# PHARMACOLOGICAL DIGEST

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## Beta-Blocker Plus Statin Curbs Heart Attack Deaths

People who survive a heart attack but develop heart failure as a result fare better when treated with a beta-blocker or a statin drug. Moreover, combination treatment with both types of drug increases the benefits. 5301 heart attack survivors were enrolled in a clinical trial of various drug treatments. A total of 1971 participants (37 percent) were treated with both statins and beta-blockers, 496 (9 percent) were given statins alone, 2004 (38 percent) received beta-blockers alone, and 830 (16 percent) were given neither treatment. A total of 770 patients died during the following three years, and 726 had another heart attack. Compared with no treatment, statin treatment alone reduced the risk of dying by 26.1 percent, beta-blockers alone yielded a decrease of 30.6 percent, and the combination of statins and beta-blockers cut mortality by 48.3 percent. Based on these findings, the researchers conclude that early initiation of statin and beta-blocker therapy for patients with a heart attack complicated by heart failure can decrease mortality.

*[Am J Cardiol. 2004;93:603-6]*

## Viagra Finds Another Use, for Lung Disease

Viagra can do more than help with erections. The drug is basically a blood-vessel dilator, and this has proven beneficial to people with pulmonary hypertension a condition in which pressure build up in the lungs' circulation can ultimately cause the heart to fail. Viagra significantly improved exercise capacity, the pumping strength of the heart, and quality of life for patients with pulmonary hypertension. Previous reports of Viagra's benefits for such patients came from clinical observations and small un-controlled studies. Viagra is a very effective medication for people with pulmonary hypertension. The researchers randomly assigned 22 patients with pulmonary hypertension to either Viagra at various doses three times daily depending on body weight, or to treatment with an inactive placebo. After six weeks, patients crossed over to the other treatment for the next six weeks. During Viagra treatment, treadmill exercise time increased by 44 percent over the level achieved on placebo. With Viagra, output from the heart also improved significantly. These benefits were accompanied by significant improvements in the breathless and fatigue components of a quality-of-life questionnaire.

*[J Am Coll Cardiol 2004; April 7]*

## Chocolate During Pregnancy has Good Impact on Baby

Eating chocolate is good for the baby. Scientists at the University of Helsinki, who asked 300 pregnant women to record their chocolate consumption and stress levels, found that daily treats had a positive impact on the baby's behavior. Six months after the infants were born the mothers who had eaten chocolate reported more reactions such as smiling and laughter in their offspring. And the babies of stressed women who had regularly consumed chocolate showed less fear of new situations than babies of stressed women who had abstained. The researchers who conducted the research

admitted they can't be certain that chocolate consumption and the babies' behavior are not linked with other factors. But they speculate that the effects they observed could result from chemicals in chocolate associated with positive mood being passed on to the baby in the womb.

*[http://www.reuters.com/newsArticle.jhtml?type=healthNews&storyID=4766985&section=news]*

## Breast Cancer Gene Test Aids Decision-Making

For women with newly diagnosed breast cancer who face a high risk of developing cancer in the other breast, genetic testing for a BRCA mutation helps them decide whether or not to undergo a double mastectomy, a new study shows. However, the high cost of testing and lack of insurance coverage threatens to make timely access to genetic testing an option for the privileged few. Women in whom hereditary breast cancer is suspected be referred for genetic testing. To examine the feasibility of this approach, Dr. Marc D. Schwartz at Georgetown University School of Medicine in Washington, DC, and colleagues studied 194 newly diagnosed patients. These women had at least a 10 percent probability of carrying a mutation in the BRCA1/2 genes that confer a high risk of breast cancer, as determined by personal and family history. Twenty-seven participants declined genetic testing. Positive test results were documented in 31 women. Among those who tested positive, 48 percent chose double mastectomy; that was a significantly higher rate than the 24 percent of those with unclear test results and 4 percent of those who declined testing. The impact of testing on the subsequent treatment decisions suggests that testing should be offered to interested high-risk patients. In some studies the likelihood of subsequent cancer in the other breast approaches 60 percent among mutation carriers. Thus, the choice to undergo bilateral mastectomy rather than breast-conserving surgery could ultimately translate into improved survival for this population of patients. The fiscal and institutional impediments to widespread availability of genetic counseling and testing for all appropriate candidates should not discourage cancer doctors from recommending it, but, rather, should commit us to the elimination of these barriers.

