THE UNIVERSITY OF CALGARY

The Relationship Between Non-Steroidal Anti-Inflammatory Drug Prescription and the Prescription of Cardiovascular Medications and Prevalence of Cardiovascular Diseases Among Senior Albertans.

by

Jeffrey Paul Schaefer

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

DEPARTMENT OF COMMUNITY HEALTH SCIENCES

CALGARY, ALBERTA

SEPTEMBER, 1999

Abstract

OBJECTIVE: The objective of this study was to assess the relationship between non-ASA non-steroidal anti-inflammatory drug exposure and the prescription of cardiovascular medications as well as the frequency of selected cardiovascular diseases. STUDY DESIGN: Cross sectional and case control analyses of administrative data was carried out for 192,866 Albertans aged 65 years and older for the year ending March 31, 1995. Medication exposure was measured in maximum daily dose equivalents (MDDE). RESULTS: For every 30 MDDE of non ASA-NSAID use there was an additional 2.47 (95%CI 2.32 - 2.65) MDDE of diuretic prescription, the odds ratios for visiting a physician for edema was 1.07 (95%CI 1.05 – 1.08), and hospitalization for congestive heart failure was 1.13 (95% CI 1.06 - 1.20). CONCLUSION: Non-ASA NSAID use is associated with increased diuretic use, increased prevalence of edema, and increased incidence of congestive heart failure in elderly subjects.

Acknowledgements

The Centre for Advancement of Health is acknowledged for funding this project. Drs. Rollin Brant, Norman Campbell, David Hogan, Eldon Shaffer, and Lloyd Sutherland are acknowledged for their personal and professional guidance and support. Gwendolyn Schaefer is acknowledged for her personal support and review of the manuscript.

Table of Contents

List of Tables

List of Figures

List of Abbreviations and Acronyms

ABC	Alberta Blue Cross
ABC-DP	Alberta Blue Cross Drug Benefit Plan
ACE	angiotensin converting enzyme
ASA	acetylsalisylic acid
CI	confidence interval
CPS	Compendium of Pharmaceuticals and Specialties
DIN	Drug Identification Number
ICD-9 CM	International Classification of Diseases - 9 Clinical Modification
MDDE	maximum daily dose equivalent
NSAID	non-steroidal anti-inflammatory drug
SD	standard deviation
yr	year(s)
ULI	unique lifetime identifier

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) comprise a class of medications that have in common analgesic, anti-pyretic, and anti-inflammatory effects. They are effective and commonly prescribed for the alleviation of symptoms associated with inflammatory and degenerative musculoskeletal diseases as well as other painful conditions. NSAIDs also have an inhibitory effect upon platelet aggregation.[1] Acetylsalicylic acid (ASA) is well known for this effect and is used for the prevention and treatment of common cardiac and vascular diseases.[2,3]

Approximately 20 different NSAIDs are available in Alberta and each agent is available in a number of formulations. The conditions for which NSAIDs are usually prescribed increase in prevalence with age and NSAIDs represent a significant proportion of drug use in the elderly. During a 6 month period in 1991, one quarter of Albertans aged 65 and older received at least one prescription for an NSAID and during this period $5 million worth of NSAIDs was prescribed to this population.[4]

The pharmacodynamic effects of NSAIDs appear to be mediated principally through inhibition of prostaglandin synthesis. Prostaglandins are endogenously generated fatty acids that play a major role in inflammatory conditions.[5] However, prostaglandin synthesis is not specific to pathological states. Normal physiology is also disrupted by inhibition of prostaglandin synthesis and the effects of NSAIDs on normal physiology are believed responsible for a number of adverse effects. Gastrointestinal hemorrhage, neutropenia, salt and water retention, renal impairment, delirium, and hypersensitivity reactions are known or suspected to be caused by NSAIDs.[6,7,8]

Much of what is known about the effects of NSAIDs on cardiovascular disease is founded upon studies of ASA. This agent has a long history of use and there is a large body of scientific literature that describes its indications and effects. In contrast to ASA, the effects of non-ASA NSAIDs on cardiovascular disease have not been well documented. Cardiovascular disease often occurs in the setting of ischemia brought about by thrombosis and atheroembolism. Platelet aggregation is required for these processes and inhibitors of platelet aggregation are suited for preventative and therapeutic intervention. Although non-ASA NSAIDs are less effective in inhibiting platelet aggregation than ASA, it does not necessarily follow that these agents have no effect on cardiovascular physiology or disease. Moreover, a significant body of research suggests that arteriosclerosis is a dynamic and to some extent an inflammatory process. [9,10,11,12] Therefore, non-ASA NSAIDs may prove beneficial irrespective of anti-platelet effect.

Alternatively, non-ASA NSAIDs may exacerbate certain cardiovascular conditions. Non-ASA NSAIDs have been shown to cause renal dysfunction that in turn may cause retention of salt and water.[13] Conditions such as hypertension, edema, and congestive heart failure may exacerbated by this process. Therefore, it may be hypothesized that non-ASA NSAIDs increases the morbidity and mortality associated with these conditions.

In summary non-ASA NSAIDs are commonly used in the elderly population. Although much is known about the effects of ASA, there is a gap in the knowledge of the effects of non-ASA NSAIDs on cardiovascular disease. From knowledge of pharmacology and pathophysiology, it is possible to hypothesize that non-ASA NSAIDs are protective of

ischemia dependent cardiovascular disorders and they are a risk factor for cardiovascular disorders that are aggravated by salt and water retention. Depending upon the net effect between protection and risk, exposure to non-ASA NSAIDs may be associated with a rate of mortality different from controls. In this paper, non-ASA NSAID prescription and cardiovascular disease will be examined in a population of senior Albertans.

Objectives

The primary objective of this study is to measure the association between non-ASA non-steroidal anti-inflammatory drug (non-ASA NSAID) use and the medical treatment and frequency of major cardiac and vascular diseases in elderly Albertans. The secondary objective of this study is to describe NSAID utilization in this population.

The study hypotheses are:

1. Seniors prescribed a non-ASA NSAID when compared to controls are more likely to be prescribed medications used for the treatment of hypertension, congestive heart failure, and edema.

2. Seniors prescribed a non-ASA NSAID when compared to controls are more likely to visit a physician or be hospitalized with a diagnosis of hypertension, congestive heart failure, or edema.

3. Seniors prescribed a non-ASA NSAID when compared to controls are less likely to visit a physician or be hospitalized for ischemic heart disease, cerebrovascular disease,

peripheral vascular disease, and thromboembolic disease.

4. Seniors prescribed a non-ASA NSAID have a mortality rate that is different from controls.

Literature Review

Pharmacology of NSAIDs

NSAIDs to varying degrees are anti-inflammatory, analgesic, antipyretic, and inhibitors of platelet aggregation. It is believed that inhibition of the enzyme cyclo-oxygenase (COX) is the primary pharmacodynamic effect of NSAIDs. COX plays an important role in the production of prostaglandins from arachidonic acid which is a phospholipid (fatty acid) present in cell membranes. Recently, it has been discovered that two isoforms of COX exist (COX 1 and COX 2) and that selective inhibition of the COX 2 isoform may confer therapeutic advantages.[14,15,16] An overview of the biochemical pathways associated with prostaglandin synthesis including the position of COX is shown in figure 1.

Prostaglandins are structurally related but have diverse and sometimes opposing effects on physiological functions. For example, a basal level of prostaglandins plays a role in the maintenance of tissues such as gastric mucosa or renal tubular function. NSAIDs can cause harm by interfering with these maintenance functions. However, when inflammatory conditions are triggered, prostaglandin levels rise and attract potentially damaging inflammatory cells. NSAIDs in this setting are beneficial in alleviating the symptoms of inflammation. One prostaglandin (prostacyclin) can inhibit platelet

aggregation while another (thromboxane) can stimulate platelet aggregation.

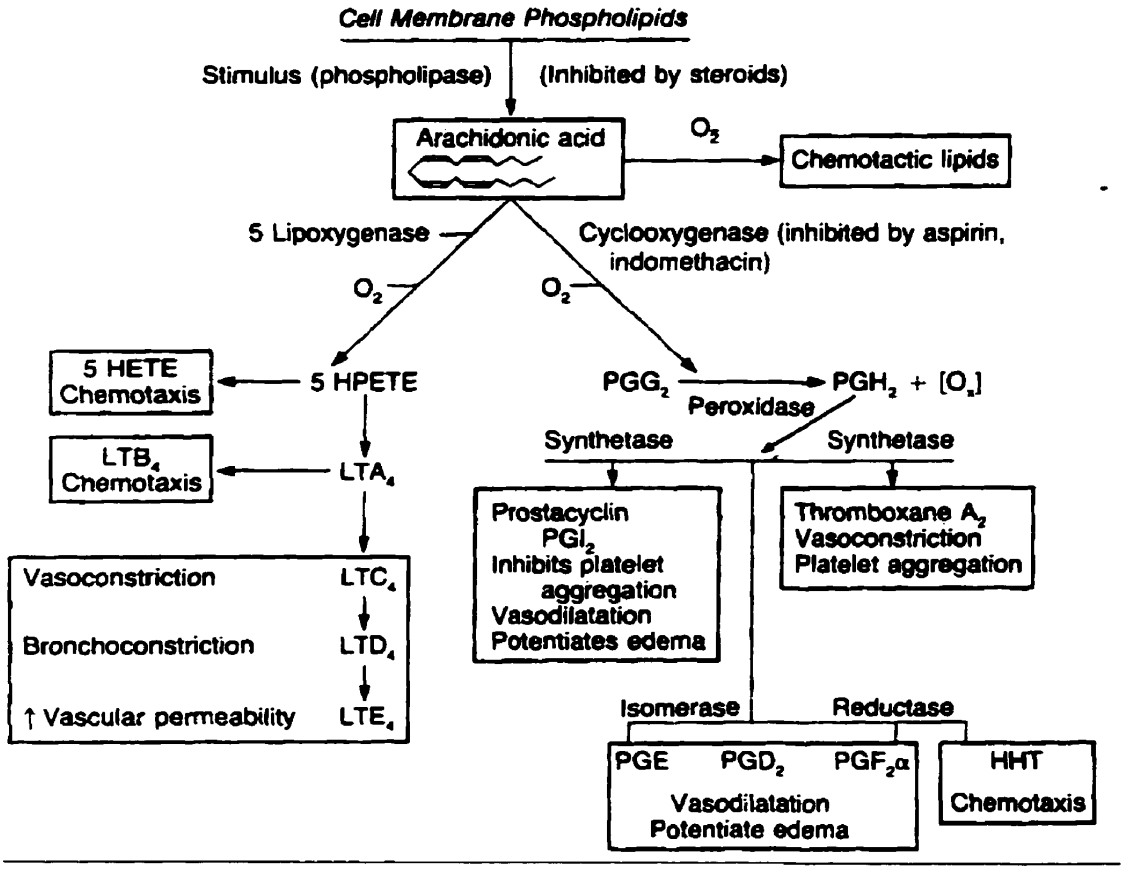

Figure 1. Biochemical pathways associated with the production of prostaglandins from arachidonic acid as well as the major actions of these substances. NSAIDs inhibit cyclo-oxygenase.[17]

A large number of NSAIDs are licensed for use in North America and they often classified according to chemical structure. A distinction is made between salicylates and non-salicylate NSAIDs. Salicylates are further classified according to the presence of an acetyl group. Acetylsalicylic acid (ASA) is the prototypical acetylated salicylate. Benorylate is another member of this class. ASA stands out among NSAIDs for a

number of reasons. First, it has a long history in medicine. Hippocrates prescribed the bark and leaves of the willow tree (rich in a substance called salicin) to relieve pain and fever and the Roman physician Galen wrote about the beneficial effects of willow leaves in 200 AD.[18]

Second, ASA is the only NSAID that acetylates COX irreversibly. Acetylation of this enzyme is believed responsible for the inhibition of platelet aggregation that is observed in vitro and that is presumed to occur in vivo. Because platelets lack the cellular machinery to synthesize new proteins they cannot recover from an exposure to ASA. Therefore, the effects of ASA on platelet dependant processes within the body do not resolve until new ones replace the exposed platelets.[19]

Lastly, aspirin is inexpensive relative to many medications. The cost of ASA 1,300 mg (maximum daily recommended dose for prophylaxis of atheroembolic stroke) is 10 cents. Diclofenac is the most commonly prescribed non-ASA NSAID in Alberta. It has a maximum daily recommended dose of 150 mg that costs $1.87.[20] ASA is also available to the public without prescription and despite its potential for adverse effects, this agent is well tolerated by most users.

