

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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CLINICAL PRACTICE

Low-Dose Aspirin in Primary Prevention of Cardiovascular Disease in Women

The final results of the Women's Health Study, a 10-year trial involving nearly 40,000 healthy women aged 45 and older, show that low-dose aspirin (100 mg every other day) has no significant effect on preventing first heart attacks [*N Engl J Med* 2005; Ridker PM]. In contrast, studies in men free of heart disease demonstrate a decided benefit and have prompted millions of healthy men to take regular doses of aspirin for primary prevention. Millions of women have been doing the same on faith. There is no longer a basis for this faith.

During the study, 477 major cardiovascular events were confirmed in the aspirin group as compared with 533 in the placebo group. The 9% relative difference between the groups was not statistically significant. The absolute difference was merely 0.23%. With regard to individual endpoints, there was a 17% relative reduction in the risk of stroke in the aspirin group, as compared with the placebo group, as a result of a 34% reduction in the risk of ischemic stroke, corresponding to an absolute risk reduction of 0.26%. Aspirin had no significant effect on the risk of fatal or nonfatal myocardial infarction or death from cardiovascular causes. Gastrointestinal bleeding requiring transfusion was more frequent in the aspirin group than in the placebo group (relative risk, 1.40; absolute increase in risk, 0.18%). Subgroup analysis showed that aspirin significantly reduced the risk of major cardiovascular events, ischemic stroke, and myocardial infarction among women 65 years of age or older.

How do these findings compare with those in men? A key trial, The Physicians' Health Study, showed that aspirin significantly reduced the risk of myocardial infarction by 44% in healthy men 50 years of age or older. There was no significant effect on stroke. The study in men used a higher dose of aspirin, 325 mg, every other day, and the risk of myocardial infarction in the placebo groups were more than four times higher in men than in women. Furthermore, a span of more than 20 years separated the studies.

A related editorial suggests that "for now it would appear reasonable to avoid prescribing "low-dose" aspirin... as a preventative measure for coronary disease in women under the age of 65 years." The author adds, "The decision to prescribe aspirin for the primary prevention of stroke and other vascular events should be left to the patient and her physician" [*Ibid*, 2005;352:1293-304].

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CLINICAL PRACTICE (continued)

Blacks with Asthma Display Decreased Steroid Responsiveness

Black subjects—those who have asthma as well as those with normal pulmonary function—appear to be less responsive to corticosteroids than their white peers. This observation may help explain the increased morbidity and mortality seen in black patients [Covar RA, *Chest* 2005;127:571-78]. A press release issued by the lead author stated, “Regardless of asthma status or severity, African-Americans in our study required higher doses of a glucocorticoid than Caucasians to inhibit proliferation of T lympho-

cytes” [*Reuters Health*, 8 February 2005].

The findings derive from a study of 395 asthmatics and 202 nonasthmatic controls who underwent tests to assess corticosteroid responsiveness. Among the asthmatics, 27% were black, while among the nonasthmatics, 52% were black. Thus, black patients with inadequately controlled asthma on standard doses of inhaled glucocorticoid may require higher doses or the addition of other agents.

Preventive Antiretroviral Use Expands Outside Work Setting

According to a recent report in *JAMA* [2005; 293:1177-78], “After years of uncertainty, the U.S. government has determined that sufficient evidence exists to sanction the use of antiretroviral drugs to prevent HIV infection following nonoccupational exposure to the virus.” Issued in January, the guidelines are intended for use in limited circumstances, when the risk of transmission is substantial. The circumstances include exposure to HIV during sexual assault, a non-occupational needle stick, or an infrequent lapse of safer sex practices. Preventive antiretroviral use is not intended for individuals who are at high ongoing risk.

The guidelines recommend a 28-day triple drug regimen initiated within 72 hours of exposure. They suggest several drugs that might be used in combina-

tion but advise against using nevirapine because it may cause liver toxicity. The Nonoccupational Postexposure Prophylaxis (nPEP) guidelines are available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5402a1.htm>. Guidelines on recommended antiretroviral regimens are available at <http://aidsinfo.nih.gov/guidelines>.

