Providing Evidence-based Clinical Information for 25 Years

CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

INSIDE

Financial Disclosure:

Clinical Cardiology Alert's physician editor, Michael H. Crawford, MD, is on the speaker's bureau for Pfizer. The peer reviewer, Rakesh Mishra, MD, reports no consultant, stockholder, speaker's bureau, or other financial relationship with any company related to this field of study.

Fish Oil Plus Statins

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Yokoyama M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomized open-label, blinded endpoint analysis. *Lancet*. 2007;369:1090-1098.

Synopsis: *EPA treatment added to statins reduces nonfatal CHD events in hypercholesterolaemic Japanese patients.*

SECONDARY PREVENTION TRIALS HAVE DEMONSTRATED REDUCED coronary heart disease (CHD) deaths in post myocardial infarction (MI) patients who consume fish or fish oil, but no prospective randomized primary prevention trials have been done. Thus, the Japan Eicosapentaenoic acid (EPA) Lipid Intervention Study (JELIS) was conducted to test the hypothesis that adding EPA to statin therapy would reduce major coronary events in hypercholesterolaemic Japanese patients. They recruited 18,645 patients with a total cholesterol of > 250 mg/dl with or without a history of CHD, who consume a large amount of fish. The patients were divided into those with CHD (3,664) and those without (14,981). They were randomized to receive EPA with statin or stain alone. All received dietary advice. The statins were either pravastatin up to 20 mg/day or simvastatin up to 10 mg/day. EPA 600 mg was administered 3 times a day after meals. The patients were followed for an average of 4.6 years. The primary endpoint was any major CHD event. Secondary endpoints included total mortality, stroke and peripheral artery disease.

Results. The primary endpoint occurred in 2.8% of the EPA group and 3.5% of the statin alone group, a relative risk reduction of 19% ($P = 0.011$). Unstable angina decreased 24% ($P = 0.014$) and all other nonfatal CHD endpoints, including MI, were significantly reduced ($P = 0.015$). The results were the same across LDL levels above or below 180 mg/dl. The primary prevention subgroup exhibited an 18% decrease in the primary endpoint in the EPA group which was not statistically significant. The secondary prevention group showed a 19% decrease which was significant (p = 0.048). All-cause mortality and stroke did not differ between groups. Total cholesterol, LDL and triglycerides

VOLUME 26 • NUMBER 6 • JUNE 2007 • PAGES 41-48

NOW AVAILABLE ONLINE
www.ahcmedia.com

decreased on therapy, but only the decrease in triglycerides was significantly greater on EPA. Neither treatment had much affect on HDL. Adverse events were more common on EPA, especially gastrointestinal (3.8 vs 1.7%), skin (1.7 vs 0.7%) and hemorrhage (1.1 vs 0.6%). The authors concluded that EPA treatment added to statins reduces nonfatal CHD events in hypercholesterolaemic Japanese patients.

COMMENTARY

This is an interesting study because despite a fish consumption that is 5 times most Western diets, supplemental EPA significantly reduced nonfatal CHD events in hypercholesterolaemic Japanese patients. Previous secondary prevention observational studies have shown that increased fish or fish oil consumption rescues fatal CHD and sudden death, but not nonfatal events. These results prompted speculation that fish oils are antiarrhythmic. Why the difference in these results? There are several potential explanations. It could be simply that the study was underpowered for fatal events. There is a low rate of death from CHD in Japan, especially in women, who comprised 69% of the study population. Most of the patients in the trial were in the primary prevention arm where the reduction in the primary endpoint did not achieve statistical significance. It could be that prospective trials avoid some of the biases of observational studies and reveal the true effect of a therapy. Fish oils contain many fatty acids and have many effects including reductions in triglycerides, thrombosis and inflammation. Perhaps EPA is less effective than fish oil. Given the high fish consumption of the Japanese, perhaps some beneficial threshold had already been crossed and further benefits from EPA therapy were more difficult to achieve. However, you can't say they didn't try. EPA levels were increased from 97 to 169 mol% after 5 years of therapy, a whopping 70% increase. Also, it had a cost in adverse effects with 25% experiencing one or more on EPA, but only 12% discontinued EPA due to adverse effects in this population. It is not known whether a lower dose would have produced similar benefits. Of interest EPA levels in most Western industrialized countries is 0.3 mol%.

Another issue with this study is that low doses of 2 statins were used. Although cholesterol levels were reduced, we don't know if any particular targets were achieved. Perhaps larger doses of statins would have accomplished the same results as adding EPA. However, the beneficial effects of EPA did not seem to be related to LDL levels, and except for triglycerides, EPA did not further change lipid levels in the study. This would argue against a statin-like effect, but doesn't mean that high dose statins couldn't achieve similar results.

