INTERNAL MEDICINE ALERT

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INSIDE

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Aspirin for Everyone?

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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

Synopsis: *Aspirin can reduce the risk of nonfatal myocardial infarction, but not mortality, in people without coronary vascular disease, at the expense of increased risk of bleeding. It should not be routinely recommended.*

Sources: Seshasai SR, et al. Effect of aspirin on vascular and nonvascular outcomes: Meta-analysis of randomized controlled trials. *Arch Intern Med* 2012;172:209-216. Mora S. Aspirin therapy in primary prevention: Comment on "Effect of aspirin on vascular and nonvascular outcomes." *Arch Intern Med* 2012;172:217-218.

Since 2009, the U.S. Preventive Services Task Force (USPSTF) has recommended the use of aspirin (ASA) "for men age 45 to 79 years when the potential benefit due to a reduction in myocardial infarctions outweighs the potential harm due to an increase in gastrointestinal hemorrhage" and "for women age 55 to 79 years when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastrointestinal hemorrhage."[1] These recommendations were based on a systematic review published in the *Annals of Internal Medicine*. Use of ASA for the secondary prevention of cardiovascular disease (CVD) is well established, but its use for primary prevention is less certain. There is an increased risk for gastrointestinal (GI) bleeding that accompanies ASA use that must be factored into the risk-benefit analysis. Since the 2009 publication, three additional articles have been published that were not included in the review.[4-6] Seshasai and colleagues have now performed a meta-analysis of randomized controlled trials (RCTs) that includes the newer data. They also looked at the evidence for ASA's role in the prevention of nonvascular disorders (e.g., cancer).

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Seshasai et al searched MEDLINE and the Cochrane Library of Clinical Trials for RCTs that had at least 1000 participants with no history of coronary heart disease (CHD) or stroke. In addition, the studies' designs had to include at least 1 year of follow-up and provide data regarding CHD, stroke, cerebrovascular disease, heart failure, peripheral vascular disease, and bleeding events. Since the initial studies often did not report data on nonvascular outcomes, they searched for subsequent analyses of secondary outcomes that included cancer and other nonvascular endpoints. They also went back to the original investigators for unpublished data on secondary outcomes. Because the original investigators used different definitions of bleeding, Seshasai et al devised a category of "clinically non-trivial bleeding" encompassing fatal bleeding, cerebrovascular or retinal bleeding, GI bleeding, and bleeding requiring hospitalization or transfusion.

Their initial search produced 680 potentially relevant articles, which were narrowed down to nine after appropriate exclusion. These nine studies include 102,621 subjects and were published between 1988 and 2010. Three of the studies enrolled medical and nursing professionals and most of the subjects resided in Western nations. Average age of the subjects was 57 years, and 54% were female. Most of the RCTs enrolled people at increased risk for CHD. Average follow-up was 6 years, during which 2169 CHD events occurred. Nonfatal myocardial infarction (MI) accounted for 1540 CHD events; 592 MIs were fatal. There were 1504 strokes and 1512 cancer deaths. There were 40,712 bleeding events, of which 10,049 were nontrivial. ASA use reduced total CVD events by 10% (odds ratio [OR] 0.90; 95% confidence interval [CI], 0.85-0.96). Nonfatal MI was the largest contributor to this with a 20% reduction in risk (OR 0.80; 95% CI, 0.67-0.96), number-needed-to-treat (NNT) 162. There was no significant reduction in fatal MI, stroke, CVD death, or all-cause mortality. There was no reduction in cancer deaths. ASA increased the risk of total bleeding events by 70% (OR 1.70; 95% CI, 1.17-2.46) and nontrivial bleeding events by 31% (OR 1.31; 95% CI, 1.14-1.50), number-needed-to-harm (NNH) 73.

