Welcome to **The Safety of COX-2 Pharmacotherapy for Patients in Pain**. This activity is accredited by the National Community Pharmacists Association (NCPA). NCPA is approved by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program will provide 1.0 contact hour of continuing pharmacy education. This program is supported by an educational grant from Pfizer Inc.
The faculty for this program is Dr. Kenneth C. Jackson.

Dr. Kenneth C. Jackson, II is a Clinical Associate Professor of Pharmacotherapy and a clinical pharmacy specialist in pain management and palliative care at the University of Utah Health Sciences Center. Dr. Jackson is currently involved in researching the role of pharmacotherapy in palliative care and chronic non-malignant pain populations. He has published numerous articles, abstracts, and book chapters relating to pain management and palliative care drug therapy. He currently serves as associate editor for the *Journal of Pain and Palliative Care Pharmacotherapy* and on the editorial board for the journal *Pain Practice*. 
Learning Objectives

- Describe differences in the mechanism of action between traditional NSAIDs and COX-2 selective NSAIDs.
- Discuss differences associated in the study design and outcomes associated with the VIGOR and CLASS trials.
- Define the potential risks for using a COX-2 selective NSAID for a patient with chronic pain.
- Discuss the FDA Subcommittees recommendations for chronic use of NSAIDs for pain.

Upon completion of this program, participants should be able to improve their patient care by being able to:

- Describe differences in the mechanism of action between traditional NSAIDs and COX-2 selective NSAIDs.
- Discuss differences associated in the study design and outcomes associated with the VIGOR and CLASS trials.
- Define the potential risks for using a COX-2 selective NSAID for a patient with chronic pain.
- Discuss the FDA Subcommittees recommendations for chronic use of NSAIDs for pain.

And now Dr. Jackson will begin this presentation on The Safety of COX-2 Pharmacotherapy for Patients in Pain.
As we begin today’s discussion considering factors associated with COX-2 pharmacotherapy and the safety issues that pertain to that, once you consider our number of economic consequences related to a variety of painful conditions, possibly the best example of that would be osteoarthritis. As you will see in the slide presented in front of you, a vast number of resources are dedicated to treating pain and symptoms associated with osteoarthritis. $76 billion are spent in direct and indirect costs associated with osteoarthritis accounting for as much as 68 million lost workdays due to pain and loss of function.
Pharmacotherapy options for treating osteoarthritis pain span quite a gamut, which you will see with this particular slide, analgesics, anti-inflammatory and intra-articular therapies are often directed to treating patients that have pain or other symptoms associated with osteoarthritis. Significant in this is the concept of anti-inflammatory pharmacotherapy, which traditionally nonsteroidal anti-inflammatory drugs or NSAIDs have been used.
The American College of Rheumatology and its subcommittee on osteoarthritis has indicated that NSAIDs are an appropriate option for patients who fail to obtain pain relief from first-line therapy such as acetaminophen. Efficacy has been established with the treatment of osteoarthritic pain with NSAIDs in a number of trials. Unfortunately, the significant drawbacks to NSAIDs have included serious gastrointestinal adverse effects and potentials for nephrotoxicity or renal toxicity.
When considering the treatment with nonsteroidal anti-inflammatory drugs, one refers back to the traditional group of medications that have been on the market for some years. And considering their conventional mechanism of action we have considered the cascade of events associated with the prostaglandin synthesis cascade originating with arachidonic acid. As you see on this slide, Cyclooxygenase-1 and Cyclooxygenase-2, often called COX-1 and COX-2, are inhibited equally in some respects by conventional nonsteroidal anti-inflammatory drugs. This inhibition leads to a decrease in prostaglandins and thromboxane. From the standpoint of COX-1 inhibition this can lead to gastrointestinal toxicity as well as impaired platelet function.
When considering Cyclooxygenase-1 and Cyclooxygenase-2 one should keep in mind the roles of these enzymes. With COX-1, it’s primarily a housekeeping enzyme that provides protection in a variety of tissues, including the gastrointestinal tract, platelets, kidney. It can be inducible and certainly can be responsible for an increased expression in infectious causes associated with macrophage proliferation. COX-2 on the other hand is primarily inducible in most tissues, including the immune system, colorectal tumors, bone, and kidney. However it’s a housekeeping enzyme in the brain and the kidney as well. In that respect it may pose difficulties from a renal toxicity profile as well.
<table>
<thead>
<tr>
<th>NSAIDs: What Are the Risks?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GI Tract</strong></td>
</tr>
<tr>
<td>- Ulcers, perforations, bleeding, obstruction strictures, enteropathy</td>
</tr>
<tr>
<td><strong>Kidney</strong></td>
</tr>
<tr>
<td>- Sodium and fluid retention</td>
</tr>
<tr>
<td>- Hyperkalemia</td>
</tr>
<tr>
<td>- Acute renal failure</td>
</tr>
<tr>
<td>- Hypertension</td>
</tr>
<tr>
<td><strong>Platelet</strong></td>
</tr>
<tr>
<td>- Inhibition of aggregation leading to increased potential for bleeding</td>
</tr>
</tbody>
</table>