*[J Cli Oncol 2004; May 15]*

## Green Tea Component Kills Leukemia Cells

A component of green tea, epigallocatechin (EGCG), seems to destroy leukemia cells by interrupting a chemical pathway that helps the cells survive. Understanding this mechanism and getting these positive early results give us a lot to work with in terms of offering patients with this disease more effective, easily tolerated therapies earlier. In a previous report, Kay's team had shown that certain cancer cells, known as chronic lymphocytic leukemia cells, release a chemical called vascular endothelial growth factor (VEGF). Coupled with other research, the findings suggested that VEGF helped the cancer cells survive. Since the green tea component has chemical activities that could affect VEGF, the researchers decided to test EGCG on leukemia cells in the lab, according to the report in the medical journal Blood. As anticipated, VEGF did, in fact, help the cancer cells survive. Treatment with EGCG, however, resulted in the death of many cancer cells. Although further studies are needed to clarify how EGCG works, the authors believe that given its relatively nontoxic nature, EGCG could be tested in certain patients with early forms of chronic lymphocytic leukemia.

*[Blood March 2, 2004 online edition]*

## Testosterone Helps Men with Heart Failure

Treatment with the male hormone testosterone appears to improve exercise tolerance and reduce symptoms in men with heart failure. The findings are based

on a study of 20 men with heart failure who were given testosterone or inactive "placebo" injections every 2 weeks for 12 weeks. Treatment with testosterone produced a significant improvement in the distance they could walk. Testosterone therapy also led to dramatic improvements in heart failure symptoms and may have had a beneficial effect on depression. None of these effects was seen with placebo. Treatment with the hormone had no major effect on muscle bulk and strength. Treatment with testosterone appeared to be safe and well tolerated, the authors note. However, one patient in the testosterone group did experience breathlessness after 8 weeks of therapy.

*[Heart, April 2004]*

## Acetaminophen Use Linked to Asthma in Women

Use of acetaminophen (Tylenol and other similar products) has been linked to asthma in several cross-sectional studies. To evaluate the effect of acetaminophen on asthma risk, data from the Nurses Health Study has been following more than 120,000 women. Although the study began in 1976, participants were first asked in 1990 about how often they took acetaminophen, which is known as paracetamol in some parts of the world. During follow-up, 346 women were diagnosed with asthma. As acetaminophen use increased, so did the risk of asthma. Compared with nonusers, women who took the drug on more than 14 days per month were 63 percent more likely to develop asthma. It would be premature to recommend acetaminophen avoidance for patients with asthma, but further research on (lung) responses to acetaminophen is necessary to confirm or refute these findings and to identify subgroups whose asthma may be modified by acetaminophen.

*[Am J Resp Cri Care Med, April 1, 2004]*

## Immune Component Blocks SARS Virus

The virus that causes SARS is susceptible to a natural immune component called interferon-alpha-2b. In contrast, ribavirin, a drug that was use extensively during the SARS outbreaks last year, seems to have no effect against the virus. Two drugs in cells infected with the virus were tested. The cells were a special type that could not produce their own interferon. Interferon-alpha-2b treatment for 72 hours significantly blocked the SARS virus from reproducing itself. Moreover, the amount of interferon needed to achieve this effect would probably be safe in therapeutic doses in humans. Ribavirin, even at high levels for several days, had no apparent effect on the SARS virus, the report indicates. Still, the researchers aren't ready to abandon ribavirin just yet, noting that it's possible the drug may have beneficial effects if given together with interferon. Based on these findings, the researchers believe that human trials of interferon for SARS are warranted.