■ COMMENTARY

One way to view the conclusions of this meta-analysis is to look at the NNT for nonfatal MI events and the NNH for nontrivial bleeding events. Is treating 162 individuals with ASA to prevent one nonfatal MI worth at least two nontrivial bleeding events? The answer to this question depends on how you (and your patients) value MI prevention (hard to prove a negative) vs nontrivial bleeding (usually very apparent when it occurs). While there is good evidence for prescribing ASA for secondary prevention of CHD, the tradeoff of increased nontrivial bleeding for reduction of nonfatal MI (and no mortality benefit) may make primary prevention less appealing. Perhaps our other methods of primary prevention (e.g., smoking cessation, control of hypertension, statin use, aggressive diabetes treatment) are more effective and have made ASA less valuable.

Limitations of this meta-analysis include the inclusion of studies done among health professionals, who may not represent the average person in your practice. Strengths include the very large sample size and the timeliness of the studies that comprise the meta-analysis.

The USPSTF recommendations include a table that indicates by age when the risks of CHD for men and the risk of stroke for women exceed the risk of GI harms.[7] It also includes links to risk calculators to help you quantify your patient's risk. Some doctors may find this time consuming, and there is no evidence to date that there are subgroups that would benefit from primary prevention. However, as Mora's commentary concludes, "it is reasonable to consider using aspirin for primary prevention in higher-risk individuals without known CVD (above 1% CVD event rate per year) if they are deemed to have a greater benefit to risk ratio and after taking into account patient preferences." I think I'll put away my bottle of baby aspirin. ■

References

1. http://www.uspreventiveservicestaskforce.org/uspstf/uspsasmi.htm. Accessed Feb. 20, 2012.
2. Wolff T, et al. *Ann Intern Med* 2009;150:405-410.

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3. Antithrombotic Trialists' (ATT) Collaboration. *Lancet* 2009;373:1849-1860.
4. Belch J, et al. *BMJ* 2008;337:a1840.
5. Ogawa H, et al. *JAMA* 2008;300:2134-2141.
6. Fowkes FG, et al. *JAMA* 2010;303:841-848.
7. http://www.uspreventiveservicestaskforce.org/uspstf09/aspirincvd/aspcvdsum.htm. Accessed Feb. 20, 2012.

Long-term Safety of Statins

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

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This article originally appeared in the February issue of Clinical Cardiology Alert. *At that time it was peer reviewed by Ethan Weiss, MD, Associate Professor of Medicine, Division of Cardiology, University of California, San Francisco, CA. Dr. Weiss is an advisory board member for Bionovo. Dr. Boyle reports no financial relationships relevant to this field of study.*

Synopsis: *There do not appear to be any safety issues with the long-term use of statins.*

Source: Heart Protection Study Collaborative Group. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: A randomised controlled trial. *Lancet* 2011;378:2013-2020.

STATINS REDUCE THE INCIDENCE OF ADVERSE CARDIOVASCULAR events. Some observational non-randomized studies have suggested that low cholesterol levels and/or statins may increase the risk of cancer or other non-cardiovascular diseases. To determine the long-term effects of simvastatin on cancer and death, the investigators from the Heart Protection Study reviewed the outcomes of their trial participants over an extended follow-up time after the original 5-year clinical trial had ended.

You may remember that the Heart Protection Study (HPS) was a trial of 20,536 patients at high risk of vascular events who were randomized to receive simvastatin 40 mg daily vs placebo. The study ran over 5 years and showed a reduction in LDL cholesterol of 1 mmol/L (39 mg/dL), which was associated with a 23% reduction in major vascular events. This paper extends the follow-up period to 11 years. Over the original 5-year study period, 85% of the simvastatin-allocated patients, and 17% of the placebo-allocated patients, were taking statins. Over the extended follow-up period of this study, approximately 74% of patients in each group were taking statins. Correspondingly, LDL cholesterol was lower in the simvastatin-allocated group after the original 5-year study period, but was the same between groups after the extended follow-up period. Thus, the long-term follow-up represents a 5-year period of randomized treatment (statin vs placebo), followed by 6 years of high rates of statin treatment in both groups. The particular focus of this study was on cancer and mortality, so the authors not only followed up the patients but also cross-referenced with the national cancer registry and with the national death index in the United Kingdom.

