

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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CLINICAL PRACTICE

Leukotriene Inhibitors as Add-On Therapy to Inhaled Steroids in Asthma

Inhaled glucocorticoids are the cornerstone of asthma management, but when control is poor, other drugs such as long-acting beta agonists and leukotriene inhibitors can be added. The combination of antileukotrienes and inhaled steroids may enhance the control of asthma by reducing bronchoconstriction and inflammation of the airways. Although this treatment is increasingly used, no systematic review of randomized controlled trials has examined the evidence supporting it. An investigator has now closed this gap by carrying out a systematic review of trials in adults and children with asthma comparing the addition of an antileukotriene—montelukast, pranlukast, or zafirlukast—or placebo to inhaled glucocorticoids [*BMJ* 2001;324:1545-48]. Discarding more than 350 citations, she selected 13 suitable trials—12 in adults and only 1 in children.

The researcher concluded that the addition of leukotriene inhibitors may modestly improve asthma control compared with inhaled glucocorticoids alone, but there is little evidence to consider their use as a substitute to increasing the dose of inhaled steroids. She adds, "In well controlled patients, the addition of antileukotrienes may be associated with superior asthma control after steroid tapering, but there is insufficient evidence to quantify the corticosteroid sparing effect" [*Ibid*]. The researcher added that extrapolation of data to children remains speculative. In general, there is a shortage of relevant trials testing antileukotrienes as add-on therapy. The bottom line: "Until further evidence is available, the gold standard of asthma treatment should remain the use of inhaled glucocorticoids at the lowest effective dose" [*Ibid*].

Expert Panel Updates Asthma Management Guidelines

The expert committee of the National Asthma Education and Prevention Program, which is coordinated by NIH's National Heart, Lung, and Blood Institute, has reported a revision of the Guidelines for the Diagnosis and Management of Asthma. The guidelines were last revised in 1997. The new information is available at www.nhlbi.nih.gov/guidelines/asthma.

The recommendations stress that strong clinical evidence has established the central role of inhaled corticosteroids to improve control of asthma for children with mild to moderate persistent asthma. The panel acknowledges the potential but small risk of delayed growth, but finds that the risk is well balanced by the effectiveness of inhaled corticosteroids. Neither as-needed beta agonists nor other

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CLINICAL PRACTICE (continued)

Panel Updates Asthma Management Guidelines (continued)

long-term control medications are as effective as inhaled steroids in improving asthma outcomes. However, in a prepared statement, the chair of the NAEPP panel cautioned that inhaled steroids alone might not be sufficient in all cases.

Therefore, the preferred treatment of adults and children older than five years now includes the addition of a long-acting inhaled beta agonist to low-to-medium doses of inhaled corticosteroids.

In younger children, the panel suggests either a long-acting inhaled beta agonist in combination with low doses of inhaled corticosteroids or medium-dose inhaled corticosteroids as monotherapy. The recommendations are unchanged on antibiotic use. Antibiotics are not recommended except as needed for comorbid conditions. The panel is uncertain as to the benefits of early treatment of asthma in preventing disease progression [*Reuters Health*, 11 June 2002].

Influenza Vaccine Encouraged for Infants

The Centers for Disease Control and Prevention's vaccine advisory committee is now encouraging parents to vaccinate children between the ages of 6 and 23 months for influenza at the start of the 2002/2003 flu sea-

son. The committee advises that children in this age group are at substantially increased risk for influenza-related hospitalizations [*Reuters Health*, 22 February 2002].

NEW DRUGS AND INDICATIONS

FDA Approves *Vfend* for Invasive Aspergillosis

Oral and intravenous formulations of *Vfend* (voriconazole) have been approved by the FDA for the primary treatment of acute invasive aspergillosis and as salvage therapy for certain rare but serious fungal infections, especially in immunocompromised patients. *Vfend* has a broader indication and more dosing options than *Cancidas* (caspofungin). *Cancidas* is second-line for aspergillosis and must be administered by intravenous infusion. The FDA turned down a request to approve *Vfend* for febrile neutropenia, but FDA advisory panel members sug-

gested that high-risk febrile neutropenia patients might benefit.

The aspergillosis indication was supported by a 12-week study in 227 patients. *Vfend* had a global response rate of 53% compared with a 32% response rate to amphotericin B. Survival rates were 71% for *Vfend* compared with 58% for amphotericin. The use of *Vfend* must take into account potentially serious drug-drug interactions. Labeling contains a bold-faced warning on visual disturbances and hepatotoxicity [*The Pink Sheet*, 3 June 2002].