The *JAMA* report notes that the most direct evidence of nPEP’s effectiveness is a case-control study of health workers with occupational exposure. Prophylaxis reduced the risk of infection by 81% [*N Engl J Med* 1997;337:1485-90]. Postexposure prophylaxis has been recommended since 1996 for health care workers with occupational exposure. Expanding that strategy to nonoccupational exposure has been controversial.

Computer Alert Reduces Venous Thromboembolism among Hospitalized Patients

A computer alert system warning that a particular patient is at high risk for venous thromboembolism has been shown to strikingly reduce the occurrence of deep-vein thrombosis (DVT) and pulmonary embolism (PE) among hospitalized patients [*N Engl J Med* 2005;352:969-77].

The investigators developed a computer program linked to a patient database to identify consecutive hospitalized patients at risk for DVT in the absence of prophylaxis. The major risk factors were cancer, prior venous thromboembolism, and hypercoagulability. Major surgery was an intermediate risk factor and advanced age, obesity, bed rest, and the use of hormone-replacement therapy or oral contraceptives were minor risk factors. Patients who had a least one major risk factor and

at least one intermediate or minor risk factor were eligible for the study. In the absence of a major risk factor, patients who had major surgery and at least two minor risk factors were also eligible.

The program randomly assigned 1255 eligible patients to an intervention group, in which the responsible physician was alerted to the risk of DVT, and 1251 patients to a control group, in which no alert was issued. More patients in the intervention group than in the control group received mechanical intervention (10% vs. 1.5%) or pharmacologic prophylaxis with heparin, enoxaparin, or warfarin (23.6% vs. 13.0%). A clinically diagnosed, objectively confirmed DVT or PE

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Computer Alert Reduces Venous Thromboembolism (continued)

at 90 days occurred in 4.9% of patients in the intervention group, as compared with 8.2% in the control group, a risk reduction of 43%. The findings suggest

that the intervention needs to be used in just 30 patients to prevent one case of DVT or PE [*Ibid*, 1034-36].

NEW DRUGS AND INDICATIONS

Symlin: Adjuvant Treatment for Diabetes

Symlin (pramlintide) injection has received approval for the control of blood sugar in adults with type 1 or type 2 diabetes. The novel agent is only to be used in addition to mealtime insulin therapy in patients who do not achieve adequate control of blood glucose levels with insulin therapy alone. It is the first adjuvant ever approved for the treatment of type 1 diabetes [*MD Consult*, 18 March 2005].

Studies in about 5300 patients with both types of diabetes served as the basis for approval. Overall, *Symlin* treatment administered before meals was associated with better control of blood glucose and with weight loss. The self-administered injection, given prior to meals, helps patients achieve lower blood glucose after meals, leading to less fluctuation during the day, and better long-term glucose control (HbA1c) compared

with patients taking insulin alone. On average, patients in these studies used less mealtime insulin.

Pramlintide is a synthetic analog of human amylin, a naturally occurring hormone that is made in the beta cells of the pancreas. In patients with type 2 diabetes who use insulin, and in patients with type 1 diabetes, those cells are either damaged or destroyed, resulting in reduced secretion of both insulin and amylin after meals.

The principal risk associated with *Symlin* therapy is severe hypoglycemia; the risk is greater in patients with type 1 diabetes. The drug should not be prescribed for patients who cannot sense when their blood glucose is low or if they have gastroparesis. *Symlin* has not been evaluated in children.

New Vaccine for Meningitis

According to a news report in *JAMA*, the licensing of a new meningococcal conjugate vaccine has prompted the government to expand recommended immunization practices. The new vaccine is expected to substantially reduce the prevalence of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups that comprise most of the cases in the U.S. [*JAMA* 2005;293:1433-34].