So what do we tell our patients now about the use of fish oils? Clearly their potential benefit outweighs any potential harm in both primary and secondary prevention populations with high cholesterol values. They are one of the few therapies that lower triglycerides. In patients with high LDL, we don't know if they have benefits beyond aggressive LDL lowering with statins. In this study the average LDL on therapy was > 130 mg/dl. Recent studies with statins clearly show the benefits of LDL levels < 130, especially in secondary prevention. I believe the jury is still out on fish oils, especially for primary prevention, but if tolerated they don't appear to be harmful and have the potential to be beneficial. ■

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
ASSOCIATE PUBLISHER: Lee Landenberger.
ASSOCIATE MANAGING EDITOR: Jennifer Corbett.
MARKETING PRODUCT MANAGER: Gerard Gernazian.

GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Clinical Cardiology Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

Subscriber Information

Customer Service: 1-800-688-2421
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: jennifer.corbett@ahcmedia.com

Subscription Prices

United States
1 year with Free AMA Category 1 credits: $289
Add $9.95 for shipping & handling.
(Student/Resident rate: $125).

Multiple Copies
Discounts are available for group subscriptions. For pricing information, please call Tria Kreutzer at (404) 262-5482.

Canada
Add GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of *25 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the cardiologist. It is in effect for 36 months from the date of the publication.

Questions & Comments

Jennifer Corbett,
Associate Managing Editor, at (404) 262-5431 or e-mail at jennifer.corbett@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statins and HDL Cholesterol

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Asztalos BF, et al. Comparison of the Effects of High Doses of Rosuvastatin Versus Atorvastatin on the Subpopulations of High-Density Lipoproteins. *Am J Cardiol.* 2007;99:681-685.

Synopsis: *Rosuvastatin and atorvastatin at their maximal doses, favorably change HDL subpopulation levels, but rosuvastatin is significantly more potent than atorvastatin for this purpose.*

THE FAILURE OF NEW DRUGS THAT RAISE HDL cholesterol to change outcomes has renewed interest in HDL subpopulations. Thus, Asztalos and colleagues analyzed HDL subpopulations in the Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial. This study showed that 40 mg/day of rosuvastatin exhibited the greatest increase in HDL (+10%) versus (+2%) for atorvastatin 80 mg/day (*Clin Ther* 2004;26:1388 and *Am J Cardiol* 2003;92:152). This was a multi-centered open-label randomized study conducted in the U.S. that compared the effects of 4 statins on various lipoprotein values. The current analysis involved serum samples from baseline and after 6 weeks of therapy, plus diet in over 300 patients in the rosuvastatin 40 mg/day group and the atorvastatin 80 mg/day group. They assayed Apo A-1 levels and 8 subpopulations of HDL. About half the subjects were men and the average age of the two groups were 56 and 58 years. Baseline lipid, lipoprotein and HDL subpopulation values were well matched between the 2 treatment groups. Apo-1 increased 5% on rosuvastatin and decreased 1% on atorvastatin ($P < .001$). Both drugs decreased total cholesterol, triglycerides and LDL cholesterol to a similar degree. HDL was increased more on rosuvastatin (10% vs 3%), as was Apo-1 (5% vs 1, $P < .001$). Increases in α-1 and α-2 HDL have been previously shown to decrease the risk of coronary heart disease (CHD) and CHD events; both of these subpopulations were increased significantly by statin treatment (24% rosuvastatin and 12% atorvastatin for α-1 and 13 vs 4% for α-2, both $P < .001$ for the difference between treatment groups). The pre α-1 subpopulation was decreased similarly by both drugs suggesting a shift of cholesterol to the larger α particles (reversed cholesterol transport). Individuals with baseline low HDLs (< 40 mg/dl men, < 50 mg/dl women) showed an even greater difference between the effects of rosuvastatin vs atorvastatin (α-1 32% vs 11% and α-2, 21% vs 5%). The authors concluded that both rosuvastatin and atorvastatin at their maximal doses, favorably change HDL subpopulation levels, but rosuvastatin is significantly more potent than atorvastatin for this purpose.

