Major Side Effects of Nonsteroidal Anti-Inflammatory Drugs: Gastrointestinal and Cardiovascular Risks of Etodolac and Interaction of NSAIDs with Cardioprotective Effects of Acetylsalicylic Acid

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

In

Pharmaceutical Sciences

Faculty of Pharmacy and Pharmaceutical Sciences
University of Alberta

Abstract

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are administered for their anti-inflammatory, analgesic, and antipyretic properties. Thus, NSAIDs are one of the most commonly prescribed group of medications to relieve pain and inflammation associated with inflammatory conditions such as rheumatoid arthritis (RA). Nevertheless, reports of cardiovascular (CV) adverse events began to emerge since early 2000 and subsequent placebo-controlled studies showed that COX-2 inhibitors like rofecoxib were associated with life threatening CV incidents. However, some meta-analyses suggested that such a risk is not restricted to highly COX 2 inhibitors, but also applies to other NSAIDs. This is while many reports suggest that Acetylsalicylic acid (ASA) reduces such a risk.

Etodolac, a generic NSAID, thus cost-effective, with a confirmed efficacy and high tolerability, is a potential alternative to other least cost-effect NSAIDs. Hence, the drug possesses high affinity for COX-2 over COX-1 isoenzyme, it is believed that etodolac demonstrate a safe gastrointestinal (GI) profile than other NSAIDs. However, it has been established that NSAIDs are heterogonous in causing CV incidents, etodolac has not been thoroughly investigated regard its CV toxicity, particularly in presence of covariates such as underlying inflammation conditions or use of ASA. It has been suggested that the concomitant use of some NSAIDs diminishes the extent of platelet aggregation effects of ASA, however, many epidemiological studies suggest that the addition of the latter reduces the CV risk attributed to the use of NSAIDs.

We hypothesized that etodolac exposure is not associated with serious GI events compared with other NSAIDs, including COX-2 selective inhibitors, and etodolac use is not associated with increased of CV risk compared with non-users, users of conventional as well as COX-2 selective NSAIDs. Also, we hypothesized that the cardioprotective effects of ASA are reduced upon

concomitant administration with other NSAIDs. To test these theories, we carried out comprehensive systematic searches and performed a meta-analysis. We searched various databases up to October 2017 for randomized and non-randomized trials that reporting myocardial/vascular, all-cause mortality and/or GI (upper/lower bleeding, obstructions, or perforations) after etodolac use. We looked, also, for molecular interaction studies between the drugs and long-term clinical outcomes based on randomized clinical trials and epidemiological observations that reported the effect estimates of CV risks (OR, RR or HR; 95% CI) of the interacting drugs alone or in combinations. Comparisons were made between outcomes after ASA alone, other NSAIDs alone and ASA with naproxen, ibuprofen, celecoxib, meloxicam, diclofenac or rofecoxib. Titles and abstracts of included studies were retrieved and screened independently by two reviewers to identify potentially relevant studies. Additionally, the reference lists of the retrieved articles were scanned for relevant studies. A standardized, pre-piloted form was used to extract data from the included studies for assessment of study quality and evidence synthesis. The combined odds ratio estimates (OR; 95% CI) of GI and CV risks of etodolac were calculated using the random effect meta-analysis model when a significant heterogeneity across included trials is detected, otherwise fixed effect model was performed.

Our analyses of published evidence suggest that etodolac demonstrate a significantly lower rate of serious GI adverse events such as ulcers and bleeding compared with other NSAIDs. Furthermore, the drug use was not associated with an increased CV risk compared with non-user or other NSAIDs, such as naproxen and celecoxib. Our results in ASA and other NSAIDs interactions showed conflicting platelet aggregation data for ibuprofen, naproxen and celecoxib. Nevertheless, for naproxen, the interaction at the aggregation level did not amount to a loss of cardioprotective effects of Aspirin. Similarly, for ibuprofen, the results overwhelmingly suggest

no negative clinical CV outcomes following the combination therapy. Meloxicam and rofecoxib neither interacted with ASA at the level of platelet aggregation nor altered clinical outcomes. The clinical outcomes data for celecoxib and diclofenac are in conflict.

We concluded that etodolac is well tolerated in terms of GI adverse events and has a safe CV profile. Also, Aspirin appears to maintain its cardioprotective effect in the presence of naproxen, ibuprofen, meloxicam and rofecoxib. The limited available data suggest that the effect of interaction at the platelet aggregation level may dissipate shortly, or the reduced platelet aggregation yielded by the interaction may be sufficient for cardioprotection; i.e., no need for near complete aggregation. In addition, cardioprotective effect of Aspirin, despite reduced platelet aggregation caused by other NSAIDs, may be through its involvement in other mechanisms such as the renin angiotensin system and/or metabolism of arachidonic acid to biologically active compounds mediated by cytochrome P450.

Preface

This thesis is an original work by Zuhair Abdulrahman Al-Qahtani, completed under supervision of Prof. Fakhreddin Jamali at the University of Alberta.

Chapter 5 of this thesis has been published as Z. Al-Qahtani, F. Jamali "Clinical Outcomes of Aspirin Interaction with Other Non-Steroidal Anti-Inflammatory Drugs: A Systematic Review" *Pharm Pharm Sci*, 21 (1s) (2018): 48s-73s. I was responsible for the data collection and analysis as well as the manuscript preparation. Dr. Fakhreddin Jamali was the supervisory author and was involved with concept formation, data review and manuscript composition.

DEDICATION

This work is wholeheartedly dedicated to:

My father Mr. Abdulrahman Al-Qahtani, although he is no longer of this world, his memories continue to regulate my life.

My beloved mother Mrs. Umrah Mohammed, who has been my source of inspiration and gave me strength when I thought of giving up, who continually provide her moral, spiritual, and emotional support.

My dearest wife Mrs. Nawal Alshehri, who has been a constant source of support and encouragement, limitless giving and great sacrifice during the challenges of graduate school and life. I am genuinely thankful for having you in my life.

My precious sons: Abdulrahman and Ibrahim, whom I can't force myself to stop loving.

Acknowledgments

I am very fortunate to have performed my graduate work at the University of Alberta; therefore, there are many people to thank for their part in my success.

First and foremost, I would like to thank my enthusiastic supervisor, Prof. Fakhreddin Jamali, for giving me the great opportunity to join his team and support throughout my master's program. He is incredibly organized, and a great problem solver, both of these qualities were immensely helpful in moving my research forward.

I would also like to thank my supervisory committee members, Dr. Hoan Linh Banh, Dr. Sherif Mahmoud and Dr. Raimar Loebenberg for their scientific guidance, many insightful suggestions and demonstrated a sincere interest in my work. I would also like to mention Dr. Maria Ospina, University of Alberta, Dr. Theresa Charrois, University of Alberta, for their valuable comments and help in study design and data analysis, and Sandra Campbell and Janice Kung, librarians at John W. Scott Health Sciences Library University of Alberta for their help in databases search.

I would like to take this opportunity to say warm thanks to my colleagues Dr. Ali Aghazadeh, Dr. Forughalsadat Sanaee, Dr. Muhammad Waheed Asghar, Hanan Allawati, and Surur Ahmed for their support and help along the way of my thesis master's program.

I would also like to acknowledge the financial support from the King Saud University and the Saudi Cultural Bureau in Canada throughout my master's program.

Not least of all, I would like to express the most profound gratitude to my whole family, my mother Mrs. Umrah, my brothers and sisters, particularly my dearest sister Musfirah and beloved brother Muhammed, for their generous support they provided me throughout my entire life and mainly through the process of pursuing the master's degree.

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List of abbreviations

AA	Arachidonic acid
ADP	Adenosine 5'-diphosphate.
AFD	Adjusted for arthritis disease
ASA	Acetylsalicylic acid
CHF	Congestive Heart Failure
COX	Cyclooxygenase
CV	Cardiovascular
CT	Closure time
CYP	Cytochrome P450 enzyme
GI	Gastrointestinal
HR	Hazard ratio
hr./h	Hours
LDL	low-density lipoprotein
LPS	Lipopolysaccharide
MI	Myocardial infarction
NA	Not available
NANSAIDs	Non-Aspirin nonsteroidal anti-inflammatory drugs
NOS	Newcastle-Ottawa quality scale
NR	Not reported
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
OD	Odds ratio
OTC	Over the counter
PFA	Platelet function analyzer
PG	Prostaglandin
PGE_2	Prostaglandin E_2
PRP	Platelet rich plasma
RA	Rheumatoid arthritis
RAS	Renin angiotensin system
RCT	Randomized controlled trials
RR	Relative risk ratio
TxB_2	Thromboxane B_2

Chapter 1

1. Introduction

This thesis deals with some aspects of Nonsteroidal anti-inflammatory drugs (NSAIDs) side effects, specifically, those with cardiovascular (CV) and gastrointestinal (GI) roots. The emphasises are on an uncommonly used and neglected NSAID, etodolac, and Acetylsalicylic acid (ASA, Aspirin), the first marketed NSAID.

1.1. Non-steroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed as well as purchased over-the-counter medications to treat acute and chronic pain and inflammation associated with a range of medical conditions [1]. It is estimated that NSAIDs are prescribed to about 25% of Canadians for short-term use, however overall use is likely much higher with over-the-counter availability [2].

Acetylsalicylic acid (ASA) was the first NSAID introduced to the market in 1899 with the name of Aspirin [3]. Indomethacin and ibuprofen were the first non-Aspirin NSAIDs made in 1964 and 1969, respectively [4]. Since then, many compounds belonging to various chemical categories have been introduced as NSAIDs [4]. Most NSAIDs have acidic properties with high bioavailability and high protein binding ability, and they metabolized by the liver and renal enzymes [4].

1.2. Classification of NSAIDs

NSIADs can be categorized based on chemical structure [Table 1] and based on their selectivity towards cyclooxygenase (COX) enzymes [Table 2].

Table 1: Chemical classification of NSAIDs (adapted from reference [5] with modification)

Chemical group	Example
Salicylates	Acetyl salicylic acid (Aspirin), sulfasalazine
Propionic acid derivatives	Ibuprofen, naproxen, ketoprofen, flurbiprofen, fenoprofen, Oxaprozin
Pyranocarboxylic acids	Etodolac
Heteroaryl acetic acid	Tolmetin, diclofenac, ketorolac
Alkanones	Nabumetone
Indoleacetic, indeneacetic acid	Indomethacin, sulindac, etodolac
Oxicams	Piroxicam, meloxicam Ketorolac
Fenamates	Mefenamic acid, meclofenamic acid
Diaryheterocycles (coxibs)	Rofecoxib, celecoxib, veldecoxib, paracoxib, etoricoxib, lumaricoxib

Table 2: Classification of NSAIDs based on COX selectivity (adapted from references [6, 7] with modification)

Non-Selective NSAIDs	Moderately COX-2 selective NSAIDs	Highly COX-2 selective NSAIDs
Acetylsalicylic acid (Aspirin)	Celecoxib	Etoricoxib
Ibuprofen	Etodolac	Lumiracoxib
Naproxen	Meloxicam	Parecoxib
Diclofenac	Nimesulide	Rofecoxib
Ketorolac		Valdecoxib
Flurbiprofen		
Ketoprofen		
Indomethacin		
Tolmetin		
Piroxicam		

1.3. Therapeutic Use of NSAIDs

NSAIDs are used to relieve symptoms like pain and discomfort associated with chronic conditions such as rheumatoid arthritis (RA) [8] and osteoarthritis (OA) [9]. NSAIDs also used for other indications such as juvenile arthritis, psoriatic arthritis, Reiter's syndrome, systemic lupus erythematosus, rheumatic fever, thrombosis, pericarditis, Kawasaki disease, gout, gouty arthritis, ankylosing spondylitis, patent ductus arteriosus and dysmenorrhea [4].

1.4. Mechanism of action of NSAIDs

In 1971, Vane and Piper described the mode of action of NSAIDs. NSAIDs exert their analgesic, anti-inflammatory and antipyretic effects through inhibition of the biosynthesis of prostaglandins (PGs) and prostanoids by preventing the binding of arachidonic acid (AA) to the COX enzyme [10]. Later, COX enzyme found to be existed in two isoforms COX-1 and COX-2 [11-13]. COX-1 enzyme is responsible for the production of prostaglandins and thromboxane, which are involved in normal physiological functions such as renal function, mucosal protection in the gastrointestinal tract, platelet aggregation in the platelets. COX-2 is induced by local injury and inflammatory mediators i.e., cytokines [4, 14]. The prostaglandins produced by COX-2 contribute to pain and fever but are also involved in renal function, tissue repair and reproduction [10]. Both COX-1 and COX-2 play a role in homeostasis: prostacyclin (PGI_2) is produced via COX-2 of endothelial cells and has antithrombotic effects, and thromboxane is produced by COX-1 found in platelets and is prothrombotic [10, 15] [Figure 1]. Lately, another COX enzyme (COX-3) has been recognized [16]. However, its function has not been fully described [17].

1.5. Adverse Effects of NSAIDs

NSAIDs at recommended therapeutic doses and for short-term are usually well tolerated.

However, high risk of developed adverse effects is associated with presence of co-morbidities, use of high doses or for longer duration [4]. Adverse effects range from mild and common to severe and infrequent: dyspepsia, gastric or duodenal ulceration, fluid retention, renal toxicity and subsequent hypertension, as well as increased incidence of CV adverse events [18].

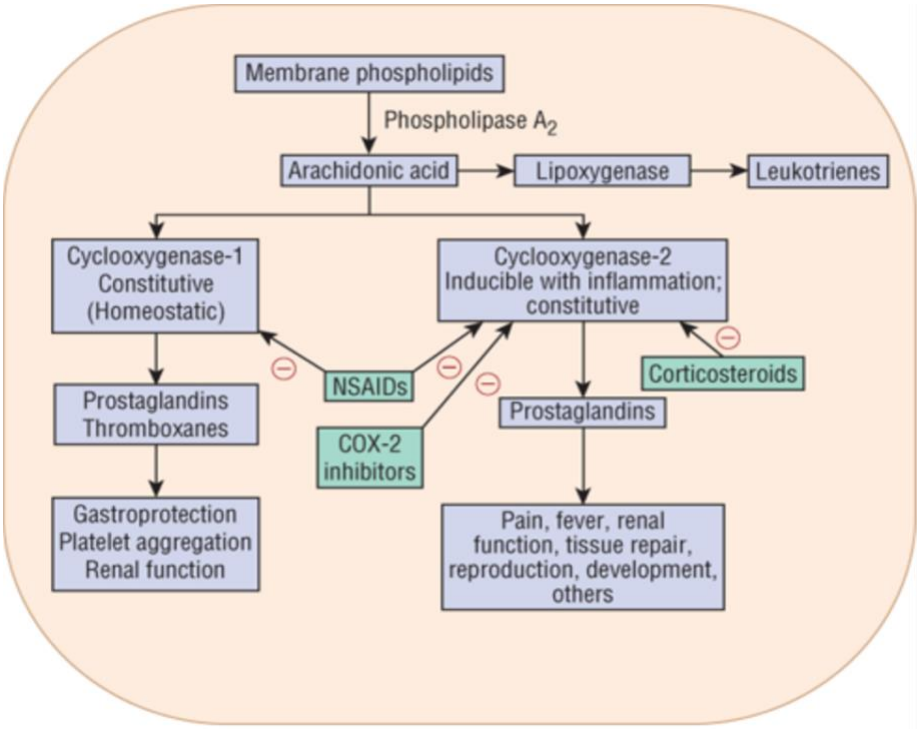


Figure 1: Pathways of prostaglandin synthesis (adapted from reference [19] with modification).

1.5.1. Gastrointestinal adverse effects

1.5.1.1. Upper GI side effects

The most common adverse effects of NSAIDs involve the GI system such as heartburn, nausea and dyspepsia are limited to the upper GI tract [4, 20]. The COX-2 selective inhibitors appear more appealing with less GI toxicity [21]. Nevertheless, the effects are mild and can be minimized with use of available gastro-duodenal-protective treatments [22]. Serious upper GI complications such as perforation or bleeding resulted from gastric or duodenal ulcers occur in up to 5% of patients in

the first year of treatment with non-selective NSAIDs [23] and less frequently associated with COX-2 selective NSAIDs [20]. However, these effects are often easy to notice and diagnose.

1.5.1.2. Lower GI side effects

Potentially more serious adverse effects of NSAIDs are often occur in the lower GI tract. These complications are not easy to notice and hard to diagnose, hence, less common events such as ulcer, bleeding, inflammation and scarring in small intestine and colon are reported [24]. These adverse effects can progress into more serious complications such as diaphragm disease [25]. Furthermore, delayed release formulations (e.g., enteric coated and sustained release) of NSAIDs may increase such risk [26]. Available protective approaches such as mucosal protective agents (e.g., misoprostol) [27], H_2-receptor blockers (e.g., famotidine) [28] or proton pump inhibitors (e.g., omeprazole) [29] can minimize the upper GI damage attributed to the use of NSAIDs but their effectiveness towards lower GI effects has not been confirmed.

1.5.2. Renal adverse effects

Prostaglandins control renal blood flow, glomerular filtration rate and salt and water excretion by the kidneys. The inhibition of PGs by NSAIDs is accounted for the deterioration in kidney's normal functions. This may be aggressive in patients with high risk such as a history of renal dysfunction or reduced perfusion [15].

Nephrotoxicity adverse events associated with the use of NSAIDs is estimated to be 1-5% among current users [30] but it can go as high as 20% among high risk patients due to co-morbidities [31]. Renal toxicity may present in different symptoms such as hyperkalemia, sodium retention, acute renal failure, declined glomerular filtration rate, nephrotic syndrome with acute interstitial nephritis, renal papillary necrosis and edema [30, 31]. These effects are dose-dependent, and many are short-term and reversible upon discontinuing the medication [4].

It has been established that any change in the renal functions may influence CV system. Various forms of CV failures caused by NSAIDs have been observed including hypertension and exacerbated heart failure [32]. Thus, care is needed with NSAIDs, of all classes, in people on antihypertensive, the elderly and others at risk of renal diseases [33].

1.5.3. Cardiovascular and cerebrovascular adverse effects

Following the APPROVe (Adenomatous Polyp PRevention on Vioxx) trial, which brought to light the increased risk of CV events with rofecoxib, a potent COX-2 selective NSAID, the CV safety of COX-2 selective inhibitors as well as traditional nonselective NSAIDs has been extensively investigated. The APPROVe trial was designed to evaluate the efficacy of treatment with rofecoxib (25 mg/day; n=1287) to reduce the risk of recurrent adenomatous polyps among patients with a history of colorectal adenomas compared with placebo (n=1299). However, the trial was stopped due to CV safety reports after 18 months of treatment. Patients treated with rofecoxib reported a greater risk of Myocardial infarction (MI) and ischemic cerebrovascular, congestive heart failure (CHF), and cardiac failure events [34]. Moreover, a clinical trial, Vioxx Gastrointestinal Outcomes Research (VIGOR), that compared the mortality rates between rofecoxib (50 mg/day) and naproxen (1000 mg/day) in 8076 RA patients, with no ASA use revealed a four-fold rise in CV risks among patients taking rofecoxib compared to naproxen (0.4% vs 0.1%) [35]. As a result of these findings, rofecoxib has been globally withdrawn.

Nonetheless, the Celecoxib Long Term Arthritis Safety Study (CLASS) trial that compared a relatively high dose of another COX-2 selective NSAID, celecoxib (800 mg/day) with ibuprofen (2400 mg/day) and diclofenac (150 mg/day) in 8059 patients with OA and RA, found no significant difference between the examined drugs in the CV incidence irrespective of concomitant use of ASA [36].

Mukherjee *et al.* suggested that both celecoxib and rofecoxib may increase the CV risk [37]. Authors explained the reason behind the different observations between VIGOR and CLASS studies may be the different comparators used in the trials; naproxen and ibuprofen or diclofenac, respectively. In VIGOR trial naproxen use was associated with a decreased of the CV risk, but rofecoxib increased the relative risk. While, in the CLASS trail, the comparator was ibuprofen or diclofenac with relatively high-risk ratio rendering the difference between them and celecoxib insignificant. In addition, use of low-dose ASA in the CLASS study and antithrombotic effect of naproxen in the VIGOR study are other plausible explanations for the differences between the two studies' outcomes [37]. Another possible reason for the observed difference between the two reported outcomes is the treatment duration , 6 months (CLASS) *vs* 12 months (VIGOR) [38].

It has been suggested that the COX-2 selective inhibitors may increase the risk of CV events primarily due to the imbalance caused by inhibition of COX-2 mediated prostacyclin production without inhibition of COX-1 mediated thromboxane production [39]. However, it has been established that both COX-2 selective and traditional nonselective NSAIDs at therapeutic doses have potential for cardiovascular toxicity [10, 40].

Recently, McGettigan and Henry reviewed the published evidence regarding CV risk profiles of NSAIDs in high, medium and low income countries [41]. The results revealed that NSAIDs including rofecoxib, etoricoxib and diclofenac have the highest CV risk compared to naproxen. While, ibuprofen, meloxicam and indomethacin demonstrated a moderate CV risk. Celecoxib and ibuprofen demonstrate CV risk in high doses only, in contrast to low doses used in clinical practice [41].

Nevertheless, the CV side effect has been addressed with many NSAIDs since the withdraw of rofecoxib. A confounding factor in identifying the latter side effect of NSAIDs is

underlying inflammatory conditions that have been determined to be associated with increased CV risks, i.e., both the inflammatory diseases and NSAIDs may result in CV complications. It is well established that inflammatory conditions, such as arthritis, adversely influence the CV system so that patients with arthritis are afflicted with CV conditions to a significantly greater extent than the general population [42]. Moreover, another risk factor for increased CV risk is a diminish in the pharmacological effect of drugs used to treat CV complications in inflammatory conditions [42].

Acetylsalicylic acid (Aspirin) is not only used for its analgesic, antipyretic and anti-inflammatory properties, but for its anti-platelet beneficial effects to reduce CV risk such as nonfatal MI or cardiac death [43]. Furthermore, low-dose ASA, alone or in combination, is recommended for the secondary prevention of acute ischemic stroke and transient ischemic attack [44-46]. Ironically, despite the acknowledge reduced in CV risk of NSAIDs, reports have appeared of an interaction between ASA and other NSAIDs at the platelets level while is the suggested mechanisms for cardioprotective effect of ASA.

1.6. Selection of NSAIDs for this study

Overall, all NSAIDs may cause GI and CV adverse events with celecoxib, COX-2 selective NSAID, and naproxen, nonselective NSAID, associated with less risks as compared with other investigated NSAIDs. Detailed studies focused on other potentially safe NSAID with favorable COX-2 selectivity such as etodolac are lacking. Also, it is unclear whether the reduced CV risk of some NSAIDs is due to concomitant use of low-dose ASA.

Previously, our team has reported that CV risk associated with NSAIDs exposure is heterogeneous in its nature as some demonstrate higher and some lower potential of causing such risk. The study concluded that meloxicam use is associated with a limited, although manageable,

vascular risk and etodolac, a COX-2-selective NSAID, also may have a similar CV safety profile to that of meloxicam [47]. Interestingly, systematic reviews and epidemiological studies, although not focusing on etodolac, also suggested a more favorable overall GI and CV safety profiles for the drug [20, 48-50].

We wish to examine available clinical data further and provide high quality, up to date evidence of GI as well as CV safety profiles of etodolac. We selected etodolac, an uncommonly used generic NSAID with a higher preference for COX-2 receptors and compared the associated risks to other non-selective NSAIDs, like naproxen, and COX-2 selective NSAIDs, like celecoxib. Also, we examined available clinical and experimental data regard short and long-term clinical consequences of adding low-dose ASA to NSAIDs regimen. We limited our study to only six non-ASA NSAIDs, i.e., ibuprofen, naproxen, diclofenac, celecoxib, rofecoxib, and meloxicam.

1.7. Etodolac

1.7.1. Chemistry

Etodolac is a chiral molecule classified chemically a member of the pyranocarboxylic acid class with a molecular formula of $C_{17}H_{21}NO_3$ and also known chemically as 2-(1,8-diethyl-4,9-dihydro-3H-pyrano[3,4-b]indol-1-yl)acetic acid [Figure 2] [4, 51].

1.7.2. Epidemiology of etodolac prescribing

In 1991, etodolac was first approved by the US Food and Drug Administration (FDA) for treating acute pain, in adults but not children. Late 1997, etodolac was approved in Canada for acute or chronic use as a general analgesic for pain associated with RA and OA as well as a general analgesic [52].

Etodolac doses of 300-400 mg daily have tended to be more effective than ASA of 3-4 g daily and provided similar efficacy to sulindac 400 mg daily [53]. Moreover, the analgesic

efficacy of etodolac 200 mg is comparable to acetaminophen 600 mg plus codeine 60 mg, and etodolac 400 mg is significantly superior to the latter combination [54]. Clinical doses of etodolac 200-300 mg twice daily for relief of low back or shoulder pain have been equated to analgesia with naproxen 500 mg twice daily [55]. In postsurgical pain, etodolac 100-200 mg was approximately equivalent to ASA 650 mg in providing pain relief, although etodolac had a longer duration of action [56]. In arthritis, recommended doses of etodolac are 300 mg two to three times daily or 400-500 mg twice daily and a total of maintenance dose of 600-1000 mg divided 2-4 times daily up to a maximum of 1200 mg per day. Maintenance can also be performed with the extended release formulation: 400-1000 mg divided 2-4 times every 24 hours up to a maximum of 1200 mg/day [57]. It has been well-known that etodolac possesses a more favourable therapeutic index between anti-inflammatory effects and gastric irritation than other NSAIDs [58].

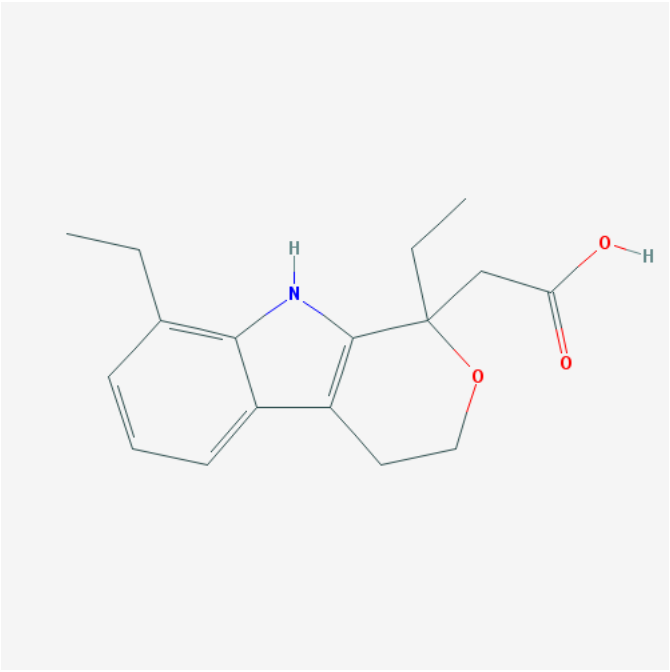


Figure 2: Chemical structure of etodolac (adapted from reference [51])

1.7.3. Pharmacodynamics properties

Etodolac is an anti-inflammatory agent with analgesic and antipyretic activity. The therapeutic effects of etodolac are achieved through inhibition of the synthesis of PG (COX enzymes) involved in fever, pain, swelling and inflammation. Etodolac is administered as a racemate. As with other NSAIDs, the S-form has been shown to be active while the R-form is inactive. Both enantiomers are stable and there is no evidence of R- to S- conversion *in vivo* [59].

Compared with other NSAIDs, etodolac has shown consistent selective COX-2 inhibition activity. A study reported that etodolac showed 1000 times more selective for COX-2 over COX-1[60]. Moreover, etodolac was three times more selective for COX-2 enzyme than meloxicam and celecoxib, COX-2 inhibitor NSAIDs [15]. Indeed, etodolac at therapeutic concentrations demonstrated similar magnitude of refecoxib, a highly selective COX-2 inhibitor NSAID [61]. Hence, the evidence for etodolac as a highly selective COX-2 inhibitor is very robust.

1.7.4. Pharmacokinetics properties

1.7.4.1. Absorption

Etodolac is administered orally and available in either tablet or capsule formulation. It follows a linear pharmacokinetic profile. Etodolac is well absorbed and its systemic bioavailability is 100% as compared to solution and at least 80% as determined from mass balance studies. After oral administration of etodolac, peak serum concentrations of 16 and 25 mg/L are attained within 2 hr. of administering 200 and 400 mg, respectively. Food does not affect the bioavailability of the drug. There are no human clinical data on the influence of antacids medication on the bioavailability of etodolac. However, animal studies indicated that the bioavailability of etodolac is not affected by the concomitant administration of the antacid drugs [62, 63].

