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An Aspirin a Day (Before a NSAID) Keeps the Doctor Away

ABSTRACT & COMMENTARY

Synopsis: *This study suggests that the beneficial effects of aspirin in preventing coronary disease and stroke may be offset by taking ibuprofen before aspirin.*

Source: Catella-Lawson F, et al. *N Engl J Med.* 2001;345:1809-1817.

Study subjects were nonsmokers without cerebrovascular disease who were randomized to 1 of 4 groups as detailed in Table 1 below. Subjects were blindly given 1 of the 2 medications, and the second medication 2 hours later. A baseline thromboxane B2 level was obtained prior to the administration of the medications, and sequentially at 2, 6, 12, and 24 hours thereafter.

After 6 days of therapy, study subjects underwent a 2-week washout period during which they received no medications. They then received the same medications but in reverse order of administration from the first protocol. Thromboxane B2 levels were again obtained prior to the administration of the medications, and sequentially at 2, 6, 12, and 24 hours thereafter.

One subgroup was randomized to receive enteric-coated aspirin before multiple doses of ibuprofen (3 times a day) or diclofenac (twice a day).

Table
Percent Inhibition of Thromboxane B2 Production

	Percent inhibition of Thromboxane B2 production 6 hours after dosing	Percent inhibition of Thromboxane B2 production 24 hours after dosing
Aspirin before ibuprofen	99%	98%
Ibuprofen before aspirin	80%	53%
Aspirin before acetaminophen	99%	96%
Acetaminophen before aspirin	99%	96%
Aspirin before rofecoxib	99%	99%
Rofecoxib before aspirin	99%	97%
Aspirin before ibuprofen (TID)	97%	67%
Aspirin before diclofenac	97%	92%

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INSIDE

COMMENT BY JEFF WIESE, MD

Aspirin reduces the risk of myocardial infarction and stroke by irreversibly inhibiting platelet cyclooxygenase.[1] Thromboxane A2, the end product of this enzyme, is a potent platelet aggregator. Inhibition of production of thromboxane A2 reduces platelet aggregation, and thereby reduces the risk for coronary thrombosis. Thromboxane B2 is a stable byproduct of thromboxane A2, and is used to measure the activity of platelet cyclooxygenase, and, thus, overall platelet aggregation.

Unlike aspirin that irreversibly acetylates cyclooxygenase, nonsteroidal medications reversibly occupy the enzyme, decreasing platelet aggregation for up to 24 hours.[2]

This study suggests that the inhibitory effect of aspirin, as measured by a reduction of thomboxane B2, is reduced when ibuprofen is given prior to aspirin. There was no reduction in the thromboxane B2 level when aspirin was given before ibuprofen. This finding is consistent with Catella-Lawson and colleagues' hypothesis that ibuprofen may reversibly occupy the cyclooxygenase enzyme when given prior to aspirin, thereby preventing aspirin from inhibiting the enzyme. Catella-Lawson et al also found that multiple doses of ibuprofen (TID dosing) inhibited aspirin's effects even if aspirin preceeded these doses each day.

There was no effect of acetaminophen, rofecoxib (a COX-2 selective inhibitor), or diclofenac (a NSAID) on aspirin's effectiveness, regardless of sequence of dosing.

Although there are no clinical end points to this study, this study suggests that the beneficial effects of aspirin in preventing coronary disease and stroke may be offset by taking ibuprofen before aspirin. Final conclusions will require clinical trials investigating the interaction of aspirin with other nonsteroidal medications. Until that time, physicians should advise patients who depend on aspirin for platelet inhibition (ie, those with coronary disease, prior stroke, and atrial fibrillation) to avoid taking ibuprofen prior to aspirin, and to exercise caution when taking multiple doses of ibuprofen. Acetaminophen, rofecoxib, or diclofenac may be safer alternatives for these patients. ❖

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Screening for Colorectal Cancer

ABSTRACT & COMMENTARY

Synopsis: *Many options exist for colorectal cancer screening, each with its own advantages and drawbacks. The best of these include fecal occult blood testing, sigmoidoscopy, and colonoscopy.*

Source: Ransohoff DF, Sandler RS. *N Engl J Med.* 2002;346: 40-44.

Some of the considerations in selection of an approach to colorectal cancer screening include costs, safety, potential discomfort, and the individual patient's fear of cancer.