COMMENTARY

There are several interesting aspects to this study. First, changes in total cholesterol, LDL, HDL and triglycerides were nearly identical between rosuvastatin and atorvastatin at their maximum recommended doses. So claims that rosuvastatin is more potent does not hold up when maximum doses are considered. This is reminiscent of what happened when atorvastatin was released with claims of increased potency over simvastatin. Suddenly the maximum dose of simvastatin was increased from 40 to 80 mg to minimize these differences. Was the impending release of rosuvastatin the driving force behind atorvastatin 80 mg? If one believes adverse events are more likely with higher doses of a drug, then rosuvastatin 40 may be preferable to atorvastatin 80. Second, although both drugs at maximum doses favorably altered the HDL subpopulations, the effect of rosuvastatin was of a much greater magnitude, especially in those with low HDL at baseline, but also in those with high triglycerides at baseline. Although observational studies suggest that the particular HDL subpopulation profile achieved with these drugs is associated with less CHD, only prospective treatment trials focusing on outcomes can establish this. Whether the differences between the 2 drugs will affect outcomes is unknown. However, this data suggests that rosuvastatin is more potent at favorably altering HDL subpopulations, which could be an advantage of this agent.

Third, the decrease in pre α-1 HDL and the increase in the cholesterol rich α particles suggest that reverse cholesterol transport may be enhanced by these statins. Pre α-1 particles avidly take up cholesterol from the periphery and deliver it to the liver. This pathway is not enhanced by the new direct cholesterol ester transport protein inhibitors, which may explain their failure to reduce atherosclerosis despite markedly raising HDL levels. Both statins showed about a 40% decrease in pre α-1 particles.

Baseline characteristics of the patients studied are worth noting to see if you can expect similar results in the patients you are treating. They had relatively normal HDL levels on average (about 50 mg/dl), but very high LDL levels (about 190 mg/dl) and moderately high triglyceride levels (about 180 mg/dl). Only about 20%

had known vascular disease and < 10% were diabetic. Whether the results observed would be found in a population with more comorbidity is not known. ■

Rosuvastatin Plus Ezetimibe

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Ballantyne CM, et al. Efficacy and Safety of Rosuvastatin 40 mg Alone or in Combination with Ezetimibe in Patients at High Risk of Cardiovascular Disease (Results from the Explorer Study). *Am J Cardiol.* 2007;99:673-680.

Synopsis: *Rosuvastatin plus ezetimibe may improve the management of high-risk patients by increasing the number that reach goal LDL cholesterol levels.*

When baseline LDL cholesterol levels are high, achievement of target levels, especially < 70 mg/dl can be difficult. Thus, the EXamination of Potential Lipid-modifying effects Of Rosuvastatin in combination with Ezetimibe versus Rosuvastatin alone (EXPLORER) study was conducted at 58 centers in the U.S., Western Europe and South Africa. The purpose of this study was to compare the efficacy and safety of adding ezetimibe 10 mg to rosuvastatin 40 mg in patients with coronary artery disease (CAD) or a CHD risk equivalent profile (10-year risk > 20%) and a fasting LDL of > 160 mg/dl but < 250 mg/dl and triglycerides < 400 mg/dl. Patients were randomized to rosuvastatin alone 40 mg/day or both drugs and the primary endpoint was the percent of patients achieving an LDL < 100 mg/dl after 6 weeks of therapy. A secondary endpoint was the percent achieving a non HDL cholesterol of < 130 mg/dl and high sensitivity CRP levels. Mean age of the 469 patients randomized was 63 years, just over half were men, almost 40% were diabetic and 97% had hypertension. More patients on combination therapy achieved an LDL < 100 mg/dl as compared to rosuvastatin alone (94 vs 79%, $P < 0.001$); the goal of < 70 mg/dl in high-risk patients (80 vs 35%, $P < 0.001$). Both treatments increased HDL about 10%. High sensitivity CRP levels also decreased more on combination therapy (46 vs 29%, $P < 0.001$). Adverse events were noted in about a third of patients with both treatments. Serous adverse events occurred in 2% or less of patients and few discontinued therapy. Myalgia was the most frequent adverse event in both groups at about 3%, but no rhabdomyolysis was observed. ALT increases were more common on combination therapy (2.5% vs 0.4%). The authors concluded that rosuvastatin plus ezetimibe may improve the management of high-risk patients by increasing the number that reach goal LDL cholesterol levels.

■ COMMENTARY

These results are most encouraging since 94% of these high-risk patients with mean LDL values of about 190 mg/dl achieved levels < 100, and 80% were < 70 mg/dl achieved levels < 100, and 80% were < 70 mg/dl on the combination of rosuvastatin 40 mg and ezetimibe 10 mg a day. Although comparisons to other trials are difficult because of differences in patient populations, these results are superior to those of simvastatin and atorvastatin plus ezetimibe. Also, it was reassuring that adverse events were few and not serious. No rhabdomyolysis was observed and myalgias were infrequent (3%) and the same in both treatment groups.

