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INSIDE

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Tennis Elbow, Anyone?

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips serves on the speakers bureau for PotomaCME.

Synopsis: *Neither physical therapy nor steroid injection improved primary outcomes of tennis elbow at 1 year; in fact, steroid injection was associated with worse outcome. Physical therapy was associated with some improvement in short-term outcomes and secondary measures.*

Source: Coombes BK, et al. Effect of corticosteroid injection, physiotherapy, or both on clinical outcomes in patients with unilateral lateral epicondylalgia: A randomized controlled trial. *JAMA* 2013;309:461-469.

THE PRIMARY AIM OF THIS STUDY WAS TO ASSESS THE LONG-TERM EFFECTS of corticosteroid therapy and physical therapy, singly and in combination, for the treatment of epicondylalgia (a.k.a., tennis elbow). This report is the result of a randomized, blinded, placebo-controlled trial with a 1-year follow-up. Recruited patients were randomized to one of four treatment groups: 1) corticosteroid injection, 2) placebo injection, 3) corticosteroid injection plus physiotherapy, and 4) placebo injection plus physiotherapy.

Participants had pain over the lateral humeral epicondyle that was provoked by at least two of the following: gripping, palpation, resisted wrist or middle finger extension, or stretching of forearm extensor muscles with reduced pain-free grip. Those who had already had injections or physical therapy were excluded.

The researcher who assessed outcomes and analyses was blinded to both injection and physiotherapy assignment. Patients were masked to injection type (corticosteroid or placebo), but could not be masked as to whether they received physiotherapy. Those who were randomized to receive an injection received a single injection of either placebo (0.5 mL of 0.9% isotonic saline) or corticosteroid and local anesthetic

medication (10 mg/mL of triamcinolone acetonide in a 1 mL injection plus 1 mL of 1% lidocaine). The injection was applied to the site of greatest palpable tenderness at the common extensor origin.

The physiotherapy groups had eight 30-minute sessions in 8 weeks with the first session scheduled prior to the injection. (For the inquiring reader, the specific elbow manipulation techniques are described by Vicenzino[1]). In addition, there was twice-daily sensorimotor retraining at home. The outcome measures at 4, 8, 12, 26, and 52 weeks were global ratings using a 6-point Likert scale, ranging from "complete recovery" to "much worse." The primary outcomes were 1-year global scores of complete recovery/much improvement and 1-year recurrence (defined as global rating scores of complete recovery/much improvement at 4 or 8 weeks, but worse after that).

All patients received standardized advice to avoid activities that caused or provoked pain and to refrain from performing strenuous activity for 2 weeks after injection. Following this 2-week rest period, they were encouraged to return to normal activities. Use of analgesics, anti-inflammatories, heat, cold pack, or braces was allowed but not encouraged.

The authors recruited 165 patients with unilateral lateral epicondylalgia over about a 2-year period. Only two patients were lost to follow-up, but four patients missed injections and several missed physiotherapy sessions.

With regard to primary outcomes at 1 year, corticosteroid injection demonstrated lower complete recovery/much improvement (83% vs 96%, $P = 0.01$) and greater recurrence (54% vs 12%, $P < 0.001$) than placebo injection. Patient-rated worst pain remained significantly higher for the corticosteroid injection compared with the placebo injection at 1 year. There were no differences between physiotherapy and no physiotherapy at 1 year for complete recovery/much improvement or recurrence. Use of an analgesic or anti-inflammatory medication did not differ between injection of corticosteroid or placebo (31% vs 28%) but was less frequent in patients allocated to physiotherapy compared with those not allocated to physiotherapy (20% vs 39%).

The short-term (secondary) outcomes were strikingly different from the primary outomes. At the 1-month follow-up, in the absence of physiotherapy, complete recovery/much improvement was greater following corticosteroid injection compared with the placebo injection. But when physiotherapy was present, there were no differences between the corticosteroid injection and placebo injection groups for the outcomes of complete recovery/much improvement at 4 weeks (although there was a medium-sized benefit for pain and disability when physiotherapy was combined with corticosteroid injection). Physiotherapy plus corticosteroid (vs corticosteroid alone) had no effect on the outcomes of complete recovery/much improvement at 4 weeks. Patients who received the placebo injection plus physiotherapy had greater complete recovery/much improvement compared with the no physiotherapy group in the short run.

