Association of selective and conventional nonsteroidal anti-inflammatory drugs with acute renal failure

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Abstract

The safety of the novel class of nonsteroidal anti-inflammatory drugs (NSAIDs), the COX-2 inhibitors, is currently debated, with the focus on their cardiovascular toxicity. Here, the association of NSAIDs with acute renal failure (ARF) was assessed in a nested case-control study using the administrative databases of Quebec.

The risk of ARF for all NSAIDs combined was highest within 30 days of treatment initiation (adjusted rate ratio (RR) 2.05, 95% confidence interval (CI) 1.61 – 2.60) and receded thereafter. After at least 30 days without an NSAID-prescription, the risk had returned to baseline. The associations with ARF were comparable for rofecoxib (RR 2.31, 95%CI 1.73 – 3.08), naproxen (RR 2.42, 95%CI 1.52 – 3.85) and non-selective, non-naproxen NSAIDs (RR 2.30, 95%CI 1.60 – 3.32), but lower for celecoxib (RR 1.54, 95%CI 1.14 – 2.09). They were dose-dependent for celecoxib, naproxen, and rofecoxib. Results were confirmed when using an alternative exposure definition. Interactions between NSAIDs and aspirin, and NSAIDs and nephrotoxic drugs could not be demonstrated conclusively.

There is a significant association for both selective and non-selective NSAIDs with ARF. Celecoxib appears to have a more favorable renal safety profile but confirmatory studies are required.

Abrégé

Les effets néfastes des agents anti-inflammatoires nonstéroïdiens (AINS) sont l'objet d'une discussion scientifique courante, surtout leur cardiotoxicité. Dans cette thèse, l'association des AINS avec l'insuffisance rénale aiguë (IRA) a été évaluée avec une étude cas-témoin imbriquée dans une cohorte en utilisant les banques des données administratives du Québec.

Le risque pour l'IRA pour tous les AINS considérés ensemble était le plus élevé pendant les 30 jours après l'institution du traitement (rate ratio ajusté (RR) 2.05, intervalle de confiance à 95 % (IC) 1.61 – 2.60). Après au moins 30 jours sans prescription d'un AINS, il n'avait plus de risque élevé avec les AINS. Les associations avec l'IRA étaient comparable pour rofécoxib (RR 2.31, 95%IC 1.73 – 3.08), naproxène (RR 2.42, 95%IC 1.52 – 3.85) et les AINS non-sélectives, non- naproxène (RR 2.30, 95%IC 1.60 – 3.32), mais plus grand en comparaison avec célécoxib (RR 1.54, 95%IC 1.14 – 2.09). Ils étaient dépendants de la dose pour célécoxib, naproxène, et rofécoxib. Les résultats étaient confirmés avec une définition alternative de l'exposition. Les analyses des interactions entre AINS et l'aspirine, et AINS et les médicaments néphrotoxicques n'étaient pas concluantes.

Une association significative était démontrée pour les AINS non-sélectives et les AINS sélectives avec l'IRA. Célécoxib semble d'être plus favorable mais des études additionnelles sont nécessaires.

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Contribution of Authors

This thesis includes the text of a manuscript that has been submitted for publication.

In fulfilling the authorship criteria, **all authors** critically reviewed drafts of the manuscript and provided useful comments.
Dr. James Brophy, as thesis supervisor, was responsible for the study as a whole, the study design and interpretation of the results.
Verena Schneider, as MSc candidate and first author, developed the research question, and was responsible for carrying out the literature review, the programming required for analysis of the databases, performing the statistical analyses, organizing the results and writing the manuscript. She also contributed to the design of the study and the definition of variables.
Linda Lévesque contributed to the study design, the definition of variables and the interpretation of the results.
Bin Zhang assisted in programming, the statistical analyses and their interpretation.
Dr. Thomas Hutchinson, as a thesis committee member, contributed to the study design and the interpretation of the results.

Dr. James Brophy also reviewed drafts of the remaining chapters that compose this thesis. Dr. James Hanley, as co-supervisor, reviewed drafts of the thesis and contributed to results that are not included in the manuscript.

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Chapter 1

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of pain and inflammation. Chemically, they are a very diverse group of drugs, but they have a common target: the enzyme cyclooxygenase (COX), which catalyzes the first step of prostaglandin formation. The therapeutic effects of NSAIDs, but also their adverse effects, are mainly due to the inhibition of prostaglandin formation. The functions of the different prostaglandins vary depending on the site (organ) and tissue distribution of specific receptors. Based on the elucidation of the mechanism of action of NSAIDs and the discovery of two isoforms of COX (COX-1 and COX-2), a novel group of NSAIDs, the selective inhibitors of COX-2 were developed. This was motivated by the observation that one isoform, COX-1, was a constitutive 'housekeeping' enzyme, whereas the second was inducible and responsible for the inflammatory reaction. Selective inhibition of the second isoform was presumed to lead to increased efficacy and superior safety, in particular with respect to gastrointestinal adverse effects, a major drawback of the conventional NSAIDs due to their inhibition of gastroprotective prostaglandins. Subsequently, selective inhibitors of COX-2 were introduced and marketed very successfully. One of these drugs, rofecoxib, was voluntarily withdrawn by its manufacturer for its cardiovascular toxicity. A second COX-2 inhibitor, valdecoxib, was removed from the market by regulatory agencies for both cardiovascular and dermatologic side effects. In comparison to conventional NSAIDs, the properties of the novel group of selective inhibitors of COX-2 are less well understood. This also includes their renal risks, a well-established safety concern of the conventional NSAIDs. The novel drug group has therefore stirred numerous investigations and a very active debate concerning their cardiovascular risks, but little or no discussion of their potential nephrotoxicity.

The study presented here is a comparison of the novel selective inhibitors of COX-2 and conventional NSAIDs and their association with acute renal failure. The results of the study could contribute to a comprehensive evaluation of the risks and benefits of this novel drug group.

1.1 History of nonsteroidal anti-inflammatory drugs: from willow bark to Vioxx® withdrawal

The bark of willow (e.g. *Salix alba*, *Salix fragilis,* and other members of the *Salicaceae* family), or extracts from similar plants (*Spiraea* species) have been used for the treatment of fever and pain in many different cultures for centuries. Evidence for its use was found as early as in the ancient Assyrian[1] as well as Egyptian culture[1,2]. The medicinal properties of the willow were also known to Greek physicians, including Hippocrates[1]. Moreover, American Indian[2] and African tribes[2,3] made use of plants containing salicylate for the treatment of various conditions, including pain and fever. They were also applied in ancient China[2].

The first account of the beneficial effects of the bark of willow in modern times dates back to 1763 and was given by the Oxfordshire Reverend Edward Stone[2,4]. He believed in the doctrine of signatures, whereby the cure for a disease was to be found close by its origin. In the case of fevers and rheumatic diseases, this meant that their cure would arise from the moist ground that favours their occurrence, which is where the willow trees grow. 100 years later, in 1876, another adherer of this doctrine, Thomas MacLagan from Dundee, reported the first clinical trial with the willow bark extract[1,5]. This had been preceded by the first isolation of the bitter tasting glycoside of salicylic acid, salicin, by the German professor of pharmacy Johann Andreas Buchner in 1828 and optimization of the process by the French pharmacist Henri Leroux in 1829. Synthetic salicylic acid had become available by 1874 thanks to Hermann Kolbe and E. Lautemann[2].

Charles Friedrich Gerhardt had already synthesized acetylsalicylic acid in 1853. This was rediscovered in 1897 by a chemist with the Bayer Company in Germany, Felix Hoffman, when he searched for an alternative, better tolerated form of the very popular salicylic acid. In 1899, his product, acetylated salicylate, was registered as Aspirin, probably named after the plant *Spirea ulmania*. The drug has then become and remained an extraordinary success, not only in terms of efficacy, but also in terms of marketing[1].

In parallel to the development of salicylate-based antipyretic drugs, quinine became the target of pharmaceutical research. Quinine had been isolated from Peruvian bark (*Cinchona officinalis*) that was the established treatment for the fever of Malaria. Based on the synthetic production of the quinine-derivative quinoline, Ludwig Knorr in 1884 synthesized a non-salicylate analgesic and anti-inflammatory drug called antipyrine. In contrast to initial assumptions, this product was not a quinine, but contained a pyrazolone and a benzene ring, and the subsequent development of antifebrile and analgesic drugs focused on compounds with these chemical features[3]. In 1887 phenacetin and in 1896 aminopyrine were introduced. 1952 marked the introduction of the pryazolone derivative phenylbutazone[3]. Numerous new NSAIDs were developed in the 1960s and 1970s, markedly indometacin in 1963[6]. This research was driven by the need for drugs providing effective relief of pain and fever, as well an acceptable side effect profile, a motive that has persisted until today.

John Vane elucidated the mechanism of action for nonsteroidal anti-inflammatory drugs (NSAIDs) when he showed in 1971 that aspirin, sodium salicylate and indomethacin inhibit prostaglandin synthesis in rodents[7]. Later, in 1982, he was honoured with the Nobel price for this discovery. Simultaneously to Vane's findings, the blockade of prostaglandin release form canine spleen by indomethacin and aspirin[8], and an inhibitory effect of aspirin on human platelet function[9] were demonstrated. The denomination fatty acid cyclooxygenase for the enzyme that is inhibited by aspirin was proposed by Hamberg in 1974[10]. Already in 1972, the existence of 2 isoformes of the enzyme cyclooxygenase (COX-1 and COX-2) was postulated[11]. Both were found to be encoded by different genes and the second isoform appeared to be inducible[11].

Based on this, it was hypothesized that sparing of the presumed physiological or 'housekeeping' isoform (COX-1) by selective inhibition of the second isoform (COX-2) would result in less side effects and even increased efficacy[12-14]. This COX-hypothesis triggered the development of new NSAIDs, the so-called COX-2 inhibitors or COXibs. Two members of this new group of NSAIDs, rofecoxib and celecoxib, became available in Canada in 1999. Further selective compounds where introduced or are under clinical

development, such as valdecoxib, etoricoxib and lumiracoxib. Meanwhile, it has been shown that COX-2 is physiologically expressed in various human tissues[15] and that COX-1 may also play a role in inflammation[16]. Consequently, the initial COX-hypothesis now appears to be rather simplistic.

Although other NSAIDs, such as alclofenac, isoxicam, and sudoxicam[6], have been withdrawn already in the past due to an unacceptable side effect profile, the withdrawal of rofecoxib due to cardiovascular toxicity attracted more public attention. In this context the function of regulatory authorities overseeing post-marketing drug safety has also been questioned and criticized[17-19]. The term Vioxx® disaster, that was used by mass media, illustrates the public perception of the withdrawal of rofecoxib. In the meantime, the regulatory approval of valdecoxib was officially reversed[20]. The removal of rofecoxib by the manufacturer was not requested by drug regulatory agencies in Canada, the United States of America[21] or elsewhere; thus rofecoxib could, at least theoretically, be re-introduced into clinical practice. Further regulatory decisions will determine the fate of the COX-2 inhibitors, therefore, currently, the future significance of these NSAIDs is uncertain.

1.2 Clinical Pharmacology of contemporary nonsteroidal anti-inflammatory drugs

Despite their long history, non-steroidal anti-inflammatory drugs remain among the most commonly used drugs today[22,23]. The newly introduced compounds celecoxib and rofecoxib were on the 10th and 11th rank among the most frequently dispensed medications in 2002 in Canada[24].

1.2.1 Which drugs are nonsteroidal anti-inflammatory drugs (NSAIDs)?

The designation 'nonsteroidal anti-inflammatory drugs' (NSAIDs) implies that the members of this drug group are drugs with anti-inflammatory effects, excluding steroids, such as cortisol. Pharmacologically, the compound acetaminophen (paracetamol) is usually also considered to be an NSAID. Here, acetaminophen will not be considered as an NSAID, because it predominantly has central nervous analgesic rather than anti-inflammatory effects.

Another term for the group of NSAIDs, aspirin-like drugs, indicates that Aspirin belongs to the NSAIDs as well. However, due to differences in its mechanism of action and predominant indication in comparison to the other NSAIDs, Aspirin will be considered separately.

Thus, here, when the term NSAIDs is used, in fact reference is made to non-aspirin, non-acetaminophen NSAIDs. Later, this NSAID-classification will be further subdivided.

1.2.2 Effects and Indications of NSAIDs

NSAIDs are known to have antipyretic, analgesic and anti-inflammatory effects[25]. Although they are usually classified as mild analgesics, e.g. for the treatment of dental pain, NSAIDs can be superior to opioid analgesics in states of postoperative pain. NSAIDs are mostly employed to treat musculoskeletal diseases, such as rheumatoid arthritis, osteoarthritis or ankylosing spondylitis. Although they provide relief from pain and the symptoms of inflammation, they do not halt the progression of the underlying disease. Furthermore, NSAIDs are effective in the treatment of dysmenorrhoea and less frequent conditions such as systemic mastocytosis, hypercalcemia in some cancer patients, as well as Bratter's syndrome. The prevention of neoplastic diseases (e.g. colon cancer) and Alzheimer's disease are potential new indications for NSAIDs[26,27].

1.2.3 Pharmacokinetic properties

The majority of NSAIDs are organic acids and are therefore rapidly and almost completely absorbed after oral administration. NSAIDs can roughly be divided into those with short (< 6 hours) and long (>10 hours) half-lives[25]. They are highly plasma protein bound and are metabolized in the liver, their metabolites are then excreted by the kidney. Only a very small proportion of the ingested dose is eliminated unchanged by the kidney, thus NSAIDs are not retained in patients with impaired renal function[28-31]. NSAIDs tend to accumulate at sites of inflammation, which is an attractive property for agents meant to interfere with inflammation[25].

1.3 Molecular pharmacology of NSAIDs

On the molecular level, NSAIDs function as inhibitors of cyclooxygenase, a key enzyme in prostaglandin formation. Accordingly, understanding the physiological functions of prostaglandins helps to explain many of the observed effects of NSAIDs, both desired and adverse. The function of cyclooxygenase, prostaglandin effects and the impact of NSAIDs are illustrated at the end of this chapter (Figure 1.1) and described in more detail in this section.

1.3.1 Cyclooxygenase substrate: Arachidonic acid

Arachidonic acid is an unsaturated fatty acid with four of its 20 carbon atoms joined by a double bound[32]. It is formed from linoleic acid (18 carbon atoms, 2 double bounds), which is essential in mammals, i.e. it has to be ingested from dietary sources. Arachidonic acid can be incorporated in cellular membranes. Stimuli can lead to the release of arachidonic acid from the cell membranes by means of phospholipases. Free arachidonic acid can either be reesterified into phospholipids, bound to proteins, or metabolised to a number of biologically active compounds. The latter are called eicosanoids and represent products from 3 different major metabolic pathways. The three pathways are the cyclooxygenase, the lipoxygenase and the cytochrome P-450 pathway. The specific arachidonic acid metabolites that are formed depend on the initial stimulus

and the pathway that is functional in the cell. Stimuli leading to eicosanoid formation can be hormonal but also non-specific, i.e. traumatic or ischemic. In the kidney, arachidonic acid can be metabolised by all three enzymatic pathways, the cyclooxygenase pathway however, is the predominant one[32].

1.3.2 Cyclooxygenase enzymology: function, structure and inhibition by NSAIDs

In the first and rate-limiting step of the cyclooxygenase pathway, the bifunctional enzyme cyclooxygenase (COX) converts arachidonic acid to prostaglandin G2 and then prostaglandin H2. The enzyme is therefore also called prostaglandin synthase G2/H2. Specific (prostaglandin) synthases then transform prostaglandin H2 to prostanoids, which engage in cellular signal transduction by acting at G protein coupled receptors[32].

As mentioned above, cyclooxygenase has 2 functions: it catalyses the formation of prostaglandin G2 from arachidonic acid (cyclooxygenase activity) and the subsequent formation of prostaglandin H2 (peroxidase activity)[33,34]. The existence of two COX-isoforms, COX-1 and COX-2, has been shown in 1980[35,36]. Both enzymes are encoded by different genes, which are located on different chromosomes, COX-1 on human chromosome 9, COX-2 on chromosome 1[37]. Depending on the species, however, both isoforms share a 60-65% amino acid sequence identity. In accordance with this, their crystal structures revealed that both are quite superimposable and structurally homologous. Both COX-isoforms are membrane bond and form homodimers. Each monomer has 3 different domains: an epidermal growth factor like domain, a membrane binding and a catalytic domain with a mainly α-helical fold. The active site is situated at the end of a hydrophobic channel that leads from the surface of the protein to the interior of the catalytic domain[38].

NSAIDs inhibit COX by binding to amino acids in a specific portion of this channel. Notably, in the COX-2 enzyme, the hydrophobic channel has a larger volume. This is

exploited by NSAIDs that are selective for COX-2, which are bulkier than conventional NSAIDs[38].

In fact, all NSAIDs, including the so-called COX-2 inhibitors, inhibit both COX-isoforms. However, individual NSAIDs differ in their selectivity for one of the other COX-isoform, i.e. their potential of inhibiting COX-1 in comparison to COX-2. NSAID-selectivity depends on the assay[36]. Therefore, the dichotomization of NSAIDs into conventional NSAIDs and selective COX-2 inhibitors is, strictly speaking, arbitrary. Particularly as some NSAIDs that are usually classified as non-selective (conventional), in fact show COX-2 selectivity, which is greater than (e.g etodolac), or similar to (e.g. nimesulide) the COX-2 inhibitor celecoxib[39]. Lipsky proposed a classification of NSAIDs into four categories[40]. According to this, the selective COX-2 inhibitor meloxicam is often classified as 'COX-2 preferential', separately from 'COX-2 specific' NSAIDs, and aspirin is classified as a 'COX-1 specific' NSAID. In fact, indomethacin is more COX-1 selective than aspirin and meloxicam appears to be more COX-2 selective than celecoxib[39], although, it is not marketed as such.

