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Low Molecular Weight Heparin for Unstable Coronary Syndromes

ABSTRACT & COMMENTARY

Synopsis: *In patients with unstable angina or non-Q-wave myocardial infarction, short-term enoxaparin reduced the incidence of subsequent ischemic events and revascularization in the first 30 days and at one year.*

Source: Goodman SG, et al. *J Am Coll Cardiol* 2000;36:693-698.

Aspirin plus heparin therapy is standard evidence-based therapy for unstable angina/non-Q-wave myocardial infarction (MI) patients admitted to the hospital. Recent studies have suggested that low molecular weight heparin (LMWH) may be superior to unfractionated heparin in the short term, but little long-term data are available. Thus, Goodman and colleagues reported on the one-year results of the Efficacy and Safety of Subantaneous Enoxaprin in Non-Q-wave Coronary Events (ESSENCE) study. They studied 3171 patients from 176 centers worldwide who had angina decubitus for less than 24 hours and evidence of coronary artery disease, but not acute Q-wave MI. The patients were randomized to enoxaparin 1 mg/kg, 12 hour SQ or unfractionated heparin 5000 U bolus followed by a continuous infusion adjusted by the activated clotting time (ACT). Aspirin was given also and heparin was continued for 48 hours—eight days (median 2.6 days). The 14-and-30 day results have already been reported.[1] This report details the one year follow-up results in 2915 (92%) survivors not lost to follow-up. The primary end point of the study was death, MI, or recurrent angina requiring hospitalization or revascularization. The percent achieving this end point is shown in the Table. The secondary end points of death or MI were not statistically significant despite a trend toward lower rates with enoxaparin. However, the rates of subsequent cardiac catheterization and revascularization were significantly lower on enoxaparin.

Goodman et al concluded that in patients with unstable angina or non-Q-wave MI, short-term enoxaparin reduced the incidence of subsequent ischemic events and revascularization in the first 30 days and at one year.

Volume 19 • Number 11 • November 2000 • Pages 81-88

Table

Frequency of the Primary End Point on the Two Treatments in ESSENCE

	14 d	30 d	1 y
Enoxaparin	16.6%	19.8	32.0
IV heparin	19.8	23.3	35.7
P value	$P < 0.02$	$P < 0.02$	$P = 0.02$

COMMENT BY MICHAEL H. CRAWFORD, MD

Despite the success of heparin plus aspirin therapy, significant numbers of patients with acute coronary syndromes have recurrent ischemic events or require revascularization. This has stimulated interest in other approaches to these patients. Initial short-term studies with the LMWH suggested that ischemic end points were less for up to 45 days but may wane after that. Other studies showed no benefits vs. unfractionated heparin of two LMWHs, nadroparin and dalparin. Thus, the ESSENCE study is of interest because it used enoxaparin, the agent with only positive reports and the most wide usage in the United States. Also, economic studies have shown that enoxaparin is cost-effective for the treatment of unstable angina. The benefits of enoxaparin were seen by 48 hours and persisted at 14, 30, and 360 days following a median treatment period of 2.6 days. The major reason for the persistent effect was the reduction in need for subsequent revascularization.

It is not clear why studies with the other two LMWH were negative, especially since one used a long-term administration protocol. However, these agents have different pharmacodynamics, which may partly explain the disparity. Also, the effects of LMWH in this clinical setting are not profound. Therefore, some of these studies may have been underpowered to detect a difference. In addition to these positive results with regard to ischemic events vs. infractionated heparin, there are several other advantages to LMWH: They are weight dosed without needing ACTs because of their predictable pharmacokinetics; they have less interactions with platelets; and heparin-induced thrombocytopenia is less frequent. A proposal for the care of unstable coronary syndromes is as follows: aspirin for all patients; LMWH for 48-72 hours for those admitted; IIb/IIIa blockers and catheterization/revascularization for high-risk patients (ST changes, serum markers elevated, rest pain). This proposal has not been tested yet but makes some sense based upon available data. ❖

Reference

1. Cohen M, et al. *N Engl J Med* 1997;337:447-452.

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Lipid-Lowering Drugs and Recurrent Ventricular Arrhythmias

ABSTRACT & COMMENTARY

Synopsis: *Lipid-lowering drugs decrease recurrent ventricular arrhythmias in patients with implantable cardioverter defibrillators.*

Source: De Sutter J, et al. *J Am Coll Cardiol* 2000;36: 766-772.

