Methods: Platelet aggregation was measured with the point-of-care MICUHLS™ cell counter (ABX Diagnostics, Irvine, CA) and the Plateletwork™ test platform (Helena Laboratories, Beaumont TX) using 20 μM ADP agonist in 20 human healthy volunteers before any drug administration (0 hours) and 4 hours following clopidogrel 450 mg oral administration. Subjets with percent platelet aggregation ≥ 70% at 4 hours after clopi-
dogrel administration were considered to be non-responders. Subjects with percent platelet aggregation < 70% at 4 hours after clopidogrel administration were considered to be responders. In vivo CYP3A4 activity at baseline and 4 hours after clopidogrel was measured by the erythromycin breath test. Results were compared using a two group t-
test.

Results: Twenty-five percent (5/20) of the subjects did not respond to a loading dose of clopidogrel. Platelet aggregation was significantly higher in the non-responders as com-
pared to responders at 4 hours after clopidogrel administration (80 ± 59% vs. 27 ± 20%, p<0.0002). The inhibitory activity of CYP3A4 in the clopidogrel non-responders was lower than in the responders (1.9 ± 0.7% vs. 2.7 ± 1.0% 3HCoCl-exhaled/hour, p=0.15).

Conclusion: This study demonstrates that clopidogrel non-responders exist and that they have lower metabolic activity of CYP3A4. These results, in addition to our previous observation that atorvastatin and potentially other CYP3A4 substrates attenuate the platelet inhibitory activity of clopidogrel, amplifies the importance of determining whether platelet aggregation inhibition targets are being met in individual patients by point-of-care platelet aggregation testing.

1009-118 Effects of Clopidogrel-Aspirin Combination Versus Aspirin Alone on Platelet Aggregation and Major Receptor Expression in Patients With Heart Failure: For the Plavix Use for Treatment of Congestive Heart Failure (PLUTO-CHF) Trial

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Background: Persistent platelet activation may contribute to thrombotic events in patients with congestive heart failure (CHF). Chronic use of platelet inhibitors would therefore represent an independent variable to improve morbidity, mortality and quality of life in this expanding population. We assessed antiplatelet properties of clopidogrel with aspirin (C-A) versus aspirin alone (A) in CHF patients with heightened platelet activity.

Methods: Patients with LVEF < 40%, or CHF symptoms in the setting of preserved systolic function and NYHA Class II-IV were screened. Patients were considered to have platelet aggregation > 80% at 4 hours after clopidogrel administration (80 ± 59% vs. 27 ± 20%, p<0.0002). The inhibitory activity of CYP3A4 in the clopidogrel non-responders was lower than in the responders (1.9 ± 0.7% vs. 2.7 ± 1.0% 3HCoCl-exhaled/hour, p=0.15).

Conclusion: This study demonstrates that clopidogrel non-responders exist and that they have lower metabolic activity of CYP3A4. These results, in addition to our previous observation that atorvastatin and potentially other CYP3A4 substrates attenuate the platelet inhibitory activity of clopidogrel, amplifies the importance of determining whether platelet aggregation inhibition targets are being met in individual patients by point-of-care platelet aggregation testing.

1009-110 Whole Blood Aggregometry as a Potential Method of Detecting Aspirin Resistance

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Background: Much attention has currently being given to the phenomenon of aspirin resistance as a potential cause of therapeutic failure for patients taking this agent. Despite this attention, little is known regarding factors that may predispose to aspirin resistance and how to identify aspirin-resistant patients.

Methods: We studied 13 healthy volunteers (mean ± s.d. age = 25.5 ± 5.9 years) in an open-label study. Each subject received a single oral 325 mg dose of aspirin. Blood samples were drawn at 0, 5, 10, 15, 20, 25, 30, 45, 60, 75, and 90 minutes and at 2, 4, 6, 8, 10, 12, 24, 48, and 72 post-dose to determine the onset of duration of aspirin effect. Platelet aggregation was assessed at each time point using whole blood impedance aggregometry with collagen (1.0 mcg/mL) and arachidonic acid (0.05 mM) as pro-aggregants. The dose of aspirin effect was defined as at least 25% inhibition of aggregation compared to baseline. The duration of aspirin effect was defined as a return of platelet aggregation to 75% of baseline.

