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CLINICAL CARDIOLOGY ALERT®

A monthly update of developments in cardiovascular disease

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New Heart Failure Clinical Trials

CONFERENCE COVERAGE

Synopsis: *Several studies were reported at the Second Annual Scientific Meeting of the Heart Failure Society of America that should influence physician practice in the care of patients with left ventricular dysfunction and heart failure.*

Source: The Second Annual Scientific Meeting of the Heart Failure Society of America, Boca Raton, FL. September 13-16, 1998.

CIBIS-II

This important trial evaluated the effects of bisoprolol, a selective beta 1 beta-blocker, in patients with heart failure. The trial was stopped prematurely at the second interim analysis because of positive results in the beta blocker arm. Approximately 2600 patients from throughout Europe with Class III or IV congestive heart failure were slowly up-titrated with bisoprolol or placebo over a period of several months. All were on an angiotensin converting enzyme (ACE) inhibitor and diuretics. Entry criteria included an ejection fraction (EF) of less than 35%; 16% of the patients were Class IV. Eighty percent were male, and more than 50% had coronary artery disease. The primary end point was all-cause mortality; a variety of traditional secondary end points were assessed. At the time the trial was stopped, all-cause mortality had decreased in the beta blocker group by 32% (P = 0.0005); death rates were 17.3% placebo vs. 11.8% bisoprolol, with a rate of 12% per year in the placebo arm and 8.2% in the beta blocker cohort. Average follow-up at trial cessation was 1.4 years. There was a 45% decrease in sudden death and a slight favorable trend in deaths from heart failure or unknown causes. There were no significant differences in outcome in subjects with an ischemic etiology (50% reduction in deaths) or different functional class. Total and heart failure hospitalizations were decreased in the beta blocker group. Virtually all secondary end points were positively affected, including in-hospital deaths. Withdrawal rates were 15% for both placebo and bisoprolol. In summary, CIBIS-2 resulted in a 32% reduction in all-cause mortality, 45% reduction in sudden death, 30% reduction in hospitalization for CHF, and 15% reduction in all-cause hospitalization. No

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significant adverse reactions occurred. The authors conclude that only 25 patients would need to be treated with bisoprolol to save one life.

COMMENT BY JONATHAN ABRAMS, MD

This important study confirms recent meta-analysis (*Circulation*, 1998;98:1184) demonstrating an advantage in death or heart failure hospitalization as well as EF in more than 3000 patients receiving a beta blocker who have congestive heart failure. While the mortality rates in CIBIS II suggest that these patients may have been less sick than traditional Class III-IV classification, the data are concordant with the recent carvedilol studies as well as outcomes in a number of small beta blocker trials. Thus, it would appear that all patients who have congestive heart failure with substantial depression of EF should be given a beta blocker unless there are contra-indications. Certainly, this is an attractive policy for stable Class II-III subjects. The question as to whether selective, non-selective, or vasodilator-beta blockers are superior is unresolved and awaits the results of ongoing trials (BEST, COMET, COPERNICUS). Very recently, the MERIT-HT study was stopped because of a major benefit of long-acting metoprolol in 4000 cases of II-IV subjects with an EF less than 40%. The data are not available yet, but this study, along with CIBIS II and the carvedilol trials, underscores that beta blockers clearly increase survival in heart failure with impaired LV systolic function.

MACH-I

This trial was an international evaluation of the T-channel calcium blocker mibefradil, recently removed from the market in the United States because of drug interactions and other toxicity. This promising calcium blocker had received considerable attention, and the results of the MACH-I trial were eagerly anticipated as to whether a calcium blocker could benefit some patients with depressed LV function and heart failure. The primary study end point was all-cause mortality, with a variety of secondary end points. Subjects with an EF of less than 35%, on diuretic and ACE inhibitor, functional Class II-IV, were enrolled after one month of up-titration. Approximately 2600 individuals were enrolled with a mean EF of 25%. Two-thirds had coronary disease; the majority were Class III (10% Class IV, 25% Class II). The study showed a nonsignificant increase in deaths of approximately 11% in the mibefradil group, with an average follow-up of 580 days. There was an early increase in mortality with the calcium channel blocker. A number of drug interactions were evaluated because of the effects of mibefradil on the cytochrome P-450 system; individuals (mostly women) who received the calcium blocker and took amiodarone or other anti-arrhythmics showed a substantially higher death rate.

