Exposure characterization and risk assessment in pharmacoepidemiology: Non-steroidal anti-inflammatory drugs and gastro-intestinal bleeding

by

Yola MORIDE

Dept. Epidemiology and Biostatistics
McGill University, Montreal

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Yola Moride Ph.D. thesis

Dept. Epidemiology and Biostatistics
McGill University, Montreal

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STATEMENT OF ORIGINALITY

The primary goal of this thesis was to link the risk of upper gastro-intestinal bleeding to antecedent use of non-steroidal anti-inflammatory drugs (NSAIDs). The data for this study are those of the RAMQ, the prescription drug database of the Quebec government. In this study, novel hypotheses on the duration of antecedent use and both risk factors for bleeding and protective factors for bleeding were evaluated. The originality of the thesis does not only reside in its methodological contributions to pharmacoepidemiologic research but also in the uniqueness of its data sources.

This thesis was the first to provide a comprehensive assessment of exposure characterization in pharmacoepidemiology by identifying patterns of drug utilization, quantifying them, and evaluating their impact in risk assessment. The analyses appraise the role of duration and recency of NSAID use allowing for the assessment of past experience with the drug as an independent risk factor of adverse event. Although previous studies on patterns of drug use described the "switching" phenomenon, they did not assess its relationship to an outcome. In addition, the methodology to include these patterns in a protocol for data analysis had to be developed. The use of patterns of drug exposure in the framework of risk assessment was unprecedented. Furthermore, the multi-dimensional nature of exposure to drugs was also considered. This study was the first to address simultaneously several of its

components in risk assessment, namely: past experience with the drug, patterns of drug utilization, concomitant medications. Furthermore, this study was the first to document the effect of past history of gastropathy on prescribing behaviours for NSAIDs and protective agents.

This study was the first to use, for pharmacoepidemiologic purposes, the Quebec prescription database, the largest available to date on the elderly population (700,000). The feasibility of linking the Med-Echo hospital discharge database to the RAMQ databases was also demonstrated. The complex methodology for the linkage was designed and is documented.

This study was the first pharmacoepidemiologic study to use "hard" data collected over a long term (3 years). In addition, it was the first to exploit the strengths of two sources of data: automated databases and patients medical charts. Hard data on drug exposure were obtained from the database and patients charts were reviewed to validate the diagnosis and collect information on concomitant variables.

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Abstract

Exposure to drugs is a complex phenomenon. A method to characterize long term patterns of drug use amenable to analysis in the framework of risk assessment was developed. The impact of patterns was assessed with the effect of non-steroidal anti-inflammatory drugs (NSAIDs) on upper gastro-intestinal bleeding (UGIB). A hospital based case-control study was conducted (244 cases age 68 and over, 615 matched controls). Objective data on all medications dispensed during the three years preceding admission were obtained from the Quebec prescription database. Patterns were expressed in terms of recency, duration and switches. Past use of NSAIDs was associated with a lower risk of UGIB. The risk decreased as the duration of use increased. Patients who switched products were at greater risk. Concomitant use of protective agents, history of gastropathy and current smoking increased the risk significantly. Patterns of drug utilization should therefore be considered to identify groups at high risk for an adverse event.

Caractérisation de l'exposition et évaluation de risque en pharmacoépidémiologie: Anti-inflammatoires non-stéroidiens et hémorragies digestives

Résumé

L'exposition aux médicaments est un phénomène complexe. Une méthode de caractérisation des profils d'utilisation a été développée afin d'être utilisée dans l'évaluation de risque. L'impact de ces profils a été évalué avec les anti-inflammatoires non-stéroïdiens (AINS) et les hémorragies digestives (HD). Une étude cas-témoin en milieu hospitalier a été réalisée (244 cas âgés de 68 ans et plus, 615 témoins appariés). Des données objectives sur tous les médicaments dispensés durant les 3 ans précédant l'hospitalisation ont été obtenues à partir de la base de données de prescriptions du Québec. Les profils ont été mesurés en termes de délai, durée et transfert. L'utilisation antérieure d'AINS est associée à un risque plus faible d'HD. Ce risque diminue avec une augmentation de la durée d'exposition. Les patients ayant changé de produits ont un risque plus élevé. L'utilisation associée de protecteurs gastriques, un antécédent de gastropathie et le tabagisme augmentent de façon significative le risque. Les profils d'utilisation des médicaments devraient donc être pris en compte dans l'identification des groupes à risque d'événement indésirable.

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SCOPE AND CONCEPTUAL FRAMEWORK

1.1 INTRODUCTION

Unlike many risk factors for a health event, exposure to drugs is heterogeneous. Patients may use a drug only once, intermittently or continuously. A drug may be a risk factor for an adverse event (AE) as well as a marker for the presence of a disease. Although pharmacoepidemiologic studies are mainly non-experimental, exposure conditions are not truly "uncontrolled" as the prescription of the drug is determined by the prescriber based on certain patient characteristics. Exposure is intentional and occurs in populations of individuals who are already sick. As a result, the complexity and variation in drug use cannot solely be expressed as a dichotomous (exposed/unexposed) variable. Rather, drug exposure is characterized by patterns of use over time. Furthermore, adding to the complexity, patients often use more than one drug concomitantly.

In the context of risk assessment, the problem is further complicated if the interest resides in the comparison of individual drugs with respect to the risk of AE. Differences between patients in baseline susceptibility or disease severity may bias observed differences in toxicity between drugs. Some patients may switch to a drug because of intolerance to another, or some drugs may be

preferentially prescribed to sicker patients. These features, specific to pharmacoepidemiology (PE), generated methodological issues, some of which addressed in the literature.

The availability of automated databases that include information on drugs dispensed to well defined populations has increased the feasibility of conducting analytic studies in non-experimental settings. Although controversies exist regarding the use of these databases in risk assessment, they do provide longitudinal data on drug exposure on a long term basis. This feature provides the empirical base to characterize patterns of drug utilization over time. Patterns of drug utilization have recently been described using data from automated databases but their impact in risk assessment remains to be determined. At present, it is not known whether patterns should be considered to identify patients at high risk for an AE. This issue is central to the scope of this thesis.

It is now well recognized that the use of non-steroidal anti-inflammatory drugs (NSAIDs) increases the risk of gastropathy. Several epidemiologic studies have been published on this issue. Although most results favour a positive association, the magnitude varies greatly between studies. Such an uncertainty justifies the need to identify subgroups of patients at high risk. NSAIDs are widely used in the population for various indications and thus, exhibit variable patterns of utilization. It has been suggested that part of the difference observed between the various studies

could be due to the different types of exposure that were actually considered (van Staa et al., 1991). However, this hypothesis remains to be verified. NSAID-gastrotoxicity therefore provides an appropriate empirical setting to evaluate the impact of patterns of drug utilization in risk assessment. NSAID use is the greatest in the elderly population. This population is also at highest risk for side effects. Interest should therefore focus on this high risk population. Yet, very few studies on NSAID-gastropathy were conducted in the elderly population.

1.2 MAIN OBJECTIVE

The main objective of the thesis is to evaluate the impact of patterns of drug utilization in non-experimental risk assessment.

1.3 METHODOLOGICAL PROBLEMS IN PHARMACOEPIDEMIOLOGY

1.3.1 Exposure characterization

In epidemiology "individuals are considered exposed if they have been exposed to a supposed cause of disease or if they possess a characteristic that is a determinant for the health outcome of interest" (Last, 1983). In pharmacoepidemiology (PE), the determinant of interest is a drug. More specifically, it refers to

its ingestion or administration. According to the definition cited above, exposure is either an event that occurred in the past (eg. asbestos) or, is a characteristic that remains unchanged over time (eg. gender). In PE, exposure is intermediate between these two extremes and varies between individuals. Exposure to drugs is a complex phenomenon: over time, individuals may start and stop the drug several times and the duration of each episode may vary.

The multi-dimensional nature of exposure may affect the assessment of the risk of adverse events (AE) in non-experimental settings as it increases the complexity of the relationship between exposure and outcome. However, the dimensions remain to be identified and methods of characterization need to be developed. These are addressed in this thesis.

Patients not only start and stop treatment but they may also switch between drugs, doses and modes of administration. Among potential reasons for switching are indication, lack of efficacy, intolerance, marketing pressure and cost. So far, three studies have been published on the description of patterns of drug utilization over time (Leufkens et al., 1990; Abenhaim et al., 1991; Walker et al. 1992). Incidentally, they all involve NSAIDs.

In the Leufkens et al. (1990) study, patterns of NSAID utilization were described in an open population. Individuals who received at least one NSAID prescription in 1987 were followed prospectively

over the year. Patterns were described in terms of total duration of use during the year and switches between products, dosages and modes of administration. The objective of this study was to describe the population of users in order to identify groups of patients at high risk for an AE.

Abenhaim et al. (1991) conducted a study to identify the predictors of switching between the various NSAIDs. Among the independent variables examined were: demographic characteristics, length of the prescription, concomitant use of protective agents and history of switches. Thus in this study, the switch was the outcome of interest.

A methodology has been proposed by Walker et al. (1992) to study switching from one product to another for the purpose of comparing toxicity between products. This study was cross-sectional and patients were not followed for any length of time. The unit of analysis was the drug. Because survival on each drug was not considered on a long term basis for each individual, switches were treated as independent variables (i.e. no distinction was made between several switches occurring in the same individual and one switch in several individuals). The objective of this study was to describe the selection process of patients receiving therapy and to document the reasons for switching. In this study, 32.7% of the switches between NSAIDs were for a lack of efficacy.

Because the study of patterns of drug utilization is very recent, published studies remain descriptive and the effect of patterns on a health outcome has not yet been determined. So far, this concept has not been applied in the framework of risk assessment. It is studied in this thesis.

1.3.2 Sources of biases in the assessment of the risk associated with drug use

History of exposure to the drug: It has been proposed that past use of the drug may be a risk modifier for current exposure (Miettinen and Caro, 1989). The risk of experiencing an AE may not be the same for a patient who has taken the drug before as for a first-time user. Presumably, past occurrence of symptoms of the AE constitutes a contra-indication for current exposure. Therefore, the population of exposed and unexposed patients may differ with respect to their baseline risk of AE due to their experience with the drug. Furthermore, methods to characterize past exposure have been inadequately described. This concept, which has not yet been studied empirically, is addressed in this thesis.

Channeling: The population of users may be heterogeneous with respect to baseline susceptibility for the AE. As a result, it is important to identify high risk groups. The selection of one drug over another is not a random process. It is the outcome of a

decision-making process based on several factors, one of which being susceptibility. This selective process has been referred to as "channeling" (Petri and Urquhart, 1991). Empirical evidence of the channeling phenomenon has been provided by Petri et al. (1991) with beta-2 agonists prescribed for the treatment of asthma. The populations of patients on each drug differed with respect to asthma severity. As a result, a higher risk of AE may wrongly be attributed to a given drug when in fact, the population of users of that drug was more susceptible to the event. History or concomitant drug use may be used as markers of disease severity. Findings from this study showed that drug history of each patient should be taken into account in the comparison of toxicity between drugs.

Protopathic bias: Exposure to a drug may be a determinant for an AE and it may also be a marker for a disease that this drug intends to treat. When an error is made in the timing between exposure and outcome, it results in a protopathic bias. One may wrongly conclude that a drug is a risk factor for the event when in fact it was prescribed because of the presence of the event. As a result, the assessment of the risk associated with drug exposure should also consider concomitant drugs as they may modify the risk of AE. An example is the concomitant use of gastro-protective agents in the treatment with NSAIDs. Protective agents (H_2 antagonists, antacids, anticholinergics) are prescribed for the treatment of gastropathy. They have been used either as an outcome definition

for gastropathy (Bigelow and Collins, 1987) or as a marker for history of gastropathy (Collier and Pain, 1985; Armstrong and Blower, 1987; Jick et al., 1987). However, the effect of the concomitant use of these drugs on the risk of AE has not been addressed. As a result, the presence of a protopathic bias has not yet been demonstrated. This phenomenon is studied in this thesis.

Indication bias: The International Study on Agranulocytosis and Aplastic Anemia Study has been conducted in order to quantify the risk of agranulocytosis and aplastic anemia associated with the use of analgesics. Published results (International Agranulocytosis and Aplastic Anemia Study, 1986) generated some criticisms that were subsequently raised in the literature (Kramer et al., 1987). It was felt that the indication for the use of analgesics may also be a risk factor for the AE of interest and that the risk should have been assessed conditionally on the patient's clinical characteristics and indications. The assessment of effect modification by these variables would have allowed the identification of high risk groups. According to the critiques, indication is important because it would generate differences in patterns of drug use. Analgesics are prescribed for numerous conditions, ranging from localized pain to rheumatoid diseases. These drugs are therefore used differently for the various indications. Differences between indications in the risk of AE may be attributable to differences in the risk between the treated conditions and/or differences between patterns of use. This

possibility was raised in the critiques but was not demonstrated empirically. Differences in risk between patterns will be examined in this thesis.

1.3.3 The adverse event

The characteristics of an event associated with drug exposure may vary with respect to severity and delay of onset. The problem is further complicated by variations in the risk between subgroups of the population (sex, age...) and between individuals (comorbidity, contra-indications...). The risk of AE is therefore a complex and multi-dimensional domain. The major challenge of pharmacoepidemiologic research is to quantify this risk.

The assessment of the risk associated with drug exposure is a two-stage process that involves: 1) the identification of possible adverse drug reactions and, 2) the quantification of the risk. The first is a major activity in the area of pharmacosurveillance while pharmacoepidemiology focuses on the second. Several methods may be applied to quantify the risk of AE but common to all approaches is the assessment of the risk relative to a reference risk.

The risk associated with exposure to drugs differs according to the framework: it is perceived differently by clinicians, etiologists and public-health practitioners. The different viewpoints and

their methodological implications in risk assessment and selection of risk estimators have been described by Abenhaim and Moride (1992).

1.3.4 Risk measures

Adverse events occur in various patterns depending on the type of drug and event under study. Examples of timing of the event are shown in figure 1.1. For each situation, risk assessment involves: 1) the selection of an appropriate measure to quantify the risk of the event and, 2) the comparison of the risk in the exposed with that in a reference population.

Several measures may be used to quantify the risk. These have been described extensively by O'Neill (1988) and their applications in the framework of drug-induced illnesses were discussed. The measures were: crude risk, occurrence per unit time exposure, life table and hazard rates. The hazard rate may increase, decrease, remain constant, or have complex patterns while the crude risk and the occurrence per unit time assume that the AE follows a constant hazard rate for the period of time considered.

The selection of the risk measure is dependent on the type of exposure and the delay of onset of the event. Miettinen and Caro (1989) added to this the type of persons potentially exposed. The

following table summarizes the most appropriate measure to be used for several patterns of occurrence:

Duration of Exposure	Delay of onset	Hazard function	Risk measure
Short or Constant	Short	Peak at the beginning	Crude risk
Constant	Short	Constant	Occurrence per Unit time
Variable	Short or long	No assumption	Life table
Variable	Short or long	Variable	Hazard rate

1.3.5 Time window

Given that most AE do not follow a constant hazard the crude risk is not an adequate measure. The concept of incidence density (or hazard rate) is more appropriate to describe the risk (O'Neill, 1988; Miettinen and Caro, 1989). There are 2 major underlying assumptions:

1) The shape of the risk function of exposed and unexposed individuals are identical. In the case of drug-related AE, there is no reason to believe that it is the case. The concepts and methods of analysis have been described in great detail by Miettinen and Caro (1989). According to these authors, when the

hazard functions are not proportional, the relative risk could be obtained for various time intervals following the start of therapy,

2) In the context of non-experimental risk assessment, it is assumed that early stages of the AE do not lead to changes in the exposure. Quantitatively, incidence density assumes that subjects who withdraw from treatment would have exhibited the same event rate as the noncensored subjects had they not been censored. According to this, censoring is not related to the effects of the drug. This assumption is likely to be violated in the context of drug-induced illnesses given that patients may interrupt treatment because of early symptoms of the AE. These patients would select themselves out of the population at risk. Alternatively, they may switch between drugs or use concomitant therapy. This process has not been adequately studied. The effect of this selection process on the risk is addressed in this thesis.

As stated by Miettinen and Caro (1989), history of exposure to the drug is important to take into account because it affects the shape of the hazard function. The incidence density might initially increase with duration of exposure. Then, there may be a point beyond which a selection process operates. Individuals susceptible to the event have already experienced symptoms (not the event under study) and select themselves out of the population at risk before becoming a case. As a result, the slope of the risk function becomes negative. It is therefore critical to define the time

associated with the highest risk (in other words, the section of the risk function where the slope is positive). These concepts have been described theoretically and specifically for cohort studies. Given that their application in case-control studies has not been addressed, they constitute the framework of this thesis.

The time window is the time during which an individual is considered exposed. Although cohort and case-control studies are conceptually the same (Rothman, 1986), they differ with respect to the operational definitions of the time window found in the literature. The contrasts that are discussed below are based on operational considerations rather than design issues. In published cohort studies, the width is defined in relation to the start of treatment. It is often fixed and corresponds to a predefined number of days following the initiation of therapy. In the case of NSAIDs, van Staa et al. (1992) found that the predefined time window is often too wide relative to the length of the prescription. As a result, exposure is over-estimated. This study showed that it results in an under-estimation of the effect.

In published case-control studies, an individual is considered exposed if he(she) used the drug within a predefined number of days preceding the event. In contrast to cohort studies, the time window is selected in relation to the outcome and does not consider time since initiation of treatment because drug exposure preceding the event is usually not available on a long term basis. The time

window is defined according to what is known about the idiosyncratic mechanism of the AE. The most likely delay of onset is determined and a fixed time window selected. As a result, on the day of the event the patient may still be on the drug or may have discontinued it. Relative to a time window defined in relation to the initiation of treatment (published cohort studies), the time window defined in relation to the event (published case-control studies) would result in an over-estimation of exposure. This could explain in part the discrepancy in the estimates of relative risks found in the literature.

In summary, several concepts must be taken into account to assess the risk associated with drug exposure. Some of them have been addressed theoretically but all remain inadequately studied. These are listed below:

1) The shape of the hazard function in order to determine the appropriate time window for the assessment of the risk,

2) The duration of exposure to control or describe differences in baseline risk,

3) The selection process (termination of treatment or switching therapy) due to early signs of the AE,

4) The effect of co-medications on the risk of AE.

So far, some of these concepts have mainly been discussed in the context of clinical trials (O'Neill, 1988) or cohort study settings (Miettinen and Caro, 1989) where the study population is followed over time. The practical implication in case-control studies has not yet been addressed. Furthermore, they have only been considered theoretically and not empirically.

These issues have not been adequately addressed in empirical settings, especially with the case-control design, largely because of the three following limitations:

1) The shape of the hazard function is not always known. Case-control studies can be conceptualized as an efficient follow-up study where cases and controls are sampled (Rothman, 1986). However, in practice, this design is not amenable to describe the hazard function, likely to be non-proportional between exposed and unexposed, because there is no information on the patients lost to follow-up.

2) Because previous experience with the drug may have an effect on the risk, cases and controls may differ with respect to susceptibility. Intuitively, it may be that controls are no longer representative of the population that generated the cases given that they would include more non-susceptible individuals as well as

those who selected themselves out of the population at risk before developing the event. Cases, on the other hand, would include the most susceptible individuals.

3) Duration of drug use cannot be used as a marker for indication given that it is expressed in relation to an outcome and not to initiation of treatment. The implication is that duration subgroups are heterogeneous with respect to indication. For example, short-time users include patients who only require the drug for a short time as well as those whose indication is supposed to be chronic but they developed the event under study early in the course of the treatment.

In this thesis will be developed methods to identify high risk groups with respect to susceptibility to AE even in the absence of a hazard function (especially using the case-control design) and to quantify the selection bias attributable to susceptibility. Ultimately, conclusions regarding the impact of these methods in risk assessment will be made.

1.4 SOURCES OF DATA ON DRUG USE

Three major sources of data on drug use can be identified: 1) market surveys, 2) third-party automated databases, 3) institutional and ambulatory databases. These sources have been

described by Melnychuk et al. (in press). A summary of the strengths and weaknesses of each of these sources is found in table 1.1. Databases are only useful for analytic research if information on drug exposure can be linked to an outcome or a marker of it.

To these sources can be added information on drug use obtained by questionnaire to the patients. These are usually collected in the course of a specific epidemiologic study. Overall, the major sources of data used in current pharmacoepidemiologic research are third-party databases and patient interviews. Studies relying on patient interviews usually consider consumption as exposure while those relying on automated databases consider dispensing, a marker for consumption. Individually, none of these sources are comprehensive.

The use of third-party databases in pharmacoepidemiologic research has been criticized by Shapiro (1989). The main areas of criticism were:

1) Lack of information on potential confounders (such as indication, smoking, alcohol consumption and over-the-counter drug use),

2) No validation of the outcome which can only be achieved by chart review,

3) Accurate information on duration and timing (time between exposure and event) can only be obtained from the patient.

From this paper was initiated a debate in the literature (Faich and Stadel, 1989; Strom and Carson, 1989; Jick and Walker, 1989; Tilson, 1989). The responses to the criticisms may be summarized as follows:

1) It has not been documented that patient interviews are more appropriate to ascertain exposure to drugs (Faich and Stadel; Strom). A poor agreement between actual medication use and that ascertained by interviews was reported. Moreover, interviews are subject to recall bias (Strom),

2) Epidemiologic studies based on interviews are not likely to provide answers in a timely and cost-effective fashion (Faich and Stadel),

3) In the current settings, studies based on automated databases have access to medical records and thus, the diagnosis can be validated (Strom).

The major response to Shapiro was that his criticisms on databases were design issues and not inherent to the databases themselves.

It is true that some information on potential confounders (such as

smoking and alcohol consumption) cannot be obtained from automated databases. However, a strategy has been developed in an attempt to minimize the problem (Ray et al., 1989; Griffin et al., 1991). In studies where the diagnosis of cases is validated by chart review, information on potential confounders also available in the charts may be ascertained at the same time. The underlying hypothesis is that if there is no association between the potential confounder and exposure among the cases, then there is no association in the controls. This assumption allows to rule out confounding but not to assess effect modification.

Other important methodological issues have never been addressed in the debate and could be central to risk assessment:

1) It is feasible with databases to ascertain the study population on the basis of exposure and achieve a follow-up over time. If exposure data are linked to an outcome, then these offer the opportunity to describe empirically the hazard function of the AE following initiation of drug therapy. This would allow to define the most appropriate time window to estimate the risk,

2) An important feature of automated databases is the availability of longitudinal hard data on drug exposure for each individual. As such, it is possible to derive the various utilization patterns of drug use in terms of discontinuation (selection out of the population at risk), switches between products and co-

prescriptions.

So far, no published studies have used these features in the framework of risk assessment. In conclusion, the criticisms of automated databases have been more on design issues which are independent of the data source itself. Well designed studies based on automated databases can be found in the literature. The major caveat is that so far, pharmacoepidemiologic studies, in the most part, have not taken advantage of one of the major strength of automated databases: the availability of hard and longitudinal data on drug use.

1.5 THE PROBLEM OF NON-STEROIDAL ANTI-INFLAMMATORY DRUG USE AND GASTROPATHY

Some of the concepts and methodological problems specific to pharmacoepidemiology have been presented in the sections above. In order to gain empirical content, these will be applied to the problem of NSAIDs and gastropathy. This problem was specifically chosen because it has been widely studied and yet, uncertainties remain regarding the assessment of the risk. Furthermore, the patterns of drug utilization that have been described in the literature apply to NSAIDs. Although a variety of AE are associated with NSAIDs, the majority of published studies are on gastropathy.

It is now well recognized that NSAIDs increase the risk of upper gastro-intestinal bleeding (UGIB). However, there is a large variation in the estimates of relative risk (RR) published in the literature. Estimates obtained from case-control studies range from 1.1 (Henry et al., 1987) to 7.4 (Holvoet et al., 1991) while those obtained from cohort studies are smaller: 1.2 (Jick et al., 1987) and 1.5 (Carson et al., 1987). Such a large variation motivates the identification of high risk groups. NSAID use and NSAID side effects are the highest in the elderly population. Yet, only a limited number of studies have focused on this high risk population.

Patterns of NSAID use over time have been described empirically in terms of duration and switches between products (Leufkens et al., 1990; Abenhaim et al., 1991; Walker et al., 1992), doses and modes of administration (Leufkens et al., 1990). However, they have not yet been considered in an analytic framework, namely in risk assessment of an AE.

In a cohort study, it was found that the risk of UGIB appears to increase until the fourth prescription and decrease thereafter (Carson et al., 1987). Recently, in case-control studies, the risk of UGIB decreases as the duration of exposure increases (Levy et al., 1988; Griffin et al., 1991). So far, duration of past exposure was assessed only in patients who were currently exposed. As such, chronic users were more likely to be currently exposed

(length-biased sampling). If most cases of UGIB have their onset early in the course of the treatment, chronic users are likely to include mostly tolerant individuals. Consequently, it would bias the measure of the risk towards the null (Kramer et al., 1987). Because in these studies, duration of past exposure was not recorded in the unexposed, it was not possible to distinguish between the effect of current exposure to NSAIDs and the differences in baseline risk between the various duration subgroups. In this thesis, a method to partition both effects is proposed.

Only a limited number of studies have examined the effect of co-medications, such as gastro-protective agents, but none were conducted in the elderly population. Timing of exposure to these drugs and exposure to NSAIDs varied between studies and none have examined their concomitant use.

1.6 RATIONALE

Several methodological issues specific to pharmacoepidemiology have been raised in the literature. Some of them, such as indication and channeling biases, have been addressed empirically. It has been suggested that past experience with the drug of interest or co-prescriptions may have an effect on the risk of AE. However, such effects have not yet been demonstrated. In addition, an

increase in the resolution of the characterization of experience with a drug may be achieved by considering patterns of drug utilization over time. Such patterns have been described prospectively in a limited number of studies but their effect in the assessment of the risk of AE has not been addressed. Because of the lack of data on the long-term use of drugs, a comprehensive assessment of the effect of gastro-protective agents on the risk associated with NSAID use has not yet been obtained. NSAID-gastropathy has been widely studied but a great uncertainty remains concerning the magnitude of the risk and the identification of high risk groups. This study therefore intends to examine the effect of patterns of NSAID utilization on the risk of UGIB. A method to characterize patterns amenable to analysis in the framework of risk assessment is proposed.

A database on prescriptions dispensed to all Quebec elderly residents has been created by the Régie de l'assurance-maladie du Québec (RAMQ). Hard data on prescribed medications is available from the largest dataset extant in the elderly. The use of this database for pharmacoepidemiologic purposes is unprecedented. The variation in the mode of utilization of NSAIDs on a long term basis has not been previously quantified in this population.

1.7 SPECIFIC OBJECTIVES

The specific objectives of the thesis are to:

1) Characterize patterns of drug utilization that are clinically relevant, quantifiable and amenable to risk assessment studies,

2) Develop a database suitable for the quantification and the study of patterns in the province of Quebec,

3) Apply the concept of patterns in a well-studied problem in order to contribute to the comprehension,

4) Provide empirical evidence of the presence of biases described in theory in the literature but not yet demonstrated,

5) Determine if NSAIDs increase the risk of gastropathy in the Quebec elderly population, using a unique data source,

6) Describe the variation in the mode of utilization of NSAIDs in the Quebec elderly population.

TABLE 1.1
Examples of existing prescription drug databases

Data Source	Size	Source Populations	Drug Range	Owner/Accessibility	Comments
Market surveys 1. IMS America Ltd. a) Nat'l prescriptions aid	1400 computerized pharmacies 600 non-computerized	Customers at sampled pharmacies	All prescribed medications, No OTC	Private/Available for cost	- The prescription is the sampling unit - Representative sample - Number of users must be estimated - No information on indication - No information on usage of medical services - Cross-sectional, no history on drugs taken
b) Nat'l disease therapeutic index		Patients of sampled physicians	All out-patients prescriptions No OTC	Private/Available for cost	- The prescription is the sampling unit - Number of users must be estimated - Information on indication
2. Nat'l disease prescriptions card service	839 pharmacies 4 million prescriptions per month	Customers at sampled pharmacies	All out-patient prescriptions No OTC	Private/ Available for cost	- The prescription is the sampling unit - Number of users must be estimated
Third party RAMQ (Quebec)	700,000 elderly	Quebec elderly residents	Drugs included in formulary	Government/On demand with cost	- All Quebec elderly residents - Longitudinal data - Linkage with morbidity databases - No in-patients prescriptions
Saskatchewan	1.1 million people 3.7 million prescriptions accumulated since 1975	Saskatchewan residents	Drugs included in formulary (1600)	Government/On demand with cost	- All Saskatchewan residents - Longitudinal data - Linkage with morbidity and mortality databases - No in-patient prescriptions
COMPASS	10 states approx. 8 million people	Medicaid enrollees	All prescriptions	Government/On demand with cost	- Non uniform populations across states - Skewed population - Loss of follow-up because of eligibility changes

TABLE 1.1 (cont'd)
Examples of existing prescription drug databases

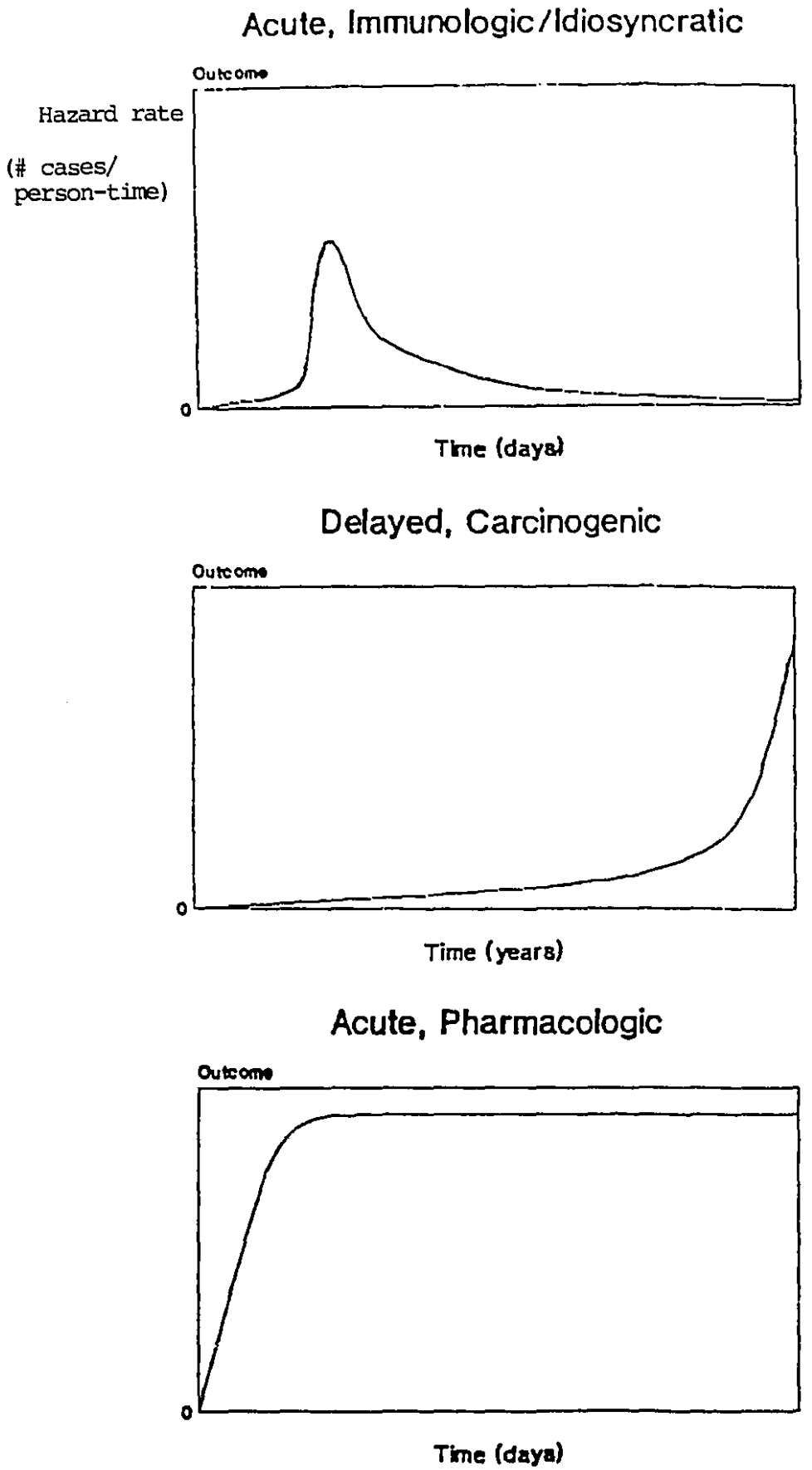
Data Source	Size	Source Populations	Drug Range	Owner/Accessibility	Comments
Hospital based	Variable	Hospital catchment population	In-patient prescriptions	Institution/Collaboration with institution	- Selected population - Selected conditions - Information on indications
Disease-specific ARAMIS	23,000 patients	Patients with rheumatologic conditions followed in 17 centers (U.S.A. and Canada)	All prescriptions Some OTC* but not systematic	American Rheumatism Association	- Prospective and systematic follow-up of patients cohorts - Longitudinal data - Comprehensive follow-up - Laboratory, therapeutic and other quantitative data
HIVIS (Human Immunodeficiency Virus Information System)	3,000 PWA** 500 PWHIV	Maryland residents who are in the HIV registry	All prescriptions	Government	- Longitudinal - Linkage with: vital records, public/private insurance companies, institution/community-based services, Medicaid, Maryland Pharmacy Assistance Programme

*OTC = over-the-counter drugs
** PWA = Persons with AIDS

Source: Melnychuk et al. (in press), reproduced with permission.

FIGURE 1.1

Examples of timing of drug effects



Source: Kramer (1991), reproduced with permission

CHAPTER 2

REVIEW OF THE LITERATURE ON NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND GASTROPATHY

2.1 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Extent of use: NSAIDs are first-line therapy for the treatment of musculoskeletal diseases. They are one of the most commonly used groups of drugs in North America (Swift et al., 1989; Roth, 1989; Fries et al., 1989). In 1987 alone, 10.6 million NSAID prescriptions were written in Canada (Gabriel and Bombardier, 1990). In Quebec, 35% of elderly residents filled at least 1 NSAID prescription in 1988 (Moride and Abenhaim, 1990).

NSAIDs and gastrotoxicity: Despite their efficacy, a number of side-effects are associated with NSAIDs, the most well known being gastropathy. The association is widely recognized and has motivated a strong class labeling specific for chronic use by the Food and Drug Administration (U.S.A.), the Committee on Safety of Medicines (U.K.), the Health Protection Branch (Canada) and the Commission Nationale de Pharmacovigilance (France).

The magnitude of the problem in the U.S. has recently been documented by Fries et al. (1991). The current number of NSAID users is 13 million and the total annual number of GI

hospitalizations in these patients is 76,000 (at a cost of $ 3.8 billion/year). The number of GI deaths ranges from 7,600 to 20,000 deaths per year. NSAID-gastrotoxicity has been referred to by Fries as the "second most deadly rheumatic disease". The wide use of NSAIDs due to the high prevalence of arthritic conditions among the elderly represents a serious public health problem.

Mechanism of toxicity: Two mechanisms of GI toxicity have been proposed: a local irritation and a systemic effect. Aspirin has been known for a long time to act as a mucosal irritant while the effect of non-aspirin NSAIDs (NANSAIDs) appears to be mainly systemic, through the inhibition of prostaglandin synthesis (O'Brien and Brunham, 1985; Cockel, 1987; Doherty, 1989).

2.2 REVIEW OF EPIDEMIOLOGIC EVIDENCE

A plethora of articles have been published on NSAIDs and gastropathy. However, only a limited number focuses on the elderly population. The purpose of this literature review is two-fold. First, it provides an update on the "state-of-the art" on this issue by reviewing the publications most frequently cited in the last 10 years, with the intent to identify the areas in need of further research. Second, the literature was reviewed in order to identify the variables that should be considered in an observational epidemiologic study on NSAID-gastropathy.

A thorough appraisal of the evidence would be lengthy and not directly related to the scope of this thesis. However, it was shown to be necessary to select the relevant covariates as well as to identify some of the deficiencies. A thorough review of the literature with an emphasis on the quantitative evaluation of the evidence can be found in appendix A. In this chapter are summarized the major elements to be considered in the study of NSAIDs in the elderly population. The evidence directly related to the scope of the thesis, i.e. exposure characterization, is described in greater detail.

2.2.1 Association between NSAIDs and gastropathy

It is now well recognized that NSAIDs increase the risk of gastropathy. A review of the estimates of relative risk obtained from various studies was done by Hawkey (1990) and Gabriel et al. (1991). However, the effect NSAIDs is not so well known in the elderly population. As shown in table 2.1, a large variation exists between the estimates of relative risk associated with non-aspirin NSAID use in the elderly published in the literature, ranging from 2.9 (Henry et al., 1991) to 11.54 (Collier and Pain, 1985). The risk associated with ASA in the elderly was quantified in only 1 study (Laporte et al., 1991) and could be computed from data published in another (Levy et al., 1988). Estimates of relative risk were 6.7 and 3.07, respectively. A number of factors

may be responsible for the discrepancy: study design, base population, definition and ascertainment of the outcome, definition and ascertainment of the exposure. Because several factors may contribute simultaneously to the difference, it is not possible to extract the independent effect of each. Studies have been compared with respect to these methodological elements and summary tables may be found in Appendix A. The major elements are discussed below.

