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THE NON-STEROIDAL ANTI-INFLAMMATORY DRUGS-MYOCARDIAL INFARCTION ASSOCIATION: AN INVESTIGATION OF KENTUCKY MEDICAID PRESCRIPTION CLAIMS

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THE NON-STEROIDAL ANTI-INFLAMMATORY DRUGS-MYOCARDIAL INFARCTION ASSOCIATION:
AN INVESTIGATION OF KENTUCKY MEDICAID PRESCRIPTION CLAIMS

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DISSERTATION
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A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
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at the University of Kentucky

By
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Lexington, Kentucky
2015

ABSTRACT OF DISSERTATION

THE NON-STEROIDAL ANTI-INFLAMMATORY DRUGS-MYOCARDIAL INFARCTION ASSOCIATION:
AN INVESTIGATION OF KENTUCKY MEDICAID PRESCRIPTION CLAIMS

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications globally. There are generally two types: selective (COX-2) and traditional NSAIDs (COX-1). They are primarily used for the treatment of pain. They gained attention after a study about their basic mechanisms highlighted their toxicity.

Several studies have reported an association between NSAIDs and risk of myocardial infarction (MI). However, the direction of the relationship is not conclusive. Further studies are needed to ascertain the direction of this relationship and evaluate the present situation with available drugs. Due to the seriousness of cardiovascular diseases as one of the leading cause of death, continuous monitoring of the NSAIDs-MI association is needed.

The purpose of this dissertation was to investigate the association between NSAIDs and MI in a younger (30-64 years) Kentucky Medicaid population with a 12 year window of data. The three specific aims were: (1) to understand the characteristics of the Kentucky Medicaid population with respect to NSAID use: (2) to evaluate the NSAID-MI relationship with a 12 year follow-up in a young heavily-burdened population for cardiovascular diseases: and (3) to investigate the MI risk of meloxicam, celecoxib and naproxen compared to no exposure.

A retrospective study was conducted employing data from January 1st 2000 and December 31st 2012. The data comprised demographic, prescription and medical files. Within this cohort, a nested case control study was conducted. Cases of MI were matched to four controls on race and gender.

The results suggested that exposure to COX 2 presented an increased adjusted risk for MI (1.138(0.983, 1.318)). However, this risk was significantly increased for COX-2 only users compared to COX-1 only users (1.221 (1.03, 1.485)) and 30-40 year olds (1.600 (1.082, 2.367)). Meloxicam, celecoxib and naproxen compared to no exposure showed meloxicam presented a non-significant different risk for MI (1.26 (0.98, 1.63)) and celecoxib presented a significantly increased risk for MI (1.52 (1.26, 1.82)).

This study considered pattern of use in determining continuous usage by looking at both continuous and sporadic users of NSAIDs and also considered patient switching patterns between classes of NSAIDs.

KEYWORDS: NSAIDS, Myocardial Infarction, Medicaid claims

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July 21st 2015
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To my late father, for his example

To my mother, for her sacrifice

To my wife, for her patience

ACKNOWLEDGMENTS

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Chapter One

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used

medications globally (Bombardier et al., 2000). There are generally two types categorized based

on their ability to inhibit the cyclooxygenase (COX) enzymes. They are selective (COX-2) and

traditional NSAIDs (COX-1)(Al-Saeed, 2011). They are primarily used for the treatment of pain.

They gained attention after a study about their basic mechanisms shed light on their toxicity

(Catella-Lawson et al., 1999). This relationship was strengthened in findings that emerged in

clinical trials and observational studies. The Vioxx Gastrointestinal Outcomes Research (VIGOR),

a clinical trial designed to examine gastrointestinal (GI) toxicity of refocoxib and naproxen in

patients with rheumatoid arthritis, found a higher incidence of myocardial infarction (MI) in

patients in the refocoxib group compared with those in the naproxen group (Bombardier et al.,

2000). Several pharmaco-epidemiologic studies confirmed and quantified these effects using

large linked databases in different countries (Garcia Rodriguez, Varas-Lorenzo, Maguire, &

Gonzalez-Perez, 2004; Daniel H Solomon et al., 2004).

NSAIDs inhibit the COX enzyme which is the first step in converting arachidonic acid to

prostaglandins, thromboxane and prostacyclin (Catella-Lawson et al., 1999). The COX enzyme

exists in two forms- COX-1 and COX-2. COX-1 produces prostaglandins responsible for

homeostatic functions such as platelet aggregation and gastric mucosa. COX-2 produces

prostaglandins that mediate pain and inflammation. The inhibition of COX-1 causes bleeding and

the inhibition of COX-2 suppresses prostacyclin which reacts with thromboxane for homeostatic

balance (Graham, 2006).

Several studies found an association between exposure to NSAIDs in general and risk of

MI. However, the direction of the relationship was not conclusive (Bombardier et al., 2000;

Silverstein et al., 2000; Daniel H Solomon et al., 2004; S. D. Solomon et al., 2005). The Bombardier et al study found a lower incidence of MI among patients in the naproxen group when compared to those in the rofecoxib group (relative risk (RR) = 0.2 [0.1, 0.7]). The Silverstein et al study found no difference in the incidence of cardiovascular events in general when celecoxib was compared to other NSAIDs. However, the event rates for this study were very low. The Solomon et al study found an increase in death from cardiovascular diseases with use of celecoxib when compared to placebo (hazard ratio (HR) =3.4[1.4, 7.8]).

In October 2004, rofecoxib was withdrawn from the market after a randomized placebo-controlled trial found it increased the rate of cardiovascular events in higher doses (Antman, DeMets, & Loscalzo, 2005; Bresalier et al., 2005). Valdecoxib was removed in 2005 due to concerns about increased risk of cardiovascular disease and stroke (Antman et al., 2005). Since these removals, other generic NSAIDs have been developed and marketed with varying degrees of study for adverse health effects (McGettigan & Henry, 2011). Additionally, some of these drugs (like meloxicam) have been studied less due to small numbers of adverse health events and population sizes.

Celecoxib is the only coxib that is still on the United States (US) market. While it is a certified COX-2 its effect on cardiovascular risk varies across the literature. It was one of the most widely prescribed NSAIDs in the US, has been in the market longer and has the largest body of evidence of use. Meloxicam, is less studied compared to other commonly used NSAIDs and has been hypothesized to have COX-2 tendencies even though it is classified as a COX-1 (McGettigan & Henry, 2011). In the Kentucky Medicaid population, it is observed that there is an increased prescription of meloxicam especially after the removal of rofecoxib and valdecoxib from the US market. This phenomenon was seen elsewhere(Barozzi & Tett, 2007). Naproxen is one of the most prescribed NSAIDs worldwide and the safest NSAID based on the literature

(Patrono & Baigent, 2014). It is a certified COX-1 and has consistently shown reduced risk for cardiovascular adverse events when compared to other NSAIDs.

Due to the seriousness of cardiovascular diseases, continuous monitoring of the NSAIDs-MI association is needed. Especially since cardiovascular diseases have been identified as one of the leading causes of death worldwide (Alwan, 2011). Since the removal of rofecoxib and valdecoxib from the US market, few studies have assessed this association for the remaining NSAIDs on the market. Furthermore, observational studies are needed to buttress the body of knowledge and give an update on the NSAID-MI association. They have the added value of providing post-market surveillance in the study of this association. This study will examine this association using 12 years of current available data with a potential longer follow-up. The Kentucky Medicaid data used for this study provides comprehensive prescription information for the subjects. A less controlled real world population would be optimal for this analysis as it represents subjects taking the medication post-marketing with all the nuances involved. This study is conducted using a real-world post-market population.

The NSAID-MI relationship has been studied before using claims databases with a focus on older cohorts. However, NSAIDs are increasingly been used among younger cohorts. This study focuses on a younger cohort (aged 30-64 years) in a population that demonstrates an increased burden for cardiovascular diseases (Rugg, Bailey, & Browning, 2008). Figure 4.1 shows the prevalence of MI in Kentucky has been consistently higher than the rest of the US for the time for which data is available. Additionally, the prevalence of chronic conditions, which are risk factors for cardiovascular diseases, continue to increase even in younger populations (CDC, 2005-2010). Finally, in most studies the data window has been less than or equal to three years. Tables 2.1 and 2.2 lists selected studies and their follow-ups. This study has a 12-year data window period allowing for the possibility of longer follow-ups (maximum 12 years) for the

patients and the observation of delayed risk. The data for this study consists of administrative

and prescription claims files for Kentucky (KY) Medicaid recipients from January 1st 2000 to

December 31st 2012. This study only considers patients in the time that they were continuously

enrolled in the Kentucky Medicaid program.

Finally, low socio-economic status has been established as a risk factor for

cardiovascular diseases (Rugg et al., 2008). This data comprises low-income patients from a

government-assisted insurance program.

This study aims to investigate the association between NSAIDs and MI using a younger

cohort with recent information from a large claims database: Kentucky Medicaid records. The

three specific aims of this study are:

1. To understand the characteristics of the Kentucky Medicaid population in terms of

    NSAID use.

2. To evaluate the NSAID-MI association with a 12-year follow-up in a young

    population that demonstrates an increased burden for cardiovascular diseases.

3. To evaluate the MI risk of meloxicam, celecoxib and naproxen compared to no

    exposure.

These three aims will make three papers that are the main body of this dissertation. The

Kentucky Medicaid data is comprised of demographic, prescription and medical files for its

recipients.

Chapter two is a literature review of the concepts used in this study. It examines

research on NSAIDs and MI. It looks at the history of the medication, the different studies used

to assess the NSAIDs-MI association and the limitations of these studies. It has a section on

administrative databases. This section outlines their advantages and disadvantages and focuses

on the Kentucky Medicaid population.

Chapter three examines the characteristics of the Kentucky Medicaid population in terms of NSAIDs use. It consists of two sections. The first section examines the Medicaid population to understand the demographic characteristics of the population. The second section examines NSAIDs use in the population. It evaluates how people use the medication and the drugs commonly used. This is an important evaluation because different providers used by the Medicaid program have varied preferred lists of medications. The demographics and NSAID use of the population were compared to national samples where applicable.

Chapter four examines the NSAID-MI relationship with a 12-year follow-up in a younger population (30-64 years) heavily burdened with cardiovascular diseases using a nested case-control design, where exposure was defined based on the NSAIDs prescribed to the patient, taking into consideration duration on the medication and whether the prescriptions were continuous or sporadic; the outcome is a hospital diagnosis of MI. The classification of users into sporadic vs continuous users is important because sporadic use of NSAIDs has been identified as a possible source of misclassification (Levesque, Brophy, & Zhang, 2005). This study makes use of both continuous and sporadic users of NSAIDs by taking into consideration patient adherence behaviors. The data for this study shows that about 50% of NSAID users in Kentucky Medicaid are continuous users while the rest are sporadic users. The analysis in this chapter accounted for several factors known to affect the NSAID-MI relationship. Demographic, comorbid conditions and concomitant medication were the main factors considered. These were compiled from an exhaustive search of the NSAIDs-MI literature. Cases were matched to four controls using incidence density sampling. Conditional logistic regression was used to estimate odds ratios and their associated confidence intervals (CI).

Chapter five evaluates the MI risk of meloxicam, celecoxib and naproxen compared to no exposure also using a nested case-control analysis. Cases were also matched to four controls

using incidence density sampling. Conditional logistic regression was used for the analysis of these comparisons. Risk factors were considered in this analysis and included as covariates in the model. Associated confidence intervals were reported for all estimates.

Chapter six discusses the findings of previous chapters, gives recommendations and implications for medical and public health practices in general and discusses the limitations of the study. This chapter also looked at areas for further research and development in the ongoing monitoring of the NSAIDs-MI association.

Chapter Two

Literature Review

NSAIDs and MI

NSAIDs were discovered in the 19th century by German scientists who recovered

salicylate from willow bark (Fuster & Sweeny, 2011). Next, indomethacin, was developed in

1960. Since then, there have been a number of drugs developed and marketed in the US. They

are commonly used for the treatment of acute and chronic pain. They are widely prescribed as

analgesics and anti-inflammatory drugs at lower and higher doses, respectively. They account

for a large volume of prescription and over- the- counter (OTC) medications worldwide (Green,

2001). In the US, they account for an estimated 5% of all prescriptions (Trelle et al., 2011). At

the turn of this century an estimated 70 million prescriptions and 30 billion OTC tablets were

sold in the US annually.

Most NSAIDs are consumed orally, yet a few are taken intravenously or in the form of a

gel. While they are differentiated in terms of potency, they are not easily differentiated in terms

of efficacy. For example, the coxibs are generally stronger than COX-1. However, there has not

been a consensus in showing one NSAID or class to be stronger than others due to the variation

in patient's reaction to the drug.   They are advantageous because they are not addictive and do

not result in sedation or respiratory depression (Green, 2001).

NSAIDs are not without side effects. The most common adverse reactions relate to

irritation, ulcers and bleeding of the upper GI tracts. It is estimated that over 103, 000 patients

are hospitalized and 16,500 die annually in the US as a result of NSAID associated GI events

(Singh et al., 2006). Another side effect is renal disease. Studies have shown that renal function,

especially in the elderly, can be impaired by some NSAIDs (Moodley, 2008).They have the ability

to also cause fluid retention. They have also been associated with adverse cardiovascular

events.

NSAIDs block the COX enzymes. COX-1 produces prostaglandins responsible for

homeostatic functions like maintenance of the GI mucosa and platelet aggregation. COX-2

produces prostaglandins that mediate pain and inflammation. The prostaglandin production is

attenuated by NSAIDs in varying degrees and is the major cause of beneficial and adverse

reactions to the drug. Inhibition of COX-2 results in a decrease in prostacyclin which is a

vasodilator and moderator of platelet activation (Daniel H Solomon et al., 2004). This decrease

in prostacyclin causes an increased production of thromboxane which is responsible for the

cardiovascular adverse events (Cannon et al., 2006).

Thromboxane is a COX-1 mediated product of arachidonic acid (Bresalier et al., 2005). It

causes irreversible platelet aggregation, vasoconstriction and smooth-muscle proliferation.

Prostacyclin is another by product of the acid which reacts with thromboxane for homeostatic

balance. The inhibition of thromboxane, by prostacyclin, constrains platelet aggregation which

has beneficial effects like the risk reduction of MI or stroke. Hence, the GI beneficial effects of

NSAIDs come from inhibition of the COX-2 enzyme while the adverse GI effects come from

inhibition of the COX-1 enzyme (Al-Saeed, 2011).

However, there are a number of other normal biologic and bodily maintenance

functions associated with the COX enzymes and prostaglandins (Green, 2001). For example,

prostaglandins protect the gastric mucosa from acid damage by maintaining adequate blood

flow. The kidneys also depend on prostaglandins for blood flow.

In 1999, COX-2 inhibitors were approved by the Food and Drug Administration (FDA)

and released in the US as a less toxic alternative to COX-1s. Their attraction was the reduction in

pain and inflammation without the GI toxicity of their counterparts. Celecoxib and rofecoxib

were the first to gain approval (Graham, 2006). They were heavily promoted and became the most widely prescribed NSAIDs. The COX-2s began to draw attention after a study about their basic mechanisms shed light on their toxicity (Catella-Lawson et al., 1999). Although they were as effective as COX-1s in relieving pain there were cardiovascular safety concerns. Concerns were discovered in 1999 during the preapproval application for rofecoxib, but these were dismissed because the FDA focused more on the reduced GI toxicity of the drug (Avorn, 2007).

Different kinds of studies have been employed in the study of the NSAIDs-MI association. The main study types are case-control and retrospective cohort studies. There has also been a prospective case-control study, several nested case-control studies and meta-analyses. There were several clinical trials done that helped fuel the need for more randomized and observational studies in the area.

Clinical Trials

Clinical trials were instrumental in uncovering the NSAIDs-MI association. The VIGOR Trial compared rofecoxib with naproxen in patients with rheumatoid arthritis and found rofecoxib was associated with a significant risk of thrombotic cardiovascular events (0.4% versus 0.1%) (Bombardier et al., 2000). However, it was not confirmed whether this was due to a protective effect of naproxen, an increased risk from rofecoxib or a combination of both. Additionally, the relative risks reported for the trial varied depending on the source of the information. The Bombardier et al study reported a fourfold increased risk while figures from the FDA files reported a five-fold increased risk (Juni et al., 2004).

The Celecoxib Long-term Arthritis Safety Study (CLASS) study compared celecoxib with other NSAIDs in patients with osteo and rheumatoid arthritis for GI toxicity (Silverstein et al., 2000). This was a pooled analysis of several trials including the SUccesive Celecoxib Efficacy and Safety Study-1 (SUCCESS-1) (Singh et al., 2006). There was no difference in the incidence of

cardiovascular events, including MIs, between celecoxib and NSAIDs when all patients were compared- 0.3% vs 0.3%. The same pattern was seen when the comparison was made in patients who were not taking aspirin. The study was re-analyzed with similar results (White et al., 2002).

The APC (Adenoma Prevention with Celecoxib) Trial which focused on the prevention of colorectal adenomas concluded patients exposed to celecoxib were at a significant risk for cardiovascular events (S. D. Solomon et al., 2005). This risk had a dose response relationship and led to the premature end of the trial after 3 years of follow-up. This study found an increase in death from cardiovascular diseases with use of celecoxib when compared to placebo (HR =3.4[1.4, 7.8]).

The APPROVe Trial (Atheromatous Polyp Prevention on Vioxx Trial) compared rofecoxib with placebo in patients with a history of colorectal adenomas and found a significant risk for cardiovascular events associated with rofecoxib (Bresalier et al., 2005). The trial occurred at 108 centers in 29 countries. This was the first relatively long-term large, multicenter, double-blind randomized trial comparing a selective COX-2 inhibitor with a placebo. Patients in the rofecoxib group had an increased incidence of cardiac events of which the majority were MIs (HR=2.8 [1.44-5.45]). The study was prematurely terminated as a result of adverse clinical events. In September 2004, Merck voluntarily withdrew rofecoxib from the market based on preliminary results of this trial.

The Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme, a pooled analysis of data from three trials, compared etoricoxib with diclofenac in patients with osteoarthritis and rheumatoid arthritis and found similar rates of thrombotic cardiovascular events for the two drugs (Cannon et al., 2006). The event rates for thrombotic cardiovascular

events for etoricoxib and diclofenac were 1.24 and 1.30 per 100 patient years respectively. The hazard ratio for etoricoxib compared with diclofenac was 0.95 (0.81, 1.11).

One of the limitations of clinical trials in the study of the NSAIDs-MI association is they were focused on older people. The average age of the cohorts in the trials was older than 50 years. Secondly, in clinical trials involving chronic conditions the follow-up time is usually short providing insufficient time to discover meaningful trends. Table 2.1 provides follow-up durations for selected trials. Clinical trials suffer from this limitation because the longer the trial the more expensive it becomes. In the trials mentioned above, those with more patients tended to have shorter follow-ups. Additionally, clinical trials can be expensive to undertake which is also a reason why they tend to be short. Finally, clinical trials are limited because they are carried out in very controlled conditions. With the heavy inclusion and exclusion criteria involved, the trial population may not be generalizable to all patients as they limit eligibility to a small minority of patients who receive treatment. As a result, the post-market population of the drugs might be very different from the trial population. Observational studies are usually able to adequately capture the effects of drugs in the post-market population.

In April 2005, the FDA requested Pfizer to withdraw valdecoxib from the market due primarily to cardiovascular concerns from trials in patients undergoing coronary-artery bypass grafting (Nussmeier et al., 2005). They allowed celecoxib to remain on the market and requested its labeling together with 18 other COX-1s describe the increased risk of cardiovascular events (Antman et al., 2005). In 2007, the FDA refused approval for etoricoxib (Avorn, 2007). Celecoxib continues to be widely used despite studies showing an increased risk of MI associated with use of the drug (Kearney et al 2006).

It was generally believed the COX-2 inhibitors were the ones with an increased risk of cardiovascular events. However, results from observational studies suggested some of the COX-

1s also increased risk when compared with other NSAIDs and no NSAID use (Garcia Rodriguez &

Gonzalez-Perez, 2005; Hernandez-Diaz, Varas-Lorenzo, & Garcia Rodriguez, 2006; McGettigan &

Henry, 2006).

