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CLINICAL CARDIOLOGY ALERT®

A monthly update of developments in cardiovascular disease

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Good News for Marine Polyunsaturated Fatty Acids, but not so Good for Vitamin E

ABSTRACT & COMMENTARY

Synopsis: *Long-term polyunsaturated fatty acids but not vitamin E were beneficial for death and combined death, nonfatal myocardial infarction, and stroke due to the decrease in risk for overall cardiovascular death.*

Source: GISSI. *Lancet* 1999;354:447-455.

The latest contribution from the gissi investigators is a study of more than 11,000 individuals with a recent myocardial infarction (MI) (less than 3 months, mean time to study entry 12 days) who were randomized to fish oil or vitamin E, or both in 2 × 2 factorial design study. There were approximately 2800 patients in each cell; supplements included N-3 polyunsaturated fatty acids (PUFA) 1 g daily; vitamin E 200 mg; the combination of the above; and neither. The study was open label and was carried out for an average of 3.5 years. The two primary end points were all-cause mortality, nonfatal MI (NFMI), and nonfatal stroke; and cardiovascular death, NFMI, and nonfatal stroke. A secondary analysis was performed for each individual event class. The trial was carried out from 1993-1995. The results were favorable for the fish oil supplement and neutral for vitamin E. Plasma lipids at six months demonstrated a decline in tryglicerides from baseline in individuals taking PUFA, and an increase in LDL cholesterol in all groups, greater in the PUFA cohort. HDL and total cholesterol increased in all groups. The primary outcome demonstrated a decrease with PUFA for all-cause death, NFMI, and stroke (P = 0.053) of 10% (P = 0.048), with a similar decrease of 11% when cardiovascular death was included. Vitamin E resulted in no difference from control, and no further reduction of events when combined with PUFA. A four-way analysis of PUFA indicated a relative decrease of 15% in the combined end point, and 20% in the secondary combined end points. Furthermore, individual event end points demonstrated a decrease in total mortality by 20%, cardiovascular death at 30%, and sudden death at 45% with N-3 PUFA.

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These represent the major benefits of this trial. Vitamin E demonstrated no differences from control, except for a decrease in cardiovascular death, but not for any of the combined end points. N-3 PUFA plus vitamin E was no more beneficial than N-3 PUFA alone. Adverse effects were relatively minor. Approximately 27% of subjects had discontinued either study drug by the end of the trial. The GISSI investigators noted that the regimen of N-3 PUFA corresponds to a large fatty fish meal every day of the week.

The data are concordant with the DART Trial reported a decade ago that analyzed fish intake on cardiovascular death and reinfarction in post-MI patients. The GISSI investigators emphasize that the study population was relatively low risk, as most of them consumed a Mediterranean diet, and many were treated with aspirin, ACE inhibitors, beta-blockers, and statins. Therefore, this Italian post-MI population represents a model approach to therapy of MI. The GISSI investigators conclude that "long term N-3 PUFA, but not vitamin E…was beneficial for death and for combined death, non-fatal MI, and stroke. All the benefit… was attributable to the decrease in risk for overall cardiovascular death."

COMMENT BY JONATHAN ABRAMS, MD

This is certainly a "good news" story with respect to dietary supplementation with marine fish oils. There are considerable epidemiologic and research data in the literature, including fish oil and fatty fish consumption, that predicted this beneficial outcome. The vitamin E results are disappointing but are concordant with all reported large trials of vitamin E supplementation available today. The mechanisms of PUFA benefits are unclear, and these benefits include antifibrinitytic and lipid modification effects. Decreased oxidation of LDL cholesterol has been suggested for vitamin E. The GISSI investigators believe without good evidence that the major effect of fatty acids was on arrhythmogenesis—not on "atherosclerotic-thrombolic events." They further suggest that the relatively ideal profile of the study cohort with respect to the Mediterranean diet and high rates of use of proven post-MI therapies would make it difficult to demonstrate a major effect of either fatty acids or vitamin E. Nevertheless, the PUFA groups did demonstrate a major benefit.