2.2.2 Study design

Three designs have been identified among the studies reviewed: case-control, cohort and nested case-control. All studies conducted in the early 1980's were case-control, the majority being hospital-based. At the end of the 1980's, the emergence of automated databases made the conduct of cohort studies feasible.

2.2.3 Gastropathy

Definition: The term "upper gastrointestinal bleeding" is very broad and non-specific. The relative contribution of NSAIDs in the set of sufficient causes may vary according to the pathology considered. The conditions varied with respect to severity, ranging from GI bleeding (Bartle et al., 1986) to life threatening

(Armstrong and Blower, 1987) or fatal peptic ulcer complications (Henry et al., 1987).

Validation: UGIB may be caused by a variety of underlying pathologies, not necessarily a gastropathy. Rupture of oesophageal varices and Mallory-Weiss syndrome are examples of sufficient causes. In order to rule out these other pathologies, diagnostic confirmation procedures have been performed. Gastroscopy appeared to be the method of choice (Clinch et al., 1983; Bartle et al., 1986; Duggan et al., 1986; Guess et al., 1988; Laporte et al., 1991; Griffin et al., 1991; Holvoet et al., 1991). Other methods were surgery, autopsy, radiology and roentgenogram (Collier and Pain, 1985; Guess et al., 1988; Griffin et al., 1991). Some of the studies based on chart review used discharge summaries only, with no other documentation (Henry et al., 1987; Jick et al., 1987; Levy et al., 1988). There was no attempt to confirm the diagnosis in 4 studies (Coggon et al., 1982; Beard et al., 1987; Carson et al., 1987; Beardon et al., 1989). Griffin et al. (1991) reported that 43% of potential cases initially ascertained from discharge diagnoses were eligible after chart review, which emphasizes the importance of diagnosis validation in the study of gastropathy.

Method of ascertainment: In the majority of studies, the outcome was ascertained from admission or discharge diagnoses, which is consistent with the fact that most studies were hospital based. Other methods were billing data for medical services (Carson et

al., 1987; Bigelow and Collins, 1989), or referral to the gastroenterology clinic (Clinch et al., 1983).

Ascertainment from admission diagnoses may be subject to referral bias if NSAID users were more likely to be admitted. Ascertainment from billing data includes non severe events that could be subject to diagnostic bias (i.e., more likely to be diagnosed in NSAID users). On the other hand, it has been documented that NSAID-related ulcers tend to be silent (Hawkey, 1990). If cases of gastropathy are ascertained solely on the basis of gastroscopic findings, detection bias would occur if NSAID users were more likely to undergo gastroscopy, which would lead to the detection of more silent ulcers in exposed patients. As a result, the strength of the association between NSAID use and gastropathy would be biased away from the null.

In principle, studies should therefore be restricted to severe events with the presence of symptoms in order to: 1) minimize referral bias and, 2) minimize the over-representation of silent ulcers in exposed cases. However, the presence of such biases has only been hypothesized and never verified empirically. Moreover, it is necessary to validate the diagnosis in order to rule out bleeding of known etiology (eg. Mallory-Weiss syndrome etc.).

2.2.4 Exposure to NSAIDs

As well, differences in the definition, characterization and ascertainment of exposure to NSAIDs may contribute to the heterogeneity of the measures of association between NSAID use and gastropathy. A comparative table of the various methods of exposure characterization found in the reviewed studies is included in Appendix A.

Definition: There is a fair amount of variation between studies in what is defined as exposure to NSAIDs; the consequence being that an individual who is considered exposed in one study may not be in another. The definition usually includes the following 2 components: 1) inclusion or exclusion of aspirin, 2) the width of the time window.

Based on the difference in the mechanism of GI toxicity (systemic effect versus mucosal irritant), it seems relevant to distinguish between the effect of ASA and NANSAIDs. Some studies have considered NANSAIDs only (Somerville et al., 1986; Beardon et al., 1989; Griffin et al., 1991), while in others, ASA was distinguished from the rest of the NSAIDs (Henry et al., 1987; Laporte et al., 1991; Holvoet et al., 1991).

Exposure quantification: The resolution of exposure quantification varied between studies and can be described in terms of the number of categories of NSAID use. Although the use of individual products has been recorded in several studies (Somerville et al., 1986; Armstrong and Blower, 1987; Beard et al., 1987; Jick et al., 1987; Bigelow and Collins, 1988; Henry et al., 1991), the majority have expressed exposure to NSAIDs as a dichotomous variable (use and non-use) in the analysis.

In some studies, the resolution of exposure was higher by being multicategorical. Categories were created on the basis of the following axes: recency of use (Coggon et al., 1982; Griffin et al., 1991), product combination (Duggan et al., 1986), recency of use and frequency (Levy et al., 1988), mode of action (long- versus short-acting) (Bigelow and Collins, 1989). Other components such as dose (Carson et al., 1987; Bigelow and Collins, 1988; Laporte et al., 1991), route and duration (Armstrong and Blower, 1987; Jick et al., 1987; Griffin et al., 1991) have not been incorporated in the categories but have been considered as covariates in a multivariate analysis.

A greater number of categories allows to better define the risk associated with NSAID use but it also results in a loss of statistical power. The majority of studies that did consider multicategorical exposure had a limited number of study subjects and consequently, reported measures of association with very wide

confidence intervals.

Patterns of use: Exposure was characterized in greater details in 3 studies by considering patterns of NSAID use over time. Patterns have been described for NANSAIDs by Leufkens et al. (1990) and Abenhaim et al. (1991) in a sample of the Dutch population. In former studies, users were distributed as follows: 74.0% incidental (≤ 30 days/year), 21.2% regular (31-210 days/year) and, 4.8% heavy users (>210 days/year). Of patients with more than 1 prescription, 71.1% switched at least once during the year. The most common switch was towards another product (42.2%), followed by dose (36.2%) and considerably less, towards another form of administration (3.5%). Walker et al. (1992) described switches between NANSAIDs, using the prescription as the unit of analysis. It was found that 16% of repeat prescriptions were a switch. There was no association between switches and sex, and switches and indication. On the other hand, switches occurred more often in the young population. Compared to the Leufkens et al. study, an additional condition was imposed: the repeat prescription had to be dispensed within 60 days. This difference may explain in part the observed discrepancy between the 2 studies. Abenhaim et al. (1991) investigated the factors that predicted switching. Among them were previous switches and length of prescription. It was not influenced by age, sex, co-prescriptions and use of protective agents. Switching was also a predictor of future switch and change of physician. So far, patterns have not been adequately described

in the elderly population.

It is important to mention that none of these studies have quantified the effect of patterns of NSAID use on gastropathy. This creates a major deficiency as the relevance of this method of exposure characterization has not yet been investigated in the framework of risk assessment.

Exposure ascertainment: Exposure to NSAIDs has been ascertained from 3 different sources: 1) interview to the patients, 2) chart review and, 3) computerized databases.

Most case-control studies were based on interviews or case notes. For current drug exposure, a 97% agreement between interviews and records has been reported by Laporte et al. (1991). In some studies, the resolution of exposure quantification exceeded the accuracy of the information. For example, details on dose (Laporte et al., 1991) obtained by interview or request for information for up to 6 months (Bartle et al., 1987) are not expected to be as accurate, especially in the elderly population. When community controls were used (Coggon et al., 1982; Somerville et al., 1986), non-comparability of information occurs because of differences in interview settings. Blinding was not specified in any of the studies reviewed, which could result in non-differential misclassification of exposure between cases and controls.

Exposure to NSAIDs has also been ascertained from third-party computerized databases. This source was used in all cohort studies. It provides data that are non-differential between cases and controls but there is no information on over-the-counter (OTC) use of drugs. This source was only used in one study involving the elderly (Griffin et al., 1991).

2.2.5 Risk quantification

Time window: Not one study has described the hazard function of gastropathy related to NSAID use. This deficiency precludes the ability to define accurately a time window for the risk period following the initiation of therapy. At present, the cut-off point is selected semi-intuitively based on the mechanism of action and delay of onset of the events. The various time windows considered in the literature are shown in table 2.2. In case-control studies, the width was selected a priori in relation to the event, ranging from the day of the event to 1 year before. In cohort studies, a maximum was set after the initiation of treatment (usually 30 days) but the width varied within the defined time window according to individual follow-up. Usually, it was the time between the date of NSAID dispensing until the date of the next dispensing, the date of the event, the number of days of treatment prescribed or the maximum (Guess et al., 1988). If a time window of 30 days is indeed too wide according to van Staa et al. (1992), then the majority of

the studies underestimated the effect of NSAID use. Differences in the width of the window may partly explain differences in estimates of relative risk.

An attempt was made to partition the time window in order to find the periods at greater risk by including duration (Carson et al., 1987; Levy et al., 1988; Griffin et al., 1991) and recency (Levy et al., 1988; Griffin et al., 1991).

The risk of gastropathy following exposure to NSAIDs has been expressed as a function of recency, duration, frequency and dose. Each of these dimensions is discussed below.

Recency: Griffin et al. (1991) reported that recent users of NSAIDs (within 30 days of the event) were at greater risk than former users (discontinuation of therapy for more than 60 days before the event): The respective ORs were 4.1 (3.5-4.7) and 1.3 (1.1-1.6). A similar trend was reported for ASA by Levy et al. (1988): 15.0 (6.4-34.0) versus 1.6 (0.6-4.2) if the drug was discontinued for more than 7 days before. These results suggest that the risk function is non proportional for exposed and unexposed individuals, and that the magnitude of the association is greatly diminished after the interruption of treatment.

The results described above clearly indicate that there is a

critical time after discontinuation of the drug when the risk becomes almost non-existent. It is not clear, however, from published data what is the length of time after discontinuation.

Duration response: It has been hypothesized that the risk of gastropathy decreases with an increase in duration of exposure due to the depletion of susceptible patients (Miettinen and Caro, 1989). There may be a point beyond which a selection process operates whereby individuals susceptible to gastropathy have already experienced symptoms (not the event under study) and select themselves out of the population at risk before becoming a case. As a result, the slope of the risk function would become negative. Duration of use has been expressed as a categorical variable in month intervals (Levy et al., 1988), or as number of prescriptions (Carson et al., 1987). Results are somewhat conflicting. The selection process may occur after the first 4 prescriptions (Carson et al., 1987), after 11 months (Levy et al., 1988), or during the first 30 days of therapy (i.e. first prescription) (Griffin et al., 1991). Nevertheless, in all studies the risk was inversely proportional to duration, with the exception of the Holvoet et al. (1991) study where there was no difference between cases and controls in duration of exposure.

It is important to note that duration was only ascertained in the recently exposed individuals. The heterogeneity in the observed risk therefore reflects both the difference in baseline risk

between chronic and occasional users, as well as the difference in the relative contribution of current NSAID use on the risk of gastropathy. Data from the literature do not allow to partition the effect of current exposure and duration. In other words, it cannot be assessed whether duration is a confounder or an effect modifier. The independent effect of the selection of susceptible patients out of the population at risk on the occurrence of UGIB can therefore not be quantified from published data.

Frequency of use: In the context of NSAID use, a large variation exists in the frequency of use because of the wide variety of indications. Frequency was used to define exposure and baseline level (Duggan et al., 1986), or was used to create 2 categories of exposure (Jick, 1981; Levy et al., 1988): heavy and occasional. Heavy users were at greater risk than occasional users. Odds ratios of 15.0 and 5.6, respectively, were reported by Levy et al.(1988) which suggests an accumulation effect.

Dose response: The dose of individual units of administration was ascertained from computerized databases. Dose categories were either data-based (Carson et al., 1987), a fraction of the recommended daily dose according to the Physicians' Desk Reference (Bigelow and Collins, 1989), or a fraction of the minimum daily dose recommended for rheumatoid arthritis (Griffin et al., 1991). All studies agreed that the risk increases with increasing doses. The dose-response was linear in the Carson et al. (1987) study.

2.2.6 Confounders, risk and effect modifiers

Variables such as age, sex, comedications, indication, comorbidity, smoking, alcohol consumption and less frequently, SES, have been considered as potential confounders. A quantitative review of the literature was made in order to assess whether there is enough empirical evidence to support this practice (appendix A).

It is typical in epidemiologic studies to consider age and sex as stratifying variables. In the domain of pharmacoepidemiology, it is very intuitive to consider these variables because it is widely recognized that drug utilization and the risk of adverse events both vary with age. In addition, these variables are important because of their relevance in describing high risk groups.

Age: Age was considered in all studies reviewed. The proportion of NSAID use differed between the age categories, the heaviest use being found in the older age group (Armstrong and Blower, 1987; Carson et al., 1987). As well, as shown in table 2.3, estimates of relative risk are heterogeneous between age groups which suggests that age is a strong effect modifier in the association between NSAID use and gastropathy.

Sex: As shown in table 2.4, the association between NSAID use and gastropathy, the association seems greater for women, with the

exception of the Armstrong and Blower (1987) and Laporte et al. (1991) studies. However, there is not enough evidence to conclude that sex is an effect modifier. The absolute number of cases increases with age but the percentage of cases taking NSAIDs only increased in those age over 65, especially women (Collier and Pain, 1985). It was concluded that the elderly, especially women, appeared to be more susceptible to the effects of NSAIDs.

History of gastropathy: History of ulcer disease was considered in several studies, either by exclusion or stratification. Results, shown in table 2.5, seem to favour a positive association between prior history of gastropathy and UGIB, and a negative association between prior history and current NSAID use (Armstrong and Blower, 1987; Griffin et al., 1991). It did not appear to be an effect modifier in the Laporte et al. (1991) study (OR for NSAID use and UGIB: 7.4 versus 8.0, for negative and positive history, respectively). The confounding or modifying effect of this factor remains to be explored further.

Protective agents: Because the association between NSAIDs and gastropathy is now well recognized in the medical community, protective agents (such as antacids, H_2 antagonists, misoprostol, sucralfate etc.) are sometimes prescribed for prophylaxis in patients thought to be at risk for a gastropathy. As a result, current use of these drugs may modify the risk of gastropathy. On the other hand, history of gastropathy appears to increase the risk

of UGIB. Prior use of these agents have been used as a marker for history of gastropathy (Collier and Pain, 1985; Armstrong and Blower, 1987; Beard et al., 1987) or as outcome definition (Bigelow and Collins, 1987).

The effect of protective agents ever used during 1 year on gastropathy was significant in the Jick et al. (1987) study: 5.1 (2.6-10.0). However, the effect of protective agents used before NSAID exposure was not significant in the Carson et al. (1987) study: 1.1 (0.6-2.3). None of the studies examined the effect of the concomitant use of these agents on the risk of gastropathy.

Comedications: Some medications are known to predispose to gastropathy or GI bleeding. Anticoagulants and corticosteroids were usually the comedications of interest. In addition, Griffin et al. (1991) considered antineoplastic drugs. Carson et al. (1987) found that the use of anticoagulants increased the risk significantly (OR=2.8; 95% CI 1.4-5.6) while there was no risk associated with corticosteroid use. Griffin et al. (1991) found that the inclusion of these drugs in the multivariate model did not significantly affect the measure of association between NSAID use and UGIB.

Concomitant conditions: A limited number of studies have assessed the effect of other conditions that could potentially predispose to UGIB such as alcohol-related conditions (Armstrong and Blower,

1987; Carson et al., 1987; Guess et al., 1988). An adjusted relative risk of 3.1 (2.0-4.9) was reported by Carson et al. (1987). However, when this variable was added in the multivariate model, alcohol-related diagnoses were not confounders. Armstrong and Blower (1987) found that cardiovascular diseases were twice as common among NSAID users, which indicates an association between comorbidity and exposure. The validity of the assessment of the effect of comedications and comorbidity was compromised by the lack of a priori hypotheses and adjustment for multiple comparisons.

Indication was considered mainly by stratification. A greater proportion of osteoarthritis and rheumatoid arthritis was found among elderly cases than controls (Collier and Pain, 1985). However, in the study by Bartle et al. (1986), there were no differences in indications between cases and controls. The addition of indication in the multivariate model did not change the effect of NSAIDs on UGIB (Carson et al., 1987). So far, findings from the literature do not provide empirical evidence of confounding by indication.

Alcohol consumption was recorded in several studies on NSAID-gastropathy (Coggon et al., 1982; Clinch et al., 1983; Bartle et al., 1986; Somerville et al., 1986; Levy et al., 1988). Although large amounts of alcohol consumption are associated with gastropathy (Tarnawski et al., 1982), its role as a confounder or

an effect modifier in the association between NSAID use and gastropathy remains unclear.

Smoking: The association between smoking and gastropathy remains unresolved. A positive association was found by Somerville et al. (1986) but the 95% C.I. included the null. The estimates of relative risk were: 1.30 (0.88-1.91) and 1.50 (1.00-1.25), respectively for hospital and community controls. In other studies, there was no significant difference between cases and controls in the proportion of smokers (Clinch et al., 1983; Bartle et al., 1986; Holvoet et al., 1991). There was no evidence that smoking was indeed a confounder or that it was interacting with another independent variable in a multiple logistic regression (Levy et al., 1988). None of these studies were conducted in the elderly population.

2.3 SUMMARY OF EVIDENCE ON NSAID-GASTROPATHY

The majority of published studies support a positive association between NSAID use and gastropathy. The elderly population appears to be at greatest risk and yet, only a limited number of studies have examined the risk in this population. Estimates of the magnitude of the association greatly vary between studies, ranging from 2.9 to 11.5. Because several factors may contribute simultaneously to the discrepancy between studies, it is not

possible to extract the effect of each.

Exposure and outcome characterization: Exposure was ascertained either from interviews or computerized databases. None of these sources is comprehensive and accurate in itself which may pose a threat to the validity of the results. Studies based on interviews tended to report a greater magnitude of the association than those based on computerized databases. Databases were only used in one study conducted in the elderly population. Recall bias and availability of information on drugs acquired OTC may explain part of the discrepancy. In addition, there was a great variation in outcomes considered. Differences in the estimates of the association may reflect in part differences in the contribution of NSAIDs in the set of sufficient conditions to cause the GI event.

Methodological considerations: The hazard function of gastropathy has not been described. As a result, it was necessary to define a time window corresponding to the risk period. Often, the selection of the time window was based on a semi-intuitive judgement and varied between studies. It has been shown that the magnitude of the association is inversely proportional to the width of the time window. Recency was addressed in only 2 studies and there is no consensus on when, after discontinuation of therapy, the risk becomes non-existant.

High risk groups: Age is an important effect modifier. Elderly

women appear to be at greater risk. The effect of smoking is controversial and that of alcohol unclear. The confounding or modifying effect of these variables have not yet been well described in the elderly population. Apart from corticosteroids, comedications do not appear to be confounders. The validity of studies that did consider comedications and comorbidity was limited by the presence of multiple comparisons without adjustment in the analysis.

Summary of the deficiencies in exposure characterization:

1) History of NSAID use has been assessed in terms of duration of use. However, because duration was only ascertained in current users it is not possible to partition the effects of current and past NSAID use. So far, there is no empirical evidence to support the phenomenon of selection of susceptible patients previously hypothesized.

2) Patterns of NSAID use were considered in 3 studies and have not been adequately described in the elderly population. Furthermore, they consisted of descriptive studies designed to examine the factors influencing patterns. None have looked at the effect of patterns on the risk of gastropathy. This constitutes a deficiency as high risk patterns may exist and could be used to identify patients at greater risk.

3) Past use of protective agents has been considered in a few studies and results are controversial with respect to the effect on gastropathy. None examined the effect of current use.

Summary of the deficiencies in the risk assessment of NSAID use:

1) Only 5 studies focused on the effect of non-aspirin NSAIDs in the elderly population and only 2 on aspirin. Furthermore, estimates of relative risk obtained from these studies are highly variable,

2) The size of the study population in some of these studies was often limited,

3) Most studies were based on interview and were thus subject to recall bias,

4) Confounders have been inadequately explored in this population. The size of the study population was large in one study and an automated database was used but the source of data necessary to assess effect modification by some covariables (smoking, alcohol consumption...) was not available,

5) Patterns of NSAID use on a long term have not been described adequately in the elderly population.

TABLE 2.1

Estimates of relative risk for the effect of NSAIDs on gastropathy published in the literature

Study	Product	Age group	Sample size	OR (95% C.I.)
Collier and Pain (1985)	NANSAIDs	≥ 65	168 cases 168 controls	11.54 (5.96-22.34)*
Henry et al. (1991)	NANSAIDs**	> 50	250 cases 250 controls	2.9 (1.8-4.8)
Laporte et al. (1991)	NANSAIDs	> 60	409 cases 1248 controls	7.7 (3.8-15.4)
Griffin et al. (1991)	NANSAIDs	≥ 65	1415 cases 7063 controls	4.1 (3.5-4.7)
Holvoet et al. (1991)	NANSAIDs	≥ 65	48 discordant pairs	7.0 (3.3-14.9)
Gabriel et al. (1991)***	NANSAIDs	≥ 60	-----	5.52 (4.63-6.60)
Levy et al. (1988)	ASA	60-69	15 cases 310 controls	3.07 (1.09-8.66)*
Laporte et al. (1991)	ASA	> 60	men: 241 cases 652 controls	6.7 (4.0-11.1)
			women: 168 cases 596 controls	6.4 (3.8-10.7)

* Crude OR derived from published data
** Excluding piroxicam
*** Meta-analysis on 8 studies

TABLE 2.2

Time windows used in published studies on NSAID-gastropathy

Case-control studies

Study	Time window *
Collier and Pain (1985) Somerville et al. (1986) Bigelow and Collins (1989)	on the day of the event
Jick (1981) Henry et al. (1987) Henry et al. (1991) Laporte et al. (1991) Holvoet et al. (1991)	7 days
Armstrong and Blower (1987)	30 days
Coggon et al. (1982) Duggan et al. (1986) Beard et al. (1987) Jick et al. (1987) Carson et al. (1987) Levy et al. (1988)	90 days
Griffin et al. (1991)	1 year
Clinch et al. (1983) Bartle et al. (1986)*** Smedley et al. (1988)	unspecified

Cohort studies

References	Maximum time window **
Guess et al. (1988) Bigelow and Collins (1989)	30 days
Beardon et al. (1989)	until end of study period (3 years)

* Defined in relation to the event
** Defined in relation to initiation of treatment
*** Probably the day of admission

TABLE 2.3

Age-specific odds ratios published in the literature on NSAID-gastropathy

Study	Age group	OR (95% C.I.)
Collier and Pain (1985)	<65 years	2.34 (0.85-6.42)
	≥ 65 years	11.54 (5.96-22.34)
	crude	4.51 (2.78-7.33)
Armstrong and Blower (1987)	<70 years	7.11 (2.16-23.40)
	>70 years	1.53 (0.69-3.38)
	crude	3.45 (1.85-6.48)
Levy et al. (1988)	18-39	4.38 (1.87-10.24)
	40-59	9.61 (3.45-26.79)
	60-69	3.07 (1.08-8.73)
	crude	5.34 (3.10-9.18)
Laporte et al. (1991)*	≤ 60 years	9.14 (5.32-15.69)
	>60 years	10.32 (6.97-15.28)
	crude	8.53 (6.30-11.56)
Holvoet et al. (1991)	≤ 60 years	10.00 (1.50-64.60)
	>60 years	7.00 (3.30-14.90)

* Derived from published data: Mantel-Hanszael OR's adjusted for sex.

TABLE 2.4

Sex-specific estimates of relative risk obtained from published studies on NSAID-gastropathy

Study	ESTIMATE OF RELATIVE RISK Men	Women	Crude
Clinch et al. (1983)	2.81 (0.55-14.32)	5.67 (1.50-21.40)	4.64 (1.69-12.77)
Armstrong and Blower (1987)*	4.35 (1.85-10.23)	2.09 (0.79-5.50)	3.45 (1.85-6.42)
Levy et al. (1988)*	4.44 (1.93-10.20)	6.05 (2.92-12.54)	5.34 (3.11-9.18)
Laporte et al. (1991)**	7.96 (5.19-12.20)	13.23 (8.35-20.96)	8.53 (6.30-11.56)
Holvoet et al. (1991)	6.7 (2.6-17.4)	8.3 (2.9-23.7)	7.4 (3.7-14.7)

* Crude odds ratios derived from published data
** Derived from published data: Mantel-Hanszael odds ratio adjusted for age

TABLE 2.5

Effect of history of gastropathy in published studies

Study	Definition of history	Relative risk (95% C.I.)
Carson et al. (1987)	Preexisting abdominal conditions	1.5 (0.9-2.5)
Laporte et al. (1991)	- Symptoms	2.6 (1.9- 3.5)
	- Peptic ulcer disease	5.5 (2.8-11.0)
	- GI bleeding	14.5 (7.5-28.2)
Jick et al. (1987)	Cimetidine, antacids (markers for history)	5.1 (2.6-10.0)
Holvoet et al. (1991)	Peptic ulcer disease	5.5 (3.2-9.6)

CHAPTER 3

METHODS

3.1 STUDY DESIGN

In order to address the objectives described in chapter 1, a hospital based case-control study was conducted. Ideally, a cohort study would have been more suitable for 2 major reasons: 1) the shape of the hazard function could have been described, thus allowing a better definition of the appropriate time window for risk assessment and, 2) the process by which NSAID users select themselves out the population at risk, or switch between products could have been quantified. In Quebec, there is a computerized database that includes information on all hospital discharges in the province: the Med-Echo database. In principle, it is possible to link the Régie de l'assurance-maladie du Québec (RAMQ) database (exposure) to the Med-Echo database (outcome) through a unique identifier. However, for confidentiality reasons, it is not feasible to engage in such a practice at present. Nevertheless, the RAMQ accepted upon request to provide information on dispensed medications for a list of identified patients. This constraint has motivated the choice of the case-control design. At present, linkage between data is unidirectional: from outcome to exposure.

Cases and their matched controls were assembled using the discharge listings from 4 hospitals in Montreal: Royal-Victoria, Notre Dame, Maisonneuve-Rosemont and Jewish General. For each selected patient, outpatient prescriptions (NSAIDs as well as all other medications) and medical services received during the 3 years preceding admission were obtained from the RAMQ databases. Information on concomitant variables were obtained from hospital charts (smoking, medical history etc.) as well as from the RAMQ database (other prescribed drugs, medical procedures received etc.). The use of NSAIDs by cases was compared to that by controls to subsequently quantify the association between NSAID use and UGIB. The study population was recruited from April 1st 1988 to March 31st 1990. The entire study period (including ascertainment of exposure) was from April 1st 1985 to March 31st 1990.

A feasibility study was conducted in 2 of the hospitals (Royal-Victoria and Notre-Dame) in order to develop the logistics of the study.

3.2 POPULATIONS

Target population: The target population consisted of Quebec elderly at risk of developing a gastropathy and at risk of being exposed to NSAIDs.

Study population: Operational definitions as well as inclusion/exclusion criteria for sampling the study population from the target population were developed during the feasibility study. For feasibility reasons, the study population consisted of a sample of Quebec elderly who were hospitalized in the 4 hospitals listed above. Controls intended to be a sample of patients who belonged to the same source population as the cases.

Base population: The base population for the present study was defined secondarily to the selection of cases. It consisted of the catchment population for severe UGIB of the 4 hospitals. This population remains theoretical and cannot be described. It could, however, be approximated by the population living in the vicinity of each hospital (Kopec and Esdaile, 1990). Further discussion on the representativeness of the study population relative to the base population is found in section 3.4 on "controls".

3.3 CASES

Definition: The illness of interest was severe UGIB that required hospitalization. More specifically, it consisted of peptic, gastric or duodenal ulcer with hemorrhage or perforation, bleeding gastritis and/or duodenitis. The conditions were acute and incident (see below).

The guidelines proposed by Jick and Vessey (1978) were used to construct the case definition. Cases were restricted to hospitalized conditions. Given that the effect of NSAIDs on GI distress has been extensively entertained in the literature and is well accepted within the medical community, detection bias may occur if patients who are NSAID users preferentially undergo diagnostic tests upon the presence symptoms or when asymptomatic. In order to minimize this detection bias, only mandatory hospitalizations (emergency admissions) for the condition were considered. The illness would be severe enough that all patients would be hospitalized regardless of NSAID use. It is likely that some cases were not admitted after having been to emergency. However, as stated by an emergency physician (Dr. Mlynaryk, Royal-Victoria hospital), it is very unlikely that the decision to admit would be differential with respect to NSAID exposure if there was bleeding in an elderly patient.

Ascertainment: The Med-Echo discharge listings at each hospital were examined. The hospitals were selected for the following reasons: 1) they are among the largest hospitals in Montreal, 2) they include populations of various socio-demographic and cultural backgrounds, 3) they were convenient in terms of location in the city. Listings sorted by International Classification of Diseases, 9th Revision (ICD-9) code were used to identify potential study subjects. Potential cases consisted of all patients 68 years old and over included in the following ICD-9 diagnostic categories:

531, 532, 533 (subcodes .0-.2, .4-.6), 578.0, 578.1 and 578.9. The diagnostic categories were selected based on 3 sources of information: 1) published literature (Guess et al., 1988), 2) expert opinion from gastroenterologists (Notre-Dame and Royal Victoria hospitals), 3) medical archivists. Charts of potential cases were reviewed and patients who met the inclusion/exclusion criteria described below were retained.

Accuracy of diagnosis: Charts of all patients retained from discharge listings were reviewed to determine if their illness complied with the case characteristics defined above. The summary sheet (filled by the physician) was used to determine the principal and secondary diagnoses. Consultation and progress notes were examined to obtain information on the onset of symptoms, characteristics of the bleed and diagnostic procedures conducted to confirm the diagnosis. If applicable, the date of the previous episode of GI illness was determined in order to apply the case definition.

In order to be eligible, the source of bleeding must have been identified as upper GI (probable or unknown were not eligible). Procedures for the validation of cases is found in section 3.9 on "validation of data and methods".

Acute: Given that the presence of a chronic ulcer would most likely influence NSAID intake, only acute cases were considered. Like in

the Levy et al. (1988) study, only conditions with symptoms present for less than 1 month prior to admission were retained in order to exclude chronic cases. ICD-9 subcodes exist for acute ulcers (.0-.2). However, as shown in the feasibility study, no patients were included in these diagnostic categories. They were all classified under: "chronic or unspecified perforation and/or hemorrhage" (subcodes .4-.6). If chronic ulcer was specified in the discharge summary, the patient was not included. However, when there was no mention of chronicity, the date of the start of the symptoms was retrieved from the chart (case report or discharge summary). According to the feasibility study, 5.5% of the patients who met the case definition had an onset of symptoms of more than 1 month before. For the purpose of this study, chronicity was defined on the basis of the onset of the symptoms rather than on the characteristics of the ulcer. Only patients who experienced symptoms for 1 month or less prior to admission were retained.

Incident: One of the criteria of causality is that the exposure must precede the outcome (Kelsey et al.,1986). In this case, the presence of the illness should not influence the probability of being exposed to NSAIDs. Rothman (1986) stated that if exposure affects the duration of the illness, then case-control studies based on prevalent cases would be unable to distinguish an etiologic role for the exposure from its effect on duration unless the effect on duration was known. Based on this argument, it was preferable to select incident rather than prevalent cases. It has

been previously determined that the slow healing phase of an ulcer lasts about 7 weeks (Peltier, 1989). Consequently, a minimum period of 3 months between 2 consecutive hospitalizations for the same condition was considered to be sufficient to treat the 2 events as independent episodes; the second one being referred to as incident. The medical history of the case was examined in order to assess prior hospitalizations for gastropathy.

Other etiology: There must be a reasonable possibility that the condition has been induced by the drug. Patients with GI bleeding of natures other than the ones listed above such as: oesophageal varices, malignant disorders that involve the GI tract, Mallory-Weiss syndrome, inflammatory colitis (such as CROHN's disease), sigmoidal diverticulosis were not be eligible as cases. Although the concomitant presence of cirrhosis and chronic alcoholism are predisposing factors, it was not felt that they were sufficient causes of GI bleeding and were therefore retained as cases (unless they were accompanied by oesophageal varices that have ruptured).

In summary, for this study, a case was a patient with a discharge diagnosis of UGIB under either of the following ICD-9 codes: 531,532,533 (subdiv. .0-.2, .4-.6), 578.0, 578.1 and 578.9. After examination of the chart for confirmation of the source of bleeding and for characteristics such as prior hospitalization, onset of illness and presumed cause, only incident acute cases were

retained, i.e. no prior hospitalization for the same condition within 3 months and onset of symptoms within 1 month prior to admission.

3.4 CONTROLS

Definition: Controls were patients hospitalized for conditions believed to be unrelated to UGIB and to NSAID use. A pool of potential controls was assembled from selected acute discharge diagnoses. According to the definition by Pearce and Checkoway (1988), it was an incidence density sampling given that controls could eventually have become cases had they developed the disease at a later date within the study period. The methodological concepts and control selection strategy are described below.

Ascertainment: Jick and Vessey (1978) identified 2 mandatory exclusions concerning the use of hospitalized controls: 1) patients admitted for conditions that are indication or contraindication for the drug of interest and, 2) patients admitted for conditions that are caused or prevented by the drug. Because NSAIDs are used for a variety of indications and have several known or suspected side-effects, these criteria were difficult to apply. In order to minimize biases due to unknown associations with NSAID use, a pool of control diagnoses was created to avoid over-representing a particular disease. Diagnoses were chosen in order to meet the

following criteria:

1) Acute,

2) Thought to be unrelated to NSAID use and UGIB,

3) Relatively frequent in the elderly population.

Based on these criteria, 3 major categories of control diagnoses were retained: pneumonia, cholecystitis and trauma (including fractures). Others included urinary tract infection, appendicitis, pancreatitis, other biliary duct illnesses, diverticulum and cholangitis. Potential controls were selected from the hospital discharge listings. Charts were reviewed in order to verify that the condition was acute and incident. An attempt was made to replace controls who did not meet the eligibility criteria. However, the pool of eligible matched controls was very restricted and in many instances, it was not possible to replace ineligible controls.

As stated by Rothman (1986), controls should be chosen in such a way that they represent those who would have navigated the same pathway of selection forces as the cases had they been ill. This concept is theoretical and is difficult to apply given that the selective forces related to UGIB admission are not defined. It was assumed that the distribution of exposure was the same in the

control series as in the random sample of the secondary base, which was equivalent to assume that there was no relationship between NSAID use and the control diagnosis (Wacholder et al., 1992). Controls were specifically chosen to be unrelated to exposure in order to ensure that they were as likely to be NSAID users as the cases, under the hypothesis of no association (Miettinen, 1985; Jick and Vessey, 1978; Rothman, 1986; Wacholder et al., 1992). Unsuspected associations with NSAID use are conceivable and strategies are available to attempt to minimize the bias brought by the inclusion of such patients. These are described below.

The selection of controls was planned taking into account the fundamentals of the case-control design. A debate on this issue was published in 1985 in the Journal of Chronic Diseases, and was followed by a series of letters to the editors in 1987. No clear consensus emerged from the literature. Concepts on the unbiased selection of controls remain theoretical and are difficult to apply in a control selection protocol. While Miettinen (1985) described the methodological concepts of the selection of controls in case-control studies, Knottnerus (1987) and Wacholder et al. (1992) translated them into operational definitions or guidelines. Jick and Vessey (1978) also included a section on the selection of controls specific for the study of drug-induced illnesses. These guidelines made up the framework of the control selection strategy used in the present study. Types of controls used in the various published epidemiologic studies on NSAID-gastrotoxicity are

described in table 3.1.

Sampling frame: As stated by Kopec and Esdaile (1990), the validity of controls can be achieved when cases may be linked to an identifiable source population. In the literature on NSAIDs, only 3 studies drew their controls from a well defined primary base population (Jick et al., 1987; Carson et al., 1988; Griffin et al., 1991). In these settings, this approach was feasible because of the availability of population-based computerized databases. All hospital based case-control studies sampled controls from a secondary base. Because the secondary base is a concept that does not have an operational definition, 2 alternatives may be considered to catch some of its members: the use of other hospitalized patients or, individuals living in the community where cases originated from. In the literature on NSAIDs, only 2 studies used community controls (Coggon et al., 1982; Somerville et al., 1986).

In the present study, settings and arguments favoured the use of hospital controls. Community controls did not seem appropriate for 3 major reasons that are described below. The first concerns validity while the 2 others are operational considerations.

1) Controls would not have hospital charts. Thus, the use of different sources of data for cases and controls would have led to non comparable information,

2) Because cases were not contemporaneous, it would be difficult operationally and lengthy to find matched controls in the community,

3) For confidentiality considerations, it was not possible to use community controls because the RAMQ does not accept to release information to a third-party even with an informed consent from the beneficiary.