Non-aspirin NSAIDs inhibit COX reversibly, whereas aspirin inhibits COX irreversibly by acetylating a Serine residue (Ser 530) of the protein[38]. This difference is most significant for platelets: As COX mediates platelet aggregation and platelets cannot synthesize new COX, their potential to aggregate is inhibited by Aspirin for their entire lifespan (approximately 10 days)[25]. Whereas COX-1 is the predominant COX isoform in platelets, COX-2 expression has also been reported, particularly in newly formed platelets[41,42]. In contrast to platelets, other cells can synthesize new COX and thereby annul the effect of irreversible COX-inhibition. By virtue of its anti-platelet-effect, aspirin is used in cardiovascular prevention.

A third COX-isoform, COX-3, probably a splice variant of COX-1, has recently been demonstrated, after it had been proposed in 1994 by John Vane. Consequently, a 'Cox continuum' has been suggested as an alternative to the simplistic COX-1/COX-2

dichotomy[43,44]. Moreover, 2 smaller, Cox-derived proteins, (PCOX) were recently discovered[45].

1.3.3 Cyclooxygenase products: Prostanoids

As already mentioned, the product of cyclooxygenase, prostaglandin H2, is transformed to active prostanoids (prostacyclin, prostaglandin D2, prostaglandin E2, prostaglandin F2 and thromboxan A2) by specific synthetases[32]. Prostanoids can be formed by virtually all cells. They have numerous and diverse, and sometimes opposing effects, depending on dose and target tissue. Prostanoids are vasoactive, modify platelet function, cardiac output and muscle tone. They inhibit gastric and intestinal secretion, have endocrine and metabolic effects and lower the threshold of nociceptors[46]. The renal effects of prostanoids are described in more detail separately.

The action of prostanoids is mediated by their individual g protein coupled receptors. Prostaglandins are quickly inactivated, they have a half-life of 3 to 5 minutes, whereas the half-life of thromboxan A2 is 30 seconds[46]. Due to their fast catabolism, arachidonic acid metabolites act predominantly in an autocrine fashion[32].

1.3.4 Prostanoids and the kidney: Molecular basis for the nephrotoxicity of NSAIDs

The predominant prostanoids in the kidney are prostaglandin E2, prostacyclin, and to a lesser degree prostaglandin F2. Due to multiple specific prostanoid receptor subtypes and their pattern of distribution, a single prostaglandin can have varying and at times apparently opposing effects[47]. Globally, renal prostanoids are involved in renin release, local vascular tone, regional circulation, sodium and water homeostasis, as well as potassium balance[48]. In normal individuals, prostaglandins are not essential for renal homeostasis. However, prostaglandin production plays an important role in pathophysiological states, such as decreased renal blood flow or volume depletion. These states can be associated with congestive heart failure, liver cirrhosis, restricted sodium

intake or diuretic use[14]. Under these conditions, renal prostanoids contribute substantially to the maintenance of renal blood flow and glomerular filtration rate. Therefore, inhibition of prostaglandin formation by NSAIDs is more likely to cause significant renal adverse events in such compromised patients[48].

1.4 Adverse effects of nonsteroidal anti-inflammatory drugs

1.4.1 General aspects and non-renal adverse effects

Side effects of salicylate and other nonsteroidal anti-inflammatory drugs have been known for a long time and have motivated the development of novel compounds, as exemplified by the COX-2 inhibitors (see Chapter 1.1). The first account of adverse events associated with salicylate may stem from 1797, when 14 men of the Royal Artillery of Quebec suffered from poisoning by oil of wintergreen (methyl salicylate) after ingestion of herbal tea. Their symptoms included vertigo, vomiting and diarrhoea, as well as respiratory distress and coma[6].

A multitude of adverse effects of the contemporary NSAIDs has been described[6,25,27]. Many of these are common to all NSAIDs and, therefore, the main adverse effects are presented together here.

Gastrointestinal damage due to NSAIDs is a major side effect and presents a large public health problem[49]. The gastrointestinal adverse effects range from mild symptoms, such as heartburn, dyspepsia and stomach discomfort, to more severe and potentially life-threatening states like gastrointestinal ulceration, bleeding or perforation. The rate of hospitalization with an upper gastro-intestinal event in users of NSAIDs was found to be 1.6 per 100 person-years of use, which is about five times the risk of non-users[27]. Randomized studies proving the effectiveness of the COX-2 selective NSAIDs provide comparable data on the occurrence of gastrointestinal adverse events. In the CLASS-study-population, the rate of upper gastro-intestinal ulcer complications was 0.8 per 100 person-years of use of celecoxib as compared to 1.5 per 100 person-years of use of diclofenac and ibuprofen[50,51]. Complicated gastro-intestinal events occurred with a rate of

0.6 per 100 person-years of rofecoxib-use and 1.4 per 100 person-years of naproxen-use in participants of the VIGOR-study[52].

Cardiovascular adverse effects include oedema, induction or aggravation of hypertension and congestive heart failure[27,53]. As already mentioned in Chapter 1.1, an association of NSAID-use with acute myocardial infarction and cerebrovascular events has been observed, particularly, but not exclusively for COX-2 inhibitors[54-58]. NSAIDs cause headaches and confusion in a relatively small number of patients[27]. NSAIDs have also been reported to cause potentially severe haematological disorders such as thrombocytopenia, agranulocytosis, aplastic anaemia and haemolytic anaemia. Skin reactions such as rashes or urticaria, photosensitivity are often reported adverse effects of NSAIDs. Life-threatening reactions, such as erythema multiforme and toxic epidermal necrolysis, are extremely rarely reported. However, severe adverse dermatological reactions were more frequently reported for the COX-2 inhibitor valdecoxib[20] and contributed to its removal from the marketplace by the FDA. Another rare adverse event associated with NSAIDs is hepatotoxicity, probably due to hypersensitivity or idiosyncrasy. Anaphylactic or anaphylactoid reactions to NSAIDs are also infrequent[27].

1.4.2 Adverse effects of NSAIDs on the kidney

The kidney plays a central role in the control of blood pressure and the body's fluid composition. NSAIDs can cause a spectrum of renal diseases[27]. These include functional renal insufficiency, nephrotic syndrome with or without interstitial nephritis, renal papillary necrosis and chronic interstitial nephritis, acute tubular necrosis, vasculitis, glomerulonephritis, and obstructive nephropathy.

The inhibition of renal prostaglandin production by NSAIDs increases vascular tone, decreases sodium excretion and has an anti-renin, as well as an anti-diuretic effect[59]. Clinically, this leads to salt retention, which in turn causes hypertension, particularly in patients who are already hypertensive and those who take diuretics or β-blockers. The

average increase of mean blood pressure is between 3 and 5 mm Hg[60]. Moreover, water retention and hyponatremia, as well as hyperkalemia can result[59].

1.4.3 NSAID-induced acute renal failure

Due to their impact on prostaglandin formation, in patients with prostaglandin-dependent renal function (see Chapter 1.3), NSAID-therapy can lead to domination of vasoconstrictive forces in the renal circulation, causing a decline in renal blood flow and renal insufficiency[59].

In general[61], acute renal failure is characterized by an abrupt decline in glomerular filtration rate and retention of nitrogenous waste products, such as blood urea nitrogen (BUN) and creatinine. Oliguria (urine output < 400 mL/day) occurs in about 50% of patients. Acute renal failure is usually diagnosed when routine biochemical serum analysis reveals a recent increase in the concentrations of BUN and creatinine. Acute renal failure can be a complication of many diseases and is divided into three categories: pre-renal (55-60% of cases), intrarenal (35-40%) and post-renal (<5%). While pre-renal failure occurs due to acute hypoperfusion of the kidney, intrarenal cases are most often caused by ischemia or nephrotoxins, and post-renal acute renal failure is triggered by an acute obstruction of the urinary collecting system. Although acute renal failure is reversible in most cases, it is associated with mortality and a prolongation of hospitalization[61]. NSAID-induced acute renal failure has been called 'acute vasomotor renal failure'[59], and it is classified as either pre-renal or intra-renal [61].

Risk factors for the occurrence of NSAID-induced acute renal failure have been identified and these are, as previously mentioned, mainly situations when renal function is vulnerable to the impact of an inhibition of prostaglandin synthesis. Two patient groups are at particular risk: the elderly and patients with underlying renal disease (chronic renal failure, nephrotic syndrome, glomerulonephritis, obstructive uropathy). Other specific risk factors include congestive heart failure, cirrhosis, volume depletion,

hypotension, haemorrhage, sepsis, postoperative conditions with third space fluid sequestration, diuretic therapy, cylosporine and contrast agents[59].

The reasons for the elderly being at high risk for NSAID-induced nephrotoxicity are age-related changes in renal function (decrease in glomerular filtration rate, renal blood flow and increased renal vascular resistance), as well as age-related changes in pharmacokinetics (increase of free drug concentration, hypoalbuminemia, decreased total body water and hepatic metabolism resulting in longer drug half-life)[59].

1.4.4 COX-isoforms, their inhibition and the kidney: experimental basis for the nephrotoxicity of all NSAIDs

The hypothesis that selective COX-2 inhibitors would only target the presumed exclusively inducible COX-2 and spare the physiological COX-1 led to the anticipation that these drugs might offer pain relief without renal complications. The distribution and roles of the COX-isoforms in the kidney have therefore been investigated. COX-2 has been localized in different substructures of the human kidney, like blood vessels, the glomerulus and the macula densa in patients older than 60 years as well as in patients with congestive heart failure[15,62]. Additionally, the importance of prostaglandins produced through COX-2 for normal renal function has been shown in animal studies. COX-2 expression was increased in states of diminished renal blood flow. The distribution pattern of COX-2 in kidneys of various animals suggests that COX-2 plays a significant role in the regulation of water and electrolyte balance in normal as well as pathophysiological situations[63].

Further insights into the significance of the COX-isoforms for human renal function has been gained by experimental studies: In healthy subjects renal blood flow was less compromised by predominant COX-2 inhibition, demonstrated when rofecoxib was compared with the non-specific conventional NSAID indomethacin[64], and celecoxib with naproxen[65]. In sodium-restricted subjects however, COX-2 selective inhibitors reduced glomerular filtration rate to the same degree as nonselective COX-inhibitors, as shown

when rofecoxib and indomethacin[66], as well as celecoxib and naproxen[63] were administered.

Based on these experimental studies, it has been assumed that in humans, the prostaglandins, which mainly play a role in situations of compromised renal blood flow, i.e. when renal function becomes prostaglandin-dependent (such as volume depletion, decreased sodium intake, and renal artery stenosis) are COX-2-derived. COX-1, on the other hand, possibly plays a role in normal renal haemodynamics. Thus, it may be concluded that, when treated with either conventional or COX-2 selective NSAIDs, patients, whose renal function is prostaglandin-dependent, are at increased risk of acute renal failure[63,67,68]. Accordingly, the risk for renal adverse events of COX-2 inhibitors was predicted to be comparable to that of conventional NSAIDs[63,69,70]. The potential of COX-2 inhibitors to cause in fact acute renal failure has become evident from case reports, predominantly from high-risk-patients[67,71-74]. However, confirmatory larger population-based studies are lacking.

1.5 Previous population-based studies of the renal risk of NSAIDs

Prior to the introduction of COX-2-selective drugs, acute impairment of renal function in association with treatment with NSAIDs had been investigated in several epidemiological studies that are reviewed here.

In a cross-sectional study[75] in 802 patients undergoing hip replacement surgery in 1995 or 1996 an impairment of renal function was marginally associated with current use of NSAIDs (odds ratio (OR) 1.4, 95% confidence interval (CI) 0.9 – 2.2). Obviously, an inference on causality is not possible from this study design.

An analysis of 88 cases with a renal biopsy in 1986 or 1987 and 176 age, sex and practice-matched controls resulted in an OR of 1.6 (95% CI 0.9 - 3.0) for renal biopsy in

users of NSAIDs at any time one year before the biopsy[76]. The outcome in this study (renal biopsy for unknown renal condition) is clearly different from NSAID-induced acute renal failure. The selection of patients (referral bias) impairs generalizability and might have distorted results, and due to the definition of exposure causality for NSAIDs is again questionable.

An Australian case-control study conducted at an unknown point in time[77] suggested an association of NSAIDs with renal failure, for NSAID-use in the week before the event (OR 1.5, 95% CI 0.80 - 2.9) and for NSAID-use within a month (OR 1.8, 95% CI 0.97 - 3.4) before the event. The results were derived from 164 patients hospitalized for various reasons with a reversible rise in serum creatinine, of which 110 could be interviewed, and 189 controls, matched on age and hospital. Higher risks were observed in persons taking drugs with a half-live of $\geq$ 12 hours (e.g. naproxen, piroxicam) compared to those with shorter half-lives (e.g. ibuprofen, diclofenac, indomethacin). Although the cases were identified by laboratory values and data on numerous covariates was collected, the study is limited by recall bias and questionable accuracy of self-reported drug exposure. Moreover, the fitness for interview required for participation lead to restriction of the study population to less severely diseased patients. The small number of cases and controls precludes precise risk estimates.

The following studies were conducted with the help of administrative databases. Additional methodological details for four studies are listed in Table 1.1 at the end of this chapter.

In an early database study from the administrative databases of Saskatchewan[78], 60 hospitalizations with adverse effects likely caused by NSAID-use were identified from the population of the province in 1983. Of these, 49 were cases of acute renal failure. Patients who had filled an NSAID-prescription at any point in time during 1983 had a relative risk of 2.3 to be hospitalized during the same year compared to non-users. No temporal relationship for NSAID-use and acute renal failure could be established from

this study. Comorbidity and use of other prescription drugs, which are essential in order to avoid confounding, were not considered in the analysis.

Later, Perez Gutthann *et al.*[79] again used the health care databases of Saskatchewan to investigate the risk for hospitalization for acute renal failure in NSAID-users in the years 1982 to 1986. 28 cases discharged from hospital with a diagnosis of acute renal failure were analyzed; patients with chronic renal failure (n=110) were excluded. 79% of the cases were ≥ 65 years old, 46% were ≥ 80 years old. The incidence of hospitalization for acute renal failure was 0.6 per 100,000 person-years for persons aged 15-64 years, in persons 65 years and older it was 4.7 per 100,000 person-years. Use of any NSAID within the last 30 days was associated with acute renal failure (OR = 4.1, 95% CI: 1.5-10.8). The risk was 3.5 times higher in persons ≥ 65 years compared to those aged 15-64 years (95% CI: 1.3 - 9.8), there was no difference between the risk in women and men. Chronic renal failure is a well-known risk factor for NSAID-induced acute renal failure. Exclusion of such high-risk patients in this study may lead to an underestimation of the NSAID-associated risks in the general population.

Griffin *et al.*[80] report a nested case-control study in Tennessee Medicaid enrolees aged 65 years and older hospitalized for acute renal failure in 1987-1991. Information on NSAID use was obtained from a Medicaid-Medicare database. Use of NSAIDs was found to increase the risk of acute renal failure by 58% (OR = 1.58, 95% CI 1.34 - 1.86). For ibuprofen, the most frequently used NSAID (35%), a dose-dependent increase of the OR for hospitalization was found, which could not be shown for other NSAIDs: for dosages of ≤ 1,200 mg/day, the OR was 0.94 (95% CI: 0.58 - 1.51), for 1,200-2,400 mg/day, the OR was 1.89 (95% CI: 1.34 - 2.67), and for ≥ 2,400 mg/day the OR was 2.32 (95% CI: 1.45 - 3.71, p for linear trend = 0.009). Risk factors for acute renal failure were old age, comorbidity, and frailty, as reflected by recent hospitalization and residence in a nursing home. Use of prescribed NSAIDs was estimated to cause 25 excess hospitalizations with renal failure per 10,000 years of use in this elderly population. In this generally well-designed study, controls were only selected if they were not hospitalized at a random date

assigned to them. This might insufficiently control for calendar time and lead to the selection of healthier controls, thus an overestimation of the NSAID-associated risk of acute renal failure.

In the Tayside region of Scotland, Evans *et al.*[81] identified 207 cases of hospitalization due to renal failure between 1990 and 1992 from a record linkage database. Most of the male (83%) and the female patients (78%) were 60 years and older. The risk of hospitalization due to acute renal failure after recent exposure (prescription within the last 90 days) was about twofold increased in comparison to both hospital and community controls (OR = 2.2, 95% CI: 1.49 - 3.25 and OR = 1.84, 95% CI: 1.15 - 2.93). There were not enough cases to allow an analysis of the risk of specific NSAIDs. Interestingly, chronic renal failure (37% of cases) did not modify the risk of a hospitalization. It appears that comorbid conditions, very important potential confounders, were not considered in the analyses of this study.

A more recent nested case-control study from the British General Practice Research Database found an incidence of 1.1 cases per 10,000 years of follow-up in 50-85 year old drug users[82]. Patients with renal disease or malignancy were excluded from the study population. The analyses were based on 103 cases and 5000 controls frequency matched on age and sex. The relative risk of acute renal failure associated with current NSAID use was 3.2 (95% CI 1.8 - 5.8). The risk increased with increasing duration of NSAID-use. The results suggest that the association of NSAIDs with acute renal failure was stronger in patients with hypertension and cardiac failure. Exposure to antihypertensive drugs, diuretics and oral corticosteroids was associated with an increased risk of acute renal failure. Patients over 70 years of age without at least two health contacts per year were excluded, probably leading to an overestimation of the risk in unexposed and thus an underestimation of the NSAID-associated risk in the general population.

1.5.1 Conclusion from previous studies

Most of these studies support the association of NSAID-use with acute renal failure on the level of the general population. Even if there are considerable differences how acute renal failure was defined, acute renal failure in association with NSAID-use clearly was infrequently observed. Therefore, only a large database study with a sufficient number of cases would be suitable in order to investigate this outcome. It is also evident from these studies that elderly patients represent a high-risk population. Given the growing number of frail elderly patients who receive NSAID-therapy, a study with contemporary data focusing on this vulnerable population is desirable.

