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INSIDE

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Transmission of Influenza H1N1: What Is Not Being Done

ABSTRACT & COMMENTARY

By Leslie A. Hoffman, PhD, RN

Department of Acute / Tertiary Care, School of Nursing, University of Pittsburgh

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

This article originally appeared in the October issue of Critical Care Alert. *At that time it was reviewed by William Thompson, MD, Associate Professor of Medicine, University of Washington, Seattle. Dr. Thompson reports no financial relationship to this field of study.*

Synopsis: *Less than one-third of health care workers with probable or possible patient-to-health care provider transmission of H1N1 reported consistently using a surgical mask or N95 respirator.*

Source: Novel Influenza A (H1N1) Virus Infections Among Health — Care Personnel — United States, April-May 2009. *MMWR Morb Mortal Wkly Rep* 2009;58:641-645.

AFTER IDENTIFYING THE FIRST 2 CASES OF NOVEL INFLUENZA (H1N1) infection in the United States in mid-April 2009, the Centers for Disease Control and Prevention (CDC) provided interim recommendations to reduce the risk of transmission in health care settings. To better understand the risk of health care providers (HCPs) becoming infected with H1N1 as a consequence of patient care and the impact of these recommendations, the CDC requested data regarding infected HCPs. As of May 13, 48 reports had been received; 26 included detailed information regarding risk factors that potentially led to the infection. Of those reporting H1N1 infection, 5 were RNs (20%), 4 were nursing assistants (16%), 4 were physicians (16%), and 12 were employed in other occupations.

Of the 26 reports, 13 (50%) HCPs were deemed to have acquired H1N1 infection in a health care setting, including 12 instances of possible or probable patient-to-HCP transmission and one instance of possible or probable HCP-to-HCP transmission. The remaining

13 cases were attributed to transmission in the community (n = 11) or an unknown source (n = 2). Among those with possible or probable patient-to-HCP transmission, only 3 reported always using a surgical mask or an N95 respirator. The individual who reported using the N95 respirator also reported never having had a fit test and did not report information on gown or glove protection. Only 5 respondents reported always using gloves. None reported always using eye protection.

■ COMMENTARY

Routine infection-control recommendations to minimize the risk of acquiring influenza include vaccination, patient isolation, and standard infection-control precautions. For H1N1, because of the previous lack of a vaccine and limited information regarding the severity and transmissibility, there were additional recommendations to use a fit-tested N95 respirator, eye protection, and contact precautions during patient care. Given the potential seriousness of infection with H1N1, it is disturbing that HCPs did not follow these guidelines. Although this report did not include information on why recommendations were not followed, similar behavior has been documented with regard to other infection-control measures, such as hand hygiene.

Many explanations have been offered for noncompliance, including the belief that infection-control practices are unnecessary or inconvenient, inadequate education, and failure to appreciate the significance of risk to self or patients. The report indicates that of the 3 HCPs who reported always using a surgical mask or an N95 respirator, 1 had not been fit-tested for the respirator and none used all the recommended personal protective equipment. These findings cannot confirm that patient-to-HCP transmission caused the reported infection or that findings would have been different if precautions were consistently followed. Although 50% of cases appeared to result from hospital-based sources, the remaining 50% appeared to result from community exposure. As the report notes, as of May 31, 2009, only 653 (6%) of 10,053 patients reported with H1N1 infection had been hospitalized.

Findings in this report are subject to several limitations. The number of cases may have been underreported and there is always potential of recall bias. Detailed information was not available for all cases and the number available for analysis was small. Nevertheless, these results highlight the need to reinforce the necessity of following recommended guidelines, reinforcing training, and being realistic about potential risk from not adhering to standard practices. ■

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Percutaneous Closure of Left Atrial Appendage vs Warfarin Therapy

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

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

Synopsis: *The efficacy of percutaneous closure of the LAA with the WATCHMAN® left atrial closure device was found to be non-inferior to that of standard warfarin therapy for prevention of stroke, cardiovascular death, and/or systemic embolism and, therefore, the device might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with non-valvular atrial fibrillation.*

Source: Reddy VY, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: A randomized non-inferiority trial. *Lancet* 2009;374:534-542.