For these reasons, it was felt that hospital controls were more suitable, which is consistent with the majority of case-control studies found in the literature. Like the cases, the presence of a disease may have influenced exposure to NSAIDs in the controls. Hence, only acute diagnoses were retained. If there was no mention of chronicity, the onset of symptoms was used as an indication of acuteness. A 1 month period was used to distinguish acute from non acute conditions. To ensure that the illness was incident, patients with a chronic disease who were returning for an acute complication or follow-up related to their chronic disease were not eligible. However, patients with a chronic condition who were hospitalized for a reason unrelated to the disease were eligible.

3.5 INCLUSION/EXCLUSION CRITERIA

Inclusion and exclusion criteria were applied to both cases and controls. These were created for feasibility considerations:

Inclusion criteria:

1) Patients had to be 68 years old and over,

2) They had to be residents of Quebec for at least 3 years.

The universal prescription programme is restricted to Quebec residents age 65 and over. In order to obtain information on drug consumption for 3 years prior to admission, patients must have been 68 years old and over and have been residents of Quebec for at least 3 years.

Exclusion criteria:

1) Patients with multiple or long-term admissions, or living in nursing homes in the previous 3 years,

2) Diagnosis of lower GI bleeding,

3) History of gastrectomy,

4) Cancer of the GI tract,

5) Allergy to acetyl salicylic acid (ASA),

6) Transfer from another hospital.

Information on dispensed medications was only available for outpatient prescriptions and extensive data truncation would occur if patients who had long-term or multiple hospitalizations before ascertainment were included. Individuals who had been admitted in a long-term care unit in the previous 3 years, hospitalized in the previous 30 days or, had individual admissions of more than 30 days were not considered. Individuals with lower GI bleeding were excluded because this condition was thought to be associated with NSAIDs and may not be independent of UGIB. Patients with a history of gastrectomy or cancer of the GI tract were excluded because the probability of a drug etiology for bleeding is minimal. Patients allergic to ASA were not considered because they were at a lower risk for exposure.

Patients transferred from another hospital were not eligible as cases for 3 reasons: 1) difficulty to find an appropriate control originating from the same base population, 2) incompleteness of medical history, 3) lack of information on time spent in the previous hospital.

3.6 MATCHING

Controls were individually matched to cases on: age (± 5 years), sex, hospital, study year and month of admission (±2). A

control:case ratio of 4:1 was intended in order to maximize the power of the study (Schlesselman, 1982). Matching variables were selected according to literature findings and intuitive judgement. Age and sex appeared to be important confounders to consider. In addition, the 4 hospitals are known to differ with respect to socio-demographic characteristics and cultural backgrounds. The Royal-Victoria and Jewish General hospitals are mainly Anglophone and are located center-west of the city of Montreal, while Notre-Dame and Maisonneuve-Rosemont are primarily Francophone and are located in the center-east of the city. It is likely that the socio-demographic structure of the catchment populations varies between hospital. Hence, it was important to match for hospital. Because of time trends in prescribing behaviour, matching was also done on study year. Seasonal variations in admission conditions at the various hospitals, which could be differential with respect to NSAID exposure, has motivated matching on month of admission. Most hospital based case-control studies published in the literature have matched on this variable.

It was initially thought that patients not eligible as cases because of other etiologies leading to UGIB could potentially be used as controls to increase the efficiency of resource utilization. Only a limited number of these patients met all egibility criteria. None of them could actually be used because they did not meet the matching criteria.

3.7 SAMPLE SIZE

At the time the study was planned, there was little information available in the literature regarding the proportion of exposure to NSAIDs in the elderly population. The studies by Laporte et al. (1991) and Griffin et al. (1991) had not yet been published. The description of patterns of NSAID utilization by Leufkens et al. (1990) was published in Pharmaceutisch Weekblad but this journal is available in Canada only after a substantial delay. Moreover, it was not restricted to the elderly population. The estimates of relative risk found in the literature were highly variable. The summary OR specific to the elderly population of 5.52 produced by the meta-analysis of Gabriel et al. (1991) was not yet available.

As a result, the initial sample size calculation was conservative and the minimum relative risk to be detected was set at 1.5, which corresponds to the estimate obtained in published cohort studies. The percentage of exposed patients in the control population was based on a descriptive study conducted by Moride and Abenhaim (1990) where it was shown that 35% of the Quebec elderly received at least 1 NSAID prescription in 1988. In the present study, a 30-day time window between admission and exposure has been selected. As a result, the prevalence of exposure was unknown but was expected to be lower. According to the sample size calculation formula found in Kelsey et al. (1986), the number of cases required

to study exposure to NSAID as a dichotomous variable with a prevalence of exposure of 35%, an alpha level of 0.05, a beta of 0.20, and 4 controls per case was 265 in order to be able to detect a relative risk of 1.5. With a control:case ratio of 4:1, the number of controls was 1060.

3.8 SOURCES OF DATA AND RECORD LINKAGE

Three major sources of data were used: 1) Med-Echo hospital discharge listings for the ascertainment of potential study subjects, 2) medical charts for the validation of the diagnosis and ascertainment of some study variables and, 3) RAMQ databases for the ascertainment of dispensed medications and medical services. Each of the data sources is described below.

Discharge listings: Discharge listings were only used for the initial ascertainment of cases and controls as well as matching. Items found in this source were not used for data analysis. The structure of the discharge listings varied according to the administrative system of the hospitals. Notre-Dame and Maisonneuve-Rosemont used the original Med-Echo database while Royal-Victoria and Jewish General used the one provided by the Health Maintenance Research Institute (HMRI) system. This distinction created some differences in logistics for the conduct of the study.

All hospitals in the province of Quebec are required to send to Med-Echo information on every discharge. Some hospitals use the information collected in the Med-Echo database while others use information processed by HMRI, a private organization, that is the intermediate between the hospital and Med-Echo. Two differences between these databases influenced the present study: 1) the time of discharge and, 2) the number of diagnostic categories. In Med-Echo, discharge was expressed as a chronological date whereas in HMRI, discharge was expressed as a period. The fiscal year (April 1st to March 31st of the next year) was divided into 13 periods. This created logistic differences in matching procedures for month of admission. It was possible to derive from Med-Echo the date of admission by subtracting the length of stay from the date of discharge. However, only the month of admission could be approximated in HMRI records from the discharge period and the length of stay. In these hospitals, the date of admission was only known with certainty from medical charts. The initial matching on month of admission was therefore revised after chart review.

HMRI included 3 types of diagnosis (main, principal and secondary) while Med-Echo only considered 2 (principal and secondary). In practice, the main diagnosis of HMRI corresponded to the principal diagnosis of Med-Echo. Consequently, the 3 categories in HMRI were collapsed into the main and secondary diagnoses. The principal diagnosis of HMRI was treated as the first secondary diagnosis. The total number of secondary diagnoses also differed between the 2

sources. In Med-Echo, the maximum number was 15 while in HMRI, it was 4, which corresponded to the first 4 secondary diagnoses listed on the summary sheet of the chart. As shown in the feasibility study, all cases were included among the first 4 diagnoses. Therefore, no cases were missed with the use of HMRI. The sensitivity of the selected diagnostic codes for ascertainment of the cases is discussed in section 3.9 on the "validation of data and methods".

In both systems, the listing sorted by ICD-9 code was used to identify potential study subjects. A list of potential cases was drawn and consisted of all patients 68 years old and over included in the ICD-9 case diagnostic categories listed above. Principal, secondary and death diagnoses were considered. Unconfirmed diagnosis (letter P) or transfer diagnosis (letter H) were not retained. A pool of potential controls was created from the discharge listings. Matching for all variables was done directly from Med-Echo listings. A posteriori matching was necessary for those based on HMRI.

Medical charts: For each admission the following documents were first consulted to obtain the required information: summary sheet, Med-Echo sheet, case history, endoscopy sheet (when applicable), transfusion requisition (when applicable). If the information was incomplete then other sources were consulted: progress notes, nursing report, consultation sheets. The order and appearance of

each form varied between hospitals but the nature of the information was very similar. The summary sheet and case history are filled by the admitting physician and coded by medical archivists. The endoscopy sheet is filled by the physician who performed the examination. The Med-Echo sheet is an administrative document. Demographic information is filled at the admission office and, information related to hospitalization (diagnoses, procedures etc.) is supplied by medical archivists based on the information appearing in the summary sheet.

Second, the medical charts were consulted in order to validate the diagnosis and obtain information on covariates such as demographic characteristics, smoking, comorbidity and history of gastropathy. The process of validation of diagnosis of the cases is described in section 3.9 on "validation of data and methods". Information on inclusion/exclusion criteria was obtained from the case history. Admissions during the previous 3 years was ascertained from admissions appearing in the chart.

RAMQ prescription database: Data on all medications dispensed in the 3 years prior to admission were obtained from the RAMQ prescription database. The universal programme is restricted to elderly and welfare recipients and is a fee-for-service (the pharmacists claim reimbursement for the drugs dispensed). In this database, the unit of observation is the prescription. It is possible to use the patient as the unit of analysis by obtaining

longitudinal information on drug exposure through a unique identifier. Key items found in this database were:

- Name of drug (generic and proprietory)
- Date of dispensing
- Number of units of administration
- Dose per unit of administration
- Prescribed number of days of treatment
- Form of administration (tablet, capsule, suppository etc.).

Drugs are grouped according to the American Hospital Formulary Service system of classification. Each code corresponds to a therapeutic class. Individual drugs are coded according to a system designed by the Health Protection Branch (Canadian government). This system differs from the other available databases (except the Saskatchewan database), which mostly use the ATC (Anatomical Therapeutic and Chemical) codes. Given the universal nature of this programme, the information is centralized and changes of pharmacist or address do not affect exposure ascertainment. The information available in the database pertains to out-patient prescribed medications that have been dispensed by the pharmacist and that are present on the list of drugs reimbursed by the RAMQ (all NSAIDs available in Canada are reimbursed). Generic names were used to distinguish between the different NSAID products. The database does not include information on drugs purchased over-the-counter (OTC). However, if a drug available OTC

is acquired with a prescription (eg. aspirin), then it is considered as a dispensing and it is included.

RAMQ medical services database: Data on all medical services received by the patients during the 3 years prior to admission were obtained from the RAMQ medical services database. The programme is universal for all Quebec residents and is a fee-for-service (the physician claims reimbursement for the medical service rendered). In the database, the unit of observation is the medical service. It includes information on the nature of the service rendered (examination, procedures etc.), the specialty of the physician, date of service and diagnosis (ICD-9 code).

Record linkage: Med-Echo and the RAMQ databases are administered by different organizations. Linkage between the RAMQ prescription and medical services databases is done routinely. However, linkage between the RAMQ and Med-Echo databases is unprecedented. As a result, the logistics to do so had to be developed. Data extracted from medical charts were linked to the RAMQ databases through a unique identifer: the Health Insurance Number (HIN). This number is acquired at birth or at the time of residency and remains unchanged throughout the life of the individual. Linkage was a two-stage process, described in figure 3.1. Patients initially ascertained in the discharge listings were identified by their chart number. Charts were consulted in order to obtain the HIN, which was subsequently submitted to the RAMQ to request information

on drugs and medical services.

The logistics for the conduct of an observational study using the Quebec databases had to be designed. The objectives of the process were: 1) the design of a feasible procedure for the linkage of data on exposure, outcome and covariates, 2) the consideration of confidentiality regulations.

The following components were addressed in chronological order: 1) initial contact with the RAMQ, 2) selection of the required variables from the prescription and medical services databases, 3) development of a strategy to link data from medical charts with those from the RAMQ databases taking into account the rules of confidentiality.

Previous work on a random sample of NSAID users (Moride and Abenhaim, 1990) allowed to make the initial contact with the RAMQ and to get acquainted with the structure and content of the databases. Members of the Evaluation Service Department of the RAMQ, who manage the RAMQ computerized databases, agreed to extract the data for the study if provided with a precise and detailed algorithm.

The procedure for data extraction for the present study was complex as it was necessary to design it in relation to confidentiality regulations. Data on outcome and some of the covariates were

obtained from the medical charts. The objective was to link these data to the information included in the RAMQ databases. The RAMQ has very strict confidentiality regulations for the release of information. It is not allowed to provide any information to a third-party even with patient's consent. As a result, neither the name of the patients nor the Health Insurance Number (HIN) could appear in the information provided by the RAMQ. However, it was possible to provide the HIN of the patients included in the study population to the RAMQ along with some information collected from the hospital charts. Linkage was then conducted on site at the RAMQ, the HIN was scrambled and an anonymous database was returned. A constraint was that it was not possible to send the original database containing all information abstracted from the medical charts in its integral form. Because the information was detailed and included numerous variables, it would have been possible in principle to trace a particular patient even in the absence of the HIN. As a result, two agreement have been reached with the RAMQ: 1) linkage would be done in two steps, 2) variables from the hospital database had to be restructured and grouped into broader categories. The steps and re-structuration of the variables are shown in the following pages:

Step 1

Before linkage		At the RAMQ
Original database	Re-structured	Linked databases
Sex	Sex	Sex
Age at admission (continuous)	Age group	Age group
HIN	HIN	Scrambled HIN
Date of admission	Date of admission	Removed
Study year	Study year	Study year
Outcome	Outcome	Outcome
Chart number	Chart number	Scrambled
Hospital	Hospital	Removed
-	-	Dispensings
-	-	Medical services (date expressed in number of days before admission)

Step 2

Before linkage		At the RAMQ
Original database	Re-structured database	Linked database
Scrambled HIN	Scrambled HIN	Scrambled HIN
Hospital	Hospital	Hospital
Smoking	Smoking	Smoking
History of gastropathy	History of gastropathy	History of gastropathy
Diagnosis	Diagnostic category*	Diagnostic category
---	---	Data from step 1

* Categories of diagnoses were created for the purpose of the sensitivity analysis described in section 3.11.8. Categories were:

1: UGIB (given to all cases)

2: Respiratory illnesses

3: Cholecystitis

4: Trauma

5: Other urinary tract illnesses

6: Other GI conditions

7: Others

Before the original data were sent to the RAMQ, several validation procedures were conducted on the HIN. The HIN contains 12 digits which corresponds to the following information:

Digits	Information
1-3	First 3 letters of the surname
4	First letter of the given name
5-6	Year of birth
7-8	For men: month of birth
	For women: month of birth + 10
9-10	Day of birth
11-12	RAMQ code

Because the date of birth was recorded from the medical charts, it was possible to verify the consistency between it and digits 5 and 6 (year of birth), 9 and 10 (day of birth) of the HIN. Digits 7 and 8 (month of birth) were verified using the information from date of birth and sex collected from the hospital charts. In case of discrepancy, the hospital was contacted and the patient traced by the chart number. The information was thus verified either from the hospital computerized system or the chart was reabstracted. Despite these validation procedures, it was found by the RAMQ that some HIN were not valid. The RAMQ returned the erroneous HINs accompanied by the medical chart number and hospital. An attempt

was made to correct the number by using the hospital computerized system. With the exception of 1 patient, all errors were typographical and could be corrected. In one instance, it could not and therefore, the patient had to be deleted.

Confidentiality procedures: In order to protect the confidentiality of selected patients, the HIN and chart number were scrambled after linkage and the database became anonymous. The study was approved by the ethics committee of each hospital under the condition that patients names would not be divulged. Confidentiality and linkage procedures met the official criteria of the RAMQ.

3.9 VALIDATION OF DATA AND METHODS

Sensitivity of case diagnostic codes: The sensitivity of the selected ICD-9 codes for the cases was assessed by comparing admission records to discharge data. Admission records were reviewed in 2 hospitals (Royal-Victoria and Notre-Dame). Ninety-two patients admitted for conditions related to the GI tract and abdomen (eg. acute abdomen, UGIB etc.) were retained. The medical charts of these patients were reviewed in order to determine the discharge diagnoses and ICD-9 codes. The codes corresponding to UGIB were all included in the list of codes for the case ascertainment (see above). All codes were either principal or among the first 4 secondary diagnoses. As a result, the selected

codes captured all potential cases (100% sensitivity).

Validation of case diagnosis: The selected ICD-9 categories were sensitive but not specific. Hence, the medical chart of each potential case identified in the discharge listings was examined in order to confirm that the diagnosis was indeed UGIB. The feasibility study has shown that most cases were diagnosed by the presence of endoscopic positive findings (87%). In a smaller proportion of patients, the diagnosis was established on the basis of occult blood positive stools or haematemesis (5%), during surgery on the digestive tract (5%) or autopsy (2.5%). The source of bleeding could not be identified in 4% of the patients.

When available, the gastroscopy report was examined in order to confirm that the source of bleeding was upper gastro-intestinal as opposed to lower and that there was bleeding. Patients who had a clot but no frank hemorrhage were also eligible as it indicated that bleeding had occurred at this location. The endoscopy report was also used to rule out other etiologies such as rupture of oesophageal varices. In rare instances, the location of the bleed had been identified during surgery. The surgery protocol was consulted as a confirmatory document.

Potential sources of errors and mitigation studies: There were 3 potential levels of errors for the diagnosis. *Level 1:* the diagnosis made by the physician. This component was intrinsic to

the system and was not validated. The study involved diseases as diagnosed by the physician and confirmed by one "objective" characteristic (see "validation of diagnosis" above). *Level 2:* completion of the summary sheet. On this sheet, the physician lists in order the diagnoses. At Notre-Dame or Maisonneuve-Rosemont hospitals, the principal and secondary diagnoses are found. At the Royal Victoria and Jewish General, it is the main, principal and secondary diagnoses. In the latter hospitals, the main diagnosis consists in the illness responsible for admission while the principal corresponds to the diagnosis that determines the length of stay. In order to avoid missing some cases, a sensitive approach was adopted. Primary and secondary diagnoses were considered. Diagnoses that did not meet the case definition were excluded after chart review. *Level 3:* coding by medical archivists. The diagnoses appearing on the summary sheet are coded by medical archivists and transmitted to Med-Echo or HMRI. A validation study was conducted in another study where a large sample of charts (over 1,000 patients) were reabstracted and the coding cross-checked (Delfino, personal communication). It was shown that the diagnosis, as coded by the medical archivists, was 90% concordant for respiratory diseases. In the present study, a small-scale validation was done during the feasibility study on 60 charts. A 89.8% concordance between the description of GI illnesses found in the charts and in the hospital discharge system was obtained. Discrepancy was found in 7 charts. In 4 instances, the diagnosis was coded as GI bleeding (578.9) when there was no evidence of

bleeding in the chart. Conversely, in 3 cases, the ulcer was coded with a subcode corresponding to: "no evidence of perforation or hemorrhage" (subcode .3) when in fact, there was bleeding. However, because the diagnosis of GI bleeding (578.9) was also present among the secondary diagnoses these cases would not have been missed.

Validation of exposure ascertainment: The universal nature of the RAMQ database ensures that exposure ascertainment is independent of the disease status of the selected patients. Any misclassification that would have occurred is expected to be non-differential. Since pharmacists claims must be included in the database before reimbursement is received, the information should be both comprehensive and accurate. The process includes an internal evaluation performed by the RAMQ. A substitution rate of 5% has been estimated (the pharmacists claim reimbursement for a drug that differs from the one actually dispensed) (RAMQ, personal communication). Nevertheless, the drug remains within the same generic class. Substitution was therefore not a concern in the present study given that proprietary names were not considered. Most claims are processed rapidly, a 3-month period is required to ensure a comprehensiveness of 95% and a 6-month period for 99%. Thus, at the time of exposure ascertainment for the study (year 1991), it was expected that the ascertainment of exposure was complete.

Validation of covariables: The presence of data on covariables, such as smoking and alcohol consumption, was assessed in the feasibility study. It was not possible to validate these data but any misclassification was expected to be non-differential with respect to exposure. However, the proportion of missing values varied between diagnoses. It was often missing for patients admitted into the department of orthopaedics but not into gastroenterology. A detailed description of differences is found in chapter 4. All charts were reviewed in order to assess alcohol consumption. This information was missing for 16% of the patients. When present, 75.2% of the patients claimed they were not drinking. These results show that the reliability of this source of information is questionnable. It is likely that patients under-estimate their alcohol consumption and their definition of drinking varies greatly. Alcohol was initially considered in the analysis but no effect was found (it did not increase the risk of UGIB and was not a confounder in the association between NSAIDs and UGIB). Due to the absence of effect and the inaccuracy of the source of information, alcohol was not considered as a covariate in the study. In addition, as shown in the literature review in chapter 2, none of the studies published on NSAIDs so far were able to find a significant effect.

Data on concomitant medications were also retrieved from the RAMQ prescription database and their validity was expected to be similar to that of NSAIDs.

A substantial amount of information was collected from admission notes in the charts. Of particular interest here was the history of GI illnesses. Intuitively, it was expected that admitting physicians were more likely to ask about history of GI problems to the cases than to the controls. In order to minimize this source of bias, hard data were sought in the RAMQ prescription database, using past exposure to protective agents as a proxy for history of gastropathy. This approach was also used by Jick et al. (1987). Two other markers were also used: history of upper GI procedures (gastroscopy, duodenoscopy, biopsy of the upper GI tract and upper GI X-ray), as well as past visit to a gastroenterologist. These were ascertained from the medical services database. The use of the latter measures is unprecedented. A comparison between the 4 measures of history (history assessed in medical charts, past visit to gastroenterologist, history of upper GI procedures and past use of protective agents) was subsequently made with respect to their independent effect on UGIB and their effect on the association between NSAID use and UGIB.

Validation of control diagnoses: Because of unsuspected associations with NSAID use, it was not known with certainty whether the selected control diagnoses were unrelated to NSAID use and to UGIB. A sensitivity analysis was conducted to assess the stability of the results by removing one major class of control diagnosis at a time.

3.10 STUDY VARIABLES

The variables considered in the present study are listed below. In order to maintain a logical sequence, variables are sorted by data source and by type (dichotomous, categorical, continuous). Each one is described in greater detail in the following sections.

RAMQ prescription database:

- Dichotomous variables:

    - Recent exposure to non-aspirin NSAIDs (NANSAIDs)
    - Recent exposure to aspirin (ASA)
    - Recent exposure to protective agents
    - Recent exposure to comedications (anticoagulants, corticosteroids, antineoplastic drugs)
    - Past exposure to NANSAIDs
    - Past exposure to ASA
    - Past exposure to protective agents

- Categorical variables:

    - Patterns of NANSAID use:
        . Recency
        . Duration

. Switching

- Continuous variables:
    - Total duration of past NANSAID use
    - Average daily dosage (ADD)
    - Number of switches between products
    - Number of switches between ADDs of the same product
    - Number of switches between modes of administration of the same product
    - Date of last switch

RAMQ medical services database:

- Dichotomous variables:
    - History of upper GI procedures
    - History of visit to a gastroenterologist

Medical chart:

- Dichotomous variables:
    - History of gastropathy

- Categorical variables:
    - Diagnostic category
    - Smoking

- Concomitant illnesses
- Past illnesses

- Continuous variables:
  - Number of concomitant illnesses

3.11 TIME WINDOW AND EXPOSURE CHARACTERIZATION

3.11.1 Definition of the time window

Based on findings from the literature as well as on the physiopathologic process of this disease, a period of 30 days was selected. Patients who had an NSAID prescription dispensed or ending within 30 days prior to the event were considered as exposed. As mentionned in chapter 1, the operational definition of the time window in case-control studies is expressed in relation to the event and not in relation to initiation of therapy. If only current use (i.e. use on the day of the event) was considered as exposure, then some exposed patients would have been wrongly classified as unexposed if the drug was discontinued at the onset of symptoms (which, according to the case definition, could occur anytime from the day of the event to one month before). In order to avoid under-estimating the proportion of exposure a time window of 30 days was selected.

Relative to the initiation of therapy, this time window therefore included a period of exposure ranging from a minimum of 1 day after initiation of treatment to a maximum of 29 days after termination. It is conceivable that a shorter time period, eg. 7 days, would have been more adequate to avoid the under-estimation effect described in chapter 1. In order to determine the effect of the width of the time window on the risk, the measure of association obtained with 30 days and 7 days prior to admission were compared.

3.11.2 Exposure characterization

In the literature, exposure to NSAIDs has been referred to as the consumption or the dispensing of an NSAID during a specified risk period preceding the event. Studies relying on patient interviews usually considered consumption while those relying on automated databases considered dispensing as evidence of exposure. The 2 sources have advantages and disadvantages which have been described in chapter 1. Operationally, the use of automated databases requires to define several parameters. Detailed information on each dispensing is available (date of dispensing, duration of the prescription, number of units of administration etc.). Consequently, there is a great discrepancy between the resolution of this information and what is known about actual consumption. In the present study, the key problem was that it was not known what dispensing sequences meant in terms of actual drug consumption. Any

interpretation may not reflect the truth. Therefore, the adopted approach was consistency. Rules were developed for the purpose of exposure characterization and are described below.

Exposure: Exposure to NANSAIDs (or ASA) was defined as NANSAID (or ASA) use within 30 days prior to the event. Operationally, it consisted of the dispensing of an NANSAID (or ASA) during the 30 days prior to admission as well as those dispensed before but ending within the 30 days. Because of the availability of long term information on drug use (3 years before admission), data truncation was not a concern and it was possible to identify all prescriptions that started before and ended within the 30 days.

Because of differences in the mechanism of action and accuracy of data (wider availability of ASA over-the-counter), NANSAIDs and ASA were studied separately.

Average daily doses: The average daily dose (ADD) was estimated from the dose per unit of administration, the quantity and the number of days of therapy. The following relationship was used:

$$ADD = \frac{\text{Dose/unit of administration} * \text{Quantity}}{\text{Prescribed number of days of therapy}}$$

Individual NSAIDs were not compared to each other. Comparison of ADDs was only made within one product. Hence, no equivalence of

ADDs between products was necessary.

3.11.3 Characterization of past exposure to NSAIDs

Past NANSAID (or ASA) use: Past NANSAID (or ASA) use was defined as the use of an NANSAID (or ASA) anytime between 31 days and 3 years before admission. Past exposure was mutually exclusive with recent exposure. If a prescription started before 30 days and ended within the 30 days then it was considered as recent exposure and not as past exposure. Although data were ascertained on a long term basis, there was truncation of the data if the patient was exposed before the 3 years. It was not possible to obtain such information and the extent of misclassification could not be assessed. Entry in the cohort is determined by an event: becoming age 65. As described in section 3.11.8 below, a sensitivity analysis was conducted to assess the impact of data truncation on the results.

Patterns of NANSAID use: In order to evaluate the impact of patterns in risk assessment, it was necessary to develop the methodology to study this issue. Two major elements were addressed: 1) the method to measure patterns and, 2) the method to consider patterns in data analysis. The objective was therefore to characterize patterns of drug use over time in a way that was

amenable to data analysis in the framework of risk assessment.

1) Method to measure patterns: Patterns of NANSAID use over a period of 1 year prior to admission were characterized. As seen before, drug utilization over time is a complex process. It was therefore necessary to extract some of its dimensions. In the literature, 2 dimensions have been considered: duration (Leufkens et al., 1990) and switches (Leufkens et al., 1990; Abenhaim et al., 1991; Walker et al., 1992). These were retained in order to assess their relevance in risk assessment. As discussed previously in chapter 1, in the context of risk assessment it is necessary to also consider the timing of exposure relative to the event. Thus, the dimension of recency was added to the 2 previous ones. In order to measure these 3 dimensions, it was necessary to have longitudinal data on drug exposure for every individual.

Recency: Recency was defined as the time between the occurrence of the event (date of admission) and exposure to the drug. In the present study, "recent" users were patients who had an NSAID prescription ending within 30 days prior to the event and "former" users were those who only had a prescription ending between 31 and 365 days before admission.

Duration: As stated above, one of the objectives of the study is to partition the effect of duration of past NSAID use and recent NSAID exposure. The 2 variables were treated as mutually exclusive

in time. Duration was ascertained for a period of 11 months, between 31 and 365 days preceding admission.

Total duration of exposure during this time period was estimated from the date of dispensing and duration of individual prescriptions, both of which are readily available in the RAMQ prescription database. It was first expressed as a continuous variable. When more than one NSAID are dispensed to a patient during a given time period, the distribution of these dispensings in time raises some problems, especially if atypical. The next prescription is not necessarily dispensed the day after termination of the previous one. Often there is an overlap or a gap between two successive dispensings. Four types of sequences may be observed and are depicted in figure 3.2:

Consecutive dispensings: the first NSAID prescription starts and ends before the next one (figure 3.2a),

Overlapping dispensings: the next prescription starts before the end of the previous one (figure 3.2b),

Nested dispensings: the next prescription starts after and ends before the previous one (figure 3.2c),

Multiple dispensings: two prescriptions or more (same or different

products) are dispensed on the same date (figure 3.2d).

The dispensing sequences observed in an automated database are theoretical and are a proxy for actual consumption patterns. As a result, there are atypical sequences, which are difficult to interpret because the patient's behaviour is unknown.

The most sensible approach is to seek expert opinion regarding likely consumption behaviour corresponding to the dispensing sequences and to adopt consistency. The proposed rules should be drug-specific. For some individuals, duration may be shorter, for others it may be longer but on average it is expected that it corresponds to the prescribed duration.

For NSAIDs, it was assumed that consumption started on the day of dispensing. The date of termination corresponded to the day of the last unit of administration. Therefore, when boundaries were set, date of start and date of termination were inclusive:

- Date of start = Date of dispensing
- Date of termination = (Date of dispensing+Duration) - 1

For single or non-overlapping prescriptions, it was assumed that the patient was compliant to the entire treatment. Duration of exposure was the sum of the number of days of each prescription. When there was an overlap between 2 prescriptions, it was assumed

that the patient did not finish entirely the first prescription. Total duration was the sum of individual durations minus the overlap. This approach was also adopted by Leufkens et al. (1990) and Strom (personal communication). In contrast, Griffin et al. (1991) used the total number of days of supply as the duration of exposure. In the present study, the maximum duration was, by design, 335 days (from 31 to 365 days prior to admission, inclusive).

Prescriptions that started before 365 days only contributed the number of days included in the year before admission. Those that started before the 30 days but ended after did not contribute any duration because they were considered as recent exposure.

Prescriptions dispensed on the same date were considered as multiple exposure. If one had a longer duration than the other, then the longest duration was retained.

Switches: A switch between products was considered to be a change in NANSAID product between 2 consecutive dispensings. In order to ensure that the medication was for the same treatment episode (indication), dates of dispensing had to be at most 60 days apart. This condition was designed by Walker et al.(1992). Two different products dispensed on the same date were not considered a switch but a multiple.

If three dispensings were considered at a time instead of 2 (figure 3.3), then two possible interpretations were possible. In the first, the patient switched from product 1 to product 2 and back to product 1. In the second, product 1 was not interrupted and product 2 was used concurrently for a short period of time (nested consumption).

Operationally, the interpretation of such scenario depends on whether a model with or without memory is used. In a model with memory, over time, the patient did not switch from product 1 to 2 because treatment with product 1 was not interrupted. Product 2 was simply incorporated and the individual was a multiple user for a short period of time (nested consumption). In the model without memory, the patient switched twice: between product 1 and 2, and between product 2 and 1. In the case of NANSAIDs, expert opinion was sought and a model without memory was the most appropriate to reflect consumption patterns. Patients who receive another dispensing before the termination of the first one most likely switched.

Several criteria were used to define a switch between products:

1) The drugs had to be different NANSAIDs,

2) The next drug had to be dispensed after the first one (Date of dispensing 2 > Date of dispensing 1),

3) The dates of dispensing had to be 60 days apart or less.

There must not necessarily be termination of treatment 1 before the end of treatment with drug 2 (date of termination 2 > date of termination 1 or date of termination 2 ≤ date of termination 1). It was assumed that treatment 1 ended the day before treatment 2 was dispensed.

The same definition was applied to switches between average daily doses and modes of administration with the additional condition that the 2 consecutive dispensings had to be for the same product. Switches between ADDs could be an increase or a decrease. The direction of the switch was recorded.

For descriptive purposes, duration and switching were expressed as continuous variables (number of days, number of switches).

In summary, several assumptions were made in the study of patterns, namely:

1) The date of dispensing corresponds to the date of the start of treatment,

2) For non-overlapping prescriptions, all units that have been dispensed have been consumed for the prescribed number of days,

3) For overlapping prescriptions, the duration of each prescription is the number of days until the dispensing of the next one,

4) In the case of a switch, individuals interrupted treatment with the first product in order to start the second. It was assumed that there was no multiple use during the days where prescribed durations overlapped.

Patterns were assessed only during the year preceding admission for 2 reasons:

1) When very long time intervals are used (eg. 3 years), one must consider the distribution of total duration in time (for eg. 100 days 3 years ago may not be the same as 100 days during the year preceding admission, or 100 days distributed over 3 years). Timing of duration and switches would have to be considered as another dimension and it was felt that the current study did not have enough power to do so,

2) To remain consistent with the Leufkens et al. study which considered duration during 1 year but did not assess the effect of patterns on the risk of adverse event.

2) Characterization of patterns for risk assessment: As mentionned in chapter 1, patterns of drug utilization may be risk modifiers. Drug utilization, as described above, is a continuous variable. The objective of the analysis was to be able to identify patterns associated with a higher risk of UGIB. Patterns were characterized in order to meet the following criteria:

- Clinically meaningful,
- Interpretable,
- Amenable to identify high risk groups,
- Quantifiable in a relatively simple way so that they could be used routinely in pharmacoepidemiologic studies.

Based on these criteria it appears that the most appropriate way to characterize patterns for risk assessment is to express them as a categorical variable. Ultimately, the risk of UGIB would be reported for each pattern. Differences between patterns in the magnitude of the association would allow to identify high risk groups.

As discussed in chapter 2, a major deficiency in published studies is that duration of drug use was assessed in currently exposed patients only. In statistical terms, the model did not include 2 independent variables but rather, 1 exposure variable with several levels. The method of analysis used in these studies would therefore not allow to report a measure of association between

NSAID and UGIB for each pattern.

As discussed above, patterns in the context of risk assessment were expressed as categorical variables. Levels for the dimension of recency were defined a priori and were based on the study by Griffin et al. (1991). For the dimensions of duration and switches, cut-off points for the various levels were based on results from the univariate analyses.

Recency: The effect of recency on the risk was assessed by characterizing this variable as 3 levels:

- None: no NANSAIDs dispensing during the year preceding the event
- Former use: NANSAIDs ending between 31 and 365 days before the event only
- Recent use: NANSAIDs dispensed or ending within 30 days prior to the event.

No use of NANSAIDs during the year prior to the event was the reference category.

Duration: Total duration of exposure between 31 and 365 days prior to the event was categorized into 4 levels:

- None: No NANSAIDs dispensed between 31 and 365 days prior to admission

- Short-term: 1-30 days of use between 31 and 365 days prior to admission

- Intermediate: 31-120 days of use between 31 and 365 days prior to admission

- Long-term: >120 days of use between 31 and 365 days prior to admission

No use of NANSAIDs between 31 and 365 days preceding the event was used as the reference category.

In the Leufkens et al. (1990) study, 3 levels were considered. The lowest cut-off point (≤ 30 days) was selected a priori because it corresponded to the duration of most NANSAID prescriptions. The second (210 days) was data-based and corresponded to the 95th percentile of the distribution of duration in that study. In the present study, the same argument was used to determine the cut-off of 30 days because it was likely to include mostly first-time users. The second cut-off was selected to ensure an adequate sample size in each category. It also corresponded to the point in the Carson et al. (1987) study beyond which there was a decrease in the risk of UGIB (i.e., 4th prescription, which would correspond to approximately 120 days).

Switches: The dimension of switching was expressed as a categorical variable. There were 3 levels that were data-based:

- None: No use of NANSAIDs between 31 and 365 days prior to admission
- Past use between 31 and 365 days prior to admission - no switch
- Past use between 31 and 365 days prior to admission - at least 1 switch between products

No use of NANSAIDs between 31 and 365 days before the event was the reference category.

3.11.4 Low doses of non-steroidal anti-inflammatory drugs

Depending on the indication, NSAIDs are prescribed at different doses. For example, low doses of ASA are prescribed in the prevention of strokes. An analgesic dose of NANSAIDs is lower than an anti-inflammatory dose. Low doses of NSAIDs may not be associated with a greater risk of UGIB. This study did not offer sufficient power to assess the risk associated with various doses of individual NANSAIDs but an attempt was made to study the risk associated with various doses of ASA. In order to address this issue, a univariate analysis was conducted to describe the distribution of the estimated average daily doses (ADDs) of ASA.

Because there was no a priori definition for low dose ASA, dose categories were data-based. The ADD of the last ASA prescription before admission was used. This approach was also used by Griffin et al. (1991). Based on the results of the univariate analysis, ADDs of ASA were categorized into 2 groups: < 650 mg/day and ≥ 650 mg/day. No use of ASA within 30 days prior to admission was the reference category.

3.11.5 Other study variables

Factors other than NSAIDs are known to affect the occurrence of UGIB and may influence the measure of association between NSAIDs and UGIB. Variables that have been confirmed as confounders in the literature (age, sex) were matched for while the confounding effect of the others was assessed in the analysis stage. Risk or effect modification was described.

Other drugs: Other drugs that have been prescribed during the 3 years, such as H_2 antagonists, antacids and anticholinergics, were ascertained from the RAMQ prescription database and were considered as potential confounders or effect modifiers. Recent and past use of these agents were distinguished because the timing of exposure to these agents may reflect different underlying processes. Recent use of these agents may reflect a protective effect if used for prophylaxis, while past use may be a proxy for history of

gastropathy. Concomitant use of drugs, such as corticosteroids, anticoagulants and antineoplastics are known to predispose to UGIB. They were considered as potential confounders.

