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CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

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INSIDE

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Risk of Statins

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Kashani A, et al. Risks Associated with Statin Therapy. *Circulation.* 2006;114:2788-2797.

DESPITE WELL-PROVEN EFFECTIVENESS, STATIN THERAPY IS underutilized. This may be due to perceived risks by physicians and patients. Thus, Kashani and colleagues prepared a meta analysis of 35 randomized controlled trials of 74,102 patients using 6 statins currently on the market. Four cerivastatin trials were analyzed separately, since it is no longer on the market. Study inclusion criteria included documented hyperlipidemia, double-blind, > 100 patients per arm, statin monotherapy vs placebo, and full documentation of adverse events.

Results: Risk of myalgias (risk difference / 1,000 patients = 2.7, 95% CI -3.2 to 8.7) creatine kinase elevation (RD = 0.2, CI -0.6 to 0.9) rhabdomyolysis (RD 0.4, CI -0.1 to 0.9) and drug discontinuation for any adverse event (RD -0.5, CI -4.3 to 3.3) were not significantly different between statin and placebo. However, the risk of transaminase elevations was higher on statins (RD 4.2, CI 1.5 to 6.9). Liver toxicity reached statistical significance in the fluvastatin and lovastatin individual trials. Individual comparisons showed a higher incidence of muscle toxicity with rosuvastatin, but because of small numbers this was not significant. Cerivastatin showed a significant increase in rhabdomyolysis (RD 12.4, CI 5.4 to 19.3, $P < 0.01$), but not myalgias or creatine kinase elevations. The authors concluded that available statins are associated with a small increased risk of hepatotoxicity, but not muscle toxicity or drug discontinuation for adverse effects. Cerivastatin was the only agent that showed an increase in rhabdomyolysis and it has been withdrawn from the market.

COMMENTARY

This study is of particular interest to me because I have found considerable patient resistance to statin therapy. Maybe this is just another "California values" issue, but I suspect many have had the same problem. The internet must be full of horror stories about statins, and my patients tell me that their herbal medicine

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retailers rail against them in favor of the "natural" compounds they sell. Thus, this article is very reassuring and I can counter my reluctant patients with data in over 74,000 subjects. The muscle toxicity issue is really put to rest by this study; the available statins just don't significantly affect the muscles. Also, as they point out, rhabdomyolysis is rare and usually associated with drug-to-drug interactions. It was reassuring to see that cerivastatin did significantly increase rhabdomyolysis; justifying its withdrawal from the market. Transaminitis was increased to about 4/1,000 patients treated with statins, but this is most often asymptomatic and reversible. Liver failure is rare, if present. Therefore, this analysis supports the conclusion of the ACC / AHA / NHLBI guidelines that screening liver enzymes and creatine kinase only be performed if patients have symptoms.

There are some limitations to the study. Clinical trial populations are usually younger and healthier than the average patient populations. How the latter are affected by statins is unknown. There is limited data on rosuvastatin since it is relatively new. There is little data on drug-to-drug interactions such as statins and fibrates. Reports of statins causing memory loss and other neurologic symptoms could not be analyzed because of insignificant data. Finally, relative risk of adverse effects at different doses could not be evaluated. This is an important point because many believe from experience that adverse effects are more common with higher doses and often abate with dose reductions, without having to stop the statin completely. More data on this observation would be useful. In the final analysis, this study confirms the safety of these highly effective agents. ■

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Questions & Comments

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Statins and Cancer

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *In older patients started on statins there was no significant increase in cancer.*

Source: Setoguchi S, et al. Statins and the Risk of Lung, Breast, and Colorectal Cancer in the Elderly. *Circulation*. 2007;115:27-33.

Studies of statin use have shown a range of effects on cancer from a protective effect to an association between cancer and statin use in elderly patients. However, these observations have not been adequately controlled for confounders. Thus, Setoguchi and associates conducted a cohort study in an elderly population using glaucoma medication init ation as a comparison group. The study was based upon linking a state drug benefit program data to a cancer registry and Medicare utilization data. All subjects were > age 65 and were excluded if they were already in the cancer registry. The population studied was those with new statin drug use after 12 months of non-use and who filled at least 3 prescriptions in 180 days and then at least 2 per 6 months. The primary endpoint was a new diagnosis of breast, lung, or colorectal cancer. The final populations included 24,439 statin users and 7,284 glaucoma drug users. Baseline characteristics were similar with regard to health care utilization, preventive activities and other ailments, but the glaucoma drug users were older. Over a mean follow-up of 3 years, there was no difference in cancer rates between the 2 groups and they were similar to reported rates in the general population (hazard ratios 0.96-1.11, all NS). The authors concluded that in older patients started on statins there was no significant increase in breast, lung, or colorectal cancer as compared to glaucoma drug users over the period of the study.