In an accompanying editorial, Brown suggests that it may take a much larger study to demonstrate a favorable effect of vitamin E. He is less sanguine about the magnitude of PUFA benefit and points out that vitamin E did reduce risk by 11% when compared to no vitamin E, but this did not result in statistical significance. One can therefore conclude that benefit will accrue to post-MI patients who ingest marine fish oils, but not necessarily in the mega-amounts used in prior trials. The benefits of vitamin E remain unproven. Unfortunately, the recently released HOPE Trial of subjects with vascular disease and diabetes also did not show a benefit for vitamin E, although the ACE inhibitor ramipril was shown to be beneficial in reducing cardiovascular risk. Another effective agent, heretofore not proven to be effective, is the fibrate gemfibrozil, which was recently reported to reduce death, recurrent MI, and revascularization rates by 22-23% in a cohort of U.S. veterans with isolated low HDL cholesterol treated with this agent for a period of five years (Rubins HB, et al. *N Engl J Med* 1999;341:410-418). Mean total and LDL cholesterol were low. There was a decrease in triglyceride levels and a modest increase in HDL throughout the study.

In conclusion, recommendations for secondary prevention now include a statin if LDL cholesterol is elevated (more than 130-135 mg/dL). In individuals with aggressive or premature coronary disease, the use of N-3 polyunsaturated fatty acids should be considered, in addition to a diet high in fatty fish consumption. It remains to be convincingly demonstrated that vitamin E is of any benefit for primary or secondary prevention. In patients with established coronary disease who have a low HDL and otherwise normal lipids, a fibrate is clearly indicated. ❖

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C-Reactive Protein and Estrogen

ABSTRACT & COMMENTARY

Synopsis: *Postmenopausal hormone replacement therapy rapidly and markedly increased the concentration of C-reactive protein, which may be a negative effect of estrogen, but reduces E-selection, which may be anti-inflammatory.*

Sources: Ridner PM, et al. *Circulation* 1999;100:713-716; Cushman M, et al. *Circulation* 1999;100:717-722.

Considerable observational epidemiological data suggest that hormone replacement therapy reduces cardiovascular events in women. However, the recently published HERS (Heart and Estrogen Replacement Study) failed to demonstrate a reduction in coronary events in women with known coronary artery disease (CAD) assigned to hormone replacement therapy vs. placebo (Hulley S, et al. *JAMA* 1998;280:605-613). Recent pathophysiological studies have linked atherosclerosis to inflammation and the inflammatory marker C-reactive protein has predicted increased risk of CAD in studies involving women. Cross-sectional studies of long-term users of hormones have shown elevated C-reactive protein levels (see Ridner and colleagues). Thus, the lack of secondary prevention benefit in HERS could be due to enhanced inflammation caused by estrogen use. Accordingly, Cushman and colleagues (second source document) tested the effects of hormone therapy on several inflammatory factors (C-reactive protein, E-selectin, Von Willebrand factor, and factor VIIIc) in 383 women, a subset of the 875 women enrolled in the postmenopausal estrogen progestin interventions (PEPI) trial. PEPI was a three-year randomized, double-blind, placebo-controlled trial comparing four hormone regimens on cardiovascular risk factors. The main trial results have been published and showed beneficial effects on serum lipids and lipoproteins. The subgroup had the inflammatory factors measured at baseline, 12, and 36 months. All four hormone regimens resulted in a sustained increase in C-reactive protein of 85%, but a decrease in E-selectin of 18% vs. placebo ($P < 0.002$). Van Willebrand and factor VIIIc were unchanged. Cushman et al conclude that postmenopausal hormone replacement therapy rapidly and markedly increased the concentration of C-reactive protein, which may be a negative effect of estrogen but reduces E-selectin, which may be anti-inflammatory. Clinical trials of cardiovascular outcomes will be needed to assess the significance of these findings.

COMMENT BY MICHAEL H. CRAWFORD, MD

After encouraging observational data on estrogens for secondary prevention, the cardiology community was deeply disappointed with the results of HERS, the first randomized clinical trial of secondary prevention with hormone replacement therapy. The results of this subgroup of PEPI may provide at least a partial explanation for the results of HERS. Of interest is the fact that coronary events were increased early in the five-year HERS, but seemed to decrease in the last two years of follow-up. This was interpreted as showing that the beneficial lipid effects of hormone therapy may take time to manifest benefit in women with known CAD. The early and marked increase in C-reactive protein may have augmented this time separation of benefits from hormones in HERS. Unfortunately, the C-reactive protein effects were sustained for the three years of PEPI, suggesting that they would probably not decrease in another two years, but you never know. Also, the potential beneficial effects of reduced E-selectin levels may take time to be of benefit. In support of this concept, the changes in E-selectin and LDL cholesterol were correlated.

