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INSIDE

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How Helpful Are Coronary Artery Calcium Scores?

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationship to this field of study.

Synopsis: *The addition of CACS to a prediction model based upon the traditional risk factors significantly improved the classification of risk and helped to place more individuals in their appropriate risk categories.*

Source: Polonsky TS, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. *JAMA* 2010;303:1610-1616.

Large prospective studies have demonstrated that coronary artery calcium scores (CACS) measured by computed tomography are of significant value in risk prediction of future cardiovascular events.[1-4] In fact, a recent publication evaluated a cohort of individuals without known cardiovascular disease (CVD) and determined that a CACS > 300 was associated with a hazard ratio for future CVD events of nearly 10-fold,[4] and including CACS in a prediction model based on traditional risk factors significantly improved the overall ability to predict future CVD events.

Polonsky and his colleagues evaluated the extent to which adding CACS to a model based on traditional risk factors correctly reclassified participants in the Multi-Ethnic Study of Atherosclerosis (MESA)[4] in terms of risk of future CVD events. This population-based cohort of individuals without known CVD totaled 6814 participants who were classified into two models. Model 1 analyzed the standard risk factors including age, sex, tobacco use, systolic blood pressure, antihypertensive medication use, total and high-density lipoprotein cholesterol measurements, and race/ethnicity, whereas model 2 used these standard risk factors plus CACS. The CACS permitted the investigators to reclassify an additional 23% of those subjects who subsequently

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experienced cardiovascular events to the high-risk category and an additional 13% without events to the low-risk category based upon their history and their CACS. Therefore, the addition of CACS to the prediction model based on traditional risk factors significantly improved the classification of risk and helped in placing more individuals in their correct risk categories.

■ COMMENTARY

The results of the Polonsky study clearly demonstrated that a significant improvement in the classification of risk for the prediction of CVD events in an asymptomatic population sample of men and women drawn from multiethnic groups occurred when CACS were added to the standard risk profile. The benefit appears to be substantially higher in the intermediate Framingham risk group; therefore, adding CACS to the standard risk factor profile for asymptomatic individuals at intermediate Framingham risk appears to be quite valuable.[5] Because some concern has been raised about the safety and cost associated with the widespread use of CACS, some cardiologists have suggested that a CACS-guided strategy may actually cost more money and prevent fewer events than would occur by simply aggressively treating all patients at intermediate risk.[6] In addition, only 4 of more than 3000 low-risk individuals were reclassified to high-risk, suggesting that CACS may not be an efficient screening tool among low-risk individuals. However, the individuals who were reclassified from high risk to low risk experienced an event rate that was higher than predicted by the model using the CACS and, although the absolute number of events was small, the data support the recommendation that patients who are at high risk should be treated vigorously regardless of their CACS; therefore, they probably should be placed in a category of patients who need not undergo CACS testing for additional risk assessment. Finally, it should be recognized that besides improving cardiovascular risk assessment, the CACS plays an important role in the appropriate lipid management of patients in certain clinical subgroups in a cost-effective manner.[7] For example, in patients with the metabolic syndrome who do not qualify for statin therapy based strictly upon NCEP ATP III recommendations, application of CACS screening could significantly improve the approach to lipid-lowering therapy, thereby reducing the frequency of subsequent CVD events.

In summary, the use of CACS plus additional risk factors significantly enhances the ability to classify a multiethnic cohort of asymptomatic persons without known CVD into clinically accepted categories of risks for future CVD events. However, it is important to recognize that the overall value of CACS appears to be greater in the intermediate-risk patient group than it is in the low-risk and high-risk patient populations. Since the medical risk of CACS is so minimal, the results of this study provides encouragement for moving to the next stage of its evaluation, which obviously is in determining its value in predicting clinical outcomes. ■

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Please call **Paula Cousins**, Senior Managing Editor, at (404) 262-5488.

In Search of Safer NSAIDs: Which Cause the Least Risk of Upper GI Bleeding?

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

Clinical Professor, University of California, San Diego

Dr. Scherger reports no financial relationship to this field of study.

