NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND CARDIOVASCULAR TOXICITY: IDENTIFYING EVIDENCE FOR CHANNELLING BIAS IN A POPULATION BASED STUDY

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ABSTRACT

The non-steroidal anti-inflammatory drug (NSAID), diclofenac, has been associated with a high risk for cardiovascular events in observational studies. However, majority of studies identifying this association were conducted when diclofenac was the only NSAID that could be obtained as a combination product (i.e., formulated with misoprostol). As a result, channelling bias might have resulted if prescribers selected the combination of diclofenac/misoprostol (Diclo-Miso) in patients with poor health status frequently than other NSAID products.

The main purpose of this study was to identify evidence for channelling bias in a cohort of patients with coronary heart disease (CHD) prescribed NSAIDs.

Three independent, retrospective analyses were carried out using Saskatchewan's health administrative databases. Patients were eligible if they were hospitalized with CHD event between January 1, 1994 and December 31, 2008. In the first analysis, a time series was conducted to examine trends in the use of NSAIDs following discharge from original hospitalization. In the second analysis, multivariate logistic regression models were constructed to identify characteristics of patients prescribed with Diclo-Miso in comparison to single-entity diclofenac. Finally, a nested case-control study was conducted to examine the risk for recurrent myocardial infarction (MI)/ Unstable Angina (UA) or death among patients prescribed with Diclo-Miso versus single-entity diclofenac. For each case, up to five controls were matched by age and sex.

Between 1994 and 2008, NSAIDs were used by 20.1% (3,099/15,393) of patients in the year following discharge from their original MI/UA hospitalization. Use of these agents was relatively stable until 2004 when the COX-2 selective agent rofecoxib was withdrawn from the market. Following this date (i.e., September 30, 2004), the use of Diclo-Miso and single-entity diclofenac appeared to follow different trends. However, available patient and disease specific factors could not explain diverging utilization trends. Further, no differences were observed in the risk of experiencing recurrent MI/UA between patients receiving Diclo-Miso (OR 0.88, 95% CI 0.72-1.08, p=0.22) or single-entity diclofenac (OR 0.78, 95% CI 0.60-1.00, p=0.06) versus patients not exposed to NSAIDs.

Based on the study's result, channelling bias does not appear to be a major threat to the analysis of cardiovascular toxicity of diclofenac products.

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LIST OF ABBREVIATIONS

NSAIDs - non-steroidal anti-inflammatory drugs

COX- cyclooxygenase

CV - cardiovascular

GI- gastrointestinal

PUD – peptic ulcer disease

PPI- proton pump inhibitor

VIGOR study – VIOXX Gastrointestinal Outcome Research Trial

CVDs – cardiovascular diseases

CHD – coronary heart disease

MI – myocardial infarction

UA – unstable angina

TXA_2 - thromboxane A_2

PGI_2 – prostacyclin

RR – relative risk

HR – hazard ratio

EML – essential medicine lists

GPRD – General Practice Research Databases

ICD – International Classification of Diseases

CCP – Canadian Classification of Diagnostic, Therapeutics & Surgical Procedures

CCI – Canadian Classification of Health Interventions

ACE – angiotensin converting enzymes

ARB – angiotensin receptor blockers

CCB – calcium channel blockers

GIS – Guaranteed Income Supplement

1. INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of medications used to manage pain and inflammation from a variety of causes [1]. Due to their effectiveness, low cost and widespread availability, NSAIDs are one of the most commonly used medications in North America [2,3]. However, over the past 10 years, mounting evidence suggests these agents increase the risk for cardiovascular events [1]. This discovery prompted a withdrawal of several NSAIDs from the market and raised serious questions about the safety of the class as a whole [4].

Many uncertainties remain about the mechanism by which NSAIDs increase cardiovascular risk. Moreover, it is not clear whether all NSAIDs exert similar risks or if certain NSAIDs are especially harmful. One of the biggest barriers to achieving a full understanding of NSAID toxicity is the quality of available evidence. A large number of studies on this issue are observational [5] because randomized trials cannot be ethically conducted to investigate toxicity as a primary endpoint. As a result, it can be difficult to assess the extent to which bias may have contributed to the findings of published reports.

The prescription NSAID diclofenac has been frequently linked with a higher risk for cardiovascular events in observational studies [5]. These findings have been widely accepted because of a plausible theory explaining its increased risk on the basis of greater selectivity for subtype 2 of the cyclooxygenase (COX) enzyme. However, an important source of bias exists in observational studies examining the cardiovascular risk associated with diclofenac. Diclofenac is unique from all other NSAIDs in one very important way; it is the only NSAID that can be prescribed as a combination product that is formulated with a gastric protective agent (until recently). To our knowledge, published observational studies have not distinguished between the single and combination product of diclofenac in their analyses [5, 6].

Research questions:

1) To what extent has the utilization of prescription NSAIDs changed since 2000 among patients discharged after a hospitalization for coronary heart disease (CHD)?
2) Are there differences in the characteristics of patients who are prescribed the combination product of diclofenac and misoprostol (Diclo-Miso) compared to those receiving diclofenac alone or other single entity NSAID products?

3) Is there evidence that patients receiving diclofenac and misoprostol (Diclo-Miso) experience more CHD events compared to those receiving single-entity diclofenac?

2. LITERATURE REVIEW

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of medications used for managing pain and inflammation. In contrast to opioids (e.g. morphine and codeine), NSAIDs have minimal central nervous system effect and can be used without concerns for addiction or dependence. Consequently, NSAIDs are used in a plethora of clinical conditions and musculoskeletal disorders requiring both short and long term relief [1]. Not only have NSAIDs been a crucial tool in pain management, they are among some of the most commonly utilized therapeutic drugs of any type. In the United States, approximately 5% of all physician visits results in a NSAID prescription [2]. Approximately 25% of Canadians are prescribed NSAIDs short term and 4% long term (greater than 6 months), [3] however three NSAIDs (ibuprofen, naproxen and aspirin) are available in Canada without prescription so overall usage is likely much higher. Patients can self-select these products without receiving advice on the potential side effects and necessary precautions required.

The fact that NSAIDs are available over the counter does not mean that they are always safe. As with most therapeutic drugs, NSAIDs can be associated with serious side effects. Numerous pharmaco-epidemiological studies and meta-analyses have documented serious hazards associated with NSAIDs, especially cardiovascular (CV) and gastrointestinal complications. In recent years however, there has been an increase in the awareness of cardiovascular risk associated with NSAIDs especially in patients with established CV disease such as myocardial infarction [1]. In fact two NSAIDs, rofecoxib (Vioxx®) and valdecoxib (Bextra®) have been withdrawn from the market due to their cardiovascular risk. Also, international guidelines are now discouraging utilization of all NSAIDs in patients with an established diagnosis of cardiovascular disease [4]. Moreover, published studies suggest the NSAIDs remaining on the market may pose different levels of cardiovascular toxicity. One of these medications, diclofenac, has frequently been linked to high rates of CV toxicity in observational studies [5, 6].

2.1 PHARMACOLOGY OF NSAIDs

NSAIDs reduce pain and inflammation by inhibiting the biosynthesis of prostaglandins through blockade of the enzyme cyclooxygenase (COX) which exists in two forms: COX 1 and COX 2 (figure 2.1) [7].

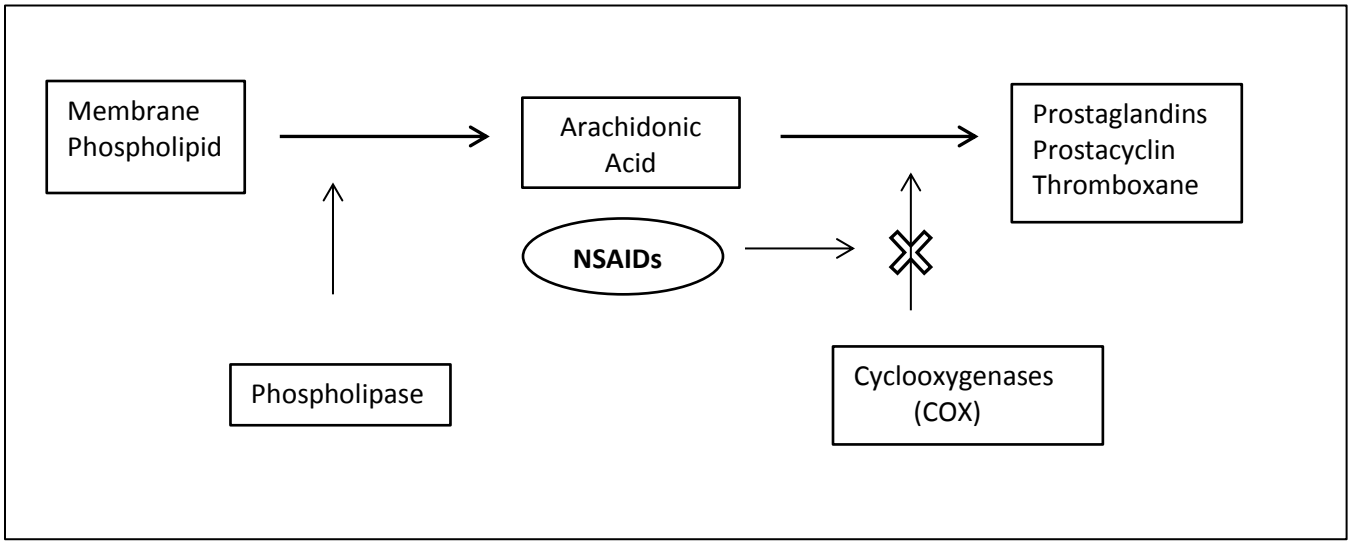


Figure 2.1: NSAIDs mechanism of action [7]

Traditional or non-selective NSAIDs inhibit both COX-1 and COX- 2 enzymes, while the newer, selective NSAIDs inhibit only COX 2 (Table 2.1). Physiologically, COX enzymes differ in their expressions and roles. COX-1 enzyme is constitutively expressed in most tissues in the body. It is involved in the production of prostaglandin which takes part in platelet aggregation, gastric cyto-protection and renal blood flow [8]. On the other hand, the COX-2 enzyme is up-regulated in inflammatory cells upon infection, injury, or activation by inflammatory cytokines. Thus it appears to be primarily responsible for producing prostaglandins that are mediators of inflammation [8]. Reducing prostaglandins through selective inhibition of the COX-2 enzymes results in similar anti-inflammatory, analgesic and anti-pyretic effects achieved with non-selective COX-2 inhibition [7, 8, 9].

Table 2.1: Non-selective and Selective NSAIDs currently available in Canada

Non- selective NSAIDs	***COX-2 Selective NSAIDs***
Aspirin Diclofenac Etodolac Flurbiprofen Ibuprofen Indomethacin Ketoprofen Ketorolac Meloxicam Mefenamic acid Naproxen Nabumetone Oxaprozin Piroxicam Sulindac Tenoxicam Tiaprofenic acid Tolmetin	Celecoxib
Combination non-selective NSAIDs	
Diclofenac and misoprostol (Diclo-Miso)	

Naproxen and esomeprazole	

Therapeutic Product Directorate - product drug database Health Canada) [10]

**Note, this product naproxen and esomeprazole was marketed in 2011 and would not be included in published studies of NSAID toxicity* [11]

2.2 NSAIDs TOXICITY

The inhibition of prostaglandin biosynthesis not only reduces pain and inflammation but it also contributes to toxicity that arises from NSAID administration. Prostaglandins are involved in many biological functions such as the maintenance of electrolyte balance, renal blood flow and vasodilation [8, 9]. The most common toxicities that are associated with prostaglandin inhibition include, gastrointestinal mucosal damage, alterations in renal blood flow and, cardiovascular toxicity [8, 9].

Gastrointestinal (GI) toxicity is the most well-known toxicity associated with NSAID use. NSAIDs can cause asymptomatic gastric mucosal damage (e.g. erosions), peptic ulcers and serious complications such as bleeding and perforation which often require hospitalization and can be life-threatening. NSAID use increases an individual's risk of peptic ulcer disease (PUD) approximately 5 - fold and upper GI bleeding approximately 4 - fold [12]. The overall incidence of these events ranges from 2% to 4%, with serious ulcer complications occurring at a rate of 1-2% of active users. As a result, NSAID toxicity is a major public health issue as over 16,500 deaths related to NSAIDs occur yearly in the United States and approximately 107, 000 hospitalizations are as a result of NSAID - related ulcer complications [13].

Several strategies have emerged to reduce the gastro-intestinal toxicity of NSAIDs. NSAIDs can be co-prescribed with acid suppressing agents such as proton pump inhibitors (PPI) or prostaglandin analogues such as misoprostol [14]. In fact, Pfizer Canada marketed the first combination tablet containing a NSAID (diclofenac) and a gastro-protective agent (misoprostol) under the name Arthrotec® [15]. Also, AstraZeneca Canada released another NSAID combination product in 2011 known as Vimovo® comprising of naproxen and esomeprazole, (a gastric acid suppressant) [11]. Prescribers who are concerned about the GI toxicity of NSAIDs can prescribe Diclo-Miso or Vimovo®, which contain two separate medications. However, Vimovo® is a relatively new product [11] that is not publicly funded in many provinces (including

Saskatchewan) [16], whereas the combination of diclofenac + misoprostol (i.e., Diclo-Miso) has been the only available NSAID/gastro-protective combination for almost two decade [17]. Notably, diclofenac can still be prescribed as a single-entity medication for patients in whom a gastro protective agent is not necessary. Consequently, Diclo-Miso has likely been prescribed to select individuals with poor health or concurrent medical conditions where the risk for adverse health outcomes of NSAIDs use is a concern.

