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CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

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CONFERENCE COVERAGE

Editor's Note: *The following reports from the annual scientific sessions of the American College of Cardiology held March 30 to April 2, 2003, were obtained by handwritten notes, press releases, and news reports.*

FACIT

ELEVATED PLASMA HOMOCYSTEINE HAS BEEN CORRELATED WITH increased rates of adverse cardiac events in patients with established atherosclerosis, and a growing body of data have suggested that reduction of plasma homocysteine with vitamin therapy reduces the risk of atherosclerotic coronary events even in those patients without overtly elevated homocysteine levels. Thus, the potential benefit of homocysteine-lowering vitamin therapy for prevention restenosis and adverse cardiac events after percutaneous coronary intervention (PCI) has been an area of interest in the interventional cardiology community. Enthusiasm for this concept was further heightened by a relatively recent study reported by Schnyder and colleagues from the University of Bern,[1] which compared angiographic and clinical outcomes in 553 patients undergoing PCI who were randomized to receive homocysteine-lowering therapy (folic acid [1 mg/d], vitamin B12 [0.4 mg/d], and vitamin B6 [10 mg/d]) for 6 months after the index procedure. The Swiss Heart Study showed significant increases in minimal lumen diameter (MLD) and reduced restenosis at 6-month angiographic follow-up, a significant reduction in the composite clinical end point (15.4% vs 22.8%, $P = 0.03$) and the need for ischemia-driven repeat revascularization, and as well as trends toward decreased death and myocardial infarction (MI) at 1-year follow-up for patients receiving folate +B12+ B6 therapy. Based on the results of this study and enthusiasm for vitamin therapy among US patients in general, many interventional cardiologists began recommending the addition of folate +B12+ B6 supplementation to the pharmacologic regimen of their post-PCI patients.

The results from FACIT were presented by Dr. Helmut Lange (Bremen Heart Center, Bremen, Germany). The FACIT investigators

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studied 626 patients who underwent successful stent implantation and were randomized to receive a vitamin preparation containing folic acid (1.2 mg/d), vitamin B12 (0.06 mg/d), vitamin B6 (48 mg/d), or placebo. The primary end point was angiographic MLD at 6 months. Secondary end points included angiographic restenosis, major adverse cardiac events (MACE), and target vessel revascularization (TVR). As in previous studies, homocysteine levels decreased in patients receiving folate +B12+ B6 supplementation. However, in contrast to the Swiss Heart Study, FACIT showed a significant reduction in 6-month MLD in patients receiving folate +B12+ B6 supplementation (1.59 mm vs 1.74 mm), as well as higher percent diameter stenosis and angiographic restenosis (35% vs 27%). In addition, higher rates of TVR (15.8% vs 10.6%) and MACE (16.8% vs 10.9%) were also reported in the folate +B12+ B6 supplementation group with clinical event curves separating within 2-3 months of follow-up. Subgroup analysis showed beneficial effects of folate +B12+ B6 supplementation on only women and diabetics. The FACIT investigators were somewhat surprised and "disappointed" to conclude that, based on the results of their study, folate +B12+ B6 supplementation after successful coronary stent implantation was associated with increased in-stent restenosis and higher rates of adverse clinical events.

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In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis. Dr. DiMarco is a consultant for Bayer and Novartis, is on the speaker's bureau for Medtronic and Guidant, and does research for Medtronic and Guidant. Drs. Crawford and Vernon report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

COMMENT BY SARAH M. VERNON, MD

The results of FACIT were unexpected, on the basis of what is known about the pathogenesis of homocysteine-induced vascular injury, the predictive value of plasma homocysteine levels on outcomes after PCI, and the beneficial effect of homocysteine-lowering therapy on cardiovascular event rates in other patient populations with vascular disease. In addition, and even more perplexing, the results of FACIT are in direct contradiction with those of the previously published Swiss Heart Study. The most obvious major difference between these 2 studies is that only 50% of patients in the Swiss Heart study underwent stent implantation compared with 100% of patients in FACIT. There are also differences in mode and timing of initiation of therapy, as well as differences in dosing of all 3 elements included in the homocysteine-lowering vitamin "cocktails" administered in the 2 studies. The Swiss study included more diabetics and patients on statins, and additional distinctions between the patients included in the 2 studies may become evident when the results of FACIT are published. As Lange pointed out in his discussion, further study will be needed to reach definitive conclusion about the use of homocysteine-lowering therapy in patients undergoing PCI. However, in the meantime, the potential untoward effects of folate + B12 and +B6 therapy as administered in FACIT would suggest that homocysteine-lowering therapy should not be initiated routinely after coronary stent implantation. In turns out that, contrary to my commentary on this issue in October,[2] despite the results of the Swiss Heart Study and the fact that folate +B12+ B6 therapy is "inexpensive, readily available, well tolerated and readily embraced by patients," there may, in fact, be a real "down-side" to recommending it for our post-PCI patients. ■

