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WHAT'S NEW

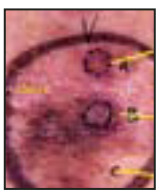
Hiring new staff this year will exempt you from the payroll tax if they were previously unemployed, Dr. Joseph S. Eastern explains. **9**

Hormone therapy statement by the North American Menopause Society has been updated. **16**

Hepatic encephalopathy may be improved with an antibiotic recently approved for that indication. **18**

Turning off the television can help patients lose weight, say Mindful Practice columnists. **27**

Impaired lung function in adults with asthma is linked to low levels of vitamin D. **32**



Partial biopsies of skin lesions can be misleading. **37**

Systemic lupus erythematosus may have link with Epstein-Barr virus. **41**

Stroke rehabilitation targeting the upper extremities may be effective years after the initial event. **43**

Health reform timeline summarizes the changes to come in 2010-2014. **50**

Law & Medicine columnist discusses disclosure of risk. **54**

Common Medications Associated With Reductions in PSA Levels

BY SUSAN LONDON

SAN FRANCISCO — Commonly used medications were associated with clinically important reductions in prostate-specific antigen levels among roughly 2,000 middle-aged and older men in a cross-sectional study.

After 1 year of regular use, PSA levels were 1% lower in users of nonsteroidal anti-inflammatory drugs (NSAIDs), 3% lower in statin users, and—an apparently novel observation—6% lower in thiazide diuretic users, according to data reported at a symposium on genitourinary cancers. The difference in PSA levels among users and nonusers of the common medications increased over time, with reductions of 6%, 13%, and 26% seen with 5 years of regular use of NSAIDs, statins, and thiazide diuretics, respectively.

"If taking these medications alters serum PSA, it could affect the quality of prostate cancer screening," said lead investigator Dr. Steven L. Chang of Stanford (Calif.) University. On the other hand, "perhaps these medications may influence prostate growth."

COURTESY DR. STEVEN L. CHANG

"If taking these medications alters serum PSA, it could affect the quality of prostate cancer screening," said lead investigator Dr. Steven L. Chang.

Using data from the National Health and Nutrition Examination Survey (NHANES) for 2003-2006, the researchers assessed associations between medication use and log-transformed PSA levels in 1,846 men aged 40 years or older who had a serum PSA measurement;

See **PSA Levels** *page 4*

Second Gene Polymorphism Reduces Activity of Clopidogrel

Affected patients 'are at significantly increased risk of recurrent ischemic events.'

BY MITCHEL L. ZOLER

ATLANTA — A second, newly recognized type of metabolic polymorphism has been found to reduce the clinical efficacy of the antiplatelet drug clopidogrel in patients with coronary disease.

In contrast, a similar antiplatelet drug, prasugrel, does not require metabolic conversion to its active form and was not associated with a change in its clinical activity related to this polymorphism, Dr. Jessica L. Mega and her associates reported in a poster at the annual meeting of the American College of Cardiology.

Clopidogrel's activity was previously shown to be affected by a polymorphism in the liver enzyme cytochrome P 2C19, estimated to occur in 2%-14% of the population. This finding formed the basis of a boxed warning imposed by the Food and Drug Administration on clopidogrel's labeling on March 12.

The newly found polymorphism also limits clopidogrel's activity and affects a cell membrane protein that controls drug efflux out of intestinal enterocytes. The homozygous polymorphism enhances efflux, thus interfering with metabolic conversion of clopidogrel. The polymorphism occurred in 27% of more than 2,900 patients with acute coronary syndrome (ACS) enrolled in a recent drug study, said Dr. Mega, a cardiologist at Brigham and Women's Hospital in Boston.

Patients with ACS who are homozygous for the polymorphism, a genotype known as C3435T, "have less platelet inhibition [from clopidogrel] and are at significantly increased risk of recurrent ischemic events in the setting of treatment with clopidogrel," the researchers said.

The analysis used data collected in the TRITON-TIMI 38 study, which com-

See **Clopidogrel** *page 3*

Genotype Poses Risk

Clopidogrel *from page 1*

pared clopidogrel and prasugrel in a randomized trial of more than 13,000 patients with ACS treated with either drug for 15 months after percutaneous coronary intervention (N. Engl. J. Med. 2007;357:2001-15). Dr. Mega and her associates focused on the 2,943 patients who had provided DNA specimens that allowed pharmacogenetic analysis. Their mean age was 60 years, and slightly more than 25% were women.