Fecal occult blood testing of stool traditionally involves 3 serial samples, an approach tested in a

number of randomized, controlled, clinical trials. However, at least 1 recent study also supported the use of a single test at the time of rectal examination. Occult blood tests probably should not be rehydrated since this increased false-positive rates. Some physicians recommend avoidance of aspirin, red meat, and horseradish prior to serial fecal occult blood testing. Colonoscopy is recommended if any occult blood test is positive since 17-46% of individuals with positive tests will have colorectal cancer or a large adenoma. Occult blood testing has been shown to reduce colorectal cancer deaths by 15-33% (similar numerically to mammography). Sigmoidoscopy is effective for finding lesions in the distal colon, and the risk of death from colorectal cancer can be reduced by 60% by the finding of a lesion within reach of the instrument, translating to a reduction of 30% for the colon as a whole. The exact reduction in risk of death from colorectal neoplasia afforded by colonoscopy is not known. However, it can be extrapolated to be much higher than either sigmoidoscopy or fecal occult blood testing. Colonoscopy does have a colon perforation rate of 2 per 1000 procedures vs. 1 per 10,000 for sigmoidoscopy. In the new millennium, there is little reason to consider barium enema as a suitable screening option for colorectal cancer due to low sensitivity for lesion detection. Virtual colonoscopy is still experimental and does not currently offer a meaningful alternative to colonoscopy.

COMMENT BY MALCOLM ROBINSON MD, FACP, FACG

All of the tests mentioned for colorectal cancer screening are considered to be cost effective—ie, they all cost less than $30,000 per year of life saved. For obvious reasons, gastroenterologists prefer colonoscopic screening. However, this is not yet verified as superior to the other 2 techniques in "competition." If sigmoidoscopy is done, the finding of an adenomatous polyp should trigger subsequent colonoscopy. At present, recommendations for a person with an average risk of colorectal cancer would be: annual fecal occult blood testing alone, sigmoidoscopy every 5 years, or a combination of the 2 tests. Colonoscopic screening, perhaps once every 10 years, is beginning to be offered as an option. In any case, whatever colorectal screening approach is selected, physicians should advise patients to reduce their risks of colorectal cancer by avoiding obesity and by limiting alcohol and red meat intake. Use of any of the available tests for colorectal cancer screening is clearly preferable to none. ❖

The Positive Effects of ARBs on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy

ABSTRACTS & COMMENTARY

Synopsis: *ARBs are associated with significant renal benefits independent of their blood pressure lowering effects.*

Sources: Brenner BM, et al. *N Engl J Med*. 2001;345: 861-869; Lewis EJ, et al. *N Engl J Med*. 2001;345:851-860; Parving HH, et al. *N Engl J Med*. 2001;345:870-878.

Yusuf and colleagues clearly demonstrated that the ACE inhibitor ramipril significantly reduced the risk of death, myocardial infarction, and stroke in a broad range of high-risk patients who were known not to have a low ejection fraction or heart failure.[1] A substudy of that trial known as the MICRO-HOPE revealed that ramipril provided protection against cardiovascular events and attenuated the increase in proteinuria commonly observed in patients with type 2 diabetes and microalbuminuria.[2]

Recognizing that diabetic nephropathy is the leading cause of end-stage renal disease and that interruption of the renin-angiotensin system has been demonstrated to slow the progression in patients with type 2 diabetes, Brenner and associates for the RENAAL Study investigators studied the effects of using an angiotensin-receptor blocking agent (losartan) on renal function in a total of 1513 patients enrolled in a multicenter, randomized, double-blind study. Losartan was added to conventional antihypertensive therapy and compared to a placebo for a mean of 3.4 years. Losartan was found to confer significant renal benefits in patients with type 2 diabetes and nephropathy by significantly reducing the incidence of: 1) a doubling of the serum creatinine concentration, and 2) end-stage renal disease; but, it was found to have no effect upon the death rate.

In the same issue of the *New England Journal of Medicine*, Lewis and colleagues for the Collaborative Study Group reported on the ability of an angiotensin-receptor blocker (irbesartan) and a calcium-channel blocker (amlodipine) to slow the progression of nephropathy in patients with type 2 diabetes independent of the capacity of these agents to lower the systemic blood pressure. This multicenter study followed patients for 2.6 years and

found that treatment with irbesartan resulted in a 20% lower incidence than the placebo group and a 23% lower incidence than the amlodipine group with respect to: 1) the doubling of the base-line serum creatinine concentration; 2) the development of end-stage renal disease; or 3) death from any cause. They concluded that irbesartan was effective in protecting against the progression of nephropathy due to type 2 diabetes independent of any reduction in blood pressure that it may cause.