Atrial fibrillation is the most common sustained cardiac arrhythmia and it is currently affecting an estimated 6 million individuals in the United States.[1] Because it occurs mainly in the elderly, its prevalence is expected to increase in parallel with the increasing age of the population and has been predicted to climb to 15.9 million Americans by 2050.[2,3] Atrial fibrillation occurs in one in four persons older than age 40,[4] and stroke, which is its most serious complication, occurs in 5% of non-anticoagulated patients every year. Stroke is the third most frequent cause of death in the United States and the leading cause of serious disability. It occurs with increasing frequency with increasing age (i.e., 23.5% of those ages 80-89 years) in patients afflicted with atrial fibrillation;[4,5] therefore, stroke prophylaxis is a crucial component of management of this arrhythmia.

Randomized controlled trials have demonstrated that warfarin is effective in preventing stroke, more so than aspirin or combination aspirin-clopidogrel;[6,7] however, warfarin is often not tolerated well and, because of its very narrow therapeutic range, its use carries a high risk for bleeding complications.[8] Also, only about 50% of patients who are eligible for long-term warfarin therapy actually receive well-controlled warfarin dosing that achieves what is universally considered to be the appropriate therapeutic result.[9] Although pharmacological alternatives to warfarin are being investigated and several of these new anticoagulants seem promising,[10] other forms of therapy (such as anatomic closure of the left atrial appendage [LAA], which is the source of thrombi in more than 90% of patients with non-valvular atrial fibrillation[11]), have demonstrated exceptionally good risk-to-benefit ratios in pilot studies.[12-15]

Reddy and colleagues performed a non-masked, multicenter, randomized, non-inferiority trial to determine the efficacy and safety of the WATCHMAN LAA closure device in patients with paroxysmal, persistent, or permanent non-valvular atrial fibrillation. A total of 707 eligible patients were randomly assigned either to percutaneous closure of the LAA and subsequent discontinuation of warfarin or to warfarin treatment. Efficacy was assessed by evaluating the primary composite endpoints of stroke, cardiovascular death, and/or systemic embolism. The authors determined that although there was a higher rate of adverse safety events in the intervention group, consisting mainly of peri-procedural complications, the efficacy of percutaneous closure of the LAA with this device was not inferior to that of warfarin therapy. The authors concluded that closure of the LAA might provide an acceptable alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with non-valvular atrial fibrillation.

■ COMMENTARY

Despite its limitations, at this time warfarin therapy is still the treatment of choice for patients with non-valvular atrial fibrillation who are both suitable and who have clear indications for long-term oral anticoagulation. However, it must be clearly recognized that even in the Reddy trial, therapeutic INR values were achieved in only 66% of the patients despite close INR follow-up. The most common primary safety complications in patients assigned to warfarin were major bleeding and hemorrhagic stroke, which occurred throughout the follow-up period. By contrast, there was a 90% reduction in the rate of hemorrhagic stroke in patients who received the WATCHMAN device, although peri-procedural complications were somewhat more frequent but usually these complications did not lead to long-term sequelae. Most patients who were treated with the LAA closure device were able to discontinue warfarin 6 months after device implantation without developing an increased risk of subsequent stroke.

Because of the therapeutic difficulties associated with long-term warfarin therapy, cardiologists are eagerly awaiting data from ongoing trials of the newer generations of direct thrombin inhibitors being used in the population of patients with non-valvular atrial fibrillation. However, larger, adequately powered studies that compare medical therapy with percutaneous closure of the LAA by percutaneous device deployment should certainly be performed, especially in high-risk patients and in those with a previous transient ischemic attack or an ischemic stroke, to determine exactly where this mechanical device might fit into our therapeutic armamentarium even if the direct thrombin inhibitors become available. At the present time, because at least one-third of patients receiving warfarin therapy are not achieving therapeutic goals, LAA closure with device therapy may appropriately become more widespread in certain patient groups, especially if the direct thrombin inhibitors prove to be ineffectual or are delayed significantly in their release to the general public. ■

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Diabetes and CV Disease: An Uneasy Truce

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque

Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis.