References

1. Schnyder G, et al. *JAMA*. 2002;288:973-979.
2. Vernon S. *Clinical Cardiology Alert*. 2002;21:73-74.

ISAR-REACT

DR. ADNAN KASTRATI (DEUTSCHES HERZZENTRUM, Munich, Germany) presented the results of Intercoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment (ISAR-REACT). This study evaluated the effectiveness of the glycoprotein IIb/IIIa inhibitor abciximab compared to placebo in low-risk patients undergoing elective percutaneous coronary interventions (PCI)—all of whom had been pretreated with high-dose clopidogrel. The clopidogrel regimen used in this study was a 600-mg oral loading dose given

at least 2 hours before the index procedure, followed by 75 mg twice daily for 3 days, then 75 mg daily for at least 4 weeks. All patients received 100 mg of aspirin. Patients with acute coronary syndromes, recent myocardial infarction (within 14 days), insulin requiring diabetes mellitus, saphenous vein procedures, or reduced left ventricular systolic function (EF < 0.30) were excluded from the study. The primary end point was a composite of death, myocardial infarction (new Q-waves or CK elevation = 3 times normal) or target vessel revascularization (TVR) at 30 days. Safety end points included major and minor bleeding, thrombocytopenia, and need for transfusion. A total of 2159 patients were randomized in the study—1079 to abciximab and 1080 to placebo. Ninety-one percent of the patients underwent stent implantation. There were no significant differences between abciximab- and placebo-treated patients with regard to the composite primary end point (4.2% vs 4.06%) or to any individual component of the composite. There were no differences between the groups with respect to bleeding events, although thrombocytopenia was more common and transfusion rates were significantly increased in the abciximab group. Kastrati concluded that in the setting of elective PCI in the low-risk nondiabetic patient who has been pretreated more than 2 hours in advance with high-dose clopidogrel, there is no additional benefit of abciximab administration. Kastrati pointed out that these data cannot be extrapolated to higher-risk patients such as those with ACS and stated that a similar trial in a high-risk PCI population was planned.

COMMENT BY SARAH M. VERNON, MD

The most recent ACC/AHA Practice Guidelines for management of ACS (2002) recommend clopidogrel as the thienopyridine of choice given its rapid onset of action and superior safely profile. Also, they recommend a loading dose of 4-8 tablets (300-600 mg) when "rapid onset of action is required." This recommendation is based, at least in part, on data from the CURE and PCI-CURE trials, which used a 300-mg loading dose of clopidogrel, and smaller studies evaluating the effect of a clopidogrel loading dose on ADP-induced platelet aggregation or ex vivo thrombus formation. Even careful reading of the guideline and its bibliography does not elucidate the origins of the recommendation for a 600-mg loading dose. More recently, the CREDO trial[1] evaluated the benefits of clopidogrel administration in patients undergoing elective stent implantation both in terms of timing and duration of clopidogrel administration, demonstrating a 38.6% reduction of adverse events in patients pretreated more than 6 hours before their index procedure and a 26.9% reduction in death, MI, and stroke when continued for 1 year. Data from CREDO has convinced operators in our catheterization laboratory to initiate clopidogrel loading as early as possible before diagnostic cardiac catheterization with a moderate-to-high likelihood of follow-on PCI.

The results from ISAR-REACT would suggest that in the low-risk elective PCI patient, pretreatment with clopidogrel (albeit at a higher dose than in CREDO) provides antiplatelet activity adequate to obviate the addition of a GP IIb-IIIa inhibitor in the management of these patients. This result is, in fact, not particularly surprising, as there have never been data demonstrating significant benefit of GP IIb-IIIa inhibitor administration in low-risk, nondiabetic patients undergoing PCI. While many interventional operators will tell you that the low-risk elective patient included in ISAR-REACT constitutes the minority of his/her practice, these patients do exist. With GP IIb-IIIa inhibitor administration rates estimated on the order of 70-90% of PCI procedures performed in the United States, it's clear that at least some of the patients receiving GP IIb-IIIa inhibitors, drugs with extremely high cost and some bleeding risk, are unlikely to obtain any real benefit from receiving them. While it's true that the results from ISAR-REACT can only be applied to a relatively narrow sector of patients undergoing PCI, perhaps they will give us the fortitude to choose clopidogrel preloading over abciximab administration for our low-risk PCI patients. ■