The major limitation of this study is the inability to assess the effects of inflammatory protein changes on cardiovascular risk. PEPI was not designed to evaluate clinical end points and there were too few women in PEPI with CAD to study outcome effects. However, to the extent that inflammatory protein pathways are casually related to cardiovascular events, these findings are of considerable interest and support the negative results of HERS. ❖

Heparin-Induced Thrombocytopenia

ABSTRACT & COMMENTARY

Synopsis: *Lepirudin reduces death, limb amputation, and thromboemboli with acceptable safety and should be given as soon as HIT is suspected.*

Source: Greinacher A, et al. *Circulation* 1999;100:587-593.

A previous study of desulfated recombinant hirudin (lepirudin) for heparin-induced thrombocytopenia (HIT) showed clinical efficacy in a highly select patient population. This study was designed to expand that experience in a broader population, including patients

with renal dysfunction. From 46 German hospitals, 112 patients with confirmed HIT (positive heparin-induced platelet activation test) and the appropriate clinical situation (50% decrease in platelets on heparin or values < 100 g/L or new thromboembolic complications [TEC]) received lepirudin as needed for 2-10 days using various bolus and infusions depending on the clinical situation. Treatment was discontinued prematurely for death (n = 7), adverse events (9), or other reasons (3); thus, 93 patients completed the protocol and were compared to historical controls of similar patients. A complete laboratory response (activated PTT ratio > 1.5 and platelet count normalization) was achieved in 65 patients (69%). From HIT diagnosis to two weeks after lepirudin cessation 11 patients died, 10 underwent limb amputation, and 20 had new TEC. The average event rate per patient-day decreased from 5.1% pretreatment to 1.5% during treatment. At 35 days after HIT diagnosis, the number of patients having more than one event was 31% on lepirudin vs. 52% in the controls (RR 0.71, P = 0.12). Adverse bleeding events were more common with lepirudin than controls at 35 days (45% vs 27%; RR 2.6, P < 0.001), but there was no difference in bleeding events requiring transfusion and no intracranial bleeding was observed. Greinacher and colleagues conclude that lepirudin reduces death, limb amputation, and TEC with acceptable safety and should be given as soon as HIT is suspected.

COMMENT BY MICHAEL H. CRAWFORD, MD

HIT typically occurs after prolonged heparin administration (5-10 days) and with heparin discontinuance it takes 7-10 days for platelet levels to return to normal. HIT-associated TEC can cause severe complications such as death, myocardial infarction, stroke, and limb amputation. However, patients frequently require heparin continuation because of underlying disease or HIT-associated vessel thrombi. Thus, lepirudin, which is a direct thrombin inhibitor that does not cross-react with HIT antibodies, may be particularly useful for the treatment of HIT. The only known alternatives—danaparoid sodium and argatroban—have not been shown to be as effective as lepirudin.

Although the event rate was considerable even on lepirudin, and the relative risk of events was not significantly reduced, it is noteworthy that 45% of the TEC occurred before treatment could be started even though the pretreatment period only accounted for 6% of the total observation time. Also, since almost all of the patients had their heparin stopped for a considerable period before treatment began, heparin cessation did not appear to be an adequate therapeutic strategy. In addition, although bleeding is generally increased on lepirudin, there was no difference in serious bleeding requiring transfusion compared to controls and no intracranial or fatal bleeds occurred.

Obviously, historically controlled studies have limitations. However, studies over the last 15 years have shown a consistent mortality of 20-30% with little, if any, progress. This rate is 2-3 times higher than the rate in this study. Also, recent studies have suggested a TEC rate of about 50%, which is almost twice the rate observed in this study. Thus, lepirudin is clearly indicated for this serious condition.