A Centers for Disease Control and Prevention advisory panel recommends that children aged 11 and 12 years, teens entering high school, and college freshman living in dormitories receive meningococcal (groups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine (*Menactra*). The new vaccine is expected to be an improvement over an older version

called *Menomune*. Because *Menactra* elicits a T cell-dependent immune response, experts expect it to offer immunity for more than eight years and prevent transmission of meningococcal infection. The old vaccine offered between three to five years of immunity and had little effect on nasopharyngeal carriage rates.

The new vaccine is expected to reduce the prevalence of meningococcal disease by between 75% and 90%. Although *Menactra* is 100% effective against targeted serogroups, there is no protection against serogroup B, which represents up to a third of all U.S. cases and half of all cases in infants. The CDC's announcement immediately created a shortage of the vaccine. Sanofi-Pasteur, the maker of *Menactra*, said it will be able to provide complete coverage in three years.

Next Season's Vaccine Will Have New Strain of Influenza Virus

According to the World Health Organization, next season's influenza vaccine will be modified to protect against a new strain of the virus that was first reported in California in January and that is spreading rapidly. The strain has been identified in more

than 20% of influenza viruses isolated from patients early in 2005 and is expected to be the dominant one circulating in the Northern Hemisphere next season [*The New York Times on the Web*, 11 February 2005].

NEW DRUGS AND INDICATIONS (continued)

Avastin Improves Vision in Wet Macular Degeneration

Avastin (bevacizumab), a monoclonal antibody against vascular endothelial growth factor (VEGF), is the first anti-angiogenic agent to receive FDA approval. In combination with intravenous 5-fluorouracil-based chemotherapy, *Avastin* is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum. The survival benefit of *Avastin* was demonstrated in well-controlled phase III trials. More recently, results reported at the 40th annual meeting of the American Society of Clinical Oncology in New Orleans indicate that the anti-angiogenic agent combined with the tyrosine kinase inhibitor *Tarceva* (erlotinib) may also be effective in the treatment of lung cancer.

Now, the results of a preliminary study suggest that *Avastin*, administered intravenously, improves

visual acuity of patients with neovascular (wet) age-related macular degeneration [*Reuters Health*, 8 March 2005]. So far, the investigators have followed 18 patients treated with the anti-angiogenic agent. Although the protocol called for six intravenous infusions given at two-week intervals, results were so encouraging that treatment was stopped after two or three infusions. Tomography showed a marked restoration of normal anatomy in the macula, and angiography showed reduced or no leakage from vessels in the retina. Two other drugs under investigation for use in age-related macular degeneration—*Macugen* (pegaptanib), now approved, and *Lucentis* (ranibuzumab)—also work by blocking VEGF, but both require intraocular injection.

DRUG SAFETY

FDA Wants Warning Labels on Eczema Products

The FDA has directed the manufacturers of two topical eczema products—*Elidel* (pimecrolimus) and *Protopic* (tacrolimus)—to add a black box to their labeling, warning that there is a potential cancer risk and that the risk increases with duration of use [*The Wall Street Journal Online*, 11 March 2005]. The FDA said that *Elidel* and *Protopic* should be used only after other eczema treatments have failed, and that they should not be used by people with immunodeficiency. Both agents are immunomodulators. In February, an FDA advisory

panel recommended that the agency require strict warnings after animal studies suggested a risk of cancer that increased with increased exposure to these agents.

The FDA will now negotiate the exact wording of the warning with the drug makers. The discussions may be protracted because the manufacturers claim their products are safe and may dig in their heels. When this occurs, the agency's options are circumscribed.

DRUG EVALUATION

Clopidogrel Plus Aspirin After MI Reduces Complications

While coronary angioplasty and stenting emerge as the treatment of choice for an acute myocardial infarction, fibrinolytic therapy continues to be widely used, especially outside the U.S. Initial reperfusion, however, fails to occur in about 20% of patients, and the artery becomes re-occluded in an additional 5% to 8% of patients during hospitalization. Both complications increase mortality. Aspirin reduces the odds of death

from vascular causes and the rate of re-occlusion, and is a mainstay of fibrinolytic therapy. An unanswered question, however, is whether the addition of clopidogrel (*Plavix*) provides further benefit.