De sutter and colleagues from the university Hospital Ghent in Belgium performed a retrospective analysis of the effects of lipid-lowering therapy on recurrent arrhythmias in patients with implantable cardioverter defibrillators (ICDs). Between 1995 and 1998, 78 patients with coronary artery disease and a history of sustained monomorphic ventricular tachycardia (VT) (75 patients), cardiac arrest (20 patients), or syn-

cope with inducible ventricular tachycardia at electrophysiologic study (3 patients) underwent implantation of a tiered therapy ICD capable of electrogram storage. Lipid-lowering drugs were prescribed at the discretion of the referring physician. At that time in Belgium, the reimbursement regulations for lipid-lowering drugs stated that the total cholesterol should be greater than 250 mg/dL after three months of adequate diet. Of the 78 patients in this study, 24 were on lipid-lowering drugs at the time of presentation with their arrhythmia, and three were started on therapy during the hospitalization for ICD implantation. The other 51 patients were not on lipid-lowering drugs before or after ICD implantation. Sixteen of the patients on lipid lowering drugs received statins and 11 were receiving fibrates.

The group of patients on lipid-lowering drugs was similar to the group not receiving these agents in terms of age, gender, history of diabetes, smoking, hypertension, previous infarction, previous revascularization, and left ventricular ejection fraction. Revascularization was performed at the time of ICD implantation in 4/27 patients on lipid-lowering drugs (group I) and 9/51 patients on no lipid-lowering drugs (group II). At discharge, group I and group II patients received angiotensin-converting enzyme inhibitors (ACEI), aspirin, digoxin, nitrates, and antiarrhythmic drugs with equal frequency, but there was a slight increase in the frequency of β–adrenergic blocker used in group I (63% vs 45%).

During a mean follow-up of 490 ± 319 days, 35/78 patients (45%) had recurrence of VT or ventricular fibrillation (VF) that was treated by their ICD. No ventricular arrhythmias were seen in the remaining 43 patients. Patients with more frequent recurrent arrhythmias, had originally presented with sustained monomorphic VT, were less frequently on β–adrenergic blocking agents, and were less likely to be receiving lipid-lowering drugs (17% for patients with recurrence vs 49% for patients without recurrence; $P = 0.004$). By multivariate analysis, the use of lipid-lowering drugs and prior hemodynamically poorly tolerated sustained monomorphic VT, remained independent predictors or recurrent arrhythmias. In the subgroup of patients receiving β–blockers, the use of lipid-lowering agents was still associated with less recurrent arrhythmia. The combined end point of cardiac death and rehospitalization was also analyzed and, again, those on lipid-lowering drugs did better. Total and LDL cholesterol levels were followed in both groups. Both groups showed a rise in total and LDL cholesterol levels after discharge. However, both initial, final, and total LDL cholesterol mean levels were lower in the group on lipid-lowering agents.

de Sutter and colleagues concluded that this observational study suggests that lipid-lowering drugs decrease recurrent ventricular arrhythmias in patients with ICDs. They propose a future randomized trial to further test the validity of this observation in a larger population.

COMMENT BY JOHN P. DiMARCO, MD, PhD

The paper by de Sutter et al provides interesting data relevant to the way we manage patients with ventricular arrhythmias. For almost 20 years, the standard approach for patients with sustained ventricular tachycardia and cardiac arrest has been based on electrophysiologic findings. Inducibility of sustained ventricular tachycardia at electrophysiologic study has been thought to be an important diagnostic sign, and therapy, both pharmacologic and nonpharmacologic, has been primarily directed toward these arrhythmias. Evidence is now accumulating that at least in patients with rapid and life-threatening arrhythmias, the arrhythmic substrate is but one factor that influences recurrence. In both the Antiarrhythmic vs. Implantable Defibrillator Study[1] and the Cardiac Arrest Study-Hamburg,[2] inducibility of an arrhythmia at a baseline EP study was not a predictor of outcome. In the CABG Patch Trial,[3] treatment of ischemia may have been responsible for the observation that ICD implantation did not decrease mortality. In larger heart failure trials, β–adrenergic blockers, ACE inhibitors, and other agents have been shown to decrease both sudden and nonsudden cardiac deaths. Finally, several trials with statins have shown a reduction in cardiac mortality in various coronary artery disease populations without a history of prior arrhythmias.