The COX-2 selective inhibitors were originally developed to overcome the risk of GI toxicity associated with traditional non-selective NSAIDs [18]. Indeed, randomized trials have confirmed the risk for GI toxicity is lower for selective than non-selective NSAIDs but not abolished completely [19]. For example, Bombardier and colleagues published a randomized control trial (RCT) in 2000, the VIGOR study, to quantify the risk for GI toxicity between rofecoxib (a selective COX-2 inhibitor) and naproxen (a non-selective COX-2 inhibitor). Among low risk patients enrolled in the study, the rate of GI complications was significantly lower with rofecoxib (0.6 per100 person-years.) versus naproxen (1.4 per100 person-years.) and the relative risk (RR) of patients in the rofecoxib group in comparison to naproxen was 0.5, (95% CI: 0.3-0.6; $P<0.001$) [19].

In contrast to the favorable effects on GI toxicity, rofecoxib appeared to be associated with an increased risk for myocardial infarction and cardiovascular mortality. Although the absolute risk for myocardial infarction and cardiovascular death was low at 0.4% and 0.2% respectively, the relative risk of placebo-treated patients compared to those receiving rofecoxib was significantly lower (RR: 0.2, 95% CI, 0.1 to 0.7) [19] . Subsequent to this study, another clinical trial which was investigating the use of rofecoxib in treating neoplastic polyps in patients with colorectal cancer (Adenomatous Polyp Prevention on Vioxx, APPROVE trial) was published with similar findings. Serious thrombotic events were more common among those receiving rofecoxib compared to placebo [RR: 1.92, 95% CI 1.19-3.11] after 18 months of treatment [20]. Following these findings rofecoxib was withdrawn from the market [21] and the safety of other NSAIDs have since been scrutinized heavily. It is now clear that cardiovascular toxicity is a potential complication of most NSAIDs and is not just restricted to selective COX-2 inhibitors [2, 5, 22].

2.2 NSAIDs AND CARDIOVASCULAR TOXICITY

The cardiovascular toxicity associated with NSAIDs has mainly been associated with myocardial infarction (MI) and stroke [23]. These findings are of great significance because of the highly prevalent use of NSAID medications and because cardiovascular diseases (CVDs) are the number one cause of death globally. In 2008, 17.3 million people died from CVDs representing 30% of all global deaths. Of these, an estimated 7.3 million were attributed to coronary heart disease (CHD) and 6.2 million to stroke. It is predicted that by 2030, an estimated 23.3 million people will die from CVDs, especially from heart disease and stroke [24]. The problem of CVD is equally striking within Canada. It is responsible for 29% of all Canadian deaths and is one of the leading causes of hospitalization, accounting for 16.9% of total all-cause hospitalizations [25].

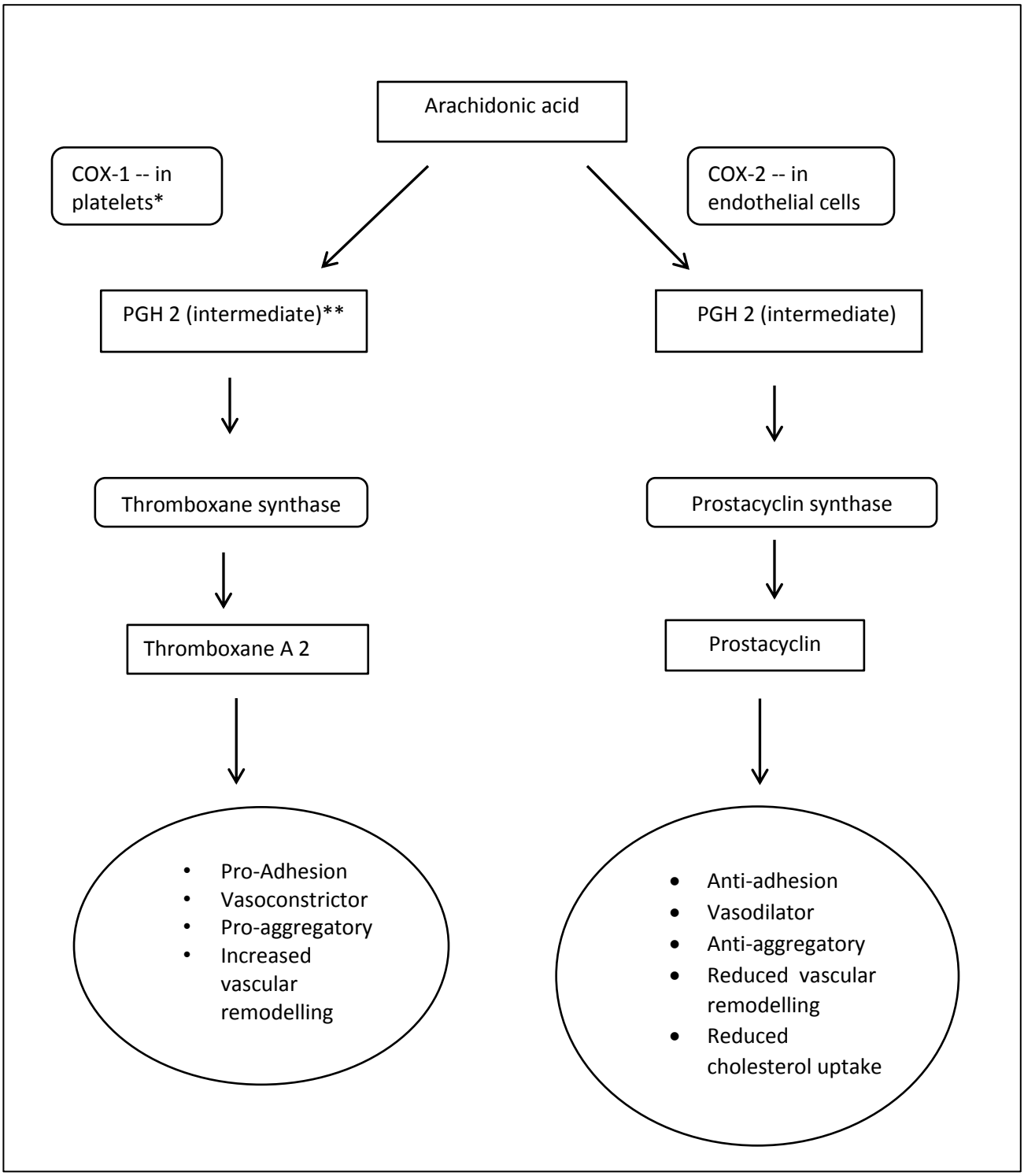
In more than 90% of individuals, the cause of myocardial infarction (MI) is the rupture, erosion or fissuring of an unstable atherosclerotic plaque. These plaques are the hallmark of CHD when they develop in the coronary arteries. After the plaque ruptures, a clot or thrombus is formed at the top of the ruptured plaque triggering a number of events including the release of thromboxane A_2 (TXA_2), platelet adhesion and obstruction of the artery [26]. Ultimately, myocardial tissue can die if the obstructed artery is not opened to re-establish blood flow to the affected area. The exact factors predisposing atherosclerotic lesions to rupture remain uncertain; however the pathogenesis of NSAIDs-induced cardiovascular toxicity may involve these pathways and/or the compensatory changes that follow.

The development of atherosclerosis is very slow. It involves multiple mechanisms including endothelial dysfunction, repression and/or induction of a variety of genes, reduced nitric oxide synthesis, inflammation, oxidation and muscle cell proliferation. Environmental and biological factors also play a role in atherosclerosis development and progression (Table 2.2) [26]. In fact a high number of Canadians exhibit important risk factors such as obesity, hypertension, dyslipidemia and diabetes. NSAIDs use among these types of individuals may contribute to a greater risk for cardiovascular diseases.

Table 2.2: Risk factors for cardiovascular disease [26]

Chronic disease	***Miscellaneous***
Obesity	Age
Hypertension	Male gender
Dyslipidemias	Tobacco usage
Diabetes mellitus	Lack of physical activity

The most commonly proposed mechanism of cardiovascular toxicity resulting from NSAIDs use is an imbalance between the production of prostacyclin (PGI_2), a potent vasodilator, and thromboxane A_2 (TXA_2), a potent vasoconstrictor. COX-1 enzymes play a role in the production of TXA_2 while COX-2 enzymes produce PGI_2 (Figure 2.2) [27]. According to this theory, COX-2 selective NSAIDs preferentially inhibit the production of PGI_2 but not TXA_2 [28]; thus, lower levels of PGI_2 cannot counteract the vasoconstriction caused by TXA_2. Further, lower levels of PGI_2 could be especially problematic among those with CHD, especially if an atherosclerotic plaque has ruptured.



*COX - Cyclo-oxygenase enzyme

**PGH 2 – Prostaglandin H2

Figure 2.2: Vascular effects of prostacyclin and thromboxane A_2 [8, 23]

The COX-2 PGI_2 theory is plausible and it provides a straight-forward reason for why COX-2 inhibitors such as rofecoxib and valdecoxib were removed from the market due to

cardiovascular toxicity. However, this theory does not explain several observations from clinical research [2]. Most importantly, in certain studies, non-selective NSAIDs have exhibited similar or greater risk of CV toxicity compared to COX-2 selective NSAIDs. Diclofenac is an example of a non-selective NSAID that has exhibited high CV risk in numerous studies [2, 5, 22].

There is a wealth of research examining NSAID use and cardiovascular outcomes. As of 2011, approximately fifty one (51) observational studies; 30 case control and 21 cohort studies have been conducted [5]. In addition, 280 randomized controlled trials of NSAIDs versus placebo and 474 randomized trials of a NSAID against another NSAID can be identified [22].

Studies examining the safety of NSAIDs mainly focus on five specific agents (Table 2.3). Among non-selective NSAIDs, naproxen, ibuprofen and diclofenac have been studied most extensively. Similarly, COX-2 inhibitors, rofecoxib and celecoxib have the most available data to evaluate [2, 5]. Currently celecoxib is the only COX-2 selective inhibitor marketed in Canada. [29] Three non-selective agents, naproxen [30] , ibuprofen [31] and aspirin can be purchased without a prescription.

Table 2.3: Most and least studied NSAIDs [2, 5]

Non-selective NSAIDs		COX-2 selective NSAIDs	
Most studied	***Least studied***	***Most studied***	***Least studied***
Aspirin	Indomethacin	Rofecoxib	Etoricoxib
Naproxen	Piroxicam	Celecoxib	Valdecoxib
Ibuprofen	Meloxicam		Lumiricoxib
Diclofenac	Etodolac		

The cardiovascular risk for the COX-2 selective NSAID rofecoxib is very consistent across published studies. According to meta-analysis of randomized controlled trials (RCT) published in 2011, rofecoxib was associated with a significantly high risk of cardiovascular events RR 2.12; 95% CI: 1.26-3.56) [2]. In addition, recent meta-analysis of observational studies also associate rofecoxib with increased cardiovascular risk, (RR 1.45; 95% CI: 1.33-1.59) [5]. The

fact that rofecoxib has a COX-2 selectivity ≥ 90% supports the theory that COX-2 selectivity is a contributing factor to an increased cardiovascular risk [32].

Celecoxib has not been associated with the same cardiovascular risks as rofecoxib, perhaps because the COX-2 selectivity of celecoxib is lower than rofecoxib [32]. However, individual trials examining the risk for cardiovascular toxicity with celecoxib have produced odds ratios as low as 0.84 (95% CI: 0.67-1.04) [34] and as high as 2.53 (95% CI: 1.53-4.18) [35]. In a meta-analysis published in 2011, a pooled rate ratio from RCTs was calculated to be 1.35 (95% CI: 0.71-2.72) for the risk of MI among celecoxib users [2]. A meta-analysis of observational studies (i.e., not RCTs) reported a slightly lower risk ratio but the impact remained statistically significantly, (RR 1.17; 95% CI: 1.08-1.27) [5]. Thus celecoxib may still confer an increased risk of CV events but this has not been confirmed from pooled RCT results. Many unresolved questions remain about the mechanisms of cardiovascular toxicity and the possible differences in risk between different NSAID medications.

The majority of non-selective NSAIDs also appear to exhibit varying degrees of cardiovascular risk [36]. Ibuprofen and diclofenac have frequently been associated with increased risk for cardiovascular toxicity while risks appear lower with naproxen [37]. Among other NSAIDs, estimates of cardiovascular risk are likely unreliable because meta-analyses tend to overestimate risk for drugs with limited studies available [5].

Naproxen appears to be associated with the least cardiovascular harm [2]. Watson and colleagues found a non-significantly lower risk of MI among individuals receiving naproxen compared to no NSAID use (OR 0.57; 95% CI: 0.31 – 1.06) [38]. Also, a meta-analysis of RCTs found no increased risk of myocardial infarction (MI) or death with naproxen use compared to other NSAIDs (RR 0.93; 95% CI: 0.69 – 1.27) [22]. Naproxen's safety may be linked to its ability to suppress platelet COX-1; naproxen exhibits a long half-life (> 12 hrs.) resulting in continued and complete suppression of platelet derived COX-1 enzymes. Indeed, it has shown the ability to inhibit ≥ 95% of COX-1 enzyme activity [32].

Ibuprofen appears to confer a higher cardiovascular risk in comparison to naproxen [39]. However, the cardiovascular risk reported for ibuprofen is sometimes conflicting as there are studies which report low risk ratios and others reporting higher risk. For example Watson and colleagues found that individuals receiving ibuprofen experienced a non-significantly lower risk for myocardial infarction (MI) compared to no NSAID use (OR 0.74, 95% CI: 0.35-1.55) [38]. In

addition, ibuprofen was associated with a low risk of recurrent MI within 7 days of starting therapy (hazard ratio (HR) 1.04; 95% CI: 0.83-1.30) [4]. In contrast, other studies have found that ibuprofen has a high risk for coronary death and MI (rate ratio 1.52; 95% CI: 1.25-1.85) [37]. Ibuprofen exhibits poor inhibition of COX-2 enzymes at low doses (≤ 1200 mg/d), but higher doses (≥ 1200 mg/d) achieve approximately 90% COX-2 inhibition [32]. These contrasting effects may explain some of the variability observed in cardiovascular toxicity with ibuprofen. Overall, the most recent meta-analysis of RCTs suggests a significantly increased risk of cardiovascular events resulting from ibuprofen use (Table 2.4), (OR 2.2; 95%CI: 1.10-4.48) [22].