Finally, a third article in the same journal by Parving and colleagues reporting for the Microalbuminuria Study Group also found that irbesartan was renal protective independent of its blood pressure-lowering effect in patients with type 2 diabetes and microalbuminuria. This multinational, randomized, double-blind, placebo-controlled study was performed on 590 hypertensive patients who were carefully followed for 2 years.

COMMENT BY HAROLD L. KARPMAN, MD, FACC, FACP

Nephropathy due to Type 2 diabetes resulted in 90,000 cases of chronic renal failure in the United States over the past year. More than 300,000 patients are now being treated by dialysis and 80,000 more have been subjected to kidney transplants. Glycemic and blood pressure control and blockade of the renin-angiotensin-aldosterone system all appear to be of special value in slowing or eliminating the occurrence of nephropathy secondary to type 2 diabetes. ACE inhibitors have clearly been demonstrated to provide protection for diabetics against cardiovascular events and have attenuated the increase observed in proteinuria in these subjects[2] and now we have convincing evidence that angiotensin-receptor blocking agents (ie, losartan and irbesartan) are also capable of conferring significant renal benefits in patients with type 2 diabetes.[4]

Unfortunately, patients at high risk for diabetic nephropathy are rarely identified early, which may explain why diabetes remains the single most important cause of end-stage renal disease in Europe, Japan, and the United States. It is, therefore, particularly important to determine the presence or absence of early diabetic nephropathy in patients with type 2 diabetes by determining whether albuminuria is present, even in patients with acceptable glycemic control, since ACE inhibitors and angiotensin-receptor blockers have now been clearly demonstrated to lower the levels of proteinuria, to decrease the rate of decline in the glomerular filtration rate, and to delay the onset of end-stage renal disease. One analysis has even suggested that an ACE inhibitor would be cost effective if prescribed for all middle-aged patients with type 2 diabetes irrespective of their base-line renal status and, although angiotensin-receptor blockers are somewhat more expensive, the same conclusions probably would hold for this class of drugs.[6] The findings of Brenner et al confirmed the results of other studies by demonstrating that angiotensin-receptor blockers lower levels of proteinuria, diminish the rate of decline in the glomerular filtration rate, and delay the onset of end-stage renal disease even in patients with well advanced renal disease.

The final detailed prospective outcome studies have not yet been performed to determine whether ACE inhibitors are better than angiotensin-receptor blockers or vice-versa; however, it now appears likely that these agents are similar with respect to their ability to diminish proteinuria and to provide protection from progressive renal damage. Therefore, type 2 diabetic patients who are initially treated with ACE inhibitors and who develop symptomatic complications such as a troubling cough should be switched to angiotensin-receptor blockers since these agents now appear to provide a similar degree of renal protection.

There now seems to be little question that ACE inhibitors and angiotensin-receptor blockers do indeed provide a significant degree of renal protection in diabetics and it would, therefore, appear that clinicians should consider prescribing one or the other to all middle-aged or older patients with type 2 diabetes irrespective of their baseline renal status. ❖

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Risk Factors for CHF Exacerbations

ABSTRACT & COMMENTARY

Synopsis: *Potentially preventable risk factors can be identified before a CHF exacerbation.*

Source: Tsuyuki RT, et al. *Arch Intern Med.* 2001;161: 2337-2342.

Using the database of the randomized evaluation of Strategies for Left Ventricular Dysfunc-

tion (RESOLVD) Pilot Study, Tsuyuki and colleagues set out to determine what exactly precipitated exacerbations of congestive heart failure (CHF) in their patients.

RESOLVD enrolled 768 patients with symptomatic CHF into a double-blind, randomized, 2-stage, multicenter trial. To enter the trial, the patients had to be New York Heart Association functional class II-IV, have an ejection fraction less than 40%, and have a 6-minute walk distance of less than 500 meters. In the first stage of the trial, patients were randomized to an angiotensin II receptor blocker (candesartan), and angiotensin-converting enzyme inhibitor (enalapril), or both. In the second stage, controlled-release metoprolol or placebo was added. The study spanned 43 weeks. Whenever a patient experienced an exacerbation of CHF, investigators completed a CHF Event Form. On this form, they recorded the signs and symptoms of CHF, their plans, and what factors they thought contributed to the exacerbation.