*[J Infect Dis, April 1, 2004]*

## Genes May Set Response to Antioxidant Vitamins

New research shows that a person's genetic make-up strongly influences his or her response to antioxidants. Theories that antioxidant vitamins protect against atherosclerosis, or hardening of the arteries, have not always panned out in clinical trials. Some studies have even linked antioxidant supplements with a worsening effect on coronary arteries. The new findings focus on the gene for haptoglobin, which is an antioxidant protein that modulates the oxidative effects of hemoglobin in body tissues. Humans have two versions of the haptoglobin gene HP-1 and HP-2. The researchers theorized that differences in how the two types function may explain paradoxical results with antioxidant supplementation. A study of vitamins involving 423 postmenopausal women, of whom 154 had diabetes. The women had

been randomly assigned to combined treatment with vitamin E 400 U and vitamin C 500 mg or placebo. In particular, the researchers looked at 299 participants whose haptoglobin type was determined and who underwent a second study of their coronary arteries about three years after an initial exam. They found that vitamin supplementation had a different effect on artery diameter depending on haptoglobin type, for the whole group and for diabetic subjects. Compared with diabetics taking placebo, the diameter increased in diabetics treated with vitamins E and C who carried the HP-1 type of haptoglobin. However, coronary diameter worsened in those with the HP-2 type. In women without diabetes, HP-1 had a favorable effect, too. The authors think that in the presence of high blood sugar levels, HP-2 haptoglobin converts vitamin C from an antioxidant into a pro-oxidant. If their findings are validated, haptoglobin typing may become a useful tool to identify individuals who will benefit from antioxidant therapy.

*[Diabetes Care April 2004]*

## Cancer Gene Blocker Shows Promise

Cancer researchers today unveiled an experimental drug that curbs the growth of a variety of tumors in animals by suppressing the action of a cancer-related gene, c-Myc. The drug, designated CX-3543, has been a very impressive compound in animal tumor models. The c-Myc gene is active in many types of tumors, and until now had been an undruggable, target. CX-3543 suppresses c-Myc activity by binding to the secondary DNA structures of the gene. CX-3543 also suppresses the growth factor VEGF that promotes formation of blood vessels supplying tumors. In animals grafted with colorectal tumors, CX-3543 produced an 85 percent reduction in c-Myc levels and up to 85 percent reduction in tumor growth, depending on the dose of drug given and when it was administered. In a very difficult to treat pancreatic cancer model, 50 percent to 90 percent of tumor growth was reduced depending on the dose of CX-3543. All of these tumors are largely driven by high levels of c-Myc. CX-3543 represents one exciting advance in taking cancer-specific gene alterations and targeting them. This is a new direction in which cancer therapy must go in the future.

*[http://www.reuters.com/newsArticle.jhtml?type=healthNews&storyID=4724140]*

## Bird Flu Prototype Virus Produced in Lab, WHO Says

A high-security laboratory has created a prototype bird flu, the first step toward making a human vaccine against the potentially deadly new virus. The WHO will give the prototype virus to three drug makers who have expressed interest in producing small sample vaccine batches and carrying out clinical trials. The clinical trials are expected to take several months, but large-scale vaccine production would only begin if a deadly pandemic broke out. Since bird flu erupted in Asia, the United Nations agency has been racing to develop a vaccine to protect humans against the H5N1 strain. Bird flu has killed 26 people in Vietnam and Thailand and decimated poultry stocks across Asia. One laboratory has produced the prototype virus. We have sent a note to vaccine manufacturers that the virus would be ready next week. In January, the WHO asked three high-security collaborating centers to produce a prototype. The three are: the Centers for Disease Control in Atlanta, Georgia, St. Jude Hospital in Memphis, Tennessee and Britain's National Institute for Biological Standards and Control. Initially 11 drug manufacturers had contacted the WHO about producing the vaccine, but only three have confirmed they want to proceed. Bird flu seems to have faded as a concern among manufacturers. They are unwilling to spend a lot of money to make up the clinical batch. Clinical trials will be conducted in the United States.