So when we consider NSAID therapy, we must think about the risks and certainly traditional NSAIDs and to a lesser extent the Cyclooxygenase-2 Selective Inhibitors have issues associated with the gastrointestinal tract and indeed that maybe in some peoples’ minds the significant gain associated with these newer agents, the prevention of ulceration and perforations, bleeding issues. There had been hope that these new agents may provide benefit for the kidney. However as we will discuss today that may not be completely true and certainly the issues with the traditional agents include sodium and fluid retention, hyperkalemia, the risk for acute renal failure and high blood pressure. In addition the NSAIDs, as a group have varying effects on platelet function, at times which has been beneficial but often times are very detrimental to individual patients.
When considering the risk factors for gastrointestinal adverse effects associated with NSAIDs the following has been suggested by The American College of Rheumatology Subcommittee on Osteoarthritis. Patients over the age of 65 with a variety of comorbid medical conditions on oral steroids, a history of having gastrointestinal bleed or a peptic ulcer disease or on any coagulant therapy.
Traditional NSAIDs and COX-2 NSAIDs

*Risk Factors for Renal Failure*

- Intrinsic renal disease
- Age $\geq 65$
- Hypertension
- Congestive heart failure
- Concomitant use of diuretics and ACE inhibitors


When considering the risk factors for renal failure, a significant morbidity associated issue with NSAID therapy as well as ulcers we are finding with COX-2 therapy, the following risk factors have been subscribed to by the following subcommittee. These would include intrinsic renal disease, age greater than or equal to 65, a history of high blood pressure, current or recent issues associated with congestive heart failure, and the concomitant use of diuretics or ACE inhibitors.
Reducing the Risk of GI Complications with NSAIDS

- Identify risk factors
- Use of gastroprotective drugs
- Safer NSAIDS
  - COX-2s?

It has been suggested that there are things that we can do to reduce the risk of GI complications in patients who require NSAID therapy. Certainly identifying the risk factors that we have discussed as well as the consideration of using gastroprotective drugs such as H2 antagonists and proton pump inhibitors. And more recently the idea of using “safer NSAIDs” and this may involve the use of COX-2 selective medications.
At this point in the presentation it maybe useful to review the NSAID class which you will note the first medication listed, or class of medications listed are the salicylates, including aspirin. A variety of other agents are listed on the subsequent bullets until the last bullet which you see as Coxibs or Celecoxib. As you will note the medications that appear before that are essentially what we would consider the traditional NSAID classification system which includes to some extent medications that some would consider having more COX-2 selectivity such as meloxicam and nabumetone.
As you can note on this slide COX-2 selectivity ranges considerably amongst the classification of agents that are known to be COX-2 selective versus those that are non-selective. On this slide, you will notice that aspirin has the least selectivity and tends to have the most ability to interfere with both the COX-1 and COX-2 enzymes. Other medications such as Celecoxib, the only currently marketed COX-2 selective agent, are much more selective for COX-2 than agents that have recently been removed from the market or even more selective for the COX-2 enzyme.

<table>
<thead>
<tr>
<th>NSAID</th>
<th>IC 50 RATIO COX-2 / COX-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>3.12</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.79</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.69</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>0.64</td>
</tr>
<tr>
<td>Etodolac</td>
<td>0.11</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>0.11</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>0.09*</td>
</tr>
<tr>
<td>Valdecoxb</td>
<td>0.04</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* Higher at higher (therapeutic) doses

