Spring 2010

Lebanon VAMC Pharmacy

Pharmacotherapy Update

Special points of interest:

- Drug class review of statins-do they increase the risk of diabetes?
- Literature Review: Dronedarone and the ATHENA Trial
- PBM Alert: Statin-fibrate combinations

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Editor Notes

Hello, all.

This issue of the Pharmacotherapy Update has a focus on drug therapy in cardiovascular disease. The literature review section reviews the recent ATHENA trial which deals with the use of dronedarone in atrial fibrillation and its suggested clinical role in the arsenal to treat AFib.

In the Drug Safety Corner we have a great review on the use of combination therapy with statin-fibrates. You will be provided with a quick overview of risk factors of rhabdomyolysis, dosing limitations for certain statin-fibrate combinations, and more.

Another timely article reviews the recent press on statin use increasing a patient's risk for diabetes on page 3 of this newsletter.

The FDA recently gave a new indication approval for rosuvastatin– check out page 4 to read all about it.

Page 5 has an entertaining article on all of the inventions pharmacists have been responsible for throughout the years.

Hope everyone enjoys the beautiful Spring weather!

Dina Norris, Pharm.D., BCPS, co-editor

Monica Gehret, Pharm.D., co-editor

Literature Review: The ATHENA Trial

By Monica Gehret, PharmD

Atrial fibrillation is the most common arrhythmia requiring treatment. It increases a patient's risk of stroke and death, as well as hospitalizations. Standard treatment for atrial fibrillation includes anticoagulation plus either rate control or rhythm control. Dronedarone was approved by the FDA in July of 2009 to treat atrial fibrillation (a.fib) and atrial flutter (a.flutter).

Dronedarone is a benzofuran derivative with a pharmacological profile that resembles amiodarone. Like amiodarone, it has characteristics of all four Vaughan-Williams antiarrhythmic classes. In other words, it blocks sodium channels, has antiadrenergic activity, prolongs action potential and refractory periods, and has calcium channel-blocking properties. It differs from amiodarone in that it does not contain an iodine group, which gives it less lipophilicity and a shorter half-life. Dronedarone is hepatically metabolized and excreted in the feces.

Three previous dronedarone trials have compared it to placebo in patients with atrial fibrillation who were in normal sinus rhythm (NSR) at the time of randomization. The primary outcome in two of these trials (DAFNE and EURIDIS/ADONIS) was time to first a.fib recurrence. In both trials, dronedarone 400mg twice daily was more effective than placebo at maintaining sinus rhythm by prolonging the time to a.fib recurrence.

The ANDROMEDA trial compared dronedarone 400mg twice daily with placebo, with a primary outcome of death from any cause or hospitalization for worsening heart failure. The patients included in this study were hospitalized with symptomatic heart failure and severe left ventricular systolic dysfunction. A.fib was not part of the inclusion criteria. ANDROMEDA was planned to last two years but was terminated early, mainly due to excess mortality from worsening heart failure in the dronedarone group.

DIONYSOS is an unpublished trial undertaken by Sanofi-Aventis, the manufacturer of dronedarone, which was completed in December 2008. This study included patients with a.fib with a primary outcome of a.fib recurrence or premature study drug discontinuation for intolerance or lack of efficacy. This trial was different from earlier trials as it compared dronedarone with amiodarone rather than placebo. Results show that more dronedarone patients reached the primary endpoint than amiodarone patients. The researchers noted that when excluding gastrointestinal adverse effects, the dronedarone group had 39% less adverse effects when compared to amiodarone, which was a significant difference. Amiodarone was more likely to cause thyroid events, neurological events, and premature discontinuation due to any adverse event.

The ATHENA trial was designed to determine if dronedarone prolongs the time to first cardiovascular hospitalization or death in moderate- to high-risk elderly patients with atrial fibrillation. The study was funded by Sanofi-Aventis, dronedarone's manufacturer, and was designed in collaboration with a steering committee. The study was a randomized, double-blind, placebo-controlled trial undertaken in 551 centers in 37 countries. It was the largest single antiarrhythmic drug trial ever conducted.

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Drug Safety Corner: Statin-Fibrate PBM Bulletin

By Lisa McKee, PharmD, BCPS

"The benefit of this combination is unclear and the potential for muscle damage is higher with the statin-fibrate combination than either statins or fibrates alone."

It is unlikely that it is news to anyone that combining HMG CoA Reductase Inhibitors (statins) and fibric acid derivatives (fibrates) has the potential to cause a drug-drug interaction that can produce muscle toxicity. This potential drug-drug interaction is well documented, however, what is new is the VA Pharmacy Benefits Management (PBM) published a bulletin in November 2009 giving guidance on the statin-fibrate combinations. The bulletin confirms that the benefit of this combination is unclear and the potential for muscle damage is higher with the statin-fibrate combination than either statins or fibrates alone. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study is comparing the statin-fibrate combination to statins alone and the results of the study are expected this year. Until the results of the ACCORD trial are available PBM advises to use the combination cautiously especially in patients with any of the following conditions:

- Advanced Age
- Impaired Renal Function
- Female Gender
- Alcoholism
- Hypothyroidism

The PBM goes on to advise high dose statin and fibrate combinations should be avoided when possible and due to limited literature available there really are not any statins or fibrates that can be considered safer than any other.

If a patient is already on the statin-fibrate combination the following steps are advised:
If LDL lowering is priority:

- Discontinue fibrate
- Continue statin
- Initiate additional agents (niacin, bile acid sequestrants) for further LDL lowering if needed

If TRIGLYCERIDE lowering is priority:

- Discontinue statin
- Continue fibrate

If both LDL and TRIGLYCERIDE lowering are needed:

- Discontinue fibrate
- Continue statin and maximize if needed for LDL lowering
- Initiate additional agents (niacin, omega-3 fatty acids) if possible for triglyceride lowering

If statin-fibrate combination benefit outweighs the risk of muscle toxicity the following is advised:

- Use lowest effective statin dose and adhere to the following dosing limits when combined with gemfibrozil:
  - Simvastatin 10mg daily
  - Lovastatin 20mg daily
  - Rosuvastatin 10mg daily
  - Atorvastatin, pravastatin and fluvastatin do not have recommended dosing limits
- Ensure normal renal (eGFR>60ml/min), liver and thyroid function
- Use caution with known statin metabolism inhibitors (macrolides, azole antifungals, protease inhibitors, cyclosporine, amiodarone, verapamil, diltiazem, etc.).
- Discuss and document in the patient's chart they have been made aware of the potential risks and benefits of combination therapy
- Educate patient to immediately notify his/her provider if muscle pain or weakness occurs

As per National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III and VA/DoD Dyslipidemia Guidelines, the following is recommended when combination therapy is used:

- Obtain a baseline creatine kinase (CK)
- Repeat CK if patient complains of muscle symptoms indicative of myopathy
- Discontinue statins and fibrates if CK reaches 10 times upper limit of normal WITH muscle complaints
- Re-challenge with a lower dose of one or the other should be considered once complaints resolve and CK returns to normal

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Statins: Decreasing Cardiovascular Morbidity and Mortality, but Causing Diabetes?

By Inga Washington, PharmD, BCPS

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Statins are the cornerstone of treatment for patients at risk for developing cardiovascular disease (CVD) as well as those with existing disease. As we know, patients with diabetes are at high risk for developing CVD and are treated to the same targets as patients with known coronary disease. It is quite unexpected, therefore, to discover that the very drugs we use to treat CVD may be inducing a risk-equivalent condition: diabetes.

The recent Justification for the Use of Statins in Primary Prevention: An Intervention Evaluating Rosuvastatin (JUPITER) trial yielded some unexpected results when significantly more patients in the intervention group developed diabetes after approximately 2 years of treatment. These results were surprising and conflicted with the West of Scotland Prevention Study (WOSCOPS) which found a reduced rate of newly diagnosed diabetes in participants treated with pravastatin. This inconsistency led to a meta-analysis of the available literature.

The authors conducted a search of the literature from 1994-2009 which yielded 2841 publications for examination for inclusion. Investigators from 9 additional trials were contacted to inquire about unpublished data that might exist regarding new onset diabetes which yielded more information. Data was collected from trials that were placebo and standard-care-controlled. Trials that were included must have determined statin effects on cardiovascular endpoints and must not have used changes in surrogate markers for evaluation, have allowed only stable patients (no patients with organ transplants or on hemodialysis), must have had 1000 or more participants, and had followed patients for more than 1 year. Trials that included diabetic patients were also excluded. Thirteen studies totaling 91,140 patients with a mean follow-up period of 4 years were included in the meta-analysis: ASCOT – LLA, HPS, JUPITER, WOSCOPS, LIPID, CORONA, PROSPER, MEGA, ASCAPS/TEXCAPS, 4S, ALLHAT, GISSI HF, and GISSI PREV. A funnel plot was performed on the included studies for heterogeneity and was found to be low, indicating a low likelihood of publication bias and that most variations were due to chance alone.

Two studies, JUPITER and PROSPER, showed an increased risk of diabetes associated with statin use. JUPITER patients were randomized to rosuvastatin 20 mg or placebo, while those in the PROSPER study received either pravastatin 40 mg or placebo. The patient populations differed dramatically between the 2 studies; JUPITER enrolled patients without CVD, whereas PROSPER examined elderly patients with CVD or at high risk for developing CVD. The method of diagnosis in PROSPER could be called into question, however, as investigators considered only 1 fasting plasma glucose (FPG) > 126 mg/dL or the use of hypoglycemic agents diagnostic for diabetes. This not in accordance with the American Diabetes Association's Standard of Care for Diabetes which requires 2 FPG readings ≥ 126 mg/dL as diagnostic. The JUPITER trial followed the Standards of Care and considered the use of hypoglycemic therapy, a positive oral glucose tolerance test (OGTT), elevated random glucose with symptoms, or 2 FPG ≥ 126 mg/dL as diagnostic.

Analysis of the available data showed 174 more cases of new onset diabetes in patients treated with statins than those in the placebo or standard-care groups. This translates to 9% increase in risk of developing diabetes. The number-to-harm analysis yielded 1 additional case of diabetes for every 255 patients treated with a statin for 4 years. There were similar risks found regardless of the use of hydrophilic (fluvastatin, pravastatin, rosuvastatin) or lipophilic statins (lovastatin, simvastatin, atorvastatin). Baseline BMI and percentage change in LDL were not found to be contributing factors. There was a stronger association between new onset diabetes and statin usage in older participants.

What does this mean for practice? Should we stop using statins due to the increased risk of diabetes? Experts on the subject resoundingly agree with the authors of the meta-analysis and say, "No." As with all treatments, the risk vs benefit must be weighed.

Does the risk of developing diabetes when treated with a statin outweigh the risk of a coronary event if not treated with a statin? In the same group of 255 patients treated for 4 years, statin therapy (with a resultant reduction in LDL of ~ 40 mg/dL) resulted in 5.4 fewer coronary events ie coronary heart disease or nonfatal myocardial infarction. Treatment with statins would also likely yield a similar decrease in the number of strokes and coronary revascularization procedures. The total benefit of preventing total vascular events vs the risk of developing diabetes is a ratio approximately 9:1. However, this also means that the benefit of statin therapy in patients at low risk of CVD, or in populations where their benefit has not been proven, the risk for diabetes associated with statin use should be considered when designing a treatment regimen.

The meta-analysis did bring to light the need for additional monitors in future clinical trials involving statins. The authors recommend that future trials include a secondary endpoint of development of diabetes and that current , long-term follow up studies include data regarding new onset diabetes. The results of the meta-analysis also show that for older patients on statin therapy, regular monitoring of glucose levels may be useful.

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Clinical Pharmacist Corner: Clinical Staff Pharmacist

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April 2000

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Food and Drug Administration: Updated Rosuvastatin Labeling

In December of 2009, the FDA voted in favor of broadening the indication for rosuvastatin, which will now be indicated for the primary prevention of cardiovascular disease. Based on the results of the JUPITER trial, the FDA felt that there is enough evidence to recommend rosuvastatin in patients with normal LDL-cholesterol levels who have elevated high-sensitivity C-reactive protein (hs-CRP) levels and one additional risk factor.

The JUPITER study was published in November of 2008. In the study, over 17,000 participants were randomized to rosuvastatin 20mg daily or placebo. The patients all had LDL levels of <130 and hs-CRP levels of 2.0mg/L or more, which is considered elevated. The study was stopped early (after about two years) due to the beneficial effect seen in the rosuvastatin group. This group had significantly less cardiovascular events, which the study defined as the composite of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. The rosuvastatin group did not have significant increases in the incidence of myopathy or cancer, although the rosuvastatin patients did have a higher incidence of diabetes, as reported by physicians. (see page 3) Basically, rosuvastatin significantly reduced the incidence of major cardiovascular events by 44% in healthy patients with elevated hs-CRP but no evidence of hyperlipidemia or cardiovascular disease.

The new rosuvastatin labeling, which was approved in February of 2010, will specifically state that in men ≥50 years old and women ≥60 years old, hs-CRP ≥2.0, and the presence of at least one additional risk factor such as hypertension, low HDL, smoking, or family history of premature cardiovascular disease, rosuvastatin is now indicated. Having elevated LDL is no longer a requirement if the above conditions are met.

Should everyone with an elevated hs-CRP level be treated with a statin? Not necessarily. This update to the rosuvastatin labeling should be interpreted with caution. In the JUPITER trial, about 50% of patients had at least one other risk factor for cardiovascular disease in addition to age, which is why the new labeling will reflect this. As it turned out, the benefit of treatment was not seen in patients without a cardiovascular risk factor in addition to age.

There are also several caveats for the JUPITER trial. The number of total cardiovascular events was small. The trial also did not compare low hs-CRP levels (<2) to high levels (>2). Caution is also warranted in evaluating hs-CRP as it may be elevated in the setting of inflammation. In patients with conditions like rheumatoid arthritis or Crohn's disease, hs-CRP is not likely to be a useful indicator of cardiovascular risk. One last thing to keep in mind is that it remains unknown if hs-CRP is a precursor to cardiovascular disease, or if it is simply elevated by the presence of cardiovascular disease. Rosuvastatin may not be widely prescribed based on its new indication, since hs-CRP is not routinely recommended or utilized as a screening tool. Updated treatment guidelines from the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) are anticipated in the near future and will serve as a further guide to interpreting and clinically utilizing this new indication for rosuvastatin.

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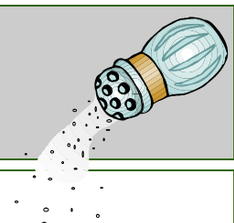
Inventions by Pharmacists



Did you know...
All of the following were invented by pharmacists:

- **Table salt** was invented by **George Duncan Bowie** & **George Weddell** in the late 1800s
  - Phosphates and sodium carbonate were added to salt to make it less prone to absorbing moisture
- **Baking powder** was invented by **Alfred Bird** in the late 1800s
- **Sir Joseph Swan** invented **the Carbon process** in 1864, allowing permanent photographs to be made
- **Sir Joseph Swan** also invented **the electric light bulb**, months before **Thomas Edison** exhibited his version of the invention in 1879
- **John Walker** invented **the match** in 1827
- **John Wheeley Lea** & **William Henry Perrins** invented **Worcestershire Sauce** in 1837
- **Luke Howard** invented the terms for **types of clouds**, such as cirrus, stratus, and cumulus
- **The fire extinguisher** was invented by **Ambrose Godfrey** in 1723
- **Coca-Cola** was invented by **John Stith Pemberton** in 1886
- **Pepsi-Cola** was invented by **Caleb Bradham** in 1893

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Literature Review: The ATHENA Trial

ATHENA included 4628 patients with paroxysmal a.fib or a.flutter. The study population had a mean age of 72 years old, was 47% female, and hypertension was the predominant underlying cardiovascular disease. This is similar to the typical elderly population at risk for hospitalization. In addition to a.fib or a.flutter, patients also had to fulfill one of the following: be 70 years or older, have arterial hypertension, have diabetes mellitus, have previously had a stroke, TIA, or embolism, have a left atrial diameter ≥ 50mm, or have a LVEF ≤ 40%. However, as the study progressed, overall mortality was lower than expected, so the steering committee changed the inclusion criteria to enrich the risk profile of the study population. About halfway through the 1.5-year long enrollment period, the inclusion criteria were changed. Basically, patients with a.fib or a.flutter who were 75 years or older, or 70-74 years old with one or more of the previous risk factors, were now included. Patients <70 years old were no longer eligible. The study excluded patients with permanent a.fib, those using other anti-arrhythmic drugs, unstable hemodynamic conditions (including decompensated heart failure within the previous four weeks), New York Heart Association (NYHA) Class IV heart failure, planned major surgery, acute myocarditis, bradycardia, previous sinus-node disease, and other non-cardiac conditions, such as severe illnesses limiting life expectancy.

Patients were randomized into study groups consisting of dronedarone 400mg twice daily or placebo and there were no significant differences between the baseline characteristics of the two groups. The follow-up was 12 months to 2.5 years with an average study duration of 21 months. The primary outcome was first hospitalization due to cardiovascular (CV) events or all-cause mortality. The secondary outcomes were all-cause mortality, CV death, or first hospitalization.

Significant differences were observed in the primary outcome with the dronedarone group having significantly more time to first hospitalization and significantly less all-cause mortality than placebo. CV death and first hospitalization were also significantly less in the dronedarone group when compared to placebo. However, although all-cause mortality was less in the dronedarone group, the incidence was not significantly different from placebo.

In terms of safety, the study drug was discontinued in 30.2% of dronedarone patients and 30.8% of placebo patients. 12.7% of the dronedarone patients discontinued due to adverse events, while only 8.1% of placebo patients discontinued because of adverse effects. This was a significant difference. Adverse events which were significantly more common in the dronedarone group included bradycardia, QT-interval prolongation, diarrhea, nausea, rash, and increased serum creatinine. Adverse events not significantly more common in the dronedarone group included pulmonary symptoms (such as interstitial lung disease), thyroid function abnormalities, and neurologic events. There was one case of torsades de pointes tachycardia following a ventricular fibrillation episode in the dronedarone group. There was no difference between serious treatment-emergent adverse events.

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Continued from page 5: Literature Review: The ATHENA Trial

In conclusion, the use of dronedarone significantly reduced the risk of hospitalization due to CV events or death in patients with paroxysmal a.fib or a.flutter. There was no significant reduction in all-cause mortality, but death from CV causes was significantly less than placebo, as was death from cardiac arrhythmia. This study likely had more favorable results than ANDROMEDA because the latter trial enrolled only patients with advanced heart failure, while ATHENA specifically excluded hemodynamic instability or NYHA Class IV HF in response to the results of ANDROMEDA. An increased serum creatinine (SCr) was also noted in ANDROMEDA. This caused an 18% reduction in creatinine clearance (CrCl), although there is no evidence that it has an effect on glomerular filtration rate (GFR).

The lack of a significant increase in the rates of thyroid or pulmonary disorders might indicate that dronedarone has a more benign side-effect profile than amiodarone. However, many amiodarone-related adverse effects present more than two years after initiating therapy, so this study might not have been of adequate duration to detect these abnormalities, especially toxic pulmonary effects.

The limitations of ATHENA include its relatively short duration and the high rate of premature discontinuation of both study treatments, at about 30%. This might have underestimated the benefit of dronedarone and also limited the likelihood of demonstrating an increase in the rate of adverse events. No other antiarrhythmic agents have been evaluated in a trial determining the rate of hospitalization due to CV events or death so this makes any comparisons difficult. Another weakness of this study is that it does not tell us how effective dronedarone is with regard to current therapy (amiodarone). We are currently awaiting the published results of the DIONYSOS trial, which compared dronedarone with amiodarone. It also had a relatively short duration, and did not look at recurrent hospitalizations or events.

One strength of this study was that it examined the unconventional combined endpoint of all-cause mortality and hospitalization for CV causes. Hospitalization is one of the main consequences of a.fib, and it can reduce quality of life as well as increase costs to society, so this seemed to be an appropriate endpoint. Less hospitalizations, as seen in this trial, was likely due to dronedarone's ability to maintain sinus rhythm longer than placebo (as seen in previous trials), and it has also shown to control heart rate in the case of an a.fib relapse. This was also the largest antiarrhythmic drug trial ever conducted in a.fib patients.

What is dronedarone's likely role in therapy? By analyzing the ATHENA trial, we can see that it included high-risk elderly patients, so we can apply it to the VA patient population, who is at high risk for complications of a.fib. The investigators excluded NYHA Class IV heart failure and hemodynamic instability due to the results of the ANDROMEDA trial. In fact, dronedarone is contraindicated in patients with with NYHA Class IV heart failure or NYHA Class II or III heart failure with a recent decompensation requiring hospitalization. Dronedarone is not likely to be effective in patients with permanent a.fib because by definition, these patients have no chance of converting to normal sinus rhythm. All dronedarone trials to date have excluded permanent a.fib.

The ATHENA trial shows us that dronedarone is likely to be useful in patients who are unable to tolerate amiodarone due to its pulmonary, thyroid, or neurologic toxicities. These patients would probably warrant a trial of dronedarone if rhythm control was the goal for a particular patient. Of note, one requirement for dronedarone use is that the patient must be in normal sinus rhythm or be scheduled for cardioversion at the time of dronedarone initiation. In the ATHENA trial, dronedarone had less adverse events, and they were also more mild. However, as discussed above, it is unknown if dronedarone may cause similar toxicities as amiodarone when used for a longer period of time than ATHENA examined. In addition, dronedarone may not be safe in patients with renal dysfunction. The discussion of the ATHENA trial noted that the increase in SCr reduces CrCl by about 18% with no effect on GFR, but provided no evidence for this claim. It also did not quantify the elevation in SCr. Frequent monitoring of renal function in patients on dronedarone is prudent, in addition to monitoring other concomitant medications which are renally cleared. Finally, the use of dronedarone in younger patients is questionable since they were not included in the second half of this study, and the overall mean age of participants included in the study was 72.

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