low dose ASA alone, the multivariate adjusted significance was 0.01. Conclusion: In a healthy population without known coronary disease, after controlling for major risk factors, the use of ASA and a statin alone remains significantly associated with lower levels of inflammation, and importantly the combination of both a statin and aspirin is a particularly strong independent predictor of lower levels of hs-CRP. These findings suggest that daily statin and aspirin therapy combined may be particularly potent in reducing inflammation in high risk individuals who have not yet had a clinical coronary event.

2:30 p.m.

**847-3**

Aspirin Resistance Is Associated With a Single Nucleotide Polymorphism in the P2Y1, ADP Receptor Gene

Brian K. Jefferson, Jennifer H. Foster, Jeannette J. McCarthy, Kandice Kotke-Marchant, Eric J. Topol, The Cleveland Clinic Foundation, Cleveland, OH, San Diego State University, San Diego, CA

**Background:** Lack of platelet aggregation response to aspirin (AR) has been reported in 5-30% of patients. Using strict criteria for AR, we have shown a threefold increased risk of death, MI and CVA. The underlying mechanisms for the variable effect of aspirin remain unclear and are likely multi-factorial. Polymorphisms in platelet surface receptors may alter the response of platelets to pharmacologic agents and play a role in aspirin sensitivity.

**Methods:** We examined 7 candidate single nucleotide polymorphisms in the COX-1, COX-2, GPIIIa, and P2Y1 (P2RY1) genes in 332 patients with a history of MI from the Gene Quest 2 database. Aspirin resistance was assessed using optical aggregetion in response to arachidonic acid and ADP. Aspirin sensitive (aggregation >20%) and resistant (aggregation <20%) subjects were compared using multiple logistic regression. DNA was genotyped using standard PCR techniques.

**Results:** In the study population, 235 (71%) were classified as aspirin sensitive and 95 (29%) were classified as aspirin resistant. Clinical comparisons between aspirin sensitive and aspirin resistant patients revealed a significant difference between the groups in age (63.3 ± 8.4 y), HDL cholesterol (39 mg/dl/35.6 mg/dl), and incidence of diabetes (22%/37%). Using logistic regression analysis, patients with the P2RY1 C/T893 genotype displayed a statistically significant 3-fold higher risk of aspirin resistance over those with the P2RY1 C/C893 genotype. The risk of aspirin resistance remained even after adjusting for the above confounding variables: Adjusted OR 2.72 (95% C.I. 1.12, 6.57). Single nucleotide polymorphisms in other candidate genes were not associated with aspirin resistance.

**Conclusions:** There are demographic differences between aspirin sensitive and aspirin resistant patients which are in agreement with previous reports. After controlling for these variables, the P2RY1 C/T893 polymorphism is associated with decreased platelet responsiveness to aspirin. Polymorphisms in the P2Y1 receptor gene may provide a genetic link in the variable clinical responsiveness of patients to aspirin and requires confirmation and elucidation of the mechanism.

2:45 p.m.

**847-4**

Asymmetric Dimethylarginine and the Risk of Coronary Heart Disease: Relationship With Traditional Risk Factors As Assessed in the Multicenter CARDIAC STUDY

Rainer H. Boger, Henrik Lenzen, Christoph Hanefeld, Aija Bartling, Karl J. Osterziel, Magda Kusus, Caroline Schmidt-Lucke, Dietrich Stroder, Jürgen Berger, Lilja Goudueva, Andreas Muge, University Hospital Hamburg-Eppendorf, Hamburg, Germany

**Background:** Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of NO synthase. In human subjects, its levels are related to endothelial dysfunction and the progression of carotid atherosclerosis. In patients with end-stage renal disease, ADMA is a strong independent predictor of death. It has been shown that ADMA is associated with chronic heart failure. It is therefore of interest to assess the relationship between ADMA concentrations and the risk for coronary heart disease (CHD) in a large population including subjects with a broad range of established coronary risk factors of both sexes and with normal renal function. We also studied the relationship between ADMA and traditional risk factors in risk determination.

**Methods:** 408 patients with established CHD and 408 controls matched for age and sex were enrolled. Besides traditional risk factors, plasma levels of ADMA and its biologically inactive regioisomer, symmetric dimethylarginine (SDMA), and L-arginine were determined.

**Results:** CHD patients had significantly higher ADMA plasma concentration than controls (median, 0.91 vs. 0.70 µmol/l; p<0.0001). ADMA was an independent predictive factor for the risk of CHD, whereas SDMA was not associated with CHD. ADMA levels significantly increased with increasing number of established cardiovascular risk factors present (p<0.01). The presence of hypertension was associated with significantly higher ADMA levels (median, 0.95 vs. 0.87 µmol/l; p<0.05), whereas hypercholesterolemia was associated with lower ADMA (0.85 vs. 1.03 µmol/l; p<0.05; probably due to the high rate of treated hypercholesterolemia), and diabetes mellitus had no significant effect on ADMA. Former smokers had higher ADMA than current smokers or non-smokers (1.16 vs. 0.70 and 0.88 µmol/l, respectively; p<0.01).

**Conclusions:** The present data show for a large group of subjects of both sexes and with a broad range of established coronary risk factors that ADMA is an independent marker of CHD. Thus, determination of ADMA may help to identify patients at risk for coronary events beyond currently established risk factors.