References

1. Steinhubl SR, et al. *JAMA*. 2002;288:2411-2420.

Indoor Smoking Ban Ordinance

SMOKING ACTIVATES PLATELET AGGREGATION, decreases endothelial-dependant vasodilatation, increases heart rate, and decreases heart rate variability. It has been shown that passive smoke increases the incidence of myocardial infarction in spouse studies. Other studies show that a smoke-free workplace decreases the number of cigarettes smoked per day in smokers. These data suggest that indoor smoking bans may reduce the risk of myocardial infarction in smokers and others. Thus, investigators took advantage of a new smoke-free ordinance in Helena, Mont, to test this hypothesis. The results were presented by Dr. Richard Sargent. On June 4, 2002, Helena passed an ordinance that banned smoking in the workplace, public places, and even the Native American casinos. This ordinance was rescinded on December 3, 2002, by a court order, resulting in 6 months of intervention data, which they compared to data from the previous 4 years (historical control). Com-

pliance with the law was excellent while it was in force. Since almost all myocardial infarctions are admitted to 1 hospital in Helena, the investigators believed that they did not miss any. However, infarctions secondary to other conditions (ie, post surgery) were excluded. In addition, seasonal variation was taken into consideration. Finally, to be included, infarction patients had to have been in Helena for at least 1 night or 1 meal. The primary end point was acute myocardial infarction per month, which was reduced by 60% during the time the ordinance was in force vs the seasonally adjusted historical control period, $P < .002$. Patients who resided in nearby counties not affected by the ordinance, who used the same hospital, showed no change in infarction rates. The investigators concluded that a ban on indoor smoking in public and workplaces had an immediate and substantial beneficial effect on acute myocardial infarction rates. They suggest that communities who wish to enact such ordinances first educate their state legislators so that the court problems they had can be avoided.

COMMENT BY MICHAEL H. CRAWFORD, MD

This is an impressive result in this simple study and points to the power of the law to affect public health. Similar results have been seen with seat belt laws, helmet laws, etc, but this is the first study showing the power of law to affect cardiovascular health. Of course, it would be preferable if people just didn't smoke or at least didn't in public places, but achievement of such an aim seems impossible despite nearly 40 years of antismoking publicity since the first Surgeon General's report in 1964. Unfortunately, the citizens of Helena, Mont, no longer benefit from this ordinance, since a court order rescinded it after 6 months. The investigators did not go into the details of the court challenge, but did state that education of the state legislature and ensuring their support probably would have avoided the court challenge. They are hopeful they can get the law reinstated soon. This would be good since it would be advantageous to see more than 6 months of data. A more robust study with the same results would be a powerful tool to help enact similar ordinances in other cities. ■

COMPANION

DRS. ARTHUR FELDMAN AND MICHAEL BRISTOW presented the Comparison of Medical, Resynchronization, and Defibrillation Therapies in Heart Failure (COMPANION) trial at the Late-Breaking Clinical Trials session at the ACC. COMPANION was a randomized trial of New York Heart Association Class 3 or 4 heart failure patients with an ECG QRS duration > 120 msec, a left ventricular ejection fraction < 35%, and an end-diastolic dimension > 60mm. Patients were randomized to either optimal pharmacologic therapy, cardiac resynchronization therapy with a biventricular pacemaker, or cardiac resynchronization therapy with a biventricular defibrillator. The randomization was in a 1:2:2 format, so that only 20% had no device. Optimal medical therapy was carefully monitored and included beta-blockers, diuretics, ACE inhibitors or angiotensin receptor blockers, spironolactone, and digoxin, whenever tolerated, for at least 1 month. A total of 1520 patients were randomized in the trial. Implant success rate for the resynchronization pacemaker or defibrillator was about 90%.

The mean left ventricular ejection fraction in each group was close to 22%. About 55% of the patients had ischemic heart disease and 45% nonischemic cardiomyopathies. The primary end point was a combination of all-cause death and all-cause hospitalizations over 12 months. Deaths and hospitalizations were reduced by both cardiac resynchronization alone and cardiac resynchronization plus defibrillation by 19%, which reached the efficacy boundaries of the trial so it was stopped early. Mortality in the medical therapy group was 19%. There was a nonsignificant 23.9% reduction in all-cause mortality with cardiac resynchronization and a highly significant reduction of 43.4% with the addition of defibrillation to resynchronization therapy. Benefit was seen in patients with both ischemic and nonischemic disease.

Feldman and Bristow conclude that cardiac resynchronization plus defibrillation therapy produces both symptomatic and mortality benefits in patients who meet these entry criteria. Resynchronization alone results in reduced hospitalization and a trend toward decreased mortality with a delayed onset of effect on mortality.

