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ACE Inhibitors and Pregnancy by Almira Koentjoro

In June, the New England Journal of Medicine (NEJM) reported increased risk of major congenital malformations in infants whose mothers had taken ACE inhibitor (ACEI) drugs during the first trimester of pregnancy.¹ Currently, ACE inhibitors are labeled as pregnancy category C (either animal studies have shown adverse effects on fetus and there are no controlled studies in women, or study in women and animals are not available) for the first trimester and labeled as pregnancy category D (there is evidence of fetal risk but the benefits may be acceptable despite the risk) for the second and third trimester of pregnancy. At this time, the findings of the NEJM have not been repeated, therefore the FDA is not going to change the pregnancy category of ACE inhibitors yet.²

Using Tennessee Medicaid data, Cooper and associates conducted a cohort study to assess the association between ACEI use during first trimester of pregnancy and risk of fetal adverse effects.¹ The study revealed that exposure to ACEI during the first trimester of pregnancy was associated with a 2.7 times greater risk for major congenital malformation compared to no exposure or exposure to other antihypertensive medications. The major malformations observed in the study were mostly related to the cardiovascular and central nervous systems. The study concluded that ACEI exposure during first trimester of pregnancy is not safe and therefore should be avoided.¹

The label of ACEI drugs has long warned health care professionals about the risk of

fetal abnormalities associated with its use during second and third trimester of pregnancy and recommended that pregnant women be taken off ACEI as soon as possible. Fetal abnormalities associated with ACE Inhibitors include oligohydramnios, renal tubular dysplasia, hypocalvaria, intrauterine growth retardation, patent ductus arteriosus, and death.^{1,3} In 1992, a study conducted by the Organization of Teratology Information Services failed to find any evidence of renal tubular dysplasia in infants whose mothers reported the use of ACEI during the first trimester of pregnancy.³ In 1992, the FDA released a warning to physicians against the use of ACEI

in second and third trimester pregnancy. Although the FDA does not plan to change the pregnancy categories for ACEI until more studies have been conducted, it is important that health care professionals consider these findings when prescribing ACEI to their patients.

1 Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors. *N Eng J Med* 2006; 354; 2443-2451.

2 FDA Public Health Advisory: Angiotensin-Converting Enzyme Inhibitor (ACE inhibitor) Drugs and Pregnancy. Available from: <http://www.fda.gov/cder/drug/advisory/ACEI.htm>.

3 Postmarketing Surveillance for Angiotensin-Converting Enzyme Inhibitor During the First Trimester of Pregnancy-United States, Canada, Israel, 1987-1995. Available from: <http://www.cdc.gov/mmwr/preview/mmwrhtml/00046949.htm>.

Zostavax[®]: The new shingles vaccine by Adam Kersten

Shingles, or herpes zoster, is the expression of the reactivated varicella zoster virus, which originally produced chickenpox. Shingles is characterized by vesicular eruptions and neuralgic pain with a dermatomal distribution. The development of shingles is related to the body's varicella-zoster virus immunity which develops after chicken pox and can decrease over time. A new vaccine was approved, Zostavax, which appears to be beneficial due to its ability to boost varicella-zoster virus immunity.¹

Zostavax is a preparation of the Oka/Merck live strain of attenuated varicella-zoster virus. It is administered as a one time dose given subcutaneously, preferably in the upper arm. When properly reconstituted each 0.65 ml dose of Zostavax contains a minimum of 19,400 plaque forming units of the Oka/Merck when stored at room temperature for up to 30 minutes. Prior to administration Zostavax should be stored frozen at all times and reconstituted immediately upon removal with only the diluent that is supplied.¹

Zostavax is indicated for the prevention of shingles in patients who are 60 years of age or older. It is not indicated for use in the treatment of active shingles or postherpetic neuralgia. Zostavax should not be administered to patients with a history of anaphylactic reactions to any component of the vaccine, a history of primary or acquired immunodeficiency, on immunosuppressive therapy, or with active untreated tuberculosis.¹

