

# PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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## PPIs for Glycemic Control

A small cross-sectional study conducted in a Spanish hospital suggests proton-pump inhibitors may help improve glycemic control in patients with type-2 diabetes.

**Methods:** Study subjects (n=97) were consecutively admitted adults (mean age, 72 years; 44% women) with diabetes who had HbA1c measured during their hospital stay. Those with a diagnosis of hyperglycemic decompensation, those with new-onset diabetes, and pregnant women were excluded. HbA1c levels were compared as a measure of glycemic control between patients receiving a PPI and those who were not.

**Results:** Of the 97 patients, slightly more than half (56%) were treated with a PPI. Acceptable glycemic control, defined as an HbA1c measure of  $\leq 7\%$ , was found in more patients receiving a PPI (prevalence ratio,\* 1.8). In addition, mean HbA1c levels were significantly lower in these patients than in those not taking a PPI (6.7% vs 7.3%;  $p=0.018$ ). Subgroup analyses found the effects of PPIs were strongest in patients taking insulin, compared with metformin (*Glucophage*), sulfonylureas, or other antidiabetic drugs.

**Discussion:** How PPIs affect glycemic control is unclear, but they may share many of the glucoregulatory effects of incretin-based therapies (e.g., increasing islet-cell mass, slowing gastric emptying, and decreasing glucagon levels).

Because PPIs have a good safety profile and are available at low cost, randomized trials of their antidiabetic efficacy appear to be warranted.

Boj-Carceller D, et al: Are proton pump inhibitors a new antidiabetic drug? A cross sectional study. *World Journal of Diabetes* 2011;12 (December 15):217–220. From Hospital Miguel Servet, Spain. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

\*See Reference Guide.

## SSRI Safety in Pregnancy

In 2006 the FDA issued a public health advisory about the risk of persistent pulmonary hypertension of the newborn (PPHN), a condition that occurs when newborns do not adapt to breathing outside of the womb, when mothers received selective serotonin reuptake inhibitors during pregnancy. That warning was based on a single study, and results of subsequent studies have been inconsistent. After review of the newer evidence, the FDA has decided that no conclusion can be reached at this time about the possible link between SSRI use in pregnancy and PPHN. Newborns with PPHN may require intensive care and mechanical ventilation. Severe PPHN can lead to organ damage, brain damage, and death. The FDA recommends that clinicians not change their current practices for treating depression during pregnancy.

Selective serotonin reuptake inhibitor (SSRI) antidepressants: drug safety communication – use during pregnancy and potential risk of persistent pulmonary hypertension of the newborn. FDA MedWatch Alert: available at [www.fda.gov/Safety/MedWatch](http://www.fda.gov/Safety/MedWatch).

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## New ACE II Receptor Antagonist

Azilsartan medoxomil, approved in early 2011 for treatment of hypertension, may have more potent blood pressure-lowering effects than other angiotensin II receptor blockers (ARBs), according to a systematic review.

Azilsartan medoxomil is one of 8 ARBs currently approved for hypertension. These drugs differ in their pharmacologic properties and effects on blood pressure. The authors of this article conducted a systematic review of preclinical and clinical studies of azilsartan, including published articles, meeting abstracts, product monographs from the FDA and the manufacturer, and studies posted on ClinicalTrials.gov.

Azilsartan medoxomil is a prodrug metabolized to azilsartan, an insurmountable, selective angiotensin II type 1 inhibitor with greater potency and a longer-lasting effect (due to slow receptor dissociation) compared to other ARBs. In animal models, the drug improved insulin sensitivity and decreased adipose tissue weight, suggesting it might be useful in treating concomitant disorders. Azilsartan has no clinically relevant pharmacokinetic interactions. Caution is indicated when prescribing with NSAIDs because of increased risk for deterioration of renal function and because NSAIDs attenuate the blood pressure-lowering effects of all ARBs.

Azilsartan has been the subject of 3 published clinical trials and several other studies reported only as abstracts. The use of 24-hour systolic blood pressure as the primary efficacy measure is a unique feature of these trials. In a 6-week clinical trial in 1275 patients, 40 mg/day azilsartan was equivalent to 40 mg/day olmesartan and superior to placebo in reducing 24-hour systolic and diastolic blood pressure and trough sitting clinic systolic and diastolic pressure. The 80-mg/day azilsartan dosage was superior to olmesartan. In a second 6-week trial in 1291 patients, 80 mg/day azilsartan was superior to both olmesartan and valsartan, and 40 mg/day azilsartan was noninferior. In the second trial, but not the first, significantly more patients receiving 80 mg/day azilsartan were considered responders, in comparison with the other treatment groups.