Patients allocated to simvastatin had a significant reduction in vascular events during the 5-year trial period. During this extended follow-up period from years 5-11, there were no differences between groups in terms of vascular events. This was to be expected because the rates of statin therapy and the lipid levels were the same in both groups. During the extended follow-up period, there were no differences between groups in terms of any of the components of the primary endpoint: stroke, major coronary events, and revascularization rate.

There was a significant reduction in mortality in the statin-allocated group during the initial 5-year study period. Mortality from vascular and non-vascular causes remained the same in each group during the extended trial follow-up period. The incidence of cancer was the same in each group, as was the body region where the cancer occurred. There were no differences in mortality between treatment groups in those with lower baseline lipid levels or in the elderly.

■ COMMENTARY

This is more good news for patients in need of statin therapy. The reports that suggested a link between statin therapy, or low LDL, and cancer or increased non-cardiovascular mortality appear to be unfounded. They were based on epidemiological observational studies, but analyses of randomized placebo-controlled trials like this one refute this hypothesis quite resoundingly. This study is congruous with the growing body of literature on long-term statin follow-up. The WOSCOPS study of pravastatin versus placebo was initially a 5-year study, and the extended follow-up of an additional 10-years showed continued reduction in cardiovascular mortality, with no increase in cancer or in non-cardiac mortality.[1] Similarly, the extended follow-up of the ASCOT-LLA study of atorvastatin 10 mg vs placebo (initial trial stopped early after 3 years for highly positive effect, extended follow-up to 11 years) showed continued reduction in mortality with no excess cancer and a *decrease* in non-cardiac mortality.[2]

In all these studies, a period of statin use for several years conferred a mortality reduction that continued for many more years. This continued legacy of treatment benefit has been consistent throughout these studies and ap-

pears to be a class effect of the statins. This confirms that statin therapy should be given early to those in whom it is warranted. There do not appear to be any long-term safety issues, at least out to 11 years. In particular, there does not seem to be an increased risk in those with low baseline LDL or in the elderly.

This long-term follow-up following an initial period of treatment and then open-label treatment is not the most robust clinical trial design. However, it is the best data we are ever likely to have. It is not ethical to have a long-term statin vs placebo trial in those who are at risk for vascular events, as the benefits of statins are clear and randomizing patients to placebo would be unethical. I am reassured by this paper, and other long-term follow-up papers, that statins are safe in the long-term. Hopefully, this paper puts the issue to rest. ■

References

1. Ford I, et al. *N Engl J Med* 2007;357:1477-1486.
2. Sever PS, et al. *Eur Heart J* 2011;32:2525-2532.

Postoperative Complications in Patients with Obstructive Sleep Apnea

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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

Synopsis: *More than half of patients undergoing noncardiac surgery and polysomnography had obstructive sleep apnea, which was associated with an increased risk of perioperative complications, including hypoxemia, ICU transfer, and prolonged length of stay.*

Source: Kaw R, et al. Postoperative complications in patients with obstructive sleep apnea. *Chest* 2012;141:436-441.

The cohort for this analysis was assembled from nearly 40,000 patients who underwent preoperative assessment over a 5-year period. The investigators cross-referenced the electronic health record with the sleep laboratory database to identify patients who had noncardiac surgery within 3 years of having a sleep study. Demographic, clinical, diagnostic, and postoperative data were collected from outpatient electronic records, inpatient hospital admission records, and surgical procedure dictation records. Obstructive sleep apnea (OSA) was defined as an apnea plus hypopnea index (AHI) of more than 5 events per hour of sleep. In patients with more than one procedure, morbidity data and postoperative outcomes were collected for the surgical procedure done closest to the date of the overnight sleep study.

