Recent Drug Safety Concerns in Pediatric Patients

The Food and Drug Administration (FDA) has recently made important labeling changes in some commonly used pediatric medications. These changes have been made in an effort to improve the safety of dosing and administration of these medications. This article will highlight these recent safety updates for infants and children.

Oseltamivir (Tamiflu) Suspension

Oseltamivir is indicated for children ≥1 year of age for influenza prophylaxis and for the treatment of uncomplicated acute illness secondary to influenza when symptoms have been present for ≤2 days. On July 11, 2011 the FDA released a drug safety communication notifying the public of a change in the concentration of oseltamivir oral suspension from 12 mg/mL to 6 mg/mL. According to the FDA, the concentration was changed in an effort to minimize prescribing, measuring, and dosing errors after safety concerns arose. Problems in accurately measuring the 12 mg/mL product were reported as the product was noted to be “frothy” after the powder was suspended in water. The new 6 mg/mL concentration was tested and found to be less frothy when suspended allowing for more accurate measuring of the dose and easier administration. In addition, the oral syringe provided in the package for medication administration was changed from having milligram measurements to milliliter measurements. This prompted the manufacturer to update the dosing information in the package insert to clearly indicate the appropriate milliliter dosage based upon patient weight.

In October 2009, the Institute for Safe Medication Practices (ISMP) released a Medication Safety Alert regarding the concentration of a compounded suspension of oseltamivir. As a result of the influenza pandemic, there was a shortage of commercially available oseltamivir suspension, and many pharmacies began to compound a suspension using oseltamivir capsules and FDA-approved compounding directions listed in the product’s labeling. These compounding instructions resulted in a more concentrated (15 mg/mL) solution than the standard 12 mg/mL commercially available product. With the new 6 mg/mL solution, the FDA-approved labeling has been updated with compounding instructions that will results in a 6 mg/mL suspension.

Genentech, the manufacturer of oseltamivir suspension, will no longer produce the 12 mg/mL suspension; however, current supplies of the older concentration will not be removed from stock, and the product is safe to use. It is extremely important for pharmacists to carefully examine the concentration of oseltamivir suspension prior to dispensing and assure the correct dosage being administered, since 2 different concentrations will be available until supplies of the 12 mg/mL are exhausted or expire. For more information concerning the dosing of this product please refer to the FDA-approved package labeling (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107838.htm).

Acetaminophen Liquid

Acetaminophen (Tylenol and various generics) is a commonly used over-the-counter (OTC) medication for the treatment of fever and pain. Acetaminophen single-ingredient pediatric formulations currently available include 2 liquid formulations: concentrated infant drops (80 mg/0.8 mL) for children ages 2 to 3 years and a liquid suspension (160 mg/5 mL) for children ages 2 to 11 years. Two single-ingredient solid dosage forms are also available: an 80 mg tablet for children ages 2 to 11 years and a 160 mg tablet for children ages 6 to 12 years.

On May 4, 2011, the Consumer Healthcare Products Association (CHPA) announced that the makers of OTC
pediatric liquid acetaminophen formulations will transition to a single standardized concentration of 160 mg/5 mL for all liquid acetaminophen products. An infant product in the new standardized concentration of 160 mg/5 mL will be made available and the concentrated infant drops (80 mg/0.8 mL) will be removed from the market. Although the mg/kg dose of acetaminophen has not changed, the volume administered will differ between the new and old infant drops, resulting in a potential for error in dosing of acetaminophen. Additionally, new acetaminophen liquid products will be packaged with different dosing devices. Infant products will come with oral syringes and flow restrictors for easier dosing and administration, and children’s products will be packaged with standard dosing cups.

The production of the standardized concentration acetaminophen liquids began in May 2011, and these products should currently be available in retail pharmacies. During the transition period, retailers and consumers may have both the old 80 mg/0.8 mL and the new 160 mg/5 mL concentrations. Careful examination of product strength should be done to ensure accurate dosing. A patient information sheet to assist providers in recommending correct acetaminophen dosing can be found on the Tylenol website at http://www.tylenolprofessional.com/index.html.

