

52% of the variation in susceptibility to ara-C cytotoxicity among the YRI cell lines.

CONCLUSION: By using a cell-based model and a whole-genome approach, we were able to identify a genetic signature for susceptibility to the cytotoxic effects of ara-C.

OI-A-1

COMBINED *CYP2C9-VKORC1* GENOTYPE GUIDED WARFARIN LOADING ENHANCES THE EFFICACY AND SAFETY OF ANTICOAGULATION. PRELIMINARY FINDINGS FROM A PROSPECTIVE, DOUBLE BLIND, RANDOMIZED, CONTROLLED STUDY. Y. Caraco,¹ I. Bejarano-Achache,¹ H. Shaoul,¹ I. Linzer,¹ S. Blotnick,¹ M. Bialer,² M. Muszkat¹; ¹Hadassah University Hospital, Jerusalem, Israel, ²The Hebrew University of Jerusalem School of Pharmacy, Jerusalem, Israel

BACKGROUND: We have recently shown that the use of *CYP2C9* genotype adjusted loading algorithms may significantly enhance the safety and efficacy of anticoagulation. The purpose of the current study was to evaluate the use of combined *CYP2C9-VKORC1* genotype to guide warfarin initiation in a prospective, double blind, randomized controlled study.

METHODS: Thirty five patients newly diagnosed with AFIB, DVT or PE with a target INR of 2-3 were randomly assigned to receive warfarin based on a validated algorithm (control group) or algorithms that were designed to take into account the combined *CYP2C9-VKORC1* genotype (study group). Patients were followed from initiation and until stable anticoagulation was reached. Both the investigators and the patients were blinded for the mode of warfarin loading or the patient's genotype. Results of genetic analysis (*CYP2C9*: 2 SNPs; *VKORC1*: 6 SNPs) for the study group patients were usually provided within 12 hours of admission.

RESULTS: Time to reach first therapeutic INR (i.e. INR>2) was significantly shorter for patients in the study as compared to patients in the control group (4.2±0.5 vs. 6.8±1.2 days, p<0.01). Stable anticoagulation was reached in the study group after 22.1±3.9 days of warfarin therapy and significantly earlier than in patients treated by the control algorithm (43.5±7.8, p<0.004). Percent time spent within the desired therapeutic range (i.e. INR 2-3) was significantly greater in the study than in the control group patients (78±8% vs. 56±12%, p<0.005).

CONCLUSION: The preliminary findings of this on-going study suggest that the prospective use of combined *CYP2C9-VKORC1* genotype to guide warfarin loading may significantly improve the safety and efficacy of anticoagulation therapy.

OI-A-2

NOVEL PROMOTER POLYMORPHISMS IN ANGIOTENSIN-I CONVERTING ENZYME (*ACE*) ASSOCIATED WITH CLINICAL OUTCOMES IN HYPERTENSIVE CORONARY ARTERY DISEASE (CAD) PATIENTS. A. D. Johnson,¹ Y. Gong,² D. Wang,¹ T. Y. Langae,² J. Shin,² R. M. Cooper-DeHoff,² N. J. Schork,³ M. A. Shriver,⁴ P. F. Binkley,¹ C. J. Pepine,² J. A. Johnson,² W. Sadee¹; ¹Ohio State University, Columbus, OH, ²University of Florida, Gainesville, FL, ³University of California, San Diego, CA, ⁴Pennsylvania State University, University Park, PA

BACKGROUND: Genetic variants of *ACE* have long been suspected as risk factors in hypertension and other diseases, and in affecting treatment outcomes. However, no definitive functional allele had been identified.

METHODS: Allelic mRNA expression and total expression of *ACE* was measured in 65 heart failure explants by RTPCR, followed by sequencing of *ACE* to identify regulatory alleles linked to allelic expression imbalance (AEI). Clinical associations for potentially functional SNPs were tested in 1032 hypertensive CAD patients from the International Verapamil SR-Trandolapril Study GENetic Substudy (INVEST-GENES) where patients were randomized to an atenolol-based β blocker strategy or verapamil SR-based calcium channel blocker strategy with trandolapril and/or hydrochlorothiazide added if necessary for BP control. Primary outcome was defined as first occurrence of death, nonfatal myocardial infarction (MI) or nonfatal stroke.

