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INSIDE

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A Guide to CV Guidelines

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD, MA

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

Synopsis: *Guidelines to assess cardiovascular risk are often inconsistent and poorly developed.*

Source: Ferket BS, et al. Systematic review of guidelines on cardiovascular risk assessment: Which recommendations should clinicians follow for a cardiovascular health check? *Arch Intern Med* 2010;170:27-40.

Among our myriad functions, family and internal medicine physicians see adults for health maintenance exams. As part of these exams, we screen patients for risk factors to predict and, perhaps, prevent disease. The particulars of these screens are almost always dictated by guidelines issued by specialty societies or governmental agencies. By their nature, guidelines can vary in quality and, at times, can contradict each other. This can occur based on what evidence the authors used to construct the guidelines or by inherent bias. So, whose guidelines should you use and trust?

These investigators from the Netherlands and Boston focused on cardiovascular (CV) risk assessment guidelines. They looked at CV guidelines that could be applied to adults without established CV disease (CVD) or already receiving treatment for diabetes, hypertension, or hypercholesterolemia and were designed to prevent a first CVD event. They performed a systematic review of the English literature from 2003 to 2006, searching MEDLINE, CINAHL, the National Guideline Clearinghouse (USA), the National Library for Health on Guidelines Finder (United Kingdom), the Canadian Medical Association Infobase, and the G-I-N International Guideline Library. An astounding 1984 citations were identified. After appropriate exclusion, 114 were fully reviewed and another 87 were excluded (again, appropriately: not the most recent version, developed before 2003, not focused on screening, not an asymptomatic population, etc.), leaving 27 for formal review.

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The authors applied the Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool to each guideline to ascertain the quality of the guideline's development. AGREE considers conflicts of interest and the reporting of the evidence search methods, evidence selection criteria, recommendations formation methods, benefits and risks, supporting evidence, external expert review, and process for updating. A single guideline might have multiple recommendations. Each guideline received a percent rigor score with 50% as the cutoff for a well developed guideline. Of the 27 guidelines, 17 received scores ≥ 50%.

The groups issuing at least one high-scoring guideline included: the National Institute for Health and Clinical Experience (NICE, UK), the Scottish Intercollegiate Guidelines Network (SIGN), the American Heart Association (AHA), the American Stroke Association (ASA), the New Zealand Guidelines Group (NZGG), the World Health Organization (WHO), the European Society of Cardiology (ESC), the Canadian Cardiovascular Society (CCS), the U.S. Preventive Services Task Force (USPSTF), the National Heart, Lung, and Blood Institute (NHLBI, USA), National Health and Medical Research Council (NHMRC, Australia), European Association for the Study of Diabetes (EASD), the Canadian Diabetes Association (CDA), the Canadian Task Force on Preventive Health Care (CTF), and the American Association of Clinical Endocrinologists (AACE). All of the USPSTF guidelines scored ≥ 95%. Not every group fared as well. For instance, the AHA's guideline on total cardiovascular risk scored 76%, but its dyslipidemia and dysglycemia guidelines (issued jointly with the American Cancer Association and the American Diabetes Association) scored only 14%.

Among the 27 guidelines, there were areas of disagreement. For instance, the USPSTF found the evidence insufficient to recommend screening for dysglycemia. The NHMRC recommended screening individuals ≥ 45 years with a body mass index (BMI) ≥ 30 kg/m^2, but found insufficient evidence to screen individuals ≥ 55 years without another risk factor. Furthermore, there were inconsistencies across guidelines regarding the use of aspirin, statins, and hypertensive agents in patients with diabetes.

■ COMMENTARY

In primary care, we want to practice evidence-based medicine, but we do not have the time to review the literature and develop our own strategies for application. We depend on expert colleagues to do this. CVD is the No. 1 killer in the Western world. To learn that CV guidelines (even well-constructed ones) are not consistent is discouraging. I have relied on the USPSTF to "guide" me, and this has worked well for me since generally they are conservative and usually noncontroversial (notwithstanding the recent update of mammography guidelines[1]). Some variation in recommendations is inevitable since, even among relatively well-off countries, there are differences in populations and what is expected of their health care systems. Certainly, depending on what populations are studied and what studies are used to develop a particular guideline, we could end up with incongruent recommendations, but we don't expect major differences.