It could be argued that, for most cardiologists, HIT is a rare disease of little importance in modern cardiology. Since most patients with HIT have been on heparin for more than five days, its incidence in cardiologic practice has decreased markedly. We no longer treat unstable angina patients with days of heparin because of pressures to reduce the length of stay and the liberal use of interventional coronary procedures. Indeed, in this study, most of the patients were noncardiac. Also, even deep venous thrombosis and other conditions are being treated more and more with low molecular weight heparin and newer antiplatelet drugs (IIb/IIIa, clopridogel, etc.). These considerations aside, when HIT does occur, it needs to be diagnosed quickly and effective treatment must be instituted as soon as possible. ❖

Standard CPR vs. ACD CPR for Out-of-Hospital Cardiac Arrest

ABSTRACT & COMMENTARY

Synopsis: *Active compression-decompression CPR administered by highly trained advanced life support personnel increases survival among victims of out-of-hospital cardiac arrest.*

Source: Plaisance P, et al. *N Engl J Med* 1999;341: 569-575.

Devices that allow active compression-decompression (ACD) of the chest have been developed to augment cardiac output during cardiopulmonary resuscitation (CPR). Plaisance and colleagues from France conducted a study testing the hypothesis that ACD CPR would improve survival and long-term neurologic outcome in victims of out-of-hospital cardiac arrest as compared to standard CPR. This report describes data at one year after arrest from their study.

Fifteen mobile ICUs in Paris and Thionville participated in the study. All teams were intensively trained in CPR using both standard and ACD approaches. Physicians were part of the emergency response team. The two CPR methods were used on odd or even days of the month, respectively. All CPR efforts were performed at the scene, not in a moving vehicle. Patients were intubated and ventilated at the start of CPR. Individual rescuers performed either standard closed chest compression or ACD in three-minute shifts to prevent fatigue. Although not specifically stated, defibrillation was apparently used as appropriate.

During the 19-month study period, 1083 calls for cardiac arrest were placed but 333 victims were either pronounced dead before CPR was initiated or were not candidates for resuscitation. Eight patients recovered with basic life support alone. The remaining 750 patients were assigned to either standard (377 patients) or ACD (373 patients) CPR. The two groups were comparable in terms of gender, age, site of arrest, and presence of known cardiac disease. Only 8% of victims received bystander CPR. The time from collapse to initiation of basic life support was 8.9 ± 6.9 and 9.5 ± 7.9 minutes in the standard and ACD CPR groups, respectively. The initial rhythm was asystole in 82%, ventricular fibrillation in 12%, and pulseless electrical activity or other in 6%.

ACD CPR was superior to standard CPR for the following outcome measures: return of spontaneous circulation (39% vs 29%); survival at 24 hours and 7 days (23% and 10% vs 14% and 5%); hospital discharge without neurologic impairment (6% vs 2%); and survival at one year (5% vs 2%). An analysis of the characteristics of the few one-year survivors showed the ACD CPR allowed survival after a longer interval of collapse without CPR and required a shorter duration of CPR for initial resuscitation. Complications were similar with both techniques except for more frequent sternal bruising with the ACD approach.

Plaisance et al conclude that ACD CPR administered by highly trained advanced life support personnel increases survival among victims of out-of-hospital cardiac arrest.

COMMENT BY JOHN P. DiMARCO, MD, PhD

One of the major problems of standard CPR is the limited amount of cardiac output and coronary flow provided by the technique. A number of approaches, including the suction device for ACD CPR, described in this paper have been developed. This paper illustrates the amount of improvement we can anticipate with these new approaches.

The French emergency medical system involved in this study differs in significant ways from systems available in many major U.S. cities. In the United States, the major emphasis has been placed on quick response times and early defibrillation by emergency responders. The introduction of automatic external defibrillators has shortened the amount of responder training required. Hopefully, by enlarging the pool of potential rescuers, the time to defibrillation will be shortened and, thus, survival improved. The French system described in this report used a mobile intensive care unit headed by a physician to respond to cardiac arrests. The response time was relatively long and, as a result, many of the victims had asystole or pulseless electrical activity as their initial rhythm. Although only a small proportion were saved, the ACD system provided a significant benefit.

