AHC Media

Vol. 31, Issue 2, February 2012
www.ahcmedia.com

Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Can Potential Acute MI Patients be Triaged Faster?

By Michael H. Crawford, MD, Editor

SOURCE: Keller T, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infraction. *JAMA* 2011;306:2684-2693.

Newer more sensitive troponin assays have the potential to identify acute myocardial infarction (AMI) earlier, but some detect troponin in 50% of normal populations, which renders them clinically useless. This study evaluates the use of troponin kinetics clinically to separate AMI patients from those with chronically elevated troponin levels. They enrolled 1818 consecutive patients suspected of having AMI and measured high sensitivity troponin I (hsTnI) and conventional troponin I (cTnI) at admission and 3 and 6 hours after. Patients were followed for 30 days and a final diagnosis of AMI was made based on current guidelines by blinded cardiologists. Critical to the diagnosis was at least a 20% rise and fall in a conventional troponin assay (I or T). The final diagnosis of MI was made in 413 (23%), of whom 56 (14%) had ST elevation MI. AUC values for the ROC curves were highest for hsTnI (0.96) followed by cTnI (0.92) on admission. The hsTnI at admission had a sensitivity of 82% and a negative-predictive value (NPV) of 95%, whereas for cTnI the values were 79% and 94%. The positive-predictive value (PPV) on admission for hsTnI was 75% and for cTnI was 81%. Samples at 3 hours improved the sensitivity of hsTnI to 98% with a NPV of 99% and identical values were observed for cTnI. Using the criteria of a hsTnI > 99th percentile at admission and a change > 266% at 3 hours improved PPV for both assays to 96%. The authors concluded that TnI measurements on admission and 3 hours later may facilitate the early triage of suspected AMI patients.

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.

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.

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.

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■ COMMENTARY

This is a relatively large observational study that compares hsTnI to cTnI and compares admission values to 3 hours post admission values and the change from admission to 3 hours for diagnosing AMI. The data analysis is comprehensive and quite complicated. Also, other biomarkers were evaluated in the study, but none, alone or in combination, were better than troponin. The study focused on suspected AMI patients because of chest pain symptoms. Only 14% of the MIs proved to be STEMIs, so the study mainly was about identifying non-STEMIs. Several conclusions can be made. First, at the time of admission hsTnI and cTnI were similar for ruling out AMI (NPV 95% vs 94%). For diagnosing AMI at admission cTnI was a little better than hsTnI (PPV 81 vs 75%). So for initial triage there is no real value of hsTnI over cTnI. Second, most low-risk patients will be held until a second troponin is done to improve diagnostic accuracy. Three hours hsTnI had a NPV of 99%, as did cTnI. So again there was no added benefit of hsTnI. Third, an evaluation of the change in troponin from admission to 3 hours showed that the PPV for both assays was increased to 96%, again demonstrating no advantage to using hsTnI. Fourth, the only subgroups that showed an advantage for hsTnI were patients with initially normal troponin and patients known to have presented very early after symptom onset (< 2 hrs). Fifth, using hsTnI routinely will result in a higher false-positive rate at admission as compared to cTnI. In summary, at this point I do not see any reason to switch to hsTnI.

There are some limitations to this study. Since troponin values were used to adjudicate the AMI diagnosis, there is the risk of incorporation bias, which would tend to increase the accuracy of troponin tests. This population was unique in at least two regards. There was a relatively high rate of AMI (23%) compared to other studies. This would also tend to increase accuracy. Also, almost all of the patients were white Europeans; so the results may not be applicable to other ethnic groups. Overall, this is a robust study which will undoubtedly influence the application of hsTnI assays in clinical settings. ■

ABSTRACT & COMMENTARY

Optimal Weight Loss Diet to Reduce Cardiovascular Risk

By Michael H. Crawford, MD, Editor

SOURCE: Gogebakan O, et al. Effects of weight loss and long-term maintenance with diets varying in protein and glycemic index on cardiovascular risk factors: The Diet, Obesity, and Genes (DiOGenes) study: A randomized controlled trial. *Circulation* 2011;124:2829-2838.

This pan-European multicultural study investigates whether after initial weight loss in overweight subjects, a subsequent diet of high or low carbohydrate (glycemic index) or protein diets helped subjects maintain their new weight better. Their initial results showed that the low glycemic, high-protein diet was superior for maintaining their weight for 26 weeks. The present study evaluated which diet best improved hsCRP, triglycerides, cholesterol levels, and blood pressure vs a control group in 932 overweight adults who lost weight on an 8-week low-calorie diet. Of the 773 randomized to one of the four diets, 71% completed the study. Average weight loss in the low-calorie period was 11 kg. Of the subsequent diets, only the low-protein high-glycemic diet resulted in weight regain (+ 1.7 kg). Weight loss reduced hsCRP, cholesterol (HDL and LDL), triglycerides, and blood pressure. During the maintenance phase, hsCRP was reduced further in the low-glycemic diets vs high and on low protein diets vs high. Cholesterol, triglycerides, and blood pressure were not differentially affected by the four diets. The authors

conclude that after weight loss, a low glycemic index and, to a lesser extent, low-protein diet may reduce inflammation associated with cardiovascular disease in overweight adults.