*[http://www.reuters.com/newsArticle.jhtml?type=healthNews&storyID=4727269]*

## Gum Inflammation Increases During Ovulation

Women who notice higher amounts of gum inflammation during certain times of the month are not imagining things. Investigators found that women tend to have higher levels of gum inflammation while ovulating, and the inflammation tends to decrease during the days before their period, and then fall even further while they are menstruating. Whether or not these changes in inflammation are significant enough to advise women to brush gingerly or avoid certain foods during certain stages of their menstrual cycles remains unclear. During the study, the researchers followed 15 women between the ages of 20 and 50 who scheduled teeth-cleaning visits several times per year. Each visit coincided with a different point in their menstrual cycles. As reported, gum inflammation fluctuated with the menstrual cycle, but the amount of plaque and other indicators of gum health did not. Women tended to report more oral discomfort during the days before or while menstruating - right around the time that their gum inflammation was decreasing. Most gum problems produce no symptoms, so many women would likely not notice if their gums had become slightly more inflamed. Some women may simply have a heightened awareness of their bodies while menstruating, causing them to report more gum symptoms in the days before and during their periods. Women's hormones fluctuate over the course of the month, and these dips and peaks may influence gum inflammation through their effects on blood vessels, white blood cells or the immune system.

*[J Periodontol, March 2004]*

## Oral Ibandronate Effective for Bone Metastases From Breast Cancer

Oral ibandronate, a third-generation bisphosphonate, is effective for treating women with bone metastases from breast cancer. Although intravenous bisphosphonates are the standard of care for metastatic bone disease, some patients suffer from infusion-related adverse events, an increased risk of renal toxicity, and the inconvenience of regular hospital visits. Oral bisphosphonate therapy is more convenient, but its use has been limited by concerns over efficacy and gastrointestinal adverse events. Oral ibandronate (Bondronat) is a highly potent, third-generation aminobisphosphonate. In two pooled phase III studies, women with bone metastases from breast cancer were randomized to receive 50 mg oral ibandronate (n = 287) or placebo (n = 277) once daily for up to 96 weeks. The skeletal morbidity period rate (SMPR), defined as the number of 12-week periods with new skeletal complications, was lower in the ibandronate group than in the placebo group (0.95 vs. 1.18; $P = .004$). The ibandronate group also fared better in terms of the mean number of events requiring radiotherapy (0.73 vs. 0.98; $P < .001$) and events requiring surgery (0.47 vs. 0.53; $P = .037$). Compared with placebo, the ibandronate group had a significant decrease from baseline in bone marker urinary c-telopeptide (CTx), a marker of bone turnover, (median change, -77.3% vs. +11.0%; $P < .001$). Based on multivariate Poisson's regression analysis, the risk of a skeletal event was lower with ibandronate than with placebo (hazard ratio, 0.62; 95% confidence interval, 0.48 - 0.79; $P < .0001$). The ibandronate group had a slightly higher incidence of mild treatment-related upper gastrointestinal adverse events compared with placebo, but there were very few serious drug-related adverse events. Long-term drug safety and tolerability is an important consideration in the selection of treatment for skeletal metastases, due to the high disease-related morbidity burden and the side effects associated with systemic cancer therapy. With its benign renal safety profile, oral ibandronate may be used in patients with existing renal impairment.