Importantly, the renal safety of the new COX-2 inhibitors has not been assessed so far on the population level. In light of an aging population and a growing number of patients with compromised renal function, the risk of NSAID-associated acute renal failure becomes increasingly relevant.

1.6 Rationale and Objectives

The safety of the novel class of NSAIDs, the COX-2 inhibitors, has attracted scientific as well as public interest recently. The debate has been mainly focused on their cardiovascular toxicity. However, in order to allow a comprehensive risk-benefit-assessment, other adverse effects should be considered as well. In this thesis, the association of NSAIDs with acute renal failure will be assessed in a high-risk population and, for the first time, also the COX-2 selective NSAIDs will be considered.

On the individual patient level, information on the comparative renal toxicity of the COX-2 inhibitors will allow a safer drug therapy for individuals in whom maintenance of renal function is the main concern when initiating NSAID-therapy.

The objective of the project is to determine the risk of acute renal failure in new users of COX-2 inhibitors in comparison with new users of conventional NSAIDs in an elderly population. The aim is to reveal the association of NSAIDs with acute renal failure focusing on individuals who recently started NSAID-treatment and to provide insight into the time- and dose-dependency of the association. Additional analyses will serve to confirm the robustness of these findings. Moreover, the modifying effects of aspirin and exposure to nephrotoxic drugs on the risk of acute renal failure in NSAID-users will be evaluated.

Acute renal failure is a well-known adverse effect of therapy with conventional NSAIDs. An evaluation of the novel class of NSAIDs might not only make a potentially important contribution to the ongoing scientific debate about their safety, but may also incite further investigations into the renal toxicity of these compounds. Ultimately, this new information may help to avoid the occurrence of a potentially serious adverse effect of therapy with NSAIDs, thereby preventing morbidity and even mortality.

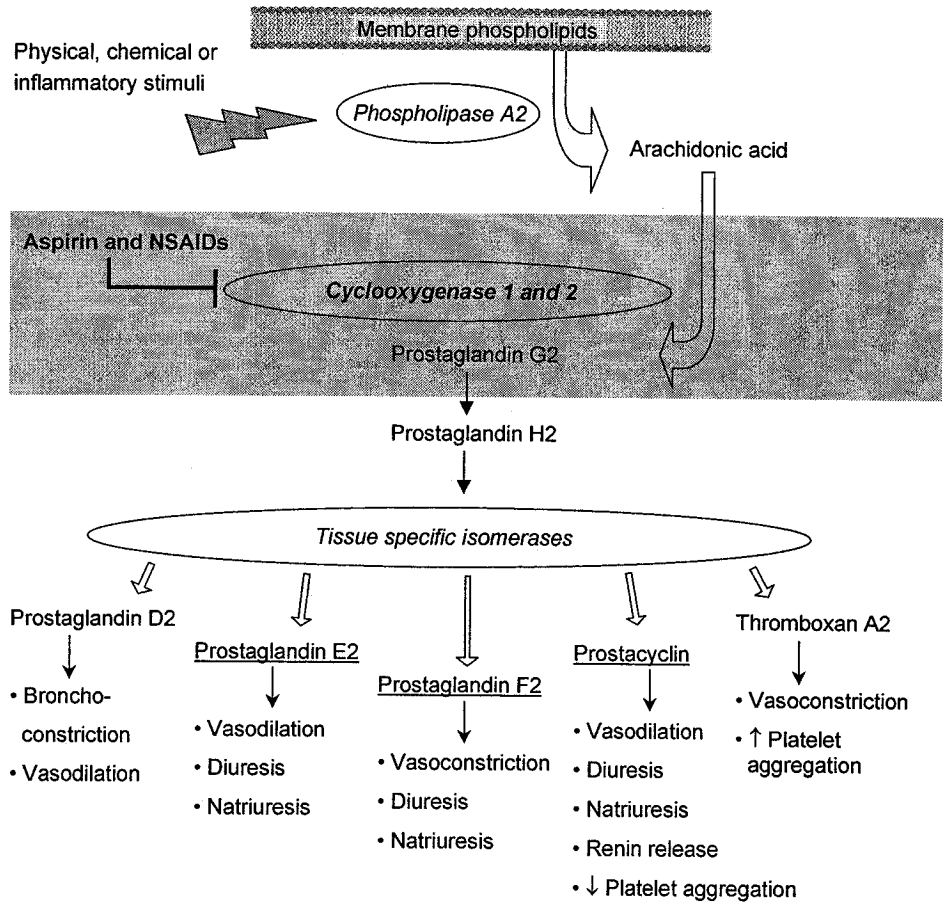
Table 1.1 Synopsis of the methodology of population based studies of the association of NSAIDs with acute renal failure.

Author	**Huerta *et al.* (2005)**[82]	**Griffin *et al.* (2000)**[80]	**Perez Gutthann *et al.* (1996)**[79]	**Evans *et al.* (1995)**[81]
Study period	1997 - ?	1987 - 1991	01/01/1982 to 31/12/1986	1990 - 1992
Study population, Setting	386,916 individuals, General practice research data base, UK	Tennessee Medicaid enrollees (n = ?), USA	228,392 health plan members, Saskatchewan	420,600 Tayside residents, Scotland
Study design	Nested case-control study	Nested case-control study	Nested case-control study	Case-control study
Number of cases and controls	103 cases 5,000 controls	1,799 cases 9,899 controls	28 cases 1,997 controls	207 cases, 1,238 community controls, 411 hospital controls
Age of study population	50-84 years	≥ 65 years, (40% of cases and 21% of controls > 85)	≥ 15 years, (79% of cases and 31% of controls > 65)	10-99 years, (61% of cases > 70)
Inclusion criteria	≥ 2 years enrollment with GP and at least 1 prescription and 1 year of enrollment thereafter	≥ 65 years, enrolled for ≥ 1 year, not from one of 19 remote counties of Tennessee (out of 95 in total)	1 prescription of an NSAID during study period, follow-up until renal disorder, death, exit health plan or end of study	Resident of Tayside and registered with a Tayside GP in May 1990
Exclusion criteria	> 70 years with less than 2 health contacts per year, diagnosis of cancer, renal disorder, cirrhosis, systemic connective tissue disease, follow-up until 85 years old, exclusion diagnosis Cases: Death ≤ 30 days after index date, non-renal	Cases: End stage renal disease, chronic renal insufficiency, acute renal failure with specific other cause or unlikely due to prostaglandin inhibition Controls: hospitalized at index date	Hospitalization for malignant neoplasm or renal disease	Death between 01/90 and 05/90

Author	Huerta *et al.* (2005)[82]	Griffin *et al.* (2000)[80]	Perez Gutthann *et al.* (1996)[79]	Evans *et al.* (1995)[81]
	hospitalization ≤ 30 days, exclusion criteria ≤ 3 months after index date			
Detection of cases	Patients with a diagnostic code in GP record indicating renal impairment considered potential cases, review of computerized record for validation	All hospitalizations with discharge diagnosis ICD-9 codes 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590.0, 590.8, 593.9, 403, 404, 250.4, 274.1, or 753.1 considered potential cases, review of medical records for validation	All hospitalizations with discharge diagnosis ICD-9 codes 580.9, 581, 583.2, 583.6 583.7, 583.8, 583.9, 584, 586 (majority of cases), or 593.9 considered potential cases, review of medical records for validation	All hospitalizations with discharge diagnosis ICD-9 codes 583.8, 584.5, 584.7, 584.8, or 584.9 considered potential cases, review of medical records for validation
Definition of acute renal failure	(1) Specialist diagnosis of renal failure and (2) serum creatinine value > 150 µmol/L or urea 17.0 mmol/L	Discharge diagnosis of renal failure in medical record, admission creatinine level ≥ 180 µmol/L and either 20% increase from baseline or 20% decline during hospitalization	All 4 criteria must be met: (1) Hospital discharge diagnosis of renal failure or acute renal failure (2) admission with uremic symptoms (3) abnormal serum creatinine (4) no diagnosis of renal disease, malignancy, or collagen-vascular disorder.	Discharge code of renal failure and 'recent evidence' for at least 20% better renal function or at least 20% improvement of renal function with treatment.
Selection of Controls	Random date during study period assigned to cohort members (index date), if included in follow-up time then potential controls,	10,000 randomly selected, random date during follow-up was index date, excluded if hospitalized at index date, no later cases.	Random date during study period assigned to cohort members (index date), if included in follow-up time then potential controls,	6 community controls, matched for sex and age, and 2 hospital controls, matched for sex, age and hospital, per case. All

Author	Huerta *et al.* (2005)[82]	Griffin *et al.* (2000)[80]	Perez Gutthann *et al.* (1996)[79]	Evans *et al.* (1995)[81]
	random selection from these controls. Frequency matched on age, sex and calendar year.		random selection from these controls.	community controls alive at end of study (!). Index date of control that of corresponding case
Definition of NSAID-exposure	Current use: supply of last prescription lasted until or ended 30 days prior to index date, recent: supply ended 31-365 days before index date, past: supply ended > 1 year before index date, non-users: no use before index date	Current use: supply included index date, recent: supply ended 1-30 days before index date, past: supply ended 31-365 days before index date, non-users: no prescription 365 days before index date	Current use: last pre-scription filled 0-30 days recent: last prescription filled 31-60 days, past: last prescription filled 61-150 days before index date, non-users: no prescription 150 days before index date	Recent exposure: ≥ 1 prescription dispensed within 90 days prior to index date Previous: ≥ 1 prescription dispensed at any time from January 1989 to the index date
NSAID categories	Individual NSAIDs (4 different drugs) other NSAIDs	Individual NSAIDs (10 different drugs), other NSAIDs, ≥ 2 NSAIDs	All NSAIDs combined	Oral NSAIDs (all combined), topical NSAIDs, Aspirin
Covariates	Age, sex, calendar year, body mass index, alcohol use, smoking, cardiovascular disease, diabetes, hospitalizations, consultations, use of prescription drugs as in Griffin et al. (2000)[80] and Perez Gutthann et al. (1996)[79].	Age, sex, ethnicity, index year, prescription drug use (cardiovascular, anti-diabetic, respiratory, immunosuppressants, selected nephrotoxic drugs and contrast agents), recent hospitalization, nursing home residence, use of other medical services	Age, sex, recent hospital-ization, a chronic disease score[83] (based on cardio-vascular, respiratory and anti-diabetic drug use), nephrotoxic comedication (34 drugs)	Primary or secondary diagnosis of acute renal failure, presence of chronic renal failure, use of topical NSAIDs and Aspirin (considered as confounders and exposure)

Figure 1.1 The role of cyclooxygenase in prostaglandin formation from arachidonic acid



Diverse specific stimuli lead to the formation of arachidonic acid from membrane phsophlipids by phospholipase A2. Arachidonic acid is metabolized by the bifunctional enzyme cyclooxygenase. Prostaglandin H2 is directly formed form prostaglandin G2 within the enzyme. Subsequently, five prostanoids result from reactions with tissue specific isomerases. The prostaniods found in the kidney are underlined. The effects of prostanoids, mediated by specific receptors, are multiple and opposing dependant on the target tissue. Here, those most relevant for renal and cardiovascular function are listed. Cyclooxygenase exisits as two isoforms, cyclooxygenase 1 and 2. Aspirin and NSAIDs (including the selective inhibitors of cyclooxygenase 2) inhibit both isoforms in varying degrees. As a result, prostanoid formation and the following reactions of the pathway are inhibited. Based on[13,48,84].

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Chapter 2

2 The databases of the health services administration of Quebec

In order to assess the occurrence of acute renal failure in users of COX-2 selective NSAIDs in comparison to conventional NSAIDs, the computerized health service databases of the province of Quebec were employed. They comprise the databases of the Régie de l'Assurance-maladie du Québec (RAMQ) as well as the hospitalization and vital statistics databases that are all administered by the Ministère de la santé de des services sociaux (MSSS) of Quebec. Numerous pharmacoepidemiologic studies have already been conducted with the help of these databases, as they are known to be a highly accurate means to determine exposure to prescription drugs[1].

Here, these databases served to form the study cohort, to determine beginning and end of follow-up time, to define covariates and exposure and to assess the occurrence of the outcome.

2.1 The databases

Provincial health insurance is available for all residents of Quebec, and for all residents aged 65 and older prescription drugs are also covered. Therefore, comprehensive health care information on virtually the whole elderly population of the province of Quebec is contained in the databases. To each individual who is covered by health care insurance and on whom data is contained in the databases, a unique encrypted identifier, the Numéro d'Assurance Maladie (NAM), is assigned. This identifier allows record linkage between different databases to synthesize information on the individual. Data were obtained for a related project[2] and were available for analysis from the databases that are subsequently described in more detail.

The beneficiary database:

This database contains information on age, and sex and date of death (if applicable) for each person covered by the provincial health insurance. Each beneficiary is represented by his or her NAM. The age of the individual is given in full years. For reasons of

confidentiality due to small numbers, the age of persons who are older than 85 years is reset to 85 years.

The eligibility database:

In addition to the NAM, the database includes a code that describes the type of the beneficiary (reason for coverage), the date of beginning of coverage, which is the date of entry in the database, and the date of termination of coverage.

Prescription drugs database:

The database consists of data on all drugs dispensed to beneficiaries as outpatients and is therefore central to the project. The NAM describes the beneficiary to whom the drug was dispensed. Moreover, her or his age group and sex as well as a regional code, the code of the CLSC (*Centre local de services communautaires*) and first three positions of the postal code of the beneficiary are included in the database. Importantly, every dispensed item is entered separately in the database.

The prescription drugs, which are eligible for coverage, are contained in the provincial drug formulary[3], which is updated biannually. The following information on drugs is available in the database:

- Date on which the drug was dispensed
- Drug identification code (*code d'identification d'un médicament*) and drug classification code according to the American hospital formulary, both as given in the applicable version of the drug formulary of Quebec
- A code for the chemical compound (*code de denomination commune*)
- The pharmaceutical form of the drug
- Information on the dosage, quantity and treatment duration
- Code indicating a new or renewal prescription and an indicator whether the prescribed drug was substituted by an equivalent pharmaceutical product
- Service fee, contribution of the beneficiary and total cost (sum of price of the drug and service fee, minus the contribution of the beneficiary)

- Professional class, encrypted identification number and specialty of the person who prescribed the drug.

Medical services database:

This database contains information on the date and nature of utilization of medical services, on an inpatient or outpatient basis. It holds the NAM and the same variables describing the beneficiary as the prescription drug database (see above). Moreover, the database contains the date of the service (treatment), a code for the type of institution where the treatment took place (e.g. doctor's office or hospital) and the role that the billing professional played when the treatment was administered. It also comprises the code for the treatment (*code d'acte*) as listed in the applicable version of the billing manuals that are published by RAMQ. The manuals consist of versions for general practitioners[4] and medical specialists[5] and are updated in irregular intervals. An identifier allows determining cases in which the treatment was administered more than once on a given date. Additionally, the diagnosis underlying the treatment is given, encoded by the ICD-9 (international classification of disease 9th edition). The treating physician is characterized by a code for professional class, encrypted identification number and specialty.

Hospitalization database (Med-Écho):

The acronym MED-ÉCHO stands for *système de Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière.* This database consists of data on all hospitalizations of beneficiaries; each hospitalization is represented by one entry. The beneficiary is described by her or his NAM, age group and sex, as well as a code for the region and CLSC. The type of institution where the patient was hospitalized is recorded by a code. The date of registration in the emergency room, the admission date, discharge date and the duration of the hospitalization are also contained in the database. For each hospitalization, one primary diagnosis and up to 15 secondary diagnoses are recorded by their ICD-9-codes. Moreover, the database contains up to 9 treatment codes as well as their corresponding dates. The treatments are encoded by the Canadian classification of diagnostic, therapeutic and surgical procedures[6].

2.2 Study population and follow-up

In this study, with the help of these databases, a population-based cohort was formed, consisting of persons above 66 years of age to whom an NSAID was newly dispensed. In particular, the eligibility database was used to verify coverage of the individual and thus representation in the prescription drugs database for the one-year period preceding the date of the first NSAID-prescription between 01.01.1999 and 30.06.2002 (cohort entry). This allowed exclusion of individuals with an NSAID-prescription in the year before their cohort entry. Coverage for the whole of the study period was also verified for all cohort members with the help of the eligibility database. Individuals whose coverage ended prior to the end of the study were censored. The beneficiary database served to determine whether an individual was deceased during the course of follow-up and thus was also censored. The hospitalization database was used to identify patients with a renal transplantation for exclusion or censoring. For the same purpose, the medical services database was used to determine whether patients were on haemodialysis. The date of the first NSAID prescription from the prescription drugs database marked the beginning of follow-up and allowed to exclude individuals with NSAID-prescriptions from 2 NSAID-categories (as defined in Chapter 3) at cohort entry.

2.3 Covariates, exposure and outcome

Certain covariates that could potentially confound the association between NSAIDs and acute renal failure were considered and defined with the help of the databases. The beneficiary database served to determine sex and age of the individual. Age was determined at cohort entry. The prescription drugs database was used to determine specific comorbid conditions (e.g. hypertension, see Chapter 3.2.2), a chronic disease score[7], drug use (corticosteroids, oral anticoagulants, psychotropics, thyroid drugs), exposure to nephrotoxic drugs, and use of aspirin. Moreover, the prescription database allowed counting of the number of different medications prescribed to the individual. Specific comorbid conditions were additionally defined with diagnoses from the hospitalization database (see Chapter 3.2.2). This database was also analyzed to assess

radio-contrast exposure (based on treatment codes), to count hospitalizations, and to assign the Charlson index[8]. The medical services database was also used to determine exposure to contrast agents (based on specific *codes d'acte*) and moreover to count the number of nephrologist visits.

Exposure to NSAIDs was defined using the prescription drugs database, the hospitalization database allowed determining the occurrence of the outcome, a hospitalization with a primary or secondary discharge diagnosis of acute renal failure or renal failure (ICD-9 code 584 or 586, chosen based on Perez Gutthann *et al.*[9], see Table 1.1).