By the 26th week, the corticosteroid injection groups demonstrated lower complete recovery/much improvement compared with the placebo injection. Physiotherapy compared with no physiotherapy demonstrated no effects on the outcomes of complete recovery or much improvement.

Adverse events overall were minor, transient, and not significantly different between injection or physiotherapy factors. Skin depigmentation (5%) and subcutaneous atrophy (4%) occurred exclusively in patients receiving corticosteroid injection, but resolved by 26 weeks.

■ COMMENTARY

Tennis elbow is common, affecting as many as 3% of the general population, with a peak prevalence between ages 30 and 50 years. Most people with this condition do not play tennis, but do engage in repetitive movements of the forearm in activities like throwing, cutting meat, swimming, gardening, typing, and brick laying.

The finding that corticosteroid injections for tennis elbow are ineffective is not new. A randomized controlled trial previously demonstrated that recurrence occurs within a year in 72% of patients receiving corticosteroid

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Questions & Comments
Please call **Neill Kimball**, Managing Editor, at (404) 262-5404.

injection compared with 8% after physiotherapy,[2] and other reports have failed to find efficacy for steroid injections.[3,4] What is new about this study are the findings that steroid injection is actually associated with worse long-term outcomes. The short-term effects of steroid injections are impressive in this study and in clinical experience, but these long-term data are compelling. As the authors put it, "This evidence does not support the clinical practice of using corticosteroid injection to facilitate active rehabilitation." Why might steroid injections actually make things worse? They could damage the tendon by impairing fibroblasts, which are important for collagen and extracellular matrix protein production.[5] Or, because they do provide short-term, immediate pain relief, they could enable excessive or inappropriate early activity.[6]

The authors set out to determine if physiotherapy combined with steroid injection could enhance the effects of the injections. Disappointingly, they found that physiotherapy (with injection or alone) provided no beneficial long-term effect on complete recovery/much improvement, recurrence, pain, disability, or quality of life. However, in the absence of steroid injection, physiotherapy resulted in short-term benefit across all outcomes and lowest recurrence rates (4.9%) and 100% complete recovery/much improvement at 1 year. In fact, most patients (about 90%) in this study got better by the end of the year. I think the take-home message is that physiotherapy results in reduced pain, is associated with reduced intake of analgesics in the long run, and doesn't appear to make things worse (which is more than you can say for steroid injections). ■

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Does Intensive Lifestyle Intervention Reverse Type 2 Diabetes?

ABSTRACT & COMMENTARY

By Jeff Unger, MD

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Dr. Unger reports no financial relationships relevant to this field of study.

Synopsis: *After 4 years, the intensive lifestyle intervention resulted in a greater likelihood of "partial remission" of type 2 diabetes.*

Source: Gregg EW, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA* 2012;38: 2489-2496.

A TOTAL OF 5145 PATIENTS WITH TYPE 2 DIABETES WERE randomized to receive either diabetes support and education (DSE), including three group sessions annually focusing on diet, physical activity, and social support, or intensive lifestyle intervention (ILI), including weekly group and individual counseling for the first 6 months followed by three sessions monthly with frequent contact sessions over 4 years. The ILI group also aimed to reduce total caloric intake to 1200-1800 kcal/day and encourage exercising 175 minutes weekly.

At 4 years, the ILI cohort experienced more weight loss vs the DSE group (-4.7% vs -4.4% from baseline). The prevalence of complete remission (defined as glucose normalization without the need for pharmacologic intervention at year 4) was low, yet more common among members of the ILI cohort (0.7% vs 0.2% of patients in the DSE cohort). Thirty percent of the patients experiencing any remission in the ILI cohort progressed to clinical diabetes each year whereas 50% of the DSE patients returned to clinical diabetes status once they achieved remission. Positive predictors for remission included: a) patients who developed any remission during the first year of the clinical trial, b) patients experiencing substantial weight loss or an increase in fitness status, c) shorter duration of diabetes prior to randomization, d) lower baseline A1c, and e) patients who were not insulin dependent.

■ COMMENTARY

Although the large database in this study supports a favorable relationship between intensive lifestyle intervention and diabetes remission, some critics may consider this "old

news." In 2009, Perreault et al enrolled participants in the Diabetes Prevention Program (DPP) and they experienced a 16% reduction in diabetes risk progression for each 1 kg of weight loss they experienced using ILI.[1] The study also demonstrated the importance of early intensive intervention in the cohort of patients with prediabetes. Those individuals who achieved normal glucose regulation during the first year of randomization were less likely to progress toward clinical diabetes due to pancreatic beta cell preservation.

