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Clinical Cardiology [ALERT]

Critical analysis of the latest clinical research in cardiovascular medicine

ABSTRACT & COMMENTARY

Colchicine in Acute Pericarditis

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

SOURCE: Imazio M, et al. A randomized trial of colchicine for acute pericarditis. *N Engl J Med* 2013;369:1522-1528.

Colchicine is indicated for treatment of recurrent pericarditis. However, its role in acute pericarditis is less clear. Previous observational series and single-center, open-label studies have suggested a benefit in acute pericarditis, but this remains to be proven. Accordingly, Imazio and colleagues performed a randomized, placebo-controlled, multicenter study of usual care (aspirin, ibuprofen, or glucocorticoids) plus either colchicine or placebo in patients with acute pericarditis.

Patients ≥ 18 years of age presenting with their first episode of acute pericarditis were enrolled. They were considered to have acute pericarditis if they had at least two of the following four clinical features: typical chest pain (pleuritic and relieved by sitting forward), typical ECG changes, pericardial friction rub, or pericardial effusion on echocardiography. Patients with idiopathic, viral, post-cardiac injury or connective tissue disease-associated pericarditis were included. Exclusion criteria included the presence of myopericarditis, tuberculous, neoplastic or purulent pericarditis, significant liver or kidney disease (creatinine > 2.5 mg/dL), blood dyscrasias, myopathy, pregnancy, lactation, and inflammatory bowel disease. Colchicine or placebo were administered for at least 3 months. The dose of colchicine was 0.5 mg twice daily, or 0.5 mg once daily for those under 70 kg and those with side effects on 0.5 mg twice daily. Usual care was either aspirin 800 mg or ibuprofen 600 mg every 8 hours. Glucocorticoids were reserved for patients intolerant of aspirin

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or ibuprofen, and were tapered over 2 weeks. All patients also received proton pump inhibitors. All patients were followed for at least 18 months, and the primary endpoint was recurrent or incessant pericarditis. Recurrent pericarditis was defined as resolution of acute pericarditis for at least 6 weeks followed by another episode. Incessant pericarditis was defined as ongoing symptoms or a repeat episode with less than 6 weeks symptoms-free. Secondary endpoints were symptom persistence at 72 hours, remission within 1 week, number of recurrences, time to first recurrence, pericarditis-related hospitalization, cardiac tamponade, and constrictive pericarditis.

A total of 240 patients were randomized to colchicine (n = 120) or placebo (n = 120). Baseline demographics were similar between groups. The average age was 52 years, 61% were male, and the vast majority were idiopathic/viral in etiology (77%). Pericardial effusion was present in two-thirds. Usual care consisted of aspirin in approximately 80%, ibuprofen in 15%, and glucocorticoids in 5%. Adherence to the study drug was closely monitored and exceeded 95% in both groups. The primary outcome of recurrent or incessant pericarditis occurred in 17% of the colchicine group and 38% of the placebo group (relative risk 0.56; $P < 0.001$). The number needed to treat (NNT) to prevent one case of recurrent or incessant pericarditis was 4. The results were similar whether patients were treated with aspirin or ibuprofen. Patients treated with colchicine, compared to placebo, had lower rates of symptom persistence at 72 hours (19% vs 40%; $P = 0.001$), pericarditis-related hospitalization (5% vs 14%; $P = 0.02$), and number of recurrences per patient (0.21 vs 0.52; $P = 0.001$). Colchicine improved the rate of remission at 1 week (85% vs 58%; $P < 0.001$) and time to first recurrence (25 weeks vs 18 weeks; $P < 0.001$). Adverse event rates and drug discontinuation rates did not differ between groups (12% vs 10% and 12% vs 8%, respectively). The authors conclude that in patients with acute pericarditis, colchicine added to conventional anti-inflammatory therapy significantly reduced the rate of recurrent or incessant pericarditis.

■ COMMENTARY

Colchicine is an old drug that has an established role in recurrent pericarditis. Recently, it has been shown to prevent pericarditis after cardiac surgery and now in the current study, it has gained a place as treatment for the first attack of acute pericarditis. The rigorous trial design strengthens the conclusions made from this dataset. The study was an investigator-initiated, randomized, placebo-controlled, multicenter trial with all events adjudicated by a blinded clinical events committee. Interestingly, the majority of patients took aspirin as the anti-inflammatory of choice, which may reflect regional practice variations. The study did not address which anti-inflammatory is the best, allowing ibuprofen or aspirin at the treating physician's discretion. The major limitations to the use of colchicine in clinical practice are nausea and diarrhea. Interestingly, in this study, there were no differences in the rates of gastrointestinal upset or drug discontinuation compared to placebo. The dose reduction in patients who develop side effects (rather than cessation) and the lower dose in smaller patients are important in maintaining patients on their therapeutic regimen. This is a low-cost, well-tolerated treatment that can improve symptoms and reduce hospitalizations for pericarditis. This will be a welcome addition to standard anti-inflammatories in patients with their first attack of acute pericarditis. ■

ABSTRACT & COMMENTARY

Is There a Benefit to Cardiac Resynchronization Therapy in Patients with a Narrow QRS and Echocardiographic Dyssychrony?