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Chapter 3

3 Manuscript and additional comments

3.1 Preface

This chapter contains a manuscript that was submitted for publication. It is presented in the form it was submitted with minor changes, mainly different formatting.

The contribution of individual authors has been listed separately on page iv.
As manuscripts are concise documents, a supplementary section (Chapter 3.3) is included, where additional aspects will be expanded and discussed.

In this study, the association of NSAIDs, considering the selective COX-2 inhibitors, with acute renal failure was investigated in a population-based nested case-control study with the administrative databases of the province of Quebec. A comparable investigation on the population level has not been conducted so far.

Particular care was taken to adjust for the potentially confounding effects of comorbid conditions, an important potential source of bias in pharmacoepidemiological studies[1], and known risk factors for acute renal failure (see Chapter 1.4 and 1.5).

The exposure to NSAIDs was assessed based on three time-windows that were chosen based on previous investigations (see Table 1.1). In contrast to these studies with three[2] or four[3-5] exposure-time categories, the exposure history in the year prior to the index date was better accounted for here, as seven mutually exclusive exposure-time categories were defined. Therefore, the association of NSAID-use and acute renal failure in the group of new NSAID-users could be determined here, which is unique to this study.

3.2 Manuscript

Title:

The association of selective and conventional nonsteroidal anti-inflammatory drugs with acute renal failure

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Abstract

Title: The association of selective and conventional nonsteroidal anti-inflammatory drugs with acute renal failure

Context: Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with acute renal failure, but the risks of selective cyclooxygenase-2-inhibitors have not been comparatively evaluated.

Objective: to assess the association between exposure to NSAIDs and hospitalization with acute renal failure.

Design, setting and patients: case-control study nested in a cohort of 121,722 elderly new NSAID-users from the administrative healthcare databases of Quebec, Canada, 1999-2002.

Main outcome measures: Rate ratios describing the incidence of hospitalization with renal failure for different NSAIDs and NSAID-exposure periods compared to unexposed individuals. These were obtained from conditional logistic regression and adjusted for sex, age, health status, health care utilization measures, exposure to contrast agents and nephrotoxic medications.

Results: 4,228 cases and 84,540 controls matched on age and follow-up time were identified. The risk of acute renal failure for all NSAIDs combined was highest within 30 days of treatment initiation (adjusted rate ratio (RR) 2.05, 95% confidence interval (CI) 1.61 – 2.60) and receded thereafter. After at least 30 days without an NSAID-prescription, the risk had returned to baseline. The association with acute renal failure within 30 days of initiation of therapy was comparable for rofecoxib (RR 2.31, 95%CI 1.73 – 3.08), naproxen (RR 2.42, 95%CI 1.52 – 3.85) and non-selective, non-naproxen NSAIDs (RR 2.30, 95%CI 1.60 – 3.32), but lower for celecoxib (RR 1.54, 95%CI 1.14 – 2.09). These risks were dose-dependent for celecoxib, naproxen, but particularly for

rofecoxib (>25 mg/day: RR 6.64, 95%CI 4.05 – 10.87; ≤25 mg/day: RR 1.94 95%CI 1.44 – 2.63; $p < 0.001$ for trend).

Conclusions:

There is a significant association for selective and non-selective NSAIDs with acute renal failure. Celecoxib appears to have a favorable renal safety profile but confirmatory studies are required.

3.2.1 Background

The analgesic and anti-inflammatory properties of nonsteroidal anti-inflammatory drugs (NSAIDs) are based on inhibition of the cyclooxygenase (COX) enzyme isoforms. Motivated by a theoretical superiority in gastrointestinal safety profile, highly selective COX-2-inhibiting NSAIDs were developed[1]. While recent attention has been focused on the cardiovascular risks of these new drugs, relatively little attention has been paid to renal toxicity. Although the cardiovascular risk associated with COX-2 inhibitors has been interpreted as a class effect, the evidence is not totally conclusive[2]. Additional evidence for a class effect with respect to other critical adverse effects, such as nephrotoxicity, may assist in this debate.

Conventional, as well as COX-2 selective NSAIDs can cause renal complications, including rises in blood pressure, peripheral oedema, sodium retention and hyperkalemia[3-6]. Although acute renal failure after exposure to conventional, non-selective NSAIDs has been shown in population-based studies[7-10], the evaluation of the renal risk of COX-2 inhibitors is currently limited to sporadic case reports[11-15], and thus, its full magnitude is unclear. Therefore, we conducted a population-based nested case-control study to evaluate the time-dependent association of NSAID-use, either non-selective or selective with acute renal failure compared to individuals not exposed to these drugs.

3.2.2 Methods

Data Source

The databases of the universal healthcare program for residents of Quebec (Canada) above 65 years of age were analyzed. These databases have been previously validated[16] and utilized for research[17-20].

We obtained information on demographics, duration of health care coverage, all dispensed prescription drugs including dose and duration. This information could be linked via an individual encrypted identifier, thereby maintaining confidentiality, to 1)

the hospitalization database, which includes up to 15 ICD9-diagnoses and seven treatment codes, 2) the physician services database, and 3) the vital statistics registry.

Cohort definition and follow-up

We conducted a nested case-control study[21]. As reported previously[19], we formed a population-based cohort of new NSAID users age 66 or older, since universal drug coverage is only available for residents older than 65. Individuals were eligible for the study cohort if they had filled one or more prescriptions for an NSAID during the cohort entry period, 1st of January 1999 to 30th of June 2002 and had not filled a NSAID-prescription for at least one year before cohort entry. Data was restricted by the province's ethics board (Commission d'accès à l'information (CAI) du Québec) to a random sample of 125,000 persons of the overall 302,964 persons fulfilling these criteria[19]. We excluded individuals, whose only anti-inflammatory during the study period was aspirin, who had a non-aspirin NSAID-prescription in the year preceding cohort entry, who had been on renal replacement therapy (haemodialysis or peritoneal dialysis) in the year before cohort entry, had had a kidney transplantation, or if they received NSAIDs from 2 different categories (see below) on the date of their initial non-aspirin NSAID-prescription.

We defined cohort entry to be the date of the initial non-aspirin NSAID-prescription, and individual follow-up started on this date. Follow-up ended on the index date, which was either the date of the outcome (see below), the end of health insurance coverage, the date of the first dialysis procedure not fulfilling the outcome definition (e.g. for chronic renal failure), the date of renal transplantation, the date of death, or the end of the study on 31st of December 2002, whichever occurred first.

Case definition

During follow-up, we identified as cases all cohort members with the *a priori* defined outcome, namely a hospitalization containing a discharge diagnosis of acute renal failure (ICD9-code 584) or unspecified renal failure (ICD9-code 586[8]). For each case, the date of admission of this hospitalization was the index date.

Control selection

For each case, we randomly selected up to 20 controls from cohort members with the same or longer duration of follow-up. Consequently, controls were matched to cases on year and month of cohort entry; they were additionally matched on age at cohort entry (± 1 year). Each control was assigned as index date the date of the outcome of its corresponding case, thus follow-up times were equal between cases and controls.

Exposure categories and assessment of exposure

We *a priori* defined 5 mutually exclusive NSAID-categories: *(1) Celecoxib* (selective COX-2 inhibitor[22]), *(2) Rofecoxib* (selective COX-2 inhibitor[22]), *(3) Meloxicam* (selective COX-2 inhibitor[22]), *(4) Naproxen* (nonselective COX-1 and COX-2 inhibitor[22], comparator in previous studies[23] and presumed favorable cardiovascular safety profile[24]), and *(5) Conventional NSAIDs* (nonselective COX-1 and COX-2 inhibitors, all NSAIDs not contained in *(1) – (4)* and excluding aspirin, but listed in the provincial drug formulary during the study period[i]). The NSAID-categories *(1) – (4)* were subdivided based on average daily doses as follows: *(1) Celecoxib*: low dose ≤ 200 mg, high dose > 200 mg; *(2) Rofecoxib*: low dose ≤ 25 mg, high dose > 25 mg; *(3) Meloxicam*: low dose ≤ 7.5 mg, high dose > 7.5 mg; *(4) Naproxen*: low dose ≤ 750 mg, high dose > 750 mg.

Exposure to NSAIDs was assessed in the year preceding the index date. Based on the dispensing dates of the NSAID-prescriptions, exposure was categorized with respect to the 1-30, 31-90 and 91-365 day-periods preceding the index date. These periods were chosen based on the observation that NSAID-induced acute renal failure occurs shortly after initiation of therapy[5]. Considering all possible combinations of the 3 periods, we created seven mutually exclusive exposure-categories (Table 3.1): *(1) Current new use* (≥ 1 NSAID-prescription only in the 1-30 days before the index date); *(2) Current and*

[i] Diclofenac, Diflunisal, Etodolac, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Mefenamic Acid, Nabumetone, Phenylbutazone, Piroxicam, Salsalate, Sulindac, Tenoxicam, Tiaprofenic acid and Tolmetin.

recent use (≥ 1 NSAID-prescription 1-30 days and ≥ 1 NSAID-prescription 31-90 days before the index date, but no NSAID-prescription 91-365 days before the index date); *(3) Current and past use* (≥ 1 NSAID-prescription 1-30 days before the index date, no NSAID-prescription 31-90 days before the index date, and ≥ 1 NSAID-prescription 91-365 days before the index date); *(4) Current continuous use* (≥ 1 NSAID-prescription in each of the 3 periods in the year before the index date); *(5) Recent use* (No NSAID-prescription 1-30 days before the index date, ≥ 1 NSAID-prescription 31-90 days before the index date, and either no or ≥ 1 NSAID-prescription 91-365 days before the index date); *(6) Past use* (No NSAID-prescription 1-30 days before the index date, no NSAID-prescription 31-90 days before the index date, and ≥ 1 NSAID-prescription 91-365 days before the index date); *(7) Unexposed* (No NSAID-prescription in any of the 3 periods in the year before the index date).

Statistical Analysis and adjustment for potential confounders

The association between NSAIDs and acute renal failure was assessed using multiple conditional logistic regression. We adjusted for the potentially confounding effects of sex, age, numerous comorbid conditions, including pre-existing renal disease[ii] and previous acute renal failure, assessed within the year preceding cohort entry using hospitalization discharge codes and prescriptions (Table 3.2). We also considered exposure to nephrotoxic drugs (diuretics, antibiotics, drugs acting on the nervous system, immunosupressants, and others[25,26]) and contrast media (procedure codes indicating intravenous application) during the 30 days preceding the index date as potential

[ii] Chronic renal failure, previous acute renal failure, renal disease (nephrotic syndrome, nephritis, renal sclerosis, cystic kidney disease, reflux), renovascular disease (sclerosis and aneurysm of renal artery), renal infection (pyelonephritis, renal abscess, urinary tract infection), conditions secondary to renal impairment (renal osteodystrophy, nephrogenic diabetes insipidus, secondary hypertension), renal manifestation of systemic diseases (hypertensive and diabetic renal disease, gouty nephropathy, hepatorenal syndrome), as well as systemic diseases and malignancy relevant for renal function (neoplasm of urinary tract and kidney, leukemia, myeloma, metastatic cancer, disorders of plasma protein metabolism, connective tissue disease, polyarteriitis)

confounders. Moreover, we assessed prescriptions of anticoagulants, corticosteroids, psychotropics, and thyroid drugs in the year before cohort entry. We determined the number of distinct drugs prescribed[27], a chronic disease score[28], the Charlson index[29], and measures of health care utilization (number of hospitalizations, outpatient physician and nephrologist encounters) in the year before the index date. As reported in previous investigations[7-9], we considered aspirin separately. We defined exposure to aspirin as overlap of the last prescription with the index date.

We assessed the stability of the incidence rate of acute renal failure by dividing the follow-up time into 16 equal intervals and tested for significance using a Poisson regression model[30].

In order to evaluate the temporal association between use of NSAIDs and acute renal failure, all NSAIDs were first analyzed collectively in an unadjusted model. All covariates were then included leading to the adjusted model. Drug switching and concurrent prescription of more than one NSAID lead to multiple different exposure-patterns, therefore, stratification of the specific drug exposure-categories other than for *current new use* was perceived to be inefficient. Consequently, in order to study the independent effects of the various NSAID-categories, we analyzed individual NSAID-categories for *current new users* only, as this allowed the most meaningful and unequivocal interpretation. Finally, we considered the average daily dose of the NSAID in *current new users*, adjusting for all potential confounders and comparing to individuals unexposed to NSAIDs in the year before their index date.

SAS, version 8.2 (SAS institute, Cary, NC) was used for data analysis.

The study was approved by the Commission d'Accès à l'Information du Québec and the Institutional Review Board of the Faculty of Medicine, McGill University.

3.2.3 Results

A cohort of 121,722 new users of NSAIDs (Figure 3.1) was followed up for an average of 2.37 years (SD ± 0.97). Overall, 288,364 person-years of observation were available for analysis. During this time, we identified 4,228 cases of acute renal failure (ICD9-code 584 and 586 in 73.7% and 26.3% of cases, respectively) and 84,540 matched controls. The average incidence of acute renal failure (1.48 cases / 100 person-years, SD ± 0.34) was stable throughout the study period (χ^2-test, p = 0.43). Case-fatality during follow-up was high (47.3%), with a median survival of 35 days (Inter-quartile range 146 days) after the diagnosis of acute renal failure.

Cases were more likely to be male and to have hypertension, diabetes, and pre-existing renal diseases including previous episodes of acute renal failure (Table 3.2). In the year before the index date, cases used more health care services and, on average, required a higher number of drugs than controls. Exposure to nephrotoxic drugs and contrast media was also more frequent in cases. NSAID-prescriptions had a median duration of 30 days (Inter-quartile range 18 days).

Overall, *current new users* of any NSAID were at highest risk for acute renal failure compared to *unexposed* individuals (Table 3.3, adjusted rate ratio (RR) 2.05, 95% confidence interval (CI) 1.61 – 2.60). *Current and recent users* appeared to have a slightly lower risk (RR 1.62, 95%CI 1.29 – 2.04). This risk decreased further with increasing duration of use (*current continuous users*, RR 1.14, 95%CI 1.01 – 1.28). The risk for those who were re-exposed to an NSAID (*current and past users*) was intermediate (RR 1.26, 95%CI 1.04 – 1.53). For individuals who had recently stopped using NSAIDs (*recent users*), the risk of acute renal failure was indistinguishable from that of the reference category (RR 0.96, 95%CI 0.85 – 1.08). *Past users* had a lower risk than *unexposed* individuals (RR 0.77, 95%CI 0.69 – 0.85).

We also examined the risks for *current new users* of specific NSAIDs. Compared to *unexposed* individuals, *current new users* of conventional NSAIDs (RR 2.30, 95%CI 1.60 – 3.32), rofecoxib (RR 2.31, 95%CI 1.73 – 3.08), and naproxen (RR 2.42, 95%CI

1.52 – 3.85) had higher risks of acute renal failure (Table 3.4). In contrast, the risk of renal failure for *current new users* of celecoxib was lower than that for the other NSAIDs, although increased compared to those unexposed (RR 1.54, 95%CI 1.14 – 2.09). There were too few *current new users* of meloxicam to reliably determine the risk of acute renal failure (RR 1.27, 95%CI 0.37 – 4.45). Notably, acute renal failure was strongly associated with use of agents from more than one NSAID category during the 30 days preceding the index date (RR 4.65, 95%CI 2.31 – 9.37). In 61.9% of these individuals, the dates of the prescriptions from the two different NSAID-categories overlapped.

In all comparisons related to dose, *current new use* of higher doses of NSAIDs was associated with a higher risk of acute renal failure compared to individuals unexposed to NSAIDs (Table 3.5). For rofecoxib, the adjusted rate ratio for > 25 mg/day was 6.64 (95%CI 4.06 – 10.87), for ≤ 25 mg/day the rate ratio was 1.94 (95%CI 1.44 – 2.63, $p < 0.001$ for trend). The risk for acute renal failure in *current new users* of celecoxib was 2.00 (95%CI 1.32 – 3.04) for users of > 200mg/day and 1.33 (95%CI 0.94 – 1.88, $p = 0.21$ for trend) for ≤ 200mg/day. Similarly, the adjusted rate ratio for users of > 750 mg/day of naproxen was 3.62 (95%CI 2.01 – 6.53) and 1.65 (95%CI 0.88 – 3.08, $p = 0.07$ for trend) for ≤ 750 mg/day. There were insufficient *current new users* of meloxicam to assess a dose-response relationship.

3.2.4 Discussion

This is the first population-based study to compare the association between both selective and non-selective NSAIDs and the risk of acute renal failure. We have demonstrated that within 1 month of a first prescription there is a twofold increase in the risk of acute renal failure with any NSAID and a fourfold increase with use of NSAIDs from more than one category, reflecting either early drug switching or concurrent use of more than one NSAID. Longer-term continuous NSAID-users remained at an increased, but lower level, of risk. After at least 30 days without an NSAID-prescription, the risk of renal failure returned to baseline. *Past users* were at lower risk than *unexposed* individuals, possibly

representing a selected population resistant to nephrotoxicity due to depletion of susceptible cases[31]. Since the number of cases exposed to individual conventional NSAIDs was limited, it was impossible to provide a detailed evaluation of the known heterogeneous renal risk[9] of individual conventional NSAIDs, other than naproxen.

This is also the first study to consider dosages of specific COX-2 selective NSAIDs. Globally, low dose rofecoxib, high dose celecoxib and nonselective NSAIDs appeared to be associated with comparable rates of acute renal failure. High dose rofecoxib appeared to be the most, and low dose celecoxib the least nephrotoxic. Compared to the other NSAIDs, celecoxib appeared to have a better renal safety profile, particularly at a dose of 200 mg/day or less.