Table 2.4: Risk ratios for serious cardiovascular events associated with NSAID use calculated from randomized controlled trials (RCT) and observational studies [5, 22]

NSAIDs		Serious Cardiovascular Events, RR (95% CI) vs non-use of NSAIDs	
		Observational Study meta-analysis (outcome)	RCT studies meta-analyses (outcome)
		McGettigan & Henry, 2011 (CV events)	Baigent et al, 2013 (MI or CHD)
Non- selective NSAIDs	Etodolac	1.55 (1.28-1.87)	nr*
	Diclofenac	1.40 (1.27-1.55)	1.70 (1.19-2.41)
	Indomethacin	1.30 (1.19-1.41)	nr
	Ibuprofen	1.18 (1.11-1.25)	2.2 (1.10-4.48)
	Meloxican	1.20 (1.07-1.33)	nr
	Naproxen	1.09 (1.02-1.16)	0.84 (0.52-1.35)
	Piroxicam	1.08 (0.91-1.30)	nr
COX-2 selective NSAIDs	Etoricoxib	2.05 (1.45– 2.88)	nr
	Rofecoxib	1.45 (1.33-1.59)	1.76 (1.31-2.37)

	Celecoxib	1.17 (1.08-1.27	*analysed together

*nr – not reported

Diclofenac, a non-selective COX inhibitor, has frequently been associated with high rates of cardiovascular risk. In fact, a recent meta-analysis of published observational studies suggest the risk associated with diclofenac use compared with either non-use or remote use (RR 1.40 95% CI: 1.27-1.55) is similar to rofecoxib (RR 1.45, 95% CI: 1.33-1.59) and higher than both ibuprofen (RR 1.18, 95% CI: 1.11-1.25) and naproxen (RR 1.09, 95% CI: 1.02-1.16) [5]. Following this meta-analysis, another observational study has been published with a strong association between diclofenac use and the risk for MI (HR 1.57, 95% CI: 1.36-1.83) that was similar to the risks associated with rofecoxib (HR 1.45, 95%CI: 1.18-1.79) [1]. These reports have suggested a consistent and profound cardiovascular risk associated diclofenac use, resulting in call for its removal from essential medicine lists (EML) in the United States, which is a list comprising of medicines that satisfy the priority health care needs of a population [1]. In theory, the increased risk associated with diclofenac is mediated by its relative COX-2 selectivity of > 90% compared to other non-selective NSAIDs [32].

In contrast, there have also been reports of diclofenac's cardiovascular risk being similar to that of other non-selective NSAIDs, ibuprofen specifically. For example, Ray and colleagues who conducted a study using databases from Tennessee Medicaid, Saskatchewan Health and United Kingdom General Practice Research databases (GPRD) on patients who were previously hospitalized for MI, revascularization or unstable angina pectoris, found that the risk of MI with diclofenac was (RR 1.26, 95% CI: 0.86-1.84) compared to ibuprofen's 1.23 (95% CI: 0.86 – 1.75) compared to individuals not exposed to NSAIDs [36]. Roumie et al also reported similar risk of cardiovascular events for diclofenac and ibuprofen after investigating the risk of CV events in the patients between the ages of 34-95 years in the United States. Diclofenac's risk was (HR) 1.01; 95% CI: 0.76 – 1.34 in comparison to ibuprofen 1.02; 95% CI: 0.90 – 1.15 [39]. Finally, a meta-analysis of randomized trials reported a similar risk in diclofenac users (RR 1.41, 95% CI: 1.12-1.78) compared to ibuprofen users (RR 1.44, 95% CI: 0.89- 2.33) [22]. Thus, although reports of diclofenac's toxicity are concerning and consistent with the COX-2 selectivity theory of cardiovascular risk, there remains a substantial amount of evidence that is contradictory.

Moreover, no information is available to explain why certain studies come to such differing conclusions.

2.3 BIAS IN OBSERVATIONAL STUDIES EXAMINING NSAID TOXICITY

Evidence for the cardiovascular risk with NSAIDs is strong [1, 2 5, 22]. However the exact mechanism by which they cause cardiovascular toxicity remains uncertain. Similarly, the extent to which cardiovascular toxicity differs among various NSAID agents (both COX-2 selective and non-selective agents) has yet to be proven. One of the major problems with published studies in this area relates to their study design. Much of the information on cardiovascular toxicity with NSAIDs comes from non-randomized studies rather than randomized controlled trials (RCT).

In non-randomized studies subjects are allocated treatment based on clinical status, risk factors, and patient or physician preference. In contrast, randomized studies assign treatments irrespective of patient factors. This fundamental difference in treatment allocation introduces a high risk of bias into all non-randomized studies [40].

Different types of bias exist; however, channelling bias is of great interest with respect to studies examining CVD toxicity with NSAIDs. "Channelling occurs when drug therapies with similar indications, either self-selected or clinically assigned, are prescribed to groups of patients with varying baseline prognoses" [41]. As a result, non-randomized studies comparing the effects of different drug therapies may contain bias due to the impact of baseline differences between groups. In the case of diclofenac, it is plausible that the combination product, Diclo-Miso, has been traditionally prescribed to individuals with a higher baseline risk for CVD compared to those receiving diclofenac alone or other types of NSAIDs as single entity products. If this higher baseline risk is not accounted for, cohorts of individuals receiving diclofenac may exhibit higher rates of MI and stroke due to the higher baseline risk among patients who have been prescribed Diclo-Miso. Upon examination of studies reporting outcomes with diclofenac users, specifically the more recent meta-analysis of observational studies [1, 5, 22], none have specifically commented on whether combination products were specifically excluded (or stratified) in the outcome analyses.

Evidence for channelling bias can be observed when contrasting the findings meta-analyses of RCTs versus non-randomized (i.e., observational) studies. The estimated risk ratios from observational studies examining diclofenac and ibuprofen were 1.40 versus 1.18

respectively [5]. However, risk ratios estimated from published RCTs were 1.41 versus 1.44 respectively [22]. Notwithstanding the wide confidence intervals and lack of comparative data, reasons for these inconsistent findings have not been found. Channelling bias has not been adequately investigated with respect to the studies examining diclofenac toxicity.

Summary

Research on the cardiovascular safety of NSAIDs has exploded since the first signal of harm in 2000. Despite the wealth of studies examining this issue and the withdrawal of several agents from the marketplace, there still remains significant uncertainty about the mechanism for cardiovascular toxicity and the differences in risk between various agents. Diclofenac has been associated with a negative cardiovascular profile that has been attributed to its COX-2 selectivity. However, studies are conflicting and it appears the issue of channelling bias has never been explored as a potential source of bias in diclofenac studies showing harm.

3. RESEARCH QUESTIONS

1) To what extent has the utilization of prescription NSAIDs changed since 2000 among patients discharged after a hospitalization for coronary heart disease (CHD)?
2) Are there differences in the characteristics of patients who are prescribed the combination product of diclofenac and misoprostol (Diclo-Miso) compared to those receiving diclofenac alone or other single entity NSAID products?
3) Is there evidence that patients receiving diclofenac and misoprostol (Diclo-Miso) experience more CHD events compared to those receiving single-entity diclofenac?

4. METHODOLOGY

4.1 DATA SOURCE

This research study was carried out using an existing health-administrative dataset containing information on a cohort of subjects in Saskatchewan who were discharged following a myocardial infarction (MI) or unstable angina (UA) hospitalization between 1994 and 2008. The government of Saskatchewan provides universal health insurance to residents and maintains health care utilization information dating back to 1975 [42]. These data have been used for high quality research in the areas of pharmaco-epidemiology, health economics, and other health related areas [36, 43, 44, 45, 46].

Health-administrative databases in Saskatchewan contain information on approximately 99% of the population including children, the elderly and women of childbearing age. The provincial drug benefit program covers 90% of provincial residents, enabling drug use and other health care utilization to be studied simultaneously through database linkage. Approximately 10% of residents are excluded from the provincial drug benefit program including registered First Nations, Armed Forces, or federal inmates because they receive benefits from federal programs [47].

The prescription drug database captures data on all medications listed in the provincial formulary that are dispensed to beneficiaries receiving treatment outside of hospitals. For each recorded dispensation, information is available on the patient, drug, prescriber, date dispensed, cost and quantity supplied. The medical services database records physician claims for payment (i.e., fee-for service claims). Physicians that are not compensated on a fee-for-service basis may submit shadow claims (or dummy billings) but it is currently unknown whether these claims are consistently and uniformly submitted by these physicians across the province. Every record in this database contains information on the patient, the date of service, the type of service, the physician, location and diagnosis. The hospital services database includes information for every discharge, transfer, or death occurring while hospitalized as well as day surgeries. Beneficiaries that have out of province hospitalizations are also captured. Hospital diagnoses collected before March 31, 2001 were coded using the *International Classification of Diseases* 9th Revision (ICD-9) and procedures were coded using Canadian Classification of Diagnostic, Therapeutics & Surgical Procedures (CCP). Following April 1, 2001, the majority of hospital diagnoses were

coded with the updated version of the ICD (ICD-10-CA) while the Canadian Classification of Health Interventions (CCI) algorithm used for procedures [47].

The vital statistics database maintains records for every birth, death, stillbirth and marriage, while the population registry contains information on all dates of initiation and termination of provincial health benefits. The population registry is updated on a daily basis [42, 47].

Beneficiary status, health services, and prescription drug use recorded in these databases can be linked using a unique health service number (HSN) given to eligible residents [47].

4.2 OBJECTIVE 1 METHOD

Objective 1: Describe changes in utilization of prescription NSAIDs between 1994 and 2008 among patients discharged after a hospitalization of coronary heart disease (CHD).

Hypothesis:

For this objective, data was presented descriptively and no formal hypothesis testing was carried out.

Study design:

A retrospective time series analysis examining NSAID use among individuals discharged following a hospitalization from coronary heart disease (CHD) between 1994 and 2008.

Study population:

Subjects were eligible for study if they satisfied the following criteria: a) were discharged from hospital following a first coronary heart disease (CHD) event between January 1, 1994 and December 31, 2007 (using a 5-year washout period); b) maintained continuous beneficiary status for at least five years preceding, and one year following the initial hospitalization. CHD event was defined as a myocardial infarction (MI) or unstable angina (UA) listed in the primary or most responsible position of the hospital discharge abstract [Table 4.1].

Table 4.1: Diagnostic codes used to identify patients discharged for myocardial infarction (MI) or unstable angina (UA) [48, 49]

ICD codes	***Disease diagnosis***	
	Myocardial infarction (MI)	Unstable angina (UA)
ICD-9	410	411
ICD-10-CA	121-122	120.0 124.0 & 124.9

**ICD- International Classification of Diseases*

Subjects satisfying these inclusion criteria were followed for a period of one-year following hospital discharge from the original CHD event. The primary endpoint was a dispensation for a prescription NSAID during this one year period. To evaluate trends in the use of NSAIDs over time, subjects were stratified into quarterly intervals according to their original discharge date. The use of NSAIDs was also examined for non-selective and COX-2 selective NSAIDs independently in addition to examining all NSAIDs combined. To facilitate comparisons over time, rates were standardized by age and sex using the 2001 Saskatchewan population as the reference.

Age and sex standardization was carried out using the following procedure. First, specific rates of the endpoint in each year were calculated within pre-defined age categories and further divided by sex, relative to the total number of eligible patients in the study sample [50]. Next, weighting for each category above were derived from the reference population defined in the first quarter (i.e., January to April) of 2001. The age and sex adjusted rate was defined by the sum of each standardized category for a given interval.

The overall study period (i.e., 1994 to 2007) was divided into three distinct periods. Period one begins on January 1st, 1994 and ends on September 30st 1998. Period one is unique because only non-selective NSAIDs were available on Saskatchewan's drug benefit list during this time. Period two begins on October 1st, 1998 and ends on September 30st, 2004. During period two, COX-2 inhibitors were newly available on the provincial benefit list in addition to non-selective NSAIDs. In period three (October 1st, 2004 to December 31st, 2007), rofecoxib

had been withdrawn from the market suggesting the risks of NSAID use were more widely appreciated [4].

4.3 OBJECTIVE 2 METHOD

OBJECTIVE #2: Identify patient characteristics associated with Diclo-Miso use (diclofenac and misoprostol) compared to the use of diclofenac alone or other single entity NSAID products.

Preamble:

Published observational studies examining cardiovascular toxicity of NSAIDs do not distinguish between individuals receiving Diclo-Miso (diclofenac plus misoprostol) versus single-entity diclofenac.

Hypothesis:

Patients prescribed the combination product Diclo-Miso exhibit higher levels of morbidity, arthritis and advanced age compared to patients receiving diclofenac alone or other single-entity NSAIDs.

Study design:

Retrospective cohort study

Study population:

Patients satisfying the inclusion criteria in objective 1 (i.e., MI or UA diagnosis at hospital discharge) were restricted to individuals who received a prescription NSAID within one year following hospital discharge. All eligible prescription NSAIDs are listed in Table 4.2.