The efficacy of Zostavax was evaluated in the Shingles Prevention Study, a double-blind, placebo-controlled trial in which 38,546 patients 60 years and older were randomly assigned to receive either a single dose of Zostavax or placebo. The results of this trial showed that Zostavax significantly reduced the risk of developing shingles when compared with placebo. The highest rate of efficacy for this medication was seen in patients 60-69 years of age and the positive results declined with increasing age.¹

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The Use of Aspirin and Plavix™ (clopidogrel) in Combination: New Findings Published in the CHARISMA Trial by Kathryn Langan

A recently published study has many health professionals rethinking the common practice of utilizing the blood thinner Plavix™ (clopidogrel) in combination with low-dose aspirin in patients at risk for cardiovascular events. Aspirin, a cyclooxygenase inhibitor, has long been used for its antithrombotic effects in preventing or decreasing the risk of myocardial infarction.¹ Clopidogrel, which was approved by the FDA in 1997, reduces atherosclerotic events by inhibiting adenosine diphosphate (ADP)-induced platelet aggregation.² Dual anti-platelet therapy of clopidogrel plus aspirin has previously been shown to reduce ischemic events in patients with unstable angina, myocardial infarction with or without ST-segment elevation, and in patients undergoing angioplasty and stenting.^{3,4,5,6} However, the authors of “The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA)” trial shed new light on the use of the two medications in combination.⁷ The trial, funded by Sanofi-Aventis and Bristol-Myers Squibb (manufacturers of Plavix™), observed 15,603 patients from

32 countries and 768 sites between October 2002 and November 2003 who were at high risk for atherothrombotic events. The study enrolled and separated patients into two subgroups; patients with documented cardiovascular disease (“symptomatic” patients); and patients without documented cardiovascular disease but who displayed multiple atherothrombotic risk factors (“asymptomatic” patients). Patients were randomly assigned to receive clopidogrel (75 mg per day) plus low-dose aspirin (75-162 mg per day) or placebo plus low-dose aspirin for a median of 28 months. The primary efficacy end point was the first occurrence of myocardial infarction, stroke, or death from cardiovascular causes. Safety end points of moderate and severe bleeding were also analyzed. Based on the clinical findings, the authors documented a 20% relative increase in the rate of primary events with clopidogrel in the subgroup of patients without documented cardiovascular disease (6.6% vs 5.5%, $p=0.20$); although not found to be statistically significant, this finding may suggest harm in this population of patients. In addition, there was a significant increase

in the rate of death from cardiovascular causes in this subgroup ($p=0.01$), as well as a significant increase in bleeding ($p<0.001$). In all, the findings did not support any benefit with clopidogrel in patients without established cardiovascular disease. The study did display significant benefit with clopidogrel in the subgroup of patients with documented cardiovascular disease. ($p=0.046$), although researchers felt the significance was marginal.

These findings led the authors to conclude that there was no significant benefit associated with clopidogrel plus aspirin as compared with placebo plus aspirin in reducing the incidence of myocardial infarction, stroke, or death from cardiovascular causes among patients with stable cardiovascular disease or multiple cardiovascular risk factors. The combination may still have a place in preventing second cardiac events after cardiovascular disease has been established, although more research is warranted to reinforce this finding. Based on results from the CHARISMA trial, dual anti-platelet therapy should be avoided as primary prevention in patients who only display cardiovascular risk factors due to the fact that the risks of the therapy may outweigh the benefits. Other preventative measures, such as aspirin alone or statins, could be considered in place of the combination of aspirin and clopidogrel in providing prevention against future cardiac events.