Combining low cost, availability, effectiveness in inhibiting platelet aggregation, and a low frequency of adverse effects makes ASA an ideal candidate for the treatment and prevention of platelet dependent conditions. Indeed, ASA has been demonstrated to reduce mortality and the frequency of recurrent ischemic events in patients with unstable coronary syndromes in a number of trials.[21,22,23] For example, ASA was associated with a

23% reduction in the risk of cardiovascular death at 35 days post presentation with an unstable coronary syndrome in the ISIS-2 trial. Primary prevention trials have been done although the data is less compelling for benefit. In The Physician's Health Study the risk of myocardial infarction was reduced by 44% in male physicians receiving aspirin 325 mg daily relative to controls. However, benefit was limited to those over 50 years of age and the total cardiac mortality was not different between the groups. Those receiving ASA were twice as likely to have a hemorrhagic stroke although this outcome did not achieve statistical significance.[24] A randomized controlled trial of British physicians failed to demonstrate a benefit with ASA used for primary prevention.[25]

Cerebrovascular disease, arterial insufficiency of the limbs and thrombophlebitis are other conditions for which the use of ASA has been studied. Numerous studies have assessed the impact of ASA on stroke related mortality. Notable among these are the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST) which demonstrated a reduction in mortality among stroke victims given ASA at time of presentation.[26,27] A meta-analysis of 145 clinical trials which included 70,000 high risk subjects found that aspirin reduced the odds of nonfatal myocardial infarction by 34%, nonfatal stroke by 31%, and vascular death by 18%.[28] ASA has been demonstrated to primarily reduce the risk of stroke in subjects with atrial fibrillation and current guidelines support its use for this indication in selected populations.[29]

With respect to atherosclerosis associated ischemia of the limbs, ASA has been demonstrated to reduce progression of disease in one randomized controlled study using angiographic endpoints.[30] It was also shown to delay the requirement for surgery in a

sub-group analysis of the Physician's Health Study.[31] Other non-NSAID antiplatelet agents have been introduced recently. Clodiprogel has shown some superiority to ASA with respect to vascular endpoints in a randomized controlled trial.[32]

While anticoagulation with heparin and warfarin is the standard of care for the prevention of deep vein thrombosis and pulmonary thromboembolism, there is a history of interest in the use of ASA for this purpose. A review of 90 clinical trials found that ASA containing regimens were superior to placebo in the peri-operative reduction of venous thrombosis and thromboembolic disease.[33]

In summary, ASA is an acetylated salicylate that has a long history in human medicine. It is inexpensive, widely available and shown to be effective in the prevention and therapy of cardiac and vascular disease.

A number of non-acetylated salicylates are available although the use of these agents is limited. Choline salicylate, choline magnesium trisalicylate, and salsalate are included in this group. A MEDLINE search from 1966 to present that included the names of these agents revealed no published articles that described an association of non-acetylated salicylates with cardiovascular disease.

The non-salicylates comprise the remaining NSAIDs that are available for human use. Because aspirin (ASA) is the predominant salicylate, the non-salicylate NSAIDs will be referred to as non-ASA NSAIDs. There are approximately 20 non-ASA NSAIDs available in Alberta. The classification of these agents has been traditionally based on chemical structure although the recent introduction of agents that are selective inhibitors

of the COX 2 isoform has generated greater interest. Selective COX 2 inhibitors became available after the study period.

The non-ASA NSAIDs available at the time of data collection included 7 structurally diverse classes. The agents are listed in Appendix 1. Structural variability is manifest mainly in pharmacokinetic issues such as elimination half-life, degree of protein binding, and routes of metabolism. The oral formulations of some non-ASA NSAIDs are available as sustained release preparations, with enteric coating, and compounded with misoprostol, an agent that has been demonstrated to reduce the risk of gastric ulcer.[34]

The pharmacodynamic effects of non-ASA NSAIDs are less variable among the non-selective COX inhibitors. They all decrease the release of mediators from immunocytes and inhibit prothrombin synthesis. They are anti-inflammatory, analgesic, and anti-pyretic. They also inhibit platelet aggregation albeit in a reversible and less effective manner than ASA.[5] The most common indication for non-ASA NSAIDs in the elderly is the amelioration of symptoms associated with degenerative and inflammatory conditions. These indications along with associated ICD-9 CM codes are listed in Appendix 2. Other indications include symptom reduction in conditions such as neoplasia, trauma, headache, dysmenhorrea, and post-operative pain. In the neonate with patent ductus arteriosus, NSAIDs have been shown to induce closure of this vascular abnormality.[35]

These agents are effective in the management of inflammatory and degenerative disease. However, there does not appear to be compelling evidence that any of the non-ASA NSAIDs are more effective than others. Individual response, adverse effect profile, and

cost are factors that physicians should consider when selecting a non-ASA NSAID.[36,37]

In general, the adverse effect profiles are similar among the non-ASA non-COX selective NSAIDs. Gastrointestinal hemorrhage, hypersensitivity reactions, exacerbation of asthma, renal impairment, elevation of liver enzymes, visual disturbances, a variety of CNS disturbances, bone marrow suppression, effects upon the pharmacokinetics of other medications, edema, aggravation of hypertension, and congestive heart failure are commonly mentioned in major texts and pharmacopoeias.[38,39] There have been attempts to systematically rank individual NSAIDs according to frequency of adverse events.[40,41] As well, clinical trials have demonstrated some differences in adverse event frequencies.[42,43] However, there is no widespread agreement regarding the relative safety profiles among these agents. The relationship between non-ASA NSAIDs and cardiovascular diseases will be discussed later in the text.

Perhaps a more difficult issue than deciding on which non-ASA NSAID to use is deciding when to introduce or discontinue NSAIDs for the individual patient. For example, exercise, acetaminophen, capsaisin cream, and intrasynovial viscosupplementation have been shown to be effective in the management of osteoarthritis.[44,45,46,47] Surgical options including osteotomy and joint replacement are also available.

NSAID Use and the Elderly

Non-ASA NSAIDs are commonly prescribed to alleviate the symptoms associated with degenerative, inflammatory, and neoplastic diseases. The prevalence of these disorders

increases with age. There is data demonstrating that NSAIDs (both ASA and non-ASA NSAIDs) are commonly used in the elderly and that there are significant medication costs associated with the use of this class of medication.

Reimbursement data for ASA and non-ASA NSAIDs from the Alberta Blue Cross Drug Benefit Plan (ABC-DP) was analyzed for a 6 month period in 1991. Of the Alberta population aged 65 and older 61,601 (26.7%) received at least one prescription for an NSAID. The total number of NSAID prescriptions reimbursed was 160,231 (2.6 prescriptions per NSAID claimant) for a cost to the ABC Drug Benefit Plan of $5.4 million dollars. The percentage of subjects receiving at least one prescription for other classes of medications was 19.9% for diuretics, 8.3% for ACE inhibitors, 8.5% for beta-receptor antagonists, 2.4% for oral corticosteroid, and 0.044% for methotrexate. NSAID exposure was assessed by the number of prescriptions rather than quantity of medication prescribed. Therefore, it was not possible to assess the relationship between medication exposure and outcomes of interest.

The frequency of NSAID prescription was studied in patients aged 65 and older using the Nova Scotia Seniors Pharmacare program database for a 1 year period ending in 1994.[48] It was found that of all NSAIDs, ASA was the most commonly prescribed, followed by diclofenac and naproxen. Often, the prescription of an NSAID will precipitate a prescription of cytoprotective medication. In this study, 17.1% of the total day's supply of NSAIDs were co-prescribed with a cytoprotective or antiulcer drug.

In summary, NSAIDs are commonly prescribed to elderly persons and the use of these

agents account for a significant health care expenditure. Few studies have been published using Canadian data.

Cardiovascular Disease in the Elderly

It may be useful to define cardiovascular disease before discussing its prevalence in the elderly. The term "cardiovascular disease" is used variably throughout the medical literature. It implies diseases of both the heart and vasculature (arteries, veins, and lymphatics). However, precision is lacking and many conditions that anatomically relate to the heart and vasculature are variably regarded by this term. For example, congenital heart disease, non-atherosclerotic conditions of blood vessels (inflammatory arteritis), thrombophlebitis and thromboembolism, lymphedema, and target organ disease (stroke, renal disease, and limb ischemia) may or may not be included by various authorities. This study will focus on the following specific cardiovascular conditions: congestive heart failure, hypertension, peripheral edema, coronary artery disease, acute myocardial infarction, atherosclerosis, aneurysm, cerebrovascular disease, deep vein thrombosis and pulmonary thromboembolism. Each of these conditions are associated with one or more International Classification of Diseases version 9 – Clinical Modification (ICD9-CM) codes and presented in Appendix 2.

Cardiovascular disease is a significant problem for Canadians. Data from Statistics Canada showed the leading causes of death in 1995 to be cancer (27.4%), diseases of the heart (27.2%), and cerebrovascular disease (7.4%).[49] Data from the original Framingham Heart Study and Framingham Offspring Study demonstrated that the incidence and prevalence of congestive heart failure doubles with each decade of life after 50 years of

age.[50] Congestive heart failure is not a benign disease. The prognosis associated with this diagnosis was studied in the Framingham population. After adjusting for age, the median time between diagnosis and death was 1.7 years for men and 3.2 years for women. Of concern was the finding that advances in the therapy for congestive heart failure between 1950 and 1980 was associated with only modest survival benefits.[51]

Hypertension and ischemic heart disease are the most common etiologies of congestive heart failure.[50] Therefore, it is expected that these conditions are significant in seniors. With respect to hypertension, there are epidemiological studies demonstrating the prevalence of isolated systolic hypertension to increase from about 8% among people in their sixties to 22% by 80 years of age.[52] The third National Health and Nutrition Examination Survey found that both the prevalence and severity of hypertension increase with age.[53] For example, among men between the ages of 50 and 69 years, the prevalence of hypertension is 35%, and fewer than one quarter of these cases represent stages 2 through 4 hypertension as defined by the Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.[54] Above the age of 69 years, the prevalence of hypertension rises to 50% and more than one third of cases fall within stages 2 through 4.

The incidence and impact of myocardial infarction also increases with age. The Worcester Heart Attack Trial demonstrated an in-hospital mortality of 5% to 8% for those 64 years of age or younger, 16% for those 65 to 74 years of age, and 32% for those older than 75 years of age.[55] It is probable that frail organ systems and co-morbidity contribute to the elevated case fatality rates observed in the elderly. An additional area of

study raises the possibility that the elderly receive sub-optimal care. For example, it was found that at least 47% of elderly myocardial infarction victims did not receive proven therapies.[56]

Peripheral edema is a significant problem in the elderly. Peripheral edema may be a sign of congestive heart failure. It may also be seen in the setting of venous insufficiency, deep vein thrombosis, low serum albumin states, inflammatory conditions, and as a consequence of non-ASA NSAID or calcium channel blocker therapy.[57] A study of 459 seniors seen in an outpatient clinic in Italy found the prevalence of pedal edema to be 8.6%. It was also found that pedal edema was associated with the presence of foot pain which in turn was associated with disability.[58] In addition to the impact of peripheral edema on health are the effects of its treatment. Diuretics prescribed for edema are associated with a number of adverse effects including electrolyte disturbances, postural symptoms, and renal insufficiency. Investigators in the Netherlands found that diuretics were prescribed to 38.3% of 1,547 elderly persons from a combined ambulatory and hospitalized population.[59] An objective of their study was to estimate the frequency with which diuretics could be safely withdrawn. Of the 218 subjects whose physician discontinued the diuretic, 41% remained diuretic free 12 months later. One interpretation of this data is that indication for starting the diuretic was transient in a significant proportion of this population. Although the investigators did not measure the association of non-ASA NSAID prescription with successful withdrawal of diuretic therapy, it was noted that 15% of the study population were using non-ASA NSAIDs.