Other factors: Data from the literature suggest that smoking is a predisposing factor. Its independent and confounding effect was assessed in this elderly population. Although indication may be a potential confounder, it was not possible to obtain data on indication because it does not appear in the prescription database. Although the diagnosis for a medical service is present in the RAMQ medical services database, it cannot be considered valid for the indication of a prescription (Strom and Morse, 1988). It was shown that the diagnosis appearing in the medical services database represented illnesses commonly found in the population and not necessarily the indication for prescribed medications. Moreover, the diagnosis was only present in approximately 50% of the medical services because this information is not required from the physicians in order to receive a fee-for-service. Contraindications for NSAID use were recorded. Among them were the use of anticoagulants, corticosteroids and antineoplastics, history of gastric problems and, diseases leading to contraindications for NSAIDs (cancer, aplastic anemia, renal failure, alcoholism, cirrhosis and hepatitis). Information on smoking, history of gastropathy and concomitant diseases was obtained from the charts.

History of gastropathy: For the purpose of this study, history of GI illnesses was assessed by chart review. Past use of protective agents (ascertained in the prescription database), history of upper GI procedures and past visit to a gastroenterologist (ascertained from the medical services database) were considered as suggestive history. History was considered positive if the patient had received an upper GI procedure or had visited a gastroenterologist between 61 days and 3 years preceding admission. All of them were characterized as dichotomous variables (i.e. positive and negative history). Each measure was treated as an independent variable. Sixty days before admission was chosen as a cut-off point in order to be reasonably certain that the procedure or visit did not pertain to the current episode of gastropathy. Past use of protective agents was defined as exposure to these drugs between 31 days and 3 years preceding admission. As with NSAID exposure, past and recent exposure were mutually exclusive. A prescription that was dispensed before the 30 days but that ended within was considered as recent exposure only. Unlike the 3 other measures, history assessed in the chart was not subject to data truncation because it was not restricted to 3 years before. It could go back very far in time and was limited by the patient's memory or information on prior admissions in the medical chart.

The variables used to characterize drug utilization and history of gastropathy are defined in table 3.2. The characterization of all study variables is summarized in table 3.3.

3.11.6 Univariate analyses

Univariate analyses were conducted in order to describe the variation in the mode of utilization of NSAIDs in the study population. A measure of central tendency was obtained for continuous variables (duration of past NANSAID use, number of days since last switch, ADDs etc.). Frequency distributions were obtained for categorical variables. The heterogeneity of the distribution of the study population into the various levels of a categorical variable was assessed by the chi-square test. No trend was assumed a priori for multi-categorical variables and, as a result, no chi-square test for trend was used. All probability (p) values were two tailed; a p value of 0.05 or less was considered to be significant.

3.11.7 Risk quantification

Bivariate analyses: Bivariate analyses were conducted in order to select potential confounders and/or effect modifiers. Variables were considered as potential confounders if they met the following conditions: 1) association with UGIB and, 2) association with recent exposure to NSAIDs in cases and controls. The covariates considered were all categorical and the heterogeneity of the distribution of cases and controls (condition 1) or exposed and unexposed (condition 2) across the various levels of the covariate

was assessed using the chi-square test. A crude odds ratio (OR) was obtained to assess the association between the variable and UGIB. The 95% confidence interval (CI) for the OR was calculated using Miettinen's test-based approximation (Kirkwood, 1988). Data manipulation and stratified analyses were conducted using the SAS statistical package (Anonymous a, 1987).

Multivariate analyses: The relative risk adjusted for selected covariates was estimated by the OR calculated from an unconditional logistic regression analysis. According to Breslow and Day (1980), the logistic regression is a valid multivariate method. Although data were matched, there was more than 1 case per combination of matching variables. Matching was therefore not considered as one to one. In this case, it is expected that estimates obtained from the conditional regression would not be biased but may be more conservative because of a greater variance. An unconditional logistic regression was therefore conducted and residual confounding was determined by fitting in the model the various matching variables.

For each variable included in the model, the estimated beta coefficient was obtained. For dummy variables and any dichotomous variable, the OR was obtained by exponentiating the beta coefficient. The 95% CI was computed by taking the estimated coefficient and adding and subtracting the proper normal deviation times the standard error, and finally exponentiating these values.

Multivariate analyses were conducted using the EGRET statistical package (Anonymous b, 1991).

Multivariate analyses were conducted to determine the extent to which various independent variables influenced the risk of UGIB in this population. A forward multivariate logistic regression strategy was adopted. The main determinants were recent NANSAID use and recent ASA use. Covariates were initially selected according to the results from the bivariate analyses. All independent variables fitted in the model were fixed effects and the risk type was multiplicative. The deviance was used as a measure of goodness-of-fit because it should approximately follow a chi-square distribution with the residual degrees of freedom. The significance of a parameter was assessed by the likelihood ratio statistic (LRS) which was the difference between the deviances of original and extended fitted models. The significance was assessed by the chi-square test and the number of degrees of freedom corresponded to the difference between the 2 models in the number of parameters. Only variables with a significant effect on UGIB were retained in the final model.

Collinearity between two parameters was assessed by examining the change in the beta coefficient and the OR of each parameter when the second was fitted. If each parameter alone had an effect but when both fitted none had an effect, then it is likely that there was collinearity between these parameters.

Interactions were fitted. The interaction terms were chosen on the basis of plausibility and statistical considerations. They always included recent NANSAID or recent ASA use as one of the interaction terms.

Strategy to assess confounding and effect modification: Confounding was assessed by comparing the crude OR with the OR obtained after the control of one or simultaneous risk factors. The significance of a risk factor was assessed by the chi-square test of the likelihood ratio. If the independent variable was a significant predictor of UGIB, then an interaction was fitted. If the interaction was significant, then the estimate of the OR for recent NANSAID or ASA use was reported for each level of the covariate.

Regression diagnostics: The unstandardized delta-betas are approximations of the amount that a given regression coefficient would change if that observation were eliminated from the regression (Anonymous b, 1991). Because all covariates were categorical, it was not appropriate to use a plot of the unstandardized delta-betas to assess the stability of the model. The deviance was used to assess the goodness of fit of the model.

Stratum-specific estimates of relative risk: A stratified analysis was conducted. In order to identify high risk patterns of NANSAID use, the magnitude of the association between recent NANSAID use

and UGIB corresponding to each duration and switching pattern was estimated by a crude OR. The Breslow-Day test was used to assess the homogeneity of the ORs. A significant heterogeneity of the ORs indicated the presence of effect modification by patterns.

Multivariate logistic regression models: The following models were fitted sequentially.

1) Exposure to NSAIDs: Recent exposure to NANSAIDs and to ASA within 30 days prior admission were the major determinants. The OR for each of the 2 classes of NSAIDs was obtained using the unexposed within 30 days as the reference category.

2) Past exposure to NSAIDs: An adjusted OR was obtained to measure the independent effect of past use of NANSAIDs and ASA, assessed over a period of 3 years prior to admission, on UGIB . The reference category was the unexposed between 31 days and 3 years prior to admission. Confounding was determined according to the strategy described above. A stratified analysis was conducted in order to obtain the crude ORs for the association between recent use of NANSAIDs and UGIB for patients who had never used the drugs in the 3 years before admission and those who did at least once during this time period.

3) Patterns of non-aspirin NSAID use

Recency: A multivariate logistic analysis was conducted to obtain an adjusted OR for the 2 levels of recency (recent and former), using the never exposed during the year as the reference category.

Duration: A stratified analysis was conducted to obtain a crude OR specific for each of the 4 patterns of duration, i.e. patients who did not use the drug between 31 and 365 days before admission, short-term, intermediate and long-term users. In contrast to the dimension of recency, the reference category for the association between recent exposure to NANSAIDs and UGIB was the unexposed within 30 days prior to the event.

Switches: Similarly, a crude OR was assessed for each switching pattern, i.e. patients who never used the drug, those who did but did not switch and, those who switched products at least once.

4) Concomitant use of protective agents: The independent effect of recent exposure to protective agents within 30 days prior to admission was assessed by fitting this variable in the multivariate logistic regression model. The reference category was no exposure to these agents during the time window. The assessment of confounding and effect modification on recent NANSAID and recent ASA use was done according to the strategy described above.

5) History of gastropathy: The independent effect of history of gastropathy was assessed by fitting the variable in the multivariate logistic model. One model was fitted for each of the four markers: History of upper GI procedures, past visit to a gastroenterologist, past use of protective agents, history assessed in the medical charts. The stability of the results was assessed.

6) Smoking: An adjusted OR was obtained for ex- and current smokers.

7) Average daily doses of ASA: An analysis was conducted to determine if there was difference in the risk between doses of ASA. An adjusted OR was obtained for each of the 2 categories of ADD of ASA (<650 , $\geq$ 650 mg/day). No exposure to ASA within 30 days prior to the event was the reference category. There was no a priori hypothesis of a dose-response relationship (eg. linear). Doses were fitted as a categorical variable in the multivariate model.

3.11.8 Sensitivity analysis

Control diagnoses: As discussed in the section on the selection of controls, a major assumption was that the control diagnoses were unrelated to exposure to NSAIDs. If there were a positive association between NSAIDs and a control diagnosis, then the OR for

the effect of NSAIDs and UGIB would be biased towards tne null. The converse would be true if there were a negative association between NSAIDs and the control diagnosis. A priori, it was felt that the selected control diagnoses were unrelated to NSAID use. However, unknown associations may exist. Six categories of control diagnoses were created: respiratory illnesses, cholecystitis, trauma, other urinary tract illnesses, other GI conditions and, the broad category of "other diagnoses". A sensitivity analysis was conducted in which each control diagnostic category was removed from the analysis one at the time. The stability of the results was assessed.

Hospital: Differences may exist between the catchment populations of the various hospitals, which would limit the generalizability of the findings. In order to appraise the extent of this selection bias, a sensitivity analysis was conducted where each hospital was removed from the analysis one at a time and the stability of the results was assessed.

Study year: Information bias due to OTC availability of drugs is of concern with the use of automated databases. It was not possible in the current settings to appraise the extent of the bias because no information on OTC drugs were available. Incidentally, ibuprofen was released OTC between the 2 study years. In order to appraise the extent of the bias for NANSAIDs, ORs were obtained specifically for each of the 2 years and the direction of the bias

was determined. It was not possible to appraise the extent of the information bias for ASA.

3.11.9 Data truncation

Data on prescriptions dispensed were assessed for a period of 3 years prior to admission. The impact of data truncation was assessed. The purpose of this analysis was to predict the direction and appraise the extent of the bias attributable to the truncation of information prior to the 3 years. So far in published studies, the maximum period of time considered was 1 year (Griffin et al., 1991) which results in an even greater truncation. The effect of data truncation was examined for the following variables: past exposure to NANSAIDs, past exposure to protective agents and history of upper GI procedures. The impact of data truncation was appraised by comparing the independent effect of these variables on UGIB as well as their effect on the association between NANSAID use and UGIB when assessed for a period of 1 year, 2 years and 3 years. The direction of the effect of the truncation of data prior to 3 years before admission could therefore be predicted. Although the truncation effect could not be extrapolated beyond the 3 years, its magnitude could be appraised.

TABLE 3.1

Controls used in published epidemiologic studies on NSAID-gastropathy

STUDY	METHOD	DESCRIPTION
Coggon et al. (1982)	Local general practices	Community
Clinch et al. (1983)	Endoscopy service	Patients without lesions
Collier and Pain (1985)	Admission registry (no diagnosis)	Admissions for surgical emergencies
Bartle et al. (1986)	Not specified	- Hospitalized medical patients - Visitors
Duggan et al. (1986)	Not specified	Surgical or dermatological clinics (first time attendance)
Somerville et al. (1986)	- Not specified - Listings of general practice of cases	- Same acute medical intake as cases - Community
Armstrong and Blower (1987)	Consecutive admissions	Not specified
Henry et al. (1987)	Health Statistics Unit (information on 4 public hospitals)	Patients with peptic ulcers who survived
Smedley et al. (1988)	Not specified	Not specified
Jick et al. (1987)	GHC pharmacy files	Unrestricted

TABLE 3.1 (cont'd)

Controls used in published epidemiologic studies on NSAID-gastropathy

Carson et al. (1988)	Members of COMPASS	Random selection of NSAID users who did not develop UGIB
Levy et al. (1988)	Selection of diagnoses (admission records)	Trauma, appendicitis, uterine prolapse, benign prostatic hypertrophy, hernia, hemorrhoids
Campbell and Steele (1991)	1. Emergency admissions 2. List of patients in the department of Surgery	1. Random 2. Uncomplicated diverticular disease
Laporte et al. (1991)	Admissions	Non-alcohol related trauma, acute appendicitis, other abdominal emergencies, elective surgery for non-painful disorders
Henry et al. (1991)	New admissions	Primary diagnoses thought to be unrelated to NSAIDs (not specified)
Griffin et al. (1991)	Medicaid enrollees	Random selection of members alive on index date
Holvoet et al. (1991)	Admissions	Next patients admitted to department of Medicine

TABLE 3.2

Glossary for the variables used to characterize drug utilization and history of gastropathy

Recent NANSAID (or ASA) use:

Non-aspirin NSAID (ASA) prescription dispensed or ending during the 30 days prior to admission.

Past NANSAID (or ASA) use:

Non-aspirin NSAID (or ASA) prescription ending between 31 days and 3 years prior to admission.

Patterns of NANSAID use:

- **Recency**

  - Recent: NANSAID prescription dispensed or ending during the 30 days prior to admission
  - Former: NANSAID prescription ending only between 31 and 365 days prior to admission (no recent use)
  - None: No NANSAID prescription dispensed or ending during the year prior to admission (non-recent, non-former).

TABLE 3.2(cont'd)

Glossary for the variables used to characterize drug utilization and history of gastropathy

- **Duration**
  - None: No NANSAID prescription ending between 31 and 365 days prior to admission
  - Short-term: NANSAID use for a duration ranging from 1 to 30 days, between 31 and 365 days prior to admission
  - Intermediate: NANSAID use for a duration ranging from 31 to 120 days, between 31 and 365 days prior to admission
  - Long-term: NANSAID use for a duration of more than 120 days, between 31 and 365 days prior to admission

- **Switching**
  - None: No NANSAID prescription ending between 31 and 365 days prior to admission
  - Past use - no switch: NANSAID prescription ending between 31 and 365 days prior to the event, no switch between products
  - Past use - switch: NANSAID prescription ending between 31 and 365 days prior to the event, at least 1 switch between products.

TABLE 3.2(cont'd)

Glossary for the variables used to characterize drug utilization and history of gastropathy

Recent use of protective agents:

Protective agent (anticholinergic, antacid or H_2 antagonist) dispensed or prescription ending within 30 days prior to the event.

History of gastropathy

- **Past use of protective agents:**

Prescription of a protective agent ending between 31 and 365 days prior to admission.

- **Past upper GI procedure:**

Upper GI procedure (gastroscopy, duodenoscopy, biopsy of the upper GI tract, X-ray of upper GI tract) received between 61 days and 3 years prior to admission.

- **Past visit to a gastroenterologist:**

Visit to a gastroenterologist between 61 day and 3 years prior to admission.

TABLE 3.3

Characterization of the variables considered in data analysis

Variable	Type	Unit
Dependent:		
UGIB	Dichotomous	Dummy variable: 0=control 1=case
Independent:		
Recent exposure to NANSAIDs or ASA	Dichotomous	Dummy variable: 0=unexposed 1=exposed
Recency	Trichotomous	Dummy variable: 0=none in year prior to admission 1=exposed only between 31 and 365 days 2=exposed within 30 days prior to admission
Past exposure to NANSAIDs (ASA)	Dichotomous	Dummy variable: 0=never during 3 years prior to admission 1=at least once during 3 years prior to admission
Duration pattern	Polychotomous	Dummy variable: 0=none in year prior to admission 1= 1- $\leq$ 30 days 2= 31-120 days 3= > 120 days
Switching pattern	Trichotomous	Dummy variable: 0=none in year prior to admission 1=exposed-no switch 2=exposed-at least 1 switch
Recent use of protective agents	Dichotomous	Dummy variable: 0=no use in 30 days prior to admission 1=exposed within 30 days prior to admission

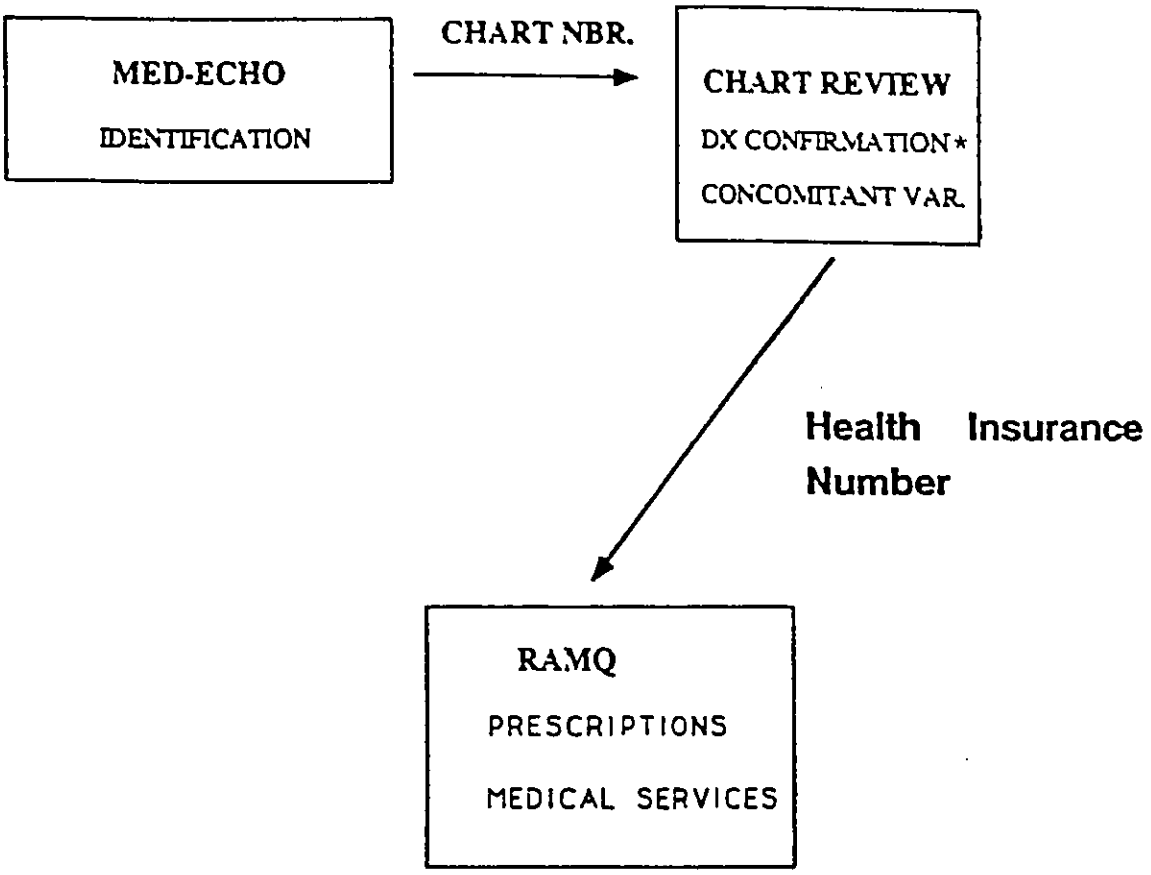
TABLE 3.3(cont'd)

Characterization of the variables considered in data analysis

Variable	Type	Unit
Past use of protective agents	Dichotomous	Dummy variable 0=none in 3 years prior to admission 1=at least once in 3 years prior to admission
Recent use of Corticosteroid Anticoagulants Antineoplastic	Dichotomous	Dummy variable 0=no use in 30 days prior to admission 1=use in 30 days prior to admission
Average daily dose of ASA	Polychotomous	Dummy variable: 0=none 1= < 650 mg/day 2= ≥ 650 mg/day
History of gastropathy	Dichotomous	Dummy variable: 0=negative 1=positive
Smoking	Trichotomous	Dummy variable: 0=never 1=ex-smoker 2=current smoker
Duration of past exposure to NANSAIDs	Continuous	Days
Nbr.switches	Count	---
Recency of switches	Continuous	Number of days since last switch
ADDs of ASA	Continuous	Multiples of 325 mg

FIGURE 3.1

Logistics for the linkage of data



* Dx confirmation = Confirmation of diagnosis of cases

FIGURE 3.2

Dispensing patterns of non-aspirin NSAIDs

Figure 3.2a Consecutive dispensings

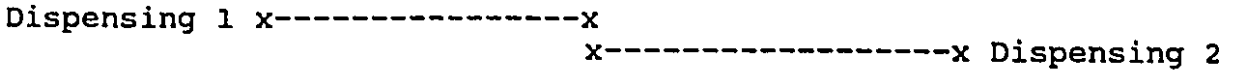


Figure 3.2b Overlapping dispensings

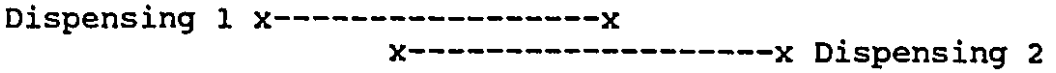


Figure 3.2c Nested dispensings

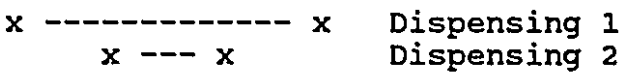
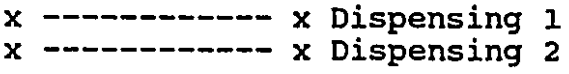
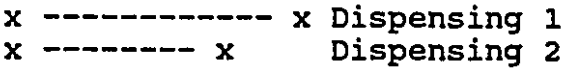


Figure 3.2d Multiple dispensings



or,



Note: These patterns all refer to consecutive dispensings of the same non-aspirin NSAID product

FIGURE 3.3

Switching patterns of non-aspirin NSAIDs

(1) First dispensing of the first non-aspirin NSAID product
(2) First dispensing of the second non-aspirin NSAID product
(3) Second dispensing of the first non-aspirin NSAID product

CHAPTER 4

RESULTS

In this chapter are reported results obtained in the study. There are 3 main sections. The first consists of the description of the study population in terms of structure, diagnoses, comorbidity etc. Second, results obtained from univariate and bivariate analyses are presented. This section also includes findings from multivariate logistic regression analyses. The third section focuses on the description of patterns of NSAID use and their effect on the risk of UGIB. Further descriptive analyses are presented in tables included in appendix B.

4.1 DESCRIPTION OF THE STUDY POPULATION

Description: The study population consisted of 244 cases and 615 controls. The sex, age group, hospital and study year distributions are displayed in table 4.1. The women:men ratio was 1.01:1 which differs from the sex ratio in the province of Quebec for people age 65 and over of 1.47:1 (according to the 1986 census). The greatest proportion of patients was found in the 75-79 age group (31.9%) and the least in the 68-69 years old (8.9%). The greatest proportion of patients was recruited at the Maisonneuve-Rosemont Hospital, and the least at the Royal-Victoria (35.6% and 15.1%, respectively). The 2 study years contributed the same

proportion of patients (51.1% versus 48.9% for the year 1988/89 and 51.1% for 1989/90).

Matching: The control:case ratio varied between matched sets and averaged 2.52:1. It was not feasible to recruit 4 matched controls per case because: 1) the pool of potential controls was not large enough initially, 2) it was not always possible to find a substitute who met all matching criteria to replace non-eligible controls.

The matching criteria of age (± 5 years), sex, hospital and study year were always met. That of month of admission had to be relaxed for 2 reasons: 1) the pool of eligible controls was not large enough, especially for very old patients, in particular men and, 2) as described in chapter 3, the exact dates of admission were not known a priori in the HMRI discharge listings (Royal-Victoria and Jewish General hospitals). An attempt was made to reorganize controls a posteriori but sometimes it was not feasible. As a result, matching was within ± 2 months for 97.8% of controls and within ± 3 months for the remainder (2.2%).

4.2 CAUSES OF NON-ELIGIBILITY

Non-eligibility was assessed at 2 levels: first, during chart review and then, during the cleaning up of the database. A total

of 1405 reviewed charts (532 potential cases and 873 potential controls) led to 252 eligible cases and 642 controls. During the cleaning up of the database, 4 other cases and 14 controls were lost for the following reasons: 1) duplication during the study period (2 cases and 9 controls) and, 2) no match (2 cases and 5 controls).

The following discussion will focus on non-eligibility at chart review. Frequencies reported below are based on the number of eligible patients before the loss during cleaning up of the database, i.e. 252 cases and 642 controls.

Sixty-four patients (12.1% of non-eligible) had up to 2 reasons to be ineligible. The unit of analysis was the cause of non-eligibility and all were treated independently.

4.2.1 Cases

The percentage eligibility was 46.6% for cases, which is consistent with the 43% obtained during the feasibility study. The relative importance of the various causes of non-eligibility is shown in table 4.2a. The most frequent causes were: 1) lower GI bleeding (21.6%), 2) unconfirmed diagnosis (20.4%) and, 3) chronicity (17.6%).

*Diagnosis:*The percentage eligibility varied between ICD-9 categories (table 4.2b). It was greater for all types of ulcers (approximately 70%), while it was much lower for gastro-intestinal bleeding (16.4%). This discrepancy reflects differences in specificity between diagnoses. As expected, the eligibility for melaena was only 7.7%. This category was selected at the design stage in order to ensure not missing any cases. The initial approach focused more on sensitivity than specificity. Table 4.2c reports the most common causes of non-eligibility by diagnosis. For all types of ulcer, it was chronicity (35.9% for gastric and, 25.0% each for duodenal and peptic ulcers) while for gastro-intestinal bleeding, it was lower GI bleeding (30.0%), which is consistent with the fact that this category is non-specific with respect to the pathologies included.

4.2.2 Controls

The percentage eligibility for controls was 71.7%. According to table 4.2a, the 3 most frequent causes of non-eligibility were: 1) chronicity (27.5%), 2) cancer of the GI tract (15.0%) and, 3) transfer from another hospital (11.3%).

Diagnosis: Causes of non-eligibility were reported for each major control diagnosis (table 4.3). Chronicity was the major cause for pneumonia and cholecystitis (62.3% and 14.9%, respectively) while

for trauma, it was transfer from another hospital (30.8%).

Non-eligibility by sex, age groups and hospital for cases and controls is found in appendix B.

In summary, the most common cause of non-eligibility for cases was lower GI bleeding. These patients were mainly found in the non-specific ICD-9 category of gastro-intestinal bleeding and melaena. For controls, the major cause was chronicity. The relative importance of the various causes varied between the selected ICD-9 categories but were similar for sexes, age groups, hospitals and study years.

In addition to non-eligibility at chart review and at cleaning up of the database, there were 17 patients (4 cases and 13 controls) who did not receive any pharmaceutical services during 3 years prior and 2 years after admission. These patients may not have received prescriptions or they may not have been in the system. Among the possible explanations for the latter are: living in a tertiary care hospital (where drugs are provided by the hospital and are not administered by the RAMQ) or, these patients paid for their prescribed medications. It was not possible to verify any of these hypotheses because of the confidentiality nature of the database (the patient identifier was scrambled). However, it is known that these patients received at least one medical service during this time period. Their presence in the medical services

database confirms their residency status. This pattern of services (presence of medical service, absence of pharmaceutical service) favours the hypothesis of data truncation rather than absence of medications, especially since these patients had received prescriptions outside the time window. As described in chapter 3, an exclusion criterion was created at the design stage to minimize such information bias whereby patients who had been admitted for long periods of time during the 3 years preceding admission were not eligible for the study. This information was perhaps not available in the chart and escaped the screening criterion. However, because it was unclear, these patients were not considered for analysis.

In accordance with confidentiality procedures, detailed information on diagnoses and hospitalization parameters was analyzed before linkage with the RAMQ databases. As a result, it was not possible to sort out these 17 patients from the initial study population for the descriptive analysis described below. However, it was taken into account in the bivariate analyses and in the analytic component of data analysis. As a result, the denominator for the description of the diagnoses (section 4.3) is based on 248 cases and 628 controls, while that of the univariate and bivariate analyses (section 4.6) is based on 244 cases and 615 controls.

4.3 DESCRIPTION OF DIAGNOSES

4.3.1 Cases

All diagnoses: After chart review and cleaning up of the database, there were 248 eligible cases. The case diagnoses were listed either as principal, secondary or death. Thirty-three cases had 2 eligible diagnoses and 6 cases had 3. Consequently, the total number of eligible diagnoses was 293. The distribution by diagnosis (principal, secondary or death diagnosis) and by hospital is described in table 4.4. The greatest proportion of diagnoses was gastric ulcers (34.8%) followed by duodenal ulcers (30.4%). Peptic ulcers accounted for the least: 4.8%. Gastritis and duodenitis were included in the broad category of gastro-intestinal bleeding.

It was possible to identify patients who died during hospitalization from the discharge listings (HMRI or Med-Echo). Of the 248 cases, 51 (20.6%) died during the admission for the gastropathy.

4.3.2 Controls

The 3 major diagnostic pools of potential controls were: trauma, respiratory illnesses and cholecystitis. These diagnoses accounted

for 30.7%, 29.9% and 15.4% respectively of the control diagnoses. The distribution of all control diagnoses is found in table 4.5. In contrast to cases, only 63 controls died (10.0%) during admission.

4.4 SYMPTOMS

4.4.1 Nature of symptoms

There were 17 different symptoms related to gastropathy (table 4.6). The majority of patients had more than 1 symptom. The distribution of the number of symptoms was: 3 (30.6%), 2 (28.6%), 4 (22.2%), 1 (16.5%) and 0 (2.0%). Symptoms were treated independently for the analysis. Melaena was the most common symptom (21.7%), followed by abdominal pain (18.7%). Symptoms were distributed more or less equally across the other categories. The most common symptom for men was melaena (25.6%) and for women was abdominal pain (20.7%). There was no significant difference in the distribution of symptoms between patients with and without a positive history of gastropathy as determined from chart review ($p<.478$). Cases with a prior history experienced more coffee ground vomiting than those with no history (5.69% versus 3.23%). They also had slightly more haematemesis (8.11% versus 5.38%).

4.4.2 Onset of symptoms

The time of onset of symptoms leading to hospital admission was recorded for both cases and controls. As shown in the table below, the proportion of patients decreased as the duration of symptoms increased.

Onset of symptoms (no. days before admission)	% cases	% controls
≤1 day	39.9	42.7
2-3 days	23.7	18.3
4-7 days	19.5	22.3
8-14 days	7.1	7.9
15-30 days	9.9	9.0

The distribution of onset of symptoms was similar for cases and controls. In approximately 40% of the patients, symptoms were reported to occur within 24 hours of the event, and in approximately 80% within 1 week.

4.5 COMPARISON BETWEEN CASES AND CONTROLS

4.5.1 Comorbidity

Because of the heterogeneity among hospitals in the number of coded

diagnoses , the secondary diagnoses appearing on the summary sheet of the medical chart were pooled with those appearing on the physician's admission notes in order to create a variable called "comorbidity".

Number of comorbid conditions: The number of comorbid conditions per patient ranged from 0 to 20 and the average was 5.31. Most patients had 2 to 8 comorbid conditions. Cases had an average of 5.74 comorbid conditions while controls had 5.14. Men had an average of 5.22 conditions while women had 5.40. The average number of comorbid conditions differed between age groups with a trend of increasing number with increasing age which is consistent with an increase in morbidity with age.

The average number of comorbid conditions differed between hospitals: RVH, 4.10; HND, 5.44; HMR, 5.10; JGH, 5.92. Differences in the age structure of the catchment populations may explain the discrepancy between hospitals. Compared to the other hospitals, a greater proportion of the study population at the JGH was 85 years old or more. Comparative figures for the proportions of patients aged 85 or more are: RVH 8.5%, HND 11.7%, HMR 14.3%, JGH 20.6%. In addition, these results may reflect differences between hospitals in the extent of history taken rather than true differences in morbidity between the various catchment populations.

Types of comorbid conditions: There were a total of 1423 comorbid conditions for cases and 3231 for controls. Using the condition as the unit of analysis, the distribution is shown in table 4.7.

The trend in the prevalence of comorbid conditions was more or less similar for cases and controls, with cardiovascular disease being the most common (27.7%) (because it included hypertension), followed by respiratory illnesses (8.7%) and other GI conditions (8.6%). The prevalence of infections among controls was twice that of cases (3.0% versus 1.2%) because it was directly related to the prevalence of pneumonia (the type of infection was coded by medical archivists in the summary sheet). Differences in comorbidity between sexes is shown in appendix B.

4.5.2 Medical history

The medical history was assessed from the physician's admission notes.

Number of conditions: The minimum number of past conditions was 0 and the maximum was 18. The average was 2.2. The greatest proportion of patients (31.1%) did not have any medical history mentioned in the chart. Cases had an average of 1.75 conditions compared to 2.36 for the controls.

Types of conditions: The distribution of diagnoses is shown in table 4.8. The most common type of past medical illness was cardiovascular disease (22.1% of patients), followed by other GI illnesses (13.3%) and diseases of the genito-urinary tract (10.1%). The distribution was similar for cases and controls. A greater percentage of controls had respiratory and genitourinary conditions. If history of such conditions was a risk factor for current episodes of these diseases, this was not unexpected given that many controls were selected in these diagnostic categories. However, a greater proportion of controls also had trauma in the past. This result was rather unexpected as it would be expected that episodes of trauma would be relatively independent from each other. However, these results suggest that the presence or absence of past illnesses in the chart is greatly influenced by the types of questions asked by the physician at admission. Probing for various diseases varies according to the admission diagnosis: orthopoedists are more likely to inquire about past trauma events, gastroenterologists about history of gastropathy etc.

The distribution of past illnesses by sex is shown in appendix B.

4.6 UNIVARIATE AND BIVARIATE ANALYSES

Univariate and bivariate analyses were based on the denominator of 244 cases and 615 controls (i.e. after excluding the 17 patients with unknown drug consumption).

4.6.1 Individual prescriptions

Duration: During the 3 years preceding admission, the total number of prescriptions dispensed to the entire study population was very similar for NANSAIDs and ASA: 3609 and 3423, respectively. For both classes, the duration of most prescriptions was 30 days. A frequency analysis, reported in table 4.9, revealed that 54.4% of NANSAIDs and 77.7% of ASA prescriptions were for 30 days.

Renewals: As shown in table 4.10, the ratio between new prescriptions and renewals was 1:1.20 for NANSAIDs and 1:2.23 for ASA. Hence, a greater proportion of ASA prescriptions were renewals compared to NANSAIDs.

Individual products: The relative importance of individual NANSAIDs during the 3 years before admission is described in table 4.11. Diclofenac accounted for the greatest proportion of NANSAID prescriptions (17.5%), followed by indomethacin (16.8%) and naproxen (16.5%).

Forms of administration: The forms of administration of the prescriptions received in the 3 years preceding admission are shown in Table 4.12. It can be noted that, for the most part, ASA was enteric-coated (98.5%). The most common forms of administration of NANSAIDs were tablets or capsules (60.2%), followed by enteric-coated capsules or tablets (20.7%). The mode of classification of the various forms of administration in the RAMQ database did not permit to distinguish between tablets and capsules. Long-acting preparations accounted for 9.9% of NANSAIDs prescriptions and suppositories for 9.2%.

4.6.2 Recent exposure to NSAIDs

Of the study population, 248 patients (28.9% of the study population) had an NSAID prescription that ended within 30 days prior to the event. Twenty seven patients (3.1%) were using NANSAIDs and ASA concurrently during this time window. The distribution of users among the various stratifying variables is shown in table 4.13. Almost twice as many cases were exposed to any NSAIDs than controls (40.6% versus 24.2%) (chi-square=22.73, p<.001). The difference between cases and controls was more important for NANSAIDs than for ASA. For NANSAIDs, the proportion of recent exposure was: 27.0% of cases versus 11.2% controls (chi-square=33.047, p<.001). For ASA, it was: 20.1% cases versus 14.8% controls (chi-square=3.577, p=.059). The crude ORs were 2.93

(2.01-4.27) and 1.45 (0.98-2.12), respectively.

There was little difference between men and women regarding recent exposure to all NSAIDs (chi-square=1.352, p=.245). However, when the 2 categories of products were considered separately, more men than women took ASA (20.6% versus 12.0%) (chi-square=11.566, p<.001), while less took NANSAIDs (13.6% versus 17.8%) (chi-square=2.916, p=.088). The greatest proportion of NSAID users was found among the 70-74 years old, both for ASA and NANSAIDs. However, the distribution was not significantly heterogeneous among age groups (chi-square=2.49, p=.115 for NANSAIDs and, chi-square=3.304, p=.552 for ASA).

The distribution of individual NANSAID products during the 30 days preceding the event is shown in table 4.14. For both cases and controls, diclofenac was the most frequent.

4.6.3 Comparison between the two time windows

As described in chapter 3, there is no consensus on the appropriate time window for the assessment of the risk of UGIB following NSAID use. In order to appraise the effect of the time window on the risk, a comparison was made between 7- and 30-day time windows.