■ COMMENTARY

With two-thirds of American adults being either overweight or obese, scientific data on appropriate diets are important. The original trial report of this study showed that caloric restriction was necessary for weight loss and diet composition had little effect. The emphasis on low-fat diets to reduce cholesterol and reduce cardiovascular risk may be thwarted if subjects substitute carbohydrates for the fat calories, resulting in little or no weight loss. As this follow-up study shows, a high glycemic index diet may also blunt the decrease in low-grade inflammation associated with weight loss and increase cardiovascular risk. Maintaining a high-protein diet also can blunt the decrease in hsCRP following weight loss, but to a much lesser extent than a high-glycemic diet. However, high-protein diets are known to improve lipid profiles. What the balance between lower LDL cholesterol and higher inflammation will do to subsequent cardiovascular risk is not known, but since cholesterol can be lowered by other means, the lower inflammation on a low-glycemic diet could be more important. In summary, this study argues for adopting low glycemic index diets with lower protein content for weight loss and maintenance.

The strengths of this study are that the subjects were otherwise healthy without diabetes, morbid obesity, and other chronic diseases. Also, the study separated the effects of weight loss from the effects of dietary composition. However, it must be emphasized that the effects of weight loss on all the metabolic, inflammatory, and blood pressure measures was greater than the effects of dietary composition. ■

ABSTRACT & COMMENTARY

Bariatric Surgery Reduces MI, Stroke, and Death

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: Sjostrom L, et al. Bariatric surgery and long-term cardiovascular events. *JAMA* 2012;307:56-65.

The prevalence of obesity is increasing throughout the western world at an alarming rate. Obesity has been associated with higher rates of cardiovascular events, although the converse association (between weight loss and reduction in cardiovascular events) has been harder to prove. In recent years, surgical treatment of obesity has advanced significantly. Compared to medical treatments, bariatric surgery results in greater and more sustained weight loss. To assess the effects of bariatric surgery on cardiovascular outcomes, the Swedish Obese Subjects (SOS) registry has been prospectively collecting data on patients undergoing bariatric surgery since 1987 in Sweden. The authors report the outcomes of 2010 patients undergoing bariatric surgery by choice (not randomization) in comparison to 2037 control subjects who were treated with standard care in 25 surgical departments and 480 primary care centers in Sweden. The inclusion criteria were men and women ages 37 to 60 years with a body mass index (BMI) ≥ 34 for men and ≥ 38 for women. The exclusion criteria of both groups were prior surgery for gastric or duodenal ulcer, prior bariatric surgery, gastric ulcer during the past 6 months, ongoing malignancy, active malignancy during the past 5 years, myocardial infarction (MI) during the past 6 months, bulimic eating pattern, drug or alcohol abuse, psychiatric or cooperative problems contraindicating bariatric surgery, and continuous steroid or anti-inflammatory treatment.

The mean BMI was 42.4 in the bariatric surgery group and 40.1 in the control group. The patients were followed for a median of 14.7 years and the primary endpoint was a combination of fatal or non-fatal MI or stroke. Secondary endpoints were MI and stroke. In the surgery group, 13.2% had gastric bypass, 18.7% had banding and 68.1% had vertical banded gastroplasty. There was significant and sustained weight loss in the surgery group of approximately 20% of body weight, with no change at all in the control group. Gastric bypass appeared to achieve slightly greater weight loss. Surgery resulted in a 17% reduction in the rate of the primary endpoint of fatal plus nonfatal MI and stroke (hazard ratio [HR] 0.67, $P < 0.001$). Cardiovascular mortality was lower in the bariatric surgery group (HR 0.47, $P = 0.002$). Bariatric surgery was associated with lower risk of MI (HR

0.71, $P = 0.02$) and stroke (HR 0.66, $P = 0.008$).

Interestingly, the beneficial effects of bariatric surgery on cardiovascular events were not related to baseline BMI, or to weight change. Other baseline variables including age, gender, blood pressure, diabetes, weight, lipid levels, blood glucose, and the presence of metabolic syndrome had no interaction on cardiovascular outcomes in the surgery group. Yet, in the control group, these parameters were predictive of outcomes, as one might expect. The only independent predictor of cardiovascular outcomes in patients undergoing bariatric surgery was a high plasma insulin level. The post-operative complication rate was 13%.

■ COMMENTARY

The SOS study adds to the growing body of literature that bariatric surgery for obese individuals leads to rapid loss of significant amounts of weight that is sustained over many years, and that this is associated with fewer incident cardiovascular events and lower mortality. This is a large dataset and the study was performed at numerous centers, which strengthen these data and suggest it is more widely applicable. However, because this study was not randomized, there may be considerable selection bias in the patients who selected surgical treatment over standard therapies. This means that although there is circumstantial evidence suggesting benefit, this has not yet been unequivocally proven. Future randomized, controlled trials are needed to confirm this. This study is not only limited by a lack of randomization, we are not given detail of the usual care in this cohort, including exercise levels, dietary interventions, or medication use. Thus, we cannot make firm conclusions from the dataset.