It's useful to consider the mechanism of action of the COX-2 inhibitor class. As we have discussed earlier COX-2 inhibition is proposed to provide significant benefits. Amongst these are the consideration that COX-2 is primarily an inducible enzyme in considerations associated with inflammation and pain, where the COX-1 system is primarily constitutive and provides protection of things such as renal blood flow and the gastric mucosa.
In general the COX-2 Selective Inhibitor Class is considered to have comparable efficacy to the traditional NSAID class, in as much this means that this group of medications provides the same kinds of analgesia and anti-inflammatory capabilities that generally well tolerated and in some peoples’ minds much better so than the traditional NSAID class. When there were several on the market there was a variety of differences associated with indications and drug interactions, and the main considerations for their use in previous years has been the concept of decreased gastrointestinal risk. There had been hope as I alluded to earlier that maybe there were some renal benefits associated with the COX-2 Selective Class that have yet to be proven and indeed as we will discuss today, probably aren’t founded. The biggest question is what is the overall safety profile of this medication class associated with treating pain and other symptoms as compared to traditional NSAIDs?
Let’s consider WR, a 59 year old male who presents to you after diagnosis of hypertension and osteoarthritis. His high blood pressure recordings were 145/90, and he describes his pain as being bilateral in the knees. This gentleman is 5’10”, 275 pounds. His previous medication use prior to his recent diagnosis included over-the-counter agents such as Naproxen three times a day and Omeprazole twice daily. In addition he has used as needed acetaminophen. He reports his pain as a 5 out of 10, on the 0 to 10 pain scale, at rest. It increases to 8 out of 10 following any kind of activity or work. He presents complaining of worsening in his gastrointestinal distress noting significant dyspepsia.
WR’s primary care physician has drawn a series of laboratory evaluations including issues associated with potentials for gastrointestinal bleeding and renal or hepatic dysfunction. He is also being evaluated for other potential disease considerations associated with his current profile, things such as diabetes and dyslipidemia. He is given a series of new prescriptions and told to discontinue his previous medications. These new prescriptions include a diuretic Hydrochlorothiazide, the ACE inhibitor, lisinopril, a different proton pump inhibitor, lansoprazole, and a COX-2 selective NSAID, Celecoxib. The patient discusses with you his recent concerns about media reports of COX-2 selective gastrointestinal and cardiovascular mortality and morbidity.
As discussed, his significant concerns are primarily how will these medications affect him with his current diagnosis of high blood pressure, is he at more risk for myocardial infarction? He wishes to discuss what are his other options, are there other analgesics that maybe more effective and although he does not mention it, he is implying that he probably would desire to have information related to some nonpharmacologic approaches to treating some his disease states, primarily his osteoarthritis pain. It is probably most beneficial at this point to entertain the discussion of the risk and benefits associated with not only treating his pain but what would happen if he was to choose not to use pharmacotherapy or other options to manage his osteoarthritis.
So on looking at the COX-2 Selective Class there are a number of safety concerns that still remain. Certainly gastrointestinal complications still occur within this class as they do with all the anti-inflammatory group. And in recent years cardiovascular complications associated with COX-2 selective medications have become more and more apparent. Issues associated with myocardial infarction, use of these medications and the immediate post-operative phase following CABG surgery, what affect do these medications have on high blood pressure and cardiorenal effects such as edema. More recently concerns about potentially life threatening reactions with certain COX-2s have come across, things like Stevens-Johnson Syndrome associated with the use of valdecoxib.
When considering the selectivity of the COX-2 versus the COX-1 enzyme system, one could look at the spectrum of inhibition in relation to the toxicity profile. As drugs become more COX-1 selective, such as aspirin, gastrointestinal complications become more difficult. It’s proposed that as COX-2 Selectivity becomes more apparent, that there may be a higher risk for cardiovascular adverse effects and we will discuss some of those issues today.
An additional significant consequence that we should consider, especially in the case of a patient such as WR, are the issues of untreated or under-treated pain. It is well known and accepted in pain circles that the following consequences are significant, especially in relation to poorly treated or untreated pain. These include physiological consequences, some of which are very significant in consideration with therapies such as COX-2 therapies. These would include things such as edema, increased blood pressure, sodium retention. Psychological variables are certainly a significant component especially with ongoing pain. These could include anxiety and depression. Immunological function may be compromised and there are studies that suggest that patients in chronic pain, especially in cancer populations, are more immunocompromised. Sociologically we know these patients tend to be ostracized and are unable to function as they once were in our society. And it's been suggested over the most recent years that acute or intermittent pain tends to lead to chronic pain.
So as we consider non-steroid anti-inflammatory therapy in relation to pain in another conditions selection of these agents should be a major consideration. Issues associated with patient’s age, the length of the pain process, nature and origin of their pain, prior attempts of self care, if there is an inflammatory component to their disease process, what side effect profile would the medication proposed have, the patient’s pregnancy or breast feeding status, potential other diseased states and/or drug therapies as well as patient preference and cost considerations.
Along these lines when considering traditional versus COX-2 therapies one needs to consider the risk factors for NSAIDs and this being, what's the level of renal parameter in the particular individual. This could include things like volume, status, cardiac failure and edema, uncontrolled hypertension, and age greater than 65 years. When considering COX-2 additional considerations should be apparent and these would include risk factors for gastrointestinal adverse event. This would include things like the history of peptic ulcer disease, or patients who are in current anticoagulant or steroid therapy.
As many of you are aware society has become much more concerned about this classification of medications in recent years. In 2004 Rofecoxib was removed voluntarily from the US market. The Food and Drug Administration’s Arthritis and Drug Safety and Risk Management Advisory Committee held meetings in February of 2005 to discuss this issue. In concert with that the Center for Drug Evaluations and Research of the FDA had an internal review of the available data recording cardiovascular safety issues with this class of medication as well as the traditional NSAIDs and provided a memo to the public on April 6th of 2005.
Adverse Event Reporting System

