



## THE EFFECT OF ST. JOHN'S WORT ON THE PHARMACODYNAMIC EFFICACY OF CLOPIDOGREL IN HYPORESPONSIVE VOLUNTEERS AND PATIENTS

ACC Poster Contributions

Georgia World Congress Center, Hall B5

Monday, March 15, 2010, 3:30 p.m.-4:30 p.m.

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Session Title: Vascular Biology/Atherosclerosis/Thrombosis/Endothelium

Abstract Category: Vascular Biology/Atherosclerosis/Thrombosis/Endothelium

Presentation Number: 1221-352

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**Background:** High platelet reactivity with suboptimal platelet inhibition during clopidogrel therapy is an independent predictor of ischemic events in coronary stented patients. We evaluated whether supplemental St. John's wort (SJW), a cytochrome P450 (CYP)3A4 and CYP2C19 inducer, enhances the pharmacodynamic efficacy of clopidogrel in clopidogrel hypo-responsive volunteers and stented patients.

**Methods:** Two studies were conducted: 1) a prospective, open-labeled, control study in 10 volunteers, and 2) a randomized, placebo controlled, double blind study in 14 post-coronary stent patients who had a suboptimal antiplatelet response to clopidogrel. Healthy volunteers, after baseline testing and a 7-day washout period, received SJW 300mg TID for 14 days. Platelet aggregation was measured at baseline before and at 2, 4, and 6 hours after a clopidogrel 300mg load and at day-21 (without maintenance therapy) after SJW therapy. The hepatic CYP3A4 metabolic activity was measured by the erythromycin breath test (0 and 4) hours at baseline and day-21. After demonstration of hypo-responsiveness, patients receiving chronic clopidogrel 75mg daily maintenance therapy were randomized to receive SJW or placebo in a 1:1 ratio. Platelet aggregation was measured before and after 14 days of SJW or placebo.

**Results:** In volunteers, SJW treatment decreased platelet aggregation after a 300mg clopidogrel load from  $59\pm 14\%$  at baseline to  $40\pm 15\%$  at 2 hours,  $p = 0.02$ ; from  $56\pm 10\%$  to  $44\pm 13\%$  at 4 hours,  $p < 0.03$ ; and from  $55\pm 14\%$  to  $37\pm 14\%$  at 6 hours,  $p = 0.01$ ; and increased hepatic CYP3A4 metabolic activity from  $2 \pm 0.4\%$  at baseline to  $3 \pm 0.6\%$   $^{14}CO_2$  exhaled/hour after 14 days,  $p = 0.002$ . In patients, SJW therapy decreased platelet reactivity measured by platelet receptor P2Y<sub>12</sub> reaction units ( $222\pm 36$  at baseline vs.  $166\pm 57$  at 14-days,  $p = 0.01$ ), and decreased platelet aggregation ( $65\pm 13\%$  vs.  $41\pm 15\%$ ,  $p = 0.0006$ ).

**Conclusion:** St. John's wort enhances the antiplatelet effect of clopidogrel in hypo-responsive volunteers and patients by induction of the hepatic CYP3A4 isoenzyme. Future studies examining the effect of SJW to enhance the potency of clopidogrel are warranted.