*[Br J Cancer. 2004;90:1133-1137]*

## SARS Vaccine Generates Cellular and Humoral Immunity in Mice

A DNA vaccine against the SARS coronavirus (CoV) generates immunity in mice and protects them against infection challenge. It was the first proof of concept to vaccinate and get immune protection against the SARS coronavirus. The research team used cDNA encoding the spike (S) glycoprotein with a truncated cytoplasmic domain, vaccinating mice at baseline, 3 weeks and 6 weeks. They evaluated immune responses 10 days after the final boost. Intracellular levels of interferon-gamma and tumor necrosis factor-alpha were significantly increased, indicating a strong CD4 T-cell response. CD8 cellular immunity was approximately seven times higher than that obtained after a sham vaccine, with neutralizing antibody titres as high as 1:150. The team challenged the mice 30 days after the final vaccination. Two days after intranasal administration of SARS-CoV, viral load in the lungs was > 1 million-fold lower in those with treated with the DNA vaccine, compared with the sham vaccine. Viral titers in the nasal turbinates were 60- to 300-fold lower. Passive transfer from immunized animals of purified IgG, but not T cells, provided immune protection. The authors thus suggest that the antibodies are primarily responsible for defending against SARS CoV infection. Because mice are less susceptible to severe SARS, the human response may be less effective than that observed in the rodents. If so, the vaccine can be readily augmented using prime-boost combinations with inactivated viral vaccine candidates or with adenoviral or poxvirus vectors.

*[Nature 2004;428:561-564]*

## Gene Therapy Shows Promise in Murine MS Model

Injection of transduced proteolipid protein (PLP), secreting fibroblasts into mice with experimental autoimmune encephalomyelitis (EAE) leads to induction of an anti-inflammatory response. In fact, the response was a striking abrogation of both clinical and histological signs of disease. The researchers note that this model bears many of the features of multiple sclerosis (MS) including demyelination and remittance and relapse. The aim of introducing the PLP-secreting fibroblasts was to produce tolerance in the EAE-inducing T cells. The continuous exposure to low levels of myelin-derived antigen ultimately rendered them anergic. The treatment, which was dose dependent, was effective when given after the first or the third relapse. It also protected naive mice from challenge with spinal cord homogenate. The goal was to treat MS patients using an allogeneic human fibroblast cell line confined in implantable chambers. The cells would secrete either our PLP- mini-protein or other myelin-derived epitopes. Furthermore, the advantages of this strategy was to have a universal cell line which can be used to treat all patients and the implant can be removed rapidly should exacerbation occur.

*[Ann Neurol 2004;55:390-399]*

## Carbenoxolone Improves Cognition in the Elderly

Treatment with carbenoxolone is associated with improved verbal fluency and verbal memory in elderly men. Chronic increases in hippocampal glucocorticoid levels have been associated with age-related cognitive impairment. The enzyme 11-beta-hydroxysteroid dehydrogenase type 1 (11B-HSD1) increases glucocorticoid activity in the brain of rats and the team posited that carbenoxolone, an 11B-HSD1 inhibitor derived from licorice root, would protect the brain from glucocorticoid neurotoxicity. They therefore conducted placebo-controlled, crossover studies of carbenoxolone 100 mg three times a day in elderly men. In 10 healthy men ages 55 to 75 years, four weeks of treatment with carbenoxolone improved scores on the Controlled Word Association Test, a measure of verbal fluency. In 12 men with well-controlled type 2 diabetes,

treatment for 6 weeks was associated with improved verbal memory, according the Rey Auditory-Verbal Learning Test scores. Amiloride was co-administered to prevent renal mineralocorticoid excess. There were no adverse effects, and blood pressure, plasma sodium and cortisol did not differ between study phases. The effect magnitude of up to 0.5 SD seem to be a worthwhile, clinically significant attainment. 11B-HSD1 may therefore afford a mechanistically tractable new therapeutic target to prevent or ameliorate age-associated cognitive dysfunction in healthy elderly subjects and in patients with type 2 diabetes.

*[Proc Natl Acad Sci USA 2004, Apr 7]*

## Interferon and Ribavirin Therapy for HCV May Be Too Short

Only about half of patients infected with genotype-1 hepatitis C virus (HCV) respond to treatment with pegylated interferon alpha-2b and ribavirin. In some patients, they suggest, this may be due to an insufficient length of therapy. To investigate, the researchers employed a large database of patients treated with a combination of ribavirin and interferon to generate a model predicting sustained viral response to this treatment. They hypothesized that the longer the virus load was undetectable in serum, the better the odds would be of such a response. Current recommendations are for 48 weeks of therapy. The model predicted that patients infected with HCV genotype 1 required continuous nondetectability of virus load in serum for 36 weeks to attain a 90% probability of a sustained response. Nondetectability for 32 weeks attained an 80% probability of a sustained viral response. The average time to clear serum of genotype-1 virus was 30.4 weeks, which indicates that the 48-week duration of therapy provided a suboptimal probability of a sustained viral response. A prospective trial is needed to prove that failure may be associated with inadequate duration of therapy. However, should this be the case, they conclude that long-term response to this combination treatment could increase by about 14%.