Of the 768 patients enrolled in the study, 180 had 1 or more exacerbations during the study period. The patients who experienced an exacerbation were similar to those who did not, except that there were proportionately more patients in functional class III in the former group. These patients also had more peripheral edema and jugular venous distention (JVD) at baseline. In the 2 days before an exacerbation, 92% of patients were on loop diuretics, 76% on digoxin, 52% on aspirin, 47% on nitrates, and 14% on β-blockers. They gained on average 1.16 kg (2 ½ lbs.). Their physical examinations had the typical findings of lung crackles (66%), JVD (55%), peripheral edema (52%), and third heart sound (36%). Five patients died.

The physicians treating these patients tried to assign cause to the exacerbations. The most commonly identified factors were excessive salt intake (22%); other noncardiac disorders, primarily upper respiratory infections and pneumonia (20%); use of study medications, usually metoprolol (15%); arrhythmia (13%); calcium channel blockers (13%); and inappropriate reductions in CHF therapy (10%). Surprisingly, noncompliance, uncontrolled hypertension, and coronary ischemia were identified in less than 10% of cases.

Tsuyuki et al recommend attending to prevention (ie, education about salt intake and influenza and pneumococcal vaccination) and avoidance of negative inotropic medications as ways to forestall CHF deterioration. They also recommend that CHF patients weigh themselves daily and report any increase, since in their experience, most patients had seemingly minor increases before their exacerbations.

COMMENT BY ALLAN WILKE, MD

A weakness of this study is that Tsuyuki et al assigned what they thought were "the factors to have contributed to the episode." It is not unusual for a physician to misclassify diagnosis. When I review an article, one of the first questions I ask myself is, "Are these patients similar to mine?" In a few ways, they are not. They were highly selected. All of these patients were on either an ACE inhibitor or an ARB. Despite this being a recommendation for CHF patients,[1] not all of mine are. Many were also on a β-blocker, another recommendation.[2] These patients were volunteers, and presumably more interested in their disease and probably more knowledgeable and compliant with their medications than mine. In other words, these were near perfect patients. If you see the glass "half-full," as I do, we have a remarkable opportunity here to improve the health of our CHF patients. ❖

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Dr. Wilke is an Assistant Professor of Family Medicine, Medical College of Ohio, Toledo, Ohio.

Pharmacology Update

Bosentan Tablets (Tracleer—Actelion)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

The fda recently approved the first oral drug for the treatment of pulmonary arterial hypertension (PAH). Bosentan is an endothelin-1 receptor antagonist developed by Actelion Pharmaceuticals. The drug will not be available in pharmacies, rather it will be dispensed via a direct distribution program by calling the company at 1-866-228-3546. Bosentan will be marketed under the tradename Tracleer.

Indications

Bosentan is indicated for the treatment of PAH in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening.[1]

Dosage

The starting dose is 62.5 mg twice daily (morning and evening) for 4 weeks. The dose is then increased to 125 mg twice daily. It may be taken without regard to meals. Higher doses are not recommended due to potential for liver toxicity. Dose adjustment is not required in patients with renal impairment. It should be used with caution in patients with mild hepatic impairment and should be avoided in those with more severe impairment. If ALT or AST levels are confirmed to be elevated between 3 to 5 times upper limit of normal (ULN), the dose of bosentan should be reduced or discontinued. If ALT or AST levels are between 5 and 8 times the ULN, treatment should be stopped. Levels should be monitored every 2 weeks, and if the levels return to pretreatment levels, dose should be continued or reinstated. If ALT or AST is > 8 times ULN, treatment should be discontinued and not reintroduced.[1]

Bosentan is available as 62.5 mg and 125 mg tablets.

Potential Advantages

Bosentan is the first oral drug for the treatment of PAH. Clinical studies indicate that bosentan improves the 6-minute walk distance. A change from baseline of 27 ± 75 m and 70 ± 56 m was reported in 2 studies compared to -8 ± 96 m and -6 ± 121 m for placebo, respectively.[1,2] In addition, bosentan produced improvements in cardiopulmonary hemodynamics such as cardiac index, pulmonary artery pressure, mean right arterial pressure, and pulmonary vascular resistance compared to placebo. Improvement in Borg dyspnea index and WHO functional class were also reported.[2] The effects appear to be maintained for 20-28 weeks.

