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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Bare-Metal or Everolimus-Eluting Stents in STEMI?

By Andrew J. Boyle, MBBS, PhD
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Dr. Boyle reports no financial relationships relevant to this field of study.

SOURCE: Sabate M, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet* 2012;380:1482-1490.

Drug-eluting stents (DES) reduce the rate of in-stent restenosis (ISR) compared to bare-metal stents (BMS). However, the first-generation DES had higher rates of late stent thrombosis than BMS, and this was more evident after primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI). However, second-generation DES show substantial benefit over their first-generation counterparts. A large recent meta-analysis of everolimus-eluting stents (EES) showed lower ISR and lower stent thrombosis than BMS. The effectiveness of EES had not been directly compared to BMS in patients presenting with STEMI. Therefore, Sabate and colleagues performed a randomized controlled trial of EES vs BMS in STEMI. Patients presenting within 48 hours of symptom onset who had ST-segment elevation or a new left bundle branch block were enrolled. Exclusion criteria were age younger than 18 years, pregnancy, patients with known intolerance to aspirin, clopidogrel, heparin, stainless steel, everolimus or contrast material, patients on chronic treatment with vitamin K antagonists, and STEMI secondary to stent thrombosis. They were randomized to receive either EES or BMS and the primary endpoint was a combination of all-cause death, myocardial infarction, or any

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Clinical Cardiology [ALERT]

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revascularization at 1 year.

A total of 1498 patients in three countries were randomly assigned to receive either an EES (n = 751) or a BMS (n = 747). They were prescribed loading doses of aspirin and clopidogrel and then maintenance doses of 100 mg and 75 mg daily, respectively. The baseline characteristics were similar between groups; mean age was 61 years, 83% were male, and 17% were diabetic. Primary PCI was performed within 12 hours of symptom onset in 85% while the others were rescue PCI, PCI after lysis, or late presenters (12-48 hours after symptom onset). Unfractionated heparin was used in 80% of cases, with few receiving bivalirudin or low molecular weight heparins. Glycoprotein IIb/IIIa inhibitors were used in 51%. The primary combined endpoint of all-cause death, any myocardial infarction, or any revascularization occurred in 11.9% and 14.2% of the EES and BMS groups, respectively (P = 0.19). There was no difference in the rate of death (3.5% in both groups; P = 1.0), myocardial infarction (1.3% vs 2.0%; P = 0.32), or total revascularization (8.0% vs 10.6%; P = 0.09). The EES group had lower rates of target lesion revascularization (2.1% vs 5.0%; P = 0.003) and target vessel revascularization (3.7% vs 6.8%; P = 0.0077) than the BMS group. In addition, the EES group had lower rates of definite (0.5% vs 1.9%; P = 0.018) and definite or probable stent thrombosis (0.9% vs 2.5%; P = 0.02). Bleeding rates were similar between groups. The authors conclude that the use of EES compared with BMS in the setting of STEMI did not lower the patient-oriented combined endpoint of death, MI, or revascularization. However, at the stent level, both rates of target lesion revascularization and stent thrombosis were reduced in recipients of EES.

■ COMMENTARY

Second-generation DES demonstrate clear benefits over first-generation DES and BMS. While the first-generation DES reduced ISR compared to BMS, there was a slightly higher risk of late stent thrombosis. Now, however, the second-generation EES show lower ISR and lower stent thrombosis. This is a win-win situation. This study is important because it extends the benefits of EES from the stable coronary artery disease and non-ST-elevation acute coronary syndrome populations to now also include the population of patients presenting with STEMI.

This is a large, randomized, controlled trial and the conclusions are strengthened by the rigorous trial design. However, a few methodological considerations warrant mention when interpreting these data. First, this was a single-blind study. The patients and the clinical events committee were blinded to the treatment allocation, but the operators could not be blinded. Second, 13% of BMS-treated patients and 16% of EES-treated patients had staged PCI for other non-culprit lesions. During the staged procedure, one-third of BMS patients crossed over and had EES implanted; none of the EES patients crossed over to BMS. This may have altered the outcome in favor of those BMS patients who crossed over. Third, follow-up is only for 1 year. Longer-term follow-up is needed to definitively exclude late complications. The precise mechanism by which second-generation DES result in significant clinical benefit over previous generations is not clear. It may relate to the thin strut cobalt-chromium design of the stent platform. Alternatively, it may relate to the second-generation polymer or to the eluted drug (everolimus). It may be a combination of all three factors. Regardless of the reason, this stent performs better than its predecessors and is now considered the standard against which other technologies should be judged. Both patients and payors will surely welcome a stent with a lower risk of stent thrombosis and lower need for repeat revascularization. ■

ABSTRACT & COMMENTARY

Renal Artery and Atrial Ablation for Resistant Hypertension and Atrial Fibrillation

By John P. DiMarco, MD, PhD
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Dr. DiMarco does research for Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

SOURCE: Pokushalov E, et al. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. *J Am Coll Cardiol* 2012;60:1163-1170.