One might predict that the higher the BMI, the greater the benefit a patient would achieve from bariatric surgery. It is fascinating that baseline weight and BMI did not predict who would achieve most benefit. Indeed, the amount of weight lost after surgery was also not predictive of reduction in cardiovascular events. Yet, we continue to select patients for bariatric surgery based on weight and/or BMI. The cardiovascular benefits may not be realized through the mechanism that we originally thought i.e., through loss of fat. Perhaps other hormonal changes following surgery are more important than the amount of body fat. Mechanistic translational studies are urgently needed to more fully understand how this treatment works. Understanding the mechanism of action may allow us to better select patients who may benefit from bariatric surgery, while not exposing those who would not derive benefit to the small but real risks of surgery. ■

ABSTRACT & COMMENTARY

Long-term Safety of Statins

By Andrew J. Boyle, MBBS, PhD

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

SOURCE: Heart Protection Study Collaborative Group. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: A randomised controlled trial. *Lancet* 2011;378:2013-2020.

Statins reduce the incidence of adverse cardiovascular events. Some observational non-randomized studies have suggested that low cholesterol levels and/or statins may increase the risk of cancer or other non-cardiovascular issues. To determine the long-term effects of simvastatin on cancer and death, the investigators from the Heart Protection Study reviewed the outcomes of their trial participants over an extended follow-up time after the original 5-year clinical trial had ended.

You may remember that the Heart Protection Study (HPS) was a trial of 20,536 patients at high risk of vascular events who were randomized to receive simvastatin 40 mg daily vs placebo. The study ran over 5 years and showed a reduction in LDL cholesterol of 1 mmol/L (39 mg/dL), which was associated with a 23% reduction in major vascular events. This paper extends the follow-up period to 11 years. Over the original 5-year study period, 85% of the simvastatin-allocated patients, and 17% of the placebo-allocated patients, were taking statins. Over the extended follow-up period of this study, approximately 74% of patients in each group were taking statins. Correspondingly, LDL cholesterol was lower in the simvastatin-allocated group after the original 5-year study period, but was the same between groups after the extended follow-up period. Thus, the long-term follow-up represents a 5-year period of randomized treatment (statin vs placebo), followed by 6 years of high rates

of statin treatment in both groups. The particular focus of this study was on cancer and mortality, so the authors not only followed up the patients but also cross-referenced with the national cancer registry and with the national death index in the United Kingdom.

Patients allocated to simvastatin had a significant reduction in vascular events during the 5-year trial period. During this extended follow-up period from years 5-11, there were no differences between groups in terms of vascular events. This was to be expected because the rates of statin therapy and the lipid levels were the same in both groups. During the extended follow-up period, there were no differences between groups in terms of any of the components of the primary endpoint: stroke, major coronary events, and revascularization rate.

There was a significant reduction in mortality in the statin-allocated group during the initial 5-year study period. Mortality from vascular and non-vascular causes remained the same in each group during the extended trial follow-up period. The incidence of cancer was the same in each group, as was the body region where the cancer occurred. There were no differences in mortality between treatment groups in those with lower baseline lipid levels or in the elderly.

■ COMMENTARY

This is more good news for patients in need of statin therapy. The reports that suggested a link between statin therapy, or low LDL, and cancer or increased non-cardiovascular mortality appear to be unfounded. They were based on epidemiological observational studies, but analyses of randomized placebo-controlled trial like this one refute this hypothesis quite resoundingly. This study is congruous with the growing body of literature on long-term statin follow-up. The WOSCOPS study of pravastatin versus placebo was initially a 5-year study, and the extended follow-up of an additional 10-years showed continued reduction in cardiovascular mortality, with no increase in cancer or in non-cardiac mortality.[1] Similarly, the extended follow-up of the ASCOT-LLA study of atorvastatin 10 mg vs placebo (initial trial stopped early after 3 years for highly positive effect, extended follow-up to 11 years) showed continued reduction in mortality with no excess cancer and a *decrease* in non-cardiac mortality.[2]

In all these studies, a period of statin use for several years conferred a mortality reduction that continued for many more years. This continued legacy of treatment benefit has been consistent throughout these studies and appears to be a class effect of the statins. This confirms that statin therapy should be given early to those in whom it is warranted. There do not appear to be any long-term safety issues, at least out to 11 years. In particular, there does not seem to be an increased risk in those with low baseline LDL or in the elderly.

This long-term follow-up following an initial period of treatment and then open-label treatment is not the most robust clinical trial design. However, it is the best data we are ever likely to have. It is not ethical to have a long-term statin vs placebo trial in those who are at risk for vascular events, as the benefits of statins are clear and randomizing patients to placebo would be unethical. I am reassured by this paper, and other long-term follow-up papers, that statins are safe in the long-term. Hopefully, this paper puts the issue to rest. ■

References

1. Ford I, et al. Long-term follow-up of the West of Scotland Coronary Prevention Study. *N Engl J Med* 2007;357:1477-1486.
2. Sever PS, et al. The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the U.K. *Eur Heart J* 2011;32:2525-2532.