COMMENT BY JOHN DiMARCO, MD, PhD

Cardiac resynchronization therapy is now being offered to many patients with left ventricular dysfunction and a widened QRS. The COMPANION trial provides further data supporting the benefit of this approach. The important observations here are that the effects of adding a defibrillator are additive to effects seen with cardiac resynchronization alone. This results in a very substantial reduction in hospitalization mortality even though patients were treated with pharmacologic therapy for heart failure.

There were several limitations in the trial. Since the devices that provide resynchronization therapy were introduced during the trial, there was an excess dropout rate among patients in the optimal medical therapy group. Complete data on those patients were not presented. In addition, the hospitalization for the device was not

counted as an end point in the trial. If there were changes in medical therapy during that initial hospitalization, that might have accounted for some of the improvement in hospitalization rates. Hopefully, once the full data from the trial become available, many other clinical questions will be answered. ■

SPORTIF III

At the late-breaking clinical trials session of the American College of Cardiology meeting Dr. Jonathan Halperin presented the results of SPORTIF III, a trial investigating the use of a direct thrombin inhibitor, ximelagatran in patients with atrial fibrillation. Ximelagatran is an oral direct thrombin inhibitor that produces the onset of anticoagulation within 2 hours after oral ingestion. In previous trials, it has been shown to have a wide therapeutic margin. It is not extensively metabolized so it has a low potential for food and drug interactions. Because of these factors, no anticoagulation monitoring is required and a single dose (36 mg b.i.d.) can be used except in the presence of severe renal dysfunction. In SPORTIF III, 3407 patients with atrial fibrillation were randomized to either adjusted dose warfarin to maintain an INR between 2 and 3 and fixed dose ximelagatran (36 mg b.i.d.). Patients had to have atrial fibrillation and at least 1 additional risk factor for stroke. Treatment was open label to simplify monitoring of prothrombin times in the warfarin group. The primary end points were strokes and systemic embolic events based on an intention-to-treat analysis. An on-therapy analysis was also reported. The hypothesis was that ximelagatran would not be inferior to warfarin in these patients.

The patients enrolled were representative of an elderly atrial fibrillation population. More than 80% had been in atrial fibrillation for more than a year. More than 90% had persistent or permanent atrial fibrillation. One-third of patients were older than 75; 40% were between 65 and 75. Sixty-five percent of the patients were male. Hypertension was seen in 66% of the patients; prior stroke, TIA, or embolism in 24% of the patients. Warfarin therapy was carefully monitored. Sixty-six percent of the INR values obtained during the study were within the prescribed therapeutic range, and 81% were within an expanded range of 1.8 to 3.2. In the intention-to-treat analysis, there were 56 strokes or embolic events in the warfarin group for an annual rate of 2.3% per year. Among the ximelagatran patients, there were 40 events for a rate of 1.6% per year. This met the statistical criteria for noninferiority. In the secondary on-treatment analysis, the relative risk reduction for stroke and systemic embolism was 41% ($P = 0.018$). Major and minor bleeding events were also evaluated. The rates for intercranial hemorrhage (0.2% vs 0.5%) and major bleeding (1.3% vs 1.8%) both favored ximelagatran, but the differences were not statistically significant. When major and minor bleeding events were combined, the rates were 25% per year on ximelagatran and 29.5% per year on warfarin ($P = 0.007$). There were no significant differences in major cardiovascular events or in all-cause mortality between the 2 groups. Liver enzyme elevation was more common with ximelagatran. A total of 6.5% of the patients on ximelagatran developed an ALT greater than 3 times the upper limit of normal vs only 0.7% on warfarin. Most of the liver enzyme elevations occurred in the first 6 months of therapy and resolved even if the drug was continued. There were no cases of hepatic failure. Halperin concluded that ximelagatran is as effective as well-controlled warfarin in preventing stroke and systemic embolism. Ximelagatran was associated with less total bleeding than was seen during warfarin therapy, but elevated liver enzymes were more common.

■ COMMENT BY JOHN DiMARCO, MD, PhD

Warfarin has been the standard for anticoagulation for more than 50 years. In the late 1980s, a number of trials conclusively showed the benefits of warfarin in patients with atrial fibrillation who were either elderly or had other risk factors. Warfarin therapy, however, has many limitations. Because the drug has many potential interactions with food and other medications, frequent monitoring of the prothrombin time is necessary. Bleeding is also common during therapy. Warfarin's onset of action is delayed, and reversing warfarin's effects can be difficult. Ximelagatran is a new antithrombotic agent. After oral administration, it is converted to melagatran, which is a direct inhibitor of thrombin. The drug is absorbed in the small intestine. Peak concentrations of melagatran are reached 30 minutes after oral ingestion. Peak ximelagatran concentrations are seen about 2 hours after absorption. In melagatran, the active metabolite is predominantly renally eliminated. In prior trials, the drug had been shown to have a wide margin of safety, and dosage adjustment is not thought to be required unless the creatinine clearance is below 30 mL/min. In this important study, ximelagatran was shown not to be inferior to warfarin. All of the measurements appear to favor ximelagatran over warfarin. Given the many disadvantages of warfarin, it is likely that ximelagatran will be an attractive option for many patients who require anticoagulant therapy.

