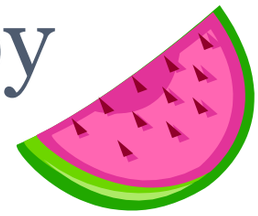
Women's Health Edition

Summer 2010

Lebanon VAMC Pharmacy

Pharmacotherapy Update



Special points of interest:

- Mammography Screening Update
- Safety of Antidepressants in Pregnancy
- Cervical Cancer Screening and Prevention
- Osteoporosis & Vitamin D
- PPIs and Osteoporosis

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Editor Notes

This edition of the newsletter focuses on women's health. As the VA is having continued growth in enrolling female veterans of childbearing age this newsletter is going to focus on some of the issues providers and other healthcare professionals will encounter in this age group.

The front page article talks about a hot topic regarding the use of antidepressants in pregnancy. There is also an article which reviews the controversial new mammography guidelines, please check out the new US guidelines. Page 4 reviews another guideline regarding PAP smear which is setting off a controversy for OBGYNs and patients everywhere.

Page 5 has a "Did you know section" that discusses pharmacy roots in the baby formula business.

Make sure to get your proper dose of sunshine each week- Page 6 has a review on the importance of Vitamin D and overall health.

The newsletter will finish off with a review of the newest relationship between osteoporosis and PPI use as well as a literature review on the "Jupiter" Trial.

Stay cool this summer!
Susan Sincavage, Pharm.D. and Dina Norris, Pharm.D., BCPS, Editors

The Safety of Antidepressants in Pregnancy

By: Megan Sculley, Pharm.D. Candidate

Although depression has been estimated to occur in approximately 12.6% of women (vs. 6.3% of men)[1], many physicians are unaware of the pharmacological options during pregnancy. As more women veterans are seeking medical care through the VA, this is becoming a more frequent scenario within our patient population.

The decision to initiate medication during pregnancy should be considered on a case-by-case basis, depending on the patient's history. Although the patient may put the needs of her baby before her own, it is important to educate her on the risks of untreated depression on the fetus. Untreated maternal illness can lead to poor compliance with both self and prenatal care, inadequate nutrition, increased alcohol or tobacco use, and preterm birth[2]. It has also been shown that children as old as 18 years of age who were born to mothers with depression have significantly higher rates of mental and behavioral disorders[3]. If medication is prescribed, a single medication at a higher dose is the recommended regimen because of the increased plasma volume and dilutional effects in pregnancy. If possible, medication should be withheld until after the first trimester, which is when the embryo is the most at risk of teratogenesis. The American College of Obstetricians and Gynecologists recommend starting an antidepressant at a low dose and titrating slowly upward until the condition seems to have subsided[4]. The Selective Serotonin Reuptake Inhibitors (SSRIs), with the exception of paroxetine, have been chosen by default as the drug class to prescribe in pregnant women, only because this drug class has the largest amount of safety data collected during pregnancy. The use of paroxetine should be avoided, if possible, during pregnancy because studies have associated it with higher risks of congenital anomalies[5], thus making it the only one of its class with a pregnancy category D.

The current system for classifying a drug in a pregnancy category is based on the risk of injury it poses on the fetus. There are five categories: A, B, C, D, and X—A being the safest, and X being the least safe. Most of the SSRIs are category C, meaning studies have shown the drug to either: (1) have *animal* teratogenic or embryocidal effects, but there are no controlled studies in women, or (2) no studies are available in either animals or women. Paroxetine was moved to category D because controlled studies in women have shown positive evidence of fetal risk.

Because of the chronic nature of depression, combined with the steep decline in levels of many hormones immediately postpartum, many women will continue taking antidepressants after giving birth. As many of

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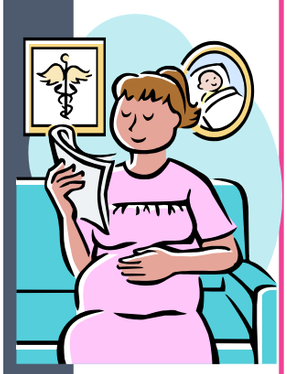

these mothers will have concerns about drugs passing into breast milk, I have also included the lactation category of all drugs as a reference.

