORPHISM AND ACE INHIBITOR VERSUS OTHER ANTIHYPERTENSIVE TREATMENTS ON CARDIOVASCULAR RISK IN HIGH-RISK HYPERTENSIVES: THE GENHAT STUDY

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Blood pressure response to treatment is influenced by genetic variation in the renin-angiotensin-aldosterone (RAS) system, but no clinical trials have tested whether cardiovascular outcomes vary across combinations of RAS genes and antihypertensive (AHYP) medications. Our objective was to determine whether the angiotensin converting enzyme (ACE) insertion-deletion (I/D) polymorphism modifies the association of AHYP medications and risk of fatal and non-fatal coronary heart disease (CHD), stroke, all-cause mortality, and combined CHD and cardiovascular disease endpoints. As an ancillary study to a double-blind, active-controlled randomized trial of AHYP treatment that recruited high-risk hypertensives, anonymized DNA specimens were genotyped in 37,939 participants using methods to enhance correct classification of ACE I/D genotypes. Participants were randomized to chlorthalidone (C) (n=13,679), amlodipine (A) (n=8069), lisinopril (L) (n=8109) or doxazosin (D) (n=8082). CHD occurred in 3096 individuals during an average 6 years of follow-up for the L, C, and A groups, and 4 years of follow-up for the D group. Hazard rates for CHD and secondary outcomes were equal across treatments. The ACE I/D variant was not associated with CHD (RR of DD versus ID + II = 0.99, 95% CI 0.91-1.07) or any secondary outcome. The hazard rate for CHD in the DD genotype was not statistically different than the ID+II genotypes by treatment (6-yr rate per 100 person-years: 11.5 vs 11.1 for L, 11.0 vs 11.4 for C, and 11.5 vs 11.4 for A; 4-year rate: 7.1 vs 7.8 L and 9.0 vs 7.6 for D). No secondary outcomes were statistically different across treatment-genotype strata. In the largest pharmacogenetics clinical trial conducted to date, the ACE I/D polymorphism was not a predictor of fatal and non-fatal CHD, nor did it modify the response to AHYP treatment.

Key Words: ACE I/D Polymorphism, Antihypertensive Treatment, Pharmacogenetics

OR-11
A NEW GORDON’S SYNDROME PEDIGREE IS CAUSED BY A NOVEL MUTATION WITHIN THE ACID MOTIF OF WNK4

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Gordon’s Syndrome (GS) is a rare familial form of hypertension characterised by hypertension and hyperkalemia. Mutations within two novel serine/threonine kinases, WNK1 and WNK4, have been identified in some GS pedigrees.

We identified an unpublished pedigree consisting of an affected father and male offspring. Southern analysis showed no evidence of large intronic deletions reported in WNK1 GS pedigrees. However, sequencing of WNK4 showed a D565H mutation, not seen in the unaffected mother. This causes a charge changing substitution within the highly conserved acidic motif that contains 3 other previously reported GS mutations. We co-expressed wild-type (WT) WNK4 with two of its known targets, NCCT (NaCl co-transporter) and the K channel, ROMK, in Xenopus oocytes. 22Na flux techniques and 2-electrode voltage clamp

Key Words: ACE I/D Polymorphism, Antihypertensive Treatment, Pharmacogenetics