

# St. John's Wort Enhances Clopidogrel Response

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ATLANTA — St. John's wort appears to convert clopidogrel hyporesponders into robust responders.

This raises the intriguing possibility that the herbal therapy might provide a "twofer": enhanced platelet inhibition in clopidogrel (Plavix) hyporesponders, plus a well-studied antidepressant effect that could be of particular value in patients with coronary artery disease, Dr. Wei C. Lau said.

"Depression plays a big role in coronary artery disease, and addressing depression is a big part of our cardiac rehab program. The next step in our



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DR. LAU

research is going to be St. John's wort versus placebo to see if we get a double whammy: a treatment that improves platelet inhibition in patients on clopidogrel while also improving the psyche," added Dr. Lau, director of adult cardiovascular and thoracic anesthesiology at the University of Michigan Cardiovascular Center, Ann Arbor.

It's now well-established that about 20% of clopidogrel-treated patients are low responders to the platelet-inhibiting drug, placing them at increased risk of major thrombotic events related to coronary stenting.

The recommended solutions at this point are to double the maintenance dose from 75 to 150 mg/day, switch to an alternative platelet inhibitor, or add another agent such as cilostazol (Pletal). But doubling the clopidogrel dose raises the associated bleeding risk, while cilostazol is a relatively expensive drug with compliance issues related to its twice-daily dosing. "I think we can do this better with St. John's wort," Dr. Lau said. "It's a dollar a pill once daily."

Clopidogrel is a prodrug activated by the cytochrome P450 isoenzyme. St. John's wort (*Hypericum perforatum*) is a potent inducer of increased metabolic activity of the CYP 3A4 enzyme, with enhanced platelet-inhibiting effects.

Dr. Lau and his coinvestigators, including Dr. Paul A. Gurbel of Johns Hopkins University, Baltimore, measured platelet function in 62 heart patients on chronic maintenance clopidogrel at the standard 75 mg once daily. They identified 19 patients as clopidogrel hyporesponders with suboptimal platelet inhibition. They randomized these 19 patients in double-blind fashion to St. John's wort at 300 mg once daily or placebo for 14 days while continuing on clopidogrel, then repeated the platelet aggregation studies.

Platelet inhibition improved by 20% in the St. John's wort group while remaining unchanged in controls. In an earlier study involving 10 clopidogrel-hyporesponsive healthy volunteers, 2 weeks of St. John's wort at 300 mg thrice daily boosted platelet inhibition by 36%.

St. John's wort's effects on the cytochrome P450 isoenzyme could in theory affect the metabolism of certain other drugs commonly prescribed in

patients with coronary disease. Dr. Lau said that he and his colleagues have demonstrated that, reassuringly, the herbal therapy does not affect LDL cholesterol levels in patients on statins. However, further studies are clearly needed to firmly establish the safety and efficacy of St. John's wort in converting clopidogrel nonresponders to responders, he added.

In an interview, Dr. Lau said the lack of effective Food and Drug Administration

oversight of herbal therapies makes him feel compelled to test every lot of St. John's wort with which he works. He has found, as have others, that concentrations of the active agent often are not as labeled and vary widely from batch to batch with some manufacturers. He has settled on the German Kira brand for its consistency. ■

**Disclosures:** Dr. Lau disclosed having no financial interests relevant to this study.

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<sup>1</sup>Robinson M, Shaw K. Proton Pump Inhibitor Attitudes and Usage: A Patient Survey, P&T April 2002 Vol127, #4:202-206  
<sup>2</sup>Jacobson BC, et al. Who is using chronic acid suppression therapy and why? Am J Gastroenterol 2003;98:151-58  
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