VA Formulary

DRUG NAME	DRUG CLASS	PREGNANCY CATEGORY	LACTATION CATEGORY
Amitriptyline HCl	TCA	C	L2*
Clomipramine	TCA	C	L2
Desipramine HCl	TCA	C	L2
Doxepin HCl	TCA	C	L5
Imipramine HCl	TCA	C	L2
Nortriptyline	TCA	C	L2
Phenelzine Sulfate	MAOI	C	Unknown
Selegiline	MAOI	C	Unknown
Tranylcypromine Sulfate	MAOI	C	Unknown
Bupropion HCl	NDRI	B	Contraindicated
Citalopram Hydrobromide	SSRI	C	L3
Fluoxetine	SSRI	C	L2 in older infants, L3 if used in neonates
Mirtazapine	Other/piperazinoazepines	C	L3
Paroxetine	SSRI	D	L2
Sertraline	SSRI	C	L2
Trazodone	Other/heterocyclic antidepressants	C	L2
Venlafaxine (ER/IR)	SNRI	C	L3

*Categories are listed as follows: L1-safest, L2-safer, L3-moderately safe, L4-possibly hazardous, L5-contraindicated.

Non-formulary Agents

DRUG NAME	DRUG CLASS	PREGNANCY CATEGORY	LACTATION CATEGORY
Amoxapine	TCA	C	L2
Duloxetine	SNRI	C	Unknown, of concern
Escitalopram	SSRI	C	L3 in older infants
Fluvoxamine	SSRI	C	L2
Maprotiline	TCA	B	L3
Nefazodone	Phenylpiperazine derivative	C	L4
Protriptyline	TCA	C	Unknown

Theoretically, the medications with fewer active metabolites, lower placental transfer (higher protein binding), and minimal interactions with other medications are preferred during pregnancy[5]. Studies on SSRIs and pregnancy have failed to provide concrete evidence as to whether or not they cause congenital defects. Those studies that *have* shown a statistically significant result have not translated into any type of clinical significance, but instead require confirmation by future studies.

Women who are already taking medication for depression should also be reviewed individually and educated on the options. In some cases, women have inappropriately discontinued their medication, without seeking medical advice first, out of concern for their babies' health. If medication is abruptly discontinued upon conception, the risk of relapse is significantly higher than in those who continue throughout pregnancy[6]. In addition, the response to medication after it is reintroduced may not be as positive as it would be if the

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Updated Mammography Recommendations

By: Christy Dayhoff, RPh

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The incidence of breast cancer increases with age and it has been estimated that the lifetime risk for breast cancer for a woman in the United States is approximately 12.3% (1 in 8 women). There are some women who are at increased risk such as those with certain gene mutations, prior history of irradiation to the chest, history of atypical hyperplasia in a previous breast biopsy or strong family history.

Controversy has been generated because The United States Preventative Services Task Force (USPSTF) recently announced that it is changing its guidelines for mammography and no longer recommends routine annual screening for the general population between the ages of 40-49. The new recommendation is that women begin routine biennial screening at the age of 50 and continue through the age of 74. This recommendation is based in part on a statistical analysis of several clinical trials which demonstrated that mammography reduced the incidence of death in women between the ages of 40-49 by about 15% but that the number of women in this age group that needed to be screened over 10 years to save one life was 1,904. In contrast, for women between the ages of 50-59, the reduction in deaths was about the same (14%) but the number of women that needed to be screened dropped to 1,339. This is also based on the fact that a woman in her 40s is less likely to be diagnosed with breast cancer that a woman in her 50s. The implementation of these new guidelines could have serious implications for how screening mammography is covered by the health insurance industry and government programs especially during this time of health care reform.

