1026-48 **Increased Serum Levels of Macrophage Migration Inhibitory Factor-Related Protein Is a Sensitive Marker for Acute Coronary Syndrome in Patients With Coronary Artery Disease**

Shoichi Miyamoto, Masaki Ikemoto, Koji Hasegawa, Noritoshi Nagaya, Shun-ichi Tamaki, Kunihisa Miwa, Masatoshi Fujita, *Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan, College of Medical Technology, Kyoto University, Kyoto, Japan.*

Background: In patients with coronary artery disease (CAD), it is important to discriminate acute coronary syndrome (ACS). There is accumulating data that ACS relates to recent activation of inflammation affecting atherosclerotic plaques. Macrophage migration inhibitory factor-related protein (MRP) is a calcium-binding protein (heterodimer), which is expressed in infiltrate macrophages during inflammatory reactions. The purpose of this study was to investigate whether MRP is useful for the diagnosis of ACS. **Methods:** We studied 92 patients with angiographically proven CAD. They comprised two groups [Group ACS, Braunwald's subclass II or III of unstable angina, and acute myocardial infarction, n=53; Group SA, stable angina, n=39]. We purified MRP from human leukocytes and then prepared rabbit monoclonal antibodies against the MRP. Serum concentrations of MRP were measured using a newly-developed enzyme-linked immunosorbent assay system. In addition, we measured serum concentrations of C-reactive protein (CRP). **Results:** There were no significant differences in age, gender and coronary risk factors between the two groups. Serum MRP levels were significantly higher in Group ACS than in Group SA [3.25±3.08 (SD) microgram/ml vs. 0.77±0.31 microgram/ml, $p < 0.0001$]. Serum CRP levels were also significantly higher in Group ACS than in Group SA (3.11±6.14 mg/dl vs. 0.19±0.20 mg/dl, p=0.0039). Sensitivity and specificity of positive serum MRP levels (> 1.2 microgram/ml) for detection of ACS were 84.9% and 89.7%, respectively. On the other hand, sensitivity and specificity of positive serum CRP levels (> 0.5mg/dl) for detection of ACS were 52.8% and 92.3%, respectively. Sensitivity was significantly ($p < 0.05$) higher in the measurements of MRP than in the measurements of CRP, while specificity was comparable in the two markers. **Conclusion:** The measurement of serum MRP levels is useful for the discrimination of ACS in patients with CAD.

POSTER SESSION

1027 Optimizing Medical Therapy Post Myocardial Infarction

Sunday, March 17, 2002, Noon-2:00 p.m.
Georgia World Congress Center, Hall G
Presentation Hour: 1:00 p.m.-2:00 p.m.

1027-38 **A Randomized Comparison of the Effects of Clopidogrel and Aspirin on Thrombotic Variables and C-Reactive Protein Following Myocardial Infarction**

Mark Woodward, Gordon D. Lowe, Lesley M. Francis, Ann Rumley, Stuart Cobbe, *Institute for International Health, University of Sydney, Sydney, Australia, Departments of Medicine and Medical Cardiology, Glasgow, United Kingdom.*

Background: Previous randomised trials have shown clopidogrel to be more efficacious than aspirin in the prevention of ischemic events amongst those at high-risk. The comparative effect of these agents on thrombotic variables and C-reactive protein remains unknown.
Methods: 184 men and women, recruited from hospitals in the United Kingdom, were randomised to 75mg/day of either clopidogrel or aspirin, 3-7 days following a myocardial infarction (MI) in the CADET trial. Treatment was continued for 6 months, with blood samples taken at randomisation, 1, 3 and 6 months for measurement of thrombotic risk factors and C-reactive protein. The study was designed to have 80% power of detecting a 10% reduction in Clauss fibrinogen level.
Results: 46 subjects had a serious adverse event (22% on clopidogrel and 28% on aspirin), of which 8 were deaths (5% and 3%), and a further 11 (5% and 7%) were withdrawn from treatment. 39 (17% and 25%) had a cardiovascular event. One month after treatment both treatment groups had significantly ($p<0.05$) reduced Clauss fibrinogen (reduced, on average, by 20% on clopidogrel and 25% on aspirin), immunonephelometric fibrinogen (14% and 14%), C-reactive protein (90% and 90%), fibrin D-dimer (29% and 26%), von Willebrand factor (23% and 28%) and factor VIII activity (19% and 18%). Only aspirin significantly reduced tissue plasminogen activator antigen (0.4% and 12%). Neither therapy significantly reduced plasma viscosity (0.0% and 1.6%). With the exception of two isolated, marginal chance findings, there were no significant differences ($p>0.05$) between any of these variables between future clinic visits (1 to 3 or 3 to 6 months). There were no significant differences ($p>0.05$) between clopidogrel and aspirin when comparing any of these variables at either 1 or at 6 months, adjusting for baseline differences. Further adjustment for age, sex, blood pressure, smoking, height and weight had no material affect on these results.
Conclusion: Similar reductions in thrombotic risk factors and C-reactive protein following a MI were observed with clopidogrel and with aspirin. The higher efficacy of clopidogrel compared to aspirin may reflect other mechanisms.