More recently, Mingrone et al demonstrated that patients undergoing bariatric surgery lost, on average, 33% of their baseline weight after 2 years.[2] No patient in this study who underwent ILI and pharmacotherapy achieved diabetes remission whereas 75% of gastric bypass and 95% of bilio-pancreatic diversion patients were diabetes free just 2 years following their surgical procedures.

ILI is not readily available to all patients. ILI patients were provided with 90 individual or group training sessions over a 4-year period. Assuming that a certified diabetes educator charges $35 per hour, 4 years of intensive lifestyle training may cost each patient $3150. Yet, less than 1% of ILI patients actually were able to experience complete remission. Although bariatric surgery is more expensive, the odds that one will lose more weight more rapidly and achieve remission sooner would suggest that qualifying patients may choose surgery over ILI coaching. ■

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Lowering Blood Pressure but Raising the Risk of Hip Fracture

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips serves on the speakers bureau for PotomaCME.

Synopsis: *The risk of hip fracture goes up for about 6 weeks immediately after older people start taking antihypertensives.*

Source: Butt DA, et al. The risk of hip fracture after initiating antihypertensive drugs in the elderly. *Arch Intern Med* 2012; 172:1739-1744.

Taking antihypertensive drugs is known to be associated with increased risk of falling and hip fracture in older people, but most of what is known about this is based on studies done in people who are taking these medications chronically. These authors set out to learn about the risk of falls and hip fractures immediately after initiation of antihypertensive drugs in community-dwelling people.

To do this, they identified all Ontario residents aged 66 years and older who got a first prescription for a thiazide diuretic, angiotensin II converting-enzyme (ACE) inhibitors, angiotensin II receptor antagonist/blockers (ARBs), a calcium channel blocker, or a beta-adrenergic blocker. They linked these patients to the national physician claims database, which provides detailed diagnostic and procedural information. Because of the richness of these data, they were able to exclude patients who were prescribed these agents for something other than hypertension (for example, cardiomyopathy or essential tremor). They also excluded those who were previously prescribed these drugs at any point in the preceding year, those with pathologic fractures, and those who were institutionalized. The main outcome was first occurrence of a hip fracture. They compared incidence of hip fracture in the first 45 days after a new antihypertensive prescription with two 45-day periods in the year before they started the treatment.

The cohort had a mean age of 81 years and was mostly women (about 81%). ACE inhibitors were the most commonly prescribed agents (30%), with ARBs being the least-commonly used (5%). There were 301,591 newly treated hypertensive elderly patients who had 1463 hip fractures during the 10-year period of data collection.

People who started an antihypertensive drug for the treatment of hypertension had a 43% increased risk of hip fracture during the first 45 days of treatment. The risks were generally consistent among the five different classes of antihypertensive drugs, but only the ACE inhibitors and beta-blockers were statistically significantly associated with increased risk as a class. Comparing risk of hip fractures for the first 2 weeks to the next 4 weeks after starting the drug showed that the hip fracture risk after starting any antihypertensive drug for the treatment of hypertension was actually highest (54%) for weeks 3-6. This increased trend was not seen with thiazide diuretics and was most pronounced for ACE inhibitors. Statistically controlling for various confounders, including psychotropic medications, did not affect these relationships.

■ COMMENTARY

What is new here is the finding that the risk of hip fracture increases immediately after starting a new anti-

hypertensive agent in older people, particularly for ACE inhibitors and beta-blockers. The authors discuss several different mechanisms, including orthostatic hypotension, confusion, venous pooling, and extracellular volume decreases, depending on the agent.

In their discussion, the authors note that treating hypertension reduces the risk of cardiovascular disease in the long run but increases the risk of fall-related injuries in the short run. They note that such falls cause functional, cognitive, and physical effects similar to those that result from myocardial infarction and stroke.[1,2] In fact, they point out that the incidence of nonfatal cardiovascular events in hypertensive elderly patients and serious fall injuries in the elderly at risk of falls is essentially the same, at 16%.[2,3] All of a sudden, the decision of when and how to treat hypertension in the elderly is not as simple as it was. At the very least, we need to advise our older patients that they will be slightly more likely to break a hip in the first 6 weeks after starting a new drug for hypertension. ■

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Pharmacology Update

Bedaquiline Tablets (Sirturo™)

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 relationships relevant to this field of study.