Synopsis: *A systematic review of 9 studies showed that the COX-2 inhibitor celecoxib and ibuprofen cause less upper GI bleeding than other NSAIDs. Diclofenac, meloxicam, ketoprofen, indomethacin, and naproxen have intermediate risk. Piroxicam and ketorolac have the highest risk. In general, drugs that have a long half-life or slow-release formulation have the greatest risk of GI bleeding.*

Source: Masso Gonzalez EL, et al. Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding. *Arthritis Rheum* 2010;62:1568-1570.

A STUDY GROUP FROM MADRID, SPAIN, CONDUCTED A SYSTEMATIC review of cohort and case-control studies to look at the relative risk of upper GI bleeding or perforation among available nonsteroidal anti-inflammatory drugs (NSAIDs). Nine studies between 2000 and 2008 with more than 50,000 patients were used in the analysis.

The relative risk (RR) overall for NSAIDs causing upper GI bleeding or perforation was 4.50 for traditional NSAIDs and 1.88 for COX-2 inhibitors. Looking at specific drugs in increasing risk order, the relative risk with celecoxib (Celebrex®) was 1.42, ibuprofen (Motrin® and others) 2.69, diclofenac (Voltaren®) 3.36, indomethacin (Indocin®) 4.15, ketoprofen (Orudis® or Oruvail®) 5.40, naproxen (Aleve® or Naprosyn®) 5.57, piroxicam (Feldene®) 9.94, and ketorolac (Toradol®) 14.54.

Among the traditional NSAIDs, the longer-acting formulations cause the greater risk overall. The risk is highest during the first 30 days of use (RR, 5.22) and lower after more than 1 year of treatment (RR, 2.90).

■ COMMENTARY

Not all NSAIDs are the same with respect to the risk for upper GI bleeding. This study, the largest to date, confirms the relative safety of the COX-2 inhibitors, with celecoxib being the only one available in the United States. There is still risk of bleeding, but much less than with traditional NSAIDs. I did not appreciate the greater than usual danger associated with the use of the IM medication ketorolac. I will be more mindful of this risk, especially with seniors.

Piroxicam probably should not be used unless a patient is doing well on it. I use a lot of naproxen and will reconsider that. Although in the intermediate risk category, it is riskier than most other NSAIDs. For short-term pain relief, ibuprofen remains a good choice. For long-term needs, the cost of celecoxib may well be worth it, especially in seniors who are more vulnerable to GI bleeding. Diclofenac looks like a good choice for chronic use of a traditional NSAID. A surprise for me in this study was the relative safety of indomethacin. I had always thought that this was a harsher medication on the stomach than other NSAIDs.

We want to always act in the best interest of our patients, and avoiding GI bleeding is of paramount importance when prescribing NSAIDs. I will keep these study results in mind and share them with patients when making treatment decisions for osteoarthritis and other conditions where NSAIDs are commonly used. ■

PO Is OK for COPD — Follow the Guidelines!

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips is a consultant for Cephalon, and serves on the speakers bureaus for Resmed and Respironics.

Synopsis: *There is no difference in rates of treatment failure, death, or readmission for COPD between patients treated with oral or intravenous steroids for exacerbation of COPD, but the IV route may be associated with increased cost and length of stay.*

Source: Lindenauer PK, et al. Association of corticosteroid dose and route of administration with risk of treatment failure in acute exacerbation of chronic obstructive pulmonary disease. *JAMA* 2010;303:2359-2367.

ALTHOUGH SYSTEMIC STEROIDS ARE WIDELY USED AND ACcepted as part of the routine treatment of COPD exacerbations, very little is known about the best route of administration or optimal dose in patients hospitalized for COPD exacerbations. The aim of this study was to compare the outcomes of patients treated with low doses of oral

steroids to those treated with higher doses of intravenous (IV) steroids. The study was carried out at 414 geographically diverse U.S. hospitals during 2006 and 2007. To be included in the study, patients had to be 40 years or older, have a principal diagnosis of COPD, or respiratory failure with acute exacerbation of COPD. They were excluded if they were admitted directly to the intensive care unit, had a secondary diagnosis of pneumonia or pulmonary embolism, were admitted for only 1 day, or were transferred to or from another acute care facility. In addition to patient age, sex, race/ethnicity, and insurance status, the authors were able to collect data about many other comorbidities and hospitalization history, as well as treatment during the hospitalization of interest for this study.