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Dr. Gerstenfeld does research for Biosense Webster, Medtronic, and Rhythmia Medical.

SOURCE: Ruschitzka F, et al and the EchoCRT Study Group. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med* 2013;369:1395-1405.

Cardiac resynchronization therapy (CRT) has been shown to reduce mortality and improve symptoms in patients with reduced ejection fraction and a wide QRS complex. However, QRS width is only an indirect measure of mechanical dyssynchrony. It has been hypothesized that patients with congestive heart failure and mechanical measures of dyssynchrony without a wide QRS would also benefit from resynchronization.

The EchoCRT study was a prospective, randomized, multicenter, clinical trial. The study enrolled patients ≥ 18 years of age with New York Heart Association (NYHA) Class III or IV heart failure, a left ventricular ejection fraction of ≤ 35%, QRS duration of < 130 msec, echocardiographic evidence of dyssynchrony, and a standard indication for a cardiac resynchronization implantable defibrillator (CRT-D). Dyssynchrony was measured by Doppler echocardiography and speckle tracking software. All enrolled patients underwent implantation of a CRT-D device with atrial, and right and left ventricular (LV) leads; those who had unsuccessful LV lead placement exited the study. Patients were then randomized to CRT-D pacing on or off (control) with customized programming in the CRT-on patients to maximize biventricular pacing. The primary endpoint was mortality or first heart failure hospitalization; a safety endpoint of freedom from complications at 6 months was also included. After enrolling 809 patients (405 to CRT-on and 404 to CRT-off), the study was terminated by the data and safety monitoring board for futility and possible harm. The mean follow-up time was 19.4 months. The mean QRS duration of randomized patients was 105 msec. The primary endpoint, death or worsening heart failure, was not significantly different between the CRT and control groups (28.7% vs 25.2%; hazard ratio [HR], 1.2; 95% confidence interval [CI], 0.92-1.47; $P = 0.15$). Mortality was actually higher in the CRT group compared to the control group (11.1% vs 6.4%; HR 1.81; 95% CI, 1.11-2.93; $P = 0.02$) with an excess of cardiovascular deaths (37 vs 17; $P = 0.004$). The hospitalization rate for worsening heart failure and change in NYHA class did not differ between groups. Freedom from complications overall was 89% at 6 months, with no significant difference between the CRT and control groups (12.5% vs 8.9%; $P = 0.11$). Inappropriate ICD shocks were more common in the CRT group compared to the control group (5% vs 1.7%; $P = 0.01$). The authors concluded that in patients with systolic heart failure and a QRS duration < 130 msec, CRT implantation did not reduce the primary endpoint of death or worsening heart failure, and may increase the mortality rate.

■ COMMENTARY

The improvements in heart failure symptoms and mortality in trials of patients with reduced ejection and wide QRS complexes undergoing CRT-D have made CRT-D an important part of the heart failure treatment armamentarium.[1] There are few options available for those patients who remain symptomatic after optimization of medical therapy, other than cardiac transplantation. This has led to the hope that other patients, namely those with narrow QRS but echocardiographic evidence of dyssynchrony, would benefit from CRT-D. The first randomized study of CRT-D in patients with heart failure and a narrow QRS[2] was negative and terminated early due to futility. A second study showed possible harm.[3] Now, EchoCRT shows not only lack of benefit, but actually an increase in mortality in patients with narrow QRS complexes undergoing CRT-D implantation. This should put to rest the question

of whether resynchronization has a role in patients with narrow QRS complexes. Clearly biventricular pacing cannot improve upon the native conduction system, and may actually cause harm through worsening interventricular dyssynchrony. In fact, one should consider that even those patients with only mild QRS widening of 120-130 msec may not benefit, particularly if an ideal pacing location is not present. In the recent MADI-CRT trial,[4] those who benefitted most had a classic LBBB and QRS duration ≥ 150 msec. While there is always a temptation to consider CRT-D in patients with QRS of 120-130 msec because there are few options available, the additional implant time and complication rate of adding two additional leads should not be underestimated. Simpler is often better. However, in patients with LBBB and QRS > 150 msec, CRT-D remains an important therapeutic option. ■

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ABSTRACT & COMMENTARY

Embolic Risk in Endocarditis

By Michael H. Crawford, MD, Editor

SOURCE: Hubert S, et al. Prediction of symptomatic embolism in infective endocarditis: Construction and validation of a risk calculator in a multicenter cohort. *J Am Coll Cardiol* 2013;62:1384-1392.

