AHC Media

Vol. 32, Issue 7, July 2013
www.ahcmedia.com

Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Another Supplement for CAD Prevention Fails

By Michael H. Crawford, MD, Editor

SOURCE: Risk and Prevention Study Collaborative Group. n-3 fatty acids in patients with multiple cardiovascular risk factors. *N Engl J Med* 2013;368: 1800-1808.

N-3 polyunsaturated fatty acids (n-3 FA) from fish have been reputed to prevent the development of cardiovascular disease (CVD) and have demonstrated some benefits in secondary prevention studies. Thus, this community-based investigator group in Italy conducted a double-blind, placebo-controlled trial of subjects with multiple risk factors for CVD (at least four, or one if diabetic) or evidence of atherosclerotic vascular disease, but without myocardial infarction (MI). Subjects were given 1 g of an n-3 FA capsule or an olive oil capsule (placebo) per day. Clinical status of the subjects was assessed yearly. The primary endpoint was the rate of death, MI, and stroke, but after low event rates were noted after 1 year, time to a CVD death and hospital admission for CVD were added. Over about 3 years, 12,513 subjects were enrolled. Almost half had diabetes and 20% had a history of vascular disease. After a median 5-year follow-up, it was noted that the CVD risk profile had improved in both groups. Drug therapy for risk factors increased over time, but to the same extent in both groups. Triglyceride levels fell more in the n-3 FA group (-28 vs -20 mg/dL, $P < 0.001$), but blood pressure, LDL cholesterol, and glucose were no different between groups. There was a slight increase in HDL cholesterol in the n-3 FA group. The primary endpoint was not different between the two groups (12% for both). At the study's end, 18% of subjects were no longer taking n-3 FA and 19% had stopped the placebo, but only analyzing the compliant subjects did not affect the outcome. Also, none of the individual endpoints in the composite primary endpoint were significantly

Financial Disclosure: *Clinical Cardiology Alert's* Editor, Michael H. Crawford, MD, reports no financial relationships relevant to this field of study, and peer reviewer, Ethan Weiss, MD, is a scientific advisory board member for Bionovo. Managing Editor, Neill Kimball, and Executive Editor, Leslie Coplin, report no financial relationships relevant to this field of study.

[INSIDE]

CVD risk calculators: Worth the effort? page 50

Can CT coronary angiography predict future ACS? page 51

Brief, high-dose statin therapy reduces lipid content in coronary plaque page 52

Clinical Cardiology [ALERT]

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road, NE Building 6, Suite 400 Atlanta, GA 30305.

POSTMASTER: Send address changes to *Clinical Cardiology Alert*, P.O. Box 105109, Atlanta, GA 30348.

SUBSCRIBER INFORMATION
1-800-688-2421
customerservice@ahcmedia.com

Editorial E-Mail:
neill.kimball@ahcmedia.com

Subscription Prices
United States
1 year with free AMA Category 1 credits: $349
Add $17.95 for shipping & handling. (Student/Resident rate: $125). Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.
Canada Add GST and $30 shipping.
Elsewhere Add $30 shipping.

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.

GST Registration Number: R128870672. Periodicals Postage Paid at Atlanta, GA, 30304 and at additional mailing offices.

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

AHC Media designates this enduring material for a maximum of 25 *AMA PRA Category 1 Credits™*. Physicians should claim only the 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.

AHC Media

different. Of the secondary endpoints, only heart failure admissions were lower in the n-3 FA group (1.5% vs 2.3%, P = 0.04). The primary endpoint occurred less frequently in women and was significantly less in the n-3 FA group women (hazard ratio, 0.82; 95% confidence interval, 0.67-0.99; P = 0.04). Finally, the results were not related to fish consumption or risk-reducing medication differences. Reported adverse events were not different between the two groups. The authors concluded that in patients at high risk for CVD, n-3 FA did not reduce mortality or morbidity over a median follow-up of 5 years.

■ COMMENTARY

First vitamin C, then folic acid, then vitamin E, then multivitamins, then niacin, and now fish oil supplements — all proven to be largely worthless for the primary prevention of CVD. This leaves us with the Mediterranean diet, exercise, and moderate alcohol consumption to recommend for our patients who want to go natural. Unfortunately, patients generally want the magic pill, not the hard stuff like diet and exercise. Also, alcohol is hard to calculate because of the narrow therapeutic-to-toxic range and the many variables affecting gastrointestinal absorption rates, so now we have to tell our patients there is no easy way — a hard sell.

The investigators were surprised by the results because the GISSI post-MI and heart failure trials showed a benefit of n-3 FA with reduced morbidity and mortality. One possible reason this trial was negative was the low rate of events (12% for the combined endpoint). One reason for this may be that the major effect in the GISSI trials was on sudden death rates. Arrhythmias are much more common in post MI and heart failure patients (excluded in this trial) and n-3 FA may reduce arrhythmias. The positive secondary endpoints were probably due to chance and they do not recommend n-3 FA for women only. Some will argue that the dose was too low or the ratio of eicosapentaenoic acid to docosahexaenoic acid was wrong, but their dose and formulation avoided adverse effects and significantly lowered triglycerides. n-3 FA probably won't hurt you and may be safer than pumping up your mercury levels with fish consumption, so I suspect many will keep at it despite this study. ■

ABSTRACT & COMMENTARY

CVD Risk Calculators: Worth the Effort?

By Michael H. Crawford, MD, Editor

SOURCE: Allan GM, et al. Agreement among cardiovascular disease risk calculations. *Circulation* 2013;127:1948-1956.