DRUG EVALUATION

Maintenance Infliximab for Crohn's Disease

Infliximab (*Remicade*), an anti-tumor necrosis factor monoclonal antibody, induces remission in patients with moderately to severely active Crohn's disease and can reduce corticosteroid requirements. However, patients relapse after a single infusion of infliximab. Preliminary results suggest maintenance therapy might be effective. Now, a large well-controlled clinical trial has

confirmed that maintenance infliximab therapy can sustain clinical remission of Crohn's disease [*Lancet* 2002;359:1541-49].

Among 573 patients with active disease who received an initial intravenous infusion of infliximab, 335 responded within the following two weeks. Responders

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Maintenance Infliximab for Crohn's Disease (continued)

were randomly assigned to receive placebo or maintenance doses of infliximab at two weeks, six weeks, and then every eight weeks. At week 30, 39% and 45% of patients who received low-dose and high-dose infliximab were in remission compared with 21% of patients who received placebo. Throughout the 54-week study, the mean time to loss of response was 38 weeks and more than 54 weeks for the two active treatment groups and 19 weeks for the placebo group. By the end of the

study, 29% of patients receiving infliximab had discontinued steroids, compared with 9% in the control group.

The lead investigator told *Reuters Health* [3 May 2002] that some patients need a repeat infusion every four to six weeks, while others can wait 10 to 16 weeks. In some patients, a 10 mg/kg maintenance dose may sustain a longer response than a 5 mg/kg maintenance dose.

Aspirin Resistance and Risk of Cardiovascular Events

Aspirin reduces the risk of cardiovascular events by about 25% in patients with arterial vascular disease, but some patients treated with aspirin do not benefit. They are described as "aspirin resistant." Possible explanations for the limited efficacy of aspirin in aspirin-resistant patients are platelet activation by pathways that are not blocked by aspirin, the need in some patients for higher doses of aspirin to achieve an optimal antithrombotic effect, and generation of thromboxane A₂ despite therapeutic doses of aspirin. Favoring the third possibility, researchers determined the extent of inhibition of thromboxane A₂ by measuring urine levels of 11-dehydro thromboxane B₂, a stable metabolite of thromboxane A₂, in 976 aspirin-treated patients at high risk of cardiovascular events. They matched 488 patients taking aspirin who had an acute MI or stroke or died from cardiovascular causes during five-years of follow-up with 488 patients taking aspirin who did not have a cardiovascular event [*Circulation* 2002;105:1650-55].

Urinary excretion of thromboxane was significantly greater in patients with a defining event than in those

who did not have an event. Among all patients, after adjustment for baseline differences, patients in the highest quartile of thromboxane excretion had a 1.8 times higher risk for the composite outcome and a 3.5 times higher risk for cardiovascular death than those in the lowest quartile. The investigators concluded, "These findings raise the possibility that elevated urinary 11-dehydro thromboxane B₂ levels identify patients who are relatively resistant to aspirin and who may benefit from additional antiplatelet therapies or treatment that more effectively blocks thromboxane production" [*Ibid*].

A leading cardiologist, Eric Topol, commenting on the work said, "Aspirin resistance has emerged as an exceptionally important issue" [*Lancet* 2002;359:1128]. He and his colleagues previously reported a significant correlation between aspirin resistance as measured by platelet aggregation and the composite primary outcome of death, myocardial infarction, or cerebrovascular accident in patients with stable cardiovascular disease.

Acarbose May Delay Onset of Type 2 Diabetes

People who develop type 2 diabetes first experience impaired glucose tolerance, which is characterized by defects in the action or secretion of insulin. Resistance to insulin progressively increases when passing from normal glucose tolerance through impaired glucose tolerance to diabetes, while secretion of insulin gradually decreases. Impaired glucose tolerance develops when insulin secretion fails to compensate for insulin resistance, resulting in hyperglycemia after a meal. Repeated hyperglycemia induces toxic effects of glucose, which further inhibit the secretion and action of insulin and contribute to progression of impaired glucose tolerance to diabetes. An intervention in the impaired glucose tolerance phase that reduces resistance

to insulin, or protects the beta cells, or both, should prevent or delay the onset of diabetes.