This paper reports the early results from a "proof-of-concept" study looking at combined renal artery denervation and pulmonary vein isolation in hypertensive patients with atrial fibrillation. The authors randomized patients with drug refractory atrial fibrillation and drug-resistant hypertension to either standard pulmonary vein isolation or pulmonary vein isolation with renal artery denervation in a single procedure. Patients were screened with magnetic resonance imaging before the study. Patients with renal artery stenosis or dual renal arteries, advanced congestive heart failure, markedly enlarged left atria, prior atrial fibrillation ablation, or treatment with amiodarone were excluded. All patients underwent pulmonary vein isolation using standard techniques. Right atrial ablation lesions were also placed in patients with a history of typical atrial flutter. Renal artery denervation was performed during the same procedure. The aortorenal artery system was mapped using the same three-dimensional navigation system and catheter that had been used for the pulmonary vein isolation. Radiofrequency lesions were applied between the first distal main artery all the way back to the renal artery origin. Up to six lesions were performed within each renal artery. High-frequency stimulation before and after each radiofrequency delivery was used to assess response.

After the procedure, all patients had a 3-month blanking period during which they were treated with propafenone or flecainide. After that, antiarrhythmic drugs were discontinued. Weekly electrocardiograms were obtained for the first month and 24-hour Holter recordings were performed at 3, 6, 9, and 12 months after the procedure. Renal function at 6 months was assessed by magnetic resonance angiography and glomerular filtration measurement. The primary endpoint of the study was documentation of more than 30 seconds of atrial tachyarrhythmia after a single ablation procedure.

This preliminary study enrolled 27 patients, with 14 randomized to pulmonary vein isolation only and 13 randomized to the combined procedure. The mean age in both groups was 56 years and most patients were male. Complete disconnection of the pulmonary veins was successfully achieved in all 27 patients. All patients randomized to renal denervation had successful elimination of any hypertensive response to high-frequency stimulation during the procedure. Pulmonary vein isolation plus renal denervation took approximately 40 minutes longer than the standard procedure, with an additional mean increase of 8 minutes of fluoroscopy time. There were no procedure-related complications either during the procedure or detected at their 6-month follow-up imaging. The patients who had the combined procedure had a 31% 1-year recurrence rate in contrast to a 71% recurrence rate in the patients who underwent pulmonary vein isolation only. Four patients in the pulmonary vein isolation only group and two patients in the combined procedure group underwent a second procedure. Renal artery denervation resulted in improved blood pressure control with documented reduction in both systolic and diastolic blood pressures, and follow-up echocardiography left ventricular mass was also reduced.

The authors concluded that renal artery denervation added to pulmonary vein isolation helps suppress atrial fibrillation in patients with drug-resistant hypertension.

■ COMMENTARY

Patients with advanced, severe, drug-resistant hypertension often have atrial fibrillation. Pulmonary vein isolation procedures in these patients have had disappointing results, presumably because they have advanced electrical remodeling of the left atrium in the setting of the chronic hypertensive stress. Recently, renal artery denervation has been introduced as an alternative therapy in patients with drug-resistant

hypertension. This paper is the first to show that a combined procedure that treats both the triggers for atrial fibrillation and the hypertension which continues to alter the left atrial substrate may be an effective approach.

This is only a small group of patients and the recurrence rate even in the combined procedure group is still quite high. However, this is the first demonstration in a randomized trial that the combined procedure may be more effective and may offer these very resistant patients a better chance at returning to sinus rhythm. We can look forward to future, more definitive studies investigating this concept. ■

ABSTRACT & COMMENTARY

Left Atrial Appendage Exclusion Device for Protection From Thromboemboli

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

SOURCE: Bartus K, et al. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: Initial clinical experience. *J Am Coll Cardiol* 2012; Sept. 28. [Epub ahead of print.]

The left atrial appendage is thought to be the source of a large proportion of emboli in patients with nonvalvular atrial fibrillation. In this paper, Bartus and his colleagues describe an innovative new device that uses a combined transseptal-epicardial approach to ligate the left atrial appendage. The LARIAT system requires both epicardial and transseptal access. First, an epicardial puncture is made and an introducing sheath is inserted into the pericardium. A transseptal puncture is then made and a delivery catheter placed in the left atrial appendage. A wire with a magnet on the tip is placed in the left atrial appendage and used to attract and establish contact with a second magnet introduced into the epicardial space. A balloon is inflated in the left atrial appendage to define the ostium and then a suture is advanced via the pericardium over the wires that are joined by the magnets and over the balloon. Once satisfactorily positioned, the suture can be closed and the transseptal catheter removed. Finally, the suture is cut and the epicardial introducer system is removed. A pericardial drain is typically left in place for a short time. The entire procedure is guided by combined transesophageal echocardiograpy and fluoroscopy.

In this initial human report, the authors report on results in 89 patients enrolled between December 2009 and December 2010. All patients had nonvalvular atrial fibrillation and a $CHADS_2$ score ≥ 1. Patients with a history of pericarditis, cardiac surgery, recent embolic events or myocardial infarctions, and unfavorable chest anatomy were excluded. Prior to randomization, patients underwent a screening contrast CT scan, and patients with markedly enlarged or unusually oriented left atrial appendages were also excluded. After the procedure, patients underwent transesophageal echocardiography at 1 day, 30 days, 90 days, and 1 year post procedure to assess for complete closure. Warfarin was continued at the discretion of the patient's physician.