This article originally appeared in the August issue of Clinical Cardiology Alert. *At that time it was reviewed by Rakesh Mishra, MD, FACC, Berkeley Cardiovascular Medical Group, Berkeley, CA. Dr. Mishra reports no financial relationship to this field of study.*

Synopsis: *The authors of this meta-analysis conclude that their results support the use of aggressive insulin-lowering therapy to reduce major CV outcomes but not all-cause mortality; further, they recommend vigilance in avoiding hypoglycemia while steadily reducing HbA1c.*

Source: Ray, K, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: A meta-analysis of randomized controlled trials. *Lancet* 2009;373:1765-1772.

THE RECENT LITERATURE IS FILLED WITH TRIALS OF type 2 diabetes (DM) treatment and cardiovascular (CV) disease, with conflicting conclusions. While intuitively reasonable, not all trials of intensive glucose management in diabetes have been found to reduce CV events or decrease CV mortality. This report is an analysis of pooled trials, each with a goal of seeing whether aggressive diabetic therapy would decrease major CV outcomes compared to usual diabetic care. After a comprehensive literature search, Ray et al chose 5 randomized, controlled trials meeting stringent criteria for inclusion in this meta-analysis: UKPDS, PROactive, ADVANCE, VADT, and ACCORD.

Diabetic subjects were randomly assigned to placebo (standard regimen) or intensive glucose lowering, with glycemic control monitoring, to achieve decreased hemoglobin A1c (HbA1c) levels. Endpoints included fatal and non-fatal myocardial infarction (MI), coronary artery disease (CAD, fatal or non-fatal), stroke, and all-cause mortality in stable patients not hospitalized. The 5 trials that met selection criteria were culled from 2400 articles selected by search engines (Medline, Cochrane Central, EMBASE) for articles published in English from 1970 to 2009. Various drugs and insulin regimens were used, including intensive insulin and metformin. Participants were mostly male and aged 53-60 years.

The aggressive insulin-treated group experienced a mean reduction of HbA1c by 0.9% lower than usual care subjects. In addition, there were 2.3 fewer MI events and 2.9 fewer CAD events for every 200 patients on intensive treatment for 5 years. However, the event rates for stroke and all-cause mortality were not statistically different from the conventional treatment. Intensive glucose control significantly reduced non-fatal MI events

by 17% (odds ratio [OR], 0.83) and CAD events by 15% (OR, 0.85). Heart failure was not different between groups, but there was pronounced heterogeneity between studies, indicating that glitazone use was associated with an excess risk of heart failure. Hypoglycemia and weight gain were more common in the intensive group (38% vs 28%). Severe hypoglycemia was much less common than moderate hypoglycemia and more common in the intensive insulin therapy subjects, who also had a weight gain of 2.5 kg compared to the standard treatment group. The authors conclude that the intensive glucose-lowering treatment has cardiovascular benefit compared with standard treatment in patients with DM. The UKPDS extension group cohort showed a reduction in MI and all-cause mortality with both metformin and sulphonylurea-insulin regimens.

■ **COMMENTARY**

This report provides an excellent database and discussion regarding the meta-analysis of 5 major studies. They assess the risk and benefits of high-dose insulin vs usual care. The 5 trials in this meta-analysis provided an assessment of 1500 events of MI, 230 CAD events, 1100 strokes, and 2900 all-cause mortality. Intensive glycemic control in the aggregate of these trials resulted in a 0.9% lower HbA1c and, importantly, a 17% decrease in non-fatal MI and a 15% reduction in CAD events. Other large studies have not been successful in lowering adverse outcomes with aggressive insulin therapy, and even suggest possible harm with intensive HbA1c lowering (ACCORD), warning that intensive glucose control may have adverse outcomes. Nevertheless, the investigators state that this meta-analysis supports the use of intensive insulin therapy with a consistent beneficial effect of intensive insulin treatment on non-fatal MI and CAD without an increase in death.

The ACCORD data demonstrated increased mortality with aggressive insulin treatment over 10 years; ACCORD also demonstrated an increased risk of CV and non-coronary death. The authors suggest a practical clinical approach might be to reduce HbA1c with measures taken to avoid moderate to moderately severe hypoglycemia. Clearly, optimum medication regimens to achieve glycemic control need to be established. However, recent data suggest that insulin itself may not be hazardous. A recent commentary regarding ACCORD suggests that the speed of insulin provision is more important than the degree of intensive insulin therapy. More interest and research in this important area are, and will be, forthcoming. At present, "optimal" diabetic therapy should provide careful insulin provision.