At the time infective endocarditis (IE) is diagnosed, an accurate predictor of the risk of embolic events would help guide the risk/benefit ratio of surgical intervention. Thus, these investigators from two regional centers in France reviewed cases of definite IE by the modified Duke criteria that did not have isolated electrophysiologic lead endocarditis or recurrent IE. Embolic events that occurred before diagnosis and the initiation of antibiotic therapy were noted, as well as supporting initial imaging data. The primary endpoint was symptomatic embolic events from the initiation of antibiotic therapy to surgery or 6 months of follow-up. Over the study period, 847 patients met inclusion criteria at the two centers, mean age was 62 years, and 72% were men. Streptococci and staphylococci organisms were causative in half the patients. Prosthetic valve IE occurred in one-fourth of the patients. Head CT scans were performed on admission in 97% and 493 patients had surgery within 30 days. The subjects were randomly divided into a development sample (n = 565) and a validation sample (n = 282). In the total population, 72 had emboli within 14 days and the central nervous system received half. After 6 months, 62% had undergone surgery and 20% had died. The 6-month embolic rate was 8.5% and was highest in the first 2 weeks. In the development group, age, diabetes, atrial fibrillation, previous embolism, vegetation length, and *Staphylococcus aureus* infection were predictive of emboli. A prediction model based on these variables performed well in the validation sample and can be programmed into a handheld device. The authors concluded that at the diagnosis of IE, a simple calculation of embolic risk can be accurately made that could be useful for therapeutic decisions.

■ COMMENTARY

Systemic emboli are common in IE and portend a poor prognosis. Prior studies have shown an association between emboli and vegetation size, staphylococcus infection, and prior embolization, which are characteristics of the infections. These factors highlight the importance of the early deployment of blood cultures and echocardiography in suspected IE. Prior emboli refers to the period before the diagnosis is made and antibiotics are started. The diagnosis of emboli could be made by clinical presentation in symptomatic patients (e.g., stroke) or by imaging in asymptomatic patients. The best imaging approach is not determined by this study, but the importance of prior emboli suggests that brain imaging should be done early to detect silent lesions. Several studies have used MRI for this purpose, but PET is promising and doesn't

require contrast. This study adds three patient characteristics that are also strongly associated with emboli: diabetes, atrial fibrillation, and age. These features are combined with the three infection features to provide a risk calculator that can be downloaded on a handheld device. The calculator can be accessed through the electronic version of the paper, in the appendix.

This study and others have shown that after antibiotic therapy is started, the risk of emboli decreases rapidly in the first 2 weeks and is unusual after 4 weeks. Surgical therapy has also been shown to reduce emboli and mortality in selected patients. If surgical therapy is to have an impact on emboli, it needs to be done early. Delays to sterilize the vegetation or other such unproven tactics put the high-risk patient at considerable risk of emboli. Delays that last longer than 2 weeks diminish the potential benefits of surgery for emboli prevention. Surgery beyond 2 weeks is usually done for hemodynamic reasons. In considering early surgery in IE, the potential benefit of surgery has to be balanced against the risk. Estimation of the former has been augmented by this study, because it better identifies the patient at high risk for emboli. Some of these factors used to predict emboli risk also predict surgical risk such as age, so the calculation of surgical risk is complicated in IE patients. If a patient is high risk for emboli and seems low risk for surgery, then early surgery makes sense.

This is a retrospective database study done at two tertiary care centers. Thus, there are referral and selection biases. The study only addresses the prediction of embolic risk by factors discernible early in the course of IE. It does not address the value of surgery, but this has been studied before and there are guidelines for deploying surgical therapy early to prevent emboli. The international guidelines specify prior emboli and vegetation length as factors favoring early surgery in IE patients. This paper adds four more factors to consider and recommends a combined risk score to help with the decision. ■

ABSTRACT & COMMENTARY

Are Eligible Patients in the Community Receiving ICDs?

Edward P. Gerstenfeld, MD

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SOURCE: Narayanan K, et al. Frequency and determinants of implantable cardioverter defibrillator deployment among primary prevention candidates with subsequent sudden cardiac arrest in the community. *Circulation* 2013;128:1733-1738.