1027-39 **Too Little Aspirin for Secondary Prevention in High Risk Patients**

Birgit Frilling, Rudolf Schiele, Anselm Kai Gitt, Steffen Schneider, Ralf Zahn, Jochen Senges, *Staedtisches Klinikum Ludwigshafen, Ludwigshafen, Germany.*

Background: Large trials have shown a significant reduction of vascular mortality in patients(pts) receiving aspirin for secondary prevention after acute myocardial infarction (AMI). About 10% of these pts do not receive aspirin after discharge. Little is known of characteristics and longtime course of these pts.
Methods: MITRA was a prospective multicenter registry of 5370 pts with AMI in Germany with a mean follow-up of 18 months. 977 pts (18%) did not receive aspirin after discharge.
Conclusions: 18% of AMI pts did not receive aspirin at discharge despite few contraindications.The majority of the pts without aspirin were at high risc for cardiovascular events. The longterm mortality of pts without aspirin was almost two times higher than in pts with aspirin.

MITRA 1994-1998

	no aspirin	aspirin	p-value
age > 70 years	48.8%	32.1%	< 0.001
no reperfusion at AMI	54.9%	38.6%	< 0.001
history of AMI	21.4%	14.7%	< 0.001
recent stroke (<3months)	2.0%	0.9%	0.005
diabetes	26.3%	19.8%	< 0.001
peptic ulcer	7.7%	3.2%	< 0.001
heart failure	43.3%	23.6%	< 0.001
renal insufficiency	3.8%	2.3%	< 0.001
mortality (18months)	19.2%	11.2%	< 0.001
non-fatal vascular event	12.8%	7.8%	0.02

1027-40 **Lower Myocardial Infarction Risk From Selective Serotonin Reuptake Inhibitors but Not Other Antidepressants**

William H. Sauer, Jesse A. Berlin, Stephen E. Kimmel, *University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, Center for Clinical Epidemiology and Biostatistics, Philadelphia, Pennsylvania.*

Background: Prior investigations have suggested that selective serotonin reuptake inhibitors (SSRIs) may reduce myocardial infarction (MI) risk, perhaps via attenuation of serotonin-mediated platelet activation or treatment of depression, particularly in smokers. We sought to validate this finding, to examine the effect in non-smokers, and to examine the effects of non-SSRI antidepressants.
Methods: A case-control study of first MI, ages 40 through 75, was conducted among 36 hospitals in a 5-county area during a 26 month period. Cases were patients hospitalized with a first MI, and controls were randomly selected from the same geographic area. Detailed information regarding medication use and other clinical and demographic data were obtained by telephone interview.
Results: 189 SSRI users were identified among the 909 cases and 3,030 controls who participated. After adjustment, using multivariable logistic regression, for age, gender, race, insurance status, exercise, body mass index, number of cigarettes smoked per day, family history, and history of coronary disease, diabetes, hypertension, and hypercholesterolemia, the odds ratio (OR) for MI among SSRI users compared with non-antidepressant users was 0.31 (95% CI: 0.12, 0.78; P=0.01) in smokers and 1.30 (95% CI: 0.78, 2.16; P=0.30) in non-smokers (test for interaction P<0.01). Smokers using SSRIs also had a reduced risk of MI relative to those using non-SSRI antidepressants (P<0.01). These non-SSRI antidepressant users did not have a reduced risk of MI compared to non-antidepressant users among either smokers or non-smokers (adjusted OR for smokers 1.67, CI: 0.79, 3.53; P=0.18; non-smokers 1.20, CI: 0.63, 2.26; P=0.58).
Conclusion: The lower risk of MI associated with SSRI use is limited to smokers, and non-SSRIs are not associated with reduced risk. This suggests that attenuation of platelet activation may be the reason for the association between SSRI use and MI protection. This benefit may be more apparent in smokers because of the altered platelet activity seen in this group.

