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.

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

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 P450, 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 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.

Pharmacology 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,” the researchers said.

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

Affected patients ‘are at significantly increased risk of recurrent ischemic events.’
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 ei-
ther drug for 15 months after percutaneous coronary in-
tervention (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 phar-
macogenetic analysis. Their mean age was 60 years, and slightly more than 25% were women.

The incidence of the primary end point—cardiovas-
cular death, myocardial infarction, or stroke—occurred in 13% of patients homozygous for the C3435T geno-
type 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 spec-
imens available, variations in the C3435 genotype had no significant effect on primary end point rates. Dr. Mega and her associates also studied 267 healthy people who had participated in other clopidogrel and prasugrel studies. A quarter tested homozygous for C3435T, and when they received clopidogrel, their re-
duction in platelet aggregation underwent an absolute 7% blunting compared with heterozygote people, a sig-
nificant difference. In this study, too, the homozygous C3435T genotype had no significant impact on the platelet effects of prasugrel.

Study Questions Dual-Antiplatelet Therapy After DES

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

Data Source: Prospective, multicenter, ran-
domized, controlled study of 2,701 Korean patients.

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

BY MITCHELL 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 con-
troversy swirling around clopidogrel’s role following percutaneous coronary interventions with drug-eluting stents. The Korean study that tried to test the long-term value of clopidogrel for pre-
venting adverse cardiovascular events fol-
lowing placement of drug-eluting stents (DES) in roughly 2,700 patients “had insuf-
ficient statistical power to allow a firm con-
cclusion,” said Dr. Seung-Jung Park at the an-
nual meeting of the American Col-
lege of Cardiology. That fact mitigated what would have otherwise been a high-
ly 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 re-
port to be dismissed and quickly forgot-
ten. But two extenuating circumstances—first, despite its problems, the study si-
multaneously 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 rozied concerns about clopidogrel’s effi-
cacy in patients who recently received a coronary stent by adding a boxed warn-
ing to the label of clopidogrel (Plavix)

alarming 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 metaboliz-
ers,” 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 vari-
ability of responsiveness to clopidogrel and aspirin” attributable to genetic differences in features such as the metabolic activation of clopidogrel, said Dr. George D. Dan-
gas, a cardiologist at the Center for In-
terventional Vascular Therapy at Co-
lumbia 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 pa-
tients who had received at least one DES and had been event free while on com-
bin ed 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 quar-
ter of the expected number—“probably be-
cause 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 as-
pirin 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 reg-
imen 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 pa-
tients and 1.3% of those on aspirin only. Rates of all-cause death and stent throm-
bo sis were nearly identical in both groups.

Many experts who heard these poten-
tially troubling findings that seemingly cast doubt on clopidogrel’s efficacy and safety as well as on prolonged dual-anti-
platelet 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 of-
er of the Harvard Clinical Research In-
stitute 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 Center, Cincinnati.

Dr. Dangas agreed that the results were inconclusive, but suggested that they may offer some guidance “until definitive stud-
ies come out.” The results were “reassur-
ning 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 serving in consulting fees or honoraria from Cordis and Medtronic Vascular. Dr. Kereiakes reported financial relationships with Reva Medical, Eli Lilly, Boston Scientific, Cordis, Devea, Abbott Vascular, Amynil, and Daiichi Sanyo, among other drug and device makers.

Results Won’t Change My Practice

Despite the study’s limited pow-
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