■ COMMENTARY

This study is also reassuring and should help allay patients' fears about statin use. Major efforts in this

study were taken to avoid bias and confounders. The new glaucoma drug users comparison group is a major strength. This group is of a similar age and is more likely to have the same health behaviors as the statin users. Also, new statin users were studied, which avoids this bias of chronic statin users who may have more healthy behaviors. The study was large and used a cancer registry as the endpoint decision maker. Finally, they looked at an older group where cancer incidence is more likely.

There were a few weaknesses to this study. Not all potential confounders could be controlled for; such as family history of cancer, aspirin use, and obesity. However, sensitivity analyses suggested that these factors would not have made a significant difference in the results. Also, follow-up was relatively short (median 2.9 years, longest 8.4 years). Only 40% were followed for more than 3 years and 60% of the cancers occurred after 3 years. So the risk of statins with use beyond this study period cannot be ascertained. However, this study should put to rest claims that statin drugs cause cancer. ■

BiV Pacing in Class IV Heart Failure

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

Dr. DiMarco is a consultant for Novartis, and does research for Medtronic and Guidant.

Synopsis: *Cardiac resychronization therapy reduces morbidity and mortality in class IV heart failure patients.*

Source: Lindenfeld J et al. Effects of Cardiac Resynchronization Therapy With or Without a Defibrillator on Survival and Hospitalizations in Patients With New York Heart Association Class IV Heart Failure. *Circulation.* 2007; 115:204-212.

This report from the COMPANION trial details the effects of cardiac resynchronization with or without defibrillation in patients with ambulatory class IV heart failure. The COMPANION trial was a randomized trial that compared optimal pharmacologic therapy, cardiac resynchronization therapy (CRT), and cardiac resynchronization therapy plus defibrillation (CRT-D) in patients with ischemic or nonischemic cardiomyopathy, class III or class IV heart failure, an ECG QRS interval of at least 120 msec, sinus rhythm and a hospitalization for the treatment of heart failure within 12, but not within one month, of enrollment. Enrolled patients were randomly assigned in a 1:2:2 ratio to pharmacologic therapy, CRT or CRT-D. This report focuses on the subset of 217 of the 1,520 COMPANION patients who were classified at the time of enrollment as having New York Heart Association class IV heart failure.

In comparison to the NYHA class III patients in COMPANION, the NYHA class IV patients had a slightly longer duration of heart failure, a lower ejection fraction, a shorter 6-minute walk distance, lower systolic and diastolic blood pressure, and decreased use of ACE inhibitors or beta blockers, the latter, presumably because of intolerance.

The primary endpoint in COMPANION was time to death or hospitalization for any cause. Time to the primary endpoint was significantly prolonged by both CRT and CRT-D compared with medical therapy among Class IV patients, as well as in the overall trial. Favorable trends for all-cause mortality were observed, but were not significant because of the relatively small size of the ambulatory class IV cohort (hazard ratios 0.67 for CRT and 0.63 for CRT-D). Time-to-death or heart failure hospitalization was also significantly improved with both CRT and CRT-D compared with medical therapy. Time-to-sudden-death was significantly prolonged by CRT-D, but not by CRT compared to medical therapy. Time-to-heart-failure-death showed favorable trends with both CRT and CRT-D, but these trends were not statistically significant.

Despite these improvements in the survival curves, mortality in this group remained high. At one year in the NYHA class IV patients, 44% of medical therapy patients had died compared with 36% of CRT patients and 30% of CRT-D patients. By 2 years, 62% of medical therapy subjects, 45% of CRT subjects and 55% of CRT-D subjects had died. Comparison with COMPANION patients classified as NYHA class III showed, as would be expected, higher rates of mortality in the ambulatory class IV patients. Many Class IV patients also showed functional improvement. At one month after implant, 67% of NYHA Class IV CRT and CRT-D patients improved at least one NYHA class compared with only 31% of medical therapy patients. Mortality benefit was seen among those who improved their functional status but was not seen in the subset of patients

who did not improve their functional status. Quality-of-life score also improved in the CRT and CRT-D patients compared with medical therapy. Only limited data were available on 6-minute walk test duration.