Our observation of the overall risk of renal failure associated with rofecoxib is generally consistent with previous predictions[32-34]. The apparently more favorable renal safety profile of celecoxib is in accordance with findings from the CLASS-study[35], where oedema, hypertension, and increased creatinine levels occurred more often in the ibuprofen and diclofenac than in the celecoxib group. More patients on rofecoxib than on celecoxib developed oedema and hypertension in the comparative SUCCESS-study[36]. Moreover, an analysis of the WHO drug safety database also revealed that rofecoxib led to more renal adverse events than celecoxib[14]. These findings do not support the assumption that the magnitude of the renal risk of NSAIDs can be predicted simply based on the relative strength of COX-1/COX-2 selectivity. We provide evidence for a class effect for all NSAIDs regardless of their COX-2 selectivity with respect to the risk of acute renal failure, as suggested earlier[5]. Nonetheless, there are important differences in the magnitude of the risk between these agents, most notably between celecoxib and the others. The pattern of risk we observed here is also in accordance with the variations in cardiovascular safety observed for selective COX-2 inhibitors[19,37-39]. Finally, the differences in risk between celecoxib and rofecoxib suggest that mechanisms other than inhibition of cyclooxygenase might be involved in the observed nephrotoxic effects of NSAIDs.

Although these results are derived from an observational design, our study does have a number of strengths. Our analysis of a population-based cohort of incident users minimizes the potential for bias compared to other designs[40]. Moreover, we carefully controlled for age, length of follow-up and most known confounders. Our results are based on a large number of non-selected subjects and show a surprisingly high number of cases of acute renal failure, highlighting the clinical importance of the renal safety of NSAIDs in the elderly. Indeed, the incidence of acute renal failure was 50% higher than that of acute myocardial infarction in the same cohort[19].

Furthermore, the validity of our study is reinforced by the consistency of our results with previous knowledge. The risk of non-selective NSAID-induced acute renal failure is known to be time-dependent[9], as well as dose-dependent [8,9]. We also demonstrated the expected strong relationship between exposure to contrast agents or nephrotoxic drugs and acute renal failure.

Our study does have several limitations. We had no measure of the severity of renal impairment, such as serum creatinine values. However, this does not affect the validity of our study addressing the risk of hospitalization for renal failure, rather than the severity of the decline in renal function. Exposure to conventional, non-selective NSAIDs might have caused physicians to more readily investigate for adverse renal events (detection bias) as their association with acute renal failure was well established previously, in contrast to the largely unstudied selective COX-2 inhibitors. However, our observation of similar risks for rofecoxib and conventional NSAIDs as well as a differential risk across COX-2 inhibitors indicates that this is unlikely to represent an important source of bias in our study. Our study could not distinguish between acute renal failure occurring before or during hospitalization. We cannot rule out that some cases represented in-hospital renal failure, and a previous investigation suggests these account for approximately 11% of potential cases[8]. However, if comorbidity rather than NSAID-exposure is the key determinant of in-hospital renal failure, then, misclassification of in-hospital cases as NSAID-associated cases is likely non-differential with respect to NSAID-exposure and would have lead to an underestimation of the true risks.

Individuals at increased risk of acute renal failure might have in fact been preferentially exposed to certain NSAIDs, leading to confounding by indication. It has been shown that patients with more severe comorbidity are preferentially prescribed COX-2 inhibitors compared to conventional NSAIDs[41]. However, this would not explain the difference between the risks associated with the use of individual COX-2 inhibitors observed here. Although the choice of the NSAID appears to be influenced more strongly by physician characteristics than by patient comorbidity[42], we cannot exclude the possibility of residual confounding by indication.

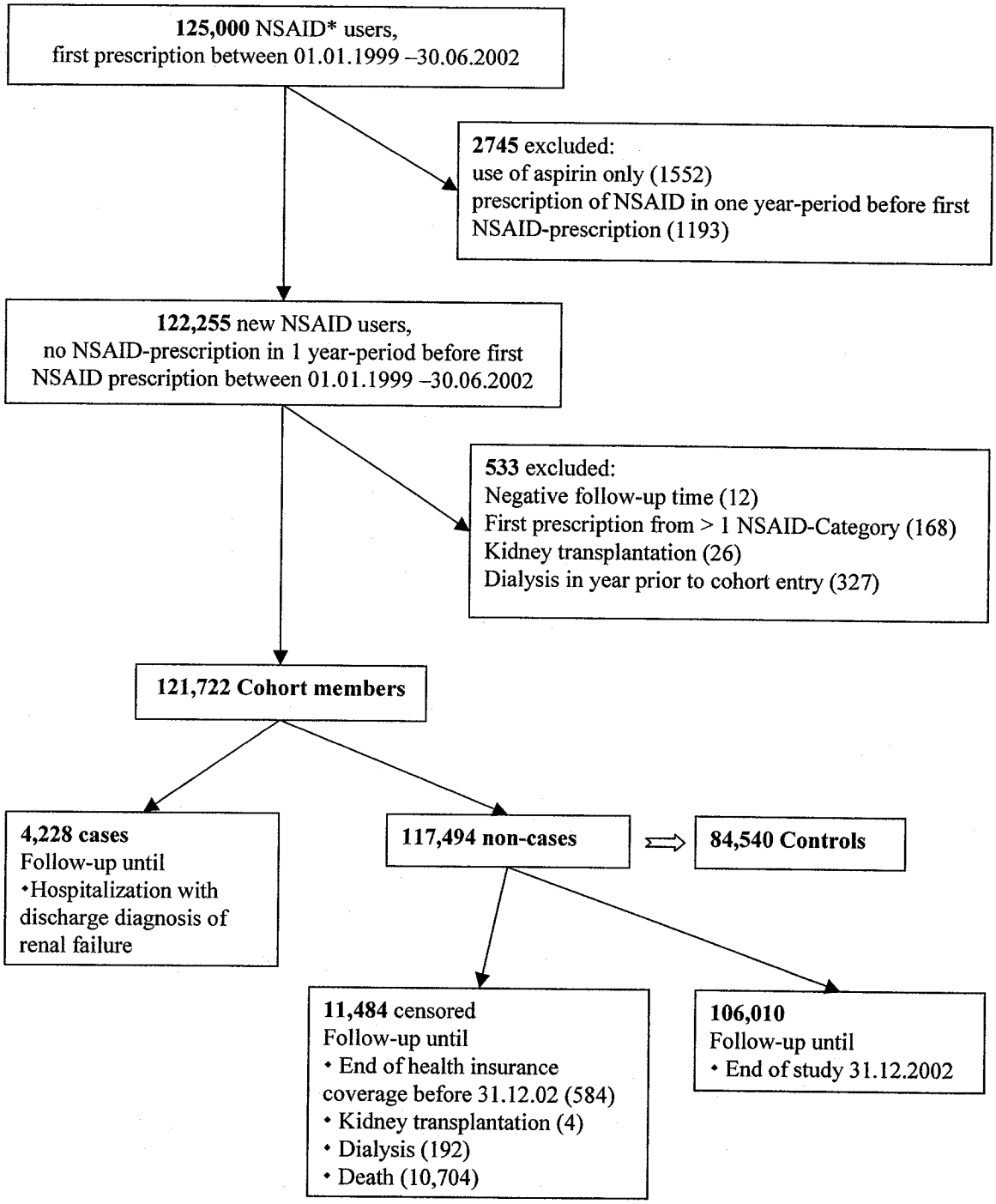
Ibuprofen and aspirin are available over-the-counter (OTC) in Canada, but they are also covered by the prescription drug plan for persons 65 years of age and older. Therefore, the proportion of OTC-NSAID-users is expected to be small. Fortunately, any resulting misclassification of NSAID-exposure, e.g. due to short-term self-medication for acute pain, is expected to be non-differential with respect to the NSAID-categories of our study. Consequently, it would bias the results toward the null. Finally, we could not consider important health determinants, such as smoking, obesity and socioeconomic status in our investigation, but these conditions seem unlikely to be differentially related to NSAID exposure. Further studies are required to confirm our observations and to firmly delineate the renal toxicity of the novel NSAIDs. For example, might low dose celecoxib represent an appropriate option for patients in whom maintenance of renal function is a priority?

In conclusion, we determined that the effect of NSAIDs on kidney function appears to be acute and recedes over time. The risk of acute renal failure shortly after treatment initiation with rofecoxib at low doses is comparable to that of conventional NSAIDs, whereas it appears to be higher at daily doses above 25 mg. For celecoxib, the risk also appears to be dose-dependent, but weaker compared to both rofecoxib and conventional NSAIDs, although this observation requires confirmation in other studies. In assessing the safety COX-2 inhibitors, one should not exclusively consider cardiovascular side effects but rather concentrate on overall risk profile, including the propensity for prognostically important renal dysfunction. The high risk of acute renal failure observed

here reinforces the wisdom of maintaining the voluntary ban on rofecoxib initially mandated by cardiovascular safety concerns. The frequent occurrence of acute renal failure observed in our study means that future trials of NSAIDs should a priori diligently monitor renal function in a manner similar to that proposed for cardiovascular outcomes. However, given the highly selective nature of the study populations and the small sample sizes in most clinical trials, population-based observational studies will continue to have an important role in the assessment of infrequent adverse effects.

3.2.5 Figure

Figure 3.1 Flow of study participants.



*Nonsteriodal anti-inflammatory drug, excluding aspirin

3.2.6 Tables

Table 3.1 Definition of exposure-time categories for cases and controls based on NSAID*-prescription(s) during the 365 days before the index date.
Presence or absence of at least one prescription is indicated with (+) or (-) respectively.

Exposure-time category	**Date of NSAID*-prescription(s)**		
	365-91 days†	90-31 days†	30-1 days†
Current new use	-	-	+
Current and recent use	-	+	+
Current and past use	+	-	+
Current continuous use	+	+	+
Recent use	**+ or -**	+	-
Past use	+	-	-
Unexposed	-	-	-

*Nonsteroidal anti-inflammatory drug

†Before the index date

Table 3.2 Characteristics of cases and controls.

	Cases (n= 4,228)	Controls (n =84,540)	Adjusted Rate ratio* (95% CI)
Age (years)† ± SD	78.1 ± 5.7	78.0 ± 5.7	1.09 (1.03 - 1.15)
Male	46.1	32.3	1.78 (1.65 - 1.90)
Female	53.9	67.7	
Comorbidity‡, %			
Hypertension	78.5	60.7	1.15 (1.05 - 1.26)
Diabetes	26.4	11.5	1.16 (1.06 - 1.27)
Heart failure	39.8	14.9	1.70 (1.57 - 1.85)
Cardiovascular disease	42.0	21.2	1.13 (1.04 - 1.22)
Artherosclerosis	7.7	2.3	1.08 (0.93 - 1.25)
Hyperlipidemia	24.9	20.1	0.79 (0.72 - 0.85)
Respiratory disease	33.0	19.5	0.86 (0.79 - 0.94)
Gastrointestinal ulcer disease	37.6	28.2	0.87 (0.81 - 0.94)
Chronic renal failure	4.8	0.7	1.49 (1.22 - 1.83)
Acute renal failure	4.2	0.5	2.41 (1.93 - 3.01)
Renal disease	1.1	0.2	0.94 (0.64 - 1.39)
Renovascular disease	0.3	0.0	2.66 (1.19 - 5.96)
Renal infection	3.5	1.4	1.05 (0.86 - 1.28)
Conditions secondary to renal impairment	0.1	0.0	2.91(0.77 - 10.97)
Renal manifestation of systemic diseases	4.0	0.7	1.33 (1.07 - 1.65)

Table 3.2 (cont).

	Cases (n= 4,228)	Controls (n =84,540)	Adjusted Rate ratio* (95% CI)
Systemic disease and malignancy relevant for renal function	3.5	0.8	1.31 (1.05 - 1.63)
Drug use‡, %			
Oral anticoagulants	12.7	4.9	0.95 (0.84 - 1.06)
Oral corticosteroids	13.7	6.6	0.96 (0.86 - 1.07)
Psychotropic drugs	19.7	15.2	0.99 (0.90 - 1.08)
Thyroid drugs	19.1	17.4	1.05 (0.96 - 1.14)
Current use of aspirin§	32.1	22.1	1.00 (0.93 - 1.08)
Nephrotoxic drugs_	73.6	49.3	1.55 (1.43 - 1.68)
Exposure to contrast media_	4.6	0.8	3.71 (3.07 - 4.49)
Comorbidity measures¶, mean ± SD			
Number of different drugs	13.9 ± 6.7	8.6 ± 5.3	1.07 (1.06 - 1.08)
Chronic disease score	8.1 ± 3.9	5.0 ± 3.5	1.05 (1.03 - 1.06)
Charlson index	1.7 ± 2.5	0.4 ± 1.2	1.18 (1.16 - 1.20)
Health care utilization¶			
> 12 physician visits	59.6	38.5	1.05 (0.98 - 1.13)
≥ 1 nephrologist visits	5.5	1.7	1.71 (1.45 - 2.01)
> 1 hospitalization	27.8	9.0	1.14 (1.03 - 1.26)

*Adjusted for all other covariates listed in the table

†At cohort entry (date of first prescription of a non-aspirin non-steroidal anti-inflammatory drug)

‡Assessed in the year before cohort entry

§Overlap of last prescription with the index date

_Dichotomous (yes or no), assessed in the 30 day-period before the index date

¶Assessed in the year before the index date

Table 3.3 Rates of acute renal failure in users of nonsteroidal anti-inflammatory drugs (NSAIDs) dependent on time, all NSAID-categories combined, relative to rates in unexposed.

Exposure-time category	**Cases (n = 4,228)**	**Controls (n = 84,540)**	**Unadjusted rate ratio (95% CI)**	**Adjusted rate ratio* (95% CI)**
Unexposed (reference category)	1,130	24,566	1.00	1.00
Current new use	382	6,576	2.31 (1.85 - 2.87)	2.05 (1.61 - 2.60)
Current and recent use	149	2,205	1.83 (1.47 - 2.26)	1.62 (1.29 - 2.04)
Current and past use	153	2,181	1.53 (1.28 - 1.82)	1.26 (1.04 - 1.53)
Current continuous use	602	8,833	1.49 (1.34 - 1.66)	1.14 (1.01 - 1.28)
Recent use	630	13,200	1.13 (1.00 - 1.26)	0.96 (0.85 - 1.08)
Past use	1,182	26,979	0.95 (0.86 - 1.04)	0.77 (0.69 - 0.85)

*Adjusted for all listed exposure-time categories and all covariates listed in Table 3.2.

Table 3.4 Rates of acute renal failure in current new users of nonsteroidal anti-inflammatory drugs (NSAIDs) by NSAID category, relative to rates in unexposed.

Exposure-time category	**Cases**	**Controls**	**Unadjusted rate ratio (95%CI)**	**Adjusted rate ratio* (95%CI)**
Unexposed (reference category)	1,130	24,566	1.00	1.00
Current new use				
Conventional NSAIDs	75	1,252	2.54 (1.82 - 3.55)	2.30 (1.60 - 3.32)
Rofecoxib	145	2,217	2.58 (1.98 - 3.36)	2.31 (1.73 - 3.08)
Celecoxib	112	2,456	1.73 (1.30 - 2.29)	1.54 (1.14 - 2.09)
Naproxen	35	478	3.12 (2.05 - 4.74)	2.42 (1.52 - 3.85)
Meloxicam	3	72	1.47 (0.46 - 4.73)	1.27 (0.36 - 4.45)
NSAIDs from > 1 Category	12	101	4.45 (2.38 - 8.33)	4.65 (2.31 - 9.37)

*Adjusted for all exposure-time categories except for current new use as listed in Table 3.3, and all covariates listed in Table 3.2. Results for other exposure-time categories are shown in Table 3.3.

Table 3.5 Rates of acute renal failure in current new users of rofecoxib, celecoxib, and naproxen by dose, relative to rates in unexposed.

Exposure-time category	**Cases**	**Controls**	**Unadjusted rate ratio (95%CI)**	**Adjusted rate ratio* (95%CI)**
Unexposed (reference category)	1,130	24,566	1.00	1.00
Current new use				
Rofecoxib†				
High dose (> 25 mg/day)	28	189	5.75 (3.68 - 8.99)	6.64 (4.05 - 10.87)
Low dose (≤ 25 mg/day)	117	2,028	2.25 (1.71 - 2.97)	1.94 (1.44 - 2.63)
Celecoxib‡				
High dose (> 200 mg/day)	39	553	2.57 (1.76 - 3.76)	2.00 (1.32 - 3.04)
Low dose (≤ 200 mg/day)	73	1,903	1.42 (1.03 - 1.95)	1.33 (0.94 - 1.88)
Naproxen§				
High dose (> 750 mg/day)	19	165	4.75 (2.79 - 8.07)	3.62 (2.01 - 6.53)
Low dose (≤ 750 mg/day)	16	313	2.16 (1.23 - 3.78)	1.65 (0.88 - 3.08)

*Adjusted for all remaining NSAID-categories listed in table 4, all exposure-time categories except for current new use listed in Table 3.3, and all covariates listed in Table 3.2.

†P < 0.001 for trend, ‡p = 0.21 for trend, §p= 0.07 for trend.

Results for remaining NSAID-categories and exposure-time categories are shown in Table 3.4 and Table 3.3, respectively.

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3.3 Additional Comments

Some aspects of the study presented before this section could not be discussed due to space limitations for a submitted article. These will be addressed subsequently.

A cohort of elderly new NSAID-users was chosen for this study, as this population is in greatest need for safe and effective anti-inflammatory therapy due to the age-dependent increase of the prevalence of rheumatic diseases and arthropathies. At the same time, the elderly are known to be at increased risk of acute renal function impairment when exposed to NSAIDs. This has been shown in the previous population-based studies as presented in Chapter 1. The health services databases of Quebec were well suited to study the association of NSAIDs with acute renal failure, as the whole elderly population of the province is represented therein, thus the results are highly generalizable.

The three exposure-time windows that were used in order to define the seven mutually exclusive NSAID-exposure-categories in this study were chosen in accordance with previous studies and case reports[4-9], which indicate that the risk of NSAID-induced renal failure is acute. Time after discontinuation of NSAID-therapy was not precisely determined for each individual. Therefore the conclusion of a time-dependent nature of the renal risk of NSAIDs must be made with caution.

