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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

Abstract & Commentary

Eplerenone Use for Mild Symptomatic Heart Failure?

By Michael H. Crawford, MD

Sources: Zannad F, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Eng J Med.* 2011;364:11- 21; Armstrong PW. Aldosterone antagonists — last man standing? *N Eng J Med.* 2011;364: 79-80.

Mineralocorticoid receptor blockers have demonstrated improved survival in class III-IV heart-failure patients (spironolactone) and post-acute myocardial infarction patients with systolic dysfunction heart failure (eplerenone). This study was a placebo-controlled, randomized trial of eplerenone for patients with class II symptoms due to systolic heart failure. Eligibility criteria included age > 54 years, left ventricular ejection fraction (EF) < 30%, or 30%-35% with an ECG QRS duration > 130 m/sec, and adequate doses of standard heart-failure therapy (ACEI/ARB and beta blocker). Patients could be enrolled if they were six months from a hospital admission for cardiovascular reasons or had a BNP > 250 pg/mL. The eplerenone dose was titrated from 25 mg daily to 50 mg daily, if tolerated. Patients with a glomerular filtration rate (GFR) between 30-49 mL/min received 25 mg every other day to start. Dosage was adjusted to keep serum potassium < 5.0 mmol/L. The primary outcome endpoint was cardiac death or hospitalization for heart failure.

Results: From 278 centers in 29 countries, 2,737 patients were recruited. Baseline characteristics in the two randomized groups were well balanced. The trial was stopped early because of a statistically significant difference at 21 months of follow-up. The primary outcome endpoint was reached in 18% of

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Clinical Cardiology [ALERT]

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the eplerenone patients and 26% of the placebo patients (HR 0.63, 95%CI 0.54-0.74, $p < 0.001$). Similar results were seen in most prespecified subgroups, including ischemic etiology, EF > 30%, and diabetics. Secondary analyses were also significantly impacted by eplerenone, such as death from any cause (HR 0.76), hospitalization (HR 0.77), and hospitalization for heart failure (HR 0.58). The number needed to treat for the primary endpoint was 19, and for death, per year of follow-up, was 51. Discontinuation of study drug for adverse events was 14% with eplerenone and 16% with placebo (p = NS). Renal failure, hypotension, and gynecomastia were not statistically more frequent with eplerenone, but increases in serum creatinine and potassium were. The authors concluded that eplerenone therapy in patients with systolic heart failure, class II symptoms, and adequate doses of standard therapy reduced the risk of death and hospitalization.

■ COMMENTARY

There is a solid mechanistic basis for this trial. Aldosterone antagonists have at least three beneficial properties. First, they are diuretics that promote volume homeostasis, which will keep heart-failure patients out of the hospital. Second, they increase potassium and magnesium levels, which would have antiarrhythmic properties in heart-failure patients and reduce arrhythmic deaths. Third, animal studies have shown that aldosterone antagonists reduce myocardial fibrosis, which could reduce ventricular remodeling and improve left ventricular function. Also, two previous large randomized trials in systolic heart failure (RALES, EPHESUS) showed reduced mortality with aldosterone-blocking drugs. Thus, it is not surprising that some benefit would be shown in a less symptomatic population. What is surprising is the magnitude of the effect; a 37% reduction in death and hospitalization.

Don't expect these results at home! There are several unique features of this study that probably augmented the observed benefit. This was a sicker, higher-risk population than the class II symptoms would suggest. All the patients were > 55 years old. Most had previous admissions for heart failure and prior myocardial infarction. Many had diabetes, atrial fibrillation, and hypertension. Most had an EF < 30%; the mean EF was 26%, which was the same as in the RALES trial. This fact emphasizes the well-known disconnection between symptoms and EF. Thus, in many ways, this population was on the sicker end of class II patients.

One-quarter of the patients had a QRS duration of > 130 m/sec, and one-quarter had left bundle branch block (LBBB). The mean QRS for the group was 122 m/sec, yet few of the patients had ICDs or resynchronization devices implanted. In the United States, these therapies would be expected to be deployed in higher numbers, which would likely reduce the impact of aldosterone antagonist therapy on death and hospitalizations. Another problem is that the study was stopped early for prespecified criteria. This tends to inflate the benefits of whatever is being studied, and many experts think that this should rarely be done.