In an invited commentary, Smith writes, "Yet concerns remain about the process by which guidelines might be developed, and a lack of congruence among their recommendations is one reason for low implementation by health care providers."[2] I want to emphasize that the authors of this review of CV guidelines did not look at the evidence that was used to develop the guidelines. They looked at how they were developed. That said, I think it's important that guidelines be developed in accordance with the AGREE tool, especially the disclosure of conflicts of interest. Smith concludes, "Further progress will depend on our ability to develop guidelines that are free from external bias, an agreement on a definition for global cardiovascular risk that is broadly applicable, and the identification of target populations in terms that take into account important regional variations in risk and health care delivery." To me, it's a matter of trust. ■

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Questions & Comments
Please call **Paula Cousins**, Senior Managing Editor, at (404) 262-5468

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New Considerations in the Work-up of Patients with Chronic Cough

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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Dr. Phillips is a consultant to Cephalon and Ventus and serves on the speakers bureaus of Cephalon and Boehringer Ingelheim.

Synopsis: *About a third of patients with sleep apnea have chronic cough. Such patients are more likely to be women and to have heartburn and rhinitis.*

Source: Chan KK, et al. Chronic cough in patients with sleep-disordered breathing. *Eur Respir J* 2010;35:368-372.

These authors set out to learn about the factors associated with chronic cough in patients with sleep-disordered breathing (SDB). To do this, they recruited a convenience sample of patients who had overnight sleep studies because of suspected sleep apnea. Patients who agreed to participate completed a questionnaire about demographics, cough symptoms and severity, and conditions commonly associated with cough. Patients were also queried about their general medical history, presence of rhinitis or hay fever, dry mouth, choking, snoring, smoking history, medications, and alcohol consumption. Chronic cough was defined as having had a cough for longer than 2 months. Cough severity was rated on a visual analogue scale. The impact of cough on quality of life was assessed with a standard questionnaire. Sleepiness was assessed with an Epworth Sleepiness Scale.

The investigators considered 108 patients for this study, but excluded nearly half of them because they were smokers, had known respiratory disease, were taking angiotensin converting enzyme (ACE) inhibitors, had a recent upper respiratory tract infection, or had sleep studies that did not show sleep apnea. Thus, the study population consisted of 55 patients. One-third of these patients had chronic cough. Patients with sleep apnea and chronic cough had impaired quality of life in all health domains. There was no relationship between the severity of the sleep apnea and prevalence or severity of cough. Five (9%) of these patients were taking proton pump inhibitors, H2 antagonist medication, or both.

Compared to those who only had sleep apnea, patients who had both sleep apnea and chronic cough were more likely to be women and to report symptoms of nocturnal heartburn (28% vs 5%; $P = 0.02$), rhinitis (44% vs 14%; $P = 0.01$), dysphagia (33% vs 11%; $P = 0.04$), and chest pain (44% vs 19%; $P = 0.05$). Of the patients with chronic cough and sleep apnea, only 22% did not report symptoms of gastroesophageal reflux or rhinitis. There was a trend for increased thyroid disease in patients with cough compared to those without. There were no significant differences in symptoms of shortness of breath, wheeze, sputum production, snoring, dry mouth, or choking between the patients with chronic cough compared to those without. There were no significant differences in sleepiness, snoring symptoms, or severity of sleep apnea between the two groups. In addition, the prevalence of CVD did not differ significantly between groups with chronic cough and those without.