ABSTRACT & COMMENTARY

Risk vs Benefit of Atrial Fibrillation Ablation Procedures

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: Shah RU, et al. Procedural complications, rehospitalizations, and repeat procedures after catheter ablation for atrial fibrillation. *J Am Coll Cardiol* 2012;59:143-149.

Shah et al used an administrative database, the California State Inpatient Database from the Healthcare Utilization Project, to analyze the short and intermediate success and complication rates associated with catheter ablation for atrial fibrillation (AF). The authors identified patients who underwent an initial AF ablation in California between January 1, 2005, and November 31, 2008. Search methods identified patients who underwent ablation for only AF and excluded patients having other electrophysiologic procedures. Comorbidities were identified through the database. Acute procedural complications were also obtained from the database and included: cardiac perforation and/or tamponade, pneumothorax, hemothorax, procedure-related stroke, transient ischemic attack, vascular access complications, and in-hospital death. Thirty-day and long-term rehospitalization rates were also identified.

During the 4-year study period, the authors identified 4156 patients who received an initial ablation for AF in the state of California. There was a steady increase in the number of initial procedures annually, with 684 cases in 2005 and 1332 in 2008. AF ablations were performed in 98 unique hospitals with a mean annual volume of 15.4 throughout the study. The mean patient age was 61.7 years, with hypertension (50.3%) and coronary artery disease (14.7%) the most common cardiac diagnoses. Only a minority of patients (20.9%) had been hospitalized with a primary diagnosis of AF during the year before ablation. The mean observation time from the initial ablation to the close of the study was 1.5 years.

During the initial hospitalization, complications were noted after 5.1% of AF ablations. The complication rate was constant during the course of the study. More than half of the complications were vascular. There was, however, only one death. In addition to these early complications, 9.4% of patients discharged were rehospitalized within 30 days after discharge. Recurrent atrial arrhythmias and late procedural complications accounted for 47% of these repeat admissions. The risk of an inpatient complication or 30-day rehospitalization was associated with the following: increased age; female gender; primary payer (Medicare vs private insurance); a history of heart failure, hypertension, renal, or lung disease; the prior number of AF hospitalizations; and hospital AF ablation volume. The latter was a strong predictor of rehospitalization with a 50% increase in the odds of complication or rehospitalization in hospitals in the lowest frequency quartile compared to those in the highest frequency quartile. After 30 days, rehospitalizations continued to be frequent. At 1 year, 39% of the patients had been rehospitalized at least once and 22% of patients had been hospitalized for either recurrent arrhythmia or a repeat ablation. Repeat ablations were performed in 17.4% of the study group with most receiving a single additional procedure.

The authors conclude that during the period of study, AF ablation procedures had only modest efficacy with a significant risk for complications and need for rehospitalization.

■ COMMENTARY

AF ablation is now one of the more common procedures performed by electrophysiologists. Evaluating the efficacy of AF ablation has been difficult. If one uses the criterion of no detectable AF off all antiarrhythmic therapy during intensive periodic monitoring, single procedure success rates are less than 65% for patients with paroxysmal AF and less than 50% for patients with persistent AF, even in experienced centers. This paper suggests that the success rates may be even lower in general practice. AF is usually managed on an outpatient basis and this report only captured recurrences if they resulted in hospitalization or a repeat ablation procedure. The observation that success rates were higher and complication rates lower in higher volume centers is also important, although not surprising. AF ablation techniques continue to evolve and only centers and operators who do enough procedures to remain current are likely to have the best outcomes. ■

ABSTRACT & COMMENTARY

Prognostic Predictors in Brugada Syndrome

By John P. DiMarco, MD, PhD

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

SOURCE: Priori SG, et al. Risk stratification in brugada syndrome: Results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. *J Am Coll Cardiol* 2012;59:37-45.

In this paper, Priori and colleagues from a consortium of 10 Italian arrhythmia centers enrolled Brugada syndrome patients to evaluate the role of programmed electrical stimulation in risk stratification and to look for other novel predictors of outcome in Brugada syndrome patients. Patients were enrolled if they were older than 18 years, had either a spontaneous or pharmacologically induced Brugada type 1 ECG pattern (coved ST segment elevation greater than 2 mm in at least two right precordial leads), and had never experienced either cardiac arrest or sustained ventricular tachycardia. All ECGs were analyzed at a central coordinating center with special attention paid to the morphology of the QRS complex and ST segment. Structural cardiac abnormalities were excluded by echocardiography and exercise testing. Patients underwent electrophysiologic (EP) study to assess the inducibility of ventricular arrhythmias. A standard protocol using three extrastimuli at two right ventricular sites was employed. A patient was considered to have an inducible arrhythmia if sustained ventricular fibrillation or sustained polymorphic ventricular tachycardia were induced. Reproducibility of arrhythmia induction was tested at the same procedure at the operator's discretion. After their EP study, physicians were free to manage their patients as they felt appropriate. During follow-up, arrhythmia events were defined as the occurrence of ventricular fibrillation or appropriate implantable cardioverter-defibrillators (ICD) interventions. Follow-up visits were made at 3 months after EP study and then every 6 months until March 2010.

