values distributed between 2.0 and 2.9 with the different devices. The 95% confidence limits around any given INR were calculated and are presented in the table.
Conclusion: There is significant device dependent variation in INR determinations with different POC testing technologies that is large enough to have significant clinical impact.

95% Confidence Limits Across Different Test Systems

Upper Limit	1.7	2.3	2.9	3.6	4.8	6.0
INR	1.5	2.0	2.5	3.0	4.0	5.0
Lower Limit	1.2	1.6	2.0	2.3	3.1	3.8

1106-83 Antiplatelet Effects of Angiotensin Converting Enzyme Inhibitors Compared with Aspirin and Clopidogrel: A Pilot Study Using Whole Blood Aggregometry

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Background: Platelet activation and subsequent aggregation play a key role in complications and progression of atherosclerosis. While specific antiplatelet agents work as well-established, effective components in secondary prevention, recent clinical trials showed a decrease in cardiovascular events also for angiotensin converting enzyme (ACE) inhibitors. Therefore, in the present study, we sought to assess the coagulative activity of cardiovascular patients grouped for treatment with either ACE inhibitors, aspirin, clopidogrel/aspirin or none of these medications.
Methods: Blood samples from 223 cardiovascular patients were analyzed by whole-blood aggregometry. Platelet aggregation was determined by the increase in impedance across paired electrodes in response to the aggregatory agents ADP and collagen, resp. These data were regarded for presence/absence of ACE inhibition or antithrombotic medication.
Results: The central finding was that platelet aggregation was attenuated by ACE inhibitors as well as by either aspirin or clopidogrel/aspirin, indicated by a lower impedance increase compared to no medication. With ACE inhibition, platelet aggregation decreased by 36% (p=0.04) following ADP induction. No significant antithrombotic effect was seen with aspirin alone (34%; p=0.10), while decrease in ADP induced platelet aggregation was extensive with clopidogrel/aspirin (90%; p=0.001). After collagen induction, there was a trend to reduced platelet aggregation with ACE inhibitor therapy (14%; p=0.20), whereas inhibition with aspirin was 20% (p=0.02) and that with clopidogrel/aspirin 31% (p=0.04) compared to untreated participants.
Conclusions: These ex vivo data on whole-blood aggregometry provide direct evidence for ACE inhibitors to decrease platelet aggregation, while confirming aspirin and clopidogrel as established antithrombotics. Antiaggregatory effects with ACE inhibition may contribute to the beneficial influence of this drug class on major clinical, cardiovascular endpoints and offer an important therapeutic option in case of aspirin/clopidogrel intolerance.

1106-84 The Effect of Drugs Which Are Known Inducers and Inhibitors of Human Cytochrome P450 3A on the Platelet Inhibitory Activity of Clopidogrel

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Background: Clopidogrel is a prodrug, which is converted to an active drug in the liver by cytochrome P450 (CYP). The metabolite forms a disulfide bond with the platelet ADP receptor, P2cyc. Platelets with a modified receptor are defective in their ability to aggregate. Two studies were undertaken to determine whether the most abundant human CYP, 3A4 activates clopidogrel.
Methods: Study 1. Twenty volunteers had platelet aggregation measured with ADP agonist (Plateletworks™) at baseline and after 6 days of clopidogrel (75 mg). After a 2 week washout period, erythromycin (250 mg qid), a CYP3A4 inhibitor, and rifampin (300 mg bid), a CYP3A4 inducer, were each given to 10 volunteers concomitant with clopidogrel. Platelet aggregation was measured at baseline and 6 days. Study 2. Clopidogrel (450 mg) was given to 5 volunteers and platelet aggregation was measured at baseline and 4 hours. Two weeks later, troleandomycin (500 mg), the most potent CYP3A4 inhibitor, and clopidogrel (450 mg) were both given. Platelet aggregation measurements were repeated at baseline and at 4 hours
Results: Study 1. Erythromycin increased platelet aggregation form 48% to 59% (p=0.005). Rifampin decreased platelet aggregation from 55% to 33% (p=0.001). Study 2. Clopidogrel initially reduced platelet aggregation from 93% to 50% (p=0.02). An erythromycin breath test showed that the addition of troleandomycin completely inhibited CYP3A4 activity: platelet aggregation was reduced from 90% to 60% (p=NS).
Conclusion: These data are consistent with the hypothesis that CYP3A4 in humans mediates the conversion of clopidogrel to an active drug. Therefore, clopidogrel will be susceptible to drug interactions with the numerous medications that are inducers or inhibitors of CYP3A4.

POSTER SESSION

1107 Effects of Statins and Lipid Therapy on Calcium Regulation in Bone and Arteries

Monday, March 18, 2002, Noon-2:00 p.m.
Georgia World Congress Center, Hall G
Presentation Hour: Noon-1:00 p.m.

