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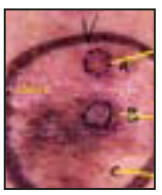

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Common Medications Associated With Reductions in PSA Levels

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;

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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-

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Mechanism Unclear

PSA Levels *from page 1*

did not have a history of prostate cancer, prostatitis, or recent prostate manipulation; and were not taking 5-alpha reductase inhibitors or hormone therapy.

Statins topped the list of the 10 medications most commonly used in the study cohort (taken by 20% of the men), according to study results, which were reported in a poster session.

They were followed by beta-blockers (13%), angiotensin-converting enzyme (ACE) inhibitors (11%), NSAIDs (9%), proton pump inhibitors (9%), calcium channel blockers (6%), selective serotonin reuptake inhibitors (6%), thiazide diuretics (5%), alpha-blockers (4%), and sulfonylureas (4%).

In multivariate analyses, PSA levels after 1 year of regular use were 1% lower in NSAID users ($P = .03$), 3% lower in statin users ($P = .01$), and 6% lower in thiazide diuretic users ($P = .03$), relative to those in the respective nonusers. The remaining medications were not independently associated with PSA levels.

The effects of statins and NSAIDs on PSA have been previously reported, but the finding for thiazide diuretics appears to be new and was somewhat surprising in magnitude, Dr. Chang commented in an interview at the symposium, which was sponsored by the American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Urologic Oncology.

Certain medication combinations also were associated with reduced PSA levels, including fixed-dose combinations of beta-blockers plus thiazide diuretics (6% reduction, $P = .03$) and ACE inhibitors plus thiazide diuretics (7%, $P = .02$), and concurrently used statins and beta-blockers (3%, $P = .03$), statins and ACE inhibitors (3%, $P = .04$), and statins and thiazide diuretics (8%, $P = .002$).

VITALS

Major Finding: NSAIDs, statins, and thiazide diuretics were associated with lower PSA levels of 1%, 3%, and 6%, respectively.

Data Source: 1,846 men aged 40 years or older who completed the National Health and Nutrition Examination Survey for 2003-2006.

Disclosures: Some of the investigators are consultants to Veridex LLC, a manufacturer of diagnostic tests.

Among the combinations, the reduction was greatest for concurrently used statins and thiazide diuretics, with a 36% difference after 5 years of regular use of both medications.

However, the link between statin use and lower PSA levels was minimized or negated in men who were concurrently taking calcium channel blockers, Dr. Chang noted.

"It's unclear as to the true mechanism behind what we are observing here, but it certainly raises a number of questions that should be addressed," Dr. Chang said.

One possibility is that these medications simply reduce PSA levels without influencing the development or growth of prostate cancer.

"In that case, patients who develop prostate cancer would be identified later because their PSA levels would be lower than in others (all other things being equal) who are not on these medications," Dr. Chang observed.

Alternatively, the medications might have some effect on the prostate gland, for example, reducing cancer development or prostate size and thereby lowering PSA levels.

In sum, Dr. Chang concluded, if the observed associations are proved to be causal, "future work is necessary to determine how medication use should be factored into prostate cancer screening. If any of these medications actually affect prostate cells, perhaps they may have a role in prevention or therapy of prostatic diseases." ■

Adoption of New, Costlier Therapies For Prostate Cancer Precedes Evidence

BY SUSAN LONDON

SAN FRANCISCO — The use of new, more expensive therapies for prostate cancer increased rapidly during a recent 4-year period, despite a lack of consensus on their effectiveness relative to that of older, less expensive therapies, researchers reported at a symposium on genitourinary cancers.

In a cross-sectional sample of 58,581 older U.S. men with nonmetastatic prostate cancer, the use of minimally invasive radical prostatectomy rose 19-fold, of intensity-modulated radiation therapy (IMRT) almost 3-fold, and of the combination of brachytherapy plus IMRT roughly 4-fold. The use of older therapies fell correspondingly.

"Despite limited comparative effectiveness data, there was a rapid increase in utilization of these more expensive therapies for prostate cancer," said lead investigator Dr. Paul L. Nguyen. "Potential benefits really must be weighed against the added costs as newer, expensive therapies are introduced."

The researchers used the linked SEER (Surveillance, Epidemiology, and End Results)–Medicare database to identify men aged 65 years or older who received a diagnosis of nonmetastatic prostate cancer between 2002 and 2005 and who were not enrolled in an HMO. Treatments were ascertained by using procedural codes.