To resolve this issue, researchers participating in the CLARITY trial enrolled 3491 patients, 18 to 75 years age, who presented within 12 hours after the on-
(Continued on Supplement page 5)

Clopidogrel Plus Aspirin After MI (continued)

set of an ST-elevation myocardial infarction, and randomly assigned them to receive clopidogrel (a 300-mg loading dose, followed by 75 mg once daily) or placebo. All patients received a fibrinolytic agent and aspirin and, when appropriate, heparin. Nearly half of the patients received tenecteplase and about 30% were treated with streptokinase. All were scheduled to undergo follow-up angiography [*N Engl J Med* 2005; 352:1179-89].

The rates of the primary efficacy endpoint—a composite of an occluded infarct-related artery on angiography, or death or recurrent MI before angiography—were 21.7% in the placebo group and 15.0% in the

clopidogrel group. The rates of major bleeding and intracranial hemorrhage were similar in the two groups. The authors of the report concluded, “In patients 75 years of age or younger who have myocardial infarction with ST segment elevation and who receive aspirin and a standard fibrinolytic regimen, the addition of clopidogrel improves the patency rate of the infarct-related artery and reduces ischemic complications.”

The authors of a related editorial offer several caveats concerning the study but conclude: “For patients who are receiving fibrinolytic therapy, a combination of aspirin and clopidogrel appears to be effective and safe” [*Ibid*, 1248-50].

Intensive Lipid Lowering in Patients with Stable Coronary Disease

Until recently, guidelines recommended that LDL cholesterol levels be reduced to below 100 mg/dl in patients with coronary heart disease (CHD). Then, on the basis of results from two trials in very high-risk patients, experts introduced a more aggressive but optional LDL cholesterol goal of less than 70 mg/dl. Now, researchers have assessed the efficacy and safety of lowering LDL cholesterol levels well below 100 mg/dl in patients with stable CHD [*N Engl J Med* 2005; 352:1425-35].

In the study, 10,001 patients with LDL cholesterol levels of less than 130 mg/dl were randomly assigned to atorvastatin (*Lipitor*), either 10 mg per day or 80 mg per day. Patients were followed for a median of 4.9 years. Mean LDL cholesterol levels at the conclusion of the trial were 77 mg/dl in those treated with high-dose atorvastatin and 101 mg/dl in those treated with low-dose atorvastatin. Persistent elevation in liver aminotransferase levels were observed in 0.2% of patients in the 10-mg group and 1.2% in the 80-mg group.

A primary event—death from CHD, nonfatal myocardial infarction, resuscitation after cardiac arrest, or

stroke—occurred in 8.7% of patients receiving 80 mg of atorvastatin, as compared with 10.9% of patients receiving 10 mg atorvastatin. Overall mortality was about the same in each group but the rate of noncardiovascular mortality favored those in the 10-mg group. The authors conclude that intensive lipid lowering in patients with stable disease provides significant clinical benefit beyond that afforded by less aggressive statin therapy, but with a greater incidence of elevated liver enzyme levels.

A related editorial observes, “Before this strategy can be adopted... clinicians will need to ask themselves how compelling the new information... is for clinical practice, and whether it is sufficient to change our current goal for LDL cholesterol in patients with stable CHD, [especially in light of the lack of effect on mortality].” The author concludes, “Until the safety and effectiveness of an 80-mg daily dose of atorvastatin have been established, patients and their physicians will need to carefully weigh the benefits of a reduction in the risk of cardiovascular events... against the uncertainty of an increase in the risk of death from noncardiovascular causes” [*Ibid*, 1483-84].