COMMENT BY JONATHAN ABRAMS, MD

This trial, while already of historic interest, does add to the database regarding whether there is a "safe" calcium channel blocker for heart failure. PRAISE II is asking whether amlodipine may be better than placebo in patients with dilated cardiomyopathy. Data from PRAISE I and several felodipine trials suggest that both amlodipine and probably felodipine are at least safe in these patients. Mibefradil had demonstrated an excellent profile in animal models and showed promise in humans with left ventricular dysfunction in acute studies. Once again, calcium blockers have been a major disappointment for long-term therapy of heart failure. The interaction with many compounds metabolized through cytochrome P-450 was unsuspected and resulted in the withdrawal of mibefradil in the United States after 10 months on the market for angina pectoris. The role of calcium blockers as therapeutic agents for congestive heart failure remains an unfulfilled promise; MACH I is another sad chapter for new and "promising" agents for heart failure.

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RALES

Recognition that ACE inhibition in patients with congestive heart failure does not provide sustained suppression of angiotensin II is well recognized. What is less known is that aldosterone levels rise over time, potentially resulting in important losses in potassium, particularly in patients on a low-sodium diet. Preliminary data indicate that both ACE inhibitors and angiotensin receptor blockers do not indefinitely suppress aldosterone levels. Other data link high aldosterone to mortality (Consensus I). Aldosterone is known to not only promote potassium loss, but it is also associated with ventricular fibrosis, sodium retention, and a variety of other actions that could be adverse in patients with depressed LV function. The RALES Trial was designed to see whether spironolactone would be beneficial in heart failure by preventing elevations in aldosterone. Sixteen hundred patients with Class III-IV heart failure were enrolled for a projected three-year follow-up. All patients were on an ACE inhibitor and a diuretic, and many were on digitalis. Spironolactone was up-titrated, beginning with 25 mg; serum potassium was carefully monitored. The target dose was 75 mg daily. Primary end point was all-cause mortality. The study was stopped by the Data Safety and Monitoring Board on August 24th, 1998, because of a significant benefit in the sprironolactone arm. No data are available at this time.

COMMENT BY JONATHAN ABRAMS, MD

Much credit must be given to Bert Pitt, MD, for the conceptualization of this trial. Details will be released at the upcoming American Heart Association meeting. In a sick population of heart failure patients, there clearly was sufficient benefit provided by spironolactone that resulted in early termination of the trial, approximately 16 months before projected completion. Hyperkalemia was noted in approximately 22-28% of individuals who reached the 50 mg or 75 mg dose, respectively. Nevertheless, the study protocol allowed for careful dosage alterations linked to potassium monitoring. The actual results will be of great interest. It may be that spironolactone, an old and little used agent, may provide an important new therapeutic adjunct for heart failure.

ATLAS

This study, initially reported at the American College of Cardiology meeting in March 1998 (*Clin Cardiol Alert* 1998;17:34), was presented in more detail by Milton Packer, MD. To reiterate, ATLAS asked the question whether high-dose ACE inhibitor was substantially better than low dose cohort. Class III patients with ejection fraction of less than 30% were followed for approximately four years. The mean high dose of lisinopril averaged 33.5 mg vs. 3.5 mg in the low dose. Primary end point was all-cause mortality. There was an 8% trend toward increased survival in the high-dose group, which was not significant. Cardiovascular deaths almost achieved significance (P = 0.07), whereas all-cause death or hospitalization was significantly reduced in the high-dose group (84 vs 80%). Other combined end point results were positive in the high-dose group, as were hospitalizations. Side effects were similar. Recurrent heart failure hospitalization was reduced by 24%. Packer concluded that high doses of ACE inhibitors would substantially reduce hospital admissions and death from congestive heart failure substantially.