- Reports of thrombotic or embolic cases
  - Rofecoxib 159
  - Celecoxib 144
  - 42 celecoxib & 60 rofecoxib cases were excluded

- Attributable thrombotic or embolic events
  - Rofecoxib 99
  - Celecoxib 102

In addition a variety of adverse events have been reported to the FDA through the Volunteer Reporting System. And note on this slide reports of thrombotic or embolic cases have been almost equal with both Rofecoxib and Celecoxib prior to Rofecoxib being removed from the US market. The attributable thrombotic or embolic events as well were very similar with approximately a 100 in both groups.
The Center for Drug Evaluations and Research in their executive summary in April 2005 came to the following conclusions. Celecoxib, Rofecoxib and Valdecoxib were associated with an increased risk of serious adverse cardiovascular events compared to placebo. They felt that the available data did not permit a rank ordering of these drugs with regard to cardiovascular risk. Data available from the large long-term controlled clinical trials provided the CDER with data to suggest that there was not a greater risk of serious adverse cardiovascular events with the COX-2 selective agents as compared to the non-selective non-steroid anti-inflammatory drugs.
I believe it’s useful to go back and look at some of this data that was used to make these decisions. As we’ll discuss there were two major landmarks studies that many of you are already familiar with. The first we’ll discuss is the VIGOR trial. This was a double-blind, randomized, stratified parallel group trial of over 8000 patients with rheumatoid arthritis. I think it’s important at this point to note that this trial only included patients with rheumatoid arthritis and this may be a consideration for evaluating the study in the future. The main important points were analysis of occurrence of gastrointestinal toxicity with Rofecoxib doses of 50 milligrams once daily compared to Naproxen doses of 500 milligrams twice daily. Aspirin use was not permitted in this trial. Following an interim analysis of 45 patients or 46 events in the Rofecoxib group and 20 patients or 20 events in the Naproxen group they were subsequently adjudicated to have had serious thrombotic cardiovascular events. These included things like myocardial infarction and unstable angina.
In the analysis of the VIGOR trial the relative risk of developing a cardiovascular event in the treatment group with Rofecoxib was 2.38 with a confidence interval of 1.39 to 4.0. This was found to be statistically significant. A subgroup analysis was subsequently performed of our patients that would be classified as “aspirin indicated” or “aspirin not indicated.” As I alluded to earlier aspirin use was not appropriate in this trial or this was designed such to be that way. They did find that there were 321 patients that should have been on aspirin. Of this 170 were in the Rofecoxib group, 151 in the Naproxen group. And as you will see with the data the relative risk increased substantially in the Aspirin indicated group up to 4.89.
There are a number of other adverse effect issues associated with Rofecoxib in the VIGOR trial and these were noted by the CDER as well as at the February 2005 FDA hearings. These included cardiorenal effects such as elevated blood pressure, changes in renal disease and heart failure. They felt that there were issues associated with hepatic dysfunction that had not previously been discussed as well as neurological considerations or consequences such as stroke and sudden death.
In addition to the VIGOR trial there are other data that suggest that Rofecoxib provides additional risk from a cardiovascular standpoint. The APPROVe trial the Adenomatous Polyp Prevention trial on Rofecoxib therapy had doses of 25 milligrams per day versus placebo indicated that the relative risk was approximately 2 in the Rofecoxib treatment group with respect to serious adverse cardiovascular events. However, it should be noted that the capital marked plots did not begin to separate until approximately 18 months in the treatment. In contrast two long-term placebo controlled trials in early Alzheimer’s disease did not indicate any significant difference in cardiovascular events with the use of Rofecoxib at a dose of 25 milligrams once daily.
Looking at Rofecoxib safety in an overview sense use of the NNT or the Numbers Needed to Treat or the NNH the Numbers Needed to Harm may be beneficial. At the FDA hearings the following data were presented and this included that a Numbers Needed to Treat of a 125 were required. So 125 patients were required for treatment of a single clinically significant upper gastrointestinal event would be prevented. In converse it would take 333 patients treated to have a myocardial infarction event. But a far fewer number of a 103 to have other types of thrombotic events.
The FDA Advisory Committee’s concerns with respect to Rofecoxib were as follows. They felt that compared to other COX-2 selective agents that Rofecoxib was associated with a high risk of cardiovascular or cardiorenal adverse effects such as increased blood pressure, fluid retention and congestive heart failure. Obviously at this point Rofecoxib has been removed from the US market and they felt that a need existed for a resubmission process and that this process must be transparent. Of note the committee did narrowly approve the risk benefit issues associated with Rofecoxib in support of future marketing in United States.
The second landmark setting the CLASS trial or the Celecoxib Long-term Arthritis Safety Study was a similarly designed study to that that we discussed earlier with VIGOR. However in this study as you'll note over 8000 patients were enrolled with either osteoarthritis or rheumatoid arthritis. As I discussed earlier with Rofecoxib's trial rheumatoid arthritis was the only disease type.
It’s been suggested that there are higher possibilities or probabilities associated with cardiovascular morbidity and mortality in patients with rheumatoid arthritis. This study used Celecoxib at doses of 400 milligrams twice daily and compared to Ibuprofen and Diclofenac. Again the outcome of significance was incidents of upper gastrointestinal toxic effects and complications associated. There are significant issues that have been proposed to be evaluated with the CLASS trial. These include the fact that the CLASS trial only included the first six months worth of trial data. The fact that important benefit and harm data may not have been reported, fortunately we do have significant data that was reported at the one year time frame through the FDA. And significant issues are raised with the use of Celecoxib or COX-2s in general for chronic use in states such as osteoarthritis pain.
At the FDA hearings in February of 2005 the 12 month data was presented and this showed that at 12 months the adverse ulcer event profile in all patients was not statistically significant between Celecoxib and the traditional NSAIDs Diclofenac and Ibuprofen.
When considering the cardiovascular risk associated with the outcomes in the CLASS trial one should consider that this is the only available data from a long-term comparison of Celecoxib to the traditional or non-selective NSAIDs. You will note that the dosage for Celecoxib was 400 milligrams twice daily and was compared to Diclofenac and Ibuprofen as I mentioned in both osteo and rheumatoid arthritis patients. This is significant because it has been suggested that as opposed to the VIGOR trial Ibuprofen and Diclofenac may not have the same degree of cardio protective abilities as Naproxen. In summation this study showed that there were no significant differences in serious adverse cardiovascular events between Celecoxib and the two non-selective NSAID comparators.
Celecoxib in Recurrent Colon Polyps