How should we apply this study to our practice? We could just add an aldosterone blocker to all symptomatic patients with systolic heart failure. This would significantly increase the complexity of patient management for many, since serum potassium has to be monitored frequently, as well as blood pressure and potential adverse events. A more selective approach would likely be more cost-effective. Obviously, patients with potassium levels > 5.0mmol/L and an estimated GFR < 30 mL/min should be excluded. If we follow the enrollment criteria for the trial, then only those > 55 years old, with EFs < 30%-35%, should be considered. Also, patients with LBBB or a QRS duration > 130 m/sec would be favored, especially

if they were not candidates for resynchronization therapy. The final issue is whether we have to use eplerenone, a branded product, or will spironolactone do? Common sense, and the previous studies would suggest, this is a class effect, about which we don't really know for sure. In addition, in men, painful gynecomastia can occur in about 10%. With eplerenone, in this trial, it was < 1% for both sexes, and rarely caused withdrawal of the study drug. Thus, if the patient could afford it, especially in men, I would use eplerenone. ■

Abstract & Commentary

Performing Cardioversion: Dabigatran Therapy vs. Warfarin

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: Nagarakanti R, et.al. Dabigatran versus warfarin in patients with atrial fibrillation: An analysis of patients undergoing cardioversion. *Circulation*. 2011;123:131-136.

The randomized evaluation of long-term anticoagulation Therapy (RE-LY) trial was a study that compared two doses of a new direct-thrombin inhibitor, dabigatran, to warfarin for stroke prevention in patients with atrial fibrillation. In this paper, the investigators report the experience with dabigatran and warfarin in patients in RE-LY who underwent cardioversion. In RE-LY, patients were randomized to one of two doses of dabigatran (110 mg or 150 mg bid; D110 and D150 groups) or warfarin. Data on cardioversions were collected during the trial. In this study, it was recommended that the assigned study drug (either dabigatran or warfarin) be continued during cardioversion. A pre-cardioversion transesophageal echo (TEE) was encouraged if the cardioversion was planned within the first 60 days after randomization. Decisions concerning additional antithrombotic agents, or the need for a TEE, were the responsibility of the patient's primary cardiologist. When a cardioversion took place, data were collected concerning pre- and post-procedure antithrombotic therapy, details of the anticoagulants used, and the method of cardioversion. TEE data, if available, were also collected. Stroke and systemic embolism and major bleeding episodes within 30 days of the cardioversion were the major outcome measures.

RE-LY enrolled 18,113 patients. During the course of the trial, 1,983 cardioversions were performed in 1,270 patients. There were 647,672, and 664 cardioversions in theD110, D150, and warfarin groups, respectively. Approximately 80% of the cardioversions were performed when the protocol's assigned study drug had been taken for at least three weeks before the cardioversion. Eighty-five to 95% of patients were continued on protocol-assigned study drugs before and after the cardioversion.

Transesophageal echocardiograms were performed before cardioversion more often in patients assigned to dabigatran than in those who received warfarin (25% vs. 13%). Among those who underwent TEE, there was no difference in the incidence of left atrial spontaneous contrast (21%, 27%, 32%) in the D110, D150 and warfarin groups, respectively, or left atrial appendage thrombus (1.8%, 1.2%, and 1.1%, respectively). Slightly more than 80% of all cardioversions were electrical, with the remainder being classified as pharmacologic. Eighty-eight percent of all cardioversions were successful, with normal sinus rhythm being restored.

The stroke and systemic embolic event rates within 30 days after cardioversion were low in all three groups (0.77%, 0.30%, and 0.60% in the

D110, D150 and warfarin groups, respectively). The stroke and systemic embolism rates were similar in patients with and without pre-procedure TEEs. Major bleeding was infrequent in all groups (1.7%, 0.6%, and 0.6% in the D110, D150 and the warfarin groups, respectively).

The authors conclude that the RE-LY trial shows that both dabigatran and warfarin, used according to the guidelines in the trial, are effective in reducing the expected incidence of stroke and systemic emboli after cardioversion in patients with atrial fibrillation.

■ **COMMENTARY**

Dabigatran is a new antithrombotic agent that has now been released in the United States. Dabigatran does not have many of the drug and food interactions that make treatment with warfarin so difficult. A single dose is used in patients with preserved renal function, and patients do not require INR monitoring. The RE-LY study enrolled over 18,000 patients and followed them for several years. As might be expected, during the course of the study, a significant number of cardioversions (over 1,900) were performed. This constitutes the largest cardioversion experience in a randomized trial that I am aware of. Although this was not a primary endpoint of the study, both doses of dabigatran seem to be as effective as warfarin in reducing the incidence of stroke and systemic embolism after cardioversion. The low incidence with all three agents suggests that there will never be a randomized trial comparing the effects of dabigatran and a standard warfarin regimen at the time of cardioversion. However, the results are such that physicians can proceed with cardioversions in patients receiving dabigatran as long as they are sure the patients have been compliant with therapy. ■

Abstract & Commentary

Five-year Follow-up of Atrial Fibrillation Ablation

By John P. DiMarco, MD, PhD

Source: Weerasooriya R, et al. Catheter ablation for atrial fibrillation: Are results maintained at 5 years of follow-up? *J Am Coll Cardiol*. 2011;57:160-166.