COMMENT BY JONATHAN ABRAMS, MD

As previously discussed in *Clinical Cardiology Alert*, the major problem with this study was the use of an extremely low dose of lisinopril in one arm and, thus, setting up an artificial construct. Most patients today are treated with 10-20 mg of lisinopril. Clearly, low doses are not as effective as higher doses. Nevertheless, the study did not demonstrate a robust decrease in any end point, which is somewhat surprising considering the marked difference in dose between the low- and high-dose groups. In general, physicians should continue to use higher doses of ACE inhibitors, as many surveys document underdosing. ❖

Intravenous Beta Blockers for Acute Myocardial Infarction

ABSTRACT & COMMENTARY

Synopsis: *Atenolol improves outcomes in acute MI treated with thrombolytics, but early IV atenolol is of little value. They recommend starting oral atenolol as soon as the patient is stable.*

Source: Pfisterer M, et al. *J Amer Coll Cardiol* 1998; 32:634-640.

In the prethrombolytic era, the early administration of intravenous (IV) beta blockers in acute myocardial infarction (MI) was shown to improve survival. However, physicians were concerned about acute negative inotropic effects and were confused by studies showing mortality reductions even if beta blockers were

started one month after MI. In the thrombolytic era, the benefits of early IV beta blockers were less conclusively shown. Thus, a prospectively planned observational analysis of the Global Utilization of Streptokinase and Thrombolysis for Occluded Coronary Arteries (GUSTO-1) data on beta blocker use is of interest. The protocol recommended atenolol be given as soon as possible after enrollment in patients without hypotension, bradycardia, or heart failure, followed by oral therapy. Five subgroups were analyzed: no atenolol; IV only; oral only; IV plus oral; Of the 41,000 patients enrolled, 75% received any atenolol. In general, those receiving atenolol were younger, had higher blood pressure, lower heart failure class, and more likely had anterior MI. Thirty-day mortality adjusted for baseline differences was lower in the atenolol-treated patients, but mortality was higher in those who received IV and oral atenolol vs. those who received only oral (RR, 1.2; $P < 0.001$). Also, intravenous atenolol use was associated with higher incidences of heart failure, shock, recurrent ischemia, and pacemaker use compared to oral atenolol. Intracranial hemorrhage rates were not lower with IV atenolol even in those patients who presented with systolic blood pressure more than 160 mmHg. In addition, reinfarction rates were unaffected by IV atenolol vs. oral atenolol and were higher in those given any atenolol. Pfisterer and colleagues conclude that atenolol improves outcomes in acute MI treated with thrombolytics, but early IV atenolol is of little value. They recommend starting oral atenolol as soon as the patient is stable.

COMMENT BY MICHAEL H. CRAWFORD, MD

This analysis of the GUSTO-1 study confirms the concerns of practicing physicians who struggled with the obvious complications of IV beta blockers for acute MI and the "evidence based medicine Gestapo's" admonition that IV beta blockers saved more lives. The concerns of real doctors caring for real patients seems to have won—IV beta blockers provide little or no additional benefit. There was a reduction in cardiac rupture-related tamponade with IV atenolol (0.6% vs 0.9%; $P < 0.001$), but this effect is inconsequentially small. On the other hand, heart failure, cardiogenic shock, heart block, recurrent infarction, and ischemia were all increased by IV atenolol. These results occurred despite the selection bias toward giving IV atenolol to the less sick individuals that one would expect in an observational study.

The data are particularly robust because 75% of the more than 41,000 patients received atenolol, 44% IV as compared to U.S. MI registry data showing 36% beta blocker use and 17% IV. Obviously, physicians in the United States have been voting with their feet on this issue, but the perceived problems with IV beta blockade early post MI may be contributing to the general low usage of beta blockers in general in the United States. Had the trialists not pushed IV therapy so hard, overall beta blocker use may have been higher in the United States.

Interestingly, the ACC/AHA guidelines for the treatment of acute MI suggest IV beta blockers especially for those with hypertension or tachycardia, yet neither subgroup did better with IV atenolol in this analysis. Also, ischemia and reinfarction were actually increased with IV atenolol use. These results fly against the common conception that beta blockers work by decreasing myocardial oxygen demand. Perhaps they have other beneficial effects not predicted by determinants of oxygen demand or perhaps lowering blood pressure is detrimental to coronary blood flow in acute MI and is ill advised. Epidemiologic studies have consistently shown that the higher your blood pressure, the better your survival with acute MI.