In a third published trial, 984 patients were treated for 24 weeks with randomly assigned

40 or 80 mg/day azilsartan or 320 mg/day valsartan. Both azilsartan doses were superior to valsartan in reducing 24-hour systolic and diastolic blood pressure; and significantly more patients were classified as responders to both azilsartan doses.

Studies available in abstract form suggest azilsartan may be effectively combined with antihypertensive agents from other classes, specifically amlodipine and chlorthalidone. The tolerability of azilsartan is similar to other ARBs and to placebo.

There is a lack of safety and efficacy data from the published trials in patients with a history of major cardiovascular events, cardiac conduction abnormalities, poor renal function, and poorly controlled type-2 diabetes—all groups that were excluded from study enrollment.

Baker W, White W: Azilsartan medoxomil: a new angiotensin II receptor antagonist for treatment of hypertension. *Annals of Pharmacotherapy* 2011;45 (December):1506–1515. From the University of Connecticut Schools of Pharmacy and Medicine, Farmington. **The authors have received funding from Takeda, the manufacturer of azilsartan medoxomil.**

**Drug Trade Names:** amlodipine—*Norvasc*; azilsartan medoxomil—*Edarbi*; chlorthalidone—*Hydone, Hygroton, Thalitone*; olmesartan—*Benicar*; valsartan—*Diovan*

## Dronedarone in Permanent AF

In a clinical trial, dronedarone (*Multaq*) was associated with increased rates of heart failure, stroke, and cardiovascular-related death in high-risk patients with permanent atrial fibrillation. The manufacturer warns against using dronedarone in such patients.

**Methods:** The randomized, placebo-controlled, multinational trial was conducted in patients with permanent atrial fibrillation or flutter, documented on a pretreatment ECG and on an ECG performed  $\geq 6$  months previously, with no documented intervening period of normal sinus rhythm. Patients were aged  $\geq 65$  years and had at least 1 additional cardiovascular risk factor, disease, or prior event. Active treatment was 400 mg dronedarone b.i.d. The trial was halted for safety reasons.

**Results:** More than 3000 patients were enrolled, and median follow-up was 3.5 months. Patients were an average age of 75 years, 69% had a  $>2$ -year history of atrial fibrillation or flutter, and about two-thirds had a history of heart failure.

The study was designed with 2 primary outcomes. The first—a composite of stroke, MI, systemic embolism, or death from cardiovascular causes—occurred in 43 patients receiving dronedarone and in 19 receiving placebo (hazard ratio,\* 2.29;  $p=0.002$ ). The second outcome—unplanned hospitalization for a cardiovascular cause or death—occurred in 127 patients receiving dronedarone and in 67 from the placebo group (hazard ratio, 1.95;  $p=0.001$ ). A total of 21 cardiovascular deaths and 23 strokes occurred with dronedarone, and there were 10 deaths and 10 strokes in the placebo group. The effects of dronedarone were consistent in all of the subgroups analyzed.

**Discussion:** In a previous clinical trial, dronedarone reduced mortality and cardiovascular disease events in patients with intermittent atrial fibrillation. The agent restores sinus rhythm, decreases blood pressure, slows the heart rate, and produces adrenergic blockade; these effects were expected to benefit patients with permanent atrial fibrillation. The authors suggest the 2 studies' results may have been inconsistent because longstanding permanent atrial fibrillation is unlikely to revert to normal sinus rhythm. Sinus rhythm was reestablished in only 3.7% of treated patients in the present study (and 1.4% of placebo controls). In this patient population, the toxic effects of dronedarone may not be offset by the benefits of maintaining sinus rhythm, and the benefit of the drug's other physiologic effects may be minimal. The increased rate of cardiovascular deaths with dronedarone was primarily due to arrhythmia. The increased stroke rate remained unexplained.

Connolly S, et al: Dronedarone in high-risk permanent atrial fibrillation. *NEJM* 2011; doi 10.1056/NEJMoa1109867. From the Population Health Research Institute, Hamilton, Ont. Canada; and other institutions. **Funded by Sanofi-Aventis. Several study authors disclosed financial relationships with commercial sources including Sanofi-Aventis.**

\*See Reference Guide.

## Dronedarone Contraindication

An FDA review of 2 clinical trials (see previous article) has found that the antiarrhythmic dronedarone (*Multaq*) increases the risk of serious cardiovascular events when used by patients with permanent atrial fibrillation. Dronedarone is indicated to reduce hospitalization in patients who are in sinus rhythm and have a history of paroxysmal or persistent, not permanent, atrial fibrillation. Patients who

receive dronedarone should also receive antithrombotic therapy. Because the agent doubles the rate of cardiovascular death, stroke, and heart failure in patients with permanent atrial fibrillation, it should not be prescribed for this population. Heart rhythm should be evaluated every 3 months in patients receiving dronedarone, and the drug should be stopped if the patient is experiencing atrial fibrillation.