1027-41 **Effects of Zoloft® on Platelet/Endothelial Biomarkers in Depressed Patients After Acute Coronary Events: Sertraline Anti-Depressant Heart Attack Randomized Trial (SADHART Platelet Substudy)**

Victor Serebruany, Alexander Glassman, Alex Malinin, Ranga Krishnan, Mitch Finkel, Charles Nemeroff, Paul Gurbel, Cathryn Clary, Wilma Harrison, Christopher O'Connor, *Johns Hopkins University, Baltimore, Maryland, Duke University Medical Center, Durham, North Carolina.*

Background: Platelets could represent a missing link between incidence of depression and adverse clinical outcomes in patients after acute cardiovascular syndromes (ACS). However, it is still not clear how modern therapies of mood disorders including selective serotonin reuptake inhibitors (SSRI's) affect platelet function in such patients. We serially assessed release of established platelet/endothelial biomarkers in patients receiving sertraline versus placebo in a frame of the SADHART trial. Methods: Plasma samples (baseline, week 6, and week 16) were collected from 5 sites in the US and Canada from patients treated with Zoloft (n=28), and placebo (n=36). Aspirin and clopidogrel were allowed in this study. Platelet factor 4 (PF4), b-thromboglobulin (bTG), platelet/endothelial cell adhesion molecule-1 (PECAM-1), P-selectin, thromboxane (TxB2), prostacyclin (6-keto-PGF1a), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin were mea-

sured by ELISA. Results: At every time point after baseline for each biomarker measured, patients undergoing treatment with sertraline exhibited substantially less platelet activation than those receiving placebo. These differences reached statistical significance for PF4 (p=0.03), and bTG (p=0.04) at week 4, and for bTG (p=0.02), PECAM-1 (p=0.01), and P-selectin (p=0.02) at week 16 after randomization. There was a trend towards inhibition of prostanoids (TxB2, and 6-keto-PGF1a), and endothelial-released adhesion molecules (VCAM-1, and E-selectin) in patients treated with sertraline as well, although these changes were not significant. Conclusion: Despite aggressive anti-platelet regimens including aspirin and clopidogrel, treatment with sertraline in depressed post-ACS patients is associated with the decreased release of platelet/endothelial biomarkers. Mild antiplatelet properties of SSRI's may represent an attractive additional advantage for using these agents in patients with depression in the context of coronary artery disease and ischemic stroke.

1027-42 The Association of Isosorbide-5-Monitrate to an ACE Inhibitor Started Early After Myocardial Infarction Improves Left Ventricular Structure and Function Over Three Months: The Delapril and Remodelling in Acute Myocardial Infarction (DRAMI) Study

Roberto Latini, Aldo P. Maggioni, Lidia Staszewsky, Violeta Labarta, Paolo Marino, Giovanni Cremonesi, Silvana Gramenzi, Giuseppe Sarcina, Sergio Piras, for the DRAMI Investigators, *Istituto Mario Negri, Milano, Italy, Centro Studi ANMCO, Firenze, Italy.*

Background. ACE inhibitor (ACEi) started early after AMI reduce mortality and morbidity. A subanalysis of the GISSI-3 study suggested additional benefit when a nitrate was associated to the ACEi. DRAMI was a multicenter, randomised, double-blind study to (1) verify whether isosorbide-5-mononitrate (IS5MN) added to an ACEi enhances its beneficial effects on LV remodelling, and (2) assess the tolerability of a new ACEi, delapril (D), in comparison to lisinopril (L).

Methods. 177 patients were randomised to D or L, with IS5MN or placebo (4 groups) within the first 36h of AMI symptoms, if they had at least 7 abnormal ECG leads and/or signs and symptoms of LV dysfunction, in absence of contraindications. Study drugs were given for 3 mos, serial echocardiographic (echo) exams were done at the site and read by a core lab.