- NCI Adenoma Prevention with Celecoxib (APC) trial
  - 2-3 fold increased risk of adverse CV events
  - Dose response
    - Mean duration of treatment of 33 months
    - Hazard ratio of 2.5 for celecoxib 200 mg BID & 3.4 for 400 mg BID
    - Composite endpoint of death from CV causes, myocardial infarction (MI), or stroke

- Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial
  - Similar to APC study
  - Unpublished and presented to the FDA advisory committee
  - Hazard ratio was 1.1 for celecoxib 400 mg QD for the composite endpoint of death from CV causes, MI, or stroke

Celecoxib has additional studies that have sent mixed messages making it difficult for clinicians to make decisions with respect to the cardiovascular morbidity profile. The National Cancer Institute’s Adenoma Prevention with Celecoxib or APC trial showed a two to three fold increased risk of adverse cardiovascular events. They noted a hazard ratio of 2.5 for the dose of Celecoxib 200 milligrams twice a day and an increased hazard ratio of 3.4 as the dose escalated to 400 milligrams twice a day. In a similar study the Prevention of Spontaneous Adenomatous Polyps or PreSAP trial you will find unpublished data was submitted to the FDA. Interestingly the hazard ratios here for Celecoxib were significantly lower than in the APC trial mentioned above.
An additional area of interest in research is the area of Alzheimer’s disease with Celecoxib and COX-2 therapy in general. The National Institute of Aging has Alzheimer’s Disease Anti-Inflammatory Prevention Trial or the ADAPT trial and in this trial they found that there was no increased risk for Celecoxib doses at 200 milligrams twice a day for the composite endpoints of death, myocardial infarction or stroke. In addition the NIA provided additional information on another small one year trial comparing the same dose of Celecoxib. And it did not demonstrate any significant increase in the risk of serious adverse cardiovascular events but they didn’t note that a trend did exist with Celecoxib therapy towards these adverse cardiovascular consequences.
White and colleagues presented information in a pooled analysis of 41 Celecoxib clinical trials in this particular meta-analysis. Nearly 5000 patients on Celecoxib were reviewed and found they have a relative risk of 1.13 per 100 patient years of a cardiovascular event compared to 1.5 in the placebo group. In summary they felt that the evidence provided in this significant number of clinical trials suggested that there is no evidence for increased risk of myocardial infarction or stroke.
Celecoxib Adverse Events: Meta-analysis

