



## Family Medicine Clinical Pharmacy Forum Vol. 5, Issue 3 (May/June 2009)

*Family Medicine Clinical Pharmacy Forum is a brief bi-monthly publication from the Family Medicine clinical pharmacists distributed to faculty and residents of the Department of Family Medicine. Our intent is to provide timely information on broad-based issues of pharmacotherapy, as well as regulatory and practiced-based issues affecting you as a prescriber. If you have suggestions for things you would like to see, please contact us.*

### **Contents**

- **Clinical Trial Updates:**
  - ACTIVE A (ASA + clopidogrel vs ASA alone in atrial fibrillation)
  - Polycap (i.e. Polypill)
- **Other Topics:**
  - 'Tis the Season for Poison Ivy
  - Clopidogrel Drug-Interaction with PPIs
  - J-Curve Revisited
  - Cholinesterase inhibitors: Not Free of AEs
  - Fenofibrate in Diabetics
  - HPV Vaccine for Women Ages 25-45

### **ACTIVE A Trial Results**

The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) trial was conducted to evaluate the role of clopidogrel plus aspirin in the prevention of stroke and other vascular events in patients with atrial fibrillation. The study consisted of three arms:

- ACTIVE W: clopidogrel plus aspirin vs. oral anticoagulation therapy (i.e. warfarin)
- ACTIVE A: clopidogrel plus aspirin vs. aspirin alone in patients with contraindications to OAC therapy or in patients unwilling to take it
- ACTIVE I: blood pressure lowering with irbesartan vs. placebo

The W arm of this study was terminated early when oral anticoagulation therapy was found to be superior to clopidogrel plus aspirin. The I arm was still on going as of May 14, 2009, when the results of the A arm were published in the New England Journal of Medicine.

ACTIVE A enrolled 7,554 patients with atrial fibrillation who had an increased risk of stroke and were unsuitable for warfarin therapy. Patients were randomly assigned to receive 75 mg of clopidogrel or placebo, in addition to aspirin. The primary outcome of the study was any major vascular event-- stroke, myocardial infarction, non-central nervous system systemic embolism, or death from vascular causes. Secondary outcomes were individual components of the primary outcome and the composite of the primary outcome and major hemorrhage.

The primary outcome occurred in 832 patients receiving clopidogrel, compared to 924 patients receiving placebo (RR 0.89; P=0.01). The authors attributed this risk reduction primarily to stroke, which occurred in 296 patients receiving clopidogrel and 408 of those receiving placebo (RR 0.72; P<0.001). Differences in the rates of myocardial infarction, non-central nervous system systemic embolism and death from vascular causes were not statistically significant. Major bleeding occurred more frequently in those receiving clopidogrel (RR 1.57; P<0.001). However, the authors point out that, when combined with the primary outcome, there was no significant difference between the overall event rate between groups (RR 0.97; P=0.54).

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Although this study has shown that clopidogrel plus aspirin is superior to aspirin alone in preventing major vascular events in patients with atrial fibrillation, it is important to consider the results as they apply to clinical practice. With an absolute risk reduction of 0.8% per year, 125 patients would have to be treated to prevent one event. Compare this to a number needed to harm of 142 (0.7% absolute risk increase), and it's clear that the benefits do not come without some risk. As always, it is important to weigh the risk versus benefit for individual patients when considering treatment.

Connolly SJ, Pogue J, Chrolavicius S, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*. 2009;360:2066-78.

Gruberg L. ACTIVE W: Atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events. MedscapeCME. 2006. Available at: <http://cme.medscape.com/viewarticle/523612>. Accessed May 31, 2009.

