

# DIS News

College of Health Professions and Biomedical Sciences  
Drug Information Service

## Literature Highlight: Effects of Soy Protein and Isoflavones on Bone Mineral Density in Late Postmenopausal Women

Due to the risks associated with hormone replacement, an increasing number of women are turning to soy products to prevent and treat osteoporosis. Isoflavones contained in soy products selectively bind to estrogen receptor- $\beta$ . Equol, a nonsteroidal estrogen that 30-50% of people are able to produce from isoflavones, also has this action. The selective binding of estrogen receptor- $\beta$  suggests that isoflavones may have positive skeletal effects similar to estrogen receptor modulators without the negative breast and uterine tissue effects of estrogen replacement therapy. Trials to determine the clinical benefit of this action are conflicting and inconclusive. This randomized, double-blind, placebo-controlled trial was performed to evaluate the effect of soy proteins and isoflavones on bone mineral density (BMD) in healthy, postmenopausal women >60 years of age.

One hundred and thirty-one women were randomly assigned to one of four treatment groups: soy protein plus isoflavone tablets, soy protein plus placebo tablets, control protein plus isoflavone tablets, and control protein plus placebo tablets. Participants were instructed to take three tablets (containing 35 mg isoflavone per pill or placebo) and 20 g protein powder daily for 12 months. Participants were asked to refrain from consuming soy products or taking medications that may affect the outcome of the study; however, exercise and other potential confounders were not controlled for. The primary endpoint was the change in BMD from baseline. The secondary endpoints were biomarkers of bone turnover and serum levels of equol.

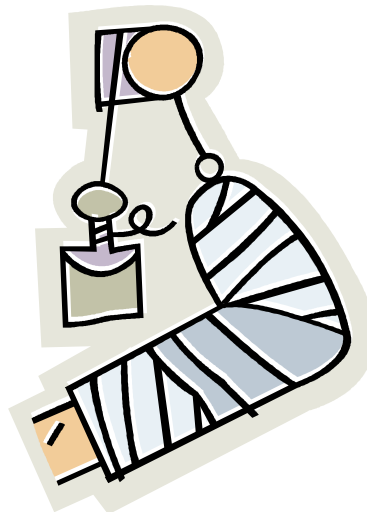
At 12 months, there was no significant difference from baseline in the change in BMD or markers of bone turnover among the treatment groups. Although 49% of the women receiving isoflavone supplements had detectable serum equol levels, there was no significant

difference in BMD between equol and non-equol producers. There was a significant correlation between markers of bone turnover and total protein intake measured in mg/kg. The most commonly reported adverse effect was gastrointestinal disturbance, but the occurrence of adverse effects did not differ among the treatment groups. The results may be limited by the small sample size and short duration when evaluating changes in BMD.

**SUMMARY:** The use of supplemental isoflavones and/or soy protein does not affect BMD in late postmenopausal women.

*Kenny AM, Mangano KM, Abourizk RH, et al. Soy proteins and isoflavones affect bone mineral density in older women: a randomized controlled trial. Am J Clin Nutr 2009;90:234-242.*

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We welcome any comments and suggestions for future newsletter topics.

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## Dronedaronone (Multaq®) for Atrial Fibrillation

The incidence of atrial fibrillation (AF) has increased over the past 20 years.<sup>1</sup> It is estimated that between 12-16 million Americans will be affected by the year 2050. AF is associated with heart disease, atrial hypertension, heart failure, and an increased risk of morbidity and mortality. The causes of AF are related to structural and electrical remodeling of the heart which can lead to voltage abnormalities and disruption of the normal atrial rhythm. Current treatments for AF focus on blocking sodium channels, beta adrenergic pathways, potassium channels, calcium channels, or a combination of all four to restore sinus rhythm (SR). Amiodarone is a multi-channel blocker that effectively maintains SR in patients with AF. The problem with amiodarone is that it has a high incidence of adverse effects and a very long half-life.<sup>1</sup> Dronedaronone, a derivative of amiodarone, was FDA approved for the treatment of AF in July 2009.<sup>2</sup> A clinical trial comparing the safety and efficacy of amiodarone with dronedaronone showed that dronedaronone has a lower risk of side effects but is slightly less effective in maintaining SR in patients with AF.<sup>1</sup> In addition, dronedaronone has a much shorter half-life (1-2 days) than amiodarone (30-55 days) making it less likely to accumulate.<sup>3</sup> Based on two large clinical trials, dronedaronone is the only AF medication associated with reducing cardiovascular mortality in patients with paroxysmal or persistent AF or atrial flutter.<sup>3,4</sup> However, dronedaronone is ineffective in late stage congestive heart failure and may lead to increased mortality in this population.<sup>1</sup> The FDA has issued a warning against its use in patients with New York Heart Association (NYHA) class III and class IV heart failure.<sup>2</sup>