Potential Disadvantages

Bosentan is contraindicated in pregnancy, as the drug is likely to produce major birth defects. Contraception other than hormonal contraceptives (oral, injectable, or implantable) must be used during bosentan therapy since the drug may reduce the effectiveness of these methods of contraception. Bosentan is an inducer of cytochrome P450 isoenzyme 3A4 that metabolizes these drugs.[1] Concomitant administration of cyclosporine or glyburide and bosentan is contraindicated. Dosage adjustment may be needed with simvastatin or other statins. Bosentan is also an inducer of CYP 2C9. Since bosentan is potentially hepatotoxic, liver aminotransferases should be measured at baseline and monthly thereafter. Bosentan also causes a dose-related decrease in hemoglobin and hematocrit. Hemoglobin levels should be monitored 1-3 months after initiation of therapy and every 3 months thereafter.[1] In one study, mean reduction in hemoglobin was 0.9 g/dL detected in the first few weeks or therapy and stabilizing in 4-12 weeks.[1] The mechanism for this effect is not known. Other side effects include headache and flushing. There are currently no published data on the effect of bosentan on survival.

Comments

Endothelin-1 is a potent peptide vasoconstrictor that has been implicated in different pulmonary diseases including pulmonary hypertension.[5] Bosentan is an endothelin-1 receptor antagonist, which has been shown to improve cardiopulmonary parameters. The efficacy of bosentan was based on 2 placebo-controlled studies involving a total of 245 patients. These patients had symptomatic, severe (WHO classes III-IV), primary pulmonary hypertension or pulmonary hypertension due to scleroderma or other connective tissue diseases or autoimmune diseases. Bosentan was added to current therapy that included vasodilators, anticoagulants, diuretics, digoxin, or supplemental oxygen. Patients on epoprostenol (prostacyclin, Flolan) were not included in these studies. The primary end point was a 6-minute walking distance. Patients on bosentan in the BREATHE-1 (Bosentan Randomized Trial of Endothelin Receptor Antagonist THErapy) trial (n = 231) had a mean increase in 6-minute walk at 4 months from 326 ± 73 m to 353 ± 115 m compared to 344 ± 76 m to 336 ± 129 m for placebo. In a smaller study (n = 32), bosentan patients improved from 360 ± 86 m to 431 ± 66 m compared to 355 ± 82 m to 350 ± 147 m at 3 months. Secondary end points included cardiopulmonary hemodynamics. In addition, clinical worsening was not reported in patients given bosentan. Similar end points have also been reported for epoprostenol when added to conventional therapy. Improvements in median walking distances at 12 weeks for epoprostenol compared to conventional therapy alone were from 270 m to 316 m compared to 240 m to 192 m in one study (n = 111) and 315 m to 362 m vs. 220 to 204 m in another (n = 81).[7,8] The results do not appear to be dramatically different although comparing across studies can be problematic.

Clinical Implications

PAH is a chronic life-threatening condition defined as abnormally high blood pressure in the pulmonary artery. This increase in pulmonary vascular resistance leads to right ventricular failure and death.[3] In untreated patients, the survival rate is 40-50% at 2 years after the onset of symptoms with a median life expectancy of 2.8 years.[6] PAH is a rare condition affecting about 100,000 people in the United States and Europe. It has been associated

with exposure to fenfluramine, dexfenfluramine, cocaine, methamphetamine, other street drugs, and certain toxins.[4] Epoprostenol is currently the most effective therapy for PAH and has been reported to improve survival,[7] however, it requires constant, 24 hour a day, intravenous administration via a central catheter with its associated risks. An orally administered drug such as bosentan offers a significant advantage. How it compares to epoprostenol in efficacy is not known since there are currently no comparative studies between these drugs. Neither treatment is a cure for this difficult-to-manage disease. ❖

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CME Questions

6. Which of the following is true for a 60-year-old man with a history of myocardial infarction?

a. Ibuprofen may be substituted for aspirin, but both should not be taken together.
b. Ibuprofen should not be taken with aspirin, regardless of sequence.
c. Ibuprofen, when given prior to aspirin or when given in multiple daily doses, may inhibit aspirin's ability to reduce platelet aggregation.
d. Rofecoxib, when given prior to aspirin or when given in multiple daily doses, may inhibit aspirin's ability to reduce platelet aggregation.