These data suggest that recurrent ischemia may be a more important trigger for threatening arrhythmias than was previously thought. It is clear that aggressive therapy of heart failure and hyperlipidemia should be important components of a strategy for reducing arrhythmia recurrence in many patients. ICD therapy remains an important backup, however, since the recurrence rate in treated patients is still unacceptably high. The major advantage of an ICD is that its efficacy is not dependent upon the cause or mechanism of the recurrent arrhythmia.

In this paper, de Sutter et al call for a randomized trial to assess the effects of lipid-lowering therapy in patients with ventricular arrhythmias. I think that we are past that time. It is clear that lipid-lowering therapy in patients with coronary artery disease is beneficial. Although it would be interesting to study the mechanism by which lipid-lowering therapy decreases arrhythmias, it seems clear that all of these patients should be treated to target levels of cholesterol. Trials that compare various lipid-lowering strategies or agents in ICD patients rather than placebo-controlled trials would be more appropriate. ❖

References

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2. Cardiac arrest study—Hamburg. *Circulation* 2000; 102:748-754.
3. CABG patch trial. *N Engl J Med* 1997;337:1569-1575.

Exercise-Induced PVDs

ABSTRACT & COMMENTARY

Synopsis: *Frequent ventricular premature depolarizations during exercise in asymptomatic, middle-aged men are associated with a long-term increase in cardiovascular death.*

Source: Jouven X, et al. *N Engl J Med* 2000;343: 826-833.

Jouven and colleagues from paris report results from a long-term study on risk factors in employees of the Paris Civil Service. The study enrolled 7746 male government workers between 42 and 53 years of age. These subjects underwent electrocardiography, provided a medical history, and had a physical examination with selected laboratory studies to exclude clinically apparent cardiovascular disease, including moderate to severe hypertension and any ECG abnormality. Subjects were then exercised using an accelerated bicycle protocol that included three workloads: two minutes at 82 W, six minutes at 164 W, and two minutes at 191 W. The test could be stopped before completion for severe symptoms, a systolic blood pressure over 250 mm Hg, a heart rate over 180 beats per minute, any ischemic changes on ECG (> 1 mm ST depression), or ventricular tachycardia. Subjects with a run of two or more consecutive ventricular beats or with more than 10% of all beats ventricular in origin, were classified as having frequent ventricular premature depolarizations (VPDs). Patients were then followed long-term for up to 27 years. Mortality data during the time the subjects were used were provided by the government department in which the subjects worked. After retirement, cause of death was obtained from the death certificate.

Complete baseline data and follow-up data were available from 6101 of the original subjects. Of these, 4.4% had ischemia and 0.8%, 2.3%, and 2.9% had frequent VPDs as defined above either before, during, or after exercise. Among the subjects with frequent VPDs during exercise and among those with evidence for ischemia, cardiovascular and total mortality rates were significantly higher than in those without. There was no increased risk associated with infrequent VPDs or with frequent VPDs before or after exercise. The crude comparative cardiovascular mortality rates were as follows: 6.4% if ischemia and frequent VPDs were both absent; 16% if ischemia with frequent VPDs was present; 16.1% if frequent VPDs without ischemia was present, and 25% if both these findings were present. The cumulative, all-cause mortality rates were 26.2%, 33.1%, 40.7%, and 50.0% for the same four groups, respectively. Patients with frequent VPDs consumed more tobacco daily but were similar to the other groups in most other clinical variables. Patients with ischemic responses to exercise were slightly older and had slightly higher mean levels of cholesterol and triglycerides than did the other groups.

Jouven et al concluded that frequent VPDs during exercise in asymptomatic, middle-aged men are associated with a long-term increase in cardiovascular death.

COMMENT BY JOHN P. DiMARCO, MD, PhD

For a number of years, it has been standard teaching that asymptomatic ventricular arrhythmias in patients with normal ventricular function are associated with a good prognosis; therefore, they did not require therapy. In the paper by Jouven et al, asymptomatic arrhythmias during exercise were associated with a 2.5-fold increase in the risk for cardiovascular death. Should these observations lead us to change our approach to patients in whom asymptomatic ventricular ectopy is detected? I believe the answer is no.