Acarbose, an α -glucosidase inhibitor, improves sensitivity to insulin and decreases postprandial hyperglycemia, thereby reducing the stress on beta cells. In this light, investigators assessed the effects of acarbose on development of type 2 diabetes in 1429 patients with impaired glucose tolerance [*Lancet* 2002; 359:2071-77]. They were assigned to either acarbose or placebo and followed for a mean of 3.3 years. Nineteen per cent of the patients in the placebo group and 31% of those in the acarbose group discontinued treatment early. The most common single cause of discontinua-

(Continued on Supplement page 4)

DRUG EVALUATION (continued)

Acarbose May Delay Onset of Type 2 Diabetes (continued)

tion in the acarbose group was gastrointestinal side effects, especially flatulence and diarrhea. A significantly smaller proportion of patients treated with acarbose developed diabetes than those treated with placebo (32% vs. 42%). The data suggest that acarbose, when

tolerated, can be used either as an alternative or, preferably, in addition to changes in lifestyle, which have already been shown to be effective, to delay development of type 2 diabetes in patients with impaired glucose tolerance.

Anti-TNF Therapy for Ankylosing Spondylitis

Ankylosing spondylitis is a chronic inflammatory rheumatic disease characterized by skeletal ankylosis and inflammation at the insertions of tendons. Although the condition has been considered a relatively benign form of arthritis, a recent study found that the rates of pain and disability among patients with ankylosing spondylitis were similar to the rates among those with rheumatoid arthritis. No therapy has been shown to slow the progression of axial disease in patients with this disorder. Tumor necrosis factor α (TNF- α) may have a role in the pathogenesis of ankylosing spondylitis. Two recently reported studies demonstrate the effectiveness of the anti-TNF- α agents infliximab (*Remicade*) and etanercept (*Enbrel*) in patients with ankylosing spondylitis.

In one study, 70 patients with active disease were assigned either to intravenous infliximab or placebo every two weeks for 12 weeks. Among those assigned to infliximab, 53% had disease regression of at least 50% compared with 9% of those on placebo. Function and quality of life also improved significantly with infliximab but not with placebo. Although treatment was generally well tolerated, three patients had potentially serious adverse effects, prompting the researchers to recommend that treatment be restricted to rheumatology clinics [*Lancet* 2002;359:1187-93].

In the second study, 40 patients with active disease were randomly assigned to receive twice-weekly subcutaneous injections of etanercept or placebo for four
(Continued on Supplement page 5)

DRUG SAFETY

Adverse Outcomes of Antiretroviral Therapy During Pregnancy

Antiretroviral therapy is recommended during pregnancy to reduce the risk of perinatal transmission and to improve maternal health. A report in *The New England Journal of Medicine* [2002;346:1863-70] described an analysis of data from seven studies of pregnant women with HIV infection to evaluate whether antiretroviral therapy during pregnancy is associated with an increased risk of premature delivery (<37 weeks of gestation) or other adverse outcomes.

Rates of premature delivery, low birth weight, low Apgar scores, and stillbirth were similar whether or not the women received antiretroviral therapy and whether or not the treated women received combination therapy or monotherapy (i.e., zidovudine or nevirapine). After adjustment for risk factors, combination antiretroviral therapy was not

associated with an increased risk of premature delivery as compared with monotherapy.

But as compared with combination therapy that did not include protease inhibitors, regimens that included these medications were associated with greater risk of very low birth weight. This finding, however, was based on small numbers of women.

The compilation of data provides reassurance that the use of combination antiretroviral therapy is not associated with an increased risk of premature delivery or other adverse outcomes in late pregnancy. Although the risk of very low birth weight appears to be higher with combination therapy that includes protease inhibitors than with regimens that do not include them, this finding requires confirmation.

Anti-TNF Therapy for Ankylosing Spondylitis (continued)

months. Treatment with etanercept resulted in significant and sustained improvement. At four months, 80% of the patients in the etanercept group had a treatment response compared with 30% of those in the placebo group. Treat-

ment response was rapid and did not diminish over time. Etanercept was well tolerated and there were no significant differences in rates of adverse events between the two groups [*N Engl J Med* 2002;346:1349-56].

Insect Repellants Against Mosquito Bites

Insect-transmitted disease remains a major source of illness and death worldwide. Mosquitoes alone transmit disease to more than 700 million people annually. In many circumstances, applying repellent to the skin may be the only feasible way to protect against insect bites. It is important to know which repellent products can be relied upon to provide predictable and prolonged protection from mosquito bites. Commercially available insect repellants contain either synthetic chemicals or plant-derived essential oils. The best known chemical insect repellent is N,N-diethyl-3-methylbenzamide (DEET). Investigators have compared the efficacy of widely available alternatives to DEET-based repellent in a controlled laboratory environment. The alternatives were a repellent containing ethyl butylacetyl-aminopropionate (IR3535), three repellent-impregnated wristbands, and a moisturizer containing a botanical claimed to have repellent effects [*N Engl J Med* 2002;347:13-18].