Patients were categorized in the high-dose IV therapy group if their first recorded dose of corticosteroids was given IV and was within a 120-800 mg/day range of the equivalent of prednisone. Patients were considered to be in the low-dose oral treatment group if they were initially treated with between 20 and 80 mg/day of prednisone by mouth. The main outcome variables were treatment failure (defined as requiring mechanical ventilation after the second hospital day), inpatient mortality, or readmission for acute exacerbation of COPD within 30 days of discharge. The authors also investigated length of stay and cost.

During the two years of study, 79,985 patients met criteria for inclusion in this analysis. A total of 73,765 (92%) were initially treated with IV steroids. There were no differences in outcomes according to route and dose of corticosteroid; 1.4% of the intravenously and 1.0% of the orally treated patients died during the hospitalization; 10.9% of the intravenously and 10.3% of the orally treated patients experienced at least one of the following: treatment failure, death during the hospitalization, or readmission for COPD within 30 days of discharge. Adjusting for confounders did not change these findings. The authors also undertook an analysis based on the likelihood of being treated with low-dose oral steroids; this model included such things as attending specialty, treatment patterns by hospital, and other treatments. In this propensity-matched analysis, the risk of treatment failure, length of stay, and cost were significantly lower among orally treated patients. When compared with those in the high-dose intravenous group, patients treated with low-dose oral steroids were marginally older, included a lower proportion of white patients, and were less likely to have private insurance. Patients treated with low doses of orally administered steroids also were sicker; they were more likely to have diabetes, heart failure, anemia, and renal failure. When compared with those initially treated intravenously, those who got low-dose oral steroids were less likely to receive early treatment with antibiotics, methylxanthine bronchodilators, to undergo arterial blood gas analysis, and to receive non-invasive ventilation in the first 2 hospital days. Treatment with low-dose orally administered steroids was more common in the Northeast, at larger hospitals, and those with teaching programs. A total of 1356 patients (22%) initially treated with low-dose oral steroids were later switched to intravenous therapy.

Other interesting characteristics of this group of patients were revealed by this analysis. Their median age was 69 years, 61% were women, 73% were white, and Medicare was the most common form of health insurance. Hypertension, diabetes, heart failure, and depression were the most frequently recorded comorbidities. Of these patients, 17% had one admission for COPD in the year before the index hospitalization, and 12% had two or more. Eighty percent were admitted directly from the emergency department, and the vast majority was cared for by general internists or family physicians. The median length of stay was 4 days, median costs were $5,021, and 30% were hospitalized for 6 days or longer.

■ COMMENTARY

COPD exacerbation is among the top 10 leading causes of hospitalization nationwide,[1] and the data here demonstrate that it is usually managed by generalists. Standard treatment includes supplemental oxygen, short-acting bronchodilators, systemic corticosteroids, and often antibiotics. Steroids have been found to improve lung function, to reduce the risk of treatment failure, and to decrease length of hospital stay for patients with COPD exacerbation,[2-4] but very little work has been done comparing the efficacy of different doses and routes of administration. Clinical guidelines produced by leading professional organizations actually recommend the use of low doses of steroids given by mouth,[5,6] and this study indicates that these recommendations are appropriate. Amazingly, however, this study also indicates that an overwhelming majority (more than 90%) of practitioners caring for patients with COPD exacerbation in the "real world" are ignoring these recommendations. As the authors of the current paper put it, "This practice does not appear to be associated with any measurable clinical benefit and at the same time exposes patients to the risks and inconvenience of an intravenous line, potentially unnecessarily high doses of steroids, greater hospital costs, and longer lengths of stay." ■

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Pharmacology Update

Denosumab Injection (Prolia™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationship to this field of study.

The first receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor has been approved for the treatment of osteoporosis. RANKL is a cytokine essential for the function of osteoclasts. Inhibiting RANKL inhibits osteoclast formation, function, and survival, thereby reducing bone turnover. Denosumab is a human IgG2 monoclonal antibody that binds to RANKL. It is marketed by Amgen as Prolia™.