Antipsychotic Drugs: Class Labeling Change
On February 22, 2011 the FDA released a drug safety communication regarding new updates to the pregnancy section in the prescribing information of all antipsychotic drugs. The FDA announced that the prescribing information for this medication class will include enhanced information on the risk of abnormal movements, extrapyramidal symptoms (EPS), and withdrawal symptoms in newborns exposed to antipsychotics in utero during the third trimester of pregnancy. Evaluation of the FDA Adverse Event Reporting System database through October 2008 revealed 69 cases of neonatal EPS or withdrawal reported after fetal exposure to maternal antipsychotic use. Symptoms of EPS and withdrawal in newborns include agitation, sleepiness, altered muscle tone, and poor feeding. These symptoms typically resolve within hours to days; however, in some newborns these effects may last longer.

Although antipsychotics are not contraindicated in pregnancy, health care providers and patients should collectively evaluate the risks/benefits of use in pregnancy. All adverse events, including EPS or withdrawal, should be voluntarily reported on the FDA MedWatch website at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm.

Fetal Risk with Antenatal Valproate Exposure
Valproate is an anticonvulsant indicated as monotherapy or adjunctive therapy in the treatment of adult and pediatric complex partial seizures that occur alone or in combination with other seizure types. In addition, valproate is commonly used in the treatment of mania and migraine headaches. Valproate products including valproate sodium (Depacon), divalproex sodium (Depakote, Depakote CP, and Depakote ER), valproic acid (Depakene and Stavzor) and various generic products are rated pregnancy category D due to their known teratogenic potential. Drugs rated as category D have demonstrated evidence of human fetal risk based on adverse reaction data but potential benefits of the drug may warrant use in pregnant women despite potential risks. Recent epidemiologic trial data led to the release of an FDA safety alert on June 30, 2011 warning patients and health care providers of the potential for neurodevelopment deficits in children exposed to valproate in utero.

A published prospective, observational, multicenter study compared the neurologic outcomes of children at 6 years of age after exposure to a single antiepileptic agent during pregnancy (carbamazepine, lamotrigine, phenytoin, or valproate). Data from an interim analysis was available for 309 children at 3 years of age. The cohort of women studied consisted of 303 pregnant women with an average maternal age at delivery of 27 to 32 years. All women had a primary diagnosis of epilepsy and were using monotherapy regimens for seizure control. There were 309 resultant live births with an average gestational age at delivery of 38 to 40 weeks. Significantly lower IQ scores at the age of 3 were found in children exposed to valproate when compared to the children exposed to the other single agent antiepileptics. The authors reported that children with valproate exposure during pregnancy had on average an IQ score 9 points lower than those exposed to lamotrigine (p=0.009), 7 points lower than those exposed to phenytoin (p=0.04), and 6 points lower than those exposed to carbamazepine (p=0.04). No difference was seen in IQ scores between the 3 antiepileptic agents (p=0.68). When the effects of antiepileptic exposure was assessed by dose (high vs. low), a significant negative correlation was seen for high dose valproate (≥1000 mg/d) and IQ scores. Among children exposed to high doses of valproate, the mean IQ score was 87 compared to 97 with exposure to low doses of valproate. No difference was seen in IQ scores between high and low doses of other antiepileptic agents.

Currently several unanswered questions about fetal valproate exposure exist. It is unknown what length of exposure or trimester of exposure places an individual at an increased risk of cognitive dysfunction. Furthermore, the long-term dysfunction or delays secondary to exposure are unknown. Despite these unanswered questions, the severity of the cognitive dysfunction identified in current data analysis has resulted in updating of the prescribing information and medication guide of valproate to include the potential cognitive risk to the fetus. Based on this increased risk of impaired cognitive development and the potential teratogenic effects of the drug, the risks and benefits of valproate during pregnancy need to be cautiously evaluated.
Conclusion
Important changes in product formulations and prescribing information and enhanced warnings affecting the pediatric population have recently been released by the FDA because of some major safety concerns. Additional information on drug safety communications and updates is available at www.fda.gov. In addition, to ensure continued safety to the public, adverse events and serious problems should be voluntarily reported to the FDA via the MedWatch system (www.fda.gov/Safety/MedWatch/HowToReport/default.htm).