RESULTS: Allelic *ACE* expression patterns revealed strong regulatory factors, most prominently in African Americans. SNPs rs7213516 and rs4290, located 5' of the *ACE* gene, were highly linked to AEI. The minor alleles of these SNPs were also associated with inter-individual differences in *ACE* mRNA expression. Both SNPs were significantly associated with primary outcome in INVEST-GENES (mostly attributable to nonfatal MI) in African Americans. The odds ratios were: rs7213516: 4.13 [1.52-11.21] (p=0.0054); rs4290: 3.91 [1.54-9.90], (p=0.0041). The effects were modifiable by drug exposure including *ACE* inhibitors.

CONCLUSION: Two *ACE* promoter SNPs for which tissue experiments suggest functional effects were strongly associated with clinical outcomes in hypertensive CAD patients. High allele frequency in African-Americans (16%) compared to Hispanics (4%) and Caucasians (<1%) suggests this allele may contribute to variation between populations in cardiovascular risk and response to *ACE* inhibitor therapy.

OI-A-3

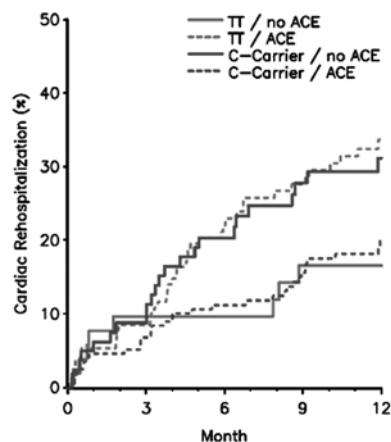
INTERACTION BETWEEN *NOS3* -786 T>C GENOTYPE AND ACE INHIBITOR THERAPY IN ACUTE CORONARY SYNDROMES. A. L. Beitelshes,¹ I. Zineh,² S. Cresci,¹ J. Wu,¹ M. R. Minton,¹ M. A. Province,¹ J. A. Spertus³; ¹Washington University, St. Louis, MO, ²University of Florida, Gainesville, FL, ³Mid America Heart Institute and University of Missouri Kansas City, Kansas City, MO

BACKGROUND/AIMS: Endothelial nitric oxide synthase (eNOS) is encoded by the *NOS3* gene. The -786 T>C variant shows reduced expression and NO bioactivity, but attempts at replication of CVD risk associations have not been conclusive. *ACE* inhibitors (*ACE*-I) increase eNOS expression and are often used after acute coronary syndromes (ACS). We hypothesized that *NOS3* -786 T>C genotype would be associated with variable *ACE*-I benefit in post-ACS patients.

METHODS: A prospective cohort of ACS patients (N=696) with 3-year mortality and 1-year cardiac rehospitalization follow-up was assessed. Age, sex, DM, CHF, HTN, ejection fraction, ACS type, coronary revascularization, genotype, *ACE*-I use, and genotype**ACE*-I interaction terms were included in Cox proportional hazards models conducted separately by race.

RESULTS: The minor allele frequency was 0.37 in whites and 0.15 in blacks, and *ACE*-I were prescribed at discharge to 70% and 74%, respectively. An interaction between *NOS3* -786 T>C and *ACE*-I on cardiac rehospitalization was identified in whites (p=0.0033) (Figure). C/C individuals treated with *ACE*-I had improved event-free survival (HR 0.25, 95% CI 0.07-0.87) compared to those not treated with *ACE*-I, while heterozygotes had no benefit (HR 1.04, 95% CI 0.51-2.13) and T/T individuals had worse event-free survival with *ACE*-I (HR 2.55, 95% CI 1.16-5.62). Results were similar in blacks (not shown). No association with mortality was seen.

CONCLUSIONS: These results suggest variable benefit of *ACE*-I treatment among post-ACS patients by *NOS3* genotype. These findings may provide insight into previous conflicting results with *NOS3*, which have not explored interactions with *ACE*-I use.