Although this analysis raises many questions that need to be evaluated in a randomized trial, two points seem clear: beta blockers are beneficial to acute MI patients in the thrombolytic era, but they should be given orally only when the patient is hemodynamically stable. ❖

Low-Energy Cardioversion After Open-Heart Surgery

ABSTRACT & COMMENTARY

Synopsis: *Temporary epicardial atrial defibrillation electrodes placed at the time of surgery can facilitate management of postoperative atrial arrhythmias.*

Source: Liebold A, et al. *Circulation* 1998;98:883-886.

Atrial fibrillation continues to be a problem after open-heart surgery. Thus, Liebold and associates tested the use of temporary epicardial wire electrodes in patients undergoing open-heart surgery. One hundred consecutive patients who were in sinus rhythm preoperatively and were scheduled for cardiac surgery with cardiopulmonary bypass were enrolled in the study. Eighty-nine patients underwent coronary artery bypass grafting alone or in combination with aortic valve replacement. Eight patients underwent isolated valve replacement, and three patients underwent various other procedures. With the patient on cardiopulmonary bypass, ring electrodes were sutured to the free right atrial wall and on the left atrial epicardium in the

space between the AV groove and the upper and lower pulmonary veins. A temporary epicardial ventricular electrode was placed on the anterior right wall. The electrodes were connected to polyurethane-coated wires that were tunneled through the skin and used for temporary pacing. Once the patients arrived in the intensive care unit, pacing threshold and impedance as well as P- and R-wave amplitudes were measured with a standard pacing system analyzer. Biatrial monophasic and biphasic defibrillating shocks of 0.3 joules were delivered, and shock impedance was measured. After surgery, patients were continuously monitored for the development of atrial fibrillation. When atrial fibrillation was detected, the patient was connected to a standard external defibrillator with a special interface module that damped the defibrillator's output to supply R-wave synchronous monophasic shocks with energies of 0.6-10.8 joules. The first shock delivered had an energy of 2 joules, and a step-up defibrillation protocol was used until sinus rhythm was restored. Sedatives or analgesics were given only if the patient requested them. The epicardial leads were left in place until just prior to hospital discharge. At that time, they were retracted transcutaneously.

It took 3.9 ± 7 minutes to place the epicardial defibrillation electrodes in the operating room. Early pacing thresholds were 2.1 ± 2 V in the right atrium and 1.9 ± 1.7 V in the left atrium. Right and left P-wave amplitudes were 2.3 ± 1.4 and 2.5 ± 1.6 mV, respectively. Monophasic test shocks revealed a mean lead impedance of 95 ± 12 ohms.

Twenty-three of 100 patients developed atrial fibrillation during their postoperative course—a mean of 2.1 ± 1.3 days after postop. Twenty of these patients were treated with internal atrial defibrillation, with 16 (80%) being converted successfully to sinus rhythm with a mean shock energy of 5.2 ± 3 joules. Eight patients developed early recurrence of atrial fibrillation. Four of these patients converted with medications, and four were treated with repeat atrial defibrillation. Five patients in the entire series had more than two episodes of atrial fibrillation. A total of 35 episodes of spontaneous atrial fibrillation were treated by internal atrial defibrillation, with an overall success rate of 31 of 35. Only six of the 20 patients required sedation or anesthesia for atrial defibrillation. General anesthesia was never required in the study. There were no complications associated with removal of the epicardial wire 5.7 ± 1.9 days postoperatively. Anticoagulation was not withheld in patients who had valve surgery.

Liebold et al conclude that temporary epicardial atrial defibrillation electrodes placed at the time of surgery can facilitate management of postoperative atrial arrhythmias. They argue that the rapid use of low energy defibrillation effectively and safely restores sinus rhythm and may be superior to approaches that use pharmacologic rate control and antiarrhythmic drugs for suppression as the primary approaches to therapy.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Atrial fibrillation is one of the most common complications encountered after cardiac surgery. In various series, it has been reported to occur in 20% to 50% of patients. Although atrial arrhythmias are not usually immediately life-threatening, they frequently prolong hospital stay and increase hospital costs. Prophylactic trials using amiodarone, several other antiarrhythmic drugs, and beta adrenergic blockers have been shown to decrease the frequency of post-operative atrial fibrillation, but it still remains a common clinical problem.