Indications

Denosumab is approved for the treatment of postmenopausal women with osteoporosis at high risk for fractures.[1] These include patients with a history of fractures or multiple risk factors for fractures, or those who have failed or are intolerant to available therapy.[1]

Dosage

The recommended dose is 60 mg given subcutaneously every 6 months. The injection sites should be upper arm, upper thigh, or abdomen. Patients should take 1000 mg of calcium and at least 400 IU of vitamin D daily.[1]

Denosumab is available as a 60 mg single-use prefilled syringe or single-use vial.

Potential Advantages

Denosumab inhibits bone resorption by blocking the formation of osteoclasts. This is a different mechanism of action than other marketed medications for osteoporosis. The drug is administered every 6 months, which may improve compliance for some women.

Potential Disadvantages

Serious adverse events associated with denosumab include hypocalcemia (< 8.5 mg/dL; 1.7% vs 0.4% for placebo), serious infections (4.2% vs 3.5%), dermatologic events (10.8% vs 8.2%), and new malignances (4.8% vs 4.3%).[1] Osteonecrosis of the jaw has been reported with denosumab. RANKL is a member of the TNF family of cytokines; the inhibition of RANKL may increase the risk of serious infection.[1]

Comments

Denosumab is the first RANKL inhibitor to be approved. Binding RANKL prevents its binding to RANK on osteoclasts and their precursors. This inhibits the formation, function, and survival of osteoclasts and results in inhibition of bone resorption and increased bone mass.[1] The efficacy of denosumab was shown in a 3-year, randomized, double-blind, placebo-controlled study in women with a baseline lumbar spine or total hip BMD T-score between -2.5 and -4.0 (mean, -2.8).[1,2] Twenty-three percent had a vertebral fracture. Study subjects were randomized to placebo (n = 3906) or denosumab 60 mg (n = 3902) given once every 6 months. The primary endpoint was the incidence of new vertebral fractures at 3 years. Secondary endpoints were the incidences of hip and nonvertebral fractures. At 3 years, vertebral fractures were reduced by 68% (2.3% vs 7.2%). Hip fractures were reduced by 40% (0.7% vs 1.2%), and nonvertebral fractures by 20% (6.5% vs 8.0%). BMD increased by 8.8%, 6.4%, and 5.2% for lumbar spine, total hip, and femoral neck, respectively. There was no significant difference between the two groups in terms of adverse events or discontinuation of treatments.[2] There are currently no published comparative trials between denosumab and any bisophosphate in terms of reducing fractures. However, in a large study in postmenopausal women (n = 1189), denosumab (60 mg every 6 months) was compared to alendronate (70 mg weekly) with change in BMD as the endpoint. At 12 months, denosumab produced larger increases in BMD at the total hip (3.5% vs 2.6%, $P < 0.001$) as well as other skeletal sites (treatment difference of 0.6%-1%).[3]

Clinical Implications

Denosumab appears to be an effective agent for reducing the risk of fracture in postmenopausal women. The magnitude of fracture risk reduction is similar to that reported for once-yearly injections of zoledronic acid and at least numerically higher than that reported for oral bisphosphonates.[4-7] The long-term safety of denosumab remains to be determined. ■

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CME Questions

36. The use of CACS in the prediction of cardiovascular risk:
a. is of no value.
b. significantly improves cardiovascular risk prediction, especially in patients in the intermediate cardiovascular risk category.
c. is of great value especially in high cardiovascular risk patients.
d. is too dangerous and costly to ever consider using and offers no benefit over traditional risk factor evaluation.

37. For in-hospital treatment of COPD exacerbation, which of the following is *true* regarding efficacy of corticosteroids in terms of death, treatment failure, or readmission for COPD within 30 days?
a. Low-dose oral and high-dose IV steroids appear to be equally effective.
b. Low-dose oral corticosteroids are more effective than high-dose corticosteroids.
c. High-dose IV corticosteroids are more effective than low-dose oral corticosteroids.
d. Steroids are not indicated for this condition.

38. Which of the following NSAIDs has the *lowest* relative risk of upper GI bleeding?
a. Diclofenac
b. Ibuprofen
c. Naproxen
d. Indomethacin

Answers: 36. b, 37. a, 38. b.

CME Objectives

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

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
Dr. Kuritzky is a consultant for Abbott, AstraZeneca, Boehringer Ingelheim, Daiichi, Sankyo, Forest Pharmaceuticals, Lilly, Novo Nordisk, Takeda.