■ COMMENTARY

Chronic cough is a vexing and common problem in primary care. In non-smokers, the commonest causes of chronic cough are asthma, gastroesophageal reflux, and rhinitis.[1] Despite comprehensive work-ups, a cause of cough is not found in up to 20% of patients who present with chronic cough.[2] Although chronic cough is already known to be commonly associated with sleep apnea and daytime sleepiness,[3,4] this is the first study to investigate the prevalence and severity of chronic cough in sleep apnea patients. The primary finding is that about a third of patients with sleep apnea have chronic cough. The possible mechanisms of the relationship between cough and SDB include gastroesophageal reflux, rhinitis, and upper airway inflammation.[3]

Since the cause of cough is never determined in many patients who report this problem, it is possible that evaluation for sleep apnea might help determine a possible cause and treatment. Although this study did not investigate whether cough would improve in patients with sleep apnea who are treated with CPAP, the authors speculate that it might. When all else fails, consider a sleep study. ■

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Aortic Stenosis — When to Operate

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

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

Synopsis: *Even if asymptomatic, early elective aortic valve replacement should be considered for increasingly symptomatic patients with severe aortic valve stenosis because they have a poor prognosis with a high event rate and a risk of rapid functional deterioration, especially if the peak aortic jet velocity is above 5.5 m/sec.*

Source: Rosenhek R, et al. Natural history of very severe aortic stenosis. *Circulation* 2010;121:151-156.

THE PROGNOSIS FOR ASYMPTOMATIC PATIENTS WITH severe aortic stenosis is usually quite favorable and a watchful waiting approach, which has been demonstrated to be quite safe, is usually the clinical approach utilized by most physicians.[1-4] However, it must be clearly recognized that when symptoms start to develop in patients with severe aortic stenosis, a very poor prognosis can be expected unless an aortic valve replacement procedure is urgently performed.[5-7] Asymptomatic patients usually are not recommended for aortic valve replacement for many reasons, including the immediate operative risk, the long-term morbidity and mortality, and the potential need for reoperation.[8] However, many clinicians have argued in favor of an earlier intervention because of the higher operative risk that occurs as patients become increasingly symptomatic,[9] the risks of late symptom reporting by stoical patients, and the risk of sudden death even though this risk is generally quite low in asymptomatic patients.[1,2]

Rosenhek and his colleagues prospectively followed 116 consecutive, asymptomatic patients with very severe isolated aortic stenosis in an attempt to define its natural history and to determine which patients should be selected for valve replacement before they became symptomatic. They concluded that in asymptomatic patients with severe aortic stenosis, the presence of a calcified aortic valve combined with rapid hemodynamic progression identified a high-risk population in whom early elective valve replacement should be considered.[2]

■ COMMENTARY

Despite being asymptomatic, patients with very severe aortic stenosis quite often have a poor prognosis with a high event rate and a significant risk of rapid functional deterioration. This study by Rosenhek et al demonstrated that event-free survival rate for patients with severe aortic stenosis (defined by a peak aortic jet velocity of 4.0-5.0 m/sec) diminished from 82% at year 1 to 39% at year 4. The survival rates were significantly worse for patients with a very severe stenosis (defined by a peak jet velocity of 5.0-5.5 m/sec): These patients had a survival rate of only 76% at year 1 and 17% a year 4. Patients with aortic stenosis and associated coronary artery disease had a worse chance of event-free survival because a more rapid hemodynamic deterioration usually occurs.[2,8] However, the presence of coronary artery disease was not found to be of statistically significant additional prognostic importance and neither was treatment with statin drugs, renin-angiotensin-aldosterone system inhibitors, or beta blockers.

Clinicians should recognize that patients with very severe aortic stenosis (i.e., defined as those patients with a peak aortic jet velocity ≥ 5.5 m/sec) tend to have more severe and rapid onset of symptoms than do those patients with a lower jet velocity. Therefore, even asymptomatic patients with very severe aortic stenosis should be considered for early elective valve replacement surgery because of the risk of rapid functional deterioration often associated with an increased event rate. All patients with aortic stenosis should be closely followed and evaluated carefully with respect to early symptom development. Additionally, they should be frequently monitored echocardiographically to determine any aortic jet velocity changes of significance. ■

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Pharmacology Update

Liraglutide Injection (Victoza®)

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.

A SECOND HUMAN GLUCAGON-LIKE PEPTIDE 1 (GLP-1) analog/receptor agonist has been approved by the FDA for the treatment of type 2 diabetes mellitus (DM2). Liraglutide is produced by recombinant DNA technology and its amino acid sequence is more similar to native GLP-1 than exenatide (97% vs 53%). It is marketed by Novo Nordisk as Victoza®.