OI-A-4

RESPONSE TO CLOPIDOGREL IN PATIENTS WITH CORONARY ARTERY DISEASE IS ASSOCIATED WITH CYP2C19 BUT NOT CYP2B6 GENOTYPE. P. Nystrom, MD,¹ Z. Desta, PhD,¹ J. Jakubowski, PhD,² L. Li, PhD,¹ J. Hilligoss,¹ J. E. Tisdale, PharmD,³ Y. Kreutz,¹ J. Miao, MD,¹ D. A. Flockhart, MD, PhD,¹ R. Kovacs, MD,¹ Y. Jin, MD¹; ¹Department of Medicine, Indiana University, Indianapolis, IN, ²Eli Lilly and Company, Indianapolis, IN, ³Department of Pharmacy Practice, Purdue University, Indianapolis, IN

BACKGROUND: Inhibitors of platelet aggregation reduce adverse cardiovascular events, but the response to clopidogrel (Clop) varies widely between individuals. Several cytochrome P450 (CYP) isoforms, including CYP2C19 and CYP2B6, have been shown to be involved in the bioactivation of Clop. We tested the hypothesis that genetic polymorphisms in CYP2C19 and CYP2B6 genes alter platelet responses to Clop.

METHODS: In an ongoing observational trial with stable outpatients on chronic dual anti-platelet therapy, subjects recorded their daily use of Clop (75 mg) and aspirin (81-325 mg) for 14 days. Pre-dose blood samples were collected on day 15. Platelet aggregation was assessed using ADP-induced light transmission aggregometry (LTA) and VerifyNow™ P2Y12 (VN) assays. Common CYP2C19 (*2, *3, *17) and CYP2B6 (*4, *6) genetic variants were determined using Taqman® assays.

RESULTS: Results from 53 subjects who completed the study demonstrated a highly variable platelet response in 20µM ADP-induced maximal platelet aggregation (MPA) (range: 15-65%) by LTA and platelet inhibition by VN (range: 0-97% inhibition). Six CYP2C19 genotypes, *17/*17 (n=4), *1/*17 (n=13), *1/*1 (n=21), *1/*2 (n=10), *2/*17 (n=2), *2/*2 (n=3), were identified and scored based on the predicted function. A statistically significant difference in MPA (P=0.016 by one-way ANOVA; R²=0.221, P<0.001 for gene-dose effects) and platelet inhibition by VN (P=0.077 by ANOVA; R²=0.175, P=0.002 for gene-dose effect) was observed among subjects with different CYP2C19 genotypes, but not for CYP2B6. Patient characteristics such as gender, race, smoking, diabetes, and concomitant medications did not appear to be associated with Clop response in this small cohort.

CONCLUSION: Variability in platelet response to clopidogrel is associated with polymorphisms in the CYP2C19 gene. CYP2C19 genotyping may enable identification of patients who respond poorly to clopidogrel.

PI-01

THE IDENTIFICATION OF A NOVEL *HNF-4A* SNP AFFECTING IN VITRO AND IN VIVO CYP2D6 ACTIVITY. C. Yeo, K. Kim, D. Cho, E. Cha, S. Lee, J. Shon, J. Shin; Department of Pharmacology & Pharmacogenomics Research Center, Busan, Republic of Korea

BACKGROUND: It has been well known that expressions of hepatic CYP450 varies widely and large part of this variability may be attributed to various genetic factors. Nevertheless, the individual variation in CYP expression and activity could not be expected solely genetic variations of CYP genes. Previous studies have demonstrated that HNF-4A is an essential transcription regulator of several CYPs. Therefore, the genetic variation of HNF-4A may contribute to the variability of CYP activities.

METHODS: The genetic polymorphism of HNF-4A was investigated in Korean subjects through direct sequencing of HNF-4A gene. Twenty SNP, including two novel nonsynonymous SNPs in exon 2, were identified. The frequency of the novel variants was assessed using pyrosequencing in Asian and Caucasians. One novel HNF-4A variant(G60D, 4749G>A) was evaluated for its functional alteration by its transactivation activity of CYP2D6 promoter. In order to evaluate the effect of this SNP on in vivo CYP2D6 activity, CYP2D6 phenotyping study using dextromethorphan was conducted in Korean healthy subjects. Urine for 8hr after dose was collected and measured dextromethorphan and dextrophan level using LC/MS/MS.