The American Cancer Society (ACS) has not changed its stance and continues to recommend routine annual screening using mammography for all women beginning at the age of 40 and that the potential benefits of screening outweighs any potential harm. Mammography does have limitations - some women may have false alarms leading to unnecessary biopsies, some cancers may be missed and some women may undergo unnecessary treatment. Mammography is less effective in women of a younger age primarily due to increased density of breast tissue making the interpretation of mammography films more difficult. However, recent data show that 17% of deaths from breast cancer occur in women who were diagnosed in their 40s and 22% occurred in women who were diagnosed in their 50s.

In summary, there is no single correct answer for any particular individual as there is no consensus agreement between the differing medical bodies regarding screening. Women should weigh risk versus benefit of annual screening with consideration given to individual risk factors for breast cancer after discussion with their physician.

Comparison of USPSTF and ACS Recommendations

Population	Women Aged 40-49 Years	Women Aged 50-74 Years	Women Aged ≥75 Years
USPSTF Recommendation	Individualize decision to begin biennial screening according to the patient's context and values.	Screen every 2 years	No recommendation.
ACS Recommendation	Screen once yearly	Screen once yearly	Screen once yearly based on individual health and presence of other serious illnesses.

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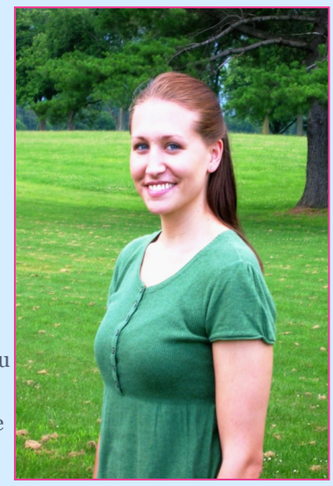
Clinical Pharmacist Corner: Ambulatory Care Resident

Monica Gehret, Pharm.D.



Education:
Doctor of Pharmacy – Wilkes University
Wilkes-Barre, PA 2009

Residency Training:
Pharmacy Practice Residency
Lebanon VA Medical Center
Lebanon, PA 2010

Future Plans:
PGY2 Ambulatory Care Residency
Lebanon, PA VA Medical Center

Advice for incoming pharmacy residents:
"Learn as much from the people around you as you can , including pharmacists, physicians, other health care professionals, and patients. Taking the knowledge you already have as a pharmacist and adding onto that with real life situations and experiences is what a PGY1 residency is all about."

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Cervical Cancer Screening and Prevention

By: Catherine Kane, Pharm.D. Candidate

With the 2006 approval of the HPV (human papillomavirus) vaccine, Gardasil®, the face of cervical cancer has been forever changed. Marketed for the use in girls and women ages 9 – 26 years of age, Gardasil® is the first vaccine of its kind – a vaccine that can prevent the development of certain types of cervical cancer (genital warts caused by types 6 and 11; and precancerous lesions caused by types 16 and 18).[1] The Gardasil® vaccination consists of three injections given at 0, 2 and 6 months. Patients most often experience injection site reactions—pain, swelling, erythema and pruritis,. Approximately 15% of patients experience syncopal episodes after vaccine administration.[1]

All female patients, regardless of their Gardasil® vaccine status should receive an annual or biannual cervical cancer screening (i.e. pap smears) beginning "approximately three years after the onset of vaginal intercourse" and "no later than the age of 21".[2] If, by the age of 30, the patient has had three consecutive negative results, they may opt to be screened every two to three years unless they have a history of cervical cancer, were exposed in-utero to diethylstilbestrol (DES – an estrogen given to pregnant women to reduce pregnancy complications shown to cause vaginal tumors in their female offspring [3]), are HIV positive or immunocompromised.[2]

Discontinuation of screening in healthy women should only be considered in women 70 or older with an intact cervix, three consecutive negative pap smears and no history of abnormal/positive pap smears within the past 10 years.[2] "Women with a history or diagnosis of cervical cancer, in-utero exposure to DES or those patients who are immunocompromised should continue cervical cancer screening as long as they are in reasonably good health and do not have life-limiting chronic conditions."[2]

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Did You Know?