Cerebrovascular disease accounted for 15,537 Canadian deaths in 1995.[49] Age is

recognized as the most significant risk factor for stroke. A population based risk factor assessment of 1,444 incidence cases of ischemic stroke in a Rochester population found that the average age of onset of first transient ischemic attack was 70 years in males.[60] Other major risk factors for stroke include hypertension and cardiac diseases (atrial fibrillation, valvular heart disease, ischemic heart disease, and congestive heart failure) both of which increase in prevalence with age. Smoking, diabetes, hyperlipidemia and other risk factors are also acknowledged.[61]

Peripheral vascular disease is a general term that refers to atherosclerotic disease of the limbs (usually legs) and aneurysm of the aorta and large extra-cranial arteries (aorta, iliac arteries, and renal arteries). Intermittent claudication is a symptom of clinically significant atherosclerosis of the arterial supply to the lower limbs. In the elderly, intermittent claudication occurs in 2 – 3 percent of men and 1 – 2 percent of women. Age is risk factor for this condition and after 5 – 10 years, 10% of affected individuals require amputation.[62]

In summary, the incidence and prevalence of cardiovascular disease in the elderly is significant. The morbidity and mortality associated with these conditions are more significant in the elderly than in younger populations.

Non-ASA NSAIDs and Hypertension

The relationship between non-ASA NSAID exposure and elevation of blood pressure has been reported in the medical literature. Numerous clinical trials of non-ASA NSAIDs have been carried out where blood pressure was the primary endpoint under study. Meta-

analyses of this literature have been carried and two are commonly referenced. The first meta-analysis used data from 54 intervention trials that included 1,324 subjects.[63] The mean age of the subjects was 46 years with no elderly patients included in the trials and 90% of the subjects had hypertension. It was found that non-ASA NSAIDs had a variable effect on mean arterial blood pressure. Of the three agents that increased blood pressure, the magnitude of effect ranged from 0.49 to 3.74 mmHg and the results were statistically significant only for indomethacin and naproxen. There were no statistically significant effects noted among normotensive subjects.

The second meta-analyses used data from 50 trials that included observations of 771 subjects.[64] The average age of the subjects from the trials was 48 years and none of the trials included elderly subjects. The pooled data revealed that non-ASA NSAIDs elevated mean supine arterial pressure by 5.0 mm Hg (95% CI, 1.2 to 8.7 mm Hg). The investigators stratified the analysis by blood pressure status. It was only among treated and controlled hypertensive subjects that a statistically significant effect was found. It was noted that the NSAIDs antagonized the effects of beta-receptor antagonists more than other anti-hypertensives and that piroxicam was the only agent for which the 95% confident interval excluded the null hypothesis.

These analyses did not have major methodological flaws according to standards used to assess systematic reviews.[65] However, the results of the analyses are not conclusive. When individual non-ASA NSAIDs were analyzed, it was found that while some agents were associated with a blood elevation, other agents either had no effect or were associated with a reduction of blood pressure. Also, a positive relationship was not found

among normotensive subjects in either of the analyses. Only modest increases in arterial blood pressure was found among those agents where differences were statistically significant and the lower limit of the confidence intervals was usually less than a 2 mmHg increase in blood pressure. However, small increases in blood pressure may be clinically relevant. The authors of the one meta-analysis noted that a 5 to 6 mmHg increase in diastolic blood pressure over a few years was associated with a 67% increase in the incidence of stroke and a 15% increase in the coronary artery disease.[64] Generalizability of the meta-analyses to elderly populations is a concern. Although there is no compelling reason to believe that elderly persons are less likely to be sensitive to the effects of NSAIDs, neither of the analyses included studies where subjects were age 65 and older.

Another approach to the question of NSAIDs and hypertension uses pharmaco-epidemiology. If non-ASA NSAIDs increase blood pressure, then patients using these agents should be at greater risk for requiring anti-hypertensive medications or require higher doses of anti-hypertensives relative to controls. A relevant study was done that included 9,411 subjects aged 65 and older who were enrolled in the New Jersey Medicaid program.[66] It was found that the odds ratio in favor of initiating anti-hypertensive medication among those receiving any amount of non-ASA NSAID was 1.66 (95% CI, 1.54 – 1.80). The odds ratios were 1.55, 1.64, and 1.82 for low, intermediate, and high users of NSAIDs respectively.

A small number of additional American pharmacoepidemiological studies that address the elderly populations have been reviewed in a recent publication.[67] Briefly, it was

found that that NSAID prescription is associated with prescription of agents commonly used to treat hypertension and that NSAID users tend to have higher blood pressures than controls. Valid reasons to anticipate differences between Canadian and American results may exist. For example, those enrolled in U.S. Medicaid Programs have very limited disposable incomes whereas Canadian programs are universal. This difference may affect the ability of subjects to fill their prescriptions. Another difference may relate to differences in the proportions of ethnic backgrounds between the countries. It is known that hypertension responds more favorably to diuretic therapy in African Americans relative to Caucasions.[54] This may suggest differences in the pathogenesis of hypertension and the response to NSAID exposure. Lastly, physician practice patterns may differ between the countries. For example, there are variations in the definition of hypertension proposed by the respective national bodies.[54,68]

Little has been published from Canadian sources. One study was located that supported a relationship between NSAID exposure and risk of prescription for cardiovascular diseases. Crude estimates of exposure were measured using administrative data in this study.[69]

In summary, data from clinical trials and epidemiological research suggest that there is an association between the use of some NSAIDs and increases in blood pressure. The effect is modest and may be most significant among those with a history of hypertension. Data from Canadian sources is limited.

Non-ASA NSAIDs and Congestive Heart Failure

It has been hypothesized that non-ASA NSAIDs may increase the risk of congestive heart failure in the elderly. Despite a large number publications that imply this relationship, a Medline search combining the terms NSAIDs and congestive heart failure for the years 1966 to present found no clinical trials where subjects were randomized to a non-ASA NSAID and clinically significant congestive heart failure was the primary outcome of interest. Of the published articles available, most of the randomized trials or cross-over trials considered the effect of NSAIDs on pharmacokinetic, hemodynamic, or biochemical outcomes such as renal prostaglandin excretion. Of those where clinical endpoints were considered, the results showed no relationship. For example, a cross-over study of 19 elderly females with controlled congestive heart failure found that subjects receiving meloxicam did not develop an exacerbation of heart failure nor did they have clinically significantly pharmacokinetic changes in concomitantly administered furosemide.[70] A study of 12 patients with compensated congestive heart failure receiving captopril were randomized to receive indomethacin or placebo. Indomethacin exposure resulted in a decreased cardiac output and renal blood flow and increased systemic vascular resistance as measured by hemodynamic monitoring. The period of observation was too short to exclude adaptation to the NSAID.[71] A study of 10 congestive heart failure patients on furosemide found that naproxen administration reduced renal prostaglandin production whereas sulindac did not have this effect.[13]

Only one pharmacoepidemiological study was published. Investigators from the Netherlands linked a prescription and hospitalization database that contained

observations on 10,519 subjects aged 55 and older who used diuretics with or without NSAIDs. The period of observation was 7 years period ending in 1992.[72] It was found that those subjects who used both agents had a relative risk of hospitalization for CHF of 1.8 (95% CI: 1.4 - 2.4) after adjusting for pertinent co-variables. Overall, the evidence supporting a relationship between non-ASA NSAID use and congestive heart failure is based on surrogate markers or pharmacoepidemiology. There is no epidemiological evidence of a relationship that was reported by Canadian sources.

Non-ASA NSAIDs and Edema

Peripheral edema is frequently listed as a potential adverse effect of NSAIDs. However, there is a paucity of original research in the published literature. A Medline search was carried out using the term edema combined with NSAIDs from 1966 to present. The development of spectacular amounts of peripheral edema during non-ASA NSAID therapy has been described in case reports.[73,74] However, clinical trials of NSAIDs where edema is an endpoint primarily concern the use of these agents in post-surgical, traumatic, or inflammatory conditions where time to resolution (not development) of edema is observed.

Non-ASA NSAIDs and Ischemic Heart Disease

While patients with apparently normal epicardial arteries may have myocardial ischemia, ischemic heart disease primarily refers to coronary atherosclerosis. The role of ASA in the treatment and prevention of ischemia secondary to coronary artery disease has been discussed under the pharmacology of NSAIDs. In summary, there is data that shows therapeutic benefit in the setting of unstable coronary syndromes as well as research

showing that ASA is effective for secondary prevention. Because all NSAIDs have to some extent an inhibitory effect on platelet aggregation, it is logical that non-ASA NSAIDs should be beneficial as well. However, there is little published data that addresses this issue.

A Medline search was carried out that combined the terms NSAIDs (excluding ASA) and myocardial ischemia from 1966 to present. After limiting the results to articles designated as clinical trials, controlled clinical trials, or randomized controlled trials, only 1 relevant article was located. A team of French investigators randomized subjects with acute myocardial infarction to receive flurbiprofen or placebo. After 6 months, the flurbiprofen group had a significantly lower rate of re-infarction (3% versus 10.5%) and the need for revascularization was lower in the treatment group (17% versus 33%).[75] There were no epidemiological articles that addressed this issue and the remaining publications examined non-clinical endpoints such as serum levels of prostaglandins or hemodynamic observations carried out over a short period of time. A particularly important question is knowing if co-prescription of ASA and non-ASA NSAIDs influence the frequency or severity of ischemic heart disease. There are no studies that have addressed this issue in the published literature.

Non-ASA NSAIDs and Cerebrovascular Disease

A Medline search of combining the terms NSAIDs excluding ASA and cerebrovascular diseases excluding migraine was carried out from 1966 to present. There were no published trials that examined the relationship between the use non-ASA NSAIDs and cerebrovascular disease.

Non-ASA NSAIDs and Peripheral Vascular Disease

A Medline search of combining the terms NSAIDs (excluding ASA) and peripheral vascular disease was carried out from 1966 to present. There were no published trials that examined the relationship between the use non-ASA NSAIDs and peripheral vascular disease.

Non-ASA NSAIDs and Thromboembolic Disease

Thromboembolic disease is meant to include deep vein thrombosis and pulmonary thromboembolism. A Medline search combining these conditions with NSAIDs excluding ASA was carried for the years 1966 to present. Two articles were located that compared a non-ASA NSAID with heparin therapy in randomized clinical trials of 60 and 90 patients.[76,77] In neither trial was there a statistically significant difference found in clinical or venographic endpoints. The authors conceded the sample sizes may have been too small to detect differences in clinical event frequencies.

In summary, non-ASA NSAID therapy has been associated with small but clinically significant increases in blood pressure in adults in clinical trials. Data in support of this association in the elderly is from observational research only. An association between non-ASA NSAID prescription and admission to hospital for congestive heart failure was observed in the elderly. There is little or no published research regarding the effect of non-ASA NSAID exposure on the incidence, progression, or prevalence of edema, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, or thromboembolic disease.