Ximelagatran has also been studied in a number of trials with venous thromboembolism for both primary and secondary prevention. Further data, however, will be needed concerning its use in other situations. In particu-

lar, for cardiologists, it will be important to have data about its use in patients with prosthetic valves and also in patients with decreased renal function. ■

Aldosterone Blockade: Another Winner

ABSTRACT & COMMENTARY

Synopsis: *When RALES and EPHESUS are considered together, one clearly can recommend the use of an aldosterone receptor blocker for all very ill patients with congestive heart failure and significant LV dysfunction, whether or not related to acute myocardial infarction.*

Source: Pitt B, et al. *N Engl J Med*. 2003;348: 1309-1321.

Following on the heels of the RALES trial, which successfully tested spironolactone in patients with severe heart failure, Pitt and associates announced the results of EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) at a late-breaking trial session at the American College of Cardiology Scientific Sessions. Simultaneously, it was published on the *New England Journal of Medicine* web site and as the lead article in the April 3, 2003, issue. Eplerenone (EPL) is a new aldosterone antagonist that selectively blocks the mineral corticoid receptor, but not the receptors for glucocorticoids, progesterone, or androgen. This drug was used in a high-risk population of post-acute MI patients with congestive heart failure. A total of 6642 patients were randomized to EPL 20-50 mg per day vs placebo and were followed for a mean of 16 months (range, 0-33). Eligible subjects were randomized between 3 and 14 days after an acute infarction; they had to demonstrate left ventricular dysfunction (LVEF of < 40%), as well as clinical heart failure, as confirmed by rales, congestion on x-ray, or a third heart sound. Diabetics could be enrolled with asymptomatic LV dysfunction only. Patients received optimal medical therapy, including ACE inhibitors (86%), beta-blockers (75%), diuretics (60%), aspirin (88%), and statins (47%). Careful potassium boundaries were followed for safety reasons; EPL was decreased or discontinued if potassium rose above 5.5. Two primary end points were used: all-cause mortality, as well as time to cardiovascular death or first hospitalization for a cardiovascular (CV) event. A multiplicity of statistical analyses were used. The study was halted by design when 1012 deaths occurred. This was an international trial involving almost 700 centers in 37 countries, with enrollment occurring during the years 2000 and 2001. The baseline cohorts consisted of 3313 evenly matched individuals. Discontinuation rates were equal in EPL and placebo. The average study medication dose was 43 mg.

The primary end point of all-cause death favored EPL, with a 15% risk reduction ($P = 0.008$). The other primary end point of cardiovascular death or hospitalization for CV events was also reduced by 15% ($P = 0.002$). Sudden cardiac death was decreased by 21% ($P = 0.03$), and hospitalizations for heart failure were reduced by EPL by 15% ($P = 0.03$). The reductions were consistent across a wide variety of sub-groups as well as geographic regions.

Safety data indicated that an incidence of serious hyperkalemia (potassium > 6.0 mE/L) with EPL was 5.5% vs 3.9% in placebo patients ($P = 0.002$). A low baseline creatinine clearance was a risk factor for hyperkalemia, which resulted in 15 EPL and 3 placebo patients requiring hospitalization.

Pitt et al conclude that EPL added to an optimal treatment regimen after acute MI "resulted in additional reduction in overall mortality and the rate of death from CV causes or hospitalization for CV events among patients with acute MI complicated by left ventricular dysfunction and heart failure." The 1-year mortality rate in placebo patients was 13.6%, which is in the mid-range for the major beta-blocker heart failure trials and greater than the recent CAPRICORN study of post-MI patients treated with carvedilol. Thus, this was a relatively high-risk post-MI population. The mortality in EPHESUS compared to RALES, which used Class III - IV patients with left ventricular dysfunction (mean EF 25%), was higher in RALES, presumably because of worse LV function (mean EF in EPHESUS was 33%) and possibly some recovery of LV function in the acute MI patients in EPHESUS. A major component of the reduction of cardiovascular mortality in EPHESUS was a 21% decrease in sudden cardiac death. Pitt et al emphasize the need to "monitor serum potassium and adjust the dose of EPL accordingly." Of note, hypokalemia was more common than hyperkalemia, and EPL reduced this risk. A potassium < 3.5 mE/L was observed in 8.4% on EPL and 13.1% on placebo ($P < 0.001$). No sexual side effects were noted with EPL (gynecomastia, impotence), presumably because of the selective nature of this aldosterone antagonist. Pitt et al conclude that 1 life would be saved by treatment of 50 individuals in a year; the number needed to decrease cardiovascular death or hospitalization at 1 year is 33.