- OA and RA trials
- Thirty-one trials included 39,605 randomized patients. Most trials lasted 12 weeks or more. Doses of celecoxib were 50 to 800 mg/day
- Forty-four cases of myocardial infarction occurred in the two largest trials (096 and 102), with 21,162 patients. Their planned duration was 12 and 52 weeks, and they had a combined actual duration of about 4.5 months
- Here 29/12,787 (0.23%) of patients taking celecoxib (200 to 800 mg) suffered a myocardial infarction, compared with 15/8,375 (0.18%) on NSAID
- The relative risk was 1.7 (0.88 to 3.2)
- NNH of 2,100 with a 95% confidence interval of 588 patients harmed to 1,337 patients where harm was prevented


Moore and colleagues presented another meta-analysis with a significant amount of unpublished data that was available from the manufacturer. In this particular analysis 31 trials included almost 40,000 patients that have been randomized to treatment. Most trials had lasted at least 12 weeks and doses varied for Celecoxib between 50 milligrams per day to as much as 800 milligrams per day. They noted that 44 cases of MI occurred in two largest trials. These were trials 096 and 102 and these comprised nearly 22,000 patients. Their plan duration had been between 12 weeks and 52 weeks, they had an actual combined duration of approximately 4½ months. In their analysis they noted that a very small percentage 29 of almost 13,000 patients using Celecoxib therapies ranging from 2 to 800 milligrams per day suffered an MI. This is compared very favorably with traditional NSAIDs with the rate of 0.18% or 15 events in a little over 8000 patients. The overall relative risk was 1.7 with an interval of 0.88 to 3.2. When Moore and colleagues calculated the Numbers Needed to Harm, they noted that the number would be 2100 with 95% confidence interval of 588 patients harmed to every 1337 patients where harm would be prevented. And in their analysis, they felt that this class of medications especially with the use of Celecoxib was beneficial.
In addition to Rofecoxib and Celecoxib, a third COX-2 had been previously on the market by the name of Valdecoxib. The CDER and the FDA felt that this had a similar overall cardiovascular toxicity profile to the current COX-2 medications as well as traditional NSAIDs. But it demonstrated an increased risk of serious adverse effects especially in short term CABG trials and they felt that it was reasonable from a public health perspective that these findings could be extrapolated to chronic use with this agent. The bigger issue was that the greater risk existed for serious and potentially life-threatening skin reactions and indeed they had 7 spontaneous reports of death from these life-threatening skin reactions. In summary, the FDA and the CDER felt that there was no documented benefit with this medication over other available agents.
The February 2005 FDA subcommittee hearings had the following recommendations: these included that Valdecoxib be voluntarily removed from the US market, that a class boxed warning and contraindication exist for all NSAIDs including the COX-2 selective and that this should highlight the potential risk or increased risk of cardiovascular events and reemphasize the serious and often life-threatening events associated with Gastrointestinal Bleeding. Based on the data available from the Valdecoxib CABG trials, they felt that a new contraindication should be class specific and be indicated for postoperative settings associated with CABG surgery with all NSAIDs.
Subcommittee Recommendations

- Chronic use of NSAIDs
  - Lowest effective dose
  - Shortest duration possible
  - Reduction of other risk factors for cardiovascular disease

- Intended to reinforce the previous bolded warning for GI risks, especially for chronic use in pain and inflammation

In addition to this they recommended that the chronic use of NSAIDs be at the lowest effective dose for the shortest duration possible and that reduction of other risk factors for cardiovascular disease be implemented. In total they intended to reinforce the previous bolded warnings for gastrointestinal risks, especially for chronic use in pain and inflammatory conditions.
COX-2s & CV Events: Possible Explanation

- May produce a pro-thrombotic vascular environment
- COX-1 and COX-2 catalyse the conversion of AA to PG
  - COX-1 is the main source of production of thromboxane A-2 (TXA-2) which mediates platelet aggregation and vasoconstriction
  - COX-2 is the main source of prostacyclin (PGI-2) which has vasodilating, anti-aggregatory and antiproliferative effects
- Selective inhibition of COX-2 causes suppression of PGI-2 without affecting TXA-2, and theoretically could predispose to hypertension and thromboembolic events

Why is it then that the COX-2 selective agents may have more risk for cardiovascular events, especially in light of the use of traditional NSAIDs over a number of years? It was been proposed that these agents may produce a prothrombotic vascular environment. If you consider back to the COX-1 and COX-2 cascade, we know that these agents are used to convert Arachidonic Acid to a variety of thromboxanes and prostaglandins. COX-1 specifically is a main source of production of thromboxane A2, which is known to mediate platelet aggregation invasive constriction. COX-2 is known to be the main source of prostacyclin, prostaglandin I2, which has vasodilatation and antiaggregatory therapy possibilities as well as being an anti-proliferative. The selective innovation of COX-2 therapy is not to cause suppression of the prostacyclin without affecting thromboxane A2 and theoretically this could predispose patients to both elevated blood pressures and thromboembolic events.
COX-2 Cardioprotective: In Vitro Data