Implantation of the resynchronization device was however more difficult in the heart failure patients in class IV compared to those in class III. Overall, 27 of 162 (17%) class IV patients did not receive a CRT device vs only 105 of 1,050 (10%) class III patients.

The authors conclude that both CRT and CRT-D are beneficial in altering mortality and morbidity in ambulatory class IV patients.

COMMENTARY

Most prior studies on resynchronization therapy and implantable defibrillators have included either no or only a small number of patients classified as having NYHA class IV heart failure symptoms. COMPANION allowed entry of Class IV patients but, in order to be eligible, patients should have been dyspneic at rest with worsening dyspnea on exertion, and yet not have had a hospitalization within the previous 30 days This is a relatively small subset of Class IV patients often referred to as ambulatory Class IV. Most patients who are chronically in Class IV have frequent hospitalizations or require inotropic support. Current guidelines do not support a role for either ICD therapy or CRT in these Class IV patients, despite the fact that there are some positive small observational studies. In the COMPANION trial, the effects seen in ambulatory class IV patients were qualitatively similar to those seen among class III patients. Although NYHA class is a somewhat subjective assessment, the data here suggest that CRT has potential benefit in ambulatory patients with advanced heart failure on optimal medical therapy who otherwise meet criteria for resynchronization.

Elevated Pulmonary Artery Pressures in CAD

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *Elevated echo-Doppler estimates of pulmonary artery pressure predict heart failure and death in CAD patients.*

Source: Ristow B, et al. Elevated Pulmonary Artery Pressure by Doppler Echocardiography Predicts Hospitalization for Heart Failure and Mortality in Ambulatory Stable Coronary Artery Disease. *J Am Coll Cardiol.* 2007;49:43-49.

Elevated estimates of pulmonary artery pressures by echo-Doppler are valuable information in many clinical situations. However, its value in coronary artery disease patients is not known. Thus, Ristow and associates evaluated the Heart and Soul Study database for echo estimates of pulmonary pressures and related them to cardiovascular (CV) outcomes. The Heart and Soul Study is a prospective cohort study on the influence of psychosocial factors on CV events in patients with known coronary artery disease (CAD). Echocardiograms were done at intake in all patients and the peak tricuspid regurgitation (TR) and pulmonic regurgitation (PR) velocity was recorded when present. The echocardiograms were read independently in a blinded fashion. The upper limit of normal for peak TR gradient was taken as 30 mmHg and 5 mmHg for the end-diastolic (ED) PR gradient. Outcomes were determined independently by patient phone calls and inspection of hospital records, death certificates and coroner's reports.

Results: Outcome adjudication was complete for 717 of 741 participants enrolled from July 2001 to December 2002. Of these 717 patients, 466 (65%) had ED PR, 573 (80%) had TR and 392 (55%) had both gradients measured. At least one TR or ED PR measurement was present in 90%. An ED PR gradient > 5 mmHg was found in 21% and 22% had a TR gradient > 30 mmHg. Several baseline characteristics differed significantly in the elevated pulmonary pressure patients; in general, they were older, sicker and had more comorbidities. Thus, multivariate adjustments were made for these differences in calculating the odds of the primary outcomes of heart failure (HF) hospitalization, CV death and all-cause mortality. During the mean follow-up of 3 years, there were 63 HF hospitalizations, 19 CV deaths, and 86 total deaths. Elevated ED PR or TR gradients were associated with higher rates of HF hospitalization and all-cause death, but not CV death. On multivariate analysis, every 5 mmHg increase in ED PR was associated with a 2.5 fold increase in HF hospitalization and a 70% increase in total mortality. Every 10 mmHg increase in TR gradient resulted in a 50% increase in HF hospitalization. Statistically both measures had similar predictive power. The authors concluded that increases in echo-Doppler measurements of ED PR or TR gradients predict HF hospitalization and death in ambulatory patients with CAD.