The Prelude Registry enrolled 308 patients. The mean age at enrollment was 47 ± 12 years and 80% were male. The Brugada type 1 ECG pattern was seen spontaneously in 56% and was induced with intravenous drug challenge in the remaining 44%. QRS fragmentation (defined as two or more spikes within the QRS complex in lead V_1 to V_3) was present in 8.1% of the patients. Genetic analysis was performed in 123 patients and an *SCN5A* mutation was identified in 20% of the tested patients. Before enrollment, 65 patients (21%) had experienced at least one syncopal spell. During follow-up of 39 ± 12 months, 14 of 308 (4.5%) of patients experienced cardiac arrest or documented ventricular fibrillation. All patients were resuscitated with either an ICD shock (13) or by an emergency medical team (1).

At electrophysiologic study, 126 of 308 patients (41%) had an inducible arrhythmia. Arrhythmias were inducible with a single extrastimulus in seven patients, with two extrastimuli in 56 patients and with three extrastimuli in 63 patients. Of note, among patients in whom short-term reproducibility was tested, only 44% of the patients had reproducible arrhythmia induction. An ICD was inserted in 98 of 126 patients with induced arrhythmia and in 39 of 182 patients without inducible arrhythmia. During follow-up, there were 14 events in the 308 patients for an annual event rate of 1.5%. Programmed electrical stimulation had no predictive value. There were five arrhythmic events among 126 patients with inducible arrhythmias (3.9%) compared to nine arrhythmic events among 182 patients with no inducible arrhythmias (4.9%). However, several factors were predictive of outcome. These included a history of syncope, a spontaneous type 1 ECG pattern, a ventricular effective refractory period < 200 msec, and QRS fragmentation. The most powerful predictor of an arrhythmic event was the presence of both syncope and a spontaneous type 1 ECG pattern.

The authors then compared their data to three other studies that looked at the natural history of patients with Brugada syndrome. They found their data to be similar to two earlier reports but considerably lower than the series reported by Brugada et al, which had an annual event rate of 4.1%.[1]

The authors conclude that the PRELUDE Registry indicates that programmed electrical stimulation should not be used to assess prognosis in patients with Brugada syndrome. The most valuable prognostic clinical factors are a history of syncope, the presence of a spontaneous type 1 ECG pattern, and QRS fragmentation.

■ COMMENTARY

Management of patients with the Brugada syndrome ECG pattern, but no documented arrhythmias, has been controversial. ICDs are the only accepted approach in patients who require treatment since no pharmacologic therapy has been shown to be effective. The event rate in asymptomatic Brugada syndrome patients is fairly low and many patients are identified as young adults. Given the complications associated with long-term ICD therapy, it would be of value if effective risk stratification were possible. Prior reports by Brugada et al suggested that programmed ventricular stimulation was an effective tool for this purpose. Unfortunately, the data presented here from a large prospective registry suggest that programmed electrical stimulation is of no benefit as a risk stratification tool since it has poor positive and negative predictive value. These new data are in agreement with data from two other reports

and the combined data should lead electrophysiologists to abandon the use of stimulation studies in these patients. Patients with syncope and a Type I ECG pattern should certainly receive an ICD. Patients with syncope and a provocable ECG pattern are also appropriate candidates. For asymptomatic patients, it is likely that a risk scoring system based on data from several combined registries will have to be devised. ■

Reference

1. Brugada P, et al. Natural history of Brugada syndrome: The prognostic value of programmed electrical stimulation of the heart. *J Cardiovasc Electrophysiol* 2003;14:455-457.

CME/CNE Instructions

To earn credit for this activity, please follow these instructions:

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5. Once the evaluation is received, a credit letter will be sent to you. ■

CME Questions

1. Which of the following characteristics confers a higher risk for sudden death in Brugada syndrome patients?
a. Inducible VT/VF on programmed stimulation
b. Syncope
c. Spontaneous Type I ECG pattern
d. b and c

2. The overall success rate of ablation for preventing paroxysmal atrial fibrillation at best is:
a. 85%.
b. 75%.
c. 65%.
d. 55%.

3. Successful bariatric surgery results in:
a. a sustained 20% weight loss.
b. reduced MI and stroke rates.
c. reduced cardiovascular death.
d. All of the above

4. Observational studies of long-term statin use repudiate the claim that they cause:
a. dementia.
b. muscle aches.
c. cancer.
d. reduced cardiovascular events.

5. The best diet for maintaining weight loss and enhancing cardiovascular protection is:
a. high protein, low carbohydrates.
b. high protein, high carbohydrates.
c. low carbohydrates, low protein.
d. high carbohydrates, low protein.

6. A highly sensitive troponin I assay is superior to conventional troponin assays for:
a. initially ruling out MI.
b. diagnosing MI by serial studies.
c. detecting MI in patients who present early after chest pain.
d. triaging patients with high initial troponin values.

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.

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, Travel Medicine Advisor.*

New, Shorter Treatment Regimen for Tuberculosis

In this issue: New treatment for TB; safety of dabigatran; quality of antidepressants; systolic hypertension treatment; and FDA actions.