*[J Infect Dis 2004;189:964-970]*

## Nasal Sumatriptan Appears Safe, Effective for Migraine in Children

Nasal sumatriptan appears to be safe and effective for the treatment of migraine in children older than 8 years of age. In a double-blind, placebo-controlled, two-way crossover trial, the researchers examined the efficacy of nasal sumatriptan in children and adolescents with migraine. Included in the study were 129 patients between the ages of 8 and 17 years from three hospital outpatient departments. The patients received a single dose of sumatriptan nasal spray or placebo at home during two attacks. The dose of sumatriptan was 10 mg and 20 mg for body weights of 20 to 39 kg and 40 kg or higher, respectively. The main outcome measure was headache relief by two grades on a five-grade scale after 2 hours of treatment. The primary endpoint was reached by 53 patients (64%) who received sumatriptan and 32 (39%) who received placebo ($p = 0.003$). At 1 hour, headache relief was also more frequent after sumatriptan than after placebo ($p = 0.014$). The difference was even more obvious in patients who received the 20-mg dose as well as in the intention-to-treat analyses. Other endpoints, including child's preference and using rescue medication, also favored sumatriptan. No serious adverse events were observed in the children. The most commonly reported adverse effect was a bad taste after sumatriptan (29%). No differences in adverse effects were seen by age or gender. Because relatively few children under the age of 12 years have been studied, the investigators suggest that more trials are needed to further document the safety of nasal sumatriptan in this age group.

*[Neurology 2004;62:883-887]*

## Calcium Channel Antagonists May Raise MMP-2 Levels

Calcium channel blockers, including felodipine, may increase matrix metalloproteinase (MMP)-2 levels and thereby protect against vascular damage in hypertension. Depressed levels of MMP-2 and MMP-9 in patients with essential hypertension may reflect abnormal extracellular matrix metabolism, which may account for the vascular fibrosis that often accompanies arterial hypertension. The researchers investigated whether 6 months of treatment with felodipine or diltiazem influenced plasma levels of MMP-2 and MMP-9 in 72 hypertensive patients. Before treatment, mean MMP-2 and MMP-9 levels were significantly lower in the hypertensive patients than in a control group of normotensive controls. Treatment with either felodipine or diltiazem was associated with normalization of blood pressure and systemic vascular resistance, the results indicate. Treatment with felodipine brought increases in MMP-2 levels but no significant change in MMP-9 levels, the report indicates. In contrast, the researchers note, treatment with diltiazem had no significant effect on either MMP-2 or MMP-9 levels. Multiple linear regression analysis failed to identify any variable (other than treatment) that was associated with MMP-2 or MMP-9 levels. Further studies of the effect of different classes of antihypertensive drugs on MMP activity could contribute to a better understanding of the effect of antihypertensive medical treatment on the chronic process of vascular remodeling in arterial hypertension. Nonetheless, the issue of whether a possible beneficial vascular protective effect of some antihypertensive agents could be translated into improved outcome in hypertension, beyond the effect of lowering blood pressure, has not yet been clarified.