- Up-regulation of COX-2 may play an essential role in the cardioprotection
- Administration of selective COX-2 inhibitors 24 hours after ischemic preconditioning abolished the cardioprotective effect of late ischemic preconditioning against myocardial stunning and MI


In vitro data suggest that COX-2 itself maybe cardioprotective and inhibition of this enzyme in and of itself may prove problematic in patients. In an animal model, Shimmura and colleagues has suggested that the up regulation of Cyclooxygenase-2 may play an essential role in this cardioprotective environment. And they noted in their experiments that administration of selective COX-2 inhibitors following the 24 hours after ischemic preconditioning would abolish this cardioprotective effect and essentially lead to the risk of Myocardial Infarction.
Let’s revisit patient WR and have the following questions for him. What types of therapy should we consider for WR? Should we provide him with Acetaminophen Therapy which he has previously used? Should we use traditional NSAID therapy, should we try a cyclooxygenase-2 selective NSAID? Would he be a candidate for Opioids or are all of these therapies potentially beneficial for WR?
Patient WR

What types of therapy should we consider for WR?

- A. Acetaminophen
- B. Traditional NSAIDs
- C. COX-2 selective NSAIDs
- D. Opioids
- *E. All of the above

It’s probably best to consider all these therapies as potential therapies for this patient. At this point we have not fully evaluated what response he may have gotten from consistent use of Acetaminophen. Previously he’s only used this on an as-needed basis. We should reevaluate the role of traditional NSAIDs, he’s used them only in over-the-counter doses and we did not know fully what his gastrointestinal history is. In addition, we are awaiting lab results to know what level of gastrointestinal toxicity he may currently have or be exposed to. Certainly in that same vein COX-2 Selective therapy may be appropriate. If indeed he is not a candidate for the previous therapies, he may be appropriate for Opioid therapy.
As we noted previously WR has reported pain ranging between 5 and 8 on the 10 point scale, as such what are the risks that are present for WR if he does not treat his pain adequately. Potential options could include worsening hypertension, fluid depletion, hepatic dysfunction, sedation or all the above.
What risks are present for WR if he does not treat his pain adequately?

* A. Worsening hypertension
B. Fluid depletion
C. Hepatic dysfunction
D. Sedation
E. All of the above

The appropriate answer being worsening hypertension indeed many patients actually have fluid accumulation or edema. We did not know that he’s at any significant risk for hepatic dysfunction with his current therapies and certainly pain in and of itself would not lead to hepatic dysfunction as well pain typically causes insomnia versus sedation.
What risks are present for WR if an antiinflammatory is considered?

A. Gastrointestinal ulceration
B. Worsening hypertension
C. Myocardial infarction
D. Renal dysfunction
E. All of the above

What risks are specifically present for WR if an anti-inflammatory is considered? Potential options include gastrointestinal ulceration, worsening high blood pressure, Myocardial Infarction, renal dysfunction, all the above.
WR is at risk for all the above. He is certainly at risk for gastrointestinal ulceration. We noted that he’s previously been on over-the-counter Proton Pump Inhibitor Therapy. He currently has high blood pressure and with his current use or previous use of the NSAID therapy, would be at risk for worsening high blood pressure. As we have noted both traditional and COX-2 therapies are associated with high risk of Myocardial Infarction. And certainly the renal dysfunction as a consequence of both his blood pressure difficulties as well as medication use could be present.
When counseling WR on the role of COX-2 selective NSAIDs, it is appropriate to discuss the potential for cardiorenal risks and potential alternatives to pharmacotherapy for pain related to OA?

A. True
B. False

When counseling WR on the role of COX-2 Selective NSAIDs, it is appropriate to discuss the potential for cardiorenal risks and potential alternatives to pharmacotherapy for pain related osteoarthritis.
When counseling WR on the role of COX-2 selective NSAIDs, it is appropriate to discuss the potential for cardiorenal risks and potential alternatives to pharmacotherapy for pain related to OA?