A total of 119 patients were screened for the procedure and 103 were thought to be eligible. On the day of the procedure, three patients were found to have adhesions and 11 patients were found to have mobile thrombi in the left atrial appendage and were excluded. Therefore, the final study group included 89 patients. Successful left atrial appendage closure was accomplished using the LARIAT system in 85 of these 89 patients (95.5%). Complete closure of the left atrial appendage was documented in all but two of these patients at follow-up. During the procedure, a single pericardial access was required in 68 of 85 patients, and in an additional 17 patients, a second pericardial access was required to obtain proper sheath orientation for delivery of the LARIAT snare. The mean time to connect the transseptal and the epicardial magnets was 1.4 ± 0.64 minutes. Transesophageal echo guidance resulted in proper position of the LARIAT snare and the ostium of the appendage in all patients. Mild chest pain was reported postoperatively by 20 of 85 patients. Only two of these, however, required treatment for pericarditis after removal

of the pigtail drain in the pericardium. One other patient developed a late pericardial effusion 2 weeks after the procedure. This was treated with pericardiocentesis and the patient recovered without further complications. During long-term follow-up, there was one sudden cardiac death and one hemorrhagic stroke. The latter patient was not on warfarin. At the 1-year follow-up, there were two additional adverse events. One patient with severe bradycardia who had refused pacemaker implantation died suddenly. One patient had a lacunar stroke.

The authors conclude that left atrial appendage occlusion with the LARIAT system provides a rapid and effective way for complete closure of the left atrial appendage. Further trials are required to see if this reliably prevents thromboembolic events in patients with atrial fibrillation.

■ COMMENTARY

Most studies have estimated that 85-90% of emboli in patients with nonvalvular atrial fibrillation arise in the left atrial appendage. Long-term oral anticoagulation has a high rate of minor and major bleeding, even with the newer oral anticoagulants. For this reason, a number of novel approaches for completely occluding the left atrial appendage are now being developed. Some recently designed surgical clips appear to be much more effective than older stapling or suture techniques, but require at least thoracoscopic access to the left chest. Several devices for occluding the left atrial appendage from a transseptal approach are undergoing trials and the Watchman device is fully released in some European countries. Endocardial devices, however, have barbs that are used to fix the device in position, but then can come loose and cause bleeding. The LARIAT system ligates the appendage from an epicardial approach and may prove safer. The preliminary data shown in this paper are quite impressive. However, we must note that one shouldn't conclude that this technique is superior or even non-inferior to oral anticoagulation until appropriate trials in which safety and stroke are the primary endpoints have been completed. The preliminary data presented here are very impressive and we can hope that the appropriate trials will soon be underway. ■

ABSTRACT & COMMENTARY

Long-Term Exercise Training in Heart Failure

By Michael H. Crawford, MD, Editor

SOURCES: Belardinelli R, et al. 10-year exercise training in chronic heart failure: A randomized controlled trial. *J Am Coll Cardiol* 2012;60:1521-1528. Whellan D. Long-term exercise training and adherence: It is not just exercise. *J Am Coll Cardiol* 2012;60:1529-1530.

Exercise training is associated with short-term improvements in functional capacity in heart failure patients, but its effect on mortality and heart failure readmissions have been mixed. Thus, these investigators from Italy and New York studied 135 stable heart failure patients who were divided into a supervised exercise training group (70% peak oxygen consumption, two times a week for 10 years) and a non-trained group. Inclusion criteria included left ventricular ejection fraction < 40% and the ability to exercise. The etiology of heart failure was ischemic in 80% and their average age was about 60 years at intake. Each patient underwent a formal re-evaluation with cardiopulmonary exercise testing every 12 months by observers blinded to the study groups. The primary outcomes were peak oxygen consumption, quality of life, mortality, heart failure exacerbation, and cardiac ischemic events. Any of the cardiovascular events ended the patients' participation in the study. Of the 135 enrolled, 123 completed the 10-year study (63 trained and 60 non-trained). Peak oxygen consumption was not different between the two groups at intake, but increased in the training group by 15% and decreased 2.5% in the non-trained group at 1 year. This difference persisted during the study and was mirrored by a slower resting heart rate in the training group. Ejection fraction was not different at intake between the two groups, but after 4 years was significantly higher in the training group (41% vs 34%, $P < 0.01$ at 5 years). Quality of life also improved significantly in the training group and was sustained for the duration. The safety of training was excellent. Clinical events were less common in the training group (12 vs 35; hazard ratio [HR] = 0.55, 95% confidence interval [CI], 0.26-0.72; $P < 0.0001$). Specifically, cardiac death was less common in the training group (4 vs 10; HR = 0.68, 95% CI 0.30-0.82; $P < 0.001$). Multivariate analysis showed that peak oxygen consumption and resting heart rate were the only independent

predictors of events. The authors concluded that moderate, supervised exercise training performed twice a week for 10 years conferred sustained improvement in exercise tolerance, quality of life, and left ventricular systolic performance in patients with heart failure due to systolic dysfunction. These improvements were associated with lower cardiac morbidity and mortality rates.