Most prior study results of catheter ablation for atrial fibrillation (AF) have had relatively short follow-up duration. In this paper, the group from the Hospital Cardiologique du Haut-Leveque in Bordeaux, France, reports their experience in 100 patients who underwent catheter ablation between January 2001 and April 2002 who were respectively followed for at least 5 years to determine long-term outcomes. Patients were excluded if they had prior AF ablation attempt, resided outside of France, had a history of atrial fibrillation for less than 6 months, or had less than one hour per week of atrial fibrillation on average. The authors' ablation protocol has been previously described. In general, radiofrequency ablation was performed using a trans-septal approach and an irrigated tip ablation catheter. All segmental pulmonary vein ostia were systematically isolated, and a cavo-tricuspid isthmus ablation lesion was placed in every patient. Linear left atrial ablation and mitral isthmus ablation lesions were used selectively in patients with persistent or longstanding, persistent atrial fibrillation. Follow-up was performed at one, three, six, and twelve months after the initial procedure, and then at annual intervals. Follow-up testing included 24-hour Holter monitoring, transthoracic echocardiography, and exercise stress testing. Patients with symptoms were encouraged to seek electrocardiographic documentation during the episode. Patients with documented recurrence were offered repeat ablation. Patients who had

documentation of atrial tachycardia or atrial flutter were considered ablation failures. Complete success was defined as the absence of symptoms or episodes of AF, atrial tachycardia, or atrial flutter of greater than > 30 seconds duration off antiarrhythmic agents.

The 100 patients in this report were selected from 552 patients who underwent catheter ablation at the author's institution during the entry period for this study. Most of the other patients were excluded because they had undergone a prior ablation (n = 256) or had inadequate histories of AF (132). The mean age in the study group was 56 years, and 86% were male. The types of atrial fibrillation were paroxysmal in 64%, persistent in 22%, and longstanding persistent in 14%. Only 36% had structural heart disease. The mean left ventricular ejection fraction was 70 ± 11%. Hypertension was present in 43 patients. The $CHADS_2$ score was 0 in 48 patients, 1 in 32 patients, and ≥ 2 in 20 patients. Patients had failed 3.5 ± 1.4 prior antiarrhythmic drugs, and 67% had unsuccessful trials of amiodarone.

In the 100 patients reported here, a total of 175 procedures were performed, with a mean number of 2 per patient. Forty-nine patients had a single procedure, 34 had 2 procedures, 13 had 3, and four had between 4 and 7 catheter ablation attempts. Recurrent AF was the major indication for a repeat procedure (60%), but other atrial tachyarrhythmias were seen in 40%. Actuarial arrhythmia-free survival rates after a single catheter ablation procedure were 39.8 ± 5.1%, 36.5 ± 5%, and 28.5 ± 4.7% at 1, 2, and 5 years, respectively. Recurrences were most frequent during the first six months. However, a late recurrence among patients who had maintained sinus rhythm for one year was observed in 28% of the patients. When all interventions were analyzed, the atrial arrhythmia-free survival rates following the last ablation procedure were 87.1% ± 3.5%, 81.4 ± 4.1% and 62.9 ± 5.4% at 1, 2, and 5 years, respectively. The most common causes for recurrent arrhythmias were either recovery of pulmonary vein conduction or gaps in linear lesions, but non-pulmonary vein foci and left atrial flutter were also noted. By multivariate analysis, predictors of recurrence were found to include valvular heart disease and history of a nonischemic dilated cardiomyopathy.

The authors conclude that although the long-term success of a single ablation procedure for AF is modest, a catheter-ablation strategy with repeat interventions, as necessary, provides acceptable long-term results in a high proportion of patients. They argue that long-term follow-up data should be openly discussed with the patients and factored into clinical decision making.

■ COMMENTARY

This paper provides important insights into the role of catheter ablation in the management of patients with AF. In patients with little or no associated heart disease, AF is primarily an electrophysiologic problem, and catheter ablation directed at the pulmonary veins, the most common source for AF, is likely to be successful. In these patients, the primary limitation to catheter ablation is the tendency for veins to reconnect. As underlying heart disease progresses, so does the atrial substrate, and catheter ablation becomes less successful. Now the appropriate comparison is not to an ablation procedure for Wolff-Parkinson-White syndrome, where ablation yields a lifelong cure, but rather to coronary interventions, which lessen symptoms, but may need to be repeated over time. The authors recognize this, and I agree with their recommendation that true long-term results should be discussed with patients so that their expectations are in line with actual results. Catheter ablation for most patients with AF represents intermediate-term palliation that may be very beneficial, but a need for repeat procedures should be expected to maintain long-term arrhythmia control. ■

Abstract & Commentary

Prosthetic Valve Thrombosis — Urgent Surgery or Thrombolysis?