A multicenter, double-blind, randomized, placebo-controlled study evaluated the efficacy of dronedaronone for maintenance of sinus rhythm in atrial fibrillation or flutter.<sup>3</sup> Twelve hundred and forty-four patients who had at least one episode of AF but were not diagnosed with permanent AF were enrolled. Patients with NYHA class III or class IV heart failure were excluded. Patients were randomly assigned to placebo or

dronedaronone 400 mg twice daily for 12 months. The primary endpoint was the time to first recurrence of atrial fibrillation or flutter. The average time to first AF recurrence for the dronedaronone group was 116 days compared to 53 days for placebo ( $p<0.001$ ). The recurrence rate was significantly lower in the dronedaronone group compared to placebo (62.3% vs. 75.2%;  $p<0.001$ ). In addition, 30.9% of the patients receiving placebo were hospitalized or died compared to 22.8% in the dronedaronone group ( $p=0.01$ ). Adverse events were similar between groups; however, the incidence of elevated serum creatinine levels and hyperthyroidism was significantly higher in patients taking dronedaronone compared to placebo ( $p=0.004$  and  $p=0.002$ , respectively). The authors concluded that dronedaronone effectively reduces the rate of recurrent atrial fibrillation. Limitations to the study include the inability to detect every episode of recurrent arrhythmia and short duration.<sup>3</sup>

Another multicenter, randomized, double-blind, placebo-controlled trial evaluated the effectiveness of dronedaronone in preventing hospitalization or death in patients with AF.<sup>4</sup> A total of 4628 patients with AF and additional risk factors for death including age greater than 70 years old, diabetes, arterial hypertension, previous stroke, systemic embolism, and transient ischemic attack were included. Patients were excluded if they had a planned major surgery or were hemodynamically unstable, diagnosed as having class IV congestive heart failure, and/or currently being treated with a class I or class III AF medication. Eligible patients were randomly assigned to placebo or dronedaronone 400 mg twice daily for a minimum of 12 months. The median duration of follow-up for all patients was 22 months and the maximum duration of therapy was 2.5 years. The primary endpoint was the first hospitalization due to cardiovascular events or death from any cause. First time hospitalization due to cardiac event or death occurred in 734 patients (31.9%) in the dronedaronone group compared to 917 patients (39.4%) in the placebo group ( $p<0.001$ ). Fewer patients in the dronedaronone group were

hospitalized due to a cardiac event compared to placebo (29.3% vs. 36.9%,  $p<0.001$ ). Significantly fewer cardiovascular deaths occurred in the treatment group compared to placebo (2.7% vs. 3.9%,  $p=0.03$ ). Overall, dronedaronone was associated with more adverse effects compared to placebo. Bradycardia, QT-interval prolongation, diarrhea, nausea, and skin-related events were reported at a significantly higher rate in the dronedaronone group ( $p<0.05$ ). The authors concluded that dronedaronone reduced the incidence of hospitalization and death due to cardiovascular events in patients with AF. Limitations to the study include the 30.2% drop out rate in the dronedaronone group and short duration.<sup>4</sup>

Dronedaronone appears to be more effective than placebo at preventing atrial fibrillation recurrence as well as preventing hospitalization and death in patients with atrial fibrillation. Dronedaronone may be a safer alternative to amiodarone; however, it is less effective and should not be used in patients with class III and IV heart failure. More studies are needed to compare the efficacy and safety of dronedaronone to alternative treatment options.

*By Ryan Davis, Pharm.D. Candidate*

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## Effient® for the Prevention of Thrombotic Events in Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

Acute coronary syndrome (ACS) primarily results from the partial or complete obstruction of a coronary artery by a thrombus.<sup>1</sup> This obstruction decreases myocardial blood flow, resulting in an imbalance in the supply and demand of blood to the heart. Percutaneous coronary intervention (PCI) is a commonly used treatment to reestablish patency in the occluded artery.<sup>1</sup> Thrombotic events following PCI are common, and the use of dual-antiplatelet therapy with aspirin and clopidogrel to prevent thrombotic events in this patient population has become the standard of practice.<sup>2</sup> Unfortunately, there are a significant number of patients that are either hypo-responsive or hyper-responsive to the anti-platelet effects of clopidogrel.<sup>3</sup>

Effient® (prasugrel) is a new thienopyridine anti-platelet agent that was FDA-approved on July 10, 2009, for thrombosis prophylaxis in patients with ACS undergoing PCI.<sup>4</sup> A loading dose (LD) of 60 mg given orally should be followed by a maintenance dose (MD) of 10 mg given orally each day in conjunction with 75 mg to 325 mg of aspirin.<sup>5</sup> A black box warning states that prasugrel has been associated with increased bleeding in patients with a history of stroke, transient ischemic attacks, body weight of <60 kg, and/or patients using other medications that increase their risk of bleeding (warfarin, heparin, fibrinolytics, and chronic use of NSAIDs). Except in patients at high risk for thrombosis, prasugrel is not recommended for use in patients 75 years of age or older. Patients who are likely to require an urgent coronary artery bypass graft should not initiate prasugrel, and it should be discontinued seven days prior to elective surgery. Common adverse drug reactions (ADRs) associated with prasugrel include hypertension (7%), hyperlipidemia (7%), backache (5%), headache (5.5%), and epis-taxis (6.2%). Serious ADRs include atrial fibrillation (2.9%), bradyarrhythmia (2.9%), major bleeding (2.2%), and leucopenia (2.8%).<sup>5</sup>

