Parameter	EZE/ S10mg (n=67)	PBO/ S80mg (n=67)	EZE/ A10mg (n=65)	PBO/ A80mg (n=62)	EZE/ P10mg (n=71)	PBO/ P40mg (n=67)	EZE/ L10mg (n=65)	PBO/ L40mg (n=65)
LDL-C*	-45.5	-44.7	-53.4	-53.8	-33.8	-31.1	-34.2	-30.5
HDL-C*	8.6	8.2	9.0***	2.8	8.4	6.1	7.9	4.8
TG**	-26.1	-22.6	-31.1	-30.6	-22.9	-19.2	-18.8	-15.3

*Mean % change **Median % change ***P<0.05 vs high dose statin (A80)

1083-143 **Does Pretreatment With Statins Before Percutaneus Coronary Intervention Reduce Myonecrosis?**

Su Min Chang, Naji Yazbek, John A. Farmer, Nasser Lakkis, Baylor College of Medicine, Houston, TX

Background: Cardiac enzyme elevation peri PCI carries a worse outcome. **Objective:** Determine if pretreatment with statins prior to PCI reduces enzyme elevation periPCI and other cardiac events (CE). **Methods:** 119 consecutive pts (63 on statins prior to PCI , 56 not)underwent PCI were followed for 6 months. We compared the peri PCI cardiac enzyme elevation above 3 times normal and 6 months CE rate (death, peri PCI myocardial infarction (MI), non fatal MI, target vessels revascularization (TVR) and unstable angina requiring hospitalization) . Of not pretreated pts , 72% were on statins at follow up as compared to 98 % of pretreated pts. **Results:** Pretreated Patients had more history of MI or revascularization (63% vs 43%, p=0.015), hyperlipidemia (80% vs 48% p=0.001), hypertension (83% vs 49% p=0.02) .The rest of baseline characteristics were similar including use of glycoprotein IIb/IIIa inhibitors (60% vs 68% p=NS) and type of lesions. Pretreatment with statins had less periprocedure enzyme elevation (2% vs 10 % p= 0.04) and lower CE rate at 6 months (21% vs 41% p=0.015). After adjusting for 15 baseline characteristics, use of statins prior to PCI was associated with a decrease in the risk of enzyme elevation and CE. (OR 0.2, CI 0.06-0.63, p=0.006). Age > 65 years and type b2/C lesions predicted worse outcome. **Conclusion:** Statins therapy prior to PCI may reduce periprocedure cardiac enzyme elevation and subsequent cardiac events. These results need to be confirmed in prospective randomized trials.

	Statins n=63	No Statins n =56
PeriPCI enzyme elevation	1 2%	6 10%
death	4 6%	2 4%
Non periPCI MI	4 6%	3 6%
TVR	1 2%	6 10%
USA	3 5%	7 13%
CE	13 21%	24 41%

1083-144 **Statins Potentiate the Anticoagulant Effects of Low Molecular Weight Heparin**

Sirisha Puppala, Katherine Zamecki, Jennifer Zimmer, Rohit R. Arora, Biren Bhatt, Jesse Houghton, Mir Chowdhury, Charles R. Spillert, New Jersey Medical School, Newark, NJ

Background: Pravastatin sodium (PS) has been shown to have an anticoagulant effect in patients. We have shown that PS has anticoagulant effects which are unrelated to a tissue factor pathway. Whether PS can potentiate the anticoagulant effects of low molecular weight heparin (LMWH, Dalteparin) is discussed.
Methods: One milliliter of citrated whole blood (CWB) was incubated for 10 minutes at 37 degrees with the following: 20 µl water (control); 16 µg/ml PS; 0.25 U/ml LMWH; 16 µg/ml PS and 0.25 U/ml LMWH combined. The clotting time (sec) was determined on a Sonoclot Coagulation Analyzer, a miniviscometer, which is sensitive to early fibrin polymer generation.
Results: The clotting times are as follows: control 355 ± 74; PS 462 ± 75;
LMWH 636 ± 191 and PS + LMWH 810 ± 119. All values were significantly different from each other (p<0.05 or less).
Conclusion: PS prolongs clotting time as does LMWH when compared to the control. In addition, the combination of PS and LMWH prolongs clotting time when compared to either alone. The enhanced anticoagulant effects of this combination of drugs may also occur when used clinically. A rapid clinical blood clotting assay capable of monitoring these apparently beneficial effects would be an asset.

1083-145 **Variability in the ABCA1 Gene but Not HMG-CoA Reductase Predicts Low-Density Lipoprotein Lowering Effects of Statins**

Gualberto Ruano, Chad Messer, Bradley Dain, Richard Judson, Carol Reed, Antonio Gotto, Genaissance Pharmaceuticals, New Haven, CT, Weill Cornell Medical College, New York, NY