There were some limitations to the study. It was a short-term trial (6 weeks) and it was open-label. Of more importance there are no outcomes data. Thus, we don't know for sure that achieving aggressive LDL goals in high-risk patients by adding ezetimibe to maximum rosuvastatin therapy will improve CHD outcomes long-term. ■

CAD in Women

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.

Source: Nicholls SJ, et al. rate of progression of coronary atherosclerotic plaque in women. *J Am Coll Cardiol.* 2007;49;1546-1551

Synposis: *Women harbor less atherosclerotic plaque within their coronary arteries, despite the greater prevalence of atherogenic risk factors.*

This study asks the question as to whether women have less obstructive coronary disease (CAD) than men. It remains unclear if the absolute burden of atherosclerotic plaque differs between men and women. The study combined 3 intravascular ultrasound (IVUS) trials to assess atheroma burden in

women vs men; the investigators also attempted to evaluate the pattern of arterial remodeling in both genders. Finally, the study attempted to answer the question as to whether anti-atherosclerotic therapies as well as plaque progression are different between men and women. The methodology included a retrospective analysis of three serial IVUS trials, Reversal, Camelot and Activate. Men and women 30-75 years of age with angiographic CAD comprising at least one stenosis > 20%, and no stenosis > 50%, were evaluated. The IVUS technique and measurements have been described in the publications. Standard evaluations included measurements of total atheroma volume (TAV), percent atheroma volume (PAV), and assessment of the atheroma volume in the most and least diseased 10mm segments in each subject. A remodeling index was calculated, and was described as constrictive or expansive. CRP was measured. Adjustments were made for factors relating to plaque burden and progression, including age, hypertension, diabetes, etc. As compared to men, women tended to have a higher BMI and were more likely to have hypertension (SBP), diabetes, higher baseline total cholesterol, higher HDL cholesterol and lower triglycerides. Mean CRP in women was 4.8 mg/l vs 2.6 mg/l, ($P < 0.001$) in men.

RESULTS: At baseline women had less atheromatous plaque as well as atheroma volume. Arterial remodeling at the site of the greatest plaque extent was similar in men and women. Restrictive and expansive remodeling was equivalent for both sexes. Women had smaller coronary arteries and lumen vol=ume. After adjustment for differences that might influence regression, there was no sex difference in total and percent atheroma volume. Thus, "Women were no more likely to undergo substantial progression… or substantial regression than men." Finally, an effort was made to evaluate the effect of risk factors on plaque progression; females were just as likely as males to undergo regression when LDL cholesterol was lowered below 80 mg/dl, SBP less than 120 mmHg, and CRP < 2mg. There was no statistical interaction between sex and changes in total atheroma volume, and no relationship between sex and changes in PAV related to HDL, SBP or CRP. The authors stated that "…despite the greater presence of risk factors, women contain less atherosclerotic plaque within their coronary arteries." In addition, women benefited to a comparable degree from intensive risk factor modification. It appears from the study that clusters of risk factors are more important than any individual one, and "despite the greater presence of established risk factors, women harbored less plaque." While the pattern of arterial remodeling at the site with the greatest degree of plaque did not differ between sexes, the authors suggest that women express plaque burden in relationship to vessel size as being smaller than in men. The authors conclude, "Women are likely to derive similar benefit from the use of medical therapies that result in intensive risk factor modification." They add that their data does not allow a determination of whether sex influences either the composition of plaque at baseline or modification following response to established therapies.

In conclusion, these data demonstrate that women harbor less atherosclerotic plaque within their coronary arteries, despite the greater prevalence of atherogenic risk factors. Nevertheless, intensive modification of risk factors has a similar favorable influence in both men and women on plaque progression.

COMMENTARY

These data provide a better window into the pathophysiology of CAD in women. A policy of aggressive risk modification is supported by these observations, and raises the bar for the treatment of women with risk factors even when the coronary artery disease is not obstructive. It would appear from these data that the coronary arteries of men and women behave in a similar fashion, including their responses to risk factors in the environment. The smaller arterial size in women may play a role in producing anginal symptoms, but the pathophysiology of CAD progression is the same as in men. Furthermore, in a recent report from the WISE study (Women's Ischemia Syndrome Evaluation), a subset of participants with normal coronary angiograms who continued to have chest pain one year after angiography had a much greater cardiovascular event rate than those without anginal symptoms. In that study, such women who had persistent chest pain at one year had twice the rate of a composite of cardiovascular events, including MI, stroke, CV death and CHF. The WISE data also support aggressive risk factor modification, as does the retrospective compilation of IVUS studies reviewed above. The recently published COURAGE trial strongly supports aggressive risk factor modification, including drug therapy as well as lifestyle changes. One can no longer conclude that chronic chest pain in women is benign. Furthermore, the IVUS analysis of coronary vessels resulted in similar findings in women as in men, with comparable responses to risk factor modification, and presumed comparable progression in the absence of vigorous control of hypertension, diabetes and dyslipidemia. ■

Obesity in Ethnic Minorities

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Razak F, et al. Defining Obesity Cut Points in a Multiethnic Population. *Circulation*. 2007;115:2111-2118.