Following the VIGOR trial, there has been accumulating evidence from several

observational studies and meta-analysis that COX-1s are associated with increased

cardiovascular risk. However, none of these results are definite and some contradict each other

leading to conflicting results. Some studies have found an increased risk with NSAIDs use (Chan

et al., 2006; Hippisley-Cox & Coupland, 2005; Johnsen et al., 2005; Mamdani et al., 2004), yet

others have found no effect (Garcia Rodriguez et al., 2004; Ray, Stein, Hall, Daugherty, & Griffin,

2002; Schlienger, Jick, & Meier, 2002). And some have even found a protective effect (Juni et al.,

2004; S. E. Kimmel et al., 2004; D. H. Solomon, Glynn, Levin, & Avorn, 2002; Watson, Rhodes,

Cai, & Guess, 2002). However, most of these studies differed in the length of use and dosage of

NSAIDs. Additionally, the endpoints for the studies differed. Some studies looked at acute MI,

some fatal MIs, some non-fatal and some looked at combinations of cardiovascular events. As a

result of the discrepancies in observational studies and clinical trials, low event rates and the

need for more studies, several researchers have undertaken meta-analysis over the years

(Garcia Rodriguez, Gonzalez-Perez, Bueno, & Hwa, 2011; McGettigan & Henry, 2011).

Observational Studies

The first epidemiologic study evaluating the NSAIDs-MI risk followed a large cohort of

164,769 women aged 50-74 years free of a history of coronary heart disease from the General

Practice Research Database (Garcia Rodriguez, Varas, & Patrono, 2000). This study found chronic

use of NSAIDs was not associated with a protective effect of MI (RR=1.32 [0.97-1.81]).

A retrospective cohort study using data from the Tennessee Medicaid program matched

a cohort of new non-aspirin NSAID users between the ages of 50 and 84 years on age, gender

and start of NSAID use with non-users (Ray, Stein, Hall, et al., 2002). The endpoint was serious coronary heart disease defined as MI or death from coronary heart disease. The study found an absence of a significant protective effect of naproxen (RR=0.95[0.82-1.09]) and other NSAIDs on risk of coronary heart disease in a high risk population. The same researchers published a study on COX-2 NSAIDs and risk of serious coronary heart disease reporting users of high dose rofecoxib were 1.7[0.98-2.95] times more likely to have coronary heart disease compared to non-users (Ray, Stein, Daugherty, et al., 2002). This risk was increased in new users 1.93[1.09-3.42]. However, there was no increased risk of coronary heart disease in users of low dose rofecoxib and other NSAIDs.

A cohort study of elderly patients older than 66 years who were dispensed selective NSAIDs, naproxen and other NSAIDs compared the rates of MI across groups (Mamdani et al., 2003).The cohort was identified from administrative health care data from Ontario, Canada. This study found no significant difference in short-term MI risk for new users of celecoxib (RR=0.9[0.7-1.2]), rofecoxib (RR=1.0[0.8-1.4]), naproxen (RR=1.0[0.6-1.7]) and other NSAIDs (RR=1.2[0.9-1.4]).

A prospective cohort study conducted with 70,971 women aged 44 to 69 years examined the influence of NSAIDs and acetaminophen on the risk of major cardiovascular events (nonfatal MI, fatal coronary heart disease, nonfatal and fatal stroke) (Chan et al., 2006). These women were free of cardiovascular disease or cancer and provided up to 12 years of follow-up. The study concluded use of NSAIDs and acetaminophen at high doses and frequency was associated with a significant increased risk of cardiovascular disease (RR =1.44[1.27-1.65]). Specifically, non-fatal MIs had the highest incidence of the four cardiovascular diseases studied (814 out of 2041) and a consistently elevated risk was found for non-fatal MI for women who frequently used NSAIDs (1.55[RR=1.26-1.90]).

A case-control study investigating the NSAIDs-MI association and the possible interaction with aspirin concluded they are associated with reduced odds in the absence of aspirin (odds ratio (OR) = 0.53 [0.42-0.67]) and there was no additional protection of aspirin (OR=0.83[0.58-1.17]) (S. E. Kimmel et al., 2004). This study accounted for OTC use of both drugs. Cases between the ages of 40 and 75 years with a first non-fatal MI were identified from 36 hospitals in a five-county region surrounding Philadelphia, PA. Approximately four controls were selected for each case. The researchers conducted another study to assess the effect of COX-2 inhibitors on the risk of non-fatal MI (Stephen E Kimmel et al., 2005). They concluded celecoxib and rofecoxib were associated with different odds of MI. The adjusted odds ratio of MI for rofecoxib compared to no NSAID use was 1.16[0.70-1.93] compared to 0.43[0.23-0.79] for celecoxib.

A matched case-control study evaluated the risk of MI among users of celecoxib, rofecoxib and NSAIDs in Medicare beneficiaries with a comprehensive drug benefit (Daniel H Solomon et al., 2004). It consisted of 54,475 patients older than 65 years who received medication from two state-sponsored pharmaceutical benefits program. It found current use of rofecoxib was associated with an elevated risk of MI compared with celecoxib (OR=1.24[1.05-1.46]) and no NSAID use (OR=1.14[1.00-1.31]).

A nested case-control study evaluating the risk of coronary heart disease from selective and non-selective NSAIDs using data from Kaiser Permanente was conducted in patients 18 to 84 years (Graham et al., 2005). 8143 cases of serious coronary heart disease (MI and sudden cardiac arrest) were risk set matched with four controls for age, sex and health plan region. This study found an increased risk of coronary heart disease with rofecoxib (RR=1.59 [1.10-2.32]) when compared with celecoxib. Additionally, the study did not find a protective effect for naproxen (RR=1.14 [1.00-1.30]) when compared with remote NSAID use.

A time-matched, nested case-control study used a computerized health insurance and vital statistics database in, Canada (Lévesque, Brophy, & Zhang, 2005). The cohort consisted of 113,927 elderly persons, aged 66 years and above, without previous MI and newly treated with NSAIDs. They found a significant increased risk of MI in current users of rofecoxib. This risk was dose dependent (RR=1.24[1.05-1.46]). There was no evidence of an increased risk with other NSAIDs.

Meta Analyses

A meta-analysis of 18 randomized control trials (RCTs) and 11 observational studies compared health effects of rofecoxib with other NSAIDs or placebo (Juni et al., 2004). The study concluded rofecoxib should have been withdrawn from the market earlier. They found a substantial increased risk of MI for rofecoxib as early as 2000 which was present for short and long term use (2.30 [1.22-4.33]). They also found a possible protective effect for naproxen was not large enough to explain the findings of the VIGOR trial. The relative risk of naproxen was 0.86 (0.75-0.99).

A systematic review of 23 controlled observational studies found cardiovascular risk was increased with use of rofecoxib, diclofenac and indomethacin (McGettigan & Henry, 2006). The risk for rofecoxib was present at high and low doses. The relative risks were 2.19 (1.64-2.91) and 1.33 (1.00-1.79) respectively. Additionally, they found naproxen did not have a protective effect as posited by previous studies with relative risk 0.97 (0.87-1.07). They updated their review with recently published data and confirmed the findings of the former study (McGettigan & Henry, 2011). The new analysis also included information on some less studied drugs like etodolac, meloxicam, indomethacin and piroxicam. In pairwise comparisons of meloxicam with naproxen the pooled relative risk was 1.11(1.00, 1.23).

A review of 16 observational studies found naproxen had a non-significant reduced risk for MI when compared to non-users of NSAIDs with pooled estimates 0.98 (0.92, 1.05) (Hernandez-Diaz et al., 2006). Diclofenac and ibuprofen had an increased risk with estimates of 1.44 (1.32, 1.56) and 1.07 (1.02-1.12) respectively. They also found an increased risk for rofecoxib especially at higher doses compared to lower doses. However, they did not find a significantly increased risk for celecoxib even at higher doses with relative risk 0.96 (0.90, 1.02).

Kearney et al (2006) conducted a meta-analysis of 138 randomized trials that included a comparison of a COX-2 and a placebo or a COX-1. For inclusion in the analysis, the trial had to be at least four weeks in duration and contain information on serious vascular events defined as MI, stroke or vascular death. They found users of COX-2 inhibitors had a 42% increased incidence of serious vascular events in placebo comparisons with rate ratio 1.42 (1.13, 1.78). This was due mainly to a two-fold increased risk of MI. Incidence of serious vascular events was not significantly different between COX-2 inhibitors and COX-1s. They concluded COX-2 inhibitors together with ibuprofen and diclofenac at high doses were associated with an increased risk of vascular events.

Garcia-Rodriguez et al (2011) concluded both NSAIDs treatment increased risk of non-fatal MI. However, they had insufficient data to assess the risk of fatal and non-fatal MIs for individual NSAIDs and whether there is a difference between other NSAIDs and the coxibs.

Summary

The literature as to whether NSAIDs affect MI risk is still unclear at least for some of the medications (Hernandez-Diaz et al., 2006). Tables 2.1 and 2.2 list clinical trials and observational studies that have evaluated the NSAID-MI relationship with their findings. Few sufficiently powered RCTs had as their primary objective the assessment of the cardiovascular effects of NSAIDs (Juni et al., 2004). The NSAIDs-MI association remains an important question, especially

given their increased use. A slight increase in risk may have considerable public health

implications. Additionally, the removal of certain drugs means the increased use of other drugs

still on the market. Uncertainty remains about the cardiovascular risk of the other NSAIDS

(Roumie et al., 2009). A recent study from Taiwan found increased MI risk associated with

current use of some NSAIDs (Shau et al., 2012).

Several studies used administrative databases to assess the NSAIDs-MI association

(Graham et al., 2005; S. E. Kimmel et al., 2004; McGettigan & Henry, 2011). These studies

employed different methods to account for the limitations of their use. One of the major

limitations is the lack of information on important confounders such as smoking, body mass

index (BMI), family history of MI and use of OTC drugs. Graham et al (2005) conducted a

telephone survey and found the missing factors were not differentially distributed by NSAID use.

In a nation-wide in-home survey of Medicare beneficiaries using different NSAIDs, they did not

differ by BMI, smoking behavior, aspirin use, or educational level (Daniel H Solomon et al.,

2004). Kimmel et al (2004) found no difference in smoking when comparing NSAID users to non-

users. Therefore, in studies of populations which did not measure these potential confounders,

it is likely they were non-differentially distributed across groups. Their impact on the study is

likely to be minimal and biased the study results towards the null or no-effect hypothesis (Ray,

Stein, Hall, et al., 2002; Daniel H Solomon et al., 2004).

Several studies have called for further studies to identify which NSAIDs minimize overall

burden of adverse cardiovascular risk (Kearney et al., 2006; Stephen E Kimmel et al., 2005;

Moodley, 2008). Additionally, due to the conflicting results obtained over the years, further

studies are warranted for a better understanding of the NSAIDs-MI association (Vanasse, de

Brum-Fernandes, & Courteau, 2009).

Table 2.1. Summary of Clinical Trials

Trial	Date	Author	Drugs	Follow up	Sample Size	Results*
VIGOR	2000	Bombardier et al	Rofecoxib, Naproxen	13 months	8076	Yes
CLASS	2000	Silverstein et al	Celecoxib, Ibuprofen, Diclofenac	17 months	8059	No
APC	2005	Solomon et al	Celecoxib, Placebo	3.1 years	2035	Yes
APPROVe	2005	Bresalier et al	Rofecoxib, Placebo	3 years	2586	Yes
TARGET	2004	Farkouh et al	Lumiracoxib, Naproxen, Ibuprofen	1 year	18325	No
MEDAL	2006	Cannon et al	Etoricoxib, Diclofenac	18 months (average)	34701	No

*Yes implies an increased risk and no implies neutral or reduced risk for MI or related events

Table 2.2. Summary of Observational Studies

Author	Drugs	Study type	Exposure Period	Outcomes	Sample Size	Results*
Ray et al 2002	Rofecoxib,Celecoxib, Naproxen Ibuprofen	RCS	1992-1994	MI and CHD	362882	NO
Mamdani et al 2003	Rofecoxib, Celecoxib, Naproxen Non-naproxen non-selective NSAIDs	RCS	1998-2001	MI	166964	NO
Chan et al 2006	Rofecxib, Celecoxib. Naproxen Ibuprofen,	PCS	1990-2002	MI, CHD AND STROKE	70971	YES
Kimmel et al 2004	Ibuprofen, Naproxen	CCS	1998-2001	MI	5208	NO
Solomon et al 2004	Rofecoxib, Celecoxib, Ibuprofen Naproxen, Other NSAIDs	CCS	1998-2000	MI	54475	YES
Graham et al 2005	Rofecoxib, Celecoxib, Naproxen	NCC	1999-2001	MI AND CARDIAC DEATH	39639	YES
Levesque et al 2005	Rofecoxib, Celecoxib, Naproxen, Meloxicam, Other NSAIDs	NCC	1999-2002	MI	113927	YES
Hippisley-Cox et al 2005	Rofecoxib, Celecoxib, Ibuprofen Diclofenac, Meloxicam, Etoricoxib Etodolac, Valdecoxib	NCC	2000-2004	MI	95567	YES
Vanasse et al 2009	Rofecoxib, Celecoxib, Other NSAIDs	NCC	1999-2002	MI	416283	YES

*Yes implies an increased risk and no implies neutral or reduced risk for MI or related events
NCC=nested case-control study, RCS=retrospective cohort study, PCS= prospective cohort study
CCS=case-control study, CHD=coronary heart disease

Limitations

There are several limitations in the study of the NSAID-MI association. These include but are not limited to stringent definition of NSAID use, short duration of follow-up and difficulty in using clinical trials in evaluating this relationship. First, several studies have used conservative rules to define drug use. In clinical trials, medication compliance rules are strictly followed. Patients are routinely monitored to make sure they take the drugs as prescribed (Bombardier et al., 2000; Silverstein et al., 2000). Failure to do so will mean exclusion from the study. Some observational studies have also followed this trend. For example, Mamdani et al (2003) allowed a 20% grace period on the previous days prescription to determine continuous use. In general most prescription lengths are 30 days which would mean that patients who fill in their prescription within 6 days from end of the previous prescription will be considered continuous users. This was considered very conservative given that patients miss several days of their prescriptions and might have extra pills from previous prescriptions which may delay their refilling of prescriptions. Additionally, the half-lives of these drugs is on average about 18hrs (almost a day) and if one has been on prescriptions for a while it will take more than 20% of the previous days prescriptions for the drug to wash out of the body system (Davies & Skjodt, 2000). Furthermore, intermittent use of NSAIDs has been identified as a possible source of misclassification in NSAID studies (Levesque et al., 2005).

Secondly there was short duration of follow-up in both clinical trials and observational studies that have investigated this relationship. A review of the literature showed that the range of follow-up for clinical trials was from 13 months to 3 years (Bombardier et al., 2000; Bresalier et al., 2005; Cannon et al., 2006). A review of observational studies showed the same pattern with the average follow-up being about 3 years (Chan et al., 2006; Graham et al., 2005; Levesque et al., 2005). It is not known how long the increased cardiovascular risk associated with NSAIDs persists and to our knowledge no studies have been done to assess this (Ross,

Madigan, Konstam, Egilman, & Krumholz, 2010). However, longer follow-ups might be able to access prolonged risk should it exist. This study has a longer period of follow-up (12 years) than most other studies with the possibility of determining long term effects that may persist even after discontinuation of the drug. This is very valuable for an observational study considering the time and money involved in carrying out a clinical trial for the same period of time.

Thirdly, several studies have called for randomized trials to ascertain and understand this relationship (Kearney et al., 2006; Stephen E Kimmel et al., 2005; Moodley, 2008; Roumie et al., 2009). However, this is difficult due to ethical considerations in withholding treatment from patients and randomizing patients to treatment groups. Since NSAIDs are mostly used in the treatment of chronic conditions, this becomes a serious problem. In the absence of clinical trials whose primary aim is the investigation of the NSAID-MI relationship more observational studies are needed to ascertain the relationship and provide timely assessments of drug safety. In this regard, observational studies of this type present value in post marketing surveillance of drugs.

Finally, not much is known about the adverse effects of meloxicam (McGettigan & Henry, 2011). Because a considerable number of study subjects were prescribed this drug, this study attempts to shed some light on this drug- that is increasing in use. Figure 3.4 shows the increase in use of meloxicam over the years. Furthermore, this study investigates celecoxib, one of the original COX-2 inhibitors released in early 2000. It was never withdrawn from the market and a follow-up of this drug is warranted.

Additionally, there is not the ability to control for many covariates that are associated with MIs. For an inclusion of many variables into a model the sample size has to also be adequate. This study has a large population and the ability to attempt to control for many covariates analytically.   And it assesses the influence of comorbidities which few studies have included in their analysis.

Secondary data are becoming increasingly popular due to the time and expenses involved in obtaining primary data and the availability of "big data". There are several challenges involved in handling secondary data which pose problems for confounding and its suitable adjustment in observational studies. Understanding and accounting for these challenges is warranted. This study describes the characteristics of large claims data and provides experience and recommendations for their efficient use.

Finally amidst all the confusion none of these studies have studied the class of NSAIDs as a whole even though the FDA deems all of them as such. Some drugs have been less studied than others.

Administrative Databases

Administrative databases are electronic records of transactions that occurred between patients and health care providers (Ferver, Burton, & Jesilow, 2009). They consist of billing codes that health care providers (e.g. hospitals and pharmacies) submit to public (e.g. Medicaid) or private (e.g. Humana) third party payers. Though primarily used for billing purposes, they are increasingly used for research. A PUBMED search for "claims data" showed their citations have increased exponentially over the years.

There are different types of claims data. They are divided into outpatient, inpatient and pharmacy claims and enrollment data. The outpatient claims contain information about the patient, date of the service, provider, and place of service, medical procedure and diagnoses codes. The inpatient claims includes begin and end dates and discharge diagnoses codes associated with the hospitalization. The pharmacy claims contain patient information, prescription dates, national drug code (NDC), day's supply and quantity of drugs dispensed. The enrollment data includes enrollment history, gender, year of birth, race, insurance plan type and geographic region.

There are several advantages of claims databases. First, they provide a comprehensive view of the patients-healthcare system interaction. This allows for an assessment of the different components of care and the associations between them (Motheral & Fairman, 1997). Secondly, they are flexible in terms of study method options. Due to their retrospective nature, the ethical issues of randomizations are avoided. They can also be useful in research that involves use of sensitive information if they are de-identified. They are less expensive (Ferver et al., 2009). Finally, they provide enough statistical power.

One of the limitations is that they are not generalizable to the population. They are limited to patients who are insured. In the case of Medicaid, they are limited to insured low income patients. Claims databases have the possibility of miscoding in the form of under-coding or over-coding. Over-coding occurs when providers include more diagnoses codes to represent a patient's medical condition. Under-coding occurs when providers limit the number of diagnoses codes because there is no incentive to report certain codes as they will not be reimbursed for such procedures (Motheral & Fairman, 1997). This can lead to misclassification of outcome. Thirdly, they lack certain information like OTC medication, smoking, body mass index (Ferver et al., 2009). This becomes a major limitation with regards to the adequate control of confounding. However, researchers have come up with proxy measures and secondary analyses methods to curb this limitation. For example, the lack of information on OTC medication varies from database to database. The extent to which this is lacking is dependent on the patients' copayment. For public insurance companies that cover everything this lack of OTC medication may be minimal. For example, in the Kentucky Medicaid, the copays can be as little as a $1. Finally, the use of claims data files can be complicated due to large, cumbersome and complex files (Scerbo, Dickstein, & Wilson, 2001).

Medicaid

Medicaid is a public, health and long-term care coverage program that is jointly financed by states and the federal government. It is the largest source of funding for medical and health related services for low-income people in the US. Federal law requires certain mandatory eligibility groups. These include qualified parents, children, pregnant women, older adults and the disabled with low income. Each state establishes and manages their own program and determines the services that are offered. There are certain mandatory benefits and states can choose to provide other optional benefits.

Kentucky Medicaid enrolls about 22% of the state population (Kentucky Cabinet for Health and Family Services, 2014). Enrollment and payments have increased steadily in the past years. Of those enrolled 92% are under managed care. Services included under the Kentucky Medicaid agreement include doctor visits, emergency and hospital care, vaccinations, prescription drugs, vision, hearing, long-term care and preventative care for children. Patients can receive these services for a small copayment. For drugs the copayments depend on whether the drug is a generic, preferred brand or non-preferred brand.

Chapter Three

Characteristics of the Kentucky Medicaid Population in terms of NSAID Use

Introduction

NSAIDs are among the most widely used medications and account for a huge volume of

both prescription and OTC medications worldwide (Green, 2001). In the US, they account for an

estimated 5% of all prescriptions (Trelle et al., 2011). They are most commonly used for the

treatment of acute and chronic pain. At the turn of this century an estimated 70 million

prescriptions and 30 billion OTC tablets were sold in the US annually.