Table 4.2: Eligible prescription NSAID in Saskatchewan between 1994-2007 categorized based on single and combination product NSAID

Single entity NSAIDs		***Combination NSAID***
Non-selective	***Selective***	
Diclofenac	Celecoxib	Diclofenac/misoprostol (Diclo-Miso)
Diflunisal	Rofecoxib	
Etodolac	Valdecoxib	
Fenoprofen		
Floctafenine		
Flubiprofen		
Ibuprofen		
Indomethacin		
Ketoprofen		
Mefanamic acid		
Meloxicam		
Nabumetone		
Naproxen		
Phenylbutazone		
Prioxicam		
Sulindac		
Tiaprofenic acid		
Tolmetin		
zomepirac		

Data analysis:

Baseline characteristics of excluded patients (i.e., no NSAID use) were compared with those of patients receiving NSAIDs. Independent sample t-tests were used for continuous variables and chi-square for discrete variables. Among patients with at least one NSAID dispensation in the one-year follow up period, multivariate logistic regression models were built

to identify differences in patient characteristics between patients receiving Diclo-Miso compared to single-entity NSAIDs.

Numerous demographic, clinical, drug, socioeconomic, and health system factors were tested. Demographic variables consisted of age, sex, and rural/urban residence. The Ministry of Health supplied an indicator of urban/rural residence based on Statistics Canada's definition of an "urban agglomeration". Specifically, individuals with postal codes occurring in an area defined as "urban" or "urban agglomeration" were considered to live in an urban setting. General comorbidity was assessed using the Deyo comorbidity Score and Chronic Disease Score. The Deyo/Charlson comorbidity was calculated at the index date and based on any hospital separations in the year before index (i.e., a discharge date within the 365 days before the index date) [51, 52]. The Chronic Disease Score is based on the number of prescriptions dispensed in the year prior to the index date [53].

Specific comorbidity was assessed using diagnoses for rheumatoid arthritis. It was hypothesized that specific arthritis diagnoses would be more commonly documented among individuals receiving the Diclo/Miso combination product because it may be perceived as safer for those receiving long-term therapy. Similarly, any diagnoses for gastrointestinal comorbidities or use of gastro-protective medications were identified separately because it was anticipated that patients receiving Diclo-Miso would have higher rates of gastrointestinal problems compared to those receiving single-entity NSAIDs (Table 4.3).

Also, the number of unique cardiovascular medication classes filled in the one year prior was served as a measure of cardiovascular morbidity, including angiotensin converting enzymes (ACE) inhibitors, angiotensin receptor blockers (ARB), beta-blockers, statins, calcium channel blockers (CCB), antiplatelets, anticoagulants, anti-arrhythmic agents, and other anti-hypertensive agents. Socioeconomic status was measured with income security benefit which is based on whether a patient receives benefits through the provincial Government of Saskatchewan Ministry of Social Services or the federal Government of Canada at index-date. Seniors and family based benefit are the two types of income security benefit utilized in this study. Seniors based benefit is characterized by additional assistance provided from the Government of Saskatchewan to senior citizens with little or no income excluding Guaranteed Income Supplement (GIS) and Federal Old Age security pension. On the other hand, family based benefit is dependent on The Government of Saskatchewan providing low-income families with children supplemental

financial assistance for necessities such as food and shelter [54]. Health services utilization was assessed with the number of physician visits in the year prior to the index date. Finally year of discharge was tested as a possible predictor of Diclo-Miso use (Table 4.3). It was anticipated that the year of discharge would interact with other variables so all first order interactions with year were investigated in the model.

Table 4.3: Potential risk factors and definition

Potential risk factor	***Variable type***	***Description***
Gender	Binary	Male Female
Age	Continuous*	
Rural/urban residence	Binary	Rural Urban
Deyo comorbidity score	Continuous*	
Chronic disease score	Continuous*	
Presence or absence of rheumatoid arthritis (RA)	Binary	Any diagnosis from hospital file or physician services within one year prior to initial hospitalization ICD 9 code for RA, 714. 0 or equivalent ICD-10/ ICD-10-CA – M05-M06 [55]
Presence or absence of GI bleed gastrointestinal, duodenal, peptic or gastro-jejunal ulcer	Binary	Any diagnosis within one year prior to initial hospitalization Gastric ulcer with hemorrhage ICD-9 code 531.0, 531.2, 531.4, 531.6 ICD-10 code K25.0, K25.2, K25.4, K25.6

		Gastrointestinal bleed (GI) ICD-9 code 578.X ICD-10 code K92.2 Duodenal ulcer with hemorrhage ICD-9 code 532.0, 532.2, 532.4, 532.6 ICD-10 code K26.0, K26.2, K26.4, K26.6 Peptic ulcer with hemorrhage ICD-9 code 533.0, 533.2, 533.4, 533.6 ICD-10 code K27.0, K27.2, K27.4, K27.6 Gastro-jejunal ulcer ICD-9 code 534.0, 534.2, 534.4, 534.6 ICD-10 code K28.0, K28.2, K28.4, K28.6
Gastro-protective medications	Binary	Prior use of PPI*, H2-RA** or misoprostol within one year prior to initial hospitalization
Cardiovascular pill burden	Binary	One point given for any class of cardiovascular medication dispensed at least once. Class of cardiovascular medication: ACE*** inhibitors, ARBs***, beta-blockers, statins, CCBs***, antiplatelet, anticoagulants, anti-arrhythmic agents, other anti-

		hypertensive agents
Year of hospital discharge	Continuous*	
Socioeconomic	Binary	Income security benefit defined as either senior or family based benefit
Physician visits	Continuous*	The number of physician visits within one year prior to initial hospitalization

*****Definition to be determined based on observation in data set

*PPI – proton pump inhibitors;

**H2-RA- histamine receptor antagonists

**ACE- angiotensin converting enzymes; ARBs – angiotensin receptor blockers; CCBs- calcium channel blockers

For all independent variables listed in table 4.3, contingency tables were constructed with the outcome of receiving Diclo-Miso (y=0, 1) described within *k* levels of the independent variables for nominal, ordinal and continuous variables. Each independent variable underwent univariate analysis against the primary endpoint of Diclo-Miso use. Variables that had a p-value of less than 0.15 became candidates for the multi-variable model. These eligible variables were added stepwise into the full model and were retained if they have a p-value of < 0.15.

For continuous variables, the following steps were taken to ensure their optimal form in the final model: A) obtain quartiles of the variable. B) Create a 4 level categorical variable using 3 cut-points based on the quartiles. C) Fit the multivariable model and replace the continuous variable (age) with the 4-level categorical variable. D) Plot the estimated coefficients (β) versus the midpoints of the groups, and plot a coefficient equal to zero at the midpoint of the first quartile. The 4 plotted points were connected to help in the interpretation process. The plot was visually inspected to ensure the relationship appears parametric [56]. All first order interactions were tested. Finally, both crude (model without potential predictors being adjusted for) and adjusted models were presented and interpretations made.

In sensitivity analyses, all other single entity NSAIDs users were tested against and used as reference to Diclo-Miso users.

4.4 OBJECTIVE 3 METHOD

OBJECTIVE #3: Determine if the risk of coronary heart disease (CHD) hospitalization is higher among patients receiving Diclo-Miso compared to those receiving single-entity diclofenac.

Preamble:

Multiple observational studies have found significant associations between diclofenac and adverse cardiovascular outcomes despite statistical adjustment for measured confounders. However, it is possible that unmeasured confounders resulting from channelling bias may have contributed to these higher rates of cardiovascular events.

Hypothesis:

Despite controlling for measured confounders available in the administrative dataset, Diclo-Miso use would be associated with recurrent coronary heart disease or death compared to single-entity diclofenac use. We assumed that all excess risk associated with Diclo-Miso was a result of residual bias (i.e., channelling bias) because misoprostol is not known to have cardiovascular toxicity.

Study design:

A nested case-control design was used to investigate the association between re-current MI/UA or death and type of NSAIDs received.

Study population:

Subjects were eligible for inclusion if they satisfied the following criteria: a) were discharged from hospital following a first coronary heart disease (CHD) event between January 1, 1994 and December 31, 2008 (using a 5-year washout period); b) were continuous health beneficiaries for at least 5 years preceding the initial hospitalization; and c) survived without recurrent hospitalization for at least 3 months following discharge. Health and drug-utilization data was collected for a period up to 15 years following the initial CHD discharge date. Subjects were followed until the earliest occurrence of recurrent myocardial infarction (MI), unstable angina (UA) or death. Subjects not reaching this study endpoint were censored upon termination of health benefits or reaching the end of the study period (December 31, 2008).

All patients experiencing a recurrent MI /UA or death between 1994 and 2008 were defined as cases. Definition of the MI or UA outcome was consistent with the inclusion criteria

(Table 4.4). The date of this event was called the CASE-INDEX date. Each case was matched to 5 control patients randomly selected using incident density sampling. Controls were matched on age (+/- 5 years), sex, and time since index event (i.e., initial MI/UA event). [43] Incident density sampling was used to identify controls; using this approach, controls can include individuals who experience an event (i.e., a case) at a future time [43]. All control subjects were assigned the same CASE-INDEX date as their corresponding case.

Exposure

Exposure to prescription NSAIDs were compared during the 3 months preceding the CASE-INDEX date. All study subjects were categorized into one of seven mutually exclusive exposure categories on the basis of their dispensation records during this period: Diclo-Miso use; single-entity diclofenac use; naproxen; indomethacin; other non-selective NSAID use; COX-2 inhibitors use; multiple NSAID use; no NSAID use (reference).

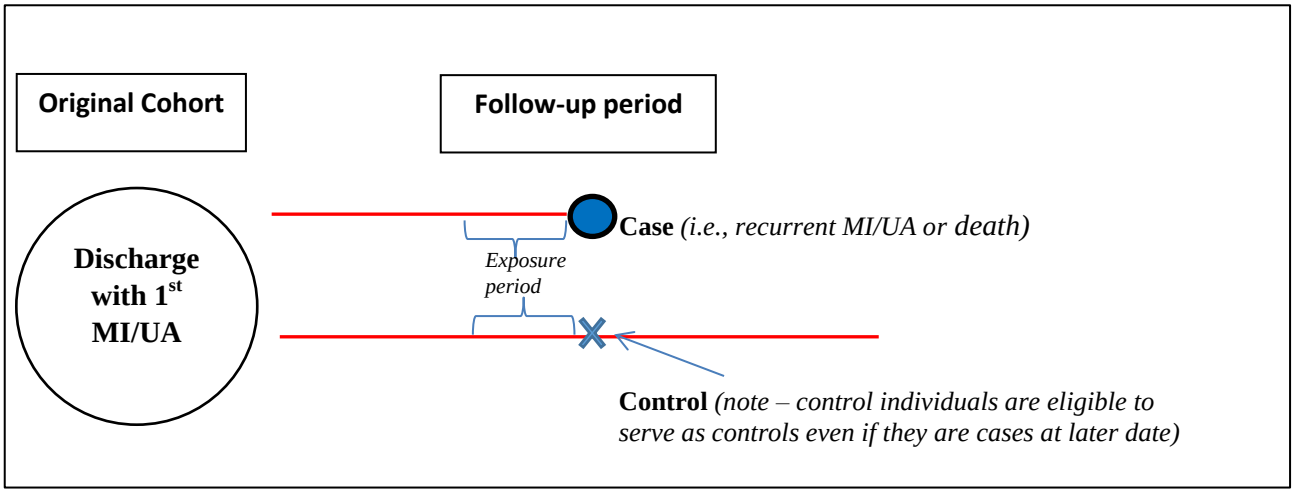


Figure 4.1: Explanation of case-control method

Data analysis:

Differences in exposure to NSAIDs prior to the CASE-INDEX date were analyzed descriptively and the odds of experiencing a recurrent MI based on specific NSAID exposures was estimated using conditional logistic regression models. Models were constructed using the same procedure outlined in objective #2; however, the specific variables to be tested in the models were slightly different because they were selected to minimize confounding for comparing the risk of MI/UA or death between NSAID groups (Table 4.4).

Table 4.4: Potential risk factors and description

Potential risk factor	***Variable type***	***Description***
Rural/ urban residence	Binary	Rural Urban
Presence or absence Hypertension	Binary	A diagnosis within two years prior to index event. One inpatient hospital separation OR two or more physician claims within two years, selected from the first diagnosis field with ICD-9 or ICD-9-CM code of 401-405 or equivalent ICD-10-CA code of I10-I13 and I15 [57]
Presence or absence of diabetes	Binary	A diagnosis within two years prior to index event. Two or more physician claims OR one inpatient hospital separation within two years, selected from the first diagnosis field with ICD-9 or ICD-9-CM code of 250 or equivalent ICD-10-CA code of E10 to E14 [57]
Modified rheumatoid arthritis	Binary	A diagnosis within two years prior to index event. 1 hospitalization RA code ever OR 3 physician diagnosis code (claims) within a 2 year period (ICD 9 code - 714. 0 or equivalent ICD-10/ ICD-10-CA – M05-M06) [55]
Hospitalizations	Continuous*	The number of hospitalizations within one year prior to initial CHD

		hospitalization
Deyo comorbidity score	Continuous*	
Chronic disease score	Continuous*	
Specific Cardiovascular medication use ACE/ ARBs Beta- blockers Statins Nitroglycerin Clopidorgrel	Binary variable for each medication	Prescription filled in exposure period, 3 months prior to CASE-INDEX date
Cardiovascular pill burden	Continuous*	One point given for each class of medication dispensed at least once Class of cardiovascular medication: ACE **inhibitors, ARBs**, beta-blockers, statins, CCBs**, antiplatelet, anticoagulants, anti-arrhythmic agents, other anti-hypertensive agents
Socioeconomic	Categorical	Income security benefit defined as either senior or family based benefit
Physician visits	Continuous*	The number of physician visits within one year prior to initial CHD hospitalization

*****Definition to be determined based on observations in data set

**ACE- angiotensin converting enzymes; ARBs – angiotensin receptor blockers; CCB= calcium channel blockers

Although a case-control design would not allow for estimates of risk associated with matched variables (age, sex, and time of follow-up), the use of these variables is intended to reduce confounding in the primary comparison of NSAID exposure; thus, it is not necessary to quantify their risk in order to meet the primary objective. The choice of a case-control design was based on the assumption that NSAID use is commonly intermittent and not restricted to a single agent. Thus, a case-control design examined the specific NSAID exposure immediately

preceding the recurrent MI or UA hospitalization. This analytic approach is consistent with the theoretical model of NSAID cardiovascular toxicity where local vaso-dilatory and anticoagulant/antiplatelet mechanisms are inhibited.