Fibrates: Generally safe, but do they improve outcomes?

Source: Jun M, et al. Effects of fibrates on cardiovascular outcomes: A systematic review and meta-analysis. *Lancet* 2010;375:1875-1884.

According to this meta-analysis, the answer to the question above very much depends upon which outcome you believe is important. Conclusions are derived from 18 trials (45,058 participants) between 1950 and 2010. Although the results of individual fibrate (i.e., gemfibrozil, fenofibrate) trials have been somewhat disappointing, the combined data look more encouraging.

For instance, in the pooled data there was a 10% relative risk reduction for major cardiovascular (CV) events, and an almost 20% relative risk reduction for nonfatal coronary events in trials of fibrate vs placebo. Surprisingly, despite these favorable effects upon CV endpoints, there was no statistically significant reduction in all-cause mortality, CV death, or cardiac death.

When compared with other interventions to reduce CV risk (e.g., BP reduction, statins, antiplatelet therapies), the degree of absolute risk reduction achieved through fibrate therapy is substantially less. As might be anticipated, in trials where subjects had a higher baseline triglyceride level, risk reduction was greater.

Most at-risk patients in the United States are already receiving statins. The ACCORD trial was the only large trial in which patients that were already being treated with a statin then received a fibrate; no additional benefit from the fibrate was discerned. Nonetheless, fibrates will continue to have a role in high-risk patients, and in patients with marked triglyceride elevation at risk for pancreatitis. ■

Glucosamine and low back pain

Source: Wilkens P, et al. Effect of glucosamine on pain-related disability in patients with chronic low back pain and degenerative lumbar osteoarthritis: A randomized controlled trial. *N Engl J Med* 2010;304:45-52.

The burden of suffering attributed to low back pain (LBP) is readily identified by all who practice primary care. Indeed, it is recognized as the largest single component of dollars expended on long-term disability in the United States. Unfortunately, there is little evidence that supports any currently available interventions to alter the natural history of LBP and restore functionality. Because glucosamine has shown promise in other forms of osteoarthritis, and because lumber osteoarthritis is commonplace in persons with LBP, a trial of glucosamine for patients with both disorders was intuitively appealing.

In this randomized, double-blind trial, subjects were randomized to either 1500 mg/day glucosamine sulfate or placebo for 6 months. Outcomes were assessed at 6 months (end of active therapy) and again 6 months later (after a 6-month hiatus in treatment).

The Roland Morris Disability Questionnaire is specifically designed to address functional status in persons suffering LBP. In addition to this metric, degree of pain reduction and quality of life were assessed.

Although glucosamine was well tolerated, it did not produce a statistically significant improvement at either the 6-month or 12-month follow-up. Unless there exists another indication for the use of glucosamine, clinicians remain without supportive data to employ it for LBP associated with lumbar osteoarthritis. ■

Effects of allopurinol upon exercise in patients with angina

Source: Noman A, et al. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: A randomised, placebo controlled crossover trial. *Lancet* 2010;375:2161-2167.

Allopurinol has been shown, in heart failure, to reduce myocardial oxygen demand. The mechanism by which this occurs is not certain, nor is it known whether such favorable effects occur in persons without heart failure. If, during exercise, an intervention could similarly reduce myocardial oxygen demand, it could prove useful in persons with angina.