Background: ABCA1 (ATP-binding cassette, sub-family A_ABC1_, member 1) is involved in Tangier disease and is known to play a role in cholesterol homeostasis but not in statin treatment. HMGCR (HMGCoA reductase) is the target for statins. We investigated whether variability in these genes may be involved in statin response using the STRENGTH study, (Statin Response Examined by Genetic Haplotype Markers, a pharmacogenetic study of statin efficacy).
Methods: 425 patients with hyperlipidemia were randomly assigned to 8 weeks of treatment with one of three statins: 80mg/day simvastatin (N=148), 80mg/day atorvastatin (N=139) or 40mg/day pravastatin (N=138). We sequenced the ABCA1 and HMGCR genes in 679 hyperlipidemic patients plus 93 other individuals. We constructed haplotype markers from unphased genotypes (Drysdale, et al, PNAS, **97**:19, 2000). Each marker was tested for an association with LDL reduction using ANCOVA models. Permutation tests were used to adjust for the multiple markers considered.
Results: We discovered 179 SNPs including 30 novel, non-synomymous SNPs in ABCA1. We found a significant association between an ABCA1 haplotype marker and LDL reduction by statin treatment (P<0.0001). The association is also seen in the individual statin groups with p-values ranging from 0.04 to 0.003. The marker includes GLU(1192) ASP plus 4 other SNPs. Patients with ≥1 copy of the marker respond with 10% less LDL reduction than those without the marker. There were no differences in baseline lipids or HDL response between individuals based on this marker.
For HMGCR, sequencing in our cohort revealed 51 SNPs. We detected no association between haplotype markers of HMGCR and statin response.
Conclusion: Genes involved in cholesterol and lipid metabolic diseases should be candidates for pharmacogenetic analysis of drug response. Drug targets, although useful for drug screening, may not influence interindividual differences in drug response.

ORAL CONTRIBUTIONS

804 Genetic Determinants of Atherosclerosis

Monday, March 31, 2003, 9:15 a.m.-10:30 a.m.
McCormick Place, Room S103

9:15 a.m.

804-1 **LOX-1 Polymorphism as a Susceptibility Genetic Marker for Atherosclerosis**

Ruggiero Mango, Fabrizio Clementi, Gianmarco Contino, Giovanni B. Forleo, Paola Borgiani, Annalisa Botta, Annamaria Nardone, Gaetano Chiricolo, Massimo Marchei, Alessia Romeo, Sabina Guarino, Clarissa Cola, Maria Rosaria D'Apice, Massimo Federici, Ibrahim Fahdi, Renato Lauro, Francesco Romeo, Giuseppe Novelli, Jawahar L. Mehta, University of Tor Vergata, Rome, Italy, University of Arkansas for Medical Sciences, Little Rock, AR

Background and Objectives: Atherosclerosis is the principal process contributing to the pathogenesis of coronary artery disease (CAD), cerebral infarction, and peripheral vascular disease. A large number of risk factors such as hypertension, hypercholesterolemia, diabetes, obesity, smoking and shear stress leads to endothelial activation and/or dysfunction, which elicit a series of cellular interactions that culminate in atherogenesis. Several biochemical and functional studies suggest that a lectin-like receptor for oxidized low-density-lipoprotein (ox-DL), termed LOX-1, may be involved in atherogenesis. A recent linkage study performed in a mouse model, identified LOX-1 as candidate susceptibility gene for human atherosclerosis. Aim of this study is to investigate the role of the LOX-1 gene in human atherosclerosis susceptibility through association studies in different populations.
Materials and Methods: We screened a group of 164 Italian individuals with angiographic CAD phenotype (CAD; n=88) or without any angiographically demonstrable disease (CAD-free; n=76) and a group of 35 individuals from Arkansas (CAD, n=14; CAD-free, n=21).
Results: We characterized five different SNPs (SNP 1-5) at the LOX-1 locus in these populations. We demonstrated that SNP4 (A to G transition) correlates with CAD with a high degree of specificity in the Italian population (X^2 = 7,37; P, 0.007; 1df) and reproduced this association also in the American group (X^2 =5.11; P, 0.0237; 1df).
Conclusion: On the basis of these data on the prevalence of LOX-1 SNPs in two different angiographically documented CAD populations, we think that LOX-1 may be a potent candidate gene for atherogenesis and endothelial dysfunction in response to ox-LDL.
Work supported by the Italian Ministry of University and Research (MIUR)

9:30 a.m.

804-2 **Genetic Determinants of Nicotine-Induced Angiogenesis**

Edwin Chang, Yan Wang, Hanh M. Bui, Johannes Jacobi, Christopher Heeschen, James J. Jang, John P. Cooke, Stanford University Medical School, Stanford, CA

Background: Nicotine is a potent angiogenic agent which induces tumor angiogenesis and plaque neovascularization. The angiogenic effect of nicotine occurs at concentrations similar to those found in plasma of moderate smokers. Nicotine action is mediated by endothelial nicotinic cholinergic receptors (nAChR). We hypothesize that stimulation of the nAChR activates signal transduction pathways and transcriptional pathways that are distinct from other angiogenic factors. Methods: We identified nicotine-regulated genes by using subtraction hybridization technology to isolate the differentially expressed genes. We also employed high-throughput microarray transcriptional profiling to examine and validate gene expression profiles. Human micro vascular endothelial cells were treated with vehicle or nicotine (10^{-8}M), and were subjected to PCR-selected subtraction hybridization. Results: Nicotine increased proliferative but decreased apoptotic indices in sub confluent proliferating endothelial cells (HUVEC and HCAECs) with respect to untreated cells. Hexamethonium blocked the anti-apoptotic effect of nicotine. In nicotine