1107-85 Simvastatin Reduces Bone Turnover in Hypercholesterolemic Subjects Independent of Its Effects on LDL Oxidation and Inflammatory Markers

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Objective: Inflammation has been recognized as a common mechanism underlying pathologic bone resorption and vascular calcification. Retrospective studies indicate that statins reduce bone fracture and coronary calcification. We investigated the effects of short-term (average of 7 and 8 weeks) statin therapy on (1) serum bone markers (bone specific alkaline phosphatase [BAP], osteocalcin [OC], and type I collagen N-telopeptide crosslinks [NTX]), and (2) their relationships to changes in oxidized LDL and selected inflammatory markers (soluble tumor necrosis factor receptors 1 and 2 [TNF R1 and R2], high-sensitivity CRP [hs-CRP].
Methods: 63 (M/F 40/23) healthy nonsmoking adults (mean ± SD, aged 51.0±8.0 y; BMI: 28.5±5.3 kg/m^2) with LDL-C between 130-189 mg/dL were randomized and treated for 8 weeks with placebo (n=17), pravastatin 40 mg/d (n=15), simvastatin 20 mg/d (n=14) or simvastatin 80 mg/d (n=17). Fasting blood samples were acquired twice at baseline, and twice at study completion.
Results: Statin therapy reduced serum BAP (group by time interaction, p= 0.004). Specifically, simvastatin 80 mg reduced BAP (-2.3 U/L, p=0.04), whereas no change was seen with simvastatin 20 mg (-0.08 U/L, p =0.71), pravastatin (+0.51 U/L, p=0.21) or placebo (0.37 U/L, p=0.51). Change in BAP (by one-way ANOVA with Student-Neuman Keuls test) in the simvastatin 80 mg group was different from the other treatment groups (p<0.05). The changes in BAP remained significant after adjustment for age, gender, and BMI. No significant differences were seen in OC or NTX. Reductions in LDL-C correlated with reductions in BAP (rho=0.25, p=0.05) across treatment groups. Statin therapy reduced LDL oxidative susceptibility (p = 0.014); however sTNF R1 and R2 and hs-CRP were unchanged. Reduction in BAP was not correlated with changes in oxidized LDL, or selected inflammatory markers.
Conclusions: Short-term use of high-dose simvastatin lowers the level of the serum bone marker BAP, suggestive of reduced bone turnover. The beneficial effects of high-dose simvastatin were unrelated to changes in LDL oxidation or certain inflammatory pathways.

1107-86 In Vivo Effects of Atorvastatin on Bone Metabolism Is Vitamin D-Dependent

Kouji Kajinami, Noboru Takekoshi, Shinobu Matsui, Hiroichi Tsugawa, Seiyu Kanemitsu, Shinji Okubo, *Kanazawa Medical University, Uchinada-machi, Japan.*

Background: Some studies reported the significant association between statin therapy and reduced risk of fracture or increased bone mineral density. However, others failed to find this association, and clinical evidence potentially related to its mechanism has not been reported.
Methods: To find the clinical variables to predict the effects of statin therapy on bone metabolism, we enrolled 34 patients (mean age 52 years) with heterozygous familial hypercholesterolemia in prospective 24-week treatment with 40 mg/day of atorvastatin. Serum levels of bone specific alkaline phosphatase (BALP) and osteocalcin (OC) were determined as bone formation marker, and urine collagen type 1 crosslinked N-telopeptide (NTx) levels as bone resorption marker, in addition to serum levels of parathyroid hormone and 1.25(OH)2 vitamin D3 (VitD).
Results: After discontinuation of any lipid-modifying therapy for more than 4 weeks, atorvastatin 40 mg/day treatment produced 40% (345 to 208 mg/dl) and 49% (267 to 136 mg/dl) reduction in total and LDL cholesterol levels, and 10% increase (51 to 56 mg/dl) in HDL cholesterol level, respectively. As a whole study group, none of examined markers showed significant alterations during treatment. However, in 14 subjects with higher VitD levels (>50 pg/ml) before treatment, significant increase of BALP (22.4 to 26.6 U/L) and small decrease of NTx (37.6 to 35.0 nMCBE/ml) were observed, whereas remaining 20 subjects with lower VitD levels did not. PTH levels did not produce significant effects on alterations of markers during treatment.
Conclusion: In vivo effects of atorvastatin on bone metabolism appears to be vitamin D-dependent.

1107-87 Maximal Lipid Lowering Therapy Decreases Calcified Plaque Volume and Increases Calcified Plaque Density

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Background: Coronary artery calcification is closely related to the history of elevated blood lipoprotein levels. We investigated the long term effect of maximal lipid lowering intervention on calcified coronary plaque characteristics in patients with familial hypercholesterolemia (FH) using computed tomography (CT).
Methods: Heterozygote FH patients (n=8, mean age: 46±7.6 years) were studied over a time period of 29 months. Patients underwent regularly LDL- apheresis (n=101±21) and received Atorvastatin (80mg/daily). Blood lipoprotein levels were measured at baseline