By: Denise Alexander, Pharm.D.

The Nestlé Company traces its roots to the advent of baby formula, which was created by a pharmacist named Henri Nestlé. Though there are endless advantages to breastfeeding, oftentimes it is necessary to bottle-feed an infant. Henri Nestlé created his baby formula in the 1860s, and it was originally tried by a premature infant that could not tolerate its mother's milk or any other substitute available. Because his formula worked, Henri Nestlé founded a company to market his product, which has now become one of the most well-known brands in the world.

There are many types of baby formulas available on the market today, and it may be confusing to choose the most appropriate product. The Food and Drug Administration (FDA) ensures that all formulas contain the necessary amounts of vitamins and minerals, so products may only differ in their fat, protein, and carbohydrate contents. Reproducing a product comparable to breastmilk is very difficult (if not impossible), as breastmilk is constantly changing to meet the baby's needs, so there is much controversy as to which products are best.

One component that should be present in formula is the omega-3 fatty acid docosahexaenoic acid (DHA), which is essential for brain development of infants. It was thought that babies could produce their own DHA when provided with other nutrients; however, studies showing improved cognition and brain function in babies fed DHA-containing formula have contradicted this theory.

Another difference between formulas lies in the protein content. Whereas some formulas provide 100% whey protein for ease of digestion, others provide a specific whey to casein ratio similar to breastmilk. Others still attempt to mimic the fats found in a baby's bloodstream after feeding by providing a different concoction to achieve the same protein blood levels. One may not be better than the other; it is best to individualize your baby's regimen based on tolerability.

Another option is a soy protein-based formula, which is mainly for babies who are unable to tolerate cow's milk-based products. Soy proteins are derived from a vegetable source rather than an animal source, and may lack specific nutrients as a result. These are not routinely recommended unless the infant is unable to use standard formula.

All in all, there are many different types of formulas that can be used if breastfeeding is not an option. Finding the optimal product for your baby's needs may require trial-and-error, but may be well worth the risk so that you can raise a happy, healthy child.

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2. Nestle Careers/History: Available from: http://www.careers.nestle.com/meet/History_1866-1905.htm

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medication had been continued. Moreover, medications should not be changed during pregnancy, as this could also lead to relapse and increase the exposure to the offspring. In the event that a woman chooses to discontinue her medication, she should be weaned slowly in order to minimize the chance of relapse. Doses should be reduced by no more than 25% every 2 weeks until the patient is no longer on the medication[4]. Ultimately, the risk of medication use should be considered in the context of the risk of relapse if treatment is discontinued.

In the event that the woman refuses pharmacologic treatment, she should be aware that both structured psychotherapy as well as electroconvulsive therapy are also viable alternatives that pose no threat to the fetus[7].

Providing pharmacologic care for a pregnant woman can be complicated, but management of depression does not have to be. Although the information is sparse, an appropriate, informed decision can be reached that will maximize the health and safety of both mother and child.

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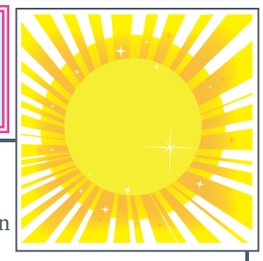
Osteoporosis and Vitamin D

By: Michele Margut, Pharm. D.



Interesting Facts About Osteoporosis

- More than 10 million people have osteoporosis, and it's not all women. According to National Osteoporosis Foundation, two million American men suffer from osteoporosis.
- 18-33% of individuals who fracture a hip may die within one year.
- Medications can cause, or contribute to, osteoporosis. The medications usually implicated are: corticosteroids, antiepileptics, aromatase inhibitors, and gonadotropin-releasing hormones.

