1007-174  Clopidogrel Regulates Platelet, Leukocyte, and Endothelial Interactions in Type 2 Diabetes Mellitus
Javdeep Sarmar, Scott A. Harding, Jehangir Din, Paul Macioca, David E. Newby, Keith A. A. Fox, University of Edinburgh, Edinburgh, United Kingdom

Introduction
Patients with diabetes mellitus have an increased risk of developing atherosclerosis and its sequelae. Atherosclerosis is now recognized to be an inflammatory disease involving multiple interactions between platelets, leukocytes and endothelial cells. We examined whether specific platelet ADP receptor inhibition with the thienopyridine clopidogrel reduced platelet-monocyte binding, monocyte activation and endothelial activation, in patients with type 2 diabetes mellitus.

Methods
Twenty patients with type 2 diabetes mellitus received clopidogrel 75mg daily for 28 days. Platelet surface P-selectin and CD40L ligand (CD40L) expression, monocyte surface CD40 and CD11b expression, platelet-monocyte binding (PMB) and platelet-neutrophil binding (PNB) were assessed by flow cytometry; platelet soluble (s)CD40L and soluble (s)E-selectin were assessed by ELISA; the chemokines RANTES and MCP-1 were assessed by flow cytometric bead array, before and after treatment.

Results
Significant reductions were seen in platelet surface P-selectin (p=0.002), PMB (p=0.007) and PNB (p=0.0025), and also monocyte surface CD40 (p=0.007) and CD11b (p=0.0024) after clopidogrel treatment. No significant change occurred in 

Conclusion
Clopidogrel acts to reduce platelet and leukocyte activation and adhesion in type II Diabetes Mellitus, suggesting a potential anti-inflammatory effect of thienopyridines. The lack of change in sE-selectin and the specific reduction in the platelet-derived chemokine RANTES suggests that these effects are platelet-driven, and not due to altered endothelial function.

1007-175  Antithrombotic Effects of Angiotensin II Receptor Blockade
David A. Vorochheimer, Mohammad Urooj Zafar, Anuragini Pandey, Ida C. Guzman, Jose Rodriguez, Bharathi Reddy, Mitchell A. Cohen, Juan J. Badimon, Mount Sinai Medical Center, New York, NY, AstraZeneca LLP, Wilmington, DE

Background: Angiotensin II accelerates the development and progression of atherosclerosis. Treatment with angiotensin receptor blockers (ARB) can reverse endothelial dysfunction, reduce oxidative stress, and inhibit inflammation. Recent large clinical trials demonstrate that ARB therapy can slow or prevent the progression of coronary artery disease. The clinical trials observed in these trials suggested benefit beyond blood pressure reduction, perhaps via alternate mechanisms. Methods: We used the Badimon perfusion chamber to study the effects of a selective angiotensin II type 1 receptor antagonist (candesartan) on platelet-endothelial wall interaction in 23 patients with cardiovascular disease and chronic stable angina, at baseline and after 6 weeks of treatment. The effects on thrombus formation were assessed in vitro in a flow chamber which mimics the rheologic conditions seen in venous blood and mildly stenotic coronary arteries. Thrombus formation was measured before and after 6 weeks of treatment with candesartan (16mg/day) in addition to other standard treatments for CAD. Results: Baseline demographic features of the population included age 61±11 years, 48% males, with the following CAD risk factors: 78% had hypertension, 62% had diabetes, and 91% had hyperlipidemia. Candesartan reduced systolic (133±20 to 115±12 mm Hg) and diastolic (80±10 to 75±8 mm Hg) blood pressure. Thrombus formation was reduced from 26×106 to 19×106 platelets/mm³, Lfibroblast-like cells/mm², α2-antiplasmin inhibitor complex and D-dimer) were determined. Thromboembolic risk and platelet activity (thrombin-antithrombin III complex and platelet factor 4), thrombotic status (thrombin-antithrombin III complex (TA) and prothrombin fragment F(1+2) and fibrinogen status (plasmin-c2-plasmin inhibitor complex and D-dimer) were determined. Thromboembolic risk and severity of aortic atherosclerosis were evaluated by transesophageal echocardiography. Results: Pts with AF, as a whole, had higher hemostatic markers and severe left atrial spontaneous contrast than those in NSR. F1+2 and fibrinogen markers in pts with severe atherosclerosis (atheroma 5 mm and/or mobile plaque) were significantly elevated as compared with that of pts without severe atherosoma. Particularly, AF pts with severe atherosclerosis showed significantly higher levels of F1+2 and fibrinogen markers than those without atherosclerosis, while markers for platelet activity were not significantly different between AF pts with and without severe atherosclerosis (Figure). Conclusion: Pts with severe atherosclerosis coexist with AF appear to have an increased risk for thromboembolism, and could benefit from more intensive antithrombotic therapy.