The authors suggest that a practical clinical approach should be to reduce HbA1c concentrations steadily while being careful to avoid severe hypoglycemia. While they acknowledge a large difference in study design among the 5 trials, they believe that intensive glucose-lowering is safe and effective for reduction of macrovascular events compared to standard treatment. The investigators suggest that their findings provide reassurance about the effectiveness of glycemic control for CV risk reduction but not a clear benefit for all-cause mortality. Also, the optimum methods to achieve glycemic control need to be established, and guidelines drawn up, with specific recommendations for reduction of HbA1c in a range of patient populations. ■

Pharmacology Update

Pitavastatin Tablets (Livalo®)

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

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

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

THE FDA HAS GRANTED MARKET APPROVAL FOR PITAVAstatin, the seventh HMG-CoA reductase inhibitor, or "statin." It is a high-potency statin similar to rosuvastatin and atorvastatin. The drug has been available in Japan since 2003 and will be marketed in the United States by Kowa Pharmaceuticals America as Livalo®.

Indications

Pitavastatin is indicated as an adjunct to diet for patients with primary hyperlipidemia and mixed dyslipidemia to reduce elevated total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG), and to increase high-density lipoprotein-cholesterol (HDL-C).[1]

Dosage

The recommended starting dose is 2 mg daily; the dose may be increased to 4 mg daily if lowering of LDL-C is inadequate. The starting dose should be reduced to 1 mg daily in patients with moderate renal impairment or end-stage renal impairment on

hemodialysis. The drug may be taken without regard to meals.[1]

Pitavastatin is available as 1 mg, 2 mg, and 4 mg tablets.

Potential Advantages

Pitavastatin is only minimally metabolized by the cytochrome P450 isoenzyme system; therefore, drug-drug interactions involving this system are unlikely.

Potential Disadvantages

Coadministration of cyclosporine, rifampin, and erythromycin results in a clinically significant increase in the systemic exposure of pitavastatin.[1] This appears to be associated with inhibition of the organic anion transporting polypeptide (OATP), resulting in reduced uptake of the drug in the liver.[2] The effect of pitavastatin on cardiovascular outcomes is not known due to limited clinical experience.

Comments

Pitavastatin is a potent HMG-CoA reductase inhibitor that is chemically similar to atorvastatin and rosuvastatin. In dose ranging studies, pitavastatin at 1 mg, 2 mg, and 4 mg showed adjusted mean reduction from baseline of LDL-C of 32%, 36%, and 43%, respectively.[1] In randomized, multicenter, double-blind, double-dummy, active-controlled, non-inferiority, phase 3 studies, pitavastatin 2 mg and 4 mg were similar to and non-inferior to (mean difference in reduction > 6%) atorvastatin (10 mg and 20 mg) and simvastatin (20 mg and 40 mg), respectively, in terms of LDL-C, TC, TG, and non-HDL-C reduction, as well as HDL-C elevation.[1] Study participants were randomized to a 12-week study after a 6- to 8-week wash-out/dietary lead-in period. The results were the same whether patients had primary hyperlipidemia or mixed dyslipidemia with or without 2 or more risk factors for coronary disease or type 2 diabetes with combined dyslipidemia. On a mg-for-mg basis, pitavastatin is 5 times and 10 times the potency of atorvastatin and simvastatin, respectively. Pravastatin appears to be less than 1/20 the potency of pitavastatin on a mg-to-mg basis.[1] Published studies of pitavastatin are primarily in Japanese patients. In patients with acute coronary syndrome (n = 252), pitavastatin 4 mg and atorvastatin 20 mg daily showed similar regression of coronary plaque volume as assessed by intravascular ultrasound.[3] Pitavastatin appears to be well tolerated. The risk of skeletal muscle adverse events (myopathy and rhabdomyolysis) appears to increase in a dose-dependent manner (1.9% [1 mg], 2.8% [2 mg], and 3.1% [4 mg]) compared to 1.4% for placebo.[1]

Clinical Implications

Pitavastatin is the newest HMG-CoA inhibitor to be added to a crowded market. Although potent, the drug has no clear benefit over currently available statins, particularly given the lack of data regarding long-term safety and effect on cardiovascular mortality and morbidity. ■

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CME Questions

53. Of health care providers who acquired H1N1 infection:
a. 50% involved acquiring the infection in a health care setting.
b. 100% reported adherence to gown and glove precautions.
c. none involved known exposure in the community setting.
d. 75% used gown and glove precautions but no mask.
e. 40% reported a comorbidity which increased their risk status.