In the last several years, there has been a tremendous interest in the use of internal atrial defibrillation. First, internal atrial defibrillation was found to be effective for converting episodes in patients with atrial fibrillation that had been resistant to attempts at transthoracic cardioversion. Subsequently, an implantable atrial defibrillator was developed, and it is now undergoing clinical trials for the management of patients with recurrent arrhythmias. This use of temporary epicardial atrial pacing and defibrillation electrodes after cardiac surgery is still another application of this concept.

The use of temporary atrial and ventricular pacing wires has long been standard after cardiac surgery. The atrial electrograms they permitted could assist in the diagnosis of various arrhythmias, and rapid atrial pacing could be used to terminate episodes of atrial flutter. However, atrial fibrillation still usually required pharmacologic management. In this paper, Liebold et al demonstrate that epicardial electrodes with a special circular design can be safely attached to the left and right atria and used for defibrillation. This permits rapid and safe termination of each episode of atrial fibrillation and prevents the deterioration associated with the rapid rates seen during the episodes. This may prevent the electrical remodeling that occurs whenever a patient stays in atrial fibrillation and may greatly facilitate management.

Liebold et al did not use anesthesia and only rarely used sedation for their patients. It has been shown that even low-energy atrial defibrillation shocks are uncomfortable for the patient. However, many of these patients are probably already receiving analgesics, and most authors report that a single shock can be tolerated by most patients. It is only when multiple shocks are required that patients usually request sedation or analgesia.

Further experience with the use of these atrial defibrillation electrodes is required before they can be routinely recommended. However, this paper presents promising data, and it may be that these electrodes and the modules to adapt standard defibrillators will be part of every postoperative unit's strategy. ❖

Hormone Replacement: Some Surprising Bad News

ABSTRACT & COMMENTARY

Synopsis: *The late trend toward a decrease in CHD events may be valid, perhaps as a result of the favorable lipid effects that induced benefit after 36-48 months.*

Source: Hulley S. *JAMA* 1998;280:605-613.

Conventional wisdom, based on a variety of small trials and many observational studies as well as meta-analyses, has suggested that hormone replacement in post-menopausal women results in approximate halving of coronary disease rates. No large, prospective randomized trial has ever been reported until the Randomized Trial of Estrogen plus Progestin in Secondary Prevention of Coronary Heart Disease in Post Menopausal Women (HERS) (Hulley S. *JAMA* 1998;280:605). The results of this long-awaited randomized trial of estrogen plus progestin (HRT) for secondary prevention of coronary heart disease in post-menopausal women sent shock waves around the world, as the results did not confirm the widely held belief that estrogen replacement would be protective against coronary heart disease (CHD). Twenty centers enrolled 2763 post-menopausal women with established CHD, beginning in 1993 and ending in early 1998. Participants had a mean age of 67; 90% were white. All underwent careful screening, and, during this study itself, the women had periodic breast and uterine examinations as well as assessment of clinical end points. Treatment consisted of conjugated equine estrogen, 0.625 mg and medroxyprogesterone (MPA) 2.5 mg, or placebo; follow-up averaged 4.1 years. Approximately 82% of those assigned to hormones were taking therapy at the end of year 1 and 75% by year 3. The primary end point was nonfatal MI or CHD death. A variety of secondary cardiovascular outcomes were assessed, as were total mortality, cancer, deep venous thrombosis, etc. Baseline lipids were abnormal, with mean LDL cholesterol of 145 and HDL of 50. The mean time since last menstrual period was 18 years. More than half of the population was overweight; less than 40% exercised regularly. Approximately 25% had been exposed to post-menopausal estrogen in the past.

The results reveal no difference between placebo and HRT in the primary end point. Furthermore, there was an actual increase in CHD events during the first 24 months of the study, compared to placebo, with decreasing CHD events vs. placebo in the last two years of the study. The risk ratio for CHD death or nonfatal MI with hormones was 1.5 in year 1, falling to 0.7 in year 3, and 0.67 in years 4 and 5. The most dangerous time for patients was in the first four months, when the risk hazard was 2.3, particularly for nonfatal MI. There was no difference in total mortality or cancer deaths. There was an almost three-fold greater likelihood of deep venous thrombosis in the HRT cohort, and there were 11 vs. four episodes of pulmonary emboli. Gallbladder disease was somewhat more common in the HRT cohort. Plasma lipids demonstrated a decrease in LDL of 14% by year 1 and an increase in HDL by 8%. These changes remained consistent throughout the trial.