Results. At randomization, 37% of the pts were in Killip class II and III, 81% received thrombolytics, 91% aspirin, 43% betablockers, 3-mo incidence of the primary combined endpoint of mortality and serious clinical events was 38.4% and 31.9% in D and L (p=NS) and 35.6% and 35.5% in IS5MN and placebo, 3-mo mortality was 10.2%, without difference between treatments. Mean (+/-SD) differences between 3-mo echo and baseline (D) are shown in the table.

Conclusion. The systematic association of IS5MN to an ACEi significantly improves LV structure and function after AMI vs ACEi+placebo, without an excess of adverse reactions. 3-mo treatment with D or L is well tolerated when started within the first 36h after AMI.

	IS5MN	placebo	p (Wilcoxon)
end diastolic vol	4.2±29.4	17.4±33.5	0.04
end systolic vol	-5.5±19.3	7.5±26.1	0.005
ejection fraction	6.7±8.2	1.9±8.8	0.01

1027-43 Stroke Reduction With Low-Medium Dose Warfarin/ Aspirin Combination Following Myocardial Infarction in the CHAMP Study

Jonathan F. Plehn, Ayumi K. Shintani, Michael D. Ezekowitz, Peter N. Peduzzi, Peter S. Rahko, Louis D. Fiore, for the CHAMP Investigators, *St. Francis Hospital, Roslyn, New York.*

Background: Following myocardial infarction (MI), 5,059 subjects (99% male, mean age=62 ±10 years) were randomly assigned to either: a) warfarin and 81 mg/day of aspirin (WAR) with a target INR=1.5-2.5 or b) aspirin 162 mg/day alone (ASA) in the VA Combination Hemotherapy and Mortality Prevention (CHAMP) Study. As previously reported, all-cause mortality and MI recurrence were unaffected by treatment over a median followup of 36 months. *Because the value of routine, low-moderate level anticoagulation in stroke prevention following MI has been controversial, we assessed the effect of WAR on stroke incidence in CHAMP.*

Results: By intention to treat analysis, subjects randomized to WAR had stroke incidence similar to ASA at 6, 12 or 36 months as indicated by relative risks (RR) and 95% confidence intervals (CI) which were non-significant (RR=0.91, CI 0.55, 0.91; RR=1.0, CI 0.65,1.55; RR=0.89, CI 0.66-1.21, respectively). However, in on-treatment analysis, when stratified by lower and higher INRs (LWAR=<2.0, HWAR=≥2.0), WAR had significant protective and apparent dose-ranging effects. Compared to ASA (n=2,537), LWAR subjects (n=1,301) with mean INR at 6 months=1.5 ± 0.3 experienced 2, 8 and 29 strokes at 6, 12 and 36 months, respectively (RR=0.12, CI 0.03,0.50; RR=0.37, CI 0.17,0.78; RR=0.60, CI 0.39,0.91) while HWAR (n=416) with mean INR =2.4±0.5 had 0 strokes at 6 and 12 months (RR=0.0, CI 0,0 for both) and 5 strokes at 36 months (RR=0.33, CI 0.14,0.82) with first stroke occurrence at 401 days following randomization. Stroke incidence or treatment effect was unrelated to either ECG MI location (anterior/ septal vs. other MIs) or qualitative echo ejection fraction.

Conclusions:1) By on-treatment analysis, low-medium dose warfarin/aspirin combination significantly reduced stroke incidence compared to aspirin throughout the study duration, 2) Stroke reduction associated with WAR was greater when INR=≥ 2.0 and was independent of infarct location or ventricular systolic function.

1027-44 Female Gender Does Not Impact Outcomes in Patients With Postinfarct Left Ventricular Dysfunction Treated With Carvedilol

Willem J. Remme, Henry J. Dargie, Ian Ford, Jose-Luis Lopez Sendon, Norman Sharpe, Antje Blank, on behalf of the CAPRICORN Investigators, *Sticares Foundation, Rotterdam, The Netherlands.*