THE FDA HAS APPROVED BEDAQUILINE, A FIRST IN CLASS DRUG for the treatment of multidrug-resistant tuberculosis. Bedaquiline, which was approved under the FDA's accelerated approval process, is a diarylquinoline antimycobacterial that inhibits the enzyme that generates energy in *Mycobacterium tuberculosis*. It is manufactured by Kemwell Pvt. Ltd in India and marketed by Janssen Therapeutics as Sirturo.

Indications

Bedaquiline is indicated in combination with other antimycobacterial drugs for patients with multidrug-resistant pulmonary tuberculosis in adults (≥ 18 years of age).[1] The drug should be reserved for use only when there are no other effective treatment regimens available. It should be given by directly observed therapy. This means that a trained health care worker or other designated individual (excluding a family member) provides the prescribed medication and watches the patient swallow every dose.

Dosage

The recommended dose of bedaquiline for the first 2 weeks is 400 mg (4 × 100 mg) once daily with food. For weeks 3-24, the dose is 200 mg (2 × 100 mg) three times per week with food with at least 48 hours between doses. Bedaquiline is given in combination with at least three other drugs that the patient's isolate has been shown to be susceptible to in vitro.[1] If these data are not available, treatment should be initiated with at least four other drugs to which the patient's isolate are likely to be susceptible. Dose adjustment is not required in patients with mild-to-moderate hepatic and renal dysfunction. Coadmistration with CYP3A4 inducers and strong inhibitors (e.g., rifampin, rifapentine) for more than 14 days should be avoided.

Bedaquiline is available as 100 mg tablets.

Potential Advantages

Bedaquiline provides a new and effective option for treating multidrug-resistant tuberculosis.

Potential Disadvantages

An increased risk of death has been associated with bedaquiline treatment compared to placebo (11.4% vs 2.5%).[1] The drug prolongs QT interval. An ECG should be done before beginning treatment and no later than 2, 12, and 24 weeks thereafter. Serum electrolytes (sodium, potassium, calcium, and magnesium) should be assessed before treatment and adjusted if abnormal. Treatment should be discontinued if ventricular arrhythmia develops or if QTcF interval is > 500 ms.

Comments

Bedaquiline is a new drug that targets mycobacterial ATP synthase and is highly active on replicating as well as dormant bacteria.[2,3] Its efficacy for the treatment of multidrug-resistant tuberculosis was evaluated in a randomized, double-blind, placebo-controlled study.[1] Subjects were mainly males (63%), median age of 34 years, 35% black, 17.5% Hispanic, 12.5% white, 25.6% of other races, 15% were HIV-positive, and

62% had cavitations in one lung. They were randomized to bedaquiline plus other drugs or placebo plus other drugs. Other drugs consisted of a combination of ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone or available alternative. Bedaquiline was taken for 24 weeks and other drugs continued for 18-24 months. The primary efficacy endpoint was sputum culture conversion and time to conversion. Treatment failure was defined as lack of conversion or discontinuation of therapy. Culture conversion status was available in 67 subjects in the bedaquiline group and 66 in the placebo group. The rate of treatment success at week 24 was 77.6% in the treatment group and 57.6% in the placebo group (P = 0.014). At week 72, rates were 70.1% and 56.1% (P = 0.092). The time to sputum conversion was 83 days for bedaquiline and 125 days for placebo. This is an ongoing trial. In a 2-year, follow-up pilot study (n = 47) where bedaquiline was added to the first 8 weeks of therapy, it not only resulted in more rapid sputum conversion but may have also helped protect against acquired resistance to the other antitubercular drugs in the regimen.[4] The most common adverse events were nausea (38%), arthralgia (33%), headache (28%), hemoptysis (18%), and elevation of liver aminotransferases of at least 3 × ULN.[1]

Clinical Implications

Multidrug-resistant tuberculosis are organisms resistant to isoniazid and rifampin.[5] Infected patients typically need to be treated for at least 20 months. The introduction of bedaquiline for the first 24 weeks of therapy increases the rate of sputum conversion. However, long-term benefits and risks remain to be established. ■

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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.

CME Instructions

To earn credit for this activity, follow these 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.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter! ■

CME Questions

1. **For treatment of epicondylalgia (tennis elbow), the best outcomes at 1 year are associated with:**
   a. corticosteroid injection plus physiotherapy.
   b. physiotherapy alone.
   c. corticosteroid injection alone.
   d. no active treatment.