Synopsis: Revisions of BMI cut-points to define obesity in ethnic minorities may be warranted.

OBESITY IS OFTEN MEASURED AS BODY MASS INDEX (BMI) and well developed cut-points for overweight and obesity have been defined largely in European populations. Evidence has emerged that these cut-points may not be appropriate for other ethnic groups. Thus, this group of investigators from Canada studied 301 Europeans, 289 South Asians, 281 Chinese and 207 Aboriginals, assessing their metabolic risk for cardiovascular (CV) disease in relation to BMI. Among 14 clinical and biochemical variables, 3 factors explained over half of the variation in the variables between ethnic groups: glucose metabolism, lipid metabolism and blood pressure. BMI cut-points were then determined for these 3 factors. Glucose and lipid factors were higher in non-Europeans and blood pressure was highest in the Chinese and lowest in the Aboriginals. When the European BMI cut-point of 30 kg/m2 was applied to the glucose factor, a similar abnormality was seen at a BMI of 21 in South Asians and Chinese, and 22 in Aboriginals. For the lipid factor it was 23 in South Asians, 26 in Chinese and Aboriginals. For blood pressure it was 29 for South Asians and 25 for Chinese. On average the cut-point to define obesity in relation to these 3 factors in non Europeans was about 24 kg/m2. The authors concluded that revisions of BMI cut-points to define obesity in ethnic minorities may be warranted and would increase the estimated burden of obesity-related disease in non-Europeans.

COMMENTARY

The links between obesity and increased CV disease are complex and not fully understood. In this analysis, glucose metabolism, lipid levels and blood pressure only explained 56% of the variability in 14 clinical and biomarkers. Clearly other factors such as lifestyle (exercise) and genetics play a role, but these are difficult to quantitate at this time. Given our current understanding, the authors' approach of defining obesity in relation to when these 3 factors become abnormal makes sense. The main message when this is done with ethnic minorities is that generally lower cut-points are found compared to Europeans. Thus, our current BMI definitions of obesity in ethnic minorities underestimate the burden of CV disease, so physicians need to take this into consideration when advising and treating patients.

The problem with this 3-factor approach is that the results are not uniform across ethnic groups. For example, the lipid metabolism factor becomes abnormal at BMI of 22 in South Asians and 26 in Chinese and Aboriginals. Thus, picking new cut-points is complex. A good rule of thumb may be that the European cut-off of 25 kg/m2 for defining overweight, be used in Asians to define obesity.

The results provide other interesting data. For example, at a BMI of 21-22 in South Asians is related to glucose and lipid metabolism levels found in Europeans at 30. This may explain their increased incidence of CAD when they live in industrialized nations. Also, Aboriginals have lower blood pressures than the other groups and it doesn't vary much with BMI.

There are some limitations to the study. It is small and only examines 3 ethnic groups in Canada. There are no outcome data, which would strengthen any conclusions about BMI levels. There are no waist or hip circumference measures or other data about abdominal fat. Finally, the study was too small to define an overweight group. Regardless, this is an important study which will impact our care of Asian minorities. ■

Anticoagulation in Atrial Fibrillation

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.

Sources: Rowan SB, et al. Trends in Anticoagulation for Atrial Fibrillation in the U.S. An Analysis of the National Ambulatory Medical Care Survey Database. *J Am Coll Cardiol*. 2007;49:1561-1565.