By Andrew J. Boyle, MBBS, PhD

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

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

Source: Keulerrs S, et al. Comparison of thrombolysis versus surgery as a first line therapy for prosthetic heart valve thrombosis. *Am J Cardiol.* 2011;107:275-279.

Thrombosis of prosthetic heart valves is one of the most feared complications of heart-valve replacement. Thrombolysis and emergency surgery are two therapeutic options for prosthetic valve thrombosis (PVT), each receiving a class II recommendation in the AHA/ACC guidelines. However, there are little data comparing these two options. Accordingly, Keuleers and colleagues retrospectively evaluated their center's experience of patients presenting with PVT over 20 years.

They identified 31 patients with PVT causing valvular obstruction. In 30 patients, this involved a mechanical valve, in the other patient, it was a bioprosthesis. The treating physician made the choice for thrombolysis vs. surgery. Success of thrombolysis was defined as complete, partial, or failure, depending on the degree of clinical improvement and the resolution of the valve leaflet obstruction. The majority of cases involved the mitral valve (n = 17), eight involved the aortic valve, and six involved the tricuspid valve.

Most patients (90%) presented with dyspnea, 42% had NYHA class IV symptoms, 33% had hemodynamic compromise on admission, and 13% presented with systemic embolization. In the majority of patients (61%), symptoms started more than 1 week prior to presentation. Importantly, sub-therapeutic international normalized ratio (INR) was present in 15 of 31 patients (48%); in nine patients, a temporary cessation of anti-coagulation within 2 months had preceded the event.

Results: Thirteen patients were treated with thrombolysis; all received rtPA with unfractionated heparin. There was immediate clinical improvement in 92%; 62% showed complete resolution and 31% showed partial resolution of echocardiographic changes. The one patient who failed thrombolysis was referred for urgent surgery. However, complications were relatively common. Recurrent PVT was seen in four patients (31%) over the following 18 months. Furthermore, stroke occurred in one patient (8%), TIA in 8%, major hemorrhage requiring surgery in 8%, and peripheral emboli in 15%.

Eighteen patients underwent immediate surgery, with two peri-operative deaths (11%) and two recurrences of PVT (11%) over a median follow-up of 76 months. Surgical patients also experienced significant complications, including acquired ventricular septal defect (n = 1), sepsis and sternitis with ICU stay > 1 month (n = 2), the need for a permanent pacemaker (n = 1), and the need for repeat surgery (n = 1). The authors conclude that thrombolysis is an attractive first-line therapy for patients with PVT, with clinical outcomes comparing favorably with the standard surgical approach.

■ COMMENTARY

The morbidity and mortality from PVT are high, and clinicians must have a high index of suspicion for this condition. It is interesting to note that the majority of patients had symptoms for over 1 week prior to presentation, and many of these had documented sub-therapeutic INR values or interruption of anti-coagulant therapy. Patients with a prosthetic valve presenting with dyspnea, especially if anticoagulation has been sub-optimal, should be carefully evaluated for PVT.

Whereas surgery has been the traditional treatment for this condition, several series have now demonstrated that thrombolysis may be an effective alternative. However, it is important to note the high rate of complications with either option. This study is limited by its small sample size and retrospective observational nature; however, the results are congruent with other series. In the absence of randomized, controlled trial evidence to support one treatment over the other, the best option, when confronted with PVT, appears to be a careful evaluation

of the individual patient, with consideration of the risks of thrombolysis or surgery in that patient. ■

Abstract & Commentary

Anomalous Coronary Arteries from the Opposite Coronary Sinus: Similar Long-term Outcomes from Medical or Surgical Treatment

By Andrew J. Boyle, MBBS, PhD

Source: Krasuski RA, et al. Long-term outcome and impact of surgery on adults with coronary arteries originating from the opposite coronary cusp. *Circulation.* 2011;123:154-162.

Coronary artery anomalies are being recognized with increasing frequency due to the increased usage of computed tomography (CT) and magnetic resonance imaging (MRI) scans in patients with chest pain syndromes. Anomalous coronary arteries that arise from the opposite sinus (ACAOS), particularly those with an inter-arterial course (IAC) between the aorta and the pulmonary artery, have been associated with sudden cardiac death (SCD) in children, adolescents, and competitive athletes. Whether this association is also true in the general adult population is not known. Furthermore, the treatment of ACAOS with IAC has increasingly become surgical, yet the benefit of surgery in adult patients is not known. Thus, Krasuski and colleagues retrospectively evaluated over 200,000 cardiac catheterizations from the Cleveland Clinic between 1966 and 2007. They identified 301 adult patients with ACAOS, of whom 54 had IAC. They stratified the cohort on the basis of medical vs. surgical treatment, and on whether or not they had IAC. Long-term mortality was confirmed with the Social Security Death Index.