Results obtained from both time windows are contrasted in tables

4.15a-b. As expected, for both cases and controls, the proportion of exposed patients was greater when a wider time window was considered. However, the difference was proportionally greater for controls than for cases. This discrepancy resulted in a lower estimate of relative risk for NANSAIDs as well as for ASA. These results indicate that an increase in the width of the time window has a greater influence on the proportion of exposure among controls than among cases which resulted in an under-estimation of the relative risk.

Bivariate analyses were conducted for various covariates and findings are summarized in table 4.19. Results are reported in greater detail below.

4.6.4 Past exposure to NSAIDs

Of the study population, 382 patients (44.5%) received at least 1 NANSAID prescription that ended between 31 days and 3 years preceding admission. The corresponding figure for ASA was 276 (32.1%). The distribution of past exposure among sexes and age groups is presented in appendix B.

Number of prescriptions: The total number of NANSAID prescriptions received by each patient during the 3 years preceding admission (excluding recent exposure) ranged from 1 to 62. The mean was 8.84

and the median was 4. The total number of ASA prescriptions ranged from 1 to 75. The mean was 11.6 and the median was 7.

Association with UGIB: The proportion of cases who received a NANSAIDs in the 3 years preceding admission was similar to that of controls (47.1% versus 43.4%) (chi-square= 0.977, p=.323). The crude OR associated with past use of these drugs was 1.16 (0.86-1.56). The association with past use of ASA was similar: chi-square= 2.420, p=.120 and the crude OR was 1.28 (0.94-1.75).

Association with recent exposure to NSAIDs: There was a strong association between past and recent use of NSAIDs. Of the patients who had been exposed to a NANSAID during the 3 years before, 33.0% were recently exposed, compared to 1.9% of those who had never been exposed before (chi-square=154.865, p<.001). The corresponding figures for ASA were 47.5% and 1.5% (chi-square=289.546, p<.001). Such a strong association is due to the fact that the 30-day time window is specific to this study and is arbitrary with respect to the course of treatment. Hence, long-term users were more likely to have been recently exposed.

4.6.5 Distribution of other potential confounders, risk and effect modifiers.

4.6.5.1 Concomitant exposure to protective agents

Recent use of protective agents was assessed. As described in chapter 3, it consisted of any prescription of these agents dispensed or ending within 30 days prior to the event. The distribution of recent use of protective agents for cases and controls is shown in table 4.16.

Association between recent use of protective agents and UGIB: Significantly more cases than controls were recent users of protective agents (18.0% versus 9.9%) (chi-square=10.720,p<.001). The crude odds ratio associated with recent use of protective agents was 2.0 (1.3-3.04).

Association between recent use of protective agents and NSAID exposure: The association with recent NSAID use was significant for NANSAIDs but not for ASA. Of recent NANSAID users, 24.4% were also using protective agents versus 9.9% of non-users (chi-square=22.296,p<.001). The association with exposure was present in both cases and controls (p=.002 and p=.009, respectively). Conversely, there was no association with ASA use: 15.0% of ASA users were also using protective agents compared to 11.7% of non-users (chi-square=1.202,p=.273).

4.6.5.2 Smoking

Information on smoking was missing in the medical charts of 110 patients (18.4% cases and 10.6% controls). Of the remaining study population, 20.0% were smokers, 25.2% had quit smoking (ex-smokers) and 54.7% were non-smokers. The distribution of smoking among cases and controls is shown in table 4.17.

Association between smoking and UGIB: The distribution of cases and controls into the 3 levels of smoking was significantly heterogeneous (chi-square=12.709, p=.002). More cases were current smokers compared to controls (22.5% versus 15.4%). The proportion of ex-smokers did not differ to a great extent between the 2 groups (22.1% versus 22.0%, respectively). The crude OR for current smokers was 2.06 (1.37-3.09), and for ex-smokers it was 1.42 (0.96-2.10).

Association between smoking and recent exposure to NANSAIDs: Opposite trends were found for cases and controls. Among cases recently exposed to NANSAIDs, a greater proportion of patients were smokers (42.6%) compared to non-smokers (23.1%). In contrast, more unexposed cases were non-smokers (71.4%). For controls, results were similar for patients exposed and unexposed to NANSAIDs; the greatest proportion being non-smokers.

4.6.5.3 History of gastropathy

Bivariate analyses were conducted for each of the four markers of history of gastropathy namely, past upper GI procedures, past visit to a gastroenterologist, past exposure to protective agents and history of gastropathy assessed in the medical chart. The method of ascertainment and respective time windows were described in chapter 3. The association between each marker and UGIB is shown in tables 4.18.

A) History of upper GI procedures

Of the study population, 146 patients (17.0%) had received such a procedure between 61 days and 3 years preceding admission: 65.4% of the procedures were diagnostic gastroscopy, 33.8% upper GI X-ray, and 0.8% duodenoscopy. Slightly more men than women had received these procedures, 18.7% versus 15.3%, but the difference was not significant (chi-square=1.820, p=0.177). The distribution into age groups was not significantly heterogeneous (chi-square=5.673, p=0.225) but point estimates suggest a decreasing trend with increasing age: 22.7% for age 68-69, 18.4% for 70-74, 16.8% for 75-79, 17.9% for 80-84 and 10.8% for ≥ 85 years.

Association between past upper GI procedures and UGIB: 24.2% of cases and 14.2% of controls had received such a procedure. The difference was highly significant (chi-square=12.467, p<.001). The crude OR for the effect of past upper GI procedures on UGIB was 1.93 (1.34-2.80).

Association between past upper GI procedures and recent exposure to NSAIDs: Patients who received such a procedure in the past were not significantly less likely to have used NANSAIDs recently than those who did not: 16.3% versus 17.1% (chi-square=0.056, p=.813). Similar results were obtained for ASA: 15.7% versus 17.3% (chi-square=0.195, p=.659).

B) History of visit to a gastroenterologist

Of the study population, 191 patients (22.2%) had seen a gastroenterologist between 61 days and 3 years preceding admission. The proportion of men and women was almost identical: 22.3% and 22.2%, respectively. Similarly, there was no difference between age groups (chi-square=1.788, p=.775).

Association between past visit to a gastroenterologist and UGIB: 30.7% of cases versus 18.9% of controls had seen a gastroenterologist before and the difference was significant (chi-

square=14.249, p<.001). The crude OR was 1.91 (1.36-2.68).

Association between past visit to a gastroenterologist and recent exposure to NSAIDs: There was no association with exposure. Findings were very similar for NANSAIDs (chi-square=0.207, p=.649) and ASA (chi-square=0.173, p=.678). These findings suggest that past visit is associated with UGIB but does not influence NSAID prescribing practices.

C) Past use of protective agents

Of the study population, 160 patients (18.6%) were exposed at least once to a protective agent between 31 days and 3 years preceding the event. There was no difference between sexes: 26.0% versus 28.9% (chi-square=0.931, p=.334) nor age groups (chi-square=6.508, p=.164).

Association between past use of protective agents and UGIB: Significantly more cases than controls had received a protective agent before: 38.5% versus 23.1% (chi-square=20.887, p<.001). The crude odds ratio was 2.09 (1.52-2.87).

Association between past use of protective agents and recent exposure to NSAIDs: 19.9% of patients who had received a protective agent at least once before had recently used NANSAIDs compared to

14.1% of those who had not. This difference was significant (chi-square=4.332, p=.037). However, there was no association between past exposure to protective agents and recent exposure to ASA: 17.4% versus 15.9% (chi-square= 0.276,p=.352).

D) History of gastropathy assessed in the charts

History of gastropathy was missing in the chart of 21 patients (2.4% of the study population), all of them controls. This finding was not surprising given that this question was always asked to patients admitted with a gastropathy but not necessarily to others. Among patients with available information, 170 (20.3%) had a positive history. A positive history was found in 23.8% of men and 16.8% women and the difference between sexes was significant (chi-square=6.287, p=.012). The distribution across age groups was not significantly heterogeneous (chi-square=4.172, p=.383) but, as with history of upper GI procedures, point estimates indicated a decreasing trend with increasing age: ranging from 26.7% for the 68-69 year old to 16.5% for the ≥85 year old.

Association between history and UGIB: According to the information appearing in the charts, 41.4% of cases had a positive history compared to 11.6% of controls. This association was highly significant (chi-square=94.834, p<.001). The crude OR was 5.37 (3.76-7.68).

Association between history and recent NSAID use: There was no significant association between history of gastropathy and exposure to NANSAIDs. 18.8% of patients who had a positive history were using NANSAIDs compared to 15.3% of those who had a negative history (chi-square=1.274, p=.259). Results were similar for ASA: 17.1% versus 16.5% (chi-square=0.034, p=.853).

In summary, the percentage of patients with a positive history was very similar between the various measures, ranging from 17% to 22.2%. All measures agreed that history of gastropathy was associated with a greater risk of UGIB and the crude ORs were similar. An exception was history obtained from the medical chart where it was 5.37. Further comparisons of these measures are found below in the section on multivariate analyses. When history of upper GI procedures, visit to a gastroenterologist and history assessed in the charts were used as markers, there was no association with recent NANSAID use. However, when past use of protective agents was used, there was an association between past use of these drugs and recent use of NANSAIDs.

4.6.5.4 Co-prescriptions

<u>Anticoagulants:</u> There was no association between recent use of these drugs and UGIB: 2.9% of cases and 2.3% of controls had recently been exposed (chi-square=0.257, p=.612). The crude OR was

1.3 (0.51-3.18). There was no association between the use of these drugs and exposure to NANSAIDs (chi-square=0.180, p=.671). None of the patients exposed to ASA were using an anticoagulant compared to 2.9% of patients who were not using ASA.

Corticosteroids: 7.8% of the cases and 6.3% of the controls were recent users of corticosteroids. The difference was not significant (chi-square=0.580, p=.446). There was a strong association between recent use of corticosteroids and recent exposure to NANSAIDs: 12.6% of those exposed to a NANSAID were also recently exposed to a corticosteroid compared to 5.7% of the unexposed (chi-square=8.678, p=.003).

Antineoplastic drugs: 1.6% of cases and 2.6% of controls had been recently exposed to these agents and there was no association with UGIB (chi-square=0.711, p=.399). Similarly, there was no association between the use of these drugs and recent exposure to NANSAIDs (chi-square=1.332, p=.248).

In this study population, there was no evidence of an association between the use of these drugs and UGIB. A significant association with recent exposure to NANSAIDs was only found with recent use of corticosteroids.

In summary, as shown in table 4.19, past NANSAID use between 31 days and 3 years prior to admission was associated with recent use

of NANSAIDs but according to the crude OR it was not significantly associated with UGIB. Past and recent use of protective agents as well as recent use of corticosteroids were associated with recent NANSAID use but not with recent ASA use. Recent and past use of protective agents were the only variables significantly associated with both recent use of NANSAIDs and UGIB. Smoking, past upper GI procedure, past visit to a gastroenterologist and history of gastropathy assessed in the charts were associated with UGIB but not with recent NANSAID or ASA use.

4.6.6 Association between independent predictors of UGIB

Association between history of gastropathy and use of protective agents:

Past upper GI procedures: Patients who had received such procedures in the past were more likely to be recent users of protective agents than those who did not: 28.1% versus 9.0% (chi-square=41.230, p<.001). Similarly, these patients were more likely to have used protective agents in the past: 67.8% versus 19.2% (chi-square=143.613, p<.001).

Past visit to a gastroenterologist: There was a very strong association between past visit to a gastroenterologist and recent use of protective agents. Of patients who had seen a specialist,

26.7% were using protective agents compared to 8.1% of those who had not (chi-square= 47.984, p<.001). Similarly, the association was very strong for past use of protective agents: 58.6% versus 18.6% (chi-square=119.721, p<.001).

Past use of protective agents: 37.7% of patients who had used protective agents during the 3 years prior to admission had been recently exposed to them compared to 2.6% of those who did not (chi-square=197.027,p<.001). These results are similar to the association between past and recent use of NSAIDs given that the 30 day time window was arbitrary. Long-term users were more likely to be recent users.

History assessed in charts: 29.4% of patients who had a positive history of gastropathy according to the charts were recent users of protective agents versus 8.23% of those with a negative history. The difference was highly significant (chi-square=55.457, p<.001). Of those who had a positive history, 58.8% had used protective agents in the past compared to 19.9% of patients with a negative history (chi-square=102.225, p<.001).

Results obtained from the various markers of history of gastropathy appear to be consistent. In this study population, patients with a positive history of gastropathy were more likely to use protective agents than to decrease NANSAID use.

Association between history of gastropathy and past NANSAID use: The association between history of gastropathy and past NANSAID use during the 3 years before admission was assessed for all measures of history.

Upper GI procedures: Patients who had used NANSAIDs in the past were not significantly more likely to have received an upper GI procedure than those who did not: 18.0% versus 15.6% (chi-square=0.795, p=.373).

History of visit to gastroenterologist: 24.3% of patients who had used NANSAIDs in the past had seen a specialist versus 19.3% of non-users. This difference was non significant (chi-square=2.935, p=.087).

Past use of protective agents: 31.6% of patients who had been exposed to NANSAIDs before also used protective agents in the past compared to 21.3% of those who were not. The difference was significant (chi-square=11.383, p<.001).

History assessed in charts: 61.8% of patients with a positive history had used NANSAIDs before compared to 58.4% of those with a negative history. The difference was non-significant (chi-square=0.641, p=.423).

These results are difficult to interpret because the timing of the

marker of history relative to past NANSAID use was not taken into account. Nevertheless, only past use of protective agents seemed associated with past NANSAID use maybe because of prophylactic purposes. As a whole, there appeared to be no collinearity between history of gastropathy and past NANSAID use.

4.7 LOGISTIC REGRESSION ANALYSES

Results from the logistic regression analyses are reported in the following section. The overall model will first be presented and then followed by a description of the effect of each variable.

4.7.1 Exposure to NSAIDs

For both NANSAIDs and ASA, the following analyses were designed to partition the effects of "recent" exposure and "past" exposure during the 3 years prior to admission. The 2 effects were fitted as independent variables in the model. The reference category consisted of patients who had not been exposed within 30 days prior to the event. Results of the multivariate logistic regression model are presented in table 4.20. Past use of ASA, recent use of corticosteroids, anticoagulants and antineoplastic drugs were not significantly associated with the risk of UGIB and were not confounders in the association bewteen NANSAID, ASA and UGIB.

Consequently, they were not retained in the final model.

The crude OR associated with recent NANSAID use was 2.93 (2.01-4.27) and that of ASA was 1.45 (0.99-2.12). In addition to recent exposure to NANSAIDs and ASA, other significant predictors of UGIB were: past exposure to NANSAIDs, history of gastropathy, and smoking. A comparison between the crude and adjusted OR showed that these parameters biased the effect of NSAID use on UGIB towards the null. The adjusted OR for NANSAIDs was 3.36 (2.05-5.52) and that for ASA was 1.65 (0.96-2.82). The addition of the matching variables in the model (i.e. sex, age group, hospital and study year) did not affect the estimates and did not improve significantly the goodness-of-fit of the model. Thus, they were not retained.

Below is described in greater details the effect of each concomitant variable on UGIB.

Past exposure to NANSAIDs: Past exposure to NANSAIDs between 31 days and 3 years preceding admission was associated with a lower risk of UGIB. It was an independent predictor and the adjusted OR was 0.66 (0.44-0.97).

The interaction between recent NANSAID use and past NANSAID use was significant (p=.015). Effect modification was evaluated by stratification. The crude OR associated with recent exposure to

NANSAIDs for patients with and without past experience with these drugs in the 3 years before admission is shown in table 4.21. Patients who had not used the drugs during the 3 years before had a greater risk of experiencing UGIB than those who had used the drugs during this time period. According to the Breslow-Day test, the ORs were significantly heterogeneous (p=.032). The wide 95% C.I. in the first estimate is due to the very small number of patients who did not use these drugs during the 3 years before but who were recently exposed (8 cases and 1 control). These results would suggest effect modification by past NANSAID use. However, a misclassification of only 1 patient in the exposure groups could change the conclusion. A sensitivity analysis was conducted in order to assess the significance of the results when the size of the smaller cell (1 patient) was increased. The OR for patients who did not use the drug in the past decreased from 22.94 (2.84-185.32) to 11.49 (2.40-55.56) when the cell size was increased to 2. The Breslow-Day test and the interaction were no longer significant (p=.088 and p=.062, respectively). These results favour an absence of effect modification. However, given the large sample size for the control group, only 1 exposed control out of 615 suggests that the true value may be 0 instead of 1. In this case, the OR would even be greater. Results from this sensitivity analysis suggest that misclassification of only 1 patient would change the significance of the results. To assess effect modification from the Breslow-Day test may be questionable. On the other hand, only 1 exposed controls out of 615 would suggest that

there may be a true effect.

History of gastropathy: The stability of the results between the various markers of history of gastropathy was assessed by comparing results from the logistic regression. The regression coefficients and estimates of relative risk obtained with each measure are shown in appendix B. In table 4.22 are summarized the estimates of relative risk obtained from each of the markers of history of gastropathy. The ORs for past upper GI procedures and past visit to a gastroenterologist were very similar: 2.02 (1.32-3.09) and 2.05 (1.38-3.04), respectively. However, when assessed in the charts, the effect of positive history was much greater 5.26 (3.47-7.95).

The magnitude of the association between recent NANSAID and ASA use and UGIB remained fairly stable across markers. So did the effect of past NANSAID use and smoking. Based on these results, history of upper GI procedures was selected as the marker for history of gastropathy in the final model.

Recent use of protective agents: Recent use of protective agents increased the risk of UGIB even when past upper GI procedures was included in the model. There was no collinearity between the 2 parameters. The OR associated with recent use of protective agents was 1.66 (1.03-2.67).

Smoking: Only current smokers had a significant risk of UGIB. The adjusted OR was 2.40 (1.57-3.67). The OR for ex-smokers was above unity but the 95% confidence interval included the null: 1.46 (0.97-2.20).

Co-prescriptions: Results indicate that the concomitant use of corticosteroids, anticoagulants or antineoplastic drugs did not have a significant effect on UGIB and did not affect the estimate of relative risk associated with NSAID use.

In summary, the effect of NANSAIDs on UGIB was greater than that of ASA. Past use of NANSAIDs in the 3 years preceding admission was an independent predictor of UGIB and it was associated with a lower risk. Stratum-specific ORs indicated that the magnitude of the association between recent NANSAID use and UGIB was greater for patients who had not used the drugs before than those who had. However, it cannot be concluded if past use of NANSAID is a true effect modifier. A positive history of gastropathy increased the risk of UGIB, whatever the marker used. Recent exposure to protective agents increased the risk independently of history of gastropathy, which indicates an absence of collinearity between the 2 variables. However, there was collinearity between past and recent use of protective agents.

4.7.2 Average daily doses of ASA

The distribution of ADDs for the 140 patients exposed to ASA is shown in table 4.23. There were no ADDs below 325mg/day. Based on these results, the ADDs were grouped into 2 categories: <650mg/day and ≥650mg/day. The distribution of patients into the 2 dose categories was assessed and results from the logistic regression are reported in table 4.24. ASA was significantly associated with UGIB only when used at the lowest ADD category. These results do not support a dose-response relationship. Possible explanations for these results are found in the discussion (chapter 5).

4.8 SENSITIVITY ANALYSES

In this section are reported results from the sensitivity analyses conducted on control diagnoses, hospitals and study years.

Control diagnoses: The distribution of patients among the diagnostic categories was described in section 4.3.2. Results of the sensitivity analysis in which each control diagnostic category was removed one at a time are presented in table 4.25. The OR for NANSAIDs obtained by including all patients was: 3.36 (2.05-5.52). The greatest OR was obtained when controls with trauma were removed and the lowest when those with cholecystitis were removed. As a whole, results remained stable with the selective exclusion of each

of the major control diagnostic categories.

For ASA use, results were fairly stable ranging from 1.41 (0.89-2.24) when respiratory illnesses were removed to 1.65 (1.06-2.57) when the category "others GI illnesses" was removed.

The stability of the results indicates that none of the control diagnostic categories were associated more or less with NSAIDs. Such consistency suggests that it is likely that control diagnoses are not associated with NSAID use. NSAID use in the control group is thus representative of the base population.

Matching variables (age group, hospital, sex and study year) were included in each model in order to ensure that the selective removal of diagnoses did not introduce confounding by these variables. None were significant and they did not alter the results.

Hospitals: Because the study was not population-based, results may have been biased due to differences in the structure of the hospital catchment populations. In order to appraise the extent of the bias, a sensitivity analysis was conducted by removing one hospital at a time. Results are reported in table 4.26. The estimates of relative risk remained stable.

Study year: The analysis was conducted for each of the study years and results are reported in table 4.27. The estimate of relative risk associated with NANSAID use was smaller in 88/89 than in 89/90: 3.16 (1.59-6.29) and 3.75 (1.78-7.93), respectively. If the misclassification of exposure due to OTC availability of ibuprofen was non-differential among cases and controls, then the OR would have been biased towards the null in 89/90. The direction of the results did not support this hypothesis. Hence, misclassification was most likely differential. If it mainly occurred among controls (i.e. more controls were in fact using NANSAIDs), then the OR would have been biased away from the null. On the other hand, misclassification occurring mainly among cases would have under-estimated the OR. Based on the results, the first situation appeared to be the most likely. Nevertheless, the magnitude of the bias, if present, was not too important because of the extensive overlap between the 95% C.I. of 88/89 and 89/90 estimates.

Results remained stable with the exception of smoking and history of gastropathy where the magnitude of the association was considerably greater in 1989-90. The actual sample size was somewhat reduced in each analysis because of missing values for smoking. Consequently, estimates are unstable.

4.9 DATA TRUNCATION

In order to appraise the direction and extent of misclassification due to the absence of data on a longer term than 3 years, the frequency of past exposure to NANSAIDs was assessed for a time window of 1 year, 2 years and 3 years preceding the event. The distribution of exposure for the 3 different time windows is presented in table 4.28. The effect of past exposure on the association between NANSAIDs, ASA and UGIB obtained from each time window is displayed in table 4.29.

The magnitude of the association between NANSAIDs, ASA and UGIB increased slightly with a wider time window. For NANSAIDs, the estimate of relative risk increased from 3.07 to 3.36. For ASA, the estimates remained stable. The effect of ASA became statistically significant (the 95% C.I. did not include the null) only when a 3 year time window was used. According to the point estimate of relative risk, there was no such trend for the independent effect of history of upper GI procedures. Past NANSAID use was associated with a lower risk of UGIB in all time windows considered. However, it became significant only when it was assessed for 3 years. As well, the interaction with recent NANSAID use was only present when data were available for 3 years.

From this analysis, it can be concluded that the effect of NANSAID and ASA use is slightly under-estimated when history of drug

exposure and gastropathy are assessed for a short period of time. An extrapolation of these results suggests that data truncation due to restricting the entry in the cohort at age 65 slightly biases the results towards the null. However, the extent of the bias is expected to be very small and it is not likely that it would have a clinical or public health significance. If the interest is on the independent effect of the other parameters, data truncation under-estimates to a significant extent the effect of past NANSAID use. It only affects slightly the effect of history of gastropathy, assessed by past upper GI procedures.

In summary, the lack of longitudinal data on individuals biases the results slightly towards the null. It can also be observed that the magnitude of the effect of past exposure to NANSAIDs increases as the time window increases.

4.10 PATTERNS OF NON-ASPIRIN NSAID USE

Bivariate analyses of patterns are first presented and are followed by an assessment of their effect on the risk of UGIB.

4.10.1 Duration

Of the study population, 80 cases (32.8%) and 151 controls (24.5%) were exposed at least once to NANSAIDs between 31 days and 1 year before admission. Duration of NSAID use between 31 days and 1 year preceding hospital admission was assessed. By definition the maximum was 335 days. The distribution of duration is shown below:

	# patients	Minimum	Maximum	Mean	Mode	Std Dev.	Median
				(no. days)			
Cases	80	5	312	132.7	30	97.3	102
Controls	151	1	325	86.9	30	85.9	52

Levels of duration: Duration of exposure to NANSAIDs during the year before was expressed as a variable with 4 levels: none in the past year, short-term (≤30 days), intermediate (31-120 days) and long-term (>120 days). The distribution of the study population into the 4 levels is presented in appendix B. It was heterogeneous among sexes (chi-square=10.009, p=.018). More men than women had never been exposed during the year (75.9% versus 70.4%). The proportion of women in the long-term use group was approximately

twice that of men (11.3% versus 5.4%). The proportion of men and women in the other categories was similar. The distribution was not significantly heterogeneous among age groups (chi-square=8.046, p=.782).

Association between duration and UGIB: The association between duration of NANSAID use in the past year and UGIB is presented in table 4.30. The distribution of cases and controls into the 4 levels of past exposure to NANSAIDs was significantly heterogeneous (chi-square= 18.352, p<.001). A greater proportion of cases were long-term or intermediate users while more controls were short-term users.

Association between duration and recent exposure to NANSAIDs: As shown in table 4.30, there was a strong association between levels of NANSAID use during the year before admission and recent exposure to NANSAIDs (chi-square=406.362, p<.001). The proportion of patients exposed within 30 days prior to the event increased as the duration of exposure during the year increased. There were more long-term users among the recently exposed and the reverse was true for the unexposed. These results provide an evidence of length-biased sampling (i.e. the probability of being recently exposed was greater for long-term users).

4.10.2 Switches between products

Switches between products were assessed between 31 days and 1 year before admission according to the method described in chapter 3. During this time period, 20 cases (25.0% of past NANSAID users during the year) and 30 controls (19.9%) switched at least once between products between 2 consecutive NANSAID dispensings less than 60 days apart.

Number of switches: The number of switches ranged from 1 to 7; the majority of patients switching only once:

Number of switches	Cases n(%)	Controls n(%)
1	12 (60.0)	17 (56.7)
2	3 (15.0)	7 (23.3)
3	1 (5.0)	3 (10.0)
4	2 (10.0)	2 (6.7)
5	1 (5.0)	0 (0.0)
6	0 (0.0)	1 (3.3)
7	1 (5.0)	0 (0.0)
Total:	20	30

Date of last switch: The distribution of the date of the last switch before the recent exposure is reported below:

	No. patients	Minimum	Maximum	Mean	Std Dev.	Median
		(no. days before admission)				
Cases	20	67	333	166.7	94.5	114
Controls	30	53	346	192.9	97.0	228

The distribution of switchers into genders and age groups is shown appendix B. The association between switching and recent exposure to NANSAIDs and UGIB is shown in table 4.31.

Association between switching and UGIB: 25.0% of cases who were NANSAID users during the year had switched once before compared to 19.9% of controls. However, the heterogeneity of the distribution of switchers and non-switchers between cases and controls was non-significant (chi-square=0.812, p=.367).

Association between switching and recent exposure to NANSAIDs: Among those who used NANSAIDs during the year, 64.0 % of switchers were also recent users of NANSAIDs compared to 45.3% of those who never switched. The association was significant (chi-square=5.479, p=.019).

According to these results, switching between NANSAIDs was not associated with UGIB but was associated with recent exposure to NANSAIDs. Patients who switched products were more likely to be recent users of NANSAIDs.

The distribution of switchers into the various levels of NANSAID use is shown below:

	Short-term 1-30 days	Intermediate 31-120 days	Long-term >120 days	Total
Switched	3 (4.1)	24 (28.2)	23 (31.9)	50
Never switched	71 (96.0)	61 (71.8)	49 (68.1)	181
Total:	74	85	72	231

The distribution was highly heterogenous (chi-square=20.182, p<.001). As expected, short-term users switched the least probably because they only had 1 prescription. The difference in the proportion of switchers between intermediate and long-term use was very small (28.2% and 31.9%, respectively).

4.10.3 Switches between average daily doses

Twelve cases (15% of past NANSAID users during the year prior to admission) and 12 controls (7.9%) increased the ADDs of the same product. The number of patients who decreased the ADDs was: 6 (7.5%) and 9 (6.0%), respectively for cases and controls. For each direction, the maximum number of switches was 3. Three patients switched both ways on separate occasions.

Date of the last increase in ADD: The distribution of the date of the last increase in ADD of NANSAIDs is found below:

	No. patients	Minimum	Maximum	Mean	Std. Dev.	Median
		(no. days before admission)				
Cases	12	70	355	192.6	105.2	205.0
Controls	12	81	338	220.6	89.3	216.5

Date of the last decrease in ADD: The distribution of the date of the last decrease in ADD of NANSAIDs is found below:

	No. patients	Minimum	Maximum	Mean	Std. Dev.	Median
		(no. days before admission)				
Cases	6	94	172	121.2	35.4	99.0
Controls	9	79	348	208.5	89.9	189.0

Association between switching ADDs and UGIB: Among NANSAID users during the year prior to admission, 12 cases (15%) and 12 controls (8.0%) had increased the dose at least once. This difference was not significant (chi-square=2.794, p=.095). Six cases (7.5%) had decreased the dose versus 9 controls (6.0%) which was not significant either (chi-square=0.204, p=.651).

Association between switching ADDs and recent exposure to NANSAIDs: All patients who had increased the ADD before were recently exposed to NANSAIDs compared to 43.5% of those who did not increase the dose. Similarly, all patients who had decreased ADD were recently exposed compared to 45.8% of those who had never decreased.

It appears that switching ADDs of NANSAIDs, whether increasing or

decreasing, was highly associated with recent exposure to NANSAIDs. Switching ADDs was not associated with UGIB, although an increase in dose may be closer to reaching significance than a decrease. Numbers were very small and thus, leading to unstable results.

4.10.4 Switches between forms of administration

Only 10 patients (6 cases and 4 controls) switched between forms of administration of the same product during the year preceding the event. The maximum number of switches between forms was 4. The types of switches encountered are described in appendix B.

Date of last switch The distribution of the date of the last switch between forms of administration is found below:

	No. patients	Minimum	Maximum	Mean	Std.Dev.
		(no. days before admission)			
Cases	6	19	343	124.2	120.8
Controls	4	46	246	165.3	86.1

Association between switching forms and UGIB: Among the 231 users of NANSAIDs during the year before admission, a slightly greater proportion of cases switched between forms of administration than controls (6.3% versus 4.0%) but the difference was not significant (chi-square=0.598, p=.440).

Association between switching forms and recent exposure to NANSAIDs: 63.6% of those who switched between forms of administration had recently been exposed to NANSAIDs compared to 48.6% of those who did not switch. Because numbers were very small, the difference was not significant (chi-square=0.943, p=0.332).

Because very few patients switched between forms of administration of the same product, it was not possible to make statistical inferences on the effect of this type switching on UGIB.

4.10.5 Multiple users

Among past NANSAID users between 31 and 365 days prior to admission, 24 patients received a prescription for a NANSAIDs and an ASA on the same day at least once: 12.5% of cases versus 4.0% of controls (chi-square=8.891, p=.003). However, it is likely that these proportions under-estimate the truth. Although small shifts in dates of dispensing were sometimes observed, it was obvious upon closer examination of data that the patient used NANSAIDs and ASA concomitantly. These patients were not recorded as multiple users.

Among past users, 22 patients (9.5% of past NANSAID users during the year) had received multiple NANSAIDs prescriptions (same or different) on the same date (7.8% cases and 10.9% controls). Only 8 patients received a prescription for 2 different NANSAIDs on the

same day (3.5% past NANSAID users). There was no association with UGIB (3.75% cases and 3.31% controls, chi-square=0.030, p=.862).

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4.10.6 Association between independent variables

Association between duration of NANSAID use and recent use of protective agents: The distribution of recent exposure to protective agents into the various levels of past exposure to NANSAIDs during the year before admission is described in table 4.32. The distribution was highly heterogeneous (chi-square=29.727, p<.001). The proportion of recent exposure to protective agents increased with duration of past exposure to NANSAIDs. It ranged from 9.2% for those who have not been exposed to NANSAIDs during the year to 27.8% for long-term users. This association was present for both cases and controls (p=.07 and p<.001, respectively).

Association between duration of NANSAID use and history of gastropathy: When history of upper GI procedures was used as a marker of gastropathy, there appeared to be no association between levels of past NANSAID use and history of gastropathy (chi-square=3.341, p=0.342) (table 4.33a). However, when history was assessed by past use of protective agents during that time period, the distribution was significantly heterogeneous (chi-square=18.223, p<.001) (table 4.33b). Approximately twice as many

intermediate or long-term users of NANSAIDs were using protective agents compared to those not exposed during the year before or exposed for a short term.

Association between switching and recent use of protective agents: 32% of patients who switched products at least once during the year had recently been exposed to protective agents compared to 17.1% of patients who were exposed but did not switch. This association was highly significant (chi-square=27.508, p<.001).

Association between switching and past exposure to protective agents: Among past users of NANSAIDs, switchers were more likely to have used protective agents than non-switchers (34% versus 24%). However, the difference was not significant (chi-square=1.893, p=.169).

4.10.7 Summary of bivariate analyses of patterns of NANSAID use

In summary, patterns of NANSAID use assessed between 31 and 365 days prior to admission were different for cases and controls. A greater proportion of cases were long-term or intermediate users while more controls were short-term users. Only 50 patients switched products. Switching was not associated with UGIB but was strongly associated with recent NANSAID use and recent use of protective agents. Switching average daily doses or forms of

administration of the same product occurred infrequently in this population of elderly and was not associated with UGIB.

4.11 LOGISTIC REGRESSION AND STRATIFICATION ANALYSES OF PATTERNS

4.11.1 Recency

Exposure to NANSAIDs was categorized into 2 levels: "recent" exposure (last prescription ending within 30 days of the event), and "former" exposure (last prescription ending between 31 and 365 days preceding admission). The unexposed during the year was the reference category. The proportion of exposure for cases and controls as well as results from the logistic regression analysis are presented in table 4.34. Compared to controls, a greater proportion of cases had recently been exposed to NANSAIDs while the converse was true for former exposure. Recent use of NANSAIDs was associated with a greater risk of UGIB. There was no significant risk associated with former use.

4.11.2 Duration

The association between NANSAID use and UGIB corresponding to each category of duration of exposure is shown in table 4.30. Point

estimates of relative risk suggest that the association decreases as the duration of exposure increases. Long-term users appear to be at lower risk than short-term users: 1.47 (0.32-6.68) and 5.58 (1.58-19.64), respectively. According to the Breslow-Day test, the ORs were not significantly heterogeneous (chi-square=2.693, p=.441).

4.11.3 Switches between products

According to the point estimates of relative risk displayed in table 4.31, patients who had switched in the past year appeared to be at greater risk for UGIB than those who used NANSAIDs but did not switch. However, because of the small number of switchers, the 95% CI of the OR was very wide and, as a result, estimates of relative risk were not significantly heterogeneous (Breslow-Day test: chi-square=3.039, p=.219).

In summary, duration of past NANSAID use during the year preceding admission or switching between products appear to affect the estimate of relative risk associated with recent NANSAID use. Because of overlapping 95% C.I., it is not possible to conclude that there is effect modification. As seen in section 4.7.1, a greater effect is obtained by ascertaining past NANSAID use on a longer term (3 years before admission).

4.12 SUMMARY OF RESULTS

1) *Exposure to NSAIDs:* Recent exposure to NSAIDs increases the risk of hospitalization for UGIB in the Quebec elderly population. The magnitude of the association was greater for NANSAIDs than for ASA. The adjusted ORs were 3.36 (2.05-5.52) and 1.56 (1.00-2.42), respectively.

2) *Past use of NANSAIDs:* Past use of NANSAIDs between 31 days and 3 years preceding admission was associated with a lower risk of UGIB. The independent effect was significant only when controlling for other factors. There was a significant interaction between past and recent use of NANSAIDs. The estimate of relative risk associated with recent NANSAID use was significantly greater for patients who were using these drugs for the first time in 3 years.

3) *Recency:* The risk associated with recent NANSAID use was significant while that associated with former use was not (in the latter, the number of days after interruption of treatment was 30 days or more).

4) *Duration:* Significantly more cases than controls were long-term or intermediate users. The risk associated with recent NANSAID use decreased as the duration of past NANSAID use increased. However, the difference between duration patterns was not significant.

5) *Length-biased sampling:* The probability of being recently exposed increases with duration of exposure.

6) *Switching:* Switching products did not occur frequently in this elderly population. Switchers were at a greater risk than non-switchers but because of the small frequency of switches, the difference was not significant.

7) *Protective agents:* Recent use of protective agents was associated with a greater risk of UGIB. The estimate of relative risk was 1.66 (1.03-2.67). Furthermore, long-term users of NANSAIDs as well as patients who switched products were more likely to use these drugs.

8) *Past history of gastropathy:* Past history of gastropathy was an independent predictor of UGIB. The estimates of relative risk for the effect of history of gastropathy remained fairly stable when the different markers of history were used (upper GI procedures, visit to a gastroenterologist or past use of protective agents). All increased the risk by a factor of approximately 2. An exception was history assessed in the charts where it was much greater (OR=5.35). There was no association between past upper GI procedure, past visit to a gastroenterologist and history assessed in the chart and recent use of NANSAIDs. However, past users of protective agents were more likely to have used NANSAIDs recently.