Sudden death accounts for 50% of cardiovascular mortality, and implantation of implantable cardioverter defibrillators (ICD) may be underutilized. The Oregon Sudden Unexpected Death Study is a community-based, prospective study of sudden cardiac arrest (SCA). The study has tracked all SCA in the Portland area since 2003. In the current study, all SCA survivors ≥ 18 years of age who had an echocardiogram prior to cardiac arrest were included. The records were reviewed to determine who was eligible for an ICD prior to the cardiac arrest, and who had and did not have an ICD placed according to the time-period appropriate guidelines based on the MADIT-II[1] and SCD-HeFT[2] studies. Patients who had a secondary prevention ICD (i.e., for pre-existing ventricular tachycardia or fibrillation) in place before the SCA, with echocardiograms performed within 40 days of an acute coronary event, or with expected survival < 1 year were excluded.

There were a total of 2093 SCAs identified between 2003 and 2012, and of these, 488 patients had a prior qualifying echocardiogram. Of these, 144 (32.1%) had LVEF ≤ 35%, 127 (28.3%) had LVEF ≤ 30%, and 304 (67.9%) had LVEF > 35%. According to time-specific guideline criteria, there were 12 primary ICD implantations among the 92 eligible candidates (13%). In addition, there were three primary prevention ICDs implanted during 2003-2005 that did not meet MADIT II criteria, increasing the primary ICD implantation rate to 15 of 95 (15.8%). Those not receiving ICDs were older than those receiving ICDs (age 67.1 ± 13.6 vs 58.5 ± 14.8 years; $P = 0.05$); there were no ICD recipients among those aged ≥ 80 years, while 16 (20%) of the nonrecipients were ≥ 80 years ($P = 0.11$). There were no significant differences in sex, race, history of myocardial infarction, or revascularization before SCA between the ICD recipients and nonrecipients. All recipients and a

majority of the nonrecipients had a clinical history of heart failure. Ten (83.3%) and 61 (76.3%) of recipients and nonrecipients, respectively, were on diuretics for symptomatic heart failure. Among ICD nonrecipients, 13.8% had dementia, 12.5% were on chronic dialysis, 25% had peripheral vascular disease (PVD), and 11.3% had diabetes mellitus. The authors concluded that a community survey of sudden cardiac arrest victims showed that 20% were eligible for prophylactic ICD implantation, but only a small proportion of these had ICDs. These data suggest that further study of the barriers to primary prevention ICD implantation is warranted.

■ COMMENTARY

In this community-based study of cardiac arrest survivors, nearly one-third had a prior echocardiogram with an EF < 35%. Yet, only 15% had a primary prevention ICD implanted. The majority (> 2/3) of patients were on chronic heart failure therapy, including diuretics, suggesting clinical heart failure symptoms. The time between the qualifying echocardiogram and the cardiac arrest was on average > 2 years, suggesting that the reduced ejection fraction was not a recent diagnosis in these patients. Why was the utilization of ICDs so low in this population? Some of the nonrecipients were older (20% > age 80) and had comorbidities such as chronic dialysis (12.5%) or dementia (13.8%). I think most would agree that an elderly patient with dementia or on chronic dialysis would not benefit from an ICD. However, most studies have shown that the rate of appropriate ICD shocks is similar in the elderly to younger patients, and that age alone should not be an exclusion to ICD placement.[3] Many physicians in the community have become disillusioned with ICDs due to problems with lead failures, inappropriate shocks, and lack of perceived benefit. It is important to recall that in the SCD-HeFT trial,[2] the mortality benefit in primary prevention ICD recipients was 7% over 5 years — thus one would need to follow 100 patients with implanted ICDs for 5 years to see seven lives saved.

The current study certainly has limitations — we cannot appreciate the number of patients who received ICDs during this time period who may have benefitted, and the clinical scenario of each patient is difficult to determine. In general, I believe we have all learned that ICD placement is a careful decision that involves risks and benefits that need to be considered and discussed with each patient. However, we should remember that the mortality benefit with ICD placement is greater than many commonly prescribed medical therapies. The finding in this study that < 10% of SCA patients survived to hospital discharge is disconcerting. If nothing else, this study should serve as a wake-up call to remember to consider ICD placement in the appropriate patient with reduced ejection fraction. In the future, better risk stratification tools and predictors of SCA are sorely needed. ■

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ABSTRACT & COMMENTARY

Esmolol in Septic Shock

By Andrew J. Boyle, MBBS, PhD

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SOURCE: Morelli A, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: A randomized clinical trial. *JAMA* 2013;310:1683-1691.