2. **According to the study by Gregg et al, which of the following does *not* predict complete regression from clinical diabetes to normal glucose tolerance in the intensive lifestyle intervention cohort during the first year following randomization?**
   a. Prolonged duration of diabetes at baseline
   b. Coexisting sleep apnea
   c. Low A1C at baseline at time of randomization
   d. Greatest improvement from baseline in fitness status
   e. Higher weight loss from baseline

3. **Antihypertensives are associated with increased risk of hip fractures in older people:**
   a. only for the first 2 weeks after initiation.
   b. after long-term (> 6 months) use.
   c. for thiazide diuretics only.
   d. which is similar to the incidence of nonfatal cardiovascular events.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda.

Peripheral Artery Disease: Helping Patients to Walk the Walk

Source: Ahimastos AA, et al. *JAMA* 2013;309:453-460.

Currently available treatments for peripheral artery disease (PAD) are only modestly effective. PAD portends increased risk of cardiovascular disease; hence, most PAD patients should be receiving pharmacotherapy with a statin and an antiplatelet agent (usually clopidogrel).

Because one of the quality-of-life limiting factors in advanced PAD is disease-mediated diminution in walking distance and walking time, incorporation of pharmacotherapy to improve these limitations is also considered important. Unfortunately, the two FDA-approved treatments (pentoxifylline and cilostazol) for symptoms of PAD provide only a modest increase in walking distance (25% or less). Smoking cessation and exercise advice remain critically important, but are too often not heeded.

Ramipril is an angiotensin-converting enzyme (ACE) inhibitor that has been used in numerous major clinical trials, including the HOPE trial, ONTARGET trial, REIN trial, and others. Use of ramipril is usually predicated on 1) its ability to lower blood pressure, 2) its ability to improve outcomes in congestive heart failure, or 3) its ability to improve albuminuria.

Based on results seen in a small pilot trial that suggested favorable results of ramipril on treadmill time in subjects with PAD, Ahimastos et al performed a larger randomized clinical trial (n = 212).

At the conclusion of the 6-month trial of ramipril 10 mg/day vs placebo, pain-free walking time had increased by more than 50% in the ramipril group, but only 10% in the placebo group.

Although the mechanism for improved function is speculative, it has been noted that ACE inhibitors increase skeletal muscle blood flow; indeed, this has been the mechanism to which improved insulin sensitivity in diabetics has been attributed. Ramipril may offer a new avenue to improve functionality in patients with PAD. ■

Long-Term Functional Outcomes After Localized Prostate Cancer Treatment

Source: Resnick MJ, et al. *N Engl J Med* 2013;368:436-445.

When prostate cancer is localized, either radical prostatectomy (RPT) or external beam radiation (EBR) can often be curative. The adverse effect profile of these two interventions, however, may be meaningfully different and such differences might also be time-dependent.

Resnick et al studied men (n = 1164) from the Prostate Cancer Outcomes Study who had been enrolled between the ages of 55-74 and had localized prostate cancer. More than 80% of the men had a Gleason score of 7 or less. The prevalence of urinary incontinence (UI) and erectile dysfunction (ED) were compared among these men at years 2, 5, and 15.

Prostatectomy subjects were five to six times more likely to have incontinence at 2 years and 5 years than EBR subjects. Similar disadvantage was seen in the prevalence of ED (two- to four-fold increased incidence in the RPT group). At the 15-year conclusion of their observations, no differences between groups remained. However, one would anticipate, for instance, a substantial incremental increase in ED as men age with or without intervention; hence, the fact that between-group differences are eliminated by 15 years provides little solace for the men who suffer the adverse effects in the interim! ■

A Relationship Between Nocturia and Hypertension

Source: Feldstein CA. *J Am Soc Hypertens* 2013;7:75-84.

Nocturia could easily be misconstrued as a "nuisance" symptom since, after all, nobody dies from nocturia … or do they? Indeed, urinary frequency and nocturia have been associated with greater risk for nocturnal falls and hip fracture; hence, nocturia can be much more than just a nuisance.

Clinicians are used to identifying nocturia as a symptom associated with benign prostatic hyperplasia, overactive bladder, uncontrolled diabetes, uncontrolled congestive heart failure, use of diuretics, and (less commonly) interstitial cystitis. What is only minimally recognized, however, is the emerging observation that hypertension is associated with nocturia.