The incidence of the primary end point—cardiovascular death, myocardial infarction, or stroke—occurred in 13% of patients homozygous for the C3435T genotype who received clopidogrel, compared with incidence rates of 8% in patients on clopidogrel with either of the other two genotype profiles (homozygous for C3435C, or heterozygous with one copy of each genotype).

In a hazard ratio analysis, patients homozygous for C3435T and on clopidogrel had a 72% increased risk for the combined cardiovascular disease end point. These patients had no significant difference in bleeding rates, compared with other patients. Among TRITON-TIMI 38 patients treated with prasugrel who had DNA specimens available, variations in the C3435 genotype had no significant effect on primary end point rates.

Dr. Mega and her associates also studied 287 healthy people who had participated in other clopidogrel and prasugrel studies. A quarter tested homozygous for C3435T, and when they received clopidogrel, their reduction in platelet aggregation underwent an absolute 7% blunting compared with heterozygote people, a significant difference. In this study, too, the homozygous C3435T genotype had no significant impact on the platelet effects of prasugrel. ■

VITALS

Major Finding: Cardiovascular death, myocardial infarction, or stroke occurred in 13% of patients homozygous for the C3435T genotype who received clopidogrel. The rate was 8% in patients on clopidogrel with either of two other genotype profiles (homozygous for C3435C or heterozygous with one copy of each genotype).

Data Source: TRITON-TIMI 38 multicenter study that randomized acute coronary syndrome patients to treatment with clopidogrel or prasugrel and included 2,943 patients with DNA available for pharmacogenetic analysis.

Disclosures: TRITON-TIMI 38 was supported by grants from Daiichi-Sankyo and Eli Lilly. Dr. Mega disclosed financial ties to Bayer Healthcare, Bristol-Myers Squibb, Eli Lilly, Schering-Plough, Johnson & Johnson, and Daiichi Sankyo.

Study Questions Dual-Antiplatelet Therapy After DES

VITALS

Major Finding: In patients who received drug-eluting stents, adverse event rates did not differ significantly between those who stopped clopidogrel after 12 months and then received aspirin only, compared with those who remained on dual therapy with clopidogrel and aspirin.

Data Source: Prospective, multicenter, randomized, controlled study of 2,701 Korean patients.

Disclosures: The study received no industry support. Dr. Park said that he and his associates had no disclosures.

BY MITCHEL L. ZOLER

ATLANTA — Results from a study branded by its principal investigator as underpowered to produce a meaningful result still sparked attention at a major cardiology meeting by fanning the controversy swirling around clopidogrel's role following percutaneous coronary interventions with drug-eluting stents.

The Korean study that tried to test the long-term role of clopidogrel for preventing adverse cardiovascular events following placement of drug-eluting stents (DES) in roughly 2,700 patients "had insufficient statistical power to allow a firm conclusion," Dr. Seung-Jung Park said at the annual meeting of the American College of Cardiology. That fact mitigated what would have otherwise been a highly surprising and troubling finding: More than a year out from coronary stenting, patients treated with aspirin alone fared no worse than and even trended toward better outcomes, compared with patients maintained on dual-antiplatelet therapy with aspirin and clopidogrel.

The underpowered study size might, in other circumstances, have caused the report to be dismissed and quickly forgotten. But two extenuating circumstances instead thrust the study into the spotlight: First, despite its problems, the study simultaneously ran in the New England Journal of Medicine (2010 March 15 [doi:10.1056/NEJMoa1001266]). Second, the report came just days after the Food and Drug Administration on March 12 roiled concerns about clopidogrel's efficacy in patients who recently received a coronary stent by adding a boxed warning to the label of clopidogrel (Plavix) alerting prescribers that certain patients do not metabolize clopidogrel effectively, thereby blunting the drug's efficacy in these people. (See related story, p. 1.) Such "poor metabolizers," the FDA said, comprise an estimated 2%-14% of the American public and perhaps as much as 50% of some Asian populations.