Cardiovascular disease (CVD) risk calculators are frequently used by clinicians to guide patient management. Unfortunately, there are more than 100 risk calculators and smaller studies have shown insistencies between them. Thus, this group of investigators from Edmonton, Alberta, Canada, studied 25 calculators from eight mainly English-speaking countries that used a range of different databases, formats, and variables. All included age, sex, smoking, blood pressure, total cholesterol, and HDL cholesterol. Diabetes was included in 18. Hypothetical patients were used to create 128 unique test subjects to which all the calculators were applied. Since some of the calculators used 5-year risk and others 10-year risk, the subjects were divided into high, medium, and low risk. In nine calculators, 10-year absolute risk was provided and compared for each subject. Each calculator was used by two investigators and agreement in risk calculation was 95%. Half the disagreement was due to errors in the calculators and half from data entry errors. The 128 patients were categorized in a mean of 2.2 risk groups with

41% crossing all three categories. The pooled concordance in risk category assignment for all paired comparisons of calculators was 67%, less for diabetes subjects, 64% vs 73% for non-diabetics. Limiting the analysis to the 10-year risk calculators did not improve concordance, 70% overall. When only the nine Framingham-derived calculators were used, overall concordance was better at 89%. When the absolute 10-year risk calculators were compared, the average calculated risk was 4-5 times higher than the lowest risk calculated for the same subject. This effect was most pronounced in those with the highest calculated risk. The authors concluded that the demonstrated inconsistency between calculators is a clinically relevant limitation to their use.

■ COMMENTARY

This study shows that if you compare any two of 25 risk calculators, the assignment of the patient's risk category (low, medium, high) will be different about one-third of the time. By sticking to calculators estimating 10-year Framingham risk, agreement increases to 89%. However, it is well known that the Framingham population is almost all Caucasians, so this degree of concordance may not be found with other populations. In fact, most of the calculators used in this study originated from English-speaking countries, so their concordance may be worse in other populations. The reasons for these discrepancies are not elucidated in the study, but likely come from different databases, different CVD endpoints, and the mathematical algorithms employed by each calculator. Using calculators that estimate absolute risk didn't improve the agreement between calculators, nor did selecting the calculators that provided the risk of only hard endpoints such as myocardial infarction and cardiac death. This data is concerning because most guidelines recommend using risk calculators even though there is no evidence that their use improves outcomes.

Surveys of physicians show that 25-50% use risk calculators. Non-use reasons include lack of time, belief that the information is not helpful, belief that calculators oversimplify things, and belief that they can accurately predict risk subjectively. One study evaluating the accuracy of physicians' subjective assessment vs the Framingham database showed that physicians were 71% accurate; four risk calculators came in at 66-81%, which supports physicians' belief in themselves. I am one of the non-believers and don't use risk calculators for all the reasons above, plus some patients fixate on their score.

One limitation of this study is that the hypothetical patients were higher risk than most primary care populations and calculated risk concordance decreased with higher risk patients. One could argue that once a patient is categorized as high risk, wide variability among calculators is moot. However, of the 28 subjects in this study who were assigned the same risk category by all 25 calculators, 79% were high risk. So, it would seem that most of the variability was actually in the low- and moderate-risk subjects. Other studies have suggested that most risk calculators overestimate risk in primary care populations. So if you are going to use risk calculators, the authors suggest that you use one targeted to your patient population and keep in mind that the results are a rough estimate. ■

ABSTRACT & COMMENTARY

Can CT Coronary Angiography Predict Future ACS?

By Andrew J. Boyle, MBBS, PhD

Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

Dr. Boyle reports no financial relationships relevant to this field of study.

SOURCE: Versteylen MO, et al. Additive value of semiautomated quantification of coronary artery disease using cardiac computed tomographic angiography to predict future acute coronary syndrome. *J Am Coll Cardiol* 2013;61:2296-2305.

Computed tomography (CT) has evolved significantly in recent years, and is now able to accurately assess coronary arteries for the presence of atherosclerosis in carefully selected patients. For example, in patients presenting with acute chest pain to the emergency department, coronary CT angiography (CCTA) has a very high negative predictive value for acute coronary syndromes (ACS). CCTA reports usually contain a coronary calcium score, the degree of luminal stenosis, and a qualitative evaluation of plaque morphology. In addition to these measures, both plaque burden and plaque characteristics that are not routinely reported have been associated with

future ACS in some studies, albeit inconsistently. Whether a more systematic approach to assessing plaque volume and geometry leads to better prediction of events has not been demonstrated in ambulant patients with stable coronary artery disease (CAD). Accordingly, Versteylen and colleagues performed a retrospective cohort study of patients with stable chest pain undergoing CCTA at two high-volume centers in the Netherlands. A total of 1650 patients underwent 64-slice CCTA and were followed up for ACS for 26 ± 10 months.

Twenty-five patients subsequently developed ACS. These were compared to 101 random controls (selected from 993 patients with CAD but without coronary event during follow-up), and their coronary arteries were evaluated using conventional CCTA reading (calcium score, luminal stenosis, morphology), and were then independently quantified using semi-automated software to derive plaque volume, burden area [defined as (plaque area)/(vessel area) × 100%], non-calcified percentage, attenuation, and vessel remodeling. Clinical risk profile was calculated with Framingham risk score (FRS). There were no significant differences in conventional CCTA parameters between controls and patients who subsequently developed ACS. However, the semi-automated plaque quantification showed that compared to controls, ACS patients had higher total plaque volume (94 mm^3 vs 29 mm^3) and non-calcified plaque volume (28 mm^3 vs 4 mm^3, $P \leq 0.001$ for both). In addition, per-plaque maximal volume (56 mm^3 vs 24 mm^3), non-calcified percentage (62% vs 26%), and plaque burden (57% vs 36%) in ACS patients were significantly higher ($P < 0.01$ for all). A receiver-operating characteristic (ROC) model predicting for ACS incorporating FRS plus conventional CCTA reading had an area under the curve of 0.64; when the ROC also incorporated semi-automated plaque quantification, the area under the curve improved to 0.79 ($P < 0.05$). The authors conclude that semi-automated plaque quantification identified several parameters predictive for ACS and provided incremental prognostic value over clinical risk profile and conventional CT reading. The application of this tool may improve risk stratification in patients undergoing CCTA.