Several plausible mechanisms can explain the nocturia/hypertension relationship: hypertension-induced alterations in glomerular filtration or tubular transport, activation of atrial natriuretic peptide from ventricular wall stress induced by hypertension, and resetting of the pressure-natriuresis relationship in the kidney, to name a few.

Feldstein indicates that the prevalence of nocturia in untreated hypertension patients may be as high as 33%. Since nocturia can be both a burdensome symptom and lead to significant morbidity (and mortality), clinicians may wish to specifically inquire about nocturia when encountering hypertension patients. ■

What Rhythm? What Artery?

By Ken Grauer, MD, *Professor Emeritus in Family Medicine, College of Medicine, University of Florida*

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

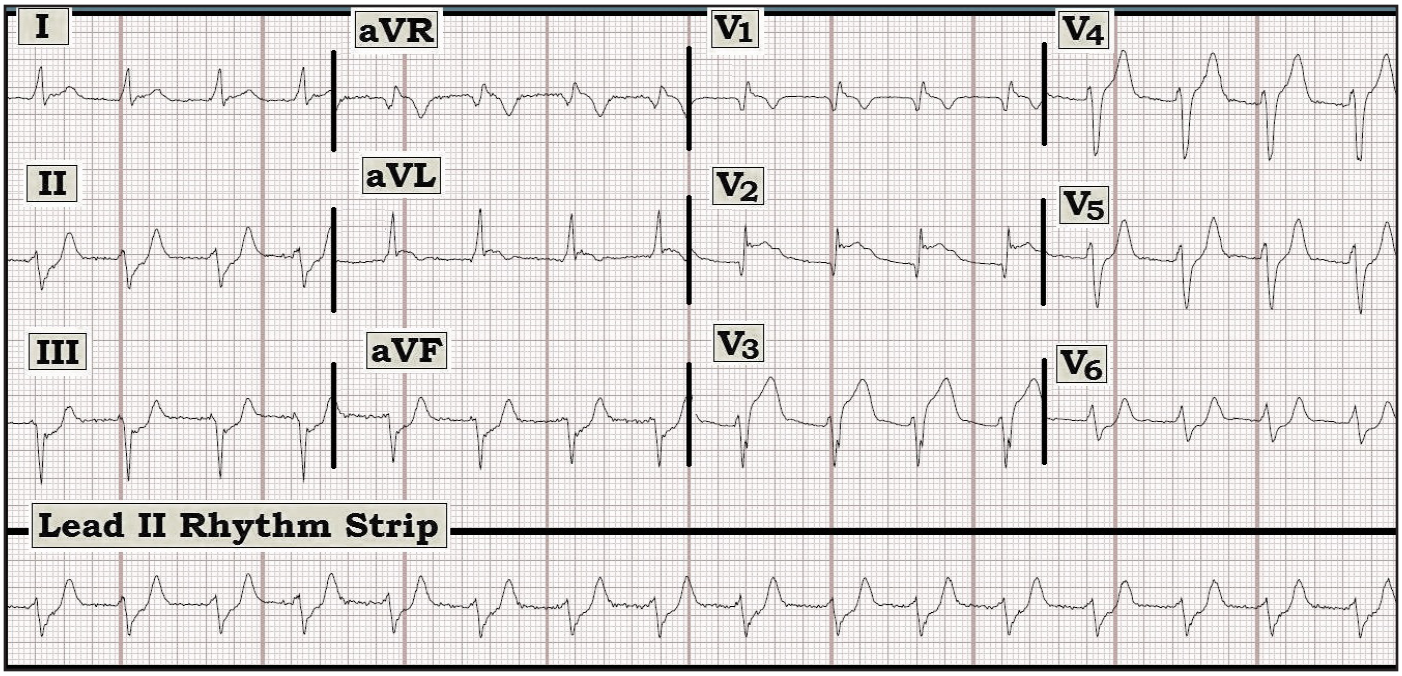

Figure — 12-lead ECG from a 55-year-old man with chest pressure.

Scenario: The 12-lead ECG and lead II rhythm strip shown above were obtained from a 55-year-old man with "chest pressure." He is hemodynamically stable. What is the rhythm? Can you identify the "culprit" artery?