54. The WATCHMAN percutaneous left atrial closure device compared to warfarin therapy for prevention of stroke in patients with atrial fibrillation:
a. had a lower rate of adverse safety events.
b. had a higher rate of long-term adverse sequelae.
c. should not be considered to be an alternative strategy to chronic warfarin therapy.
d. proved to be non-inferior.

55. Tight glycemic control in diabetics reduces:
a. myocardial infarction.
b. stroke.
c. total mortality.
d. All of the above

Answers: 53. a, 54. d, 55. a.

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.

Procalcitonin and antibiotic use

Source: Schuetz P, et al. *JAMA* 2009; 302:1059-1066.

PROCALCITONIN (PCT) IS A LABORATORY metric that helps to distinguish bacterial from viral infections. PCT measurement has been previously shown to help identify bacterial infections in patients presenting with otitis media and other respiratory infections. Although it has been around for more than a decade, with multiple clinical trials corroborating its utility, PCT is not a widely used laboratory test.

Schuetz et al performed a randomized controlled trial of patients presenting to hospitals in Switzerland (n = 1359) with symptoms of a severe lower respiratory infection. Patients were randomized to treatment with a PCT-based plan vs treatment according to the clinical judgment of the treating physician.

In the PCT group, choice of therapy was dictated by the level of PCT. For patients with very low PCT, it was suggested that antibiotics not be initiated, and if they had already been started, that they be discontinued. For patients with high PCT, it was suggested that antibiotics be initiated, or continued if already initiated. Particular antibiotic choice was based on clinician use of established treatment guidelines.

The primary endpoint of the study was the number of adverse outcomes within 30 days of randomization; adverse outcomes included pneumonia, abscess, ARDS, ICU admission, and death. Fewer patients in the PCT group incurred an adverse event. Additionally, the number of antibiotics used in the PCT group was dramatically reduced compared to the regular care group.

In an increasingly resistance-conscious clinical world, where cost issues also weigh heavily, application of PCT testing to enhance appropriate antibiotic use is very appealing. ■

Effect of CYP 2C19 variants on clopidogrel

Source: Shuldiner AR, et al. *JAMA* 2009;302:849-857.

CLOPIDOGREL (CPG) AND ASPIRIN ARE widely utilized as antiplatelet agents for both primary and secondary prevention of CVD. Because platelet activation, adhesion, and aggregation are modulated by multiple redundant pathways, it should come as no surprise that any single pharmacologic intervention might be imperfect in its ability to curtail platelet activity. Additionally, even when an antiplatelet agent is mechanistically highly effective, intra-individual variations in metabolism and genetics exert great influence on pharmacokinetics.

CPG must be converted into an active metabolite by the P450 2C19 pathway to functionally impair platelet activity. The impact of genetic variations in 2C19 activity may be examined in vitro through platelet aggregometry. If the laboratory discerns meaningful differences in platelet activity related to genetic variations in 2C19, the next question would be whether such factors impact clinical endpoints.

Chromosomal analysis indicates a strong relationship between genetic variations in 2C19 activity and platelet aggregability in response to clopidogrel, consistently predicting incomplete CPG activity upon platelets.

After confirmation of the 2C19-clopidogrel relationship, a population of individuals undergoing PCI (after which clopidogrel treatment is standard) were followed for 1 year. During this year, those with genetic variants impairing the antiplatelet activity of CPG were more than twice as likely to incur a CV ischemic event or death. In the future, therapeutic choices may be directed by knowledge of such genetic variation. ■

Dabigatran vs warfarin: Less bleeding?

Source: Connolly SJ, et al. *N Engl J Med* 2009;361:1139-1151.