Methods

Study Design

Cross-sectional and case-control research designs were used in this analysis of administrative data. Data was obtained from Alberta Health and Alberta Blue Cross (ABC) for the fiscal year ending March 31, 1995. Variables under consideration included demographic data (age, sex, and mortality) provided by ABC, medication prescription and utilization as measured by reimbursement under the ABC Drug Benefit Plan (ABC-DP), and presence of risk factors or diseases as reported by physicians and hospitals to Alberta Health.

Ethics and Scientific Review

This project was approved by The University of Calgary Conjoint Scientific Review Committee and the Conjoint Research Medical Ethics Board of the Faculty of Medicine at The University of Calgary and the Affiliated Teaching Institutions on April 6, 1995. The Alberta Health Research Review Committee approved the protocol on June 28, 1996.

Subject Selection

The population under consideration (study population) included all persons aged 65 years and older who received reimbursement for any medication under the ABC-DP during the period April 1, 1994 to March 31, 1995. According to Statistics Canada there were 266,805 persons age 65 and older that resided in Alberta during 1996 census.[78] Based on previous research, it was estimated that the study population would account for approximately 70% of all individuals aged 65 and older residing in Alberta during the

study period.[4]

Medications of Interest

Medication Selection

Medications indicated for the treatment of the ischemic heart disease, hypertension, congestive heart failure, and edema were assessed. These agents included: acetylsalicylic acid (ASA), non-ASA NSAIDs, angiotensin converting enzyme (ACE) inhibitors, beta-receptor antagonists, calcium channel blockers, digoxin, diuretics, and other antihypertensive agents. Additional medications were considered for the purpose of assigning selected disease or risk factor states. A subject prescribed any quantity of an hypoglycemic medication, anti-hyperlipidemic agent, or nicotine replacement therapy was classified as having diabetes mellitus, hypercholesterolemia, or as a smoker respectively. Smoking status was also assigned using ICD-9 CM codes (see Appendix 2). Cephalexin (an antibiotic) was selected for comparison purposes in some analyses. The medications of interest are listed in Appendix 1. A total of 96 medications of interest were considered in the analysis of which there were 825 individual formulations.

All oral, inhaled, rectal, and topical formulations of the medications of interest were considered. Except for insulin, parenteral formulations were excluded from consideration because parenteral formulations of NSAIDs and cardiovascular medications are rarely used in the outpatient setting. Also, there were only two parenteral formulations that were reimbursed in the database (ketorolac and furosemide) and exclusion of these agents was felt unlikely to significantly affect the analyses. Complementary therapies such as

nutritional supplementation or use of medication beyond its approved indication were not considered in the analysis.

Medication Identification

The Drug Identification Number (DIN) was used to identify medications for which reimbursement was provided by Alberta Blue Cross. The Health Protection Branch of Health Canada assigns a DIN to each medication and medical device marketed in Canada.

Medication Quantification

It was hypothesized that the relationship between NSAIDs and the outcomes of interest would be related to the quantity of NSAID used during the year or other selected period of interest. The indications for NSAIDs are varied and can include conditions where short term therapy is desirable (e.g. injuries or exacerbations of inflammatory disease) or where long term therapy is required (e.g. advanced osteoarthritis or degenerative disk disease). Also, 17 different non-ASA NSAIDs were used by the subjects with variable doses and frequencies of administration. Because of the heterogeneity of exposure, a common unit of NSAID exposure was required for the analysis of NSAIDs as a class. Previous studies used a count of prescriptions.[4] This method is imprecise in that a prescription may have any dose, duration, frequency of medication exposure or number of refills depending on physician practice. Another method uses the mass of the medication (e.g. milligram) as a standard unit for comparison. This method suffers from variability of efficacy between equivalent quantities of medication. For example, a typically prescribed quantity of ketorolac is 10 mg four times daily whereas the

equivalent anti-inflammatory dose of naproxen may be 500 mg twice daily.

The standard unit of medication exposure used in this study takes advantage of the pharmaceutical industry practice of stating the maximum daily dose of their medication that can be used for prolonged periods in the Compendium of Pharmaceuticals and Specialties (CPS).[39] With respect to NSAIDs, this dose is selected by balancing therapeutic effects (anti-inflammatory effect) and adverse effects (GI intolerance, edema, and other known or possible effects). For each medication of interest the CPS was consulted and the maximum daily recommended dose was recorded. The quantity of each drug reimbursed to each beneficiary was then totaled and this sum was divided by the maximum daily recommended dose. The result was labeled the maximum daily dose equivalent (MDDE).

For example, the maximum daily recommended dose for ketorolac was 40 mg per day. If a beneficiary was reimbursed for 100 tablets of ketorolac 10 mg, the exposure to this NSAID was (100 tablets x 10 mg / 40 mg/day = 25 MDDE). The advantage of this method is that it can be used for most medications and it has a basis in biological effect. A disadvantage of the method is that it cannot distinguish a maximum dose - short duration exposure from low dose - long duration exposure. Data on average dose and duration of use was not available in the ABC database. The maximum daily dose recommended indicated by the CPS is listed in Appendix 1 where applicable. Calculation of the MDDE was done for all medications of interest except for: warfarin, insulin, oral hypoglycemic agents, nicotine replacement therapy, and antihyperlipidemic agents. It was not necessary to estimate an MDDE for these agents because they were

used as markers of disease or risk factor states. For example, reimbursement for any quantity of insulin was used as a surrogate marker of diabetes mellitus.

Medication costs were calculated using the amounts reimbursed to subjects by the ABC-DP.

Diseases and Risk Factors of Interest

The diseases of interest included: cardiovascular conditions (congestive heart failure, edema, ischemic heart disease, hypertension), cerebrovascular disease, peripheral vascular disease, and thromboembolic disease (deep venous thrombosis and pulmonary thromboembolism). Other conditions which are known or suspected risk factors for the diseases of interest were also considered for the purpose of analysis and included: diabetes mellitus, hyperlipidemia, and smoking status. ICD-9 CM codes were used to identify the disease and risk factors of interest in the databases. These are listed in Appendix 2.

Mortality

All subjects who ceased to be members of the ABC-DP due to death were identified anonymously by ABC in a separate database. Only the date of de-registration was provided.

Period of Study

This study considered patient demographics, medication use, disease status and mortality during the fiscal year April 1, 1994 to March 31, 1995. Representatives from Alberta Health suggested that a minimum of 6 – 12 months should elapse between the last day of

the fiscal year and downloading of data from their mainframe computer. This period of time is necessary to allow for entry of claims from beneficiaries and physicians and to allow for updating of data with respect to mortality.

Data Acquisition

Data was requested from Alberta Health on May 27, 1996. The study required that data be abstracted the following sources: the ABC-DP, the Alberta Health Medical Services Claims database, and the Alberta Hospitalization (Acute Care Facilities) database. Each subject was assigned a unique identifying number that was mathematically based on the unique lifetime identifier (ULI) provided to residents by the Government of Alberta. The identifying codes provided were completely anonymous except for the subject's age and gender. The data was received on December 17, 1996. The cost of the data was $3,000.00 + 7% GST = $3,210.00.

Funding

This project was funded by the Centre for Advancement of Health, Foothills Provincial General Hospital.

Data Storage and Security

The data was provided and stored on a single compact disk containing four ASCI type data files and one explanatory file. The files required approximately 500 megabytes of disk space. The compact disk was downloaded to a single microcomputer that was maintained in a locked single user office environment at The University of Calgary.

Database Inspection and Coding

ABC Database

The ABC database contained information on 4,173,774 prescription reimbursements for 192,866 beneficiaries. Data provided included: anonymous recipient ULI, gender, age, drug identification number (DIN), date of prescription, date of payment, net amount paid, and drug quantity.

Inspection of the age and gender fields revealed internal inconsistencies that were associated with less than 2% of the subjects. Common examples included: the beneficiary may have been recorded as age 75 in 20 reimbursements and age 78 in 1 reimbursement, or a zero value (0) was present in a fraction of the reimbursements associated with a claimant. There did not appear to be other inconsistencies in the database. The frequency of subjects associated with a discrepant age or gender was low and it was usually possible to determine where a clerical error had occurred. Therefore, it was decided to assign the most probable age and sex based on the most commonly reported values for these variables rather than exclude these subjects from the analysis.

A small percentage (1.1%) of the entries in the database refer to the correction of errors in the reimbursement process. These administrative corrections are notable for the negative value in the cost field and proximity to an entry that responsible for the reversal.

Physician Services Database

The Physicians Services database contained information on 4,095,712 physician encounters for 124,040 beneficiaries. Data provided included: anonymous recipient ULI,

date of service, service code, functional center type (ambulatory care, laboratory, inpatient, office), diagnostic code 1, diagnostic code 2, diagnostic code 3, and amount paid.

Hospitalization Database

The Hospitalization database contained information regarding 75,236 hospitalizations for 43,246 ABC-DP claimants. Thirty-two fields of information were supplied including: anonymous recipient ULI, date of admission, date of discharge, discharge status, length of stay, diagnostic codes x 16 fields, and up to 10 fields of procedure codes.

Registration Database

The Registration database contained information relating to 7,333 subjects who were deleted from the ABC-DP due to death.

Database Linkage

Data was merged from the ABC, Physician Services, Hospitalization, and Registration databases using the anonymous unique identification code.

Cross Sectional Analysis

The cross sectional analysis was carried out using data available between April 1, 1994 and March 31, 1995. With respect to the association of non-ASA NSAID prescription with the prescription of cardiovascular medications, all exposure to the medications of interest were summed for each subject. Covariates such as age, gender, ASA prescription, and the presence of selected disease or risk factor states were obtained from the ABC, Physician Services, and Hospitalization databases.

Case Control Analysis

Because the specific date associated with each drug remuneration, physician service, and hospitalization was available for the period under observation, it was possible to perform a case control analysis. This technique was used to assess the association between non-ASA NSAID prescription and hospitalizations for acute disease states. Among the diseases of interest, four conditions usually present acutely: 1) acute myocardial infarction, 2) congestive heart failure requiring hospitalization, 3) cerebrovascular diseases, and 4) thromboembolic diseases. Cases of these conditions were defined to be present in subjects where two conditions were met: 1) the disease was reported in the Hospitalization database January 1 to March 31, 1995 and, 2) there was no mention in the Hospitalization database of the disease between April 1 – December 31, 1994. In effect, the first presentation of the disease of interest occurred during the last three months of the study period. Controls were defined as those in whom there was no mention of the disease of interest during the study period. For the cases, medication exposure was summed for the three months preceding admission to hospital for the disease of interest. For the controls, medication exposure was summed for three months preceding the midpoint of the period during which cases were admitted to hospital (February 15, 1995).

Limitations of the Data

The ABC database contained information regarding medication use that was associated with reimbursement under the ABC-DP. Therefore, it was not possible to know of medication use outside of this context. Examples would include the use of over the counter preparations such as ASA and ibuprofen which were the only agents of interest

that were available without prescription. Medications provided during hospitalization were not included in the database nor is it possible to know what was actually consumed versus discarded by patients.

A second limitation of the data is that only subjects who received a reimbursement for medication under the ABC-DP were included in the study. The ABC database was the primary database to which all others were linked. Therefore, there was no data available for subjects who visited a physician or had been hospitalized if they did not receive reimbursement under the ABC-DP. The converse of this limitation is that there is no demographic data regarding the Albertans who were eligible for reimbursement but received none. The use of administrative data is presented in the context of validity and bias of the results in the discussion section of the manuscript.

Statistical Methodology

Sample Size

The primary objective of this study was to compare the use of cardiovascular medication and frequencies of selected cardiovascular conditions among elderly subjects exposed to non-ASA NSAIDs and non-exposed elderly subjects using administrative data provided by Alberta Health. In as much as the sample size was not a random selection from the population of those aged 65 and older but based on what Alberta Health was able to provide, this sample was a convenience sample. However, data was available for 192,866 Alberta seniors from which 71,015 received at least one prescription for a non-ASA NSAID. The power to detect small differences in medication use or frequencies or cardiovascular disease was high. For example, the power to detect a 1% difference in

disease frequencies is greater than 99% using a 2 tailed test and an alpha of 0.0005.[79] Approximately 20 primary hypotheses were tested in this project. There were 3 – 7 covariates considered with each primary hypothesis which accounts for approximately 100 statistical procedures. Statistical significance was defined at an alpha of less than 0.0005 consistent with a Bonferroni adjustment for multiple statistical testing.