Under the ideal conditions provided by a controlled environment, DEET-based products provided complete protection for the longest time. Higher concentrations of DEET provided longer-lasting protection. A formulation containing 23.8% DEET, the highest concentration tested, had a mean protection time of 301.5 minutes. No non-DEET repellent was able to provide protection that lasted more 1.5 hours. Only a soybean oil-based repellent protected for a period (about 90 minutes) similar to that of the DEET product with the lowest concentration (4.75%). The soybean-based product could be an alternative to DEET to protect children against bites. The IR3535-based and citronella-based repellents protected for 25 minutes or less. The authors of the report concluded that currently available non-DEET repellants cannot be relied on to provide prolonged protection in environments where mosquito-borne diseases are a substantial threat.

DRUG SAFETY (continued)

New Warnings for Use of Simvastatin, Tamoxifen, and Erythropoietin

■ Revised labeling states in bolded type that the risk of myopathy and rhabdomyolysis associated with simvastatin (*Zocor*) increases in proportion to dose. The incidence in clinical trials has been about 0.02% at 20 mg, 0.07% at 40 mg, and 0.3% at 80 mg. The Warnings section of the label adds the anti-arrhythmic amiodarone to the list of drugs that may increase the risk of myopathy or rhabdomyolysis; verapamil continues to be listed as problematic [*The Pink Sheet*, 10 June 2002].

■ A boxed warning has been added to tamoxifen to emphasize links with uterine malignancies, strokes, and pulmonary embolisms. The warning urges physicians to exercise caution when deciding whether to use tamoxifen to reduce the risk of invasive breast cancer in patients with ductal carcinoma in situ or patients at high risk of developing breast

cancer. It states that while it has been known that tamoxifen is associated with an increased risk of endometrial cancer, new data suggest that there is also an increased risk of developing a rare and aggressive uterine sarcoma. The new label also says that the benefits of tamoxifen outweigh its risks in women who already have breast cancer, but that physicians should discuss the potential benefits versus the potentially serious adverse events with patients who are considering taking tamoxifen to reduce the risk of developing breast cancer [*Reuters Health*, 28 June 2002].

■ Johnson & Johnson announced that the number of patients who developed pure red-blood cell aplasia, a rare disorder, when treated with erythropoietin has risen to 124 worldwide, including one death. The drug company said that it has not yet identified

(Continued in box, Supplement page 6)

DRUG EVALUATION (continued)

Incremental Progress in the Treatment of Cancer

■ A Phase III trial has demonstrated that women with advanced breast cancer who have failed anthracycline therapy achieve significantly improved survival with a combination of oral capecitabine (*Xeloda*) and docetaxel (*Taxotere*). The researchers randomly assigned 511 women to the combination or to docetaxel alone. Women receiving the combination had significantly improved median time to disease progression compared with women who received docetaxel alone (6.1 months vs. 4.2 months). These women also had better overall median survival and a better tumor response rate. The treatments resulted in different side effect profiles. Combination therapy produced more grade 3 adverse events than did monotherapy. But grade 4 adverse events with docetaxel alone, in a higher dose than that used in combination therapy, were slightly more common than with the combination [*J Clin Oncol* 2002;20:2812-23]. The *Taxotere-Xeloda* combination received regulatory approval in the U.S. last September.

■ A Phase III randomized trial presented at the May meeting of the American Society of Clinical Oncology has shown significant benefits for advanced colorectal

cancer patients treated with oxaliplatin (*Eloxatin*) compared with irinotecan (*Camptosar*). In the study, a treatment regimen consisting of oxaliplatin combined with infused 5-fluorouracil (5-FU) and leucovorin achieved higher overall survival rates and a longer time to disease progression in previously untreated, advanced colorectal cancer than irinotecan with 5-FU and leucovorin. *Eloxatin* is available in several countries but is not yet approved in the U.S. Last year, an FDA advisory panel rejected a regimen of oxaliplatin with 5-FU and leucovorin as first-line treatment of metastatic colorectal cancer. The new study may change that. The median time to disease progression in the oxaliplatin arm was 8.8 months compared with 6.9 months in the irinotecan arm. One year after starting treatment, 71% of patients who received oxaliplatin were still alive, compared with 58% who received irinotecan. Furthermore, patients in the oxaliplatin arm experienced fewer side effects than those in the irinotecan arm. The oxaliplatin-5FU-leucovorin regimen was also more effective than a regimen consisting of oxaliplatin and irinotecan. Another study of oxaliplatin, as second-line treatment of metastatic colorectal cancer, is in progress.