There are generally two types of NSAIDs- selective (COX-2) and non-selective (COX-1)

categorized by their ability to inhibit the COX enzyme (Al-Saeed, 2011). The COX enzyme

produces prostaglandins which are attenuated by NSAIDs in varying degrees and is the major

cause of beneficial and adverse reactions to the drug. They are responsible for a number of

normal biologic and bodily maintenance functions (Green, 2001).

COX-1s were the first ones on the market. In 1999, COX-2s were approved by the FDA

and released in the US. Their attraction was they could reduce pain and inflammation without

the GI toxicity of COX-1s. However, they had a minimal effect on platelet aggregation. Celecoxib

and rofecoxib were the first of the COX-2s to gain approval (Graham, 2006). They were heavily

promoted and became the most widely prescribed NSAIDs. A study about their basic

mechanisms shed light on their toxicity and gave much attention to the medications (Catella-

Lawson et al., 1999). Although they were as effective as COX-1s in relieving pain, there were side

effects which were investigated in clinical trials and observational studies that succeeded these

findings (Bombardier et al., 2000).

In October 2004, rofecoxib was withdrawn from the market after a trial found it

increased the rate of cardiovascular events in some doses. In April 2005, the FDA requested

Pfizer to withdraw valdecoxib from the market due primarily to cardiovascular concerns from

trials in patients undergoing coronary-artery bypass grafting (Nussmeier et al., 2005). They

allowed celecoxib to remain on the market and requested its labeling together with 18 other

NSAIDs describe the increased risk of cardiovascular diseases (Antman et al., 2005). In 2007, the

FDA refused approval for etoricoxib (Avorn, 2007). Celecoxib continues to be widely used

despite studies showing an increased risk of MI associated with the drug (Kearney et al 2006).

The controversies surrounding NSAIDs are still unclear (Hernandez-Diaz et al., 2006;

Trelle et al., 2011). However, they are still widely used given the increase in chronic diseases.

The removal of certain drugs meant the increased use of other drugs for which uncertainty

remains (McGettigan & Henry, 2011). For example, in Australia the withdrawal of rofecoxib from

the market led to the increased use of meloxicam. Due to their increasing and widespread use, a

study of the present use of NSAIDs is warranted for an understanding of the pattern of use and

possible repercussions (Barozzi & Tett, 2007).

This study aims to document the characteristics of a younger (30-64 years) Medicaid

population and their use of NSAIDs. The study will look at geographical factors of NSAID use and

trends over the years.

Methods
A retrospective cohort study, was conducted to examine NSAIDs use among Kentucky Medicaid

enrollees between the ages of 30 and 64 years who had taken NSAIDS between January 1st 2000

and December 31st 2012.

Data Source
Data for this study represents administrative and prescription claims files of Kentucky

Medicaid enrollees between the above mentioned dates. The enrollees are of low-income socio-

economic status. Enrollment and patient demographic information are included in an

enrollment file. Prescription files contain dates, drug name, quantity, dose and number of days supply.

The final data comprises persons aged 30 to 64 years. Patients were eligible if they were enrolled in Kentucky Medicaid between January 1st 2000 and December 31st 2012, had date of birth and gender and filled prescriptions during the study. Enrollees were followed until observance of the first of either end of eligibility, end of medication use, 65th birthday, death or the end of the follow-up period (December 31, 2012). For this study continuous use of NSAIDs was considered consecutive prescriptions with a gap of less than 30 days between them. This was done because patients usually miss a couple of days when on medications and the half-lives of the drugs considered was on average about 18 hours (Davies & Skjodt, 2000). Additionally, a distribution of medication gaps showed that this was a reasonable decision. Figure 3.1 shows the study design.
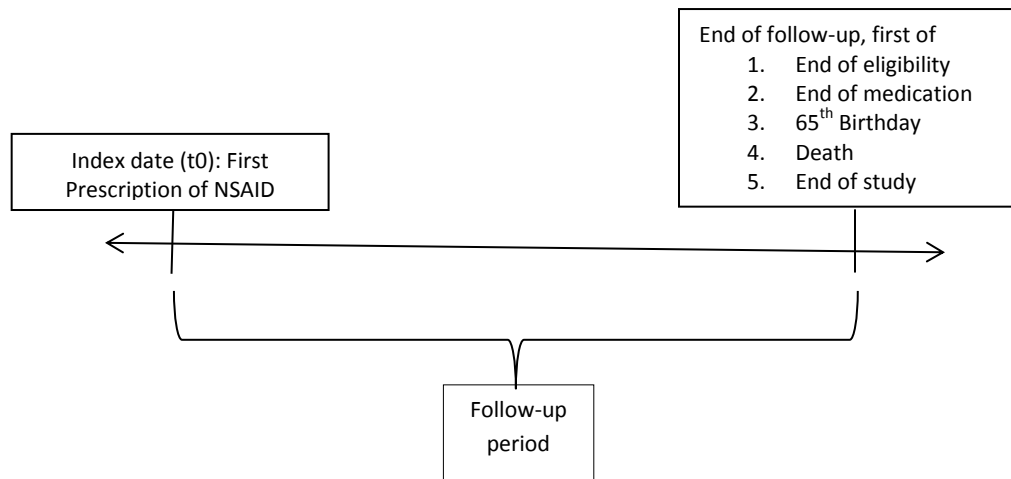
Figure 3.1 Study Design

Medicare Part D is a federal program that subsidizes the cost of prescription drugs for beneficiaries in the US (Medicare, 2014). It was enacted as part of the Medicare Modernization

Act in 2003 and went into effect in 2006. As a result, there are people in the Medicaid program who are dually eligible for both Medicare Part D and Medicaid after the age of 65. Such dually eligible individuals are transferred to Medicare Part D for their prescription drug coverage. As a result, subjects were removed from the study cohort when they turned 65 years due to lack of information on prescriptions.

Churning is a phenomenon that is present in large claims databases especially Medicaid (Saunders & Alexander, 2009). This is the tendency for subjects to move in and out of the system as indicated by different effective dates. Primarily, in the Kentucky Medicaid program, any time a subject's enrollment is touched it ends the segment and starts a new one. Some reasons for this include but are not limited to changes in eligibility and other demographic factors. For example, if a subject is continuously enrolled for a period and they make a name or address change, then that period is divided into two segments. A segment is defined by specific effective and end dates which mark the beginning and end respectively. For this study, consecutive segments with no gaps were considered as one segment. The Medicaid database also included overlapping segments. For example, a patient might have a segment with effective and end dates of 1-1-2002 and 4-17-2003 respectively. Then they might have another segment with effective and end dates of 2-1-2002 and 9-30-2002. Since the second segment is completely contained in the first segment then the first was taken and the second discarded. In the event of partial overlap of segments, the earliest effective date was chosen as the effective date for the combined segment and the latest end date was chosen as the end date of the combined segment.

For this study, patients who were enrolled in the program prior to January 1st 2000 had their beginning dates shifted to that date and patients who were in the program past December 31st 2012 had their follow-up end dates changed to that date.

Due to segment changes, some subjects were missing demographic information or had information change between segments. If the missing information in one segment was found in another segment then the information was updated. For example, a subject with five segments might have race available for two of the five segments. Their race was updated in the three segments with what was found in the two segments. Additionally, there were patients who had different demographic information in their segments. To overcome this situation, frequencies were taken for the possible options and the option with the highest frequency was used. For example, if a patient was male for four out of six segments then the patient was considered a male. This procedure was used for gender, race and county of residence. The rational for doing this for county was that the county where the subject spent the most time might have an effect on access to health care and economic opportunities.

Kentucky consists of 120 counties which were divided into the Appalachian, Central and Delta (Western) regions. The Appalachian part of the state was mostly the eastern half while the central was mostly the metropolitan areas of Louisville, Lexington and Northern Kentucky together with their surrounding areas. The delta region was the western part of the state. The map in figure 3.2 shows the division of the state into the three regions (Bostic, 2007).
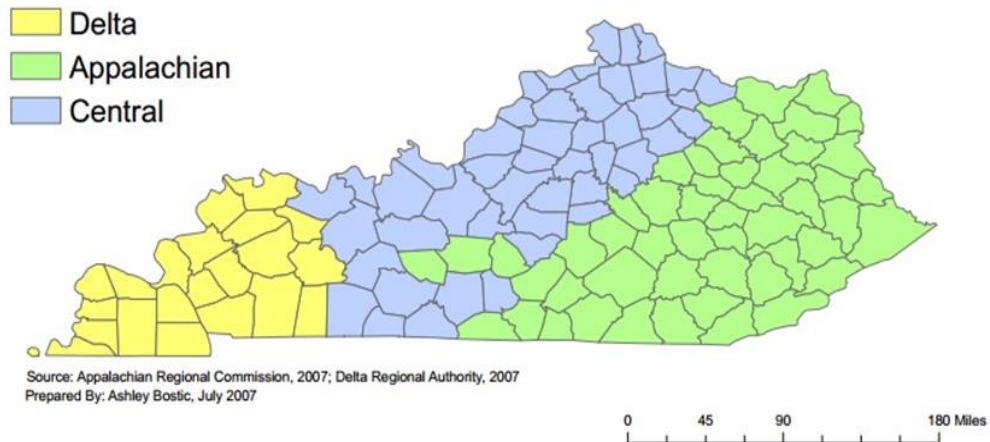
Figure 3.2 Map of Kentucky by Region

Outcome

The primary outcome for this study was the type of NSAID as determined by the first NSAID prescription of the patient. Subjects were categorized into one of two groups COX-2 or COX-1. For classification purposes, the first exposure carried forward to the rest of the study. Subjects who had taken rofecoxib, celecoxib, valdecoxib or etodolac were classified as COX-2 users and the rest were classified as COX-1 users. All NSAIDs were identified by their national drug codes (NDC) and classified into one of the two types described above. NSAIDs and their different brand names were identified using MULTUM which provides trusted drug information (Multum, 2013). Table 3.1 lists the different medications and the classes they fall into.

Table 3.1 List of Medications and their Drug Class

Drug	Class
Celecoxib	Cox-2
Etodolac	Cox-2
Rofecoxib	Cox-2
Valdecoxib	Cox-2
Diclofenac	Cox-1
Diflunisal	Cox-1
Fenoprofen Calcium	Cox-1
Flurbiprofen Sodium	Cox-1
Ibuprofen	Cox-1
Indomethacin	Cox-1
Ketoprofen	Cox-1
Ketorolac Tromethamine	Cox-1
Meclofenamate Sodium	Cox-1
Meloxicam	Cox-1
Naproxen	Cox-1
Piroxicam	Cox-1

Statistical Analysis

SAS 9.3 was used for both data management and statistical analysis. Frequencies and

percentages are presented for the covariates by outcome. Rates of new NSAID use, pattern of

use, trends in use and duration of use are also presented.

The Institutional Review Boards of the University of Kentucky (IRB Number 12-0999-

P2H) and the State of Kentucky Cabinet for Health and Family Services (CHFS-IRB-DMS-FY13-15)

approved this study.

Results

As shown in Figure 3.3, there were 325,281 individuals 18 or older who had ever

received an NSAID prescription between January 1st 2000 and December 31st 2012. Individuals

were excluded from the study for several reasons. There were 53,692 subjects excluded because

of age restrictions, one because they were missing important demographic covariates and

31,281 because they were not talking the NSAIDs of interest. The final study population was

240,307 individuals with 958,042 person-years of NSAID exposure. Of these 136,938 (57%) were

new users defined as having at least 6-months of non NSAID use before initiation of an NSAID.

The distribution of demographic variables by outcome is presented in Table 3.2. In both

groups the majority of the population were female (66.5% vs. 68%). There was a differential

proportion in the use of the types of NSAIDs by blacks compared to whites and others. For

blacks the proportion of people using COX-2s was less than that of those using COX-1s (4.3% vs

10.1%). Additionally, the pattern in the distribution of race was different for the two medication

classes. For the COX-1s, most of the users were whites followed by others and then blacks. This

pattern was not seen for COX-2s, where there was a decrease in use from whites to others and

then blacks. Baseline age was also differentially distributed among the two exposure groups.

Though both groups have a decrease in the proportion of users with increase in age, the

proportion distribution of 30-40 year olds was different in the two groups. This was the only age

group where the proportion of COX-1 users was greater than COX-2 users (30.0% vs. 50.9%).

Region was also differentially distributed in both groups with the highest proportion of users

from the Appalachian region, followed by the Central and Delta regions respectively. This

pattern was the same for subjects on both COX-1 and COX-2. Continuous use of medication was

similar between the groups with 55.7% of continuous users among COX-2 users and 58.3%

among COX-1 users.

There were 68,687(28.6%) subjects of the final cohort who were exposed to the two

types of NSAIDs during the study. Of these 33,956 (49.44%) started on a COX-2 before switching

to a COX-1 and the rest did the reverse. The median time to switch was the same for the two

distributions (30 days). However, the range was different with those switching from a COX-1 to a

COX-2 having a longer range. The ranges were 10 to 3596 days for switching from COX 1-2 versus 30 to 3346 days for switching from COX 2-1.

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┌─────────────────────────────────────────┐
│   KY Medicaid enrollees aged 18 and older who │
│   have taken an NSAIDS between 2000 and 2012 │
│                N=325,281                 │
└─────────────────────────────────────────┘
                    │         ┌──────────────────────────────────────┐
                    │         │ Exclusion Criteria                   │
                    │         │   • Age restriction (53,692)         │
                    ├─────────│   • Missing covariate(1)             │
                    │         │   • Not taking NSAIDs of interest (31,281) │
                    │         │              N=84,974               │
                    │         └──────────────────────────────────────┘
                    ▼
┌─────────────────────────────────────────┐
│  KY Medicaid enrollees aged 30 to 64 who have taken │
│  NSAIDS of interest between 2000 and 2012 │
│                N=240,307                 │
└─────────────────────────────────────────┘
           │                              │
           ▼                              ▼
┌────────────────────┐          ┌────────────────────┐
│   COX-1 Users      │          │   COX-2 Users      │
│   N=198,148        │          │   N=42,159         │
└────────────────────┘          └────────────────────┘
           │                              │
           ▼                              ▼
┌────────────────────┐          ┌────────────────────┐
│  New COX-1 Users   │          │  New COX-2 Users   │
│   N=117,552        │          │   N=19,386         │
└────────────────────┘          └────────────────────┘
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Figure 3.3 Patient identification and cohort entry

Figure 3.4 shows the trends in the number of NSAID prescriptions in the Kentucky Medicaid population for selected NSAIDs from 2000 to 2012. The graph shows the popularity of the coxibs (celecoxib and rofecoxib) as they were introduced into the market in 2000. Both celecoxib and rofecoxib were highly prescribed at the time with about a hundred thousand prescriptions each. However, this popularity declined over the years, post 2002, to below twenty thousand prescriptions. This decline gave rise to an increase in prescription of other

drugs namely ibuprofen, naproxen and most recently meloxicam. Diclofenac saw a short lived

increase but has remained mostly constant in this population.

Table 3.2 Characteristics of the population by Outcome

	COX2 (N = 47810)	COX1 (N = 192497)
Gender		
Female	31795 (66.5%)	130937 (68.0%)
Race		
White	40663 (85.1%)	158000 (82.1%)
Black	2038 (4.3%)	19346 (10.1%)
Other	5109 (10.7%)	15151 (7.9%)
Baseline Age		
30-<40	14346 (30.0%)	97998 (50.9%)
40-<50	14245 (29.8%)	50058 (26.0%)
50-<60	13509 (28.3%)	34303 (17.8%)
60-<65	5710 (11.9%)	10138 (5.3%)
Region		
Appalachian	30888 (64.6%)	91629 (47.6%)
Central	12157 (25.4%)	83261 (43.3%)
Delta/Western	4764 (10.0%)	17600 (9.1%)
Cont. Users		
Yes	26647 (55.7%)	112167 (58.3%)

1. All percentages are column percentages

NSAIDs Prescriptions
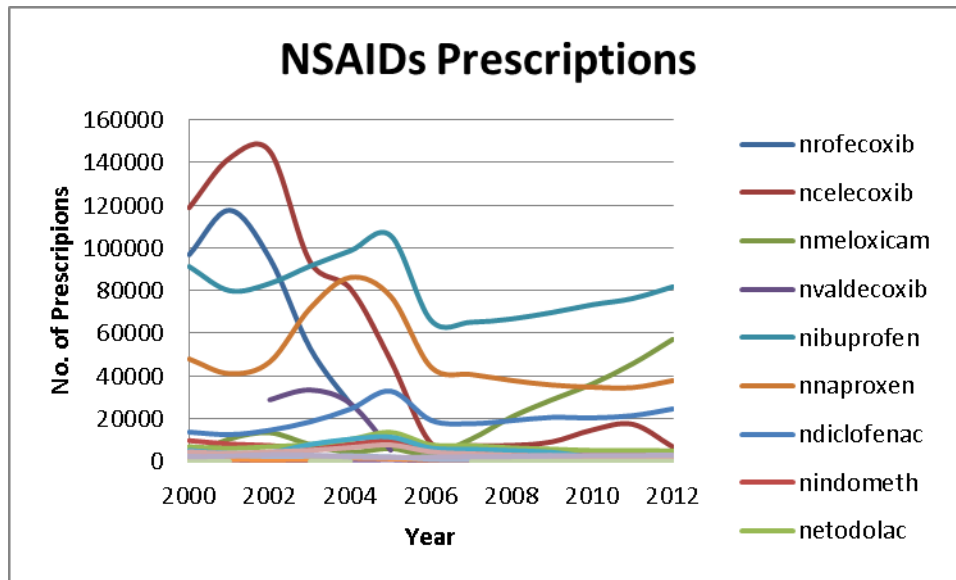
Figure 3.4. Trends in NSAID use 2000-2012

The decrease in popularity of the coxibs has meant the increase in popularity of other

NSAIDs. Naproxen and diclofenac saw an associated increase in popularity with the former

becoming the second most commonly prescribed NSAID in the population post 2003. Of

interesting note is the increased use of meloxicam in this population. This drug, which has been

less studied compared to other NSAIDs (McGettigan & Henry, 2006), has grown in popularity to

overcome the coxibs and diclofenac and become more prescribed than naproxen.

In this population there is also an emerging gradual increase in new users of NSAIDs

following a steep decline in the early 2000s. The line in Figure 3.5 shows the trend in the rates of

new NSAID use in the Kentucky Medicaid population from 2000 to 2012, while the bars show

the population of NSAID users for the corresponding years. Even though the prevalent

population has been fairly constant over the years, there is a slight emerging increase in new

use of NSAIDs in this population from 4.9% in 2007 to 6.3% in 2012.

New User Trend
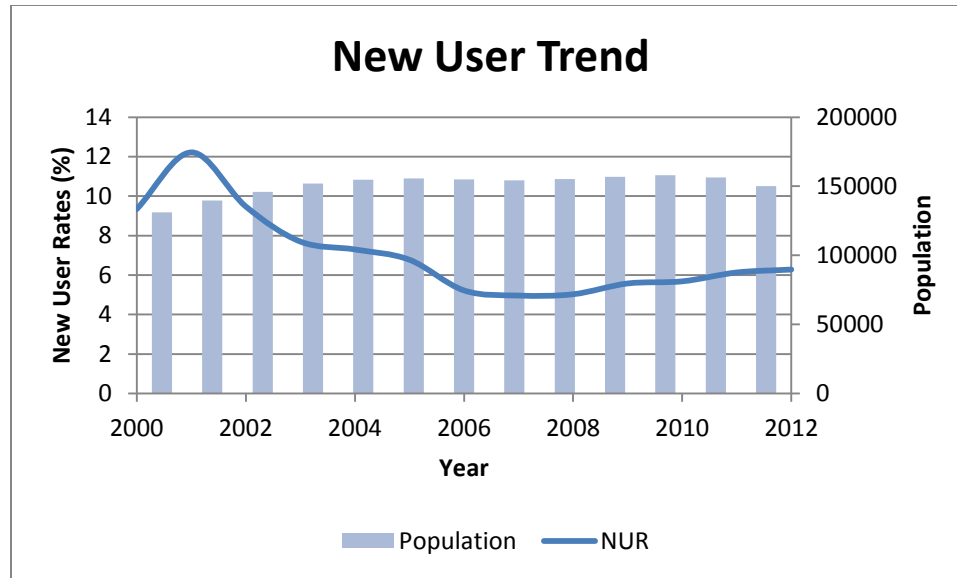
Figure 3.5 Rate of New NSAID use in the KY Medicaid population 2000-2012

Discussion

The controversial nature of NSAIDs exposure is still discussed in the scientific

community (Gever, 2014). Several studies have had as their aim the investigation of these and

have had conflicting results. As a therapeutic class they share the side effects of gastrointestinal

ulceration, hypersensitivity reactions, inhibition of uterine motility and prostaglandin-mediated

renal function (Antman et al., 2005). Additionally, some of these drugs have been associated

with an increased risk for MI (S. E. Kimmel et al., 2004). Some studies have highlighted the need

for more studies to investigate this relationship. Given the seriousness of some of the side

effects and their effect on the public health, an understanding of NSAID use is warranted.