Hulley and associates speculate that the late trend toward a decrease in CHD events may be valid, perhaps as a result of the favorable lipid effects that induced benefit after 36-48 months. Furthermore, they speculate that the early hazard of HRT could be due to a prothrombotic effect of hormone therapy. They question whether a different progestin might have produced different results. Finally, they emphasize that the HERS Trial is substantially different from previously reported hormone studies by its duration, the randomized placebo-controlled nature, and studying women primarily for CHD events.

COMMENT BY JONATHAN ABRAMS, MD

The HERS Trial is a disappointment to the many who believed that post-menopausal estrogen replacement would have a significant favorable effect on coronary artery disease. Perhaps the most important message is stated by Petitti, who wrote an accompanying editorial and concluded "commitment to randomized trials as the standard of proof must be especially strong when the public health implications are so great." Thus, in spite of a large amount of observational "evidence" and the collective wisdom of many "experts" (including myself, *Clin Cardiol Alert*, 1998;21:218-222). The results do not confirm a favorable effect of HRT in older post-menopausal women with established CHD.

There have already been commentaries about this

trial and speculations as to why HERS was not positive. Some commentators believe that the early adverse trend within the first 12-24 months (reversing to a favorable trend in the last two years of the study) implies that the duration of the HERS study was not long enough and that a longer period of HRT might demonstrate a favorable effect on CHD morbidity and mortality. Some suggest that MPA is the culprit, attenuating and perhaps canceling out the positive effects of estrogen; certainly, the literature is in conflict regarding whether progesterones do or do not add additional protection to estrogen with respect to the vessel wall. Hulley et al and Petitti speculate that the pro-thrombotic effects of the hormone combination were particularly active in the early years of the study, resulting not only in increased coronary events but also in a higher rate of deep venous thrombosis, particularly in year 1. Down-regulation of estrogen receptors by MPA is a possibility. Furthermore, it is possible that a different progestin might have resulted in a more favorable outcome. Whatever the reasons, the HERS data stand on their own, representing a well-conducted, double-blind placebo controlled trial that was unable to show benefit of combination hormone replacement in spite of favorable lipid effects over the course of the study. Another factor could well be that the study women were older, averaging 67 years at entry and 18 years post-menopausal before beginning HRT. Thus, the extent of the existing coronary vascular disease might have been substantial and less amenable to favorable effects of HRT over a relatively short period than might be true in younger women.

There has always been considerable emphasis that women who use hormones in the post-menopausal years may be different than those who do not. Many demographic characteristics, including socio-economic class, lifestyle, and general health, have been shown to be more favorable in HRT users. The concepts of prevention bias and compliance bias are germane to this discussion, implying that HRT users are healthier in many ways and are more likely to be compliant with their medications. Both these factors are impossible to unravel from the available observational data, but they clearly imply that HRT women might have a substantially better prognosis unrelated to the administration of estrogens.

It should not be forgotten that the vascular biology story regarding estrogen is extremely positive. The conventional wisdom that HRT is beneficial to the cardiovascular system is not disproven by HERS, but, certainly, the hypothesis has suffered a serious setback. Nevertheless, use of HRT for post-menopausal symptoms, uro-gynecologic problems, osteoporosis, and possible slowing of dementia is well founded. At the present time, there is no mandate for women with vascular disease to be placed on hormones in hopes that their overall CHD risk will be reduced, although this is still a possibility, as suggested by the last 24-month experience of the HERS Trial. Few adverse outcomes were noted in this trial other than the expected increase in venous thrombosis and a trend toward more pulmonary emboli, which abated over the last two years. Thus, physicians are urged to carefully counsel post-menopausal women with vascular disease regarding HRT, providing a full list of risks and benefits. Such treatment is appropriate for many, if not most, women who wish to prevent one or more of the adverse sequalae of the menopause.