Indications

Liraglutide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with DM2.[1]

Dosage

The recommended dose is 0.6 mg given as a subcutaneous injection once daily, independent of meals.[1] This lower dose is recommended to reduce gastrointestinal symptoms. After one week the dose should be increased to 1.2 mg. If glycemic control is not achieved, the dose can be increased to 1.8 mg. The injection should be given in the abdomen, thigh, or upper arm. To reduce the risk of hypoglycemia, there should be a dose reduction of concomitant antidiabetic drugs that stimulate insulin secretion.

Liraglutide is available as a prefilled multidose pen (6 mg/mL, 3 mL) that is calibrated to deliver 0.6 mg, 1.2 mg, or 1.8 mg.

Potential Advantages

Liraglutide has an elimination half-life of 13 hours and is suitable for once-daily administration. It can be given independent of meals. It appears to be more effective in achieving glycemic control and may be better tolerated than exenatide.[2]

Potential Disadvantages

The most common adverse events are gastrointestinal in nature (e.g., nausea, 28.4%; diarrhea, 17.1%; and vomiting, 10.9%).[1] These were the primary reasons for withdrawal from clinical trials (5% vs 0.5% for comparators). Pancreatitis and thyroid C-cell tumors are rare but serious adverse events associated with liraglutide.

Comments

GLP-1 and glucose-dependent insulinotropic polypeptide are hormones responsible for the incretin effect resulting in insulin secretion in response to oral glucose ingestion, inhibition of glucagon secretion, and delay in gastric emptying. The incretin effect may be diminished in DM2. GLP-1 receptor agonists (e.g., exenatide, liraglutide) and DPP-4 inhibitors (sitaglitin, saxaglitin) have been developed as incretin-based therapies. The approval of liraglutide was based on five double-blind trials, a 52-week monotherapy trial that compared the drug to glimepiride and four 26-week add-on studies.[1,3-7] In the short-term studies, liraglutide or placebo was added to glimepiride, metformin, metformin + rosiglitazone, or metformin + glimepiride. The primary endpoint was the change in HbA1c and secondary endpoints included change in fasting plasma glucose (FPG) and body weight. In the 52-week trial (n = 745), liraglutide (1.2 mg and 1.8 mg) was compared to glimepiride (8 mg).[5] Liraglutide showed statistically significant adjusted mean differences in HbA1c of -0.3% and -0.6% (for 1.2 mg and 1.8 mg, respectively) compared to glimepiride. Differences in FPG were -10 and -20 mg/dL and weight reductions were -3.2 and -3.6 kg. Systolic blood pressure was reduced by 3.64 mm Hg,

while glimepiride was associated with a small mean increase in systolic BP. In the short-term studies (n = 3246), the addition of liraglutide showed a statistical difference in HbA1c of -0.9% to -1.4%, and -28 to -38 m/dL in FPG. Significant weight reduction was reported with the liraglutide + metformin compared to glimepiride + metformin. Liraglutide as monotherapy or added to metformin significantly reduced fat mass and fat percentage compared to glimepiride.[8] When liraglutide or exenatide was added to existing oral antidiabetic drugs (n = 464), liraglutide was shown to be more effective than exenatide in terms of glycemic control (HbA1c reduction of 1.12% vs 0.79%, and FPG reduction of 29 mg/dL vs 11 mg/dL). However, postprandial glucose levels were better with exenatide. The addition of liraglutide or insulin glargine to metformin and glimepiride produced similar improvement in glycemic control.[7] Liraglutide was better tolerated in terms of the frequency of nausea and minor hypoglycemia. Liraglutide is generally well tolerated. Common adverse events are gastrointestinal in nature (nausea, diarrhea, vomiting). These generally decline after several weeks of use and do not appear to be dose-dependent.[9]

Clinical Implications

Type 2 diabetes mellitus is a multifaceted progressive disorder. As the disease progresses, it becomes more difficult to maintain glycemic control. Liraglutide appears to be an improvement over the existing GLP-1 agonist, exenatide. GLP-1 agonists are considered tier 2 drugs in the ADA guidelines. ■

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CME Questions

9. A systematic review of guidelines for screening for cardiovascular risk assessment found that guidelines:

a. are always developed in total compliance with the Appraisal of Guidelines Research and Evaluation (AGREE) tool.
b. are always free of conflicts of interest.
c. always make identical recommendations.
d. None of the above

10. The prevalence of chronic cough in patients with sleep apnea is approximately:

a. 15%.
b. 35%.
c. 55%.
d. 75%.