The endpoints for this study were significant postoperative complications, including postoperative hypoxemia, respiratory failure, congestive heart failure, myocardial infarction (MI), atrial fibrillation, delirium, death within 30 days, and hospital length of stay (LOS). Postoperative hypoxemia was defined as oxygen desaturations with a < 90% or > 4% reduction from last recorded value, or by arterial blood gas postoperatively. Postoperative respiratory failure was defined as the need for mechanical ventilation longer than 24 hours, endotracheal reintubation, or tracheostomy. Postoperative congestive heart failure was defined as new pulmonary edema, jugular venous pressure > 10 mmHg, use of diuretic or afterload/preload reducing agents, or physician documentation. Postoperative MI was defined as the appearance of new Q waves > 0.04 sec wide and 1 mV in depth accompanied by elevated levels of troponin T (0.03 ng/mL) and creatine kinase-MB (> 100 IU/L).

A propensity score for the likelihood of sleep apnea for each patient was calculated using logistic regression. The propensity model used in this study included age, sex, race, BMI, use of general anesthesia, American Society of Anesthesiology class, and several comorbidities and their interactions as covariates. The model was statistically quite strong as a predictor of sleep apnea.

The final cohort for the analysis was 471 patients. Of these, 282 (59.8%) had OSA. Patients with OSA were older, (55.9 vs 46.3 years), predominantly male (44.7% vs 21.7%), and heavier (BMI 38.3 vs 33 kg/m^2). They had a higher American Society of Anesthesiologists risk class, and many more medical comorbidities (i.e., COPD, hypertension, diabetes mellitus, coronary artery disease) than patients without OSA. Most of the surgeries were intermediate risk, with abdomino-pelvic and orthopedic procedures dominating. No differences existed between the types of anesthesia used in the two groups, and general anesthesia was more commonly used overall by far (> 80%). After adjustment for the propensity score, the presence of OSA was associated with a higher incidence of overall complications (odds ratio [OR], 6.9; P = 0.003), postoperative hypoxemia (OR, 7.9; P = 0.009), ICU transfer (OR, 4.43; P = 0.069), and longer LOS (OR, 1.65; P = 0.049). Severity of OSA measured by the AHI was not associated with postoperative complications. The median LOS was 2 days in the OSA group and 1 day in the control group.

■ **COMMENTARY**

The two take-home messages from this study are that sleep apnea is very common in perioperative patients and that it is associated with an increased risk of complications, notably increased LOS, ICU transfer, and hypoxemia.

This study is important because it is the largest study to date to determine the prevalence of polysomnographically determined OSA in the general surgical population. Although several previous reports have reported that OSA is a risk factor for increased postoperative morbidity and mortality,[1-4] most have based the diagnosis of OSA on screening questionnaires. A confounder in previous reports has likely been the presence of undiagnosed and unrecognized sleep apnea in the "control group." Because all of the patients in this analysis had sleep studies, those patients who were characterized as not having sleep apnea in this report probably did not. (On the other hand, this cohort was likely "enriched" by sleep apneics, because sleep studies were ordered on the basis of clinical suspicion). A further strength of the current study is that the authors used a propensity score that controlled for factors associated with OSA, including BMI.

Because the prevalence of obesity is increasing in this country, the prevalence of OSA is increasing as well. Between 1990 and 1998, there was a 12-fold increase in the diagnosis of OSA in surgical outpatients.[5] The American Society of Anesthesiologists has published clinical guidelines for the perioperative management of OSA,[2] but these are mostly based on consensus and are not widely used. Further, they are focused on the patients' care while in the facility.