COMMENTARY

That elevated estimates of pulmonary pressures are a bad prognostic sign in CAD patients is not surprising. What is unique about this study is the use of ED PR. This is a simple measurement available in most adults that is derived from one short axis parasternal view. TR gradients must be obtained in multiple views and the highest taken because of variations in jet direction. ED

PR gradient was as useful as TR, but it was obtainable in fewer patients (65% vs 80%). However, one or both measures were available in 90% of their patients. ED PR is also attractive because it is an estimate of end diastolic pulmonary pressure, which is a surrogate for left ventricular filling pressure. Thus, it is not surprising that it was good at predicting HF hospitalizations (OR 2.7), but so was TR gradient (OR 3.4).

There are some potential limitations to this study. The population was largely male. There were few CV deaths, so the power to predict this outcome was reduced. Neither the ED PR nor the TR gradients were corrected for estimated right atrial pressure, which would have more accurately reflected pulmonary artery pressures. This is surprising since this group popularized using inferior vena cava measurements to estimate right atrial pressure. They argue that in this ambulatory population most would have normal right atrial pressures and it would add little to the predictive value of the gradients. This may be true, but it would have been nice to see it proven. Also, they did not try to estimate pulmonary vascular resistance by measuring cardiac output by echo-Doppler. This would have been interesting, but would have added complexity to the study.

The authors recommend that echocardiographic laboratories routinely measure ED PR and TR gradients to estimate pulmonary pressures and I agree with them. This is a simple addition that provides powerful information to the clinician. ■

The Alcohol Paradox

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque

Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis.

Synopsis: *Moderate alcohol consumption is associated with a decreased risk for MI and heart failure.*

Sources: Djoussé L, Gaziano JM. Alcohol Consumption and Risk of Heart Failure in the Physicians' Health Study I. *Circulation*. 2007;115:34-39. Beulens JW, et al. Alcohol Consumption and Risk for Coronary Heart Disease among Men with Hypertension. *Ann Int Med.* 2007;146:10-19.

Many epidemiologic- and population-based studies have convincingly shown that mild to moderate alcohol consumption (no more than 2 drinks per day) is associated with decreased cardiac mortality and morbidity. However, physicians and guidelines do not support the use of alcohol in secondary or primary prevention. Two pertinent studies have recently been reported; one in a large population of hypertensive men, the other in a cohort of individuals without congestive heart failure. The results, not surprisingly, support the many previous studies and databases confirming that mild to moderate alcohol consumption on a regular basis is cardio-protective. One report comes from the Physicians Health Study I (PHS I), which enrolled 22,000 males, free of heart failure, followed prospectively from 1982 to 2005 with annual questionnaires. Participants in the PHS I longitudinal study received serial questionnaires about alcohol consumption; those with incident heart failure were contacted every 6 months. Frequent alcohol consumption was associated with older age, smoking, hypertension, and atrial fibrillation. Over an average period of 18.4 years, 904 incident cases of HF (heart failure) occurred, with a decreased incidence in men consuming more than 7 drinks per week. The hazard ratio for these moderate drinkers was 0.62 (0.41-0.96, $P = 0.012$ with adjustments for multiple risk factors). Of note, there was no significant association between HF and moderate alcohol consumption in HF patients who did not have underlying coronary artery disease. The incidence rates of heart failure were highest for zero consumption; those in the highest category of alcohol consumption had the greatest event-free survival. Adjusted hazard ratios were 0.88-1.05 for no drinking, 0.80 (0.68-0.94) for 1-4 drinks per week, and 0.62 (0.4-0.95) for greater than 7 drinks per week. Myocardial infarction incidence tracked with alcohol use rates; the lowest hazard ratio occurred in the highest-alcohol-consumption group. Multivariate analysis demonstrated comparable results, with relative risk of 1.1, 0.94, and 0.69 from the lowest to highest alcohol groups, $P = 0.003$. Prior myocardial infarction and coronary artery disease correlated with heart failure far better than those with no history of coronary artery disease. In fact, HF without antecedent myocardial infarction had a weaker inverse association with alcohol. The authors point out that the lifetime risk of heart failure is estimated to be 20% in individuals over 40 years of age.