Results: The number of referrals for ACAOS is increasing exponentially. The rates of surgery for ACAOS are also increasing exponentially. Patients with ACAOS that had an IAC, compared to those who did not have an IAC, were younger (52 ± 13 vs. 59 ± 13 years; $p = 0.001$), presented with chest pain more commonly (82% vs. 62%; $p = 0.01$), had less extensive atherosclerosis ($p = 0.01$) despite similar coronary risk factors profiles, and were significantly more likely to undergo surgical intervention (52% versus 27%; $p < 0.001$). However, there was no difference in survival between those with and those without an IAC (median 9.2 vs. 9.3 years; $p = 0.45$).

Of the 54 patients with ACAOS and IAC, just over 50% (n = 28) underwent a surgical intervention. The surgical intervention included bypass of the anomalous vessel with the use of an arterial graft in 10 patients (with concurrent ligation of the native vessel in 1 case), bypass with the use of a saphenous venous graft in 10 patients (with concurrent ligation of the native vessel in 1 case), reimplantation in five patients, and surgical unroofing in three patients. There were no peri-operative deaths. Compared to medically managed patients, surgically managed patients had more extensive coronary atherosclerosis ($p = 0.03$) but were less likely to have diabetes mellitus (0% vs. 23%; $p = 0.01$) and were more likely to have had an abnormal stress test (94% vs. 46%; $p = 0.002$). Survival did not appear to differ after 10 years between patients treated surgically and those treated medically (92.9% vs. 92.3%; $p = 0.65$). The authors conclude that in patients with an anomalous coronary artery from the opposite sinus of Valsalva, surgical management appears to have been favored recently. Despite no peri-operative mortality, a positive impact on long-term survival was

not observed. The impact of surgery in older adults with anomalous coronary arteries arising from the opposite coronary sinus with IAC deserves further study.

■ COMMENTARY

The management of patients with ACAOS has been problematic because of the paucity of data in this area. The studies linking ACAOS with sudden cardiac death were small and usually involved younger competitive athletes. This interesting study utilizes a large dataset of adult patients undergoing cardiac catheterization and casts doubt on the need for surgery for ACAOS. The study has significant inclusion bias, because the patients were referred for coronary angiography and thus were likely to have been symptomatic, at least to some degree. This is especially true in the earlier decades of the study. Whether these results can be generalized to the asymptomatic patient who is diagnosed incidentally by non-invasive imaging for some other reason remains unknown. Although the median survival was short (around nine years) and there was low surgical mortality, surgery resulted in no demonstrable mortality benefit at 10 years. Further prospective studies are needed to confirm the most appropriate management strategy. ■

CME Questions

9. Cardioversion is safe when performed on:

a. dabigatran 100 mg/day.
b. dabigatran 150 mg/day.
c. adjusted warfarin.
d. All of the above

10. In all comers, 5-year freedom from atrial fibrillation after a single ablation procedure is:

a. 14%.
b. 29%.
c. 58%.
d. 84%.

11. Improved survival has been shown for which of the following treatments for anomalous coronary artery arising from the opposite cusp?

a. Medical therapy
b. Arterial graft or reimplantation
c. Saphenous vein graft
d. None of the above

12. Thrombolysis for thrombosed prosthetic valves showed immediate clinical benefit in:

a. 54%.
b. 67%.
c. 79%.
d. 92%.

13. Which of the following is a confirmed cardiac source of thrombotic stroke?

a. Left atrial appendage thrombus
b. Left atrial pouch
c. Patent foramen ovale
d. Atrial septal aneurysm

14. Aldosterone antagonists reduce death in systolic heart-failure patients in which of the following classes?

a. I
b. II
c. III-IV
d. B and C

Answers: 9. (d); 10. (b); 11. (d); 12. (d); 13. (a); 14. (d)

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.

[IN FUTURE ISSUES] Left Atrial Septal Pouch and Stroke

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.*
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Spironolactone may save the day with resistant hypertension

Source: Engbaek M, et al. The effect of low-dose spironolactone on resistant hypertension. *J Am Soc Hypertens* 2010;4: 290-294.

Although the definition of resistant hypertension (r-HTN) has some variation, in the United States it is most commonly defined as inability to achieve target blood pressure with optimized doses of three antihypertensive agents, including a diuretic. Depending upon the population studied, as many as 15%-18% of subjects entering clinical trials — who presumably receive some of the best care medicine has to offer — are ultimately determined to have r-HTN.