Where to go from here? Awareness is an important first step. Patients who are obese, sleepy, hypertensive, have witnessed apneas, or big necks are at high risk for sleep apnea. The American Society of Anesthesiologists recommends longer postoperative monitoring in OSA patients after ambulatory surgery and 7 hours of monitoring after the last episode of airway obstruction or hypoxemia while breathing room air in an unstimulated environment prior to discharge from the facility.[2] And our colleagues in anesthesiology will likely make sure that this happens. But what happens after discharge? In a recent study, Liao et al reported a higher AHI and oxygen desaturation index among OSA patients on the third postoperative night compared with preoperatively or on the first postoperative night.[6] This is very likely due to the use of respiratory depressants, especially opioids[7] and/or Rapid-Eye Movement sleep rebound.[6] Options here are to delay discharge, increase at-home monitoring, or reduce respiratory depressant use. None of these choices is particularly attractive, but neither are postoperative complications. ■

References

1. Sharma VK, et al. *Ann Intern Med* 2003;139:707-708.
2. Gross JB, et al. *Anesthesiology* 2006;104:1081-1093.
3. Hwang D, et al. *Chest* 2008; 133:1128-1134.
4. Memtsoudis S, et al. *Anesth Analg* 2011;112:113-121.
5. Namen AM, et al. *Chest* 2002;121:1741-1747.
6. Liao P, et al. *Sleep* 2009;A223:0684.
7. Rosenberg J, et al. *Anaesthesia* 1999;54:323-328.

Pharmacology Update

Exenatide Extended-Release for Injection (Bydureon™)

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 A ONCE-WEEKLY TREATMENT FOR type 2 diabetes. The new product is a subcutaneously administered extended-release form of the glucagon-like peptide-1 receptor agonist, exenatide. Exenatide extended-release is marketed by Amylin Pharmaceuticals and Alkermes PLC as Bydureon.

Indications

Exenatide-extended-release injection (ExQW) is indicated as an adjunct to diet and exercise to improve glycemic control in adult type 2 diabetics.[1]

Dosage

The recommended dose is 2 mg given by subcutaneous injection once weekly.[1] It may be administered without regard to meals.

Exenatide-extended-release for injection is supplied as a 2 mg single-dose vial for suspension.

Potential Advantages

Compared to twice daily administration of exenatide, the once-weekly formulation provides improved glycemic control and less nausea.[1,2] Patents who switched from twice-daily exenatide (ExBID) to ExQW showed additional reduction in HbA1c.[3]

Potential Disadvantages

Common adverse events include nausea (27%), diarrhea (16%), vomiting (11%), injection site pruritus (18%), and constipation (10%).[1] Similar to immediate-release exenatide, the extended-release formulation carries the box warning for risk of thyroid C-cell tumors, including medullary thyroid carcinoma.[1] It is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or patients with multiple endocrine neoplasia syndrome type 2. Exenatide has been associated with pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis. Six percent (6%) of patients develop anti-exenatide antibodies. Serious hypersensitivity has been reported during post marketing surveillance.

Comments

The once-weekly formulation is made by encapsulating exenatide in microspheres of poly-(D,L-lactide-co-glycolide).[4] When injected subcutaneously, the suspension of these microspheres forms an amalgam that releases the drug over about 10 weeks with a peak around 2 weeks (therapeutic level) and another at week 6-7 (steady state).[1] The approval of exenatide extended-release injection was based on a comparative study with twice-daily exenatide (DURATION-5).[1,2] This 24-week study randomized 252 participants (with mean baseline HbA1c 8.5% and 8.4% for the two groups) to ExQW 2 mg every week for 24 weeks or exenatide 5 µg twice daily for 4 weeks and 10 µg twice daily for 20 weeks. The primary outcome was change in HbA1c from baseline at week 24. At week 24, ExQW resulted in a greater reduction in HGbA1c (-1.6 vs -0.9 %, $P < 0.0001$). There was also a greater reduction is fasting plasma glucose (-25 mg/dL vs -5 mg/dL, $P < 0.001$). Similar weight loss was observed between the two groups and mild-to-moderate nausea was less frequent with ExQW 14% vs 35%. Injection site pruritus was higher with ExQW compared to exenatide twice daily (18% vs 1%). Glycemic control was maintained over 1 year along with positive effects on blood pressure and lipid profile.[3] In a 26-week study, ExQW was also compared to metformin, pioglitazone, and sitagliptin as monotherapy in drug-naïve type 2 patients.[5] Participants (n = 820) were randomized to ExQW 2 mg weekly, metformin 2 g/d, pioglitazone 45 mg/d, or sitagliptin 100 mg/d. At 26 weeks, ExQW was similar to metformin and pioglitazone but better than sitagliptin. Patients on the maximum daily dose of sitagliptin or pioglitazone showed improved or maintained glycemic control when switched to ExQW.[6] Similarly, the addition of ExQW to metformin was more effective than the addition of sitagliptin or pioglitazone.[7]