Osteoporosis is characterized by reduction in bone mass and strength. It increases the risk of fractures due to skeletal fragility. Factors that increase the risk of osteoporosis are family history, smoking, drinking more than 3 drinks per day and being underweight. Being that most of these are modifiable factors, it's important to empower patients to make positive lifestyle changes.

The diagnosis of osteoporosis is based on the measurement of bone mineral density. A dual energy x-ray absorptiometry (DEXA) scan is used to confirm or establish a diagnosis and predict future risk. Results of this test can also be used to determine when to start pharmacological treatment.
The key with osteoporosis is ***prevention!***

1. Get enough calcium and vitamin D! How much is enough? At least **1200 mg calcium** daily for everyone and **800-1,000 IU vitamin D*** for people > 50 years old and 400 IU for adults under 50. Current research has shown that pregnant and lactating women may require dose as high as 2000-6000 IU/day; a specific dosage has not been discerned.
   *Newer data from NIH sets a safe upper at 2,000 IU/day of vitamin D supplementation
2. Weight bearing exercise is important for bone strength. **YES, this includes stair climbing**!
3. Eliminate factors that increase your risk such as smoking, drinking, being underweight.

Vitamin D— "The Sunshine Vitamin"

What is vitamin D?

Vitamin D is chemically similar to a steroid, and reserves its place as the only vitamin that is also a hormone. It is obtained in humans through diet or produced in the body by exposure to sunlight. Calciferols, as they are collectively known, encompass vitamin D1-D5. Vitamin D3 (cholecalciferol) and Vitamin D2 (ergocalciferol) are the relevant forms for humans. Ergocalciferol is found in plants and yeast. Cholecalciferol is synthesized in the skin and is more than three times as potent. There are few foods that contain vitamin D naturally, however some foods are supplemented. Salmon, canned tuna contain vitamin D, as do fortified milk, cereal or yogurt. Just 5-30 minutes of exposure to sunlight twice weekly without sunscreen is adequate for the body to produce enough vitamin D. Sunlight will only cause the body to produce as much vitamin D as is needed, so there is no risk of overdosing.

Role of vitamin D

Vitamin D is responsible for maintaining calcium homeostasis, bone density, and preventing osteoporosis. Since vitamin D controls calcium absorption, it has a role in maintaining muscle strength and bone and teeth building. Deficiencies cause bone to break down in order to supply calcium to the rest of the body. Muscle weakness can be a symptom of deficiency. It is important it monitor and appropriately supplement vitamin D in the body.

Monitoring

25-hydroxyvitamin D (25-OH) level is the blood test to determine a vitamin D deficiency. This is the major circulating form, however it is biologically inactive and must be converted in the kidneys to the active form, 1,25 dihydroxyvitamin D (1,25 $(OH)_2$). When assessing vitamin D status, using the 25-OH level provides a more accurate picture of the body's vitamin D stores.

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Proton Pump Inhibitors & Osteoporosis

By: Kevin Koons, Pharm.D., BCPS

It is well publicized and accepted that the use of proton pump inhibitors (PPI) has changed and improved the treatment of many acid-related disorders. This is clearly reflected in the 113 million prescriptions filled for this class of medications in 2009.[1] However, PPI use seems to have rampantly expanded beyond approved indications with an estimated 53-69% of PPIs being prescribed outside of standard treatment guidance.[1] Despite what appears to be an attractive short term safety profile, concerns have been raised over the long-term safety of these medications, particularly with difficulties in discontinuing this therapy. Concerns over the absorption of calcium and its implications on the risk of fractures in patients with or at risk of osteoporosis has been raised by multiple studies.[2] Osteoporotic fractures have the potential to place a significant burden one's health, including an increased risk of morbidity and mortality.[3] A recent study published as a part of the ongoing Women's Health Initiative (WHI) in the *Archives of Internal Medicine* attempted to help further define the extent to which we should be concerned.