PHARMACOGENOMICS

TPMT Genotype and Early Treatment Response to Mercaptopurine in Childhood ALL

A common feature in the management of children with acute lymphoblastic leukemia (ALL) is adjustment of therapy according to the risk of treatment failure conferred by different prognostic factors. Early response to chemotherapy, including mercaptopurine, as

measured by minimal residual disease, is now thought to be an important prognostic factor.

Since their introduction to leukemia therapy, some fifty years ago, thiopurines have played an essential
(Continued on Supplement page 6)

TPMT Genotype and Early Treatment Response in Childhood ALL (continued)

role in treatment protocols. As prodrugs, thiopurines require bioactivation to form thioguanine nucleotides, which are thought to be the major cytotoxic compounds. Bioactivation is in competition with inactivation of thiopurines by thiopurine S-methyltransferase I (TPMT). The *TPMT* locus is subject to genetic polymorphism with heterozygous individuals (about 6% to 11% of white people) having intermediate TPMT activity and homozygous mutant individuals (about 0.2% to 0.6% of white people) having very low TPMT activity.

An important role for genetically determined TPMT activity in the cytotoxic effects of mercaptopurine and treatment was first suggested in 1990. Later, investigators demonstrated a tendency toward better event-free survival for children with intermediate and low TPMT activity compared with that of homozygous wild-type TPMT phenotypes. However, the impact of *TPMT* genotype on mercaptopurine-mediated antileukemic effects in the early course of childhood ALL has not yet been determined and is the subject of a recent report in *JAMA* [2005;293:1485-89].

In the study, all patients homozygous for a mutant *TPMT* allele and consequently deficient in TPMT activity were treated with a 10-fold reduced dose of mercaptopurine to avoid hematopoietic toxicity. No dosage adjustments were made for heterozygous patients. On assessment of minimal residual disease on treatment day 78, significant differences were observed between wild-type and heterozygous patients. For heterozygous patients, this translated into a nearly threefold reduction in risk of having measurable minimal residual disease. At the same time, however, hematopoietic toxicity did not differ between heterozygous patients and those with homozygous wild-type *TPMT*.

The researchers suggest that their findings may provide a rationale for increasing mercaptopurine dose according to *TPMT* genotype in the early course of childhood ALL. Since this strategy will affect *TPMT* wild-type individuals, "it could have an impact on the majority of patients and, therefore, substantially influence overall treatment results."

DRUG DELIVERY

Long-Acting Injectable Naltrexone for Alcohol Dependence

Alcohol dependence is a common disorder, increasingly recognized as a chronic disease, involving genetic susceptibility and social and environmental factors. Although naltrexone, an opioid antagonist, has been shown to be effective for treatment of alcohol dependence, clinical use has been limited, in part because of variability in treatment response. One reason for variability has been poor compliance with the daily medication regimen. To overcome this problem, investigators have studied the efficacy and tolerability of a long-acting intramuscular formulation of naltrexone for treatment of alcohol-dependent patients [*JAMA* 2005;293:1617-25].

More than 600 patients who were diagnosed as being actively drinking alcoholics were randomly assigned to receive long-acting naltrexone, 380 mg or 190 mg, or matching placebo, each administered monthly for six months and combined with 12 ses-

sions of low-intensity psychosocial intervention. Patients in all three treatment groups substantially reduced the number of heavy drinking days relative to pretreatment levels.

Compared with placebo, an intramuscular injection of higher-dose naltrexone decreased the event rate of heavy drinking days by 25%, while the lower-dose decreased the rate by 17%. Statistical significance was attached only to the higher-dose. Men and patients who were abstinent at the outset of the trial exhibited greater treatment effects. Discontinuation due to adverse events occurred in 14.1% of patients receiving higher-dose naltrexone, 6.7% of those receiving lower-dose naltrexone, and 6.7% of those assigned to placebo. While the findings offer a new treatment option for people with alcohol dependence, they also highlight the importance of psychosocial intervention and the need to focus efforts on patients with a goal of abstinence.