The classification of NSAIDs in five categories based on COX-2 selectivity and known cardiovascular safety profile allows a comparison of the findings with other pharmaco-epidemiologic studies of COX-2 inhibitors, particularly those of their cardiovascular risks. Moreover it enabled an assessment of the consistency of the observations with a related study[10]. The same reasoning guided the choice of the cut-off points for the two dose levels of individual NSAIDs. In particular the selection of a daily dose of > 25 mg of rofecoxib as high dose, a regimen that is approved for short-term therapy of acute pain only, might appear questionable because it should rarely be observed. However, the use of such high doses of rofecoxib for longer than one week was relatively common in the population of the Tennessee Medicaid program at the time of this study[11].

The COX-2 selective compounds available in Quebec during the study period celecoxib, rofecoxib and meloxicam, were separately considered in the analyses. It was known prior to the study, that rofecoxib and celecoxib had been prescribed to numerous patients. Therefore it was likely that the number of cases and controls exposed to both agents would allow a sufficiently precise estimation of the related drug risk even if the drug class were stratified. Unfortunately, another COX-2 selective compound, valdecoxib, was not yet approved in Quebec during the study period. An investigation of the association of valdecoxib with acute renal failure would represent additional evidence for a class effect and might support this study. However, its recent removal from the market currently appears to be permanent. Thus it is questionable whether there is sufficient data to allow such an analysis and its results would be of little practical value.

In the analysis, conventional NSAIDs were not stratified by individual drugs. Nevertheless, a dose-response analysis for this NSAID category would have been possible. For this, a cut-off point for high and low doses could have been selected for each of the drugs and cases and controls could have been grouped into users of high and low doses of conventional NSAIDs accordingly. Although a valid approach that has been used before[3], this analysis was not conducted here, as the focus of this study was the evaluation of the novel compounds. The same applies to a calculation of the cumulative NSAID-dose for individuals, which would have allowed to evaluate the existence of a threshold dose for acute renal failure as well as chronic adverse effects of NSAIDs. Moreover, NSAIDs could have been grouped by their elimination half-life instead of their COX selectivity, as done earlier[3,12,13].

Interestingly, some pharmacokinetic properties of celecoxib are different from those of other NSAIDs, which might have contributed to the lower risk of acute renal failure that was observed with celecoxib. In particular, in patients with chronic renal failure, as reflected by a glomerular filtration rate of 34-48 ml/min, the area under the plasma concentration-time curve (AUC) appeared to be 47% lower than in normal individuals, although no relationship between kidney function and drug clearance could be

established for celecoxib[14]. Thus, in patients with impaired renal function the potential for a nephrotoxic effect of celecoxib might be self-limiting. Differences between the potency of the drugs could also have contributed to the observed differences between the renal risks of individual NSAIDs, i.e. some NSAIDs elicit the same effect at lower doses in comparison to others. Rofecoxib might appear more nephrotoxic because a daily dose that was defined as low (e.g. 25 mg) might in fact be as effective as 400 mg of celecoxib, which was categorized as a high dose in this study. Consequently, the estimated rate ratios would have to be adjusted for 'strength of the NSAID'. However, the comparisons between NSAIDs in this study served to determine differences between drugs in the way they are used in clinical practice, thus no such corrections were made.

Filling of a prescription does not mean that the individual, who was prescribed a drug, did in fact take the drug at all, or ingested it as directed. Non-compliance, here, probably is non-differential across NSAIDs. In most non-compliant NSAID-users exposure to the drug is likely overestimated. This fortunately will lead to results that are biased towards the null.

Finally, sulindac was shown to act as allosteric inhibitor of the γ-secretase complex, which produces the amyloidogenic peptide, Aβ, etiologically relevant for Alzheimer's disease[15]. Moreover, several NSAIDs decrease the production of Aβ, which appears not to be mediated by COX-inhibition. The latter effect, however, was not seen with all investigated NSAIDs[16]. These examples from current neuropathological research illustrate that NSAIDs, at least *in vitro*, can have targets other than COX. They also indicate that the potential to cause effects that are not COX-mediated varies across NSAIDs. Thus, mechanisms completely unrelated to COX-inhibition might have contributed to the nephrotoxic effects and particularly the differences between NSAIDs observed here.

3.3.1 Impact of NSAID use on public health

The prevalence of NSAID use and the risks associated with each of the NSAID-categories that were observed during the study period allow the estimation of the

proportion of cases that occurred due to NSAID-use in the study population (population attributable fraction, AF_p[17,18])

$$AF_p = p_c * (SMR - 1) / SMR \quad (3.1)$$

with p_c being the exposure prevalence among cases in the scenario of a stratified analysis (as proposed by Miettinen[17]) and SMR the risk ratio standardized to the exposed. The SMR can be replaced by the rate ratio, in case the risk ratio is uniform across strata and the disease is uncommon.

From a public health perspective, this measure is useful in order to determine the actual number of cases that were caused by the exposure and could have been prevented had the population not been exposed. Moreover, it provides a basis for estimating the number of cases likely to arise from comparable populations. Particularly in the context of the assessment of the safety of NSAIDs such figures could be of interest as they describe the burden of disease caused by specific adverse events.

In this cohort of 122,172 elderly new NSAID-users, an estimated 196 excess cases (95% CI 131 - 258) of acute renal failure occurred due to *current new use* of NSAIDs during the study period. This is based on an adjusted relative risk for acute renal failure of 2.05 (95% CI 1.61 – 2.60) and a prevalence of use in 382 of 4228 cases (0.09%), which results in a population attributable fraction of 4.63% (95% CI 3.10% - 6.09%). For the corresponding confidence interval, both the confidence interval of the adjusted relative risk and the confidence interval for the probability of exposure have to be considered. The latter is calculated based on the observed proportion of exposed cases based on the binomial distribution with the standard formula:

$$95\%\ CI(p_c) = p_c \pm 1.96 \sqrt{((p_c * (1 - p_c))/n)} \quad (3.2)$$

p_c denotes the proportion of exposed cases and n the number of cases

Assuming a constant case fatality rate for NSAID-induced acute renal failure across NSAIDs, the corresponding number of deaths likely caused by NSAID-use can be estimated with the help of the case-fatality rate observed in this study as well. In current new users, NSAIDs caused an estimated excess of 93 deaths (95% CI 60 – 126) if the observed case-fatality rate of 47.3% is assumed for the 196 excess cases. The corresponding confidence interval is obtained from the confidence interval of the population attributable fraction and the confidence interval for the probability of death, which is again calculated with the help of formula 3.2, only in this case, p_c is replaced by the proportion of cases who died.

The confidence interval for the probability of exposure and for the probability of death are both conservative estimates, thus the resulting confidence limits for the population attributable fraction and the resulting cases and deaths are wide. In the same way, the population attributable fraction as well as the number of excess cases and excess deaths was determined for all exposure time-categories based on table 3.3 (Table 3.6). As a consequence of the protective effect observed for *past users* of NSAIDs, which is discussed in Chapter 3.2.4, the number of cases prevented by NSAID use is estimated in this group. Additionally, these measures were obtained from individual NSAID-categories for current new users based on Table 3.4 (Table 3.7). They were also calculated for different doses of NSAIDs based on Table 3.5 (Table 3.8).

Interestingly, it appears that from the population health perspective, use of high doses of rofecoxib, which is very strongly associated with acute renal failure (adjusted RR 6.64; 24 excess cases), is less important than the use of low doses of the drug (adjusted RR 1.94), to which 57 excess cases could be attributed. Obviously, this is due to the much higher prevalence of the latter exposure. This also illustrates that, for example, by restricting or eliminating the seemingly 'dangerous' use of high doses of rofecoxib, the gain in terms of safety for all users might be limited.

Overall, the impact of use of NSAIDs on the overall caseload of acute renal failure is smaller than suggested by the estimated rate ratios. Acute renal failure is a condition known to be associated with a high mortality. Therefore, even small differences between individual NSAIDs lead to a number of deaths. These would be preventable if high-risk patients were not treated with these drugs, or at least minimized if a 'safer' NSAID was chosen. However, because NSAIDs are associated with other adverse effects, such as gastrointestinal and cardiovascular toxicity, the safer NSAID is not obvious from this study.

Table 3.6 Measures for impact of NSAID-induced acute renal failure on population health: estimated population attributable fraction calculated according to formula 3.1, number of excess cases and excess deaths in the study population during follow-up for different exposure-time categories.

Exposure-time category	**Cases**	**Population attributable fraction (95% CI)**	**Number of excess cases in study population (95% CI)**	**Number of excess deaths in study population (95% CI)***
Current new use	382	4.63% (3.10% - 6.09%)	196 (131 - 258)	93 (60 - 126)
Current and recent use	149	1.35% (0.67% - 2.08%)	57 (28 - 88)	27 (13 - 43)
Current and past use	153	0.75% (0.12% - 1.45%)	32 (5 - 61)	15 (2 - 30)
Current continuous use	602	1.75% 0.13% - 3.35%	74 (6 - 141)	35 (3 - 69)
Recent use	630	-0.62% (-2.82% - 1.18%)	-26 (-119 - 50)	-12 (-58 - 24)
Past use	1182	-8.35% (-13.17% - -4.69%)	-353 (-557 - -198)	-167 (-272 - -91)

*Based on the observed case-fatality rate of 47.3%

Table 3.7 Measures for impact of NSAID-induced acute renal failure on population health: estimated population attributable fraction calculated according to formula 3.1, number of excess cases and excess deaths in the study population during follow-up due to for current new users of individual NSAID-categories.

Exposure-time category	**Cases**	**Population attributable fraction (95% CI)***	**Number of excess cases in study population (95% CI)***	**Number of excess deaths in study population (95% CI)*†**
Current new use				
Conventional NSAIDs	75	1.00% (0.52% - 1.52%)	42 (22 - 64)	20 (10 - 31)
Rofecoxib	145	1.94% (1.22% - 2.69%)	82 (51 - 114)	39 (24 - 55)
Celecoxib	112	0.93% (0.33% - 1.38%)	39 (14 - 58)	19 (4 - 34)
Naproxen	35	0.49% (0.19% - 0.81%)	21 (8 - 34)	10 (4 - 17)
Meloxicam	3	0.02% (-0.27% - 0.12%)	1 (-11 - 5)	0 (-6 - 2)
NSAIDs from > 1 Category	12	0.22% (0.07% - 0.40%)	9 (3 - 17)	4 (2 - 8)

*Sum of cases differs from sum of all cases in current new users as shown in Table 3.6 due to rounding

†Based on the observed case-fatality rate of 47.3%

Table 3.8 Measures for impact of NSAID-induced acute renal failure on population health: estimated population attributable fraction calculated according to formula 3.1, number of excess cases and excess deaths in the study population during follow-up due to for current new users of rofecoxib, celecoxib and naproxen by dose.

Exposure-time category	Cases	Population attributable fraction (95% CI)		Number of excess cases in study population (95% CI)*	Number of excess deaths in study population (95% CI)*†
Current new use					
Rofecoxib					
High dose (> 25 mg/day)	28	0.56%	(0.50% - 0.60%)	24 (21 - 25)	11 (10 - 12)
Low dose (≤ 25 mg/day)	117	1.34%	(0.85% - 1.72%)	57 (36 - 73)	27 (17 - 34)
Celecoxib					
High dose (> 200mg/day)	39	0.46%	(0.22% - 0.62%)	20 (9 – 26)	9 (4 - 12)
Low dose (≤ 200 mg/day)	73	0.43%	(-0.11% - 0.81%)	18 (-5 – 34)	9 (-2 - 16)
Naproxen					
High dose (> 750 mg/day)	19	0.33%	(0.23% - 0.38%)	14 (10 - 16)	7 (9 - 26)
Low dose (≤ 750 mg/day)	16	0.15%	(-0.05% - 0.26%)	6 (-2 - 11)	3 (-1 - 5)

*Sum of cases differs form sum of all cases in rofecoxib, celecoxib, or naproxen users as shown in Table 3.7 due to rounding

†Based on the observed case-fatality rate of 47.3%

3.4 References for 3.1 and 3.3

This list contains the references from Chapter 3.1 and 3.3. The references for the manuscript that is presented in Chapter 3.2 are listed in Chapter 3.2.7.

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Chapter 4

4 Additional results

The most important findings of the project were reported in the manuscript that is presented in Chapter 3.2 of this thesis. However, additional analyses were conducted that were not included in the manuscript due to space limitations. These are the subject of this chapter. The same definitions as in Chapter 3 were employed unless stated otherwise. In particular, the same cases and controls were analyzed and covariate definitions remained unchanged. In this chapter, results obtained by a second way of defining exposure to NSAIDs are presented, as well as an analysis of the interaction of NSAID-exposure with use of aspirin and the interaction of NSAID-exposure with exposure to nephrotoxic drugs. These findings will be discussed in Chapter 5.

4.1 Results from analyses based on a different exposure definition

Preliminary data analyses were conduced based on a less complex exposure definition than that employed in the manuscript that is reproduced in Chapter 3 (see Table 3.1). Three mutually exclusive exposure-time categories were defined based on NSAID-prescriptions in the year preceding the index date. *Current users* were cases and controls in which the last NSAID-prescription overlapped with the index date, i.e. the duration of the last NSAID-prescription was up to the index date or longer. *Past users* were cases and controls whose last prescription ended before the index date (no overlap). Individuals without any NSAID-prescription in the year before their index date were considered *unexposed* and served as reference group for all comparisons. Thus, the latter category was identical to the reference category of the exposure definition applied earlier. Based on this exposure definition, for all NSAID-categories combined, *current use* of NSAIDs was associated with an increased risk of acute renal failure (Table 4.1, adjusted RR = 1.26, 95% CI 1.14 - 1.41), whereas *past use* appeared to be protective (adjusted RR = 0.84, 95% CI 0.76 - 0.92).

As before, individual NSAID-categories (see Chapter 3.2 for definition) were only considered for current users (Table 4.2). In comparison to *unexposed* cases and controls, *current use* of conventional non-aspirin, non-naproxen NSAIDs was associated with acute renal failure (adjusted RR = 1.33, 95% CI 1.03 - 1.71). *Current use* of rofecoxib (adjusted RR = 1.58, 95% CI 1.39 - 1.81), as well as naproxen (adjusted RR = 1.81, 95% CI 1.31 - 2.51) were also associated with acute renal failure. However, for *current use* of celecoxib (adjusted RR = 0.99, 95% CI 0.86 - 1.12) and meloxicam (adjusted RR = 0.89, 95% CI 0.46 - 1.73) no association was found. *Current use* of NSAIDs from more than one of the NSAID-categories concomitantly was particularly strongly associated with acute renal failure (adjusted RR = 3.09, 95% CI 1.98 - 4.80).

Current use of Rofecoxib, celecoxib and naproxen were stratified by average daily doses (Table 4.3), dose levels were defined as described previously (see Chapter 3.2). As before (Chapter 3.2), the low number of current meloxicam-users precluded a dose-response analysis. For all three drugs, the association with acute renal failure was stronger with higher doses when compared to *unexposed* cases and controls. For current users of > 25mg/day of rofecoxib the adjusted rate ratio was 2.41 (95% CI 1.67 - 3.48), for ≤ 25 mg/day it was 1.53 (95% CI 1.34 - 1.76, $p < 0.001$ for trend). For current use of high doses of celecoxib (> 200 mg/day), the adjusted rate ratio was 1.21 (95% CI 0.99 - 1.48), whereas for low doses it was 0.90 (95% CI 0.77 - 1.05, $p = 0.36$ for trend). The adjusted rate ratio for current use of > 750 mg of naproxen per day was 2.34 (95% CI 1.47 - 3.74) and 1.49 (95% CI 0.97 - 2.30, $p < 0.001$ for trend) for a daily dose of ≤ 750 mg.

Technical note

In comparison to the results from Chapter 3, the adjusted models reported in here do not contain the variable representing diseases of renal blood vessels (renovascular diseases). Its inclusion in the adjusted models led to a non-satisfactory fit of the model. Although the variable is a significant predictor of the outcome (see Table 3.2), only 11 of cases and 23 of the controls in fact had the condition. When the analyses presented in Chapter 3 where repeated under omission of the variable, as expected, virtually identical results

were obtained (not reported here). Consequently, the findings from both exposure definitions are comparable as if the same adjustments were made.

4.2 Interaction of aspirin with NSAIDs

In order to assess whether use of aspirin would potentiate the effect of NSAIDs on renal function, the interaction of aspirin with NSAIDs was studied. Only current use of NSAIDs was considered relevant in this context. For all analyses, exposure to aspirin was defined as current use of aspirin, which was previously defined as an overlap of the last aspirin-prescription with the index date (see Chapter 3). The interaction was investigated for both definitions of NSAID-exposure.

No statistically significant interaction was found when the more complex definition of exposure based on seven mutually exclusive categories as introduced in Chapter 3 was employed (Table 4.4). For *current continuous use* of any NSAID, the interaction approached statistical significance (p for interaction = 0.06), indicating a lower risk for users who took aspirin concomitantly. The interaction of aspirin with the individual NSAID-categories was further investigated in the category of *current new use* of NSAIDs (Table 4.5). Again, aspirin showed no interaction with exposure to drugs from any of the five NSAID-categories or concurrent use of NSAIDs from more than one category. Finally, the interaction of aspirin with different dose levels of NSAIDs was tested (Table 4.6). No interaction could be shown for *current new use* of high or low doses of rofecoxib, celecoxib, or naproxen.