■ COMMENTARY

The results of this study are remarkable and very different from the recently reported Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial, which showed no reduction in cardiac mortality with exercise training, despite a small but significant increase in peak oxygen consumption in the training group.[1] There are several differences between the two studies that may explain the results. First, this trial involved exercise training sessions supervised by a cardiologist, whereas HF-ACTION involved self-directed home-based exercise. Adherence to the program was 88% in this trial vs about 60% in HF-ACTION. Second, peak oxygen consumption increased 4% in HF-ACTION and 15% the first year in this study. Third, HF-Action was a 2.5 year study vs 10 years in this study. Some parameters, such as ejection fraction, took 5 years to improve in this study. Fourth, there may have been crossovers to supervised exercise training in HF-ACTION. Fifth, there were differences in medical and device therapy in the two studies. Beta-blocker use was 94% in HF-ACTION and 46% in this study. ICD use was 40% in HF-ACTION and 7% in this study. The authors focus on the supervision aspect as the key difference between the studies. The accompanying editorial suggests that the community aspects of the training sessions, which also included education, may have played a large role in the favorable outcomes.

Importantly, there is no way to be certain that the reduction in events was causally related to the exercise training. The study was underpowered for outcomes assessment; it was powered for changes in peak oxygen consumption. However, the only independent predictors of the outcomes were related to exercise training: peak oxygen consumption and resting heart rate. It is noteworthy that HF-ACTION had 2331 subjects vs 123 in this study. So perhaps the reduction in outcomes in this study was an alpha or type I statistical error, which is more common in small studies. Clearly, a larger trial would have to be done to confirm the outcome results.

Despite these weaknesses, this is a compelling study. Exercise training was safe and seemed highly effective. So why not adopt it? The feasibility and cost of such a program in the United States for almost all heart-failure patients would not be favorable under our current health care system. However, we can certainly refer most patients to cardiac rehabilitation programs and encourage them to continue these programs on their own if possible. Also, it may be worth encouraging community groups to continue this effort if health care agencies can't fund it. At a minimum, it uniformly improves exercise performance and quality of life. ■

Reference

1. O'Connor CM, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;301:1439-1450.

ABSTRACT & COMMENTARY

Multivitamins Do Not Prevent Cardiovascular Events

By Andrew J. Boyle, MBBS, PhD

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

SOURCE: Sesso HD, et al. Multivitamins in the prevention of cardiovascular disease in men: The Physicians' Health Study II randomized controlled trial. *JAMA* 2012;308:1751-1760.

Billions of dollars are spent annually in the United States on multivitamins in the hope they will improve health. The Physicians' Health Study II is a large, prospective, randomized, controlled trial that studied the effects of vitamins on the health of males aged 50 years or older. In a 2 × 2 × 2 × 2 factorial design, 14,641 men were randomized to multivitamins, vitamin E, vitamin C, and beta-carotene vs respective placebos. The authors have previously published that vitamins

E and C had no effect on cardiovascular disease (CVD) incidence or mortality. In this paper, they present the data on multivitamins and CVD.

The baseline characteristics were similar between multivitamin and placebo groups; mean age was 64 years, 42% had hypertension, 6% diabetes, 3.6% were smokers, and 77% were taking aspirin (probably because of participation in the Physicians' Health Study I, which studied aspirin and cardiovascular disease), 5% had pre-existing cardiovascular disease, and 9% had pre-existing cancer. The median follow-up was 11 years. The rates of major cardiovascular events were 11.0 per 1000 person-years in the multivitamin group and 10.8 per 1000 person-years in the placebo group. Men taking a daily multivitamin experienced no benefit for the primary endpoint of major cardiovascular events (hazard ratio [HR] 1.01; $P = 0.91$). There was a similar lack of significant benefit for the secondary endpoints of total myocardial infarction [MI] (3.9 and 4.2 events per 1000 person-years for multivitamin and placebo, respectively; HR 0.93; $P = 0.39$) and total stroke (4.1 and 3.9 events per 1000 person-years; HR 1.06; $P = 0.48$) compared with men taking placebo. Secondary endpoint analyses showed no difference in the incidence of heart failure, angina, revascularization, or sub-types of stroke, although the authors did find a reduction in MI death (HR 0.61; $P = 0.048$). The effect of a daily multivitamin on total MI, total stroke, and other cardiovascular endpoints did not differ between men with and without baseline CVD. The authors conclude that among this population of U.S. male physicians, taking a daily multivitamin did not reduce major cardiovascular events, MI, stroke, and CVD mortality after more than a decade of treatment and follow-up.