1.7.4.2. Distribution

Similar to other NSAIDs, the drug is highly plasma protein bound in healthy subjects (> 99% bound, primarily to albumin). The estimated volume of distribution after a single oral dose of 400 mg is 0.4 L/kg, slightly higher than that reported for other NSAIDs such as ibuprofen, naproxen and fenoprofen [64]. The free fraction is less than 1% and is independent of etodolac total concentration over the dose range studied. It is not proven whether etodolac is excreted in human milk; however, based on drug's physical-chemical properties, excretion into breast milk is likely. Data from *in vitro* studies show that the etodolac free fraction is not significantly altered by drugs such as acetaminophen, ibuprofen, indomethacin, naproxen, piroxicam, chlorpropamide, glipizide, glyburide, phenytoin, and probenecid.

1.7.4.3. Metabolism and excretion

Etodolac is extensively metabolized in the liver. However, the role, if any, of a specific cytochrome P450 (CYP450) system in the metabolism of etodolac is unknown. Numerous etodolac metabolites have been identified in human plasma and urine. The metabolites include 6-, 7-, and 8-hydroxylated-etodolac and etodolac glucuronide. More than 60% of the metabolites are hydroxylated with glucuronic conjugation.

Etodolac is excreted primarily in the urine, however, 16 % of the dose recovered from feces. The mean oral clearance of etodolac following oral dosing is 49 (± 16) mL/h/kg. Approximately 60% of etodolac dose is excreted within 24 hr. and nearly 90% is recovered within 7 days. Approximately 1% of a drug dose is excreted unchanged in the urine with 72% of the dose excreted into urine as parent drug plus metabolite: etodolac glucuronide (13%), 6-, 7-, and 8-hydroxylated metabolites (5%), hydroxylated metabolite glucuronides (20%) and other metabolites (33%). The elimination half-life of etodolac is approximately 7 hr. in healthy subjects

is similar for both enantiomers. Although renal elimination is a significant pathway of excretion for etodolac metabolites, no dosing adjustment in patients with mild to moderate renal dysfunction is generally required [65, 66].

1.7.5. Drug interaction

There is no clinical pharmacokinetic interactions between etodolac and other highly plasma bound drugs such as warfarin, glyburide, and phenytoin [52]. Moreover, etodolac has no clinically relevant interactions with other arthritis medications including methotrexate.

1.7.6. Adverse effects

It has been well documented that the most common adverse effects seen with NSAIDs are GI related. Nevertheless, etodolac is generally well tolerated at doses used in the treatment of RA and degenerative joint disease. In arthritic patients treated with etodolac, most adverse reactions were mild and transient. The most common GI related adverse events occurring in less than 10% of arthritic patients are: abdominal pain (3-9%), diarrhea (3-9%), dyspepsia (10%), flatulence (3-9%), nausea (3-9%), constipation (1-3%), gastritis (1-3%), melena (1-3%) and vomiting (1-3%). Other common non-GI related adverse events include asthenia/malaise (3-9%), dizziness (3-9%), depression (1-3%), nervousness (1-3%), pruritus (1-3%), rash (1-3%), blurred vision (1-3%), tinnitus (1-3%), dysuria (1-3%) and urinary frequency (1-3%).

The most serious GI related adverse events of NSAIDs are perforation, ulcerations and bleedings that require hospitalization and sometimes resulting in death. Initial reports have suggested that the incidents of perforation, ulcerations and bleedings are lower in etodolac compared with traditional non-selective NSAIDs [50]. A recent meta-analysis of 29 randomized controlled trials revealed significantly fewer clinical upper GI events (perforation, ulcerations and bleedings) of etodolac treatment (600-1000 mg / day) in OA and RA patients (RR 0.32, 95% CI:

0.15-0.71) [20]. It was also confirmed by an endoscopic examination of healthy volunteers. The study reported that etodolac showed no significant increase in GI erosion compared to placebo even at the highest dosage of 1000 mg/day whereas ibuprofen, naproxen and indomethacin showed significant increase [67].

In comparison to COX-2 selective and non-selective NSAIDs, CV related adverse effects associated with etodolac use have not been thoroughly investigated. Nevertheless, few studies reported a positive CV safety profile of the latter. Warner et al. [50] compared etodolac (≥ 800 mg/day) with naproxen (≥ 1000 mg/day) in a historical cohort analysis among 38,258 patients for 6 years. They used celecoxib (≥ 200 mg/d) and rofecoxib (≥12.5 mg/d) as positive controls. As compared to naproxen, the increased risk of MI was not significant for etodolac (OR, 1.32, 95% CI 0.81-2.16, p = 0.27) but was so for celecoxib (OR=2.18, 95% CI 1.09-4.35, P=0.03) and rofecoxib (OR = 2.16, 95% CI 1.04-4.46, P=0.04). The authors' conclusion on the safety of etodolac that confirms another report [41], of course, is on the assumption that naproxen does not increase the risk of MI. The same observation also reported when ibuprofen is used as a positive control [49].

Etodolac has a high COX-2 selective affinity, yet no significant renal adverse effects in either healthy or patients with moderately impaired renal functions were reported [68, 69]. Shand *et al.* investigated anti-inflammatory doses of etodolac and renal adverse effects compared with placebo, ASA and other NSAIDs. The results revealed that the renal function abnormalities, i.e., blood urea nitrogen and serum creatinine levels, among etodolac users were not significantly different compared with those receiving placebo. Moreover, etodolac group had a significantly lower incidence of blood urea nitrogen results than either ASA or sulindac groups [70].

1.8. Acetylsalicylic acid (ASA)

1.8.1. Chemistry

Acetylsalicylic acid is comprised of the active compounds acetic acid and salicylic acid, forming ASA with molecular formula of $C_9H_8O_4$ [Figure 3] [51].

1.8.2. Epidemiology of Aspirin prescribing

Acetylsalicylic acid was the first NSAIDs introduced to the market in 1899. As a salicylate derivative, ASA possesses the three properties of NSAIDs: analgesic, antipyretic, and anti-inflammatory. Thus, it uses in the temporary relief of various pain and inflammation signs and symptoms associated with various conditions (including RA, juvenile rheumatoid arthritis, systemic lupus erythematosus, OA, and ankylosing spondylitis), and is also used to reduce the risk of death and/or nonfatal MI in patients with previous infarction or unstable angina pectoris [3, 71].

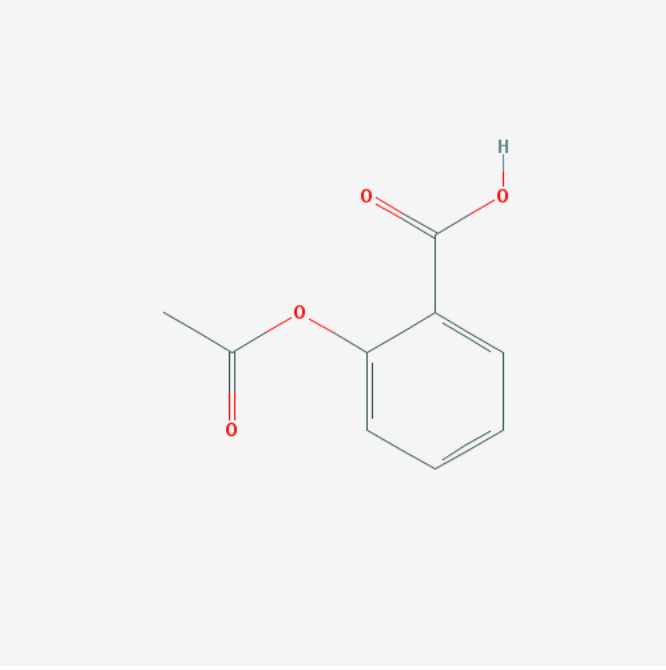


Figure 3: Chemical structure of ASA (adapted from reference [51])

Acetylsalicylic acid is indicated at doses of 3 g daily (every 4-6 hours) for anti-inflammatory efficacy in RA and OA conditions. However, it became increasingly clear that clinically relevant ASA actions, i.e., antithrombotic, analgesic, antipyretic, and partially the anti-inflammatory effects of ASA, can be obtained at much lower doses, i.e., 1-2 g daily. While, the use of the lowest effective dose (75–100 mg/day for long-term treatment) is currently the most appropriate strategy to maximize its antiplatelet properties [72].

1.8.3. Pharmacodynamics properties

Acetylsalicylic acid inhibits the biosynthesis of PGs by means of an irreversible acetylation and consequent inactivation of COX; thus, ASA inactivates COX permanently. ASA is a more potent inhibitor of both PG synthesis and platelet aggregation than its other salicylic derivatives due to the acetyl group on the ASA molecule, which irreversibly inactivates COX through acetylation. This prevents the conversion of AA to thromboxane A_2 and subsequently the platelets aggregation is inhibited for their lifespan (7-10 days) [73]. Thus, chronic administration of low-dose regimens, ranging between 75-100 mg, is required to inhibit two essential stages in the pathophysiology of thrombosis and MI; platelet activation and aggregation [74].

1.8.4. Pharmacokinetics properties

1.8.4.1. Absorption

Orally administered ASA is generally absorbed rapidly and completely in the stomach and small intestine. Thus, Peak plasma levels occur in 30-40 min after ingestion, and the inhibition of platelet function is apparent by 1 hour. However, this may vary according to the dosage form, i.e., enteric-coated tablets may take up to 4-8 hours to reach peak plasma levels. The oral bioavailability is approximately 40-50% over a wide range of doses, however, low

bioavailability has been reported for enteric-coated tablets [75]. Food does not appear to decrease the bioavailability of ASA.

1.8.4.2. Distribution

Acetylsalicylic acid is highly bound to plasma albumin (99.5%). At antiplatelet and analgesic doses, volume of distribution amounts to about 0.2 L/kg, but at high doses the volume of distribution is increased to about 0.5 L/kg [76].

1.8.4.3. Metabolism and elimination

Acetylsalicylic acid is rapidly hydrolyzed primarily in the liver to salicylic acid, which is conjugated with glycine (forming salicyluric acid) and glucuronic acid and excreted largely (> 98%) in the urine. The speed of renal excretion ultimately determines the plasma level and half-life of salicylate. The plasma half-life is approximately 3 hours for doses of 300-650 mg while with doses of 1-2 g, the half-life is increased to 5-9 hours. The approximate recovery rates of salicylate and its metabolites at a single dose (0.5-1 g) in urine are as follows: 70-75% salicyluric acid, including glucuron-conjugated products, 10% salicylic acid, 1-2% gentisic acid, and < 1% gentisuric acid [77, 78].

1.8.5. Drug interaction

Acetylsalicylic acid dose not apparent to interact with proton-pump inhibitors, angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers. However, some other NSAIDs, used chronically and at full doses, might interfere with antiplatelet activity of low-dose ASA. The type of NSAID might be relevant for optimizing CV prevention, especially for patients requiring chronic anti-inflammatory/analgesic treatment, such as elderly patients with OA [79]. It is worth to mention that the timing of dosing of some NSAIDs, like ibuprofen, and low-dose ASA is important for preserving the cardioprotective effect of ASA. Thus, it is recommended that for

single doses of ibuprofen to be taken at least 8 hours before or at least 30 minutes after low-dose ASA. Nevertheless, this strategy might not be practical with the chronic administration of other NSAIDs.

1.8.6. Adverse effects

ASA, as other nonselective NSAIDs, is expected to induce GI toxicity in dose-dependent fashion (30-1,300 mg daily), as revealed in randomized clinical trials [80]. It is important to note that such a risk is appeared to increase with formulations that are designed to release in the intestine; e.g., enteric coated and sustained release [81]. Some animal studies reported that the use of the latter formulations may shift the GI side effect of NSAIDs including ASA from easy noticeable upper segments to the less accessible lower part of the GI tract [26].

Chapter 2

2. Thesis rationale and hypotheses

2.1. Rational

The CV safety of nonsteroidal anti-inflammatory drugs (NSAIDs), precisely cyclooxygenase-2 (COX-2) inhibitors, has attracted scientific as well as public interest since the withdrawal of rofecoxib in 2004. In 2005, the US Food and Drug Administration (FDA) issued a warning for the users of selective COX-2 inhibitors as well as non-selective NSAID diclofenac [82]. Later, it was found that the NSAIDs risk could be lowered with the concomitant use of low-dose Acetyl salicylic acid (ASA) [83]. Consequently, the FDA issued a warning on the cardiovascular (CV) risk included all NSAIDs, but excluded low-dose ASA users [84].

Nevertheless, many epidemiological studies on the CV risk of NSAIDs, including generic drugs, have suggested that not all member of the class exhibit the same level in causing such incidences [40]. Recently, our group has reported that meloxicam, a generic NSAID, is associated with a low increased of CV risks compared with other NSAIDs [47]. These findings confirmed results of a previous report [41]. McGettigan and Henry reviewed the published evidence regarding CV risk profiles of NSAIDs in high, medium and low-income countries. As compared to naproxen, the results showed that meloxicam and indomethacin demonstrated a moderate elevation of the risk while etodolac did not [41]. Therefore, it can be established that the CV risk of NSAIDs cannot be generalized to the entire class or explained with COX-2 selectivity alone; rather there may be some other pharmacological or pharmacokinetic explanations that need to be investigated.

Etodolac is a generic, uncommonly used, NSAID possess high COX-2 inhibitory properties [61]. The FDA approved etodolac in 1991, and since then etodolac has been marketed

as a general analgesic and for acute and chronic treatment of signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) [85, 86]. Later, etodolac has been introduced in Canada for the same indications [87]. Nevertheless, safety reports were focused only on the GI toxicity of the drug. Thus, few clinical trials have been conducted to explore its CV risk.

Many reports covering the CV effects of NSAIDs lack crucial details to enable meaningful conclusions. For instance, some previous systematic reviews that included etodolac in their comparisons, have reported composite CV outcomes regardless of the nature of the reported adverse events, duration of use, doses and type of comparators (placebo vs active control). Notably, most of these reports have even ignored the influence of underlying inflammatory conditions as well as concomitant use of ASA while reporting combined CV risk estimates [40, 88, 89]. It is well established that inflammatory diseases, such as arthritis, are associated with a significantly greater CV risk than general population [90]. Moreover, some systematic reviews and meta-analyses that reviewed published evidence regarding CV risk of NSAIDs have reported pooled estimates of combined of different risk estimates, like, odds ratio (OR), risk ratio (RR) and hazard risk (HR). Overall, their findings exhibited that rofecoxib and diclofenac had the highest overall risks while ibuprofen and naproxen had the lowest overall risks [91]. Furthermore, of the less studied NSAIDs, they concluded that etodolac had demonstrated high overall CV risks [91]. It is worth to mention that, however, these three risk estimates (HR, OR, and RR) are relative measures of the CV effects, authors failed to justify combining them all together since reported HRs deal with different time data unlike RR or OR [92].

The association between etodolac exposure and significant increase of CV risk is still controversial due to lack of head-to-head comparison trials and poorly conducted systematic reviews and meta-analyses, therefore, in this thesis, CV toxicity profile of etodolac will be assessed

as compared to conventional and COX-2 selective NSAIDs. Additionally, CV risks associated with concomitant use of low-dose ASA with etodolac and other NSAIDs will be evaluated. In order to allow a comprehensive risk assessment, other adverse effects should be considered as well, thus, gastrointestinal (GI) adverse effects will be assessed.

Daily administration of low-dose ASA has been shown to be beneficial in preventing recurrent CV events. Although unproven, the cardioprotective effect of ASA may diminish by the concomitant use of other NSAIDs, such as ibuprofen. Hypothetically, it is well known that some NSAIDs interact, on the platelet level, with ASA since the drugs bind and inhibit the COX enzymes which lead to inhibition of prostanoids biosynthesis including PGs, prostacyclins, and thromboxanes [4]. This is while many observational studies and clinical trials suggest that ASA reduces CV risk attributed to the use of other NSAIDs. Thus, the clinical therapeutic outcomes of such an interaction need to be evaluated. Moreover, a differentiation between NSAIDs is essential as not all NSAIDs carry the same potential of influencing anti-platelet effects of ASA.

2.2. Thesis hypotheses

- Etodolac exposure is not associated with an increased CV risk or serious GI toxicity, such as ulcer or bleeding. Also, the type of comparator used in a study, underlying inflammation conditions and concomitant use of low-dose ASA are significant factors in estimation of such risks.
- The cardioprotective benefits of ASA are reduced upon concomitant administration of ASA with other NSAIDs.

2.3. Thesis objectives

- A systemic review and meta-analysis of available clinical trials and observational studies to determine the risk of CV and GI adverse events among users of etodolac in comparison with conventional NSAIDs such as naproxen as well as other COX-2 selective NSAIDs such as celecoxib. The aim was to reveal the association of etodolac, a generic COX-2 selective NSAID, with GI (mild or serious), myocardial infarction and vascular events focusing on individuals who recently started etodolac treatment and to provide insight into the effect of underlying inflammatory diseases and use of low-dose ASA on the association. Additional sensitivity analyses were conducted to confirm the robustness of these findings.
- A systemic review of available clinical data to test whether co-administration of ASA with other NSAIDs has significant negative clinical outcomes, i.e., loss of cardioprotective effect of ASA.

Chapter 3

3. Systematic review

3.1. Introduction

Lately, systematic reviews are becoming demanded due to challenges facing clinicians to keep up with modern medicine. There is too much information around for health-care providers and decision makers to keep up to date. More importantly, high-quality data are often not easy to find. Thus, developing a summary of the available literature and performing a critical scientific review of the obtained data is becoming more crucial. According to the Cochrane manual for Systematic Reviews and Meta-Analysis [93], "a systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question". It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing reliable findings from which conclusions can be drawn and decisions made.

The key characteristics of a systematic review are:

(a) a clearly stated set of objectives with an explicit, reproducible methodology;

(b) a systematic search that attempts to identify all studies that would meet the eligibility criteria;

(c) an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and

(d) systematic presentation, and synthesis, of the characteristics and findings of the included studies.

3.2. Meta-analysis

Meta-analysis is the use of statistical techniques for summarizing and reviewing included published quantitative research in a systematic review. This quantitative analysis allows combining the available data of individual observations and enables to analyze a wide variety of research questions. Furthermore, meta-analysis provides more precise effect estimates with higher statistical power than individual included studies.

3.3. Planning a systematic review and meta-analysis

The ultimate goal of systematic reviews is to answer a clearly formulated research question through systematic and explicit methods to identify, select, and critically apprise all relevant studies. Meta-analysis aims to integrate the review results into a common effect estimate. Conducting a systematic review and meta-analysis can be summarized in ten essential stages [94-98]:

1. Define a clear clinical question. Research question should state five main points:
    i. Population (patients) group of interest.
    ii. Interventions (exposures) being investigated.
    iii. Comparator (control) group intervention(s).
    iv. Outcomes (endpoints) of interest.
    v. Study design(s).
2. Define exclusion and inclusion criteria for included studies and if any limitations will be applied.
3. Plan the search methods. It is important that the methods of systematic review (with or without meta-analysis) to be implemented should be established and documented in advance since systematic reviews are retrospective. Thus, publication of search and

analysis protocol for a review prior to conduct the search of the available data reduces the impact of reviews' biases, for instance; reporting bias, consequently improve quality and increase confidence that policy or practice informed by the findings of a systematic review is based on best-quality of available evidence. In addition, published protocol provides transparency in the review process, reduces the potential for duplication, and allows peer reviewers of the planned methods by comparing of manuscript findings with the review protocol.

4. Perform a comprehensive systematic search using pre-defined search terms in order to capture all available studies addressing the research question in the medical literature. Ideally, at least 2 electronic databases should be used, and grey literature, hand-searching, and reference lists should be checked.
5. Screen titles and abstracts to identify potential studies according to the eligibility criteria. Then, full-texts of relevant studies should be retrieved and assessed against eligibility criteria. This stage should be done independently by at least 2 reviewers and any disagreement should be resolved through consensuses process.
6. Assess internal validity of included studies, i.e., whether the included studies have minimized bias in their study design. The Cochrane collaboration has developed a validation tool to help assess methodological quality of included studies [99]. In section 3.4, I will be more elaborate on assessing the risk of bias in included studies.
7. Perform the data extraction independently by 2 members of the research team using standardized forms developed a priori to eliminate discrepancies. Reviewers may contact authors for unpublished data or answers to any questions during data extraction.

8. Meta-analysis can add more value to the review (section 3.5). However, reviews must ensure that outcomes of the included studies were measures in similar fashion and reported consistently. Moreover, reviews must ensure that participants, interventions, comparisons and outcomes are homogeneous enough to enable meaningful conclusions, i.e., qualitative assessment of heterogeneity. In section 3.6, I will illustrate the importance of heterogeneity in systematic reviews and meta-analysis.
9. Interpretation of the results of meta-analysis give an answer and conclusion to the clinical research question. Reporting systematic reviews can be tricky; however, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement offers an outline of what should be reported in a published systematic review [100].
10. Maintain and update the review. Since a systematic review's conclusions on a given subject are driven by the best available and most up-to-date evidence, which is often dynamic and continually evolving, it is important to maintaining and updating these reviews as new clinical trials emerged.

3.4. Assessment of Risk of bias

The methodological quality (validity) of the included studies is essential as it may influence the overall credibility of a meta-analysis. Consequently, assessing methodological quality of included clinical trials is an important component of a systematic review, and should influence the analysis, interpretation and conclusions of the review.

Generally, the validity of any included study has two elements. First element is 'external validity' which relates to whether study's findings can be generalized to answer the clinical research question at hand. The second element of a study's validity is 'internal validity' which

relates to whether it answers its research question 'correctly', that is, in a manner that is free from bias.

The study design plays significant role on assessing the methodological quality of included studies. Randomized Controlled Trails (RCTs) are often considered high quality evidence which makes their interpretation relatively easy. However, the restrictions applied of the involved group of patients may compromised the generalization of their findings. On the other hand, observational trials are less standardized, subsequently more heterogeneous in methodological quality. However, they reflect the clinical practice of the real-world situations.

Many tools have been developed for assessing the methodological quality of studies for use in the context of a systematic review. Most tools are either scales, in which various components of quality are scored and combined to give a summary score; or checklists, in which specific questions are asked [101]. However, the Cochrane Collaboration encourage reviews' authors to use the domain-based evaluation in which critical assessments are made separately for different domains. The Cochrane tool for assessing risk of bias was developed to assess the validity of included RCTs in a systematic review [99].

a) Randomized Controlled Trials (RCTs)

Two review's authors should independently assess the risk of bias of included RCTs by considering the following six main domains [99]:

1. **Selection bias**: random sequence generation and allocation concealment.
2. **Performance bias**: blinding of participants and personnel.
3. **Detection bias**: blinding of outcome assessment.
4. **Attrition bias**: completeness of outcome data.
5. **Reporting bias**: possibility of selective outcome reporting.

6. **Other sources of bias**.

b) Observational (non-randomized) Trials

To assess risk of bias of observational studies scoring systems are used. The Newcastle-Ottawa Scale (NOS) is the scoring system for non-randomized studies. The scale allocates stars, maximum of nine, for the presence of the following [102]:

a) Cohort Studies

1. **Selection** *(max: 4 stars)*:
    1) Representativeness of the exposed cohort
    2) Selections of the non-exposed cohort
    3) Ascertainment of the exposure
    4) Demonstration that the outcome of interest was not present at start of study
2. **Comparability** *(max: 2 stars)*: Comparability of cohorts on the basis of the design or analysis.
3. **Outcome** *(max: 3 stars)*:
    1) Assessment of outcome
    2) Duration of follow-up
    3) Adequacy of follow up of cohorts

b) Case Control Studies

1. **Selection** *(max: 4 stars)*:
    1) Adequacy of case definition
    2) Representativeness of the cases
    3) Selection of Controls
    4) Definition of Controls

2. **Comparability** *(max: 2 stars)*: Comparability of cohorts on the basis of the design or analysis.
3. **Exposure** *(max: 3 stars)*
    1) Ascertainment of exposure
    2) Same method of ascertainment for cases and controls
    3) Non-Response rate

Any disagreements between the review's authors over the risk of bias in certain studies should be resolved by discussion and consensus.

3.5. Statistical analysis of meta-analysis

The results of systematic review are presented as combined odds ratio (OR) ± 95% confidence interval (95% CI), which was calculated from individual patients' data reported in eligible studies. We used Review Manager-5® 2014 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark [103]) to calculate these OR ± 95% CI. The significance of difference between OR' was noted, by a universal rule for reading OR, if 95% CI is not overlapping 1.00 (OR for reference group) it's significantly different from control/placebo.

Most meta-analyses are based on one of two statistical approaches, the fixed-effect model or the random-effects model. Fixed-effect (common-effect) model is based on assumption that there is only one treatment effect, beyond random error. Contrariwise, the random effect model is based on assumption that the true treatment effects are not identical but follow specific distribution [96].

In our meta-analysis we performed random-effects model since we assume that the studies have enough in common that it makes sense to synthesize the information, however there is no clear reason to assume that they are 'identical' in the sense that the true effect size is exactly the same in all the studies. Additionally, since we included studies with fairly different sample sizes,

we do not want the overall estimate to be overly influenced by large studies[96, 104]. Yet, fixed-effect model was carried out and reported to compare the overall estimates and as request by advisory committee members.

3.6. Heterogeneity

Heterogeneity is defined as any variability seen across the included studies in the systematic review. It could be clinical, which is variability in the participants, interventions and outcomes studied, methodological, which is variability in study design and risk of bias, or statistical heterogeneity. The latter is a result of clinical and/or methodological diversity across included studies; thus, we will refer to statistical heterogeneity simply as heterogeneity [105].

The heterogeneity can be judged graphically or statistically. In forest plot (a graphical summary of the meta-analytic statistics), if confidence intervals (95% CI) for the results of individual studies (horizontal lines) have poor overlap, this generally indicates the presence of heterogeneity. I^2 statistic, which measures the percentage of variation that in not due to chance, is a useful statistical measure to quantify the level of heterogeneity present in each outcome and also help in determining whether to pool the data or not [96]. According the Cochrane manual for Systematic Reviews and Meta-Analysis, the following is a guide to interpretation of I^2 statistic [96]:

- 0% - 40%: not important
- 30% - 60%: moderate heterogeneity
- 50% - 90%: substantial heterogeneity
- 75% - 100%: considerable heterogeneity

It can be challenging to apply the previous method to determine the heterogeneity, therefore, any value for I^2 greater than 50% accompanied by $P < 0.10$ for the Q-test was considered as being indicative of substantial heterogeneity, and we provided a narrative synthesis.

Another statistical test included in the forest plot in a review is chi-squared (χ^2, or Chi^2). It assesses whether observed differences in results are compatible with chance alone. A high P value (or a small Chi^2 statistic) suggests that the heterogeneity is insignificant, and we can go ahead and perform meta-analysis. While, a low P value (or a large Chi^2 statistic) suggests evidence of heterogeneity, variation in effect estimates beyond chance. Thus, meta-analysis should not be considered [94, 96, 105].

3.7. Subgroup analyses

Heterogeneity of the treatment effect can be investigated through subgroup analysis. Subgroup analyses may be done for subsets of studies (such as different study designs) or for patients (such as young and old patients or males females)[96] .

We planned to carry out subgroup analysis for effect of dose (low versus high doses), effect of underlying inflammatory diseases and effect of low-dose ASA on primary outcomes. However, due to lack of necessary individual patient data, subgroup analyses were not performed.

3.8. Publication bias

Historically, the nature and direction of study's results control over publication of research findings. Therefore, publication bias is considered the most critical form of reporting bias and major threat to the validity of systematic reviews.

Systematic review authors should ensure that several sources (at least two databases) are searched. However, comprehensive searches do not necessarily remove reporting bias because of included studies may present results or cite sources selectively. Thus, authors should include data

from studies that have been completed but not published, as well as data available to the researchers but missing from reports of included studies. Potential sources of unpublished data include the World Health Organization's International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/), as well as the ClinicalTrials.gov (https://clinicaltrials.gov) results database, and pharmaceutical companies' voluntary trial registers and results databases for drugs that have received regulatory approval. Other sources concern regulatory agencies (the FDA and the European Medicines Agency) and contacting trialists and sponsors [106].

Funnel plot is a simple graphical display of the intervention effect estimates from individual studies (vertical axis) against sample size (horizontal axis)[106]. In the absence of bias, funnel plot will have symmetrical appearance. While, if there is bias, funnel plot will have an asymmetrical appearance, and the effect estimate of a meta-analysis will tend to overestimate the overall intervention effect [107].