COMMENT BY JONATHAN ABRAMS, MD

The idea that aldosterone is a significant adverse player in patients with left ventricular dysfunction is relatively new and somewhat surprising to many physicians. In fact, aldosterone blockade reduces coronary vascular inflammation and attenuates fibrosis in animals. EPL has been shown to decrease oxidative stress, improve endothelial function, decrease platelet aggregation, increase endothelin, decrease matrix metaloproteinase activation, and to improve post-MI remodeling in animal models. Sympathetic drive and heart rate variability are favorably affected by aldosterone blockers; free radicals are reduced. Thus, it is obvious that aldosterone is more than a hormone that solely affects sodium retention. Aldosterone causes increased tissue ACE and angiotensin II, as well as NFKB activation and enhanced oxidative stress. Elevated aldosterone levels have been shown to be adverse in animals, as well as humans with depressed left ventricular systolic function, in part related to stimulation of increased fibrosis within the myocardium. When RALES and EPHESUS are considered together, one clearly can recommend the use of an aldosterone receptor blocker for all very ill patients with congestive heart failure and significant LV dysfunction, whether or not related to acute myocardial infarction. Whether these compounds will be more beneficial in subjects with less severe heart failure and better LV function than these 2 studies remains to be determined. Furthermore, it must be stressed that the efficacy of EPL in the EPHESUS trial is in addition to an ACE inhibitor and a beta-blocker. There is no role for aldosterone receptor blockade without "best medical therapy" for heart failure and major LV dysfunction. Aside from hyperkalemia, potentially a greater problem with subjects on an ACE inhibitor and poor renal function, there is little downside with these drugs. Furthermore, we have had a very long experience with spironolactone, which has a relatively benign safety record other than its estrogen and androgen actions. Pitt et al are to be congratulated for championing the aldosterone hypothesis, as well as designing and completing 2 major trials in the period of 4 years that have favorably impressed the medical community. ■

A to Z Trial (Aggrastat to Zocor)

THIS LONG-AWAITED INVESTIGATION REPORTED ON THE heparin anticoagulation therapy (A phase) of the A to Z Trial at the ACC Annual Meeting; the statin component is still ongoing. This is a trial of 4000 individuals with an acute coronary syndrome (ACS). Two questions were asked: which is the more effective antithrombotic therapy, the low-molecular-weight heparin (LMWH) enoxaparin (ENOX) or unfractionated heparin (UFH); and is aggressive statin therapy in ACS more beneficial than later statin initiation? Patients with ACS, characterized by chest pain within 24 hours of at least 10 minutes duration, associated with ST changes and/or positive biomarkers. Patients could not have had been on lipid-lowering therapy within 6 weeks. They were randomized to a heparin within 24 hours. Exclusion criteria included a creatinine of > 2.0 mg/dL or abnormal liver function tests. Enrollment took place from December 1999 to May 2002. Approximately 2000 patients were randomized to each of the 2 strategies. All patients received tirofiban. The heparin regimen included ENOX 1 mg per kg every 12 hours vs UFH for 24-48 hours. The primary end point was 7-day CAD death, recurrent myocardial infarction, or refractory ischemia associated with ECG changes or positive biomarkers. The main goal was to demonstrate noninferiority of ENOX over UFH. More than half the patients underwent early PCI. The use of ACE inhibitors and beta-blockers was robust. The event rates were ENOX 8.4% and UFH 9.4%, (*P* = non significant for superiority and equivalent for noninferiority). All secondary end points, including death, MI, or refractory ischemia, were nonsignificant, but trended positive for ENOX. Mortality was 0.9% UFH and 1.1% ENOX, (*P* = not significant). Bleeding events were low, 3.1% for ENOX and 2.2% for UFH (*P* = non significant). Major bleeds were 0.4% for UH and 0.9% for ENOX, with a < 1% requirement for transfusions. Most of the major bleeds were associated with invasive procedures. This study concludes that enoxaparin is an attractive alternative to the use of unfractionated heparin with efficacy end points trending in favor of the LMWH. Both agents were found to be quite safe. The statin arm is continuing.