The interaction of aspirin with exposure to NSAIDs was also investigated when NSAID-exposure history was defined by three mutually exclusive categories (see Chapter 4.1). While no interaction of aspirin with *current use* of any NSAID could be shown (Table 4.7, p for interaction = 0.35), when current use was stratified by NSAID category, in current users of rofecoxib, a statistically significant interaction with aspirin was found: In users with concomitant aspirin-use, the RR was 1.85 (95% CI 1.51 - 2.25) as compared to 1.46 (95% CI 1.25 - 1.71; p for interaction = 0.04) in users without aspirin. Current

aspirin-use did not modify the association of exposure to NSAIDs from the other categories with acute renal failure (Table 4.8). In parallel to the results reported above, the interaction with aspirin was further investigated by stratifying of rofecoxib, celecoxib and naproxen by dose (Table 4.9). No interaction of aspirin with high doses of rofecoxib was observed (p for interaction = 0.60). However, the interaction of rofecoxib with aspirin was again statistically significant for *current users* of low doses of rofecoxib: The risk was higher in users of aspirin (RR 1.80, 95% CI 1.46 - 2.20) than in no-users of aspirin (RR 1.41, 95% CI 1.20 - 1.65; p for interaction = 0.04). For exposure to high and low doses of celecoxib and naproxen, no interaction with current use of aspirin was found.

Technical note

In the tables, results from models containing interaction terms for all current exposure categories are presented. Statistical models with interaction terms for less than all current exposure categories (i.e. omission of interaction term with *current continuous use*, *current and recent use*, and *current and past use*) lead to essentially the same results for the coefficients. As before (see Chapter 4.1), in the adjusted models, the variable representing renovascular disease was omitted.

4.3 Interaction of nephrotoxic drugs with NSAIDs

NSAIDs could be associated with a different risk of acute renal failure in individuals who are prescribed nephrotoxic drugs concomitantly as compared to individuals who do not receive nephrotoxic drugs. In order to assess this potential interaction, interaction terms for all current use categories were included in the statistical models. Both definitions of NSAID-exposure were separately considered.

When exposure to NSAIDs was defined by seven mutually exclusive categories, the association of NSAIDs with acute renal failure was not materially altered by exposure to nephrotoxic drugs (Table 4.10). Stratification of current new use by NSAID-categories (defined in Chapter 3) did not reveal any interaction with nephrotoxic drugs (Table 4.11).

For *current new use* of celecoxib, the interaction approached statistical significance (p for interaction = 0.07), indicating a protective effect of concomitant exposure to nephrotoxic drugs. Moreover, as expected based on the findings for individual NSAIDs, the assessment of two dose levels for rofecoxib and naproxen did not reveal any interaction (Table 4.12). For current new users of celecoxib, however, use of high doses and nephrotoxic drugs concomitantly was associated with a lower risk for acute renal failure than use of high-dose celecoxib alone (RR 1.42, 95% CI 0.85 - 2.39 vs RR 3.72, 95% CI 2.07 - 6.68; p for interaction = 0.01).

The interaction of exposure to nephrotoxic drugs with NSAID-exposure as defined by 3 mutually exclusive categories (see Chapter 4.1) was assessed in the same fashion. For current users of any NSAID (Table 4.13), for the individual NSAID-categories (Table 4.14), as well as rofecoxib, celecoxib and naproxen stratified by dose (Table 4.15), no modifying effect of concomitant nephrotoxic drug-use was observed.

See Chapter 4.2. for a Technical note.

Table 4.1 Rates acute renal failure in users of nonsteroidal anti-inflammatory drugs (NSAIDs) dependent on time, all NSAID-categories combined, relative to rates in unexposed.

Exposure-time category*	**Cases (n = 4,228)**	**Controls (n = 84,540)**	**Unadjusted rate ratio (95%CI)**	**Adjusted rate ratio† (95%CI)**
Unexposed (reference category)	1,130	24,566	1.00	1.00
Current use	1,094	16,210	1.58 (1.44 – 1.75)	1.26 (1.14 – 1.41)
Past use	2,004	43,764	1.02 (0.94 – 1.12)	0.84 (0.76 – 0.92)

*NSAID-exposure was defined by three mutually exclusive categories (see Chapter 4.1)

†Adjusted for all covariates listed in Table 3.2, except for renovascular diseases

Table 4.2 Rates of acute renal failure in current users of nonsteroidal anti-inflammatory drugs (NSAIDs) by NSAID category, relative to rates in unexposed.

Exposure-time category*	**Cases**	**Controls**	**Unadjusted rate ratio (95%CI)**	**Adjusted rate ratio† (95%CI)**
Unexposed (reference category)	1,130	24,566	1.00	1.00
Current use				
Conventional NSAIDs	91	1,474	1.52 (1.20 - 1.92)	1.33 (1.03 - 1.71)
Rofecoxib	470	5,734	1.96 (1.73 - 2.21)	1.58 (1.39 - 1.81)
Celecoxib	434	8,122	1.23 (1.09 - 1.40)	0.99 (0.86 - 1.12)
Meloxicam	10	229	1.00 (0.53 - 1.89)	0.89 (0.46 - 1.73)
Naproxen	59	499	2.98 (2.23 - 3.99)	1.81 (1.31 - 2.51)
NSAIDs from > 1 Category	30	152	4.56 (3.06 - 6.80)	3.09 (1.98 - 4.80)
Past use	2,004	43,674	1.03 (0.94 - 1.12)	0.84 (0.76 - 0.92)

*Timing of NSAID-exposure was defined by 3 mutually exclusive categories (see Chapter 4.1)

†Adjusted for all covariates listed in Table 3.2, except for renovascular diseases

NSAID-categories are defined in Chapter 3.

Table 4.3 Rates of acute renal failure in current users of rofecoxib, celecoxib, and naproxen by dose, relative to rates in unexposed.

*Exposure-time category**	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)
Unexposed (reference category)	1,130	24,566	1.00	1.00
Current use				
Rofecoxib‡				
High dose (> 25 mg/day)	41	319	3.12 (2.23 - 4.36)	2.41 (1.67 - 3.48)
Low dose (≤ 25 mg/day)	429	5,415	1.89 (1.66 - 2.14)	1.53 (1.34 - 1.76)
Celecoxib§				
High dose (> 200 mg/day)	139	2,034	1.56 (1.30 - 1.88)	1.21 (0.99 - 1.48)
Low dose (≤ 200 mg/day)	295	6,088	1.11 (0.97 - 1.28)	0.90 (0.77 - 1.05)
Naproxen_				
High dose (> 750 mg/day)	28	170	4.12 (2.72 - 6.23)	2.34 (1.47 - 3.74)
Low dose (≤ 750 mg/day)	31	329	2.37 (1.61 - 3.49)	1.49 (0.97 - 2.30)

*Timing of NSAID-exposure was defined by three mutually exclusive categories (see Chapter 4.1), †Adjusted for all covariates listed in Table 3.2, except for renovascular disease, ‡ $p < 0.001$ for trend, § $p = 0.36$ for trend, _ $p < 0.001$ for trend

Results for *past use*, *current use* of conventional NSAIDs, meloxicam and NSAIDs from more than one NSAID category are shown in Table 4.2.

Table 4.4 Interaction of aspirin with NSAIDs: Risk of acute renal failure in current users of NSAIDs.

*Exposure-time category**	Aspirin				No Aspirin				p-value for inter-action
	Cases (n = 2059)	Controls (n = 19,627)	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	Cases (n = 2169)	Controls (n = 64,913)	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	
Unexposed‡	358	5,758	1.00	1.00	772	18,808	1.00	1.00	
Current new use	120	1,504	2.29 (1.82 - 2.90)	2.00 (1.56 - 2.58)	262	5072	2.29 (1.74 - 3.02)	2.14 (1.58 - 2.90)	0.62
Current and recent use	41	513	1.91 (1.50 - 2.42)	1.76 (1.36 - 2.28)	108	1692	1.58 (1.11 - 2.24)	1.32 (0.91 - 1.94)	0.19
Current and past use	51	539	1.51 (1.22 - 1.86)	1.25 (0.99 - 1.57)	102	1642	1.49 (1.10 - 2.01)	1.28 (0.92 - 1.78)	0.89
Current continuous use	233	2,408	1.41 (1.24 - 1.60)	1.06 (0.92 - 1.22)	369	6425	1.54 (1.31 - 1.81)	1.29 (1.08 - 1.53)	0.06

*Timing of NSAID-exposure was defined by seven mutually exclusive categories (see Table 3.1)

†Adjusted for all covariates listed in Table 3.2, except for renovascular disease

‡Reference category

Table 4.5 Interaction of aspirin with NSAIDs: Risk of acute renal failure in current new users of NSAIDs, by drug category.

*Exposure-time category**	Aspirin				No Aspirin				p-value for interaction
	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	
Unexposed‡	358	5,758	1.00	1.00	772	18,808	1.00	1.00	
Current new use									
Conventional NSAIDs	23	238	2.97 (1.81 - 4.89)	2.85 (1.65 - 4.92)	52	1,014	2.42 (1.67 - 3.49)	2.13 (1.43 - 3.16)	0.44
Rofecoxib	51	535	2.73 (1.91 - 3.90)	2.59 (1.75 - 3.84)	94	1,682	2.48 (1.85 - 3.32)	2.18 (1.58 - 3.00)	0.61
Celecoxib	29	591	1.36 (0.88 - 2.09)	1.33 (0.84 - 2.11)	83	1,865	1.89 (1.39 - 2.57)	1.64 (1.18 - 2.28)	0.14
Naproxen	12	101	3.45 (1.81 - 6.56)	2.59 (1.25 - 5.37)	23	377	2.90 (1.78 - 4.74)	2.33 (1.36 - 4.01)	0.65
Meloxicam	1	13	2.13 (0.27 - 16.69)	2.26 (0.28 - 18.31)	2	59	1.35 (0.33 - 5.6)	1.03 (0.22 - 4.73)	0.72
NSAIDs from > 1 Category	4	26	4.08 (1.40 - 11.89)	2.88 (0.80 - 10.31)	8	75	4.51 (2.12 - 9.59)	5.84 (2.63 - 13.00)	0.88

*Timing of NSAID-exposure was defined by seven mutually exclusive categories (see Table 3.1)

†Adjusted for all covariates listed in Table 3.2, except for renovascular disease

‡Reference category

Table 4.6 Interaction of aspirin with NSAIDs: Risk of acute renal failure in current new users of rofecoxib, celecoxib and naproxen stratified by dose.

*Exposure-time category**	Aspirin				No Aspirin				p-value for inter-action
	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	
Unexposed‡	358	5,758	1.00	1.00	772	18,808	1.00	1.00	
Current new use									
Rofecoxib									
High dose (> 25 mg/day)	9	40	6.53 (3.06 - 13.93)	8.39 (3.64 - 19.32)	19	49	5.46 (3.25 - 9.18)	6.04 (3.42 - 10.68)	0.50
Low dose (≤ 25 mg/day)	42	495	2.38 (1.63 - 3.48)	2.19 (1.44 - 3.32)	75	1,533	2.16 (1.58 - 2.95)	1.82 (1.30 - 2.56)	0.42
Celecoxib									
High dose (> 200 mg/day)	7	128	1.46 (0.66 - 3.21)	1.33 (0.58 - 3.06)	32	425	3.07 (2.04 - 4.62)	2.27 (1.44 - 3.59)	0.25
Low dose (≤ 200 mg/day)	22	463	1.29 (0.80 - 2.09)	1.29 (0.77 - 2.15)	51	1,440	1.48 (1.04 - 2.11)	1.37 (0.93 - 2.00)	0.83
Naproxen									
High dose (> 750 mg/day)	5	38	3.56 (1.34 - 9.43)	2.36 (0.78 - 7.13)	14	127	5.05 (2.75 - 9.25)	4.21 (2.16 - 8.23)	0.37
Low dose (≤ 750 mg/day)	7	63	3.26 (1.44 - 7.39)	2.65 (1.05 - 6.80)	9	250	1.71 (0.84 - 3.48)	1.28 (0.58 - 2.81)	0.21

*Timing of NSAID-exposure was defined by seven mutually exclusive categories (see Table 3.1)

†Adjusted for all covariates listed in table 3.2, except for renovascular disease

‡Reference category

Table 4.7 Interaction of aspirin and NSAIDs: Risk of acute renal failure in current users of NSAIDs, based on 3 exposure-time categories.

Exposure-time category*	**Aspirin**				**No Aspirin**				**p-value for inter-action**
	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	
Unexposed‡	358	5,758	1.00	1.00	772	18,808	1.00	1.00	
Current use	380	4,152	1.55 (1.34 - 1.78)	1.33 (1.14 - 1.55)	714	12,058	1.56 (1.39 - 1.74)	1.23 (1.09 - 1.39)	0.35

*Timing of NSAID-exposure was defined by three mutually exclusive categories (see Chapter 4.1)

†Adjusted for all covariates listed in Table 3.2, except for renovascular disease

‡Reference category

Table 4.8 Interaction of aspirin and NSAIDs: Risk of acute renal failure in current users of NSAIDs, stratified by drug.

*Exposure-time category**	Aspirin				No Aspirin				p-value for inter-action
	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	
Unexposed‡	358	5,758	1.00	1.00	772	18,808	1.00	1.00	
Current use									
Conventional NSAIDs	25	361	1.20 (0.79 - 1.83)	1.04 (0.66 - 1.64)	66	1,113	1.64 (1.25 - 2.15)	1.48 (1.10 - 1.98)	0.19
Rofecoxib	179	1,489	2.07 (1.73 - 2.49)	1.85 (1.51 - 2.25)	291	4,245	1.83 (1.59 - 2.12)	1.46 (1.25 - 1.71)	0.04
Celecoxib	153	2,086	1.22 (1.01 - 1.47)	1.04 (0.85 - 1.27)	281	6,036	1.20 (1.04 - 1.39)	0.96 (0.82 - 1.12	0.49
Naproxen	12	113	1.86 (1.01 - 1.47)	1.57 (0.81 - 3.04)	47	386	3.44 (2.49 - 4.76)	1.89 (1.31 - 2.73)	0.62
Meloxicam	2	49	0.68 (0.17 - 2.81)	0.64 (0.15 - 2.66)	8	180	1.16 (0.57 - 2.36)	0.99 (0.47 - 2.10)	0.59
NSAIDs from > 1 Category	9	54	2.85 (1.40 - 5.81)	1.92 (0.89 - 4.18)	21	98	5.50 (3.41 - 8.87)	4.01 (2.36 - 6.81)	0.12

*Timing of NSAID-exposure was defined by three mutually exclusive categories (see Chapter 4.1)

†Adjusted for all covariates listed in Table 3.2, except for renovascular disease

‡Reference category

Table 4.9 Interaction of aspirin and NSAIDs: Risk of acute renal failure, current use of rofecoxib, celecoxib and naproxen by dose.

*Exposure-time category**	Aspirin				No Aspirin				p-value for interaction
	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	
Unexposed‡	358	5,758	1.00	1.00	772	18,808	1.00	1.00	
Current use									
Rofecoxib									
High dose (> 25 mg/day)	15	79	3.34 (1.91 - 5.84)	2.77 (1.47 - 5.20)	26	240	2.93 (1.94 - 4.43)	2.26 (1.44 - 3.54)	0.60
Low dose (≤ 25 mg/day)	164	1,410	2.00 (1.66 - 2.42)	1.80 (1.46 - 2.20)	265	4,005	1.77 (1.52 - 2.05)	1.41 (1.20 - 1.65)	0.04
Celecoxib									
High dose (> 200 mg/day)	34	496	1.13 (0.79 - 1.62)	1.00 (0.68 - 1.45)	105	1,538	1.74 (1.41 - 2.15)	1.30 (1.04 - 1.64)	0.22
Low dose (≤ 200 mg/day)	119	1,590	1.24 (1.01- 1.53)	1.05 (0.84 - 1.31)	176	4,498	1.01 (0.85 - 1.20)	0.82 (0.69 - 0.99)	0.08
Naproxen									
High dose (> 750 mg/day)	6	40	2.55 (1.06 - 6.10)	2.02 (0.77 - 5.31)	22	130	4.75 (2.98 - 7.57)	2.45 (1.44 - 4.17)	0.73
Low dose (≤ 750 mg/day)	6	73	1.46 (0.63 - 3.39)	1.29 (0.52 - 3.20)	25	256	2.74 (1.79 - 4.21)	1.56 (0.96 - 2.54)	0.71

*Timing of NSAID-exposure was defined by three mutually exclusive categories (see Chapter 4.1)

†Adjusted for all covariates listed in Table 3.2, except for renovascular disease

‡Reference category

Table 4.10 Interaction of nephrotoxic drugs with NSAIDs: Risk of acute renal failure in current users of NSAIDs, based on 7 exposure-time categories.

*Exposure-time category**	Nephrotoxic drugs				No nephrotoxic drugs				p-value for interaction
	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	
Unexposed‡	819	11,322	1.00	1.00	311	13,244	1.00	1.00	
Current new use	282	3,384	2.12 (1.68 - 2.67)	1.97 (1.53 - 2.54)	100	3,192	2.25 (1.69 - 3.00)	2.24 (1.65 - 3.03)	0.34
Current and recent use	113	1,174	1.69 (1.33 - 2.14)	1.64 (1.27 - 2.12)	36	1,031	1.70 (1.18 - 2.44)	1.58 (1.08 - 2.30)	0.85
Current and past use	115	1,211	1.31 (1.06 - 1.61)	1.22 (0.97 - 1.52)	38	970	1.54 (1.10 - 2.15)	1.39 (0.98 - 1.96)	0.52
Current continuous use	99	3,188	1.25 (1.11 - 1.41)	1.17 (1.03 - 1.33)	503	5,645	1.25 (1.00 - 1.55)	1.00 (0.79 - 1.26)	0.20

*Timing of NSAID-exposure was defined by seven mutually exclusive categories (see Table 3.1)

†Adjusted for all covariates listed in Table 3.2, except for renovascular disease

‡Reference category

Table 4.11 Interaction of nephrotoxic drugs with NSAIDs: Risk of acute renal failure in current new users of NSAIDs, by drug.