Clinical Implications

ExQW provides a more convenient and effective form of exenatide for the treatment of type 2 diabetes. It also may be a useful add-on therapy for patients not adequately controlled on monotherapy. There are no clinical data indicating that exenatide reduces macrovascular risk. ■

References

1. Bydureon Prescribing Information. San Diego, CA: Amylin Pharmaceuticals, Inc; January 2012.
2. Blevins T, et al. *J Clin Endocrinol Metab* 2011;96: 301-310.
3. Buse JB, et al. *Diabetes Care* 2010;33:1255-1261.
4. DeYoung MB, et al. *Diabetes Technol Ther* 2011;13: 1145-1154.
5. Russell-Jones MK, et al. *Diabetes Care* 2012;35:252-258.
6. Wysham C, et al. *Diabet Med* 2011;28:705-714.
7. Bergenstal RM, et al. *Lancet* 2010;376:431-439.

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 Questions

1. **The meta-analysis of aspirin use for the primary prevention of cardiovascular disease (CVD) made what conclusion?**
   a. Aspirin reduced the rate of total CVD events.
   b. Aspirin reduced the rate of fatal myocardial infarction.
   c. Aspirin reduced the rate of stroke.
   d. Aspirin reduced the rate of all-cause mortality.
   e. Aspirin reduced the rate of cancer mortality.

2. **Observational studies of long-term statin use repudiate the claim that they cause:**
   a. dementia.
   b. muscle aches.
   c. cancer.
   d. reduced cardiovascular events.

3. **Unrecognized obstructive sleep apnea in the perioperative period is associated with increased risk of:**
   a. ICU transfer.
   b. atrial fibrillation.
   c. death.
   d. hypercarbia.

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

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

Supplementation in Older Adults with Wounds

Source: Sallit J. Rationale for zinc supplementation in older adults with wounds. *Ann Long-Term Care: Clin Care Aging* 2012;20:39-41.

Zinc deficiency is defined as a serum zinc level < 60 mg/dL. Unfortunately, there is some question about the reliability of zinc levels to accurately reflect zinc status, since some persons with prototypic symptoms of zinc deficiency (loss of appetite, diarrhea, hair loss, delayed wound healing, and smell and taste disturbances) have normal zinc levels. Residents of long-term care facilities are at risk for zinc deficiency, both because they may be consuming diets that are lower in zinc and also because they may not absorb zinc from the diet as well as younger persons. For instance, one clinical trial of patients from nursing homes (n = 617) found that almost half had subnormal zinc levels. Some medications can compound the issue — diuretics can deplete zinc.

The roles of zinc in wound healing are diverse, including collagen and protein synthesis, cell proliferation, and immune function. The body's demands for zinc are thought to increase at the time of injury, and continue through the early inflammatory phase; hence, zinc deficiency at this time can delay wound healing.