Answers: 9. d, 10. 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.

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
Dr. Kuritzky is a consultant for Sucampo Pharmaceuticals, Takeda, Boehringer Ingelheim; and is a consultant and on the speaker's bureau for Novo Nordisk, Lilly, Daiichi Sankyo, Forest Pharmaceuticals, Cephalon, Novartis, and Sanofi Aventis.

Remission of type 2 diabetes with bariatric surgery

Source: Wilson JB, Pories WJ. Durable remission of diabetes after bariatric surgery: What is the underlying pathway? *Insulin* 2010;5:46-55.

The burgeoning population of individuals with type 2 diabetes corresponds to a parallel increase in obesity. Although bariatric surgery produces prompt and sustainable weight loss, the post-surgical rapidity with which derangements of diabetes resolve defies explanation by weight loss alone.

Bariatric surgical procedures that eliminate food contact with the duodenum and jejunum — as opposed to gastric banding type procedures — produce not only substantial weight loss, but also provide remission of type 2 diabetes within days. Indeed, as many as 80% of type 2 diabetes patients leave the hospital with no diabetes medications, and more than 75% remain diabetes-free 5 years later. Similar reversion to normal glucose handling has also been seen in patients with impaired glucose tolerance who have bypass surgery.

Post-surgical benefits of bariatric surgery include resumption of normal menstrual function, BP and lipid improvements, and reductions in diabetes-related mortality. Studies of gastric banding conclude that weight loss is responsible for these favorable outcomes. In contrast, bariatric bypass surgery, although enjoying benefits attributable to weight loss, has other operant mechanisms: One report of intestinal bypass in lean type 2 diabetics found resolution of diabetes without weight loss.

The GI tract has been increasingly recognized as a critical player in glucose dysregulation, as evidenced by evolution of the incretin mimetics and DPP-4 inhibitors. Resolution of dysglycemia within a few days — prior to meaningful weight loss — is characteristic of bariatric bypass surgery. ■

Ipratropium and cardiovascular events in COPD

Source: Ogale SS, et al. Cardiovascular events associated with ipratropium bromide in COPD. *Chest* 2010;137: 13-19.

Bronchodilators (i.e., inhaled beta agonists and anticholinergics) are the foundation of symptomatic care for COPD. Metered-dose inhaler administration of ipratropium (IPR) is generally very well tolerated, and associated with few, if any, adverse symptoms. Nonetheless, there remains some conflict about the cardiovascular safety of anticholinergic bronchodilators in COPD. One meta-analysis suggested as much as a 53% increased relative risk for MI in COPD patients treated with IPR; in contrast, a large randomized prospective trial with tiotropium (n = 6000, approximately) did not find any signal for increased cardiovascular events.

Ogale et al performed a cohort study comprised of newly diagnosed COPD patients (n = 82,717) attending an Illinois VA hospital.

Risk for a cardiovascular event was 29% higher in COPD patients treated with IPR than comparators. Risk was time-related: Those with at least a 6-month interval since last exposure to an anticholinergic were not at greater risk. The mechanism by which anticholinergics might increase cardiovascular risk is not clear, although a dose-response relationship between IPR and supraventricular tachyarrhythmia incidence noted in the Lung Health Study intimates a possible connection. ■

Home vs office BP measurement

Source: Beitelshees AL, et al. Comparison of office, ambulatory, and home blood pressure antihypertensive response to atenolol and hydrochlorthiazide. *J Clin Hypertens* 2010;12: 14-21.

In untreated subjects with hypertension (HTN), 24-hour ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBP) have been shown to provide better indication of risk than office blood pressure (OBP). On-treatment BP measurement using the same techniques shows similar associations: ABPM is better than HBP, which is better than OBP for risk prediction. Since not all patients can be availed of ABPM, HBP monitoring has received increased advocacy.