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The Shingles Prevention Study evaluated 21,000 of the enrolled patients for safety and found that serious adverse effects occurred at similar rates in patients vaccinated with active medication or placebo. However, in a substudy done from 0 to 42 days after injection, significantly more patients had serious adverse events in the active group compared with the placebo group (1.9% to 1.3%). The nature of these serious adverse effects was not specified. The most common adverse effects reported during this trial were injection-site adverse experi-

ences which occurred significantly more often in patients receiving Zostavax, when compared with those patients receiving placebo (48% to 17%).² Zostavax is supplied as a single dose vial of vaccine and a single dose vial of diluent. The manufacturer’s supplied price for Zostavax is \$152.50 per dose.³

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Guidelines for the Management of Atrial Fibrillation (ACC/AHA/ESC)

by Ted Tamisica

On August 15, 2006 the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) released revisions to the 2001 guidelines for the management of patients with atrial fibrillation. Atrial fibrillation (AF) is defined as a supraventricular tachyarrhythmia with signs of uncoordinated atrial activation leading to compromised mechanical function. Atrial fibrillation is the most common type of arrhythmia encountered in the clinical setting. It is estimated that 2.3 million people in North America are diagnosed with paroxysmal or persistent AF¹.

The standard ACC/AHA/ESC format on classifications of recommendations and level of evidence was used in this study. The following recommendations were revised since the 2001 publication to include the outcomes of recent clinical trials and the advances in AF therapy. The guidelines are quite extensive, however, this article will focus on the following Class I recommendations: pharmacological rate control during atrial fibrillation, prevention of thromboembolism, maintenance of sinus rhythm, postoperative atrial fibrillation, and acute myocardial infarction.

Recommendations for pharmacological rate control during atrial fibrillation²

- In most cases, patients with persistent or permanent AF should receive either a beta blocker or nondihydropyridine calcium channel antagonist.
- IV beta blockers or nondihydropyridine calcium channel antagonists are recommended to slow the ventricular response to AF in the acute setting, in the absence of preexcitation. Caution should be used in hypotensive or heart failure states.
- IV administration of amiodarone or digoxin can be used to control heart rate in AF and HF patients who lack an accessory pathway.
- Adjustment in therapy may be needed for those patients who experience AF symptoms during times of activity or exercise.
- Digoxin is effective in controlling rate in AF patients who have symptoms while at rest, and is indicated for patients who have heart failure, left ventricular dysfunction or who are inactive.

Recommendations for the prevention of thromboembolism²

- Antithrombotic therapy should be provided to all patients with atrial flutter or AF, unless contraindicated.

- Risk of stroke, bleeding and any other complications should be considered before therapy is initiated.
- Patients who are at high risk of stroke or have multiple moderate risk factors should receive anticoagulant therapy with a vitamin K antagonist.
- High risk factors include prior thromboembolism and rheumatic mitral stenosis.
- Moderate risk factors include: 75 years or older; HTN, HF, DM, and impaired LV systolic function.
- The goal INR for patients without a mechanical heart valve is 2 to 3. If the patient has a mechanical heart valve, the goal INR should be at least 2.5.

Recommendations for the maintenance of sinus rhythm²

- Treatment of underlying or reversible causes of AF should be considered before resorting to antiarrhythmic drug therapy.

Recommendations for postoperative atrial fibrillation²

- Patients undergoing cardiac surgery may receive treatment with an oral beta blocker to prevent postoperative AF, unless otherwise contraindicated.
- Patients who develop postoperative AF may receive an AV nodal blocking agent to achieve heart rate control.

Recommendations for acute myocardial infarction²

- In cases where patients experience severe hemodynamic compromise or intractable ischemia, or unsuccessful rate control with pharmacological therapy, direct current cardioversion is recommended.
- IV Amiodarone can be used in patients with acute MI to improve LV function and to slow rapid ventricular response due to AF.
- IV beta blockers and nondihydropyridine calcium antagonists are effective treatment options to slow a rapid ventricular response in patients with acute MI, without LV dysfunction, bronchospasm or AV block.
- In cases where the patient has AF and acute MI, continuous IV infusion or intermittent subcutaneous injections of unfractionated heparin may be utilized to lengthen the PTT to 1.5 to 2 times the control value.