Safety data with Pioglitazone and Bladder Cancer

Introduction
Pioglitazone is a thiazolidinedione (TZD) that is used for the treatment of type 2 diabetes mellitus (T2DM), in combination with diet and exercise. It is a peroxisome proliferator-activated receptor – gamma (PPARY) modulator that increases insulin sensitivity in muscle, fat, and liver cells. Pioglitazone can be used as monotherapy; however, it is often added to metformin, sulfonylureas, or insulin regimens resulting in a reduction of A1C by 0.5% to 1.4%. Initial doses of 15 mg to 30 mg daily are used and can be titrated up to a maximum dose of 45 mg. Pioglitazone is also available in combination with metformin or glimepiride to decrease pill burden in patients who are on stable medication doses. The most common side effects of pioglitazone are weight gain and peripheral edema. It carries a boxed warning contraindicating its use in patients with New York Heart Association (NYHA) Class 3 or 4 Heart Failure (HF) and cautioning against its use in patients with symptomatic HF.

In a recent animal study, pioglitazone induced urothelial bladder tumors in male rats but female rats and mice were unaffected. In another animal study, PPARY and combined PPARY/γ agonists also showed similar results, adding to the possibility of urothelial changes in monkeys. In rats, activation of the PPARY receptor in the bladder can cause urinary solid formations, leading to cytotoxicity, necrosis, regenerative proliferation of the bladder epithelial wall, and subsequently bladder tumors. In humans, toxic precipitates do not lead to regeneration of the epithelium. If urinary solids form, they are very painful and immediately removed through clinical intervention so there is rarely progression to malignant cells.

The PROactive study (PROspective pioglitAzone Clinical Trial In Macrovascular Events), was conducted to determine whether pioglitazone decreased morbidity and mortality in patients with established macrovascular disease. At the conclusion of the trial, the adverse events summary showed a statistically insignificant (p=0.069) increase in patients with bladder cancer in the pioglitazone arm versus the placebo arm (14 vs. 6). These results differed from the Food and Drug Administration’s (FDA) adverse event reporting system (AERS), which showed hazard ratios (HR) indicative of a definite risk for bladder cancer with pioglitazone (HR 4.30 [95% confidence interval (CI) 2.82 to 6.52]). Subsequently, Takeda, the manufacturer of pioglitazone, initiated a 10-year, observational cohort study to address the long-term risk of bladder cancer associated with pioglitazone in patients with T2DM. The following is a summary of the 5-year interim analysis.

Clinical Evidence
This cohort study used 193,099 patients from the Kaiser Permanente Northern California (KPNC) diabetes registry. Patients were eligible to participate in the study if they were ≥40 years of age and diagnosed with T2DM between January 1997 and December 2002. Patients were not eligible if they had any of the following at the time of entry into the cohort: previous bladder cancer, newly diagnosed bladder cancer within 6 months of KPNC membership, no prescription benefits, or a >4 month gap between prescription benefits or membership benefits. Upon entry, patients were categorized as “ever use” (n=30,173) or “never use” (n=162,926). “Ever use” was defined as filling ≥2 prescriptions for a diabetic medication within a ≤6 month time period. “Never use” was defined as having only 1 prescription <6 months prior to trial entry.

The objective of the study is to determine if there is a link between bladder cancer and pioglitazone use. Patients were stratified based on length of therapy (12 months, 12 to 24 months, >24 months) and cumulative dose exposure (1 to 10,500 mg, 10,501 to 28,000 mg, and >28,000 mg). The primary outcome was the incidence of newly diagnosed bladder cancer with the use of pioglitazone. The incidence of bladder cancer was characterized as in situ bladder cancer or papillary urethral neoplasm with low grade malignant potential. The SEER (Surveillance, Epidemiology, and End Results) guidelines were used to categorize the cancer as local, regional, distant, or undetermined. Diagnosis of cancer was collected from January 1997 to April 2008.