DRUG SAFETY (continued)

Warnings for Simvastatin, Tamoxifen, and Erythropoietin (continued)

what is causing the immune system to attack the protein-based drug but suggested that subcutaneous delivery might play a role and pointed out that all of the cases so far have been in patients with renal dis-

ease. J & J stated that its version of erythropoietin, sold only outside the U.S., should be given intravenously in patients with chronic renal failure [*Ibid*, 1 July 2002].

Risk of Lactic Acidosis with Metformin Therapy

A report in *JAMA* [2002;287:2504-05] suggests that metformin may often be inappropriately prescribed for patients with type II diabetes who have renal dysfunction or congestive heart failure. Metformin has been associated with sometimes-fatal lactic acidosis in such patients. The investigators did a retrospective review of randomly selected charts of patients receiving metformin through a medical-center based outpatient pharmacy. Among 100 patients using metformin, 22 were found to have either congestive heart failure requiring treatment or renal insufficiency. In only

two cases did documentation show that the contraindications were considered.

Another survey of metformin prescribing arrived at similar findings [*Arch Intern Med* 2002;162:434-37]. The authors concluded, "Many patients are treated with metformin despite having clinical conditions that place them at risk for developing lactic acidosis. To minimize this risk, it is essential that physicians develop a better understanding of the prescribing guidelines for metformin."

Efforts to Prevent Type 1 Diabetes and Its Complications

The Diabetes Control and Complications Trial (DCCT) proved that intensive insulin treatment of patients with type 1 diabetes for 6.5 years reduced the risks of retinopathy, nephropathy, and neuropathy by 35% to 90%, compared with conventional insulin treatment [*N Engl J Med* 1993;329:977-86]. The absolute risks of retinopathy and nephropathy were proportional to the mean glycosylated hemoglobin (HbA_{1c}). Intensive treatment was most effective when begun early, before complications were detectable.

Now, in a Special Communication, The Writing Team for Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group report that intensive treatment in the DCCT for 6.5 years continues to yield benefit up to seven years later, even though the two groups (intensive or conventional therapy) have long since become virtually indistinguishable in terms of glycemic control [*JAMA* 2002;2563-69].

Risk reductions at the end of DCCT were achieved at a median HbA_{1c} level difference of 1.8% (9.1% for conventional treatment and 7.3% for intensive treatment). These risk reductions have been maintained even though the difference in HbA_{1c} between treatment

groups was only 0.4% one year later, continued to narrow, and became statistically nonsignificant by five years (8.1% vs. 8.2%).

While a reduction in the risk of complications of type 1 diabetes appears to be within reach, the prevention of type 1 diabetes seems a long way off. A much heralded effort with early insulin intervention in high-risk nondiabetic relatives of patients with type 1 diabetes has failed [*N Engl J Med* 2002;346:1685-91].

In the study, the investigators enrolled 339 first- and second-degree relatives of diabetic patients who tested positive for islet cell antibodies and had a projected five-year risk of developing diabetes of more than 50%. The subjects were randomly assigned to close observations or to low-dose subcutaneous ultralente insulin twice daily plus annual four-day continuous intravenous infusions of insulin. Median follow-up was 3.7 years. The annualized rate of progression to diabetes was 15.1% in the intervention group as compared with 14.6% in the observation group. The authors of the report concluded, "In persons at high risk for diabetes, insulin at the dosages used in this study does not delay or prevent type 1 diabetes" [*Ibid*].

Preoperative Beta-Blocker Use May Improve CABG Surgery Outcome

Beta-adrenergic blockade improves acute outcomes and long-term prognosis in ischemic heart disease. Beta-blocker therapy also reduces perioperative events among high-risk patients undergoing major noncardiac and vascular surgery. However, no well-controlled study has examined whether β -blocker therapy is useful when used preoperatively in patients undergoing coronary artery bypass graft surgery (CABG). Although extrapolation of the cardioprotective benefits of β -blockers to this setting is plausible, concerns exist that treatment might depress myocardial contractility and/or exacerbate underlying reactive airway disease.