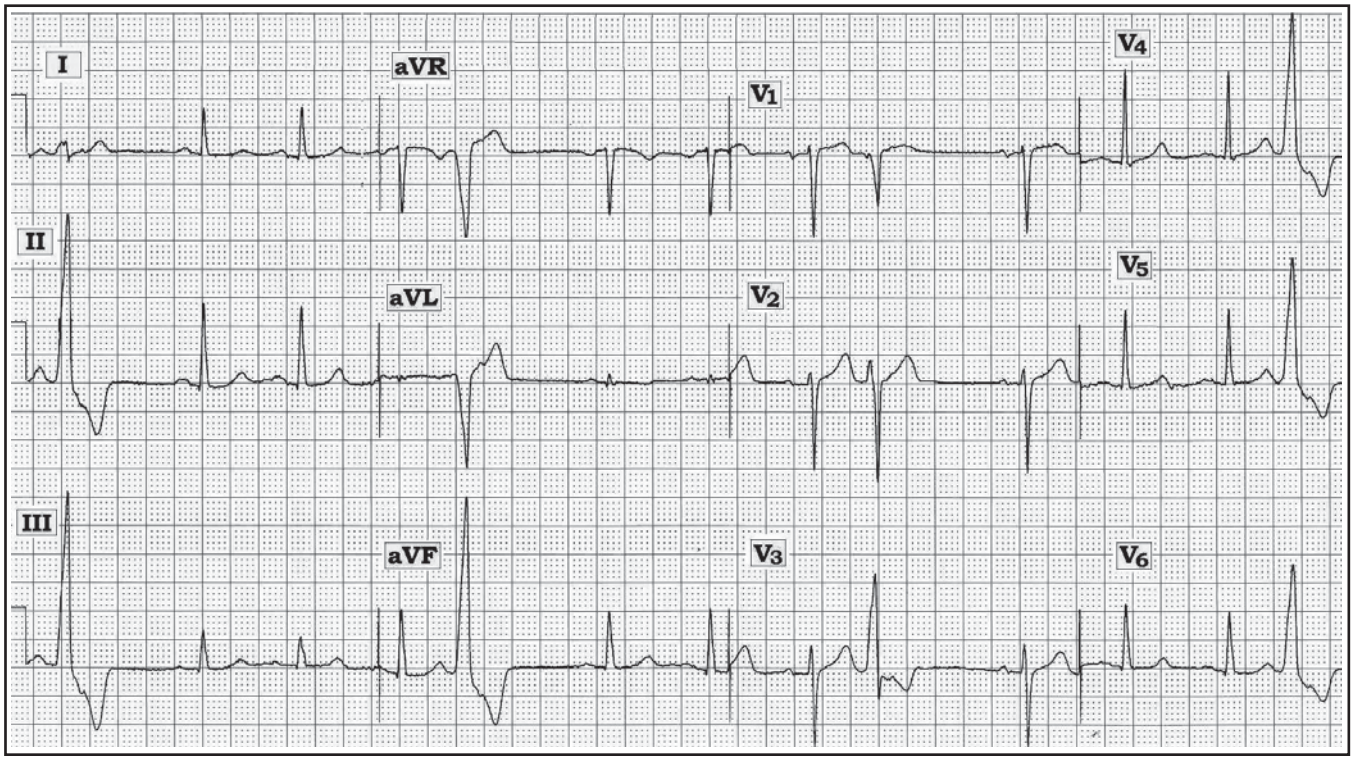
HCTZ and atenolol (ATN) are two of the most commonly prescribed antihypertensive agents in the United States. Beitelshees et al performed a randomized controlled trial to assess the relative accuracy of OBP and HBP compared to the gold standard ABPM in subjects (n = 418) treated with HCTZ, atenolol, or the combination.

For both systolic and diastolic BP, correlation with ABPM was significantly better for HBP than OBP. For example, OBP overestimated treatment effects on SBP by 4.6 mm Hg compared with HBP. Recent HTN consensus groups have endorsed routine HBP monitoring; these data support the role of HBP monitoring as a better risk predictor than OBP. ■

What Is the Frequency?

