St. John’s Wart Can Reverse Resistance to Clopidogrel

BY BRUCE JANCIN  Denver Bureau

ORLANDO, Fla. — St. John’s wart converts clopidogrel-resist- ing platelets back to responders, Wei C. Lau, M.D., reported at the annual meeting of the American College of Cardiology. The mechanism by which the herbal product enhances clopidogrel’s antiplatelet effect and transforms clopi- dogrel nonresponders into responders lies in the fact that St. John’s wart boosts hepatic cytochrome P450 3A4 metabolic activity. Clopidogrel (Plavix) is activated by this hepatic en- zyme. Individuals having inherently low P450 3A4 activ- ity will show clopi- dogrel resistance. So will patients taking drugs that are cytochrome P450 3A4 inhibitors, ex- plained Dr. Lau, an anesthesiologist at the University of Michigan, Ann Arbor.

He told this newspaper he would recommend using St. John’s wart “with discretion” to convert clopidogrel-resistant pa- tients into responders rather than increasing the dosage of the an- tplatelet agent to 600 mg/day or more, as some physicians now do in an effort to overcome the resis- tance despite the expense and in- creased bleeding risk.

He added that the need for care in using St. John’s wart for this purpose stems from the fact that doing so will speed up the metabol- ism of any other drugs the pa- tient might be taking that are de- pendent upon the cytochrome P450 3A4 enzyme pathway. One such very widely used drug is ator- vastatin. The St. John’s wart:ator- vastatin interaction would render any given dose of the statin equiv- alent to a considerably lesser dose. In an earlier study, he showed that clopidogrel resistance, as de- fined by relative inhibition of adenosine diphosphate–induced platelet aggregation, is quite com- mon. Indeed, in a group of 37 sub- jects, 40% were healthy volunteers and 23 had coronary artery disease, 19% were clopi- dogrel-resistant while another 23% were clopidogrel low responders. Dr. Lau further showed that clopi- dogrel’s antiplatelet effect corre- lated inversely with cytochrome P450 3A4 activity (Circulation 2004;109:166-71).

Having previously observed anecdotally that clopidogrel-resis- tant patients taking St. John’s wart seemed to lose their resistance, Dr. Lau and coinvestigators set about in the new study to find the mechanism of benefit. He had six healthy, clopidogrel-resistant sub- jects take 360 mg of St. John’s wart three times daily for 24 hours. Then he measured platelet aggre- gation by point-of-care whole blood aggregometry prior to a single 450 mg dose of clopidogrel and again 2, 4, and 6 hours later. The subjects were converted to clopidogrel by showing marked enhancement of platelet inhibition at 4 and 6 hours compared with testing done prior to taking St. John’s wart. Moreover, erythromycin breath test measurements of he- patic cytochrome P450 3A4 ac- tivity performed 4 hours after taking clopidogrel showed a greater than 1.5-fold increase in conjunction with the use of St. John’s wart.

Patients on Long-Term Clopidogrel Need Not Stop Drug for Surgery

BY MITCHEL L. ZOLER  Philadelphia Bureau

WASHINGTON — Pa- tients on long-term clopi- dogrel treatment don’t need to stop the drug before surgery, Richard E. Kuntz, M.D., said at a meeting sponsored by the Cardiovascular Research Institute at Washington Hospital Center. “There is growing experi- ence that it’s safe to perform surgery on a patient taking clopidogrel. At our institu- tion, surgeons will operate on these patients. There is no significant difference in morbidity and mortality” during surgery, said Dr. Kuntz, a cardiologist at Brigham and Women’s Hos- pital in Boston.

“Surgeons make more of a big deal about clopidogrel than they need to,” he added. This approach to dealing with patients on long-term treatment with the an- tiplatelet drug clopidogrel (Plavix) was endorsed also by Ron Waksman, M.D., of the division of cardiology at the Washington Hospital Center.

“If we push our surgeons, they’ll do surgery without waiting to stop clopi- dogrel,” said Dr. Waksman, who chaired the meeting.