NUMEROUS PROSPECTIVE TRIALS have confirmed that anticoagulant therapy with warfarin (WRF) provides substantial stroke risk reduction for patients with atrial fibrillation (AF). Overall, AF patients enjoy as much as a two-thirds reduction in risk of ischemic stroke when WRF has been compared with placebo in clinical trials. These benefits notwithstanding, utilization of WRF is complex and entails significant risk of bleeding. Direct thrombin inhibitors (DTIs) such as ximelagatran have previously demonstrated comparable stroke risk reduction in AF as WRF, with less risk of serious bleeding; additionally, DTIs do not require ongoing monitoring to assure a therapeutic range, simplifying the level of involvement required of the patient. Unfortunately, clinical trials with earlier DTIs (e.g., ximelagatran) showed a significant risk of hepatotoxicity, precluding clinical use in the United States.

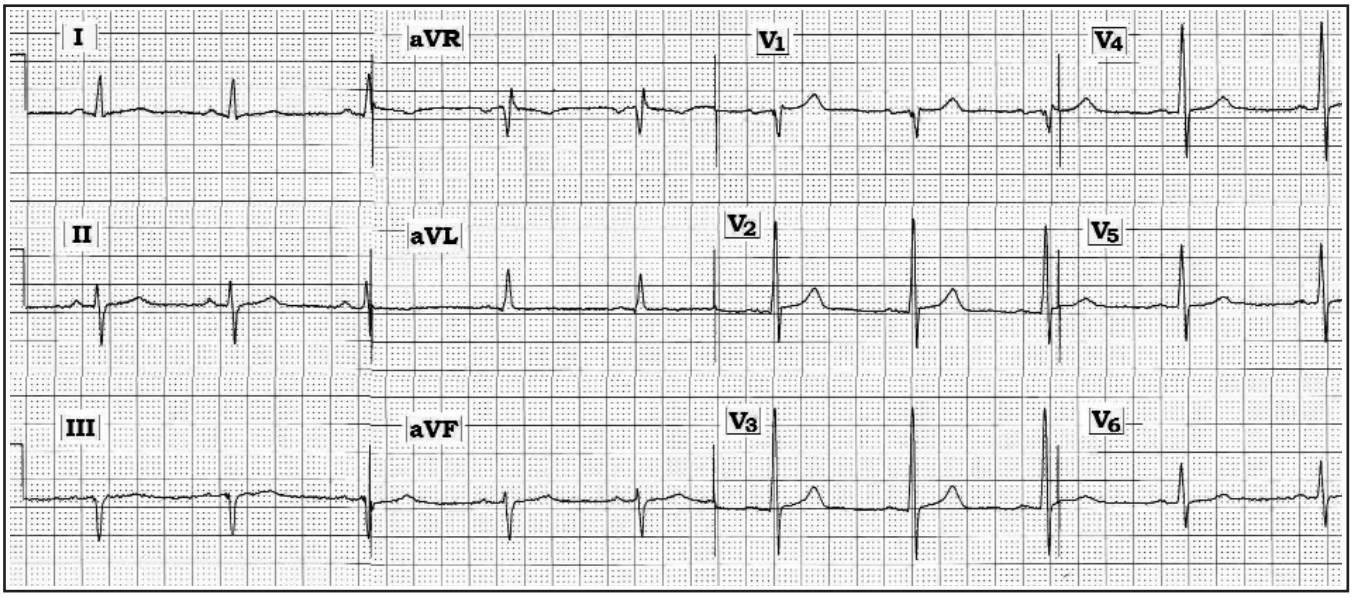
Dabigatran (DAB) is an oral DTI administered twice daily. Based upon favorable results from pilot trial data in AF and venous thromboembolism, a major clinical trial (n = 18,113) was undertaken to compare warfarin with DAB in AF.

After a median follow-up of 2 years, DAB provided risk reduction as great as or superior to WRF, with similar or fewer bleeding events. The orally administered DTI class shows great promise as an alternative to WRF. ■

Has There Been an Infarct?

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 tracing shown above was obtained from a 50-year-old man with a history of longstanding hypertension.

Interpretation: The rhythm is normal sinus rhythm at 60/minute. Intervals are normal. There is significant left axis deviation (LAD) sufficient to qualify as left anterior hemiblock (LAHB), since the QRS complex in lead II is predominantly negative (which places the QRS axis at more negative than -30º). There is no chamber enlargement.