■ COMMENTARY

This study is a very large, well-conducted study that is consistent with prior literature showing no benefit of multivitamin supplementation on cardiovascular outcomes. With high statistical power, they showed no impact on the incidence of any CVD, and they showed no difference in event rates in those with pre-existing CVD. The size and rigorous design strengthen the conclusions that can be drawn from this study. Placing these data in context with the literature, it appears that multivitamins do not affect the incidence of CVD in the populations studied. It should be noted, however, that this was a study of generally healthy physicians, and there was not likely to be any major dietary vitamin deficiencies. In addition, the population of this study was entirely male, so the results may not be generalizable to women or those with dietary deficiencies. At the end of the paper, the authors hint that there may be a reduction in risk of cancer with multivitamins, but these data will be presented in a subsequent manuscript. For now, there is no reason to recommend multivitamins for patients for primary or secondary prevention of CVD events. ■

ABSTRACT & COMMENTARY

NSAIDS Post Myocardial Infarction

By Michael H. Crawford, MD, Editor

SOURCE: Olsen AM, et al. Long term cardiovascular risk of nonsteroidal anti-inflammatory drug use according to time passed after first-time myocardial infarction: A nationwide cohort study. *Circulation* 2012;126:1955-1963.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) early after myocardial infarction (MI) has been shown to increase the risk of death or recurrent MI, but little is known about the long-term risks. Thus, this group from Denmark evaluated their national database and identified more than 99,000 patients who survived 30 days after discharge following their first MI. Of these patients, 44% filled at least one prescription for NSAIDs during a 5-year follow-up period between 1997 and 2009 when the study ended. All NSAIDs were only available by prescription, except ibuprofen. Ibuprofen was available from late 2001 on, but only in 200 mg doses with a maximum of 100 tablets. The primary outcomes were all-cause mortality and cardiac death or readmission for MI. The use of any NSAIDs was associated with an increased risk of death (HR 1.59, 95% CI, 1.49-1.69) after 1 year and HR 1.63 (CI, 1.52-1.74) after 5 years. Cardiac death or MI was also increased (HR 1.30, CI, 1.22-1.39) after 1 year and HR 1.41 (CI 1.28-1.53) after 5 years. Diclofenac exhibited the highest increase in mortality (HRs 2.07-2.73 over first 5 years). The authors concluded that the use of NSAIDs was associated with an increased risk of coronary events for more than 5 years after the first MI.

■ COMMENTARY

This population-wide observational study strongly

suggests that all NSAIDs should be avoided after MI because there is a persistent increase in coronary events even after 5 years. Although naproxen exhibited the least increase in events, it has a higher likelihood of causing gastrointestinal (GI) bleeding than celecoxib, and bleeding in post-MI patients is not safe. Of course, this study does not establish causation, but there are potential mechanisms that would make the assumption of causation biologically plausible.

This is one of several cardiovascular studies to come from epidemiologists in Denmark who are mining their national databases. Such studies have the strength of large numbers, but suffer from a lack of comprehensive clinical factors that can produce unmeasured confounders. However, they believe this is unlikely because their sensitivity analysis suggests that if such a factor was present in the population at a frequency of 20%, it would have to raise the risk of mortality by about four-fold to influence the results. In fact, they repeated their analysis after excluding patients with rheumatoid arthritis and it did not change the results.

It is highly unlikely that there will ever be a randomized, controlled trial on this issue. So at this point, all NSAIDs should be avoided if possible post MI. If they do need to be used, naproxen may be the best choice unless the patient is at high risk of GI bleeding. Also, the adverse effects of NSAIDs have been shown to be dose related, so the lowest dose for the shortest time should be used. Since most NSAIDs in the United States are available over the counter, physicians must instruct their post-MI patients about this issue. ■

CME Questions

1. Which of the following should be avoided in post-MI patients?
   a. Sex
   b. Exercise
   c. NSAIDs
   d. Coffee

2. Supervised regular exercise training in heart failure patients results in:
   a. lower mortality.
   b. better quality of life.
   c. fewer readmissions for heart failure.
   d. All of the above

3. In patients with resistant hypertension undergoing ablation therapy for atrial fibrillation, what will decrease atrial fibrillation recurrences?
   a. Renal artery denervation
   b. Renal artery atherectomy
   c. Steroids
   d. Hydralazine

4. The LARIAT device for reducing thromboemboli in atrial fibrillation does what to the left atrial appendage?
   a. Obliterates it
   b. Ligates it
   c. Clips it shut
   d. Removes it

5. In the Physicians' Health Study, which of the following reduces cardiac events?
   a. Vitamin C
   b. Vitamin E
   c. Multivitamins
   d. None of the above

6. Second-generation drug-eluting stents for STEMI reduced which events vs bare-metal stents?
   a. Target vessel revascularization
   b. Total revascularization
   c. Death
   d. MI

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.

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Beta-Blocker Use in Situations Other than Just Post-MI

Source: Bangalore S, et al. *JAMA* 2012; 308:1340-1349.

Current standard-of-care management of post-myocardial infarction (MI) patients includes long-term use of a beta-blocker, unless otherwise contraindicated. The length of the leash on this concept is not long, however, as prospective data confirming benefits of beta-blockers post-MI are limited to just a few years. Since clinicians have not been given concrete advice about when to *stop* beta-blockers, most patients are kept on beta-blockers indefinitely. Perhaps our indecisiveness is bolstered by anxieties related to the potential consequences of beta-blocker withdrawal in persons with known coronary artery disease (CAD).