Cardiac patients are prone to develop sepsis in the intensive care unit (ICU) setting. The physiological changes associated with septic shock, such as tachycardia and hypotension, may be particularly deleterious to cardiac patients. Therefore, knowledge of ways to ameliorate these physiological changes may benefit cardiologists. Morelli and colleagues addressed the issue of whether beta-adrenoceptor blockade would be beneficial by reducing tachycardia or deleterious by reducing inotropy in patients with septic shock. They performed a single-center, randomized, open-label study of patients in ICU with septic shock, a heart rate > 95/min, and requiring high-

dose norepinephrine to maintain mean arterial blood pressure (MAP) > 65 mmHg. They excluded minors, those on beta-blocker therapy prior to randomization, patients with significant cardiac impairment (cardiac index < 2.2 L/min/m^2 and pulmonary capillary wedge pressure > 18 mmHg) or valve disease and pregnant women. All patients had a pulmonary artery catheter and arterial line, and received fluid resuscitation to achieve a right atrial pressure ≥ 8 mmHg. Patients were randomized to a continuous infusion of esmolol, titrated to heart rate 80-94/min for the duration of ICU stay, vs usual care. The primary endpoint was attaining heart rate 80-94/min. Secondary endpoints included hemodynamic parameters and 28-day survival.

A total of 154 patients were randomized to receive esmolol infusion (n = 77) vs usual care (n = 77). Baseline demographics were similar between groups; the mean age was 68 years and 54% were male. Pneumonia was the most common source of sepsis. There was a wide spectrum of bacteria isolated as the causative organisms, with *Klebsiella* being the most common and *Staphylococcus aureus* being isolated in 8%. The target heart rate was achieved in 100% of patients receiving esmolol with a mean reduction of 18 beats/min (P < 0.001 vs usual care). Patients receiving esmolol showed improved hemodynamic parameters compared to usual care, including significant improvements in stroke volume, systemic vascular resistance, and left ventricular stroke work index. Fluid requirements were lower in the esmolol group (3.98 L/d vs 4.43 L/d; P < 0.001) and norepinephrine requirements, which were equivalent at baseline, were also reduced. Renal function improved in the esmolol group, but not in the usual care group. Unadjusted mortality at 28 days was lower in the esmolol group (49.4% vs 80.5%; P < 0.001). Multivariable analysis showed that SAPS II score and esmolol were the only independent predictors of survival. The authors conclude that for patients in septic shock, open-label use of esmolol compared to usual care was associated with reductions in heart rates to target levels, without increased adverse events, and that the observed improvements in mortality and other secondary endpoints warrant further investigation.

■ COMMENTARY

Heart rate control in septic shock is controversial. Studying patients in the ICU is inherently difficult because of the heterogeneous nature of the diseases that caused them to be there, and also because of the myriad comorbidities that may confound their clinical course and treatment. Thus, randomizing patients to a particular treatment regimen is mandatory in such studies to exclude biases. In addition, the high acuity of such patients makes blinding of treatment difficult, and titrating to a heart rate goal makes a placebo problematic to deliver. The randomized, open-label design of this trial is therefore appropriate and the authors should be commended on completing such a study. However, the open-label design does allow for some confounding of the results.

Several aspects of this study should be highlighted. First, they excluded patients with significant cardiac impairment (cardiac index < 2.2 + wedge pressure > 18 mmHg) and patients on beta-blockers prior to randomization. Therefore, the results may not be generalizable to all cardiac patients. Second, the doses of esmolol used were modest, with the mean being 100 mg/hr, and the dose used did not predict mortality at 28 days. Third, the heart rate goal was arbitrarily chosen, and the optimal heart rate in patients with septic shock remains unknown.

How should one incorporate these data into clinical practice? It is reasonable in patients with septic shock, in whom tachycardia may be producing deleterious cardiac effects, to try low-dose esmolol to reduce the heart rate. There were no safety concerns raised by this study, and this may allow reduction in vasopressor doses. However, routine use of esmolol to reduce mortality based on the secondary endpoints of this study would be premature. ■

CME Instructions

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4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
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CME Questions

1. A recent study of esmolol in septic shock showed:
   a. increased mortality.
   b. increased stroke volume.
   c. worsening renal function.
   d. All of the above

2. Early colchicine therapy continued for 3 months in acute pericarditis patients:
   a. was poorly tolerated.
   b. increased subsequent hospitalizations.
   c. reduced recurrent attacks.
   d. All of the above

3. A new embolic risk calculation in infective endocarditis:
   a. focuses on echocardiographic findings.
   b. requires an admission head CT.
   c. excludes prosthetic valve patients.
   d. includes patient characteristics.

4. In a community survey, what proportion of patients eligible for a primary prevention ICD received one?
   a. 4%
   b. 9%
   c. 13%
   d. 20%

5. A trial of cardiac resynchronization therapy in systolic heart failure patients with QRS duration < 130 msec showed:
   a. fewer deaths.
   b. fewer rehospitalizations for heart failure.
   c. more device complications.
   d. more inappropriate shocks.

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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Goldilocks Unable to Find Amount of Antioxidants That's Just Right

Source: Bjelakovic G, et al. *JAMA* 2013; 310:1178-1179.