*[Am J Hypertens 2004;17:273-276]*

## Aspirin Curbs Daily Life Ischemia Via Platelet/Thrombin/Cytokine Inhibition

In patients with daily life ischemia, 300 mg of aspirin daily reduces the number and duration of ischemic events through the combined inhibition of platelet activation, thrombin generation, and the inflammatory procoagulant cytokine, macrophage colony stimulating factor (MCSF). The investigators note that these findings are clinically relevant, as daily life ischemia and MCSF plasma concentrations, are both known to predict adverse outcomes in individuals with chronic coronary artery disease (CAD). In the trial, The investigators treated 40 patients with chronic stable CAD and demonstrable ischemia on 48-hour Holter monitoring with 300 mg aspirin or placebo daily for 3 weeks in a double-blind crossover fashion. The total number of ischemic episodes fell from 339 during placebo to 251 during aspirin treatment and the total duration of episodes fell from 1765 minutes to 1305 minutes ($p<0.01$ for both). Aspirin therapy also significantly reduced systemic concentrations of key hemostatic and inflammatory markers, namely urinary thromboxane B2 (TxB2), the thromboxane metabolite, 11-dehydro-TxB2, plasma prothrombin fragment F1+2, MCSF, and interleukin (IL)-6 ($p < 0.05$ for all). Excretion of 11-dehydro-TxB2 with and without aspirin was related to MCSF levels ($p < 0.01$), and the percentage decline of MCSF with aspirin therapy correlated with the reduction in 11-dehydrdo-TxB2 ($p < 0.05$) and with the decline in ischemic burden compared with placebo ($p < 0.05$). Daily life ischemia in addition to platelet activation, thrombin generation and inflammation are determinants of prognosis, and thus their reduction by 300 mg of aspirin may prevent transient coronary flow reductions and improve long term prognosis in this group of patients.

*[Heart 2004;90:389-393]*

## Inhaled Corticosteroids May Increase Nonvertebral Fracture Risk

Patients with chronic obstructive pulmonary disease (COPD) who use high doses of inhaled corticosteroids (ICS) have an increased risk of nonvertebral fractures compared with those who do not use ICS. Patients with COPD are frequently treated with ICS. However, the impact of ICS use on fracture risk remains unclear in these patients. The authors cite earlier research showing negative effects of ICS on biochemical markers of bone turnover and increased fracture risk in patients with COPD independent of ICS use. From a cohort of 40,157 Veterans Affairs patients with a new diagnosis of COPD between Oct. 1, 1998. and Sept. 30, 1999, who were treated during a one-year follow-up, the investigators identified 1,708 cases with nonvertebral fractures and matched them to 6,817 control patients. Average age was 62.7 years, and 94% of patients were male. Prescription records were used to quantitate ICS exposure and to convert it to beclametbasone equivalents. Conditional logistic regression models revealed that exposure to ICS at any time during follow-up was not associated with an increased fracture risk (adjusted odds ratio [OR], 0.97; 95% confidence interval [CI], 0.84 - 1.11). However, the risk of fracture was increased in current users of high-dose ICS (at least 700 µg daily) compared with patients with no exposure (adjusted OR, 1.68; 95% CI, 1.10 - 2.57). In patients with COPD, current use of high-dose ICS was associated with an increased risk of nonvertebral fractures. The increase in the risk of fracture associated with ICS use found in this study does not by itself warrant the stopping of treatment in patients with COPD. However, evidence from this and other epidemiologic studies of ICS dose and the risk of fractures indicate that providers should consider prescribing the lowest effective dose of ICS in the management of COPD.