Spironolactone (SPIR) is an aldosterone antagonist with modest diuretic activity. It has been shown to be effective in reducing blood pressure independent of aldosterone status; that is, one does not have to be a "high aldosterone" subject to enjoy meaningful BP reduction.

Engbaek et al report on 344 r-HTN subjects (mean BP 169/88, while already on three other medication), who were treated with SPIR 25 mg or 50 mg QD. They found a prompt and sustained mean BP reduction with SPIR: a 17/7 mm Hg reduction at 1 month, 24/10 mm Hg reduction at 3 months, and 26/11 mm Hg reduction at 6 months, all of which were statistically significant. The two most predictable adverse effects of SPIR, hyperkalemia and gynecomastia, were infrequent: 4.1% and 5.2%, respectively. Other clinical trials corroborate the utility and tolerability of SPIR to manage r-HTN. Clinicians should be reassured that < 10% of participants discontinued SPIR secondary to adverse events. ■

Fish oils: Where's the beef?

Source: Kromhout D, et al. n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med* 2010;363: 2015-2026.

Observational data indicate that populations with high intake of fish oil have less cardiovascular disease (CVD) endpoints, spurring clinical trials to elucidate the relationship. A 2008 meta-analysis suggested that in persons with existing coronary heart disease (CHD), supplements of fish oils (n-3-fatty acids, e.g., eicosapentaenoic acid and docosahexaenoic acid) reduced CHD mortality by as much as 20%. This beneficial effect has been attributed to a reduced vulnerability to arrhythmia provided by fish oils; disappointingly, the inclusion of fish oil supplements in study subjects with implantable cardioverter-defibrillators did not confirm an anti-arrhythmic effect.

To clarify the potential role of fish oil supplementation for CHD patients, the Alpha Omega Trial enrolled men and women age 60-80 with a history of myocardial infarction (n = 4837). Study subjects were randomized to fish oil supplementation or placebo for 40 months.

Fish oil supplementation did not provide a statistically significant reduction in CVD events. Because many of the study subjects were receiving other interventions to reduce CVD risk (e.g., statins, antiplatelet agents, BP drugs), the authors posit that it is possible that these results, which are divergent from earlier trials, reflect the lesser available margin for improvement in persons already receiving other good tools for CVD risk reduction. ■

Gait speed and survival in older adults

Source: Studenski S, et al. Gait speed and survival in older adults. *JAMA* 2011;305:50-58.

The frailty of senior citizens is often portrayed on-stage by slow, stiff gait. This representation may be much more than theatre. Indeed, according to this pooled analysis of a very large data set (34,485 community-dwelling senior citizens), gait speed is linearly associated with mortality among persons age 65 years and older.

Gait speed in the studies was calculated by timing the study subjects while they walked distances varying from 2.4 to 6 meters by simply dividing the distance covered by elapsed time, recorded as meters/second. After obtaining baseline gait speed, study subjects were followed for 6-21 years.

For each 0.1 meter/second increase in baseline gait speed, there was a 12% higher rate of survival. This was independent of gender, BMI, smoking, blood pressure, or self-reported health.

Should clinicians wish to consider using gait speed as a health predictor, the method is simple: The patient is asked to walk over a predetermined distance with the instructions "Walk at your usual pace, as if you were walking down the street."

No particular encouragement or stimulus to promote intensification of effort is necessary. ■

Rifaximin for IBS without constipation

Source: Pimentel M, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med* 2011;364:22-32.

It has been recognized for more than a decade that most patients with IBS have abnormal lactulose hydrogen breath tests results, consistent with small bowel bacterial overgrowth. Neomycin treatment, which can re-establish bowel flora, has shown modest efficacy in IBS, but is limited by tolerability issues. Other systemic antibiotics have not provided consistent symptomatic improvement in IBS. A previous pilot trial of rifaximin found that 10 days of treatment provided symptomatic improvement as measured 10 weeks later.

The TARGET trials are two identical double-blind, placebo-controlled trials of subjects with IBS without constipation. Patients were randomly assigned to rifaximin 550 TID or placebo for 2 weeks. Symptoms were monitored for up to 10 weeks. The primary outcome was the proportion of individuals reporting adequate relief of global IBS symptoms. The main secondary outcome was relief of bloating. Additional outcomes included abdominal pain and stool consistency.

Rifaximin provided a statistically significant improvement in global symptoms, bloating, abdominal pain, and stool consistency. Consonant with a very favorable tolerability profile seen in prior clinical trials, the safety profile of rifaximin was similar to placebo in this report. It is anticipated that systemic effects of rifaximin will be rare, since only a miniscule proportion of administered drug enters the systemic circulation.

Short-term treatment with rifaximin can provide statistically significant improvements for patients with IBS without constipation. ■

Pre-exposure HIV prophylaxis for men who have sex with men

Source: Grant RM, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010;363:2587-2599.