This was a very unusual study. A large cohort of men without cardiac symptoms or history were identified, tested, and then followed for a very long period of time. Even in the groups with positive findings, the annual cardiovascular mortality rates were considerably less than 1% per year through the first 20 years of the study. This low-event rate means that any response to the risk factors identified must be both safe and inexpensive to warrant implementation. Treatment of standard risk factors such as increased lipids, hypertension, and tobacco use would qualify, but antiarrhythmic therapy certainly would not.

Why were the frequent VPDs associated with increased mortality in this cohort? Several explanations might be considered. Standard ECG stress testing has a sensitivity of only 60-70% for detecting angiographically documented coronary lesions. Therefore, some of the VPDs might have been due to ischemic heart disease not detected by the test. The subjects only underwent a limited screen for cardiac disease. Mild or moderate hypertensive heart disease or an early nonischemic cardiomyopathy would not have been detected but could be associated both with PVCs and an increased mortality during follow-up.

Tobacco abuse can result in increased vascular reactivity even before clinically detectable fixed coronary obstruction develops and this also may result in increased ectopy.

The Cardiac Arrhythmia Suppression Trial showed that treating ventricular ectopy, a known risk factor, in moderate to high risk populations was counterproductive. Treating VPDs in an asymptomatic individual based on the data shown here would also be incorrect. ❖

ACEI Dosage Optimization in Heart Failure

ABSTRACT & COMMENTARY

Synopsis: *Optimization of angiotensin-coverting enzyme inhibitors in a heart failure program can markedly reduce readmissions and lower the cost of care in heart failure patients.*

Source: Luzier AB, et al. *Am J Cardiol* 2000;86: 519-523.

Since the atlas trial was published, there has been increased interest in the effects of optimizing angiotensin converting enzyme inhibitors (ACEIs) in heart failure patients. Thus, Luzier and colleagues conducted a prospective intervention study in 110 patients with systolic left ventricular dysfunction entered into a multidiscliplininary heart failure disease management program. They were divided into three groups. Group A consisted of 28 patients on at least recommended doses of ACEI (captopril 150 mg, enalapril 20 mg, lisinopril 20 mg, or quinapril 40 mg daily), which averaged 30 mg of enalapril or its equivalent daily. Some patients were up-titrated so the final average dose of enalapril was 36 mg daily. The 82 patients (75%) considered to be on suboptimal ACEI or none were divided into group B, which consisted of 51 patients in whom the recommendation to increase ACEI was accepted by the treating physician, and those in whom it was not were in group C. In group B, ACEI was initiated in 26 (51%) patients and was increased in the rest to a mean of 16 mg daily for the group. Mean ACEI dose in Group C was 6 mg/d. Readmission rates at 90 days follow-up were: group A = 14%, B = 19%, and C = 29% ($P = 0.02$), and at 180 days were A = 31%, B = 35%, and C = 63% ($P < 0.007$). The higher readmission rate in group C was associated with higher direct costs. Luzier et al concluded that optimization of ACEI in a heart failure program can markedly reduce readmissions and lower the cost of care in heart failure patients.

COMMENT BY MICHAEL H. CRAWFORD, MD

Several studies have documented suboptimal ACEI usage in heart failure patients and optimization of ACEI is believed to be an important aspect of multidisciplinary heart failure management programs. The bar for ACEI dosages was raised by the ATLAS trial,[1] which showed that doses of lisinopril greater than 30 mg/d resulted in better outcome than less than 5 mg/d. However, the lisinopril dose in other successful trials was 20 mg/d and this is the recommendation of the AHCPR guidelines. Unfortunately, ATLAS did not test this dose. An analysis of this discrepancy by Drs. Nicklas, Cohn, and Pitt[2] recommend that physicians continue to use ACEI dosages from randomized clinical trials (i.e., lisinopril 20/d) rather than the high doses used in ATLAS. The rationale for this recommendation was that the difference in benefits between high-and low-dose ACEI in ATLAS was small and it is likely that the intermediate doses used in randomized clinical trials would have the same effect as higher doses.