Summary Statistics

Measures of central tendency used to describe the data included means and medians. Expressions of variability include ranges, quartiles, standard deviations, standard error of the means, and confidence intervals as described in a standard textbook of biostatistics.[80]

Hypothesis Testing

Formal techniques used to test for differences between groups included Fisher's exact test in cases where the data was binary and Student's t-test when the dependent variable was continuous.

Statistical modeling was carried out using logistic regression analysis when outcome data was binary and linear regression analysis when the outcome data was continuous. The technique of backward elimination was used to remove explanatory variables that were not contributory to the models. The dataset under consideration was restricted to NSAID exposures greater than 0 MDDE for some analyses. This technique was used to examine the potential effect that selection bias may have had on the association between NSAID exposure and the outcome variables under consideration. Stata was used for all statistical analyses.[81]

Results

Demographics

The ABC database contained information on 192,866 subjects. This cohort of subjects defined the study population. There were 266,905 persons aged 65 and older residing in Alberta during 1996. Assuming the change in size of the population of elderly Albertans between 1995 and the 1996 census to be small, the study population accounted for 72% of all elderly Albertans. In the study population, males numbered 84,336 (44%) and females numbered 108,530 (56%). The mean age was 74.5 yr (median: 73 yr, SD: 6.84). The mean age of the females was 74.9 years (SD: 7.00) and the mean age of the males was 73.9 years (SD: 6.59). The age distributions of all subjects and gender sub-groups are presented in figure 2.

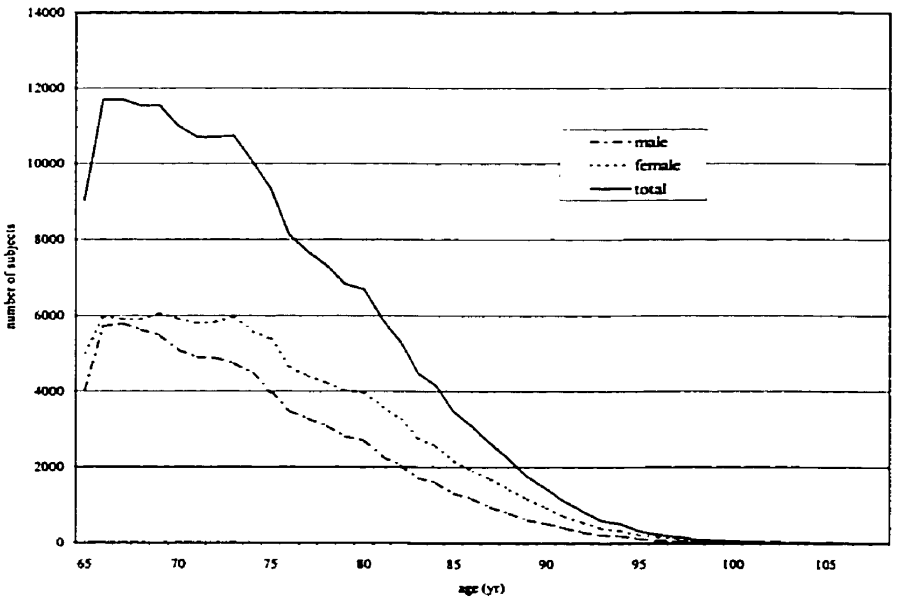

Figure 2. Age distribution of study population and gender sub-groups.

Prescription of NSAIDs

During the study period 228,290 prescriptions for non-ASA NSAIDs were reimbursed to the study population. The mean number of non-ASA NSAID prescriptions per person was 1.18 / yr. The number of subjects that received at least one prescription for any NSAID was 95,332. The number of subjects that received at least one prescription for a non-ASA NSAID was 71,015 and those receiving at least one prescription for ASA numbered 39,926. A total of 15,609 subjects received prescriptions for both ASA and a non-ASA NSAID.

Study subjects were prescribed a variable number of different non-ASA NSAIDs during the study period as shown in table 1. 15,140 (7.85%) subjects received prescriptions for

Table 1. Study population stratified by number of different non-ASA prescribed during the study period.

Number of different non-ASA NSAIDs	Number of subjects	Percentage of study population
0	121,851	63.1791
1	55,875	28.9709
2	12,269	6.3614
3	2,350	1.2185
4	434	0.2250
5	70	0.0363
6	13	0.0067
7	3	0.0016
12	1	0.0005
Total	192,866	100.0000

more than one type of non-ASA NSAID. A small number of subjects received greater than 2 different non-ASA NSAIDs and one subject received 12 different non-ASA NSAIDs. The data concerning this subject did not appear to contain administrative or

typographical errors. It was possible to query the database for instances where more than one non-ASA NSAID was prescribed to a subject on the same day. There were 1,906 instances where 2 non-ASA NSAIDs were prescribed on the same day and 19 instances where 3 non-ASA NSAIDs were prescribed on the same day. ASA was not included in this analysis because of its role in the prevention of stroke and recurrent myocardial infarction.

Non-ASA NSAID prescription was stratified by demographic variables. The mean quantity of non-ASA NSAIDs prescribed to the study population was 28.55 MDDE/yr. The mean MDDE prescribed to each age group is presented in figure 3. The graph

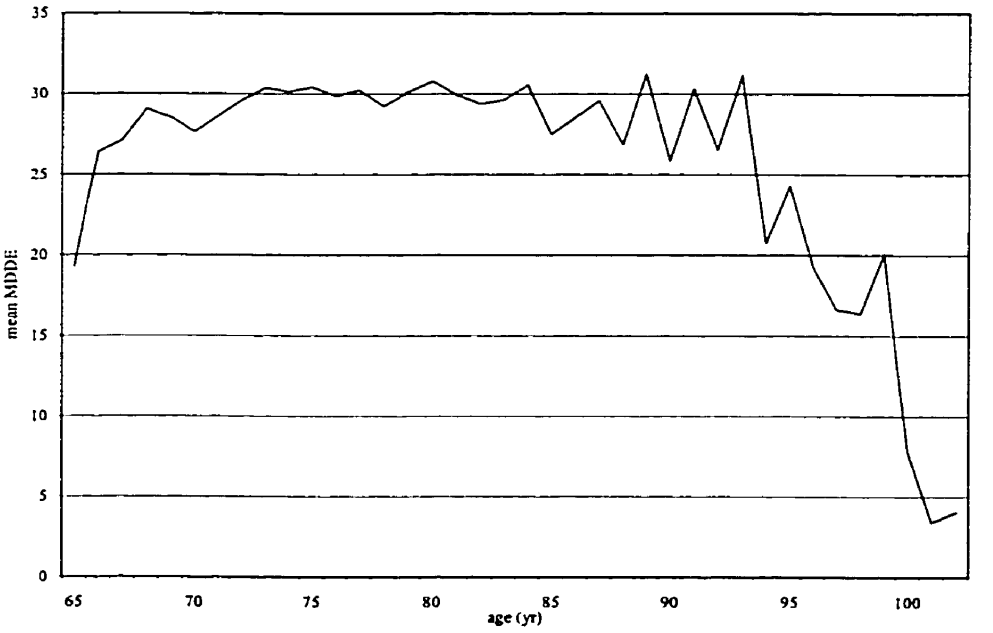

Figure 3. Mean non-ASA NSAID prescription measured in maximum daily dose equivalents (MDDE) by age for study population. (n=192,866).

suggests a fairly constant utilization up until age 90 after which there is a decline. Linear

regression analysis revealed that over the entire range of age, there was a slight increase in utilization with age estimated at 0.14 MDDE / subject / yr (95%CI: 0.09 - 0.18). Age restricted analyses revealed that between 65 and 90 years there was an increase in use of 0.19 MDDE / subject / yr (95% CI: 0.14 – 0.24) and between 91 and 106 years there was a decline in prescription of 1.66 MDDE / person / yr (95% CI of decline: 2.50 - 0.79). The average MDDE prescribed to those age greater than 100 varies widely owing to the small numbers (44 subjects age > 100 years). The mean utilization of non-ASA NSAIDs was not statistically different (t-test, $p = 0.058$) between males (28.9 MDDE / male / year) and females (28.3 MDDE / female / year).

Quantity and Cost NSAIDs

The quantity of NSAIDs and their associated cost to the ABC-DP over the 12 month study period is presented in table 2. Data regarding 18 NSAIDs including ASA is included. Summarized are the: number of subjects who received at least one prescription for the selected medication, the percentage of the study population that received at least one prescription for the selected medication, the total MDDE for the study population, the mean MDDE for subjects who received at least one prescription for the selected medication, the total reimbursement to the study population, and the mean reimbursement to subjects who received at least one prescription for the selected medication. The agents are ranked by frequency of use in descending order.

A total of 8.8 million MDDE of ASA and non-ASA NSAIDs were prescribed with an associated cost to the ABC-DP of $8.3 million. 5.5 million MDDE of non-ASA NSAIDs

Table 2. Reimbursement of NSAIDs by the ABC Drug Benefit Plan for the year ending March 31, 1995. Aggregate and mean values per study subject are presented.

Medication	Number of subjects prescribed this agent	Percentage of study population prescribed this agent	MDDE	Mean MDDE per subject prescribed this agent	Total reimburse-ment for this agent	Mean reimburse-ment per subject prescribed this agent	Mean reimburse-ment per MDDE for this agent
ASA	39,966	20.72	3,287,606	82.3	$1,277,032	$31.95	$0.39
diclofenac	27,754	14.39	1,869,829	67.4	$2,907,393	$104.76	$1.55
naproxen	12,355	6.41	640,198	51.8	$620,408	$50.22	$0.97
indomethacin	10,688	5.54	348,228	32.6	$652,935	$61.09	$1.88
ibuprofen	8,804	4.56	487,075	55.3	$160,887	$18.27	$0.33
ketoprofen	8,804	4.56	732,130	83.2	$932,209	$105.88	$1.27
ketorolac	4,998	2.59	109,607	21.9	$261,836	$52.39	$2.39
tiaprofenic acid	4,438	2.30	387,020	87.2	$464,889	$104.75	$1.20
tenoxicam	2,819	1.46	230,318	81.7	$272,037	$96.50	$1.18
sulindac	2,723	1.41	235,974	86.7	$228,666	$83.98	$0.97
piroxicam	2,439	1.26	269,844	110.6	$205,171	$84.12	$0.76
flurbiprofen	1,656	0.86	92,578	55.9	$128,989	$77.89	$1.39
diflunisal	642	0.33	47,982	74.7	$50,817	$79.15	$1.06
floctafenine	632	0.33	21,550	34.1	$41,457	$65.60	$1.92
mefenamic acid	370	0.19	9,945	26.9	$21,839	$59.02	$2.20
phenylbutazone	239	0.12	4,436	18.6	$2,835	$11.86	$0.64
tolmetin	199	0.10	15,451	77.6	$32,774	$164.69	$2.12
fenoprofen	100	0.05	4,623	46.2	$11,911	$119.11	$2.58
Total for all agents			8,794,393		$8,274,086		
Mean for all agents				60.8		$76.18	$0.94
Total for non-ASA			5,506,787		$6,997,054		
Mean for non-ASA				59.6		$78.78	$1.27

were prescribed with an associated cost of $7.0 million. The number of subjects who received each agent varied widely. ASA was prescribed to 39,966 subjects whereas diflunisal was prescribed to 100 subjects. The sum of the number of subjects column exceeded the total population because some subjects received more than one type of NSAID.