These results are concordant with data from the Kaiser Permanente Cardio-Vascular Health Study, which showed a 40% lower risk of coronary artery disease related heart failure and much less for non-coronary artery disease HF. Other reports have been less robust. The authors identify a number of biologic mechanisms responsible for these observations, including beneficial effects on HDL, insulin sensitivity,

inflammation, endothelial function, coagulation, and atrial natriuretic peptide. No differences were found between the different types of alcoholic beverages. The authors conclude that their data shows "an inverse association between moderate alcohol consumption and incident heart failure." They speculate that alcohol use "may lower the risk of heart failure, especially in coronary artery disease-related heart failure."

The second study was of alcohol use in men with hypertension and came to similar conclusions. These data are from the Health Professional Follow-Up study (HPFS), a group of almost 12,000 men with hypertension studied between 1986 and 2002. The enrollees were all health professionals, although physicians were excluded. Subjects were categorized by preexisting hypertension or the development of hypertension after entering the study. Overall, 9,000 men with hypertension were diagnosed during the follow-up period, 2,700 men had hypertension at baseline. Thus, 11,700 patients with were eligible for this observational study. Patients were comprehensively evaluated by extensive questionnaires regarding alcohol consumption. Ethanol intake was calculated as were the number of days per week that individuals typically drank. Estimated mean alcohol intake was 12.5 grams per day (one drink). Primary end-points were incident non-fatal MI and fatal coronary heart disease (CHD) or stroke. CHD risk factors were assessed. Alcohol consumption and other dietary variables were updated every 4 years and anti-hypertensive medication was tracked. Of interest, only liquor consumption was associated with improved CHD outcomes. Approximately half of the study population were on hypertensive medications, more with greater alcohol use. Heavier alcohol consumption was associated with smoking and a lower prevalence of diabetes. Liquor and beer were used in the greatest quantity. During follow up of 16 years there were 653 myocardial infarctions (MI) (279 fatal, 374 non fatal). Low-quantity drinkers were comparable to abstainers. There was an approximate dose-dependant-inverse relationship between alcohol consumption and the risk for MI in adjusted models. The hazard ratio for consumption of 15-30 grams of alcohol per day was 0.70 (CI, 0.53-0.97). There was an inverse association for MI as low as 0.51 for consumption of 10-15 grams per day. There was no significant association for ischemic stroke. Liquor consumption was most strongly related to a lower risk for MI, (hazard ratio 0.59). Hazard ratio for red wine was 1.01, and 0.89 for white wine. Drinking frequency was inversely associated with risk for MI, with an adjusted hazard ratio of 0.64 for daily drinking. Alcohol consumption decreased somewhat after the initial diagnosis of hypertension, but 80% of men did not alter the intake by more than an average of one half drink per day following hypertension diagnosis.

In summary, their analysis of 12,000 men with hypertension indicates that alcohol use was associated with a decreased risk for fatal and non fatal MI but not for total death or CHD death. There was no statistical increase in other medical conditions, particularly cancer. The authors suggest that "approximately one half of the association of alcohol consumption with CHD is mediated by an increase in HDL." Controlling for age, smoking, BMI, etc., did not change the results. The authors conclude that moderate alcohol consumption is associated with a decrease risk for MI in men with or without hypertension, with no adverse affect from alcohol. "Men with hypertension who drink moderate and safely may not need to change their drinking habits."

COMMENTARY

These data are reassuring for those of us who like to have one or 2 glasses of wine on a daily basis. It has been long recognized and recommended that 1-2 drinks per day is a healthy maximum, and these reports robustly confirm these recommendation. In fact, in the modest number of individuals who were heavy drinkers, there appeared to be little adverse health effects (although benefits seen for moderate drinking were greater). These 2 very large data sets utilized careful and detailed statistical methods. Confounding information could be missed, as the alcohol intake records were done by repeated questionnaire. Nevertheless, there appears to be no "smoking gun" that would be responsible for these results being false or misleading.