The observation that excess oxidative stress is associated with diverse pathologic consequence has been consistently coupled with the obvious next intellectual step: antioxidants *should* be beneficial to prevent these consequences. Unfortunately, no Goldilocks has stepped forward to inform us which antioxidant is too much, which is too little, and which is just right. Or maybe the antioxidant hypothesis is just a fairy tale, after all?

This is not the first time that observational hypotheses have disappointed. In two clinical trials of antioxidant supplementation in persons at risk for lung cancer (combined n > 45,000), the first trial found an *increase* in lung cancer and mortality, and the follow-up trial was discontinued almost 2 years early because of similar outcomes.

This most recent Cochrane systematic review included 78 trials (n = 296,707) performed in both primary and secondary prevention modes. The "bottom line" is worth quoting: "Antioxidant supplements are not associated with lower all-cause mortality. Beta carotene, vitamin E, and higher doses of vitamin A may be associated with *higher* all-cause mortality." Some naysayers would suggest that we have not yet fulfilled the Goldilocks systematic approach: Maybe we used too little, maybe we used too much, or maybe we used the wrong formulation, and have not yet found the approach that's "just right." For now, the science does not support a role for antioxidants in primary or secondary prevention. ■

Antipsychotics Are Associated with Increased VTE Risk

Source: Wu CS, et al. *J Clin Psychiatry* 2013;74:918-924.

Antipsychotics have suffered a beleaguered course of late: literature showing little efficacy advantage of newer vs older agents, concerns about increased mortality associated with their use, etc. A recent report suggests that antipsychotic treatment is also associated with a clinically meaningful increase in risk for venous thromboembolism (VTE), comprised of deep vein thrombosis plus pulmonary embolism.

Wu et al performed a case-control study of enrollees in the National Health Insurance Research Database of Taiwan to compare cases of confirmed VTE (n = 2162) with age-matched controls without VTE (n = 12,966). Initial analysis looked simply at the relative risk of antipsychotic use in persons with VTE vs controls. Second-step analysis adjusted for confounders.

Overall, the adjusted odds ratio for VTE in current antipsychotic users was 1.52 (i.e., current users were 52% more likely to experience VTE than controls); the odds ratio was substantially worse (3.26: a more than 3-fold increase in risk) for new users. These concerning results were attained even after correction for confounding factors such as utilization of thrombogenic medications (e.g., oral contraceptives) and medical comorbidities associated with increased VTE risk (e.g., congestive heart failure). Analysis of different classes of antipsychotics did not find any particular distinction among them. The mechanism by which antipsychotics might increase VTE risk is uncertain, although the authors posit that antipsychotic-induced sedation could lead to less physical activity with subsequent venous stasis. In any case, these data suggest vigilance for VTE in persons prescribed antipsychotics, especially in the early months of use. ■

Physician Visits for Itching

Source: Shive M, et al. *J Am Acad Dermatol* 2013;69:550-556.

If results from the National Ambulatory Medical Care Survey conducted by the CDC are correct, pruritus as a presenting complaint in ambulatory care may merit more of our attention. In a retrospective review of data from 1999-2009, there were approximately 7 million office visits per year in which pruritus (or itching) was indicated as a presenting symptom. In comparison, there were almost 18 million visits per year for low back pain. Since itch may or may not have been specifically indicated when syndromes such as a drug allergic reaction occur, the authors suggest that these numbers likely *underestimate* the true prevalence of pruritus.

The consequences of pruritus may range from minor nuisance to intolerable. Indeed, patients taking opioid analgesia frequently mention pruritus as a treatment-limiting adverse effect. Fortunately, clinicians have a diversity of agents to treat pruritus, including multiple generations of antihistamines as well as steroids (topical and systemic). Finally, it has been

recognized for more than 2 decades that doxepin — traditionally used as an antidepressant — has antihistaminic potency as much as 50 times greater than the most potent "traditional" antihistamines such as hydroxyzine. Because of this antihistaminic potency, doxepin is often used in refractory urticaria, when other antihistamines have failed, even though sedation is common at typical therapeutic doses. ■

Consequences of Non-Adherence in Treated Hypertensives

Source: Cummings DM, et al. *J Am Soc Hypertens* 2013;7:363-369.

The relationship between elevated blood pressure (BP) and stroke is linear and continuous. An abundance of clinical trial data indicate that treatment of hypertension (HTN) by means of numerous diverse classes of antihypertensives lowers stroke risk by ≥ 40%. Clinical trials, however, are not "real life." The Reasons for Geographic and Racial Disparities in Stroke (REGARDS) study is examining a large population (n = 30,239) of southeastern men and women with HTN. Their assessment of the relationship between self-reported degree of antihypertensive medication adherence and serious outcomes (stroke/TIA) from a subset population (n = 15,071) is quite sobering.

