Genetic Variation in Cyclooxygenase-1 Associates With the Antplatelet Effect of Aspirin in Stable Coronary Artery Disease

Aino Lepantalo, Jussi Mikkelsen, Julio Resendz, Leena Heinonen, Pekka J. Karhunen, Riitta Lassila, Whuuri Research Institute, Helsinki, Finland, University of Tampere, Tampere, Finland

Impaired antithrombotic effect of aspirin may be a risk factor for coronary events in stable coronary artery disease (CAD). The pharmacogenetics of the COX-1, the target of the antithrombotic effect of aspirin, have not been studied previously. In the current series, we have analysed platelet responses in stable CAD patients on aspirin. The platelet responses were determined with optical aggregometry as well as PFA-100. The phenotypes were related to patient characteristics as well as COX-1 genotype. Patients were randomized to 2 groups. Group A received 4 weeks of oral amiodarone: 200mg Tds for 1 week prior to DCCV, then 200mg Tds week 2, 200mg Bd week 3 and 200mg Qd week 4. Group B received placebo. We took blood samples from 101 patients with stable CAD on aspirin (100mg/day). The antplatelet effect of the treatment regimen was studied in whole blood with PFA-100 and in platelet-rich plasma with turbidometric aggregations using arachidonic acid (AA)-induced (12.5 ìmol/L) aggregation to identify the exact response. We used 170s. closure time (CT-CEP) for PFA-100 and aggregation slope of 10%min/100iu for AA as predetermined cut-off points for aspirin response. 7% (AA) and 22% (CT-CEP) of patients were defined as poor aspirin responders. Individuals carrying one 1687A (AA) and/or 2033A (CT-CEP) heterozygous or homozygous variant had shorter mean CT-CEPI (221s., 261s., 81s.) compared to carriers of the common (80%) haplotype (261s., 67s., p<0.03). In addition, platelets of individuals from the rare haplotype group showed more preserved mean AA-induced maximal aggregation (31% ± 5%) compared to the common haplotype (21% ± 1.3%, p<0.02).

We conclude that impaired response to aspirin measured with PFA-100 and aggregometry is common among individuals with angiographically proven severe CAD and is associated with common genetic variation of COX-1.

Short Burst Oral Amodarone Improves Cardioversion Success Rates for Patients in Persistent Atrial Fibrillation

Christopher J. Bogg, Eric Clark, Ranjit S. More, Eric Clark, St. Mary's Hospital, Portsmouth, United Kingdom

Background: Increasing efforts have been made to improve the success rates for external direct-current cardioversion (EDC) for patients in persistent atrial fibrillation (AF). The pharmacogenetics of the COX-1, the target of the antithrombotic effect of aspirin, have not been studied previously. In the current series, we have analysed platelet responses in stable CAD patients on aspirin. The platelet responses were determined with optical aggregometry as well as PFA-100. The phenotypes were related to patient characteristics as well as COX-1 genotype. Patients were randomized to 2 groups. Group A received 4 weeks of oral amiodarone: 200mg Tds for 1 week prior to DCCV, then 200mg Tds week 2, 200mg Bd week 3 and 200mg Qd week 4. Group B received placebo. We took blood samples from 101 patients with stable CAD on aspirin (100mg/day). The antplatelet effect of the treatment regimen was studied in whole blood with PFA-100 and in platelet-rich plasma with turbidometric aggregations using arachidonic acid (AA)-induced (12.5 ìmol/L) aggregation to identify the exact response. We used 170s. closure time (CT-CEP) for PFA-100 and aggregation slope of 10%min/100iu for AA as predetermined cut-off points for aspirin response. 7% (AA) and 22% (CT-CEP) of patients were defined as poor aspirin responders. Individuals carrying one 1687A (AA) and/or 2033A (CT-CEP) heterozygous or homozygous variant had shorter mean CT-CEPI (221s., 261s., 81s.) compared to carriers of the common (80%) haplotype (261s., 67s., p<0.03). In addition, platelets of individuals from the rare haplotype group showed more preserved mean AA-induced maximal aggregation (31% ± 5%) compared to the common haplotype (21% ± 1.3%, p<0.02).

We conclude that impaired response to aspirin measured with PFA-100 and aggregometry is common among individuals with angiographically proven severe CAD and is associated with common genetic variation of COX-1.

Effect of Atorvastatin and Sildenafil on Endothelial Function in Patients With Erectile Dysfunction and Increased Cardiovascular Risk

Giuseppe M. Rosano, Cristiana Vitale, Giuseppe Mercuro, Roberto Patrizi, Giuseppe Marazzi, Elena Cerquati, Massimo Fini, San Raffaele Roma, Roma, Italy, University of Cagliari, Cagliari, Italy

Erectile Dysfunction is often associated with a cluster of risk factors for coronary artery disease and with a reduced endothelial function. Acute administration of phosphodiesterase-5 inhibitors (PDE5) improves endothelial function in patients with ED. Tadalafil is a newer PDE5 inhibitor with a long half life that allows chronic administration and chronic therapy with Tadalafil has been suggested to be beneficial in patients with ED. We hypothesized that chronic therapy with T may improve endothelial function in patients with ED and increased cardiovascular risk. To this end we randomized 32 patients with ED to receive either T 20 mg on alternate days or matching placebo (P) for 1 month. Brachial artery flow-mediated dilation (FMD) was assessed at baseline, at 1 month and at 6 months. At 1 month FMD was significantly improved by T (from 4.2±3.2 to 9.3±3.7%, p=0.01 vs. baseline), but was not affected by P (from 4.1±2.8 to 4.0±3.4%, p=0.09 vs. baseline). At 6 months the benefit in FMD was sustained in patients that received T (9.1±3.9% vs. 4.2±3.2%, p=0.01 vs. baseline; 9.3±3.9% vs. 9.3±3.7%, p=1 month, p=NS) while no changes in FMD were observed in patients randomized to P. In conclusion, chronic therapy with T improves endothelial function. The benefit of this therapy seems to be sustained after discontinuation of therapy. Larger studies are needed in order to assess the clinical implications of this scheme of therapy.