Specifically, continuous monitoring of NSAIDs use is warranted to curb any potential adverse

effects that they might have.

This study finds that new use of NSAIDs is gradually increasing in the Kentucky Medicaid

population after a decline due to bad publicity. In 2007 new use had dipped to 4.9% but by 2012

new use had increased to 6.3%. There is a high proportion of younger people who are using the

drugs and they account for this gradual increase in use. From table 3.2, the 30-40 year olds

make up the highest percentage of users in both the COX-1 and COX-2 groups. In this cohort, the

30-40 year olds and the 40-50 year olds were the majority of the incident population of NSAID

users. In 2000, the 30-40 year olds accounted for about 30% of the incidence use population and

by 2012 they accounted for about 60% of the incidence population. Even the enrollees who are

less than 50 years of age are helping to propagate the incidence and prevalence of use in the

population.

This study does not have a wash out period and assumes that an incident prescription of

NSAID in the Medicaid program is an incident use of NSAID. This may not be the case as we do

not have information on OTC medications.

The use of NSAIDs especially in young populations should be closely monitored to track

the possible occurrence of any harmful side effects which might have public health implications

if left unattended.

Using the National Health and Nutrition Examination Survey (NHANES) data, the

prevalence of NSAIDs use for the 30 to 64 year age range used in this study was estimated at

4.4% for the study period. A significant proportion of the population uses these drugs and they

account for a huge volume of prescription medications nationally. As such any adverse side

effects caused by them will have considerable public health implications.

This population compares to the national sample in the NHANES data in several ways. In

both populations women use the medication more than men. More people also use more COX-1

NSAIDS compared to COX-2. About one-third of the NHANES population was on COX-2s

compared to one-fifth of the Kentucky Medicaid population. One precaution in these

comparisons is that the NHANES data mostly measure prevalence of medication use while the

Kentucky Medicaid data measures both incidence and prevalence. This will explain the higher

proportion of people in the older age groups in the NHANES data compared to the higher

proportion in the younger age groups in the Kentucky Medicaid population.

While race and region may not directly influence access to NSAIDs they might serve as a

proxy for underlying socio-economic factors that serve as an indicator of access. The

Appalachian region of the state leads the rest of the state in use of both COX-1s and COX-2s but

more so the COX-2s. This might be indicative of the prevalence of chronic conditions in that part

of the state compared to the others. It is generally believed this section of the state is

responsible for the low ranks in national health indices as it has a high prevalence of diseases.

This will make geographical location important as a predictor for NSAID drug use in the Kentucky

Medicaid population. Additionally, race was also differentially distributed especially for blacks

which might also be indicative of socio-economic factors.

Based on the literature, the trends in NSAID use for this population mirrors that of the

general US population. Of all the NSAIDs studied the most commonly used medication presently

is ibuprofen. It has consistently achieved one of the highest numbers of prescriptions over the

study period (Figure 3.4). This is understandable as ibuprofen has been around for a long time

and is available under a bunch of generic and trade names. There are over a thousand NDCs

associated with this drug alone. The commonly used Advil falls under this group of drugs.

However, in the early 21st century, COX-2 inhibitors were very popular. They were leading in the

number of prescriptions in this population. This popularity saw a decline after some studies

highlighted their cardiovascular risk. It is hypothesized that this decline was due to the negative

publicity associated with these drugs in terms of their increased risk for MI (Bombardier et al.,

2000; Mukherjee, Nissen, & Topol, 2001). The decline coincides with the publication of research

articles attesting to the increased risk of MI with use of these drugs. This risk was first posited in

2001 with several other studies supporting and disputing said risk over the years. This led to an

increase in popularity of other NSAIDs. However, studies have also highlighted the

cardiovascular risks of other NSAIDs. This calls for further studies of these drugs and an

understanding of their use in the general population.

Further research into the determinants of the relationship between NSAIDs and their

potential side effects is warranted. Further research will look at factors that potentially affect

these relationships. For example, one of the side effects of NSAIDs is cardiovascular diseases

which have been identified as a leading cause of death worldwide (Alwan 2011). As a result,

anything that would exacerbate this risk is of grave public health concern. Considering that

NSAIDs are widely used in the population even a small increase in adverse side effects will have

considerable public health implications.

Chapter Four

Understanding MIs in a Younger Medicaid Population

Introduction

NSAIDs are among the most widely used medications and account for a huge volume of

both prescription and OTC medications worldwide (Greene 2001). They are effective for the

management of inflammatory, arthritic and other musculoskeletal conditions (Rahme, Pilote, &

LeLorier, 2002). They are most commonly used for the treatment of acute and chronic pain.

There are generally two types of NSAIDs categorized on their ability to inhibit the COX

enzyme; they are selective (COX-2) and traditional NSAIDs (COX-1)(Al-Saeed, 2011). In 1999,

COX-2s were approved by the FDA and released in the US as a less toxic alternative to COX-1s.

Their attraction was they could reduce pain and inflammation without the upper GI toxicity

identified in other NSAIDs. Celecoxib and rofecoxib were the first to gain approval (Graham

2006). They were heavily promoted and quickly became the most widely prescribed NSAIDs. A

study about their basic mechanisms shed light on their toxicity and gave much attention to the

medications (Catella-Lawson et al 1999). This study highlighted suppression of prostacyclin by

inhibition of the COX-2 enzyme. Although they were as effective as other NSAIDs in relieving

pain, there were cardiovascular concerns such as MI and stroke.

The inhibition of the COX enzyme is the first step in converting arachidonic acid to

prostaglandins, thromboxane and prostacyclin (Catella-Lawson et al., 1999). COX-1 produces

prostaglandins responsible for platelet aggregation and gastric mucosa. COX-2 produces

prostaglandins that mediate pain and inflammation. The inhibition of COX-1 causes bleeding and

that of COX-2 suppresses prostacyclin which reacts with thromboxane for homeostatic balance

(Graham, 2006). This inhibition of prostacyclin causes an increased production of thromboxane

which is responsible for adverse cardiovascular events (Cannon et al., 2006). This mechanism of

action has been reported to be sufficient to explain the clinical effects of NSAIDs (Patrono & Baigent, 2014).

Several studies have evaluated the NSAIDs-MI association. The VIGOR Trial reported an increased risk for MI with use of rofecoxib compared to naproxen (Bombardier et al 2000). However, it was not confirmed whether this association was due to a protective effect of naproxen, an increased risk from rofecoxib, or a combination of both. Several other studies and trials on the NSAIDs-MI association have found conflicting results. The CLASS study compared celecoxib with other NSAIDs in patients with osteoarthritis and rheumatoid arthritis and found no difference in cardiovascular events between the groups (Bresalier et al., 2005; Farkouh et al., 2004; Silverstein et al., 2000; S. D. Solomon et al., 2005).

The APPROVe trial was terminated as a result of adverse clinical events such as MI, unstable angina, death from cardiac causes, ischemic stroke, ischemic attack, peripheral arterial thrombosis, peripheral venous thrombosis, and pulmonary embolism. The study found use of rofecoxib was associated with a significant increased cardiovascular risk when compared to a placebo in patients with a history of colorectal adenomas (RR=1.92; 1.19-3.11)(Bresalier et al., 2005). While this study looked at a combination of cardiovascular events, MI was the majority of such events. In September 2004, Merck voluntarily withdrew rofecoxib from the market based on preliminary results of this trial. In April 2005, the FDA requested Pfizer to voluntarily withdraw valdecoxib from the market. This was due primarily to cardiovascular concerns (MI, cardiac arrest, stroke and pulmonary embolism) produced from trials in patients undergoing coronary-artery bypass grafting (Nussmeier et al., 2005). The FDA allowed celecoxib to remain on the market and requested its labeling together with other NSAIDS describe the increased risk of cardiovascular events (Antman et al., 2005; FDA, 2005). At the time, this was a black-box warning that was not preceded by investigations for all the medications involved. In 2007, the

FDA refused approval for etoricoxib because of the possible implications of approving another COX-2 inhibitor with potentially dangerous cardiac side effects (Avorn, 2007). Celecoxib is still widely used despite studies showing an increased risk of MI associated with the drug (Kearney et al., 2006).

Results of some observational studies have suggested that some COX-1s also increased cardiovascular risk (Garcia Rodriguez & Gonzalez-Perez, 2005; Hernandez-Diaz et al., 2006; Juni et al., 2004; McGettigan & Henry, 2006). Following the VIGOR trial, there has been accumulating evidence from several large observational studies and meta-analysis that NSAIDs are associated with increased cardiovascular risk. However, these results are not conclusive lending to conflicting results and the need for more studies in this area. While some studies have found an increased cardiovascular risk with NSAIDs use (Chan et al., 2006; Hippisley-Cox & Coupland, 2005; Johnsen et al., 2005; Mamdani et al., 2004), others have found no effect (Garcia Rodriguez et al., 2004; Mamdani et al., 2003; Ray, Stein, Daugherty, et al., 2002; Schlienger et al., 2002) . And some have even found a protective effect with use of some NSAIDs (Juni et al., 2004; S. E. Kimmel et al., 2004; D. H. Solomon et al., 2002; Watson et al., 2002). As a result of the discrepancies in the different studies, low event rates and the need for more meaningful studies, several researchers have undertaken meta-analysis over the years (Garcia Rodriguez et al., 2011; McGettigan & Henry, 2011). The Garcia Rodriguez et al. study concluded that use of NSAIDs increased the risk of non-fatal MIs but did not have a substantial effect on fatal ones. The McGettigan study found that there were different levels of cardiovascular risk among the most widely used NSAIDs. These studies and their results and methods are listed in tables 2.1 and 2.2.

Whether NSAIDs affect MI risk is still unclear (Gever, 2014; Hernandez-Diaz et al., 2006; Trelle et al., 2011). The NSAIDs-MI association remains an important question, especially given

their increased use in an aging population with a high prevalence of chronic diseases.

Additionally, the removal of refocoxib and valdecoxib from the market means the increased use

of other drugs on the market (e.g. meloxicam) for which the cardiovascular risks are not well-

defined (McGettigan & Henry, 2011). A recent study from Taiwan found increased MI risk

associated with current use of some NSAIDs including commonly used drugs like ibuprofen and

diclofenac (Shau et al., 2012). Recently, the FDA convened an advisory committee meeting to

assess NSAID safety in an effort to re-evaluate decisions made nearly a decade ago in light of

present evidence (Gever, 2014).

Cardiovascular disease is a leading risk factor for death worldwide (Alwan, 2011). As a

result, continuous monitoring of the NSAID-MI relationship is needed because an agent that

potentially affects such an important risk factor poses considerable public health consequences.

Kentucky is one of the states with the highest prevalence of cardiovascular diseases in the US

(CDC, 2005-2010). According to the Behavioral Risk Factor Surveillance System (BRFSS), from

2005 to 2010 the MI prevalence for Kentucky has been between 5% and 6.5% with the lower

bound of the 95% CI greater than the median percentage for all the other states over the same

period of time. Figure 4.1 shows the prevalence of MI in Kentucky compared to the US from

2005 to 2010.

This study is different in that it investigates the NSAIDs-MI association in a younger

population (30-64 years) heavily burdened with cardiovascular diseases. Also, this study has

more recent data compared to other studies done over a decade ago and it has a longer window

of data (12 years). Secondly this study investigates a possible class effect of NSAIDS which has

been posited by some researchers (Antman et al., 2005). The investigation of a class effect was

done by comparing COX-2s to COX-1s on their risk for MI. Additionally, this study takes into

consideration latent socio-economic factors, by accounting for the geographical region of the

patients. It also considered switching patterns of medication classes. Finally, this study accounts

for continuous and sporadic use of the medications in the cohort. The intermittent use of

NSAIDs has been identified as a limitation in the study of the NSAIDs-MI association (Levesque

et al., 2005).

While most other studies that have evaluated the NSAID-MI relationship have focused

on age as an important high risk factor for MI, this study highlights socio-economic risk factors

that affect the disease especially in a state like Kentucky where the prevalence of cardiovascular

diseases is very high compared to the rest of the US. As such, the Kentucky population serves as

an important case study for the investigation of this association.

Figure 4.1 Prevalence of MI in KY and US
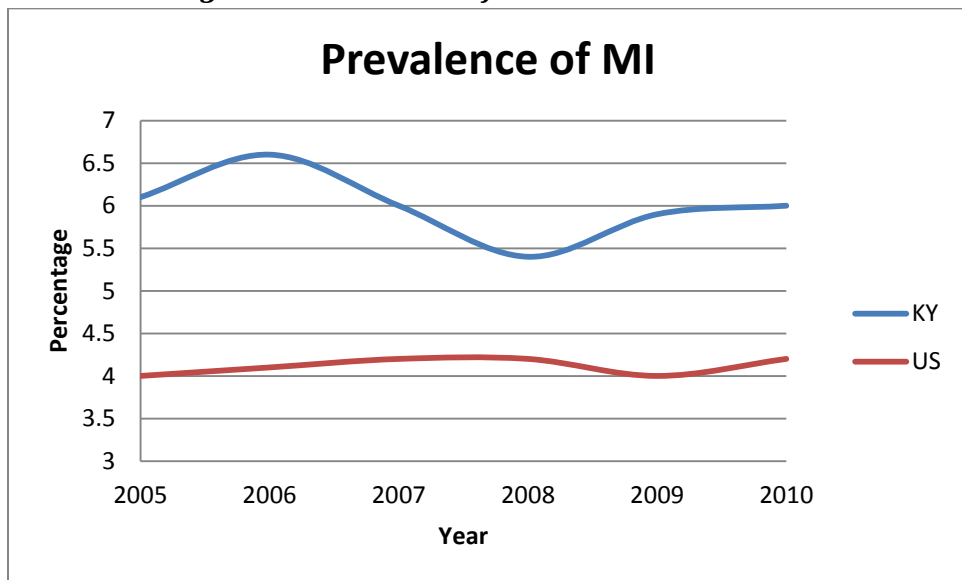
1. Percentages are weighted to population characteristics.
2. Data obtained from BRFSS.

Due to the overall health status of the state, younger groups of patients also have an

increased burden for cardiovascular diseases compared to the rest of the country (CDC, 2005-

2010). From 2005-2010, the rates of MI in Kentucky for the different age groups is at or higher

than the median for the US. This study aims to investigate the NSAIDs-MI relationship in a younger Medicaid population with the aim of understanding the literature-defined and socio-economic risk factors in patients exposed to the drug and assessing the possibility of a residual risk after discontinuation of the drug.

Methods

Study overview

A retrospective cohort study, using the new users design (defined below), was conducted to examine the NSAIDs-MI relationship among younger (30-64 years) Kentucky Medicaid enrollees who were prescribed NSAIDs between January 1st 2000 and December 31st 2012 (Ray, 2003). Only patients with an NSAID prescription of interest were selected for entry into the cohort. Within this cohort we conducted a nested case-control study. The primary objective of this study was to compare MI events (cases) to non-MI events (controls) between users of COX-2 and users of COX-1.

Data Source

Data for this study included administrative and prescription claims of Kentucky Medicaid linked with hospital discharge information and death dates collected between January 1st 2000 and December 31st 2012. Enrollment and patient demographic information were included in an enrollment file. Prescription files contained dates, drug name, quantity, dose and days of supply. Hospital and outpatient files included admission and discharge dates for hospitalizations, outpatient and emergency department visits. Diagnoses associated with hospitalizations and visits were identified using the International Classification of Diseases, Ninth Revision; Clinical Modification (ICD-9-CM).

The subjects for this study included persons aged 30 to 64 years at NSAIDs initiation who were enrolled in Medicaid between 2000 and 2012, had information on demographic

covariates, had at least one outpatient encounter or filled at least one NSAID prescription and

did not have evidence of serious medical illness in the 6-month baseline period before they

began taking NSAIDs. We restricted patients 65 years and older from entering the cohort

because of the introduction of Medicare Part D in 2006. Serious medical illnesses included HIV

infection (ICD-9-CM 042.x-044.x and 079.53) and organ transplant (ICD-9-CM V42.x). Patients

with serious medical illnesses were excluded because they already have a compromised

immune system (Graham et al., 2005).

Enrollees were followed until observance of study outcome (MI), disenrollment from

the program, their 65th birthday, death or the end of the follow-up period (December 31, 2012),

whichever came first. Only the first occurrence of the study outcome was observed as an

outcome. Figure 4.2 shows the study design.
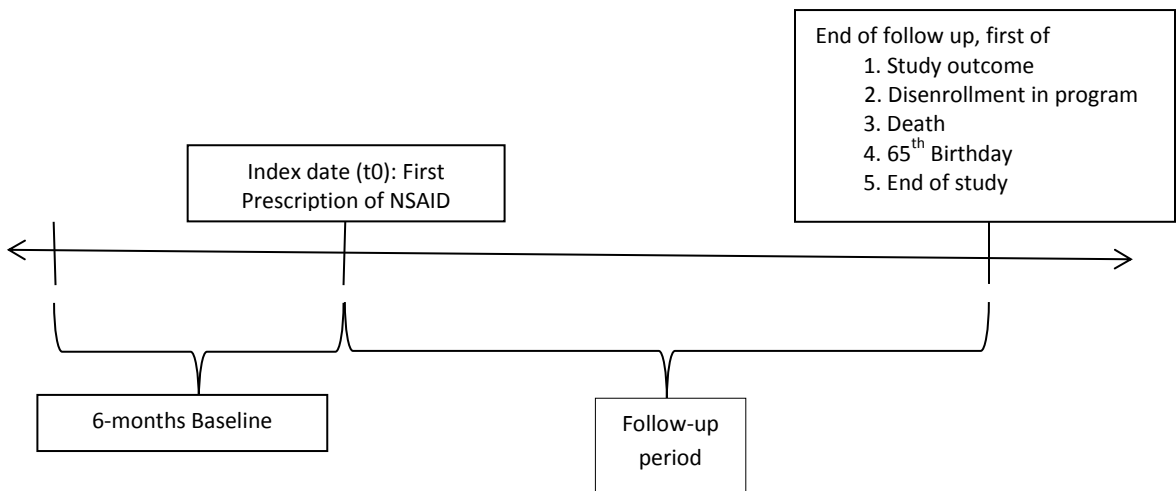
Figure 4.2 Study Design

Exposure classification

The primary exposure was the type of NSAID (COX-2 versus COX-1) used on the index

date, which was the first prescription of an NSAID after the 6-months baseline period defined

below. The COX-2 and COX-1 users were considered as the exposed and comparison groups

respectively. The COX-2 drugs of interest were rofecoxib, celecoxib, valdecoxib and etodolac.

The COX-1 drugs of interest were diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen,

indomethacin, ketoprofen, ketorolac, meclofenamate, naproxen and piroxicam. These drugs

were identified from the literature as the most commonly used in the study of the NSAIDs-MI

association (McGettigan & Henry 2011). Meloxicam was not considered in this study because it

is usually classified as a COX-1 but not much is known about it. Other studies have hypothesized

that it has a higher COX-2 then COX-1 selectivity (Antman et al., 2005; McGettigan & Henry,

2011; Singh et al., 2006). Figure 3.4 shows the trends in use of meloxicam over the study period.

All NSAIDs of interest were identified by their national drug codes (NDCs) and classified into the

two types using MULTUM (Multum, 2013). The list of drugs studied and their classifications are

presented in table 3.1.

Only new users were included in the analyses. For this study, a new user was defined as

someone who had no prescription of the study drugs in the 6-month baseline period preceding

their first NSAID prescription (index date). A baseline period of 6-months was used as it was

deemed sufficient for any previous use to have left the body and for collecting of baseline

covariates. This period of non-use is synonymous to a wash out period as used in clinical trials.

New users are less susceptible to biases introduced by prevalent users (Ray 2003). These include

but are not limited to the healthy user effect and the effect of prevalent use of drugs on the

covariates measured at study entry.

The primary way in which observational studies differ from clinical trials is that patients

determine whether they take the treatment. As a result, patients will discontinue treatment if

they have adverse reactions to it. This phenomenon of not having an adverse reaction to the

treatment is what has been termed the "healthy user effect"(Ray, 2003). On the other hand,

prevalent users can cause misclassification of events if they occur early during exposure. Prevalent users also do not allow for control of certain risk factors that may be affected by the treatment.