*[Am J Respir Crit Care Med. 2004;169:855-859]*

## Non-Aspirin NSAIDs May Be Cardioprotective

The use of non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) appears to reduce the risk of myocardial infarction (MI) in patients not taking prophylactic aspirin. However, they do not seem to provide any extra protection to aspirin users. In fact, NSAIDs may reduce the risk of MI, but they should not be used for this purpose. Only aspirin should be used to specifically prevent MI. The researchers examined the effects of such agents, particularly ibuprofen, on MI risk, in the presence or absence of aspirin. They conducted a case-control study. This involved more than 1000 subjects who had had a first nonfatal MI and about four times as many controls. In nonusers of aspirin, NSAIDs led to a significant reduction in MI risk (adjusted odds ratio 0.53). Results were similar with both ibuprofen and naproxen. For those using aspirin, but not non-aspirin NSAIDs, the corresponding odds ratio was 0.79. However, using both aspirin and non-aspirin NSAIDs did not appear to provide increased protection. Moreover, in those who took non-aspirin NSAIDs at least four times a week, the corresponding odds ratio for aspirin versus no aspirin use was 2.04. The outcome was similar when ibuprofen and aspirin use was considered. Nevertheless, the researchers note that confidence intervals were very wide and thus the findings cannot definitively determine the cardiac risk in such combination users in general or ibuprofen users in particular. Overall, the fact that such agents could reduce the risk of MI may be important to factor into the decision process for the choice of pain relievers and arthritis medications when balanced against the risk of bleeding complications from these drugs. Additional studies, the team concludes, are needed to determine the clinical impact of using the drugs along with aspirin for cardioprotection. In an accompanying editorial, Drs. Jeptha P. Curtis and Harlan M. Krumholz of Yale University School of Medicine, New Haven, Connecticut,

agree that the issue is not resolved. They point out however that in patients who have a strong preference for ibuprofen and a need for aspirin, it is reasonable to reassure them that the preponderance of the evidence does not clearly demonstrate that this combination is harmful.

*[Am J Coll Cardiol 2004;43:985-993]*

## Antimicrobial Therapy for Endometritis Appears Effective

Results of a prospective study support the antimicrobial treatment of subacute endometritis and indicate that prior pelvic inflammatory disease (PID) as well as current cervical infection is a risk factor for endometritis. The researchers analyzed endometrial biopsies from 207 women at risk for endometritis. Thirty-seven (18%) had histologic evidence of the condition. In this study, as in others, both Chlamydia trachomatis and Neisseria gonorrhoeae were more common in women with (43% of 37) than without (25% of 170) endometritis. However, a new finding is that histologic endometritis was more common among women with prior PID, both in the group with (43%) but also in those without (28%) cervical C. trachomatis or N. gonorrhoeae infection. In women without prior PID, endometritis was present in 23% with and 12% without current C. trachomatis or N. gonorrhoeae infection. In the treatment trial, 153 of the women with histologic endometritis but without clinical evidence of current PID received oral cefixime 400 mg, azithromycin 1 g, and metronidazole 500 mg twice daily for 7 days. After antimicrobial treatment, significant reductions occurred in abnormal bleeding, mucopurulent cervicitis, uterine tenderness, and histologic endometritis. Endometritis was reduced in all groups. Although the treatment results are encouraging, the authors note that all subjects received antimicrobial therapy. It is possible that the histologic endometritis would clear after menses without antimicrobials.

*[Am J Obstet Gynecol 2004;190:305-313]*

## U.S. Consumer Group Calls for Lipid-Lowering Drug Crestor to Be Banned

A consumer group asked the U.S. government to ban AstraZeneca's cholesterol-lowering statin drug "Crestor", citing reports of dangerous reactions and one death. Crestor (rosuvastatin) was introduced in Canada in February 2003 and in Europe in March 2003. The drug hit the U.S. market in September. Since the drug's launch, seven patients who took it developed life-threatening rhabdomyolysis, and nine experienced kidney failure or damage. One 39-year-old U.S. woman died from kidney damage and rhabdomyolysis, a known side effect of Crestor and other statins. Cases of rhabdomyolysis led to the 2001 withdrawal of Bayer AG's Baycol, which was linked to more than 100 deaths. AstraZeneca spokesman provided the information that more than 1 million patients have taken Crestor, and side effects so far "totally mirror the experience" in the company's clinical trials that supported Crestor's approval. The drug's risks are comparable to other statins. While both the muscle and kidney problems were seen in premarketing trials of Crestor, the FDA concluded the drug's benefits outweighed its risks at doses of 5 to 40 milligrams. Safety concerns had led AstraZeneca to drop plans to market an 80-milligram dose. Public Citizen, which had urged the FDA not to approve Crestor in the first place, said the post-marketing information showed serious side effects occurred even in patients taking the lower doses.

*[http://www.reuters.com/newsArticle.jhtml?type=healthNews&storyID=4459144&section=news]*