During a 5-year window of observation, study participants were grouped into four categories of adherence using the Morisky scale, which translates into general groupings of high, good, moderate, and low adherence. Perhaps not surprisingly, mean systolic BP in the high adherence group was substantially better than the low adherence group (131 mmHg vs 138 mmHg). Incidence of stroke or TIA was 8% higher in the lowest adherence group compared to the highest. Good BP control has meaningful payoff; every decrement of adherence less than that is costly. ■

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Long-Term Risk-Reduction Benefits of Sigmoidoscopy and Colonoscopy

Source: Nishihara R, et al. *N Engl J Med* 2013;369:1095-1105.

Participants from two large observational studies provide an opportunity to evaluate the risk reduction accrued from either colonoscopy (COL) or sigmoidoscopy (SIG). The Nurses' Health Study (n = 121,700 female nurses) and the Health Professionals Follow-up Study (n = 51,529 male health professionals) have more than 20 years' prospective follow-up of their participants. During this interval, there were 1185 cases of colon cancer and 474 deaths from colon cancer.

Skeptics have long held fast to the tenet that SIG had an advantage over COL: proven risk reduction for colon cancer mortality for the former. Although the intuitive additional advantage of examining the entire colon with COL seemed a no-brainer, purists argued that whether COL was truly better than SIG was not yet proven, and that since COL was associated with greater risks (perforation, adverse effects from sedation, etc.), there was reasonable basis to continue with SIG as a preferred method. In accord with this philosophy, noting the many missed opportunities for colon cancer screening and prevention, advocacy groups rallied around the call-to-action, "The best colon cancer screening test is whichever one you can get done!"

These data may change that perspective, since the risk reduction for colon cancer death was almost twice as great for COL as SIG (hazard ratios, 0.59 vs 0.32). The "no-brainer" part of the equation was also resoundingly confirmed: COL reduced mortality from proximal colon cancer by more than half compared to no risk reduction through SIG. ■

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Warfarin Outperforms Dabigatran in Patients with Mechanical Heart Valves

Source: Eikelboom JW, et al. *N Engl J Med* 2013;369:1206-1214.

The atrial fibrillation (AF) headlines have been filled with celebration over the efficacy of factor Xa inhibitors (e.g., rivaroxaban, apixaban) and direct thrombin inhibitors (e.g., dabigatran) for prevention of thrombotic events. Since warfarin — though highly effective, exhaustively studied, and time-tested — also has distinct clinical burdens (e.g., need for monitoring, food interactions, drug interactions), agents that were at least as efficacious for thrombotic risk reduction — with fewer of these same clinical burdens — were welcomed.

Success in AF, however, does not necessarily translate into other pathologies. Eikelboom et al studied patients with recent mitral or aortic mechanical valve replacement (n = 252). Subjects were randomized to dabigatran or warfarin. About one-fourth of these patients also had AF.

The trial had to be discontinued early because of untoward events in the dabigatran group: stroke occurred in 5% of the dabigatran group vs none in the warfarin group, and major bleeding was twice as common on dabigatran (4% vs 2%). Although earlier trials in animals were encouraging, these data indicate that warfarin is safer and better tolerated in patients with recent surgery for prosthetic mechanical heart valves. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Reglan Safe in Pregnant Women for Nausea and Vomiting

In this issue: Reglan safe in pregnancy; battle brewing over naming of biosimilar drugs; and FDA actions.

Reglan safe in pregnancy

Use of the anti-nausea medication metoclopramide (Reglan) in pregnancy is not associated with an increased risk of major congenital malformations, spontaneous abortion, or stillbirth. These were the findings of large, register-based cohort study from Denmark. The safety of metoclopramide in pregnancy has been of concern because it is increasingly used to treat pregnant women with nausea and vomiting. Metoclopramide-exposed pregnant women were matched with unexposed women in a 1:4 ratio, with more than 40,000 exposed women in the cohort, of whom more than 28,000 received the drug in the first trimester. The drug was not associated with major malformations or any of more than 20 individual malformations. There was no increase in spontaneous abortion, stillbirth, preterm birth, low birth weight, or fetal growth restriction (*JAMA* 2013; 310:1601-1611). ■