Patients were classified into exposure categories based on their new-user or first NSAID exposure. Patients were not re-classified for claim changes. Preliminary results show that the characteristics of the subjects in the two possible switch groups (COX-1-2 and COX-2-1) were similar by outcome. Furthermore, these results showed the proportion of people who switched were similar for the two possible switches- from a COX2-1 and vice versa (51.3% vs 48.7%).

Duration of exposure was taken into consideration by summing up the number of days supply for the patients prescriptions during their time in the study. There were some patients with very large number of days supply on their prescriptions. As a result, a decision was made that if a prescription had a number of days supply greater than 90 days then the number of days supply will be reduced to 90 days. This was done because prescriptions in the Kentucky Medicaid data usually run from 30 to 90 days.

Finally, patients were classified as continuous versus sporadic drug users. For this study, continuous use of NSAIDs was defined as consecutive prescriptions with a gap of less than 30 days between prescriptions. Otherwise, they were considered sporadic users. This was done because patients usually miss a couple of days when on medications and the half-lives of the drugs under consideration is on average about 18 hours (Davies & Skjodt, 2000). Furthermore, a distribution of medication gaps showed that this was a reasonable decision.

To compensate for the fact that patients were not re-classified for claim changes, switching was considered in a separate analysis. Once a patient was classified as a COX-1 or COX-2 user at study entry, there is the possibility that they could switch from a COX-1 to a COX-2 and vice versa. As a result, switching patterns for the two possible switches were compared to

those patients who did not switch and stayed on their original classification throughout the study. Alternatively, exposure was considered as a four category variable; those who took only COX-1, those who took only COX-2, those who switched from COX-1-2 and those who switched from COX-2-1.

Outcome

The primary outcome was admission for MI during the study as identified from hospital discharge diagnosis codes (ICD-9-CM 410.xx) in the primary and secondary diagnoses positions. This algorithm was validated by a hospital stay of more than 2 days but less than 180 days, unless the patient died (Petersen, Wright, Normand, & Daley, 1999; Roumie et al., 2009; Daniel H Solomon et al., 2004). Two days was chosen because shorter stays were unlikely for an accurate diagnosis of MI. Several studies have validated this algorithm for claims data ICD-9-CM diagnosis and found greater than 90% for positive predictive value and sensitivity (Graham et al., 2005; Metcalfe et al., 2013; Roumie et al., 2009; Wahl et al., 2010) . This algorithm has a specificity greater than 90% (Brouwer et al., 2013). A recent study showed the changes in sensitivity, specificity, positive and negative predictive values with different algorithms for ascertaining MI cases from claims data (Brouwer et al., 2013). The algorithm, of a MI admission identified from the first and second diagnosis positions with a stay of more than 2 days, was used as it was common in the literature and highlighted as optimal (Brouwer et al., 2013; Levesque et al., 2005; Roumie et al., 2009). Given the high sensitivity and specificity for this algorithm, the false negative and positive rates were expected to be relatively low.

For every MI case, we randomly selected four controls from individuals in the study cohort and matched them for gender and race using incidence density sampling. This is an efficient approach which produces unbiased estimates of the relative risk (Richardson 2004). The process involves matching cases to controls who were at risk at the time of case occurrence.

For example, if a case occurred in 2003, only persons who had entered the cohort at or before 2003 and had not become a case by then will be eligible to be chosen as controls. Controls matched to a case could later become cases themselves. It solves the problem of controls providing excess person time to the study than cases.

A SAS macro by Richardson (2004) with some edits was used for the incidence density sampling. Instead of using age for the macro, date of first NSAID prescription was used as date of entry into the cohort. Last date in the cohort was the first of either end of segment, 65th birthday, MI event date, death or end of the study. For matching on race and gender, estimated probabilities were generated using logistic regression with MI as the outcome and race and gender as the inputs. The probabilities were then multiplied by a hundred and rounded to the nearest whole number to form categories which were used for the matching in the macro. This was done as an alternative method to incorporate matching using propensity scores.

Covariates

Baseline covariates were measured in the 6-months prior to the index date. This was done to reduce bias that might arise because of varying lengths of covariate assessment (Solomon et al 2004).

The study covariates included age at initiation, gender, race, state region of residence, co-morbid conditions, concomitant medication (other non-NSAID medications).

Demographics

Demographic variables were identified from patient enrollment data. Age at initiation was calculated as the difference between the patient's year of birth and year of index date. Gender and race were reported in the Medicaid file. The enrollment file also contained the patient's county of residence. This was used to determine Kentucky residence as a categorical

variable with options: Appalachian, Central and Delta or Western. Figure 3.2 shows the division of the state into the three regions.

Comorbid Conditions

Comorbid conditions that occurred during the 6-month baseline period were obtained from Medicaid medical files. The ICD-9-CM codes were used in coding algorithms for the Elixhauser and Charlson comorbidities (Quan et al., 2005). These algorithms identify comorbidities from administrative data and they have been validated for such use. Claims data have a stipulated number of diagnoses and for Medicaid, there are up to ten diagnoses reported. The following comorbid conditions were assessed based on the literature: angina, cerebrovascular disease , chronic pulmonary disease (COPD) , congestive heart failure , coagulopathy , coronary revascularization , diabetes , hypertension , hypercholesterolemia , osteoarthritis , previous MI , and rheumatoid arthritis (Baron et al., 2008; Shau et al., 2012). Table 4.1 lists the comorbid conditions with their corresponding ICD-9-CM codes.

Concomitant medication

Several methods are used to assess disease severity in the use of claims data. The use of concomitant medication is one such method and this was identified from the prescription claims file as those that overlap the index date of NSAID use within a 60 day window centered at the index date. The main drug classes considered were statins, beta-blockers, anticoagulants, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB) and diuretics. These were all considered based on the literature (Cannon et al., 2006; Graham et al., 2005; Daniel H Solomon et al., 2004). Table 4.2 lists the drug classes and the medications that were considered in those classes. The concomitant medications were all identified using MULTUM (Multum, 2013).

Table 4.1 Comorbid conditions and ICD-9-CM Codes

Comorbid Condition	ICD-9-CM Code
Angina	413.0,413.9
Cerebrovascular Disease	430.x – 438.x
Chronic Pulmonary Disease	490.x-496.x
Congestive Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x
Coagulopathy	286.x, 287.1, 287.3-287.5
Coronary Revascularization	414.x
Diabetes	250.xx
Hypertension	401.xx – 405.xx
Hypercholesterolemia	272.0
Osteoarthritis	715.xx
Previous MI	410.x
Rheumatoid Arthritis	446.5, 710.0 –710.4, 714.0—714.2,714.8,725.x

Table 4.2 Drug classes and medications

Drug Class	Medications
Statins	Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin Pitavastatin
Beta Blockers	Kerlone, Zebeta, Tenormin, Toprol-xl, Bystolic, Brevibloc, Sectral, Innopran XL, Corgard, Betapace, Inderal, Coreg, Labetalol, Timolol, Carteolol, Levatol, Sorine, Trandate, Pindolol
Anticoagulants	Clopidogrel, Fondaparinux, Hepharin, Ticlopidine, Warfarin, Enoxaparin, Dalteparin
Calcium Channel Blockers	Amlodipine, Clevidipine , Isradipine, Felodipine, Nicardipine , Nifedipine, Nimodipine, Nisoldipine, Verapamil , Diltiazem, Mibefradil A, Fluspirilene
ACE Inhibitors	Captopril, Zofenopril, Enalapril , Ramipril , Quinapril , Perindopril , Lisinopril , Benazepril, Imidapril, Zofenopril, Trandolapril, Fosinopril (Fositen/Monopril)
ARB Medications	Valsartan, Telmisartan, Losartan, Irbesartan, Azilsartan, Olmesartan, Candesartan, Eprosartan
Diuretics	Furosemide, Ethacrynic acid, Torsemide, Hydrochlorothiazide, Acetazolamide, Methazolamide, Chlorothiazide, Indapamide, Metolazone, Bumetanide, Amiloride, Eplerenone, Spironolactone, Triamterene

Statistical Analysis

SAS 9.3 was used for both data management and statistical analyses.

This paper examined the NSAID-MI association using patients with a baseline washout period of 6 months (180 days). The baseline period was used to identify baseline characteristics and give patients an equal amount of time for these characteristics to be evaluated.

Comparisons were presented of cases and controls in tables using frequencies and percentages. Tables comparing cases and controls by exposure were also presented to see differences in case status by exposure for the demographic and risk factors. Conditional logistic regression was used to evaluate the association between NSAID use and MI taking into consideration confounders and risk factors not used for matching. Duration of exposure and continuous use were also considered. COX-2 users were compared to COX-1 users. Age was assessed as an effect modifier by running the model for the different age categories and comparing the parameter estimates. The estimated odds ratios approximate the relative risk. Covariates were determined based on the literature and characterization of the population. The same model was considered with switching pattern as the exposure. Parameter estimates with their associated 95% confidence intervals were presented for all comparisons.

The Akaike Information Criteria (AIC) was used to assess model fit and the variance inflation factor (VIF) was used to evaluate multi-collinearity. The VIFs for all the variables used in the accepted range that does not indicate multi-collinearity in models (greater than 5 or 10).

Missing data were not an issue as patients missing demographic information were excluded from the study (Figure 4.3). For comorbid conditions and concomitant medications, a patient did not have them if the code(s) for those indications were not in their files.

We conducted sensitivity analysis to see the differences between the population that was used for the study and those excluded due to the new users design. This comparison was presented using frequencies and percentages.

The Institutional Review Boards of the University of Kentucky (IRB Number 12-0999-P2H) and the Kentucky Cabinet for Health and Family Services (CHFS-IRB-DMS-FY13-15) approved this study.

Results

Figure 4.3 shows the patient disposition of the study. There were 325,281 subjects 18 or older who had taken an NSAID in the Kentucky Medicaid program between January 1st 2000 and December 31st 2012. Of these 232, 645 (71.5%) were between 30 and 64 years at NSAID initiation, taking an NSAID of interest and had all their demographic covariates. These formed a cohort of which 184,835 (79.4%) were COX-1 users and 47,810 (20.6%) were COX-2 users. Patients with a 6-month baseline period without any NSAID prescriptions prior to their first prescription were considered new users and formed the final cohort. The COX-1 users were reduced to 106,558 (57.7%) of which 1,084 (1.02%) had an MI. There were 22,718 (47.5%) COX-2 users in the final cohort of which 420 (1.84%) had an MI. A total of 129,276 people contributed 514,525 person-years of observation time to the study. The mean age at NSAID initiation of the cohort was 42.2 years with a standard deviation of 9.7 years. From this cohort, there were 1504 cases of MI matched to 6016 controls using incident density sampling matching on gender and race. Of the 1504 cases, 658 (43.75%) had an MI after last exposure to the drug.

Figure 4.4 shows the trend in NSAIDs initiations by type for the study population. The popularity of COX-2s is seen by the peak in their prescriptions around 2000 and their subsequent decline. The prescription of COX-1s has been mostly constant over the years.

Table 4.3 shows the baseline characteristics of the MI cases and controls. It shows the balance in the variables used for matching. The distribution in age at initiation is different for cases and controls. Amongst cases, initiation of medication started later compared to controls. The modal age group for controls was 30-40 years and that of cases was 50-60 years. For

controls there is a progressive decline in initiation as age increases. However for cases, there is

an increase and then a decrease as age increases.

KY Medicaid enrollees aged 18 and older who
have taken an NSAIDS between 2000 and 2012
N=325,281

Exclusion Criteria
- Age restriction (53,692)
- Missing covariate(1)
- Not taking NSAIDs of interest (38,943)
N=92,636

KY Medicaid enrollees aged 30 to 64 who have taken
NSAIDS of interest between 2000 and 2012
N=232,645

COX-1 Users
N=184,835

COX-2 Users
N=47,810

New COX-1 Users
N=106,558

New COX-2 Users
N=22,718

MI
N=1,084

NMI
N=105,474

MI
N=420

NMI
N=22,298

Figure 4.3 Patient identification and cohort entry

The majority of cases (58.3%) were from Appalachia as opposed to 34.0% and 7.6% from the

Central and Delta regions respectively. The same pattern was repeated for controls. The

proportion of patients with risk factors among the MI cases was significantly higher than the

controls for all the comorbid conditions and concomitant medications. And in some cases there

is almost a doubling or more of proportions. For example, 6.4% of the MI cases had angina

compared to only 1.8% of the sampled controls.

To investigate if risk factors for MI varied by the type of NSAID, we investigated the

distribution of these factors in MI cases and controls by exposure group. Table 4.4 displays the

results. Among female patients who took a COX-2, there was a higher percentage of MI cases

than controls (58.6% vs 52.9%) but amongst those exposed to COX-1 the reverse was true

(50.3% vs 54.5%). The same pattern, of higher percentages of MI cases than controls amongst

COX-2 users, was repeated for the categories of race with the exception of others. For patients

in the other race category, there was a higher percentage of cases compared to controls among

those exposed to COX-1s (12.2% vs 9.6%) but a higher percentage of controls compared to cases

among those exposed to COX-2s (13.3% vs 12.4%). The distribution of age at initiation was

different with a divide at 50 years. For those less than 50 who were exposed to COX-2, there

was a higher percentage of controls compared to cases. The percentage of control patients in

the 30-<40 and 40-<50 age groups were 31.2% and 34.6% respectively compared to MI case

percentages of 16.4% and 31.4% in the same groups respectively. For those older than 50 years

in the same exposure group, there was a higher percentage of cases compared to controls. For

those exposed to COX-1s, the same pattern repeated itself. Region repeated the same pattern

that was seen in the overall comparison of cases and controls presented in table 4.3, where

there were more MI cases in the Appalachian region followed by the Central and Delta regions,

for the two exposure groups. In both categories, there was a higher proportion of cases than

controls for each of the levels of region with the exception of the Delta region for those exposed

to COX-2s and the Central region for those exposed to COX-1s. In those two scenarios there

were more controls than cases. For all of the risk factors the percentage of MI cases with the

risk factor was higher than that of controls in both exposure groups.

Figure 4.4. Graph showing the trend in NSAIDs initiation in the KY Medicaid Population 2000-2012
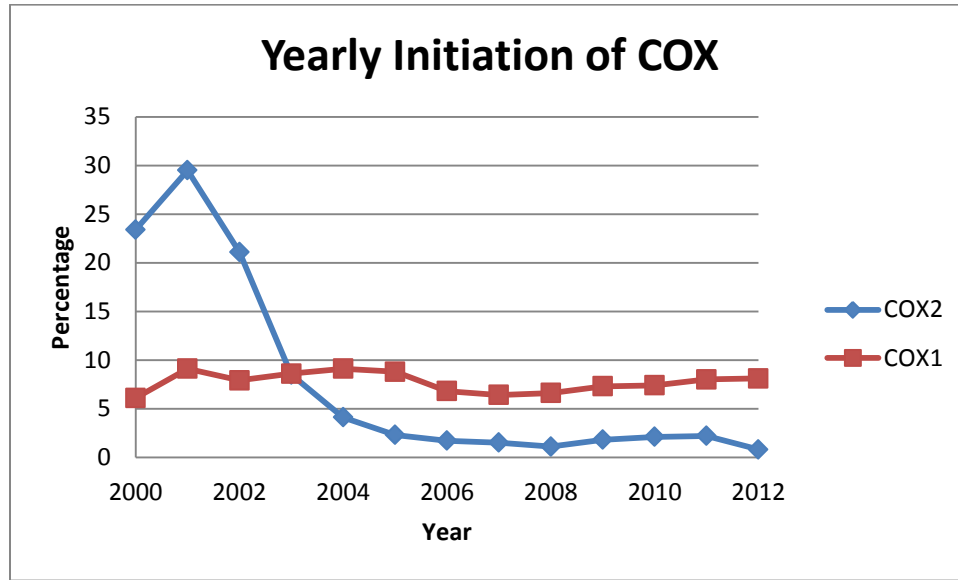
Table 4.3 Characteristics of the MI cases and matched controls from the base population

	NMI (N = 5661)	MI (N = 1504)	P-Value
Gender			**0.2952**
Female	3063 (54.1%)	791 (52.6%)	
Race			**0.1427**
White	4665 (82.4%)	1223 (81.3%)	
Black	399 (7.0%)	97 (6.4%)	
Other	597 (10.5%)	184 (12.2%)	
Age			**<.0001**
30-<40	2305 (40.7%)	254 (16.9%)	
40-<50	1781 (31.5%)	461 (30.7%)	

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50-<60	1357 (24.0%)	658 (43.8%)	
60-<65	218 (3.9%)	131 (8.7%)	
Region			**0.2649**
Appalachian	3172 (56.0%)	877 (58.3%)	
Central	2049 (36.2%)	512 (34.0%)	
Delta/Western	440 (7.8%)	115 (7.6%)	
Angina	100 (1.8%)	97 (6.4%)	**<.0001**
Cereb. Disease	109 (1.9%)	106 (7.0%)	**<.0001**
COPD	1009 (17.8%)	464 (30.9%)	**<.0001**
Cong. Heart Failure	165 (2.9%)	149 (9.9%)	**<.0001**
Coagulopathy	38 (0.7%)	35 (2.3%)	**<.0001**
Coron. Revascul.	254 (4.5%)	333 (22.1%)	**<.0001**
Diabetes	681 (12.0%)	483 (32.1%)	**<.0001**
Hypertension	1280 (22.6%)	686 (45.6%)	**<.0001**
Hypercholestrol.	268 (4.7%)	150 (10.0%)	**<.0001**
Osteoarthritis	376 (6.6%)	174 (11.6%)	**<.0001**
Previous MI	65 (1.1%)	112 (7.4%)	**<.0001**
Rheumatoid Arth.	83 (1.5%)	40 (2.7%)	**0.0015**
Anticoagulants	211 (3.7%)	220 (14.6%)	**<.0001**
Beta-Blockers	681 (12.0%)	321 (21.3%)	**<.0001**
Statins	792 (14.0%)	490 (32.6%)	**<.0001**
C-C Blockers	561 (9.9%)	308 (20.5%)	**<.0001**
ACE/ARB	973 (17.2%)	505 (33.6%)	**<.0001**
Diuretics	1026 (18.1%)	469 (31.2%)	**<.0001**

1. All percentages are column percentages
2. Missing observations are not included in the frequency calculations
3. Comorbid conditions were identified using the Charlson and Elixhauser Indices
4. Concomitant medications were identified using active ingredients and NDC codes
5. Cereb. = Cerebrovascular, Cong. = Congestive, Coron. = Coronary, Hypercholestrol. = Hypercholesterolemia, Arth. = Arthritis

Conditional logistic regression was used to model the sampled data including all

variables in tables 4.3 and 4.4, continuous use and duration of exposure with the exception of

those used for matching in the incident density sampling and age. The unadjusted and adjusted

results are presented in table 4.5.