■ COMMENTARY

This study adds to the growing body of literature that CCTA not only can non-invasively define coronary anatomy, but also has powerful predictive ability for future ACS events. Several studies have shown the utility of CCTA in patients with acute chest pain, and this study extends these findings into patients with stable CAD. It is perhaps intuitive that higher plaque burden is predictive of future plaque rupture events. The early identification of such patients may allow intensification of lipid-lowering and antiplatelet medications in order to prevent such events. An important limitation to this study is the retrospective nature of its observations. The information gleaned from this study should be hypothesis-generating and will not alone be enough to change practice. However, this study sets the stage for future clinical trials using CCTA to guide therapy in patients with stable CAD. As we search for more personalized and more cost-effective medicine, we look for novel strategies to improve risk stratification and early disease identification to more accurately direct therapy. The use of these novel CCTA parameters may help predict future events, but how this should alter management remains to be tested in future clinical trials. ■

ABSTRACT & COMMENTARY

Brief, High-Dose Statin Therapy Reduces Lipid Content in Coronary Plaque

By Andrew J. Boyle, MBBS, PhD

Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

SOURCE: Kini AS, et al. Changes in plaque lipid content after short-term, intensive versus standard statin therapy: The YELLOW Trial. *J Am Coll Cardiol* 2013; [Epub ahead of print].

Statin therapy has multiple beneficial effects on coronary plaque, including prevention of plaque progression and reduction in thrombotic events. It is not clear if the beneficial effect on clinical events is due to reduction in lipid content of plaque. To assess the short-term effects of intensive statin therapy on the lipid content of coronary artery plaque, Kini and colleagues performed a prospective, randomized trial in patients with multivessel coronary artery disease

(CAD) wherein patients were randomized to either intensive statin therapy (rosuvastatin 40 mg daily) or standard-of-care lipid-lowering therapy. Using an innovative trial design, they studied patients with multivessel disease who were undergoing percutaneous coronary intervention (PCI) to one lesion, and had at least one other obstructive lesion (defined as fractional flow reserve [FFR] < 0.80) in another vessel. These non-target lesions (NTLs) were evaluated at baseline with FFR and intravascular ultrasound (IVUS). In addition, the authors also performed near-infrared spectroscopy (NIRS), which is an intra-arterial imaging system performed in a similar manner to IVUS, but using near-infrared light rather than ultrasound, that is able to identify lipid content within the vessel wall. Eighty-seven patients with chronic stable angina were randomized to intensive statin therapy (n = 44) or standard care (n = 43). After 6-8 weeks, repeat angiography, FFR, IVUS, and NIRS were performed at the same NTL previously imaged. These repeated measurements were performed before any additional PCI. Then, as indicated clinically, PCI was performed immediately after in lesions with FFR < 0.8. The primary endpoint was the change in lipid-core burden index at the 4 mm max segment (LCBI4mm max), wherever this occurred within the lesion.

Baseline demographics and angiographic features were similar between groups. Baseline LDL cholesterol was 82.8 ± 26.9 mg/dL in the standard therapy group and 79.1 ± 25.3 in the intensive therapy group (*P* = ns). Mean C-reactive protein was 1.7 and FFR was 0.73 in each group. At follow-up, median reduction in LCBI4mm max was greater in the intensive vs standard group (-149.1 [-210.9, -42.9] vs +2.4 [-36.1, 44.7]; *P* = 0.01). Serum LDL level in the intensive group was correspondingly lower compared to the standard therapy group (58.4 ± 26.3 vs 81.9 ± 27.9 mg/dL, respectively; *P* = 0.001). C-reactive protein and angiographic diameter stenosis did not change. FFR increased to > 0.8 in four patients in the intensive group and two patients in the standard group, and these patients avoided PCI. Clinical event rates were low and were not different between groups. Three patients in the intensive group required dose reduction. The authors conclude that short-term, intensive statin therapy may reduce lipid content in obstructive lesions, and these hypothesis-generating findings warrant confirmation in larger studies with longer follow-up.

■ COMMENTARY

This study shows that it takes just a few weeks for high-dose statins to favorably affect the lipid content in plaque. The very dynamic nature of atherosclerotic coronary plaque, and the beneficial effects of statins in the short term, are generally under-appreciated. Although this study was not powered to study clinical endpoints, it is likely that these changes will reduce the vulnerability of those plaques for progressing to acute coronary syndromes. However, the authors highlight the need for future clinical trials to confirm this. It is noteworthy that these were stable CAD patients and their average LDL was below the guideline goal of 100 mg/dL. Yet, they still derived visible benefit from intensive statin therapy. This is congruous with other studies showing the benefits of stains extend beyond simply lowering serum LDL.