When a long-term care facility resident sustains a wound, although it is reasonable to ascertain zinc status through serum levels and treat accordingly, it appears equally reasonable based upon a high level of suspicion of zinc deficiency to simply supplement zinc at moderate doses (15-30 mg/d), since such dosing is well tolerated. Indeed, a clinical trial at slightly higher supplementation doses (25-50 mg/d × 3 months) has documented a beneficial effect on wound healing in zinc-deficient individuals. The authors suggest that 40 mg/d be the maximum dose administered to non-deficient persons, due to tolerability issues (diarrhea, nausea, vomiting, vertigo). ■

Association of Psoriasis with CV Risk Factors

Source: Shapiro J, et al. Psoriasis and cardiovascular risk factors: a case-control study on inpatients comparing psoriasis to dermatitis. *J Am Acad Dermatol* 2012;66:252-258.

In the last decade, the recognition that rheumatoid arthritis (RA) is associated with adverse cardiovascular (CV) outcomes has been increasingly highlighted, to the point that some voices suggest including the presence of RA as a formal CV risk factor of similar impact to having a low HDL. Psoriasis (PSR) and RA share some common features, especially including their responsiveness to similar disease-modifying therapies, suggesting common pathophysiology. The mechanism by which RA imparts increased CV risk is unclear, though it is commonly attributed simply to the deleterious effects of chronic inflammation. Might PSR also be associated with CV risk?

To examine this issue, Shapiro et al performed a case-control study that compared PSR inpatients (n = 1079) to age- and gender-matched inpatient controls who had other non-psoriatic dermatitis issues, such as atopic dermatitis and contact dermatitis (n = 1079).

Multivariate logistic regression found that PSR was associated with greater odds ratio (OR) for diabetes (OR = 1.43) and hypertension (OR = 1.31). Although PSR was associated with CVD, the association was no longer present when correcting for obesity and hypertension. Although the pathogenesis of increased CV risk associated with PSR is uncertain, the fact that PSR produces systemic effects on tumor necrosis factor alpha and other inflammatory markers may be critically linked. ■

Occupational Stress and Hypertension

Source: Rosenthal T, Alter A. Occupational stress and hypertension. *J Am Soc Hypertens* 2012;6:2-22.

The consequences of job-related stress (JRS) have been the object of a great deal of research. Of course it is difficult to determine the best measurement tool for JRS, and it is equally difficult to explain how similar levels of JRS are interpreted and managed differently by different individuals. Some of the data on JRS and its relationship to blood pressure suggest that JRS need not necessarily be perceived to be associated with adverse effects. Nonetheless, several lines of evidence lead to the conclusion that identification of JRS is replicable and consequential in some settings.

For instance, a review of data from 34 studies on professional drivers (e.g., bus drivers) found a consistently increased risk of heart disease and hypertension, attributed to a wide range of psychological and physical stressors. To describe the inherent stressful conflict of bus drivers, the authors remind us that the drivers are constantly dealing with the competing agendas of staying on time and optimizing safety.

Despite the large amount of descriptive data that help us identify the negative impact of job stress on health, there is little substantive information that anyone has found highly effective methods to improve outcomes from JRS. It is likely that reducing JRS and its consequences will require interventions on a public health level. ■