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 66-year-old woman with chest discomfort. What is going on in this tracing?

Interpretation

The difficulty interpreting this 12-lead tracing results from the lack of a lead II rhythm strip. There are a total of 13 beats on this 3-channel, simultaneously recorded 12-lead tracing. QRS morphology of the normal, sinus-conducted complexes changes every 3-4 beats with each lead change. This makes it challenging to distinguish the new QRS morphology of sinus beats resulting with each lead change from the frequently occurring premature ventricular contractions (PVCs) that are seen on this tracing. Looking along the lower row of beats, the first complex in lead III is a PVC. The 5th, 9th, and 13th beats are also PVCs. Each of these beats occurs early, is obviously widened, and not preceded by a premature P wave. In contrast, even though QRS morphology of the 1st complex in leads V_3 and V_6 differs markedly from QRS morphology just preceding the lead change, we know that the 1st complex in leads V_3 and V_6 is a sinus beat, because the QRS is of normal duration, it is on time (rather than early), and the QRS is preceded by a sinus P wave. The rhythm is therefore ventricular quadrigeminy (sinus rhythm with every 4th beat a PVC). Assessing Q-R-S-T morphology of the sinus-conducted beats suggests that this ECG is otherwise normal. ❖

In Future Issues: **BMI, Metabolic Syndrome, and Cardiac Death in Middle-aged Men**

PHARMACOLOGY WATCH

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Oral Treatments for Relapsing-remitting MS

In this issue: Two oral medications for relapsing-remitting MS in phase III development; antihypertensives find new uses; *Ginkgo biloba* does not prevent cognitive decline in elderly; and FDA Actions.

Oral medications for relapsing-remitting MS

Two new oral medications are effective treatments for relapsing-remitting multiple sclerosis (MS) according to three studies published on-line in the *New England Journal of Medicine*. Fingolimod and cladribine differ in the mechanism of action but both reduce the number of potentially auto-aggressive lymphocytes that are available to enter the central nervous system. In the Cladribine Tablets Treating Multiple Sclerosis Orally (CLARITY) trial, two different doses of cladribine were compared to placebo with the endpoint being relapse at 96 weeks. Both doses were more effective than placebo at preventing relapses and reducing brain lesion count on MRI ($P < 0.001$ for all comparisons). The drug was associated with lymphocytopenia and a higher risk of herpes zoster.

Fingolimod was compared to placebo in the FREEDOMS trial and compared to injectable interferon in the TRANSFORMS trial. The 24-month FREEDOMS trial compared two doses of fingolimod to placebo and similarly found a lower rate of relapse ($P < 0.001$ for both doses) and disability progression ($P = 0.02$ for both doses). The drug also reduced the number of new lesions found on MRI. Significant side effects included bradycardia, AV block, macular edema, elevated LFTs, and mild hypertension. When compared to interferon, fingolimod was associated with significantly lower annualized relapse rates at both doses tested ($P < 0.001$ for both comparisons), although there was no significant difference with respect to progression of disability. Two fatal infections occurred with the higher dose of fingolimod (disseminated primary varicella zoster and herpes simplex encephalitis). (All three studies published on-line at www.NEJM.org, Jan. 20, 2010).

An accompanying editorial calls the arrival of oral formulations of MS drugs "welcome news for the estimated 2.5 million people worldwide with this chronic, disabling disease." While suggesting these drugs "support a change in treatment approach to directly prevent immune-related injury," the editorial also suggests that long-term goals of MS therapy are currently lacking (published online at www.NEJM.org, Jan. 20, 2010). Both drugs are in phase III trials for treatment of MS; cladribine is currently approved in parenteral form for treatment of hairy cell leukemia. ■

Antihypertension drugs for AF and dementia?