Within the study, there were multiple confounding variables with the potential to increase the apparent incidence of bladder cancer. A nested case-control study was conducted to determine if the confounding variables would impact the results of the cohort study. The variables included are race/ethnicity, smoking history, duration of diabetes, and occupational exposures. For every individual with bladder cancer, 1 control was matched for gender, age (within ± 2.5 years), and time of entry into the cohort study (± 6 months).

The results showed that 90 of 30,173 patients who had ever used pioglitazone and 791 of 162,926 who had never used pioglitazone developed bladder cancer. After adjustment for age, sex, and use of other diabetes medications, there was a minimal increase in the incidence of bladder cancer associated with pioglitazone use (HR 1.2 [95% CI 0.9 to 1.5]).
There were no statistically significant differences observed when further categorized by gender (men HR 1.1 [95% CI 0.9 to 1.5]; women 1.4 [95% CI 0.8 to 2.6]). It was noted that risk of bladder cancer with pioglitazone was slightly increased with longer duration of exposure and a higher cumulative dose when compared to those who never used pioglitazone. For more accurate interpretation, the results were adjusted for only age and sex, as well as fully adjusted for the additional confounders. When adjusted for both age and sex, the risk of bladder cancer increased by 30% if pioglitazone was used for 12 to 24 months (HR 1.3 [95% CI 0.9 to 2.0]). Additionally, the risk increased by 50% if exposure was >24 months (HR 1.5 [95% CI 1.1 to 2.0]). The results of the fully adjusted models showed similar results; >24 months exposure (HR 1.4 [95% CI 1.03 to 2.01]). When adjusted for gender, men had an increased risk of bladder cancer if pioglitazone exposure extended >24 months (HR 1.6 [95% CI 1.2 to 2.3]) and the cumulative dose was >28,000 mg (HR 1.8 [95% CI 1.2 to 2.6]). A post hoc analysis was conducted to evaluate exposure to pioglitazone >48 months. When adjusted only for age and sex, there was an increased incidence in the risk of bladder cancer (HR 1.7 [95% CI 1.1 to 2.7]). However, the results were not statistically significant when the data was fully adjusted (HR 1.6 [95% CI 0.96 to 2.7]). Of the patients diagnosed with bladder cancer, there were more in situ cancers in the pioglitazone-exposed group compared to the group never exposed to pioglitazone. Although the use of pioglitazone was associated with an increased risk of bladder cancer, the group exposed to pioglitazone had a lower incidence of regional or advanced disease at diagnosis (3%) compared to the non-exposed group (9%); this result did not reach statistical significance (p=0.1). The authors of this interim analysis concluded that there was not a statistically significant increase in the risk of bladder cancer in patients receiving pioglitazone for <2 years. There is a possible association between longer duration of treatment and higher cumulative doses with pioglitazone that will hopefully be addressed at the conclusion of the 10-year analysis.

**New FDA Dosing Recommendations for Erythropoiesis-Stimulating Agents**

Recently, the FDA has changed the dosing recommendations for erythropoiesis-stimulating agents (ESAs) for the treatment of anemia in chronic kidney disease (CKD) patients. These changes have been made due to new evidence showing increased risks for cardiovascular (CV) events such as stroke, thrombosis, and death associated with ESA use.

**Introduction**

In the United States, it is estimated that over 20 million adults have CKD. These patients may become anemic due to decreased erythropoietin production from the kidneys. Chronic kidney disease patients with anemia may be at an increased risk for cardiovascular disease (CVD), increased hospitalizations, and decreased quality of life. Anemia is associated with difficulty breathing, angina, intolerance to cold, tachycardia, and fatigue. These signs and symptoms may be due to decreased oxygen delivery to tissues. The goal of treatment is to decrease the signs and symptoms of anemia, decrease the need for blood transfusion, improve quality of life, and increase oxygen delivery to tissues. Partial correction of hemoglobin (Hgb) using ESAs has been recommended to decrease these effects and improve quality of life. Erythropoiesis-stimulating agents work by stimulating the production and differentiation of mature erythrocytes through interactions with erythroid progenitor cells. They are indicated for the treatment of various types of anemia, including anemia associated with CKD and chemotherapy. Currently, there...
are 2 types of ESAs available in the United States, epoetin alfa (EpoGen, Procrit) and darbepoetin alfa (Aranesp). Iron deficiency caused by blood loss or ESA therapy is another complication of CKD-associated anemia. Erythropoiesis-stimulating agents may cause iron deficiency due to the increased iron demand associated with increased red blood cell production. Iron supplementation in patients with iron deficiency is considered first line therapy to avoid iron-restricted erythropoiesis. In some patients, iron replacement may be enough to achieve desired Hgb levels without the use of ESAs.