Battle over naming of biosimilar drugs

A battle is shaping up between biotech companies and the Generic Pharmaceutical Association (GPhA) over the naming of biosimilar drugs. Biosimilars, or "follow-on biologics," are products whose active ingredient is an approved version of a previously approved biopharmaceutical. Since biologics are generally manufactured in a complex process that may include molecular clones and proprietary cell lines, it is virtually impossible for the manufacturers of a biosimilar to match the process step-by-step. This results in small differences between the innovator product and the follow-on product (hence the name "biosimilar"). With billions of dollars of revenue at stake, biotech companies, such as Genentech and Amgen, have been lobbying federal and state legislators to tighten the rules regarding use of biosimilars. There has also been concern that the FDA might prohibit biosimilar manufacturers from using the same generic name as the original drug, a move that biotech companies would endorse and the GPhA would strongly oppose. A bipartisan group of senators recently entered the fray by penning a letter to the FDA urging the agency to allow biosimilars to share the name of the innovator product. Led by Republican John McCain and Democrats John Rockefeller and Tom Harkin, six senators urged the FDA to follow the intent of the Biologic Price Competition and Innovation Act, suggesting that if biosimilars were not allowed to share the same name it would undermine "the safety and accessibility of affordable biosimilars." The FDA had been in support of allowing biosimilars to share generic names, but the sudden removal of a page from the FDA website that contained a 2006 statement supporting same-name biosimilars prompted the concern of the senators. ■

FDA Actions

The FDA is recommending that hydrocodone-containing pain medications (Vicodin, Norco,

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Lortab, and others) be upgraded from schedule III to schedule II. The move would put significant restrictions on the drugs, including requiring a physician signature for each prescription, no refills, and no phone or fax prescriptions. Hydrocodone would join other powerful opioids including oxycodone, morphine, fentanyl, and methadone in the more restricted schedule II category. The FDA is reacting to the epidemic of prescription drug abuse and addiction that has decimated some communities in this country and has led to the overdose by tens of thousands, including teenagers and young adults. Prescription drug overdoses now outnumber illegal drug overdoses 3:1. The Drug Enforcement Agency has been pushing for stronger controls on hydrocodone for years, but physician and pharmacy organizations have successfully argued that the change unfairly impacts legitimate patients and would increase physician and pharmacy workloads. Hydrocodone/acetaminophen combination drugs were the most frequently prescribed medications in the United States last year. The change is likely to take effect by mid-2014.

Meanwhile, the FDA has approved an extended-release hydrocodone product for the management of severe pain requiring daily, around-the-clock treatment. The drug is an extended-release formulation of hydrocodone that is dosed twice a day. It is available in six strengths — 10, 15, 20, 30, 40, and 50 mg capsules. Because of concerns of addiction and abuse, and the greater risk of overdose and death associated with extended-release and long-acting formulations, hydrocodone extended-release should be reserved for patients in whom alternative treatment options are ineffective, not tolerated, or one otherwise provides inadequate pain management. The approval of hydrocodone extended-release was controversial given that the drug is not packaged as a tamper-proof capsule, theoretically allowing it to be crushed, chewed, or even injected. Experience with abuse of extended-release oxycodone (OxyContin) prompted the FDA to require Purdue Pharmaceuticals to reformulate the drug into a tamper-proof capsule in 2010. Some in the FDA felt this new formulation of hydrocodone should be similarly packaged, but the drug was approved without such restrictions. Hydrocodone extended-release will be schedule II, and marketed by Zogenix Inc. as Zohydro.

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The FDA has approved two new drugs to treat pulmonary arterial hypertension (PAH). Macitentan is a dual endothelin-receptor antagonist, while riociguat is a first in class soluble guanylate cyclase stimulator. Macitentan is a once-daily pill that is approved to treat PAH. Its safety and efficacy was established in a 2-year, randomized, placebo-controlled trial of 742 patients. Patients in the active treatment group had delayed progression of the disease and improved symptoms. Macitentan is manufactured by Actelion Pharmaceuticals and will be marketed as Opsumit. Riociguat is also an oral agent given three times a day. It is approved for PAH and also for chronic thromboembolic pulmonary hypertension (CTEPH), the first drug to be approved for this latter indication. Safety and efficacy for PAH was shown in a trial of 443 patients in which treated patients had improved 6-minute walk times after 12 weeks. It was shown to be effective for CTEPH in a study of 261 patients in which treated patients had improved walk times at 16 weeks. Riociguat is marketed as Adempas by Bayer HealthCare.

An FDA advisory group has recommended approval of simeprevir and sofosbuvir, two long-awaited agents to treat hepatitis C virus (HCV). Both are oral drugs and have higher cure rates compared with currently available agents. Simeprevir is a protease inhibitor, similar to currently available agents such as telaprevir and boceprevir, while sofosbuvir is a new type of hepatitis c antiviral called a nucleotide analogue (or "nuke"). Sofosbuvir has been highly anticipated as clinical trials suggest that it results in sustained virological responses as high as 90%, and may eventually be part of an all-oral regimen for HCV along with ribavirin. The FDA is expected to approve both drugs by mid-December. Simeprevir will be marketed by Johnson & Johnson while sofosbuvir will be marketed by Gilead Sciences. ■