With regard to the end point of rehospitalization, this ACEI dose optimization study supports the recommendation for intermediate doses since there was no difference in outcome between groups A (36 mg/d enalapril) and B (16 mg/d), but group C (6 mg/d) did worse. One caveat to this study is that half of the group B patients were not on ACEI at initiation into the study, but 96% were after the intervention. So this is not just a study of dose optimization, because it includes initiating ACEI for half the patients. This clouds the results with regard to dose optimization.

The reason given for why patients were either not on ACEI or at low doses in group B was fear of adverse effects: 14 were intolerant to ACEI; of these, 11 with cough were put on losartan and three with renal insufficiency were put on hydralazine/nitrates. These patients were included in group B and contribute to the outcome results. Thus, ACEI optimization in this study also included recognized alternative therapy. ❖

References

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2. Nicklas JM, et al. *J Cardiac Failure* 2000;6:165-168.

Ethanol for HOCM

ABSTRACT & COMMENTARY

Synopsis: *Septal infarction by intracoronary ethanol injection is beneficial for symptomatic hypertrophic obstructive cardiomyopathy patients refractory to pharmacologic therapy.*

Source: Lakkis NM, et al. *J Am Coll Cardiol* 2000; 36:852-855.

Early reports on the benefits of ethanol injection into septal perforator arteries of patients with hypertrophic obstructive cardiomyopathy (HOCM) were encouraging. Thus, the report of Lakkis and colleagues of the one-year follow-up of their first 50 patients treated is of interest. All their patients were refractory to medical therapy with persistent dyspnea and a resting gradient greater than 40 mm Hg, or a dobutamine (5-20 mg/kg/min) gradient greater than 60 mm Hg due to asymmetric septal hypertrophy and systolic anterior motion of the anterior leaflet of the mitral valve. The procedure consisted of identifying the septal arteries supplying the septal bulge by contrast echocardiography, followed by 2-5 mL of ethanol to fill the vessel. All septal branches were injected until the resting gradient was less than 20 mm Hg. All patients had pacemaker backup either temporary or permanent and were observed in the CCU for 24 hours. In 7/50 patients, the procedure was redone and mean hospital stay was three days. The mean number of arteries injected was 1.7 and all patients experienced chest pain and rises in creatine kinase. NYHA class III or IV symptoms were present in 90% of the patients before treatment and all were class I-II at one year. Also, mean exercise treadmill times increased from 271 to 407 seconds at one year ($P = 0.02$). Mean resting gradients decreased from 74 to 6 mm Hg at one year ($P < 0.001$), and dobutamine gradients from 84 to 30 mm Hg. On echo-ejection fraction was unchanged, septal thickness decreased from 2.1 cm to 1.5 cm ($P < 0.001$) and mitral regurgitation decreased from mild-moderate to zero-trivial ($P < 0.01$). There were two deaths; one died of a dissected left main coronary artery despite emergency bypass surgery and one died suddenly 10 days after the procedure. Complete heart block requiring a pacemaker developed in 11 patients; 20 had new right bundle branch block; 14 had right bundle plus left anterior hemiblock; and six had left bundle branch block. Lakkis et al concluded that septal infarction by intracoronary ethanol injection is beneficial for symptomatic HOCM patients refractory to pharmacologic therapy.

COMMENT BY MICHAEL H. CRAWFORD, MD

Several more aggressive therapies exist for HOCM patients who remain systematic on beta blockers and calcium antagonists. The least aggressive is dual chamber pacing adjusted to reduce the outflow gradient and increase cardiac output. The most aggressive are surgical septal myectomy and mitral valve replacement. Since the results of septal infarction in this report are better than those reported with pacing and equivalent to the results of myectomy or valve replacement without the risks of surgery, should septal infarction be the preferred treatment?

There are some caveats to septal infarction therapy. First, there were two early deaths, which represent a 4% periprocedure mortality and one late death at 22 weeks. Second, the procedure was painful despite premedication with narcotics and resulted in several days of hospitalization. Third, according to the text, all of the 50 patients developed conduction abnormalities or already had a pacemaker and 11 required a new permanent pacemaker. Given these complications, it would seem reasonable to try dual chamber pacing first in drug refractory HOCM patients and consider ethanol septal infarction for those that fail pacing therapy. ❖

Secondary Prevention with Antioxidants—The SPACE Stories—News from the Antioxidant World: Real or Chance?