COMMENT BY JONATHAN ABRAMS, MD

This trial does not unequivocally support superior efficacy for LMWH. Nevertheless, the composite triple end point of death, MI, or refractory ischemia is favorable for ENOX when the ESSENCE, TIMI IIB, INTERACT, and A to Z trials are combined.

This study was the first to include a large number of ACS patients receiving a IIb/IIIa inhibitor and an invasive approach was used in 60% of patients, clearly increasing bleeding rates. Another ongoing trial, SYNERGY (ACS patients who undergo early angiography and are randomized to LMWH or UFH) should provide more data on bleeding risks. In the meantime, physicians can use either ENOX or UFH, according to preferences. The ACC ACS Guidelines rate ENOX as a IIa indicator. ■

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21. The incremental value of a defibrillator to a biventricular resynchronization therapy in patients with class III-IV heart failure is:
a. reduced hospitalization.
b. reduced mortality.
c. reduced pharmacologic therapy.
d. increased ejection fraction.

22. A reduction in passive smoke exposure in a community:
a. reduces pneumonia incidence.
b. reduces all-cause mortality.
c. reduces the frequency of acute MI.
d. All of the above

23. The potential advantages of ximelagatran vs warfarin include:
a. less bleeding events.
b. no INR monitoring.
c. less food and drug interactions.
d. All of the above

24. An aldosterone antagonist in addition to ACE inhibition and beta-blockers in post-MI heart failure patients:
a. reduced all-cause mortality.
b. reduced sudden cardiac death.
c. reduced hospitalization for heart failure.
d. All of the above

25. In acute coronary syndrome patients treated with tirofiban, enoxaparin vs unfractionated heparin showed:
a. similar cardiovascular event rates.
b. similar bleeding complications.
c. similar mortality.
d. All of the above

26. In postcoronary stent patients, treatment with folate, B12, and B6 6-month coronary angiography showed:
a. reduced minimal lumen diameter.
b. reduced major adverse cardiovascular events.
c. reduced target vessel revascularization.
d. All of the above

27. In low-risk percutaneous coronary intervention patients treated with 600 mg of clopridogrel > 2 hours prior to the procedure, abciximab therapy:
a. reduced cardiovascular events.
b. increased the need for blood transfusion.
c. reduced all-cause mortality.
d. All of the above

Answers: 21(b); 22(c); 23(d); 24(d); 25(d); 26(a); 27(b)

PHARMACOLOGY WATCH

Counterfeit Procrit Uncovered by FDA Surveillance

In one of the more bizarre stories of the year, the FDA has uncovered files of counterfeit Procrit (epoetin alfa—Johnson & Johnson) in routine surveillance. To make matters worse, the fake vials have been contaminated with bacteria and many contain no active ingredient. Johnson & Johnson is sending out a "Dear Doctor" letter to warn health care professionals about the counterfeit vials including the lot numbers of the suspected counterfeits. Fake Procrit was also discovered last summer in United States. At that time, counterfeiters apparently purchased 2000 U/mL vials and labeled them as the higher priced 40,000 U/mL vials. More information is available at the Johnson & Johnson/Ortho Biotech web site including pictures of the counterfeit vials.

Pharmaceutical Marketing Campaigns in Full Swing

Love 'em or hate 'em, direct-to-consumer (DTC) advertisements of pharmaceuticals are big business. The Kaiser Family foundation reports that spending on DTC ads increased nearly 10-fold in 10 years, from $260 million to $2.5 billion in 2000. More than 80% of respondents report seeing or hearing a drug ad in the last 3 months according to an FDA survey, and the Kaiser study reports that one third of patients have asked their doctor about an ad they saw on TV or in print. Unfortunately, drug ads are increasingly unregulated. The FDA is tasked with reviewing DTC ads for false or misleading statements, but according to a recent review in *Consumer Reports*, the agency has only 30 reviewers to handle 30,000 submissions each year. By the time false or misleading ads are pulled from the airways, they have often run their lifespan, with new ads appearing in their place. But are the pharmaceutical companies getting $2.5 billion of value from these ads? Apparently. A recent FDA survey of physicians revealed that when patients initiate a discussion about a prescription drug they've seen advertised, they asked for a prescription more than 50% of the time. Some 66% of physicians said they were not pressured to prescribe a drug in that situation. However, when a specific brand name drug was requested, physicians felt pressured to prescribe it more than 50% of the time. Despite this, physicians are split on the effect of DTC ads on their patients and practice, with 32% feeling negative about the ads, 40% feeling positive, and 28% feeling that DTC advertising has no effect on the practice (www.fda.gov/cder/ddmac/presentations.htm).