ASA was the most commonly prescribed NSAID accounting for 3.3 million MDDE and a cost of $1.3 million. Among those who received at least one prescription for ASA, an average of 82.3 MDDE per year was prescribed with an associated cost of $31.95 per year. The most commonly prescribed non-ASA NSAID was diclofenac which was prescribed to 14.4% of the study population. Diclofenac accounted for 44.0% of all non-

ASA NSAID MDDE. This agent was associated with a reimbursement of $104.76 per year to the average recipient of this agent. Other commonly prescribed agents were naproxen and indomethacin.

The mean MDDE per subject prescribed any NSAID was 60.8 per yr. The cost associated with the average user of any NSAID varied from $11.86 to $119.11 per yr and was explained in part by the quantity of the agent prescribed. However, there were exceptions where the price of the agent appeared to impact on reimbursement costs. For example, the average user of fenoprofen was reimbursed $119.11 for 46.2 MDDE ($2.58 / MDDE) which was more costly than the average user of diclofenac who was reimbursed $104.76 for 67.4 MDDE ($1.55 / MDDE). ASA was the least expensive agent for its average recipient.

For each class of medication of interest, the total quantity prescribed in MDDE, average MDDE per study population, cost, and average cost per MDDE is presented table 3. The mean MDDE per subject was calculated by dividing the total MDDE by 192,866 subjects. The average cost per MDDE was calculated by dividing the total cost attributable to each class of medication by the number of MDDE prescribed. The individual agents comprising each class is listed in appendix 1. The most commonly prescribed classes of cardiovascular medications were diuretics and calcium channel blockers while the most expensive agents were ACE-inhibitors and calcium channel blockers. Digoxin and diuretics were the least expensive of the cardiovascular agents of interest. NSAIDs are included in the table for comparative purposes.

Table 3. Total quantity of NSAIDs and selected cardiovascular medication prescribed and amount reimbursed by Alberta Blue Cross to Albertan aged 65 and older for fiscal year ending March 31, 1995. (n-192,866)

Category	Total MDDE	Mean MDDE per subject	Total cost	Average cost per MDDE
diuretics	7,921,601	41.07	$4,418,669	$0.56
non-ASA NSAIDs	5,506,787	28.55	$6,997,054	$1.27
calcium channel blockers	4,651,485	24.12	$13,500,085	$2.90
digoxin	3,477,633	18.03	$951,974	$0.27
ACE inhibitors	3,466,089	17.97	$9,986,719	$2.88
ASA	3,287,606	17.05	$1,277,032	$0.39
beta receptor blockers	2,628,699	13.63	$3,059,261	$1.16
other antihypertensives	424,797	2.20	$999,073	$2.35

Non-ASA NSAIDs and Cardiovascular Medication Prescription

Odds Ratios for Dichotomized Variables

Subjects were stratified according to reimbursement of non-ASA NSAID and selected cardiovascular medications. Reimbursement for at least one prescription of a non-ASA NSAID qualified as an exposure. Reimbursement for at least one prescription of a cardiovascular medication of interest qualified as a case. Odds ratios along with the associated 95% confidence intervals (Cornfield) and Chi square tests were calculated for each class of cardiovascular medication and are presented in table 4. The odds ratios were statistically different from the null hypothesis in all cases except for calcium channel blockers. However, the magnitude of the associations were small in all cases. The odds ratio for the association between non-ASA NSAID exposure and prescription for medications used to treat the symptoms of peripheral vascular disease was the highest.

Quartiles of non-ASA NSAID Exposure

The subjects were stratified by level of non-ASA NSAID exposure. The reference group

included only those who received no reimbursement for a non-ASA NSAID. Those

Table 4. Odds ratios for the association between non-ASA NSAID exposure and prescription of cardiovascular agents of interest. 95% confidence intervals (Cornfield method) and p – value associated with Chi square test are presented.

Cardiovascular Medications	Odds ratio	95% confidence interval	p - value
ACE inhibitors	0.91	0.89 - 0.93	< 0.00005
beta receptor antagonists	0.95	0.93 - 0.97	= 0.0001
calcium channel blockers	0.99	0.97 - 1.01	= 0.3301
digoxin	0.81	0.79 - 0.84	< 0.00005
diuretics	1.06	1.04 - 1.08	< 0.00005
other anti-hypertensives	1.08	1.04 - 1.13	= 0.0001
agents for peripheral vascular disease	1.36	1.27 - 1.46	< 0.00005

receiving at least one prescription for a non-ASA NSAID were categorized by quartile of exposure. Table 5 summarizes the outcome of this stratification procedure.

Table 5. Stratification of study population by exposure to non-ASA NSAIDs.

Group	Abbreviation	Exposure (MDDE)	Number of subjects	Percent of study population
Reference	R	0	121,851	63.2
Quartile 1	Q1	>0 - 15	18,363	9.5
Quartile 2	Q2	>15 - 40	17,568	9.1
Quartile 3	Q3	>40 - 106.6	17,278	9.0
Quartile 4	Q4	>106.6	17,806	9.2
Total			192,866	100.0

Graphical Presentation

The quantity of cardiovascular medication prescribed for each strata of exposure to non-ASA NSAIDs is presented in figure 4. The relationship between the prescription of non-ASA NSAIDs and cardiovascular medications can be described as a J-curve where the reference group received more cardiovascular medications than the first quartile of

exposure. Among those receiving non-ASA NSAIDs the relationship was direct. The J-curve was not present for cephalexin, a medication not known to have any association with cardiovascular disease. Diuretics, calcium channel blockers, and ACE inhibitors were prescribed most frequently. Cephalexin and other anti-hypertensives were used less frequently.

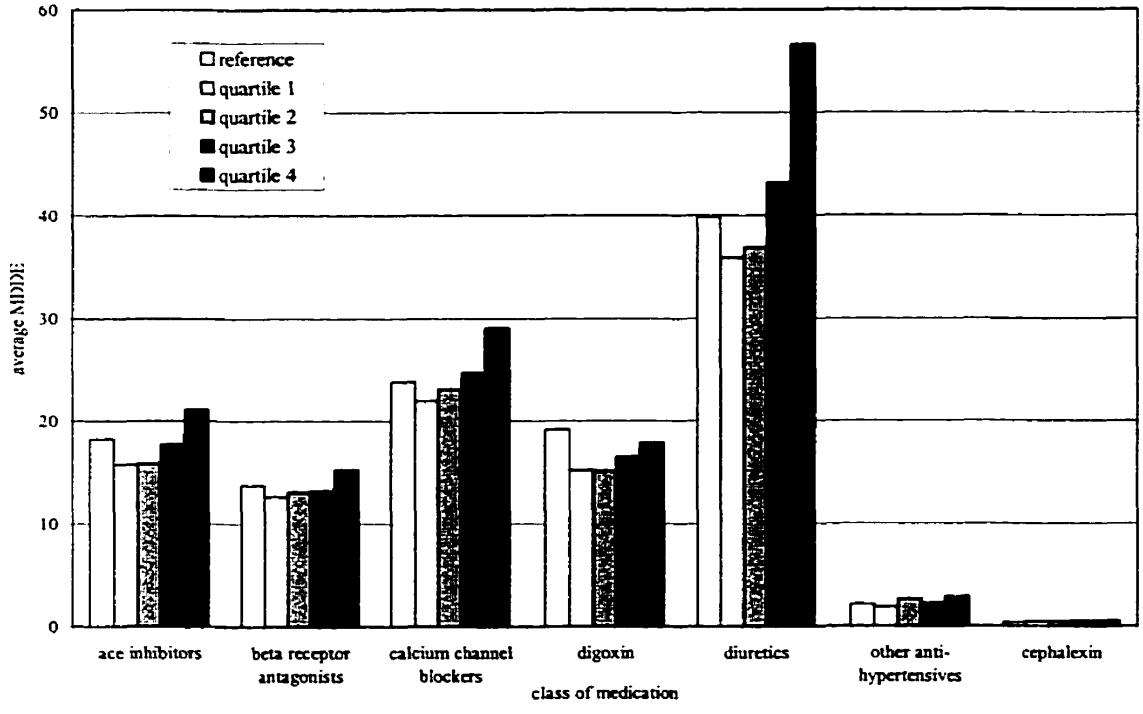

Figure 4. Prescription of selected medications according to exposure to non-ASA NSAID for study population over the 12 month period of observation.

Regression Analysis

Linear regression analysis was used to described the association between non-ASA NSAID reimbursement and the reimbursement of cardiovascular medications and cephalexin. The results of this analysis are presented in table 6. Simple linear regression

analysis was performed for the entire study population (crude regression coefficients) and a restricted analysis was performed for those subjects who received at least one prescription for a non-ASA NSAID. The restricted analysis was carried out to control for a bias that has likely occurred in the subject selection process. Specifically, the dataset provided by Alberta Health excluded outcome data for those who received no medications under the ABC DP. Therefore, the reference group (those not exposed to non-ASA NSAIDs) received at least one medication that was not a non-ASA NSAID but excluded subjects who received no medications any kind. This exclusion is likely to have resulted in a reference group with more cardiovascular illness than the actual population that was free of non-ASA NSAID use during the study period.

Multiple linear regression analysis was carried out with the addition of age, sex and ASA exposure to the models. The demographic variables did not influence the outcome of the association between non-ASA NSAIDs and the medications of interest and these results were not included in the table.

The crude regression coefficients were statistically significant for all associations except digoxin. The association for diuretic therapy was the largest and most clinically significant among the medications. For every 30 days of maximum dose non-ASA NSAID use, there was an additional 2½ days of diuretic prescription. Cephalexin was included in the analysis as a control medication. There was no biological reason to anticipate a relationship between non-ASA NSAID prescription and this antibiotic and the relationship for this medication approached the null hypothesis. When the analysis was restricted to those who received at least one prescription for a non-ASA NSAID, the

strength of the association increased for the cardiovascular medications. These relationships reached clinical significance for calcium channel blockers and ACE inhibitors. ASA was added to the models because it is an NSAID. The addition of this agent generally decreased the strength of the relationship between non-ASA NSAID and the cardiovascular medications. Simple linear regression for the association between ASA and non-ASA NSAID among those exposed to non-ASA NSAIDs resulted in an odds ratio of 0.80 (0.67 - 0.93).

Table 6. Linear regression analysis describing the relationship between 30 MDDE of non-ASA NSAID exposure and additional MDDE of medications of interest. The regression coefficients includes all subjects, the restricted odds ratios includes only those subjects (71,015) that were reimbursed for a non-ASA NSAID. The restricted regression coefficients with ASA exposure included in the models are presented in the last column.

Medication	Crude regression coefficients (95% CI)	Restricted regression coefficients (95% CI)	Restricted regression coefficients with ASA in model (95%CI)
ACE inhibitors	0.53 (0.43 - 0.62)	0.89 (0.77 - 1.01)	0.84 (0.72 - 0.96)
beta receptor antgonists	0.27 (0.18 - 0.36)	0.43 (0.31 - 0.54)	0.38 (0.27 - 0.49)
calcium channel blockers	0.89 (0.78 - 1.01)	1.16 (1.07 - 1.31)	1.04 (0.89 - 1.18)
cephalexin	0.03 (0.02 - 0.03)	0.02 (0.01 - 0.02)	0.02 (0.01 - 0.02)
digoxin	-0.08 (-0.22 - 0.05)	0.43 (0.27 - 0.59)	0.37 (0.21 - 0.53)
diuretics	2.47 (2.32 - 2.65)	3.08 (2.89 - 3.28)	2.99 (2.78 - 3.19)
other antihypertensives	0.13 (0.08 - 0.19)	0.15 (0.05 - 0.25)	0.14 (0.04 - 0.24)

Non-ASA NSAIDs and Cardiovascular Conditions in the Ambulatory Setting

Prevalence of Cardiovascular Conditions

The numbers of subjects who visited a physician at least once in an ambulatory care setting are presented for each diagnosis of interest in table 7. During the year, a diagnosis of hypertension was reported for 36.3% of the study subjects, 19.0% had degenerative or

inflammatory conditions of the musculoskeletal system, and 11.5% had coronary artery disease. The ICD-9 CM diagnosis codes associated with these conditions are listed in appendix 2

Table 7. Number of subjects who visited a physician for a diagnosis of interest in an ambulatory care setting.