This study has several strengths, including its randomized controlled design, the use of an independent data safety and monitoring board, and the use of a blinded core laboratory to analyze the imaging studies. These aspects strengthen the conclusions that can be drawn from the data. However, this was a small trial and was not powered to detect clinical endpoints. Despite these limitations, this study confirms the safety of high-dose statins in the short term, and sets the stage for larger clinical trials powered to assess hard clinical endpoints from high-dose statins in stable CAD patients. ■

ABSTRACT & COMMENTARY

Heparin Bridging or Continued Warfarin for Device Surgery?

By John P. DiMarco, MD, PhD

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

Dr. DiMarco does research for Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

SOURCE: Birnie, et al, for the BRUISE CONTROL Investigators. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med* 2013;368:2084-2093.

Many laboratories have changed their practice to perform some procedures without stopping warfarin anticoagulation, but trial evidence supporting this practice has been lacking. In this paper, investigators from 17 centers in Canada and one in Brazil report the results of a trial comparing continued warfarin with heparin bridging in high-risk patients undergoing device procedures. Patients at the centers scheduled for a pacemaker or implantable cardioverter-defibrillator (ICD) procedure of any type who were on chronic warfarin were eligible for enrollment. Patients were then randomly assigned in a 1-to-1 ratio to continued warfarin treatment or warfarin interruption with bridging therapy with heparin. The target INR on the day of surgery in the continued-warfarin group was 3 or lower in most patients but up to 3.5 in patients with mechanical valves. Patients in the heparin-bridging group discontinued warfarin 5 days before the procedure and then received either low molecular-weight heparin or intravenous unfractionated heparin for 3 days before the procedure. Intravenous heparin was stopped at least 4 hours before surgery. For those who received low molecular-weight heparin, the last dose was given the morning of the day before the procedure. Heparin was restarted 24 hours after the procedure and continued until a therapeutic INR had been achieved on warfarin. Clopidogrel was stopped 5 days before the procedure, except for those patients with drug-eluting or recently implanted bare-metal coronary stents. Aspirin was continued. The primary outcome measure was a clinically significant device-pocket hematoma defined as one that either required surgical drainage, prolonged hospitalization, or interruption of anticoagulation therapy.

The study was terminated after a second interim look by a data safety monitoring board. The entire cohort included 681 patients. The final comparison group was 326 patients assigned to heparin bridging and 335 patients assigned to continued warfarin. Low molecular-weight heparin was used in 89% of the patients and intravenous heparin in 11%. Postoperatively, 82% of the patients received low molecular-weight heparin and 17% intravenous heparin. In the heparin-bridging group, the median INR on the day of surgery was 1.2. In the continued-warfarin group, the median INR was 2.3. Surgery had to be postponed in eight patients in the continued-warfarin group because the INR on the day of surgery was above 3.5. In the heparin-bridging group, three patients had postponements because of INRs higher than the desired target.

Clinically significant hematomas occurred in 12 of 343 patients in the continued-warfarin group (3.5%) compared with 54 of 338 patients (16%) in the warfarin-bridging group. The most common endpoint was a non-surgical hematoma requiring interruption of anticoagulation, but an increase in prolonged hospitalizations and surgical evacuations was also noted in the heparin-bridging group. Although not statistically significant, there were also six infections related to the device system in the heparin-bridging group compared to only two in the continued-warfarin group. There were two neurologic events in the continued-warfarin group; one stroke and one TIA. Both patients, however, had unplanned subtherapeutic INRs on the day of the procedure despite continuing warfarin therapy. Patient satisfaction scores were better in the continued warfarin group.

The authors conclude that for most patients, cardiac device-related procedures can be safely performed with continued warfarin therapy avoiding the increased risk of hematoma associated with heparin bridging.

■ COMMENTARY

Many electrophysiology (EP) laboratories have gradually shifted their practice to perform ablation and device procedures in patients on warfarin with INRs still in the low therapeutic range. Heparin therapy after a device procedure has been associated with increased risk of hematoma and this was confirmed in this study. When a hematoma develops, the patient often has to stop anticoagulation until the hematoma has started to resolve, and this may take many days. Surgical re-exploration to drain a hematoma is also often difficult since it's rare to identify a discrete bleeding site after the pocket has been reopened. Another factor that makes device-related hematomas a management problem is the fact that they cannot

easily be controlled with direct pressure. Once a clot has developed, the device itself is floating in clot and this prevents the tissue-to-tissue contact that might stop the bleeding.

The authors have done a significant service to the EP community. This paper should lead to a revision of the current guidelines and provide benchmark data to which implanters can compare their results. ■

ABSTRACT & COMMENTARY

Air Travel Emergencies and the Physician Passenger

By John P. DiMarco, MD, PhD
Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

SOURCE: Peterson, DC. Outcomes of medical emergencies on commercial airline flights. *N Engl J Med* 2013;368:2075-2083.

Most physicians who travel will encounter one or more emergencies during air travel. This paper reviews the experience of a medical communication center that serves five domestic and international airlines over a 34-month period. The communication center is contracted by subscribing airlines to provide medical consultations using radio or satellite telephone communications. It is staffed by emergency physicians who are trained in telemedicine and the management of in-flight medical emergencies. For each event, data were entered into an electronic database. Follow-up data were obtained from airline personnel.