Table 4.4 Characteristics of the MI cases and matched controls from the base population by exposure

	COX2 (N=1869)		COX1 (N=5296)	
	NMI (N = 1449)	MI (N = 420)	NMI (N = 4212)	MI (N = 1084)
Gender				
Female	766 (52.9%)	246 (58.6%)	2297 (54.5%)	545 (50.3%)
Race				
White	1203 (83.0%)	351 (83.6%)	3462 (82.2%)	872 (80.4%)
Black	53 (3.7%)	17 (4.0%)	346 (8.2%)	80 (7.4%)
Other	193 (13.3%)	52 (12.4%)	404 (9.6%)	132 (12.2%)
Age				
30-<40	452 (31.2%)	69 (16.4%)	1853 (44.0%)	185 (17.1%)
40-<50	501 (34.6%)	132 (31.4%)	1280 (30.4%)	329 (30.4%)
50-<60	406 (28.0%)	171 (40.7%)	951 (22.6%)	487 (44.9%)
60-<65	90 (6.2%)	48 (11.4%)	128 (3.0%)	83 (7.7%)
Region				
Appalachian	983 (67.8%)	290 (69.0%)	2189 (52.0%)	587 (54.2%)
Central	351 (24.2%)	103 (24.5%)	1698 (40.3%)	409 (37.7%)
Delta/Western	115 (7.9%)	27 (6.4%)	325 (7.7%)	88 (8.1%)
Angina	35 (2.4%)	33 (7.9%)	65 (1.5%)	64 (5.9%)
Cereb. Disease	31 (2.1%)	30 (7.1%)	78 (1.9%)	76 (7.0%)
COPD	272 (18.8%)	144 (34.3%)	737 (17.5%)	320 (29.5%)
Cong. Heart Failure	47 (3.2%)	45 (10.7%)	118 (2.8%)	104 (9.6%)
Coagulopathy	12 (0.8%)	15 (3.6%)	26 (0.6%)	20 (1.8%)
Coron. Revascul.	79 (5.5%)	103 (24.5%)	175 (4.2%)	230 (21.2%)
Diabetes	183 (12.6%)	125 (29.8%)	498 (11.8%)	358 (33.0%)
Hypertension	354 (24.4%)	196 (46.7%)	926 (22.0%)	490 (45.2%)
Hypercholestrol.	78 (5.4%)	55 (13.1%)	190 (4.5%)	95 (8.8%)

Osteoarthritis	112 (7.7%)	55 (13.1%)	264 (6.3%)	119 (11.0%)
Previous MI	22 (1.5%)	27 (6.4%)	43 (1.0%)	85 (7.8%)
Rheumatoid Arth.	26 (1.8%)	16 (3.8%)	57 (1.4%)	24 (2.2%)
Anticoagulants	66 (4.6%)	46 (11.0%)	145 (3.4%)	174 (16.1%)
Beta-Blockers	200 (13.8%)	92 (21.9%)	481 (11.4%)	229 (21.1%)
Statins	235 (16.2%)	140 (33.3%)	557 (13.2%)	350 (32.3%)
C-C Blockers	208 (14.4%)	87 (20.7%)	353 (8.4%)	221 (20.4%)
ACE/ARB	299 (20.6%)	128 (30.5%)	674 (16.0%)	377 (34.8%)
Diuretics	315 (21.7%)	133 (31.7%)	711 (16.9%)	336 (31.0%)

1. All percentages are column percentages
2. Missing observations are not included in the frequency calculations
3. Comorbidities were identified using the Charlson and Elixhauser comorbidities
4. Concomitant medications were identified using active ingredients and NDC codes
5. Cereb. = Cerebrovascular, Cong. = Congestive, Coron. = Coronary, Hypercholestrol. = Hypercholesterolemia, Arth. = Arthritis

Table 4.5 Result for the Conditional Logistic Regression model

	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**
COX-2	1.116(0.982, 1.270)	1.138(0.983, 1.318)
COX-1	Ref	Ref

1. Models adjusted for region, angina, cerebrovascular disease, COPD, congestive heart failure, coagulopathy, coronary revascularization, diabetes, hypertension, hypercholesterolemia, osteoarthritis, previous MI, rheumatoid arthritis, anticoagulants, beta-blockers, statins, calcium channel blockers, ACE/ARB, diuretics, continuous use and duration of exposure

Though exposure to COX-2 presented an increased odds for MI when compared to COX-

1 and accounting for the risk factors listed above, this risk was not statistically significant in both

the unadjusted and adjusted models. The adjusted and unadjusted odds ratios with their

associated CIs were 1.116(0.982, 1.270) and 1.138 (0.983, 1.318) respectively

Table 4.6 Unadjusted and adjusted OR Estimates for Covariates

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Region	1.037(0.924, 1.164)	1.161(1.019, 1.324)
Angina	3.395(2.571, 4.483)	0.975(0.686, 1.386)
Cereb. Disease	3.535(2.707, 4.615)	1.575(1.142, 2.173)
COPD	2.109(1.855, 2.398)	1.426(1.228, 1.655)
Cong. Heart Failure	4.418(3.486, 5.598)	1.118(0.839, 1.490)
Coagulopathy	2.593(1.694, 3.967)	1.236(0.721, 2.117)
Coron. Revascul.	5.465(4.589, 6.509)	2.265(1.782, 2.879)
Diabetes	3.596(3.136, 4.125)	2.085(1.774, 2.450)
Hypertension	2.828(2.506, 3.193)	1.322(1.126, 1.552)
Hypercholestrol.	2.235(1.816, 2.749)	0.866(0.676, 1.111)
Osteoarthritis	1.849(1.532, 2.232)	1.139(0.919, 1.411)
Previous MI	6.960(5.098, 9.502)	1.668(1.150, 2.419)
Rheumatoid Arth.	1.456(1.009, 2.101)	1.698(1.124, 2.566)
Anticoagulants	3.600(2.982, 4.347)	1.582(1.233, 2.030)
Beta-Blockers	2.053(1.772, 2.380)	1.035(0.869, 1.234)
Statins	2.947(2.584,3.361)	1.501(1.276, 1.765)
C-C Blockers	2.207(1.898, 2.566)	1.367(1.141, 1.638)
ACE/ARB	2.469(2.174, 2.804)	1.108(0.939, 1.307)
Diuretics	2.114(1.857, 2.405)	1.048(0.890, 1.234)
Continuous Use	1.566(1.396, 1.757)	1.598(1.379, 1.851)

1. Cereb. = Cerebrovascular, Cong. = Congestive, Coron. = Coronary, Hypercholestrol. = Hypercholesterolemia, Arth. = Arthritis

Model fit statistics were evaluated for this model. Additionally, the adjusted model was

evaluated for multi-collinearity of the variables used in the model. The VIFs for all the variables

used were evaluated and found to be small (less than 2) and within the accepted range to not

worry about multi-collinearity (greater than 5 or 10).

Table 4.6 lists the unadjusted and adjusted odds ratios for the covariates used in the model.

Region and continuous use were also evaluated as these were new variables in this study.

Region was significantly associated with risk of MI in the Kentucky Medicaid population exposed

to NSAIDs. Patients in Appalachia had significantly increased odds for MI compared to those in

the other two regions combined and accounting for all risk factors in this study (1.161[1.019,

1.324]). Continuous use was also significantly associated with risk of MI. Patients in the

continuous use group had significantly increased odds for MI compared to those in the sporadic

use group and accounting for all risk factors (1.598 [1.379, 1.851]). Most of the other comorbid

conditions and concomitant medications were also significantly associated with MI risk with the

exception of angina, congestive heart failure, hypercholesterolemia, osteoarthritis, beta-

blockers, ACE inhibitors and diuretics.

Age at initiation was considered an effect modifier to see how the risk for MI varied for

the different age groups and the model above was done for the different age groups. The

unadjusted and adjusted ORs for the models are presented in table 4.7. Exposure to COX-2 was

not significantly different from exposure to COX-1 in risk for MI for all of the age groups with the

exception of the 30-40 year olds where both the unadjusted and adjusted results showed

significant increased risk for MI with exposure to COX-2 compared to COX-1. The adjusted and

unadjusted results with their associated CI for the 30-40 year group were 1.657 (1.201, 2.285)

and 1.600 (1.082, 2.367) respectively. In general, odds for MI with exposure to COX-2 compared

to COX-1 decreased with increase in age.

Table 4.7 Results of the conditional logistic regression by Age group

Age Group	N	Unadjusted OR(95% CI)	Adjusted OR(95% CI)
All	1504	0.982 (0.865, 1.115)	0.975 (0.848, 1.122)
30-<40	254	1.657 (1.201, 2.285)	1.600 (1.082, 2.367)
40-<50	461	1.178 (0.939, 1.477)	1.177 (0.914, 1.516)
50-<60	658	0.736 (0.607, 0.892)	0.729 (0.590, 0.901)
60-<65	131	0.964 (0.642, 1.448)	0.934 (0.569, 1.531)

1. Models adjusted for region, angina, cerebrovascular disease, COPD, congestive heart failure, coagulopathy, coronary revascularization, diabetes, hypertension, hypercholesterolemia, osteoarthritis, previous MI, rheumatoid arthritis, anticoagulants, beta-blockers, statins, calcium channel blockers, ACE/ARB, diuretics, continuous use and duration of exposure

The effect of switching from one class of medication to the other was also considered as 53% of patients in the original cohort switched between medication classes. Switching was considered comparing the two possible switch groups and those who were only on COX-2s to those who were only on COX-1s. Among those who switched there was not a significant difference in risk for MI between the two possible switches (COX-1-2 and COX-2-1) when compared to patients who had only taken COX-1s. The unadjusted and adjusted ORs for those who switched from COX-2-1 compared to those who only took COX-1 were 1.040(0.882, 1.226) and 1.104(0.915, 1.331) respectively. The unadjusted and adjusted ORs for those who switched from COX-1-2 were 0.810(0.696, 0.942) and 0.947(0.800, 1.122) respectively. COX-2 only users presented a marginally significant increased risk for MI when compared to COX-1 only users. The unadjusted and adjusted risks were 1.208 (1.014, 1.430) and 1.221(1.003, 1.485) respectively. Table 4.8 presents the results.

We conducted sensitivity analysis to see the differences in the population that was used for the study and those excluded. The results are presented in table 4.9. The two populations were similar in their demographic information and concomitant medication use with comparable rates. There were some differences in the MI risk factors. This difference might be attributed to the fact that we did not have time to collect this information since it was collected

at baseline. However the MI rates in two groups did not differ significantly. The MI rates in the

included and excluded populations were 1.16% and 1.40% respectively.

Table 4.8 The effect of Switching

Switch	Unadjusted OR(95% CI)	Adjusted OR(95% CI)
COX-2-1	1.040 (0.882, 1.226)	1.104 (0.915, 1.331)
COX-1-2	0.810 (0.696, 0.942)	0.947 (0.800, 1.122)
COX-2 Only	1.208 (1.014, 1.438)	1.221 (1.003, 1.485)
COX-1 Only	1.000	1.000

1. Models adjusted for region, angina, cerebrovascular disease, COPD, congestive heart failure, coagulopathy, coronary revascularization, diabetes, hypertension, hypercholesterolemia, osteoarthritis, previous MI, rheumatoid arthritis, anticoagulants, beta-blockers, statins, calcium channel blockers, ACE/ARB, diuretics, continuous use and duration of exposure

Table 4.9 Characteristics of the Included and Excluded populations

	Included Participants (N = 129277)	Excluded Participants (N = 102836)
Gender		
Female	87111 (67.4%)	70649 (68.7%)
Race		
White	105983 (82.0%)	86054 (83.7%)
Black	12320 (9.5%)	8298 (8.1%)
Other	10974 (8.5%)	8484 (8.3%)
Age		
30-<40	63611 (49.2%)	45437 (44.2%)
40-<50	32616 (25.2%)	29706 (28.9%)
50-<60	24484 (18.9%)	21073 (20.5%)
60-<65	8566 (6.6%)	6620 (6.4%)
Region		
Appalachian	64479 (49.9%)	54214 (52.7%)

Central	52863 (40.9%)	39125 (38.0%)
Delta/Western	11931 (9.2%)	9493 (9.2%)
Angina	2127 (1.6%)	907 (0.9%)
Cereb. Disease	2675 (2.1%)	1104 (1.1%)
COPD	21667 (16.8%)	9099 (8.8%)
Cong. Heart Failure	3349 (2.6%)	1256 (1.2%)
Coagulopathy	1145 (0.9%)	391 (0.4%)
Coron. Revascul.	5700 (4.4%)	2184 (2.1%)
Diabetes	14951 (11.6%)	6469 (6.3%)
Hypertension	28842 (22.3%)	12394 (12.1%)
Hypercholesterol.	5389 (4.2%)	1900 (1.8%)
MI	1504 (1.16%)	1437 (1.40%)
Osteoarthritis	8020 (6.2%)	3798 (3.7%)
Previous MI	1524 (1.2%)	621 (0.6%)
Rheumatoid Arth.	2313 (1.8%)	1163 (1.1%)
Anticoagulants	5326 (4.1%)	3249 (3.2%)
Beta-Blockers	13656 (10.6%)	10595 (10.3%)
Statins	16476 (12.7%)	11762 (11.4%)
C-C Blockers	11591 (9.0%)	10706 (10.4%)
ACE/ARB	21177 (16.4%)	16284 (15.8%)
Diuretics	22657 (17.5%)	19122 (18.6%)

1. All percentages are column percentages
2. Missing observations are not included in the frequency calculations
3. Comorbidities were identified using the Charlson and Elixhauser comorbidities
4. Concomitant medications were identified using active ingredients and NDC codes
5. Cereb. = Cerebrovascular, Cong. = Congestive, Coron. = Coronary, Hypercholestrol. = Hypercholesterolemia, Arth. = Arthritis

Discussion

The data from this nested case-control study showed that the overall odds of MI did not differ significantly between those taking COX-1 and COX-2s in a young cardiovascular disease burdened Medicaid population. This study was designed to investigate the risk of MI in patients taking COX-2 compared to COX-1. This result is consistent with hypotheses which have questioned a class effect between classes of NSAIDs. Antman et al (2005) raised the question about a true class effect in discussing the risks of NSAIDs. Furthermore, several studies have showed that there was no difference in risk of MI when individual COX-2 drugs were compared with their COX-1 counterparts (Back, Yin, & Ingelsson, 2012; Stephen E Kimmel et al., 2005; Mamdani et al., 2003).

However, this study is different because it carried out a class comparison in a younger (30-64 years) post-market population taking into consideration switching patterns and differentiating between continuous and sporadic users. It is important from a clinical perspective as patients need to be monitored for adverse events both during exposure to the drugs and after exposure. Of the 1504 cases, 658(43.75%) has an MI after their last exposure to the drugs. Furthermore, patients have to be considered in the pattern of their adherence which is sometimes different from the pattern of adherence that is followed during clinical trials. This study investigates that by taking into consideration the switching patterns of the patients.

Even though there was not a significant difference in risk for MI with exposure to COX-2 was compared to COX-1 we think there is a clinical difference. We calculated the numbers needed to harm which show that for every 50 patients between the age of 30 and 65 years taking a COX-2 one additional patient will have an MI in the time frame. Given the high prevalence of the use of these drugs in the general population the number of patients needed to harm could have considerable implications for public health.

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This inter-class comparison is important because after the removal of the coxibs from the market the remaining NSAIDs were made to contain a blanket warning about the cardiovascular risk with regards to their use. Up until recently, the FDA is still involved in discussions with researchers as to whether these warnings are still relevant and should still stay on the boxes (Gever, 2014). This study shows that a class warning may be relevant for the class of drugs used within certain age groups. As such continuous monitoring of this risk should be done from time to time to see where we are at.

While there was no overall difference in risk for MI between the NSAID classes, there was a difference in risk when switching patterns were considered and for certain age groups. Age at initiation was investigated as a potential effect modifier. Patients in the 30-40 year old group presented a significantly increased risk for MI when COX-2 users were compared to COX-1 users. The other age groups did not show a significant difference in risk for MI between COX-1s and COX-2s. Patients in the 30-40 year old group presented a 60% increased risk while patients in the 40-50 year old group presented an 18% increased risk for MI with the former been significant and latter not significant.

Switching from one class of medication to the other was considered as more than 53% of the cohort used for this study had switched between a COX-1 and a COX-2 or vice versa. Among those who switched in the two possible groups there was not a difference in odds when the possible switches were compared to those only on COX-1s during their time in the study. However, there was a marginally significant increased risk for MI when COX-2 only users were compared to COX-1 only users. While there was not an overall difference in risk when comparing Cox-2 to COX-1 NSAIDs, this study found a significant difference in risk when COX-2 only users were compared to COX-1 only users. COX-2 only users presented a 22% increase in risk for MI when compared to COX-1 only users.

Switching medications is a common phenomenon in the general population. Patients switch medications for different reasons. One of these reasons is reactions to the medication they are taking. A possible explanation for the increased risk is that those who are switching are already sicker to begin with compared to those who did not. Further research into switching patterns between NSAIDs medications and the possible ramifications is warranted.

Region and continuous use were also evaluated in this study and found to be significantly associated with risk for MI in the Kentucky Medicaid population. Patients in the Appalachian region had significantly increased risk when compared to those in the other two regions. Patients in the continuous use group had significantly increased risk when compared to those in the sporadic use group. This highlights the fact that the disease burden usually seen in Appalachia is also present in the Medicaid population exposed to NSAIDs. The combination of chronic continuous drug use and region could have potential public health implications if not monitored adequately.

The pattern of NSAID prescriptions in this cohort mirrors the rest of the country in the popularity and decline of the coxibs. The decline started around 2002 which corresponds to the time when research studies highlighting the cardiovascular effects of NSAIDs were being published. In the last few years the new users initiation/new prescriptions in Kentucky Medicaid has leveled out.

Understanding the cardiovascular risk associated with NSAID use and the factors associated with said risk is essential given their widespread use in the general population. This is especially important in light of recent health care laws where it is anticipated that more people will be exposed to these medications. An understanding of exposure and risk factors in a younger population will help public health practitioners in preparing for an older population.

Additionally, understanding these factors in a heavily burdened population would enable

practitioners to be able to assess this scenario and come up with more preventative measures.

Furthermore, it should be taken into consideration that the cohort was limited to those

less than 65 years to accommodate for loss of information due to the initiation of Medicare part

D and allow for uniform cohort enrollment over the duration of the study. However, even

amongst this young cohort (30-64 years), there was a heavy use of NSAIDs. This increased use

warranted a need for the study of the MI risk associated with NSAID use in this population.

A major strength of this study is the large sample size in the original cohort. This allowed

for the use of the new user design with a large enough sample left for the nested case-control

analysis. However this could also be a limitation because if not handled adequately there is the

potential for meaningful associations to be lost in the milieu of data. With very large sample

sizes most associations tend to be significant due to the law of large numbers. Secondly, this

study has a long window of available data. This study had twelve years of Kentucky Medicaid

data which allowed for the possibility of longer follow-ups. The average length of follow-up for

this study was 3.9 years which is more than most other studies in this area.   Thirdly, this study

takes into consideration switching between medication classes, which is a very common

phenomenon among patients as shown by the data.

There are several limitations to this study. A secondary database was used to define

both exposure and outcome. This could lead to possible misclassification of both exposure and

outcome due to missing information. There was also the lack of information on OTC medication.

However the effect of this is expected to be low given the comprehensive nature of the

program. Although some of the NSAIDS could be obtained over the counter, the fact that the co-

pay was low was an economic incentive to purchase the drugs through the program. As such, it

is believed that this will not have a significant effect on the results as most patients will want to

maximize the financial benefits of the program. Regardless, some exposure misclassification is expected and this will probably bias the results towards the null effect.

Another limitation of this study is the lack of information on smoking –identified as potentially the largest lifestyle confounder-, obesity and other lifestyle factors. However, some studies have shown that these lifestyle factors were not differentially distributed by exposure group. We used COPD as a proxy for smoking and found no differential distribution between the exposure groups in the controls (27.4% vs 23.9%). Additionally, it has been hypothesized that these lifestyle factors affect medical risk factors such as hypertension and angina which are both accounted for in this study (Ray, Stein, Hall, et al., 2002).

Finally, loss of patients due to use of the new users design could also be a limitation. However, this was done to curb the biases that are inherent in studies of this nature that use prevalent users.

This study did not show a significantly overall increased risk for MI when NSAID COX-2 users are compared to COX-1 users in a nested cohort of the Kentucky Medicaid population. However when the analysis was done for the different age groups there was a significantly increased risk for MI in the 30-40 year old group even though they account for 16.9% of the total number of cases. Further studies are needed to ascertain this relationship especially given the increased risk of cardiovascular diseases in this population and the importance of risk factors that further increase said risk. More research is needed for methods to identify further risk of exposure in populations that are already at increased risk for certain outcomes especially in large databases.

This study also showed that the increased risk from exposure to COX-2 NSAIDs that had been posited in older populations is also present in some younger populations. The youngest age group studied (30-<40 years) presented significantly increased MI risk for COX-2 users

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compared to COX-1 users. This has significant public health consequences especially when taken in light of the present health care landscape and the fact that cardiovascular risk increases with age.   Although this is an observational study, the evidence it presents in combination with the literature highlights the cardiovascular risk of COX-2s especially when compared to COX-1s and investigated in a heavily burdened population. Given the wide spread use of NSAIDs in the general population, extreme caution should continue to be taken especially in those patients who already present risk factors for cardiovascular diseases.

Chapter Five

Comparison of Meloxicam with Celecoxib and Naproxen

Introduction

Meloxicam is one of the NSAIDs that has been less studied compared to its counterparts

because of low use in some populations (Levesque et al., 2005; McGettigan & Henry, 2011). In

the Kentucky Medicaid population there is an increased prescription of the drug especially

following the removal of rofecoxib and valdecoxib from the US market (Figure 3.4). They were

withdrawn in 2004 and 2005 respectively due to adverse events. It is assumed that this

increased prescription indicates increased use in the same population. It is hypothesized that

this drug has replaced the popularity of those withdrawn that used to be more popular. This

phenomenon was also seen in Australia where meloxicam replaced both rofecoxib and celecoxib

after the publicity about their adverse events (Barozzi & Tett, 2007; McGettigan & Henry, 2006).