*A. True
B. False

The appropriate answer is true. As we have noted in patients such as WR, there are potential cardiorenal effects associated with COX-2 Selective NSAIDs as well as traditional NSAIDs. And there certainly are potential alternatives to drug therapy in patients with osteoarthritic pain.
At this point, it may be useful to consider trials associated with the use of COX-2 selective agents specifically for considerations in hypertension and osteoarthritis. Sowers and Colleagues in 2005 published a double-blind randomized control trial comparing lower doses than previously described. These doses included Celecoxib 200 milligrams daily, Rofecoxib 25 milligrams daily and Naproxen 500 milligrams twice daily. This was for 12 weeks with the primary outcome of 24 hour blood pressure control in patients with type 2 diabetes, hypertension, and osteoarthritis. As noted the outcomes were primarily associated with hypertension and in blood pressure, it was noted that Rofecoxib and Celecoxib both raised blood pressure but Rofecoxib more significantly. This held true when Rofecoxib was compared to Naproxen as well.
Walton and Colleagues noted similar findings in a study comparing patients with osteoarthritis and hypertension. This was a patient population over the age of 65 years who were using comparisons of Celecoxib and Rofecoxib. Again the primary outcome was associated with blood pressure. You would notice with this study that the greatest increase is associated with systolic blood pressure and Rofecoxib therapy specifically in groups with ACE inhibitor therapy and beta-blockers. Of note significant issues arose with Rofecoxib and edema, this was found to be statistically significant when compared to Celecoxib.
COX-2: Use in Geriatric OA & HTN

Outcomes
- SBP: significant increase (change > 20 mm Hg plus absolute value ≥ 140 mm Hg) at any time point rofecoxib 14.9% vs celecoxib 6.9% ($p < 0.01$)
  - Greatest increase in SBP with rofecoxib – ACE inhibitors and beta blockers
  - No significant increase seen with calcium channel blockers or diuretic monotherapy for either COX-2
- Edema (new or worse): rofecoxib 7.7% vs celecoxib 4.7% ($p < 0.05$)

Walton and colleagues had a similar study in patients with hypertension. This again was in geriatric patients using the dosing platform that we had seen previously with Celecoxib 200 milligrams a day compared to Rofecoxib 25 milligrams per day. Again edema was found to be statistically and significantly more problematic in the Rofecoxib group. However as you will note Celecoxib did have a 5% incidence of edema.
Walton and colleagues conducted another trial in geriatric hypertensives who had osteoarthritic pain. This was a large randomized control trial, similarly designed. It was a 6 week RCT with a parallel group double-blinded patients as noted, whoever the age of 65 with osteoarthritis. They were taking antihypertensive medications and they were receiving Celecoxib with doses of 200 milligrams per day, of rofecoxib 25 milligrams per day.
In this study Walton and colleagues found that edema was more common in patients with Rofecoxib therapy. Almost 10% of patients having edema with this agent versus nearly 5% on Celecoxib, this was found to be a statistically significant difference. As well they noted significant increases in systolic blood pressure and this was more common in patients on Rofecoxib therapy. Changes in diastolic blood pressure were not as significant between the two agents. And indeed there was no statistical significance between, difference between Rofecoxib and Celecoxib diastolic blood pressure changes.
In a presentation presented to the CDER and the FDA by Graham and colleagues at the February 2005 FDA Advisory Panel Meeting, he suggested that the following considerations be considered for dose selection with COX-2 therapy with an eye towards a risk of acute Myocardial Infarction. You will note that he states that doses equal to or less than 200 milligrams per day of Celecoxib have no apparent effect on cardiovascular morbidity. You will also note that Valdecoxib has doses less than 20 milligrams a day no apparent effect. Rofecoxib on the other hand even at low doses appears to have a probable increased risk and this is probably the most significant issue associated with the FDA’s decision to ask the company to resubmit data to provide additional quantifications of its risk even at lower doses in chronic use.
CV Risk Factor Considerations

- **Strong Risk to Avoid COX-2**
  - All patients with symptomatic CVD
  - Dx left ventricular hypertrophy
  - Genetic lipid disorders
  - Dx of diabetes with renal disease

- **Moderate Risk to Avoid COX-2**
  - Strong family history of CVD (1st degree relative: i.e. a male with CVD before 55 years, or female before 65 years)
  - Those who are obese (BMI > 30 kg/m²)
  - Dyslipidemia
  - Hypertension

It maybe useful to consider the following information as an overall cardiovascular risk factor evaluation. It’s probably a strong risk, it would be best to avoid COX-2 selective agents in patients who are symptomatic with cardiovascular disease, have a diagnosis of left ventricular hypertrophy, have genetic lipid disorders or diagnosis of diabetes especially with renal disease. Moderate risk factors to avoid COX-2 therapy would include a strong family history especially first to be relatives with cardiovascular disease before the age of 55 or in females before the age of 65, patients who are obese, patients who are dyslipidemic or who have high blood pressure. As we revisit our case and discuss the issues associated with WR, he certainly fits these profiles and would be best to avoid COX-2 therapy unless we are able to modify his risk factors.
Thank you for participating in this activity. It’s been my pleasure to present this information and I hope you found it useful.