**RECONSIDERATION OF THE ROLE OF STATINS IN PRIMARY PREVENTION; POTENTIAL OF ADVERSE EFFECT RELATED TO GENETIC VARIABILITY**

**J.L. Mehta**, A. Deshmukh, E. Price

UAMS, Little Rock, AR, USA

Statins have been the cornerstone of therapy of CAD for >10 years with emphasis on high dose. We first drew attention to the rise in fasting plasma glucose (FPG) with statin use based on a follow-up of 345,417 patients from Veterans Affairs VISN 16 database (J Invest Med 2009,57:495). Increase in FPG and HBA1C with statins has been now confirmed in several studies leading to FDA advisory in February 2012. While statins save lives in secondary prevention trials, their use in primary prevention was raised into question by in a meta-analysis (Arch Int Med 2010;170:1024). A 2011 Cochrane review of treatment with statins among persons without documented CAD came to similar conclusions. We believe that the widely variable benefits of statins may relate to genetic variation in pleiotropic anti-inflammatory pathways relating to statins. For example, genetic polymorphisms in the LXRA gene may limit the pleiotropic anti-inflammatory benefits of statins. In a study of 68 patients, we found that individuals with rs12221497 G/A genotype (15% of patients) manifested a pro-inflammatory effect when given atorvastatin. Wild type G/G carriers experienced 11% decrease in CRP while the variant G/A carriers experienced a 25% increase in CRP, p=0.047. In the Cholesterol and Pharmacogenetics (CAP) study wherein 933 subjects were treated with simvastatin, carriers of the rs12221497 G/A genotype (20% of subjects) demonstrated a diminished and more variable CRP response. Since diabetes is an inflammatory disorder, it is possible that patients who developed high FPG while taking statins had the genetic susceptibility- exacerbated by statins.