During the study period, the communication center received calls about 11,920 in-flight medical emergencies. There were an estimated 744 million airline passengers during this period for a rate of 16 medical emergencies per 1 million passengers. The incidence of medical emergencies was one per 604 flights. The most commonly reported problems were syncope and presyncope (37%), respiratory symptoms (12%), and nausea and vomiting (10%). Seizures (5%) and possible stroke (2%) were also notable reasons for the emergency. The aircraft was diverted in 875 of the 11,920 (7.3%) cases. The rest of the flights continued to their original destination. For 31% of the passengers involved in the initial medical emergencies, the situation had resolved by landing and emergency medical service (EMS) personnel were not requested. Of the patients who were met by EMS personnel, 37% were transported to a hospital emergency room and 901 patients were admitted to the hospital. There were 36 deaths that resulted from these medical emergencies and 30 occurred during flight. The mean age of passengers who died was 59 ± 21 years with a range of 1 month to 92 years. There were 61 obstetrical or gynecologic emergencies in this study. Of these, 61% occurred in pregnant women at < 24 weeks of gestation who had signs of possible miscarriage. Eleven cases involved women in labor > 24 weeks gestation and three of these resulted in aircraft diversion. Flight personnel requested and received on-board assistance by physicians (48%), nurses (20%), EMS providers (4%), and other health care professionals (4%). Aircraft diversion and hospitalization rates were higher if the assistance of medical personnel was requested, probably reflecting the more serious nature of the events. The most common reasons for hospital admission were possible stroke, respiratory symptoms, and cardiac symptoms. The most commonly used medications were oxygen, intravenous saline, and aspirin. Antiemetics were used in patients with nausea and vomiting, and patients who received an antiemetic had a lower rate of aircraft diversion. An automatic external defibrillator (AED) was applied in 137 patients. The most common reasons for AED application were syncope or presyncope and chest pain. An AED was applied in 24 cases of cardiac arrest, but a shock was delivered in only five cases with one return of spontaneous circulation. Eight other initially unconscious patients in whom an AED was applied had spontaneous return of circulation even though no shock was indicated or delivered.

The authors conclude that health care professionals who travel on commercial flights should be prepared for a potential role as a volunteer responder to in-flight medical emergencies. A knowledge of the common problems encountered and the resources available on planes would be

valuable in this situation.

■ COMMENTARY

I always dread the overhead announcement asking, "Is there a physician on the flight?" when I'm traveling, but it's happened to me at least a half dozen times. When I responded, the experience has been highly variable. On several occasions, I was one of a large group of responders, and an anesthesiologist or an emergency medicine doctor took over the situation quite efficiently. On two other occasions, I had to deal with prolonged chest pain episodes and had to decide whether the aircraft should be diverted. Fortunately, I've yet to be confronted with an obstetric emergency while flying. In that case, I might put the AED on myself! What is clear to me is that physicians are likely to be called upon to render assistance and they should be willing and at least minimally prepared to do so.

This paper outlines the medical emergencies that one is likely to be confronted with during travel. Physicians should also go to the online supplement to look at the list of medications and tools available in medical kits on board. Even without recent training or experience in emergency or critical care, many of us will be able to work with the ground consultant in managing the situation. In some instances, a serious emergency will be managed with more direct routing, bypassing the usual air traffic control delays. This shortens flight time and diversion will only rarely be necessary. However, even under ideal conditions, it may be quite some time before the plane can be landed anywhere safely, and we should all be willing to step in to bridge this gap when asked. ■

CME Questions

1. Pocket hematomas are less likely if which of the following is done with device implantation?
   a. Continue therapeutic range warfarin
   b. Continue warfarin with INR 1.8-2.3
   c. Unfractionated heparin bridging
   d. Low molecular-weight heparin bridging

2. The most common emergency medical problem on commercial flights is:
   a. obstetrical conditions.
   b. acute respiratory distress.
   c. syncope and pre-syncope.
   d. chest pain.

3. Which coronary CT finding best predicts future acute coronary syndromes in stable coronary artery disease patients?
   a. Calcium score
   b. Percent luminal stenosis
   c. Qualitative plaque characteristics
   d. Measured plaque volume

4. Which of the following dietary supplements is of proven value in the primary prevention of coronary artery disease?
   a. Vitamin E
   b. Fish oils
   c. Folic acid
   d. None of the above

5. Short-term, high-dose statins may reduce:
   a. LDL cholesterol.
   b. in-stent restenosis.
   c. plaque lipid core.
   d. A and C

6. Coronary artery disease risk prediction calculators are most accurate when they use:
   a. hard endpoints (e.g., death).
   b. 10-year Framingham risk.
   c. quantitative vs qualitative risk.
   d. physician judgment is substituted.

CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss the most current information related to cardiac illness and the treatment of cardiac disease;
- explain the advantages and disadvantages, as well as possible complications of interventions to treat cardiac illness;
- discuss the advantages, disadvantages, and cost-effectiveness of new and traditional diagnostic tests in the treatment of cardiac illness; and
- discuss current data regarding outpatient care of cardiac patients.

AHC Media

Dear *Clinical Cardiology Alert* Subscriber:

This issue of your newsletter marks the start of a new continuing medical education (CME) semester.

Clinical Cardiology Alert, sponsored by AHC Media, provides you with evidence-based information and best practices that help you make informed decisions concerning treatment options. Our intent is the same as yours — the best possible patient care.

The objectives of *Clinical Cardiology Alert* are:

- discuss the most current information related to cardiac illness and the treatment of cardiac disease;
- explain the advantages and disadvantages, as well as possible complications of interventions to treat cardiac illness;
- discuss the advantages, disadvantages, and cost-effectiveness of new and traditional diagnostic tests in the treatment of cardiac illness; and
- discuss current data regarding outpatient care of cardiac patients.

Here are the steps for earning credit for this activity:

1. Read and study the activity, using the provided references for further research.
2. Log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. *First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice, or renewal notice.*
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

If you have any questions about the process, please call us at (800) 688-2421, or outside the U.S. at (404) 262-5476. You can also fax us at (800) 284-3291, or outside the U.S. at (404) 262-5560. You can also email us at: customerservice@ahcmedia.com.