A randomized, multi-centered, double-blind, placebo-controlled trial compared the safety and efficacy of prasugrel

to clopidogrel in preventing thrombotic events in patients with ACS undergoing PCI.<sup>2</sup> Seven hundred and seven centers in 30 countries randomized 13,608 patients who were scheduled for a PCI to receive either prasugrel (LD=60 mg, MD=10 mg daily) or clopidogrel (LD=300 mg, MD=75 mg daily). Both treatment groups received aspirin with a recommended daily dose of 75 mg to 162 mg. The median duration of therapy was 14.5 months. There was a significant decrease in the rate of death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke in patients with ACS receiving prasugrel compared to patients receiving clopidogrel (-9.9% vs. -12.1%;  $p<0.001$ ). Significantly more patients treated with prasugrel experienced a fatal thrombolysis in myocardial infarction (TIMI) major bleed than those treated with clopidogrel (0.4% vs. 0.1%;  $p=0.002$ ). Treating patients with a history of stroke or transient ischemic attack with prasugrel resulted in more harm than benefit. Patients who were 75 years of age or older and/or weighed <60 kg had no net benefit from prasugrel. When patients with any of these three risk factors were excluded from the analysis, there was no significant difference in the incidence of major bleeding between the prasugrel and clopidogrel treatment groups. The incidence of serious ADRs unrelated to hemorrhage was not statistically different between the two treatment groups; however, there was a significant difference between the prasugrel and clopidogrel groups in the incidence of neutropenia (<0.1% vs. 0.2%;  $p=0.02$ ) and colonic neoplasms (0.2% vs. 0.1%;  $p=0.03$ ). The doses used in this study resulted in higher, more consistent levels of active metabolite, higher mean inhibition of platelet aggregation, and lower patient response variability (fewer hypo-responders) in patients given prasugrel compared to those given clopidogrel. The authors concluded that prasugrel reduces the rate of ischemic events following PCI, but it is associated with a greater risk of bleeding compared to clopidogrel.<sup>2</sup>

Prasugrel's superior anti-platelet effects compared to clopidogrel provide it a unique place in thrombotic prophylaxis. Its black box warning urges prescribers to use prasugrel with discretion in patients who have a history of stroke or transient ischemic attacks, are 75 years of age or older, and/or

weigh <60 kg. As long as these precautions are observed, prasugrel is a safe and highly effective anti-platelet treatment for the prevention of thrombosis in patients with ACS undergoing PCI.

**By**

**Cassandra Stiff, Pharm.D. Candidate**

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## Renal and Retinal Effects of Enalapril and Losartan in Type 1 Diabetes

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It has been well documented that angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) can reduce the progression of advanced stage diabetic retinopathy and nephropathy in patients with type 1 or type 2 diabetes. However, whether ACE inhibitors or ARBs can slow the progression of diabetic retinopathy and nephropathy if administered before the onset of disease has not been determined. A double-blind, randomized, placebo-controlled study evaluated the effect of enalapril and losartan on the progression of diabetic nephropathy and retinopathy in normotensive patients with type 1 diabetes.

Two hundred and eighty-five patients were randomly assigned to either 10 mg of enalapril daily, 50 mg of losartan daily, or placebo. The study was conducted for five years, but a dose increase was initiated at year two due to data supporting progression rate reduction of nephropathy and retinopathy at higher doses. The primary endpoints were a reduction in the rate of kidney and reti-

nal damage measured by mesangial fraction volume, a measure of kidney damage, and visual inspection of the retina via photograph. Retinal disease progression was quantified by step classifications ranging from step one, mild disease progression, to step 16, advanced disease progression.

Renal and retinal biopsies were completed for 90% and 82% of the patients, respectively. The renal biopsy showed no significant difference between groups in mesangial fractional volume per glomerulus. The losartan group had a higher incidence of microalbuminuria ( $p=0.01$ ) and higher albumin excretion rates ( $p=0.03$ ) compared to placebo. Compared to baseline, retinal photographs revealed that 25% of patients in the enalapril group ( $p=0.02$ ), 21% in the losartan group ( $p=0.008$ ), and 38% in the placebo group had retinopathy progression of two steps or more, suggesting that ACE inhibitors and ARBs may significantly reduce the progression of diabetic retinopathy. Side effects from the treatment groups were fairly mild, and

chronic cough was the most common side effect for both groups.

**SUMMARY:** Enalapril and losartan may reduce the progression of diabetic retinopathy in normotensive patients with type 1 diabetes without previous retinal damage; however, enalapril and losartan do not reduce the progression of kidney damage in this population.

*Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med 2009;361:40-51.*

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