1007-176  Elevated Levels of Hemostatic Markers in Patients With Atrial Fibrillation and Aortic Atherosclerosis
Keiko Nakazawa, Tadakazu Hori, Tomoki Kameyama, Noriko Shirokawa, Hidetsugu Asamori, Hiroshi Inoue, Toyama Medical and Pharmaceutical University, Toyama, Japan

Background: Patients (pts) with atrial fibrillation (AF) are at risk for thromboembolism, and their prothrombotic profiles might be associated with coexistent cardiovascular disease, rather than AF alone.

Methods: In 63 pts with AF and 42 pts with normal sinus rhythm (NSR) who underwent transesophageal echocardiography, plasma levels of markers for platelet activity (thromboglobulin and platelet factor 4), thrombotic status (thrombin-antithrombin III complex (TA) and prothrombin fragment F(1+2)) and fibrinogen status (plasmin-c2-plasmin inhibitor complex and D-dimer) were determined. Thromboembolic risk and severity of aortic atherosclerosis were evaluated by transesophageal echocardiography. Results: Pts with AF, as a whole, had higher hemostatic markers and severe left atrial spontaneous contrast than those in NSR. F1+2 and fibrinogen markers in pts with severe atherosclerosis (atheroma ≥5 mm and/or mobile plaque) were significantly elevated as compared with that of pts without severe atheroma. Particularly, AF pts with severe atherosclerosis showed significantly higher levels of F1+2 and fibrinogen markers than those without atherosclerosis, while markers for platelet activity were not significantly different between AF pts with and without severe atherosclerosis (Figure). Conclusion: Pts with severe atherosclerosis coexist with AF appear to have an increased risk for thromboembolism, and could benefit from more intensive antithrombotic therapy.

1007-177  Predictors of Major Hemorrhage Following Initiation of Warfarin Therapy
Henri克 Saint-Jacques, Anne S. Hellkamp, David E. Kandzari, Christopher M. O’Connor, Robert Daly,花开 Kopecky, Anatoly Langer, Vorschere, Patrick T. O’Gara, Valentine Fuster, Robert M. Califf, Robert A. Harrington, Duke Clinical Research Institute, Duke University Medical Center, Durham, NC

Background: Despite documented benefits of oral anticoagulant therapy for patients (pts) at risk for embolic events, use of warfarin remains low mostly secondary to concerns for major hemorrhage (MH). Objective: We identified pts characteristics that predict MH after initiation of a uniform dosing of warfarin. Methods: Among pts in the Courmadin Aspirin Reinfusion Study (CARS) who were randomized to a daily fixed dose of warfarin (1 mg combined with aspirin 80 mg), INR levels were measured at the end of the first week of therapy by a core laboratory using the same thromboplastin reagent (ISI=0.97). MH was defined as intracranial hemorrhage or spontaneous bleeding that required surgical intervention, a decrease in hemoglobin ≤2 g/dl, or sufficient to require transfusion, or bleeding that contributed to death, impaired sight or hearing. Multivariable Cox proportional hazard model was developed to assess the relationship between baseline pts characteristics and MH. Results: MH occurred among 64 out of 2,913 pts over median (25th,75th percentile) = 151 (81, 340) days after initiation of therapy. MH was associated with increasing age, non-white ethnicity, higher INR levels and BMI, and use of aspirin agents. Concomitant use of beta blockers had a protective effect. Conclusion: These data identify important pts characteristics that are predictive of warfarin-associated MH. Clinicians are encouraged to account for these modifiable risk factors and identify high-risk groups when initiating warfarin therapy.

Predictors of major hemorrhage among 2913 patients following initiation of warfarin therapy.

<table>
<thead>
<tr>
<th>Variables</th>
<th>P-value</th>
<th>HR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>0.0001</td>
<td>1.32 (1.17, 1.50) for 5 years increase</td>
</tr>
<tr>
<td>INR</td>
<td>0.0001</td>
<td>1.15 (1.07, 1.23) for 0.5 unit increase</td>
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<tr>
<td>Beta blockers use</td>
<td>0.002</td>
<td>0.45 (0.27, 0.74)</td>
</tr>
<tr>
<td>Non-white race</td>
<td>0.006</td>
<td>0.29 (1.26, 4.16)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.051</td>
<td>1.05 (1.00, 1.09) for each unit increase</td>
</tr>
<tr>
<td>Adrenergic agents</td>
<td>0.061</td>
<td>2.31 (0.96, 5.52)</td>
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