On behalf of AHC Media, we thank you for your trust and look forward to a continuing education partnership.

Sincerely,

Lee Landenberger
Continuing Education Director
AHC Media

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

Volume 18, Number 7 Pages 13-14 July 2013

Food Allergy in IBS: Patch Testing

Source: Stierstorfer MB, et al. Food patch testing for irritable bowel syndrome. *J Am Acad Dermatol* 2013;68:377-384.

We have, as yet, no fully satisfactory etiologic explanation for the symptom complex recognized as irritable bowel syndrome (IBS). Yet, demonstration of various derangements — hypersensitivity to neurogenic stimuli, altered bowel flora, dysregulation of serotonin — has been seen in subgroups of persons with typical IBS. Results from IBS trials of non-systemic antibiotics (e.g., rifaximin) demonstrate improvements in IBS symptoms and support bacterial flora imbalance in some, but not all, IBS subjects.

IBS patients commonly report foods that exacerbate symptoms. Could these food sensitivities represent actual food allergy, and contribute etiologically to IBS? A variety of commonplace foods and food additives have been documented to cause allergic *cutaneous* contact dermatitis (type-4 hypersensitivity). Could similar responses lead to inflammatory changes in the gut and symptoms of IBS?

Stierstorfer et al performed patch testing in IBS subjects (n = 51) using up to 40 different foods or food additives that have been previously recognized as implicated in food hypersensitivity. Fifty-eight percent of subjects had one or more patch test results indicating possible food sensitivity, and when the "offending" food was eliminated from the diet, about two-thirds of subjects reported symptomatic improvement. Food allergy may play a more important role in IBS than previously recognized. ■

A Relationship Between Atrial Flutter and Sleep Apnea

Source: Bazan V, et al. Obstructive sleep apnea in patients with typical atrial flutter: Prevalence and impact on arrhythmia control outcome. *Chest* 2013;143:1277-1283.

Commonly recognized consequences of obstructive sleep apnea (OSA) include increased risk for hypertension, cardiovascular events, and arrhythmias, the most common of which is atrial fibrillation (AFib). Less well understood is the relationship between atrial flutter (AF) and OSA. Even though invasive treatment through catheter ablation is highly effective for AF, over the long term, as many as one-third of AF ablation patients develop postoperative AFib, which of course has its own toxicities.

Bazan et al evaluated a preoperative population of AF patients with polysomnography, none of whom had previously been diagnosed with or suspected of OSA. Overall, 82% of subjects were diagnosed with OSA, almost half of whom were graded as severe OSA.

Over the ensuing 12 months, use of continuous positive airway pressure (CPAP) in OSA patients who had received catheter ablation for AF resulted in a dramatic reduction in new postoperative AFib: from 46% (untreated) to 6% (treated).

OSA appears to be more commonplace in AF than previously recognized. Although a much larger randomized clinical trial will be necessary for confirmation, this small study suggests that for AF patients with OSA who are undergoing catheter ablation, CPAP substantially reduces the likelihood of postoperative AFib. ■

Beyond Hypertension: Metabolic Effects of Telmisartan

Source: Takagi H, et al. Telmisartan as a metabolic sartan: The first meta-analysis of randomized controlled trials in metabolic syndrome. *J Am Soc Hypertens* 2013;7:229-235.

It has not gone unnoticed that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) can sometimes have a favorable effect on glucose metabolism in diabetics and prediabetics. Experts have opined that it is perhaps vascular dilation in the skeletal muscle compartment from renin-angiotensin-aldosterone system blockade that produces increased glucose utilization. One of the ARBs, telmisartan, in addition to its blood pressure-lowering effect, has been noted to have peroxisome proliferator-activated receptor (PPAR)-gamma activation activity, distinct from the other members of this drug class. PPAR-gamma activation could favorably impact metabolic syndrome, but individual clinical trials of telmisartan have been inconclusive in this regard.

Takagi et al performed a meta-analysis of clinical trials (n = 10) of telmisartan in patients (n = 546) with metabolic syndrome. Favorable effects were seen for

fasting glucose, insulin, and A1c. Of the 10 trials analyzed, only three included data on adiponectin, but results were also favorable for this metric.

Large clinical trials of telmisartan in patients with established vascular disease (e.g., TRANSCEND, n = 5926) have shown a nonsignificant trend toward less new onset diabetes, but the number of metabolic syndrome subjects in this trial was not specified.

Whether favorable changes seen in metabolic syndrome patients treated with telmisartan are sufficient to improve "hard" outcomes (myocardial infarction, cerebral vascular accident, diabetes mellitus) would require a very large clinical trial. ■

Risk of New Onset Diabetes with Statins

Source: Danaei G, et al. Statins and risk of diabetes: An analysis of electronic medical records to evaluate possible bias due to differential survival. *Diabetes Care* 2013;36:1236-1240.

The oft-quoted "9% increase in new onset diabetes (NODM) due to statins" sounds pretty scary. What is left out of the aforementioned quote, however, is that the increased risk is a *relative*, not *absolute*, increase. To make the issue more concrete: In one of the largest meta-analyses (n = 91,000), we learned that statins increase risk for diabetes. Among 45,521 statin-treated patients, there were 2226 NODM cases (compared to 2052 of 45,619 placebo recipients); the incidence of NODM then was 4.89% in the statin group, compared to 4.5% in the placebo group, for an underwhelming risk increase of 0.39%. This would translate into a number needed to treat of 250 patients receiving a statin to induce one new case of diabetes. Not nearly so scary, huh?