It has long been a dilemma as to whether physicians should recommend a daily glass of wine to high-risk or overt CHD individuals. The concern about alcoholism has so far overpowered the argument that such a recommendation should be made by the physician. Nevertheless, it seems that patients who are well known to their doctor, have no addictive behaviors, and who are most interested in maximizing health benefits, could be safely advised of the data in the literature, including these 2 studies, which confirm a rather striking benefit in habitual, low-quantity drinkers, particularly if HDL is low. In addition to the general population studies of

alcohol consumption, we now know these data reflect a lower likelihood of congestive heart failure in patients who have underlying coronary disease, as well as clear-cut benefits for individuals who have or will develop hypertension. The alcohol paradox remains and is unlikely to disappear. Perhaps it is reasonable to revisit our policies and guidelines with a multi-representative task force to see if some of the benefits of alcohol can be safely steered toward individuals at risk for CHD. ■

Long QT Genes in SIDS

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Synopsis: *Sudden arrhythmic death associated with genetically determined long QT syndrome is a significant cause of SIDS.*

Source: Arnestad M, et al. Prevalence of long-QT Syndrome Gene Variants in Sudden Infant Death Syndrome. *Circulation.* 2007;115:361-367.

THE CAUSE OR CAUSES OF THE SUDDEN INFANT Death Syndrome (SIDS) have remained mysterious. In this article, Arnestad et al report the frequency of long QT syndrome (LQTS) gene variants and mutations in infants dying with SIDS. The authors evaluated 252 cases of unexpected infant death that occurred in the Southwestern region of Norway over a 6-year period. The cases were categorized as either pure SIDS, borderline or probable SIDS (ie, minor coexisting disease) or clearly due to infection or violence. The pure and probable SIDS patients, the patients with infectious or violent deaths and another group of 137 adults who died from noncardiac causes in the same acute geographic region were screened genetically for mutations/variants in the genes known to be associated with LQTS. The study was reviewed by a Norwegian ethics committee and this group mandated complete anonymity of the samples. This restriction prevented further contact with families of the victims in whom gene variants were identified.

Genomic DNA was extracted from blood or frozen tissue samples. Genetic techniques were used to amplify the coding sequences of 7 of the genes that have been identified as causes of long QT syndrome. Genetic variants identified were classified as either mutations, rare variants, and common (not clinically relevant) genetic variants. Mutations defined as genetic variants were not identified in ethnically matched controls nor in previously recorded control populations. Rare genetic variants were those that are absent in Norwegian controls, but reported in less than 0.7% of other white control populations or in nonwhite populations. Common genetic variants are those identified in greater than 0.7% of Norwegian or other white control populations.

There were 201 cases classified as either pure or borderline SIDS with a median age at the time of death of 3.5 months. Mutations and rare variants in the LQTS genes were identified in 26 of 201 cases (12.9%). The genes most frequently involved were SCN5A (13 cases, 50%), followed by KCNQ1 (5 cases, 19%), KCNH2 (5 cases, 19%), CAV3 (3 cases, 11%), and KCNE2 (1 case, 4%). One subject was identified who carried variants in both SCN5A and CAV3. Eleven different mutations and 9 rare variants were identified. The sodium channel variants identified were associated with an increased persistent sodium current or accelerated inactivation when assayed in vitro. In contrast, potassium channel variants identified in the SIDS cases may have been incidental findings since 4 of the 9 mutations identified in 6 cases had no evidence for channel dysfunction when assayed in vitro. In addition to the mutations and rare genetic variants identified, 13 common variants were detected. These were considered not to be related to SIDS. As a result, the overall data suggest that 19 of the 201 SIDS victims (9.5%) were carriers of functional defect likely to be the cause of sudden arrhythmic death.

The authors conclude that sudden arrhythmic death associated with genetically determined long QT syndrome is a significant cause of SIDS. They argue that an early ECG taken the third and fourth week of life, at a time when the QT interval is stable, would identify most of these infants and could lead to the initiation of effective preventive therapy.

■ COMMENTARY

Sudden infant death syndrome has remained a frustrating clinical problem. Current opinion now holds that the syndrome has multiple causes, but defining a cause in an individual case often proves difficult. Prospective identification of infants at high risk would be a major advance. This paper provides

further support for the concept that a significant fraction of SIDS cases are caused by ion channel mutations that result in unstable cardiac repolarization. It is striking in this paper that most of the mutations involve sodium channel defects, one of the less frequent causes of long QT syndrome in older children and adults. However, patients with sodium channel defect related LQTS often have their clinical events during sleep and this is certainly consistent with the pattern seen in SIDS.