In the absence of data from a randomized, prospective, long-term trial, observational data may provide some clues about the relative benefit (or lack thereof) of beta-blockers in at-risk populations. To that end, Bangalore et al report on the outcomes of three different at-risk populations from a CAD registry: post-MI patients (n = 14,043), CAD patients without history of MI (n = 12,012), and patients with CAD risk factors but no known CAD (n = 18,653). Study subjects were enrolled in 2003-2004, and followed for approximately 4 years.

Beta-blocker use was not associated with improved outcomes in *any* of the three subgroups, even the one group we take for granted that there will be beneficial effects: the post-MI group. In the 1990s, the term "cardioprotective" was sometimes used in reference to beta-blockers. Although this may be true for the few short years immediately after an MI where older clinical trials have found a benefit, whether such benefits persist, or extend to other at-risk groups, remains to be determined. ■

Long-Term Sexual and Psychological Adverse Effects of Finasteride

Source: Irwig MS. *J Clin Psychiatry* 2012;73:1220-1223.

Cutaneous dihydrotestosterone is etiologically involved in the development of male pattern baldness. Since finasteride blocks the conversion from testosterone to dihydrotestosterone, it is commonly used to treat the disorder. Systemic alpha-reductase inhibitors like finasteride are occasionally associated with sexual side effects, but only recently has there been the suggestion that finasteride-associated sexual side effects might persist beyond the time treatment is administered. Additionally, recent FDA labeling changes have added depression as a recognized adverse effect of finasteride treatment. Although mechanisms to explain persistent adverse sexual effects are unclear, some animal data suggest persistent diminution in penile relaxation and contraction subsequent to finasteride.

From a population of young men (mean age 31 years) with male pattern baldness (n = 91), Irwig compared men who reported sexual dysfunction for at least 3 months after finasteride cessation to men with male pattern baldness who had not used finasteride. Outcomes of interest were depression scores and suicidal thoughts.

Depression, depressive symptoms, and suicidal thoughts were all substantially more common in the former finasteride users than controls. For example, 75% of former users had a Beck Depression Inventory Score of at least 14 (confirming depression) as opposed to 10% of controls. It is important that clinicians recognize the potential for enduring adverse sexual and psychological symptoms associated with finasteride. ■

Novel CV Risk Markers: How Much Cluck for the Buck?

Source: The Emerging Risk Factors Collaboration. *N Engl J Med* 2012;367:14: 1310-1320.

The c-reactive protein (CRP) debate has no end in sight. While traditional risk stratification tools like the Framingham Risk Score remain well established to distinguish high- and low-risk groups, the intermediate-risk group is the population in which further refinement in risk score might be helpful. Tools like CRP and fibrinogen, when applied to persons of intermediate Framingham risk, might help identify a subgroup that merits consideration for interventions like statins.

The Emerging Risk Factors Collaboration analyzed data from prospective cohort studies (n = 246,669) that included persons free of CV disease at baseline in whom CRP, fibrinogen, and components of Framingham risk score were available. Among persons with an intermediate Framingham risk score (10-20% risk of CV event over the next 10 years), the ad-

dition of either CRP or fibrinogen to risk assessment would result in reclassification of approximately 5% from intermediate to high risk. Such risk status elevation would justify statin treatment. According to current outcomes data, statin intervention in this population would prevent one CV event for every 440 intermediate-risk persons screened. Results were similar for fibrinogen.

The results obtained are "modeled" results rather than actual outcomes. CRP and fibrinogen testing are readily available. Yet, the number needed to test for avoidance of one CV event — more than 400 — is substantial. The authors do not offer an opinion on the *propriety* of such an investigation as CRP or fibrinogen; rather, they simply provide a metric to help quantify how much cluck for the buck one might anticipate. ■

Antidepressants and Auto Accidents

Source: Orriols L, et al. *J Clin Psychiatry* 2012;73:1088-1094.

DRIVING SIMULATION TESTS PERFORMED with *healthy, non-depressed volunteers* indicate varying degrees of deleterious effect on driving skills with tricyclics (TCA) and mirtazapine, but less so with selective serotonin reuptake inhibitors (SSRIs) and venlafaxine. In direct contrast, but perhaps more pertinent to clinical medicine, trials of driving performance in *depressed patients* on antidepressants suggest better driving skills on SSRIs or mirtazapine than TCAs or venlafaxine. To gain more insight into the effects of antidepressant treatments on auto crashes, Orriols et al reviewed the database of accidents accrued by the French police force from 2005-2008 (n = 210,818).

Being on an antidepressant increased the odds ratio of being the at-fault driver by 34% compared with persons not on antidepressants. The immediate time period around initiation or change of treatment was particularly high risk. Subgroup analysis found the greatest risk among persons receiving serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine) and the least risk among TCA recipients (e.g., amitriptyline). Even though driving simulation tests suggest that depressed patients who are being treated perform better than untreated patients, clinicians must still exercise vigilance and should consider informing patients — especially upon initiation of or change in treatment — about driving risks. ■

A Different Kind of Fish Story

Source: Rizos EC, et al. *JAMA* 2012;308:1024-1033.