Chapter 4

4. The Effect of COX-2 Selective Etodolac on Myocardial, Vascular, And Gastrointestinal Risks: Systematic Review and Meta-Analysis

4.1. Introduction

With demonstrated efficacy in relieving symptoms pain [108] and musculoskeletal disorders [41], nonsteroidal anti-Inflammatory drugs (NSAIDs) are among the most commonly used groups of medication. They are administered for their anti-inflammatory, analgesic and antipyretic properties [4].

The NSAIDs use is associated with a range of adverse events [4] including but not limited to renal toxicity, fluid retention, exacerbation of hypertension, gastrointestinal (GI) complications [109] and cardiovascular (CV) events [18]. Thus, all NSAIDs, including prescription COX-2 selective, have the same warning for serious GI and CV events from different regulatory agencies [110]. However, it has been established through many epidemiological studies that, with regard to the nature and severity, CV risks are not homogenous across all NSAIDs [41, 111]. Recently, a systematic review has been done on the effect of meloxicam on the CV/renal risks has shown that meloxicam is associated with a limited increase in CV risk, mainly vascular in nature, compared to other NSAIDs [47]. These findings go alongside with earlier reports. McGettigan and Henry reviewed the published evidence regarding CV risk profiles of NSAIDs in high, medium and low income countries [41]. The results showed that meloxicam and indomethacin demonstrated a moderate elevation of risk ratio (RR) while etodolac did not increase RR significantly as compared to naproxen [41].

Etodolac, an uncommonly used nonsteroidal anti-inflammatory drug (NSAID) which possess high COX-2/COX-1 inhibitory properties [61] is marketed since early 1990s for acute or

chronic use as general analgesic for pain in the rheumatoid arthritis (RA) and osteoarthritis (OA) [85]. In clinical practice, etodolac has shown clear efficacy and minimal serious side effects, particularly GI related. Chen *et al.* reviewed the published evidence regarding the clinical effectiveness and cost effectiveness of COX-2 selective NSAIDs [20]. The results exhibited that etodolac is equally effective compared to non-selective NSAIDs and equally or superior GI tolerability [20].

Etodolac is one of many NSAIDs, including piroxicam, indomethacin, and meloxicam, that have not been thoroughly investigated in relation to their CV safety. However, some available reports of its pair-wise analysis indicated that etodolac has CV safety pattern as some low risk NSAIDs, for instance naproxen and ibuprofen [91]. Warner *et al.* compared etodolac with naproxen in a retrospective cohort study among 38,258 US veteran patients [50]. They found that the risk of myocardial infarction (MI) associated with etodolac use was not significantly increased compared to naproxen (OR 1.32, 95% CI 0.81-2.16, p = 0.27). They included celecoxib and rofecoxib as positive controls and found that the MI risk was significantly increased as compared to naproxen, (OR 2.18, 95% CI 1.09-4.46, p= 0.03) and (OR 2.16 95% CI 1.04-4.35, p=0.04), respectively [50].

We, therefore, hypothesized that etodolac is not associated with serious GI or CV risks. Accordingly, we conducted a systematic review and meta-analysis of all available randomized controlled trials (RCTs) and observational studies that reported any GI or CV adverse events after administration of etodolac.

4.2. Methods

A systematic literature review and meta-analysis were performed according to the Cochrane Handbook for Systematic Reviews of Intervention [112] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA) [100]. This review followed a predefined published protocol [113].

Trial registration number PROSPERO 2016: CRD42016047313

4.2.1. Study eligibility criteria

Randomized and nonrandomized studies that compared the CV and GI events in etodolac users with those observed in the nonusers of NSAIDs or users of other NSAIDs. Studies had to report GI/CV adverse events data among participants and include a comparator group consisting of placebo, other NSAIDs or no treatment. Studies were included if they reported relevant digestive system adverse events (nausea, vomiting, diarrhea, dyspepsia, eructation, flatulence, or abnormal stools) or other confirmed GI adverse events (ulcers, bleeding, perforation or obstruction) or relevant confirmed CV events (including myocardial infarction, heart failure, stroke and/or major adverse cardiac events).

The identified studies were excluded if: (1) they were animals studies, review article, thesis, survey, case-reports, conference abstracts, editorial or commentary; (2) had no eligible outcomes or did not report direct comparisons of individual NSAIDs, i.e., not a comparative trial; (3) use of combination of other than ASA, drug switching, dose adjustment, and/or use of extra-oral route of administration, or use of sustain release (SR) formulations had occurred; (4) patient missing prescription follow-up before the anticipated index date.; (5) hazard ratio was used as the measure of the risk. (6) adverse events rate among etodolac users and the comparison group are not available or accessible elsewhere.

4.2.2. Data sources and searches

The following databases were searched up to October 2017: MEDLINE, EMBASE, The Cochrane Library (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Methodology Register, Health Technology Assessment, and NHS Economic Evaluation Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), Web of Science. The search terms were compiled from different generic names of etodolac, randomized controlled trials, and placebo. Details of the search strategy are available as an online supplementary appendix. Supplementary searches were undertaken to identify grey literature, completed and ongoing trials in the following resources: NIH ClinicalTrials.gov, Health Canada's Clinical Trials Database, PROSPERO International prospective register of systematic reviews and ProQuest Dissertations & Theses Global. The bibliographies of included studies were searched for relevant additional studies. Abstract and unpublished studies were not included.

4.2.3. Study selection and data extraction

Both authors independently screened all titles and abstracts of studies to identify studies that potentially meet the inclusion criteria. The full texts of these potentially eligible studies were retrieved and independently assessed for inclusion in the systematic review and meta-analysis according to the predetermined criteria. Disagreements were resolved through discussion and consensus. Both investigators independently extracted the following data for each study using a predefined data collection form: study information (authors, location, publication date, study design, number of participants, and study duration); patient characteristics (age, sex, class of NSAIDs, history of MI or peptic ulcers, health condition requiring NSAIDs therapy); intervention and comparator/control (drugs and dosage), outcomes (events/total for all study population or

subgroups); study methods (randomization, sequence concealment, blinding, loss to follow-up and other risk of bias). The number of events for etodolac and compared groups were recorded for each endpoint. We contacted authors for missing data when necessary.

4.2.4. Quality assessment

The risk of bias in the included RCTs was evaluated using the Cochrane Collaboration's tool [112]. This tool evaluated the risk of bias due to random sequence generation, concealment of allocation, blinding, completeness of outcome data, elective reporting and other source of bias. While, the methodological quality of the included observational studies (cohort and case-control studies) was tested using the Newcastle-Ottawa Quality Assessment Scale (NOS) [114].

4.2.5. Primary and secondary outcomes

The primary outcomes for this review were the association between etodolac and GI toxicity as well as confirmed CV adverse events. The secondary outcomes were the association between etodolac and all-cause of mortality. Upon the review of the included observational studies (cohort/case-control studies), we categorized the reported outcomes in the eligible studies according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) classification codes for 2016 (Table 2) [115].

4.2.6. Data synthesis and statistical analysis

Extracted data were combined for meta-analysis with a random effect model which accounts for both within and between study variability to provide more conservative estimates. However, fixed-effect model was reported when there is no heterogeneity across studies ($I^2 = 0\%$). Data analyses were undertaken using Review Manager (RevMan 5.3) software (The Cochrane Collaboration, Copenhagen, Denmark). The summary effect size was calculated as an odd ratio (OR), together with its 95% confidence intervals (95% CI). Forest plots were constructed to summarize the OR

estimates and their 95% CIs. All tests were two sided and used a significance level of $P < 0.05$. We presented the results by subgroups to show the estimated effects of individual NSAIDs. Heterogeneity among studies, i.e., the variation in outcomes across studies and between the outcomes, was assessed using both the Cochrane's Q and the I^2 statistic. A value for I^2 greater than 50% accompanied by $P < 0.10$ for the Q-test was considered as being indicative of substantial heterogeneity and a narrative synthesis was provided [112]. We evaluated the presence of publication bias with funnel plots and Egger's test if 10 or more studies were included in the meta-analysis [116].

4.3. Results

4.3.1 Eligible studies

The search strategy identified 2,065 potentially eligible citations, of which 591 duplicate citations were removed. A total of 1,944 records were excluded after screening their titles and abstracts. We screened the full texts of the 121 remaining studies and 40 studies were considered as potentially eligible and included in this systematic review. Finally, 26 RCTs with 5,874 participants and 8 observational studies (2 cohort and 6 case-control studies) with 6,405 participants that reported GI/CV adverse events data were found eligible and contributed in the final quantitative meta-analysis [Figure 4].

The excluded studies consisted of 29 trials because they did not report GI/CV events; 14 due to inadequate outcome analysis, i.e., only combined endpoints were reported, 16 studies because they did not have direct comparisons of individual NSAIDs, 13 studies because of sustained release formulations, 9 because of drug switching, dose adjustment, combination of other than ASA, or use of other than oral had occurred, had duplicate data, full text is not in English or not available.

The details of the individual RCTs that conducted to assess the GI safety profile of etodolac compared to other NSAIDs (ASA, naproxen, piroxicam, indomethacin, celecoxib, ibuprofen, and nabumetone) are given in Table 3. The shortest duration of included RCT was 12 hours and the longest was 156 weeks. Patients with chronic musculoskeletal conditions (RA or OA) were 75% of all included patients. The average age of participants in included RCTs ranged from 23.59 to 67.5 years. Twenty RCTs recruited more females than males (the percentage of female ranged from 51% to 90%).

The details of the individual observational studies that reported CV adverse events among etodolac users and characteristics of the studies' participants are presented in Tables 4 and 5, respectively. All of the studies had age- and sex-matched subjects as well as comorbidities such as a history of CV diseases, DM and/or RA, and therapies such as antihypertensive drugs and antiplatelet drugs. The duration of included observational studies was as follows: cohort trials: 3 and 11 years of follow-up, case-control studies: 4-11 years. The average age of participants in included obsessional studies was ranged from 58.9-70.21 years and the percentage of females ranged from 45% to 48.86%.

4.3.2. Quality of included studies

The overall risk of bias of individual trials was low for most of the included RCTs. However, 75% of included RCTs suffered from insufficient information regard randomization process (random sequence generation and allocation concealment). Thus, we were not able to assess the selection bias. All included RCTs used double-blinding, however, information regard outcomes assessment blinding was not provided. The risk of bias due to incomplete outcome data or selective outcome reporting was assessed as low in 24 out of 26 of the included RCTs. A detailed assessment of the risk of bias of the included RCTs is presented in Table 6 and Figure 9.

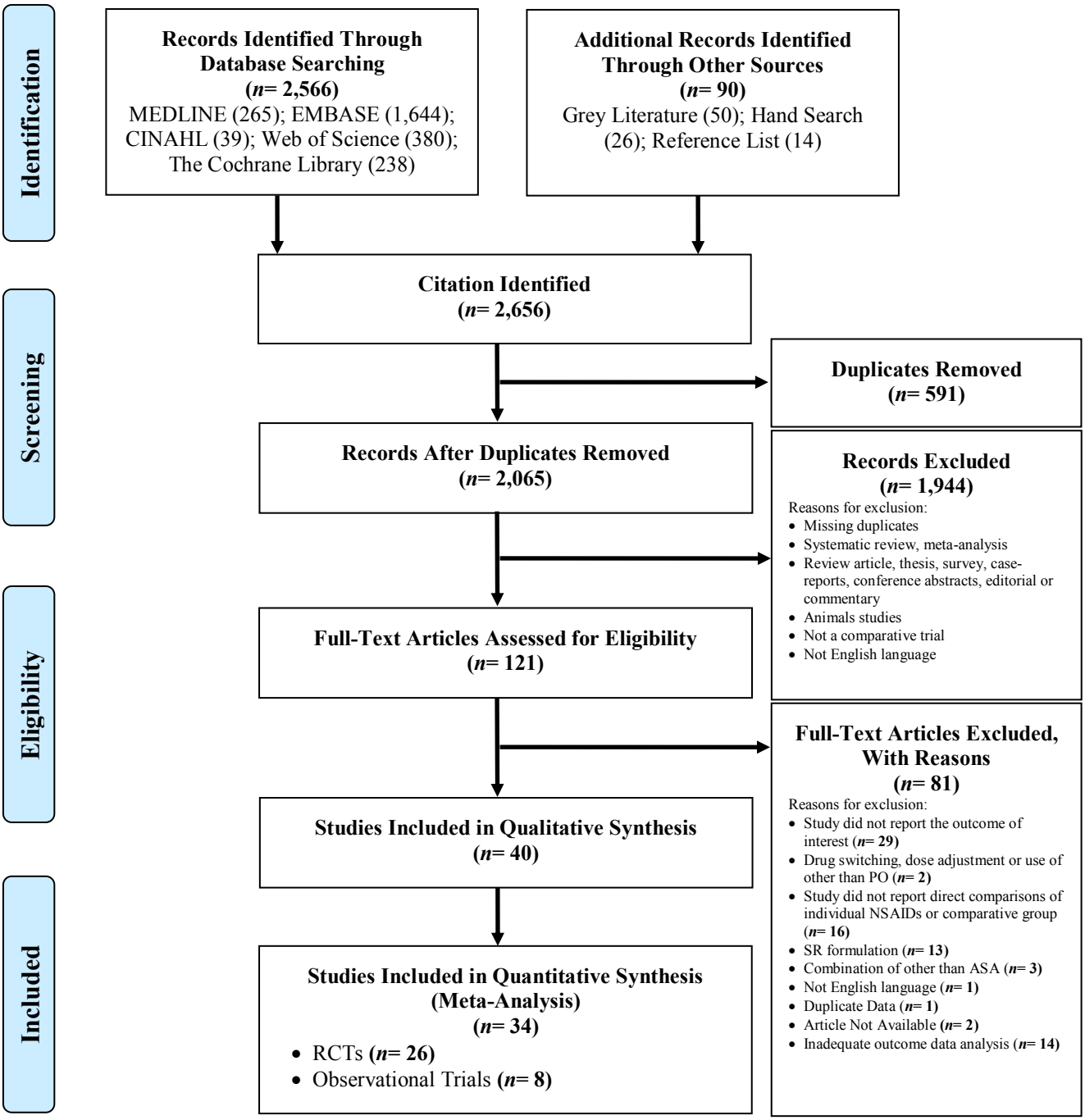


Figure 4: PRISMA [100] flow chart of study selection.

The overall quality of the included observational studies was high and was tested using the Newcastle-Ottawa scale (NOS) method. The cohort studies scored 7-9 out of total 9, while the included case-control studies scored 6-8 out of total 9. A detailed assessment of the methodological quality of the included observational studies is presented in Table 5.

4.3.3. Gastrointestinal outcomes

Twenty-six studies (5,874 participants) were contributed to the meta-analysis of GI adverse events [Table 3, Figures 5-8]. The risks of minor GI adverse events like nausea, vomiting, stomach discomfort or constipation among all participants who received different etodolac doses compared with other NSAIDs, like naproxen, celecoxib or ibuprofen were OR 0.87 (95% CI 0.68-1.12; heterogeneity: $P = 0.07$, $I^2 = 36\%$) [Figure 5]. Subgroup analysis according to available data of individual NSAIDs, suggested that the risks of minor GI adverse events among etodolac users were not significantly different than naproxen users, OR 1.36 (95% CI 0.80-2.31; heterogeneity: $P = 0.96$, $I^2 = 0\%$) [Figure 7].

The risks of bleeding and/or ulcers among etodolac users were 83% lower compared with other NSAIDs users such as ibuprofen or indomethacin users, OR 0.17 (95% CI 0.07-0.41; heterogeneity: $P = 0.95$, $I^2 = 0\%$) [Figure 6]. Moreover, the risks of combined GI adverse events, including ulcers, were 40 % lower in etodolac users compared with users of anti-inflammatory doses of ASA, OR 0.56 (95% CI 0.34-0.92; heterogeneity: $P = 0.0004$, $I^2 = 62\%$) [Figure 8]. However, the heterogeneity test indicates significant variation in outcome across included studies. We did not find eligible studies that compared etodolac GI adverse effect with non-users.

4.3.4. Cardiovascular outcomes

We found eight studies (6,405 participants) that reported the effect of etodolac exposure of any duration on the CV risks (7 studies reported MI, Cerebrovascular accidents (CVA) and/or death

risks, while 1 study reported heart failure (HF) risk). As compared with no exposure, etodolac use was found to exhibit no significant increase of CV risks. OR 1.62 (95% CI 0.84-3.13; heterogeneity: $P = 0.50$, $I^2 = 86\%$) [Figure 10]. However, our analysis of studies that adjusted for arthritis conditions revealed that etodolac exposure was not associated with a significant increased risk than non-users, OR 1.18 (95% CI 0.77-1.81; heterogeneity: $P = 0.40$, $I^2 = 0\%$). Etodolac was found to exhibit an insignificant increased of CV risks compared with other NSAIDs, including naproxen and celecoxib, OR 1.10 (95% CI 0.98-1.24; heterogeneity: $P = 0.50$, $I^2 = 0\%$) [Figure 11]. However, Subgroup analysis by individual NSAIDs showed that CV risks among etodolac users were not significantly elevated compared with naproxen users, OR 1.10 (95% CI 0.92-1.31; heterogeneity: $P = 0.20$, $I^2 = 28\%$) [Figure 12]. In addition, available data exhibited that the CV risk of etodolac was not significantly different than other COX-2 selective NSAIDs such as celecoxib or meloxicam, OR 1.10 (95% CI 0.93-1.29; heterogeneity: $P = 0.82$, $I^2 = 0\%$) and OR 96 (95% CI 0.73-1.28; heterogeneity: $P = 0.99$, $I^2 = 0\%$) [Figures 13 and 14], respectively. No eligible study was found that reported a concomitant use of low-dose ASA.

We found only 2 observational studies that reported Cerebrovascular accidents (CVAs) and/or mortality rate among etodolac users. Both studies concluded that etodolac exposure was not associated with increased CVA risk compared with celecoxib, COX-2 selective NSAID, HR 1.07 (95% CI 0.93-1.24) [117] or non-exposure, HR 1.11 (95% CI 0.83-1.47) [118].

4.3.5. Publications bias

The funnel plots generated by graphing OR against the standard error of the log of OR appear symmetric for all RCTs that reported minor GI outcomes [Figures 15 and 16]. As expected, in a few cases, some of the smaller studies had more extreme OR; this does not necessarily suggest

publication bias but instead could reflect that the smaller study was of lesser quality or was perhaps conducted among a particularly high-risk population [119]. Because we found only 8 observational studies that reported CV adverse events of etodolac exposure, we did not undertake funnel plot test to evaluate publication bias as the number of included observational studies in the meta-analysis was less than 10.

4.3.6. Sensitivity analysis

The results of sensitivity analyses according to sample size and risk of bias are presented in Table 7. The estimated effects for minor, complicated GI (bleedings/ulcers) risks and CV adverse events were robust and we did not indicate any major influence on the estimated effects between selective COX-2 etodolac and other NSAIDs by sensitivity analyses.

4.3.7. Potential bias

Our analysis suggests that etodolac was not associated with GI toxicity. Moreover, etodolac exposure was associated with significantly fewer complicated GI adverse events (ulcers and bleedings) than other NSAIDs like ASA or ibuprofen.

We did not find a significant number of CV events among etodolac users compared with other NSAIDs, OR 1.10 (95% CI 0.98-1.24; I^2 = 0%). Our analysis, however, suggests that etodolac exposure was associated with a comparable CV risks as associated with naproxen, OR 1.10 (95% CI 0.92-1.31; I^2 = 28%). Furthermore, there was no difference in CV risks between etodolac and celecoxib users, OR 1.10 (95% CI 0.93-1.29; I^2 = 0%). However, in general, these results were based on a small number of studies, and therefore they should be interpreted with caution.

4.4. Discussion

Based on 34 clinical and epidemiological trials that included 582 GI and 360 CV events, this meta-analysis demonstrates that etodolac exposure was associated with a significantly lower GI risk and with no increased of CV risk compared with other NSAIDs, for instance, naproxen. Etodolac has been little studied in relation to its CV safety; however, this systematic review constitutes the most comprehensive overview to date, assessing CV risk as well as GI risk associated with etodolac use. Of all included studies, 9 RCTs were contributed to the quantitative meta-analysis of the GI risks of etodolac. Our analysis suggests that etodolac was associated with a limited GI risk mainly uncomplicated adverse events in its nature, such as diarrhea, dyspepsia, flatulence, nausea, abnormal stools and vomiting. The magnitude of the risk was not significant compared with other NSAIDs, for instance; naproxen or celecoxib. Interestingly, low doses of etodolac (300 mg/day) were associated with significantly lower risk of uncomplicated side effects compared to ibuprofen (2,400 mg/day) or celecoxib (200-400 mg/day). But, the probability of these complications increases with higher doses (>1000 mg/day). Nevertheless, etodolac was not associated with a significant complicated GI adverse events, in particular ulcers or bleedings. In fact, the risk of ulcers or bleedings among etodolac users was 83% lower than other NSAIDs, for instance; ibuprofen, piroxicam and indomethacin. Our analysis of GI toxicity exhibits that etodolac is very safe drug compared with other available NSAIDs.

The reduced GI events with etodolac use have been confirmed in a historical cohort study [120], patients prescribed ≥ 800 mg/day or naproxen ≥ 1000 mg/day were followed up for 3 years. The clinically significant upper GI (CSUGI) events were identified and confirmed by endoscopy. Authors reported 13 CSGIU events (6 systematic GI ulcer and 7 upper GI bleeding events) in etodolac users compared with 28 events (9 systematic GI ulcer, 17 upper GI bleeding events and

2 perforations) among naproxen users. They concluded that CSGIU risk among etodolac users was 76% lower than patients prescribed naproxen, (OR 0.24, 95% CI 0.09-0.63, $P = 0.01$). However, the concomitant used of low-dose ASA increased events rates with both drugs, (OR 0.75, 95% CI 0.28-1.99). Similarly, studies overwhelmingly suggest that etodolac use is associated with minimal gastric and duodenal gastric damage confirmed by endoscopy compared with naproxen [67, 121-125], ASA [126] or none NSAIDs users [127].

Etodolac is a chiral molecule classified chemically as pyranocarboxylic acids group [4]. It was known as one of the traditional NSAIDs, nonselective NSAID, however, it has been shown that etodolac possess high COX-2 inhibitory property [7]. García Rodríguez *et al.* investigated *in vitro* the magnitude of inhibition of therapeutic doses of the most commonly used NSAIDs on whole blood COX-1 and COX-2 activates. Etodolac was found to inhibit COX-2 enzyme by nearly 90% at therapeutic concentrations where celecoxib, COX-2 selective NSAID, was found to inhibit approximately 70% of COX-2 activity at therapeutic doses [61]. It is important to mention that celecoxib, a moderately COX-2 selective NSAID [6], has been shown to be associated with minimal GI adverse events compared with non-selective NSAIDs [128]. In an RCT, Ishiguro *et al.* investigated the safety of celecoxib compared with placebo and etodolac in postoperative pain patients. Authors concluded that the safety of celecoxib is similar to placebo. Interestingly, reported overall adverse events, in particular, GI adverse events like nausea, constipation and diarrhea, are relatively similar in celecoxib, placebo and etodolac groups, 2.4%, 4.8% and 4.1%, respectively. Etodolac users were experiencing GI side effects similar or lower than placebo. The better overall GI safety profile of etodolac compared to other NSAIDs is possibly because of its high COX-2 selectivity property.

It is important to mention that the overall level of evidence of available RCTs is good. The majority of the included RCTs were conducted between 1983 and 1997 which can explain – partially – the poor reporting of the randomization and blinding of outcome assessment personnel in the manuscript. The risk of bias of the random sequence generation and the allocation concealment was not apparent due to an insufficient description. Therefore, the selection bias might be present. Nevertheless, all included RCTs were at low risk of other sources of bias like performance bias, attrition bias and reporting bias. This suggests that etodolac is a safe drug in term of GI profile and included trials have a low risk of bias. Thus, our interpretations would have a low overall bias.

Although we have not included studies that investigated microbleeding associated with etodolac use as they often reported continues outcomes, it is timely to mention that GI blood loss associated with chronic use of anti-inflammatory doses of etodolac is significantly lower compared with naproxen, ibuprofen, indomethacin [129, 130], piroxicam [131], and ASA [132].

Our comprehensive search returned only eight observational studies that reported CV adverse events after etodolac use. Our analysis suggests that etodolac demonstrated insignificant increased CV risks compared with other available NSAIDs. This meta-analysis suggests that the CV (MI/HF) risks of etodolac exposure were similar to naproxen, a relatively CV safe NSAID [133].

Many systematic reviews and meta-analyses have concluded that CV risk associated with NSAIDs exposure is heterogeneous [20, 47, 91, 134]. Nevertheless, uncertainty remains about uncommonly used NSAIDs like etodolac. Our analysis agrees with the limited number of studies that have looked for, and found, that etodolac is not associated with an increased CV risk compared with naproxen. For example, Warner *et al.* reported that etodolac is not associated with an

increased AMI risk compared with naproxen, (OR 1.32, 95% CI 0.81-2.16, $P = 0.27$) [50]. The same observations were reported when ibuprofen has been used as a reference group [49]. Furthermore, Motsko *et al.* concluded that neither long nor short-term exposure to etodolac or naproxen was not associated with an increased CV risk, overall use: etodolac (HR 0.82, 95% CI 0.48-1.40) and naproxen (HR 0.86, 95% CI 0.53-1.40), long term use (> 180 days) etodolac (HR 1.26, 95% CI 0.35-4.56) and naproxen (HR 1.15, 95% CI 0.35-3.77) or short term use (≤ 180 days) etodolac (HR 0.73, 95% CI 0.41-1.30) and naproxen (HR 0.83 95% CI 0.48-1.42) [49]. Similarly, Arfè *et al.*, have reported that etodolac, selective COX-2 inhibitor, does not increase the risk of HF compared with past users [135]. However, the authors pooled data generated following the use of all NSAIDs assuming an across the class side effect profile.

Our analysis highlights the problem of pooling data without considering the heterogeneity across included studies. There are only two published reviews reported an increased CV risk among etodolac users [91, 136]. McGettigan and Henry reviewed the published evidence regarding major CV events of NSAIDs in different doses of different background risk of CV events [91]. They concluded that etodolac users, of the less studied NSAIDs, were at higher risk of overall CV. However, authors based their conclusions on analyses of different CV risks estimates (HR, OR, and RR) extracted from only 5 trials [61, 137-140]. As expected, authors failed to justify combining them all together. In fact, HR deals with time-event data and unproven to be combined with OR and RR. Furthermore, it has been established that conducting a meta-analysis using summary information from published papers or trial reports is often difficult as the most appropriate summary statistics are typically not presented [112]. In fact, only one cohort study reported the increased CV risks among etodolac users [137]. Abraham *et al.* investigated etodolac exposure and risks of MI or CVA and reported that the risk of MI or CVA were 1.5-2.7 folds

among etodolac users as well as naproxen users in the same population [137]. A case-control study investigated the CV risks of some NSAIDs in presence and absence of a history of CV diseases. The results suggest that etodolac exposure is not associated with an increased overall CV risk compared with naproxen, OR 1.00 (95% CI 0.86-1.16) and OR 0.91 (95% CI 0.84-0.98, P = 0.27), respectively [140]. It is important to mention that the heterogeneity, i.e., variability across included studies, was 58% which may represent substantial heterogeneity. This is maybe because of, but not limited to, combining different studies designs in the meta-analysis i.e., cohort studies and case-control studies. Varas-Lorenzo *et al.* reported the same conclusion [136]. Authors concluded that etodolac use was associated with increased of AMI events, OR 1.55 (95% CI 1.16-2.06). However, they based their analysis on three studies, only one trial reported an increased risk [137], while the other two studies did not find any significant increase of the CV risk [61, 139].

When reported, chronic etodolac therapy did not adversely affect renal function in patients with arthritis. Shand *et al.* investigated anti-inflammatory doses of etodolac exposure and renal risks compared with placebo, ASA and other NSAIDs. Authors reported renal function results based on ten double-blind, placebo-controlled trials in patients with RA or OA, from 4 to 52 weeks and a total of 1,382 patients received etodolac [70]. They concluded that renal function abnormalities, i.e., blood urea nitrogen and serum creatinine levels, among etodolac users were not significantly different compared with those receiving placebo. Moreover, etodolac group had a significantly lower incidence of blood urea nitrogen results than either ASA or sulindac groups. The same pattern was observed in healthy subjects [68, 69] and even in patients with moderate renal impairment [68].