5. RESULTS

5.1 COHORT DESCRIPTION

The original cohort provided by the Saskatchewan Ministry of Health contained records for 42,360 patients who were discharged from hospital with a coronary heart disease (CHD) event and /or a coronary revascularization procedure between 1994 and 2008. A total of 21,038 patients were excluded because they received a revascularization procedure in the absence of a diagnosis of MI or UA. The remaining 21,322 patients were discharged with a diagnosis of myocardial infarction (MI) or unstable angina (UA). From those MI or UA patients, 19,717 patients made up the "Base Cohort" containing patients with a first hospital discharge diagnosis of myocardial infarction (MI) or unstable angina (UA) and continuous beneficiary coverage for 5 years prior to first MI/UA [Figure 5.1].

Myocardial infarction was identified in 64.7% (12,774 /19,717) of the discharged population, and 64.4% (8,230/12,774) were males. The average age was 68 years old (range 18-87, SD ±11.15) and the majority were 65 years or older (69.7% or 13,761/19,717). Also more than half of the patients in the base cohort resided in rural areas (52%, 10,267/19,717) and 31.1% (6,127/19,717) were receiving seniors based benefit.

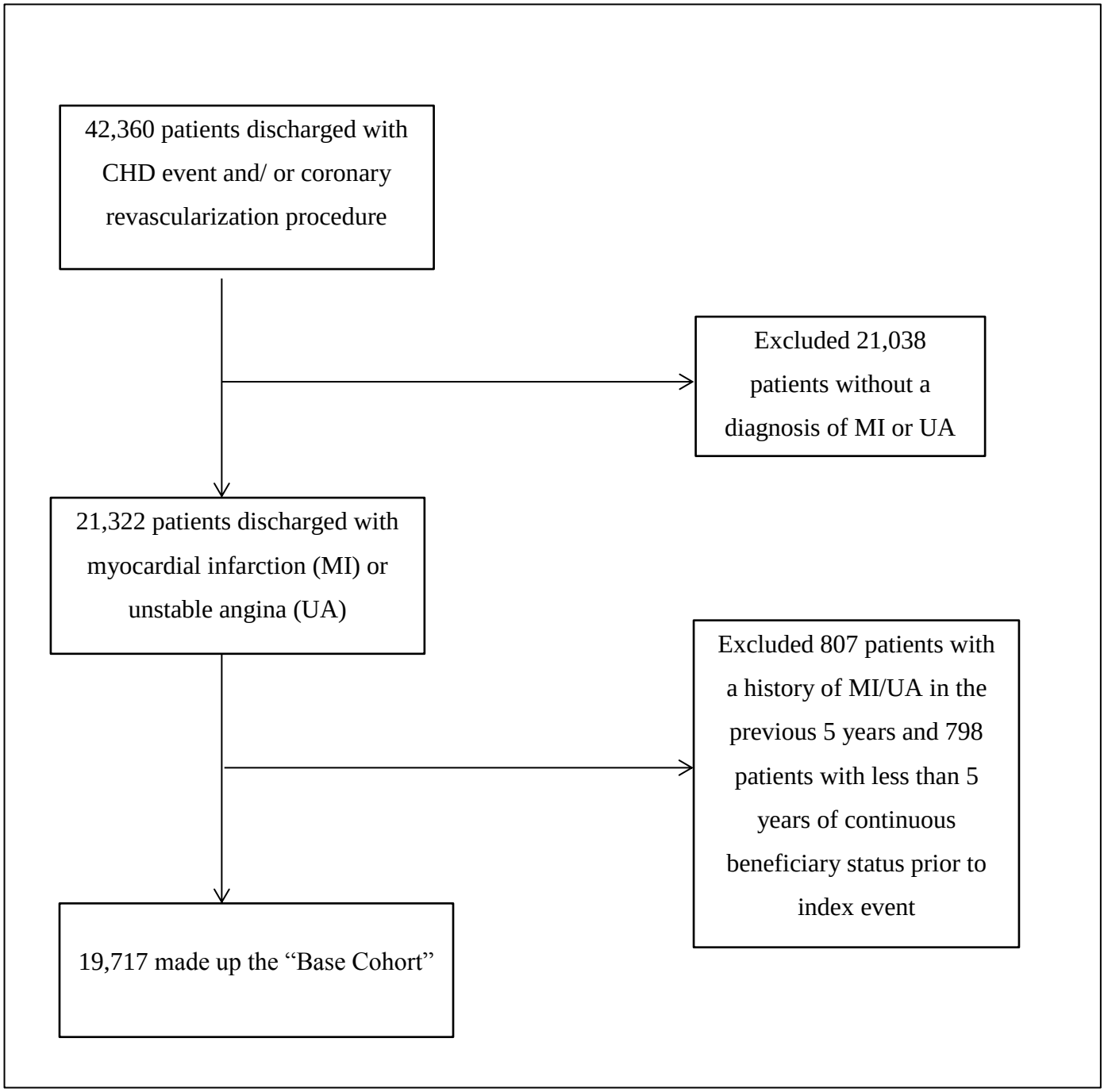


Figure 5.1: Flow diagram illustrating patients in "base cohort"

5.2 OBJECTIVE 1 RESULTS

<u>Objective 1</u>: Describe changes in utilization of prescription NSAIDs between 1994 and 2008 among patients discharged after a hospitalization for coronary heart disease (CHD)

From the 19,717 patients experiencing their first MI or UA, 15,393 of those beneficiaries could be followed for at least one year after discharge [Figure 5.2]. The mean age of this cohort was 67 years old (SD ± 11.33), 62% (9,563/15,393) were male and 61.3 % (9,442/15,393) received a diagnosis of MI on the index hospitalization.

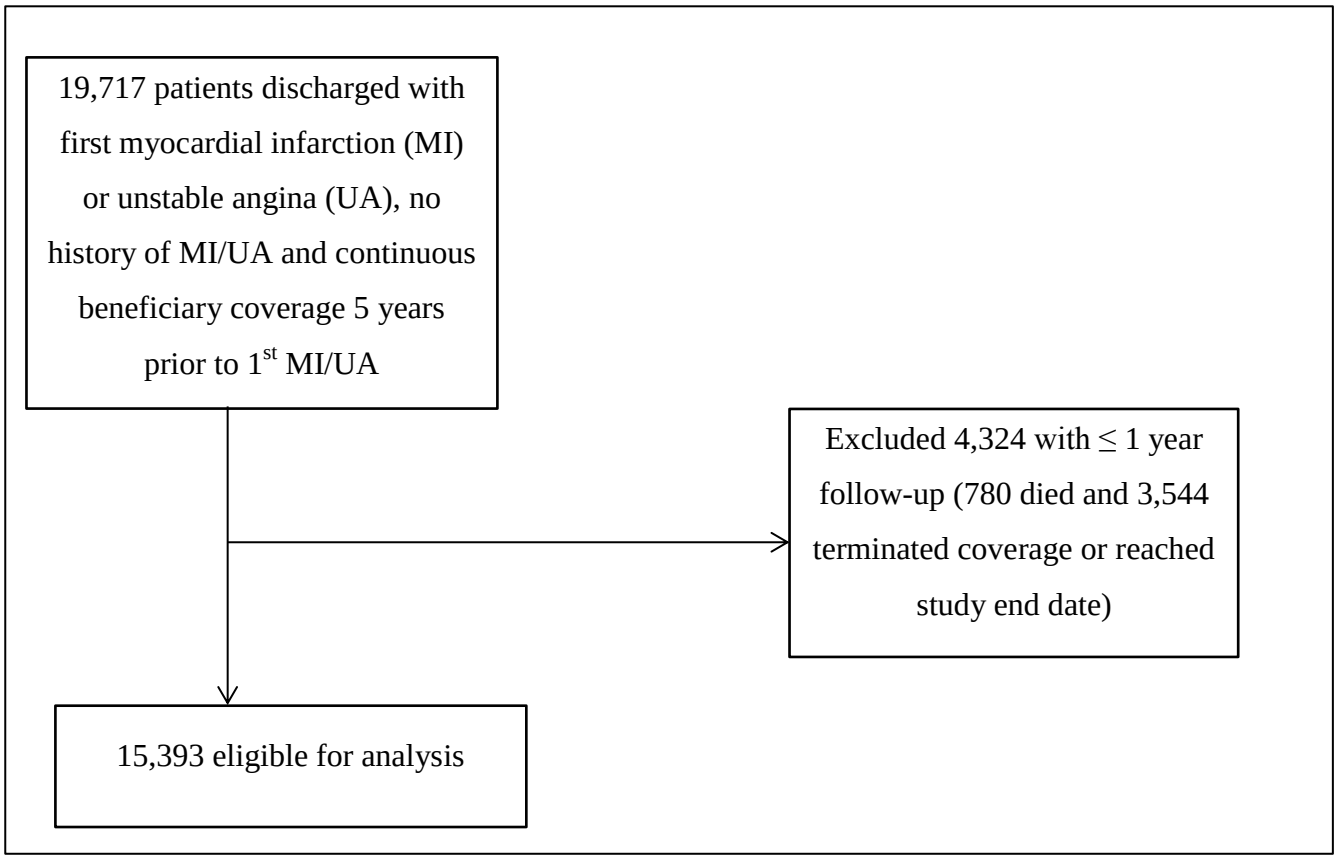


Figure 5.2: Flow chart showing how patients were included and excluded from the base cohort to satisfy objective 1

Overall, 20.1% (3,099/15,393) of patients received at least one NSAID dispensation during the 365 days following hospital discharge. Eleven percent (1,737/15,393) received two or more NSAID dispensations during the follow-up year and 8.2% (1,274/15,393) received at least three. The most commonly dispensed NSAIDs were diclofenac (33.1%, 1,028/3,099), indomethacin (16.9%, 526/3,099), naproxen (14.7%, 456/3,099), celecoxib (11.4%, 356/3,099)

and rofecoxib 8.1% (254/3,099). Other NSAIDs accounted for the remaining 15.4% (479/3,099). Among diclofenac users (n=1,028), the use of the single-entity product (n=525) was similar to the combination product, Diclo-Miso (n=503), accounting for 16.9% and 16.2% of those with at least one NSAID dispensation respectively (Figure 5.3).

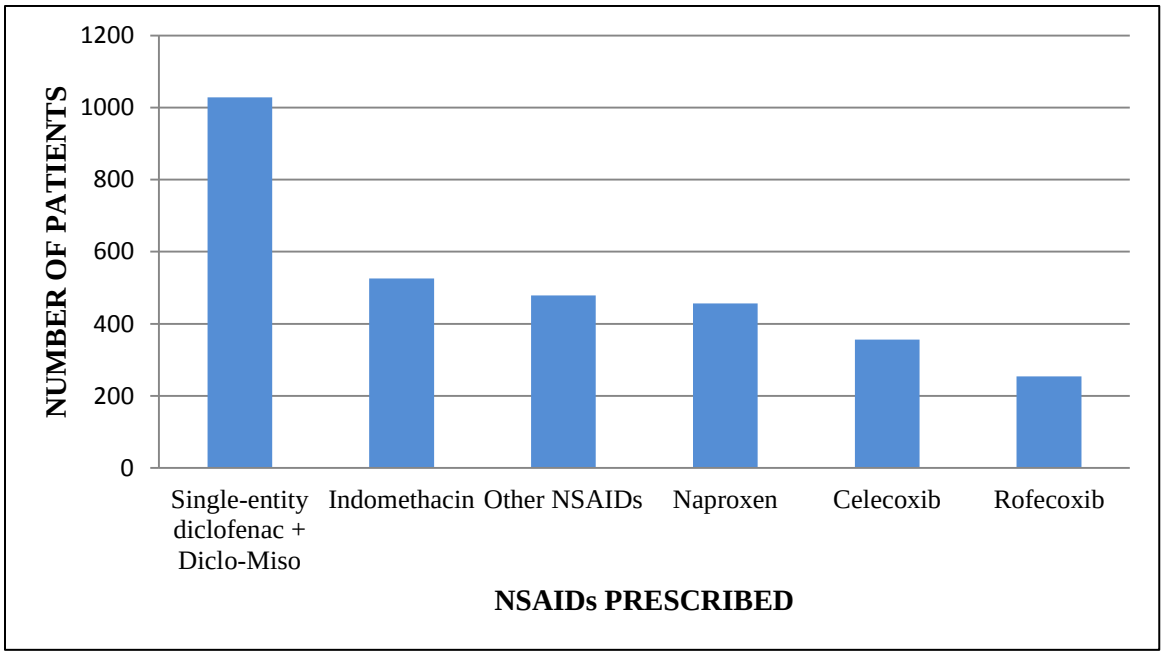


Figure 5.3: Number of patients prescribed with NSAIDs within 1 year of MI/UA discharge

Following age and sex standardization, the percentage of patients receiving at least one NSAID dispensation in the one-year follow-up period was plotted over time (Figure 5.4). During the first period when only non-selective NSAIDs were available, 19.2% of discharged patients received at least one NSAID dispensation in the one year follow-up period. In the second period, corresponding to the new availability of COX-2 inhibitors, 21.7% received an NSAID. In the final period of analysis (October 1st, 2004 to December 31st, 2007) following rofecoxib's withdrawal from the market, NSAID use was observed in 15.9% of eligible patients.