7. Options for colorectal cancer screening could reasonably include:

a. colonoscopy every 10 years.
b. sigmoidoscopy every 5 years.
c. annual fecal occult blood testing.
d. All of the above

8. In the study of CHF, the most common cause of exacerbations was:

a. excessive salt intake.
b. cardiac ischemia.
c. pneumonia.
d. metoprolol.
e. noncompliance with medication.

By Louis Kuritzky, MD

Oral Triptans in Acute Migraine Treatment: A Meta-Analysis of 53 Trials

Migraine is a commonplace disorder that typically results in recurrent attacks of disabling headache. Triptans have become the foundation of abortive therapy for most migraneurs, yet little guidance is available to choose the most appropriate triptan from among the available, and soon to be available, agents. In this meta-analysis, Ferrari and colleagues reviewed data from 24,089 patients who had been included in double-blind, randomized, controlled clinical trials of oral triptans in migraine.

Sumatriptan (SUM) is the most widely used triptan, and hence serves as the most convenient and familiar comparator. Efficacy measures included response at 2 hours, pain free at 2 hours, recurrence within 24 hours, and sustained pain-free status (free of headache at 2 hours, without recurrence within 24 hours).

Eletriptan (ELE) demonstrated a higher placebo-subtracted 2-hour response rate and pain free at 2 hours rate than SUM, but frovatriptan (FRO) was slightly less efficacious than SUM for response at 2 hours. Sustained pain-free status was statistically significantly greater for rizatriptan (RIZ), ELE, and almotriptan (ALM). Placebo-subtracted adverse events rates were significantly lower for ALM.

As a group, all triptans demonstrate similar efficacy and adverse event profiles. Modest differences between agents might be helpful in initial product selection. ❖

Ferrari MD, et al. Lancet. 2001;358: 1668-1675.

Simvastatin and Niacin, Antioxidant Vitamins, or the Combination for the Prevention of Coronary Disease

It has been suggested that cardiovascular risk is separately and independently related to both changes in LDL and HDL. The oft-quoted relationship between lipid subfractions suggests that for each 1% reduction in LDL, one might achieve a 1-1.5% decline in cardiovascular end points, and that for each 1% increase in HDL a 2-4% reduction in cardiovascular end points. This study (n = 160) evaluated the hypothesis that for persons with existing coronary artery disease (CAD), lipid-altering and antioxidant treatments might provide independent and additive benefits. Inclusion criteria included established CAD plus a low HDL.

Treatments received by the subjects included simvastatin, slow-release niacin, and/or antioxidants (800 IU vitamin E, 1000 mg vitamin C, 25 mg beta carotene, 100 µg selenium daily). Patients were followed for 3 years, with end points of stenosis status and clinical cardiovascular events.

Risk of death from coronary causes, confirmed MI or stroke, or revascularization for worsening ischemia (the composite primary end point of the trial) was 90% lower in the simvistatin + niacin group than the placebo group. No statistically significant effects were shown for use of antioxidants. Brown and colleagues suggest that the combination of simvastatin and niacin may represent a major advance of traditional monotherapies, and that there is little to support the commonplace practice of antioxidant supplementation for CAD modulation. ❖

Brown BG, et al. N Engl J Med. 2001; 345:1583-1592.

Decreased Rate of Coronary Restenosis After Lowering of Plasma Homocysteine Levels

The potential etiologic relationship of homocysteine (HCST) to cardiovascular disease end points has generated much recent scrutiny. There has not been a major clinical trial indicating that homocysteine modification effects cardiovascular outcomes. Schnyder and colleagues examined the effect of folic acid-based treatment (FBT)—ie, 1 mg folic acid, 400 mcg vitamin B12, and 10 mg pyridoxine daily—upon post-coronary angioplasty patients (n = 205) administered over 6 months.

FBT produced a 35% reduction in homocysteine levels (from 11.1 to 7.2). Minimal luminal diameter was greater and degree of stenosis was less severe in FBT recipients.

FBT treatment produced an impressive halving of the rate of restenosis, and a comparably favorable reduction in the need for revascularization of the target lesion.

Administration of moderate supplementation with folic acid, vitamin B12, and pyridoxine is inexpensive and well tolerated. Schnyder et al suggest that such treatment should be considered "adjunctive therapy" after coronary angioplasty. Though folate is likely to be the most prominently involved constituent, it is possible that pyridoxine and/or vitamin B12 also exert effects. ❖

Schnyder G, et al. N Engl J Med. 2001;345:1593-1600.

In Future Issues: NSAIDs Protect Against Alzheimer's Disease