Short course treatment for latent TB

Three months of two drugs administered once weekly is as effective as 9 months of daily isoniazid (INH) for the treatment of latent tuberculosis infection (LTBI), according to a new study. An international team of researchers randomized nearly 8000 patients with latent tuberculosis (TB) to 3 months of directly observed once-weekly therapy with rifapentine 900 mg plus INH 900 mg or 9 months of self-administered daily INH 300 mg. The primary endpoint was confirmed TB after 33 months of follow-up. In the modified intention-to-treat analysis, TB developed in 0.19% of the once-weekly combination group and in 0.43% of the INH only group. Rates of completion were much higher with the short course, once-weekly regimen (82.1% in the combination-therapy group and 69.0% in the INH only group, $P < 0.001$). Rates of hepatotoxicity were higher in the INH only group. The authors conclude that use of rifapentine plus INH given once a week for 3 months is as effective as 9 months of INH in preventing tuberculosis and has a higher treatment-completion rate (*N Engl J Med* 2011;365:2155-2166). Based on this study and others, the CDC has issued a new recommendation on the use of short-course combination therapy for latent TB infection. The recommendation states, "The new regimen is recommended as an equal alternative to the 9-month INH regimen for otherwise healthy patients ≥ 12 years who have LTBI and factors that are predictive of TB developing (e.g., recent exposure to contagious TB)." It also recommends that the new regimen may be considered for other categories of patients when it offers advantages. Daily INH continues to be the preferred regimen for children between the ages of 2 and 11 (*MMWR Morb Mortal Wkly Rep* 2011;60:1650-1653). ■

Bleeding concerns with dabigatran

Dabigatran (Pradaxa), Boehringer Ingelheim's blockbuster anticoagulant, is the subject of a December 7, 2011, Drug Safety Communication by the FDA regarding serious bleeding events. The FDA is evaluating postmarketing reports of serious bleeding events that may lead to serious or even fatal outcomes. Experts are working to determine whether the reports of bleeding associated with the drug are occurring more commonly than would be expected based on observations from large clinical trials. The drug was approved in October 2010 to reduce the risk of stroke in patients with non-valvular atrial fibrillation. More than a million prescriptions have been filled by nearly 400,000 patients since approval. ■

All antidepressants are created equal

When it comes to choosing an antidepressant, all modern drugs are roughly equivalent, according to a new study in the *Annals of Internal Medicine*. Researchers performed a large meta-analysis of 234 studies that looked at the treatment of major depressive disorder (MDD) with second-generation anti-

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depressants. There were no differences among the drugs with regard to efficacy or effectiveness for the treatment of acute, continuation, and maintenance phases of MDD. There were also no significant differences when accompanying symptoms were taken into account or other factors such as age, sex, ethnicity, or comorbid conditions. There were differences among the drugs with regard to onset of action, adverse effects, and some quality-of-life issues. There was also a significant difference in cost and dosing convenience. Drugs considered in the study were bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine. The authors suggest that familiarity with the broad spectrum of antidepressants is prudent given the difficulty of predicting which medication will be effective and tolerated by any given patient (*Ann Intern Med* 2011;155:772-785). ■

Benefits of treating systolic hypertension

Older adults with isolated systolic hypertension gained about 5 months of life when treated with chlorthalidone-based stepped care 2 decades after completion of the Systolic Hypertension in the Elderly Program (SHEP) trial. SHEP, conducted between 1985 and 1990, was a clinical trial of patients aged 60 years or older (mean age 72) with isolated systolic hypertension who were randomized to chlorthalidone-based antihypertensive therapy or placebo. Over a mean follow-up of 4.5 years, chlorthalidone-based therapy resulted in prevention of approximately 1 of 2 admissions for heart failure, 1 out of 3 fatal or nonfatal strokes, and 1 of 4 coronary heart disease events, but there was no effect on all-cause mortality or cardiovascular death. At the end of the trial, all participants were advised to receive active therapy. The new study reviewed cardiovascular death and all-cause mortality in SHEP trial participants 22 years after the study ended. Life expectancy gain between the active treatment group and placebo group was 105 days (95% confidence interval [CI], -39 to 242; $P = 0.07$) for all-cause mortality and 158 days (95% CI, 36-287; $P = 0.009$) for cardiovascular death. Each month of active treatment was associated with approximately 1 day extension in life expectancy. The authors conclude that treatment of isolated systolic hypertension with chlorthalidone stepped-care therapy for 4.5 years was associated with longer life expectancy at 22 years of follow-up (*JAMA* 2011;306:2588-2593). This study may help convince older patients with systolic hypertension that compliance with diuretic-based hypertensive therapy is worth the effort as it will prolong their lives. ■

Aliskiren and ACEIs/ARBs don't mix

Aliskiren (Tekturna), Novartis' direct renin inhibitor, should not be combined with an ACE inhibitor or angiotensin receptor blocker (ARB) to treat hypertension, according to the manufacturer. Novartis recently terminated the ALTITUDE trial when it was found that patients with type 2 diabetes or impaired renal function who were given the combination of aliskiren with an ACEI or ARB had a higher incidence of nonfatal stroke, renal complications, hyperkalemia, and hypotension. More information can be found at www.novartis.com/newsroom/media-releases/en/2011/1572562.shtml. ■

FDA actions

The FDA approved generic atorvastatin (Lipitor) on November 30, 2011. Ranbaxy Laboratories will make the first generic in 10, 20, 40, and 80 mg strengths. Atorvastatin as Lipitor was first marketed in 1997 and became the best-selling prescription medication in history with sales of more than $125 billion. It has dominated the statin market in recent years, representing nearly a quarter of Pfizer's annual revenue, and the giant pharmaceutical company aggressively defended their patent against multiple challenges. Ranbaxy has 180 days of exclusivity on generic atorvastatin after which time multiple manufacturers are expected to seek approval for their generic version of the drug.