The potential for bias in our meta-analysis has been minimized by obtaining access to detailed individual patients' data from included trials that recorded GI and CV and outcomes. Since

most events occurred in trials with small sample size, sensitivity analyses indicated that our results were not significantly influenced by uncertainties about the quality of those trials. In addition, there was no evidence that our results depended on whether included trials had been published, although some unpublished trials of which we were unaware might have affected particular findings.

Etodolac is COX-2 selective NSAIDs [4], thus, is expected to be associated with a significantly lower GI risk, in particular ulcers and bleedings, than what has been reported for other drugs of the class. Our analysis of the available data suggests that etodolac might not be associated with an increased risk of major vascular events, but this result should be interpreted with caution. First, etodolac is not a commonly used NSAID, thus, limited data are available, and no certain conclusion can be made. Secondly, we do not know whether the associated CV risk with etodolac would be different in patients treated with low-dose ASA.

Previously our group has highlighted the issue of ignoring effect of underlying inflammatory diseases (RA or OA) and concluding that CV complications in such conditions are solely due to NSAIDs effect [4, 6, 47]. It is well established that patients with inflammatory conditions, arthritis, in particular, are at greater risk of increased morbidity and mortality mainly due to CV complications [42, 90]. However, some of available reports that addressed the association of CV adverse events and etodolac exposure underestimated effect of the inflammatory conditions. Interestingly, with the exception of one study (Lindhardsen *et al.*), our analysis of available studies that adjusted for arthritis conditions exhibits that etodolac use was not associated with an increased CV risk compared with no exposure, OR 1.22 (95% CI 0.93-1.60; heterogeneity: $P = 0.61$, $I^2 = 0\%$) [Figure 10]. Nevertheless, including the latter study did not result in a significant increase of the risk, OR 1.62 (95% CI 0.84-3.13; heterogeneity: $P < 0.0001$, $I^2 = 86\%$), but a

substantial heterogeneity. It is worth mentioning that Lindhardsen *et al.* compared their outcomes between patients who were taking the drug and general population. Thus, it is likely that authors did not account for underlying inflammatory conditions as a covariant in control group. Conclusively, it is important to note that NSAIDs are heterogeneous in causing CV adverse events, particularly if they used in low therapeutic doses [4], or with low-dose ASA [141].

This review turns attentions toward issue of prescribing only few NSAIDs without considering the variability of patient's response to other available NSAIDs. For instance, Generic NSAIDs like etodolac, thus, cost-effective, is associated with a significantly lower GI adverse events and no increased in CV risk than what has been reported for other available NSAIDs, including naproxen and celecoxib. Thus, arthritic patients who have no history of CV diseases but with high risk of GI toxicity or had a history of ulcers associated with NSAIDs use may recommend using etodolac as a safe alternative.

In this review, we aimed to identify all available evidence on the safety of etodolac exposure using broad search criteria in many databases. We, thus, included both RCT and non-RCT as we aimed to provide evidence of CV adverse events that would not be adequately studied with RCT alone, and we anticipated a low yield from RCT. Unfortunately, this reduces the quality of the included studies, particularly as in many of these studies the relevant reported adverse events data were secondary outcomes only, and therefore little details were often provided.

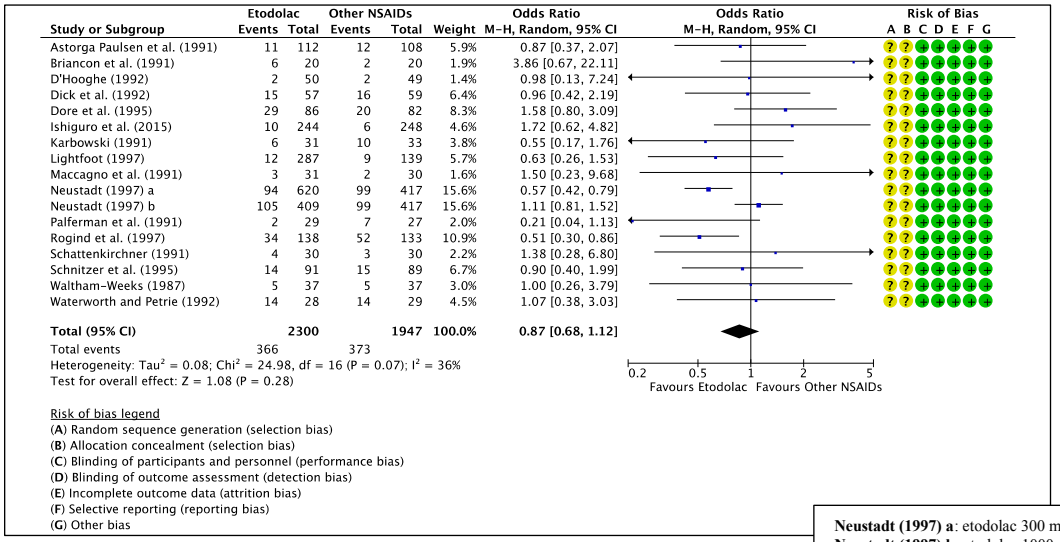
This study is not without limitations. As with any systematic review, the limitations reflect those of the included studies. However, most of RCTs included in this review scored low overall risk of bias, details regard randomization process and blinding were not often reported. Also, most non-RCTs relied on recorded events, where the definition of exposure relies on the recording of a drug being prescribed or dispensed rather than actually consumed. Thus, misclassification is

possible. An additional weakness was the inability in many studies to measure directly consumption of non-prescription ASA and other NSAIDs. It is possible that unrecorded exposure to ASA or anti-inflammatory drugs might account for some of the observed heterogeneity. Other possible causes of across study heterogeneity include the different ages and baseline risks of the study populations and varying ingested doses of drugs. From a statistical standpoint, the degree of heterogeneity was significantly high in some outcomes which requires us to perform random-effects models. Indeed, the heterogeneity may result in increased variability in the risk estimates and, thus, mask the true effects.

4.5. Conclusion

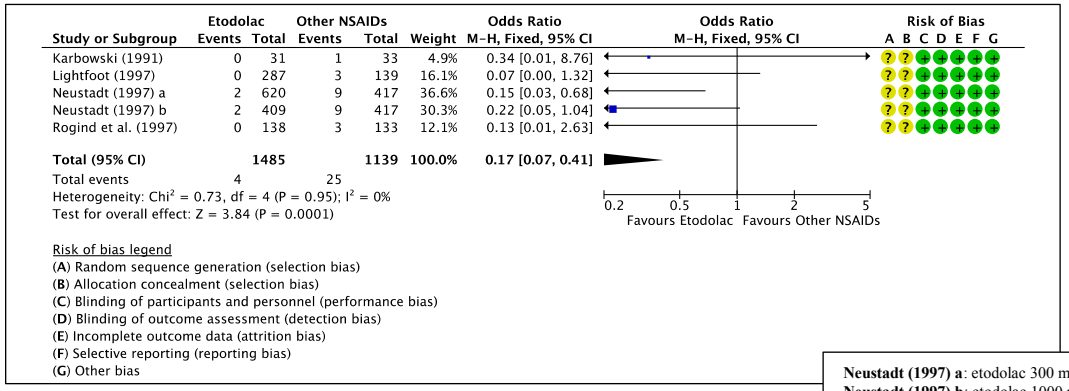
The extent and nature of GI as well as CV risks associated with NSAIDs use are heterogeneous. Etodolac is generally well tolerated in terms of its overall GI adverse events. Moreover, the drug is associated with a significantly fewer complicated ulcers and bleedings events compared with other NSAIDs. Besides, etodolac use has demonstrated a safe CV profile compared with other NSAIDs, such as naproxen. Nevertheless, our conclusion regarding other NSAIDs may not be unequivocal since we did not include all available studies but only the ones that were find eligible according to our criteria. Further clinical trials on the CV safety of available generic NSAIDs like etodolac are desired to establish the exact magnitude and nature such a risk. Important covariates such as the underlying arthritis conditions, dose dependency and ASA co-administration must be considered.

Figure 5: Forest plot showing the risk of minor GI adverse events (*nausea, vomiting, diarrhea, dyspepsia, eructation, flatulence, or abnormal stools*) in those who received etodolac compared with those who received other NSAIDs.



Neustadt (1997) a: etodolac 300 mg/day; ibuprofen 2400 mg/day,
Neustadt (1997) b: etodolac 1000 mg/day; ibuprofen 2400 mg/day.

Figure 6: Forest plot showing the risk of serious GI adverse events (*ulcers and/or bleeding*) in those who received etodolac compared with those who received any other NSAIDs.



Neustadt (1997) a: etodolac 300 mg/day; ibuprofen 2400 mg/day,
Neustadt (1997) b: etodolac 1000 mg/day; ibuprofen 2400 mg/day.

Figure 7: Forest plot showing the risk of GI adverse events in those who received etodolac compared with those who received naproxen.

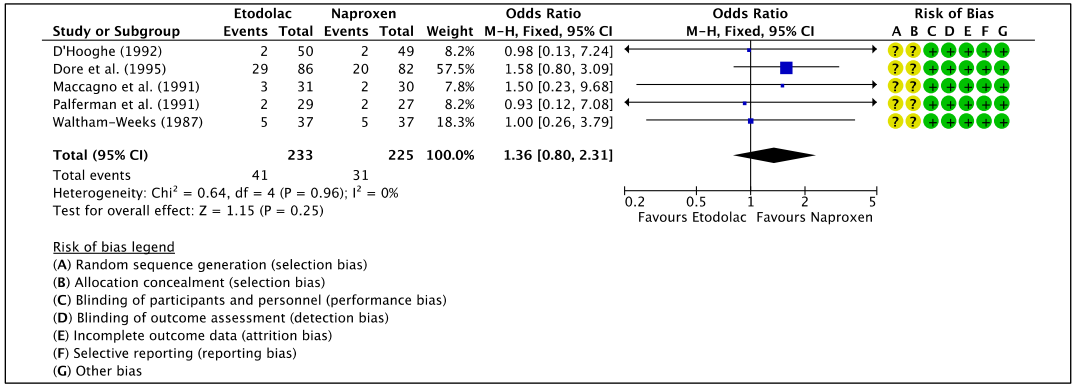
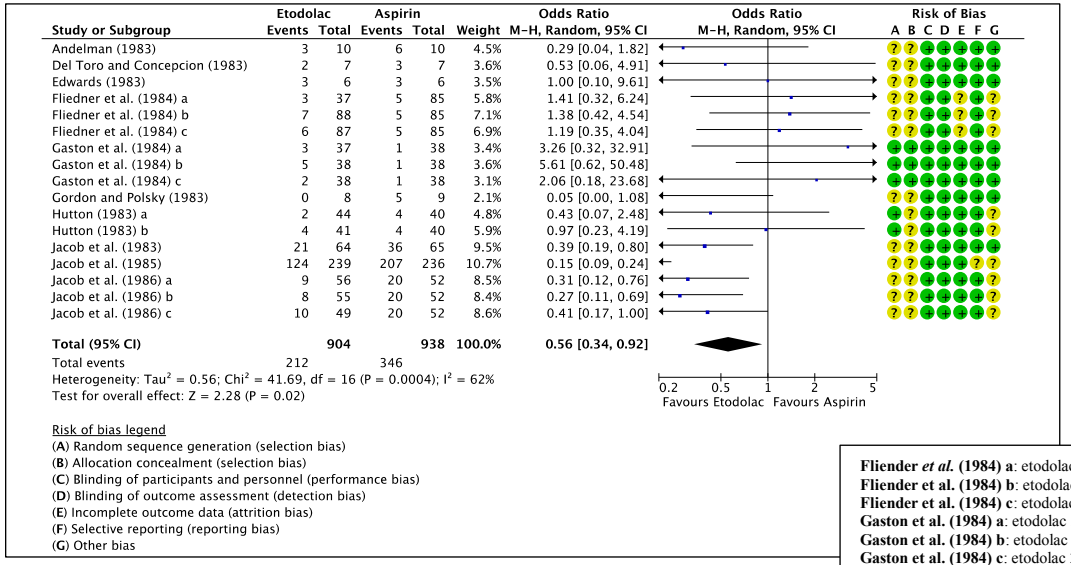


Figure 8: Forest plot showing the risk of combined GI adverse events (*including ulcers*) in those who received etodolac compared with those who received ASA.



Fliender *et al.* (1984) a: etodolac 50 mg; ASA 650 mg,
Fliender et al. (1984) b: etodolac 100 mg; Aspirin 650 mg,
Fliender et al. (1984) c: etodolac 200 mg; ASA 650 mg,
Gaston et al. (1984) a: etodolac 50 mg; ASA 650 mg,
Gaston et al. (1984) b: etodolac 100 mg; ASA 650 mg,
Gaston et al. (1984) c: etodolac 200 mg; ASA 650 mg,
Hutton (1983) a: etodolac 100 mg; ASA 650 mg,
Hutton (1983) b: etodolac 100 mg; ASA 650 mg,
Jacob et al. (1986) a: etodolac 50 mg/day; ASA 3.9g/day,
Jacob et al. (1986) b: etodolac 100 mg/day; ASA 3.9g/day,
Jacob et al. (1986) c: etodolac 200 mg/day; ASA 3.9g/day.

Figure 9: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included RCTs.

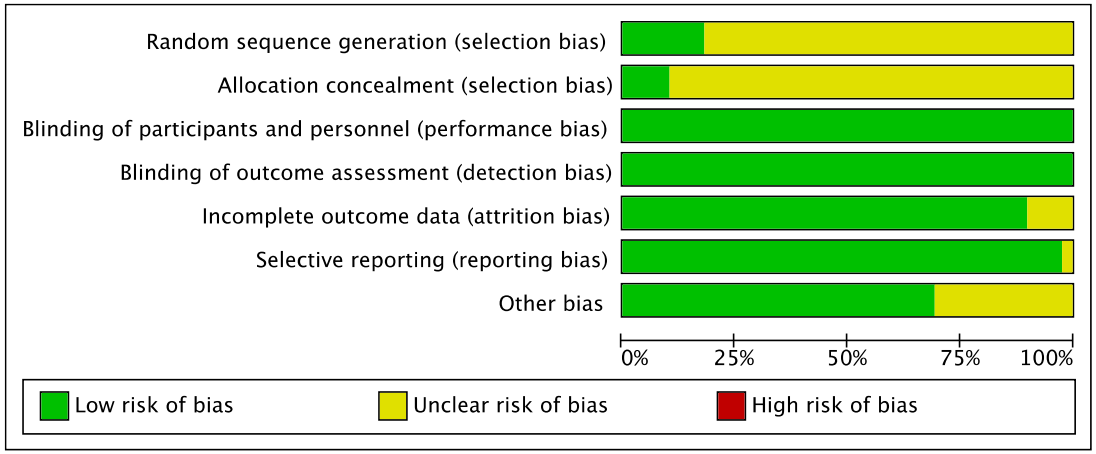
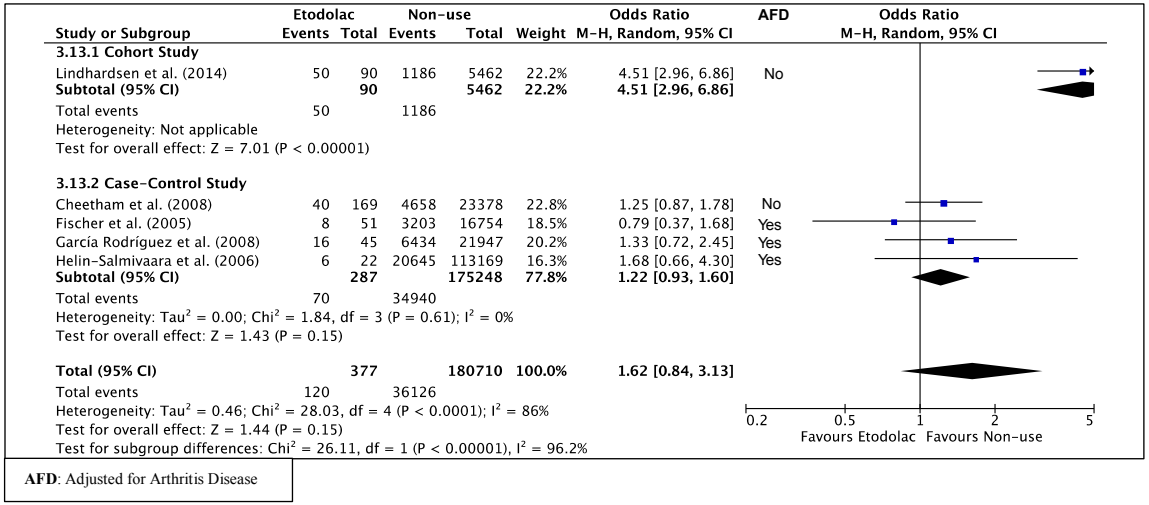
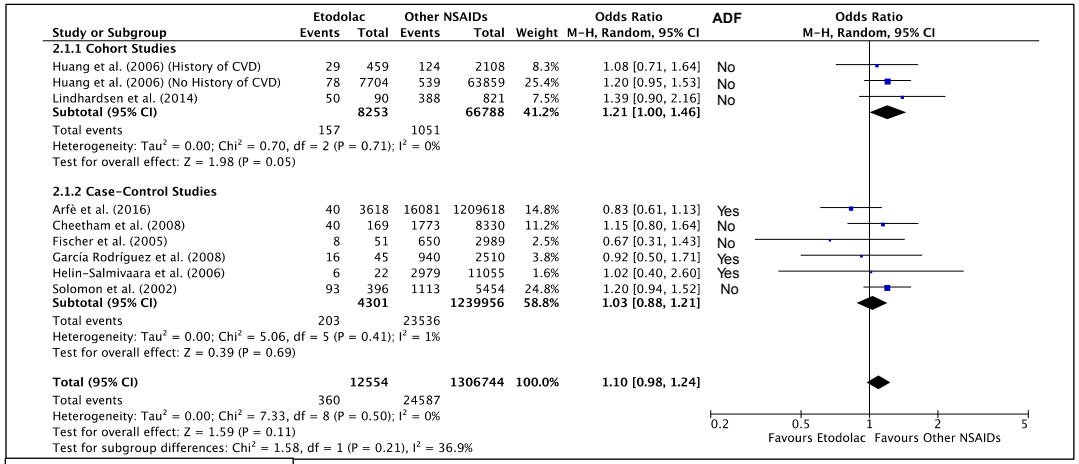


Figure 10: Forest plot showing the risk of CV adverse events (*MI*) in those who received etodolac compared with no exposure (*stratified by study design*).



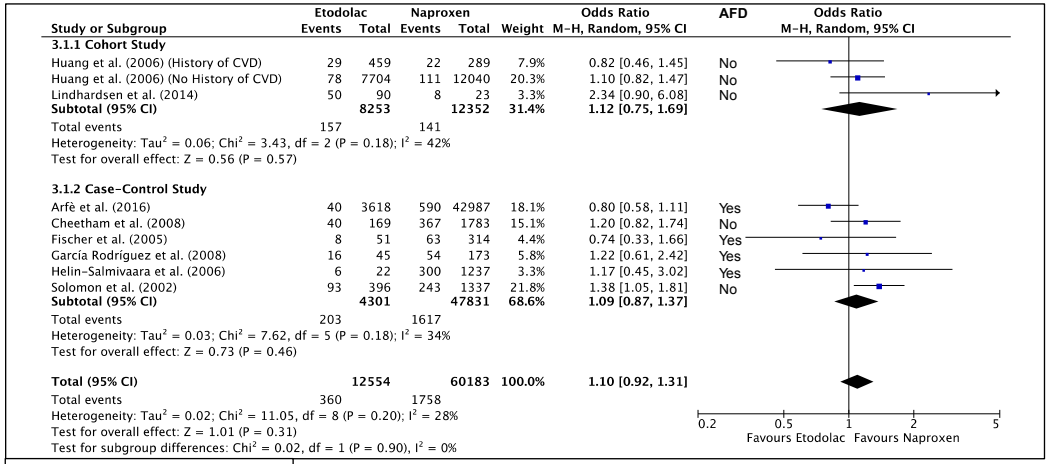
AFD: Adjusted for Arthritis Disease

Figure 11: Forest plot showing the risk of CV adverse events (*MI/HF*) in those who received etodolac compared with those who received of any NSAID (*stratified by study design*).



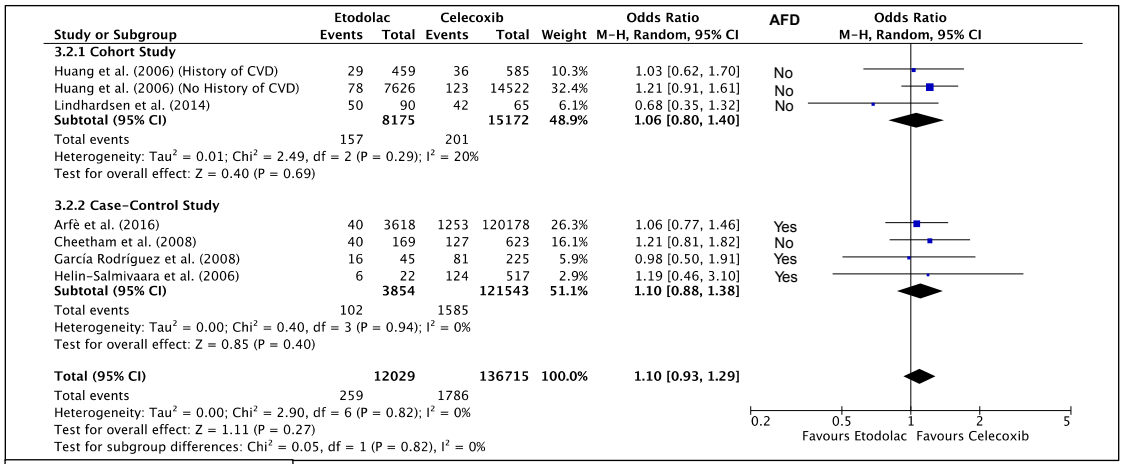
AFD: Adjusted for Arthritis Disease

Figure 12: Forest plot showing the risk of CV adverse events (*MI/HF*) in those who received etodolac compared with those who received naproxen (*stratified by study design*).



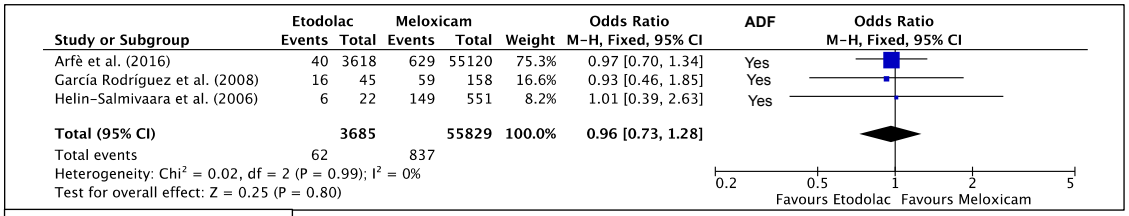
AFD: Adjusted for Arthritis Disease

Figure 13: Forest plot showing the risk of CV adverse events (*MI/HF*) in those who received etodolac compared with those who received celecoxib (*stratified by study design*).



AFD: Adjusted for Arthritis Disease

Figure 14: Forest plot showing the risk of CV adverse events (*MI/HF*) in those who received etodolac compared with those who received of Meloxicam (*study design: Case-Control*).



AFD: Adjusted for Arthritis Disease

Table 3: Characteristics of Included Randomized Controlled Trials

Author (year)	Condition	Study duration (weeks)	Intervention, dosage (*n*)	Mean age ± SD (years)	Female, *n* (%)	Drug comparisons	Outcome reported
Astorga Paulsen *et al.* (1991)	OA (knee)	8	Etodolac 600 mg/day (112); Piroxicam 20 mg/day (108)	58	87 (78)/83 (77)	Piroxicam	Digestive system (diarrhea, dyspepsia, eructation, flatulence, nausea, abnormal stools, or vomiting)
Briancon *et al.* (1991)	RA	12	Etodolac 400 mg/day (20); Piroxicam 20 mg/day (20)	56	16 (80)/18 (90)	Piroxicam	Digestive system (diarrhea, dyspepsia, enterocolitis, eructation, nausea, or vomiting)
D'Hooghe (1992)	Acute Sport Injuries	1	Etodolac 900 mg/day (50); Naproxen 1000 mg/day (49)	39	27 (54)/15 (31)	Naproxen	Digestive system (dyspepsia)
Dick *et al.* (1992)	OA (knee)	6	Etodolac 600 mg/day mg (57); Piroxicam 20 mg/day (59)	58	41 (72)/38 (64)	Piroxicam	Digestive system (dyspepsia, abdominal pain, or nausea)
Dore *et al.* (1995)	OA (knee)	4	Etodolac 800 mg/day (86); Naproxen 1000 mg/day (82); Placebo (86)	63.7	52 (60)/ 52 (63)/ 56 (65)	Naproxen	Digestive system (dyspepsia, flatulence, or constipation)
Ishiguro *et al.* (2015)	Postoperative pain	44	Etodolac 200 mg/dose (224); Celecoxib 200-400 mg/dose (248); Placebo (124)	53.2±15.7/ 50.2±16.3/ 53.7±14.8	106 (43.4)/ 91 (36.7)/ 56 (45.2)	Celecoxib	Digestive system (constipation, diarrhea or nausea)
Karbowski (1991)	OA (knee)	6	Etodolac 600 mg/day (31); Indomethacin 150 mg/day (33)	54	19 (61.3)/ 20 (60.61)	Indomethacin	Digestive system (dyspepsia, flatulence, abdominal pain, nausea, stomach ulcer, or melaena)
Lightfoot (1997)	RA	12	Etodolac 400 mg/day (140) or 600 mg/day mg (147); Piroxicam 20 mg/day (139)	57±11/ 58±9/ 56±10	105 (75)/ 103 (70)/ 96 (69)	Piroxicam	Digestive system (diarrhea, dyspepsia, nausea, ulcer or bleeding)
Maccagno *et al.* (1991)	Acute Gout Episode	1	Etodolac 600 mg/day (31); Naproxen 1000 mg/day (30)	55±10/ 54±8	9 (29)/ 5(17)	Naproxen	Digestive system (abdominal pain or dyspepsia)

TABLE 3. Continued…

Neustadt (1997)	RA	156	Etodolac 300 mg/day (620); 1000 mg/day (409); Ibuprofen 2400 mg/day (417)	53.2±11.1/ 53±11.1/ 53.1±10.6	440 (71)/ 283 (69)/ 299 (72)	Ibuprofen	Digestive system (dyspepsia, diarrhea, nausea, abdominal pain, stomach ulcer or bleeding)
Palferman *et al.* (1991)	OA (knee)	6	Etodolac 600 mg/day (29); Naproxen 1000 mg/day (27)	61.6±10.9/ 64.5±7.3	17 (59)/ 18 (67)	Naproxen	Digestive system (dyspepsia, abdominal pain, nausea, or stomach cramps)
Rogind *et al.* (1997)	OA (hip, knee)	8	Etodolac 600 mg/day (138); Piroxicam 20 mg/day (133)	67±10.7/ 67.5±11.5	110 (79.7)/ 103 (77.4)	Piroxicam	Digestive system (upper/lower abdominal pain, nausea ulcer or bleeding)
Schattenkirchner (1991)	RA	12	Etodolac 400 mg/day (30); Piroxicam 20 mg/day (30)	56.1±10.2/ 52.8±11.6	23 (77)/ 23 (77)	Piroxicam	Digestive system (dyspepsia, abdominal pain, nausea, or vomiting)
Schnitzer *et al.* (1995)	OA (knee)	4	Etodolac 800 mg/day mg (91); Nabumetone 1500 mg/day (89); Placebo (90)	63.81 ±10.62/ 62.38 ±11.14/ 65.26 ±10.16	64 (70.3)/ 62 (69.7)/ 59 (65.6)	Nabumetone	Digestive system (dyspepsia, abdominal pain, diarrhea or nausea)
Waltham-Weeks (1987)	RA	6	Etodolac 400 mg/day (37); Naproxen 1000 mg/day (37)	51.57 ±11.72/ 55.56 ±8.62	9 (42.9)/ 14 (77.8)	Naproxen	Digestive system (dyspepsia, abdominal pain, diarrhea, nausea, melaena gastro-enteritis, or excessive thirst)
Waterworth and Petrie (1992[142])	OA (knee)	6	Etodolac 600 mg/day (28); Piroxicam 20 mg/day (29)	59.8±10.1/ 59.3±7.2	12 (43)/ 20 (69)	Piroxicam	Digestive system (dyspepsia, abdominal pain, diarrhea or nausea)
Andelman (1983)	OA (hip, knee)	12	Etodolac 384 mg/day (10); ASA 4,322 mg/day (10); Placebo (10)	61.4/ 60.1/ 62.4	1 (10)/ 3 (30)/ 3(30)	ASA	Digestive system (dyspepsia, abdominal pain, nausea, vomiting, GI cramps, diarrhea, constipation or indigestion)