Gray *et al,* performed a prospective cohort study which followed 161,806 women that were enrolled in the WHI. The cohorts were defined based on use of PPI, histamine-2 receptor antagonists, or non-users and then followed for osteoporotic fractures and bone mineral density changes for a period of 7.8 years on average. Hazard ratios were calculated for each group using Cox proportional hazards models. In the final analysis the use of PPI was not associated with an increase in the risk of hip fracture (HR, 1.00; 95% CI 0.71-1.40). However, there was an increase in the risk of clinical spine (HR, 1.47;95%CI, 1.18-1.82) and forearm/wrist (HR, 1.26; 95% C, 1.05-1.51) fractures. The HR ratio for all fractures with PPI use was 1.25 (95% CI, 1.15-1.36), meaning there is an approximate 25% increase in the risk of fractures with use of PPIs relative to nonusers. H2 antagonists were not associated with an increase in risk of any one category of fracture; however, their use was associated with a small 8% relative increase in risk of total fractures versus nonusers. A robust change in bone mineral density in PPI or H2 antagonist users was not apparent.

There were several limitations to the data generated. One example is that the baseline characteristics of the different cohorts had some significant differences. In general, PPI users tended to have a greater degree of multiple comorbidities that extended beyond gastrointestinal issues. In addition, results were likely confounded by many of the patients being actively enrolled in treatment programs as part of the WHI specifically targeting osteoporosis. Overall, this article provides evidence that supports the need for appropriate risk versus benefit evaluation for initiation and continuation of PPI therapy.

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Literature Review: The Jupiter Trial

By: Heather Ulrich, Pharm.D, BCPS, CDE

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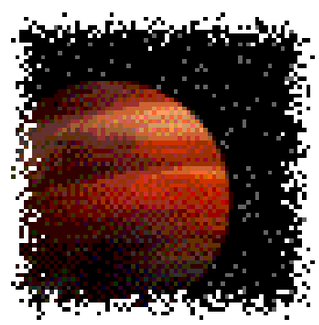
There is overwhelming literature to support the use of statins to prevent morbidity and mortality in patients with cardiovascular disease or risk factors such as hyperlipidemia or diabetes. However, as many as 50% of heart attacks and strokes occur in healthy individuals without established cardiovascular disease or risk.[1] It is on this premise that the Jupiter trial was designed to answer the question: can statin therapy prevent cardiovascular events in healthy people with normal cholesterol levels but increased levels of C-reactive protein (CRP).

Background: CRP is a marker of chronic low-level inflammation which has emerged as an independent predictor of myocardial infarction, ischemic stroke, and vascular death.[2,3] The addition of CRP to traditional risk factors, has been shown to reclassify up to 30% of individuals.[4] Studies have demonstrated that statins lower CRP and support the hypothesis that these agents may have anti-inflammatory effects that produce benefits beyond LDL lowering.[5,6] The JUPITER trial is the first study to prospectively look at the impact of statin therapy on CRP and risk for cardiovascular events.

Study design: JUPITER was a randomized, double-blind, placebo controlled multicenter trial conducted at 1315 sites in 26 countries. Astra-Zeneca, the manufacturer of rosuvastatin, provided funding and support for data collection and monitoring, but had no stated role in data analysis or manuscript development.

Patient population: Men ≥ 50 years old and women ≥ 60 years old were eligible for the study if they had no history of cardiovascular disease or events and had a LDL cholesterol <130 mg/dl and a CRP >2.0mg/L. Other inclusion criteria were written informed consent and a triglyceride level of <500 mg/dl.



Exclusion criteria included:

- Previous or current use of statin or other lipid-lowering therapy
- Current use of post-menopausal hormone-replacement therapy
- Hepatic dysfunction, creatinine >2.0mg/dl
- Diabetes, uncontrolled hypertension, uncontrolled hypothyroidism
- Recent history of cancer (exception for skin cancer)
- Recent history of alcohol or drug abuse
- Inflammatory conditions or use of immunosuppressant agents

Methods: Following a 4 week run-in phase with placebo, patients were randomized to receive rosuvastatin 20mg daily or placebo. Follow-up visits, which included laboratory monitoring, pill counts, and structured interviews, were conducted at 13 weeks, then every 6 months.