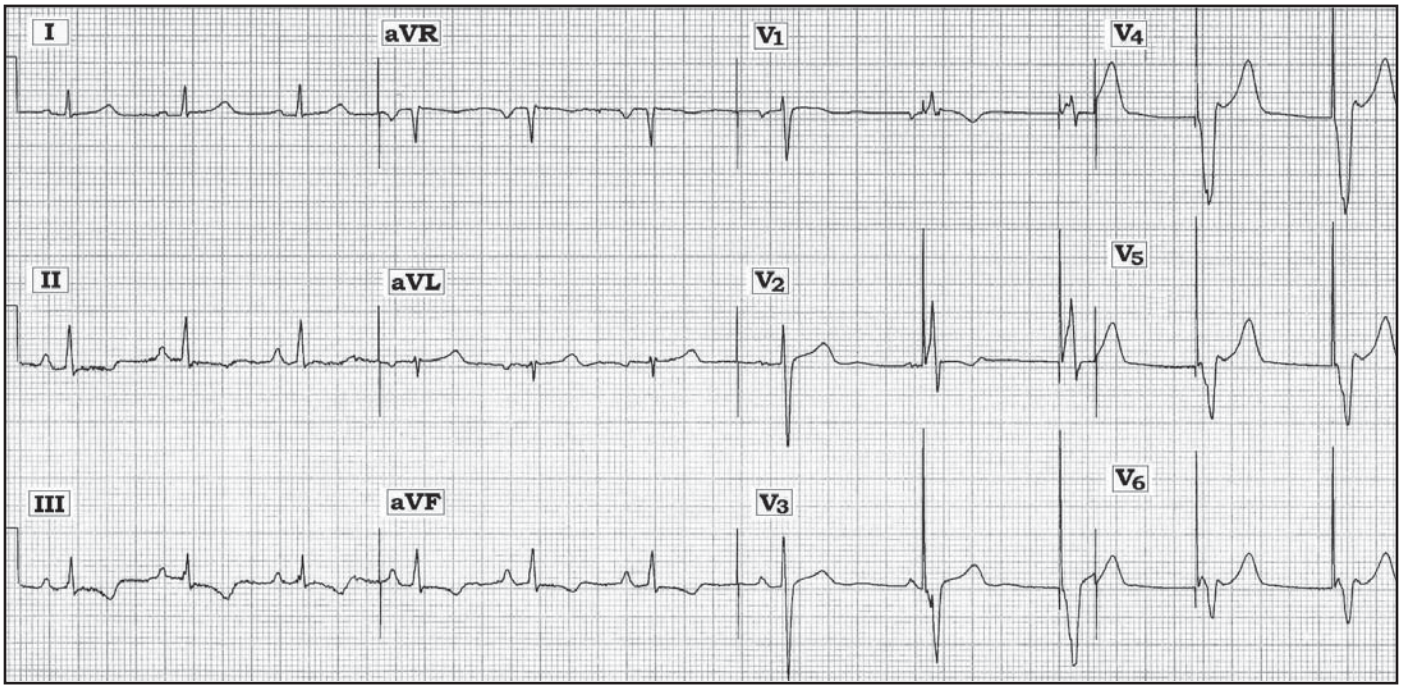
To address this question, the authors randomized subjects (n = 65) with chronic stable exercise-induced angina to high-dose allopurinol (600 mg/day) or placebo. Inclusion criteria required consistency of time to ischemia on baseline Bruce protocol exercise treadmill testing. Subjects received 600 mg/day allopurinol for 6 weeks (or placebo) and were then crossed over.

Allopurinol did produce a statistically significant increase in time to ST depression, as well as time to onset of chest pain, with no adverse effects. As a result, the authors suggest that there may be a role for allopurinol based upon cost, efficacy, and safety. Before embarking upon utilization of allopurinol for angina, clinicians must recognize that allopurinol is known to cause (rarely) a hypersensitivity vasculitis, which has a case fatality rate of approximately 25%. ■

Paced Abnormality?

By Ken Grauer, MD, *Professor, Department of Community Health and Family Medicine, University of Florida*

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.



Scenario: The ECG shown above was obtained from a 77-year-old woman with chest discomfort and a permanent pacemaker. Do you see any abnormality on this paced tracing?

Interpretation: A lot is seen on this 12-lead ECG obtained from an elderly woman with chest pain and a permanent pacemaker. Definitive interpretation is problematic in view of the lack of a lead II rhythm strip, unavailability of prior tracings for comparison, and minimal information about her clinical situation and the type of pacemaker she has, but valid concern should nevertheless be raised that something acute may be in progress. Four pacer spikes are seen on this ECG, all occurring at the end of the tracing. The pacemaker R-R interval is regular and measures 950 msec (corresponding to a paced rate of 65/min). Each pacer spike successfully captures the ventricles. In addition to effective capture function, we presume appropriate pacemaker sensing is present by the observation that the initial part of the tracing shows a spontaneous normal sinus rhythm at a slightly faster rate (of about 70/min, corresponding to an R-R interval of 840 msec). The sinus rate gradually slows after the sixth beat in the tracing. When it does, the pacemaker appropriately takes over. These events are best seen in lead V_3. The first QRS complex in this lead is a spontaneous sinus beat. The third (and last) complex in lead V_3 is paced. The middle complex in lead V_3 represents a fusion beat, with QRS morphology intermediate between that of the sinus-conducted first beat seen at the beginning of this lead, and the purely paced complex seen at the end. Fusion beats are common in pacemaker tracings, especially when the patient's underlying spontaneous rhythm is similar to the rate that the pacer is set at. The short PR interval preceding the middle beat in lead V_3 reflects partial conduction by the sinus P wave, which is then interrupted by the pacing spike that occurs at precisely the appropriate escape interval (i.e., 950 msec after the preceding spontaneous QRS complex). ECG changes of ischemia or infarction can only be assessed from spontaneous beats on a pacer tracing. Inferior ST-T wave depression seen here should therefore raise concern about a possible acute process in this elderly woman with chest pain. ■