The remarkable findings on this tracing lie with assessment of Q-R-S-T morphology. There is a deep Q wave (QS complex) in lead III; a subtle r' in lead V_1 with some concave upward J-point ST segment elevation in V_1,V_2; early transition between V_1-to-V_2 (with a surprisingly tall R wave already by lead V_2); and persistence of S waves throughout the precordial leads. The significance of these findings in our descriptive analysis is uncertain. Isolated Q waves (even when deep) are often found in leads III and/or aVF without necessarily implying that there has been prior inferior infarction. Unless there are Q waves in each of the 3 inferior leads (II, III, and aVF), we tend to interpret this finding as a "Q wave in lead III of uncertain significance." A terminal r' in lead V_1 and persistence of S waves across the precordial leads are findings that are often associated with pulmonary disease — but the rest of this tracing is not suggestive of this. Slight J-point ST elevation with upward concavity in a few isolated anterior leads, in the absence of other evidence of acute infarction, is usually a benign finding.

The most eye-catching finding on this tracing is the abrupt early transition caused by the unexpectedly tall R wave in lead V_2. Possible reasons for this finding include posterior infarction, cardiomyopathy, abnormal body habitus or anatomic chest wall abnormality, and lead misplacement. Clinical correlation (and comparison with a prior tracing) is essential to determine which of these possibilities may be operative. ■

In Future Issues: **Sex Differences in Mortality After Acute Coronary Syndromes**

PHARMACOLOGY WATCH

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

WHO Issues Global Alert on Antiviral Use

In this issue: WHO recommendations for antiviral use for H1N1 flu; antibiotic use trends for acute respiratory tract infection; denosumab clears FDA Expert Panel; FDA Actions.

Antiviral Recommendations for H1N1

The World Health Organization (WHO) has issued a global alert and response regarding the use of antivirals for pandemic H1N1 flu, reiterating that antivirals should be used to prevent severe illness and death in children and adults. The neuraminidase inhibitor oseltamivir (Tamiflu®) is recommended for patients who initially present with severe illness or whose condition begins to deteriorate. H1N1 remains sensitive to the neuraminidase inhibitors such as oseltamivir despite isolated reports of resistance earlier this year. The WHO recommends that clinicians in communities where the virus is circulating widely assume that patients with flu-like symptoms have H1N1 and not wait for laboratory confirmation. Most patients with pandemic flu experience typical flu symptoms and recover within a week. These patients do not need antivirals. But in patients with severe illness, studies have shown that early treatment, within the first 48 hours, is associated with better clinical outcomes. WHO also states that if oseltamivir is unavailable zanamivir (Relenza®) may be used in its place. This recommendation applies to all patient groups including children and pregnant women. The WHO statement comes in response to an article in the *British Medical Journal* suggesting neuraminidase inhibitors provide minimal benefit for children with seasonal influenza and have little effect on asthmatic exacerbations or use of antibiotics (Shun-Shin M, et al. *BMJ* 2009;339:b3172). ■

Antibiotic Use Declines Overall, While Use of Broad-Spectrum Increases

Physicians are prescribing fewer antibiotics for acute respiratory tract infections (ARTIs), but if an antibiotic is used, it is more likely to be a broad-spectrum drug. Using data from 1995 to 2006, antibiotic trends were reviewed from a national database for ARTIs, which included otitis media (OM). Children younger than age 5 were seen less frequently for ARTI than in the past, and they were less likely to be prescribed an antibiotic (36% reduction; 95% confidence interval [CI], 26%-45%). Among children age 5 or older, ARTI visit rates remained stable but antibiotic prescription rates decreased by 18% (95% CI, 6%-29%). Excluding otitis media, antibiotic prescription rates decreased by 41% among all age groups. Prescription rates for a penicillin, cephalosporins, and sulfonamide/tetracycline decreased while the rate of prescriptions for azithromycin increased, making it the most commonly prescribed macrolide for ARTI and OM. Among adults, quinolone prescriptions also increased. The authors conclude that overall antibiotic prescription rates for ARTI decreased in the last 10 years; however, prescription rates for