THE IDEA THAT OMEGA-3 POLYUNSATURATED fatty acids — a.k.a. fish oil — are beneficial stems from *some* positive randomized clinical trials. But the word "some" is limiting in the previous sentence, since some other trials do not report benefit. Rizos et al performed a systematic review and meta-analysis based on 28 studies (n = 68,680) in which adults were treated with omega-3 fatty acids for primary or secondary prevention of cardiovascular disease.

Studies were reported between 1999-2010, and averaged 2 years of follow-up, although some data went as long as 6.2 years. The majority of trials were secondary prevention trials, which — because they represent a higher risk group — might be anticipated to more readily demonstrate risk reduction.

Contrary to popular opinion, this meta-analysis was unable to confirm any positive effects of omega-3 fatty acids, whether the metric was all-cause mortality, cardiac death, sudden death, MI, or stroke. Most of the trials used combinations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), leaving open the possibility that an EPA or DHA individually might have produced different results. The authors conclude that their data support neither the routine inclusion of omega-3 fatty acids in clinical practice nor guideline recommendations that advocate their use. ■

Risk of Cancer in RA Patients Treated with Disease-Modifying Drugs

Source: Lopez-Olivo MA, et al. *JAMA* 2012;308:898-908.

IN THE EARLY YEARS OF TREATMENT EXPERIence with biologic response modifiers (BRMs) for rheumatoid arthritis (RA), concern was raised that the immune-modulating effects responsible for dramatic symptomatic improvement might also lead to increased risk for cancer. Indeed, based on excess cases of lymphoma reported in the Adverse Event Reporting System database among children and adolescents treated with BRMs, the FDA recommended a warning label for all TNF-inhibitors. Should we be worried about cancer risk in patients treated with BRMs?

Lopez-Olivo et al performed a data analysis on randomized, controlled trials (n = 63 trials) of BRM treatment in RA patients in which a BRM was compared with placebo or another traditional therapy such as methotrexate (n = 29,423). A wide variety of BRMs was included in the analysis (e.g., abatacept, adalimumab, anakinra).

This dataset was restricted to trials with at least 6 months' duration. No signal for increased risk of cancer was discerned. Although a trend for increased risk of lymphoma was found, the numbers did not achieve statistical significance. It is not possible to determine whether longer-term outcomes in relation to BRMs will be impacted by cancer risk, since this dataset is comprised of studies of 3 years' duration or less. Additionally, whether RA patients who have already suffered a cancer are at greater risk of recurrence subsequent to BRM treatment is unknown. The dramatic RA disease remission we have come to commonly see thanks to treatment with BRMs appears to be safe from an increased risk for cancer. ■

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Menopausal Hormone Therapy and the Risk for VTE, AD

In this issue: Menopausal hormone therapy and risk of VTE and AD; patients' understanding of chemotherapy benefits; and FDA actions.

Hormone therapy and VTE risk

The different drug formulations of menopausal hormone therapy (HT) may determine the risk of venous thromboembolism (VTE), according to a new study. It is known that combined estrogen-progesterone therapy has a higher risk of VTE than estrogen-only therapy, and oral therapy has a higher risk than transdermal therapy. Now, a follow-up study from the Million Women Study with more than 3.3 million patient-years of follow-up looks at the varying risks of different HT combinations. The risk of VTE was again found to be significantly higher for combination estrogen-progesterone therapy compared to estrogen-only therapy (relative risks [RR] = 2.07 [95% confidence intervals (CI) 1.86-2.31] vs 1.42 [1.21-1.66]). Transdermal estrogen-only therapy resulted in no excess risk for VTE (RR 0.82 [0.64-1.06]). Among users of combination estrogen-progesterone, the risk of VTE varied by progestin type with significantly greater risk for preparations containing medroxyprogesterone compared to other progestins (2.67 [2.25-3.16] vs 1.91 [1.69-2.17]; *P* heterogeneity = 0.0007). The risk of VTE was significantly higher (2 times the risk) in the first 2 years after starting combination HT than later years. Five-year risks for pulmonary embolism (PE), both fatal and nonfatal, were calculated as: 1 in 664 for never users of hormone therapy, 1 in 475 for current users of oral estrogen-only, 1 in 390 for users of estrogen-progesterone containing norethisterone/norgestrel, and 1 in 250 for users of estrogen-progestin therapy containing medroxyprogesterone. The authors conclude that VTE risk varies considerably by HT formulation and is greatest in users of oral estrogen-progesterone therapy containing medroxyprogesterone. One case of PE could be avoided for every 1295 current users of oral HT if estrogen-only rather than estrogen-progesterone was used. Among combined HT users, one PE in 700 women could be avoided by use of a progestin other than medroxyprogesterone (*J Thromb Haemost* published online Sept. 10, 2012. doi: 10.1111/j.1538-7836.2012.04919.x). These data follow on the Women's Health Initiative, which also showed a higher risk of breast cancer for combination hormone replacement therapy vs estrogen-only therapy, but this risk is offset by the risk of endometrial cancer in women with an intact uterus on unopposed estrogen. ■