Meloxicam has been hypothesized to have a dual nature with regards to NSAID classification. In

the literature, it has been classified as both a COX-1 and a COX-2 (Antman et al., 2005; Graham,

2006; Moodley, 2008).

Celecoxib was one of the first coxibs released in the US by Pfizer (Chan et al., 2006;

Kearney et al., 2006). While it is a certified COX-2, its effect on cardiovascular risk varies across

the literature. It was heavily promoted and marketed for its less harmful GI adverse side effect.

It is one of the most widely prescribed NSAIDs in the US (Graham, 2006). Additionally, it has

been on the market longer and has the largest body of evidence of use to be studied compared

to the other COX-2s.

The APC trial was instrumental in uncovering the cardiovascular risk of celecoxib. This

study found that patients exposed to celecoxib had an increased risk for cardiovascular diseases

and was halted prematurely as a result of the findings (S. D. Solomon et al., 2005). This study

found an increase in death from cardiovascular diseases with use of celecoxib when compared

to placebo (hazard ratio=3.4[1.4, 7.8]). MI was one of the cardiovascular diseases studied.

The CLASS study compared celecoxib with other NSAIDs in patients with osteoarthritis

and rheumatoid arthritis and found no difference in cardiovascular events, including MIs

(Bresalier et al., 2005; Cannon et al., 2006; Silverstein et al., 2000). Additionally, this was a

pooled analysis that included results from several trials including the SUCCESS-1 (Singh et al.,

2006). There was no difference in the incidence of cardiovascular events between celecoxib and

other NSAIDs- 0.3% vs 0.3%.

Several other studies in different countries have highlighted the cardiovascular risk of

celecoxib in different comparisons (Graham et al., 2005; Johnsen et al., 2005). However, there

are other studies that have not found an increased risk (McGettigan & Henry, 2006). In a study

of elderly patients, celecoxib was not found to have increased MI risk compared to controls

(Mamdani et al., 2003). In a systematic review of 16 observational studies, a significantly

increased risk for MI was not found with use of celecoxib (Hernandez-Diaz et al., 2006).

After the other coxibs were withdrawn from the market, the FDA allowed celecoxib to

remain on the market and requested its labeling together with 18 other tNSAIDS describe the

increased risk of cardiovascular events (Antman et al., 2005; FDA, 2005). Celecoxib continues to

be widely used despite studies showing an increased risk of MI associated with the drug

(Kearney et al., 2006).

Naproxen is one of the most prescribed NSAIDs worldwide (Patrono & Baigent, 2014). It

has been hypothesized to be a stronger antiplatelet agent when compared to other NSAIDs

(Rahme et al., 2002). It is a certified COX-1 and the safest of all NSAIDs with regards to

cardiovascular safety according to the literature. It has been posited to have a cardio-protective

effect when compared to other NSAIDs (Bombardier et al., 2000; Garcia Rodriguez & Gonzalez-

Perez, 2005; Juni et al., 2004; Topol, 2004). While this is debatable, at the very least it has a consistent reduced risk for cardiovascular adverse events when compared to the other NSAIDs (Hernandez-Diaz et al., 2006).

The VIGOR Trial compared rofecoxib with naproxen in patients with rheumatoid arthritis and found rofecoxib associated with a significant risk of cardiovascular events (0.1% versus 0.4%) (Bombardier et al., 2000). However, it was not confirmed whether this was due to a protective effect of naproxen, an increased risk from rofecoxib or a combination of both.

In comparisons with no NSAID use, naproxen has been found to have a significantly increased risk for MI (Graham et al., 2005). The adjusted odds ratio was 1.14 (1.00-1.30). A cohort study of elderly patients older than 66 years who were dispensed selective NSAIDs, naproxen and other NSAIDs, compared the rates of MI across groups (Mamdani et al., 2003). Members of the cohort were identified from administrative health care data from Ontario, Canada. This study found no significant difference in short-term MI risk for new users of naproxen (RR=1.0[0.6-1.7]) and other NSAIDs (RR=1.2[0.9-1.4]). Several other studies have endorsed the reduced risk of MI with exposure to naproxen (Juni et al., 2004; Kearney et al., 2006; McGettigan & Henry, 2006).

Several researchers have called for further studies to identity which NSAIDs minimize overall burden of adverse cardiovascular risk (Kearney et al., 2006; S. E. Kimmel et al., 2004; Stephen E Kimmel et al., 2005; Moodley, 2008). Cardiovascular disease is a leading risk factor for death worldwide (Alwan, 2011). As a result, continuous monitoring of the NSAID-MI relationship is needed because an agent that potentially affects such an important risk factor poses considerable public health consequences.

This study aims to assess the cardiovascular safety of meloxicam, celecoxib and naproxen, with a 12 year follow-up, by comparing them with no exposure and considering time at risk for MI.

Methods

Study overview

A retrospective cohort study was conducted to examine the risk of MI among younger (30-64 years) Kentucky Medicaid enrollees who were prescribed meloxicam, celecoxib and naproxen between January 1st 2000 and December 31st 2012. Only patients with these three prescriptions were selected for entry into the cohort. Within this cohort we conducted a nested case-control study. The primary objective of this study was to compare MI cases to controls between users of meloxicam, celecoxib and naproxen compared to patients with no exposure.

Data Source

Data for this study included administrative and prescription claims of Kentucky Medicaid linked with hospital discharge information and death dates collected between January 1st 2000 and December 31st 2012. Enrollment and patient demographic information were included in an enrollment file. Prescription files contained dates, drug name, quantity, dose and days of supply. Hospital and outpatient files included admission and discharge dates for hospitalizations, outpatient and emergency department visits. Diagnoses associated with hospitalizations and visits were identified using ICD-9-CM codes.

Subjects included persons aged 30 to 64 years enrolled in Medicaid between 2000 and 2012, had demographic information and had at least one outpatient encounter or filled NSAID prescription. We restricted patients 65 and older from entering the cohort because of the introduction of Medicare Part D in 2006.

Cases of MI were identified based on admission for MI as identified from hospital discharge diagnosis codes (ICD-9-CM 410.xx) in the primary and secondary diagnoses positions which was validated by a hospital stay of more than 2 days but less than 180 days, unless the patient died (Roumie et al 2009, Solomon et al 2004, Petersen et al 1999). Two days was chosen because studies have validated this algorithm for claims data ICD-9-CM diagnosis and found high positive predictive value, specificity and sensitivity (Brouwer et al., 2013; Graham et al., 2005; Metcalfe et al., 2013; Roumie et al., 2009; Wahl et al., 2010) .

Case-control Analysis

Cases were patients aged 30-64 years with a first MI identified in the cohort. We matched four controls to each case by age of diagnosis, gender and race using incident density sampling. All controls were alive and enrolled in Kentucky Medicaid at the time their matched case was diagnosed. We derived an index date for each control, which was the date of MI for their matched case.

A SAS macro by Richardson (2004) with some edits was used for the incidence density sampling. For matching on age at diagnosis, race and gender, estimated probabilities were generated using logistic regression with MI as the outcome and age, race and gender as the inputs. The probabilities were multiplied by a hundred and rounded to the nearest whole number to form categories which were used for matching. This was done as an alternative method to incorporate matching using propensity scores.

Exposure classification

The exposure was the NSAID used before the index date, which was the date of MI for a case and its matched controls. The NSAIDs of interest were meloxicam, celecoxib and naproxen. All drugs were identified by their national drug codes (NDCs) and classified into one of the two types using MULTUM (Multum, 2013). Patients who did not use a drug of interest before their

index date were classified as having no exposure and formed the control group for exposure

classification. Patients were classified based on their first NSAID exposure prior to their index

date which was carried forward to the end of the study. Patients were not re-classified for claim

changes. Additionally, duration of exposure or drug use was considered by summing up the

number of days supply for the prescriptions from entry in the study till the index date. This was

then classified into five categories with a sixth category of no use for those patients who did not

use a drug before the index date. The five duration-of-drug-use categories were 0-30 days, 31-

90 days, 91-180 days, 180-365 days and more than 365days. Finally, patients were classified into

continuous, sporadic and non-drug user groups. Continuous use of NSAIDs was considered

consecutive prescriptions with a gap of less than 30 days between prescriptions prior to the

index date. If there were gaps of more than 30 days the patient was considered a sporadic user

and patients with no drug use prior to the index date were in the non-drug use group.

Covariates

Baseline covariates were measured prior to the index date. The study covariates

included state region of residence, co-morbid conditions and concomitant medication (other

non-NSAID medications).

Demographics

Demographic variables were identified from patient enrollment data. The enrollment

file contained the patient's county of residence. This was used to determine Kentucky residence

as a categorical variable with options: Appalachian, Central and Delta or Western. Figure 3.2

shows the division of the state into the three regions.

Comorbid Conditions

Comorbid conditions were obtained from Medicaid medical files. The ICD-9-CM codes

were used in coding algorithms for the Elixhauser and Charlson comorbidities (Quan et al.,

2005). These algorithms have been validated to identify comorbidities from administrative data.

Claims data have a stipulated number of diagnoses and for Medicaid, there are up to ten

diagnoses reported. The following comorbid conditions were assessed based on the literature:

angina, cerebrovascular disease , COPD , congestive heart failure , coagulopathy , coronary

revascularization , diabetes , hypertension , hypercholesterolemia , osteoarthritis , and

rheumatoid arthritis (Baron et al., 2008; Shau et al., 2012). Table 4.1 lists the comorbid

conditions with their corresponding ICD-9-CM codes.

Concomitant medication

Several methods are used to assess disease severity in the use of claims data. The

use of concomitant medication is one such method and this was identified from the prescription

claims file. The main drug classes considered were statins, beta-blockers, anticoagulants,

calcium channel blockers, ACE inhibitor, ARB and diuretics. These were all considered based on

the literature (Cannon et al., 2006; Graham et al., 2005; Daniel H Solomon et al., 2004). Table

4.2 lists the drug classes and the medications considered in those classes. Concomitant

medications were identified using MULTUM (Multum, 2013).

Statistical Analysis

SAS 9.3 was used for both data manipulation and statistical analyses.

This paper assessed the risk of MI after use of meloxicam, celecoxib (a widely used COX-

2) and naproxen (a widely used COX-1) compared to no exposure using patients in the cohort.

Comparisons were presented of cases and controls in tables using frequencies and

percentages. Tables comparing cases and controls by the three different exposure groups and

no exposure were also presented to see differences by exposure for the demographic and risk

factors considered. Conditional logistic regression for matched case-control studies was used to

evaluate the association between NSAID use and MI taking into consideration confounders and

risk factors not used for matching. Continuous use and categories for duration of exposure were also accounted for. Due to the rareness of the outcome and the incidence density sampling, the estimated ORs approximate the relative risk. Covariates were determined based on the literature and the characterization of the population.

The Institutional Review Boards of the University of Kentucky (IRB Number 12-0999-P2H) and the Kentucky Cabinet for Health and Family Services (CHFS-IRB-DMS-FY13-15) approved this study.

Results

There were 149,917 patients between the ages of 30 and 64 years who were prescribed meloxicam, celecoxib or naproxen during the study period. We identified 2,198 first cases of MI which were matched to 8,792 controls by age at diagnosis, gender and race using incident density sampling.

Table 5.1 shows the characteristics of the MI cases and controls. Cases and controls were well matched on age at diagnosis, race and gender as evidenced by the non-significant p-values showing the lack of differences in the levels of these variables.

The majority of the cases (59.6%) were from the Appalachian region as opposed to 32.6% and 7.9% from the Central and Delta regions respectively. The same pattern was repeated for the controls with 58.8% from the Appalachian region, 33.3% from the Central region and 8.0% from the Delta. There was not a large difference in regional percentages between cases and controls. Even though we did not match on region, the distribution of cases and controls among the three regions was well balanced. This table also highlights the risk factors considered. The proportion of patients with risk factors among cases is significantly higher than controls for all of the comorbid conditions and concomitant medications. And in some cases

there is more than a doubling or more of these proportions. For example, 23.9% of the MI cases

had a coronary revascularization compared to 5.7% of controls.

Table 5.1 Characteristics of the MI cases and matched controls

	NMI (N = 8792)	MI (N = 2198)	P-Value
Gender			**0.9465**
Female	4821 (54.8%)	1207 (54.9%)	
Race			**0.2732**
White	7276 (82.8%)	1831 (83.3%)	
Black	364 (4.1%)	102 (4.6%)	
Other	1152 (13.1%)	265 (12.1%)	
Age			**0.3953**
30-<40	1156 (13.1%)	263 (12.0%)	
40-<50	2597 (29.5%)	675 (30.7%)	
50-<60	3857 (43.9%)	973 (44.3%)	
60-<65	1182 (13.4%)	287 (13.1%)	
Region			**0.7968**
Appalachian	5167 (58.8%)	1309 (59.6%)	
Central	2924 (33.3%)	716 (32.6%)	
Delta/Western	701 (8.0%)	173 (7.9%)	
Angina	206 (2.3%)	163 (7.4%)	**<.0001**
Cereb. Disease	202 (2.3%)	135 (6.1%)	**<.0001**
COPD	1514 (17.2%)	574 (26.1%)	**<.0001**
Cong. Heart Failure	247 (2.8%)	219 (10.0%)	**<.0001**
Coagulopathy	67 (0.8%)	34 (1.5%)	**0.0006**
Coron. Revascul.	503 (5.7%)	525 (23.9%)	**<.0001**
Diabetes	1137 (12.9%)	573 (26.1%)	**<.0001**
Hypertension	2140 (24.3%)	813 (37.0%)	**<.0001**
Hypercholesterol.	447 (5.1%)	208 (9.5%)	**<.0001**
Osteoarthritis	687 (7.8%)	210 (9.6%)	**0.0077**

Rheumatoid Arth.	139 (1.6%)	50 (2.3%)	**0.0252**
Anticoagulants	458 (5.2%)	356 (16.2%)	**<.0001**
Beta-Blockers	1310 (14.9%)	506 (23.0%)	**<.0001**
Statins	1732 (19.7%)	761 (34.6%)	**<.0001**
C-C Blockers	1399 (15.9%)	483 (22.0%)	**<.0001**
ACE/ARB	1973 (22.4%)	740 (33.7%)	**<.0001**
Diuretics	2156 (24.5%)	718 (32.7%)	**<.0001**

1. All percentages are column percentages
2. Missing observations are not included in the frequency calculations
3. Comorbidities were identified using the Charlson and Elixhauser comorbidities
4. Concomitant medications were identified using active ingredients and NDC codes
5. Cereb. = Cerebrovascular, Cong. = Congestive, Coron. = Coronary, Hypercholesterol. = Hypercholesterolemia, Arth. = Arthritis

Table 5.2 shows the characteristics of the cases and controls by the different exposure groups. There were 679 (6.2%) patients exposed to meloxicam prior to their index date, 2786 (24.4%) to celecoxib, 4224 (38.4%) to naproxen and 3301 (30.0%) not exposed to any of the three medications. The four groups almost follow the same pattern for gender, race and region. Most of the patients in the four groups were female with the exception of the no exposure group where females were slightly lower than males (49.7%). The pattern for race was consistent across the groups with whites been the majority composition followed by others and then blacks. Additionally, across all the groups most patients were from the Appalachian region followed by the Central and Delta regions. The distribution for age at diagnosis was also similar for the groups. The modal age group for the four exposure groups was the 50-60 years. There was a steady increase in the percentage of patients as age increased up to the modal age group and then there was a decline.

Cases of MI were similarly distributed among the exposure groups with celecoxib having

a slightly higher rate (22.1%) followed by naproxen (20.3%) and then meloxicam and no

exposure with rates of 18.9% and 17.8% respectively. Meloxicam had higher or comparable

rates than celecoxib for almost all of the comorbid conditions but lower rates for the

concomitant medications considered in this study. Naproxen users had the lowest rates for all

the risk factors studied even when compared to the no exposure group.

Table 5.2 Characteristics of the MI cases and matched controls by Exposure

	MEL (N = 679)	CELE (N = 2786)	NAP (N = 4224)	NO EXP (N= 3301)
Gender				
Female	411 (60.5%)	1637 (58.8%)	2339 (55.4%)	1641 (49.7%)
Race				
White	561 (82.6%)	2360 (84.7%)	3432 (81.3%)	2754 (83.4%)
Black	32 (4.7%)	50 (1.8%)	244 (5.8%)	140 (4.2%)
Other	86 (12.7%)	376 (13.5%)	548 (13.0%)	407 (12.3%)
Age				
30-<40	84 (12.4%)	279 (10.0%)	657 (15.6%)	399 (12.1%)
40-<50	192 (28.3%)	825 (29.6%)	1418 (33.6%)	837 (25.4%)
50-<60	340 (50.1%)	1361 (48.9%)	1827 (43.3%)	1302 (39.4%)
60-<65	63 (9.3%)	321 (11.5%)	322 (7.6%)	763 (23.1%)
Region				
Appalachian	403 (59.4%)	1939 (69.6%)	2313 (54.8%)	1821 (55.2%)
Central	232 (34.2%)	616 (22.1%)	1596 (37.8%)	1196 (36.2%)
Delta/Western	44 (6.5%)	231 (8.3%)	315 (7.5%)	284 (8.6%)
MI	128 (18.9%)	625 (22.4%)	856 (20.3%)	589 (17.8%)
Angina	30 (4.4%)	65 (2.3%)	103 (2.4%)	171 (5.2%)
Cereb. Disease	21 (3.1%)	74 (2.7%)	97 (2.3%)	145 (4.4%)
COPD	142 (20.9%)	474 (17.0%)	751 (17.8%)	721 (21.8%)

Cong. Heart Failure	27 (4.0%)	102 (3.7%)	135 (3.2%)	202 (6.1%)
Coagulopathy	6 (0.9%)	25 (0.9%)	30 (0.7%)	40 (1.2%
Coron. Revascul	56 (8.2%)	192 (6.9%)	245 (5.8%)	535 (16.2%)
Diabetes	120 (17.7%)	392 (14.1%)	608 (14.4%)	590 (17.9%)
Hypertension	208 (30.6%)	577 (20.7%)	982 (23.2%)	1186 (35.9%)
Hypercholesterol.	52 (7.7%)	131 (4.7%)	207 (4.9%)	265 (8.0%)
Osteoarthritis	79 (11.6%)	245 (8.8%)	280 (6.6%)	293 (8.89%)
Rheumatoid Arth.	19 (2.8%)	45 (1.6%)	56 (1.3%)	69 (2.1%)
Anticoagulants	46 (6.8%)	194 (7.0%)	210 (5.0%)	364 (11.0%)
Beta-Blockers	122 (18.0%)	495 (17.8%)	597 (14.1%)	602 (18.2%)
Statins	169 (24.9%)	623 (22.4%)	835 (19.8%)	866 (26.2%)
C-C Blockers	109 (16.1%)	568 (20.4%)	649 (15.4%)	556 (16.8%)
ACE/ARB	173 (25.5%)	697 (25.0%)	943 (22.3%)	900 (27.3%)
Diuretics	190 (28.0%)	819 (29.4%)	1001 (23.7%)	864 (26.2%)

1. All percentages are column percentages
2. Missing observations are not included in the frequency calculations
3. Comorbidities were identified using the Charlson and Elixhauser comorbidities
4. Concomitant medications were identified using active ingredients and NDC codes
5. Mel= Meloxicam, Cele= Celecoxib, Nap= Naproxen, No exp=No Exposure, Cereb. = Cerebrovascular, Cong. = Congestive, Coron. = Coronary, Hypercholestrol. = Hypercholesterolemia, Arth. = Arthritis

Conditional logistic regression was used to model the sampled data including all

variables with the exception of those used for matching in the incident density sampling.

Duration of exposure categories and continuous use were also included in the model. The

unadjusted and adjusted results are presented in table 5.3. Exposure to meloxicam did not

present significantly increased risk for MI when compared to no exposure and accounting for

risk factors. The unadjusted and adjusted odds ratio of MI when meloxicam was compared to no

exposure were 1.10 (0.88, 1.38) and 1.26 (0.98, 1.63) respectively. The unadjusted and adjusted

odds ratio of MI when celecoxib was compared to no exposure were 1.36 (1.19, 1.55) and 1.52

(1.26, 1.82) respectively. The unadjusted and adjusted odds ratio of MI when naproxen was compared to no exposure were 1.20 (1.06, 1.37) and 1.47 (1.24, 1.73) respectively. Celecoxib and naproxen presented significantly increased risks for MI when compared to no exposure for both the adjusted and unadjusted estimates. Meloxicam though presenting an increased risk was not significantly different from no exposure. The estimates for meloxicam's risk for MI are lower than both celecoxib and naproxen in the unadjusted and adjusted scenarios.