Synposis: *Appropriate and seemingly inappropriate use of anticoagulation is occurring among patients with atrial fibrillation.*

ROWAN ET AL DESCRIBE RESULTS FROM THE National Ambulatory Medical Care Survey

(NAMCS) Database with regard to the use of warfarin anticoagulation in patients with atrial fibrillation (AF). The NAMCS Database for the 1994 to 2003 time period contains data from 40.5 million AF patient visits. Among all AF patients, age and the use of rate control agents only were associated with anticoagulant usage. The overall frequency of warfarin anticoagulation in patients with AF increased from 40.3% of all patients between 1994 and 1997 to 49.1% between 2001 and 2003. Of interest, the use of anticoagulation increased by 80% in the 18 to 59 year old population, decreased by 8% in the 60 to 75 year old population and increased by 45% in the 76 and older population. Patients with co-morbid conditions associated with thromboembolic phenomena showed a higher use of anticoagulation in all age groups. Patients taking rate control agents more frequently received anticoagulation than patients taking rhythm control agents only. Finally, among patients thought to be at low risk for a thromboembolic event, i.e., individuals under 65 years of age without congestive heart failure, previous cerebrovascular events, hypertension or diabetes, 30% of the patients were anticoagulated. The authors argue that both appropriate and seemingly inappropriate use of anticoagulation is occurring among patients with atrial fibrillation.

COMMENTARY

This paper provides an interesting view of the use of warfarin anticoagulation in patients with atrial fibrillation the United States. The National Ambulatory Medical Care Survey Database provides data from a very large number of patient visits allowing true national patterns to be detected. However, interpreting the data in a paper like this is somewhat difficult. In the late 1980's a series of trials demonstrated the benefit of warfarin in patients with atrial fibrillation and identified risk factors for embolic events. These and later studies also characterized risk factors for bleeding associated with warfarin therapy. The data from these trials have led to the increase in warfarin use documented here. It must be remembered however that about 1/3 of elderly patients have true contraindication to warfarin and so the attainable goal will never be 100% usage. Since many of the risk factors for embolic events (ago, co-morbidities, etc.) overlap with risk factors for bleeding, physicians continue to be often faced with a difficult clinical decision. One other limitation in the survey here is that the database doesn't provide a good reason why so many " low risk patients" were anticoagulated, particularly if they were seeing a cardiologist. It is likely that a substantial number of these latter patients were symptomatic younger individuals in whom a cardioversion was planned or was being considered. Use of warfarin in such patients would be completely appropriate. Unfortunately, the data available in a database like NAMCS does not allow us to answer questions such as this.

Brugada Syndrome in Children

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Probst V, et al. *Circulation.* 2007; 115:2042-2048

Synposis: *In children affected by Brugada syndrome there is no male predominance, a very strong linkage to febrile episodes and a high incidence of SCN5A mutations.*

Probst et al reports on the clinical characteristics of 30 children in whom a diagnosis of the Brugada syndrome was made before age 16. The patients were collected from 13 tertiary hospitals in European countries. The diagnosis of Brugada syndrome was made because of either syncope thought due to arrhythmia (n=10), aborted sudden death (n=1), symptomatic supraventricular arrhythmias (n= 1), an abnormal ECG (n=1) or an ECG obtained during family screening for Brugada syndrome (n=17). All patients showed either a Brugada type 1 ECG spontaneously (n=17) or after drug challenge (n=13). The group included 17 boys and 13 girls. Among the 12 symptomatic patients, there were 8 boys and 4 girls. The age at diagnosis for the entire group was 8.5 years. In 25 patients, one other family member with Brugada syndrome was also identified. Genetic screening for mutations in the SCN5A gene was performed in 21 patients and a mutation was found in 15. Most episodes of syncope took place at rest with only one patient reporting syncope during exercise. Fever, however, was an important precipitant. Episodes of syncope or sudden death were associated with fever in 5 of 11 cases. Four of the patients had supraventricular tachycardia which caused syncope in 3 patients. Sinus node dysfunction was documented in 2 patients. Drug challenge with either intravenous flecainide or ajmaline was performed in 16 of 30 patients and all had a type 1 Brugada syndrome response. No complications from drug challenge were reported. Electrophysiologic study was only performed

in 6 patients. Three had inducible ventricular tachycardia or ventricular fibrillation. Treatment was variable. Five patients received an ICD. Two of these patients had appropriate ICD shocks during follow-up and one patient developed an ICD infection necessitating removal of the device. One patient diagnosed at age 1, who was not being treated, had an episode of sudden death. Four patients were treated with quinidine with a mean follow-up of 28 + 24 months. None of these patients developed side effects and none developed symptomatic arrhythmias or syncope while on therapy.

The authors present their findings as the largest series of children affected by Brugada syndrome. In contrast to adult population, there is no male predominance, a very strong linkage to febrile episodes and a high incidence of SCN5A mutations. They argue these observations should influence decision making in caring for family members of adults with Brugada syndrome.