Ambulatory Antibiotic Reduction: Take the Good with the Bad

The national campaign to reduce antibiotic use in ambulatory practice seems to be working, but there is good news and bad news. Researchers from UCSF and Harvard reviewed the rates of overall antibiotic use in the National Ambulatory Medical Care Survey between 1991-1992, and compared those rates to usage between 1998-1999. The use of antibiotics decreased in the latter time period especially for the treatment of respiratory tract infections such as the common cold and pharyngitis (visits with a

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prescription decreased from 13% to 10% in adults, and from 33% to 22% among children). The use of broad-spectrum antibiotics increased over the same time span; however, including the macrolides azithromycin and clarithromycin, quinolones, amoxicillin-clavulanate, and second- and third-generation cephalosporins. The use of these antibiotics increased from 24% to 48% of all antibiotic prescriptions among adults and from 23% to 40% among children. An accompanying editorial reiterates the CDC's Campaign for Appropriate Antibiotic Use in the Community, which encourages prescribing antimicrobials only when they are likely to be beneficial to the patient, selecting agents that will target the likely pathogen, and using these agents in the correct dose and for the proper duration. The editorial suggests that we have been effective at decreasing the overall use of antibiotics, but less successful at promoting targeted therapy, ie, using narrow spectrum antibiotics whenever appropriate to reduce the likelihood of resistance in a population (*Ann Intern Med*. 2003;138:525-533,605-606).

Nefazodone Under Attack Once Again

Public Citizen, the national nonprofit watchdog organization, has petitioned the FDA to remove the antidepressant nefazodone (Serzone—Bristol-Myers Squibb) from the US market. The petition is based on evidence of liver toxicity associated with the drug including liver failure and death. Nefazodone was recently pulled from the European market after reports of a worldwide total of 28 cases of liver failure of which 18 patients died. The move in Europe was voluntary on the part of Bristol-Myers Squibb because of the call for increased liver enzyme monitoring requirements in several European countries. In this country, the FDA has required a black box warning on nefazodone since January 2002. Despite these concerns, nefazodone, which is a SSRI antidepressant, continues to be relatively popular, with more than 4 million prescriptions written last year. Bristol-Myers Squibb has no plans to withdraw the drug in this country at present.

Lindane Receives Black Box Warning

The FDA has issued a Public Health Advisory concerning the use of lindane for the treatment of scabies and lice. The boxed warning is the result of concern of potential neurotoxicity especially in children. The new advisory states that lindane is a second-line treatment and updates information about its potential risk in children and adults who weigh less than 110 pounds. The advisory also states that reapplication of lindane lotion or shampoo is not appropriate even if itching continues after the single treatment. The FDA is also requiring package sizes to be limited to 1 and 2 oz in order to minimize the potential for product access in a single treatment. Lindane, also known as gamma benzene hexachloride, is an industrial pesticide, has been in use for decades, and has been banned in several countries. Neurologic side effects include dizziness, seizures, and even death. The drug is currently approved for the treatment of lice and scabies in patients who have failed or are intolerant of other therapies. First-line agents for scabies include permethrin cream (Nix, Elimite, Acticin) and malathion lotion (Ovide) and for lice pyrethrum with piperonyl butoxide shampoo and cream rinse permethrin cream rinse (Nix and Rid).

Aspirin Could Help Reduce Colorectal Adenomas

Two different studies in the same issue of the *New England Journal of Medicine* suggest that daily doses of aspirin reduce the risk of colorectal adenomas. In the first study, 635 patients with previous colorectal cancer were randomized to receive either 325 mg of aspirin per day or placebo. The study was terminated early when a significant reduction in colorectal adenomas was shown during the planned interim analysis. After an average of 12.8 months of follow-up, 1 or more adenomas were found in 17% of patients in the aspirin group and 27% patients in the placebo group ($P = 0.004$). The mean number of adenomas was lower in the aspirin group ($P = 0.003$) and the time to detection of the first adenoma was longer in the aspirin group than in the placebo group ($P = 0.022$). In the second study, 1121 patients with a recent history of adenomas were randomized to placebo (372 patients), 81 mg of aspirin (377 patients), or 325 mg of aspirin (372 patients). Follow-up colonoscopy was done approximately 3 years after randomization. The incidence of 1 or more adenomas was 47% placebo group, 38% in the 81 mg aspirin group, and 45% in the 325 mg aspirin group (global $P = 0.04$). The risk of larger polyps including adenomas measuring > 1 cm or with tubulovillous or villous, or severe dysplasia was also lowest in the 81 mg aspirin group. An accompanying editorial suggests that inhibition of COX-2 may prevent inflammation, increased cell proliferation and angiogenesis. The author also cautions that prophylactic aspirin is not a substitute for colorectal cancer screening (*N Engl J Med*. 2003; 348:883-890, 891-899,879-880). ■