Table 5.3 Result for the Conditional Logistic Regression model comparing Meloxicam, Celecoxib and Naproxen to No Exposure

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Meloxicam	1.10 (0.88, 1.38)	1.26 (0.98, 1.63)
Celecoxib	1.36 (1.19, 1.55)	1.52 (1.26, 1.82)
Naproxen	1.20 (1.06, 1.37)	1.47 (1.24, 1.73)
No Exposure	Ref	Ref

1. Models adjusted for region, angina, cerebrovascular disease, COPD, congestive heart failure, coagulopathy, coronary revascularization, diabetes, hypertension, hypercholesterolemia, osteoarthritis, rheumatoid arthritis, anticoagulants, beta-blockers, statins, calcium channel blockers, ACE/ARB, diuretics, continuous use and duration of exposure

We investigated the risk for MI for different categories of duration of use compared to no use. The results are presented in table 5.4. There was a consistent, though not always significant, increased risk for MI across all duration of use groups when compared with no use. The unadjusted results for the first two duration categories were not significant but all the adjusted estimates were significant at the 5% level. In general, the risk increased as usage increased in both the adjusted and unadjusted analysis with the exception of a small dip for the 31-90 days category for the adjusted estimates.

Table 5.4 Duration of Exposure and Risk for MI

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
0-30 days	1.11 (0.96, 1.28)	1.47 (1.24, 1.73)
31-90 days	1.15 (0.98, 1.35)	1.39 (1.14, 1.70)
91-180 days	1.30 (1.09, 1.55)	1.63 (1.32, 2.01)
181-365 days	1.41 (1.18, 1.68)	1.77 (1.43, 2.18)
Greater than 365 days	1.54 (1.32, 1.80)	2.05 (1.68, 2.49)
No Exposure	Ref	Ref

1. Models adjusted for region, angina, cerebrovascular disease, COPD, congestive heart failure, coagulopathy, coronary revascularization, diabetes, hypertension, hypercholesterolemia, osteoarthritis, rheumatoid arthritis, anticoagulants, beta-blockers, statins, calcium channel blockers, ACE/ARB, diuretics, continuous use and duration of exposure

Discussion

The data from this nested case-control study showed that there is a difference in risk of MI when meloxicam, celecoxib and naproxen are compared to no exposure. There is an apparent hierarchy in risk with celecoxib showing the most risk followed by naproxen and then meloxicam. This was an observational study with young patients 30-64 years from a population heavily burdened with cardiovascular diseases. In the unadjusted and adjusted analysis meloxicam was not significantly different from no exposure in risk for MI but celecoxib and naproxen were. However, there is quite considerable overlap between the confidence intervals for the MI risks of meloxicam, celecoxib and naproxen when compared to no exposure.

This study suggests a hierarchy in risk of MI for different NSAIDs. This study puts meloxicam below naproxen and celecoxib in terms of MI risk. In that regard, this study suggests that meloxicam is more likely a COX-1 drug than a COX-2 possibly because of reduced COX-2 selectivity. An understanding of meloxicam is important because in some populations (including the one studied) it has replaced other NSAIDs in terms of prescription popularity following the

bad publicity concerning cardiovascular adverse effects. In chapter three, the popularity of meloxicam to surpass the other NSAIDs was seen. This study is consistent with two other studies that have found no significant increased risk for MI with exposure to meloxicam when compared with non-use (Garcia Rodriguez et al., 2004; Levesque et al., 2005). However, it should be noted that meloxicam had the smallest number of cases of all the exposure groups studied.

This is an observational study and is therefore at risk of bias and possible confounding. However, this analysis accounted for many potential confounders including, comorbidities and concomitant medications and we expect that this may have reduced the impact of any such occurrences. The ability to account for so many potential confounders was made possible by the large sample size of the cohort.

The cases and controls were well matched on race, gender and age of diagnosis, and accounting for total duration on drugs categories and whether the exposure was continuous or sporadic compared to no exposure. The measure of our outcome (whether patients had an MI or not), as recorded by ICD-9-CM codes has been validated by several studies and found to have high sensitivity, specificity and positive predictive value. Dose was not analyzed because this can vary from day to day depending on the levels of pain that the patient is experiencing (Hippisley-Cox & Coupland, 2005). Duration of exposure served as a proxy for cumulative dose. Additionally, rofecoxib was the coxib that has been consistently shown to have a dose response relationship and it is not included in this study. Celecoxib has been identified as having no dose response relationship (Hernandez-Diaz et al, 2006; Levesque et al, 2005).

While this is an observational study and is not conclusive, our results suggest that meloxicam is more of a COX-1 than a COX-2 and adds to the literature in terms of classifying this drug that has been dually classified for a long time. Additionally, this study adds to the body of literature about meloxicam which is very scarce.

Chapter Six

Discussion & Conclusion

This chapter provides a summary and discussion of the conclusions of the other chapters in this dissertation. It also includes individual and public health implications, strengths and limitations and recommendations for future research. There were four other chapters presented in this dissertation apart from the introduction. These include:

1. A literature review of the NSAIDs-MI association

2. An understanding of NSAIDs prescription practices in the Kentucky Medicaid population

3. A comparison of COX-1 and COX-2 exposure in the Kentucky Medicaid population with regards to risk of MI; and

4. A comparison of Meloxicam, Celecoxib and Naproxen to no exposure for risk of MI

Chapter two was a comprehensive literature review that focused on the different studies that have been employed in the study of the NSAIDs-MI association and their findings. The purpose of this review was to provide a framework of the studies that have been employed and the methods used in these different studies. This review showed that the main study types that have been employed were clinical trials, case-control and retrospective cohort studies, nested case-control studies and meta-analysis. There was not a consensus in the direction of the NSAIDs-MI relationship across studies. Some studies found increased risks for MI when certain NSAIDs were compared to others or placebo use, some found a protective effect and some found no effect. These differing results have aided the controversy in the study of this relationship. Additionally, a number of studies have employed electronic databases in the study of the NSAID-MI association. Furthermore, most of the studies have employed older populations with a short term follow-up. There was a shortage of studies that had a long term follow-up and employed a younger cohort of patients. Finally, there was a limited number of studies that had explored the cardiovascular risk of meloxicam.

In chapter three, the purpose was to understand the prescription of NSAIDs in the Kentucky

Medicaid population. Post-market populations tend to be different from clinical trial populations

in terms of adherence to prescription medications. This study found that the trends in the

prescription of NSAIDs have changed over the years with some medications gaining popularity

as their counterparts loose popularity. Specifically, the coxibs have declined in prescription

popularity while other drugs like meloxicam have increased in popularity. This trend has been

identified by other studies (Barozzi & Tett, 2007). Secondly, this study found that patients did

not always adhere to their medication prescriptions. There were gaps between prescriptions. As

a result, these gaps were taken into consideration in the models used. Patients with gaps less

than 30 days were considered to be continuous users based on the distribution of the

prescription gaps. Also, it highlighted the prevalence of switching between medications which

was taken into consideration in the analysis. To our knowledge no other study has done this.

Thirdly, this study found that new use of NSAIDs was gradually increasing in the Kentucky

Medicaid population due to the increase in use of young users. Fourthly, the trends in use of

NSAIDs in the study population mirrored that of the general US population. The increase in the

popularity of the coxibs and their subsequent decrease was seen.

Finally, this study showed the importance of region as a proxy for underlying socio-

economic factors in the Kentucky Medicaid population. The Appalachian region leads the rest of

the state in use of both classes of drugs which might be indicative of the prevalence of chronic

conditions in that region of the state which is known to have high prevalence of diseases as

indicated by low ranks in national health indices (CDC, 2005-2010).

This chapter also described the reasoning for some of the methods in the study. Specifically,

it explains the changes in the Medicare program that led to patients being censored at 65 years.

It also explained the concept of churning in claims data and how that was handled for this study.

For this study, consecutive segments with no gaps were combined and overlapping segments were also combined to form one continuous segment.

Chapter four was a nested case-control study comparing patients exposed to COX-2 drugs to those exposed to COX-1s for their risk of MI. This study found that even though there was an increased risk for MI when COX-2s were compared to COX-1s, this risk was not significant. The unadjusted and adjusted relative risk for MI were 1.116 (0.982, 1.270) and 1.138 (0.983, 1.318) respectively. This sheds some light on the question as to a class effect with regards to risk of MI from exposure to NSAIDs.

 While there was no significant overall class effect, it was found that there was a difference in risk when the same model was considered for the different age at initiation groups. Patients in the 30-40 year old group presented a significant increased risk for MI when COX-2 users were compared to COX-1 users. The unadjusted and adjusted risk estimates were 1.657 (1.201, 2.285) and 1.600 (1.082, 2.367) respectively. This was the only age group that showed a significant increased risk. Additionally, this chapter considered switching between the classes of medication as most of the cohort had switched. It found that patients who were in the two possible switch groups (COX-1-2 and COX-2-1) did not have a significantly increased risk for MI when compared to those who had only taken COX-1s. This may be due to an interaction effect that is not allowing the mechanism to act in favor of one NSAID or the other. However, patients in the COX-2 only group had a marginally significant increased risk for MI when compared with those in the COX-1 only group. The unadjusted and adjusted risks were 1.208 (1.014, 1.438) and 1.221 (1.003, 1.485) respectively. This increased risk is clinically important.

Chapter five was also a nested case-control study comparing patients exposed to meloxicam, a drug for which there is ambiguity in its classification and much less studied, celecoxib, the only coxib presently on the US market, and naproxen to no exposure for risk of

MI. Naproxen is a certified COX-1 and celecoxib is a certified COX-2. It was found that risk for MI for meloxicam was lower than celecoxib and naproxen when the three were compared to no exposure and accounting for risk factors. The unadjusted and adjusted risk for MI when meloxicam was compared to no exposure were 1.10 (0.88, 1.38) and 1.26 (0.98, 1.63) respectively. Two other studies comparing meloxicam with no use have found no significant increased risk for MI (Garcia Rodriguez et al., 2004; Levesque et al., 2005). There is an apparent hierarchy in risk with celecoxib showing the most risk followed by naproxen and then meloxicam. In both the adjusted and unadjusted analysis, meloxicam was not significantly different from no use with regards to risk for MI but celecoxib and naproxen were.

While this is an observational study and not conclusive, it suggests that meloxicam is similar to COX-1s than COX-2s as it is similar to naproxen than celecoxib. Even if it is a COX-2 inhibitor it can be considered a safe one.

There are several biases inherent in this study. These include but are not limited to the large number of patients excluded from the study due to the incorporation of the new users design and the degree of naiveness of the new users. There are potential cases that could have been missed in the patients excluded. However, if they had been included in the study it would make collection of baseline covariates burdensome.

Implications

The results from this study have major implications for patients taking NSAIDs as well as for public health efforts, given the prevalence of NSAID use in the population. The results found that there is not a significant overall class difference between COX-1s and COX-2s. Though not significant the risk is increased. However, there was a significant increased risk for MI for those taking COX-2s when compared to COX-1s in the youngest age group (30-40 years) and when COX-2 only users were compared to COX-1 only users. The increased risk for MI is of clinical

significance; at least for the youngest age at initiation group and the patients who were only

exposed to COX-2s. Clinical consideration should be made by doctors and other health care

providers in the prescription of NSAIDs and subsequent monitoring of said prescriptions;

especially to certain groups of people. This potential increased risk has significant public health

implications especially considering that cardiovascular disease is the leading cause of death

worldwide. Given the seriousness of cardiovascular diseases as a leading cause of death

worldwide, anything that exacerbates that risk is of considerable public health importance. As a

result, the increased risk seen in this study exacerbates the risk for cardiovascular diseases and

thus has considerable public health implications.

Additionally, in this population region which was included in the study as a proxy socio-

economic indicator was significantly associated with MI taking into consideration exposure and

other risk factors. The MI risk with exposure to NSAIDs varies across the state and is higher in

the Appalachian region. From a Kentucky perspective, extra efforts should be put in place to

monitor the NSAIDs-MI association in the Appalachian region which is significantly associated

with risk of MI. Low socio-economic status has been identified as a risk factor for cardiovascular

diseases and the significance of region points to that (Rugg et al., 2008).

In chapter five, both an increased and a significant risk for MI were found when

celecoxib and naproxen were compared to no exposure. However, meloxicam was not

significantly different from no exposure in terms of MI risk in both the unadjusted and adjusted

analysis. There is a slight increased risk for MI but it was not statistically significant. In the

literature, all NSAIDs have been shown to have increased risk for cardiovascular events when

compared to no NSAID use. Since all these medications are still being marketed and used, their

ongoing monitoring with regards to the risk for MI is important. Particularly, increased

monitoring should be implemented for those in the Appalachian region who are chronic users of these drugs.

If ignored there could be potential economic consequences associated with health costs and lost productivity due to illness. Especially considering that the highest risks were seen in the youngest age group in the cohort.

Strength and Limitations

A major strength of this study was the comparatively longer study period with recent data. This study had a recent 12 year window of data. The average length of follow-up for this study was 3.9 years, which allowed for evaluation of both short and long term risks associated with exposure to NSAIDs. Additionally, this study provides an update on the NSAIDs-MI association. To our knowledge this is one of the longest study periods in the study of the NSAID-MI association. The large cohort obtained from an electronic database can be considered a strength as it allows for adequate control of confounding.

Secondly, this study investigated the NSAIDs-MI association in a younger post-market cohort from a population with a high prevalence of cardiovascular diseases. This allowed for the incorporation of patient medication adherence behavior into the analysis of the NSAIDs-MI association. This study takes into consideration patient behavior in determining continuous use and also accounts for switching which is a common phenomenon in the general population. Patients switch between medications for many different reasons.

Thirdly, this study was able to assess the MI risk of meloxicam which has been less studied in the literature. This was made possible because of increased use in this cohort. One of the reasons why it had not been studied much in the past was lack of sufficient use.

A major limitation of this study was the lack of information on important confounders associated with the NSAIDs-MI study. This study lacked information on OTC medication, smoking

and BMI. Some of the medications in this study, like meloxicam and ibuprofen, are available

OTC. The small amount of copay involved with this program serves as an incentive for patients

to maximize its use. As a result, it is hoped OTC medications will not affect the results

significantly. Smoking is important in studies of this kind as it has been identified as a potential

lifestyle confounder. To account for the lack of information on smoking, COPD was used as a

proxy. Additionally, hypertension and angina were accounted for in the analysis and they have

been identified as significantly affected by smoking (Ray, Stein, Hall, et al., 2002). BMI was

another important confounder that was missing in this study. Given its prevalence in the state of

Kentucky it is highly unlikely that it will be differentially distributed between patients who are

exposed to different types of NSAIDs.

However, the lack of information on important confounders is a limitation that is

common to most US studies using electronic databases in this area of research. Their European

counterparts tend to do a better job in capturing such information in electronic databases. For

example, the General Practice Research Database (GPRD) (now known as Clinical Practice

Research Datalink (CPRD)) in the United Kingdom has the most comprehensive longitudinal

patient level data (Lawson, Sherman, & Hollowell, 1998).

Additionally, several studies using administrative databases to assess the NSAIDs-MI

association have employed different methods to account for these limitations (Graham et al.,

2005; S. E. Kimmel et al., 2004) . Graham et al conducted a telephone survey and found the

missing factors were not differentially distributed by NSAID use. In a nation-wide in-home

survey of Medicare beneficiaries using different NSAIDs, they did not differ by BMI and smoking

behavior (Daniel H Solomon et al., 2004). Therefore, in studies which did not measure these

potential confounders, it is likely they were non-differentially distributed across exposure

groups. Their impact on the study is likely to be minimal and biased the study results towards the null or no-effect hypothesis (Ray, Stein, Hall, et al., 2002; Daniel H Solomon et al., 2004).

Another limitation is the use of electronic database to define both exposure and outcome. This could lead to possible misclassification of both. Administrative databases suffer from miscoding in the form of under-coding. This is usually done at the discretion of health care providers for various reasons. Due to the seriousness of the outcome, it is highly unlikely that it will be missed by a health care provider at the hospital due to its seriousness. However, there is still the likelihood of a silent MI as they are higher in patients with cardiovascular risk factors (Valensi, Lorgis, & Cottin, 2011). Additionally, due to the economic incentive of having very low copayments, the misclassification of exposure will be small as most low income patients will utilize a $1 copay program rather than go out and buy medications on their own. Though very much minimized, there is still the possibility of misclassification of both the exposure and the outcome. Additionally, this study only used MI cases that had been admitted to a hospital. Missing cases due to silent MIs and sudden death would have resulted in incomplete case identification. Also, there is the possibility that a patient sustained an MI during hospital admission in which case it will not be included in the admission charts. However, the algorithm used for identification of the outcome has been validated for use in such scenarios. It was found to have high sensitivity, specificity and positive predictive value.

There are several challenges involved in using electronic databases for the purposes of research. Specifically, the conversion of the database from raw files to analysis datasets can be very cumbersome and involve some resources for adequate management. There are several things to watch out for. Adequate secure storage space and data management are fundamentally important to undertake the task to convert raw electronic flat files to analysis datasets, as was undertaken for this study. Last but not least, security is of utmost importance

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given the nature of the dataset. In short one would need sufficient coding experience, and a large and secure enough location to store the dataset.

Future Research

The NSAIDs-MI association should be given major attention by healthcare practitioners especially in light of present health care laws in the US. Continuous monitoring should happen to see the trends in this association and to keep the risk in check. More so as more people have access to health care and there is increased use of this class of drugs.

One possible area of future research is to increase the quality of data contained in publicly available electronic databases. The lack of information on important lifestyle confounders like smoking and BMI is a major limitation on their use. With the implementation of a national health insurance program and projected increased use of the healthcare system, researchers can increase efforts for electronic claims databases to contain such comprehensive patient level information which will make future research involving these variables more meaningful. Additionally, this will allow for comprehensive data patients over the whole age spectrum and the overall effect of these medications can be investigated in the entire population as opposed to different sections depending on what the choice of electronic data source allows.

This dissertation used data from the Kentucky Medicaid database which is comprised mostly of low income patients. Therefore, the results might not be generalizable to the general population exposed to NSAIDs. Future studies investigating NSAIDs exposure should consider a broader population within states and nationally. A national database with comprehensive patient level data will be very instrumental in such research. Collaboration between researchers and clinicians for future studies will greatly aid this effort.

Another area of research is an investigation of the switching patterns between different classes of NSAIDs by patients and the possible ramifications. This study took switching pattern into consideration and found that risk for MI varied by the kind of switch that was done by the patients.

The NSAIDs-MI association should remain an important priority for health care practitioners and public health professionals as continuous monitoring will help reduce the associated risks for MI which in turn will potentially reduce cardiovascular risk as a result of exposure to NSAIDs.

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Teaching Assistant
Mathematics Department, Berea College, Berea, KY, Spring 2004 – Spring 2007

<div align="center">**PUBLICATIONS AND PRESENTATIONS**</div>

Zimmerman, RS, Cupp, PK, Abadi, MH, Donohew, RL, Gray, C,. **Gordon, L**, & Grossl, AB (2014). The effects of framing and fear on ratings and impact of anti-marijuana PSAs. *Substance Use & Misuse, 49(7), 824-35*.

Gordon, L. Using Classification and Regression Trees (CART) in SAS® Enterprise Miner™ for Applications in Public Health, April 2013 Presented at **SAS Global Forum 2013** (Best Contributed Paper).

Gordon, L. The Keouk County CAFO Study: A Complementary Analysis Using Classification Trees in SAS® Enterprise Miner™, October 2012 Presented at **SESUG 2012.**

Gordon, L. Using the SAS® System and SAS® Enterprise Miner™ for Data Mining: A Study of Cancer Survival at the Mayo Clinic, April 2010 Presented at **SAS Global Forum 2010.**

Colon-Rentas, O, **Gordon, L,** Ludguier, DM, Reitsma, P, Sanchez, Song, B. The Impact of the Sleeper Effect and Relapse on the Dynamics of Cigarette Smoking Among Adolescents, August 2006 Presented at **Joint Society for Industrial and Applied Mathematics (SIAM) and Society for Mathematical Biology (SMB) Conference.**

AWARDS

- SAS Student Ambassador 2013
- Teaching/Research Assistantships
- South East SAS User Group (SESUG) 2012 Student Scholarship
- Dean's List
- Pi Mu Epsilon
- Vincit Qui Patitur Honor Society
- Senior Mathematics Award 2007
- Society of Industrial and Applied Mathematics (SIAM) Poster award winner 2006
- 2004 Nelson Mandela Award for service and support

PROFESSIONAL ACTIVITIES

- American Statistical Association