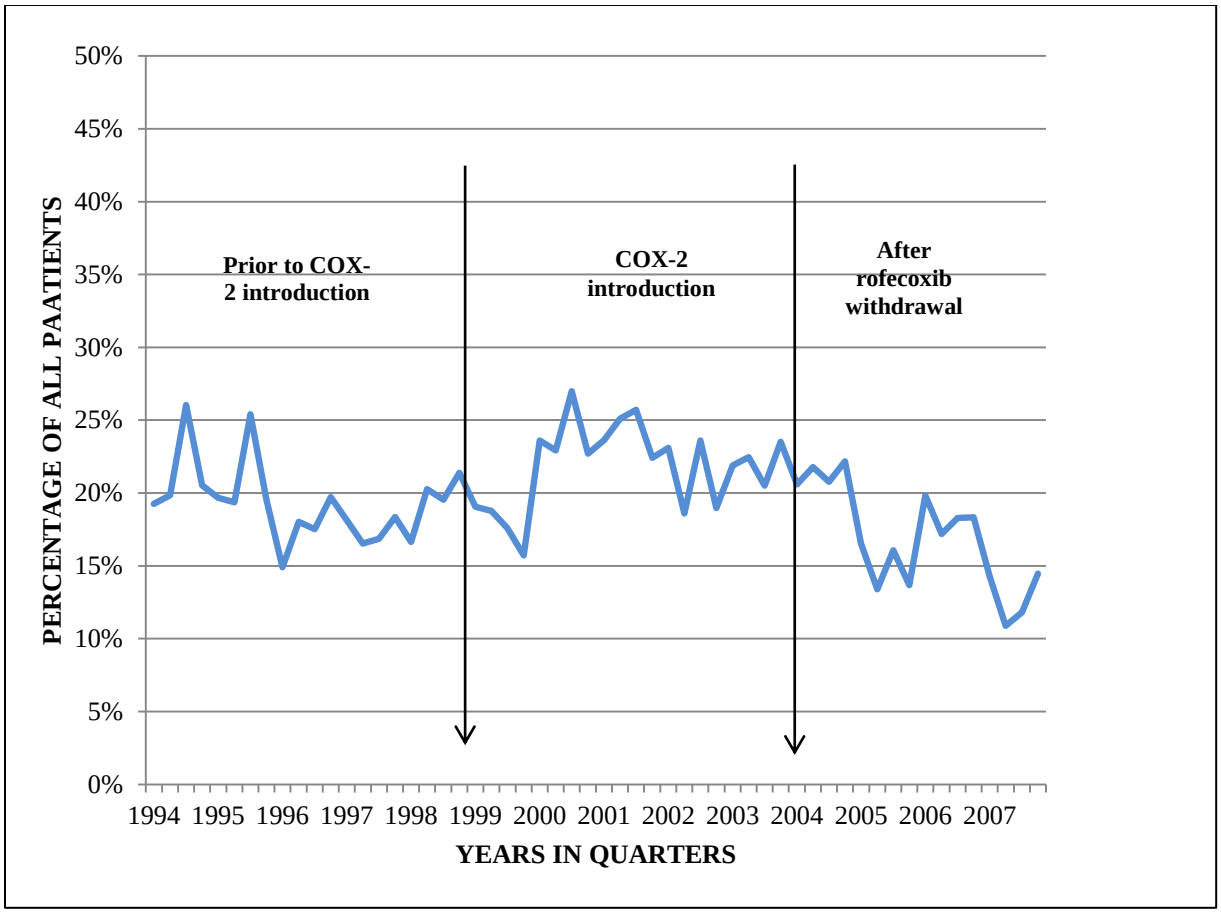


Figure 5.4: Percentage of patients receiving at least one prescription NSAID within one-year following a coronary heart disease hospitalization in Saskatchewan, Canada between 1994 and 2007

Individual NSAID agents were also examined to determine if they followed similar trends compared to the aggregate analysis. In general, the use of NSAIDs appeared to decline or stabilizes over time with the exception of Diclo-Miso (Figure 5.5). The use of Diclo-Miso appeared to increase while the use of single-entity diclofenac product did not appear to change between these two periods. The impact of calendar year on diclofenac use was examined in objective 2.

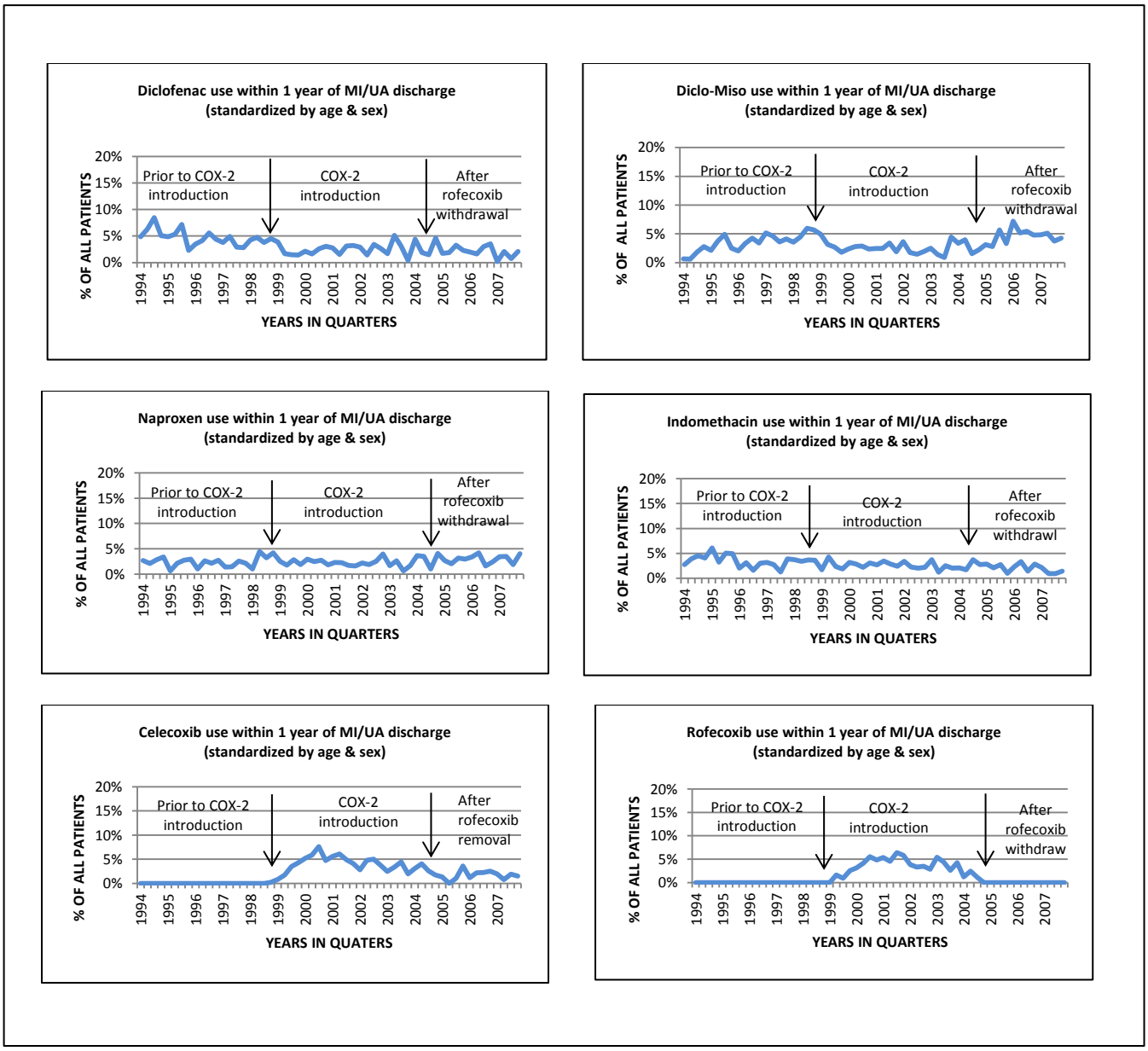


Figure 5.5: Percentage of patients receiving at least one prescription NSAID within one-year following a coronary heart disease hospitalization in Saskatchewan, Canada between 1994 and 2007

5.3 OBJECTIVE 2 RESULTS

<u>Objective 2</u>: Identify patient characteristics associated with Diclo-Miso use compared to the use of single-entity diclofenac or other single entity NSAID products.

Among the 15,393 patients examined in objective one, 3,099 received at least one NSAID dispensation in the one-year follow-up period. Among these patients, 1,084 received at least one dispensation of Diclo-Miso or diclofenac. Fifty six patients were excluded due to the use of both Diclo-Miso and diclofenac leaving 525 patients receiving single-entity diclofenac and 503 receiving Diclo-Miso exclusively (Table 5.6).

Baseline characteristics of patients receiving either single-entity diclofenac or Diclo-Miso differed for chronic disease score ($p=0.03$), physician visits in prior year ($p=0.02$), use of cardiovascular medications in prior year ($p=0.04$), and year of hospital discharge ($p<0.01$). For each of these factors, individuals on Diclo-Miso appeared to demonstrate higher levels of comorbidity. In addition, Diclo-Miso use appeared to be used more frequently in the final period compared to single-entity diclofenac.

Table 5.6: Characteristics of patients prescribed NSAID products (Diclofenac/Misoprostol (i.e., Diclo-Miso), single-entity diclofenac, other single-entity NSAIDs)

Baseline characteristics	**Diclo-Miso (%)**	**Single-entity Diclofenac (%)**	**Other NSAIDs**	**P-values**
Total patients	503	525	2540	--
Gender				
Males, no. (%)	269 (53.5)	312 (59.4)	1485 (58.5)	0.04
Mean ± SD* age	67 ± 10.96	66 ± 10.40	68 ± 10.93	--
Age 65 or older, no. (%)	341 (67.9)	340 (64.8)	1748 (68.8)	0.65
Rural/ urban residence				
Rural, no. (%)	302 (60.0)	325 (61.9)	1410 (55.5)	0.06
Deyo Comorbidity Score [51, 52]				
0	430 (85.5)	452 (86.1)	2184 (85.9)	0.77
≥ 1	73 (14.5)	73 (13.9)	356 (14.0)	

Chronic Disease Score [53]				
≤3	106 (21.1)	130 (24.8)	569 (22.4)	0.77
4 - 5	120 (23.9)	140 (26.7)	643 (25.3)	
6 - 7	116 (23.1)	129 (24.6)	629 (24.8)	
≥ 7	161 (32.0)	126 (24.0)	699 (27.5)	
GI medication use (1 year prior to initial CHD hospitalization)**				
No use	340 (67.6)	382 (72.8)	1844 (72.6)	0.02
Any use	163 (32.4)	143 (27.2)	696 (27.4)	
Use of cardiovascular medications in prior year to initial CHD hospitalization***				
< 3	214 (42.5)	240 (45.7)	1027 (40.4)	0.25
3 -4	220 (43.7)	239 (45.5)	1208 (47.6)	
> 4	69 (13.7)	46 (8.8)	305 (12.0)	
Rheumatoid arthritis diagnosis (1 year prior to initial hospitalization)				
RA disease, no. (%)	12 (2.4)	8 (1.5)	58 (0.2)	0.89
GI bleed diagnosis (1 year prior to initial hospitalization)****				
GI bleed, no. (%)	6 (1.2)	9 (1.7)	25 (0.1)	0.67
Income security benefit				
No benefit	346 (65.9)		1624 (64.90	0.56
Any benefit (senior or family based)	188 (37.4)	179 (34.1)	916 (36.1)	
Year of hospital discharge				
Before 1999	282 (56.1)	351 (66.9)	1080 (42.5)	<0.0001
1999 - 2004	132 (26.2)	136 (25.9)	1266 (49.8)	

After 2004	89 (17.7)	38 (7.2)	194 (7.6)	
Health Services Number of physician visits (1 year prior to initial (1 year prior to initial hospitalization)				
< 10	140 (27.8)	180 (34.3)	880 (34.6)	0.003
≥ 10	363 (72.2)	345 (65.7)	1660 (65.3)	

*SD= standard deviation;

**GI meds= gastrointestinal medication (proton pump inhibitors, H2 antagonists or misoprostol);

***Cardiovascular medications (angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), Beta blockers, statins, calcium channel blockers (CCBs), anti-platelets, anti-coagulants, anti-arrhythmic agents and other anti-hypertensive agents);

****GI bleed= gastrointestinal bleed

During the model building process where Diclo-Miso was the dependent variable, rheumatoid arthritis and GI bleed diagnoses were excluded because of insufficient numbers of patients with these diagnoses. All other variables except rural-urban residence, Deyo comorbidity score, and income security benefit satisfied the requirement of p-value ($p=<0.15$). The final model contained gender, age, year of hospital discharge and the interaction term year of hospital discharge versus age group.

Year of hospital discharge was the only significant variable in the multivariate model, (Table 5.7). Also within the final model, there was a significant interaction between the terms age and year of hospital discharge ($p=0.003$). However, upon further examination, the interaction was not deemed an effect modifier. In other words, the impact of year was consistent within both age groups (above and below 65 years).