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

broad-spectrum antibiotics increased significantly (Grijalva CG, et al. *JAMA* 2009;302:758-766). This study points out the success of multiple campaigns to decrease antibiotic use for ARTIs, which are primarily caused by viruses. However the increasing use of broad-spectrum antibiotics is concerning. ■

Denosumab Receives Conditional Approval from FDA Expert Panel

Denosumab is a new human monoclonal antibody that suppresses osteoclast function and thus inhibits bone resorption. It is being evaluated by the FDA for treatment of osteoporosis in men and women, and although it has not yet been approved, a recent FDA Expert Panel has given conditional approval paving the way for full FDA approval this fall. Two recently published, industry-sponsored studies suggest the drug is effective in 2 different populations. In the first study, more than 1400 men receiving androgen-deprivation therapy for nonmetastatic prostate cancer were randomly assigned to receive denosumab 60 mg SQ every 6 months or placebo for 2 years. The primary endpoint was change in bone mineral density (BMD) at the lumbar spine, with secondary endpoints of change in BMD in the hip as well as fracture incidence. At 24 months, BMD increased in the lumbar spine with denosumab (5.6% increase vs 1% decrease for placebo; $P < 0.001$). BMD was also increased in the total hip, femoral neck, and distal radius, and the effect was maintained for 36 months. New fracture rate was also decreased with treatment (1.5% vs 3.9% with placebo; $P = 0.006$). Rates of adverse events were similar in both groups (Smith MR, et al. *N Engl J Med* 2009;361:745-755).

In the second study, 7868 postmenopausal women with low BMD were randomized to denosumab 60 mg SQ every 6 months or placebo for 36 months. The primary endpoint was new vertebral fractures. Denosumab was associated with a reduction in vertebral fractures (2.3% vs 7.2% placebo; $P < 0.001$), a reduction in hip fractures (0.7% vs 1.2% placebo; $P = 0.04$), and a smaller reduction in nonvertebral fractures. There was no increase in risk of cancer, infection, cardiovascular disease, delayed fracture healing, hypocalcemia, or osteonecrosis of the jaw in this study (Cummings SR, et al. *N Engl J Med* 2009; 361:756-765).

These last findings are important because the FDA's Expert Panel expressed concerns about infection and cancer data in giving a recommendation to approve denosumab when the FDA votes on the drug in October. If approved, which seem likely, denosumab will be marketed by Amgen under the trade name Prolia™. ■

FDA Actions

The FDA is requiring new boxed warnings on TNF-blockers regarding the risk of lymphoma and other malignancies in children and adolescents who have received the drugs. The new labeling will include warnings regarding cases of leukemia in adults, adolescents, and children, as well as new onset psoriasis. The labeling will also include a revised Medication Guide to reflect the safety information. Products subject to the new boxed warning are infliximab (Remicade®), etanercept (Enbrel®), adalimumab (Humira®), and the recently approved agents certolizumab pegol (Cimzia®) and golimumab (Simponi™). These TNF-blockers are used to treat rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ankylosing spondylitis. The warning is based on reports of nearly 50 cases of various cancers associated with the drugs, of which half were lymphomas.

The FDA has approved a new dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes. Bristol-Myers Squibb and AstraZeneca's saxagliptin (Onglyza™) is the second DPP inhibitor approved after sitagliptin (Januvia®). It is the first drug approved since the FDA changed its standards for diabetes drug approvals, requiring evidence of cardiovascular safety. While saxigliptin has not shown evidence of higher rates of cardiovascular disease, the FDA is requiring post-marketing studies to specifically look at cardiovascular safety in high-risk populations. Saxigliptin is dosed once daily and is approved as monotherapy or in combination with metformin, sulfonylureas, or thiazolidinediones.

The FDA has announced that it is reviewing adverse event reports of liver injury in patients taking the weight-loss drug orlistat, marketed as the prescription drug Xenical® and over the counter as Alli®. The agency has received 32 reports of serious liver injury in patients taking the drug in the last 10 years. Of these, 6 resulted in liver failure. Almost all of the reports are from outside the United States. The FDA is not recommending patients discontinue the drug, but is suggesting that those who have used orlistat should consult a health care professional if they develop jaundice, fever, fatigue, brown urine, or other symptoms of liver injury. ■