COMMENTARY

Brugada syndrome was first described about 15 years ago. Over 1500 adults with Brugada syndrome have been reported. Arrhythmias in the Brugada syndrome are thought to be due to reduction in the inward sodium current. In areas where these is a strong outward current, such as the right ventricular epicardium, these leads to a shortened action potential and arrhythmias. Most patients with Brugada syndrome present after puberty with the most common appearance of symptoms between age 30 and 50. In adults there is a strong male predominance. This report documents that Brugada syndrome can occur in children and result in life-threatening symptoms. It appears likely that gender related changes in cardiac ion channels result in the male dominant pattern seen in adults.

Several observations in this series are of clinical value. First, quinidine appears to be a reasonable choice for therapy in children in whom placement of an ICD would be problematic. Second, fever is an important risk factor. Observation with monitoring and vigorous attempts to keep fevers under control should be the rule in children with known Brugada syndrome. Finally, in asymptomatic individuals with a Type I ECG pattern only with provocation, careful observation without therapy seems justified. ■

CME Questions

32. Fish oil therapy reduces
A. death rates
B. triglyceride levels
C. HDL cholesterol
D. the side effects of statins

33. Rosuvastatin plus ezetimibe vs. statin alone resulted in
A. more patients achieving target LDL cholesterol levels
B. fewer side effects than with statin alone
C. higher HDL levels
D. all of the above

34. Rosuvastatin 40mg vs. atorvastatin 80mg
A. were equipotent at lowering LDL cholesterol
B. rosuva raised HDL more
C. rosuva favorably altered the HDL subpopulation profile
D. all of the above

35. Brugada syndrome in children
A. occurs predominantly in females
B. syncope is commonly precipitated by fever
C. quinidine often leads to torsade
D. has a uniformly bad prognosis

36. Patient surveys show that warfarin use in atrial fibrillation
A. has increased recently
B. increased usage was more common in those <age 60
C. 30% of low risk patients were on warfarin
D. all of the above

37. Atherosclerotic plaque in women as compared to men
A. is less extensive in general
B. is less responsive to treatment
C. is less likely to progress
D. all of the above

38. BMI cut-offs for defining obesity in relation to CV disease risk factors should be ____ in Asians.
A. the same as for Europeans
B. higher
C. lower
D. insufficient data to determine

Answers: 32.(b) 33.(a) 34.(d) 35.(b)36.(d) 37.(a) 38.(c)

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.

Risk With Preventative Antibiotics Outweighs Benefit for Most

Sweeping new changes have been made to the guidelines for prevention of endocarditis in patients undergoing dental procedures. The new recommendations dramatically reduce the indications for dental prophylaxis and reduce the number of patients who need preprocedure antibiotics. The guideline was issued by the American Heart Association in conjunction with the American Dental Association, Infectious Diseases Society of America, and the Pediatric Infectious Diseases Society and was published online April 19, 2007, in *Circulation*. The guidelines reflect evidence that the risk of taking preventative antibiotics outweighs the benefit for most patients. It is also been found that infectious endocarditis (IE) is more likely to result from frequent exposure to random bacteremias from activity such as flossing and brushing than from dental work. Specifically, the guidelines say that prophylactic antibiotics are no longer required for patients with mitral valve prolapse, rheumatic heart disease, bicuspid valve disease, calcified aortic stenosis, or congenital heart conditions such as ventricular septal defect, atrial septal defect, and hypertrophic cardiomyopathy. There are still patients who are at extremely high risk of IE who should continue to receive prophylactic antibiotics: patients with artificial heart valves, a history of infective endocarditis, congenital heart disease including unrepaired or incompletely repaired cyanotic congenital heart disease, including those with palliative shunts and conduits, those with a completely repaired congenital heart defect with prosthetic material during the first 6 months after the procedure, repaired congenital heart defect with residual defect at the site or adjacent to the site of a prosthetic patch or prosthetic device, or a cardiac transplant patient with a cardiac valvulopathy. Antibiotic prophylaxis is no longer recommended for any other form of congenital heart disease. Dosing regimens are essentially the same as previous recommendations and include oral amoxicillin 2 gm 30 to 60 minutes prior to procedure. Oral alternatives include cephalexin, clindamycin, azithromycin or clarithromycin. Parenteral regimens include ampicillin, cefazolin, ceftriaxone, and clindamycin. The guideline also no longer recommends antibiotics to prevent IE in patients undergoing genitourinary or gastrointestinal tract procedures (*Circulation* 2007, doi:10.1161/CIRCULATIONAHA.106.183095). The full guideline is available at http://www.ada.org/prof/resources/ topics/infective_endocarditis_guidelines.pdf. ■