The authors' recommendation that infants receive a screening ECG between 3 and 4 weeks of age would require a change in current pediatric practice. In any screening program, there is always a fear of causing harm by false-positive findings. However, as genetic testing for long QT syndrome has become more sophisticated, the value of screening becomes greater since a reliable follow-up test for those infants with QTC intervals over 470 msec is now available. Costs of such a program will have to be carefully evaluated, if such a testing program is to become standard. ■

CME Questions

12. Cardiac resynchronization therapy reduces death and heart failure hospitalizations in patients categorized as?
A. Class III
B. Ambulatory class IV
C. Decompensated class IV
D. A & B

13. Genes known to be associated with long QT syndromes are found in what percent of sudden infant death victims?
A. 5
B. 10
C. 15
D. 20

14. Commercially available statins increase the incidence of?
A. Liver function test abnormalities
B. Creatine kinase elevations
C. Cancer
D. Rhabdomyolysis

15. Routine transthoracic echocardiography measurement of TR and ED PR gradients can predict what in CAD patients?
A. All-cause mortality
B. Cardiovascular death
C. Heart failure hospitalizations
D. A & C

16. Which level of alcohol consumption reduces the risk of heart failure and myocardial infarction?
A. none
B. 1-2 drinks/day
C. 3-4 drinks/day
D. >4 drinks/day

Answers: 12. (d) 13.(b) 14.(a) 15.(d) 16.(b)

CME Objectives

The objectives of *Clinical Cardiology Alert* are:

• To present the latest information regarding diagnosis and treatment of cardiac disease;

• To discuss the pros and cons of these interventions, as well as possible complications;

• To discuss the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• To present the current data regarding outpatient care of cardiac patients. ■

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Higher HDL Cholesterol in Statin Therapy, Key to Slowing Atherosclerosis?

Aggressive statin therapy is associated with slowed progression and even regression of atherosclerosis. A new study suggests that, when monitoring statin therapy, increases in HDL cholesterol may be as important as decreases in LDL cholesterol in preventing disease progression. Researchers from the Cleveland Clinic reviewed 4 large studies from United States, North America, Europe and Australia in which 1,455 patients with angiographic coronary disease underwent serial intravascular ultrasonography while receiving aggressive statin therapy for 18 or 24 months. During therapy, mean LDL levels dropped from 124.0 mg/dl to 87.5 mg/dl, and mean HDL levels increased from 42.5 mg/dl to 45.1 mg/dl, and LDL to HDL ratios were reduced from a mean of 3 to 2.1 ($P < 0.001$ for all). These changes were accompanied by a small, but statistically significant decrease in atheroma volume as measured by intravascular ultrasound. The largest decrease in atheroma volume was associated with patients with LDL cholesterol less than the mean of 87.5 mg/dl, and percentage increases in HDL cholesterol of greater than 7.5%. The authors conclude that when treating with statins, decreases of LDL cholesterol and increases in HDL cholesterol are independently associated with regression of atheroma volume. They also note that these changes were not associated with reductions in clinical events or improved clinical outcomes and that more research is needed (*JAMA*. 2007; 297:499-508).

Citalopram Useful for Depression in CDA Patients

Major depression affects up to one quarter of patients hospitalized with coronary artery disease and these patients have a worse prognosis than non-depressed patients. A new study from Canada compares the efficacy of citalopram vs interpersonal psychotherapy in reducing depressive symptoms among these patients. The study randomized 284 patients with CAD and major depression to 12 weeks of interpersonal psychotherapy plus clinical management vs clinical management only, and a second randomization compared 12 weeks of citalopram 20-40 mg/day vs placebo. The main outcomes were scores on objective depression scales. Citalopram was superior to placebo in reducing depression scores ($P = 0.005$), but interpersonal psychotherapy was ineffective, being no better than clinical management. The authors conclude that citalopram administered in conjunction with weekly clinical management was effective in treating depression whereas there was no evidence of value for interpersonal psychotherapy. The authors suggest that citalopram or sertraline (based on previous studies) should be considered as first-step treatment for patients with CAD and major depression (*JAMA*. 2007;297:367-379). An accompanying editorial agrees that citalopram and sertraline are safe and effective for treatment of depression in patients with coronary heart disease, and suggests physicians should actively screen for signs and symptoms of depression in these patients. However, there is not yet

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any evidence that treating depression in this patient population reduces subsequent cardiac events (*JAMA*. 2007;297:411-412).