Whether younger healthy women at risk for CHD should be placed on HRT, or perhaps estrogen alone, remains an unresolved question. It may be that use of hormones relatively soon after menopause might be critical with respect to slowing down the atherosclorotic process. Unfortunately, data are not available and may not be for some time. The Women's Health Initiative is addressing this question, but completion is not scheduled until the year 2005. Finally, the question of whether a progestin should be used in conjunction with estrogen replacement is unresolved. There are data suggesting that MPA may not be the ideal compound. Protection of the uterus from unopposed estrogen remains a critical problem in HRT; many to most women today are given both compounds. While HERS does not provide a smoking gun to discard the protective effects of progestin, it does give considerable stimulus to the search for a potentially better progestin than MPA itself. ❖

CME Questions

28. A trial of the beta 1 selective blocker bisoprolol in heart failure was stopped prematurely because:

a. of increased mortality in the beta blocker group.
b. of reduced mortality in the beta blocker group.
c. of high withdrawal rates in the beta blocker group.
d. the sponsor declared bankruptcy.

29. The T-channel calcium blocker mibefradil:

a. is metabolized by the P-450 system.
b. increased mortality 11% in a heart failure study.
c. has been withdrawn from the U.S. market.
d. all of the above

30. The RALES study of class III-IV heart failure was stopped early because:

a. mortality was reduced in the spironolactone group.
b. mortality was increased in the spironolactone group.
c. serious hyperkalemia was noted in more than 50% of the patients on spironolatone.
d. sudden death rates were higher on spironalactone.

31. Acute intravenous atenolol use with thrombolytic therapy of acute MI:

a. reduces early mortality significantly vs. later oral atenolol.
b. reduces heart failure, shock, and recurrent MI.
c. reduces intracranial hemorrhage in those with systolic BP of more than 160 mmHg.
d. is of little or no additional value vs. later oral atenolol.

32. Surgically placed atrial electrodes are useful for:

a. diagnosing rhythm disorders.
b. pacing the atria.
c. defibrillating the atria.
d. all of the above

33. Hormone replacement therapy for secondary prevention in post-menopausal women with established coronary heart disease:

a. reduced subsequent MI and death vs. placebo.
b. reduced the incidence of deep venous thrombosis.
c. increased cardiac events during the first 24 months.
d. had no effect on cholesterol levels.

34. Which is most correct concerning lisinopril dosage for heart failure therapy?

a. Higher doses increased survival significantly
b. Higher doses reduced cardiac deaths significantly
c. Higher doses reduced death and hospitalization significantly
d. Higher doses markedly increased side effects

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Medical Economics, Inc.	Five Paragon Drive
	Montvale, NJ 07645

12. For completion by nonprofit organizations authorized to mail at special rates. The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes: *(Check one)* ☐ Has Not Changed During Preceding 12 Months ☐ Has Changed During Preceding 12 Months *(If changed, publisher must submit explanation of change with this statement)*

PS Form **3526**, July 1995 *(See instructions on Reverse)*

13. Publication Name: Clinical Cardiology Alert — 14. Issue Date for Circulation Data Below: September 1998

15. Extent and Nature of Circulation	Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*	1694	1756
b. Paid and/or Requested Circulation (1) Sales Through Dealers and Carriers, Street Vendors, and Counter Sales *(Not Mailed)*	0	0
(2) Paid or Requested Mail Subscriptions *(Include Advertisers' Proof Copies/Exchange Copies)*	1523	1556
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*	1523	1556
d. Free Distribution by Mail *(Samples, Complimentary, and Other Free)*	20	20
e. Free Distribution Outside the Mail *(Carriers or Other Means)*	0	0
f. Total Free Distribution *(Sum of 15d and 15e)*	20	20
g. Total Distribution *(Sum of 15c and 15f)*	1543	1576
h. Copies Not Distributed (1) Office Use, Leftovers, Spoiled	151	180
(2) Return from News Agents	0	0
i. Total *(Sum of 15g, 15h(1), and 15h(2)*	1694	1756
Percent Paid and/or Requested Circulation *(15c / 15g × 100)*	99	99

16. This Statement of Ownership will be printed in the November issue of this publication. ☐ Check box if not required to publish.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Donald R. Johnston, Publisher — Date: 9/25/98

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions *(including fines and imprisonment)* and/or civil sanctions *(including multiple damages and civil penalties).*

Instructions to Publishers

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2. Include in items 10 and 11, in cases where the stockholder or security holder is a trustee, the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check box. Use blank sheets if more space is required.
3. Be sure to furnish all information called for in item 15, regarding circulation. Fee circulation must be shown in items 15d, e, and f.
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