Based on these data, it appears that the ACD system will become a useful secondary tool for emergency response teams. Early defibrillation should still be the first priority. When the initial defibrillation attempts are unsuccessful or if the initial rhythm is asystole, use of ACD CPR may permit salvage of a small number of patients. ❖

Exaggerated QT Prolongation After Cardioversion

ABSTRACT & COMMENTARY

Synopsis: *Dofetilide produced greater QT interval increases in sinus rhythm than during atrial fibrillation. Monitoring of rhythm and QT changes after restoration of sinus rhythm is required until steady state has been reached.*

Source: Choy AMJ, et al. *J Am Coll Cardiol* 1999;34: 396-401.

Choy and colleagues measured the effects of intravenous dofetilide on QT intervals during both atrial fibrillation and sinus rhythm. Twelve patients with hypertension and atrial fibrillation or flutter who were scheduled for elective cardioversion were recruited for the study. Atrial fibrillation or flutter had been present for between 24 hours and 12 months. Patients received either 5.25 g/kg or 8 g/kg intravenous dofetilide over 100 minutes. QT intervals were measured in leads V_2 and V_3, with the mean volume for five consecutive beats reported. Only one patient was converted to sinus rhythm with intravenous dofetilide. Electrical cardioversion was attempted in the remaining 11 patients. Three patients failed electrical cardioversion and their data were excluded. The remaining nine patients were scheduled to

receive a second identical dofetilide infusion the following day. In four patients, however, the infusion was terminated before its completion because of QT prolongation to greater than 500 msec in two ECG leads. The nine study patients were divided into two groups: group I (infusion terminated early) and group II (infusion completed). During atrial fibrillation in all nine patients, dofetilide produced a modest increase in QT that was not significant (baseline and 100 min infusion values: 386 ± 49 and 420 ± 60 msec, P = NS). The four group I patients showed an exaggerated QT response during sinus rhythm. After only 20 minutes, QT had increased from 432 ± 15 at baseline to 580 ± 63 msec (P < 0.01). Among the five group II patients, dofetilide produced a change in QT from 412 ± 52 at baseline to 459 ± 62 msec at end infusion (P = NS). One patient in group I developed asymptomatic, recurrent runs of torsades de pointes that lasted for 10 minutes after stopping the infusion. Plasma dofetilide concentrations were similar on both infusion days. Heart rate was slower in sinus rhythm, with the slowest heart rates noted in the four group I patients. Atrial natriuretic peptide and plasma norepinephrine levels fell after cardioversion in both groups.

Choy et al conclude that the IKr blocker, dofetilide, produced greater QT interval increases in sinus rhythm than during atrial fibrillation. Monitoring of rhythm and QT changes after restoration of sinus rhythm is required until steady state has been reached.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Dofetilide is a new type III antiarrhythmic drug that has recently received FDA approval for use in patients with atrial fibrillation. Dofetilide blocks the rapidly acting, outward potassium current, IKr, and prolongs repolarization and the QT interval. Unlike sotalol, dofetilide has no beta-blocking activity and does not result in bradycardia. Unlike amiodarone, dofetilide results in only rare extracardiac toxicity. Dofetilide has no major negative inotropic effects and has been used safely in patients with heart failure. The major toxicity observed during clinical trials with dofetilide has been QT prolongation and torsades de pointes.

In this paper, Choy et al report that dofetilide produces more QT prolongation and toxicity during sinus rhythm than during atrial fibrillation. This would be consistent with the clinical observation made with other QT-prolonging drugs that serious arrhythmias occur most commonly in the period immediately after cardioversion. Unfortunately, the mechanism for this increased response is unexplained. In this study, patients were to receive identical infusions of dofetilide, yet QT prolongation was more marked when the patients were in sinus rhythm. It is hard to know if the changes in heart rate, the small residual concentrations of dofetilide still present from the first infusion, or some electrophysiologic changes in the ventricles after restoration of sinus rhythm were responsible. The small number of patients in this study also limits our ability to interpret the data since mean QT changes of up to 10-15% did not reach statistical significance.

Dofetilide will be marketed with strict guidelines for administration. Dosage adjustment based on renal function and initiation of therapy during in-hospital monitoring will be recommended. The data presented in this paper support this conservative approach. ❖

Stroke Following Cardiac Surgery

ABSTRACT & COMMENTARY

Synopsis: *Strokes after cardiac surgery are more common after initial normal neurologic recovery and atrial fibrillation was related to these later strokes only if a low cardiac output state was induced.*

Source: Hogue CW, et al. *Circulation* 1999;100: 642-647.