Men who have sex with men (MSM) are a high-risk group for acquisition of HIV, but other than safe sex practices, there has been little encouraging information about chemoprophylaxis. Certainly clinicians have some degree of confidence in the efficacy of post-exposure HIV prophylaxis post-needle stick in the health care setting, but the only population in which pre-exposure prophylaxis has been studied utilized tenofovir vaginal gel in women in Africa, reporting a 39% reduction in HIV infection.

HIV-seronegative men (or transgender women) who have sex with men (n = 2499) were randomized to a combination antiretroviral treatment (emtricitabine and tenofovir) or placebo once daily. They were followed for up to 2.8 years (median 1.2 years).

During follow-up, all subjects were seen every 4 weeks, during which they were counseled on safe sex practices, sexually transmitted diseases (STDs), and STD risk reduction.

At the conclusion of the trial, 36 of 1224 pre-exposure prophylaxis patients sero-converted vs 64 of 1217 placebo subjects (a 44% reduction in HIV incidence). Tolerability of the active antiviral treatment was excellent. The risk reduction demonstrated in this trial seems all the more remarkable because the reduction in unsafe sex practices attributed to the repetitive sexual health education and counseling during the trial would tend to minimize benefits of the medication. ■

Treating venous thromboembolism with rivaroxaban

Source: The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499-2510.

The treatment of acute venous thromboembolism commonly is managed successfully with enoxaparin followed by intermediate to long-term prevention of recurrent thromboembolism with warfarin.

Despite a proven track record of efficacy, warfarin has limitations, including the need for ongoing monitoring, problematic interactions with medications and food, and risk of significant bleeding, which occurs in 1%-2% of patients using long-term warfarin.

Rivaroxaban is a direct factor X inhibitor administered orally once daily. It is effective both acutely (hence, it may be utilized instead of heparin during the acute phase of venous thromboembolism) and chronically. Because it does not have any interactions with food and does not require monitoring, it provides many fewer obstacles to successful patient management than warfarin or heparin-warfarin combinations.

The EINSTEIN Investigators reported on two trials: One compared rivaroxaban with enoxaparin + warfarin for acute venous thromboembolism (n = 3449), and the other compared rivaroxaban with placebo in subjects who had completed 6 months of warfarin treatment for DVT.

For acute venous thromboembolism, rivaroxaban was non-inferior to enoxaparin + warfarin. In the long-term trial, rivaroxaban was superior to placebo. Rivaroxaban appears to provide an attractive alternative treatment for venous thromboembolism. ■

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Escitalopram for Menopausal Hot Flashes

In this issue: Escitalopram for menopausal hot flashes, rifaximin for IBS without constipation, herpes zoster vaccination, antiepileptics drugs and fracture risk, and FDA Actions.

Escitalopram for hot flashes

Since the Women's Health Initiative was published in 2003, the use of hormone therapy for the treatment of postmenopausal hot flashes has dropped dramatically. Both selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) have been studied to relieve postmenopausal symptoms, but no agent has been conclusively shown to be effective. A new study suggests that escitalopram (Lexapro™) may offer some relief.

In a study recently published in the *Journal of the American Medical Association*, 205 menopausal women were randomized to 10-20 mg per day of escitalopram or matching placebo for 8 weeks. The primary outcome was the frequency and severity of hot flashes with the average hot flash frequency at nearly 10 per day at baseline. Escitalopram resulted in 1.41 fewer hot flashes per day compared to placebo ($P < 0.001$), although both the active drug group and placebo groups noted reductions. Escitalopram also reduced hot flash severity. There was no difference among women of different races, and the discontinuation rate was small. The authors concluded that escitalopram 10-20 mg per day compared with placebo resulted in fewer and less severe menopausal hot flashes at 8 weeks (*JAMA* 2011;305:267-274). Whether the same effect can be expected with racemic citalopram (Celexa™) is unknown. ■

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Rifaximin for IBS without constipation

Rifaximin, an oral, nonsystemic (poorly absorbed) broad-spectrum antibiotic, may help relieve symptoms of irritable bowel syndrome according to two identically designed studies published in the *New England Journal of Medicine*. A total of 1060 patients who had IBS without constipation were randomized to rifaximin 550 mg three times daily for 2 weeks or matching placebo. The primary endpoint was a proportion of patients with adequate relief of global IBS symptoms; the secondary endpoint was relief of bloating. Significantly more patients in the rifaximin group had adequate relief of IBS symptoms during the first 4 weeks of treatment (40.7% vs 31.7%; $P < 0.001$), as well as improvement in bloating (40.2% vs 30.3%; $P < 0.001$). The incidence of adverse events was similar in the two groups. The authors concluded that among patients who had IBS without constipation, treatment with rifaximin for 2 weeks provided significant relief of the IBS symptoms of bloating, abdominal pain, and loose or watery stools (*N Engl J Med* 2011;364:22-32).