The pattern of relative use of treatment modalities remained constant between 2002 and 2005, with external-beam radiation therapy used most commonly, followed by brachytherapy, and then by surgery. But there were major shifts within each modality in the specific therapies used, Dr. Nguyen reported at the symposium, which was sponsored by the American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Urologic Oncology.

Among men who had surgery, the proportion who had minimally invasive (laparoscopic or robotic) radical prostatectomy increased 19-fold, from 1.5% in 2002 to 28.7% in 2005. Meanwhile, the proportion having open prostatectomy fell.

Among men who had external-beam radiation therapy, the proportion who had IMRT almost tripled, from 28.7% to 81.7%. At the same time, the use of 3D-conformal radiation therapy decreased.

Finally, among men who had brachytherapy, the proportion also treated with IMRT roughly quadrupled, from 8.5% to 31.1%. Meanwhile, the proportion receiving brachytherapy plus 3D-conformal radiation therapy fell, and the proportion receiving brachytherapy alone was unchanged, said Dr. Nguyen, director of prostate brachytherapy at the Dana-Farber Cancer Institute and Brigham and Women's Hospital, both in Boston.

Compared with men who had open prostatectomy, men who had minimally invasive radical prostatectomy were more likely to be highly educated, reside in a high-income neighborhood, and live in the Northeast or the West; were more likely to have a high tumor grade, a clinical T1 stage, and limited comorbidity; and were more likely to be Asian and less likely to be black or Hispanic.

All of these factors were also associated with receiving IMRT as opposed to 3D-conformal radiation therapy, except for race/ethnicity. IMRT recipients were more likely to be Asian and more likely to be white, but less likely to be black.

"Comparative effectiveness research into these more expensive therapies has been pretty limited. Certainly, there are no randomized trials that tell us that the more expensive therapy is better than the less expensive therapy," Dr. Nguyen commented.

An analysis suggesting that IMRT is cost effective (Int. J. Radiat. Oncol. Biol. Phys. 2006;66:408-15) was published after the use of this therapy was already widespread. "So we have to ask ourselves, did we do this backwards, because … it was after the fact that we found it was cost effective," he said. "What if we had found out it wasn't?"

The findings have important implications for guiding the use of future technologies, such as proton therapy, Dr. Nguyen observed. "Even if there is a clinical benefit to these more expensive therapies, it's still fair to ask [whether] these benefits [will] outweigh the added costs," he said. ■

Disclosures: *Dr. Nguyen reported having no conflicts of interest related to the study.*

Urethritis Common in Asymptomatic Men

BY MELINDA TANZOLA

ATLANTA — Urethritis is relatively common even in men reporting no urethral symptoms, according to study findings suggesting that routine genital examination may help diagnose unsuspected sexually transmitted diseases.

Of 236 men, aged 16-63, recruited from a Seattle emergency department waiting room who reported having no urethral symptoms, 16% had microscopic evidence of inflammation and nearly half of those men (7% of the total group) had discharge visible upon examination. Another 2% of men had visible discharge without microscopic evidence of inflammation, Catherine M. Wetmore reported at a conference on STD prevention sponsored by the Centers for Disease Control and Prevention.

"Conventional wisdom suggests that women frequently experience asymptomatic reproductive tract infections but that men are generally more aware of potential signs/symptoms of infection," she noted in a statement. Yet urethral discharge was visible in nearly 10% of these men reporting no urethral symptoms. Moreover, 80% of men with visible discharge had microscopic evidence of urethral inflammation (at least five polymorphonuclear neutrophils per high-power field over at least three fields on a urethral gram-stain).

Ms. Wetmore, of the University of Washington, Seattle, and her colleagues also evaluated the incidence of sexually transmitted infections (STIs) in these men. Nearly one in five men (18%) with asymptomatic urethritis, and 4% of men without urethritis, had detectable STIs, including *Mycoplasma genitalium* (9% and 2%), *Chlamydia trachomatis* (8% and 2%), and *Trichomonas vaginalis* (3% and 1%). No cases of gonorrhea were detected.

Patients were an average of 37-39 years old; 52% were African American, 33% were white, 2% were Asian/Pacific Islander, and the remainder were other races.

In a multivariate analysis, factors independently associated with an increased risk of asymptomatic urethritis included having a detected STI, older age, race (African American vs. white), having a greater number of recent sex partners, being uncircumcised, having had recent anal sex, and having voided at least 2 hours before the exam.

Ms. Wetmore noted that her findings suggest that a genital exam may provide an opportunity to diagnose and treat unsuspected sexually transmitted infections. ■

Disclosures: *Ms. Wetmore reported having no conflicts of interest.*