In Future Issues:

Can We Diagnose Gout Without Needling Our Patients?

PHARMACOLOGY WATCH

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

Aggressive Modification of Cardiovascular Risk Factors

In this issue: Aggressive approach to CVD reduces MI, folic acid and vitamin B12 for CAD, corticosteroids for acute exacerbations of COPD, prescription drug abuse among young adults, and ARBs and cancer risk.

CVD decreases with aggressive treatment

Aggressive modification of cardiovascular risk factors seems to be paying dividends, at least for a large population of insured patients in Northern California. In an analysis of nearly 18.7 million patient-years between 1999 and 2008, the rate of myocardial infarction (MI) increased in 1999 and 2000 and then decreased significantly every year thereafter (287 cases/100,000 person-years in 2000, decreasing to 208 cases/100,000 person-years in 2008; 24% relative decrease over the study period). The rate of ST-segment elevation MI decreased over the study period (133 cases/100,000 person-years in 1999 to 50 cases/100,000 person-years in 2008; $P < 0.001$) and the 30-day mortality rate decreased from 1999 to 2008 as well (adjusted odds ratio, 0.76; 95% confidence interval, 0.65-0.89). This occurred despite more aggressive diagnosis of MI.

The authors conclude, "The lower incidence of myocardial infarction — particularly ST-segment elevation myocardial infarction — is probably explained, at least in part, by substantial improvements in primary-prevention efforts, …" including statins and aggressive blood pressure reduction, as well as use of cardioprotective medications such as aspirin (*N Engl J Med* 2010;362:2155-2165).

An accompanying editorial points out that while these trends are generally the case in the United States, there are significant geographic differences. "The risk among residents of Oklahoma, the lower Mississippi corridor, and Appalachia, for example, is double that among other Americans, … " suggesting socioeconomic factors play a role. Hypertension and diabetes rates have increased slightly over the last decade, while smoking rates have decreased. Perhaps even more importantly, statin use has increased significantly (among those between age 45 and 64 years, statin use in men increased from 2.5% to 16.8% and from 1.9% to 13.5% in women; among those 65 years of age or older, statin use increased from 1.9% to 38.9% in men and from 3.5% to 32.8% in women). Aspirin, beta-blockers, and ACEIs/ARBs have also contributed to the decline in cardiovascular mortality in the United States (*N Engl J Med* 2010;362:2150-2153). ■

Folic acid and vitamin B12 for CAD

Unfortunately, lowering homocysteine with folic acid and vitamin B12 does not seem to be a benefit to patients with coronary artery disease. In a study from the United Kingdom, more than 12,000 survivors of myocardial infarction were randomized to 2 mg folic acid plus 1 mg vitamin B12 daily vs matching placebo, with the main outcomes being first major vascular event such as coronary event, stroke, or noncoronary revascularization. Folate and vitamin B12 were effective at reducing homocysteine levels by 28%; however, there was no difference in the rate of major vascular events over the 6.7 years of follow-up (25.5% active treatment vs 24.8% placebo; $P = 0.28$). Individually, there was no effect on major coronary events, stroke, or noncoronary

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revascularizations, nor was there a survival benefit from active treatment. Interestingly, the authors also looked at incidence of cancer and found no difference in that outcome either. The authors conclude that long-term reductions in blood homocysteine levels with folic acid and vitamin B12 do not have a beneficial effect on vascular or cancer outcomes (*JAMA* 2010;303:2486-2494). ■