Results: The onset of aspirin effect was within 30 minutes for 9 subjects and within 90 minutes for the other 4 subjects in response to collagen. In response to arachidonic acid, the onset of effect was within 30 minutes for 12 subjects and within 45 minutes for 1 subject. By 24 hours, the aspirin effect had worn off in 2 subjects in response to collagen and in 2 additional subjects by 48 hours post-dose. Inhibition of platelet aggregation remained significant and persisted throughout the 72-hour study in all patients.

Conclusion: Whole blood aggregometry may be a useful tool in detecting aspirin resistance. Using this method, we have determined that a 24-hour dosing interval may be insufficient in maintaining the antplatelet effects of aspirin in a significant number of patients. In these patients, twice daily dosing of aspirin may be needed to maintain therapeutic efficacy. Future studies are needed in patients with cardiovascular disease to identify the prevalence of aspirin resistance in this population.

1009-152 Demographic and Clinical Predictors of Excessive Anticoagulation Following Initiation of Warfarin Therapy

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Background: Anticoagulant therapy with warfarin has established efficacy in the prevention of thromboembolic events. However, its potential benefits are limited by the risk of excessive anticoagulation and subsequent serious or fatal hemorrhages. We sought to identify patient characteristics that predict excessive international normalized ratio (INR) response to initiation of a uniform warfarin dosing regimen.

Methods: Among patients (pts) in the Coumadin Aspirin Reinforcement Study (CARS) who were randomized to treatment with warfarin 3mg daily, excessive INR response was defined as INR >4.0 after one week of therapy. The dose of warfarin was fixed, and INR measurements were performed at the end of first week of therapy by a core laboratory using the same thromboplastin reagent (International Sensitivity Index, ISI=0.97). A logistic regression model was used to assess the relationship of baseline characteristics with excessive INR response.

Results: Out of 2,980 treated pts, 167 (5.6%) had an INR >4.0. Pts with excessive INR had significantly lower body weight or were older, of Asian ethnicity, or on fibrillate therapy. Blacks had a much lower risk of excessive INR than other races.

1009-153 Unexpected Amiodarone and Warfarin Interaction at the 17th to 20th Week After the Initiation of Amiodarone

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Background: Amiodarone and warfarin interact and warfarin dose is reduced when amio-
darone is initiated. Whether further adjustments in warfarin dosage can be anticipated is unclear.

Objective: To determine whether and when adjustment of warfarin dosage after initiation of amiodarone is needed.

Method: We retrospectively reviewed Anticoagulation Clinic patients who initiated amio-
darone while on warfarin therapy to determine the timing of amiodarone and warfarin interactions. INR readings were analyzed for 40 weeks after initiation of amiodarone. INR >5.0 were defined as Grade I interactions, INR > upper target but < 5.0 were defined as grade II interactions.

Results: Of 524 patients, 24 had amiodarone started while on warfarin. Fourteen had their warfarin dose reduced when amiodarone was started. After the initiation of ami-
darone, Grade I interaction were observed in 47% (41/87) of clinic visits during the first 8 weeks and 53% (20/38) from the 17th to 20th week. There were 84% (7/87) grade 1 interactions observed during the first 8 weeks and 13% (5/38) Grade I interactions from weeks 17th to 20th week (see figure).

Conclusions: Amiodarone and warfarin interaction was bimodal with peaks in INR dur-
ing the first two months and during the 17th-20th weeks after initiation of amiodarone. In addition to warfarin dose adjustment during initiation of amiodarone, more frequent INR checks may be also necessary 17 to 20 weeks later.