TABLE 3. Continued…

Del Toro and Concepcion (1983)	RA	12	Etodolac 329 mg/day (7); ASA 4,600 mg/day (7); Placebo (7)	48/50/57	4 (57.14)/ 6 (85.71)/ 4 (57.14)	ASA	GI adverse events
Edwards (1983)	RA	12	Etodolac 394 mg/day (6); ASA 4,414 mg/day (6); Placebo (6)	51/55/55	3 (50)/ 2 (33.33)/ 4 (66.66)	ASA	GI adverse events
Fliedner *et al.* (1984)	Oral surgery	12 hours	Etodolac 50 mg (37), 100 mg (87), or 200 mg (86); ASA 650 mg (83); Placebo (87)	24.4/24.3/ 23.9/24.3/ 24.5	20 (54.1)/ 59 (67.82)/ 44 (51.2)/ 45 (54.22)/ 54 (62.1)	ASA	Digestive system (epigastric pain, nausea or vomiting)
Gaston *et al.* (1986)	Oral surgery	12 hours	Etodolac 50 mg (37), 100 mg (38), or 200 mg (38); ASA 650 mg (38); Placebo (38)	24.4/24.3/ 24.6/24/ 24.3	20 (54.1)/ 24 (63.2)/ 18 (47.4)/ 18 (47.4)/ 19 (50)	ASA	Digestive system (epigastric pain, nausea or vomiting)
Gordon and Polsky (1983)	RA	14	Etodolac 332 mg/day (8); ASA 3,758 mg/day (9); Placebo (8)	54/58/55	2 (25)/ 0 (0)/ 1 (12.5)	ASA	Digestive system (heartburn, nausea or constipation)
Hutton (1983)	Oral surgery	12 hours	Etodolac 100 mg (44), or 200 mg (41); ASA 650 mg (40); Placebo (43)	23.59/ 23.27/ 24.43/ 24.23	32 (72.7)/ 24 (58.5)/ 25 (62.5)/ 33(76.7)	ASA	Digestive system (nausea or vomiting)
Jacob *et al.* (1983)	RA	12	Etodolac 307 mg/day (64); ASA 3,871 mg/day (65); Placebo (65)	50.4±10.5/ 52±10.5/ 53.2±10.3	41 (64.1)/ 47 (72.31)/ 48 (73.85)	ASA	Digestive system (nausea, vomiting, diarrhea, constipation, heartburn, flatulence, abdominal pain, dyspepsia, melena, indigestion, bloating, rectal bleeding, epigastric pain, bad breath, increased bowel movement or cramps)

TABLE 3. Continued…

Jacob *et al.* (1985)	RA	51	Etodolac 300-600 mg/day (239); ASA 4,800 mg/day (236)	49±11.4/ 49±10.7	180 (75)/ 170 (72)	ASA	Digestive system (nausea, epigastric pain, heartburn, diarrhea, indigestion, constipation, abdominal cramps, abdominal bloating, vomiting or abdominal pain)
Jacob *et al.* (1986)	RA	6	Etodolac 50 mg/day (56), 100 mg/day (55), or 200 mg/day (50); ASA 3,900 mg/day (52); Placebo (51)	52±12/ 54±10/ 52±11/ 53±12/ 53±13	36 (64.3)/ 28 (51)/ 30 (60)/ 29 (55.8)/ 36 (70.6)	ASA	GI adverse events

Table 4: Characteristics of Included Observational Studies in Qualitative and/or Quantitative Analysis

Author, Year	Condition	Study duration (years)	Type of study	Exposure definition	NSAID comparisons	Outcome reported (ICD-10)	Covariates (adjusted)
Cheatum *et al.* (1999)	RA or OA	NR	Cohort	All 1,826 patients diagnosed with either RA or OA who have been using an NSAID for the last 6 months, need NSAID therapy but cannot tolerate GI side effects; or have been diagnosed with clinically significant gastric or duodenal lesions related to NSAID therapy.	Etodolac Fenoprofen Diclofenac Naproxen Sulindac Ibuprofen Indomethacin Flurbiprofen Ketoprofen ASA	Gastroduodenal ulcers (confirmed by endoscopy)	Age, type of arthritic disease, duration of disease, duration of NSAID use, severity of GI symptoms
Weideman *et al.* (2004)	NR	3	Cohort	All 16,286 patients who received etodolac (≥ 800 mg/day) or naproxen (≥ 1000 mg/day) between January 1, 1999 and December 31, 2001.	Etodolac Naproxen	CSUGI (confirmed by endoscopy)	Age, sex, duration of NSAID use, RA, CHF, DM, use of low-dose ASA, history of ulcer
Warner *et al.* (2008)	NR	6	Cohort	Any NSAID exposure before the index date.	Etodolac Naproxen Celecoxib Rofecoxib	Coronary artery disease (I20-I25), previous coronary revascularization (Z95.1-Z95.5), previous myocardial infarction (I21, I22), congestive heart failure (I50), diabetes mellitus (E10-E14), hypertension (I10) and hyperlipidemia (E78).	Age, sex, diabetes mellitus, hypertension, hyperlipidemia, prior congestive heart failure, coronary artery disease, history of myocardial infarction, prior coronary revascularization, antiplatelet therapy

TABLE 4. Continued…

Motsko *et al.* (2006)	NR	3	Cohort	Short-term exposure was defined as use of NSAID (≤ 180 days), and long-term exposure (> 180 days).	Etodolac Naproxen Ibuprofen Celecoxib Rofecoxib	Acute myocardial infarction (I21, I22)	Age, sex, atrial fibrillation, angina, cancer, COPD, diabetes mellitus, heart failure, HIV/AIDS, lupus, osteoarthritis, peripheral vascular disease, renal failure, respiratory failure, rheumatoid arthritis, prior acute myocardial infarction, prior stroke, antiarrhythmic drugs, ASA, β-adrenoceptor antagonists, calcium channel antagonists, antidiabetic drugs, digoxin, estrogen, other antihypertensives, loop diuretics, methotrexate, nitrate, PVD drugs, warfarin, ACE inhibitors/ARBs, antiplatelet drugs, antirheumatic drugs, corticosteroids, cholesterol-lowering drugs, other diuretics/anticoagulants

TABLE 4. Continued…

Huang *et al.* (2006)	NR	3	Cohort	Chronic use was defined as use of an NSAID for ≥180 days.	Etodolac Nabumetone Ibuprofen Naproxen Celecoxib	Acute Myocardial infarction (I21-I22), Angina (I20), Cerebrovascular accident (I60-I69), Transient ischemic attack (G45)	Age, sex, accumulated duration of use based on prescription data, and pre-existing cardiovascular events and/or hypertension (I10-I15), dyslipidemia (E78.1), diabetes mellitus (E10-E14), congestive heart failure (I50.0), and/or chronic renal disease (N03-N26)
Lindhardsen *et al.* (2014)	RA (ICD10: M05M06)	12	Cohort	Any NSAID exposure during follow-up period.	Etodolac Ibuprofen Diclofenac Celecoxib Piroxicam Rofecoxib Naproxen Ketoprofen Nabumetone Indomethacin	Myocardial infarction (I21-I22), stroke (I60, I61, I63 and I64) or cardiovascular death (I00-I99 listed as the primary cause of death)	Age, sex, socioeconomic index, diabetes, hypertension, heart failure, ischaemic heart disease, atrial fibrillation, chronic obstructive pulmonary disease

TABLE 4. Continued…

Abraham *et al.* (2007)	NR	3	Cohort	The first NSAID prescription during follow-up period.	Etodolac Rofecoxib Valdecoxib Celecoxib Nabumetone Meloxicam Naproxen Naproxen sodium Ibuprofen	Myocardial infarction (I21, I22), cerebrovascular event (I60-I69)	Age, gender and race, hypertension, a history of ischemic heart disease, diabetes, congestive heart failure, peripheral arterial disease, previous MI or CVA, coronary or carotid revascularization procedures, atrial fibrillation, chronic renal failure and rheumatological diseases, anticoagulants, anti-platelet agents, statins, low-dose ASA use, acetaminophen and steroids
Lee *et al.* (2007)	OA	3	Case-control	Any NSAID exposure during follow-up period.	Etodolac Celecoxib Rofecoxib Naproxen Ibuprofen Diclofenac Indomethacin	Angina (I20), ischemic heart disease (I24-I25), myocardial infarction (I21, I22), cerebrovascular event (I60-I69)	Event risk score and comorbidities.

TABLE 4. Continued…

Cheetham *et al.* (2008)	NR	3	Case-control	All patients who filled at least one prescription for an NSAID between January 1, 1999, and December 31, 2001. NSAID exposure was defined as: current users, if the duration of their most recent NSAID prescription overlapped the index date, Remote users, if the supply ended ≥ 60 days before the index date, or recent users were those individuals whose NSAID prescriptions ended between 1-60 days before the index date.	Etodolac Celecoxib Diclofenac Ibuprofen Indomethacin Nabumetone Naproxen Piroxicam Rofecoxib Sulindac	Acute myocardial infarction (I21, I22), Intermediate Coronary Syndrome (I20)	Age, sex, Health Plan region, major CVE, angina, HF, other IHD, cardiac arrhythmias, noncardiac hospitalization, other cardiovascular hospitalizations, antiplatelets, anticoagulants, antiarrhythmics, antidiabetics, antihypertensives, loop diuretics, and antihyperlipidemics.
García Rodríguez *et al.* (2008)	NR	4.1	Case-control	NSAID exposure was classified to: current NSAID exposure, when the most recent prescription lasted until index date or ended in the 7 days before the index date, recent NSAID exposure when it ended between 8-90 days before the index date or past, when it ended between 91-365 days before the index date and nonuser, when there was no recorded use in the year before the index date.	Etodolac Celecoxib Diclofenac Etoricoxib Ibuprofen Indomethacin Meloxicam Piroxicam Rofecoxib	Myocardial infarction	Age, sex, calendar year, BMI, general practitioner visits, referrals, smoking, Townsend score, IHD, DM, RA, COPD, and anticoagulants, antihypertensive, oral steroids, ASA use

TABLE 4. Continued…

Helin-Salmivaara *et al.* (2006)	NR	4	Case-control	Patients with first-time MI who admitted between January 1, 2000 and December 31, 2003. NSAID exposure was defined as: current users, the supply of the prescription started before and extended beyond the index day, recent users, the supply of the prescription ended 1-30 days before the index day and past users, the supply of the prescription ended 31 days to 2 years before the index day.	Etodolac Indomethacin Diclofenac Naproxen Nimesulide Ibuprofen Piroxicam Ketoprofen Tolfenamic acid Nabumetone Meloxicam Etoricoxib Rofecoxib Celecoxib	Acute myocardial infarction (I21, I22)	Age, sex, hospital catchment area, DM, RA, CAD, hypertension, and the use of a ß-blocker, a statin, hormone replacement therapy, clopidogrel
Solomon *et al.* (2002)	NR	5	Case-control	Patients who were exposed to one of the study oral NSAID within 6 months before the index date.	Etodolac Naproxen Ibuprofen Ketorolac Indomethacin Sulindac Oxaprozin Diclofenac Flurbiprofen Ketoprofen Nabumetone Piroxicam Fenoprofen Tolmetin	Acute myocardial infarction (I21, I22)	NSAIDs exposure, age, sex, ethnicity, Medicaid enrollment, nursing home use, DM, hypertension, CHF, Charlson Comorbidity Index, number of different drug prescriptions, number of hospitalizations

TABLE 4. Continued…

Arfè *et al.* (2016)	NR	11	Case-control	Any NSAID exposure during follow-up period. NSAID exposure classified as current users: NSAID availability within 14 days before the index date, recent users: NSAID availability within 15-183 days before the index date, or past users otherwise (reference).	Etodolac Ketorolac Etoricoxib Indomethacin Rofecoxib Sulindac Piroxicam Acemethacin Diclofenac Dexibuprofen Nimesulide Ibuprofen Naproxen Valdecoxib Nabumetone Tiaprofenic acid Lornoxicam Tenoxicam Ketoprofen Aceclofenac Meloxicam Diclofenac, combination Proglumethacin Flurbiprofen Celecoxib Dexketoprofen Oxaprozin	Heart failure (I11.0, I11.00, I11.01, I13.0, I13.00, I13.01, I13.2, I13.20, I13.21, I50, I50.0, I50.00, I50.01, I50.1, I50.11, I50.12, I50.13, I50.14, I50.19, I50.9)	Age, sex, AMI, alcohol abuse, asthma, AF, chronic liver disease, chronic respiratory disease, DM, HF, hyperlipidaemia, hypertension, iron deficiency, anaemia, IHD, kidney failure, obesity, OR, Rheumatoid arthritis, inflammatory polyarthritis, smoking, stroke, valvular disease, endocarditis, ace inhibitor/angiotensin II antagonists, anticoagulants, ASA, ß-blocker, calcium channel blockers, cardiac glycosides, CYP 2C9 inducers/inhibitors, diuretics, glucocorticoids, nitrates, platelet aggregation inhibitor, vasodilators

TABLE 4. Continued…

Fischer *et al.* (2005)	NR	6	Case-control	Patients with first-time MI who admitted between January 1995 and April 2001. Current NSAID exposure was defined as most recent prescription of the last one NSAID ended before or after the index date.	Etodolac Acemetacin Diclofenac Diflunisal Fenbufen Fenoprofen Flurbiprofen Ibuprofen Indomethacin Ketoprofen Mefenamic acid Nabumetone Naproxen Piroxicam Sulindac Tenoxicam Tiaprofenic acid	Myocardial infarction	Age, sex, Smoking, Body mass index, Hypertension, Hyperlipidemia, Diabetes mellitus, Ischemic heart disease, Arrhythmias or Heart failure, Arterial thrombosis, Kidney diseases, Rheumatoid arthritis, Systemic Lupus Erythematosus

NR, not reported

Table 5: Characteristics of Patients in Observational Studies Included in Meta-Analysis

Author, Year	No. of subjects (case/control)	Mean age ± SD (years) (case/control)	Female, *n* (%) (case/control)	Concomitant drug use	Diseases	NOS
Huang *et al.* (2006)	History of CV 29/430 No history of CV 78/7,626	70.21 ± 13.59	984 (48.86)	NR	CV events, hypertension, dyslipidemia, diabetes mellitus, congestive heart failure, chronic renal disease	Selection: 4 stars; Comparability: 2 stars; Exposure: 3 stars
Lindhardsen *et al.* (2014)	50/40	58.9 ± 14.4/ 58.9 ± 14.4	NR	ß-blocker, Lipid lowering agent, renin–angiotensin system blocker, Loop diuretic, Spironolactone, Vitamin K antagonist, Clopidogrel, ASA, Thiazide, Calcium channel blocker, NSAID, Gastroprotective agent,	Hypertension, Ischaemic heart disease, Heart failure, Atrial fibrillation, Diabetes, Chronic obstructive pulmonary disorder, Chronic kidney disease	Selection: 3 stars; Comparability: 2 stars; Exposure: 2 stars
Cheetham *et al.* (2008)	40/129	68.8	18 (45)	Antiplatelets, anticoagulants, antiarrhythmics, antidiabetics, antihypertensives, loop, diuretics, digoxin, nitrates, antihyperlipidemics	Major CV events (MI, cardiac arrest, and revascularization procedures), angina, congestive heart failure , other ischemic heart disease (atherosclerosis and ischemia), cardiac arrhythmias, other CV hospitalizations (major CV procedures, peripheral vascular disease, valve disease, cerebrovascular disease, and peripheral vascular procedures), and non-CV hospitalizations.	Selection: 4 stars; Comparability: 2 stars; Exposure: 2 stars

TABLE 5. Continued…

García Rodríguez *et al.* (2008)	16/29	NR	NR	Anticoagulants, Antihypertensives, Oral steroids, ASA	Ischemic heart disease, diabetes mellitus, rheumatoid arthritis, chronic obstructive pulmonary disease	Selection: 4 stars; Comparability: 2 stars; Exposure: 2 stars
Helin-Salmivaara *et al.* (2006)	6/16	NR	NR	ß-blocker, HMG-CoA-reductase inhibitor, hormone replacement therapy in females, clopidogrel	Diabetes mellitus, rheumatoid arthritis, hypertension, coronary artery disease	Selection: 3 stars; Comparability: 2 stars; Exposure: 3 stars
Solomon *et al.* (2002)	93/303	NR	NR	NR	Diabetes mellitus, hypertension, congestive heart failure	Selection: 3 stars; Comparability: 1 star; Exposure: 2 stars
Arfè *et al.* (2016)	40/3,578	NR	NR	ACE inhibitor/angiotension II antagonists, anticoagulants, ASA, β-blockers, calcium channel blockers, cardiac glycosides, CYP2C9 inducers, CYP2C9 inhibitors, diuretics, glucocorticoids, nitrates, platelet aggregation inhibitor, vasodilators	Acute myocardial infarction, alcohol abuse asthma, atrial fibrillation and flutter, chronic liver disease, chronic respiratory disease, diabetes, heart failure, hyperlipidaemia, hypertension, iron deficiency anaemia, ischaemic heart disease, kidney failure, obesity osteoarthritis, other cardiovascular disease, rheumatoid arthritis and inflammatory polyarthritis, smoking stroke, valvular disease and endocarditis	Selection: 3 stars; Comparability: 2 stars; Exposure: 2 stars

TABLE 5. Continued…

Fischer *et al.* (2005)	8/43	NR	NR	NR	Hypertension, Hyperlipidemia, Diabetes mellitus, Ischemic heart disease, Arrhythmias or heart failure, Arterial thrombosis, Kidney diseases, rheumatoid arthritis, Systemic Lupus Erythematosus	Selection: 2 stars; Comparability: 2 stars; Exposure: 2 stars

NR, not reported

Table 6: Risk of bias summary: review authors' judgements about each risk of bias item for each included RCT.

Author, Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete data outcome	Selective reporting	Other source of bias
Astorga Paulsen *et al.*, 1991	Unclear	Unclear	Low	Low	Low	Low	Low
Briancon *et al.*, 1991	Unclear	Unclear	Low	Low	Low	Low	Low
D'Hooghe, 1992	Unclear	Unclear	Low	Low	Low	Low	Low
Dick *et al.*, 1992	Unclear	Unclear	Low	Low	Low	Low	Low
Dore *et al.*, 1995	Unclear	Unclear	Low	Low	Low	Low	Low
Ishiguro *et al.*, 2015	Unclear	Unclear	Low	Low	Low	Low	Low
Karbowski, 1991	Unclear	Unclear	Low	Low	Low	Low	Low
Lightfoot, 1997	Unclear	Unclear	Low	Low	Low	Low	Low
Maccagno *et al.*, 1991	Unclear	Unclear	Low	Low	Low	Low	Low
Neustadt, 1997	Unclear	Unclear	Low	Low	Low	Low	Low
Palferman *et al.*, 1991	Unclear	Unclear	Low	Low	Low	Low	Low
Rogind *et al.*, 1997	Unclear	Unclear	Low	Low	Low	Low	Low
Schattenkirchner, 1991	Unclear	Unclear	Low	Low	Low	Low	Low
Schnitzer *et al.*, 1995	Unclear	Unclear	Low	Low	Low	Low	Low
Waltham-Weeks, 1987	Unclear	Unclear	Low	Low	Low	Low	Low
Waterworth and Petrie, 1992	Unclear	Unclear	Low	Low	Low	Low	Low
Andelman, 1983	Unclear	Unclear	Low	Low	Low	Low	Low
Del Toro and Concepcion, 1983	Unclear	Unclear	Low	Low	Low	Low	Low
Edwards, 1983	Unclear	Unclear	Low	Low	Low	Low	Low
Fliedner *et al.*, 1984	Unclear	Unclear	Low	Low	Unclear	Low	Unclear
Gaston *et al.*, 1984	Low	Low	Low	Low	Low	Low	Low
Gordon and Polsky, 1983	Unclear	Unclear	Low	Low	Low	Low	Low
Hutton, 1983	Low	Unclear	Low	Low	Low	Low	Unclear
Jacob *et al.*, 1983	Unclear	Unclear	Low	Low	Low	Low	Low
Jacob *et al.*, 1985	Unclear	Unclear	Low	Low	Low	Unclear	Unclear
Jacob *et al.*, 1986	Unclear	Unclear	Low	Low	Low	Low	Unclear

Figure 15: Funnel plot of etodolac compared with other NSAIDs, *outcome: minor GI adverse events*.

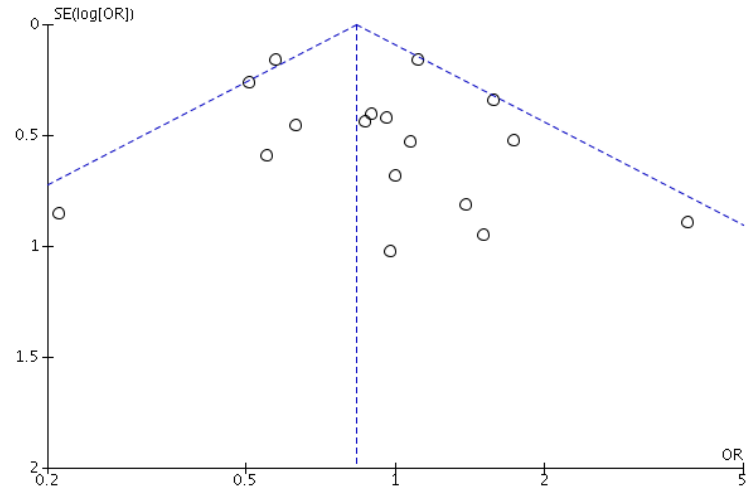


Figure 16: Funnel plot of etodolac compared with ASA, *outcome: combined GI adverse events*.

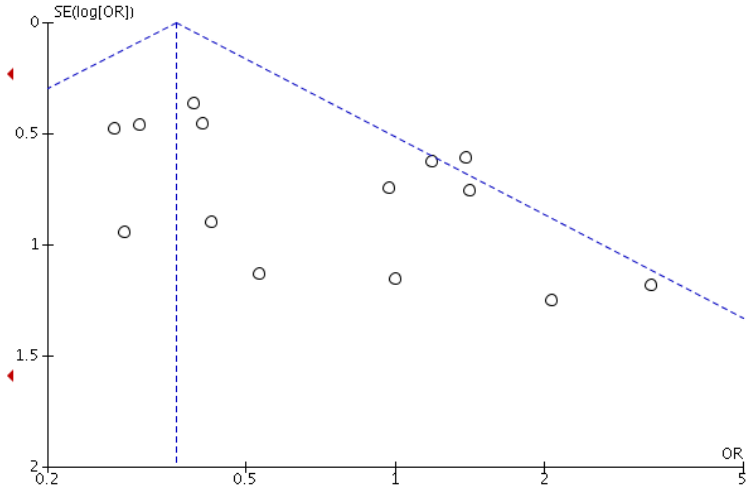


Table 7: Sensitivity analysis by sample size and risk of bias.

	Studies removed from the primary meta-analysis	Included studies	Event/Total	OR (95% CI)	Heterogeneity
Sample Size					
Gastrointestinal outcomes					
Minor GI adverse events (*vs* other NSAIDs)	8	9	324/2,044	0.86 (0.64-1.16)	$P = 0.02$ $I^2 = 55\%$
Minor GI adverse events (*vs* naproxen)	3	2	31/136	1.50 (0.79-2.84)	$P = 0.66$ $I^2 = 0\%$
GI adverse events (*vs* ASA)	8	4	175/589	0.40 (0.20-0.79)	$P = 0.001$ $I^2 = 75\%$
Serious GI adverse events (*bleedings/ulcers*) (*vs* other NSAIDs)	1	3	4/1,454	0.16 (0.06-0.41)	$P = 0.91$ $I^2 = 0\%$
Cardiovascular outcomes					
CV adverse events (*vs* non-users) *	4	1	40/169	1.25 (0.87-1.78)	NA
CV adverse events (*vs* other NSAIDs)	4	4	280/12,346	1.10 (0.97-1.26)	$P = 0.38$ $I^2 = 5\%$
CV adverse events (*vs* naproxen)	4	4	280/12,346	1.07 (0.87-1.33)	$P = 0.11$ $I^2 = 47\%$
CV adverse events (*vs* celecoxib)	3	3	187/11,872	1.14 (0.96-1.36)	$P = 0.89$ $I^2 = 0\%$
CV adverse events (*vs* meloxicam) *	2	1	40/3,618	0.97 (0.70-1.34)	NA
Risk of bias					
Gastrointestinal outcomes					
General GI events (*vs* other NSAIDs) **	16	0	-	-	-
Minor GI adverse events (*vs* naproxen) **	5	0	-	-	-
General GI events (*vs* ASA)	9	1	10/113	3.59 (0.96-13.39)	NA
Serious GI adverse events (*bleedings/ulcers*) (*vs* other NSAIDs) **	3	0	-	-	-
Cardiovascular outcomes †					
CV adverse events (*vs* nonusers)	1	4	112/326	1.91 (0.93-3.94)	$P = 0.00001$ $I^2 = 87\%$
CV adverse events (*vs* other NSAIDs)	2	6	259/12,107	1.09 (0.95-1.26)	$P = 0.52$ $I^2 = 0\%$

TABLE 7. Continued…

CV adverse events (*vs* naproxen)	2	6	259/12,107	1.04 (0.86-1.25)	$P = 0.33$ $I^2 = 13\%$
CV adverse events (*vs* celecoxib)	0	6	259/12,029	1.10 (0.93-1.29)	$P = 0.82$ $I^2 = 0\%$
CV adverse events (*vs* meloxicam)	0	3	62/3,685	0.96 (0.73-1.28)	$P = 0.99$ $I^2 = 0\%$

Sensitivity analyses according to sample size excluded the studies with <50 (RCTs) or < 100 (non-RCTs) participants.
Sensitivity analyses according to risk of bias excluded the studies with high risk of bias on one or more domain, or with unclear risk of bias on three or more domains.
* The sample size was less than 100 in 2 out of 3 of included studies in the main analysis, thus only one study was included. ** There were three domains at unclear risk of bias according to Cochrane handbook for the included studies, so all studies were removed. † The total scores were > 7 starts according to the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis.

Chapter 5

5. Clinical Outcomes of Aspirin Interaction with Other Non-Steroidal Anti-Inflammatory Drugs: A Systematic Review

5.1. Introduction

Acetylsalicylic acid (ASA) is in clinical use since mid 19th century. In addition to being an effective analgesic, antipyretic and anti-inflammatory agent, it is used, among other indications, for its anti-platelet property to reduce all-cause mortality, cardiac death, and nonfatal myocardial infarction (MI) [43]. Moreover, low-dose ASA, alone or in combination, is recommended for the secondary prevention of acute ischemic stroke and transient ischemic attack [44-46]. The anti-platelet effect of ASA is largely accounted for the irreversible inhibition of platelet cyclooxygenase-1 (COX-1) enzyme. COX-1 is an enzyme that catalyzes Arachidonic Acid (AA) to produce several prostaglandins (PG), among them thromboxane A_2 (TxA_2), a promoter of platelet aggregation [143, 144]. The inhibition of the COX-1 dependent TxA_2 by ASA, measured by plasma thromboxane B_2 (TxB_2) is recommended to be near completion to significantly inhibit platelet function *in vivo* [145-147].

The non-Aspirin nonsteroidal anti-inflammatory drugs (NANSAIDs), such as ibuprofen and naproxen, are among the most commonly used medications for a variety of indications ranging from headaches to arthritis. NANSAIDs bind and inhibit the COX enzymes which lead to inhibition of prostanoids biosynthesis including PGs, prostacyclins and thromboxanes [4]. Thus, the concomitant use of some NANSAIDs appear to interact with the ASA's anti-platelet function, thereby, although unproven, may reduce its CV protection benefits [148]. This, however, seems contradictory to the observations that the elevated CV risks of some NANSAIDs is lowered by addition of low-dose ASA to the regimen [61, 149].

We, therefore, hypothesized that the CV benefits of ASA are reduced upon chronic concomitant administration of NANSAIDs. We tested the hypothesis through a comprehensive systematic search of available literature data to assess the CV risks of concomitant use of NANSAIDs and ASA.