Disease	Number of subjects	Percent of study population
coronary artery disease	22,143	11.5%
congestive heart failure	11,245	5.8%
cerebrovascular disease	5,202	2.7%
edema	2,195	1.1%
hypertension	69,918	36.3%
indication for NSAID	36,594	19.0%
peripheral vascular disease	2,805	1.5%

Graphical Presentation

The number of subjects who visited a physician for a diagnosis of interest was stratified according to non-ASA NSAID exposure and the results are presented in figure 5. There appears to be a direct relationship between non-ASA NSAID exposure and the prevalence of edema and degenerative or inflammatory musculoskeletal conditions. The relationship is indirect for coronary artery disease. A J-curve describes the relationship for hypertension and congestive heart failure. The relationship between non-ASA NSAID exposure and peripheral vascular disease is less clear.

Regression Analysis

The association between exposure to non-ASA NSAIDs and the prevalence of selected cardiovascular diseases was assessed using logistic regression analysis. The odds ratios

for crude association as well as models that included co-variables are presented in table 8.

There was a small but clinically significant association demonstrated for edema (odds ratio 1.07, 95%CI 1.05 – 1.08). The addition of clinically relevant co-variables to the regression models did not significantly change the magnitude of the associations.

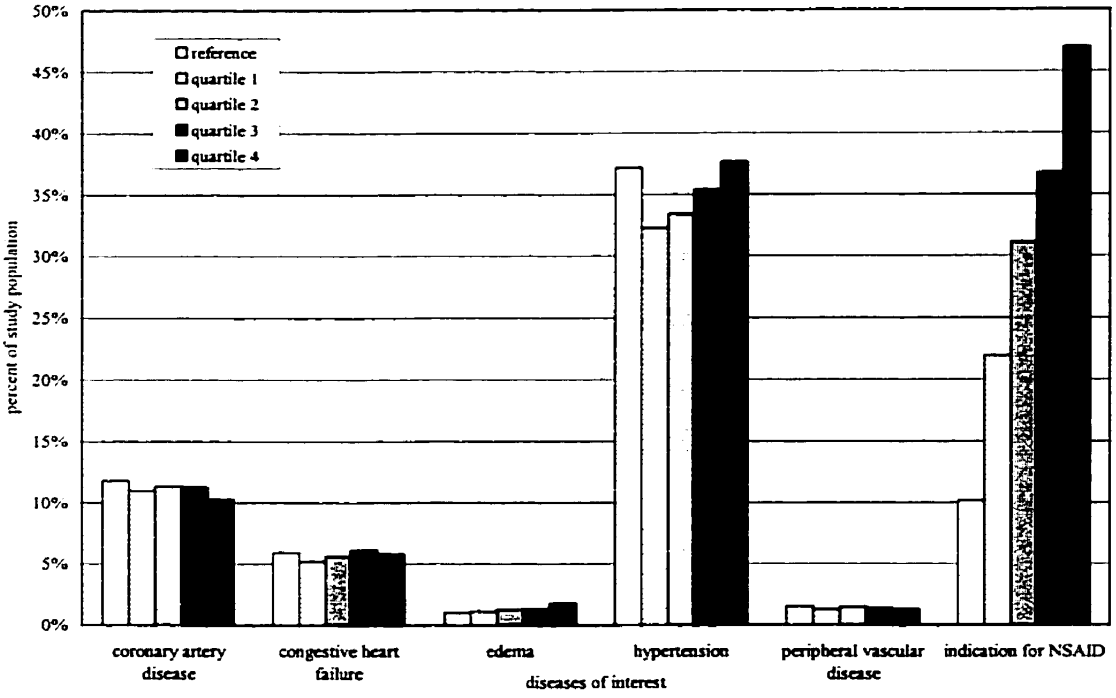

Figure 5. Prevalence of subjects who visited a physician in an ambulatory care setting with a diagnosis of interest over study period.

Exploratory Analysis: Restriction to Exposed Quartiles.

The possibility of selection bias is discussed in the demographics and discussion sections. Restriction may be used to reduce the effect of selection bias and an exploratory analysis

was done by considering only those who were prescribed a non-ASA NSAID.

Table 8. Odds ratios describing the association between increments of 30 MDDE exposure to non-ASA NSAIDs and the 1 year period prevalence of subjects who visited a physician in an ambulatory care setting for diagnoses of interest. Presented are the odds ratios describing the crude association as well as odds ratios associated with co-variables. An asterisk (*) denotes an associated $p < 0.0005$.

Disease	Crude	ASA	ASA, demographics	ASA, demographics, cardiovascular risk factors	ASA, demographics, cardiovascular risk factors, cardiovascular medications
coronary artery disease	0.98*	0.97*	0.97*	0.97*	0.96*
congestive heart failure	1.00	1.00	1.00	1.00	0.98*
edema	1.07*	1.07*	1.06*	1.07*	1.05*
hypertension	1.00	1.00	1.00	1.00	0.98*
peripheral vascular disease	0.98	0.98	0.98	0.98	0.97
indication for NSAID	1.28*	1.28*	1.28*	1.28*	-

Regression analysis for the association between an additional 30 MDDE of non-ASA NSAID exposure and congestive heart failure and hypertension was carried out. The crude odds ratio congestive heart failure was 1.01 (95% CI: 1.00 - 1.02) and for hypertension was 1.03 (95% CI: 1.02 - 1.03). Adjusting for age, sex, ASA exposure, diabetes mellitus, evidence of smoking, and hypercholesterolemia did not significantly change these relationships.

Hospitalizations

Prevalence of Cardiovascular Conditions in the Hospital Setting

The number of subjects noted to have a diagnosis of interest during at least one admission to hospital were summarized. This data is presented in table 9. Among the cardiovascular diseases of interest, the period prevalence of congestive heart failure in the hospital setting was the highest (4.3%). The prevalence of indications for which non-

ASA NSAIDs are prescribed was similar (5.0%).

Graphical Presentation

The frequency with which subjects were hospitalized with a diagnoses of interest were stratified by non-ASA NSAID exposure for the study period. The relationships were

Table 9. Number of subjects where a condition of interest was noted during hospitalization from April 1, 1994 to March 31, 1995. (n=192,866)

Disease	Number of subjects	Percent of study population
acute myocardial infarction	2,366	1.2%
congestive heart failure	8,384	4.3%
cerebrovascular disease	3,602	1.9%
indication for NSAID	9,695	5.0%
peripheral vascular disease	2,672	1.4%
thromboembolic disease	683	0.4%

graphed and presented in figure 6. A direct and linear relationship was present between exposure to non-ASA NSAIDs and the prevalence and inflammatory diseases of the musculoskeletal system in the hospital setting. The relationship between exposure to non-ASA NSAIDs and the prevalences of myocardial infarction and cerebrovascular diseases may be indirect whereas the relationship for thromboembolic disease is less clear. This analysis does not adjust for demographic variables, risk factors for cardiovascular diseases, and other medical therapies.

Case-control Analysis

The associations between exposure to non-ASA NSAIDs and hospitalizations was assessed using case-control methodology. This methodology offers an advantage over

the cross section analysis by allowing for inferences to be made regarding cause and effect.

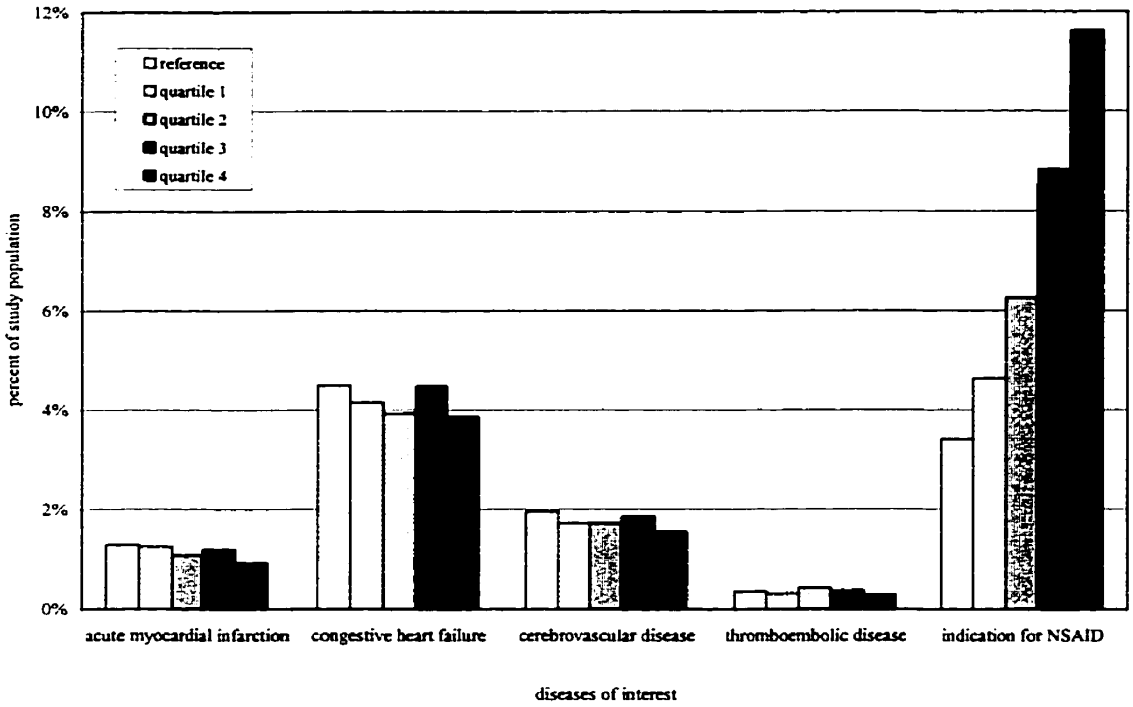

Figure 6. Prevalences of diagnoses of interest in the hospitalized setting for levels of non-ASA NSAID exposure over the study period.

The associations were assessed using logistic regression analysis for the presence of the conditions of interest. The crude odds ratio for describing the association between non-ASA NSAIDs and the presence of disease are presented in table 10 along with the odds ratios obtained when relevant co-variables are included in the model for each condition. There was a clinically and statistically significant association for hospitalization with congestive heart failure (odds ratio 1.13, 95%CI 1.06 - 1.20). This association did not significantly change when co-variables such as demographics, risk factors for disease,

and exposure to ASA were included in the model.

Table 10. Odds ratios for the association between increments of 30 MDDE non-ASA NSAIDs exposure and selected cardiovascular diseases using case-control methodology. Crude odds ratios and odds ratios adjusted for the addition of co-variables are presented. Demographics include age and gender, risk factor include the presence of diabetes, positive smoking history and hypercholesterolemia, selected medications include those using ACE inhibitors, calcium channel blockers, diuretics and digoxin. One asterisk (*) denotes $p < 0.001$ and two asterisks (**) denotes $p < 0.0005$.

Disease	Crude	ASA	ASA, demographics	ASA, demographics, risk factors	ASA, demographics, risk factors, selected medications
acute myocardial infarction	0.93	0.93	0.96	0.97	0.94
congestive heart failure	1.13**	1.12**	1.15**	1.17**	1.12*
cerebrovascular disease	1.04	1.03	1.05	1.06	1.07
thromboembolic disease	1.23	-	-	-	-

Mortality

A total of 7,333 subjects died during the period of observation. The mortality rate was stratified by exposure to non-ASA NSAIDs. The relationship is graphed and presented in figure 7. Overall, there appears to be an inverse relationship between non-ASA NSAID exposure and mortality.