Corticosteroids for exacerbations of COPD

Giving corticosteroids orally in lower doses is as effective as giving the drugs intravenously at higher doses for the treatment of acute exacerbation of COPD (ae-COPD), according to a recent study in the *Journal of the American Medical Association*. The records of nearly 80,000 patients in more than 400 hospital admissions for ae-COPD who received steroids were reviewed. The primary outcomes were treatment failure, defined as the initiation of mechanical ventilation, inpatient mortality, or readmission within 30 days. The vast majority of patients (92%) received IV steroids. After multivariate adjustment, the death rate was similar in the two groups (1.4% IV therapy vs 1.0% oral) and the composite outcome was also similar (10.9% IV vs 10.3% oral). In a propensity-matched analysis, the risk of treatment failure was actually significantly lower among orally treated patients (odds ratio, 0.84; 95% confidence interval, 0.74-0.95), as was the length of stay and cost. Of the orally treated patients, 22% were switched to IV therapy later in the hospitalization.

The authors conclude that for patients admitted for ae-COPD, low-dose steroids administered orally are as effective, and may be safer, than higher-dose IV steroids (*JAMA* 2010;303:2359-2367). An accompanying editorial suggests that rather than doing large non-inferiority studies to confirm these findings, sufficient evidence exists to change practice now with continued comparative effectiveness research via linked registries (*JAMA* 2010;303:2409-2410). ■

Prescription drug abuse in young adults

Prescription drugs are the new drugs of abuse among young adults. While drug use in general seems to be dropping in high schools, prescription drug abuse is skyrocketing. The recently published National Youth Risk Behavior Survey from the Centers for Disease Control and Prevention (CDC) showed that 1 of 5 high school students in the United States reported abusing a prescription drug at some time in their lives. The most commonly mentioned drugs were OxyContin®, Percocet®, Vicodin®, Adderall®, Ritalin®, and Xanax®. Prescription drug abuse was most common among white students (23%), followed by Hispanic students (17%), and then black students (12%). Not surprisingly, high school students were most likely to abuse drugs in their senior year (*MMWR* 2010;59:1-142). While many teens get their prescription drugs from medicine cabinets of family and friends, others order them online, and recently many drug dealers have begun specializing in prescription drugs.

Many young adults, however, seek opioids and benzodiazepines from physicians, especially in emergency departments (ED). A new report from *MMWR* reports that ED visits for nonmedical use of opioid analgesics increased 111% from 2004 to 2008 and increased 29% from 2007 to 2008 alone. The highest number of ED visits was recorded for oxycodone, hydrocodone, and methadone. ED visits for benzodiazepines also increased 89% over the same period. In 2008, the rates of visits for both opioids and benzodiazepines increased sharply after age 17 and peaked in the 21-24 year age group. During the 2004-2008 study period, the largest increase in ED visits to obtain drugs occurred among persons age 21-29 years. Findings were from the CDC and the Substance Abuse and Mental Health Services Administration, reviewing data from the Drug Abuse Warning Network (*MMWR* 2010;59:705-709). ■

ARBs and cancer risk

Do angiotensin receptor blockers (ARBs) increase the risk of cancer? In a widely reported study, researchers from Case Western Reserve performed a meta-analysis of 5 trials for which cancer data were available from more than 61,000 patients. Telmisartan was the ARB used in nearly 86% of the studies. Patients randomly assigned to receive ARBs had a rate of new cancer occurrence of 7.2% vs 6.0% for placebo (relative risk [RR], 1.08; 95% confidence interval [CI], 1.01-1.15; $P = 0.016$). The risk ratio was higher when the analysis was limited to trials where cancer was the prespecified endpoint (RR, 1.11; 95% CI, 1.04-1.18; $P = 0.001$). There was no difference in the rate of cancer deaths between the two groups. The authors conclude that this trial suggests that ARBs are associated with a modestly increased risk of new cancer diagnosis, but it is not possible to draw conclusions about the exact risk of cancer associated with each particular drug and further research is warranted (*Lancet Oncology* 14 June 2010; early online publication). ARBs are involved in the regulation of cell proliferation, angiogenesis, and tumor progression, which are possible mechanisms for these findings. ■