### **Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease**

A recent trial published in the *Lancet* looked at a combination capsule of three blood pressure lowering drugs, hydrochlorothiazide (12.5 mg), atenolol (50 mg), and ramipril (5 mg), a cholesterol lowering drug, simvastatin (20 mg), and aspirin (100 mg) given to patients ages 45-80 years who had only one cardiovascular risk factor. There were 2053 participants in the trial, with 412 in the group actually taking Polycap, and the remainder in other control groups. The study then assessed outcomes related to lipid lowering, blood pressure decrease, heart rate and anti-platelet effects, and safety after an average of 12 weeks of use. Lipid lowering effects were measured using LDL, platelet effects were approximated based on urinary 11-dehydrothromboxane B2, and safety was estimated by discontinuation rates.

The study found that Polycap lowered blood pressure a similar amount to when just the three blood pressure medications were used, with or without aspirin, and that it significantly lowered LDL cholesterol, although not as much as with just simvastatin alone. The systolic blood pressure after taking Polycap was 7.4 mmHg (95% CI 6.1 – 8.1 mmHg) lower than the control group and the diastolic was 5.6 mmHg (95% CI 4.7 – 6.4). The LDL decreased by an average of 27 mg/dL (95% CI 24 – 30 mg/dL). The urinary 11-dehydrothromboxane B2 was also not significantly different across the groups, demonstrating the presence of the anti-platelet effects of the aspirin in the Polycap. With regard to the safety of the Polycap, it was found to be similar to that of the control groups with no evidence of adverse effects being linked to increasing number of medications given in one dosage form. The Polycap had a 16% discontinuation rate while other discontinuation rates in the study ranged from 10% to 22.5%.

Based on these early results, the Polycap may be a promising new “multi-vitamin” type approach to reducing cardiovascular risk and disease. Furthermore, the blood pressure effects in individuals without hypertension from the Polycap can be extrapolated to show a 24% cardiovascular disease risk reduction and a 33% risk reduction in strokes. The same extrapolations can be made for the LDL effects, showing a potential 27% risk reduction for cardiovascular disease and 8% decrease in the risk of strokes. A larger, higher powered trial focused on cardiovascular risk reduction is planned.

Indian Polycap Study (TIPS), Yusuf S, Pais P, Afzal R, et al. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomized trial. *Lancet*. 2009 Apr 18;373(9672):1341-51.

### **Poison Ivy Prevention**

**Barrier creams and lotions:** Bentoquatam is available in many products that are designed to prevent the uroshiol from coming into contact with the skin and causing a rash. The  
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5% preparation has been shown to prevent the rash associated with poison ivy and to reduce the severity of the reaction. The cream/lotion should be applied to the skin less than one hour before anticipated contact and washed off within four hours. A common available product containing bentoquatam is Ivy Block.

**Skin cleansers:** Skin cleansers can be used to wash the uroshiol off the skin after exposure and prevent or reduce the severity of the reaction. For maximum effectiveness the cleansers should be used as soon as possible after exposure to the plant, generally within 30 minutes. There is a question of cost effectiveness with these products because they have not been very significantly more efficacious than much less expensive cleansers like common soap. Available products include Technu and Zanfel.

**Hyposensitization:** Leaf chewing, thought to originate with the Indians, and oral and injectible commercially prepared extracts are thought to decrease sensitivity to uroshiol exposure. There is a general lack of efficacy and safety data, however. Regimens vary, but one example is 0.0001% Rhus toxicodendron solution administered as a 3 mL dose once per week for three weeks, followed by monthly maintenance administration. Administration is suggested to begin in March and extend through September. Hyposensitization is reported to last no longer than one month if maintenance dosing is not used. Available products include Oral Ivy and other compounded products available at many compounding pharmacies.

Essig, Maria. Barrier creams and lotions for the prevention of poison ivy, oak, or sumac rash. WebMD. 25 Sept. 2007.

Tanner, T. Rhus (toxicodendron) dermatitis. Prim Care. 2000 Jun; 27(2):493-502.

Stein M, Parsons E. Effectiveness in oral Rhus toxicodendron solution for poison ivy prevention. International Journal of Pharmaceutical Compounding. 2003 Jul/Aug; 7(4): 272-275.