When to Stop Anticoagulation Before Surgery?

For patients on warfarin who have been bridging therapy with low molecular weight heparin (LMWH) prior to surgery, when is the best time to stop anticoagulation? A new study suggests that the evening before surgery is too late. Researchers in Ontario, Canada, looked at 80 patients who were scheduled for surgery or invasive procedures and were bridged with LMWH. All 20 patients had normal renal function and were given enoxaparin 1 mg/kg of body weight twice daily with the last dose administered the evening before surgery. Blood anti-factor Xa heparin levels were measured shortly before surgery, an average of 14 hours after the last dose. Two-thirds of patients had anti-Xa heparin levels of 0.5 U/ml or higher shortly before their invasive procedure. Patients with higher BMIs were more likely to have higher levels as were patients with lower creatinine clearances. The authors conclude that preoperative bridging with twice daily enoxaparin results in high residual anti-Xa heparin levels if the last dose is given the evening before surgery. They recommend that the last dose be given the morning on the day prior to surgery (*Ann Int Med.* 2007;146:184-187).

Drug Warnings: Ranibizumab and Bevacizumab

Both of Genentech's anti-angiogenic agents, ranibizumab (Lucentis) and bevacizumab (Avastin), have been the subject of new warnings from the company and the FDA. Ranibizumab, which is used for the treatment of neovascular (wet) macular degeneration, has been associated with increased risk of stroke in elderly patients. The drug, which is administered as an monthly intraocular injection, was found to be associated with a 1.2% risk of stroke at the recommended dose of 0.5 mg compared to a 0.3% risk associated with the lower-than-recommended 0.3 mg dose ($P = 0.02$) at an average follow-up of 230 days. Patients who had a history of stroke were at the highest risk. Bevacizumab, which is approved for treatment of non-small cell lung cancer and metastatic colorectal cancer, was recently found to be associated with increased risk of gastrointestinal perforation and potentially fatal pulmonary hemorrhage. Gastrointestinal perforation was seen as a complication of patients treated for colorectal cancer, while pulmonary hemorrhage was seen in patients receiving chemotherapy plus bevacizumab for lung cancer. Other bleeding complications seen in bevacizumab-treated patients including GI hemorrhage, subarachnoid hemorrhage and hemorrhagic stroke.

Growth Hormone Treatment, More Harm Than Good

The January 16, 2007, *Annals of Internal Medicine* includes a review of the safety and efficacy of growth hormone in the healthy elderly. The review was undertaken because growth hormone is widely recommended and sold as an anti-aging agent in this population. The authors reviewed 31 articles, which included a total of 220 participants who received growth hormone. The mean age was 69 and patients were generally overweight. Treatment duration mean was 27 weeks. Growth-hormone-treated patients compared to placebo- treated patients were noted to have decreases in overall fat mass and increases in overall lean body mass, but weight did not change significantly. Total cholesterol decreased, although not significantly, after adjustment for body composition changes. Bone density and other lipid levels did not change. Those treated with growth hormone were significantly more likely to experience soft tissue edema, and arthralgias, carpal tunnel syndrome, and gynecomastia as well as a slightly increased rate of diabetes and impaired fasting glucose. The authors conclude that growth hormone use in the elderly is associated with small changes in body composition and an increased rate of adverse events and cannot be recommended (*Ann Int Med*. 2007; 146:104-115).

FDA Actions

The FDA has warned against unsupervised use of topical anesthetic products for cosmetic procedures. The agency has received multiple reports of adverse events associated with patients applying excess amounts of topical agents containing lidocaine, tetracaine, benzocaine, and prilocaine. Two women who used topical anesthetics with lidocaine and tetracaine died after applying the creams to their legs and wrapping their legs in plastic to increase absorption. Healthcare professionals are cautioned to prescribe topical anesthetics with caution in the lowest concentration consistent with pain relief goals and to advise patients in their safe use.

The FDA has approved Roche's orlistat for over-the-counter use to facilitate weight loss. The drug, available in prescription form under the trade name "Xenical," blocks absorption of fat by inhibiting pancreatic lipase thus preventing triglyceride absorption in the small bowel. The over-the-counter version will be available as a 60 mg dose, half the prescription dosage. Orlistat over-the-counter will be marketed as "Alli." ■