A Helpful Hand from aVR

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

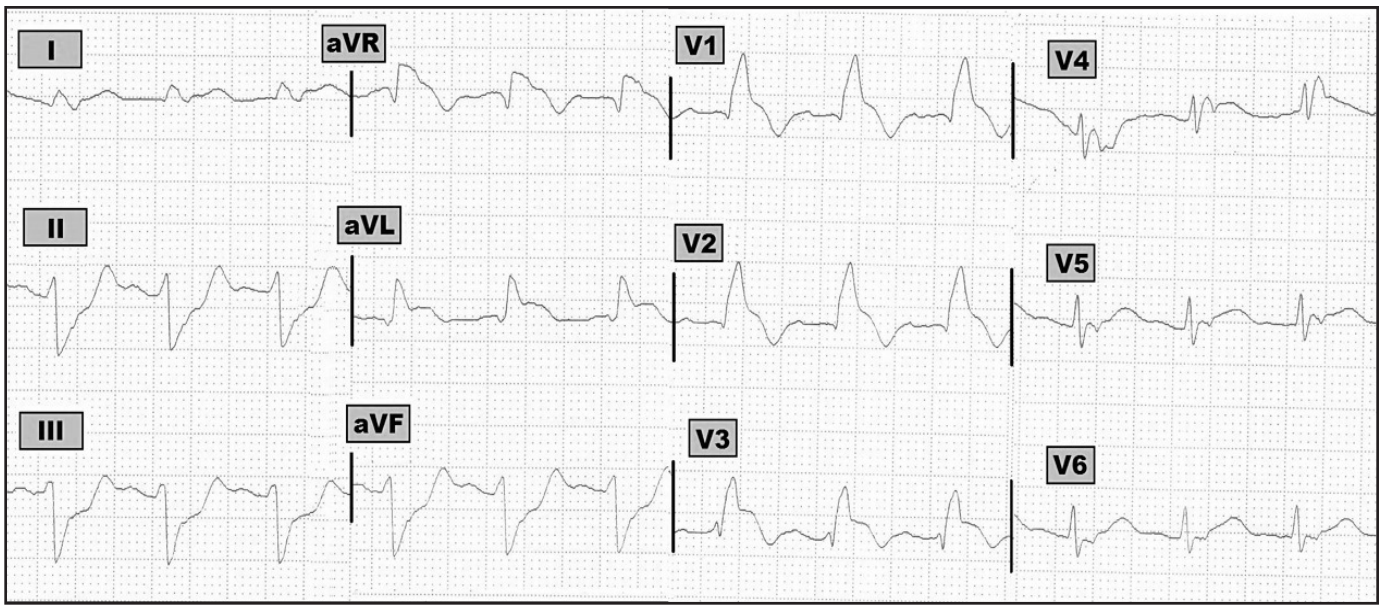

Figure — 12-lead ECG obtained from a patient with new-onset chest pain.

Scenario: The 12-lead ECG shown above was obtained from a patient with new-onset chest pain. Where is the acute lesion likely to be?

Interpretation: The rhythm is sinus tachycardia at about 100/minute. The PR interval is relatively long given the fast rate (though not quite satisfying criteria for 1st degree AV block). The QRS complex is wide in the pattern of right bundle branch block (RBBB). There is marked left axis deviation consistent with left anterior hemiblock — which makes the conduction defect at least a bifascicular block. There are small q waves in leads aVL, V1, and V2, with the most remarkable finding being the marked ST elevation in multiple leads (including leads I, aVR, aVL, and V1-through-V6). In addition, there is reciprocal ST depression in each of the inferior leads. Obviously, extensive myocardial infarction is acutely ongoing. Specifically, there very likely is acute occlusion of the left main coronary artery. This is an indication for urgent cardiac catheterization.

This tracing provides an excellent example of one of the very few instances when lead aVR may prove highly insightful. Most of the time, the remote right-sided and superior lead location of aVR provides little clinically useful information beyond suggesting on rare occasions that there may be lead misplacement or dextrocardia. It is helpful to be aware of two additional situations in which recognition of ST elevation in lead aVR may be instructive: 1) in the presence of diffuse ST depression, the finding of ST elevation in lead aVR suggests the patient has either three-vessel or left main coronary artery disease; and 2) in patients with acute coronary syndrome who have acute left main coronary artery occlusion. The findings in the Figure are highly suggestive of the latter situation. This is because the patient has new-onset chest pain; there is marked and diffuse ST segment elevation in multiple leads with reciprocal ST depression in the remaining leads; there is significant conduction system disease including RBBB (which is highly characteristic of acute left main occlusion); and there is more than 1 mm of ST elevation in lead aVR. ■

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