Multaq (dronedarone): drug safety communication – increased risk of death or serious cardiovascular events. FDA MedWatch Alert: available at [www.fda.gov/Safety/MedWatch](http://www.fda.gov/Safety/MedWatch).

## ADHD Medications: Safety in Adults

Stimulant medications and atomoxetine can increase blood pressure and heart rate, which could in turn increase risk of MI, stroke, and sudden cardiac death. However, a large cohort study of young and middle-aged adults found ADHD medications were not associated with increases in cardiovascular events.

**Methods:** The study, funded by several Federal government agencies, examined ADHD medication use and serious cardiovascular events in persons aged 25–64 years. (A parallel study was conducted in younger patients, aged 2–24 years.) Participants were >150,000 patients who were continuously enrolled in health plans with pharmacy coverage, received ADHD medication between 1986 and 2005, and were free of diseases likely to be fatal in the near term. Medication use was defined as filling a prescription, regardless of indication, for a stimulant (i.e., methylphenidate, amphetamines, or pemoline) or atomoxetine. Each patient was matched for age, gender, and other factors with 2 stimulant nonusers from the same institutions. Study endpoints were MI, sudden cardiac death, or stroke.

**Results:** During the follow-up period (median, 1.3 years per patient), 1357 MIs, 296 sudden cardiac deaths, and 575 strokes occurred. Crude incidence rates ranged from 0.3 to 1.34 per 1000 patient-years. After adjustment for confounding factors (e.g., age, gender, smoking, concurrent medications), rates of cardiovascular events did not differ between users and nonusers of ADHD drugs. Results were similar for all medications, for all individual study endpoints including hemorrhagic and ischemic stroke, and regardless of diagnosis, patient age, and history of cardiovascular disease. New users of the medications were not at increased risk compared with non-users.

There was no association of cardiovascular risk with increasing duration of current use or with use during any window of time. Even in worst-case scenarios that assumed risks were at the upper end of the confidence intervals, elevations were small. The parallel study in young patients had similar results.

**Discussion:** More than 1.5 million U.S. adults were treated with stimulants in 2005, the end date of the study, and in recent years, use of these medications has increased more rapidly in adults than in children. Adverse event reports have resulted in the questioning of the cardiac safety of ADHD medications, and although epidemiologic studies did not support those reports, concern persisted. Although the limitations inherent to population-based cohort studies make it impossible to completely rule out a modest increase in risk, the present results support the cardiac safety of ADHD medications. However, treated adults should continue to be monitored for other possible adverse effects such as weight loss and insomnia.

Habel L, et al: ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. *JAMA* 2011;306 (December 28):2673-2683. From Kaiser Permanente Northern California, Oakland; and other institutions. **Funded by the Agency for Healthcare Research and Quality; and other sources. Several study authors disclosed financial relationships with commercial sources.**

**Drug Trade Names:** atomoxetine—*Strattera*; methylphenidate—*Ritalin*; pemoline—*Cylert*

## Fenofibrate, Heart Attack, and Stroke

The lipid-lowering agent fenofibrate (*Trilipix*) lowers LDL cholesterol and increases HDL cholesterol, but according to an FDA review, it may not reduce a patient's risk of heart attack or stroke. In the large randomized ACCORD trial of adjunctive fenofibrate in patients receiving simvastatin, no significant difference was found in rates of serious cardiac events, such as heart attack and stroke, between those who received combination therapy and simvastatin monotherapy. Females who received fenofibrate in the ACCORD trial had higher rates of cardiac events than those who received monotherapy, although this result was not found in a trial of fenofibrate vs placebo. Fenofibrate also did not lower cardiac morbidity or mortality in patients with type 2 diabetes. Based on their findings, the FDA will require Abbott Laboratories, the manufacturer of *Trilipix*, to conduct a trial evaluating the cardiovascular effects in patients who are already treated with a statin and are at high risk for cardiac events.

FDA drug safety communication: review update of *Trilipix* (fenofibric acid) and the ACCORD lipid trial. FDA MedWatch Alert: available at [www.fda.gov/Safety/MedWatch](http://www.fda.gov/Safety/MedWatch).

**Drug Trade Names:** fenofibrate—*Trilipix*; simvastatin—*Zocor*

## Reference Guide

**Hazard Ratio:** A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that one group has half the risk of the other group.

**Prevalence Ratio:** A comparison of disease prevalence in two groups: usually 1 group at risk for the disease or with a specific attribute and the general population or a group without the attribute or risk factor.

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