Different classes of blood pressure (BP) medications may have different benefits according to two new studies. In the first study, researchers from the United Kingdom performed a nested

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case-control analysis to evaluate whether different antihypertensive drug classes may alter the risk for atrial fibrillation. The researchers reviewed records from a large patient population, specifically patients who were on a single agent for lowering BP. A lower odds ratio (OR) for atrial fibrillation was noted with ACE inhibitors (OR, 0.75; 95% confidence interval [CI], 0.65-0.87), angiotensin receptor blockers (ARBs) (OR, 0.71; 95% CI, 0.57-0.89), and beta-blockers (OR, 0.78; 95% CI, 0.67-0.92) compared with current exclusive therapy with calcium channel blockers. Although the researchers were unable to assess why patients were receiving one class of blood pressure medicine over another, they concluded that long-term therapy with ACE inhibitors, ARBs, or beta-blockers reduces the risk for atrial fibrillation compared with calcium channel blockers. These findings generally relate to patients with mild hypertension, since patients on multiple drugs were excluded from the study (*Ann Intern Med* 2010;152:78-84).

In the second study, researchers from Boston set out to investigate whether ARBs reduce the risk of Alzheimer's disease and dementia or reduce the progression of both diseases. More than 800,000 predominately male participants, age 65 or older with cardiovascular disease, were studied. Patients were divided into three cohorts (ARBs, lisinopril, and other cardiovascular drugs as a comparator) and followed over 4 years, with adjustments for age, diabetes, stroke, and cardiovascular disease. Hazard rates for dementia in the ARB group were 0.76 (95% CI, 0.69-0.84) compared to the cardiovascular comparator, and 0.81 (95% CI, 0.73-0.90) compared to the lisinopril group. In patients with pre-existing Alzheimer's disease, ARBs were associated with significantly lower risk of admission to a nursing home. The combination of the ARB and ACE inhibitor was better than ACE inhibitor alone in preventing dementia and reducing admission to nursing home. The authors conclude that ARBs are associated with a significant reduction in the incidence and progression of Alzheimer's disease and dementia compared to ACE inhibitors or other cardiovascular drugs (BMJ 2010;340:b5465, doi: 10.1136/bmj.b5465, published on-line Jan. 12, 2010). An accompanying editorial points out that several studies have shown that treatment with any antihypertensive is associated with a lower risk of cognitive decline or incident dementia in older adults. What is not clear is whether some antihypertensives also have other biological mechanisms that help prevent dementia. It is plausible that ARBs are more neuroprotective than other drugs because of their effect on type 2 angiotensin receptors in the brain (*BMJ* 2010:340;b5409, doi: 10.1136/bmj.b5409, published on-line Jan. 12, 2010). ■

Ginkgo does not prevent cognitive decline

The National Center for Complementary and Alternative Medicine (NCCAM) was founded during the Clinton administration as part of the National Institutes of Health to investigate complementary and alternative medicines. Many of the NCCAM-funded studies, however, have shown no benefit from complementary or alternative treatments, and that is the case with a new study looking at *Ginkgo biloba* and cognitive function in older adults. *Ginkgo biloba*, which is widely marketed as an aid to preventing cognitive decline and dementia, was previously found to have no benefit in reducing the incidence of Alzheimer's disease or dementia overall (*JAMA* 2008;300:2253-2262).

In a new study sponsored by NCCAM, researchers set out to determine whether *Ginkgo biloba* slows the rate of global or domain-specific cognitive decline in older adults. More than 3000 participants age 72-96 years were enrolled and randomized to *G. biloba* 120 mg or placebo twice daily. Rates of change over time in two different objectives cognitive tests, as well as neuropsychological tests, were the primary endpoints. There was no difference in the decline in cognitive scores between *Ginkgo biloba* and placebo in any of the domains including memory, attention, and visuospatial abilities, language, or executive functions. There was also no difference in the rate of change in the standardized cognitive exams. The authors conclude that compared to placebo, *Ginkgo biloba* did not result in less cognitive decline in older adults (*JAMA* 2009;302: 2663-2670). ■

FDA Actions

Novo Nordisk has received approval to market liraglutide, a once-daily injection for the treatment of type 2 diabetes in adults. The drug is a glucagon-like peptide-1 receptor agonist similar to exanatide (Byetta®). The company is required to perform additional post-marketing cardiovascular studies as well as a 5-year epidemiological study to evaluate the risk of thyroid cancer. Liraglutide will be marketed under the trade name Victoza®. ■