We assessed the CV risks of users of ASA alone, NANSAID alone and ASA plus NANSAIDs and compared the outcomes of the studies reporting *in vitro*/*in vivo*/*ex vivo* ASA-NANSAIDs interactions with those reporting clinical outcomes of the combination. The present analysis focuses on only six commonly used NANSAIDs, i.e., ibuprofen, naproxen, diclofenac, celecoxib, rofecoxib, and meloxicam.

5.2. Methods

This systematic review with a trial registration number of PROSPERO 2018 CRD42018084556 has been carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as listed in the appendixes [100].

5.2.1. Search strategy

The study focus was only on ibuprofen, naproxen, diclofenac, meloxicam, celecoxib and rofecoxib. Both authors independently searched published studies indexed in MEDLINE, EMBASE, CINAHL, Web of Science, and the Cochrane Library (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Methodology Register, Health Technology Assessment, and NHS Economic Evaluation Database) from inception to October 2017. The search terms were compiled from the names of individual NANSAIDs, acetylsalicylic acid, Aspirin, cyclooxygenase, COX, cardiovascular, myocardial infarction, stroke, cerebrovascular, cardioprotection, platelet, platelet aggregation, platelet aggregation inhibit, anti-platelet effect, blood platelets, and drug interaction.

The detailed search strategy is provided in the appendixes. We also searched the Clinical Trials Registry platforms for ongoing studies for any additional relevant references. The bibliographies of included studies were searched for relevant additional studies. Abstracts and unpublished studies were not included.

5.2.2. Study selection and data extraction

Both authors examined the titles and abstracts of studies to identify studies that potentially meet the inclusion criteria. The inclusion criteria were as follows: (i) Randomized controlled trials (RCTs) or observational studies (cohort or case-control studies) that include treatment with ASA alone, NANSAID alone and concomitant use of NANSAIDs with ASA. The association between the treatments and risk of CV (MI), cerebrovascular events (stroke) or all-cause mortality were assessed for studies that included odds ratios (ORs), relative risks (RRs), hazard ratios (HRs) with 95% confidence interval (CI). (ii) molecular interactions trials (*in vitro*, *in vivo* or *ex vivo*) in human addressing the interaction at the platelet level between NANSAIDs and ASA. The full texts of these potentially eligible studies were retrieved and independently assessed for eligibility. Disagreements were settled through discussion and consensus. Extracted information included study information (authors, location, publication date, type of study, number of participants, and study duration), patient characteristics (age, sex, previous CV events including stroke, ASA use, and NANSAIDs use), intervention and comparator (drugs and doses) and outcomes (events/total for all study population or subgroups). The identified studies were excluded if: (i) they were reviews, questionnaire, thesis, letters, simulated studies, meeting summary, conference abstracts, editorial or commentary articles; (ii) had no eligible outcomes or did not report direct comparisons of individual NANSAIDs; or (iii) used of extra-oral route of administration (e.g., topical use for analgesia) or combination of other than NANSAIDs with ASA had occurred.

5.2.3. Quality assessment

The methodological quality of the included observational studies (cohort and case-control studies) was appraised using scales adopted from the Newcastle-Ottawa quality scale (NOS) [114]. Based on the study design (cohort or case-control study), each study was evaluated using the appropriate scoring system. Eight items in the included cohort and case-control studies were identified and assessed. Cohort and case-control studies with 6-9, 3-5, and 0-2 points were identified as good, fair or poor quality, respectively.

5.3. Results

5.3.1. Eligible studies

Our search strategy yielded 3,563 potentially relevant articles from which 3,498 were found ineligible because they were not epidemiological studies or molecular interactions experiments. Sixty-five articles underwent full-length article review. Twenty-five of these were excluded because they did not report the outcome of interest (MI or stroke), 5 were excluded because they did not report direct comparison of individual NANSAIDs with or without use of ASA, and 3 were excluded because of combination other than ASA with NANSAIDs or use of formulation other than oral. Twelve studies (5 cohort studies and 7 case-control studies) with 80,845 events met our eligibility criteria and were included in the analysis [61, 83, 149-158]. The eligible studies scored good quality based on the calculated NOS scores (cohorts, 8-9/9 and case-controls 6-8/9) [Table 16].

Twenty molecular interactions studies addressing the interactions between NANSAIDs and ASA were included. The detailed flow chart of search methodology and selection process is shown in Figure 17. Table 8 compares the outcomes of both platelet effects and clinical outcomes. Data on the selected NANSAIDs are provided in Tables 9-14. The detailed characteristics of

molecular interactions experiments studies are described in Table 15. The clinical data on the interactions between ASA and different type of NANSAIDs are summarized in Table 16.

5.3.2. Platelet aggregation

The 20 eligible molecular interaction studies with the information on the interactions indicated that, in general, the anti-platelet effect of ASA is reduced in the presence of ibuprofen, naproxen or celecoxib [Tables 8 and 15]. However, meloxicam, rofecoxib and diclofenac do not interfere with the anti-platelet effect of ASA.

5.3.3. Cardiovascular outcomes

The 12 studies [61, 83, 149-156] listed in Tables 8 and 16 reported CV risks of ASA alone as well as in combination with various NANSAIDs. The results suggest that the addition of naproxen to an ASA regimen does not result in a loss of beneficial effects of the latter [Tables 8 and 10]. Similarly, the reported ibuprofen-ASA interaction at the level of platelets does not seem to diminish the cardioprotective effect of ASA [Table 8]. However, 2 of the 10 eligible studies have reported diminished clinical benefit of ASA caused by ibuprofen [150, 157]. Indeed, one of the 2 studies [150] has made the same observation for celecoxib and diclofenac [Table 8]. As depicted in Table 9, there are only two studies [157, 158] that found changes in all-cause mortality for ASA plus ibuprofen compared with ASA alone users. One of these studies [158] found that addition of ibuprofen did not increase the risk of all-cause mortality (HR, 0.84; CI 0.70-1.01) but the other one [157] did (HR, 1.93; CI 1.30-2.87). The latter also found an increased risk of CV mortality for the combination (HR, 1.73; CI 1.05-2.84).

A trend towards an increase in the rate of recurrent MI has been reported in one cohort study when subjects exposed to ASA and ibuprofen (HR, 1.50; CI 1.33-1.70) compared with ASA alone users (HR, 0.98; CI 0.94-1.03) [150]. A retrospective cohort study has also concluded that

patients with history of CV diseases had increased risk of mortality when exposed to ASA plus ibuprofen compared with users of ASA alone [157].

Table 8: Summary of *in vitro*, *in vivo*, *ex vivo* and clinical data on the interactions between ASA and different type of NANSAIDs

NANSAIDs	Anti-platelet effect of ASA diminished				Beneficial effect of ASA in reducing CV risks diminished	
	in vitro		*in vivo/ex vivo*		Clinical data	
Ibuprofen	No [159]	Yes [159-161]	No [162]	Yes [163-169]	No [61, 151-156, 158]	Yes [150, 157]
Naproxen		Yes [170]	No [171]	Yes [167-170, 172]	No [61, 83, 150-152, 156]	
Diclofenac	No [159, 160]		No [163, 164, 171]		No [152, 156]	Yes [61, 150]
Celecoxib		Yes [160]	No [165, 167, 168, 173]	Yes [174]	No [61, 149]	Yes [150]
Rofecoxib		NA	No [163, 175]		No [61, 149, 150]	
Meloxicam	No [159]		No [176]		No [61, 83]	

NA, not available

5.4. Discussion

This is, to the best of our knowledge, the first systematic review that compares published ASA-NANSAIDs interaction at the platelet level with its long-term clinical outcomes. We have used broad inclusion criteria in many databases to capture molecular interactions experiments, RCTs and observational studies for a range of NANSAIDs and ASA users. However, no RCTs data were found.

We found that a NANSAID-ASA interaction at the platelet level does not necessarily amount to a loss of beneficial effects of ASA. Indeed, for naproxen, studies have consistently reported no negative clinical outcomes after addition of the drug to the ASA regimens [Table 10]. Similarly, studies overwhelmingly suggest that ASA maintains it beneficial effects after addition of ibuprofen to the regimen [Table 9].

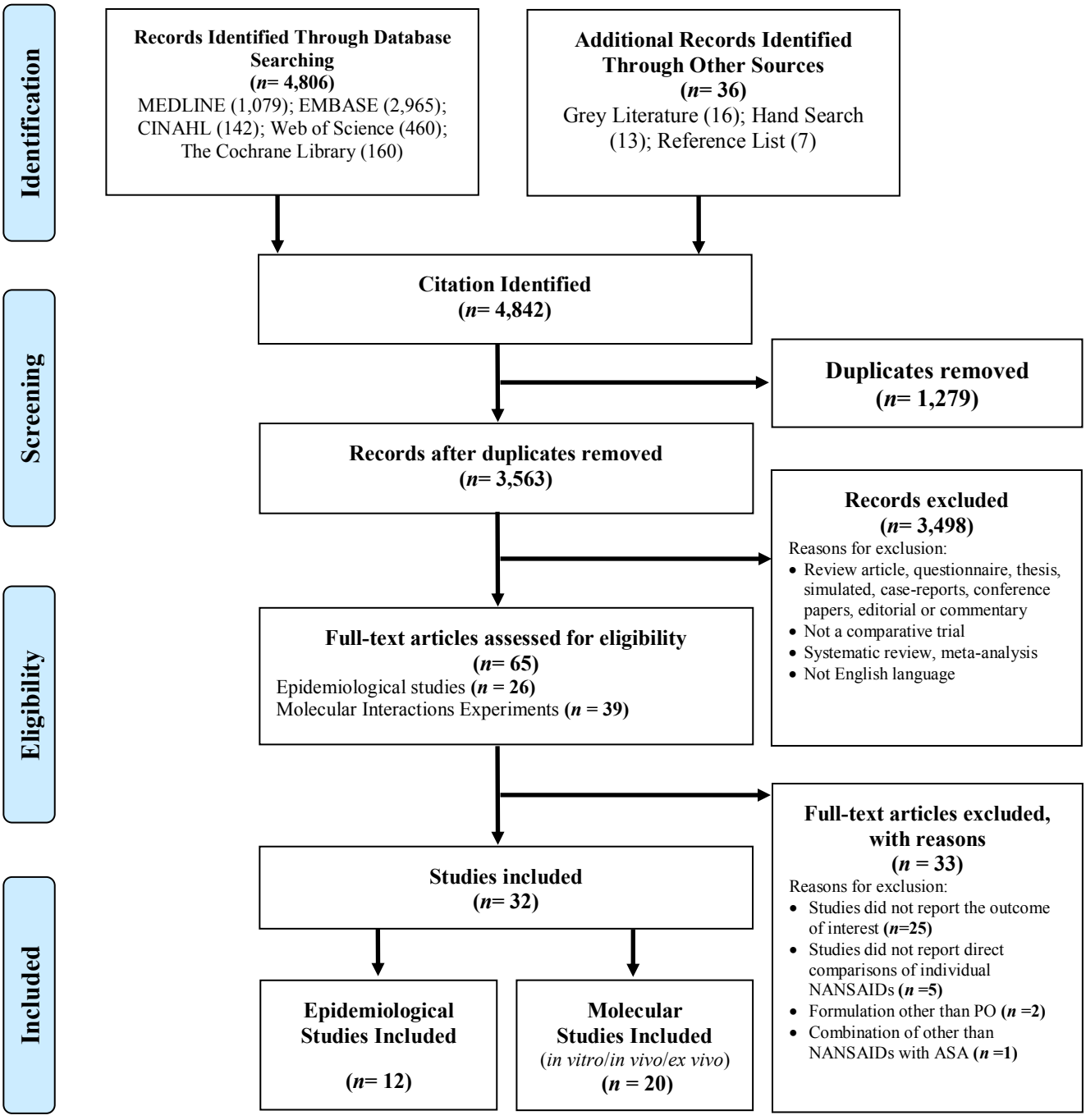


Figure 17: PRISMA [100] flow chart of study selection.

As expected, the cardioprotective effect of ASA is not diminished by meloxicam and rofecoxib, two NANSAIDs that do not interact with ASA at the platelet level [Table 8]. Interestingly, diclofenac for which its lack of effect on the anti-platelet action of ASA has been repeatedly reported appears to diminish the clinical benefit of the latter as reported by 2 of eligible 4 studies [Table 8].

Despite the limited number of eligible studies, meloxicam [61, 83] [Table 11] and rofecoxib [61, 149, 150] [Table 12] do not appear to diminish the cardioprotective effect of ASA. This is not unexpected since these drugs do not interact with the anti-platelet properties of ASA [Table 8].

The data for celecoxib are not as conclusive as those available for naproxen and even ibuprofen since we found only 3 eligible studies. Two studies that suggest no loss of the beneficial effect of ASA [61, 149] contradict the other one [150]. The reason for the conflicting results is unclear but it may be of relevance to mention that the latter study [150] stands out as the one that has also observed diminishing clinical benefit of ASA for ibuprofen, diclofenac as well. Nevertheless, in light of the conflicting data and the limited eligible studies, one cannot draw an unequivocal conclusion as to the clinical outcome of celecoxib-ASA interaction. Similarly, one cannot draw a definite conclusion regarding diclofenac as we found only 4 eligible studies, two in each side of the controversy. This is interesting since diclofenac does not interact with ASA at the platelet level [Table 8], thus, the loss of cardioprotective effect caused by the drug-drug interaction is unexpected.

The observation that not all NANSAIDs interact with ASA at the clinical level despite the fact that with the exception of meloxicam, rofecoxib and diclofenac, they interact with ASA at the platelet level [Table 8] highlights the heterogeneity of NANSAIDs [4] that is often ignored. For,

example, Arfè *et al.* [135] who studied the risk of heart failures causes by NANSAIDs in 4 European countries noticed that only approximately one-half of the drugs used were significantly cardiotoxic. Nevertheless, they calculated the current use of any NANSAIDs, toxic or not, and concluded that the use of any NANSAID was associated with 19% increased heart failure risk.

The heterogeneity of NANSAIDs is confirmed in a crossover study [163] in which patients received 81 mg of immediate-release ASA followed 2 h later by ibuprofen, rofecoxib, or diclofenac for 6 days. This was followed by a washout period of 14 days, after which the same 2 medications were administered in reverse order for another 6 days. The inhibition of COX-1 was assessed by measuring serum TxB_2 level, platelet aggregation induced in platelet-rich plasma and COX-2 activity by the measuring the formation of lipopolysaccharide-stimulated PGE2 in whole blood. They noticed no significant interaction between ASA and rofecoxib or diclofenac. However, ibuprofen significantly interacted with ASA given before or after the NANSAID. The ASA-ibuprofen interaction has been confirmed by others [159-161, 164-169].

Although we have not made a comparison between molecular interactions studies and clinical trials for all NSAIDs, it is timely to reemphasize that their interaction with ASA is heterogeneous in nature. For example, naproxen, celecoxib, piroxicam, indomethacin, mefenamic acid, tiaprofenic acid, nimesulide, oxaprozin, flufenamic acid and dipyrone do interact, while loxoprofen, diclofenac, rofecoxib, etoricoxib, lumiracoxib, etodolac, ketorolac, meloxicam, acetaminophen, flurbiprofen, sulindac, and sodium salicylate do not [Table 15].

It has been suggested that the ASA-NANSAIDs interaction is due to a competition to bind to the Arginine-120 residue of the COX-1 channel which may prevent the acetylation of the serine-529 residue by ASA [170, 177]. Nevertheless, the interference of NANSAIDs with the anti-platelet effect of ASA seems to have no long-term consequences as the CV protection of ASA remains

unaffected by concomitant use of, at least, naproxen and ibuprofen. We put forward three plausible explanations for the disconnect between the results of the short-term platelet experiments and those of observational studies. (i) The interaction at the platelet level may be short-lived so that the effect dissipates shortly after its occurrence. (ii) There is no need for near complete inhibition of TxB2 inhibition to benefit from the cardioprotective properties of ASA so that despite a reduction in the extent of anti-platelet effect, the beneficial effect persists, or (iii) the CV effect of ASA may not be exclusively due to the drug's anti-platelet properties.

For all, except one eligible study, the CV risk was assessed after > 30 days exposure to the combination while typically, the effect of NANSAIDs on the anti-platelet activity of ASA is studied after short exposure times. Thus, the data on the therapeutic outcome of the short-term exposure to ASA-NANSAIDs are limited. However, the results published by Kimmel *et al.* [155] based on a case-control study that assessed the risk only one week before the date of onset of MI are useful in this context. They have reported that addition of NANSAIDs to ASA regiment does not increase the CV risk within one week post combination therapy. To this, one may add the fact that, to the best of our knowledge, there is no published report suggestive of a quick negative clinical CV outcome in individual patients who took NANSAIDs therapy while on ASA. Furthermore, data from a small size clinical trial, suggest that the effect of naproxen and diclofenac on the ASA-induced inhibition of platelet aggregation is short-lived [171]. In a randomized placebo-controlled trial, Galliard-Grigioni *et al.* treated healthy subjects with 100 mg ASA daily in combination with either three doses of either 1 g acetaminophen, 50 mg diclofenac, 250 mg naproxen or placebo, and assessed the platelet function. Initially, naproxen enhanced, and diclofenac reduced the anti-aggregatory action of ASA while acetaminophen had no effect. After

4 days of treatment, however, the platelet aggregation was equally inhibited by all ASA-NANSAID combinations.

In practice, a near complete inhibition of TxB2, thereby platelet aggregation is aimed to obtain cardioprotective effects of ASA [160]. This is while the anti-platelet action of ASA is shown to be dose-dependent [178], i.e., low doses of the drug may not completely inhibit TxB2. Nevertheless, ASA has been shown to be cardioprotective after low doses [Table 16]. This may suggest that to benefit from the CV properties of ASA, a complete inhibition of TxB2 is not needed. Thus, a reduced platelet aggregation activity of ASA resulted from combination therapies with NANSAIDs, unless proven through appropriately designed clinical trials, may have no significant clinical consequences.

In addition to its anti-platelet effect, ASA may reduce CV risks through other mechanisms. Both inflammation and some NANSAIDs appear to increase CV risks [4]. Through animal studies, it has been shown that inflammatory conditions impair the balance of vasodilator/vasoconstrictor components of renin-angiotensin system (RAS) within the heart [179]. The RAS is a major regulator of human physiology and has a key role in the CV homeostasis. Interestingly, NANSAIDs appear to be void of significant effects on RAS, instead, they are able to restore the imbalances that are resulted by inflammation [179]. Alternatively, an altered protective/toxic balance of the cardioactive CYP450-mediated metabolites of arachidonic acid has been reported to be involved in the cardiotoxic effects of NANSAIDs [180]. Whether ASA influences the RAS or the CYP450-mediated metabolites of arachidonic acid, remains unknown. Nevertheless, the possibility of CV protection by ASA through mechanisms other than its platelet effect is plausible.

The current analysis has limitations some of which are inherent to the nature of included studies. First, we have found that the published clinical evidence was sparse and has substantial

limitations. To highlight this point, we were unable to assess the heterogeneity since some studies reported RR/OR while other did HR. Second, the primary outcomes of some studies that we included in our review were not CV (MI or stroke) risks as they reported the latter as secondary outcomes. Last, we were unable to perform meta-analysis as the same reference (ASA alone, NANSAID alone or nonusers) or outcome (OR, RR or HR) had not been used across the eligible studies.

5.5. Conclusion

Low-dose ASA is widely used to prevent MI and other CV diseases. However, there is evidence that concurrent use of some, but not all NANSAIDs, may inhibit the anti-platelet effect of ASA. Naproxen, meloxicam and rofecoxib do not appear to influence the cardioprotective effect of ASA. Similarly, a large body of evidence supports that ibuprofen co-administration with ASA does not antagonize the anti-platelet effect of ASA. Altogether, it appears that the NANSAID-ASA interaction at the level of platelets does not necessarily amount to a loss of beneficial effects of ASA. The limited available data suggest that the effect of the drug-drug interactions on the platelet aggregation may dissipate shortly. In addition, it is plausible that the reduced platelet aggregation resulted by the interaction may be sufficient for cardioprotection; i.e., no need for near complete aggregation. In addition, the cardioprotective effect of ASA despite reduced platelet aggregation caused by NANSAIDs may be through its involvement in other mechanisms such as the RAS and/or metabolism of arachidonic acid to biologically active compounds mediated by CYP450.

Table 9: Reports of concomitant ibuprofen/ASA use regarding CV/all-cause mortality risks.

Beneficial effect of ASA in reducing CV risks NOT diminished		Beneficial effect of ASA in reducing CV risks diminished	
Reference	**Conclusions (RR/OR/HR (95% CI))**	**Reference**	**Conclusions (RR/OR/HR (95% CI))**
[61]	RR for MI: ASA+ibuprofen, 1.22 (0.83-1.78); ASA alone, 1.04 (0.96-1.12); ibuprofen alone, 1.02 (0.80-1.32).	**[150]**	HR for MI: ASA+ibuprofen, 1.50 (1.33-1.70); ASA alone 0.98 (0.94-1.03).
[151]	RR for MI: ASA+ibuprofen, 1.28 (1.16-1.40); ibuprofen alone, 1.12 (1.06-1.19).	**[157]**	HR for all-cause mortality: ASA+ibuprofen, 1.93 (1.30-2.87) *vs* ASA alone; HR for CV mortality: 1.73 (1.05-2.84) *vs* ASA alone.
[152]	HR for MI: ASA+ibuprofen, ever exposed, 1.01 (0.58-1.76), ≥ 30 days: 1.13 (0.54-2.39), ≥ 60 days: 1.83 (0.76-4.42) *vs* nonexposed subjects.		
[153]	OR for MI: ASA+ibuprofen, 0.74 (0.57-0.97); ASA alone, 0.87 (0.75-1.00).		
[154]	RR for MI: ASA+ibuprofen, 0.61 (0.50-0.73) *vs* ASA alone users.		
[155]	OR for MI: ASA+ibuprofen, 1.01 (0.47-2.20) *vs* ASA alone; ASA+ibuprofen, > 4 times/week, 2.03 (0.60-6.84); ASA+ibuprofen, < 4 times/week, 0.60 (0.21-1.66).		
[156]	OR for MI: ASA+ibuprofen, 1.08 (0.74-1.58) *vs* ASA alone users.		
[158]	HR for death: ASA+ibuprofen, 0.84 (0.70-1.01) *vs* ASA alone users.		

RR, Risk Ratio; OR, Odds Ratio; HR, Hazard Ratio; CV, Cardiovascular; MI, Myocardial Infarction. Ratios for ASA are listed when the assessment is made *vs* nonusers; for others, the ratio is 1 as ASA is used as the reference.

Table 10: Reports of concomitant naproxen/ASA use regarding CV risks.

Reference	Beneficial effect of ASA in reducing CV risks NOT diminished Conclusions (RR/OR/HR (95% CI))
[61]	RR for MI: ASA+naproxen, 1.26 (0.60-2.62); ASA alone, 1.04 (0.96-1.12); naproxen alone, 1.00 (0.68-1.47).
[83]	OR for MI: ASA+naproxen, 1.04 (0.65, 1.67); naproxen alone, 1.21 (0.93-1.56).
[150]	HR for CV: ASA+naproxen, 0.94 (0.52-1.70); ASA alone 0.98 (0.94-1.03).
[151]	RR for MI: ASA+naproxen, 1.28 (1.07-1.53); naproxen alone, 1.11 (1.01-1.23).
[152]	HR for MI: ASA+naproxen, ever exposed, 1.04 (0.58-1.76), ≥ 30 days, 1.13 (0.54-2.39), ≥ 60 days, 1.83 (0.76-4.42) *vs* nonexposed subjects.
[156]	OR for MI: ASA+naproxen, 0.96 (0.49-1.86) *vs* ASA alone users.

RR, risk ratio; OR, odds ratio; HR, hazard ratio; CV, Cardiovascular; MI, Myocardial Infarction. Ratios for ASA are listed when the assessment is made vs nonusers; for others, the ratio is 1 as ASA is used as the reference.

Table 11: Reports of concomitant meloxicam/Aspirin use regarding CV risks.

Reference	Beneficial effect of ASA in reducing CV risks NOT diminished Conclusions (RR/OR/HR (95% CI))
[61]	RR for MI: ASA+meloxicam, 0.78 (0.41-1.51); ASA alone, 1.03 (0.95-1.12); meloxicam alone, 1.61 (1.09-2.40).
[83]	OR for MI: ASA+meloxicam, 0.70 (0.39, 1.25); meloxicam alone, 1.41 (1.03-1.92).

Table 12: Reports of concomitant rofecoxib/ASA use regarding CV risks.

Beneficial effect of ASA in reducing CV risks NOT diminished	
Reference	**Conclusions (RR/OR/HR (95% CI))**
[61]	RR for MI: ASA+rofecoxib, RR 1.51 (0.92-2.47); ASA alone, 1.04 (0.96-1.12); rofecoxib alone, 1.47 (1.06-2.05).
[149]	RR for MI: no history of MI, ASA+rofecoxib, 1.12 (0.88-1.42); rofecoxib alone, 1.30 (1.08-1.57); previous MI, ASA+rofecoxib, 1.50 (1.07-2.09); rofecoxib alone, 1.75 (1.23-2.50).
[150]	HR for CV: ASA+rofecoxib, 1.10 (0.61-1.98); ASA alone 0.98 (0.94-1.03).

RR, risk ratio; OR, odds ratio; CV, Cardiovascular; MI, Myocardial Infarction

Table 13: Reports of concomitant celecoxib/ASA use regarding CV risks.

Beneficial effect of ASA in reducing CV risks NOT diminished		Beneficial effect of ASA in reducing CV risks diminished	
Reference	**Conclusions (RR/OR/HR (95% CI))**	**Reference**	**Conclusions (RR/OR/HR (95% CI))**
[61]	RR for MI: ASA+celecoxib, 1.13 (0.63-2.03); ASA alone, 1.04 (0.96-1.12); celecoxib alone, 1.44 (1.04-2.01).	**[150]**	HR for CV: ASA+celecoxib, 1.78 (1.30-2.44); ASA alone, 0.98 (0.94-1.03).
[149]	RR for MI: no history of MI, ASA+celecoxib, 0.88 (0.70-1.11); celecoxib alone, 1.11 (0.94-1.32); previous MI, 1.27 (0.94-1.71); celecoxib alone, 1.59 (1.17-2.18).		

RR, risk ratio; OR, odds ratio; HR, hazard ratio; CV, Cardiovascular; MI, Myocardial Infarction

Table 14: Reports of concomitant diclofenac/ASA use regarding CV risks.

Beneficial effect of ASA in reducing CV risks NOT diminished		Beneficial effect of ASA in reducing CV risks diminished	
Reference	**Conclusions (RR/OR/HR (95% CI))**	**Reference**	**Conclusions (RR/OR/HR (95% CI))**
[152]	HR for MI: ASA+diclofenac: ever exposed, 0.99 (0.58-1.76), ≥ 30 days: 0.80 (0.54-1.20), ≥ 60 days, 1.00 (0.61-1.65) *vs* non-exposed subjects.	**[61]**	RR for CV: ASA+diclofenac, 1.41 (1.03-1.93); ASA alone, 1.03 (0.96-1.12); diclofenac alone, 1.79 (1.52-2.12).
[156]	OR for MI: ASA+diclofenac, 1.16 (0.82-1.65) *vs* Aspirin alone users.	**[150]**	HR for MI: ASA+diclofenac, 1.74 (1.44-2.08); ASA alone, 0.98 (0.94-1.03).

RR, risk ratio; OR, odds ratio; HR, hazard ratio; CV, Cardiovascular; MI, Myocardial Infarction

Table 15: Main characteristics of the included molecular interactions studies that reported the influence of NANSAIDs on the anti-platelet action of ASA in human blood samples (*in vitro)*, healthy volunteers (*in vivo)* or isolated platelets (*ex vivo)* studies.