The FDA has approved Prevnar 13 for adults age 50 and older to prevent pneumonia and invasive disease caused by *Streptococcus pneumoniae*. The vaccine was previously approved for children up to 5 years of age. The approval was based on head-to-head studies with Pneumovax 23 which is already approved for use in adults. According to the FDA, "for the 12 common serotypes, Prevnar 13-induced antibody levels were either comparable to or higher than the levels induced by Pneumovax 23." Prevnar 13 is manufactured by Wyeth Pharmaceuticals.

Dronedarone (Multaq) should not be prescribed to patients with permanent atrial fibrillation (AF), based on results from the PALLAS trial which showed that the drug doubles the risk for cardiovascular death, stroke, and heart failure in such patients. The FDA is requiring revised labeling for the antiarrhythmic drug and has issued a Drug Safety Communication after a safety review was completed. If dronedarone is to be prescribed, the FDA recommends ECGs every 3 months and immediately stopping the drug if the patient is found to be in AF. The drug is indicated to reduce hospitalization for AF in patients in sinus rhythm with a history of non-permanent AF (paroxysmal or persistent AF). Dronedarone is manufactured by Sanofi-Aventis. ■

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 17, NUMBER 2 PAGES 3-4 FEBRUARY 2012

Establishing the CV Safety Profile of ADHD Meds in Children and Young Adults

Source: Cooper WO, et al. *N Engl J Med* 2011;365:1896-1904.

CASE REPORTS OF ADVERSE CARDIOVASCULAR (CV) events in children and young adults taking attention deficit-hyperactivity disorder (ADHD) medications have included myocardial infarction (MI), stroke, and sudden death. These individual cases, however, neither prove causation nor provide insight into event frequency, since the denominator is unknown. Because of the seriousness of these events, a clearer understanding of their epidemiology is important.

Cooper et al performed a retrospective cohort study based on data from four large health plans, which included data from more than 1 million persons 2-24 years of age. Among this population, there were data on 373,667 person-years of ADHD drug treatment in these children and young adults.

In this entire population, there were 81 serious CV events (rate = 3.1/100,000 person-years). However, persons currently using ADHD drugs did *not* demonstrate an increased risk for CV events compared to non-users; in fact, the hazard ratio (HR) demonstrated a trend (not statistically significant) toward *fewer* serious CV events in persons taking ADHD medications (HR = 0.75). Whether CV events were looked at in composite (MI + stroke + sudden death) or individually, the same generally favorable trend was seen (HR = 0.70, *P* = NS). Similarly, former users of ADHD medications were at no greater risk for CV events than never-users. This study was not funded by industry, but by the federal agencies AHRQ and FDA. ■

If You're Already on a Statin, Does Adding Niacin Help?

Source: AIM-HIGH Investigators. *N Engl J Med* 2011;365:2255-2267.

RESULTS FROM INTERVENTION TRIALS WITH statins for secondary prevention of cardiovascular (CV) events are consistently impressive. Nonetheless, significant residual risk remains; that is, even though statin treatment reduces risk of events by as much as 20-30% over 5 years, persons with existing CV disease are still at substantially greater risk of having another CV event than age-matched controls without CV disease. Observational studies suggest that increasing high-density lipoprotein (HDL) might provide an even greater incremental CV risk reduction than LDL modulation, although evidence from interventional trials is conflicting.

The AIM-HIGH trial enrolled patients with existing CV disease (n = 3414) who were already receiving simvastatin (plus ezetimibe if LDL goals were not attained with simvastatin alone). Study subjects were randomized to extended-release niacin or placebo.

Although intended to conclude after 4.6 years, the study was stopped early (at 3 years) subsequent to the recommendation by the data and safety monitoring board that the trial be discontinued due to both a lack of positive efficacy as well as an unanticipated elevation of ischemic stroke in niacin recipients. Adding niacin to statins in persons with stable atherosclerotic vascular disease does not reduce CV events. ■

Adverse Effects on Semen from SSRI Treatment of Premature Ejaculation

Source: Koyuncu H, et al. *Int J Impot Res* 2011;23:257-261.

SEVERAL TREATMENTS HAVE BEEN SHOWN to be highly effective in management of premature ejaculation (pEJ), including behavioral therapy, systemic modulation of serotonin, and topical agents. The most popular current treatment is sustained use of selective serotonin reuptake inhibitors (SSRIs), which typically increase intravaginal latency (the time from intromission to ejaculation) from pretreatment times of < 1 minute to over 5 minutes. There has been little study of the impact of SSRI treatment on parameters such as semen, perhaps because most of the pEJ trials have been short-term. Studies in which SSRIs are added to semen preparations in vitro have shown adverse changes in sperm motility and viability, prompting consideration of potential adverse effects from systemically administered SSRIs.