Hormone therapy and AD risk

Does the timing of menopausal HT affect the risk of Alzheimer's disease (AD)? Several studies have suggested the timing of postmenopausal HT is critical, especially during the first 5 years after menopause when hormones appear to be somewhat neuroprotective. The Women's Health Initiative (WHI) study clearly showed that starting HT after age 65 had no effect on cognition and in fact may be harmful. Now a new study confirms that starting HT immediately after menopause may have neuroprotective benefits. In a follow-up from the Cache

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County study, 1768 women provided a detailed history on age at menopause and use of HT between 1995 and 2006. During this interval, 176 women developed AD. Women who used any type of HT within 5 years of menopause were at 30% less risk of AD (95% CI, 0.49-0.99), especially if they used it for 10 years or more. By contrast, woman who started HT 5 or more years after menopause did not have a decreased rate of AD. Confirming the WHI findings, rates of dementia were nearly doubled among those who began combination estrogen-progesterone compounds later in life. The authors conclude that the association of HT and the risk of AD may depend on the timing of use. HT appears to be beneficial during the critical window near menopause, but may be associated with an increased risk if initiated later in life. (*Neurology* 2012;79:1846-1852). An accompanying editorial suggests that AD and coronary heart disease share common risk factors. WHI data show that women assigned to HT close to menopause had a reduction in the risk of coronary heart disease, whereas women given HT later in life had increased risk. The same seems to be true for the risk of AD. Two soon-to-be published studies will provide evidence regarding hormone effects on cognition in younger postmenopausal women (*Neurology* 2012;79:1840-1841). The decision to initiate HT in postmenopausal women is generally based on severity of symptoms, risk of breast cancer, risk of venous thromboembolic disease, and other factors. Benefits on cognition and potential protection against AD may now need to be added to the equation. ■

Chemotherapy often misunderstood

Chemotherapy for metastatic lung or colon cancer may provide palliation and prolongation of life by weeks or months, but a new study shows that most patients with these diseases erroneously think that chemotherapy is curative. Researchers studied nearly 2000 patients in the Cancer Care Outcomes Research and Surveillance study who were alive 4 months after diagnosis of stage IV lung cancer or colorectal cancer. All patients received chemotherapy. Overall, 69% of patients with lung cancer and 81% of those with colorectal cancer did not report understanding that chemotherapy "was not at all likely to cure their cancer." This misunderstanding about the benefits of chemotherapy was more prevalent among nonwhite and Hispanic patients as compared to non-Hispanic white patients (odds ratio [OR] for Hispanic patients 2.82, 95% CI, 1.51-5.25; OR black patients 2.93, 95% CI, 1.80-4.78). Patients who rated communication with their physician favorably also had a higher OR (1.90; 95% CI, 1.33-2.72). Educational level, functional status, and the patient's role in decision making were not associated with inaccurate beliefs about chemotherapy. The authors conclude that "many patients receiving chemotherapy for incurable cancers may not understand that chemotherapy is unlikely to be curative." This misunderstanding suggests that patients "have not met the standard for true ongoing informed consent" and may not accept toxic treatment with no reasonable hope of cure. The data also suggest that patients rate their doctors as better communicators if they are more optimistic. The authors suggest that honest communication is "a marker of quality of care" but may cause lower patient ratings (*N Engl J Med* 2012;367:1616-1625). ■

FDA actions

The FDA has approved a new drug for the treatment of chronic myelogenous leukemia (CML). Omacetaxine mepesuccinate is a protein translation inhibitor that was originally identified in the 1970s as a potential treatment for CML as well as other hematologic conditions and even solid tumors. It was eventually dropped from development as the tyrosine kinase inhibitors (TKIs) became the mainstay of therapy. Emerging resistance to imatinib and other TKIs has led to renewed interest in the drug. It was recently approved for chronic, accelerated, or blast-phase Philadelphia-chromosome-positive CML that is resistant or in patients who are intolerant of other therapies including TKIs. Approval was based on a study of patients in chronic or accelerated-phase CML who had been treated with two or more TKIs. Omacetaxine is administered by subcutaneous injection. It is marketed by Teva Pharmaceuticals as Synribo. It joins Pfizer's bosutinib (Bosulif), which also was recently approved for the same indication.

The FDA has approved perampanel as adjunctive treatment for partial onset seizures in patients 12 years of age and older. The drug is the first in its class of noncompetitive AMPA receptor antagonists that are taken orally once daily. Approval was based on data from three Phase 3 studies of nearly 1500 patients with partial-onset seizures which found that perampanel, when used as an adjunctive therapy with other anti-seizure medications, significantly reduced seizure frequency. The drug comes with a boxed warning regarding serious neuropsychiatric events including agitation, aggression, anxiety, paranoia, euphoria, anger, and irritably. Perampanel is marketed by Eisai Inc. as Fycompa. ■