9) *Average daily doses of ASA:* This study did not detect a dose-response relationship for the effect of recent ASA use. Low ADDs of ASA (ADDs <650 mg/day) were associated with a significant risk of UGIB but not those greater or equal to 650 mg/day.

10) *Other risk factors:* Among the other potential risk factors for UGIB, only smoking was associated with an increase in the risk. Recent use of comedications, such as corticosteroids, anticoagulants or antineoplastic drugs did not have an effect on UGIB and were not confounders.

TABLE 4.1

Structure of the study population

	No. patients	% Study population
Cases	244	28.4
Controls	615	71.6
Men	427	49.7
Women	432	50.3
68-69	75	8.7
70-74	201	23.4
75-79	274	31.9
80-84	179	20.8
≥ 85	130	15.1
Total:	859	

TABLE 4.2a

Causes of non-eligibility of potential cases and controls

	FREQUENCY n (%) Cases	Controls
Lower GI bleeding	71 (21.6)	1 (0.4)
Unconfirmed diagnosis	67 (20.4)	2 (0.8)
Chronic	58 (17.6)	75 (30.4)
Cancer of the GI tract	27 (8.2)	37 (15.0)
Transfer	23 (7.0)	28 (11.3)
Past gastric surgery	18 (5.5)	22 (8.9)
Allergic to ASA	13 (4.0)	15 (6.1)
Long-term or multiple admissions in past 3 years	9 (2.7)	7 (2.8)
Non-incident	7 (2.1)	8 (3.2)
Cirrhosis	6 (1.8)	3 (1.2)
Non-resident	2 (0.6)	11 (4.5)
Alcoholism	2 (0.6)	----
Elective admission	2 (0.6)	5 (2.0)
NSAIDs side-effect	1 (0.3)	----
Error in coding of diagnosis	0 (0.0)	3 (1.2)
Cause missing	13 (3.8)	16 (6.5)
For cases: other pathologies responsible for UGIB	20 (6.1)	----
For controls: gastropathy	---	13 (5.3)
Total:	342	247

TABLE 4.2b

Non-eligibility by case ICD-9 diagnosis

Diagnosis	No. charts reviewed	No. eligible	Eligibility %
Ulcer:			
- gastric	138	97	70.3
- duodenal	109	77	70.6
- peptic	20	13	65.0
Haematemesis	72	27	37.5
Melaena	39	3	7.7
GI bleeding	214	35	16.4
	592	252	42.6

TABLE 4.2c

Most frequent cause of non-eligibility by case ICD-9 diagnosis

Diagnosis	Cause	Relative importance
- Gastric ulcer	chronicity	35.9%
- Duodenal ulcer	chronicity	25.0%
- Peptic ulcer	chronicity	25.0%
- GI bleeding	lower GI bleeding	30.0%

TABLE 4.3

Most frequent cause of non-eligibility by control ICD-9 diagnosis

Diagnosis	Cause	Frequency (%)
Cholecystitis	Chronic	62.3
	Transfer	10.7
	Past stomach surgery	10.7
Pneumonia	Chronic	14.9
	Cancer of the GI tract	13.5
	Past stomach surgery	12.2
Trauma	Transfer	30.8
	Cancer of the GI tract	15.4
	Gastropathy	7.7
	Multiple admissions	7.7
	Long-term or multiple admissions	7.7

TABLE 4.4

Distribution of the case diagnoses

Diagnosis * (ICD-9)	RVH(1)	HND(2)	HMR(3)	JGH(4)		Total
531.0	1	1	1	6		9
531.1	0	0	0	6		6
531.2	0	0	0	0		1
531.4	12	13	27	19		71
531.5	1	4	8	0		13
531.6	0	0	0	2		2
					Subtotal	102
532.0	0	1	1	7		9
532.1	0	0	2	3		5
532.2	0	0	2	0		2
532.4	17	9	13	22		61
532.5	2	3	2	3		10
532.6	1	0	0	1		2
					Subtotal	89
533.0	0	0	0	3		3
533.1	0	0	0	0		0
533.2	0	0	0	0		0
533.4	1	2	4	3		10
533.5	0	0	1	0		1
533.6	0	0	0	0		0
					Subtotal	14
578.0	0	0	34	2		36
578.1	3	0	2	4		9
578.9	8	19	8	9		44
					Subtotal	89
No. of dx	46	52	105	90	Total	293
No. of cases	40	45	83	80		248

* 531 Gastric ulcer
532 Duodenal ulcer
533 Peptic ulcer
578.0 Hamatemesis
578.1 Malaena
578.9 Gastro-intestinal bleeding (unspecified)

(1) Royal-Victoria Hospital
(2) Hôpital Notre-Dame
(3) Hôpital Maisonneuve-Rosemont
(4) Jewish General Hospital

TABLE 4.5

Distribution of control principal diagnoses

Diagnostic category	No. Controls (%)
Trauma	189 (30.7)
Respiratory	184 (29.9)
Cholecystitis	97 (15.4)
Urinary tract	56 (9.1)
Other GI	33 (5.4)
Other	65 (8.8)
Missing	4 (0.7)
Total:	628

Other GI tract disorders consisted of:

	No. Patients	% Patients
Appendicitis	19	3.0
Hernia	5	1.0
Occlusion	1	0.2
Diverticulum	2	0.3
Peritonitis	2	0.4
Cholangitis	2	0.3
Other biliary duct cond.	1	0.2
Pancreatitis	1	0.2
Total:	33	

TABLE 4.6

Distribution of symptoms of cases

Nature of symptom	Frequency (%)
Melaena	21.7
Abdominal pain	18.7
Nausea	7.4
Vomiting	6.7
Hematemesis	6.5
Dizziness	5.9
Coffee ground stool	5.5
Anemia	5.2
Shortness of breath	5.2
Weakness	4.4
Coffee ground vomiting	4.3
Bloody diahrrea	2.1
Loss of appetite	1.9
Syncope	1.7
Diarrhea	1.7
Constipation	0.8
Weight loss	0.2

TABLE 4.7

Distribution of comorbidity of cases and controls

	CASES		CONTROLS	
	Number	% comorbidity	Number	%comorbidity
Gastric ulcer	35	2.5	-	-
Duodenal ulcer	19	1.3	-	-
Peptic ulcer	13	0.9	-	-
Gastr./duoden.	62	4.4	-	-
GIB	59	4.1	5	0.2
CVD	383	26.9	906	28.0
Other GI illnesses	121	8.5	277	8.6
Respiratory	119	8.4	285	8.8
Endocrinologic	99	7.0	262	8.1
Osteo-muscular	91	6.4	177	5.5
Genitourinary	80	5.6	202	6.3
Sensory organs	77	5.4	230	7.1
Trauma	39	2.7	216	6.7
Mental disorder	33	2.3	131	4.1
Infection	17	1.2	97	3.0
Tumour	24	1.7	55	1.7
Hematologic	55	3.9	68	2.1
Other	97	6.8	320	9.9
Total:	1423		3231	

Legend

Gastr.:	Gastritis
Duoden.:	Duodenitis
GIB:	Gastrointestinal bleeding
CVD:	Cardiovascular disease

TABLE 4.8

Medical history of cases and controls

Diagnosis	All patients combined %	Cases %	Controls %
CVD*	22.1	24.3	21.5
Other GI	13.3	14.2	13.0
Genito-urinary	10.1	6.7	11.1
Trauma	7.8	3.7	9.1
Tumour (other than GI)	7.3	7.8	7.1
Respiratory	6.9	3.0	8.0
Sensory organs	6.1	3.0	7.0
Musculo-skeletal	2.0	2.3	2.0

* Cardio-vascular disease

TABLE 4.9

Frequency distribution of individual non-aspirin NSAID and ASA prescriptions

Prescribed Duration (days)	NANSAIDs n=3609 (%)	ASA n=3423 (%)
7	6.2	4.6
10	6.5	1.0
15	9.1	1.4
20	3.4	0.6
25	4.5	3.8
30	54.4	77.7
>30	6.0	8.7

Note: Frequency distribution of the total number of prescriptions dispensed during the 3 years prior to admission

TABLE 4.10

Distribution of new and renewed individual prescriptions

Product	New n(%)	Renewed n(%)	Total
NANSAIDs	1639 (45.4)	1970 (54.6)	3609
ASA	1061 (31.0)	2363 (69.0)	3425

Note: Frequency distribution of the total number of prescriptions dispensed during the 3 years prior to admission

TABLE 4.11

Distribution of individual products, 3 years before admission

Product	No. prescriptions (%)
Diclofenac sodium	632 (17.5)
Indomethacin	606 (16.8)
Naproxen	594 (16.5)
Ibuprofen	533 (14.8)
Ketoprofen	372 (10.3)
Piroxicam	372 (10.3)
Sulindac	256 (7.1)
Flurbiprofen	102 (2.8)
Diflunisal	49 (1.4)
Tiaprofenic acid	37 (1.0)
Tolmetin	26 (0.7)
Fenoprofen	22 (0.6)
Mefenamic acid	2 (0.1)
Total:	3609

Note: Total number of non-aspirin NSAID prescriptions dispensed to the study population during the 3 years prior to admission

TABLE 4.12

Distribution of the forms of administration of non-aspirin NSAIDs and ASA, 3 years before admission

	NANSAIDs (n=3609)	ASA (n=3423)
Tablets or capsules	60.2	1.3
Enteric-coated	20.7	98.5
Long-acting	9.9	0.2
Suppositories	9.2	N/A*

* N/A: Non-applicable

Note: Total number of prescriptions dispensed to the study population during the 3 years prior to admission

TABLE 4.13

Exposure to NSAIDs within 30 days prior to admission

	All NSAIDs	ASA	NANSAIDs
	n (% study population)		
Cases	99 (40.6)	49 (20.1)	66 (27.0)
Controls	149 (24.2)	91 (14.8)	69 (11.2)
Men	131 (30.7)	88 (20.6)	58 (13.6)
Women	117 (27.1)	52 (12.0)	77 (17.8)
68-69	18 (24.0)	10 (13.3)	12 (16.0)
70-74	68 (33.8)	39 (19.4)	40 (19.9)
75-79	81 (29.6)	47 (17.2)	41 (15.0)
80-84	49 (27.4)	26 (14.5)	26 (14.5)
≥ 85	32 (24.6)	18 (13.8)	16 (12.3)

TABLE 4.14

Distribution of the individual non-aspirin NSAID products during the 30 days prior to admission

Product	All patients n(%)	Cases n(%)	Controls n(%)
Diclofenac	55 (23.8)	30 (24.6)	25 (22.9)
Naproxen	38 (16.5)	17 (13.9)	21 (19.3)
Ketoprofen	33 (14.3)	20 (16.4)	13 (11.9)
Indomethacin	29 (12.6)	15 (12.3)	14 (12.8)
Piroxicam	27 (11.7)	18 (14.8)	9 (8.3)
Ibuprofen	25 (10.8)	7 (5.7)	18 (16.5)
Sulindac	9 (3.9)	4 (3.3)	5 (4.6)
Flurbiprofen	8 (3.5)	6 (4.9)	2 (1.8)
Diflunisal	3 (1.3)	2 (1.6)	1 (0.9)
Tolmetin	2 (0.9)	2 (1.6)	0 (0.0)
Tiaprofenic acid	2 (0.9)	1 (0.8)	1 (0.9)
Total:	231	122	109

Note: The number of prescriptions exceeds the number of exposed individuals because some patients had more than 1 prescription that ended within 30 days prior to the event

TABLE 4.15a

Crude odds ratio for the effect of non-aspirin NSAID use on upper gastro-intestinal bleeding at different time windows

Time window	Cases		Controls		Crude Odds ratio	95% C.I.
	Exposed	Unexposed	Exposed	Unexposed		
7 days	56	188	48	567	3.52	2.31 - 5.35
30 days	66	178	69	546	2.93	2.03 - 4.24

TABLE 4.15b

Crude odds ratio for the effect of aspirin use on upper gastro-intestinal bleeding at different time windows.

Time window	Cases		Controls		Crude Odds ratio	95% C.I.
	Exposed	Unexposed	Exposed	Unexposed		
7 days	44	200	76	539	1.56	1.04 - 2.34
30 days	49	195	91	524	1.45	0.99 - 2.12

TABLE 4.16

Association between recent use of protective agents and recent use of non-aspirin NSAIDs

Use of protective agents *	Cases		Controls	
	Exposed**	Unexposed	Exposed	Unexposed
	n (%)			
None	46 (69.7)	154 (86.5)	56 (81.2)	498 (91.2)
Recent	20 (30.3)	24 (13.5)	13 (18.8)	48 (8.8)
Total	66	178	69	546

* Recent exposure to protective agents (prescription ending within 30 days prior to admission

** Recent exposure to NANSAIDs (prescription ending within 30 days prior to admission)

TABLE 4.17

Distribution of recent exposure to non-aspirin NSAIDs

by smoking levels

Smoking level	Cases		Controls		Crude	
	Exposed	Unexposed	Exposed	Unexposed	Odds ratio	95% C.I.
	n (%)					
Smokers	46 (42.6)	9 (9.9)	7 (10.8)	88 (18.1)	2.06	1.37-3.09
Ex-smokers	37 (34.3)	17 (18.7)	14 (21.5)	121 (24.9)	1.42	0.96-2.10
Non-smokers	25 (23.1)	65 (71.4)	44 (67.7)	276 (56.9)	Reference	
Total:	108	91	65	485		

TABLE 4.18

Comparison between the four markers of history of gastropathy

	History of gastropathy				
	Cases		Controls		
	Positive	Negative	Positive	Negative	Crude OR (95% C.I.)
Upper GI procedure (1)	59	185	87	528	1.93 (1.34-2.80)
Visit to gastroenterologist (2)	75	169	116	499	1.91 (1.36-2.68)
Past use of protective agents (3)	94	150	142	473	2.09 (1.52-2.87)
History assessed in charts (4)	101	143	69	525	5.37 (3.76-7.68)

(1) Upper gastro-intestinal procedure received between 61 days and 3 years prior to admission
(2) Visit to a gastroenterologist between 61 days and 3 years prior to admission
(3) At least 1 prescription for a protective agent between 31 days and 3 years prior to admission

TABLE 4.19

Summary of bivariate analyses

Covariate	Association with NANSAIDs	ASA	UGIB	Crude OR (95% C.I.)
Past NANSAID use	**	N.A.	N.S.	1.06 (0.86-1.56)
Past ASA use	N.A.	**	N.S.	1.28 (0.94-1.75)
Concomitant use of protective agent	**	N.S.	**	2.00 (1.30-3.04)
Smoking	N.S.	N.S.	*	Ex: 1.42 (0.96-2.10) Current: 2.06 (1.37-3.09)
History of gastropathy:				
a) past UGI procedure	N.S.	N.S.	**	1.93 (1.34-2.80)
b) visit to gastroenterologist	N.S.	N.S.	**	1.91 (1.36-2.68)
c) past use of protective agents	*	N.S.	**	2.09 (1.52-2.87)
d) history assessed in charts	N.S.	N.S.	**	5.37 (3.76-7.68)
Comedications:				
a) anticoagulants	N.S.	N.S.	N.S.	1.03 (0.50-2.11)
b) corticosteroids	*	N.S.	N.S.	0.94 (0.60-1.47)
c) antineoplastic drugs	N.S.	N.S.	N.S.	1.45 (0.72-2.90)

* Significant at the .05 level
** Significant at the .01 level

N.S. Non-significant
N.A. Non-applicable

TABLE 4.20

Multivariate logistic regression analysis

Independent predictors of upper-gastrointestinal bleeding*

Parameter	B coefficient	Std. Error	P value	Crude OR (95% C.I.)	Adjusted OR (95% C.I.)
NANSAIDs	1.212	.253	<.001	2.93 (2.01-4.27)	3.36 (2.05-5.52)
ASA	0.499	.274	.069	1.45 (0.99-2.12)	1.56 (1.00-2.42)
Past NANSAID use	-0.412	.204	.043	1.16 (0.86-1.56)	0.66 (0.44-0.97)
Protective agents	0.510	.244	.037	1.28 (0.94-1.75)	1.66 (1.03-2.67)
Ex-smokers	0.382	.209	.067	1.42 (0.96-2.10)	1.46 (0.97-2.20)
Smokers	0.878	.217	<.001	2.06 (1.37-3.09)	2.40 (1.57-3.67)
Hx of gastropathy**	0.700	.218	.001	1.93 (1.34-2.80)	2.02 (1.32-3.09)

Deviance 741 DF = 808.777

Interactions:

- Recent NANSAID use * Past use of NANSAIDs in previous 3 years: LRS(1df)=5.95, p=.015
- Recent NANSAID use * Recent use of protective agents: LRS(1df)=0.64, p=.423
- Recent NANSAID use * History of gastropathy: LRS(1df)=0.12, p=.725
- Recent NANSAID use * Smoking: LRS(2df)=1.31, p=.519

* Non-use during the 30 days preceding the event is the reference category
** History of gastropathy assessed by past upper GI procedures

TABLE 4.21

The relative risk for hospitalization for upper gastro-intestinal bleeding associated with recent use of non-aspirin NSAIDs for patients with and without past use of these drugs in the last 3 years

Use of NANSAIDs in past 3 years	Cases		Controls		Crude Odds Ratio	95% CI
	Exposed	Unexposed	Exposed	Unexposed		
None	8	121	1	347	22.73	2.84 - 200.00
At least once	58	57	68	199	2.98	1.88 - 4.72

Breslow-Day test for homogeneity of ORs: chi-square=4.575, p=.032

TABLE 4.22

Multivariate logistic regression analysis

Comparison between the 4 measures of history of gastropathy

Parameter	UGI procedures	Past visit to a Gastroenterologist	Past use of protective agents	Hx assessed in charts
NANSAIDs	3.36 (2.05-5.52)	3.43 (2.08-5.65)	3.34 (2.05-5.49)	3.58 (2.14-6.01)
ASA	1.56 (1.01-2.42)	1.55 (1.00-2.40)	1.58 (1.02-2.44)	1.57 (1.00-2.47)
Past NANSAID use	0.66 (0.44-0.97)	0.65 (0.44-0.97)	0.61 (0.41-0.92)	0.68 (0.45-1.02)
Protective agents	1.66 (1.03-2.67)	1.57 (0.96-2.54)	1.16 (0.68-1.97)	1.08 (0.64-1.81)
Ex-smoker	1.46 (0.97-2.20)	1.42 (0.95-2.14)	1.44 (0.96-2.17)	1.30 (0.84-2.00)
Smoker	2.40 (1.57-3.67)	2.39 (1.56-3.66)	2.25 (1.47-3.45)	2.24 (1.44-3.49)
Positive history of gastropathy	2.02 (1.32-3.09)	2.05 (1.38-3.04)	2.26 (1.50-3.41)	5.26 (3.47-7.95)

TABLE 4.23

Distribution of average daily doses of

ASA within 30 days prior to admission *

Average (mg/day)	Multiple of 325mg/day	No. prescriptions	Percent
325	1	61	43.6
650	2	35	25.0
975	3	7	5.0
1300	4	26	18.6
1625	5	0	0.0
1950	6	4	2.9
2275	7	2	1.4
2600	8	1	0.7
2925	9	2	1.4
3250	10	1	0.7
3575	11	1	0.7
Total		140	

* Last ASA prescription before admission

TABLE 4.24

Multivariate logistic regression analysis

Average daily doses of ASA

Average Daily Dosage * (mg/day)	Cases	Controls	Odds Ratio**	95% CI
	n(%)			
≥650	25 (10.2)	54 (8.8)	1.32	0.74 - 2.33
<650	24 (9.8)	37 (6.0)	1.92	1.05 - 3.51
Unexposed	195 (79.2)	524 (85.2)	Reference	

* Estimated from dose per unit of administration, prescribed duration of treatment and quantity.

** Adjusted odds ratio

TABLE 4.25

Sensitivity analysis

Effect of control diagnoses

	All included (n=749)	Respiratory illnesses (n=582)	Cholecystitis (n=675)	Trauma (n=593)
NANSAIDs	3.36 (2.05-5.52)	3.16 (1.86-5.36)	3.05 (1.82-5.10)	3.81 (2.24-6.47)
ASA	1.56 (1.01-2.42)	1.41 (0.89-2.24)	1.60 (1.02-2.51)	1.57 (0.99-2.49)
Protect. ag.*	1.66 (1.03-2.67)	1.66 (0.99-2.79)	1.96 (1.19-3.24)	1.48 (0.89-2.46)
Hx of NANSAIDs	0.66 (0.44-0.97)	0.64 (0.42-0.96)	0.67 (0.45-1.01)	0.64 (0.42-0.96)
Ex-smokers	1.46 (0.97-2.20)	1.77 (1.14-2.75)	1.52 (0.99-2.31)	1.31 (0.85-2.00)
Smokers	2.40 (1.57-3.67)	2.48 (1.58-3.89)	2.14 (1.39-3.30)	2.82 (1.77-4.49)
Hx of UGI proc.**	2.02 (1.32-3.09)	2.02 (1.27-3.20)	2.14 (1.38-3.33)	1.83 (1.16-2.87)

	Urinary tract (n=697)	Other GI illnesses (n=718)	Other (n=698)	Missing (n=745)
NANSAIDs	3.38 (2.04-5.60)	3.48 (2.11-5.77)	3.19 (1.92-5.28)	3.36 (2.04-5.52)
ASA	1.55 (1.00-2.41)	1.65 (1.06-2.57)	1.63 (1.05-2.55)	1.55 (1.00-2.40)
Protect. ag.	1.65 (1.02-2.68)	1.64 (1.01-2.66)	1.63 (1.00-2.66)	1.64 (1.02-2.65)
Hx of NANSAIDs	0.65 (0.43-0.96)	0.67 (0.45-1.00)	0.69 (0.46-1.03)	0.65 (0.44-0.97)
Ex-smokers	1.49 (0.98-2.26)	1.37 (0.91-2.07)	1.37 (0.91-2.07)	1.46 (0.97-2.20)
Smokers	2.24 (1.46-3.44)	2.43 (1.57-3.74)	2.34 (1.52-3.60)	2.45 (1.60-3.76)
Hx of UGI proc.	1.97 (1.28-3.04)	2.09 (1.35-3.23)	2.00 (1.29-3.08)	2.05 (1.33-3.14)

* Recent use of protective agents
** History of upper gastro-intestinal procedures (marker of history of gastropathy)

Note: The actual sample size does not correspond to the total sample size minus the number of controls in the diagnostic category because there were also 110 patients with no information on smoking.

TABLE 4.26

Sensitivity analysis

Effect of hospitals

	Royal-Victoria (n=636)	Notre-Dame (n=607)	Maisonneuve-Rosemont (n=536)	Jewish General (n=468)
NANSAIDs	3.13 (1.85-5.29)	3.23 (1.85-5.65)	3.58 (1.92-6.70)	3.55 (1.93-6.56)
ASA	1.66 (1.03-2.66)	1.38 (0.85-2.24)	1.48 (0.87-2.51)	1.82 (1.05-3.14)
Prot.ag. *	1.77 (1.05-2.98)	1.41 (0.81-2.46)	1.62 (0.94-2.82)	1.95 (1.07-3.54)
Past NANSAID use	0.66 (0.43-1.02)	0.78 (0.50-1.20)	0.52 (0.32-0.85)	0.66 (0.41-1.08)
Ex-smoker	1.33 (0.85-2.08)	1.36 (0.87-2.12)	1.76 (1.08-2.88)	1.44 (0.86-2.42)
Smoker	2.26 (1.42-3.61)	2.75 (1.71-4.42)	2.18 (1.28-3.71)	2.30 (1.37-3.87)
Hx of UGI proc. **	1.57 (0.98-2.52)	2.51 (1.57-3.99)	2.01 (1.20-3.35)	2.20 (1.28-3.79)

* Recent use of protective agents
** History of upper gastro-intestinal procedures (marker of history of gastropathy)

TABLE 4.27

Sensitivity analysis

Effect of study years

	88/89 (n=369)	89/90 (n=380)
NANSAIDs	3.16 (1.59-6.29)	3.75 (1.78-7.93)
ASA	1.73 (0.94-3.19)	1.43 (0.76-2.68)
Prot.ag. *	2.01 (0.94-4.26)	1.59 (0.84-3.00)
Past NANSAID use	0.68 (0.39-1.18)	0.56 (0.31-1.00)
Ex-smoker	0.90 (0.49-1.64)	2.50 (1.39-4.49)
Smoker	2.05 (1.12-3.76)	3.18 (1.71-5.90)
Hx of UGI proc. **	1.37 (0.70-2.67)	2.99 (1.66-5.37)

* Recent use of protective agents
** History of upper gastro-intestinal procedures (marker of history of gastropathy)

TABLE 4.28

Distribution of past exposure to non-aspirin NSAIDs into 3 different time windows

	Past exposure to NSAIDs					
	31 days-1 year		31 days-2 years		31 days-3 years	
	Exposed*	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Cases	80	164	95	149	115	129
Controls	151	464	224	391	267	348

* Recent exposure to NANSAIDs (prescription ending within 30 days of the event)

TABLE 4.29

Effect of data truncation

	Odds ratio (95% C.I.)		
	31 days - 1 year	31 days - 2 years	31 days - 3 years
Recent NANSAIDs	3.07 (1.80-5.24)	3.17 (1.85-5.43)	3.36 (2.05-5.52)
Recent ASA	1.55 (1.00-2.39)	1.54 (1.00-2.37)	1.56 (1.01-2.42)
Past NANSAID use	0.79 (0.49-1.26)	0.79 (0.49-1.27)	0.66 (0.44-0.97)
Recent protective agents	1.65 (1.02-2.66)	1.56 (0.96-2.52)	1.66 (1.03-2.67)
Ex-smokers	1.44 (0.96-2.16)	1.41 (0.94-2.12)	1.46 (0.97-2.20)
Smokers	2.41 (1.58-3.69)	2.42 (1.58-3.70)	2.40 (1.57-3.67)
History of * gastropathy	1.94 (1.27-2.95)	2.01 (1.31-3.08)	2.02 (1.32-3.09)
Deviance (741 DF)	812.286	804.479	808.777
Interactions:			
Recent NANSAIDs and Past NANSAID use	LRS=0.123 p=.726	LRS=4.678 p=.031	LRS=5.946 p=.015

* Past upper gastro-intestinal procedures

TABLE 4.30

The relative risk for upper gastro-intestinal bleeding associated with recent use of non-aspirin NSAIDs for each pattern of duration of use

Level of duration	No. patients	Cases exposed*	Cases unexposed	Controls exposed	Controls unexposed	Odds Ratio**	95% confidence interval
			n		n		
None (1)	628	12	152	9	455	3.99	1.65 - 9.66
Short (2)	74	7	8	8	51	5.58	1.58 - 19.64
Intermediate (3)	85	17	15	18	35	2.20	0.90 - 5.41
Long (4)	72	30	3	34	5	1.47	0.32 - 6.68

* Recent exposure to non-aspirin NSAIDs within 30 days prior to the event
** Crude odds ratio associated with recent exposure to non-aspirin NSAIDs for each pattern

(1) No prescription of non-aspirin NSAIDs ending between 31 and 365 days prior to admission
(2) At least 1 prescription of non-aspirin NSAIDs ending between 31 and 365 days prior to admission: 1-30 days
(3) At least 1 prescription of non-aspirin NSAIDs ending between 31 and 365 days prior to admission: 31-120 days
(4) At least 1 prescription of non-aspirin NSAIDs ending between 31 and 365 days prior to admission: > 120 days

TABLE 4.31

The relative risk for upper gastro-intestinal bleeding associated with recent use of non-aspirin NSAIDs for each switching pattern.

Switching pattern	No. patients	Cases		Controls		Odds Ratio**	95% confidence interval
		exposed*	unexposed	exposed	unexposed		
None (1)	628	12	152	9	455	3.99	1.65 - 9.66
Non-switchers (2)	181	18	2	14	16	2.45	1.30 - 4.61
Switchers (3)	50	36	24	46	75	10.29	2.02 - 52.36

* Recent exposure to non-aspirin NSAIDs
** Crude odds ratio between recent use of non-aspirin NSAIDs and upper gastro-intestinal bleeding for each pattern

(1) No prescription of non-aspirin NSAIDs ending between 31 and 365 days prior to admission
(2) At least 1 prescription of non-aspirin NSAIDs ending between 31 and 365 days prior to admission, no switch between products
(3) At least 1 prescription of non-aspirin NSAIDs ending between 31 and 365 days prior to admission, at least 1 switch between products

TABLE 4.32

Association between recent use of protective agents and duration patterns of non-aspirin NSAIDs

Duration pattern	All patients		Cases		Controls	
	Exposed*	Unexposed	Exposed	Unexposed	Exposed	Unexposed
	no. patients					
None (1)	58	570	24	140	34	430
Short-term (2)	8	66	2	13	6	53
Intermediate (3)	19	66	7	25	12	41
Long-term (4)	20	52	11	22	9	30

* Recent use of protective agents (prescription ending within 30 days prior to the event)

(1) No prescription of non-aspirin NSAIDs ending between 31 and 365 days prior to admission
(2) At least 1 prescription of non-aspirin NSAIDs ending between 31 and 365 days prior to admission: 1-30 days
(3) At least 1 prescription of non-aspirin NSAIDs ending between 31 and 365 days prior to admission: 31-120 days
(4) At least 1 prescription of non-aspirin NSAIDs ending between 31 and 365 days prior to admission: > 120 days

TABLE 4.33a

Association between history of upper GI procedures and duration of past non-aspirin NSAID use during the year before admission

Past UGI procedure	Duration pattern of NANSAID use							
	Never Exposed		Short-term 1-30 days		Intermediate 31-120 days		Long-term >120 days	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Positive	41	66	4	5	7	9	7	7
Negative	123	398	11	54	25	44	26	32
Total	164	464	15	59	32	53	33	39

TABLE 4.33b

Association between past use of protective agents and duration of past non-aspirin NSAID use during the year before admission

	Duration pattern NANSAID use							
	Never Exposed		Short-term 1-30 days		Intermediate 31-120 days		Long-term >120 days	
Past prot. agents	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Positive	64	90	5	15	12	23	13	14
Negative	100	374	10	44	20	30	20	25
Total	164	464	15	59	32	53	33	39

TABLE 4.34

The relative risk for upper gastro-intestinal bleeding according to recency of use of non-aspirin NSAIDs

Recency of use	Cases (n=244)	Controls (n=615)	Odds Ratio*	95% Confidence Interval
	n	n		
Recent (1)	99	149	2.54	1.63 - 3.96
Former (2)	17	82	0.82	0.49 - 1.39
None (3)	128	384	1.0	Reference

* Adjusted odds ratio

(1) Last prescription ending less than 30 days before the GI event.

(2) Last prescription ending between 31 and 365 days before the GI event.

(3) Reference group: No prescription of non-aspirin NSAIDs during the year preceding admission (non-recent, non-former).

CHAPTER 5

DISCUSSION

5.1 STUDY FINDINGS

Findings on which is based the following discussion are summarized in chapter 4, section 4.12. Each element is addressed in greater detail in the following sections of this chapter. The discussion consists of the interpretation of the results as well as of a comparison with previous findings from the literature when applicable. The strengths and limitations of the study are discussed thereafter. Finally, recommendations for future research are made.

5.1.1 Association between NSAID use and UGIB

NANSAIDs: In this elderly population, recent users of NANSAIDs were 3.36 times more likely to be hospitalized for UGIB than non-users. This estimate of relative risk was compared to those found in the literature for the elderly population. The estimate was similar to that reported by Griffin et al. (1991) of 4.1 but was smaller than those reported by Laporte et al. (1991) and Holvoet et al. (1991): 7.7 and 7.4, respectively. The estimate was also smaller than the summary OR of 5.52 obtained for individuals age 60 and over in the meta-analysis by Gabriel et al. (1991). As discussed in chapter 2,

differences between studies regarding various factors could explain the discrepancies namely, time window, method of exposure ascertainment, age structure of the study population etc.

It is interesting to note that both studies that used automated databases (the present study and that by Griffin et al.) found smaller estimates of relative risk than those based on interviews. In the literature, it has been reported that estimates obtained from cohort studies were smaller than from case-control studies. This study suggests that the difference is not a design issue but is related to the source of information on drug use.

ASA: The estimate of relative risk associated with recent use of ASA was 1.87, which was smaller than those previously reported. Levy et al. (1988) found 3.07 while Laporte et al. (1991) obtained 6.7 for men age 60 and over, and 6.4 for women. Several possible explanations for the difference between NANSAIDs and ASA may be considered. The first one is a true difference while the other 3 are biases. These are described below:

1) In this study population, and probably generalizable to the entire Quebec elderly population, most prescribed ASA was enteric-coated, which could explain the smaller relative risk. However, the very small number of users of non-coated ASA does not allow to verify this hypothesis. This association is indirect and inferences regarding differences in toxicity between modes of

administration cannot be made.

2) The difference could also be due to misclassification of exposure due to the availability of ASA over-the-counter (OTC). However, patient interviews were conducted in both the Laporte et al. and Holvoet et al. studies and ascertainment included OTC drugs. Yet in these studies, the risk associated with NANSAIDs use was also greater than with ASA use.

3) Indication bias may also be present. The illnesses for which patients use NANSAIDs may increase the risk of UGIB compared to those for which ASA is used. None of the studies that compared both classes of products controlled for indication.

4) Similarly, the doses at which NANSAIDs are used may be greater than those of ASA, maybe because of differences in indication. Doses of NANSAIDs and ASA were not compared in this study.

In summary, these results confirm that NANSAIDs and ASA increase the risk of UGIB in the elderly population. The magnitude of the risk associated with NANSAIDs was lower than that of published case-control studies based on interviews but similar to the one that used automated databases. This study also supports previous findings from comparative studies whereby the effect of NANSAIDs was greater than that of ASA. It was not possible to document whether there was a true difference in the risk due to differences

in the form of administration or dose, or whether it was due to misclassification biases. Regardless of the reason, these results demonstrate that it is important to distinguish between NANSAIDs and ASA because of the difference in the risk of UGIB as well as differences in patterns of utilization (eg. men versus women), which suggest different indications.

5.1.2 Past NSAID use

Results obtained in this study provide empirical evidence that patients who used NANSAIDs for the first time in 3 years were at greater risk of experiencing UGIB than those who used them during this time period. The estimate of relative risk associated with past use was 0.66 (0.44-0.97). Such an effect was not present with past use of ASA. Comparison with previous findings cannot be made because none of the studies published so far examined the independent effect of past experience with the drug.

Furthermore, the estimate of relative risk between recent NANSAID use and UGIB was greater for first-time users than for those who used the drugs in past 3 years. It is hypothesized that past users who were also recent users tolerated the drug well, and past users who were intolerant selected themselves out of the population at risk because of symptoms of gastropathy. This selection process is similar to the well known "healthy worker effect" in

epidemiology. In chapter 1 was described one of the assumptions of the concept of incidence density namely, that early stages of the adverse event do not lead to changes in exposure and that censoring is not related to exposure (O'Neill, 1988). Results found in this study suggest that this assumption is violated in the framework of the risk associated with drug exposure.

Another reason for the difference in relative risk is the reference population. In the group of patients with no past exposure in the 3 years prior to the event, the reference population consisted of individuals who were not exposed before and not currently exposed. These patients are probably healthier, which would over-estimate the relative risk.

The effect of past NANSAID use was independent of that of history of gastropathy because the lower risk remained after controlling for history of gastropathy. This suggests that other factors may be responsible for the selection out of the population at risk, such as symptoms (before developing severe UGIB).

However, because NANSAIDs are widely used among the elderly, there were very few patients who were using the drugs for the first time in 3 years. Past exposure is thus an independent predictor of UGIB but the assessment of its modifying effect is limited by the small number of patients who used NANSAIDs for the first time in 3 years. Nevertheless, these findings show that past experience with the

drug should therefore be taken into account in the assessment of the risk of UGIB.

5.1.3 Patterns of non-aspirin NSAID use

Recency: According to the estimate of relative risk, there was no risk associated with former exposure to NANSAIDs (last exposure between 31 days and 365 days before admission). Effects of a similar direction were found for NANSAIDs by Griffin et al. (1991) where there was a small significant risk associated with former use (defined as exposure between 60 and 365 days before the index date) of 1.3 (1.1-1.6). The estimate of relative risk for current use (on the day of admission) was 4.1 (3.5-4.7).

Results from the present study indicate that the risk becomes non-significant more than 30 days after the discontinuation of treatment. In the Griffin et al. study, there was still a small risk more than 60 days after discontinuation. Such a discrepancy between findings does not allow us to determine the period at risk after the discontinuation of the drug.

Duration: The estimate of relative risk for UGIB decreased as the duration of NANSAID use during the year before admission increased. The difference in risk observed was much smaller than that reported by Griffin et al. (1991) where estimates of relative risk were: 7.2

(4.9-10.5) for incidental users, 3.7 (2.7-5.2) for 31-90 days and 3.9 (3.3-4.6) for duration greater than 90 days. The reference group in that study consisted of never exposed during the year. Factors influencing the reference risk consisted of no current exposure to NSAIDs as well as no past experience with NSAIDs. Therefore, as described in chapter 2, the assessment of duration in recently exposed individuals only, does not allow to partition the effect of recent exposure to NSAIDs and that of patterns of NSAID use.