Table 5.7: Crude univariate and multivariate results for potential risk factors in receiving Diclo-Miso versus diclofenac reporting odds ratio, P-value and 95% CI

Potential risk factors	**Crude, univariate**			**Adjusted, multivariate**		
	Odds ratio	***95% CI***	***P-value***	***Odds ratio***	***95% CI***	***P-value***
Gender						
Male (ref)	1.00			1.00		
Female	1.27	0.99-1.63	0.05	1.21	0.95-1.57	0.13
Age (categorical)						
< 65 (ref)	1.00			1.00		
≥ 65	1.15	0.88-1.48	0.30	1.23	0.95-1.63	0.12
Year of hospital discharge						
Before1999 (ref)	1.00			1.00		
1999 - 2004	1.44	1.09-1.89	0.01	1.50	1.14-1.98	0.004
After 2004	3.16	2.08-4.78	<0.001	3.25	2.14- 4.94	<0.001
Interaction terms						
Age ≥65 * Year of hospital discharge (1999 -2004)	-	-	-	2.23	1.43-3.47	0.003
Age ≥65 * Year of hospital discharge (after 2004)	-	-	-	0.72	0.33-1.58	0.60
Variables not included in the multivariable model						
Rural/urban residence						
Rural (ref)	1.00					
Urban	1.08	0.84-1.40	0.54	-	-	-
Chronic Disease Score						

Categorical						
≤3 (ref)	1.00			-		
4 - 5	1.05	0.73-1.49	0.78	-	-	-
6 – 7	1.10	0.77-1.57	0.59	-	-	-
≥7	1.56	1.10-2.21	0.01	-	-	-
Deyo Comorbidity Score						
0 (ref)	1.00					
≥ 1	1.05	0.74-1.50	0.78	-	-	-
GI meds (1 year prior to initial CHD hospitalization)*	1.28	0.97-1.67	0.07	-	-	-
CV meds (1 year prior to initial CHD hospitalization) **				-	-	-
< 3 (ref)	1.00			-	-	-
3 -4	1.03	0.79-1.33	0.81			
> 4	1.68	1.11-2.55	0.01			
Income security benefit						
none (ref)	1.00					
Any benefit (senior or family based)	1.15	0.89-1.49	0.27	-	-	-
Number of physician visits (1 year prior to initial CHD hospitalization)						
< 10	1.00					
≥ 10	1.35	1.04-1.76	0.03	-	-	-

*GI meds= gastrointestinal medication (proton pump inhibitors, H2 antagonists or misoprostol);

**CV meds = Cardiovascular medications (angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), Beta blockers, statins, calcium channel blockers (CCBs), anti-platelets, anti-coagulants, anti-arrhythmic agents and other anti-hypertensive agents);

Predictors of Diclo-Miso use were re-examined using the same procedures among a larger cohort including the use of any single-entity NSAID versus Diclo-Miso (Table 5.8). The variables that had <0.15 and thus considered as components of the final model were gender, age, rural/urban residence, year of hospital discharge and physician visits (Table 5.8). All the variables were significant with a p-value of <0.05 except age and physician visits. Therefore a person's gender, place of residence and year of hospital discharge might be predicting factors in being prescribed with Diclo-Miso versus single-entity NSAIDs.

In testing for interaction terms, there was a significant difference recorded between the terms year of hospital discharge and age group (Table 5.8). There was also a significant between Year of hospital discharge and rural/urban residence (Table 5.8). These interaction terms however were not considered an effect modifier.

Table 5.8: Crude univariate and multivariate results for potential risk factors in receiving Diclo-Miso versus any single-entity NSAIDs reporting odds ratio, P-value and 95% CI

Potential risk factors	**Crude, univariate**			**Adjusted, multivariate**		
	Odds ratio	***95% CI***	***P-value***	***Odds ratio***	***95% CI***	***P-value***
Gender						
Male (ref)	1.00			1.00		
Female	1.22	1.01-1.48	0.04	1.25	1.03-1.53	0.02
Age (categorical)						
< 65 (ref)	1.00			1.00		
≥ 65	0.95	0.77-1.17	0.65	0.92	0.74-1.14	0.44
Rural/urban residence						
Rural (ref)	1.00			1.00		
Urban	0.83	0.68-1.01	0.06	1.25	1.02-1.52	0.03
Year of hospital discharge						
Before1999 (ref)	1.00			1.00		
1999 - 2004	0.62	0.50-0.76	<0.00	0.59	0.48-0.74	<0.00

After 2004	2.06	1.55-2.75	1 <0.001	1.98	1.48-2.64	1 <0.001
Number of physician visits (1 year prior to initial CHD hospitalization) 10 (ref) ≥10	1.00 1.37	1.11-1.69	0.003	1.00 1.01	0.99-1.01	0.12
Interaction terms Age ≥65 * Year of hospital discharge (1999-2004) Age ≥65 * Year of hospital discharge (after 2004)	- -	-	- -	0.71 0.63	0.50-1.01 0.37-1.05	0.01 0.02
Rural/urban residence* Year of hospital discharge (1999-2004) Rural/urban residence * Year of hospital discharge (after 2004)	- -	-	- -	1.61 1.39	1.14-2.26 0.82-2.36	0.04 0.28
Variables not included in the multivariable model						
Chronic Disease Score Categorical ≤3 (ref) 4 - 5 6 - 7	1.00 1.00 0.99	0.75-1.33 0.74-1.32	0.99 0.95	- -	- -	- -

≥ 7	1.24	0.95-1.62	0.12	-	-	-
Deyo Comorbidity Score						
0 (ref)	1.00			-	-	-
≥ 1	1.04	0.79-1.37	0.76	-	-	-
GI meds (1 year prior to initial CHD hospitalization)*	1.27	1.03-1.56	0.02	-	-	-
CV meds (1 year prior to initial CHD hospitalization)**						
< 3 (ref)	1.00					
3 -4	0.87	0.71-1.07	0.19	-	-	-
> 4	1.08	0.80-1.46	0.59	-	-	-
Income security benefit						
none (ref)	1.00			-	-	-
Any benefit (senior or family based)	1.05	0.86-1.29	0.57	-	-	-

*GI meds= gastrointestinal medication (proton pump inhibitors, H2 antagonists or misoprostol);

**CV meds= cardiovascular medications (angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), Beta blockers, statins, calcium channel blockers (CCBs), anti-platelets, anti-coagulants, anti-arrhythmic agents and other anti-hypertensive agents);

5.4 OBJECTIVE 3 RESULTS

<u>Objective 3</u>: To identify evidence for bias in a non-randomized comparison of Diclo-Miso versus single-entity diclofenac using conventional methods.

From the 19,717 patients making up the base-cohort, 4,174 could not be followed for the minimum duration of 90 days due to death (n=1,408), termination of health coverage (n=645), and reaching the end of the observation period (n=2,121) (Figure 9). Of the 15,543 patients eligible for analysis 62.1% (9,645/15,543) were males and the mean age was 67 years old (SD ± 11.40). The average length of follow-up was 6.41 years (range: 3 months – 15 years). Almost

half of the cohort (i.e., 48%, 7,482/15,543) experienced a recurrent MI/UA event or died during the follow-up period.

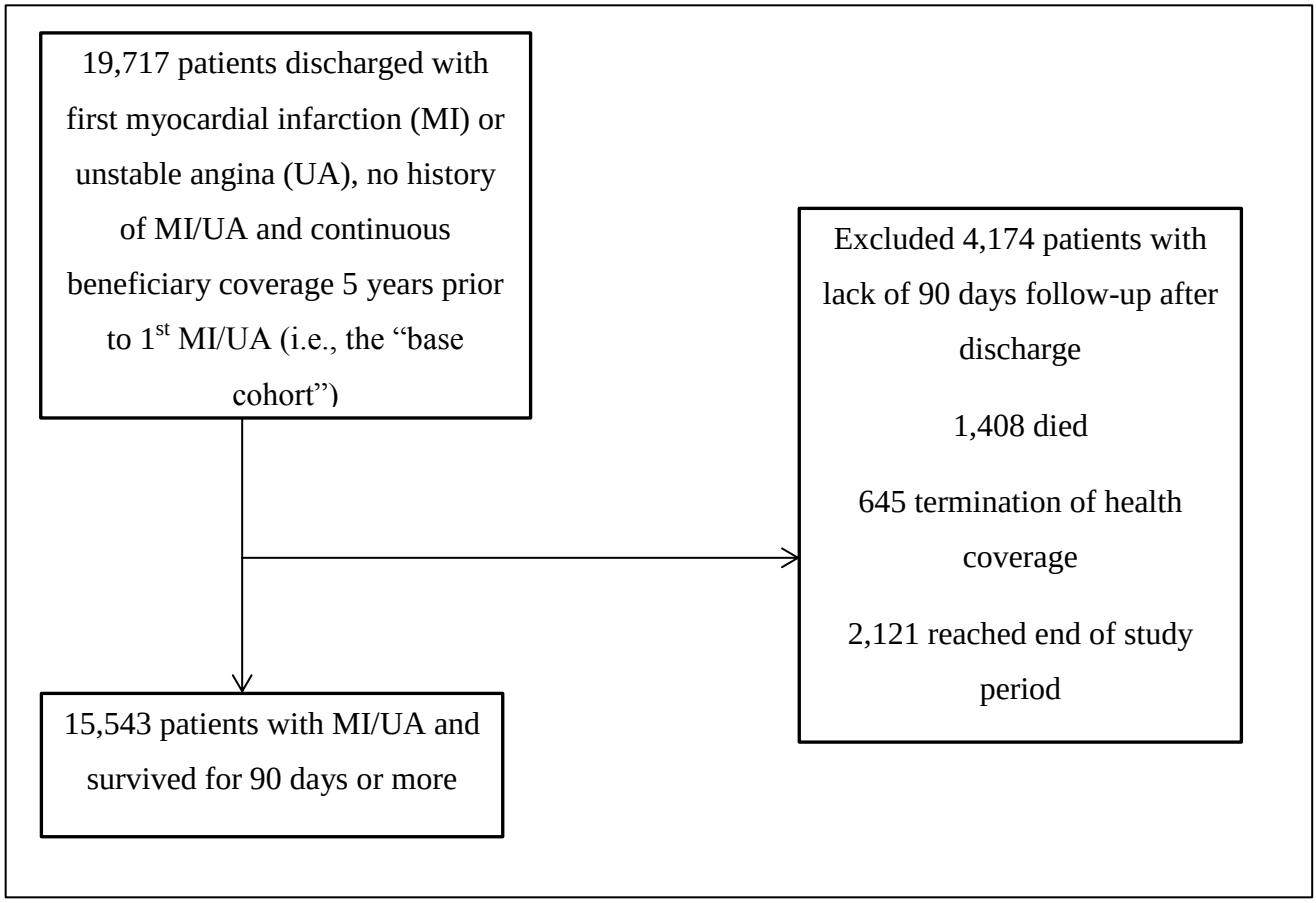


Figure 5.6: Flow chart of showing how many patients were included and excluded from the cohort to satisfy objective

Compared to patients who did not experience an outcome (i.e., recurrent MI/UA or death) patients developing MI/UA or death were significantly different for all baseline characteristics in with the exception of rural/urban residence and number of hospital visits (Table 5.9)

Table 5.9: Baseline characteristics of NSAID users 3 months after discharge for 1st MI/UA

Baseline characteristics	***Cohort description***		
	MI/UA or death outcome	***Satisfied inclusion criteria but no outcome experienced***	***P-values***
Total (n)	7,482	8,061	-
Gender, n (%)			
Male	4,533 (60.6)	5,112 (63.4)	<0.01
Female	2,949 (39.4)	2,949 (36.6)	
Age ,mean (SD)*	71 ± 9.1	64± 12.3	-
Demographics, n (%)			
Rural	3,848 (51.4)	4,113 (51.0)	0.62
Urban	3,634 (48.6)	3,948 (49.0)	
Clinical disease, n (%)			
Hypertension	136 (1.8)	69 (0.9)	<0.01
Diabetes	178 (2.4)	59 (0.7)	<0.01
Rheumatoid arthritis	13 (0.2)	3 (0.03)	0.01
Chronic Disease Score			
≤ 3 (ref)	1,761 (23.5)	3,016 (37.4)	<0.01
4 - 5	1,810 (24.2)	2,165 (26.9)	
6 - 7	1,809 (24.2)	1,564 (19.4)	
≥ 7	2,102 (28.1)	1,316 (16.3)	
Deyo comorbidity score			
0	5,968 (79.8)	7,455 (92.5)	<0.01
≥ 1	1,514 (20.2)	606 (7.5)	
Year of hospital discharge			
Before 1999	4,316 (57.7)	2,492 (30.9)	<0.01
1999 - 2004	2,792 (37.3)	3,722 (46.2)	
After 2004	372 (5.0)	1,847 (22.9)	

Number of hospital visits (1 year prior after initial CHD hospitalization)			
< 10	7,470 (99.8)	8,055 (99.9)	0.12
≥ 10	12 (0.2)	6 (0.1)	
Number of physician visits (1 year prior after initial CHD hospitalization)			
< 10	2,688 (35.9)	4,211 (52.2)	<0.01
≥ 10	4,794 (64.1)	3,850 (47.8)	
Income security benefit			
None (ref)	4,437 (59.3)	6,141 (76.2)	<0.01
Any benefit (senor or family based)	3,045 (40.7)	1,920 (23.8)	

*SD=standard deviation

Five controls were matched on age and sex for 99.3% (7,431/7,482) for 7,482 cases and at least one control was identified for 99.7% (7,467/7,482) of cases. Therefore, the final comparison was undertaken with 7,482 cases and 37,203 controls. At baseline, cases and controls were well matched for most characteristics (Table 5.10). However, cases appeared to exhibit a slightly higher level of comorbidity as evidenced by 28.1% (2,102/7,482) having a chronic disease score of 7 or greater compared to 17.9% (6,666/37,203) with similar chronic (Table 5.10).