### **Proton-pump Inhibitors and Clopidogrel**

At the Society of Cardiovascular Angiography and Interventions (SCAI) 2009 Scientific Sessions the results of a late-breaking clinical trial, Clopidogrel Medco Outcomes, were presented. This retrospective cohort study involved over 16,700 patients who received clopidogrel post-stenting. It compared major adverse cardiovascular events (MACE) among members of the Medco Health Solutions pharmacy and medical claims database who either didn't make a prescription claim for a PPI 12 months post-PCI or filed claims for various PPIs, including esomeprazole, omeprazole, pantoprazole, lansoprazole or rabeprazole. Also of note, this is the first study that has looked at all PPIs; previous studies were on omeprazole alone.

In those who received PPIs, the one-year risk of MACE was 25.1% higher compared to those who did not (HR 1.51, CI 1.39-1.64). This effect was reported to be consistent among each PPI when looked at individually, which is suggestive of a class effect. However, since this study was retrospective and many variables were not controlled (including whether or not patients were receiving OTC PPIs), it doesn't give us a direct answer, but instead shows us where more research needs to be done.

Wood S. Possible "class effect" of proton-pump inhibitors on top of clopidogrel therapy. Theheart.org. Accessed June 1, 2009. Available at <http://www.theheart.org/article/967075.do>.

### **J-Curve Revisited**

A post-hoc analysis of BP data from the Treating to New Targets cholesterol trial has reinvigorated the debate about the J-Curve. J-Curve is the term referring to the paradoxical increase in morbidity and mortality with an excessive decrease in blood pressure. In this analysis, the investigators wanted to determine whether the J-Curve relationship existed between BP and CV events among patients undergoing aggressive management of other CV

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risk factors. In TNT, men and women aged 35-75 years with CAD and LDL<130 were randomized to conventional treatment with atorvastatin 10 or 80 mg. Compared with reference BPs, SBP >130 to 140 mmHg and diastolic >70-80 mmHg, patients with SBP <110 had a 3-fold increase risk of CV events whereas those with DBP <60 had 3.3 fold increased risk of events. Low BP may lead to underperfusion of coronary arteries during diastole, increasing risk of MI. Low DBP also results in high pulse pressures, leading to stiff arteries and vascular disease. Although there is pathophysiological support for the J-Curve hypothesis, it is important to note that the study could suffer from confounding by reverse causation – that is, patients with low BP might be sicker to begin with.

Messerli FH, American Society of Hypertension 2009 meeting (abstract), San Francisco

### **Adverse Effects of Cholinesterase Inhibitors**

AEs from cholinesterase inhibitors (CEIs) receive little attention. One little appreciate AE is that they can provoke symptomatic bradycardia and syncope. This was a population based cohort study from Ontario. All residents of Ontario aged 66 and older with dementia were divided into 2 cohorts – new users of CEIs and those who had not received any. Cohort entry was defined as date of first dispensed CEI. The study examined outcomes of first hospital visit for syncope, hospital visits for bradycardia or AV block, and pacemaker insertion. Hospital visits for syncope were more frequent in people receiving CEIs than controls (HR 1.76 [1.57-1.98]), as were hospital visits for bradycardia (HR 1.69 [1.32-2.15]), permanent pacemaker insertion (HR 1.49 [1.12-2.000] and hip fracture (HR 1.18 [1.04-1.34]). Results were consistent when additional analyses in which subjects were matched based on baseline comorbidities. In the face of little supportive evidence for efficacy, it seems this is one more reason to avoid prescribing CEIs routinely.

Arch Intern Med 2009;169:867-73.

### **Fenofibrate in Diabetics**

Results from a prespecified analysis of the FIELD (Fenofibrate Intervention in Event Lowering in Diabetes) study were recently published in the Lancet. The analysis showed that participants receiving fenofibrate had a lower risk of first amputation and minor amputation than those receiving placebo.