The most recent analysis of NODM compiled data from the electronic medical records of 500 United Kingdom general practices (n = 285,864). Similar to the above mentioned meta-analysis, the absolute annual incidence in the United Kingdom dataset was 1.59% in statin users compared to 1.13% in nonusers.

Statins can cause NODM, but in trials of secondary prevention, risk of NODM is far outweighed by risk reduction for cardiovascular events. ■

Perimenstrual Asthma: A High-Risk Phenotype

Source: Rao CK, et al. Characteristics of perimenstrual asthma and its relation to asthma severity and control: Data from the severe asthma research program. *Chest* 2013;143:984-992.

Some women with asthma note a worsening of asthma related to onset of menses. In the National Heart, Lung, and Blood Institute Severe Asthma Research Program (SARP), 17% of women (92/483) reported that menses were a trigger for their asthma symptoms. Exploration of perimenstrual asthma (PMA) as a distinct phenotype has been prompted by the recognition of an association between PMA and asthma acuity. Indeed, near-fatal and fatal asthmatic events have been linked to PMA.

Evaluation of women identified with PMA from SARP found that nearly twice as many PMA subjects met criteria for classification as severe asthma than women without PMA. In addition, levels of asthma control were worse in PMA subjects, and they experienced greater urgent health care utilization. Aspirin sensitivity was found three times more often in PMA patients (30% vs 10%), as were nasal polyps (16% vs 5%).

At the current time, PMA is not a widely appreciated entity. In the United States, there are still approximately 5000 asthma deaths per year. Any phenotypic prototype that can help to identify an asthma population at greater risk of fatal or near-fatal asthma might be a step toward reducing the mortality burden of asthma. ■

What's the Durability of Lifestyle Change in Type 2 Diabetes?

Source: Jakicic JM, et al. Four-year change in cardiorespiratory fitness and influence on glycemic control in adults with type 2 diabetes in a randomized trial: The Look AHEAD trial. *Diabetes Care* 2013; 36:1297-1303.

Embarking on lifestyle change is widely reinforced early on by numerous incidental happenstances. First, response to diet is most prominent in the early weeks of dieting. Second, relative gains in fitness and strength are most obvious in the early weeks of dieting. Third, most support programs providing advisors for diet, exercise, and psychological aspects are "front-loaded" (greater frequency/intensity at first) to try and establish optimum patterns early on. Fourth, as one gains positive initial steps, observers and friends tend to be avid supportive "cheerleaders," a response that diminishes as the going gets tougher, occasional ground is lost, or ground gained is less visible.

Jakicic et al report on the outcome at 4 years in the Look AHEAD Research Group trial. Overweight or obese type 2 diabetics (n = 3942) were randomized to intensive lifestyle intervention (ILI) or standard care. ILI included weekly instructional/support sessions × 24, continuing with lesser (but still frequent) support on diet and exercise throughout 4 years time. Goal exercise time was 175 minutes a week of brisk walking or the equivalent. As perhaps is intuitive, the intervention group achieved and maintained better fitness levels, better A1c, and better weight control. Structured ILI programs can provide sustained benefits in overweight and obese type 2 diabetics. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media.

Executive Editor: Leslie Coplin.
Editor: Stephen Brunton, MD.
Managing Editor: Neill L. Kimball.
This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: neill.kimball@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305.

AHC Media

PHARMACOLOGY WATCH

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

Is Naproxen the Safest NSAID for the Heart?

In this issue: NSAIDs and cardiovascular risk; new antithrombotic guidelines; warfarin during surgery; Pfizer selling Viagra online; azithromycin and cardiovascular risk; and FDA actions.

NSAIDs associated with less vascular risk

Naproxen may be the safest anti-inflammatory — at least when it comes to cardiovascular risk — according to a new study. Researchers from the United Kingdom undertook a meta-analysis of 280 trials of non-steroidal anti-inflammatory drugs (NSAIDs) vs placebo and 474 trials of one NSAID vs another. Main outcomes were major vascular events, major coronary events, stroke, mortality, heart failure, and upper gastrointestinal (GI) complications including bleeding. All NSAIDs and COX-2 inhibitors (coxibs) increased major vascular events except for naproxen (rate ratio [RR], coxibs 1.37 [95% confidence interval (CI), 1.14-1.66; $P = 0.0009$] and diclofenac 1.41 [95% CI, 1.12-1.78; $P = 0.0036$] mostly due to an increase in major coronary events). Ibuprofen also significantly increased the risk of major coronary events (RR 2.22, 95% CI, 1.10-4.48; $P = 0.0253$), but not major vascular events. Naproxen did not significantly increase the risk of major vascular events. Coxibs and diclofenac also significantly increased risk of vascular death, and there was a nonsignificant increase with ibuprofen, while there was no increase with naproxen. Heart failure risk was roughly doubled by all NSAIDs. The risk of upper GI complications was lowest with coxibs and highest with naproxen (coxibs 1.81, 95% CI, 1.17-2.81; $P = 0.0070$; diclofenac 1.89, 95% CI, 1.16-3.09; $P = 0.0106$; ibuprofen 3.97, 95% CI, 2.22-7.10; $P < 0.0001$, and naproxen 4.22, 95% CI, 2.71-6.56; $P < 0.0001$). The authors conclude that the vascular risks of diclofenac and possibly ibuprofen are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk (but higher GI risk) than other NSAIDs (*Lancet* published online May 30, 2013). The authors speculate that high-dose naproxen has fewer cardiovascular effects because it is the strongest inhibitor of COX-1, resulting in near complete suppression of platelet thromboxane biosynthesis (thus blocking platelet aggregation) throughout the 12-hour dosing interval. ■