The primary outcome was the occurrence of a first major cardiovascular event, which was defined as nonfatal myocardial infarction or stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from a cardiovascular cause. Secondary endpoints included individual components of the primary outcome and death from any cause. The study was event-driven, in that it was designed to continue until 520 events occurred. This provided 90% power to detect a 25% reduction in the primary outcome. Analysis was done on an intention to treat basis using Cox proportional hazard models.

Results: 17,802 individuals met eligibility criteria and were randomized to one of the two study groups. 38.2% of subjects were women and 25.2% were black or hispanic. Median cholesterol levels at baseline were: LDL 108 mg/dl, HDL 49 mg/dl, and TRG 118 mg/dl. Median CRP level was 4.2 in the active treatment group and 4.3 in the placebo group. It should be noted that although this was a study designed to look at a healthy population, 41.4% of individuals were classified as having the metabolic syndrome, 16% were current smokers, and 11% had a family history of premature heart disease.

Although the study was anticipated to run 5 years, it was stopped early after a median follow-up of 1.9 years due to treatment benefit that exceeded prespecified boundaries. As anticipated, rosuvastatin significantly lowered LDL and CRP levels. Treatment with Rosuvastatin was associated with a statistically significant decrease in first major cardiovascular events (0.77 vs. 1.36 per 100 person years, hazard ratio 0.56). Significant differences were also noted for all individual components of the primary outcome, with the exception of hospitalization for unstable angina. The rates of death from any cause were 1.00 and 1.25 per 100 person years with rosuvastatin and placebo, respectively (HR 0.80, p=0.02). The number needed to treat to prevent one first time event in 2 years of therapy was 95 (31 for 4 years, 25 for 5 years). Total adverse effects, including LFT abnormalities and common side effects of statins, such as muscle weakness or pain, did not differ significantly between groups. Only one case of rhabdomyolysis was reported for a 90 year old patient with influenza and pneumonia in the treatment group. There was, however, a higher incidence of physician-reported diabetes with rosuvastatin therapy.

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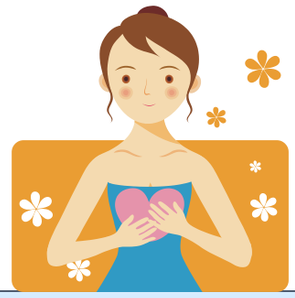

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Results were consistent across prespecified subgroups including those based on age, race, gender, and Framingham risk score. Subjects that had elevated CRP but no other major risk factors experienced benefits similar to those of higher risk participants. An a-priori subanalysis published following the original report demonstrated that benefits were greatest when both LDL and CRP were reduced (65% reduction when both targets were achieved vs. 33% when one or neither target reached).[7] A substudy which included 6801 women aged 60 years and up demonstrated that treatment with rosuvastatin decreased the relative risk for major cardiovascular events in women by 46% as compared with placebo.

Implications: It has been estimated that if statins were broadly recommended based on the JUPITER inclusion criteria, an additional 6-8 million adults in the US would be treated.[8] Although one cost-analysis deemed such a recommendation cost-effective, it is difficult to make firm conclusions without further data on long term efficacy and safety.[8] Further investigation is warranted to determine specific recommendations for screening and treatment of elevated CRP. Perhaps the JUPITER trial, which gives weight to the inflammatory hypothesis of atherosclerosis, will pave the way for studies of other anti-inflammatory medications. And, since it included enough women to determine statistical significance, we now have evidence that women may benefit from this treatment as well.

The primary prevention of cardiovascular disease is key to reducing morbidity and mortality in our society. Reduction of modifiable risk factors, such as obesity, smoking and sedentary lifestyle, remains paramount in the overall prevention of heart disease, and should remain the focus of public health efforts, regardless of the role of statin therapy.

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