Clinical Evidence
There are 4 major studies on the use of ESAs in adults with CKD, and the results from these trials have shown that higher Hgb targets did not result in better clinical outcomes. In fact, patients in the higher target group had an increased risk of cardiovascular events and death in the CHOIR study and increased risk of stroke in the TREAT study. The benefits associated with higher Hgb targets compared to lower targets were modest in the 4 trials. The Normal Hematocrit trial showed decreased blood transfusions and improvement in physical function scores in the higher Hgb group, while other trials showed improvements in subscales of quality of life measures such as fatigue, vitality, and general health. The results from these trials are summarized in Table 1. It is important to note that the Normal Hematocrit and the CHOIR trials were both stopped early due to safety concerns in the higher Hgb groups.

Of the 4 studies reviewed, TREAT was the most recent and largest ESA study done on CKD patients with anemia. It evaluated whether using darbepoetin to raise Hgb levels in CKD patients not undergoing dialysis with type 2 diabetes (T2DM) and anemia would lower the incidence of CV events, end stage renal disease (ESRD), and death. The results from TREAT showed that there was no significant difference in the time to a CV event, death, or ESRD between darbepoetin and placebo. However, the incidence of stroke, a secondary endpoint, was higher with darbepoetin compared to placebo. The authors concluded that in CKD patients with T2DM and anemia, not requiring dialysis, the potential benefit of ESAs do not outweigh the increased stroke risk. This study was unique because it is the only trial to include a placebo arm, and it led to the recent changes in ESA dosing recommendations by the FDA. It was always assumed that treating anemia with ESAs would improve patient outcomes, which is the reason why previous trials did not include a placebo arm.

Some of the strengths of this trial include the use of a placebo group, the large number of patients included, and management of comorbid conditions according to accepted guidelines. Although this was a well-designed trial, there were also some limitations. One limitation is the clinical applicability of the results to all CKD patients with anemia since it only included CKD patients with T2DM not on dialysis. Also, according to the study protocol, patients in the placebo group received rescue darbepoetin when the Hgb level dropped below 9 g/dL. At the end of the study, 46% of the placebo subjects received 1 or more doses of darbepoetin. The use of darbepoetin as rescue therapy in the placebo group could have confounded the results. Additionally, the average darbepoetin dose was 176 ug/month, which is higher than the doses observed in clinical practice. It was also noted that more patients randomized to placebo received intravenous iron than patients in the darbepoetin group (20.4% vs. 14.8%, respectively, p<0.001). This could have contributed to the results of the study because iron repletion is an important factor in anemia treatment.

<table>
<thead>
<tr>
<th>trial/Design/Population</th>
<th>Hemoglobin Targets in g/dL</th>
<th>Endpoints/Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Hematocrit* (1993-1996)</td>
<td>14 (n=618) vs. 10 (n=615)</td>
<td>Primary Endpoint</td>
</tr>
<tr>
<td>Design</td>
<td>Prospective, open-label, MC, R</td>
<td>Time to death or 1st non-fatal MI:</td>
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<tr>
<td></td>
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<td>-32.7% high Hgb vs. 26.7% low Hgb (RR 1.3, 95% CI 0.9 to 1.9)</td>
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<tr>
<td>Population</td>
<td>CKD patients on HD with CHF or CAD, Hct 30 +/- 3% on epoetin alfa</td>
<td>Key Secondary Endpoints</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. RBC transfusion:</td>
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<tr>
<td></td>
<td></td>
<td>-21% in high Hgb vs. 31% in low Hgb (p&lt;0.001)</td>
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<tr>
<td></td>
<td></td>
<td>2. Changes in QoL measures:</td>
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<tr>
<td></td>
<td></td>
<td>-Physical function score at 12 months increased by 0.6 point for each % point increase in Hct (p=0.03),</td>
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<td></td>
<td>3. Incidence of thrombosis of vascular access sites</td>
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<tr>
<td></td>
<td></td>
<td>-39% in high Hgb vs. 29% in low Hgb (p&lt;0.001)</td>
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<tr>
<td>Comments</td>
<td>Higher Hgb goal is not recommended in patients with cardiac disease on HD.</td>
<td></td>
</tr>
</tbody>
</table>
**CHOIR** (2003-2006)