This study showed that past experience with NANSAIDs was associated with UGIB, independently of recent use. Duration was defined in relation to the date of admission. Long-term users were more likely to be recent users because of length-biased sampling. Because the risk decreases with an increase in duration of use, to measure duration only in the recently exposed patients would bias the magnitude of the association towards the null. Furthermore, because of the inability to partition the effects of recent and past exposure, as well as length-biased sampling, it appears that the assessment of duration of use in recent users only using the never exposed during the year as the reference group is not appropriate to assess the modifying effect of past experience.

Based on these results, it can also be concluded that descriptive studies on drug utilization that are based on cross-sectional data

would over-estimate the proportion of long term users.

Studies on patterns found in the literature are population-based. Hence, for comparison purposes, figures obtained in the control group will be used. Of controls who were exposed between 31 and 365 years prior to admission, 39.1% were short-term users, 35.1% were intermediate users and 25.8% were long-term users. This is in contrast to the Leufkens et al. (1990) study where 74.0% of NANSAID users in a period of 12 months were short-term users. Three factors may explain the discrepancy between findings:

1) The age structure of the 2 populations differs. Patients of all ages were included in the Leufkens et al. study. It was possible to derive from published data the distribution of levels for patients above the age of 60. According to the calculations, it was found that 49.5% of patients in this age group were incidental users, which is still greater than what was found in the present study.

2) In the present study, duration of exposure was determined in relation to an event (date of admission) and data before 365 days were truncated. Therefore, it did not consider time since initiation of therapy. Individuals in the Leufkens et al. study were followed prospectively and the date of entry was chronological, starting at the beginning of the study year.

3) The Leufkens et al. study was population-based whereas in the present study, controls were a non-random sample of the secondary base. Even if the control population is a valid sample of the secondary base, exposure patterns in the control population are not expected to reflect exposure patterns of the entire Quebec elderly population (see discussion below on selection bias).

4) The time period was 1 month longer in the Leufkens et al. study (12 months versus 11 months), and the youngest individual was 60 years old which could inflate the proportion of incidental users in the Dutch population.

Switches between NANSAIDs: Patients who switched at least once between products appeared to be at greater risk than those who did not. In the present study, 19.9% of controls who had used a NANSAID between 31 and 365 days prior to admission switched at least once between products. The proportion was two times greater in the Leufkens et al. (1990) study where 42.2% of patients switched at least once between NANSAIDs during this time period. Previous work conducted on a random sample of the Dutch population (Abenhaim et al., 1991) reported that 26.9% of patients switched, which is closer to the results found in this study. However, the 3 studies are not comparable for the following reasons:

1) In the Leufkens et al. study, the denominator consisted of patients who received more than 1 NANSAID prescription. In the

present study, it was not felt that the denominator should include only these patients because it is the switch that influences the number of prescriptions and not the converse.

2) Here, included in the definition of a switch was the condition that the dates of dispensing of the 2 consecutive NANSAID prescriptions had to be 60 days apart or less. This condition was not used by Leufkens et al. nor by Abenhaim et al.

3) Leufkens et al. used the ATC codes (i.e. the World Health Organization Anatomical Therapeutic Chemical classification) to refer to individual NANSAID products whereas generic names were used in the present study.

4) Age structure: Walker et al. (1992) reported that switches occurred more frequently in the young population. All ages were considered in the Leufkens et al. study, which could explain the greater proportion of switchers in that population.

Switches between average daily doses: A greater proportion of controls who used NANSAIDs between 31 and 365 days prior to admission increased the ADD of a given product than decreased. In contrast, in the Leufkens et al. study, a slightly greater number of switches were reductions in ADD. Here, only 20% of patients who switched ADDs switched more than once compared to the Leufkens et

al. study where it was one third. Several factors may be responsible for the discrepancy between the 2 studies:

1) A different measure of dosage was used by Leufkens et al. It consisted of the prescribed daily dose divided by the defined daily dose ratio (DDD). The DDD is a measure that consists of the average daily dosage for the drug when used in its main indication. The numerator of this estimator corresponds to the average daily dosage used in the present study. However, the differences between the measures used in the 2 studies should not cause non-comparability of the results as far as switches are concerned because the DDD used by Leufkens et al. is constant within each product.

2) Possible explanations for the discrepancy are the same as those for switching between products namely, definition of a switch, time period, denominator and base population (especially, the age structure).

Switches between forms of administration 2.6% of controls who used NANSAIDs between 31 and 365 days before admission switched between forms of administration compared to 3.5% in the Leufkens et al. study. Here 60% of switchers switched more than once while in the Leufkens et al. study most switches were incidental.

To summarize, switching products was more common than switching doses. Overall, there appears to be a smaller proportion of patients who switched products than in published studies. The reason for the discrepancy most likely resides in the definition of a switch (different in both the Leufkens et al. and Abenhaim et al. studies) and the age structure of the population (compared to the Leufkens et al. study).

Effects of patterns of NANSAID use on the risk of UGIB The magnitude of the association between NANSAIDs and UGIB decreases as the duration of use increases. Patients who switched products at least once were at greater risk than those who did not switch. However, it cannot be concluded from the results that patterns are effect modifiers because the ORs were not significantly heteregeneous. The absence of a significant difference was due to the fact that the majority of NANSAID users in this elderly population were not short-term users and did not switch frequently. As a result, the variation in patterns of NANSAID use during the year preceding hospitalization was small which decreased the efficiency of the study. It may have been useful to characterize patterns on a longer term (eg. 3 years). However, this would have required the inclusion of an additional dimension: timing of patterns. This study did not offer the power to do so.

Walker et al. (1992) documented the reasons for switching and did

not find evidence to support a hypothesis that drugs frequently switched to because of patient intolerance for previous drugs would themselves show higher probabilities of discontinuation for intolerance, nor that drugs switched to for lack of efficacy of previously given NSAIDs would show lower apparent efficacy. These findings suggest that patients who switch are not more susceptible to UGIB, which would explain the absence of a significant difference between the estimates of relative risk.

5.1.4 Concomitant exposure to protective agents

Recent users of protective agents were 1.68 times more likely to experience UGIB than non-users. These data provide empirical evidence of the presence of a protopathic or susceptibility bias. One may wrongly conclude that these drugs increase the risk of UGIB. However, it is likely that individuals used these drugs because they were already experiencing symptoms of gastropathy.

Furthermore, the recent use of these drugs increased with an increase in duration of NANSAID use and switching between products. These results indicate that the elderly who use NANSAIDs on a long term remain on the drug and, if intolerant, use protective agents rather than discontinue or switch. Susceptibility bias in the association between NANSAIDs and UGIB would therefore be better appraised by the use of protective agents than by switching.

Because the effect of recent use of protective agents on UGIB remained even after controlling for history of gastropathy, it strengthens the allegation that even if patients experienced a gastropathy in the past, they do not modify therapy with NANSAIDs but supplement it with protective agents.

On the other hand, because NSAID-gastrotoxicity is well recognized within the medical community, physicians may prescribe more frequently protective agents to long-term users of NSAIDs for prophylactic purposes. At present, it is not known whether protective agents should be used as a marker for gastropathy or for susceptibility (as perceived by physicians who believe that some patients are in high risk groups).

5.1.5 History of gastropathy

Patients with a positive history of gastropathy, assessed by history of upper GI procedures, were at a greater risk of experiencing UGIB by a factor of approximately 2. When history was assessed as past visit to a gastroenterologist, similar results were found. None of the studies reviewed used these measures as markers for history of UGIB. As a result, the estimate obtained cannot be compared with previous findings. According to the results, past upper GI procedures and past visit to a

gastroenterologist are predictors of UGIB but not of NANSAID prescription.

When history was assessed in the charts, an estimate of relative risk of 5.35 was found. It is likely that this effect is over-estimated due to differences in the accuracy of the information. The admitting physician would inquire specifically about history of gastropathy in patients admitted for UGIB but not necessarily in patients admitted for an unrelated illness. If absent from the chart, it was coded as absent history. This would lead to a differential misclassification between cases and controls. However, it was useful to confirm the direction of the effect because this method of ascertainment (patient's interview by the physician) was completely independent of the others which were derived from the RAMQ databases. It is likely that the reliability of these data is lower than the hard data obtained from the RAMQ databases but on the other hand, there was no truncation before the 3 years preceding admission. Nevertheless, these results agree with those found in the Laporte et al. (1991) and Holvoet et al. (1991) studies which both reported an OR of 5.5 for history of peptic ulcer disease. In these studies, patients were interviewed and it was not mentionned whether interviewers were blinded or not. Recall bias may also inflate the estimates of the effect and the differential misclassification may have occurred in these settings as well.

When past use of protective agents was used as a marker, the estimate of relative risk was 2.68. The collinearity between past and recent use of protective agents suggests that they were in fact measuring the same underlying phenomenon. The effect was stronger for past use because of the greater prevalence in this wider time window compared to the 30 days of recent use (18.6% versus 12.2%). It is likely that recent use of protective agents is a continuation of treatment that started before the 30-day window. In the Jick et al. (1987) study, patients who ever used cimetidine and antacids were 5.1 times (2.6-10.0) more likely to experience a gastropathy. Carson et al. (1987) found no association between protective agents dispensed before NSAID use and UGIB (relative risk=1.1, 95% C.I.=0.6-2.3). The estimate found in the present study was therefore smaller than that found in the Jick et al. study but greater than in the Carson et al. study.

Results indicate that history of gastropathy does increase the risk of UGIB by a factor of approximately 2. Past use of protective agents does not seem to be a good marker because it does not allow to partition the marker effect (protopathic bias) and the real protective effect of these agents when used for prophylaxis. Past upper GI procedures and past visit to a gastroenterologist produced estimates of relative risk that were very similar while history assessed in the chart over-estimated the effect.

History of gastropathy was not associated with recent use of

NANSAIDs. Conversely, it was associated with recent use of protective agents. These results suggest that history of gastropathy does not influence prescribing behaviour for NANSAIDs and instead, patients use protective agents. Opposite results were found by Griffin et al. (1991) study where there was a negative association between history of gastropathy and current use of NSAIDs. In that study, the association was determined from hospital charts in cases only.

A possible explanation for the absence of an association between history of gastropathy and recent NANSAID use is the reliability of the markers used. Past upper GI procedures is sensitive but is non-specific, i.e. most patients with a gastropathy receive such diagnostic procedures but these procedures are also conducted for other pathologies. Past visit to a gastroenterologist is also non-specific and is less sensitive than the previous marker because not all patients with a gastropathy consult a specialist. However, history assessed in the charts was also not associated with recent NANSAID use. This measure was not derived from automated databases and yet, results are the same as those obtained with the previous markers. Such consistency between the measures would favour a true absence of association between history of gastropathy and recent use of NANSAIDs.

Unlike NANSAIDs, the effect of past and recent use of protective agents were not independent of each other and both increased the

risk of UGIB. It is therefore likely that past use of protective agents does not specifically reflect a history of gastropathy.

5.1.6 Average daily doses of ASA

As discussed in chapter 3, it has been hypothesized that low doses of ASA may not be associated with a greater risk of UGIB. There was no estimated ADD below 325 mg dispensed to the patients of the study population, and the majority of prescribed ASA was enteric-coated.

The distribution of the ADDs of ASA was not heterogeneous between cases and controls and this study did not support a dose-response relationship. Doses of ASA were considered only in the Holvoet et al. (1991) study and were expressed as a dichotomous variable: < 2 grams/week and > 2 grams/week. Although a dose-specific OR was not reported by Holvoet et al., the distribution of the population into the dose categories was not heterogeneous between cases and controls, which suggests no dose-response as well.

Four factors may explain the absence of a dose difference. The first one is a true effect and the other three are potential biases. These are described below:

1) Enteric-coating may be responsible for the absence of a

difference between doses. However, because of the small number of non enteric-coated ASA prescriptions, it was not possible to verify for this effect.

2) Because the exact drug regimen was not known, the ADD had to be estimated from the number of units of administration, dose per unit of administration, and number of days of therapy. This estimation may result in an extensive misclassification that could mask an existing trend. It was not possible to compare the distribution of estimated ADD with previous studies because of a lack of published data.

3) Because ASA can be purchased OTC at a relatively low cost, there may be differential misclassification of exposure among the dose categories. For example, if more low doses of ASA were purchased OTC than higher doses. It was not possible to verify this hypothesis. However, if this were the case then the estimate of relative risk for low doses of ASA would be biased towards the null. Results from this study do not support this given that the risk associated with the low dose category was greater.

4) Compliance: Higher ADDs are associated with a greater number of tablets per day. As a result, compliance may be reduced in higher dosages. Exposure would therefore be over-estimated in the higher doses.

In summary, the absence of a dose-response relationship may be attributable to differential misclassification between the dose categories due to OTC availability of ASA and/or compliance. There is also the possibility of a true absence of dose-effect due to enteric-coating. None of these hypotheses could be verified in the study. The scarcity of data in the literature and findings from this study suggest that this issue should be explored further.

5.1.7 Concomitant medications

This study was unable to demonstrate that recent use of corticosteroids, anticoagulants or anti-neoplastic drugs were associated with an increased risk of UGIB. Carson et al. (1987) reported a relative risk of 1.4 for corticosteroid use that was non-significant according to the 95% C.I. (0.8 to 2.2) whereas the effect of anticoagulants was significant 2.8 (1.4-5.6). Bigelow and Collins (1989) also reported a significant relative risk for the use of anticoagulants and/or corticosteroids of 1.7. Holvoet et al. (1991) found no difference between cases and controls in the use of corticosteroids, which suggests no effect. However, the prevalence of exposure was small and thus, the power to detect an effect was very small.

5.1.8 Smoking

Smoking increased the risk of UGIB. Compared to ex-smokers, only current smokers had a significant risk. The magnitude of the association was greater than that previously reported by Somerville et al. (1986) of 1.30 (0.88-1.91) using hospital controls. Bartle et al. (1986) and Holvoet et al. (1991) found that smoking did not have any effect on UGIB but these studies were not restricted to the elderly population. The absence of data on smoking in the medical charts was not differential between cases and controls which does not support a bias introduced by differential misclassification.

5.1.9 Exposure to NSAIDs

The prevalence of exposure to NSAIDs obtained in the present study was compared to figures found in the literature for the elderly population. It should be kept in mind that results obtained from various studies were not totally comparable because of different time windows used for exposure ascertainment. In the following section, comparisons are made always acknowledging the factors that could potentially jeopardize the comparability of prevalence figures.

NANSAIDs: For the purpose of comparability, results obtained using

a 7-day time window were used in the comparison with previous findings. In this study, it was found that 23.0% of cases and 7.8% of controls had been exposed to NANSAIDs within 7 days prior to admission. For the same time window, Laporte et al. (1991) reported slightly lower figures: 20.5% of cases and 4.2% of controls (pooling both genders together). The time window was smaller in the Griffin et al. study (1991) (exposure was ascertained on the day of the event). Yet, the proportion of NANSAID use was much greater: 34% of cases and 13% of controls. The corresponding figures in the Collier and Pain (1985) study were 47.0% of cases and 7.1% of controls.

Such a discrepancy between studies is not due to a difference in time window because, as shown in the present study, it would have biased the results in the other direction (a wider time window results in greater proportion of exposure). It is also not due to the source of information because the Laporte et al. study is based on interview and yet, results are similar. The study by Griffin et al. used automated databases and results differed from those obtained in this study.

Individual products The most widely used NANSAID was diclofenac which is consistent with the Dutch population (Leufkens et al., 1990) and results found by Laporte et al. (1991). Indomethacin came second, followed by naproxen. In the Dutch population, the second was ibuprofen. The probable reason for the discrepancy is

that all ages were included in the Leufkens et al. study which resulted in a greater variability of indications.

ASA: For the purpose of comparability, results obtained using a 7-day time window were used in the comparison with previous findings. For cases, the prevalence of exposure to ASA was lower than that to NANSAIDs: 18.0% were recent users of ASA versus 27.0% for NANSAIDs. However, the reverse was true for controls: 12.4% were recent users of ASA versus 7.8% for NANSAIDs. The difference between cases and controls in the proportion of exposure to ASA was greater in the Laporte et al. (1991) study: 33.0% of cases versus 9.7% of controls. The larger difference between cases and controls observed in the latter study is likely to be due to recall bias.

Sexes: A greater proportion of women than men had been exposed to NANSAIDs: 17.8% versus 13.6%, whereas the reverse was true for ASA: 12.0% versus 20.6%. Among the studies reviewed, only the Laporte et al. (1991) stratified prevalence figures according to sexes. The use of NANSAIDs was also greater for women than for men over 60: 11.0% versus 5.9%. However, contradictory results were found for ASA. In the Laporte et al. study, a greater proportion of women than men had been exposed to ASA (17.5% for women versus 13.7% for men) while it was the reverse in the present study. Because exposure was ascertained by interviews in the Laporte et al. study, it also included over-the-counter (OTC) drugs which

could explain the discrepancy between results. If this were the case, then exposure misclassification due to OTC availability of ASA would be differential between men and women.

Age groups: Studies found in the literature agree that exposure to NSAIDs increases with age. Results obtained in the present study could not support this contention. The trend may therefore not exist in the age range included in the elderly population.

5.2 LIMITATIONS OF THE STUDY

5.2.1 Causal associations with UGIB

NSAIDs: A significant association between NSAID use and UGIB was found in this study. This association appeared to be causal for the following reasons:

1) *Biological plausibility:* A vast amount of research has been conducted to describe the biological process involved in NSAID-gastropathy. In the present study, the risk associated with ASA was smaller than that of NANSAIDs. It is biologically possible that this difference is due to the enteric-coating but, as discussed above, it may also be attributable to biases.

2) *Consistency:* These results are in accordance with the majority of published case-control studies that were conducted in various settings where the use of NSAIDs increases the risk of UGIB in the elderly population.

This study did not detect a dose-response relationship for ASA because of the possible biases or true absence of effect, as described in section 5.1.1.

In summary, the causal relationship between NSAID use and severe UGIB is reasonably well established. However, the reality of the

difference in the risk between NANSAIDs and ASA has not yet been elucidated.

Protective agents: The association between recent use of protective agents and UGIB is not biologically plausible. It is due to a protopathic bias. These agents were prescribed because of symptoms of GI problems or as prophylaxis.

Past exposure to NANSAIDs: Only possible explanations could be given regarding the lower risk of UGIB associated with past NANSAID use because the reason for interrupting treatment is not known. It could be due to intolerance as well as indication. There may be a selection bias whereby individuals who remain exposed are those who tolerate the drugs well while the susceptible patients selected themselves out of the population at risk (depletion of susceptibles). These results do not support the phenomenon of gastric adaptation previously suggested by Graham et al. (1988).

Switching between NANSAIDs: The reasons for switching between products, dosages or forms of administration were not documented. It is possible that patients switch because they were not tolerant and thus, were more susceptible to develop UGIB.

5.2.2 Selection bias

The study was restricted to patients who had been hospitalized for UGIB and who met the case definition. Differential admission or detection may have occurred if NSAID users were more likely to be hospitalized for UGIB than non-users. An attempt was made to minimize this bias by selecting cases that were severe enough to require hospitalization regardless of their drug exposure status. As confirmed by a gastroenterologist, bleeding in an elderly patient is a sufficient cause for admission.

The base population was secondary and corresponded to the hospital catchment populations for severe UGIB. Because the study was not population-based, it is not known with certainty whether controls were drawn from the same base as the cases. It is uncertain that a control would have been enrolled as a case had he(she) been diagnosed with UGIB at the time of the study.

It was not feasible to select a random sample of the study base, the major limitation being that the secondary base (i.e. the hospital catchment population for UGIB) was difficult to define. Hence, a non-random subset was selected. Controls were matched to cases on hospital in order to increase the probability that they originated from the same base as the case. It was assumed that the distribution of exposure was the same in the control series as in the random sample of the secondary base. This was equivalent to

assume that there was no relationship between NSAID use and the control diagnoses. Intuitively, it was felt that the control diagnoses were not associated. It is likely that the hospital catchment population differed according to diagnoses. The catchment population for UGIB was different from the catchment population for fractures. The assumption mentionned above would be violated only if NSAID prescribing practices differed between catchment populations. Because it was not possible to quantify this variation, a variety of control diagnoses were selected in order to attempt to minimize the extent of the bias. In addition, a sensitivity analysis was conducted to assess the effect of each control diagnosis and results remained stable. Results obtained by removing each control diagnostic category one at a time remained stable. It is therefore reasonably safe to conclude that none of the control diagnoses were associated with NSAID use.

As previously stated, exposure in controls should be representative of the secondary base. The distribution may differ from that obtained from a random sample of the population because they are sick individuals. They be more or less likely to take NSAIDs or have different utilization patterns and co-prescriptions if they have frequent contacts with a physician.

As described by Wacholder (1992), 2 conditions had to be met:

1) Cases would have been admitted to the same hospital for the

control diseases and conversely, controls would have been admitted as cases had they developed the disease. It is likely that this condition was not met given that the catchment population may vary according to specialties or services, especially geographically. However, this would not be a concern if it can be assumed that the prescribing patterns of NSAIDs were similar among the bases with respect to region, SES or ethnicity in this study. It is likely that this would be a greater problem in the comparison of individual NSAID products rather than for NSAIDs as a whole. Here, the problem may be more important for protective agents, where marketing pressures may vary among regions. The greatest number of patients come from urban regions and regional differences may arise between the island of Montreal and suburbs (mainly Montérégie). SES may vary according to the catchment areas of the various diagnoses. However, there was no evidence form the literature that SES was a confounder in the association between NSAID use and UGIB.

2) Exposure should be unrelated to the reason for admission of the control. This condition is likely to be met because there is no firm or intuitive evidence that patients with a fracture, pneumonia or cholecystitis would be more likely admitted if they were NSAID users than if they were not.

An alternative would have been to use a random sample of the Quebec elderly in order to obtain information on exposure patterns at the population level. However, this approach was not appropriate for

the following reasons:

1) non-comparability of information on exposure due to unknown data truncation (long-term hospitalization),

2) no information on smoking could have been obtained in the controls. The association between these factors and NSAID use in the cases only, as done by Griffin et al. (1991), would have allowed to assess confounding but not effect modification,

3) the exclusion criteria could not have been applied in the controls, which would have led to non-comparable populations,

4) If prescribing practices vary between regions, SES or ethnic groups, then a population sample would not have been representative of the base from which originated the cases.

A prospective population-based study was not feasible because linkage from the Med-Echo discharge database to the RAMQ databases could not be done. Hence, a secondary base population had to be used.

Within the constraints of feasibility, the case-control design was the most appropriate. Hospital-based was better than community-based for reasons described above. Results favour the absence of a bias brought by the control diagnoses or by differences between

the hospital catchment populations.

5.2.3 Information bias

Misclassification: The measure of exposure was the dispensing of a prescription for an NSAIDs, which is a proxy for actual drug consumption. Two major factors reduce the accuracy of this proxy, namely: 1) the availability of these drugs without prescription and, 2) poor compliance.

NSAIDs may be acquired through other distribution channels. ASA and ibuprofen are available OTC. In addition, samples of NSAIDs may be distributed at the physician's office. The acquisition of the drugs through these channels would result in an under-estimation of actual exposure. The estimate of relative risk was lower than that found in case-control studies conducted in elderly populations based on interviews (which include OTC drugs). It could be concluded that OTC exposure biased the results towards the null but too many other differences between the studies may contribute to the discrepancy in results (eg. recall bias, time window etc.).

If there was under-estimation of exposure due to OTC availability of drugs, the proportion of exposed patients should be greater in studies based on interviews than on databases. Comparing with the

Laporte et al. (1991) study at the same time window, it is true for the cases (33.% versus 18%) but not for controls (9.7% versus 12.4%). Because a discrepancy is present in the cases and not in the controls, it seems that recall bias rather than misclassification of exposure is responsible for the difference between studies.

In addition, the sensitivity analysis has shown that there was no difference between study years despite the fact that ibuprofen was released OTC between the 2 years. These results suggest that OTC may not be an important factor in the assessment of exposure to NANSAIDs. However, for ASA it may play a larger role and could explain why the RR found with ASA was smaller than with NANSAIDs. However, such a difference was also found in other studies relying on interviews which included the assessment of OTC ASA. Given that elderly do not pay for their medications when prescribed, it is expected that few drugs are purchased OTC. A study from France, where prescribed medications are also free of charge, has shown that only 3% of medications, including ASA, among elderly were not prescribed (Avouac, 1989).

Because these data were collected for administrative purposes, it is certain that any misclassification of exposure occurring in the database would be non-differential between cases and controls.
A major assumption in this study was that everything that was acquired was actually consumed. This assumption is violated due to

non-compliance to the prescribed regimen. Non-compliance would therefore result in an over-estimation of exposure during the defined time period. Griffin et al. (1991) suggested that these sources of bias are likely to be non-differential between cases and controls and would bias the results towards the null (under-estimation). However, in the present study, it is plausible that non-compliance would be differential between cases and controls, being influenced by the presence of symptoms of adverse events. If cases discontinued therapy because of the presence of symptoms before the 30 days, they were not eligible for the study (according to the case definition). If they discontinued after, they were considered exposed. On the other hand, if controls discontinued a treatment that was supposed to end within the 30 days, it was unknown because symptoms of gastropathy could not be recorded. This would have resulted in an over-estimation of exposure in the controls. As a result, the OR would have been biased towards the null. As a whole, non-compliance is likely to have biased the results towards the null whether it was differential or not between cases and controls. In any event, the extent of the bias due to non-compliance is not expected to be too large in this population because most patients were on a long-term therapy.

The accuracy of using dispensing as evidence of exposure is limited by these 2 factors (i.e. OTC and compliance). These limitations exist in all studies that use automated databases. Another

alternative would be patient interviews. This method of ascertainment is less desirable because of several factors, namely:

1) the response rate in the elderly is expected to be poor, especially if the patient is hospitalized. This has been documented by Kelsey et al. (1989),

2) the reliability of the resolution of the characterization of exposure would be much lower, especially for dosages and dates of dispensing of several drugs,

3) the accuracy of longitudinal data on drug exposure would be much lower. Patterns and duration of use were derived from the total duration for a period of one year based on the dates of dispensing of the various products. Hard data on the dates obtained from the database are expected to be more accurate than the total duration reported by an elderly patient during an interview. It is likely that interviews would not have been adequate to obtain reliable data on drug use for 3 years preceding hospital admission.

Data truncation: The RAMQ database is limited to prescriptions dispensed to the elderly in the community. It does not include drugs received in acute or long-term care institutions. As a result, misclassification of exposure would occur. In order to minimize this information bias patients in nursing homes or with prolonged hospitalizations during the previous 3 years were

excluded. A bias could be introduced if NSAID users were more likely to be hospitalized for long periods of time. This bias, non-differential between cases and controls, would result in an under-estimation of exposure to NSAIDs and is expected to bias the results towards the null. In addition, Quebec residents may live outside of the province for significant periods of time before they loose their residency status. This is particularly a problem in the winter, where a significant number of elderly move to Florida for several months. In principle, several renewals cannot be dispensed on the same date. However, deviance exists in the system due to arrangements between the pharmacist and the patient. It is not known whether this bias would be differential between cases and controls. If other factors related to NSAID use and UGIB also influence moving to warmer regions (eg. SES, previous history of gastropathy or arthritis) then information bias could be differential. The importance of this source of bias cannot be appraised because the number of Quebec elderly who spend long time periods outside of Quebec is not documented.

Alcohol consumption could not be assessed accurately. This is a concern especially to assess confounding in the association between NSAIDs and gastropathy. However, based on findings found in the literature, there is no evidence that alcohol is a confounder. Even if effect modification by alcohol could also not be reported, it would not jeopardize the validity of the study.

5.2.4 Indication bias

The indication for the use of drugs was not available and may have introduced confounding in the results, although previous studies have not found this (Collier and Pain, 1985; Bartle et al., 1986; Carson et al., 1987). Furthermore, the variation in indications in the elderly population is likely to be smaller than when all ages are considered. Duration of exposure could not be used as a proxy for indication because it was determined in relation to the event. A patient was exposed to NSAIDs for a short time period either because of an indication that requires a short treatment or, was ascertained early in a treatment that was supposed to be chronic.

5.2.5 Time window

It has been argued that a time window of 30 day preceding the event may not be appropriate. If too long, it would result in an underestimation of the effect. However, no exact definition of the appropriate time window can be provided until the hazard function of UGIB following NSAID use is documented. Operationally, in the case-control design, the time window does not refer to time since initiation of treatment but also include a time since discontinuation. To limit the assessment of exposure to current does not seem appropriate because drug exposure should precede the onset of symptoms.

It was necessary to assume proportional hazard functions for exposed and unexposed subjects within each pattern of exposure. It may be that the appropriate time window to define the risk period associated with NANSAID use differs between the different patterns. However, at present, the presence and/or extent of the difference remains unknown.

5.3 STRENGTHS OF THE STUDY

5.3.1 Validation of diagnosis

Unlike many studies relying on automated databases, all charts were individually reviewed to validate the diagnosis. This practice was proven to be necessary because the percentage eligibility of cases originally ascertained from ICD-9 codes was only 45.6%.

5.3.2 Exclusion criteria

Several exclusion criteria were applied in order to minimize selection and information bias. Patients transferred from another hospital were excluded to ensure that they originated from the hospital catchment population. As mentionned above, patients with previous long-term hospitalizations were excluded to minimize data truncation. Symptoms had to be present for less than 30 days to ensure that exposure preceded the outcome.

These validity issues would not have been possible to consider if only a computerized database had been used to conduct the study.

5.3.3 Unique data source

The universal nature of the program avoids any data truncation due to changes in eligibility. With the exception of the Saskatchewan database, this feature is not present in other databases such as COMPASS or Medicaid. Although there is a potential for data truncation due to long-term hospitalizations or moving out of the province for long periods of time, the extent of the bias should not be as important as data truncation due to eligibility.

Entry in the cohort is determined by an event: becoming 65 years old. Hence, data on drug exposure prior to this age are not available. Hard data on a very long term (3 years) were sought. In order to ensure that misclassification of exposure due to data truncation would be non-differential among age groups, the minimum age for inclusion in the study was 68. No allowance for this factor was made in previous studies where the minimum age in the study population corresponded to the minimum age at entry in the cohort. With this restriction, the extent of the bias is expected to be minimum for NSAIDs because most prescriptions are for 30

days.

In order to predict extent of bias, sensitivity analysis showed that data truncation reduced the efficiency of detecting a significant effect of past NANSAID use on UGIB but not for history of gastropathy, assessed by upper GI procedures or past use of protective agents. The magnitude of the bias was small.

Cohort studies that use automated databases are limited by the quality and depth of data available in those databases. Case-control studies, which often use interviews to determine exposure, suffer from numerous biases in the determination of exposure. In this study, a case-control design was selected, using hospital records for the identification of cases and controls, validation of diagnosis and data on some potential confounders, as well as records from a computerized prescription database for exposure determination. This study was the first to incorporate the benefits of both sources. Griffin et al. (1991) also reviewed hospital records but only for the cases. It was therefore not possible to assess effect modification by some of factors.

5.3.4 History of gastropathy

No gold standard was available to assess past history of gastropathy. As a result, 4 different measures were used and their

effects compared. These were: history of upper GI procedures (including gastroscopy, duodenoscopy, upper GI X-ray etc.), past visit to a gastroenterologist, history of protective agents use and history assessed in the medical chart. According to the literature, the comparison of several markers is unprecedented. The independent effect on UGIB was similar for history assessed by past upper GI procedures and past visit to a gastroenterologist. These results demonstrate the presence of differential misclassification between cases and controls when only hospital records are used.

5.4 GENERALIZABILITY OF THE RESULTS

Results are consistent with those obtained in several epidemiologic studies conducted in other elderly populations. Inferences made in the present study apply to the elderly population receiving prescribed NSAIDs as outpatients. The elderly represents the largest group of NSAID users and are at special risk for untoward GI problems. Such findings should not be extrapolated to the younger population as patterns of use, indications and comedications are likely to be different.

5.5 RECOMMENDATIONS FOR FUTURE RESEARCH

In the literature, it has been suggested that some NSAID products are more toxic than others. Hence, the variability in drug utilization patterns between products may be greater than between individuals. Patterns may be useful to compare the toxicity between individual NSAID products by accounting for susceptibility bias. However, a larger sample size would be needed in order to distinguish between the various products.

Because of the effect of past experience with the drug on the risk of UGIB, further studies are needed to document past toxicity in current users and reasons for discontinuation in former users.

A major deficiency in the literature is that the hazard function for UGIB after the initiation of NSAID use is unknown. So far, the time windows to define the risk period have been selected semi-arbitrarily. As a result, the width of the time windows varies to a great extent between studies. Because the width of the time window has a great influence on the estimation of the effect, results from the various studies are not comparable. A prospective study should be conducted in order to describe the hazard function necessary to assess the risk during and after termination of treatment with NSAIDs. The appropriate time window could therefore be defined and the duration of surveillance for the adverse event could be determined.

The use of protective agents was considered as a whole and the major limitation was the inability to partition between the prescription of these drugs for prophylaxis and for the treatment of a gastropathy. In order to distinguish between the 2 effects, timing of the dispensing of protective agents should be considered in relation to the the dispensing of NSAID use. If prescribed before or after NSAIDs then it is more likely that it is to treat a gastropathy than when it is dispensed concurrently, where it is probably for prophylaxis in high risk patients.

As shown in this study, the use of protective agents increased with duration of NANSAID use. It is not known whether these drugs were prescribed for prophylactic purposes or for the treatment of a gastropathy. It would therefore be useful to document the indication for the use of protective agents in order to describe the differences in susceptibility between patients of the different patterns.

As in any case-control study, the greatest concern was the validity of the selection of cases and controls. It was assumed that controls and cases originated from the same base population and a sensitivity analysis suggests that it was met. Several factors that could violate this assumption were discussed. In order to avoid such a bias, it would be more desirable to conduct a population-based study. If feasible, a cohort study would be more preferable. Study subjects would be selected on the basis of

exposure and followed in time. However, in the context of risk assessment, such a design would be preferable only if access to patients charts could be obtained in order to verify the diagnosis, apply the exclusion criteria and obtain information on potential confounders. Given that the probability of being exposed during the time window increases with duration, duration of use would be based on personal time and not chronological time. Nevertheless, attention should be given to correct for data truncation before entry in the cohort.

If interests resides on the effect of ASA, then information bias due to OTC availability is of concern. Information obtained from databases should be supplemented by patient interviews in order to obtain information on OTC drugs. A specific study should be conducted in order to investigate if there is a true difference between ASA and NANSAIDs controlling for the form of administration and correcting for the differential bias due to OTC availability of ASA.

5.6 CONCLUSIONS

The results obtained from this case-contol study allow to evaluate the impact of patterns of drug utilization in non-experimental risk assessment. This, it can be recalled, was the main objective of the thesis. Patterns of drug utilization that are clinically

relevant, quantifiable and amenable to be used in pharmacoepidemiologic studies were characterized empirically.

In this study, patterns of non-aspirin NSAIDs (NANSAIDs) were associated with the risk of hospitalization for upper gastro-intestinal bleeding (UGIB). Patients who used these drugs in the past were at a lower risk than first-time users. Furthermore, the risk decreased with an increase in duration of exposure. The effect may be due to the selection of susceptible patients out of the population at risk, a process analogous to the "healthy worker effect" that has been described in the epidemiologic literature. In the elderly, most NANSAID users are not short-term and patients do not switch products frequently. Instead, they use gastro-protective agents. This study provides the first empirical evidence of the importance of patterns of drug utilization in risk assessment. The identification of high risk groups should therefore take into account not only the drug of interest but also past experience with the drug as well as comedications. Further studies are needed to document past toxicity in current users and reasons for discontinuation in former users.

The system of linkage of data that was developed makes the conduct of pharmacoepidemiologic studies based on automated databases feasible in Quebec. In this elderly population, recent NANSAID use and a prior history of gastropathy were the major factors associated with hospitalizations for UGIB. Recent use of

protective agents was also associated with a greater risk of UGIB. This association reflects prescribing practices or early symptoms of gastropathy rather than a true effect of these drugs. This was an empirical evidence of the presence of a susceptibility or protopathic bias previously described in the pharmacoepidemiologic literature.

These results suggest that clinicians should inquire about past experience with the drug whenever they intend to prescribe it and follow first-time users carefully.

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APPENDIX A

Literature review on NSAID - gastropathy

Tables of the elements to be considered in risk assessment

TABLE 1

Description of published case-control studies on the effect of NSAIDs on gastropathy.