The ACC/AHA/ESC Practice Guidelines for Atrial Fibrillation are an attempt to help health-care professionals select the most appropriate therapy for their patient based on current acceptable protocols. These practice guideline recommendations represent professional opinions based on current practices and scientific data and are intended to improve the quality of patient care. For more specific information on the revised guidelines please contact the Creighton University Drug Information Center at 402-280-5100.

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Changes in Varicella Vaccine Recommendations by Jessica McCunn

Varivax™, a live, attenuated varicella (chickenpox) vaccine, is given to prevent chickenpox. Chickenpox virus can spread from person to person through the air, or by contact with fluid from chickenpox blisters. The vaccine will prevent most people from getting chickenpox, and will prevent the occurrence of shingles years later.

In June, the Advisory Committee on Immunization Practices (ACIP) to the Centers for Disease Control and Prevention (CDC) recommended changes in the administration of varicella vaccinations. The changes included routine two-dose varicella vaccination of children and a second dose catch-up varicella vaccination for children, adolescents and adults who previously only had one dose. Revised recommendations also included a wider use of the vaccine for adolescents, adults, and HIV-infected children and approved criteria for evidence of immunity to varicella.

The currently recommended guidelines are as follows:

Children younger than 13 years of age should receive two doses of varicella vaccine. A second dose for children four to six years old is given to improve protection from the disease. The first dose should be given at 12-15 months old and the second dose given at 4-6 years old (before kindergarten or first grade).

A second dose “catch-up” varicella vaccine is recommended for children, adolescents, and adults who had previously received one dose. This catch-up second dose can be given at any time after 3 months following the first dose to improve individual protection and decrease school outbreaks.

Varicella vaccination of HIV-infected children. Specific individuals should receive two doses of single antigen varicella vaccine at a minimum interval of 3 months. Those individuals include HIV-infected children \geq 12 months of age in CDC clinical classes N, A, or B with CD4+ T-lymphocytes \geq 15% and without evidence of varicella immunity.

Prenatal assessment and postpartum vaccination. Women should be assessed prenatally for varicella immunity. Upon completion or termination of pregnancy, those women without immunity should receive the first dose of varicella vaccine before leaving the health care facility and the second dose should be given 4 to 8 weeks later.

Vaccination of people \geq 13 years of age. All people \geq 13 years of age without evidence of immunity should be vaccinated with two doses of varicella at a 4-8 week interval.

Second dose varicella vaccine for outbreak control. During a varicella outbreak, people who have received one dose, should receive a second dose if appropriate time has passed since the first dose. (3 months for people 12 months to 12 years of age and at least 4 weeks for people \geq 13 years of age).

The ACIP also revised the criteria for evidence of immunity to varicella to include any of the following:

Documentation of age-appropriate vaccination:

Preschool-aged children \geq 12 months of age: one dose

School-aged children, adolescents, and adults: two dose

Laboratory evidence of immunity or laboratory confirmation of disease

Born in the USA before 1980

A healthcare provider diagnosis of varicella or healthcare provider verification of history of varicella disease

History of herpes zoster based on healthcare provider diagnosis

This information has been recommended and voted on by the ACIP. However, the recommendations are under review by the Director of CDC and the Department of Health and Human Services. These recommendations will become official when published in CDC's Morbidity and Mortality Weekly Report.

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Email: druginfo@creighton.edu

Creighton University Drug Information Center
2500 California Plaza
Omaha, NE 68178

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Faculty:

Amy Friedman Wilson, PharmD. Director of Drug Information Services

Philip J. Gregory, PharmD. Assistant Professor, Pharmacy Practice

Linda K. Ohri, PharmD. Associate Professor, Pharmacy Practice

Edited by Drug Information Clerkship Students, Creighton University

Adam Kersten	Kathryn Langan
Almira Koentjoro	Jessica McCunn
	Theodore Tamisiea