The issue of when to stop clopidogrel recently became critical for patients who take the medication after they have received drug eluting coronary stents.

A report last year detailed four anecdotal cases of pa- tients who developed clinically significant coronary thrombosis within a drug- eluting stent after their clopi- dogrel and aspirin regimens were stopped (Lancet 2004;364:1519-21). In three of these cases, patients had stopped their antiplatelet medications before under- going surgery.

These reports have made many experts wary about discontinuing the use of aspir- in and clopidogrel in their patients. Although standard prac- tice when placing drug-elut- ing coronary stents is to treat patients with clopidogrel for 2-3 months (for stents) or 6 months (for paclitaxel-eluting stents), Dr. Kuntz recommended continuing the drug even longer.

To prevent stent throm- bosis, patients with a drug- eluting stent should contin- ued clopidogrel “as long as possible, as long as they can afford it,” Dr. Kuntz said.

Intensive Statin Therapy Most Effective in Elderly Patients

BY MITCHEL L. ZOLER  Philadelphia Bureau

ORLANDO, Fla. — Intensive statin treatment produced a bigger benefit in el- derly patients at high risk for coronary artery disease than in younger patients, based on an analysis from the PROVE IT-TIMI 22 study.

Intensive statin treatment that lowered serum levels of LDL cholesterol to less than 70 mg/dL also was safe in elderly patients, leading to no increased rate of liver enzyme or muscle abnormalities, Kausik K. Ray, M.D., reported at the annual meeting of the American College of Cardiology. These findings show that the updated guidelines of the National Cholesterol Edu- cation Program, which suggested low- ering LDL-cholesterol levels to less than 70 mg/dL in patients with a very high risk of coronary disease, are applicable to pa- tients who are aged at least 70 years, said Dr. Ray, a cardiologist at Brigham and Women’s Hospital in Boston.

To assess the role of age in intensive LDL-cholesterol reduction, Dr. Ray and his associates used data collected in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in My- ocardial Infarction 22 (PROVE IT-TIMI 22) trial (N. Engl. J. Med. 2004;350:1495- 504). This study randomized more than 4,000 patients with acute coronary syn- drome to treatment with either an inten- sive (80 mg of atorvastatin daily) or moder- ate (40 mg of pravastatin daily) lipid-lowering regimen, and showed that patients whose LDL-cholesterol levels dropped below 70 mg/dL had better out- comes during 2 years of follow-up com- pared with patients who had higher levels of LDL cholesterol.

The new analysis focused on the 3,784 patients (915 of the total study cohort) who were free from death, MI, or unstable angina 30 days after they started treat- ment. This group included 634 patients aged at least 70 years, and 3,150 patients who were younger than age 70.

During the remaining 23 months of fol- low-up, patients aged 70 or older who were in the intensive-treatment group had a 20% reduced risk of death, MI, or un- stable angina compared with similarly aged patients in the moderate-treatment group.

The benefit from aggressive treatment was virtually identical in younger patients. Those younger than 70 years in the ag- gressive arm had a 21% drop in events compared with similarly aged patients in the moderate-treatment group.

Another way to assess the outcomes was to focus on how patients fared if their LDL-cholesterol level dropped below 70 mg/dL after the first 30 days on treatment, abnormal liver enzymes were not part of which treatment arm the patients were in. By this measure, older patients got more bang for their statin buck than did younger patients.

In contrast, among younger patients, those whose LDL-cholesterol level dropped below 70 mg/dL had a subse- quent 8.1% event rate, compared with a 10.4% rate among younger patients who failed to achieve this LDL-cholesterol tar- get. The difference between these groups was also statistically significant but the abso- lute difference was only 2.3%.

Safety measures were similar in the old- er and younger patients. The incidence of abnormal liver tests, an appar- ent aminotransferase level at three times or more above the upper limit of normal, occurred in 2% of all patients regardless of their age. The incidence of patients taking creatinine kinase, a marker of muscle ab- normalities, was 6% in younger patients and 3% in older patients.