Stroke after cardiac surgery continues to be a problem and is associated with high mortality. Thus, Hogue and colleagues sought to identify risk factors for early and later stroke in 2972 patients aged younger than 50 years in whom epicardial echocardiography was used to identify ascending aorta atherosclerosis. The surgical approach was modified to avoid atheroma during aorta manipulations. Stroke was defined as new permanent neurological defects that could not be attributed to metabolic or other problems, and they were classified as early (immediately after surgery) or later (occurring after initial normal neurologic recovery). The incidence of stroke was 1.61% (48/2972) and 65% were later. Multivariate analysis showed that prior neurologic events (odds ratio 12, P < 0.001), aortic atherosclerosis (OR = 2, P = 0.004), female sex (OR = 0.7, P = 0.004), and duration of cardiopulmonary bypass (OR = 1.1, P = 0.005) were independent predictors of early stroke. Later stroke risk factors also included diabetes (OR = 2.8, P = 0.008) and low cardiac output associated with atrial fibrillation (OR = 1.7, P = 0.033). In-hospital mortality was 41% in those with early strokes, 13% in those with late strokes, and 3.7% in the nonstroke patients (P < 0.001). Hogue et al conclude that strokes after cardiac surgery were more

common after initial normal neurologic recovery and atrial fibrillation was related to these later strokes only if a low cardiac output state was induced. Also, all strokes were more common in women, those with prior strokes, and those with atherosclerosis.

COMMENT BY MICHAEL H. CRAWFORD, MD

The major finding of this study was the low rate of stroke (1.6%) in an older cohort in whom epiaortic echo was used to guide aorta cannulation. Previous studies have found stroke rates of 3-6% in similar populations. Unfortunately, epiaortic echo was used in all the patients, rather than being randomly assigned vs. no echo assessment. Thus, we cannot be sure that the aortic echos made the difference or some other technical advance or population characteristic was the reason for the lower rates. This study and others strongly suggest that intraoperative ascending aorta evaluation may reduce preoperative stroke rates. The results are more impressive when you consider that some of the strokes may have been present preoperatively and missed because no formal preoperative neurological assessment was done, but post-operative patients suspected of stroke were evaluated by neurologists.

Another deficiency of the study was a failure to evaluate cognitive function before and after surgery. Previous studies have suggested that mild intellectual impairment occurs in up to 6% of post-operative patients, resulting in a total stroke plus milder impairment rate of 10-15%.

Much has been made of the morbidity and mortality associated with post-operative atrial fibrillation that occurs frequently after cardiac surgery. Yet in this study, atrial fibrillation alone was no more likely to be associated with stroke than no atrial fibrillation (1%). However, the presence of low cardiac output plus atrial fibrillation raised it to 4% (P = 0.004). On the other hand, we do not know how the patients with atrial fibrillation were managed in this study. It is possible that they were aggressively managed with heparin, transesophageal echo, and cardioversion, if appropriate. Aggressive treatment would reduce the rate of strokes from this cause.

In conclusion, it is clear that more attention needs to be paid to the condition of the ascending aorta in cardiac surgery patients. Whether preoperative echo, intraoperative echo, or experienced palpitation is the best approach is unknown. Also, if echo is employed, should it be transesophageal or epiaortic? In addition, women and patients with prior stroke are at higher risk of early and late strokes. Interestingly, diabetes and age were not predictive, which Hogue et al suggested may be due to assessing the patients for aortic atherosclerosis. In previous studies in which age and diabetes were risk factors, they may have been serving as markers for atherosclerosis. In descending order of importance, perioperative stroke seems related to a history of prior stroke, female sex, and aortic atherosclerosis. ❖

Alcohol Consumption and Sudden Cardiac Death

ABSTRACT & COMMENTARY

Synopsis: *Men who consume mild to moderate amounts of alcohol had a reduced risk of SCD as compared to those who consumed less or more.*

Source: Albert CM, et al. *Circulation* 1999;100: 944-950.