*Exposure-time category**	Nephrotoxic drugs				No nephrotoxic drugs				p-value for inter-action
	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	
Unexposed‡	819	11,322	1.00	1.00	311	13,244	1.00	1.00	
Current new use									
Conventional NSAIDs	54	614	2.39 (1.65 – 3.47)	2.37 (1.58 – 3.54)	21	638	2.54 (1.54 – 4.19)	2.23 (1.32 – 3.77)	0.83
Rofecoxib	112	1,135	2.49 (1.88 – 3.32)	2.33 (1.71 – 3.19)	33	1082	2.20 (1.47 – 3.31)	2.26 (1.49 – 3.44)	0.88
Celecoxib	80	1,333	1.48 (1.08 – 2.02)	1.38 (0.99-1.93)	32	1132	2.00 (1.32 – 3.03)	2.08 (1.35 – 3.22)	0.07
Naproxen	22	220	2.68 (1.63 – 4.42)	1.97 (1.13 – 3.43)	13	258	3.89 (2.11 – 7.20)	3.56 (1.85 – 6.84)	0.13
Meloxicam	3	38	1.78 (0.54 – 5.87)	1.58 (0.44 – 5.72)	0	34	0	0	0.94
NSAIDs from > 1 Category	11	44	6.13 (3.07 – 12.26)	6.74 (3.09 – 14.71)	1	57	1.20 (0.17 – 8.76)	1.28 (0.17 – 9.46)	0.13

*Timing of NSAID-exposure was defined by seven mutually exclusive categories (see Table 3.1)

†Adjusted for all covariates listed in Table 3.2, except for renovascular disease

‡Reference category

Table 4.12 Interaction of nephrotoxic drugs with NSAIDs: Risk of acute renal failure in current users of NSAIDs, by dose.

*Exposure-time category**	Nephrotoxic drugs				No nephrotoxic drugs				p-value for inter-action
	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	
Unexposed‡	819	11,322	1.00	1.00	311	13,244	1.00	1.00	
Current new use									
Rofecoxib									
High dose (> 25 mg/day)	22	77	6.94 (4.13 - 11.65)	8.06 (4.55 - 14.30)	6	112	3.74 (1.60 - 8.77)	4.52 (1.89 - 10.83)	0.25
Low dose (≤ 25 mg/day)	90	1,058	2.12 (1.57 - 2.87)	1.94 (1.40 - 2.70)	27	970	2.01 (1.29 - 3.11)	2.01 (1.27 - 3.16)	0.89
Celecoxib									
High dose (> 200 mg/day)	23	283	1.90 (1.19 - 3.03)	1.42 (0.85 - 2.39)	16	270	3.97 (2.30 - 6.87)	3.72 (2.07 - 6.68)	0.01
Low dose (≤ 200 mg/day)	57	1,050	1.31 (0.93 - 1.86)	1.32 (0.91 - 1.91)	16	853	1.30 (0.75 - 2.23)	1.41 (0.80 - 2.48)	0.82
Naproxen									
High dose (> 750 mg/day)	12	68	4.58 (2.36 - 8.91)	3.14 (1.49 - 6.62)	7	97	5.23 (2.33 - 11.74)	4.57 (1.95 - 10.71)	0.49
Low dose (≤ 750 mg/day)	10	152	1.75 (0.88 - 3.47)	127 (0.59 - 2.75)	6	161	2.95 (1.25 - 6.97)	2.72 (1.10 - 6.75)	0.18

*Timing of NSAID-exposure was defined by seven mutually exclusive categories (see Table 3.1)

†Adjusted for all covariates listed in Table 3.2, except for renovascular disease

‡Reference category

Table 4.13 Interaction of nephrotoxic drugs with NSAIDs: Risk of acute renal failure in current users of NSAIDs, based on 3 exposure-time categories.

*Exposure-time category**	Nephrotoxic drugs				No nephrotoxic drugs				p-value for interaction
	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	
Unexposed‡	819	11,322	1.00	1.00	311	13,244	1.00	1.00	
Current use	863	9,476	1.35 (1.21 - 1.50)	1.27 (1.13 - 1.42)	231	6734	1.46 (1.24 - 1.72)	1.25 (1.06 - 1.49)	0.92

*Timing of NSAID-exposure was defined by three mutually exclusive categories (see Chapter 4.1)

†Adjusted for all covariates listed in Table 3.2, except for renovascular disease

‡Reference category

Table 4.14 Interaction of nephrotoxic drugs with NSAIDs: Risk of acute renal failure in current users of NSAIDs, by drug.

*Exposure-time category**	Exposure to nephrotoxic drugs				No exposure to nephrotoxic drugs				p-value for interaction
	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	
Unexposed‡	819	11,322	1.00	1.00	311	13,244	1.00	1.00	
Current use									
Conventional NSAIDs	67	779	1.31 (1.00 - 1.72)	1.35 (1.01 - 1.81)	24	695	1.52 (0.99 - 2.32)	1.28 (0.82 - 2.00)	0.84
Rofecoxib	375	3,294	1.71 (1.50 - 1.96)	1.63 (1.40 - 1.88)	95	2440	1.69 (1.35 - 2.12)	1.46 (1.15 - 1.85)	0.40
Celecoxib	345	4,917	1.03 (0.90 - 1.18)	0.97 (0.84 - 1.13)	89	3205	1.18 (0.94 - 1.49)	1.03 (0.81 - 1.31)	0.69
Naproxen	45	263	2.63 (1.88 – 3.67)	1.78 (1.22 - 2.59)	14	236	2.67 (1.53 - 4.66)	1.88 (1.04 - 3.43)	0.87
Meloxicam	8	134	0.87 (0.43 - 1.79)	0.92 (0.43 - 1.94)	2	95	0.87 (0.21 - 3.55)	0.80 (0.19 - 3.33)	0.87
NSAIDs from > 1 Category	23	89	3.76 (2.36 - 5.99)	3.00 (1.79 - 5.05)	7	63	4.58 (2.09 - 10.07)	3.31 (1.46 - 7.52)	0.84

*Timing of NSAID-exposure was defined by three mutually exclusive categories (see Chapter 4.1)

†Adjusted for all covariates listed in Table 3.2, except for renovascular disease

‡Reference category

Table 4.15 Interaction of nephrotoxic drugs with NSAIDs: Risk of acute renal failure in current users of NSAIDs, by dose.

*Exposure-time category**	Exposure to nephrotoxic drugs				No exposure to nephrotoxic drugs				p-value for interaction
	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	Cases	Controls	Unadjusted rate ratio (95%CI)	Adjusted rate ratio† (95%CI)	
Unexposed‡	819	11,322	1.00	1.00	311	13,244	1.00	1.00	
Current use									
Rofecoxib									
High dose (> 25 mg/day)	33	170	2.92 (1.99 - 4.28)	2.63 (1.73 - 4.02)	8	149	2.37 (1.15 - 4.86)	1.88 (0.89 - 3.98)	0.44
Low dose (≤ 25 mg/day)	342	3,124	1.64 (1.43 - 1.89)	1.57 (1.35 - 1.83)	87	2,291	1.64 (1.30 - 2.08)	1.43 (1.12 - 1.83)	0.49
Celecoxib									
High dose (> 200 mg/day)	101	1,223	1.19 (0.96 - 1.48)	1.12 (0.89 - 141)	38	811	1.95 (1.39 - 2.74)	1.53 (1.07 - 2.19)	0.13
Low dose (≤ 200 mg/day)	244	3,694	0.97 (0.83 - 1.13)	0.92 (0.78 - 1.08)	51	2,394	0.91 (0.67 - 1.22)	0.83 (0.61 - 1.12)	0.51
Naproxen									
High dose (> 750 mg/day)	22	89	3.71 (2.29 - 6.01)	2.30 (1.34 - 3.97)	6	81	3.38 (1.46 - 7.83)	2.48 (1.02 - 6.00)	0.89
Low dose (≤ 750 mg/day)	23	174	2.05 (1.31 - 3.21)	1.46 (0.88 - 2.43)	8	155	2.30 (1.11 - 4.75)	1.58 (0.72 - 3.45)	0.87

*Timing of NSAID-exposure was defined by three mutually exclusive categories (see Chapter 4.1)

†Adjusted for all covariates listed in Table 3.2, except for renovascular disease

‡Reference category

Chapter 5

5 Discussion

In this section, the analyses presented in Chapter 4 will be discussed. For a discussion of other aspects of the study, see Chapters 3.2.5 and 3.3.

5.1 Association of NSAIDs with acute renal failure based on two different NSAID-exposure definitions

When NSAID-use was defined based on three mutually exclusive exposure categories (see Chapter 4.1) the association of NSAIDs with acute renal failure, as reported in Chapter 3, was confirmed. This exposure definition reveals an average treatment risk, because the duration of use is less well accounted for in contrast to the exposure defined by seven mutually exclusive categories. Consequently and in accordance with the results presented in Chapter 3, which indicate that the risk of acute renal failure in association with exposure to NSAIDs recedes with increasing treatment duration, the associations observed in Chapter 4.1 for all NSAID-categories are weaker. In particular, the statistical significance of the association of high-dose celecoxib with acute renal failure is marginal. This could be due to a lower risk as well as a longer average duration of celecoxib use in comparison to other NSAIDs. Based on the findings from Chapter 3, probably both have contributed to the observed result for celecoxib. An association of meloxicam with acute renal failure was not observed with both exposure definitions. However, it cannot be excluded with certainty, because the power for its detection was limited by the low number of users. Both exposure definitions also led to the observation that past use of NSAIDs is protective. As argued earlier (see Chapter 3.2) this might be due to a depletion of patients susceptible to the adverse effects of NSAIDs from the group of NSAID-users. However, the observed effect is comparatively strong, suggesting there might be other contributing causes. Interestingly, in a previous study, a comparable observation was made in NSAID-users, whose last prescription ended between 30 and 365 days before the index date (OR = 0.87 (95% CI 0.74 – 1.01)[1].

The same exposure definition (three categories) was employed in a related study[2]. In comparison to myocardial infarction, the outcome of interest there, the association of

current use of rofecoxib with acute renal failure is stronger and a risk for conventional NSAIDs is demonstrated here.

Based on both exposure definitions, conventional NSAIDs, rofecoxib, naproxen and high-dose celecoxib were shown to be associated with acute renal failure. Moreover, higher doses of rofecoxib, celecoxib as well as naproxen pose a greater risk for acute renal failure.

5.2 Interaction of aspirin with NSAIDs

A potential modifying effect of aspirin on the association of NSAIDs with acute renal failure was shown for rofecoxib, indicating a higher risk for individuals who used both drugs. In previous population-based studies an association of aspirin use with acute renal failure was weak[1,3], which is in accordance with this study (see Table 3.2), or was not found[4,5]. The interaction of aspirin with other NSAIDs was not assessed in these studies.

Apparently, the observed interaction was mainly based on users of low dose rofecoxib, who formed the majority of individuals in the category of rofecoxib users. However, this result was only obtained when the exposure definition based on three categories was used (see Chapter 4.2). This could mean that the duration of rofecoxib use determines whether aspirin is harmful or not in these patients. Unfortunately, the small numbers of *current and recent users* as well as *current and past users* and *current continuous users* precluded meaningful results from stratification by individual drugs in order to elucidate the association over time. Moreover, in *current continuous users*, globally, a trend toward a protective effect of aspirin use was observed, thus it is unlikely that the findings for rofecoxib would be confirmed. Additionally and importantly, the number of *current new users* of rofecoxib (see Table 4.5), is much smaller than the number of *current users* of rofecoxib (see Table 4.8). The definition of aspirin use employed here does not consider dose or duration of use. Thus, aspirin use could have differed systematically in users of different NSAIDs. For instance, users of COX-2 selective NSAIDs might have been prescribed higher doses of aspirin. Finally, the investigation of the interaction of

Aspirin and NSAIDs involved performing multiple statistical tests, therefore the role of chance in detecting an association between rofecoxib and aspirin cannot completely be discounted.

These findings suggest the possibility that aspirin might modify the association of rofecoxib-use with acute renal failure, but the evidence from this study is not very firm.

5.3 *Interaction of nephrotoxic drugs with NSAIDs*

Although in this study, use of nephrotoxic drugs was found to represent a strong independent risk factor for acute renal failure (see Table 3.2), for NSAIDs other than celecoxib, no interaction with nephrotoxic drugs was observed in this study. For current new users of high-dose celecoxib, however, the risk of acute renal failure was lower in concurrent users of nephrotoxic drugs. This finding is surprising and inconsistent with a previous study[1], as well as the fact that in general concomitant drug use leads to a higher risk of adverse events, e.g. caused by pharmacokinetic drug interactions. With celecoxib, that *in vitro* is metabolised by the isoform 2C9 of the enzyme Cytochrom P 450 (CYP) and inhibits CYP 2D6, such interactions are likely[6]. Moreover, the modifying effect of nephrotoxic drug use for celecoxib was not found when exposure was defined by three instead of seven categories. This indicates that an interaction occurs when treatment with celecoxib is initiated. However, the detection of this interaction involved numerous statistical tests, thus, the possibility that it was found by chance has to be considered as well.

Because the renal risk of celecoxib was also lower than for other NSAIDs in this study, celecoxib appears to be an NSAID with properties that are different from others and that await elucidation. The reason why an interaction of celecoxib with nephrotoxic drugs was observed here, is therefore unclear, and can hardly be supported by current knowledge.

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Chapter 6

6 Conclusion

In this thesis, the association of NSAIDs with acute renal failure was assessed. Congruent with previous population-based studies and experimental findings, conventional NSAIDs were shown to be associated with acute renal failure. In comparison to previous studies, here, for the first time, analyses included the COX-2 inhibitors. Two specific agents were investigated: Celecoxib and rofecoxib. A third agent, meloxicam, was only infrequently prescribed and could not be thoroughly investigated. The magnitude of the association with acute renal failure within 30 days of initiation of therapy was comparable for rofecoxib, naproxen and non-selective, non-naproxen NSAIDs, but lower for celecoxib. The association was found to be strongest shortly after treatment initiation and receded thereafter. In addition, the time-and dose dependent nature of the NSAID-associated renal risk was demonstrated, the latter was confirmed when a different exposure definition was employed. The modifying effect of aspirin use and exposure to nephrotoxic drugs could not be conclusively determined.

Based on the large number of cases, in particular in comparison to the number of myocardial infarctions that occurred in the same cohort during the same period of time, it appears that the acute renal toxicity of NSAIDs is a safety concern that has received insufficient attention so far, in particular in the elderly, who were not represented in the randomized clinical trials that lead to the approval of the COX-2 inhibitors. Moreover renal toxicity might evolve to become an additional criterion to guide regulatory decisions on the fate of the COX-2 inhibitors, in particular whether to revise approved daily doses or to tolerate a renewed marketing of rofecoxib at all.

These findings have to be confirmed by other investigations, e.g. analyses of other databases or large clinical trials. Further experimental studies could provide more insight into possible mechanisms responsible for the nephrotoxic potential of the COX-2 inhibitors as well as for the differences observed between the two individual agents that were considered here.

Appendices

Appendix 1: NSAIDs included in the Quebec formulary during the study period

Classification of NSAIDs (Mechanism of action)	**Therapeutic compound**
Aspirin (Irreversible, non-specific COX-1 and COX-2 inhibitors)	Acetylsalicylic acid (Aspirin)
Conventional NSAIDs (Reversible, non-specific COX-1 and COX-2 inhibitors)	Diclofenac Diclofenac / misoprostol Diflunisal Etodolac Fenoprofen Flurbiprofen Ibuprofen Indomethacin Ketoprofen Mefenamic acid Nabumetone Naproxen Phenylbutazone Piroxicam Salsalate Sulindac Tenoxicam Tiaprofenic acid Tolmetin
COX-2 selective NSAIDs (Reversible, specific COX-2 inhibitors)	Meloxicam[1] Celecoxib[2] Rofecoxib[3]

[1]Included in formulary in April 2001
[2]Included in formulary in October 1999
[3]Included in formulary in April 2000

Appendix 2: Ethics Approval Comission d'accès á l'information

Commission d'accès à l'information du Québec

Siège social
575, rue St-Amable, bureau 1.10
Québec (Québec) G1R 2G4
Téléphone: (418) 528-7741
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Québec, le 10 novembre 2004

Monsieur James Brophy
Centre universitaire de santé de McGill
(Hôpital Royal Victoria)
687, avenue des Pins Ouest
Ross Pavillon 4.12
Montréal (Québec) H3A 1A1

N/Réf. : 04 11 14 (03 02 55)

Monsieur,

Le 4 mars 2003, vous avez obtenu de la Commission une autorisation (dossier 03 02 55), pour votre étude sur l'innocuité d'une nouvelle classe de médicaments anti-inflammatoires, les inhibiteurs de la cyclooxygenase-2 (COX-2) chez les personnes âgées, à recevoir communication de renseignements nominatifs détenus par la Régie de l'assurance maladie du Québec (RAMQ) et le ministère de la Santé et des Services sociaux (MSSS).

Vous désirez ajouter un projet à votre programme de recherche. En conséquence, vous nous avez transmis une demande d'autorisation de revoir les mêmes renseignements pour ce nouveau projet dont l'objectif est de quantifier le risque d'insuffisance rénale aiguë en association avec les inhibiteurs spécifiques de la COX-2, comparativement aux AAINS conventionnels. Vous désirez également déterminer le risque rénal des agents considérés individuellement ainsi que vérifier si le risque d'insuffisance rénale aiguë dépend de la dose cumulative et si l'aspirine modifie ce risque.

Après étude de cette demande et conformément à l'article 125 de la *Loi sur l'accès aux documents des organismes publics et sur la protection des renseignements personnels*, nous vous autorisons à recevoir de la RAMQ, du MSSS et de l'Institut de la statistique du Québec (ISQ), à titre de mandataire du MSSS, les même renseignements nominatifs que ceux déjà reçus dans le cadre du dossier 03 02 55 et qui sont reproduits pour référence en annexe.

Cette autorisation est cependant assortie des conditions suivantes que vous devez respecter :

Appendix 3: Ethics Approval Faculty of Medicine of McGill University Institutional Review board

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