Background: CAPRICORN, a randomised double blind placebo-controlled study of carvedilol in patients with left ventricular dysfunction after myocardial infarction on ACE inhibition, demonstrated improvement in survival, non-fatal MI and in the combined endpoint of cardiovascular mortality or non-fatal MI or hospitalisation for heart failure. Although conflicting, previous heart failure trials have suggested a sex/beta-blocker interaction. This abstract aims to determine whether gender differences impact on the effects of carvedilol in CAPRICORN. **Methods:** 1959 patients with acute MI and an LV ejection fraction <= 40 % were included in 163 centres in 17 countries. 259 women and 716 men were randomised to carvedilol and 260 and 724 respectively to placebo. Carvedilol did not affect withdrawal rates in either sex. Analyses were done on ITT basis and for time to first event. Mean follow-up was 1.3 years. **Results:** In women carvedilol reduced all-cause mortality by 27 %, HR 0.73 (95 % CI 0.49-1.09) and in men by 22 %, HR 0.78 (0.58-1.06). The second co-primary endpoint all-cause mortality or cardiovascular hospitalisations was reduced in women by 17 %, HR 0.83 (0.63-1.08) and in men by 3 %, HR 0.97 (0.81-1.15). All cause mortality or non-fatal MI was reduced by 32 % (0.46-0.98) in women and by 27 % (0.56-0.95) in men. Non-fatal MI was reduced by 25 % (0.34-1.66) in women and by 47 % (0.32-0.88) in men, whereas the combined endpoint of CV death or non-fatal MI or hospitalisation for heart failure decreased by 15 % (0.62-1.17) in women vs 21 % (0.63-0.98) in men. Hospitalisation for heart failure fell by 11 % (0.58-1.37) in women and by 16 % (0.62-1.13) in men. Interaction p values were all non significant. **Conclusion:** The analysed mortality and morbidity endpoints confirm that carvedilol had comparable effects in women and in men. Although women were underrepresented as in most large scale trials, the consistent findings suggest a uniform protective role for carvedilol irrespective of gender.

POSTER SESSION

1049 ACE Inhibitors/Angiotensin II Receptor Antagonists for Myocardial Protection

Sunday, March 17, 2002, 3:00 p.m.-5:00 p.m.
Georgia World Congress Center, Hall G
Presentation Hour: 4:00 p.m.-5:00 p.m.

1049-31 Effects of Losartan and Quinapril on Myocardial Infarct Size and Endothelial Function

Boqing Zhu, Richard E. Sievers, Amanda E. Browne, Randall J. Lee, Kanu Chattejee, William Grossman, William W. Parmley, *University of California, San Francisco, San Francisco, California.*

Background:We previously showed that the angiotensin II receptor blocker losartan reduced infarct size and arrhythmias in a rat model of ischemia-reperfusion. The angiotensin converting enzyme inhibitor quinapril has a strong affinity for tissue. We evaluated the individual and combined effects of losartan (L) and quinapril (Q) in a rat model of ischemia-reperfusion. Methods: Eighty Sprague-Dawley rats were randomized into 4 groups: one control (C) and three pretreatment groups (L,Q,LQ) which were given 40 mg/kg/day of losartan or/and 2.4 mg/kg/day of quinapril in drinking water for 6 weeks respectively. After pretreatment, rats were subjected to 17 min of LAD occlusion and 120 min of reperfusion with hemodynamic and ECG monitoring. Results: Hemodynamic changes were the same, except group LQ had lower blood pressure. Effective refractory period (ERP) in the 4 groups were similar. Ventricular fibrillation threshold (VFT) in the three pretreatment groups was higher than controls. VF episodes per rat in the three pretreatment groups were lower than controls. Infarct size was significantly reduced by losartan and losartan plus quinapril. Calcium ionophore (A23187) induced endothelium-dependent maximum vasorelaxation (Vasorelax) in groups L and LQ was higher than controls. Conclusions: Six weeks of pretreatment with losartan and/or quinapril reduced arrhythmias; losartan or losartan plus quinapril decreased infarct size and increased endothelium-dependent vasorelaxation.

(*P<0.05, **P<0.01 when compared with the control group)

Groups	VFT(mA)	VF Episodes	Infarct size(%)	Vasorelax(%)
Control (C)	0.36±0.05	2.4±0.2	43±4	-50±7
Losartan (L)	1.27±0.25*	1.6±0.3*	30±6*	-68±9*
Quinapril (Q)	1.23±0.19*	1.1±0.3**	43±3	-64±6
Losartan+Quinapril (LQ)	1.29±0.39*	0.5±0.2**	30±4*	-70±6*