Gonococcal Infections, CDC's Updated Treatment

The CDC has issued updated treatment recommendations for gonococcal infections and associated conditions due to the high level of resistance of gonorrhea to fluoroquinolones. The agencies Gonococcal Isolate Surveillance Project demonstrates that fluoroquinolone-resistant gonorrhea is continuing to spread and is now widespread

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

throughout United States. Therefore, fluoroquinolones such as ciprofloxacin, ofloxacin, or levofloxacin are no longer recommended. Current recommended regimens for gonococcal infections of the cervix, urethra, and rectum are ceftriaxone 125 mg IM and a single dose or cefixime 400 mg orally in a single dose plus treatment for chlamydia if chlamydial infection is not ruled out. Uncomplicated gonococcal infections of the pharynx should be treated with ceftriaxone 125 mg IM plus treatment for chlamydia, if chlamydial infection is not ruled out. Disseminated gonococcal infection should be treated with ceftriaxone 1 g IM or IV every 24 hours. Pelvic inflammatory disease may be treated with parenteral and oral therapy. Parenteral therapy regimens include cefotetan or cefoxitin plus doxycycline or clindamycin plus gentamicin. An alternative regimen is ampicillin/sulbactam plus oral doxycycline. Oral therapy can be considered in women with mild to moderate disease. With the loss of fluoroquinolones, cephalosporins are the mainstay of most regimens. For patients who are highly allergic to cephalosporins, spectinomycin may be considered although it is not generally available in this country. Another option is azithromycin, however, prescribing should be done in consultation with an infectious disease specialist due to concerns over emerging antimicrobial resistance to macrolides. The CDC's full recommendations are available online at www.cdc.gov/std/treatment/2006/updated-regimens.htm. ■

Head Lice — Malathion First-Line Treatment

Malathion should be first-line treatment for children who have lice according to a new review in the journal *Pediatrics*. Head lice have become resistant to nearly all first-line treatments in United States including permethrin, which has been considered first-line treatment for years. Malathion, in the formulation containing isopropyl alcohol and terpineol, is safe and effective for lice and all existing points within the life cycle, and generally requires a single treatment, reducing the duration of infestation, and lost time from school and work. Concern about flammability seems to be over emphasized, as there have been no reported cases of bodily injury related to burns (*Pediatrics* 2007. 119:965-974).

Statins, May Cut the Risk of Cataracts

Statins, the cholesterol wonder drugs, have been associated with a number of other benefits including reduction of inflammation within the arteries, improved bone density, reduction in the risk of colon cancer, renoprotective effects, and reduction in the risk of Alzheimer's disease and other dementias. Now, a new study suggests that the drugs may also cut the risk of cataracts by 50%. Researchers from Australia reviewed the rate of cataract development in 3,654 elderly patients. After 10 years, after controlling for age, gender and others factors, the hazard ratio for any type of cataract in statin users was 0.52. In subgroups, there was a decreased risk of nuclear cataracts (HR = 0.66) and cortical cataracts (HR =0.76), but neither of these reached statistical significance. The authors conclude that there may be a protective influence of statins on cataracts and this needs to be further explored (*Am J Ophthalmol* 2007; 143:687-689). ■

FDA Actions

Sanofi Aventis has been approved to produce a vaccine to prevent bird flu in humans. The vaccine against the H5N1 virus will not be produced commercially, but will instead be stockpiled by the U.S. government for distribution in case of the outbreak. The FDA admits that the vaccine is not optimal, requiring a higher dose than normal flu vaccine, and 2 shots which must be given 28 days apart. But until other vaccines are developed, this vaccine will be used as the "interim measure."

The FDA is recommending updating black box warning regarding suicidality in young adults (under age 24) starting on antidepressants, calling for appropriate monitoring and close observation. The new recommendation should also include the statement that there was no increase in suicidality in adults over the age of 24, and a decrease in the risk in adults over the age of 64.

The FDA has approved generic versions of 2 of the most popular drugs of the last decade, Ambien (zolpidem) and Zoloft (sertraline). Zolpidem will be available in 5 mg and 10 mg immediate-release tablets. Thirteen manufactures have received approval to market the product. Sertraline is approved in the 25 mg, 50 mg and 100 mg strengths, and will be produced by Ranbaxy Laboratories.

The FDA has issued a warning about the health risks of dietary supplements touted as sexual enhancement products and treatments for erectile dysfunction that have been distributed under the trade names True Man and Energy Max. Both drugs have been sold throughout United States. Energy Max was found to contain an analogue of sildenafil, the active ingredient in Viagra, while True Man was found to contain an analogue of sildenafil and vardenafil, the active ingredient in Levitra. Both drugs can have serious interactions with nitrates. ■