Reference	Year	Type of study (species)	Subjects	Treatments	Analyzed parameters	Conclusions
[161]	2017	*in vitro* (human)	Healthy volunteers (n = 6)	ASA only, ibuprofen (6 min after ASA) or loxoprofen (6 min after ASA) plus ASA groups were added to PRP.	Platelet aggregation by aggregometry and serum TxB_2 levels	Ibuprofen interferes with the anti-platelet effect of low-dose ASA; however, loxoprofen do not when given 6-12 h before ASA.
[159]	2013	*in vitro* (human)	Healthy volunteers (n = 6)	ASA, ibuprofen, loxoprofen, indomethacin, diclofenac, etodolac, mefenamic acid, naproxen, meloxicam, or flurbiprofen were added alone to PRP, then ASA was added before and after each NANSAID to PRP.	Platelet aggregation by aggregometry	Only ibuprofen and mefenamic acid do significantly interfere with the anti-platelet effect of ASA when taken after.
[160]	2013	*in vitro* (human)	Healthy volunteers (n = 7)	Ibuprofen, naproxen, diclofenac, ketorolac, flufenamate, piroxicam, dipyrone, celecoxib, nimesulide, acetaminophen or oxaprozin were added alone or together with ASA to PRP.	Platelet aggregation (induced by AA), plasma TxB_2 concentrations by aggregometry	Celecoxib, dipyrone, ibuprofen, flufenamic acid, naproxen, nimesulide, oxaprozin, and piroxicam do significantly interfere with the anti-platelet activity of ASA. While diclofenac, ketorolac and acetaminophen do not.
[170]	2005	*in vitro, in vivo* and *ex vivo* (human)	Healthy volunteers (aged 23-30 years, n = 4)	The volunteers received ASA (100 mg, once daily) for 6 days. Then they received either single or multiple doses of the combination of ASA 2 h before naproxen (500 mg, twice daily) for another 6 days. After a washout period of 14 days, the treatments were administered in reverse order.	Serum TxB_2, urinary 11 dehydro-TxB_2 excretion rates, platelet aggregation by aggregometry, LPS-stimulated PGE_2 production in whole blood	Naproxen interferes with the inhibitory effect of low-dose ASA on platelet aggregation.
[174]	2016	*in vivo* (human)	Healthy volunteers (aged 18-50 years)	ASA and celecoxib (alone or together) or control (saline) were added to the PRP.	Platelet aggregation (induced by AA) by aggregometry	Celecoxib interferes to a limited extent with the anti-platelet effect of low-dose ASA.

TABLE 15. Continued…

[167]	2014	*ex vivo* (human)	Healthy volunteers (*n* = 5)	Platelets were pre-incubated with ibuprofen, naproxen, or celecoxib for 10 min. then ASA was added to each group.	COX-1 acetylation, TxB_2 formation	A single therapeutic dose of ibuprofen or naproxen followed by ASA do reveal a potent drug-drug interaction, but not between celecoxib and ASA.
[167]	2014	*in vivo* (human)	Healthy volunteers (*n* = 7)	Subjects received a single dose of ibuprofen (600 mg), naproxen (500 mg), or celecoxib (200 mg), then a single dose of ASA (325 mg) was given 2 h after the NANSAID.	COX-1 acetylation, platelet aggregation (induced by AA), platelet TxB_2, urinary 11-dehydro TxB_2	
[169]	2013	*ex vivo* (human)	Healthy volunteers (*n* = 30)	The Volunteers were randomly allocated in two groups. First group received two daily doses of naproxen (500 mg), ibuprofen (600 mg) or placebo. Second group received one daily dose of meloxicam (15 mg), etoricoxib (90 mg) or placebo. Both groups received ASA (80 mg) 2 h after 2nd or 3rd dose of study medication.	*ex vivo* thrombocyte function, CT (seconds) was measured using the PFA-100 CT	Ibuprofen and naproxen interfere with anti-platelet effect of ASA, but etoricoxib and meloxicam do not.
[172]	2011	*in vivo* and *ex vivo* (human)	Healthy volunteers (aged 23-37 years, *n* = 9)	Subjects received either a combination of ASA (100 mg) 2 h before or after naproxen (220 mg, twice a day), or ASA alone for 6 days separated by 14 days of washout.	Serum TxB_2 and platelet aggregation (induced by AA and collagen)	Naproxen interferes with the anti-platelet activity of ASA. The interaction was similar when naproxen giving 2 h before or after low-dose of ASA.
[164]	2009	*in vivo* (human)	Healthy volunteers (aged 26-58 years, *n* = 12)	The volunteers were randomly assigned to either ASA (30 mg, once daily) for 7 days, slow release diclofenac (50 mg, three times daily) or ibuprofen (800 mg, three times daily) for 1 day. ASA (80 mg, once daily) was given after a washout period of 14-42 days with each treatment group for 7 days.	Serum TxB_2 levels	Only ibuprofen interferes with the anti-platelet activity of ASA.
[171]	2009	*ex vivo* (human)	Healthy volunteers (aged 21-58 years, *n* = 11)	The volunteers received during 4 different study periods (≥10 days washout period) either acetaminophen (1 g, three times daily), diclofenac (50 mg, three times daily), naproxen (250 mg, three times daily) or placebo plus ASA (100 mg, once daily) for 4 days.	PFA-100 CT	Regular daily co-administration of acetaminophen, diclofenac or naproxen do not interfere with the anti-platelet activity of ASA.

TABLE 15. Continued…

[168]	2008	*ex vivo* (human)	Healthy volunteers (n = 24)	The volunteers received randomly either naproxen (550 mg), ibuprofen (400 mg), celecoxib (200 mg), indomethacin (25 mg), tiaprofenic acid SR (300 mg) or sulindac (200 mg), ASA (300 mg) or placebo for 2 days.	PFA-100 CT	Ibuprofen, indomethacin, naproxen, and tiaprofenic acid interfere with the anti-platelet activity of ASA but not sulindac or celecoxib.
[166]	2008	*in vivo* (human)	Healthy volunteers (aged 21-32 years, n = 10)	The volunteers were randomly assigned to receive either ibuprofen (400 mg), ASA (325 mg) or ibuprofen (400 mg) plus one dose of ASA (325 mg, 2 h later). A minimum of 6 days washout period was allowed between treatments.	Platelet aggregation by aggregometry	Administration of ibuprofen before ASA interferes with the inhibitory effect of ASA on platelet aggregation.
[165]	2006	*in vivo* and *ex vivo* (human)	Osteoarthritis and stable ischaemic heart disease patients (aged 45-73 years, n = 29)	The patients were undergoing long term treatment with ASA (100 mg, daily), and received celecoxib (200 mg, twice daily), ibuprofen (600 mg, three times daily) or placebo for 7 days.	Serum TxB_2, urinary 11 dehydro-TxB_2 excretion rates, platelet aggregation by aggregometry, LPS-stimulated PGE_2 production in whole blood	Ibuprofen interferes with anti-platelet effect of ASA but not celecoxib.
[181]	2005	*ex vivo* (human)	Healthy volunteers (aged 18-45 years, n = 28)	The volunteers were randomly assigned to receive either lumiracoxib (400 mg, once daily) or placebo for 11 days. Both treatment groups received ASA (75mg, once daily) form day 5 to 11 (6 days).	Platelet aggregation (induced by AA and collagen), Serum TxB_2 levels, urinary TxB_2 and prostacyclin excretion rate	Lumiracoxib does not interfere with anti-platelet effect of low-dose ASA.
[162]	2005	*in vivo* (human)	Healthy volunteers (aged 19-54 years, 58-100 kg, n = 47)	The volunteers received ASA (81 mg, once daily) for 8 days. On day 9, subjects received either ibuprofen (400 mg, three times daily) or placebo (three times daily) for 10 days.	Serum TxB_2 levels	No clinically meaningful loss of cardioprotection was found in healthy volunteers who received OTC doses of ibuprofen with low-dose ASA.
[176]	2004	*in vivo* (human)	Healthy volunteers (aged 20-47 years, 55-87 kg, n = 16)	The volunteers received meloxicam (15 mg, once daily) alone for 4 days, then ASA (100 mg, once daily 2 h later) was added for another 6 days. After a washout period of 14 days, subjects received only ASA (100 mg, once daily) for 2 days.	Platelet aggregation by aggregometry, serum TxB_2	Meloxicam does not interfere with the inhibitory effect of low-dose ASA on platelet aggregation.

TABLE 15. Continued…

[173]	2002	*in vivo* (human)	Healthy volunteers (aged 18-48 years, 48.7-86 kg, *n* = 17)	The volunteers received celecoxib (200 mg, twice daily) or placebo for 4 days. On day 5, all volunteers received ASA (325 mg) with either celecoxib (20 mg) or placebo.	Serum TxB_2 levels, platelet aggregation (induced by ADP, AA and collagen)	Celecoxib does not interfere with anti-platelet effect of ASA.
[163]	2001	*ex vivo* (human)	Healthy volunteers (aged 18-65 years, *n* = 12)	The volunteers received ASA (81 mg) 2 h before single dose of either ibuprofen (400 mg), acetaminophen (1000 mg), or rofecoxib (25 mg) for 6 days. After a washout period of 14 days, the same medications were given in the reverse order for 6 days.	Serum TxB_2, platelet aggregation (induced by AA in PRP), LPS-stimulated PGE_2 production in whole blood, prostaglandin I_2	Only ibuprofen interferes with anti-platelet effect of ASA.
[163]	2001	*ex vivo* (human)	Healthy volunteers (aged 18-65 years, *n* = 10)	The volunteers received ASA (81 mg) 2 h before single dose of either ibuprofen (400 mg, three times daily) or delayed-release diclofenac (75 mg, twice daily) for 6 days.	Serum TxB_2, platelet aggregation by aggregometry	
[175]	2000	*ex vivo* (human)	Healthy volunteers (aged 18-38 years, 45.2-103.7 kg, *n* = 24)	The volunteers received either rofecoxib (50 mg, once daily) or placebo for 10 days and ASA (81 mg, once daily) for 7 days (days 4-10).	Serum TxB_2, platelet aggregation by aggregometry	Rofecoxib does not interfere with the inhibitory effect of low-dose ASA on platelet aggregation.
[182]	1984	*in vivo* (human)	Healthy volunteers (aged 22-32 years, *n* = 6)	The volunteers received sodium salicylate (1500 mg) and,1 h later, ASA (500 mg). After 2 weeks, subjects received only ASA (500 mg).	Serum TxB_2 concentrations	Sodium salicylate does not interfere with the inhibitory effect of ASA.

PRP, Platelet Rich Plasma; AA, arachidonic acid; TxB_2, thromboxane B_2; PFA, platelet function analyzer; PGE_2, prostaglandin E_2; LPS, lipopolysaccharide; COX-1, cyclooxygenase-1; h, hours; CT, closure time; OTC, over the counter; ADP, adenosine 5'-diphosphate.

Table 16: Main characteristics of the included epidemiological studies.

Reference	Year	Country	Type of study	Participants (events, *n*)	Duration	F%, age (years), history of CV/stroke events, ASA use, NANSAIDs use	comparison, *n*	Outcomes	Quality Assessment (NOS)
[150]	2015	Denmark	Cohort	61,971 patients (CV, 18,568)	3.5 years	36.8%, 67.7 (SD, 13.6) years, 4.9%, 18.0%, rofecoxib 0.8%, celecoxib 1.2%, diclofenac 9.9%, ibuprofen 23.1%, naproxen 1.7%, other 6.6%	Overall NANSAID use, 9,194	**Primary**: Admission or death of GI bleeding **Secondary**: CV death, nonfatal recurrent MI, and ischemic stroke, transient ischemic attack, or systemic arterial emboli	Selection: 4 stars; comparability: 2 stars; exposure: 2 stars
[151]	2008	UK	Cohort	729,294 NSAID users: 443,047 controls (MI, 5,690)	6.1:5.6 years	54.1%, 58.0 years: 58.2 years, 7.4%/3.1%: 6.9%/3.4%, 76.2%, ibuprofen 31.1%, diclofenac 39.6%, naproxen 9.1%, meloxicam 3.8%, indomethacin 3.6%, piroxicam 2.0%, mefenamic acid 1.9%	Control cohort (matched by disease risk score), 443,047	MI	Selection: 4 stars; comparability: 2 stars; exposure: 2 stars
[152]	2005	Canada	Cohort	18,503 patients (AMI, 535)	239.7 days	42.3%:45.1%, 74 years, 23.0%/6.5%: 18.9%/5.6%, NA, ibuprofen 9.1%, naproxen 30.4%, diclofenac 36.1%	Unexposed, 14,424	AMI	Selection: 4 stars; Comparability: 2 stars; Exposure: 3 stars
[157]	2003	UK	Cohort	7,107 patients (mortality, 3,813)	3.3 years	NA, 27-100 years, 50.5%/23.8%, 100%, ibuprofen 187, diclofenac 206, other 429	Unexposed, 6,285	All-cause mortality or CV mortality	Selection: 4 stars; Comparability: 2 stars; Exposure: 2 stars

TABLE 16. Continued…

[158]	2003	USA	Cohort	70,316 patients (mortality, 12,096)	3 years	48.3%, 75 years (53.9%), 30.5%/13.2%, 96.1% (66,739), ibuprofen 844, other 2,733	Unexposed, 66,739	Mortality within 1 year after discharge	Selection: 4 stars; Comparability: 2 stars; Exposure: 2 stars
[83]	2017	UK	Case-control	9,291 cases: 30,676 controls (MI, 9,291)	13 years	41.7%: 43.1%, 67.4 years (±11.9): 66.3 years (±11.6), 24.7%: 9.9%, 34.6%: 21.0%, diclofenac 1,020:2,846, meloxicam 248:655, naproxen 277: 886, other 1,246:3,843	Remote users (no exposure > 60 days prior index date but within 1 year), 4,184:15,488	MI	Selection: 3 stars; comparability: 2 stars; exposure: 2 stars
[61]	2008	UK	Case-control	8,852 cases: 20,000 controls (MI, 8,852)	4.1 years	NA, 50-84 years, NA, NA, celecoxib 81:144, diclofenac 353:483, ibuprofen 143:314, indomethacin 29:45, meloxicam 59:99, naproxen 54:119, refecoxib 98:139	Control cohort (matched by sex, age within 1 year, and calendar year), 20,000	MI	Selection: 4 stars; Comparability: 2 stars; Exposure: 2 stars
[149]	2007	Canada	Case-control	3,423 cases: 68,456 controls (MI, 3,423)	2.3 years	52.1%:67.1%, 78.2 years (5.4), 16.9%/2.0%: 6.2%/0.9%, 35.7%:21.8%, 71.4%	Control cohort (matched by sex, age within 1 year, and calendar year), 68,456	Nonfatal or fatal MI	Selection: 3 stars; Comparability: 2 stars; Exposure: 3 stars

TABLE 16. Continued…

[153]	2005	UK	Case-control	8,688 cases: 33,923 controls (MI, 8,688)	7 years	37.1%:37.2%, <50 years 7.6%:7.7%, 50-69 years 42.4%:42.8%, 70-89 years 50.0%: 49.5%, 30.1%: 12.1%, NA, diclofenac 260:834, ibuprofen 176:656, naproxen 63:251, indomethacin 36:124, piroxicam 30:114, ketoprofen 18:109, fenbufen 16:19, nabumetone 10:56, mefenamic acid 9:26, etodolac 8:43, flurbiprofen 6:34, tiaprofenic acid 6:26	Unexposed, 3,203: 13,551	The first MI	Selection: 3 stars; Comparability: 2 stars; Exposure: 2 stars
[154]	2004	USA	Case-control	3,859 cases: 10,239 controls (MI, 3,859)	52,139 patients-months: 156,417 patients-months	97.5 % (±2.5): 97.6% (±0.15) male, NA, NA, 100%, ibuprofen 3,859	Control cohort (sex, race, age, and LDL cholesterol level), 10,239	MI	Selection: 4 stars; Comparability: 1 star; Exposure: 1 star
[155]	2004	USA	Case-control	1,055 cases: 4,153 controls (MI, 1,055)	1067 days	44.5%/34.4%:66.6%/54.7%, 57.01 (±9.12)/58.07 (±9.24): 51.14 (8.64)/53.16 (±9.46) years, 15.0%/18.8%: 4.0%/3.7%, 27%, 30% (78% non-prescription NANSAID)	Control (no history of MI), 1,357:2,796	MI	Selection: 4 stars; Comparability: 2 stars; Exposure: 2 stars
[156]	2004	UK	Case-control	4,975 cases: 20,000 controls (MI, 4,975)	2 years, 4 months	35%, 55% >70 years, 38%/14%: 17%/8%, 27%:14%, 61%:59%	Control cohort (sex, age, and calendrer year), 20,000	MI	Selection: 3 stars; Comparability: 2 stars; Exposure: 2 stars

CV, cardiovascular; GI, gastrointestinal; MI, myocardial infarction; LDL, low-density lipoprotein; NA, not available; NOS, Newcastle-Ottawa quality scale.

Chapter 6

6. Summery and Suggestions

6.1. General conclusion

Our analyses suggest that use of etodolac is associated with a significantly fewer complicated GI risks, particularly ulcers and bleedings, compared with other available NSAIDs, such as naproxen and ibuprofen. We also found that etodolac caused a limited of common uncomplicated GI related adverse events that associated with NSAIDs use such as nausea, diarrhea or vomiting. This study confirmed that a generic NSAID like etodolac with high COX-2 selective properties (1000 folds over COX-1) caused to limited, mainly uncomplicated in its nature, hence manageable, GI side effects than other commonly used traditional or COX-2 selective NSAIDs, such as naproxen [122] or celecoxib [183].

The magnitude and nature of the CV risk associated with NSAIDs are heterogeneous across the class. Our analyses revealed that etodolac exposure demonstrated a safe CV profile compared with other NSAIDs, such as naproxen. Furthermore, CV risk associated with etodolac was comparable with no exposure groups when adjust for underlying inflammatory diseases. These findings confirmed that covariates like the underlying inflammatory conditions play a significant role in estimation of CV risk associated with NSAIDs exposure as they are commonly prescribe for patients with RA or OA. We also found that CV risk associated with NSAIDs is affected by other covariates such as NSAIDs doses as well as concomitant use of ASA.

We also investigated the long-term effects of the short-term pharmacodynamic interactions between ASA and other NSAIDs. We found that the interaction on the platelet level is not necessarily account for total loss of cardiprotective effect of low-dose ASA. In general, we found

conflicting conclusions regard ASA-NANSAIDs molecular interactions (*in vitro/in vivo/ex vivo*) data for ibuprofen, naproxen and celecoxib. However, for naproxen, the interaction at the platelet level did not amount to a loss of cardioprotective effects of ASA. Similarly, for ibuprofen, the results overwhelmingly suggest no negative clinical CV outcomes following the combination therapy. Meloxicam and rofecoxib neither interacted with ASA at the level of platelet aggregation nor altered clinical outcomes. The clinical outcomes data for celecoxib and diclofenac are in conflict. We concluded that the effect of the molecular interaction at the platelet site may dissipate shortly, or the reduced of the platelet aggregation yielded by the interaction may be sufficient for cardioprotection; i.e., no need for near complete aggregation. In addition, cardioprotective effect of ASA, despite reduced platelet aggregation caused by NANSAIDs, may be through its involvement in other mechanisms such as the renin-angiotensin system and/or metabolism of arachidonic acid to biologically active compounds mediated by cytochrome P450.

6.2. Future directions

The following are my recommendations for future studies to confirm and extend our analyses presented in this thesis:

a. Large clinical trials

Further experimental studies could provide more insight into risks associated with NSAIDs exposure in high risk populations such as RA patients. To demonstrate which of available NSAIDs are less toxic and investigate mechanisms responsible for the risks.

b. Network meta-analysis

I recommend performing network meta-analysis to investigate unknown pharmacodynamics interactions between ASA and other NSAIDs. I also recommend investigating the mechanisms of the interactions on platelet sites and whether or not ASA involves in other anti-aggregation mechanisms beyond its well-known platelet site.

c. Pharmacoeconomic analysis

I recommend conducting a full cost-benefit analysis regard risks that associated with available NSAIDs (generic *vs* brand). Although methodologically challenging, it would be very useful to conduct some longer-term studies which sought to quantify the impact of underlying inflammatory conditions in clinical trials.

6.3. Limitations and suggestions

Although the studies included in this thesis were carefully and intellectually prepared, I am still aware of their limitations and shortcomings. An important limitation in the meta-analysis was finding all of the studies on CV effect that associated with etodolac use. A critical issue is "the file-drawer effect" which is a study is conducted without a significant result, and it is not published. This is may be due to that some generic NSAIDs, hence not actively marketed, such as etodolac and meloxicam, may have favorable safety profiles as compared with other NSAIDs.

Finally, in the systematic reviews, some conclusions are made based on limited available data due to our narrow inclusion criteria which required inclusion of etodolac in the included studies. It would be better for future research to use a broaden inclusion criteria.

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Appendixes

Appendix-I: Chapter 4: List of literature search terms and key words

MEDLINE (Ovid)

1. etodolac.mp. or exp Etodolac/ (703)
2. (etodolac OR ecridoxan OR edolan OR entrang OR etodin OR etodolic acid OR etonox OR etopan OR etopan xl OR hypen OR lodins OR lodine lp OR lodine retard OR lodine sr OR lodine xl OR lenone OR ay 24,236 OR ay 24236 OR ay24,236 OR ay24236 OR leonine OR osteluc OR ramodar OR sdx 101 OR sdx101 OR tedolan OR toselac OR ultradol OR zedolac).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (778)
3. 1 or 2 (778)
4. randomized controlled trial.pt. (497429)
5. clinical trial.pt. (548139)
6. randomi?ed.ti,ab. (557885)
7. placebo.ti,ab. (208217)
8. dt.fs. (2116475)
9. randomly.ti,ab. (299939)
10. trial.ti,ab. (535870)
11. groups.ti,ab. (1873450)
12. or/4-11 (4552758)
13. animals/ (6511768)
14. humans/ (17827266)
15. 13 not (13 and 14) (4646034)
16. 12 not 15 (3956970)
17. 13 and 16 (294)
18. remove duplicates from 17 (265)

EMBASE

1. etodolac.mp. or exp etodolac/ (2611)
2. (etodolac OR ecridoxan OR edolan OR entrang OR etodin OR etodolic acid OR etonox OR etopan OR etopan xl OR hypen OR lodins OR lodine lp OR lodine retard OR lodine sr OR lodine xl OR lenone OR ay 24,236 OR ay 24236 OR ay24,236 OR ay24236 OR leonine OR osteluc OR ramodar OR sdx 101 OR sdx101 OR tedolan OR toselac OR ultradol OR zedolac).mp.[mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (2733)
3. 1 or 2 (2733)
4. exp clinical trial/ (1269575)
5. randomi?ed.ti,ab. (715917)
6. placebo.ti,ab. (262301)
7. dt.fs. (3495788)
8. randomly.ti,ab. (368045)
9. trial.ti,ab. (681601)
10. groups.ti,ab. (2388377)
11. or/4-10 (6558136)
12. animal/ (1816968)
13. human/ (18946796)
14. 12 not (12 and 13) (1383139)
15. 11 not 14 (6393225)
16. 3 and 15 (1670)
17. remove duplicates from 16 (1644)

The Cochrane Library (via Wiley)

Search Name: etodolac in Title, Abstract, Keywords or etodolac OR ecridoxan OR edolan OR entrang OR etodin OR etodolic acid OR etonox OR etopan OR etopan xl OR hypen OR lodins OR lodine lp OR lodine retard OR lodine sr OR lodine xl OR lenone OR ay 24,236 OR ay 24236 OR ay24,236 OR ay24236 OR leonine OR osteluc OR ramodar OR sdx 101 OR sdx101 OR tedolan OR toselac OR ultradol OR zedolac and clinical trial OR randomi* OR placebo OR randomly OR trial OR groups and humans not animal (Word variations have been searched)

Last Saved: 24/10/2017 01:10:03.363

ID	Search	Results
# 1	etodolac:ti,ab,kw or etodolac OR ecridoxan OR edolan OR entrang OR etodin OR etodolic acid OR etonox OR etopan OR etopan xl OR hypen OR lodins OR lodine lp OR lodine retard OR lodine sr OR lodine xl OR lenone OR ay 24,236 OR ay 24236 OR ay24,236 OR ay24236 OR leonine OR osteluc OR ramodar OR sdx 101 OR sdx101 OR tedolan OR toselac OR ultradol OR zedolac AND clinical trial OR randomi* OR placebo OR randomly OR trial OR groups AND humans NOT animal (Word variations have been searched)	238 (Cochrane Database of Systematic Reviews (CDSR) (19), Database of Abstracts of Reviews of Effect (DARE)(8), Cochrane Central Register of Controlled Trials (CENTRAL) (204), Cochrane Methodology Register (CMR)(3), Health Technology Assessment Database (HTAD)(2), NHS Economic Evaluation Database (NHSEED) (2), Cochrane Groups (0))

CINAHL

Search Strategy:

Search ID#	Search Terms	Results
S3	(clinical trials OR randomi* OR placebo OR randomly OR trial OR groups OR human NOT animal) AND (S1 AND S2)	(39)
S2	clinical trials OR randomi* OR placebo OR randomly OR trial OR groups OR human NOT animal	(1,939,735)
S1	etodolac OR (etodolac OR ecridoxan OR edolan OR entrang OR etodin OR etodolic acid OR etonox OR etopan OR etopan xl OR hypen OR lodins OR lodine lp OR lodine retard OR lodine sr OR lodine xl OR lenone OR ay 24,236 OR ay 24236 OR ay24,236 OR ay24236 OR leonine OR osteluc OR ramodar OR sdx 101 OR sdx101 OR tedolan OR toselac OR ultradol OR zedolac)	(74)

Web of Science

Search Strategy:

Set	Results	Search history
# 5	380	#4 AND #3 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*
# 4	8,044,311	**TOPIC:** (clinical trials) *OR* **TOPIC:** (randomi*) *OR* **TOPIC:** (placebo) *OR* **TOPIC:** (randomly) *OR* **TOPIC:** (trial) *OR* **TOPIC:** (groups) *OR* **TOPIC:**(human) *NOT* **TOPIC:** (animal) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*
# 3	908	#2 OR #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*
# 2	908	**TOPIC:** (etodolac or ecridoxan or edolan or entrang or etodin or etodolic acid or etonox or etopan or etopan xl or hypen or lodins or lodine lp or lodine retard or lodine sr or lodine xl or lenone or ay 24,236 or ay 24236 or ay24,236 or ay24236 or leonine or osteluc or ramodar or sdx 101 or sdx101 or tedolan or toselac or ultradol or zedolac)

		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 1	771	**TOPIC:** (Etodolac) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*

PubMed (May 1, 2018)

This searched was planned to screen for any relevant studies published after October 2017. We, therefore, carried out a PubMed search using the following key words "etodolac AND gastrointestinal adverse events OR ulcer adverse events OR bleeding adverse events OR cardiovascular adverse events OR myocardial infarction adverse events OR cerebrovascular adverse events" and restricted our search to published clinical trials conducted in humans between 2017/11/01 and 2018/05/01 in English language. We found 379 studies, and none met the inclusion criteria of this review.

Search Details

("etodolac"[MeSH Terms] OR "etodolac"[All Fields]) AND (gastrointestinal[All Fields] AND adverse[All Fields] AND events[All Fields]) OR (("ulcer"[MeSH Terms] OR "ulcer"[All Fields]) AND adverse[All Fields] AND events[All Fields]) OR (("hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields] OR "bleeding"[All Fields]) AND adverse[All Fields] AND events[All Fields]) OR (("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields]) AND adverse[All Fields] AND events[All Fields]) OR (("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields]) AND adverse[All Fields] AND events[All Fields]) OR (cerebrovascular[All Fields] AND adverse[All Fields] AND events[All Fields]) AND (("2017/10/01"[PDAT] : "2018/05/01"[PDAT]) AND "humans"[MeSH Terms]

Grey Literature Search

Database/ Website Name	URL or Path	Date searched	Search terms used	# of Relevant Documents	Comments
ClinicalTrials.gov (US National Institutes of Health)	https://clinicaltrials.gov	23-Oct-2017	Etodolac	**23**	23 trials were included in additional records identified through other sources
ProQuest Dissertations & Theses Global	http://www.proquest.com/products-services/pqdtglobal.html	23-Oct-2017	Etodolac	**20**	20 trials were included in additional records identified through other sources.
Health Canada's Clinical Trials Database	https://health-products.canada.ca/	23-Oct-2017	Etodolac	**0**	No trials were found.
PROSPERO International prospective register of systematic reviews	https://www.crd.york.ac.uk/	23-Oct-2017	Etodolac	**7**	7 trials were included in additional records identified through other sources.

Appendix-II: Chapter 4: References for studies included in the systematic review and/or meta-analysis and studies excluded from the review.