Escitalopram is an SSRI sometimes used to treat pEJ. To elucidate the effects of escitalopram on semen, subjects with lifelong pEJ (n = 25) and normal baseline semen analysis were enrolled. Additionally, at baseline all subjects had normal scrotal ultrasound, CBC, glucose, hormone levels, lipid levels, and genito-rectal examinations.

At 1 month, no alterations in semen were detected. However, at 3 months there were multiple statistically significant changes: sperm count decreased (68 million/mL to 26 million/mL), number of motile spermatozoa decreased by more than 50%, and the number of morphologically normal sperm decreased by over 50%. In the absence of a control group, these findings cannot be considered definitive. Additionally, it is possible that sperm function might return to pretreatment levels upon drug discontinuation. However, the prominent effects on semen within a short interval merit our awareness. ■

Comparing Two High-Intensity Statin Regimens: Atorvastatin and Rosuvastatin

Source: Nicholls SJ, et al. *N Engl J Med* 2011;365:2078-2087.

Between statin head-to-head trials are uncommon. The PROVE-IT trial convincingly demonstrated that intensive LDL reduction with atorvastatin (achieved LDL = 62 mg/dL) vs pravastatin (achieved LDL = 95 mg/dL) improved outcomes in persons with acute coronary syndromes. In persons with stable atherosclerotic disease, however, it remains controversial whether high-dose statin treatment reduces mortality when compared with "standard" dosages, even though it has been shown to reduce CV events.

Results from clinical trials are sometimes hampered by the limitations of time: In a 5-year window of opportunity, are the long-term effects of intervention adequately represented? Such time limitations have prompted consideration of surrogate markers, which might more promptly reflect the anticipated long-term effects of intervention. Accordingly, Nicholls et al performed a controlled trial (n = 1039) to compare, by means of intravascular ultrasound, the effects of high-dose atorvastatin (80 mg/d) vs rosuvastatin (40 mg/d) on coronary atherosclerosis.

At 2 years, atheroma regression was similar between the two agents, despite the superior performance of rosuvastatin for attained LDL (62.6 mg/dL vs 70.2 mg/dL) and HDL (50.4 mg/dL vs 48.6 mg/dL). Maximal doses of these statins appear to perform similarly for the endpoint of regression of atherosclerosis. ■

The Effect of Adiposity on Insulin Pharmacodynamics

Source: Porcellati F, et al. *Diabetes Care* 2011;34:2521-2523.

It is probably not a surprise to clinicians that adiposity and efficacy of therapeutic insulins are related. We are accustomed to seeing type 2 diabetes (DM2) associated with being overweight and obesity, and watching control of diabetes become more difficult if obesity worsens. The question addressed by Porcellati et al is not whether insulin requirements are affected by obesity, but rather are various insulins differently affected by obesity.

To that end, DM2 subjects (n = 18) were studied using infusions of glucose to maintain constant plasma levels. Three different insulins — NPH, insulin glargine, and detemir — were compared. The threshold at which glucose infusion rates were meaningfully different was a body mass index (BMI) > 29 kg/m^2, at which point all three insulins demonstrated less efficacy to control glucose. That is, as BMI goes up, insulin sensitivity goes down.

Within this study group, however, there was a statistically significantly greater reduction in insulin sensitivity with detemir than with either NPH or insulin glargine. Ultimately, this means that in patients with progressively greater BMI, a higher dose of detemir may be required to achieve glucose control than the other two forms of basal insulin. Some clinical trials have also reflected this requirement for greater doses of detemir than comparators in patients with obesity. Nonetheless, because the amount of data addressing this issue remains small, whether there are meaningful differences that need to be considered when addressing insulin needs of obese DM2 patients in reference to choice of basal insulin is still considered a matter of controversy. ■

Psoriasis Predisposes to Serious Infections

Source: Wakkee M, et al. *J Am Acad Dermatol* 2011;65:1135-1144.

As the use of systemic immune-modulating treatments for rheumatoid arthritis (RA) has evolved, the risk for serious infectious disease complications related to their use has become more evident. Since many of the drugs used to treat RA are now used for patients with psoriasis (PSR), it is logical to evaluate PSR patients for risk of serious infectious diseases.

Wakkee et al looked at a database comprised of PSR patients (n = 25,742) and controls (n = 128,710) from a Dutch registry compiled from 1997-2008. They examined the incidence of infectious disease events resulting in hospitalization during this interval.

Overall, persons with PSR were more than twice as likely to be hospitalized for a serious infectious disease than controls; multivariate analysis (adjustment for confounding issues like age, diabetes, COPD) modified this hazard ratio slightly (down from 2.08 to 1.54).

Perhaps the greatest surprise from this trial was that the use of systemic antipsoriatic medications was *not* associated with risk for infectious disease. Apparently then, it is PSR itself which imposes an increased risk of infectious diseases, not the immunosuppressive agents increasingly used to treat it. ■

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

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