Authors	Outcome	Study population	Matching	Findings
Coggon et al. (1982)	Haematemesis Melena	277 matched pairs patients from local community clinics	Age, Sex	ASA used more often by cases than by controls ($p<.001$)
Clinch et al. (1983)	Peptic ulcer	100 cases 50 controls (normal endoscopy)	none	Significant association between lesion and Non-aspirin NSAID use ($p=.002$)
Collier and Pain (1985)	Peptic ulcer perforation	Hospital based 269 cases 269 controls (surgical emergencies)	Age, Sex	Significant difference between cases and controls in ingestion of NSAIDs ($p<.001$)
Bartle et al. (1986)	Acute UGIB	Hospital based 57 cases 123 controls (1/2 hospitalized 1/2 visitors)	Age, Sex	42.1% of cases versus 18.1% of controls were taking NSAIDs ($p<.005$)
Duggan et al. (1986)	Peptic ulcer	180 cases 180 controls (surgical and dermatologic outpatients)	Age, Sex, SES	Statistical and clinical significant association with non-aspirin NSAIDs OR=5 (1.4-26.9)

Somerville et al. (1986)	Bleeding peptic ulcer	≥ 60 years 230 cases 230 hospital controls 207 community controls	Age, Sex	Significant difference in non-aspirin NSAIDs use (p<.001)
Armstrong and Blower (1987)	Life threatening complications of peptic ulcerations	Hospital based 235 cases 1246 controls (admitted to hospital with no peptic ulcer disease)	none	60.0% of cases versus 9.9% of controls were non-aspirin NSAID users
Henry et al. (1987)	Fatal peptic ulcer complication	80 cases 160 controls (survivors)	Age, Sex, Site of ulcer, Nature of complication	No evidence that NSAID use was associated with an increase in mortality OR= 1.1 (0.6-2.1)
Smedley et al. (1988)	Bleeding and perforated peptic ulcer	Hospital based 272 cases 272 controls (type not specified)	Age, Sex	20% of cases versus 6% of controls were NSAID users (p=.003)
Jick et al. (1987)	Hospital admissions for perforated peptic ulcers	GHC, > 10 years old 6 controls/case (number not specified)	Age, Sex, GI history, Date of entry in health plan	No significant association OR= 1.20 (0.45-3.50)
Levy et al. (1988)	Major UGIB	Hospital based 18-69 years old 57 cases 2417 controls (independent of exposure)	none	26% of cases versus 4% of controls had taken ASA regularly OR = 15 (6.4-34)

Laporte et al. (1991)	UGIB	Hospital based 875 cases 2682 controls (acute clinical disorders)	Age, Sex, Centre, Time from admission	Significant association with NSAID use OR = 7.2 (5.4-9.6)
Henry et al. (1991)	UGIB	2 studies: A) ≥ 50 years Hospital controls 1:1 ratio (numbers not specified) B) All ages Hospital controls 1:2 ratio	Age, Sex Age, Sex	Significant association OR= 2.9 (1.8-4.8) OR = 3.1(2.3-4.1)
Holvoet et al. (1991)	UGIB	Hospital based 161 cases 161 controls (next patient admitted to dept. Internal Medicine)	Age, Sex	Significant association - non-aspirin NSAID use OR = 7.4 (3.7-14.7) - ASA OR = 2.2 (1.3-4.0)

TABLE 2

Description of published cohort studies on the effect of NSAID on gastropathy

Authors	Outcome	Study population	Findings
Beard et al. (1987)	Gastro-oesophageal bleeding	GHC Puget Sound, >64 years old 6.1 x 10^6 person-days exposed 38.0 x 10^6 person-days unexposed	Non-significant rate difference: 1.3 hospitalizations/10^6 (-0.2 - 3.4)
Jick et al. (1987)	Perforated peptic ulcer	GHC Puget Sound, >10 years old 23.4 x 10^6 person-days exposed 558.6 x 10^6 person-days unexposed	No significant association with NSAID use: RR_{adj} = 1.2 (0.50-2.8)
Carson et al. (1987)	UGIB	COMPASS 47,136 persons exposed 44,634 persons unexposed	Significant association RR_{adj} = 1.5 (1.1-1.9)
Guess et al. (1988)	Fatal UGIB or perforation	Saskatchewan residents 134,060 users 834,051 non-users	Age-specific rates Rate highest in women >75 years
Beardon et al. (1989)	GI events	Prescription Pricing Division 25,959 users non-users population matched for age, sex, general practitioner (number not specified)	Attributable risk was significant only for ≥ 60 years old
Bigelow and Collins (1989)	General GI upset	Wisconsin Medicaid ≥ 65 years 18,771 users 59,134 non-users	NSAID use positively related to general GI upset

TABLE 3

Description of published nested case-control studies on NSAIDs and gastropathy.

Authors	Outcome	Study population	Matching	Findings
Henry et al. (1987)	Death from peptic ulcer complications	Hospital based Cohort: patients with peptic ulcer complications 80 deaths 160 survivors	Age, sex, ulcer site, nature of complication	39% of cases versus 37% of controls were NSAID users Non-significant association: NANSAID: OR= 1.1 (0.6-2.1) ASA : OR=1.2 (0.6-2.4)
Carson et al. (1987)	UGIB	Saskatchewan Cohort: patients exposed to only 1 NSAID during the observation period number of cases and controls not specified	none	-Linear dose-response relationship (p<.01) -Quadratic duration-response (p<.001)
Griffin et al. (1991)	Peptic ulcer disease	Cohort: Tennessee Medicaid Elderly 1415 cases hospitalized 7065 controls (stratified random sample of cohort)	Birth year, sex, race, nursing home status	34% of cases versus 13% of controls were NANSAID users OR=4.1 (3.5-4.7)

TABLE 4

Estimates of excess risk of UGIB associated with NSAID uses

Study	Drugs	Outcome	Reference risk /100,000 persons	ER (95% C.I.) /100,000 persons
Jick (1981)	Aspirin	Hosp. adm. for major GIB	13.0	15.0
Beardon et al. (1989)	NANSAIDs	GI events	males: 9110 females: 8020	2250 (1380-3120) 4680 (4000-5360)
		GI hem./perf.	males: 710 females: 750	790 (490-1090) 810 (470-1150)

TABLE 5

Estimates of excess rates of UGIB associated with NSAID use

Study	Drugs	Outcome	Reference rate /10^6 person-days	ER (95% C.I.) /10^6 person-days
Beard et al. (1987)	NANSAIDs	hosp. for gastro-esophageal bleeding	3.4	1.3 (0.2-3.4)*
Jick et al. (1987)	NANSAIDs	hosp. perf. gast. + duod. ulcers	0.09	0.15 (-0.06 - 0.36)
Carson et al. (1987)	NANSAIDs	UGIB	2.77	1.46**
Guess et al. (1988)	NSAIDs	fatal UGIB	0.051	1.11

* We could not duplicate this value from published results
** Insufficient data published to calculate a 95% C.I. with the approximate method.

We used an approximate estimation of the 95% C.I. of the rate difference. The number of exposed and unexposed cases can each be assumed to have a Poisson distribution (Rothman, 1986).

TABLE 6

Incidence rate ratios and relative risks
in studies of NSAID-gastropathy

	Reference	Outcome	RR (95% C.I.)
Incidence rate			
	Beard et al.(1987)*	hosp.eosaphageal bleeding	1.1 (0.7-1.7)
	Jick et al.(1987)	perforated peptic ulcer	1.2 (0.5-2.8)
	Carson et al.(1987)	UGIB	1.5 (1.1-1.9)
Relative risk			
	Eliakim et al.* (1987)	bleeding in patients with duodenal ulcers	5.5 (4.0-7.5)
	Beardon et al.* (1989)	GI events	1.5 (1.5-1.6)

* Crude estimates derived from published data

TABLE 7

Published odds ratios for the effect of NSAIDs on gastropathy

Study	Drug	Outcome	OR (95% C.I.)
Coggon et al. (1982)	ASA	Haematemesis	3.7 (2.2-6.4)
Clinch et al. (1983)*	NSAIDs	GI adverse events (lesions) Maelena	4.6 (1.7-12.8)
	NANSAIDs	"	3.9 (1.4-10.7)
Collier and Pain (1985)*	NSAIDs (not specified if incl. ASA)	PU perf.	7.3 (4.2-12.5)
Duggan et al. (1986)	NANSAIDs ASA	Peptic ulcer	5.0 (1.4-26.9) 3.0 (0.7-21.3)
Somerville et al. (1986)	NANSAIDs	Bleeding PU	2.7 (1.7-4.4)
Bartle et al. (1986)*	NSAIDs	"	3.2 (1.6-6.3)
	NANSAIDs	GI bleeding hosp.	4.3 (2.8-12.3)
	ASA	"	2.7 (1.2- 6.0)
Armstrong and Blower* (1987)	NANSAIDs	Life threat. complications of peptic ulcer	13.7(9.9 -18.9)
Henry et al. (1987)	NANSAIDs ASA	Fatal PU complications	1.1 (0.6-2.1) 1.2 (0.5-1.9)
Jick et al. (1987)	NANSAIDs	Hosp. adm. perforated gast. + duod. ulcers	1.2 (0.45-3.5)
Levy et al. (1988)	NANSAIDs ASA	major UGIB	9.1 (2.7-31.0) 15.0 (6.4-34.0)

Study		Drug	Outcome	OR (95% C.I.)
Henry et al. (1991)	A)	NANSAIDs	hosp. UGIB	2.9 (1.8-4.8)
	B)	"	"	3.1 (2.3-4.1)
Laporte et al. (1991)*		NANSAIDs	UGIB	9.89**
		ASA		7.2 (5.4-9.6)
Griffin et al. (1991)		NANSAIDs	hosp. PUD	4.1 (3.5-4.7)
Holvoet et al. (1991)		NANSAIDs	UGIB	7.4 (3.7-14.7)
		ASA	"	2.2 (1.3- 4.0)

* Derived from published data
** adjusted for age and sex by the Mantel-Haenszel method

TABLE 8

Severity of outcome in studies on NSAID-gastropathy

Study		Exposure	Outcome	Estimate of RR (95% C.I.)
Clinch et al. (1983)		NANSAIDs	Endoscopic lesions	3.86 (1.39-10.68)
Beardon et al. (1989)		NANSAIDs	GI event	men: 1.25 women: 1.58
Laporte et al. (1991)		NANSAIDs	UGIB	9.89
Beard et al. (1987)		NANSAIDs	hospitalized for gastro-oesophageal bleeding	1.88
Bartle et al. (1986)		NANSAIDs	Hospitalized GIB	4.32(2.84-12.25)
Holvoet et al. (1991)		NANSAIDs	Hospitalized UGIB	7.4 (3.7-14.7)
Jick (1981)		ASA	hosp. adm. major UGIB	2.1
Jick et al. (1987)		NANSAIDs	perforation	1.20 (0.45-3.5)
Beardon et al. (1989)		NANSAIDs	GI bleed/perf.	men: 2.11 women: 2.08
Henry et al. (1991)	A)	NANSAIDs	hosp. bleeding or perforation	2.9 (1.8-4.8)
	B)	"	"	3.1 (2.3-4.1)
Collier and Pain (1985)		NSAIDs	PU perforation	7.25 (4.22-12.45)
Henry et al. (1987)		NANSAIDs	Life threat. complications	13.7 (9.9-18.9)

TABLE 9 - Case definition and ascertainment in studies on NSAID-gastropathy

STUDY	DEFINITION OF CASES	CONFIRMATION	INCLUSION CRITERIA	EXCLUSION CRITERIA	METHOD OF RECRUITMENT
1- Jick et al. (81)	- Patients hospitalized for major and minor GI bleeding - Outpatients admitted because of serious GI bleeding Major = Transfusion req't Minor = No transfusion req't	?	- Consecutive patients admitted in medical wards	- Known disease predisposing to GI bleeding	Database
2- Coggon et al. (82)	- GI bleeding defined symptomatically as haematemesis and melaena	None	- Patients admitted to City Hospital with haematemesis and melaena between Nov. 76 and Feb. 80	- Clinically trivial bleeding - Doubtful occurrence of bleeding - Death soon after admission - Patients too confused to cooperate	Admissions
3- Clinch et al. (83)	Patients referred for OGD with lesions: - Ulcers (acute and chronic) - Benign gastric ulcer - Duodenal ulcer, duodenitis, gastritis, oesophagitis	Gastroscopy: mucosa had to be grossly red and inflamed for Dx of oesophagitis, gastritis, duodenitis	- All cases referred for endoscopy where lesion was found	- Patients on medications besides NSAIDs that might have caused the lesion - Suspected malignant lesion	Referrals to GI clinic
4- Collier and Pain (85)	Perforated peptic ulcers (gastric and duodenal)	- Operative findings (87%) - Radiological findings (5.6%) - Necropsy (7%)	- All patients admitted to one hospital with perforated peptic ulcers between 1973 and 1982	None	Admissions
5- Bantle et al. (86)	Acute non-variceal UGIB	- Presence of haematemesis and/or black stool on admission - All patients had gastroscopy	- All patients admitted to gastroenterology service in one hospital between Nov. 15, 1982 and June 21, 1983	None	Admissions
6- Duggan et al. (86)	Duodenal or gastric ulcers but not both	Gastroscopy	All patients presenting for first time at gastroenterology unit (not specified if outpatients or inpatients or both)	Patients with both duodenal and gastric ulcers	?

STUDY	DEFINITION OF CASES	CONFIRMATION	INCLUSION CRITERIA	EXCLUSION CRITERIA	METHOD OF RECRUITMENT
7- Sommerville et al. (86)	- Presence of haematemesis or melaena - Diagnosis of bleeding gastric or duodenal ulcers	?	Admitted between April 83 and March 85 with primary diagnosis of haematemesis or melaena	- Unable to reply clearly to questionnaire - Early discharge/interviewer not available - Death before interview - Refusal of consent	Admissions
8- Armstrong and Blower (87)	Death from or requirement for emergency surgery for bleeding or perforation of benign peptic ulcer	- For deaths (at home or before operation): coroner's autopsy - For those presenting with haematemesis or melaena: - at surgery - gastroscopy (0.85%)	Consecutive series of patients who died or required emergency surgery for bleeding or perforation of benign peptic ulcer between Jan 83 and Dec. 85	- Gastric carcinoma - Bleeding ulcers that settled without surgical intervention	?
9- Beard et al. (87)	Gastrooesophageal bleeding Diagnoses: gastritis, gastric ulcer with bleeding, haematemesis, peptic ulcer with bleeding	None	- Members of GHC - > 64 years from 77-83 - Hospitalized for gastrooesophageal bleeding	- Disseminated cancer - GI bleeding secondary to severe trauma or chronic alcoholism - GIB occurring while in hospital or resulted from recorded duodenal ulcer - current steroid or anticoagulant therapy - Presence of diagnosed bleeding disorder	Discharges (ICD-8)
10- Henry et al. (87)	Death from peptic ulcer complication	Review of notes of all patients who had died during their hosp. adm. and whose records contained any mention of P.U. complication in discharge diagnoses	Patients who had admission of death from P.U. complication between Jan. 80 and June 86	None	Admissions
11- Smedley et al. (88)	Admission for bleeding and perforated peptic ulcer	?	?	?	Admissions

STUDY	DEFINITION OF CASES	CONFIRMATION	INCLUSION CRITERIA	EXCLUSION CRITERIA	METHOD OF RECRUITMENT
12- Jick et al. (87)	Hospital admission for perforated ulcer with the following discharge diagnoses: (531.2 -.3, 532.2 -.3, 533.2 -.3)	Confirmed with discharge summary	- Members of GHC - ≥ 10 years - Admitted between Jan. 1, 1977 and Dec. 31st, 1983	- Previous surgery at perforation site - Malignant disorder that might involve the stomach - other known etiological factors (eg. car accident)	Discharges
13- Carson et al. (87)	Diagnosis of UGIB during a day at risk	None	- Members of COMPASS from states of Michigan + Minnesota (eligible to Medicaid benefits) - March-Aug. 80 - Diagnosis of UGIB during days at risk (within 30 days of Px in E)	- Patients who had been given aspirin - Patients with no claim for medical service in 1980 - Diagnosis of UGIB in 1980 prior to the 6-month observation	Billing data inpatients and outpatients (ICD-9)
14- Levy et al. (87)	Admission for frank haematemesis or melaena, discharged with UGIB, gastric ulcer, gastritis without known earlier predisposition: UGIB, gastric ulcer, gastritis	Presence of discharge diagnosis in discharge summaries	- 18-69 years - First episode of major UGIB (frank haematemesis, melaena or both) no more than 1 month before admission - No endoscopic or radiologic evidence of duodenal ulcer - no symptoms referable to upper GI tract that had lasted more than 30 days	- History of PUD, cirrhosis, oesophageal varices, chronic alcoholism, cancer, corticosteroid, anticoagulant H_2 antagonist	Discharge summaries
15- Guess et al. (88)	Hospitalizations with fatal UGI haemorrhage and/or perforation. More specifically: Gastric, duodenal or peptic ulcer with bleeding and/or perforation, gastritis and duodenitis, (except alcoholic or atrophic gastritis), haematemesis, melaena or unspecified haemorrhage of GI tract UGI perforation = perforation of duodenum or stomach confirmed at surgery or autopsy	Review of written hospital discharge summaries and autopsy reports UGIB: (1) described in discharge summary as UGIB, haematemesis or melaena or (2) documented by gastroscopy, surgery or autopsy as originating from duodenum or stomach	- Members of Saskatchewan health plan in 1983 with one of the discharge diagnoses of UGIB	- Discharge summaries with cancer, aplastic anaemia, acute hepatitis or chronic active hepatitis, cirrhosis or alcoholism, current use of anticoagulants - Surgical procedure within a month of UGIB or perforation	Discharge diagnoses Database (primary and secondary)

STUDY	DEFINITION OF CASES	CONFIRMATION	INCLUSION CRITERIA	EXCLUSION CRITERIA	METHOD OF RECRUITMENT
16- Beardon et al. (89)	- Disease of digestive system - Symptoms involving the digestive system - Diagnosis of perforation or haemorrhage of peptic ulcer	None	- Patients with admission diagnosis between Jan. 1st, 83 and Dec. 85. - Members of Edinburgh Prescription Pricing Division on completion of mandatory one-year retention period	None	Database of inpatient morbidity
17- Bigelow and Collins (89)	GI upset A. Diagnostic codes indicative of GI upset presumed to be attributable to NSAID use B. Bills submitted for H_2 antagonists and antacids (markers)	—	- Members of Wisconsin Medicaid Billing Data from April 1, 84 - March 31, 87 - ≥ 65 years - Received services for which a bill was received by Medicaid	- History of GI upset during first 90 days: diagnostic codes indicative of GI upset, bill submitted for H_2 antagonists or antacids during first 90 days of observation - Patients with fewer than 90 days' worth of bills submitted (not sufficient observation period to determine prior hx of GI upset) - Diagnostic codes indicative of alcohol abuse at any point during period of observation - Diagnostic codes indicative of GI difficulties but not presumed to be causally related to NSAID use - Prescription of H_2 antagonists or antacids started on same day or day after initiation of NSAID drug therapy	Database: diagnostic codes or bills for H_2 antagonists and antacids
18- Campbell and Steele (91)	Severe complications of diverticular disease: pericolic abscess, generalized peritonitis, bleeding requiring surgical intervention and fistula formation	—	- Admitted between 83 and 88	- No adequate drug history available from case notes	Admissions

STUDY	DEFINITION OF CASES	CONFIRMATION	INCLUSION CRITERIA	EXCLUSION CRITERIA	METHOD OF RECRUITMENT
19- Laporte et al. (91)	- Hospitalization with haematemesis and melaena - Primary diagnosis of acute UGIB - At least one diagnosis of benign gastric ulcer, duodenal ulcer, acute lesions of gastric mucosa, erosive duodenitis	- Endoscopy - Surgery	- Patients presenting at participating hospitals between Feb. 1st, 87 and Dec. 31, 88	- Other endoscopic diagnoses: oesophageal varices, anastomotic ulcers, gastric carcinoma, Mallory Weiss syndrome - History of liver cirrhosis or coagulopathy - People on holiday from other countries - Illiterate - Not reliably interviewed - Death	?
20- Henry et al. (91)	Admitted with UGIB or ulcer perforation	Endoscopy with 24 hours of admission	A) ≥ 50 - Admitted with UGIB or ulcer perforation to 2 public hospitals: between 85 and 87 B) All ages - Consecutive admission with haemorrhage or perforation to all public hospitals mid-88 --> mid-90	?	?
21- Griffin et al. (91)	- Hospitalized with diagnosis of confirmed peptic ulcer or UGIB (gastric or duodenal) - UGIB of unknown causes: haematemesis, presence of blood in nasogastric aspirate, melaena Codes: Gastric, duodenal, peptic, gastrojejunal ulcer, other disorders of stomach and duodenum, GI haemorrhage	Peptic ulcer: - Surgery - Endoscopy - Roentgenogram - Autopsy UGIB: Review of hospital records	- Member of Tennessee Medicaid Program - ≥ 65 years - Confirmed peptic ulcer or UGIB - 1984 --> 86 - Enrolled ≥ 365 days before hospitalization	- Esophageal varices - Gastric cancer - Other known causes	Database: Hospital discharge(ICD-9) and state death certificate database
22. Holvoet et al. (1991)	Hospitalized with peptic oesophagitis, gastric erosion, gastric ulcer or duodenal ulcer	Endoscopy within 48 hours of admission	May 1st 87 to May 1st 89	Oesophageal varices, Mallory-Weiss, upper GI neoplasia, vascular malformation	Admission

TABLE 10 - Exposure characterization in studies on NSAID-gastropathy

	DEFINITION		QUANTIFICATION				ASCERTAINMENT		CHARACTERIZATION
Reference	NSAIDs	Consideration of Multiple Drug Use	Number of categories	Dose	Route	Duration	Method	Types of Drugs	Time Window
1- Jick et al. (81)	Combined	No	Dichotomous	Yes	Yes	Yes	Clinical records, interview	---	1 week before
2- Coggon et al (82)	Aspirin Paracetanol	No	8 - sometimes in past 2 days - sometimes in past week - sometimes in each of past 2 weeks - Regularly ≥ 3 months for aspirin and paracetamol	No	No	Yes	Interview	Taken	3 months before admission
3- Clinch et al. (83)	- NSAIDs at least 1 week - Individual products	Yes*	Dichotomous	Yes*	Yes*	Yes*	- Referring doctor's letter - Admitting doctor's case history - Nursing records (family doctor when not enough information)	Not specified	Not specified but at least 1 week before admission
4- Collier and Pain (85)	Combined	No	Dichotomous	No	No	No	Retrospective note review	Ingestion	On admission
5- Bartle et al. (86)	Individual*	Yes*	2 - ASA - non-asp. NSAID	Yes*	No	Yes*	Interview	Use	Not specified (but presumed at least 6 months)
6- Duggan et al. (86)	Regular use (≥ 2 doses weekly in last 3 months)	Yes*	6 - Aspirin alone - Aspirin as compound preparation containing aspirin and caffeine - Paracetamol alone - NSAIA alone - NSAIA and aspirin or aspirin and caffeine - Others: - irregular - non-respondents - < 2 doses/week	No	No	Yes (frequency, quantity)	Questionnaire	Consumption	3 months

* = Recorded but NOT considered in analyses

	DEFINITION		QUANTIFICATION				ASCERTAINMENT		CHARACTERIZATION
Reference	NSAIDs	Consideration of Multiple Drug Use	Number of categories	Dose	Route	Duration	Method	Types of Drugs	Time Window
7- Sommerville et al. (86)	- NANSAIDs - Individual products*	Yes*	Dichotomous	No	No	No	- Questionnaire - Case notes and general practice records for those not directly questioned	Use	- Day of interview for community controls - Day of event for cases and hospital controls
8- Armstrong and Blower (87)	- Individuals products*	Yes*	Dichotomous	No	No	Yes	- Questioned by admitting physician - GP record for those who died	Use	1 month [although analyzed a duration of 3 years (?)]
9- Beard et al. (87)	- Individuals products*	Yes	Dichotomous	No	No	Yes (number of prescriptions)	Database	Prescription	30 days
10- Henry et al. (87)	3 categories: - Aspirin - NSAIDs - Corticosteroids	No	Dichotomous	No	No	No	Clinical notes	Use	Week before admission
11- Smedley et al. (88)	Combined	No	Dichotomous	No	No	No	?	Ingestion	?
12- Jick et al. (87)	Individual products*	No	Dichotomous	No	No	Yes	Database	Prescriptions for all outpatient drugs (incl. OTC)	90 days = current users (but went back ≥ 5 years for duration)
13- Carson et al. (87)	Combined	Yes (but excluded from study)	Dichotomous	Yes (low, medium, high)	No	Yes (number of prescriptions)	Database Billing data	Outpatient drugs dispensed	30 - 90 days

= Recorded but NOT considered in analyses

	DEFINITION		QUANTIFICATION				ASCERTAINMENT		CHARACTERIZATION
Reference	NSAIDs	Consideration of Multiple Drug Use	Number of categories	Dose	Route	Duration	Method	Types of Drugs	Time Window
14- Levy et al. (88)	3 categories: - Aspirin - Acetaminophen - Others	No	3 - Regular (≥ 4 days during 7 days before) - Occasional - Discontinued (last use 8-90 days before)	No	No	Yes (frequency)	Questionnaire	Use of prescriptions for indications such as pain, headache, backache, fever, cough, colds, arthritis, muscle spasms, menstrual cramps, stomachache	90 days before index day
15- Guess et al. (88)	Combined	No	Dichotomous	No	No	No	Database	Prescribed medications	Variable time window Smallest of: 1. 30 days 2. Nbr. of days until next NSAID prescription 3. Nbr. of days to the end of 1983 4. Nbr. of days to date of death
16- Beardon et al. (89)	5 Ibuprofen Indomethcain Naproxen Osmosin Piroxicam	No	Dichotomous	No	No	No	Database	Written prescriptions	Variable From date of first prescription to end of study period
17- Bigelow and Collins (88)	Individual products	No	2 - long-acting (hall-life > 12 hours) - short-acting	Yes % of maximum recommended daily dose 3 categories: Full, therapeutic, low	No	Yes (Control for individual period of observation)	Database	Bills for service received	1 episode = 30 days Total observation period variable for each patient (variable nbr. of episodes)

= Recorded but NOT considered in analyses

	DEFINITION		QUANTIFICATION				ASCERTAINMENT		CHARACTERIZATION
Reference	NSAIDs	Consideration of Multiple Drug Use	Number of categories	Dose	Route	Duration	Method	Types of Drugs	Time Window
18- Campbell and Steele (91)	Yes	No	Dichotomous	No	No	No	Case notes	---	On admission
19- Laporte et al. (91)	Yes	No	Dichotomous	Yes	No	No	Interview - Open questions and list of common symptoms to prompt - Relative invited to help to recall - Only information confirmed by patient was collected	All	28 days before admission
20- Henry et al. (91)	Individual products* a) Combined b) Piroxicam vs other NSAIDs	No	Dichotomous	Yes*	No	Yes*	Interview - Mixture of open followed by closed questions	Use	Week before admission

21- Griffin et al. (91)	- Non aspirin NSAIDs - Individual products	Yes (sum doses)	4 Current: supply ending on or after index date Indeterminate: supply ending 1-60 days before index date Former: px in 365 days before index date but supply ended > 60 days before index date Non users: No px in 365 days before index date	Yes ADD = qty/days 4 categories 0.5 1.0 1.5 2.0 > 3.0 standard doses	No	Yes (quantity, days)	Database	Prescriptions filled for outpatients and nursing home residents	365 days before index date
22. Holvoet et al. (1991)	Individual products* NANSAIDs ASA	No	Dichotomous	Yes ASA: <2g/week >2g/week	No	Yes < 1 week 1week-1mo. 1mo.-1year >1 year Unknown	Interview	Prescriptions and OTC	7 days before admission

* = Recorded but NOT considered in analyses

TABLE 11

Effect of history of gastropathy in published studies

Study	Definition of history	Relative risk (95% C.I.)
Carson et al. (1987)	Preexisting abdominal conditions	1.5 (0.9-2.5)
Laporte et al. (1991)	- Symptoms	2.6 (1.9- 3.5)
	- Peptic ulcer disease	5.5 (2.8-11.0)
	- GI bleeding	14.5 (7.5-28.2)
Jick et al. (1987)	Cimetidine, antacids (markers for history)	5.1 (2.6-10.0)
Holvoet et al. (1991)	Peptic ulcer disease	5.5 (3.2-9.6)

TABLE 12

Confounding by comedications

Study	Comedications	Association with gastropathy	Association with NSAIDs
Collier and Pain (1985)*	corticosteroids	3.1 (1.4-6.7)	2.9 (1.3-6.7)
Carson et al. (1987)	anticoagulants corticosteroids	2.8 (1.4-5.6) 1.4 (0.8-2.2)	---
Bigelow and Collins (1989)	anticoagulants and/or corticosteroids	1.7 ($p<.001$)	

* Crude estimate derived from published data

APPENDIX B

Descriptive analyses

Additional Tables

TABLE 1

Causes of non-eligibility of cases by sex

Cause	Men	Women
Lower GI bleeding	18.6	23.8
Unconfirmed diagnosis	18.6	21.7
Chronic	15.0	19.6
Cancer of the GI tract	10.7	6.4
Past gastric surgery	7.9	3.7
Transfer	6.4	7.4
Allergic to ASA	5.0	3.2
Non-incident	2.9	1.6
Long-term or multiple admissions in past 3 years	2.1	3.1
Alcoholism	1.4	0.0
Non-resident	0.7	0.5
Elective admission	0.7	0.5
Other pathologies	6.4	5.8
Total:	140	189

TABLE 2

Causes of non-eligibility of cases by age group

Age group	Cause	Frequency (%)
68-69	Lower GI bleeding	18.9
	Unconfirmed diag.	18.9
	Cancer of GI tract	10.8
70-74	Chronic	18.0
	Lower GI bleeding	17.0
	Transfer	13.0
75-79	Unconfirmed diag.	23.1
	Lower GI bleeding	22.0
	Chronic	20.9
80-84	Lower GI bleeding	26.6
	Unconfirmed diag.	23.4
	Chronic	18.8
$\geq$ 85	Unconfirmed diag.	33.3
	Lower GI bleeding	25.0
	Chronic	13.9

TABLE 3

Causes of non-eligibility of controls by sex

	Percent causes	
	Men	Women
Chronic	26.8	28.3
Cancer of the GI tract	14.2	18.8
Past gastric surgery	11.8	5.8
Transfer	8.7	14.2
Non-resident	4.7	4.2
Allergic to ASA	3.9	8.3
Long-term or multiple admissions in past 3 years	3.9	1.7
Cancer of site related to admission dx	3.9	2.5
Elective admission	3.9	0.0
Non-incident	2.4	2.5
Error of diagnostic code	1.6	0.8
Past surgery for current admission	0.8	0.8
Cirrhosis	0.8	1.7
Lower GI bleeding	0.0	0.8
Unconfirmed diagnosis	0.0	1.7
Total:	127	120

TABLE 4

Main causes of non-eligibility of controls by age group

Age group	Cause	Frequency (%)
68-69	Chronic	28.6
	Transfer	14.3
	Past stomach surgery	14.3
70-74	Chronic	33.7
	Transfer	10.1
	Allergic to ASA	9.0
75-79	Chronic	25.5
	Transfer	14.6
	Cancer of the GI tract	14.6
80-84	Cancer of the GI tract	31.0
	Chronic	28.6
	Gastropathy	11.9
$\geq$ 85	Cancer of the GI tract	22.9
	Past stomach surgery	14.3
	Transfer	11.4
	Chronic	11.4

TABLE 5

Main causes of non-eligibility of controls by hospital

Hospital*	Cause	Frequency (%)
RVH	Chronic	29.0
	Allergic to ASA	18.4
	Past stomach surgery	13.2
HND	Chronic	36.2
	Transfer	15.9
	Unknown reason	13.0
HMR	Chronic	37.5
	Transfer	18.1
	Cancer of the GI tract	9.7
JGH	Cancer of the GI tract	30.9
	Past stomach surgery	16.2
	Diag. of gastropathy	13.2

* RVH = Royal-Victoria Hospital
HND = Hôpital Notre-Dame
HMR = Hôpital Maisonneuve-Rosemont
JGH = Jewish General Hospital

TABLE 6

Distribution of case principal diagnosis

	Number of cases	% cases
Gastric ulcer	72	29.0
Duodenal ulcer	67	27.0
GI bleeding	27	10.9
Gastroduodenitis	13	4.2
Peptic ulcer	6	2.4
Other	63	25.4
	248	

TABLE 7

Distribution of case principal diagnoses other than upper GI bleeding

	Number of cases	% cases
CVD	16	25.4
Respiratory	10	1.6
other GI disorders	10	1.6
Malignant tumours (excl. GI)	6	9.5
Mental disorders	4	6.3
Endocrinologic	3	4.8
Others	14	22.2
	63	

Other GI disorders included:

	Number of cases
Oesophagitis	3
Pyloric stenosis	1
Metaplasia of intestinal mucosa	1
Hernia with occlusion	1
Intestinal adhesion	1
Alcoholic lesion of the liver	1
Acute pancreatitis	1
Chronic peptic ulcer	1
Total:	10

TABLE 8

Distribution of comorbidity of men and women

	% Comorbidity	
	Men	Women
CVD*	29.01	26.43
Respiratory	9.77	7.53
Other GI**	9.77	7.38
Endocrinologic	7.14	8.35
Genito-urinary	6.57	5.56
Sensory organs	5.83	7.34
Trauma	5.04	5.90
Osteo-muscular	4.21	7.25
Mental	3.29	3.75
Infection	2.19	2.70
Tumour	2.15	1.26
Hematologic	2.10	3.16
UGIB	1.40	1.35
Gast/Duod.	1.31	1.43
Gastric ulcer	0.83	0.72
Duodenal ulcer	0.61	0.25
Dermatologic	0.57	1.56
Peptic ulcer	0.44	0.13
Other	7.76	7.80

* Cardio-vascular disease
** Other gastro-intestinal disorder

TABLE 9

Medical history

comparison between men and women

Past illness	Percentage Men	Women
CVD*	25.0	18.8
Other GI	14.8	11.5
Genito-urinary	11.0	9.0
Trauma	5.1	11.1
Tumour (other than GI)	7.0	7.6
Respiratory	7.7	6.0
Sensory organs	4.2	8.3
Musculo-skeletal	2.0	2.0

* Cardio-vascular disease

TABLE 10

Distribution of past NSAID use, between 31 days and 3 years prior to admission

	All NSAIDs n (%)	NANSAIDs* n (%)	ASA n (%)
Cases	145 (59.4)	115 (47.1)	88 (36.1)
Controls	362 (58.9)	267 (43.4)	188 (30.6)
Men	258 (60.4)	177 (41.5)	155 (36.3)
Women	249 (57.6)	205 (47.5)	121 (28.0)
68-69	35 (46.7)	32 (42.7)	16 (21.3)
70-74	130 (64.7)	103 (51.2)	74 (36.8)
75-79	166 (60.6)	118 (43.1)	96 (35.0)
80-84	108 (60.3)	80 (44.7)	55 (30.7)
≥85	68 (52.3)	49 (37.7)	35 (26.9)
Total:	507 (59.0)	382 (44.4)	276 (32.1)

* Non-aspirin NSAIDs

TABLE 11

Exposure to protective agents within 30 days prior to admission

	No.patients	% study population
Cases	44	18.0
Controls	61	9.9
Men	51	11.9
Women	54	12.5
68-69	11	14.7
70-74	34	12.4
75-79	34	12.4
80-84	18	10.1
≥ 85	8	6.2
Total:	105	12.2

TABLE 12

Distribution of duration non-aspirin NSAIDs

between 31 and 365 days prior to admission

	Never exposed	Short Term ≤ 30 days	Intermediate 31-120 days	Long-term >120 days
Cases	164 (67.2)	15 (6.2)	32 (13.1)	33 (13.5)
Controls	464 (75.5)	59 (9.6)	53 (8.6)	39 (6.3)
Men	324 (75.9)	37 (8.7)	43 (10.1)	23 (5.4)
Women	304 (70.4)	37 (8.6)	42 (9.7)	49 (11.3)
68-69	57 (76.0)	5 (6.7)	8 (10.7)	5 (6.7)
70-74	137 (68.2)	19 (9.5)	22 (11.0)	23 (11.4)
75-79	200 (73.0)	28 (10.2)	26 (9.5)	20 (7.3)
80-84	134 (74.9)	15 (8.4)	15 (8.4)	15 (8.4)
≥ 85	100 (76.9)	7 (5.4)	14 (10.8)	9 (6.9)
Total:	628	74	85	72

TABLE 13

Distribution of patients who switched non-aspirin NSAIDs between 31 and 365 days before admission

	Nbr. Switchers	past NANSAID users*	Percent
Cases	20	80	25.0
Controls	30	151	19.9
Men	18	103	17.5
Women	32	128	25.0
68-69	2	18	11.1
70-74	15	64	23.4
75-79	13	74	17.6
80-84	10	45	22.2
≥ 85	10	30	33.3
Total:	50	231	21.6

* Patients who were exposed to non-aspirin NSAIDs between 31 and 365 days prior to admission.

TABLE 14

Description of switches between forms of administration

between 31 and 365 days prior to admission

Product	Type of switch	No. switches
Indomethacin	Caps. ---> L.A. caps.	4
	L.A. caps. ---> Caps.	3
	Supp. ---> Caps.	3
	Caps. L.A. ---> Supp.	1
	Supp. ---> Caps. L.A.	1
Naproxen	Tabl. ---> Supp.	1
	Supp. ---> Tabl.	1
Piroxicam	Caps. ---> Supp.	1
	Supp. ---> Caps.	1
Ketoprofen	L.A. tabl. ---> Supp.	1

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