Interpretation: There are two key issues to address regarding this tracing. The first relates to determining the rhythm. Given that the patient is hemodynamically stable, there is at least a moment to contemplate what is seen. The QRS is slightly widened (to ~0.11 second). No *P* waves are seen. The rate is about 100/minute. Although the rhythm appears to be regular, careful measurement (with calipers) indicates that there is in fact slight variation in R-R intervals. This leaves us with the differential diagnosis of an almost regular wide rhythm at 100/minute in a hemodynamically stable patient with obvious ST-T wave abnormalities. The three entities to consider are: 1) a fascicular type of ventricular tachycardia; 2) accelerated AV nodal rhythm; or 3) atrial fibrillation. Because of the subtle irregularity in the rhythm and QRS morphology that "looks to be" supraventricular, we favor atrial fibrillation as the etiology of the rhythm. That said, we fully acknowledge that one cannot be certain of the rhythm from this single tracing. Moreover, this unfortunate patient has other more pressing concerns at the moment. Definitive rhythm diagnosis will almost certainly be revealed in this hemodynamically stable patient with ongoing monitoring over the next few minutes.

Of most concern about this tracing is the obvious extensive anteroseptal ST-elevation myocardial infarction. One should suspect a very proximal left anterior descending coronary artery occlusion because 1) there is marked ST elevation not only in leads V2 and V3, but also in leads V1, aVL, and aVR; 2) there are conduction abnormalities (right bundle branch block and left anterior hemiblock); 3) there is a non-sinus rhythm; and 4) Q waves are present in septal leads V1 and V2, with the Q in V1 in the presence of right bundle branch block strongly suggesting septal involvement. Acuity and extent of the infarct is further supported by marked reciprocal ST depression (in the inferior leads) and hyperacute T waves in multiple leads. This patient is at high risk of developing complete heart block *and/or* cardiogenic shock. Acute reperfusion is urgently needed.

For more information about coronary anatomy/infarct localization, please visit: https://www.kg-ekgpress.com/ecg_-_coronary_anatomy-mi_localization/. ■

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Aspirin Use and Age-Related Macular Degeneration

In this issue: Aspirin use and AMD risk; using NSAIDs and antihypertensive agents; and FDA actions.

Does aspirin cause AMD?

Does regular aspirin use put patients at risk for age-related macular degeneration (AMD)? That is the finding in a highly publicized study from Australia published in *JAMA Internal Medicine* (formerly *Archives of Internal Medicine*). A prospective analysis was conducted from an Australian population-based cohort that included four examinations in 15 years as well as questionnaires regarding aspirin use. Of the 2389 participants with follow-up available, 257 (10.8%) were regular aspirin users and 63 of these (24.5%) developed neovascular (wet) AMD. Regular aspirin users were more likely to develop neovascular AMD: The 15-year cumulative incidence was 9.3% in aspirin users and 3.7% in non-users. After adjustment for age and multiple cardiovascular risk factors, regular users of aspirin had an odds ratio of neovascular AMD of 2.46 (95% confidence interval [CI], 1.25-4.83). The association showed a dose response effect, with daily users at higher risk. Aspirin was not associated with geographic atrophy (dry AMD). The authors conclude that "regular aspirin use is associated with increased risk of incident neovascular AMD independent of a history of cardiovascular disease and smoking." (*JAMA Intern Med* published online Jan. 21, 2013. doi:10.1001/jamainternmed.2013.1583). A related editorial points out that age-related AMD is the leading cause of blindness in Western countries, and this study suggests that regular aspirin is associated with an approximate 2.5-fold greater risk in incident AMD. The study is not a randomized trial, and although there is some biological plausibility in the association between aspirin use and development of AMD, this study is "not sufficiently robust to be clinically directive." (*JAMA Intern Med* published online Jan. 21, 2013. doi:10.1001/jamainternmed.2013.2530.) The take-home message for now is that for patients who are likely to benefit from aspirin (secondary prevention of cardiovascular disease), practice should not change. However, for those patients who take aspirin for indications that are less compelling, we may want to rethink the recommendation until good trials on the relationship between aspirin use and AMD can be assessed. ■

NSAIDs and antihypertensive agents

Mixing certain antihypertensive agents with nonsteroidal anti-inflammatory drugs (NSAIDs) increases the risk of renal failure, according to a new study. In a retrospective cohort study of nearly 500,000 users of antihypertensive drugs in the United Kingdom, rate ratios of acute kidney injury associated with current use of certain antihypertensive agents with NSAIDs were assessed. After a mean follow-up of 5.9 years, 2215 cases of acute kidney injury were identified. Overall, current use of a single antihypertensive (either diuretics, angiotensin-converting enzyme inhibi-