New antithrombotic guidelines

A new guideline from the American Academy of Neurology gives primary care doctors guidance on periprocedural management of antithrombotic medications in patients with a history of stroke. Among the recommendations is that stroke patients undergoing dental procedures should routinely continue aspirin. Aspirin should also be considered for continuation in stroke patients undergoing invasive ocular anesthesia, cataract surgery, dermatologic procedures, transrectal ultrasound-guided prostate biopsy, spinal/epidural procedures, and carpal tunnel surgery. Aspirin should possibly be continued during other procedures such as virtroretinal surgery, EMG, transbronchial lung biopsy, colonoscopic polypectomy, upper endoscopy and biopsy/sphincterotomy, and abdominal ultrasound-guided biopsies. For stroke patients on warfarin, the guideline recommends continuation of the drug

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) 262-5404. E-mail: neill.kimball@ahcmedia.com.

during dental procedures and probably during most dermatologic procedures. Other more invasive procedures should warrant discussion. The guideline states there is insufficient evidence to support or refute periprocedural heparin-bridging therapy to reduce thromboembolic events in chronically anticoagulated patients. Bridging therapy is probably associated with increased bleeding risk as compared with warfarin cessation, but the risk difference compared with continuing warfarin is unknown (*Neurology* 2013;22:2065-2069). ■

Continuing warfarin for surgery

In related news, a new study suggests that continuing warfarin for pacemaker or defibrillator surgery is safer than heparin bridging. Nearly 700 patients with an annual risk of thromboembolic events of ≥ 5% who required pacemaker or defibrillator surgery were randomized to continued-warfarin treatment or bridging therapy with heparin. The primary outcome was clinically significant device-pocket hematoma, which occurred in 12 of 343 patients (3.5%) in the continued-warfarin group as compared with 54 of 338 (16.0%) in the heparin-bridging group. There was one episode of cardiac tamponade and one myocardial infarction in the heparin-bridging group and one stroke and one TIA in the continued warfarin group. This study was stopped early after interim analysis found that the primary outcome occurred four times as often in the heparin-bridging group. These findings suggest that a strategy of continued warfarin therapy at the time of pacemaker or defibrillator surgery markedly reduced incidence of clinically significant device pocket hematoma as compared with heparin bridging (*N Engl J Med* 2013;368:2084-2093). ■

Pfizer launches own Viagra website

Pfizer is aggressively pursuing the online market for sildenafil (Viagra) by launching its own "Viagra home delivery" website. The drug will be available online directly from Pfizer but will still require a doctor's prescription. This move is also designed to counter online marketing of counterfeit Viagra, the most commonly counterfeited drug in the world. Pfizer plans to make Viagra available online at approximately $25 a pill. Meanwhile, the company has lost patent protection for its other version of sildenafil citrate marketed for pulmonary hypertension under the trade name Revatio. This version of the drug is only available in 20 mg strength, but is otherwise identical to Viagra, which is available in 25, 50, and 100 mg strengths. It is yet to be seen whether physicians will prescribe generic 20 mg sildenafil off label for erectile dysfunction. ■

Azithromycin and cardiovascular risk

Does azithromycin increase cardiovascular (CV) risk? A recent observational study showed that azithromycin was associated with a 2-3 times higher risk of death from CV disease in patients at high risk for CV disease (*N Engl J Med* 2012;366:1881-1890). A new study looks at the risk of the drug vs placebo and a comparator antibiotic (penicillin V) in Danish adults ages 18-64. As compared with no use of antibiotics, use of azithromycin was associated with a significantly increased risk of CV death (rate ratio 2.85; 95% CI, 1.13-7.24); however, when compared to penicillin V, there was no increased risk (crude rate CV death 1.1/1000 person years azithromycin vs 1.5/1000 penicillin V). With adjustment for CV risk, current azithromycin use was not associated with increased risk of CV death compared with penicillin V in a general population of young and middle-aged adults. (*N Engl J Med* 2013;368:1704-1712). This study is reassuring, suggesting that the increased risk of death is probably due to the illness rather than the drug, especially in low-risk populations. However, the risk of the macrolides still should be considered among patients with a high baseline risk of CV disease. ■

FDA actions

The FDA has approved a new once-daily combination inhaler for the treatment of chronic obstructive pulmonary disease (COPD). The product combines the long-acting beta-agonist (LABA) vilanterol with the steroid fluticasone furoate. Vilanterol is a new LABA and fluticasone furoate is reported to have longer lung retention time compared to the proprionate allowing for once-daily dosing. The product is a dry powder that is delivered via the Ellipta device. The new inhaler was evaluated in 7700 patients with COPD and showed improved lung function and reduced exacerbations compared to placebo. Vilanterol/fluticasone furoate is marketed by GlaxoSmithKline in collaboration with Theravance as Breo Ellipta.

The FDA has approved a new cholesterol combination drug, combining ezetimibe and atorvastatin. The drug is indicated for lowering cholesterol in patients with primary or mixed hyperlipidemia and in those with homozygous hypercholesterolemia. It is approved in four strengths, each containing 10 mg of ezetimibe with 10, 20, 40, or 80 mg of atorvastatin. The combination reduces LDL cholesterol levels up to 61% in clinical trials. Like the previously marketed simvastatin/ezetimibe, there is no evidence that the combination improves cardiovascular outcomes over a statin alone. The combination will be marketed by Merck as Liptruzet. ■