**Design**
Prospective, open-label, MC, R

**Population**
CKD patients not on dialysis with no previous history of epoetin alfa, Hgb < 11

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOIR*</td>
<td>Time to composite of MI, stroke, CHF hospitalization, or death -17.5% in high Hgb vs. 13.5% in low Hgb (HR 1.34, 95% CI 1.03 to 1.74, p=0.03)</td>
</tr>
</tbody>
</table>

**Key Secondary Endpoints**
1. Time to renal replacement -No significant difference (p=0.15)
2. QoL measures (LASA, KDQ, SF-36) -Subscale of emotional role in SF-36 was higher in low Hgb vs. high Hgb (p=0.01).
3. Adverse events -Significantly more patients in the high Hgb vs. low Hgb group reported adverse events (54.8% vs. 48.5%, p<0.02); CHF occurred significantly more in the high Hgb group.

**Comments**
There was an increased risk of CV events and death, no improvement in QoL, and more frequent adverse events with a higher Hgb target.

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**CREATE** (2000-2004)

**Design**
Prospective, open-label, MC, R

**Population**
CKD stage 3 or 4 patients not on dialysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREATE</td>
<td>Time to composite of 8 CV events: -19.3% in high Hgb vs. 15.6% in low Hgb (HR 0.78, 95% CI 0.53 to 1.14, p=0.20)</td>
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</tbody>
</table>

**Key Secondary Endpoints**
1. Death from any cause, changes in LV mass index, or time to renal replacement -No significant difference
2. QoL measures (SF-36) -At 2 years, better general health and vitality scores observed with high Hgb vs. low Hgb (p=0.008 and p=0.01, respectively).
3. Adverse events -Higher incidence of hypertension (p=0.005) and headache (p=0.03) in high Hgb group

**Comments**
There was no decrease in risk of death or CV events with epoetin use, however, there was an increased risk of stroke with epoetin use.

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**TREAT** (2004-2009)

**Design**
Prospective, DB, PC, MC, RCT

**Population**
CKD patients not on dialysis with T2DM, Hgb ≤ 11

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary Endpoint</th>
</tr>
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<tbody>
<tr>
<td>TREAT</td>
<td>1. Time to composite of death or CV event -31.4% in darbepoetin vs. 29.7% in placebo (HR 1.05, 95% CI 0.94 to 1.17, p=0.41) 2. Time to composite of death or ESRD -3.4% in darbepoetin vs. 30.5% placebo (HR 1.06, 95% CI 0.95 to 1.19, p=0.29)</td>
</tr>
</tbody>
</table>

**Secondary Endpoints**
1. Fatal or non-fatal stroke -6.0% in darbepoetin vs. 2.6% in placebo (HR 1.92, 95% CI 1.38 to 2.68, p<0.001)
2. Improvement in QoL measures (FACT-Fatigue, SF-36) -Improvement in fatigue scores in 54.7% darbepoetin vs. 49.5% placebo (p=0.002)

**Comments**
There was no decrease in risk of death or CV events with darbepoetin use, however, there was an increased risk of stroke with darbepoetin.