An accompanying editorial points out that the benefit from rifaximin was sustained over 10 weeks after a short 2-week treatment course, but also points out that benefit of the drug was a mere 9%-12% improvement over placebo, barely clinically relevant. Still, for patients who have IBS without constipation who have not responded to other therapies, a single treatment

cycle could be tried (*N Engl J Med* 2011;364: 81-82). ■

Herpes zoster vaccination rates and incidence of shingles

The herpes zoster vaccine cuts the rate of shingles by 55% in the elderly population according to a new report in the *Journal of the American Medical Association*. Researchers at Kaiser Permanente in Southern California performed a retrospective cohort study of health plan members, 75,000 of whom were vaccinated against shingles (age 60 and older) and 225,000 age-matched controls who did not receive vaccine. The rate of herpes zoster was 6.4/1000 person-years in the vaccinated group and 13.0/1000 person-years in the unvaccinated group (hazard ratio, 0.45; 95% confidence interval, 0.42-0.48). Reduction in herpes zoster occurred in all age groups and among individuals with chronic disease. The rate of ophthalmic herpes zoster and hospitalizations for herpes zoster were also significantly reduced.

The authors of the study concluded that among immunocompetent community-dwelling adults age 60 and older, receipt of the herpes zoster vaccine was associated with a lower incidence of herpes zoster (*JAMA* 2011;305:160-166). The study is important because only 10% of those aged 60 and older received the shingles vaccine in 2009, whereas nearly one of three people in the United States will develop shingles in their lifetime. ■

Fracture risk with antiepileptic drugs

Most antiepileptic drugs (AEDs) are associated with an increased risk of nontraumatic fracture according to a retrospective match cohort study. Nearly 16,000 patients with a history of prior AED use (carphenazine, clonazepam, ethosuximide, felbamate, gabapentin, lamotrogine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, topiramate, valproic acid, or vigabatrin) were compared to up to three matched controls each. Rates of fractures of the wrist, hip, and vertebrae were measured between 1996 and 2004. A significant increase in fracture risk was found for most AEDs, with an adjusted odds ratio of 1.24 for clonazepam to 1.91 for phenytoin. The only AED not associated with increased fracture risk was valproic acid.

The authors concluded that most AEDs are associated with an increased risk of nontraumatic fractures in individuals age 50 or older. They suggested that the risk of fracture with newer AEDs needs to be determined, as well as the effect of bone protective medications in this population (*Arch Neurol* 2011;68:107-112). The mechanism of increased fracture risk in patients using AEDs is unknown, but may be related to accelerated vitamin D catabolism, calcium absorption, or an effect on osteoblasts. ■

FDA Actions

The FDA has approved vilazodone hydrochloride for the treatment of depression in adults. The drug is a selective serotonin reuptake inhibitor as well as a partial agonist of the 5HT 1a receptor. The drug was approved in dosages of 10 mg, 20 mg, and 40 mg for major depressive disorder or major depression. Vilazodone is touted as having fewer sexual side effects than other antidepressants. It carries the same boxed warning as other antidepressant regarding suicidal thinking and behavior in children, adolescents, and young adults. Vilazodone will be marketed by Clinical Data Inc. as Viibryd™.

The FDA is limiting the amount of acetaminophen in combination prescription pain medications. The new requirement limits the amount of acetaminophen to 325 mg in each tablet or capsule. Common medications that will be affected include codeine (acetaminophen with codeine), oxycodone (Percocet®), and hydrocodone (Vicodin®). Over-the-counter acetaminophen products are not affected. This action is being taken to limit acetaminophen-related liver failure. It is felt that lowering the amount of acetaminophen in these products will have minimal effect on efficacy for treating pain. The change will be phased in over 3 years.

The FDA has approved a new transmucosal form of fentanyl for the treatment of breakthrough pain for adults with cancer. The drug is indicated for the management of breakthrough pain in patients with cancer ages 18 and older, who use opiate pain medication around the clock. Breakthrough pain is defined as pain that comes on suddenly for short periods of time and is not alleviated by the patient's normal pain management plan. Patients must be opioid-tolerant to qualify for use with transmucosal fentanyl. The drug is available only through a Risk Evaluation and Mitigation Strategy (REMS) program, which is intended to minimize risk of misuse, abuse, addiction, and overdose. Fentanyl sublingual tablets are available as 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, and 800 mcg strengths. Fentanyl sublingual tablets are marketed by ProStrakan Inc. under the trade name Abstral®. ■