"We see tremendous variability of responsiveness to clopidogrel and aspirin" attributable to genetic differences in features such as the metabolic activation of clopidogrel, said Dr. George D. Dangas, a cardiologist at the Center for Interventional Vascular Therapy at Columbia University in New York. "How can we have a question of [clopidogrel treatment] duration in patients who are not responding? I'm not sure that makes much sense. Perhaps patients in Dr. Park's study were hyporesponders" to clopidogrel.

The Korean study enrolled 2,701 patients who had received at least one DES and had been event free while on combined antiplatelet therapy with aspirin and clopidogrel for at least 12 months. The mean age was 62, and 70% were men. A median of 13 months after stent placement, the patients were randomized to continue on 75 mg clopidogrel plus 100-200 mg aspirin daily, or aspirin alone. Follow-up continued for a median of 19 months, but the total number of end point events remained low—about a quarter of the expected number—probably because the study involved low-risk patients, said Dr. Park, professor of medicine in the Heart Institute at Asan Medical Center in Seoul, South Korea.

The primary end point, the combined rate of MI or cardiac death, occurred in 1.8% of patients on clopidogrel and aspirin and in 1.2% of those on aspirin only, a nonsignificant 65% relative increased risk of events among patients on the dual-antiplatelet regimen vs. aspirin alone.

For two other outcome measures, the worse performance by the combined regimen just missed statistical significance. The combined rate of MI, stroke, or death from any cause occurred in 3.2% of combined-treatment patients and in 1.8% of aspirin-alone controls, and the rate of MI, stroke, or cardiac death tallied in 2.7% of the aspirin plus clopidogrel patients and 1.3% of those on aspirin only. Rates of all-cause death and stent thrombosis were nearly identical in both groups.

Many experts who heard these potentially troubling findings that seemingly cast doubt on clopidogrel's efficacy and safety as well as on prolonged dual-antiplatelet therapy following coronary stenting dismissed the findings as unreliable.

"The answers are not definitive. The lack of power is the primary concern," said Dr. Laura Mauri, chief scientific officer of the Harvard Clinical Research Institute in Boston.

"We won't know [how long to treat these patients with clopidogrel] until we have an adequately powered study," said Dr. Dean J. Kereiakes, CEO of the Ohio Heart Health Center, Cincinnati.

Dr. Dangas agreed that the results were inconclusive, but suggested that they may offer some guidance "until definitive studies come out." The results were "reassuring that perhaps in patients who did well over the first year [following placement of DES], it might be okay to consider taking them off clopidogrel," he said. ■

Disclosures: *Dr. Dangas reported financial relationships with several pharmaceutical and device companies, including Daiichi-Sankyo, Sanofi-Aventis, Boston Scientific, AstraZeneca, and Cordis. Dr. Mauri reported receiving consulting fees or honoraria from Cordis and Medtronic Vascular. Dr. Kereiakes reported financial relationships with Reva Medical, Eli Lilly, Boston Scientific, Cordis, Devax, Abbott Vascular, Amylin, and Daiichi Sankyo, among other drug and device makers.*

MY TAKE

Results Won't Change My Practice

Despite the study's limited power, it generates some interesting hypotheses. Perhaps we need to consider the level of risk that patients face from major adverse events following coronary stenting with DES when evaluating dual-antiplatelet therapy. The new results suggest that in low-risk patients, this balance tips in favor of stopping dual-antiplatelet drug therapy a year after stenting. It's not clear what mechanism might produce the apparent risk from clopidogrel treatment beyond 1 year in this study.

Asian populations have a high prevalence of cytochrome P2C19 genes that produce little or no active enzyme needed to metabolize clopidogrel to its active form. This may mean that many patients in the study were genetically unable to benefit from clopidogrel treatment.

The new results suggesting that some low-risk patients may not benefit from continued clopidogrel treatment are not convincing. I am sufficiently uncertain that I'm not willing to change my practice, even in low-risk patients. My approach has been to have a low threshold for continuing dual-antiplatelet therapy in DES patients. Until now, all data supporting this approach came from observational studies. This is no substitute for prospective, controlled studies, so the Korean study is a laudable first step. What's needed are larger studies with longer follow-up, such as the Dual Antiplatelet Therapy (DAPT) study, with an expected enrollment of more than 20,000 patients.

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