The FIELD study was a 5 year multinational randomized control trial enrolling 9,795 participants, aged 50-75 with type 2 diabetes mellitus who were not taking statin therapy at study entry. The primary outcome was coronary events—coronary heart disease death or non-fatal myocardial infarction. Secondary outcomes included total cardiovascular events—the composite of cardiovascular death, myocardial infarction, stroke, and coronary and carotid revascularization. Tertiary outcomes reported were vascular and neuropathic amputations, progression of renal disease, and laser treatment for diabetic retinopathy.

The primary outcome was overall non-significant. However, there was a significant 24% reduction in non-fatal MI, with a non-significant increase in CHD mortality in those receiving fenofibrate. The secondary outcome of revascularization was also significantly reduced by 21% in the fenofibrate group. All other secondary outcomes were non-significant.

Fenofibrate was found to have a positive impact on all microvascular (tertiary) outcomes. The study showed a 30% reduction in the requirement for laser treatment for retinopathy. Patients receiving placebo were more likely to progress from normo- to microalbuminuria or from micro- to macroalbuminuria than those receiving fenofibrate. The later group also had more participants regress during the study. As stated earlier, patients receiving fenofibrate also

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had a lower risk of first amputation and minor amputation than those receiving placebo. All of these findings were significant.

Also of note, more patients in the placebo group were placed on statin therapy during the study. This reinforces evidence suggesting that statin therapy has a negligible effect on certain outcomes.

The pleiotropic effects of fenofibrate, along with its lipid lowering abilities, render it a useful treatment for type 2 diabetic patients for multiple reasons.

Ansquer JC, Foucher C, Aubonnet P, Le Malicot K. Fibrates and microvascular complication in diabetes- insight from the FIELD study. *Curr Pharm Des.* 2009;15:537-552.

Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet.* 2005;366:1849-1861.

Rajamani K, Colman PG, Li LP, et al. Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial. *Lancet.* 2009;373:1740-1741.

### **Safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years**

The HPV vaccine is currently recommended for use in women up to age 26 by the CDC, however there have been questions regarding possible efficacy in older women. Merck, the manufacturer of the Gardasil HPV vaccine, recently released an interim analysis on the use of the quadrivalent HPV vaccine in women aged 24-45 years.

This study is a multi-center, parallel, randomized, placebo-controlled, double-blinded trial with the objective to test the safety, immunogenicity, and efficacy in the above age group. There are 3819 women aged 24-45 are enrolled in the study. Exclusion criteria include pregnancy, hysterectomy, history of genital warts or past/present cervical disease. The primary endpoints are the combined incidence of infection of at least 6 months duration and external genital disease related to HPV 6, 11, 16, 18 or of 16 or 18 alone. Secondary endpoints are combined incidence of infection related to HPV 6 or 11 with a duration of 6 months or more and cervical and external genital disease. The duration of the trial is set to be 4 years, however three interim analyses were conducted after a mean of 2.2 years: per-protocol efficacy analysis, population naïve to the relevant type, and intention to treat. The results were that the per-protocol showed a 90.5% efficacy, naïve to the relevant type population had 74.6% efficacy, and intent to treat had 30.9% efficacy for the primary endpoint. Adverse effects were comparable between the vaccine and placebo.

Although the vaccine is efficacious, there are many other factors to consider. The CDC still only recommends the vaccine for females ages 11 – 26 and most insurance companies will not cover the \$360 cost for women outside of that age range. At least 50% of sexually active men and women acquire HPV at some point in their life; however 90% of cases are cleared naturally by the body's immune system within two years. Cost effectiveness is still not established and more information should after the full duration of the study.

Munoz N, Manalastas R, Pitisuttithum P, Treusukosol D, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomized, double-blind trial. *Lancet* 2009; 373:1949-1957.

HPV vaccine information for young women. Centers for Disease Control and Prevention. [www.cdc.gov/std/hpv/STDFact-HPV-vaccine-young-women.htm](http://www.cdc.gov/std/hpv/STDFact-HPV-vaccine-young-women.htm). Accessed June 10.2009.

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