Although heavy alcohol consumption is associated with an increased risk of sudden cardiac death (SCD), the risk of more moderate alcohol consumption is unclear. Thus, Albert and associates evaluated the Physician's Health Study database of more than 22,000 apparently healthy men aged 40 years or older who were followed for an average of 12 years. The purpose of this study was to assess the effects of aspirin and beta-carotene on cardiovascular disease and cancer end points. At enrollment and at 84 months, a questionnaire regarding number of alcoholic drinks consumed was administered. SCD occurred in 141 subjects. Alcohol consumption was evenly distributed between one drink or less per month to one per day, but there were few men who consumed two or more per day. After controlling for confounders, men who consumed 2-4 drinks per week (relative risk 0.40, P = 0.004) or 5-6 drinks/week (RR 0.21, P = 0.002) at baseline had a significantly reduced risk of SCD compared to those who consumed more or less alcohol. In fact, the relationship between alcohol consumption and SCD was "U" shaped. By contrast, the risk of nonfatal cardiac events was linear, with the lowest risk recorded for those who drank 1-2 drinks/day (P = 0.02). Albert et al conclude that men who consume mild to moderate amounts of alcohol (2-6 drinks/week) had a reduced risk of SCD as compared to those who consumed less or more.

COMMENT BY MICHAEL H. CRAWFORD, MD

SCD is the most common cause of death in adults younger than 65 years of age. Out-of-hospital resuscitation is not going to be the answer; thus, prevention makes sense. In this regard, this study is of interest. Prior prospective studies have shown a reduction in coronary

events with moderate alcohol consumption, but not in SCD. However, case-controlled studies have shown a reduction in both. It may be that the prospective studies were underpowered for SCD, a deficiency that the Physician's Health Study did not have with 20,000 participants.

The "U" shape of the curve relating alcohol consumption to SCD contrasts to the linear relation between alcohol intake and other coronary events. Presumably, the difference is that high alcohol intake is arrhythmogenic. The mechanism for the beneficial effect of alcohol is not known, but some studies have suggested that reduced plaque rupture, thrombosis, and autonomic nervous system activity or increased HDL levels may play a role. Clearly more study is needed about mechanisms to develop an approach with the benefits of alcohol, but without the risks of alcohol.

There are several limitations to this study. One is the lack of knowledge of the type of alcohol imbibed. Thus, we cannot accept or refute the red wine hypothesis. Also, we don't know the pattern of alcohol ingestion, but presumably most physicians do not binge drink and the 5-6 drinks/week is spread out. Obviously, binge drinking has its own risks (i.e., holiday heart syndrome). In addition, there may be confounders that accompany moderate alcohol intake that may explain the results in part. Finally, the study was done on healthy, upper socioeconomic class men and may not be applicable to women and other segments of the U.S. male population. However, for the weary physician who has battled disease and HMOs all day, they should go ahead and have that one cocktail as long as they are not on call or planning to operate heavy machinery. ❖

CME Questions

17. Which of the following supplements was shown in GISSI to reduce cardiovascular events?
a. Vitamin E
b. N-3 polyunsaturated fatty acids (fish oil)
c. Vitamin C
d. All of the above

18. The potential reason for the negative findings in the Heart and Estrogen Replacement Study of secondary prevention is that estrogen:
a. increases LDL cholesterol.
b. increases the Von Willebrand factor.
c. increases C-reactive protein.
d. All of the above

19. Currently the best treatment for heparin-induced thrombocytopenia is:
a. switch to low-molecular-weight heparin.
b. coumadin.
c. clopridogel.
d. lepirudin.

20. The best initial therapy for cardiac arrest is:
a. prompt defibrillation.
b. standard CPR.
c. compression-decompression CPR.
d. IV amiodarone.

21. The major adverse effect of dofetilide, a new type III antiarrhythmic agent, is:
a. beta blockade.
b. extra cardiac toxicity.
c. negative inotropic effect.
d. QT prolongation and torsades de pointes.

22. Which is most true concerning stroke following cardiac surgery?
a. The majority occur after initial normal neurologic recovery.
b. Most are related to post-operative atrial fibrillation.
c. The incidence is 10-15%.
d. Preoperative neurological exam is predictive.

23. Which is most correct concerning alcohol consumption and cardiac events?
a. Moderate consumption reduces sudden cardiac death rates.
b. Moderate consumption reduces nonfatal events.
c. Benefits are only seen with red wine intake.
d. a and b.