ABSTRACT & COMMENTARY

Synopsis: *A major reduction in cardiovascular morbidity and mortality in end-stage renal disease patients can be achieved with vitamin E supplementation.*

Source: Boaz M, et al. *Lancet* 2000;356:1213-1218.

The antioxidant hypothesis remains the focus of considerable attention. Pathogenetic mechanisms for many vascular disease phenomena are readily attributed to oxidant stress, which also contributes to inadequate nitric oxide bioavailability. The concept that widely available vitamins with antioxidant properties might be an inexpensive, safe, and effective therapy for primary or secondary cardiovascular prevention, is attractive. However, recent randomized, clinical trial data are very sobering with respect to supporting the antioxidant

hypothesis: More than 20,000 patients in the HOPE and GISSI-P trials[1,2] showed no benefit for vitamin E in patients with cardiovascular disease or in high-risk diabetics without overt cardiac disease. The CHAOS trial data, published several years ago, did suggest a benefit with vitamin E supplementation in patients with coronary artery disease undergoing angioplasty.[3] However, this study has been widely criticized for a variety of reasons and is not considered to be reliable.

The SPACE trial (Secondary Prevention with Antioxidants of cardiovascular disease and end stage renal disease), was carried out in five Israeli dialysis centers in high-risk end stage renal disease (ESRD) subjects with documented cardiovascular disease. The hypothesis was that vitamin E supplementation would decrease new vascular events due to decreases in oxidant stress and oxidation of LDL cholesterol. Stable dialysis patients between the ages of 40-75 and a documented history of cardiovascular disease were randomized to vitamin E 800 IU/d or matching placebo in this double-blind, randomized trial. An event rate of 30% over two years in the placebo group was postulated. The primary end point was a composite consisting of myocardial infarction (MI), stroke, unstable angina, and new peripheral vascular disease. The patient groups appeared to be well matched at baseline, although the cohorts were rather small, consisting of just under 100 patients each.

The results indicated a robust reduction in the primary end point of 54% (P = 0.014). If sudden death was included, there was a 46% reduction in relative risk, (34 end points with placebo vs 18 in the vitamin E group). An adjustment was made for smoking, as the vitamin E cohort had a greater percentage of active smokers (24% vs 14%). The results in smokers were similar to the overall primary outcome. The major end point affected by vitamin E was new MI, which demonstrated a 70% reduction (P = 0.016). When sudden deaths were considered as a fatal MI, the reduction was 55% (P = 0.04). Non-fatal was reduced by 66% (P = 0.08). No obvious variables could be detected to indicate a different baseline in those individuals who did or did not have an MI during this study. The Kaplan Meier event curve separation began at approximately 300 days, widening at study termination, with some patients being followed for 600-700 days.

Although there were trends toward a reduction in incident peripherial vascular disease, ischemic stroke, and unstable angina (62%, 49%, and 15% relative risk reduction, respectively), these were nonsignificant due to the small numbers of events and the small cohort size. Side effects were few, and not clearly related to vitamin E. The mean annual MI rate in the placebo patients in SPACE was 12.3%, substantially higher than CHAOS, GISSI, and HOPE. The latter two had MI rates of 2.5 and 3.8% per year, respectively, both lower than CHAOS. Overall mortality was not reduced in the SPACE study due to a "nonsignificant increase in noncardiac mortality in patients who receive vitamin E." Vitamin E may have contributed to hemorrhage; otherwise, details were not provided. Boaz and colleagues point out that high-dose vitamin E supplementation has been shown in experimental studies to reduce the atherogenic profile, including monocyte super oxide release, lipid oxidation, platelet aggregation, smooth muscle cell proliferation, and possibly "stabilization of atherosclerotic plaque." They state, "our study is not the final word," and did not make specific therapeutic recommendations. Boaz et al call for a major clinical trial to further evaluate the vitamin antioxidant approach in ESRD patients.