To shed light on this question, researchers analyzed data from 629,877 patients who underwent CABG between 1996 and 1999. During that period, the percentage of cases in which preoperative β -blocker therapy was used increased from 50% to 60%. The investigators found that patients who received a β -blocker had

lower mortality than those who did not (unadjusted 30-day mortality, 2.8% vs. 3.4%; odds ratio, 0.80). Preoperative use remained associated with slightly lower mortality after adjusting for patient risk and treatment center effects (OR, 0.94; 95% confidence interval, 0.91-0.97). This small treatment advantage was seen among the majority of patient subgroups. Among patients with a left ventricular ejection fraction of less than 30%, however, preoperative β -blocker therapy was associated with a trend toward a higher mortality rate (OR, 1.13; 95% CI, 0.96-1.33).

The researchers pointed out that the measured effect (0.11%, absolute risk reduction) of β -blockade on 30-day mortality predicts saving approximately 500 lives per year. They caution, however, "Although these results are promising, we believe that, ideally, they should be confirmed in a large, randomized clinical trial of preoperative β -blocker use" [*JAMA*; 2002;287:2221-27].

BIOTECHNOLOGY

Therapeutic Angiogenesis for Intermittent Claudication: Proof of Principle

Peripheral artery disease (PAD) affects up to 15% of adults over the age of 55. Agents such as recombinant basic fibroblast growth factor (FGF), which promote angiogenesis and proliferation of endothelial cells, could benefit PAD patients. A recent report supports the hypothesis that recombinant FGF improves treadmill performance in patients with intermittent claudication of the leg caused by infra-inguinal obstructive atherosclerosis [*Lancet* 2002;359:2053-58].

The investigators found that a single intra-arterial infusion of recombinant FGF significantly increased peak walking time at 90 days as compared with a placebo infusion. Walking time increased by 0.60 minutes with placebo and by 1.77 minutes with FGF, from about 5 to 7 minutes. The authors of the report concluded that intra-arterial recombinant FGF resulted in a significant increase in peak walking times at 90 days, but repeat infusion at 30 days was no better than a single infusion.

PHARMACOECONOMICS

Cost Effectiveness of Aspirin, Clopidogrel, or Both for Secondary Prevention

Both aspirin and clopidogrel (*Plavix*) reduce the rate of cardiovascular events in patients with coronary heart disease, but clopidogrel is far more expensive than aspirin. Clopidogrel was shown to reduce the relative risk of ischemic stroke, myocardial infarction, or death from vascular causes in patients with cardiovascular disease by 8.7% as compared with aspirin, and the addition of clopidogrel to aspirin for patients with acute coronary syndromes reduced the relative risk of death from cardiovascular causes, reinfarction, or stroke by 20% as compared with aspirin alone. Do the enhancements offered by clopidogrel justify the additional cost? The purpose of a recently reported study was to perform a cost-effectiveness analysis of the long-term use of aspirin, clopidogrel or both for secondary prevention in patients with established coronary disease. [*N Engl J Med* 2002;346:1800-06].

The investigators used a computer simulation of the U.S. population to estimate incremental cost effectiveness over a 24-year period of four strategies in patients over 35 years of age with coronary disease: (1) Aspirin for all eligible patients (i.e., those who are not aspirin intolerant); (2) Aspirin for all eligible patients and clopidogrel for those who are aspirin intolerant; (3) Clopidogrel for all patients; and (4) The combination of aspirin for all eligible patients plus clopidogrel for all patients.

The analysis indicated that the extension of aspirin therapy from current levels of use to all eligible patients for 25 years would have an estimated cost-effectiveness ratio of \$11,000 per quality-adjusted life year (QALY) gained. The addition of clopidogrel for the 5% of patients who are ineligible for aspirin would cost about \$31,000 per QALY gained. Clopidogrel alone in all patients or in routine combination with aspirin had an incremental cost of \$130,000 per QALY gained. Health economists consider the last two scenarios to be financially unattractive. The use of clopidogrel would cost less than \$50,000 per QALY gained if its price in the U.S. were reduced by at least 70%.

The authors of the report concluded, "Aspirin for secondary prevention of coronary disease is attractive from a cost-effectiveness perspective under a wide range of assumptions. Clopidogrel, as currently priced, has an attractive cost-effectiveness ratio for patients with contraindications to aspirin but not for patients who can tolerate aspirin" [*Ibid*].

A related editorial takes issue with the authors' conclusions, stating "The cost of the additional therapeutic benefits of clopidogrel is certainly high; however, to accept uncritically that it is 'unattractive' seems to me to be potentially dangerous" [*Ibid*, 1819-21].