Table 5.10: Baseline characteristics of NSAID users for cases and controls 3 months after discharge for 1st MI/UA

Baseline characteristics	***Cases (%)***	***Controls (%)***
Total patients (n)	7,482	37,203
Gender		
Male	4,533(60.6)	22,563 (60.6)
Female	2,949 (39.4)	14,640 (39.4)
Age, mean (SD)*	70 ± 0.04	70± 0.04
Demographics		
Rural	3,848 (51.4)	19,399 (52.1)
Urban	3,634 (48.6)	17,804 (47.9)
Clinical disease		
Hypertension	136 (2.0)	421 (1.1)
Diabetes	178 (2.4)	321 (1.0)
Rheumatoid arthritis	13 (0.2)	22 (0.1)
Chronic Disease Score		
≤ 3	1,761 (23.5)	11,578 (31.1)
3 - 5	1,810 (24.2)	10,561 (28.4)
6 - 7	1,809 (24.2)	8,398 (22.6)
≥ 7	2,102 (28.1)	6,666 (17.9)
Deyo score		
0	5,968 (79.8)	33,378 (89.7)
≥ 1	1,514 (20.2)	3,825 (10.3)
Year of hospital discharge		
Before 1999	4,316 (57.7)	21,485 (57.8)
1999 - 2004	2,794 (37.3)	14,057 (37.8)
After 2004	372 (4.9)	1,661 (4.5)
Number of hospital visits (1		

year prior to initial CHD hospitalization)		
< 10	7,470 (99.8)	37,170 (99.9)
≥ 10	12 (0.2)	33 (0.1)
Number of physician visits (1 year prior to initial CHD hospitalization)		
< 10	2,688 (35.9)	16,725 (44.9)
≥ 10	4,794 (64.1)	20,478 (55.0)
Drugs taken within 90 days of discharge		
Nitroglycerin	6,133 (82.0)	14,730 (39.6)
ACE/ARB**	4,947 (66.1)	11,272 (30.3)
Beta blockers	4,628 (61.9)	11,614 (31.2)
Statin	2,689 (35.9)	6,265 (16.8)
Clopidogrel	810 (10.8)	1,862 (5.0)
Income security benefit		
None	4,437 (59.3)	24,350 (65.5)
Any benefit (senor or family based)	3,045 (40.7)	12,853 (34.5)

*SD=standard deviation

** ACE = angiotensin converting enzyme; ARB= angiotensin receptor blocker

All the variables tested on univariate analysis except rural/urban residence were significantly associated with the outcome of recurrent MI/UA or death using a threshold of p=<0.15 (Table 5.11). After multivariable adjustment, neither diclofenac (adjusted OR 0.78, 95% CI 0.60-1.00, p=0.06) or Diclo-Miso (adjusted OR 0.88, 95% CI 0.72-1.08, p=0.22) were significantly associated with an increased risk for death or recurrent MI/UA compared to no NSAID use. Further, no significant increase in risk was observed among patients receiving Diclo-Miso compared to single-entity diclofenac (adjusted OR 1.11, 95% CI 0.81-1.56, p=0.50). In contrast, increased risk for the outcome was observed for patients receiving multiple NSAID

(adjusted OR 1.67, 95% CI 1.22-2.29, p=<0.01), patients receiving indomethacin [adjusted OR 1.34 (1.07-1.67), p=0.01] and naproxen [adjusted OR 1.30 (1.04-1.63), p=0.02], (Table 5.11). Estimates for the risk of MI/UA or death were not substantially impacted by multivariate adjustment.

Patients who were prescribed beta blockers and nitroglycerin within 3 months after discharge, Chronic Disease Score (CDS), physician visits, and income security benefits were significant predictors receiving Diclo-Miso while patients who were prescribed ACE/ARBs 90 days after discharge showed borderline significance (Table 5.11).

Table 5.11: Potential risk factors for recurrent Myocardial Infarction, Unstable Angina or death among NSAID users

Potential risk factors	***Crude, univariate***			***Adjusted, multivariate***		
	Odds ratio	***95% CI****	***P-value***	***Odds ratio***	***95% CI****	***P-value***
No use (ref)	1.00			1.00		
Diclofenac	0.84	0.64-1.08	0.17	0.78	0.60-1.00	0.06
Diclo-Miso	0.99	0.81-1.20	0.88	0.88	0.72-1.08	0.22
Naproxen	1.36	1.09-1.69	0.01	1.30	1.04-1.63	0.02
Indomethacin	1.53	1.23-1.89	0.001	1.34	1.07-1.67	0.01
Other non-selective	1.20	0.96-1.48	0.10	1.15	0.93-1.44	0.20
COX-2 selective agents	1.06	0.93-1.20	0.38	0.92	0.81-1.05	0.21
Multiple uses	1.97	1.45-2.68	0.00	1.67	1.22-2.29	0.002
Chronic Disease Score						
≤ 3 (ref)	1.00			1.00		
4 - 5	1.14	1.06-1.23	0.001	1.09	1.02-1.18	0.02
6 - 7	1.47	1.36-1.58	0.001	1.29	1.20-1.39	<0.01
≥7	2.17	2.03-2.34	0.001	1.78	1.65-1.92	<0.01
Number of physician visits (1 year prior to initial CHD hospitalization)						

< 10	1.00			1.00		
≥ 10	1.50	1.42-1.59	0.001	1.22	1.15-1.30	<0.01
ACE/ARB**	1.06	01-1.12	0.02	1.05	1.00-1.02	0.05
B-blockers	0.76	0.72-0.80	0.001	0.79	0.74-0.83	<0.01
Statin	0.68	0.64-0.72	0.001	0.67	0.63-0.71	<0.01
Nitroglycerin	1.92	1.82-2.03	0.001	1.84	1.74-1.95	<0.01
Income security benefit						
None (ref)	1.00			1.00		
Any benefit (senior or family based)	1.34	1.27-1.41	0.001	1.25	1.18-1.32	<0.01
Rural/urban residence	0.97	0.92-1.02	0.25	--	--	--

*CI= confidence interval
**ACE = angiotensin converting enzyme; ARB= angiotensin receptor blocker

6. DISCUSSION

The purpose of this study was to perform a retrospective analysis of prescription NSAIDs used to identify evidence for channelling bias between Diclo-Miso and diclofenac products. Between 1994 and 2004, the utilization of all NSAIDs remained relatively stable among patients who had been hospitalized with cardiac event in Saskatchewan. However, following the removal of rofecoxib from the market in 2004 (due to concerns over cardiac toxicity), the utilization of Diclo-Miso appeared to increase while single-entity diclofenac and other NSAIDs remained stable or decreased. This difference in utilization may have been a result of channelling bias in that Diclo-Miso and single-entity diclofenac were prescribed to different types of patients. Evidence for a unique prescribing pattern of Diclo-Miso following 2004 was confirmed using multivariate regression models; year of discharge was strongly associated with the odds of receiving Diclo-Miso compared to single-entity diclofenac. However, no significant associations were observed with any of the other patient characteristics examined. In addition, the risk of death or recurrent cardiovascular morbidity did not differ between Diclo-Miso and single-entity diclofenac using conventional methods to control for channelling bias and confounding. Based on these results overall, evidence for channelling bias with respect to the integration of Diclo-Miso and single-entity diclofenac could not be confirmed.

The overall use of NSAIDs among cardiac patients was not drastically impacted by the emergence of COX-2 selective agents on the Saskatchewan market. This low impact may have been a result of restrictions associated with their use. Provincial drug coverage for COX-2 selective agents was restricted to patients with a history of ulcers, age 65 or older, concurrent prednisone or warfarin therapy or intolerance to other NSAIDs [58]. As a result, widespread prescribing of COX-2 selective agents may have been discouraged by these coverage restrictions. However, individuals could have obtained these medications without provincial coverage. In this situation, claims for COX-2 inhibitors would not have been captured by the prescription drug plan file. Fortunately, a high percentage of subjects in our study were eligible for coverage based on age (i.e., ≥65 years); thus, it is expected that this limitation of the data source did not drastically influence our results.

Diclo-Miso use increased following the withdrawal of rofecoxib from the market. This trend was the first possible indicator of potential channelling bias in our study. In the absence of

bias, Diclo-Miso would have been expected to follow similar utilization pattern as the other single-entity NSAIDs, especially diclofenac. If bias was present, it was hypothesized that patients receiving Diclo-Miso would be older and exhibit higher levels of comorbidity. However, the result of this study failed to indicate a clear preference for Diclo-Miso among patients with increased levels of comorbidity or advanced age. Although some variables representing comorbidity were associated with Diclo-Miso use in the univariate analyses, none of these associations persisted after multivariate adjustment.

A comparison of health outcomes between individuals receiving Diclo-Miso versus single-entity diclofenac also failed to reveal evidence for channelling bias. It was hypothesized that patients receiving Diclo-Miso would exhibit higher rates of recurrent MI/UA and death due to channelling bias. In the absence of bias, no differences in health outcomes were expected because misoprostol (i.e., the gastro-protective agent (i.e., found in Diclo-Miso) has no known impact on cardiac toxicity at prescribed doses [59]. However, the risk for MI/UA or death was not statistically different between patients taking Diclo-Miso versus single-entity diclofenac. This result corresponded to the findings of objective #2 which failed to identify significant differences in patient characteristics between cohorts exposed to these diclofenac products.

Evidence for channelling bias has been identified previously in utilization studies of COX-2 inhibitors. Following the approval of these agents in Canada, rates of hospitalization for gastrointestinal (GI) bleeding increased significantly despite evidence suggesting COX-2 selective agents were safer than traditional NSAIDs [50]. It was assumed that higher rates of bleeding were a result of channelling these agents to older/sicker patients [50]. A similar study suggested channelling bias was responsible for an observed risk of GI bleeding with a non-selective NSAID meloxicam [60].

The results of this study indicated diclofenac products (of any kind) did not increase the risk for cardiac toxicity. The odds of experiencing a recurrent MI/UA or death compared to no NSAID use was 0.88 (95% CI 0.72-1.08) for patients receiving Diclo-Miso and 0.78 (95% CI 0.60-1.00) for patients receiving single-entity diclofenac. In contrast, published meta-analyses have reported significant risk with diclofenac based on RCTs (1.41 RR, 95% CI 1.12-1.78, p=0.003) [22] and observational studies (1.40 RR, 95% CI 1.27-1.55, p=<0.0001) [5].

The exact reasons for these contrasting estimates of harm remain unidentified. One possible factor could have been related to the duration of exposure to diclofenac products. Olsen and colleagues found that diclofenac had the highest risk (3.26 hazard ratios, 95% CI 2.75-3.86) for recurrent MI or death within the first 1-7 days of use [4]. Dose was another factor which was not investigated in our study but Gislason and colleagues found that doses <100mg were not significantly associated with death (0.89 HR, 95% CI 0.66-1.20, p=0.45) or recurrent MI (1.27 HR, 0.92-1.76, p=0.15) compared to patients receiving higher doses (i.e., ≥100 mg per day) [27]. Although these factors were not specifically examined in our study, diclofenac cohorts were directly compared to patients receiving other NSAIDs and it was assumed that the percentage of individuals receiving high doses or extended duration of exposure would be similar for all classes of NSAID products. Yet, other NSAID medications were associated with higher risks compared to diclofenac. As a result, other unidentified factors likely played an important role in these contrasting results.

7. LIMITATION

This study was conducted using Saskatchewan health administrative data, which are widely recognized for their accuracy and comprehensiveness [47]. However, despite the use of these robust databases, several limitations must be acknowledged. First, the results of this study may not be generalizable to other populations because the sample was restricted to patients experiencing a cardiac event whereas NSAIDs are used by many different types of patients with or without chronic conditions. Although the study inclusion criteria would have undoubtedly excluded many NSAID users, individuals eligible for this study exhibited coronary heart disease (CHD) at baseline, which is a known risk factor for NSAID induced cardiac toxicity. Therefore, this study population was considered an ideal model for testing and comparing the cardiovascular risks of NSAID medications. It is also possible that Saskatchewan-specific prescribing patterns and drug coverage policies may reduce the generalizability of these findings. Second, the period of observation (i.e., 1994-2008) included the introduction of COX-2 selective NSAIDs and also the withdrawal of rofecoxib from the market. Overall NSAID use was negatively impacted by the latter event, which may have confounded the assessment of channelling bias between Diclo-Miso and single-entity diclofenac. Third, ibuprofen became available without a prescription in 1993, one year prior to the beginning of the study period (i.e., in 1994). Although ibuprofen's availability as an over-the-counter product likely resulted in an underestimate of NSAID use overall, it was not expected to confound the specific comparison of Diclo-Miso versus single-entity diclofenac. Fourth, it is possible that differences in NSAID toxicity may have been confounded by the extent of exposure. It is known that the length of time an individual receives an NSAID along with the dose (i.e., high versus low doses) likely impacts the risk for cardiac toxicity [4, 27]. However, it was assumed that the percentage of individuals receiving high doses and/ or long-term therapy would be similar between all types of NSAIDs examined.

Lastly, one of the major limitations of population-based databases is the lack of clinical information available [61]. This limitation may have confounded the assessment of frailty or comorbidity. As a result, the risk associated with diclofenac and/or Diclo-Miso may have been confounded by differences in the health status of study patients receiving various NSAID products. However, a rigorous approach was used to match patients by age, sex, and discharge

year and exposure to NSAIDs was identified in the 90 days preceding each study outcome. In addition, several confounding variables were accounted for in the final analysis.

8. CONCLUSION

The results of this study indicate that channelling bias has not been an important threat to the assessment of cardiac toxicity of NSAIDs using observational studies. Thus, diclofenac must still be considered an NSAID with important risks. However, the results of this study provided further conflicting information relating to the risks associated with the use of diclofenac. Future studies are needed to clarify the reasons for differences in estimated risk associated with diclofenac.

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