Logistic regression analysis confirmed this relationship. For every additional 30 MDDE of non-ASA NSAID exposure, the crude odds ratio for mortality was 0.92 (95% CI: 0.91 - 0.93). Adjusting for ASA exposure, age, sex, diabetes mellitus, evidence of smoking, and hypercholesterolemia changed the odds ratio by less than 0.02.

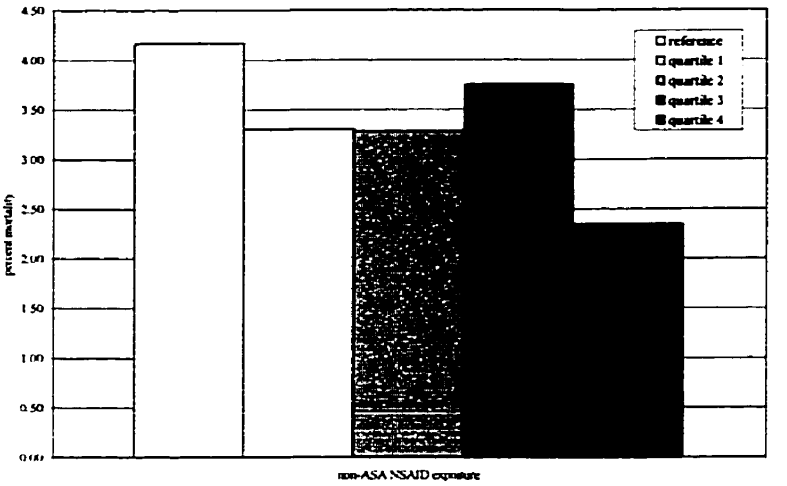

Figure 7. Mortality for study population for each level of exposure to non-ASA NSAIDs.

Discussion

Demographics

Alberta Health provided data describing prescription drug use, physician services, hospitalizations, and mortality on Albertans aged 65 and older who received a benefit under the ABC-DP. The ABC database was the primary database to which the Physician Services, Hospitalization, and Registration databases were linked using anonymous unique identification codes.

The age distribution of the subjects was consistent with the direct relationship between age and mortality. Females accounted for 56% of the study population which is consistent with census data.

Approximately 75% of those aged 65 years and older were present in the ABC database. There was no data that described the remaining quarter of the elderly population in any of

the databases. It is important to note that the inclusion of 192,866 out of an estimated population of 266,905 elderly subjects was not due to random selection. Subjects included into the analysis must have been reimbursed under the ABC-DP. Therefore, they were diagnosed with at least one condition that required medical therapy. This is significant when considering the makeup of the reference group used in the analyses.

The reference group consisted of those in the ABC database who were not prescribed a non-ASA NSAID. By definition, those included in this group must have been treated for other conditions. Conversely, those not treated for other conditions could not be included in the reference group. This is in contrast to the NSAID exposed groups where those not treated for other conditions could be included. Because inclusion into the reference group depends on the presence of other medically treatable disease whereas inclusion into the NSAID exposed groups was not conditional upon the presence of medically treatable disease, there is a potential for selection bias to influence the analyses.

The direction and magnitude of the effect of any selection bias owing to the inclusion criteria depends on the relative frequency of diseases of interest among those not included in the analysis and those of the reference group included in the analysis. If those not included in the ABC database are indeed healthier than those in the reference group, then the reference group will have had a higher frequency of non-ASA medication use and disease than those not exposed to NSAIDs in general. Moreover, comparisons to those exposed to NSAIDs will have been biased toward the null hypothesis. Another manifestation of this selection bias is the J-curve phenomenon. Inspection of the figures 3 and 4 revealed linear trends among those exposed to non-ASA NSAIDs that were not

extended to the reference group.

The above consideration of selection bias assumes that those not included in the analysis were healthier than those included in the reference group. While this seems to be a logical conclusion from the criteria used to include subjects, it may be useful to consider the likely populations of subjects that were not included in more detail. Three populations may be hypothesized.

First, individuals who did not receive a prescription during the observation period would be excluded. This population would consist of persons who did not require medication, those who had clinically occult conditions or in whom a diagnosis had not been made (e.g. hypercholesterolemia or hypertension), and those with clinically apparent disease who did not visit a physician. Overall, this population of patients is likely to have been relatively healthy and independent.

Second, it is possible that some individuals may have received and filled a prescription for medication covered under the plan for but did not claim any benefits. This population may have include those covered by alternative insurance plans of wealthy individuals who declined enrollment into the ABC-DP. The relative health of those that filled a prescription but did not claim a benefit is speculative. It is known that socioeconomic status correlates with health. Therefore, it can be hypothesized that this population is also relatively healthy.

The third group of seniors excluded from the study are those who were institutionalized during the study period. Medications dispensed within chronic care facilities are covered

under the hospital pharmacy budgets rather than the Alberta Blue Cross Drug Benefit Plan. Persons residing in a chronic care facility are more likely to have a significant burden of physical or psychological disease than their peers. According to a Government of Alberta publication, there were 13,522 long-term care beds in the province as of March 31, 1997.[82] This did not include assisted living facilities where medications would be reimbursed under the Alberta Blue Cross Drug Benefit Plan. This represents 5.1% of the 1996 census population or only 24% of those not included in this study.

The criteria used to include subjects into the study, a consideration of the characteristics of those not included, and the emergence of J-curves provides evidence of a selection bias toward the null hypothesis and provides a rationale for the use of restricted analyses.

NSAID Utilization

Number of Prescriptions

The number of prescriptions (reimbursements) for non-ASA NSAIDs is summed for the study population. Because the number of prescriptions provided to the subjects is insensitive to the actual quantity of medication prescribed, this analysis was done mainly to compare our results with those obtained by others. Non-ASA NSAIDs were frequently prescribed to the study population. Over 228,000 prescriptions for a non-ASA NSAID was claimed over the 1 year under study. Using Alberta Blue Cross data covering a 6 month period ending June 30, 1991 Hogan found that 109,591 prescriptions were received by the same population. After indexing this result to the observation period (109,591 * 2 half-years = 219,182) and considering growth of the population, the findings were comparable to the 1991 results.

Number of Agents per Subject

Most of those receiving a prescription for a non-ASA NSAID used 1 or 2 different agents over the study period. There are a number of reasons why patients may substitute one non-ASA NSAID for another. Lack of efficacy, adverse effect, changing to a less expensive agent, withdrawal of a medication by the manufacturer, and publication of comparative literature are medically valid reasons for changing therapies. Other potential reasons include patients visiting multiple physicians with different prescribing habits, failing to document previously used medications and effects, and prescribing more than one non-ASA NSAID concurrently.

Of concern are the 1,925 instances where multiple non-ASA NSAIDs were prescribed on the same day. It is recommended that the concurrent use of non-ASA NSAIDs be avoided owing to an increased frequency of adverse effects without an increase in efficacy.[83]

Cost and Quantity

Alberta seniors used a significant quantity of non-ASA NSAIDs over the year of observation. Over 5.5 million maximum daily dose equivalents were reimbursed with an associated cost of $7 million. Except for diuretics, non-ASA NSAIDs were prescribed in greater MDDE than other cardiovascular classes of medication. ASA accounted for 3.3 million MDDE during the study period. The large quantity of non-ASA NSAIDs prescribed to this most likely relates to the high prevalence of conditions for which non-ASA NSAIDs are usually prescribed. As expected, there was a strong relationship between non-ASA NSAID prescription and the prevalence of degenerative and

inflammatory conditions.

Determinants of Use

It is worthwhile to consider factors that influence non-ASA NSAID use. Severity of symptoms, patient preferences, and the physician's estimate of expected benefit and risk of complication are likely to influence prescribing habits. Another factor that will influence the strength of the relationship between the degenerative musculoskeletal disease and NSAID prescription is the availability of data showing efficacy of other treatments. For example, it was only within the last 6 years that a randomized clinical trial showed acetaminophen to be as effective as ibuprofen in the treatment of mild – moderate osteoarthritis.[45] In contrast to opinion of the last century, exercise was also shown in randomized clinical trials to be beneficial in osteoarthritis.[44,84] New therapies such as intrasynovial lubricants and glucosamine / chondroitin preparations are showing promise.[85,86] Lastly, joint replacement surgery is an established therapy for advanced degenerative disease of hips and knees.

Eighteen different NSAIDs were identified in the database of which ASA was most commonly prescribed. Of the non-ASA NSAIDs diclofenac was most commonly prescribed to the subjects. Ketoprofen and naproxen were the next commonly prescribed agents accounting for less than half the MDDE and reimbursement costs. The remaining agents were used less frequently including an agent that was reimbursed to as few as 100 subjects.

The question arises as to the evidence available in support of individual non-ASA

NSAIDs. A review of the literature does not indicate that one non-ASA NSAID is more efficacious than others.[87] There is some literature that demonstrates differential frequencies of a limited number of adverse events.[88] The American College of Rheumatology echoes these conclusions in a recent consensus statement.[89] Therefore, the differential frequency with which some non-ASA NSAIDs are prescribed cannot be attributable to evidence of efficacy or safety. If there is little difference in clinical effect between agents, cost would normally be the next consideration in the selection agent. The cost per MDDE for each agent is presented in table 2. There is no evidence that the less expensive agents were used more frequently by the study populations. Therefore, the choice of agent must depend on factors other than knowledge of clinical evidence or cost. Physician perceptions of efficacy, frequency and severity of adverse effects, patient preferences, tradition, and effect of pharmaceutical marketing strategies are possible reasons that explain the variation in use of non-ASA NSAIDs in this study.

One such example where physician perception may have been more influential than scientific evidence is the case of phenylbutazone induced agranulocytosis. Although prescribing data was not readily available, this agent appears to have been popular enough to be included in randomized controlled trials in the 1970's. Case reports of phenylbutazone induced agranulocytosis has appeared intermittently in the medical literature as early as 1965 and this agent is now one of the most infrequently used NSAIDs. However, epidemiological literature published in 1986 estimated the actual risk of agranulocytosis. Not only was the risk of agranulocytosis found to be very low at about 1 per million weeks of exposure, the risk was found to be the same for butazones

and the most commonly used agent in Alberta, diclofenac.[90]

Another example where the medical evidence appears to play a secondary role in prescribing habits is the use of indomethacin in the management of acute gouty arthritis. A Medline search from 1966 to present using the terms indomethacin and gout found only 4 publications where indomethacin was compared to another NSAID in a randomized clinical trial. In none of the trials was indomethacin found to be superior to the alternative arm.[91,92,93,94] Despite the lack of efficacy data indomethacin has been cited as drug of choice in major medical texts.

It is difficult to estimate the effect of pharmaceutical marketing practices on prescribing habits. It is interesting to note that the most commonly used agent was marketed as a compound containing 200 micrograms of misoprostol, an agent demonstrated to have efficacy in the prevention of NSAID induced gastropathy.[95] No other agents were marketed in this manner.

In summary, there was wide variation in frequency of use among the non-ASA NSAIDs. There is little scientific evidence that supports the use of one agent over another and the most commonly used agents were not the least expensive. Therefore, physicians appear to be selecting non-ASA NSAIDs based on reasons other than medical evidence or cost.

Non-ASA NSAIDs and Cardiovascular Medication Use

The association between use of non-ASA NSAIDs and selected cardiovascular medications was measured using two statistical methodologies. A traditional epidemiological approach uses contingency tables. This methodology allows for the

calculation of odds ratios for outcomes based on exposure or non-exposure status. The results from this analyses were statistically significant for most of the cardiovascular medications. However, the odds ratio for the association of any non-ASA NSAID exposure and any cardiovascular medication utilization were usually close to the null hypothesis and the clinical significance of these values are doubtful. The odds ratio for agents used to treat peripheral vascular disease was highest among the contingency table analysis. This positive association does not provide evidence that non-ASA NSAIDs protect against NSAIDs. