Rosiglitazone: An Update

Background
The Food and Drug Administration (FDA) is currently considering the fate of rosiglitazone, a thiazolidinedione (TZD) first linked to an increase in cardiovascular events in 2007. The May/June 2007 edition of the RxPress (http://pmpr.pharm.uic.edu/dig/rx/2007%20v8n3%20MayJun.pdf) summarizes the initial paper, a meta-analysis by Nissen and colleagues, as well as preliminary data (an unplanned interim analysis) from the prospective, multicenter, randomized, open-label RECORD (Rosiglitazone Evaluated for Cardiac Outcomes in Diabetes) trial. At the time, the meta-analysis found an increased risk of myocardial infarction with rosiglitazone vs. comparator therapies (odds ratio [OR] 1.43, 95% confidence interval [CI] 1.03 to 1.98; p=0.03), which was not confirmed by interim data from RECORD. The purpose of this article is to summarize the FDA advisory committee recommendations and recent literature concerning the cardiac safety of rosiglitazone.

Literature Update
The RECORD trial was published in full in June 2009. The overall results were not different from those revealed during the unplanned interim analysis in 2007. Briefly, RECORD involved subjects with type 2 diabetes receiving sulfonylurea or metformin monotherapy with an A1C of >7% to 9% who were randomized to the addition of rosiglitazone (n=2220) or the combination of metformin plus a sulfonylurea (n=2227, control arm). A third agent could be added if A1C exceeded 8.5% on combination therapy. Subjects were treated for a mean of 5.5 years and the primary outcome measure was time to first occurrence of cardiac hospitalization or cardiovascular death based on a noninferiority analysis of rosiglitazone compared to control therapy. Noninferiority was established if the upper limit of the CI did not exceed 1.2. Individual components of the composite endpoint were evaluated separately as well. The primary endpoint occurred in 321 (14.6%) of 2200 rosiglitazone recipients and 323 (14.5%) of 2227 recipients in the control group (hazard ratio [HR] 0.99, 95% CI 0.85 to 1.16); therefore, the criteria for noninferiority was met. Rosiglitazone was associated with an increased risk of heart failure (HR 2.10, 95% CI 1.35 to 3.27; p=0.0010).

The RECORD trial has been highly criticized. One of the main points of contention has been power. Power was based on an event rate of 11% for the primary endpoint, but the actual rate was 2.5%; therefore the trial may have been underpowered (unable to show a difference if one truly existed). There is the potential for clinician bias (practitioners participating in the trial may have had an expectation of how the trial would end based on the interim analysis) since the interim results were reported, a move undertaken by GlaxoSmithKline to counter the Nissen meta-analysis in 2007. Furthermore, data were unavailable for subjects who crossed over to rosiglitazone therapy from the control group. Overall, the results are not viewed as definitive.

Nissen and Wolski published an update of their 2007 meta-analysis to shed additional light on the cardiac safety of rosiglitazone. The updated analysis included 56 trials involving more than 35,000 patients with diabetes. In order to be included, trials must have been randomized and controlled with at least 24 weeks of therapy and data available for cardiovascular events. The primary source of trials was the GlaxoSmithKline database, but the authors also searched Medline and the FDA website. The main outcome measures were myocardial infarction and cardiovascular mortality.

Rosiglitazone was associated with a significantly higher risk of myocardial infarction vs. comparator therapies...
(OR 1.28, 95% CI 1.02 to 1.63; p=0.04). No difference was found in cardiovascular mortality (OR 1.03, 95% CI 0.78 to 1.36; p=0.86). The authors also performed an analysis excluding data from the RECORD trial; the results were similar. The authors concluded that rosiglitazone appears to be associated with an increased risk of myocardial infarction, and the risks of therapy outweigh any potential benefits.

At approximately the same time the updated Nissen meta-analysis was published, Dr. David Graham (of the FDA) and colleagues published an observational study to evaluate the cardiovascular safety of rosiglitazone as compared to pioglitazone. The design was a retrospective, observational cohort study involving Medicare Part D beneficiaries at least 65 years of age who received a prescription for either TZD from July 2006 to June 2009. Endpoints included myocardial infarction, stroke, heart failure, and all-cause mortality, as well as a composite of acute myocardial infarction, stroke, heart failure, or death.

Overall, 227,571 subjects initiated TZD therapy during the specified time period and were enrolled in the cohort. The mean age was 74.4 years with a median follow-up of 105 days. A total of 8667 endpoints occurred among subjects in the cohort. In the adjusted analysis, rosiglitazone was associated with a significantly higher risk of stroke (HR 1.27, 95% CI 1.12 to 1.45), heart failure (HR 1.25, 95% CI 1.16 to 1.34), and death (HR 1.14, 95% CI 1.05 to 1.24) compared to pioglitazone. There was no increased risk of myocardial infarction with rosiglitazone (HR 1.06, 95% CI 0.96 to 1.18). The risk for the composite endpoint was 1.68 (95% CI 1.27 to 2.08) excess events per 100 person-years, which corresponded to a number-needed-to-harm of 60 (number of people who must be treated for 1 year with rosiglitazone to see an additional composite endpoint). The authors concluded that rosiglitazone therapy was associated with an increased risk of stroke, heart failure, and death, as well as the composite of acute myocardial infarction, stroke, heart failure, or all-cause mortality when compared to pioglitazone.

**Regulatory Actions**

On July 14, 2010 members of the Endocrine and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the FDA voted to keep rosiglitazone on the market. The committee members met for 2 days and heard 18 presentations about the safety of rosiglitazone. Options available to the committee members for the final vote and the number voting for each option are summarized in table 1.

<table>
<thead>
<tr>
<th>Option</th>
<th>Vote count</th>
</tr>
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<tbody>
<tr>
<td>Remove cardiac warnings from label</td>
<td>0</td>
</tr>
<tr>
<td>Keep rosiglitazone on the market with current labeling</td>
<td>3</td>
</tr>
<tr>
<td>Allow continued marketing with stronger warnings</td>
<td>7</td>
</tr>
<tr>
<td>Keep rosiglitazone on the market with stronger warnings and restricted access</td>
<td>10</td>
</tr>
<tr>
<td>Remove the drug from the market</td>
<td>12</td>
</tr>
</tbody>
</table>

A final decision from the FDA is pending; however, historically, the agency follows the recommendations of their advisory committees. The agency did place a partial hold on the TIDE trial on July 21, 2010. TIDE (Thiazolidinedione Intervention with Vitamin D Evaluation), initiated in May 2009, is a phase IV, randomized, double-blind study comparing rosiglitazone and pioglitazone in terms of cardiac safety. A major goal of the trial is to determine the safety of rosiglitazone as compared to pioglitazone to allow more firm conclusions about the safety of rosiglitazone. New enrollment is suspended pending notification of institutional review boards (IRBs) as to the safety information presented at the advisory committee meeting. Subjects currently enrolled may continue therapy; however, it is likely that they will need to be re-consented as determined by individual IRBs. The European equivalent to the FDA, the European Medicines Agency (EMA), has announced it too will be reviewing the safety of rosiglitazone.

**Summary**

The future of rosiglitazone is in question. Recent literature confirms past concerns about the cardiovascular safety of the drug; however, the data demonstrating risk come from an observational study and a meta-analysis. The RECORD trial failed to identify excess cardiovascular events with rosiglitazone compared to other therapies with the exception of heart failure, a well-known TZD class effect. RECORD has been highly criticized and appears to have been underpowered to detect such a difference in cardiovascular hospitalization or cardiac death. Many had hoped that the TIDE trial would answer the question of cardiovascular safety of rosiglitazone compared to pioglitazone; however, this appears somewhat unlikely now. The TIDE trial is on partial hold by the FDA and IRBs will ultimately weigh in on the ethics of continuing the trial. Advisory committees to the FDA have recommended that rosiglitazone remain on the market with increased warnings and/or restrictions. Ultimately, the FDA will make a determination on the drug, but it is unknown when this will occur.

For a comprehensive overview and timeline of the
The study was designed so that individuals were assigned to 1 of 9 groups. The first group was given a daily polypill (formulated as a capsule) containing atenolol 50 mg, ramipril 5 mg, hydrochlorothiazide 12.5 mg, simvastatin 20 mg, and aspirin 100 mg (n=412). The remaining groups were given simvastatin 20 mg alone (n=202), aspirin 100 mg (n=205), hydrochlorothiazide 12.5 mg (n=205), hydrochlorothiazide 12.5 mg + ramipril 5 mg (n=209), hydrochlorothiazide 12.5 mg + atenolol 50 mg (n=207), ramipril 5 mg + atenolol 50 mg (n=205), hydrochlorothiazide 12.5 mg + ramipril 5 mg + atenolol 50 mg (n=204), and hydrochlorothiazide 12.5 mg + ramipril 5 mg + atenolol 50 mg + aspirin 100 mg (n=204). The authors hypothesized that the polypill would be non-inferior to simvastatin and the combination of the 3 combined antihypertensive agents, with or without aspirin. The primary outcomes were change from baseline in blood pressure, LDL, heart rate (for the effects of atenolol), and urinary 11-dehydrothromboxane B2 for the antiplatelet effects of aspirin. Safety was measured by rates of discontinuation.

The results of the study showed that there was a similar decrease in blood pressure between the polypill and the combinations containing the 3 antihypertensive agents, with or without aspirin (decrease in blood pressure with aspirin: 6.1/4.2 mmHg [95% CI 4.4/3.2 to 4.7/5.2]; no aspirin: 6.6/4.8 mmHg [95% CI 4.9/3.7 to 8.2/5.8]; polypill: 7.4/5.6 mmHg [95% CI 6.1/4.7 to 8.6/6.4]; p<0.001 for noninferiority). The decrease in LDL was slightly less with the polypill compared with simvastatin alone, 23.3% vs. 27.7%, respectively; p=0.041. The reduction in heart rate was the same between the polypill group vs. the groups that contained atenolol (7 beats per minute); however, both were significantly greater than the groups without atenolol (p<0.001). The polypill showed a similar reduction in mean urinary 11-dehydrothromboxane B2 levels when compared to aspirin alone or the group containing 3 antihypertensive agents plus aspirin; however, the comparison did not meet the pre-defined noninferiority margin (p=0.57). The polypill was well-tolerated. The rates of discontinuation did not differ significantly between the 9 groups; however the discontinuation rate was approximately 16% with the polypill, which was higher than predicted.

In relation to the goal of the study, the author of TIPS concluded the following:

1. Can a polypill (or capsule) be formulated so that it can deliver an effect similar to the additive effects of each component taken separately?
2. What degree of reduction in blood pressure and low density lipoprotein (LDL) cholesterol can be achieved in people with normal levels of risk factors?
3. Will a polypill with 5 components be tolerated?
4. Will unexpected interactions arise when these drugs are given as a single pill?
5. Does aspirin reduce the blood-pressure lowering effects of the anti-hypertensive medications?
3. Will a polypill with 5 components be tolerated? The polypill was well-tolerated over the 12-week period and the rates of discontinuation were similar among all 9 groups.
4. Will unexpected interactions arise when these drugs are given as a single pill? There were no interactions noted.
5. Does aspirin reduce the blood-pressure lowering effects of the anti-hypertensive medications? Aspirin did not have an effect on blood-pressure lowering of the 3 anti-hypertensive medications.

Although the results of TIPS are promising, the clinical implications are limited by the use of surrogate endpoints for the primary outcome; therefore, it is difficult to determine if the results correlate to clinical effects. The study was conducted in India so it is unknown as to whether the results can be extrapolated to other ethnic groups. Finally, a long-term study measuring clinical outcomes (i.e., heart attacks, strokes) is needed to assess whether the polypill would be effective in improving cardiovascular outcomes and mortality.

The polypill controversy
Advocates of the polypill estimate that there will be a 48% relative risk reduction in stroke and a 62% relative risk reduction in coronary heart disease. The polypill may increase adherence and reduce costs to the patient.

Opponents of the polypill have many concerns. Some experts question the feasibility of the polypill. A large phase III study is needed to determine the full safety profile of the polypill and how adverse effects should be managed. For example, does the physician stop the polypill if an adverse effect is seen or how does a physician know which component is causing the adverse effect? Additionally, a large outcomes trial is necessary to determine if the polypill is effective in reducing death, myocardial infarction, and stroke. The dosage of the polypill is also an issue. The polypill used in TIPS has 1 dose. The FDA requires that combination pills be available in every dose combination of each drug. This would result in hundreds of dosage combinations of the polypill. Another challenge is patients’ perceptions of the polypill. The availability of 1 pill to prevent stroke and coronary heart disease might discourage patients from maintaining healthy lifestyle modifications. Finally, is it appropriate to treat relatively healthy individuals with a pill that contains multiple medications?

Conclusion
TIPS demonstrated the potential for the polypill to improve markers of cardiovascular disease. Larger studies are needed to determine the feasibility of the polypill and clinical outcomes. Currently, in a collaborative effort called Single Pill to Avert Cardiovascular Events (SPACE), several polypill trials are underway in Europe. The newest study, Use of a Multidrug Pill in Reducing Cardiovascular Events (UMPIRE), is designed to determine adherence to the polypill. The polypill in UMPIRE consists of aspirin, a statin, and 2 anti-hypertensive agents. The study consists of 2000 patients that are at an increased risk of cardiovascular events compared to individuals enrolled in TIPS. The polypill comes in 2 strengths. Individuals with a prior myocardial infarction will be given a tablet containing aspirin 75 mg, simvastatin 40 mg, atenolol 50 mg, and lisinopril 10 mg. The polypill given to individuals with a history of stroke contains the same amounts of aspirin, simvastatin, and lisinopril; atenolol is replaced by hydrochlorothiazide 12.5 mg. Although the primary outcome of UMPIRE is adherence, the results will be combined with the trials in the SPACE collaboration, which will include over 7000 patients and have enough power to show cardiovascular outcomes data.

In TIPS 2, which is currently in progress, the low-dose polypill used in TIPS is being compared with a polypill containing twice the amounts of the components. The larger doses are more similar to the doses of the individual drugs that have been proven to reduce clinical events. This study will have approximately 500 individuals and is expected to be completed by the end of the year. The investigators of TIPS 2 plan to present their findings at the American College of Cardiology meeting in 2011.

Children with Hyperlipidemia - Screening and Treatment Recommendations

Introduction
Historically, only children with certain disease states associated with accelerated atherosclerosis were screened and treated for hyperlipidemia. However, with the rising incidence of pediatric obesity, recommendations from the American Academy of Pediatrics (AAP) for hyperlipidemia screening and treatment were updated in 2008 to also include children with multiple risk factors associated with cardiovascular disease (CVD). An overview of the updated screening and treatment recommendations is discussed below.

Associated with the metabolic syndrome, familial combined hyperlipidemia (FCH) is characterized by an increase in triglycerides, LDL, and apolipoprotein B along with decreased high-density lipoprotein (HDL) levels. In this condition, triglycerides generally range from 250 to 750 mg/dL and total cholesterol levels range from 250 to 500 mg/dL. There appears to be a direct correlation with childhood obesity and FCH; both are on the rise. The updated AAP recommendations for lipid screening include the factors that place children at risk for this form of hyperlipidemia.

Screening recommendations
Children with high-risk disease states should continue to be screened and treated for hyperlipidemia. Table
2 lists the disease states associated with accelerated atherosclerosis. Additionally, screening is recommended for children with a positive family history of CVD or those with an unknown family history. The presence of other CVD risk factors also mandates lipid screening. Table 3 lists patient factors that require lipid screening in children. Screening should occur between the ages of 3 and 10 years since cholesterol levels decrease during puberty and increase thereafter. A fasting lipid profile that includes total cholesterol, triglycerides, and HDL should be measured. The LDL concentration can be calculated from these values. If levels are considered normal for the child’s age and gender, the lipid profile can be rechecked in 3 to 5 years.

Table 2. Disease states associated with accelerated atherosclerosis.

- Familial hypercholesterolemia
- Type 1 and 2 diabetes
- End-stage renal disease
- Kawasaki disease
- Heart transplantation
- Human immunodeficiency virus (HIV)
- Post-cancer treatment survivors
- Chronic inflammatory diseases
- Congenital heart disease

Table 3. Patient factors that require lipid screening.

- Positive family history of dyslipidemia
- Family history of premature CVD (men ≤55 years of age or women ≤65 years of age)
- Unknown family history
- BMI ≥85th percentile for age and gender
- Hypertension (BP ≥ 95th percentile for age and gender)
- Cigarette smoking

CVD=cardiovascular disease; BMI=body mass index; BP=blood pressure.

**Treatment recommendations**

**Lifestyle modification**

Regardless of risk factors and concomitant disease states, the AAP recommends that all children over the age of 2 years consume a healthy diet comprised of low fat dairy products, fruit, vegetables, whole grains, and lean protein. Total daily fat intake should be limited to <30% of total calories with saturated fat intake limited to <10% of total calories. Total cholesterol intake should not exceed 300 mg per day. Intake of trans fatty acids should be less than 1% of total calories. Consumption of fruit juices, sugar-sweetened foods and beverages, and salt should be limited. Children should be encouraged to engage in physical activity for at least 1 hour per day and screen time (television, video and hand-held games) should not exceed 2 hours per day.

Children with lipid disorders should further limit daily saturated fat intake to <7% of total calories and daily cholesterol intake to <300 mg. A 12.5% reduction in total cholesterol has been observed in obese children who lost 10% of their baseline body mass index with 5 months of dietary changes and exercise. A 6 month trial of lifestyle modifications should be given before pharmacologic therapy is considered.

Other non-pharmacologic interventions include use of supplemental soluble fiber, at a dose that is determined by the child’s age, if the child is 15 years or younger (daily dose = child’s age + 5 g/day). Intake of plant stanols and sterols added to a variety of foods including margarine and yogurt can also help reduce LDL levels. However, clinicians should be aware that these agents can interfere with absorption of fat-soluble vitamins and beta-carotene.

**Pharmacologic treatment**

In the updated guidelines, pharmacotherapy is recommended for children as young as 8 years with elevated LDL levels despite lifestyle modification. Pharmacologic treatment can be instituted in children younger than 8 years who present with extremely elevated LDL concentrations that occur in high risk disease states such as familial hypercholesterolemia. The LDL concentrations at which pharmacologic treatment is recommended and the corresponding treatment goals are summarized in table 4.

Table 4: Recommended LDL concentrations and goals for pharmacologic treatment of children and adolescents.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Recommended cut points</th>
<th>LDL goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No other risk factors for CVD</td>
<td>LDL levels persistently &gt;190 mg/dL</td>
<td>&lt;160</td>
</tr>
<tr>
<td>Other risk factors present including obesity, HTN, cigarette smoking, positive family history of premature CVD</td>
<td>LDL levels persistently &gt;160 mg/dL</td>
<td>&lt;130 but 110 is preferable</td>
</tr>
<tr>
<td>Children with diabetes</td>
<td>Treatment should be considered when LDL levels are &gt;130 mg/dL</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

LDL=low-density lipoprotein; CVD=cardiovascular disease; HTN=hypertension.

Due to the adverse effects of bile acid-binding resins, niacin, and cholesterol-absorption inhibitors, statins have emerged as frontline pharmacotherapy for management of hyperlipidemia. With the exception of rosuvastatin, all other statins are approved by the FDA.
for use in children. Pravastatin is the only agent that is FDA-approved for use in children as young as 8 years. Table 5 provides a summary of the approved dosing of statins in children. Adolescent females receiving statin therapy should be counseled on pregnancy prevention since statins are contraindicated in pregnancy.

Table 5. Statins approved for use in children and adolescents.

<table>
<thead>
<tr>
<th>Statin</th>
<th>Age (years)</th>
<th>Starting dose (mg)</th>
<th>Maximum daily dose (mg)</th>
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<tbody>
<tr>
<td>Atorvastatin</td>
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<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>10 to 17</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>10 to 17</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>8 to 13</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>14 to 18</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>10 to 17</td>
<td>10</td>
<td>40</td>
</tr>
</tbody>
</table>

Although statins are recommended for treatment of hyperlipidemia in children, it should be noted that there are no long-term prospective data available demonstrating effects of statins on morbidity or mortality in children. There is also a lack of information regarding safety and lifetime use of statins, as the longest follow up study evaluating statin use in children was 2 years.

**Summary**

The criteria for lipid screening in children have been expanded to include patients with a positive CVD family history, an unknown family history, and/or a personal history of multiple CVD risk factors. This will certainly detect a greater number of children with lipid disorders. Pediatricians will be faced with a new challenge of managing an otherwise chronic adult condition. Emphasis should be placed on lifestyle modifications before instituting pharmacologic management. Referral to a dietitian and an exercise program can help increase the likelihood of a successful outcome. Although statins have shown efficacy in treating hyperlipidemia in children, data are lacking regarding the safety of long-term use or their effects on morbidity and mortality in this particular patient population. Conversely, this class of drugs is better tolerated than other agents used to treat hyperlipidemia and can effectively reduce lipid levels in children at high risk of adverse CVD outcomes.