Included Studies

RCTs

1. Andelman, S.Y., *Etodolac, aspirin, and placebo in patients with degenerative joint disease: A twelve-week study.* Clinical Therapeutics, 1983. **5**(6): p. 651-661.
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5. Hutton, C.E., *The effectiveness of 100 and 200 mg etodolac (Ultradol), aspirin, and placebo in patients with pain following oral surgery.* Oral Surgery, Oral Medicine, Oral Pathology, 1983. **56**(6): p. 575-80.
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8. Jacob, G., M. Sanda, and J. Mullane, *Long-term evaluation of the efficacy and safety of etodolac in the treatment of rheumatoid arthritis.* Advances in Therapy, 1985. **2**(3): p. 82-95.
9. Gaston, G.W., R.D. Mallow, and J.E. Frank, *Comparison of etodolac, aspirin and placebo for pain after oral surgery.* Pharmacotherapy, 1986. **6**(5): p. 199-205.
10. Jacob, G., et al., *Minimum effective dose of etodolac for the treatment of rheumatoid arthritis.* Journal of Clinical Pharmacology, 1986. **26**(3): p. 195-202.
11. Waltham-Weeks, C.D., *Etodolac versus naproxen in rheumatoid arthritis: A double-blind crossover study.* Current Medical Research and Opinion, 1987. **10**(8): p. 540-547.
12. Astorga Paulsen, G., et al., *Efficacy and tolerability comparison of etodolac and piroxicam in the treatment of patients with osteoarthritis of the knee.* Current Medical Research & Opinion, 1991. **12**(6): p. 401-12.
13. Briancon, D., J. Peterschmitt, and G. Laviec, *Double-Blind Parallel-Group Evaluation Of The Safety And Efficacy Of Etodolac Capsules Compared With Piroxicam Capsules In Patients With Rheumatoid-Arthritis.* Acta Therapeutica, 1991. **17**(1): p. 35-47.
14. Karbowski, A., *Double-blind, parallel comparison of etodolac and indomethacin in patients with osteoarthritis of the knee.* Current Medical Research And Opinion, 1991. **12**(5): p. 309-317.
15. Maccagno, A., E. Di Giorgio, and A. Romanowicz, *Effectiveness of etodolac ('Lodine') compared with naproxen in patients with acute gout.* Current Medical Research and Opinion, 1991. **12**(7): p. 423-429.
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18. D'Hooghe, M., *Double-blind, parallel-group evaluation of etodolac and naproxen in patients with acute sports injuries.* Clinical Therapeutics, 1992. **14**(4): p. 507-516.
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24. Neustadt, D.H., *Double blind evaluation of the long-term effects of etodolac versus ibuprofen in patients with rheumatoid arthritis.* Journal of Rheumatology - Supplement, 1997. **47**: p. 17-22.
25. Rogind, H., et al., *Comparison of etodolac and piroxicam in patients with osteoarthritis of the hip or knee - A prospective, randomised, double-blind, controlled multicentre study.* Clinical Drug Investigation, 1997. **13**(2): p. 66-75.
26. Ishiguro, N., et al., *Efficacy and safety of celecoxib compared with placebo and etodolac for acute postoperative pain: a multicenter, double-blind, randomized, parallel-group, controlled trial.* Nagoya Journal of Medical Science, 2015. **77**(1-2): p. 81-93.

Cohort studies

1. Huang, W.F., et al., *Cardiovascular events associated with the use of four nonselective NSAIDs (Etodolac, Nabumetone, Ibuprofen, or Naproxen) Versus a Cyclooxygenase-2 Inhibitor (Celecoxib): A population-based analysis in taiwanese adults.* Clinical Therapeutics, 2006. **28**(11): p. 1827-1836.
2. Lindhardsen, J., et al., *Non-steroidal anti-inflammatory drugs and risk of cardiovascular disease in patients with rheumatoid arthritis: A nationwide cohort study.* Annals of the Rheumatic Diseases, 2014. **73**(8): p. 1515-1521.

Case-control studies

1. Solomon D.H., et al., *Nonsteroidal anti-inflammatory drug use and acute myocardial infarction.* Archives of Internal Medicine, 2002. **162**(10): p. 1099-1104.
2. Fischer LM, et al., *Current use of nonsteroidal antiinflammatory drugs and the risk of acute myocardial infarction*. Vol. 25. 2005: PHARMACOTHERAPY. p503-p510.
3. Helin-Salmivaara, A., et al., *NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case–control study from Finland.* European Heart Journal, 2006. **27**(14): p. 1657-1663.
4. García Rodríguez, L.A., S. Tacconelli, and P. Patrignani, *Role of Dose Potency in the Prediction of Risk of Myocardial Infarction Associated With Nonsteroidal Anti-Inflammatory Drugs in the General Population.* Journal of the American College of Cardiology, 2008. **52**(20): p. 1628-1636.
5. Warner, J.J., et al., *The Risk of Acute Myocardial Infarction With Etodolac Is Not Increased Compared to Naproxen: A Historical Cohort Analysis of a Generic COX-2 Selective Inhibitor.* Journal of Cardiovascular Pharmacology and Therapeutics, 2008. **13**(4): p. 252-260.
6. Arfè, A., et al., *Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study.* BMJ (Clinical Research Ed.), 2016. **354**: p. i4857-i4857.

<u>Excluded studies:</u> categorized by reasons for exclusion

Studies Did Not Report the Outcome of Interest (total number of events/patients at risk)

1. Nelson, S.L. and S.A. Bergman, *Relief of dental surgery pain: a controlled 12-hour comparison of etodolac, aspirin, and placebo.* Anesthesia Progress, 1985. **32**(4): p. 151-6.
2. Scott, R., E. Ellis, 3rd, and L.G. Upton, *Double-blind evaluation of etodolac (200 mg, 400 mg) compared with zomepirac (100 mg) and placebo on third molar extraction pain.* Oral Surgery, Oral Medicine, Oral Pathology, 1986. **62**(6): p. 638-42.

3. Ciompi, M.L., et al., *Etodolac versus diclofenac: double-blind cross-over study in rheumatoid arthritis.* International Journal of Clinical Pharmacology Research, 1989. **9**(3): p. 217-22.
4. Chikanza, I.C., et al., *A comparative study of the efficacy and toxicity of etodolac and naproxen in the treatment of osteoarthritis.* British Journal of Clinical Practice, 1994. **48**(2): p. 67-69.
5. Akbulut, N., et al. *Comparison of the effect of naproxen, etodolac and diclofenac on postoperative sequels following third molar surgery: A randomised, double-blind, crossover study*. Medicina oral, patologia oral y cirugia bucal, 2014. **19**, 149-56 DOI: 10.4317/medoral.19518.
6. Arnold, J.D., et al., *Etodolac, aspirin, and gastrointestinal microbleeding.* Clinical Pharmacology and Therapeutics, 1984. **35**(5): p. 716-721.
7. Salom, I.L., et al., *Gastrointestinal microbleeding associated with the use of etodolac, ibuprofen, indomethacin, and naproxen in normal males.* Journal of Clinical Pharmacology, 1984. **24**(5-6): p. 240-246.
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9. Salom, I.L., et al., *Gastrointestinal microbleeding associated with the use of etodolac, ibuprofen, indomethacin, and naproxen in normal males.* Journal of Clinical Pharmacology, 1984. **24**(5-6): p. 240-246.
10. Brater, D.C., et al., *Effect of etodolac in patients with moderate renal impairment compared with normal subjects.* Clinical Pharmacology & Therapeutics, 1985. **38**(6): p. 674-679.
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12. Jallad, N.S., et al., *Gastrointestinal blood loss in arthritic patients receiving chronic dosing with etodolac and piroxicam.* American Journal of the Medical Sciences, 1986. **292**(5): p. 272-6.
13. Lanza, F., J. Panagides, and I.L. Salom, *Etodolac compared with aspirin: an endoscopic study of the gastrointestinal tracts of normal volunteers.* Journal of Rheumatology, 1986. **13**(2): p. 299-303.
14. Lanza, F., J. Panagides, and I.L. Salom, *Etodolac compared with aspirin: an endoscopic study of the gastrointestinal tracts of normal volunteers.* Journal of Rheumatology, 1986. **13**(2): p. 299-303.
15. Davoli, L., et al., *Piroxicam-beta-cyclodextrin in the treatment of low-back pain. Controlled study vs etodolac.* Current Therapeutic Research - Clinical and Experimental, 1989. **46**(5): p. 940-947.
16. Fioravanti, A., et al. *Single-blind, randomized, parallel-group study of etodolac and naproxen in patients with osteoarthritis*. Current therapeutic research - clinical and experimental, 1989. **46**, 648-653.
17. Taha, A.S., et al., *Evaluation of the efficacy and comparative effects on gastric and duodenal mucosa of etodolac and naproxen in patients with rheumatoid arthritis using endoscopy.* British Journal of Rheumatology, 1989. **28**(4): p. 329-332.
18. Russell, R.I., *Endoscopic Evaluation of Etodolac and Naproxen, and Their Relative Effects on Gastric and Duodenal Prostaglandins.* Rheumatology International, 1990. **10**: p. 17-21.
19. Taha, A.S., et al., *Effect on gastric and duodenal mucosal prostaglandins of repeated intake of therapeutic doses of naproxen and etodolac in rheumatoid arthritis.* Annals of the Rheumatic Diseases, 1990. **49**(6): p. 354-358.
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25. Svendsen, K.B., et al., *A comparison of the effects of etodolac and ibuprofen on renal haemodynamics, tubular function, renin, vasopressin and urinary excretion of albumin alpha-glutathione-S-transferase in healthy subjects: A placebo-controlled cross over study.* European Journal of Clinical Pharmacology, 2000. **56**(5): p. 383-388.
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27. Garcia Rodriguez, L.A. and L. Barreales Tolosa, *Risk of Upper Gastrointestinal Complications Among Users of Traditional NSAIDs and COXIBs in the General Population.* Gastroenterology, 2007. **132**(2): p. 498-506.
28. Imamura, H., et al., *Evaluating the effects of diclofenac sodium and etodolac on renal hemodynamics with contrast-enhanced ultrasonography: a pilot study.* European Journal of Clinical Pharmacology, 2013. **69**(2): p. 161-165.
29. Iwabuchi, T., et al., *Increased gastric mucus secretion alleviates non-steroidal anti-inflammatory drug-induced abdominal pain.* The Tohoku Journal Of Experimental Medicine, 2013. **231**(1): p. 29-36.

Drug Switching, Dose Adjustment, and/or Use of Extra-Oral Route of Administration Had Occurred

1. Ryder, S., I. Salom, and G. Jacob, *Etodolac (Ultradol): The safety profile of a new structurally novel nonsteroidal anti-inflammatory drug.* Current Therapeutic Research - Clinical and Experimental, 1983. **33**(6 I): p. 948-965.
2. Pareek, A., et al., *Comparative evaluation of efficacy and safety of etodolac and diclofenac sodium injection in patients with postoperative orthopedic pain.* Current Medical Research & Opinion, 2011. **27**(11): p. 2107-15.

Full-text not in English language

1. Homma, M., et al. *Long-Term Clinical Study of Etodolac in Patients with Rheumatoid Arthritis*. Rinsho iyaku (journal of clinical therapeutics and medicines), 1991. **7**, 129-154.

Duplicate Data

1. Shand, D.G., et al., *The effect of etodolac administration on renal function in patients with arthritis.* Journal of Clinical Pharmacology, 1986. **26**(4): p. 269-74.

SR Formulation

1. Jubb, R.W., P. Platt, and T.R. Price, *Double-blind comparison of etodolac sustained-release tablets and piroxicam capsules in patients with rheumatoid arthritis: An interim report.* Current Therapeutic Research - Clinical and Experimental, 1992. **52**(6): p. 769-779.
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Appendix-III: Chapter 5: List of search terms and key words used

MEDLINE

1. acetylsalicylic acid.mp. or exp Aspirin/ (47960)
2. Aspirin.mp. or exp Aspirin/ (65534)
3. ASA.mp. (24069)
4. 1 or 2 or 3 (87880)
5. exp Anti-Inflammatory Agents/ or exp Anti-Inflammatory Agents, Non-Steroidal/ or NSAID*.mp. or exp Cyclooxygenase Inhibitors/ (500344)
6. nonsteroidal antiinflammatory.mp. (4610)
7. nonsteroidal anti-inflammatory.mp. (15647)
8. non-steroidal antiinflammatory.mp. (913)
9. non-steroidal anti-inflammatory.mp. (15062)
10. (Ibuprofen or naproxen or ketoprofen or flurbiprofen or fenoprofen or oxaprozin or etoldolac or tolmetin or diclofenac or ketorolac or nabumetone or indomethacin or sulindac or piroxicam or meloxicam or mefenamic acid or meclofenamic acid or rofecoxib or celecoxib or veldecoxib or paracoxib or etoricoxib or lumaricoxib).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (90791)
11. (cyclooxygenase* or cyclo-oxygenase* or COX*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (196883)
12. 5 or 6 or 7 or 8 or 9 or 10 or 11 (683969)
13. cardiovascular.mp. (517392)
14. myocardial infarction.mp. or exp Myocardial Infarction/ (241926)
15. exp Stroke/ or stroke*.mp. or exp Cerebrovascular Disorders/ (481036)
16. (cardioprotect* or cardio-protect*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (19351)
17. 13 or 14 or 15 or 16 (1140235)
18. exp Platelet Aggregation/ or platelet*.mp. (262607)
19. blood platelets.mp. or exp Blood Platelets/ (78062)
20. exp Platelet Aggregation Inhibitors/ or exp Platelet Aggregation/ or platelet aggregation inhibit*.mp. or exp Blood Platelets/ (186906)
21. anti platelet effect*.mp. (264)
22. 18 or 19 or 20 or 21 (324684)
23. 17 or 22 (1419931)
24. Interaction.mp. (724108)
25. Drug interaction.mp. or exp Drug Interactions/ (164791)
26. Interact*.mp. (1503338)
27. 24 or 25 or 26 (1563966)
28. 4 and 12 and 23 and 27 (3728)
29. ((NSAID* or Ibuprofen or naproxen or ketoprofen or flurbiprofen or fenoprofen or oxaprozin or etoldolac or tolmetin or diclofenac or ketorolac or nabumetone or indomethacin or sulindac or piroxicam or meloxicam or mefenamic acid or meclofenamic acid or rofecoxib or celecoxib or veldecoxib or paracoxib or etoricoxib or lumaricoxib) adj3 (interact* or inhibit*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (15311)
30. ((cyclooxygenase* or cyclo-oxygenase* or COX*) adj3 (interact* or inhibit*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (36297)
31. ((aspirin or ASA or acetylsalicylic acid) adj3 (interact* or inhibit*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4517)
32. 29 or 30 or 31 (45379)

33. 28 and 32 (1161)
34. remove duplicates from 33 (1079)

EMBASE

1. acetylsalicylic acid.mp. or exp acetylsalicylic acid/ (194594)
2. Aspirin.mp. or exp acetylsalicylic acid/ (200287)
3. ASA.mp. or exp acetylsalicylic acid/ (225835)
4. 1 or 2 or 3 (235264)
5. exp nonsteroid antiinflammatory agent/ or NSAID*.mp. (537163)
6. nonsteroidal antiinflammatory.mp. (5560)
7. exp antiinflammatory agent/ or nonsteroidal anti-inflammatory.mp. (1643638)
8. non-steroidal antiinflammatory.mp. (1926)
9. non-steroidal anti-inflammatory.mp. (19822)
10. mefenamic acid.mp. or exp mefenamic acid/ (5640)
11. meclofenamic acid.mp. or exp meclofenamic acid/ (2834)
12. (ibuprofen or naproxen or ketoprofen or flurbiprofen or fenoprofen or oxaprozin or etoldolac or tolmetin or diclofenac or ketorolac or nabumetone or indomethacin or sulindac or piroxicam or meloxicam or rofecoxib or celecoxib or veldecoxib or paracoxib or etoricoxib or lumaricoxib).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (166401)
13. (cyclooxygenase* or cyclo-oxygenase* or COX*).mp. [mp=title, abstract, heading word, drug trade name, original
    title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (284223)
14. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (1876062)
15. cardiovascular.mp. (874842)
16. myocardial infarction.mp. or exp heart infarction/ (378320)
17. stroke*.mp. (370234)
18. Cerebrovascular.mp. or exp cerebrovascular disease/ (556732)
19. (cardioprotect* or cardio-protect).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (25495)
20. 15 or 16 or 17 or 18 or 19 (1726649)
21. platelet*.mp. (291091)
22. blood platelets.mp. or exp thrombocyte/ (104209)
23. Platelet Aggregation Inhibitors.mp. or exp antithrombocytic agent/ (314999)
24. Platelet Aggregation.mp. or exp thrombocyte aggregation/ (61352)
25. platelet aggregation inhibit*.mp. (2390)
26. anti platelet effect*.mp. (421)
27. 21 or 22 or 23 or 24 or 25 or 26 (586844)
28. 20 or 27 (2171471)
29. exp drug interaction/ or Interaction.mp. (1524352)
30. Interact*.mp. (1914430)
31. 29 or 30 (2067908)
32. 4 and 14 and 28 and 31 (17752)
33. ((NSAID* or Ibuprofen or naproxen or ketoprofen or flurbiprofen or fenoprofen or oxaprozin or etoldolac or tolmetin or diclofenac or ketorolac or nabumetone or indomethacin or sulindac or piroxicam or meloxicam or mefenamic acid or meclofenamic acid or rofecoxib or celecoxib or veldecoxib or paracoxib or etoricoxib or lumaricoxib) adj3 (interact* or inhibit*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (17171)
34. ((cyclooxygenase* or cyclo-oxygenase* or COX*) adj3 (interact* or inhibit*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (43788)
35. ((aspirin or ASA or acetylsalicylic acid) adj3 (interact* or inhibit*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (5681) 33 or 34 or 35 (55160)

36. 32 and 36 (3017)
37. remove duplicates from 37 (2965)

CINAHL

Wednesday, November 01, 2017 4:53:55 PM

#	Query	Limiters/Expanders	Last Run Via	Results
S5	(Interaction OR Drug interaction OR Interact*) AND (S1 AND S2 AND S3 AND S4)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	142
S4	Interaction OR Drug interaction OR Interact*	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	117,174
S3	cardiovascular OR myocardial infarction OR stroke* OR cerebrovascular OR cardioprotect* OR cardio-protect* OR platelet* OR platelet aggregation OR platelet aggregation inhibit* OR antiplatelet effect* OR blood platelets	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	256,163
S2	NSAID* OR nonsteroidal antiinflammatory OR nonsteroidal anti-inflammatory OR non-steroidal antiinflammatory OR non-steroidal anti-inflammatory OR (Ibuprofen OR naproxen OR ketoprofen OR flurbiprofen OR fenoprofen OR oxaprozin OR etoldolac OR tolmetin OR diclofenac OR ketorolac OR nabumetone OR indomethacin OR sulindac OR piroxicam OR meloxicam OR mefenamic acid OR meclofenamic acid OR rofecoxib OR celecoxib OR veldecoxib OR paracoxib OR etoricoxib OR lumaricoxib) OR (cyclooxygenase* OR cyclo-oxygenase* OR COX*)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	66,609
S1	acetylsalicylic acid OR aspirin OR ASA	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	15,169

Web of Science

Set	Results	Save History / Create Alert / Open Saved History	Edit Sets	Combine Sets AND OR Combine	Delete Sets Select All Delete
# 5	460	#4 AND #3 AND #2 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	Edit		
# 4	2,772,324	**TOPIC:** (Interaction) *OR* **TOPIC:** (Drug interaction) *OR* **TOPIC:** (Interact*) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	Edit		
# 3	1,135,107	**TOPIC:** (cardiovascular) *OR* **TOPIC:** (myocardial infarction) *OR* **TOPIC:** (stroke*) *OR* **TOPIC:** (cerebrovascular) *OR* **TOPIC:** (cardioprotect*) *OR* **TOPIC:** (cardio-protect*) *OR* **TOPIC:** (platelet*) *OR* **TOPIC:** (platelet aggregation) *OR* **TOPIC:** (platelet aggregation inhibit*) *OR* **TOPIC:** (antiplatelet effect*) *AND* **TOPIC:** (blood platelets) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	Edit		
# 2	283,167	**TOPIC:** (NSAID*) *OR* **TOPIC:** (nonsteroidal antiinflammatory) *OR* **TOPIC:** (nonsteroidal anti-inflammatory) *OR* **TOPIC:** (non-steroidal antiinflammatory) *OR* **TOPIC:** (non-steroidal anti-inflammatory) *OR* **TOPIC:** (Ibuprofen OR naproxen OR ketoprofen OR flurbiprofen OR fenoprofen OR oxaprozin OR etoldolac OR tolmetin OR diclofenac OR ketorolac OR nabumetone OR indomethacin OR sulindac OR piroxicam OR meloxicam OR mefenamic acid OR meclofenamic acid OR rofecoxib OR celecoxib OR veldecoxib OR paracoxib OR etoricoxib OR lumaricoxib) *OR* **TOPIC:** (cyclooxygenase* OR cyclo-oxygenase* OR COX*) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	Edit		
# 1	79,382	**TOPIC:** (acetylsalicylic acid) *OR* **TOPIC:** (Aspirin) *OR* **TOPIC:** (ASA) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	Edit		
				AND OR Combine	Select All Delete

EBM Reviews search (via Wiley)

Search Name: acetylsalicylic acid OR Aspirin OR ASA in Title, Abstract, Keywords and NSAID* OR nonsteroidal antiinflammatory OR nonsteroidal anti-inflammatory OR non-steroidal antiinflammatory OR non-steroidal anti-inflammatory OR Ibuprofen OR naproxen OR ketoprofen OR flurbiprofen OR fenoprofen OR oxaprozin OR etoldolac OR tolmetin OR diclofenac OR ketorolac OR nabumetone OR indomethacin OR sulindac OR piroxicam OR meloxicam OR mefenamic acid OR meclofenamic acid OR rofecoxib OR celecoxib OR veldecoxib OR paracoxib OR etoricoxib OR lumaricoxib OR cyclooxygenase* OR cyclo-oxygenase* OR COX* and cardiovascular OR myocardial infarction OR stroke* OR cerebrovascular OR cardioprotect* OR cardio-protect* OR platelet* OR platelet aggregation OR platelet aggregation inhibit* OR antiplatelet effect* OR blood platelets and Interaction OR Drug interaction OR Interact* (Word variations have been searched)
Last Saved: 01/11/2017 22:00:04.558
ID Search
#1 acetylsalicylic acid or Aspirin or ASA:ti,ab,kw and NSAID* or nonsteroidal antiinflammatory or nonsteroidal anti-inflammatory or non-steroidal antiinflammatory or non-steroidal anti-inflammatory or Ibuprofen or naproxen or ketoprofen or flurbiprofen or fenoprofen or oxaprozin or etoldolac or tolmetin or diclofenac or ketorolac or nabumetone or indomethacin or sulindac or piroxicam or meloxicam or mefenamic acid or meclofenamic acid or rofecoxib or celecoxib or veldecoxib or paracoxib or etoricoxib or lumaricoxib or cyclooxygenase* or cyclo-oxygenase* or COX* and cardiovascular or myocardial infarction or stroke* or cerebrovascular or cardioprotect* or cardio-protect* or platelet* or platelet aggregation or platelet aggregation inhibit* or antiplatelet effect* or blood platelets and Interaction or Drug interaction or Interact* (Word variations have been searched)

Results: 160
1. Cochrane Database of Systematic Reviews (25)
2. Database of Abstracts of Reviews of Effect (1)

3. Cochrane Central Register of Controlled Trials (134)
4. Cochrane Methodology Register (0)
5. Health Technology Assessment Database (0)
6. NHS Economic Evaluation Database (0)
7. About the Cochrane Collaboration (0)

PubMed (May 01, 2018)

This PubMed search aimed to screen for any relevant studies published after October 2017. We, therefore, carried out PubMed search using the following keywords " Aspirin AND NSAIDs" and restricted to publication date from 2017/11/01 to 2018/05/01. We found 148 studies, and none met the inclusion criteria of this review

Search Details

("aspirin"[MeSH Terms] OR "aspirin"[All Fields]) AND ("anti-inflammatory agents, non-steroidal"[Pharmacological Action] OR "anti-inflammatory agents, non-steroidal"[MeSH Terms] OR ("anti-inflammatory"[All Fields] AND "agents"[All Fields] AND "non-steroidal"[All Fields]) OR "non-steroidal anti-inflammatory agents"[All Fields] OR "nsaids"[All Fields]) AND ("2017/11/01"[PDAT] : "2018/05/01"[PDAT])

Grey Literature Search					
Database/ Website Name	**URL or Path**	**Date searched**	**Search terms used**	**# of Relevant Documents**	**Comments**
Cochrane Central Register of Controlled Trials (CENTRAL)	http://onlinelibrary.wiley.com/cochranelibrary/search	01-Nov-17	acetylsalicylic acid OR Aspirin OR ASA in Title, Abstract, Keywords and NSAID* OR nonsteroidal antiinflammatory OR nonsteroidal anti-inflammatory OR non-steroidal antiinflammatory OR non-steroidal anti-inflammatory OR Ibuprofen OR naproxen OR ketoprofen OR flurbiprofen OR fenoprofen OR oxaprozin OR etoldolac OR tolmetin OR diclofenac OR ketorolac OR nabumetone OR indomethacin OR sulindac OR piroxicam OR meloxicam OR mefenamic acid OR meclofenamic acid OR rofecoxib OR celecoxib OR veldecoxib OR paracoxib OR etoricoxib OR lumaricoxib OR cyclooxygenase* OR cyclo-oxygenase* OR COX* and cardiovascular OR myocardial infarction OR stroke* OR cerebrovascular OR cardioprotect* OR cardio-protect* OR platelet* OR platelet aggregation OR platelet aggregation inhibit* OR antiplatelet effect* OR blood platelets and Interaction OR Drug interaction OR Interact*	**134**	We added this to the Cochrane library search results as the CENTRAL is one database included in Cochrane library
ProQuest Dissertations & Theses Global	https://search-proquest-com.login.ezproxy.library.ualberta.ca/pqdtglobal/results/D2EEE14FBB414B59PQ/1?accountid=14474	02-Nov-17	all(acetylsalicylic acid OR Aspirin OR ASA) AND all(NSAID* OR nonsteroidal antiinflammatory OR nonsteroidal anti-inflammatory OR non-steroidal antiinflammatory OR non-steroidal anti-inflammatory OR Ibuprofen OR naproxen OR ketoprofen OR flurbiprofen OR fenoprofen OR oxaprozin OR etoldolac OR tolmetin OR diclofenac OR ketorolac OR nabumetone OR indomethacin OR sulindac OR piroxicam OR meloxicam OR mefenamic acid OR meclofenamic acid OR rofecoxib OR celecoxib OR veldecoxib OR paracoxib OR etoricoxib OR lumaricoxib OR cyclooxygenase* OR cyclo-oxygenase* OR COX*) AND all(cardiovascular OR myocardial infarction OR stroke* OR cerebrovascular OR cardioprotect* OR cardio-protect* OR platelet* OR platelet aggregation OR platelet aggregation inhibit* OR antiplatelet effect* OR blood platelet) AND all(Interaction OR Drug interaction OR Interact*)	**16**	We added all 16 to the additional records identified through other sources

GREY LITERATURE SEARCH, Continued…

Health Canada's Clinical Trials Database	https://health-products.canada.ca/ctdb-bdec/search-recherche.do;jsessionid=1D954BB5AFD48D432664B0D0818697F4	02-Nov-17	**Medical Condition**: cardiovascular OR cerebrovascular **Drug Name**: acetylsalicylic acid OR Aspirin AND NSAID	**0**	
PROSPERO International prospective register of systematic reviews	https://www.crd.york.ac.uk/PROSPERO/#searchadvanced	06-Nov-17	acetylsalicylic acid OR Aspirin OR ASA AND NSAID* OR nonsteroidal antiinflammatory OR nonsteroidal anti-inflammatory OR non-steroidal antiinflammatory OR non-steroidal anti-inflammatory OR Ibuprofen OR naproxen OR ketoprofen OR flurbiprofen OR fenoprofen OR oxaprozin OR etoldolac OR tolmetin OR diclofenac OR ketorolac OR nabumetone OR indomethacin OR sulindac OR piroxicam OR meloxicam OR mefenamic acid OR meclofenamic acid OR rofecoxib OR celecoxib OR veldecoxib OR paracoxib OR etoricoxib OR lumaricoxib OR cyclooxygenase* OR cyclo-oxygenase* OR COX* AND cardiovascular OR myocardial infarction OR stroke* OR cerebrovascular OR cardioprotect* OR cardio-protect* OR platelet* OR platelet aggregation OR platelet aggregation inhibit* OR antiplatelet effect* OR blood platelet AND Interaction OR Drug interaction OR Interact*	**2**	Both records were not relevant.

Appendix-IV: Publication from this thesis

Zuhair Al-Qahtani and Fakhreddin Jamali. "Clinical Outcomes of Aspirin Interaction with Other Non-Steroidal Anti-Inflammatory Drugs: A Systematic Review" *Pharm Pharm Sci*, 21 (1s) (2018): 48s-73s.