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Table abbreviations: CAD=coronary artery disease, CHF=chronic heart failure, CHOIR=correction of hemoglobin and outcomes in renal insufficiency, CI=confidence interval, CKD=chronic kidney disease, CREATE=cardiovascular risk reduction by early anemia treatment with epoetin beta, CV=cardiovascular, DB=double-blind, ESRD=end-stage renal disease, FACT=functional assessment of cancer therapy, Hct=hematocrit, HD=hemodialysis, Hgb=hemoglobin, HR=hazard ratio, KDQI=KDOQI anemia guideline, KDIGO=Kidney Disease: Improving Global Outcomes, LASA=linear analogue self-assessment, LV=left ventricular, MC=multicenter, MI=myocardial infarction, PC=placebo-controlled, QoL=quality of life, R=randomized, RBC=red blood cell, RCT=randomized clinical trial, RR=relative risk, SF-36=36-item short form health survey, T2DM=type 2 diabetes mellitus, TREAT=trial to reduce cardiovascular events with aranesp therapy.

**Recommendations for ESAs**
Previously, the labeling for ESAs recommended a Hgb target of 10 to 12 g/dL in CKD patients with anemia. Currently, the Kidney Disease Outcomes Quality Initiative (KDOQI) anemia guideline recommends that clinicians aim for a Hgb target of 11 to 12 g/dL (Hgb target should not exceed 13 g/dL) in CKD patients with or without dialysis. However, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for anemia are expected to be published in early 2012. The purpose of the KDIGO guideline will be to update the KDOQI anemia guideline.

**Study**
Study was terminated prematurely due to safety concerns.
and include the data from recent trials on ESAs.

The new recommendation for ESAs is to individualize anemia treatment by using the lowest dose of ESA to reduce the need for blood transfusions. The labeling no longer includes a Hgb target range. Instead of a target range, it states that in CKD patients not undergoing dialysis, ESAs should be used only if the Hgb level is less than 10 g/dL. The dose of ESAs should be decreased or stopped if the Hgb level is greater than 10 g/dL. For CKD patients that are on dialysis, the label suggests that ESAs be started when Hgb drops below 10 g/dL and the dose should be reduced or stopped if the Hgb level approaches or exceeds 11 g/dL. The FDA also mandated that the prescribing information be updated with the new boxed warning for CKD patients. These warnings state that there is no clinical evidence on a target Hgb, ESA dose, or regimen that does not increase the risk of death or CV events. In fact, in clinical trials of CKD patients, Hgb targets of greater than 11 g/dL increased the risk of death, stroke, or CV events. The new boxed warning still contains information for cancer patients. In trials of breast cancer (CA), non-small cell lung CA, head and neck CA, lymphoid CA, and cervical CA patients, the use of ESAs decreased overall survival and increased the risk of the malignancy progressing or recurring. As with CKD patients, the lowest ESA dose required to reduce the need for blood transfusions should be used in cancer patients only when the anemia is due to myelosuppressive chemotherapy. ESAs should be stopped after the chemotherapy has been completed, and they should not be used at all if the goal of therapy is cure. The FDA continues to require a Risk Evaluation and Mitigation Strategy (REMS) from the manufacturers. Healthcare providers and hospitals must be certified in the ESA APPRISE Oncology Program to prescribe or dispense ESAs. Other elements of the APPRISE Program include patient medication guides, communication between Amgen and healthcare providers, and documentation that the discussion of risk vs. benefits of ESAs between the healthcare provider and patient has occurred.

Conclusion
The true net clinical benefit of ESAs in CKD patients with anemia is unknown at this time. Therefore, it will be important for clinicians weigh the risks of stroke, CV events, and death associated with ESAs against the benefits of fewer blood transfusions and modest improvements in quality of life. Clinicians should optimize other therapies such as iron repletion in symptomatic CKD patients with anemia before considering ESAs. Future studies on ESAs and iron supplementation are needed to assess the risk-benefit profile of iron alone or in combination with ESAs in anemic CKD patients. The results from TREAT showed that the risks and benefits of ESAs can only be reliably evaluated when trials include a placebo arm. More trials like TREAT will be needed to evaluate the safety and efficacy of ESAs in patients with anemia; therefore, the FDA is requiring that Amgen conduct more trials.

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