RESULTS: The allelic frequency of HNF-4A G60D variant was about 2% in Koreans and lower in Chinese and Vietnamese, but not

founded in Caucasian. This variation resulted in the loss of DNA binding activity leading to the loss of transactivation for HNF-4A target gene *CYP2D6*. Subjects with heterozygous mutation of *HNF-4A* G60D seemed likely to show a lower urinary metabolic ratio (dextromethorphan/dextrophan ratio in 8hr urine) than those with wild genotype (p=0.08).

CONCLUSION: The null allelic variant, *HNF-4A* G60D, was identified in Asians. Results in these in vitro and in vivo functionality studies suggest that *HNF-4A* G60D variant may contribute to the interindividual variability of CYP2D6 expression and more accurately predict *in vivo* CYP2D6 activity.

PI-02

COMPARISON STUDY OF NOVEL PDE-5 INHIBITOR, UDENAFIL, DISPOSITION BETWEEN HEALTHY ELDERLY AND YOUNG ADULT MALE SUBJECTS. C. Yeo, D. Cho, K. Liu, J. Shon, J. Shin; Department of Pharmacology & Pharmacogenomics Research Center, Busan, Republic of Korea

BACKGROUND: Udenafil is a novel cGMP-specific PDE 5 inhibitor that is currently available in South Korea for the treatment of erectile dysfunction(ED). In the prior clinical trials, udenafil was generally well tolerated and showed the efficacy of ED and frequency of adverse events comparable to other PDEIs. This study was to evaluate the effect of age on the pharmacokinetics and safety of udenafil.

METHODS: A open, parallel, single oral dose study were conducted in healthy elderly and young adult male subjects after a single oral dose of 100mg of udenafil. Pharmacokinetic parameters and safety of udenafil were compared between 12 young subjects (mean age 23 years; range 21-27 years) and 12 elderly subjects (mean age 69 years; range 65-78 years). Blood and urine samples were collected up to 60 h after dose. The assays of udenafil and its main metabolite, DA-8164, were conducted using LC/MS/MS and pharmacokinetic parameters were estimated with WinNonlin®. Analysis of variance (anova) was used to compare udenafil and DA-8164 AUC and C_{max} in the young vs the elderly groups.

RESULTS: The C_{max} of udenafil and its metabolite, DA-8164 in elderly (214.0±100.3ng/ml, 124.4±40.8ng/ml) seems likely to be lower than that in young (292.8±96.6ng/ml, 164.6±55.4ng/ml), while t_{1/2} were prolonged in elderly when compared with young (16.6±3.2h vs 11.6±1.6h). Finally, no significant difference in AUC_{inf} was observed between the elderly(1858.8±694.6ng-hr/ml and 1768.0±634.7ng-hr/ml) and the young subjects (2100.6±419.8ng-hr/ml and 2072.2±652.4ng-hr/ml) for both udenafil and its metabolite. While, all adverse events(1 migraine and 3 hot flushing) were reported only in elderly and were mild.

CONCLUSION: Oral disposition of udenafil in elderly was not different significantly when compared with that in young, in contrast to other PDEIs. However, vascular adverse events were reported only in elderly group. This information would be useful for dosage regimen of udenafil in elderly group.

PI-03

ENOXAPARIN DOSE REDUCTION IN ELDERLY PATIENTS WITH ACUTE CORONARY SYNDROME (ACS) : THE EFFECT ON 3-MONTH ACS RECURRENCE. A. Levin, M. Ben-Artzi, P. Beckerman, G. Haber, D. Varon, A. Ben-Yehuda, M. Muszkat; Hadassah University Hospital, Jerusalem, Israel

BACKGROUND: The recommended enoxaparin dosage in ACS is 1mg/kg/12hr, however, in elderly patients reduction of enoxaparin dosage is common, despite the lack of specific recommendations. The aim of this study was to determine the effect of enoxaparin dosage reduction on 3-month ACS recurrence in elderly patients without severe renal dysfunction.

METHODS: Design: Prospective observational. Setting: The Internal Medicine ward in a tertiary care general hospital. Population: Consecutive patients with ACS treated with enoxaparin bid. Patients with creatinine clearance (CrCl) <30 ml/min were excluded. Outcome: 3-month ACS recurrence.