COMMENT BY JONATHAN ABRAMS, MD

The results of SPACE, if validated by larger trials, are of considerable importance, indicating that a major reduction of cardiovascular morbidity and mortality in ESRD subjects can be achieved with vitamin E supplementa- tion. There are few obvious limitations of this study, other than the small number of patients followed over a short time period; the degree of relative risk reduction for MI and other end points are so robust that they cannot be ignored. Boaz et al believe that the baseline risk was equivalent in the two groups. However, information regarding left ventricular function, active myocardial ischemia, or lipid profiles are not provided. There is no question that the ESRD patients were high risk; 42% of the entire cohort had diabetes and a comparable number had hypertension. Prior MI was documented in 49% of the vitamin E cohort and 57% of the placebo patients; no quality of life or clinical classification was provided; therefore, it is possible that the two groups may have had a different burden of morbidity in spite of relatively comparable major prior cardiovascular disease. The group size of just under 100 patients each also presents a problem, allowing for the probability of a significant type I error. Given the large decrease in the primary end point, it is somewhat surprising that overall mortality was not affected by the study. The reasons for this are not clear and although unlikely, could possibly be due to an increased hazard with high-dose vitamin E. The dose used in this study was higher than in all three of the prior trials, although some patients in CHAOS did receive 800 IU.

What should the clinician do with these data? While the SPACE study is substantially less persuasive than HOPE, which recommended ACE inhibitors for all patients who meet the HOPE criteria, these data do sug-

gest that ESRD patients who have a history of cardiovascular disease should be considered for high-dose vitamin E supplementation. In the SPACE trial, all such individuals were treated for hyperhomocysteinemia with vitamin B complex-folate supplementation. Given the enormous burden of morbidity and mortality in these patients and the lack of clear cut evidence that antioxidant vitamin supplementation or B vitamins carry any significant harm, it does appear reasonable for physicians to prescribe vitamin E in the doses used in SPACE. Many questions are unanswered regarding antioxidant vitamins, including whether synthetic or natural vitamins are better; whether the right vitamin molecule has been used in the major studies; whether vitamin C should be used in conjunction with vitamin E; and whether it is even reasonable to hypothesize that intake of vitamin supplements will be able to attenuate or even reverse the profound oxidant stress that is systemic in the vessels of individuals with many types of cardiovascular disease, including diabetes, hypercholesterolemia, and of course, ESRD patients.

A large clinical trial should be quickly launched testing vitamin E, and possibly the combination with vitamin C in ESRD. Given the differences in the patient populations in SPACE, GISSI-P, and HOPE, it is not appropriate to extend these observations to primary or secondary prevention in patients with coronary artery disease in the absence of renal failure. ❖

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CME Questions

23. Low molecular weight heparin vs. unfractionated heparin in acute non-Q-wave coronary syndromes after one year reduced:

a. death, MI, and recurrent angina.
b. death and MI.
c. death.
d. MI.

24. In patients with CAD and an ICD, lipid-lowering therapy reduced:

a. recurrent ventricular tachyarrhythmias.
b. cardiac death and rehospitalization.
c. LDL cholesterol.
d. All of the above

25. Frequent VPDs on exercise testing in subjects without apparent CAD predicted cardiovascular mortality:

a. better than ischemia on ECG.

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10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
American Health Consultants	3525 Piedmont Road, Bldg. 6, Ste 400 Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Medical Economics Data, Inc.	Five Paragon Drive Montvale, NJ 07645

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

PS Form **3526**, September 1998 — *See instructions on Reverse)*

13. Publication Name: Clinical Cardiology Alert — 14. Issue Date for Circulation Data Below: November 2000

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)*			1708	1632
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	1457	1382
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	0	0
	(4)	Other Classes Mailed Through the USPS	0	0
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			1457	1382
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	0	0
	(2)	In-County as Stated on Form 3541	0	0
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			13	13
f. Total Free Distribution *(Sum of 15d and 15e)*			13	13
g. Total Distribution *(Sum of 15c and 15f)*			1470	1395
h. Copies Not Distributed			238	237
i. Total *(Sum of 15g, and h.*			1708	1632
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			99	99

16. Publication of Statement of Ownership
Publication required. Will be printed in the November issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Publisher — Date: 10/11/00

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

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 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 the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
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5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

PS Form **3526**, September 1999 *(Reverse)*

b. equally to ischemia on ECG.
c. less well than ischemia on ECG.
d. best when it was present with ECG ischemia.