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tors [ACEIs], or angiotensin receptor blockers [ARBs]), along with an NSAID was not associated with increased rate of acute injury. However, combining a diuretic with either an ACEI or ARB along with an NSAID increased the rate of acute kidney injury significantly (rate ratio 1.31, 95% CI, 1.12-1.53). This 31% increased risk of acute kidney injury was driven by a nearly two-fold increased risk in the first 30 days of use. The authors conclude that triple therapy consisting of diuretics with an ACEI or ARB along with an NSAID was associated with an increased risk of acute kidney injury, especially at the start of treatment (*BMJ* published online January 8, 2013. doi.org/10.1136/bmj.e8713). ■

FDA actions

An advisory committee to the FDA has recommended moving hydrocodone/acetaminophen (Vicodin, Norco) from schedule III to schedule II later this year. The move would put the drug in the same category as morphine and oxycontin, and would require a handwritten, tamper-proof prescription for every prescription and refill. Vicodin — the most widely prescribed drug in this country — is at the center of the controversy regarding prescription drug abuse, which has become "epidemic" in this country, according to the CDC. The United States consumes 99% of all the hydrocodone produced worldwide, and deaths attributable to prescription opioid abuse skyrocketed in the last 2 years, outpacing deaths from illegal opioid drugs, including heroin. The move is supported by some advocacy groups, including an endorsement by the American Academy of Pain Medicine, but not by others. Some physicians are concerned that the schedule change will be a major inconvenience for legitimate pain patients and their physicians, who will be required to write a tamper-proof prescription for each refill of the drug.

The FDA has approved an over-the-counter version of topical oxybutynin for the treatment of overactive bladder in women ages 18 and older. The approval is for women only, with oxybutynin available to men by prescription only. The anticholinergic drug has been used for years by prescription for this indication. In studies of more than 5000 subjects, it was determined that consumers can understand the labeling and "properly select whether the product is right for them." Merck will market the product as a patch that is replaced every 4 days under the trade name Oxytrol for Women.

The FDA has lowered the recommended doses for zolpidem (Ambien) for women. The agency based its recommendation on findings that the popular insomnia drug might impair alertness the next morning if taken at recommended doses. The recommendation is also based on findings that zolpidem stays in the body longer than previously thought, especially in women who process the drug somewhat slower. The new recommended maximal dose for women has been lowered from 10 mg to 5 mg for the immediate-release product, and from 12.5 mg to 6.25 mg for the extended-release (Ambien CR). The FDA further recommends that zolpidem and all insomnia drugs should be used at the lowest dose needed to treat symptoms in both men and woman.

The FDA has approved alogliptin for the treatment of type 2 diabetes. The drug is the fourth dipeptidyl peptidase-4 inhibitor after sitagliptin (Januvia), saxagliptin (Onglyza), and linagliptin (Tradjenta). Takeda Pharmaceuticals has been seeking approval for more than 5 years, dealing with the FDA's tighter standards for new diabetes drugs. The approval was based on 14 trials involving about 8500 patients as well as five ongoing postmarketing trials. The agency also approved two additional combinations of alogliptin with metformin and pioglitazone. Alogliptin alone will be marketed as Nesina, alogliptin/metformin will be marketed as Kazano, and alogliptin/pioglitazone will be marketed as Oseni. Both combination products carry boxed warnings (for lactic acidosis associated with metformin and heart failure associated with pioglitazone). All three are distributed by Takeda Pharmaceuticals.

Johnson & Johnson is one step closer to approval of canagliflozin, the first of a new type of diabetes drug. The Endocrionologic and Metabolic Drugs Advisory Committee voted 10 to 5 in favor of approving the drug while still expressing some concern about the cardiovascular safety of the agent. Canagliflozin is an oral inhibitor of the sodium glucose cotransporter 2 (SGLT2) that reduces reabsorption of glucose in the kidney, resulting in increased urinary glucose excretion with a consequent lowering of plasma glucose levels as well as weight loss. If eventually approved by the FDA, it would be the first SGLT2 inhibitor on the U.S. market. The FDA denied a similar drug 1 year ago (dapagliflozin) because of increased risk of bladder and breast cancer. The favorable vote was based on clinical trials of more than 10,000 patients worldwide which showed that the drug improves blood sugar levels and led to modest weight loss as well as reduction in blood pressure. ■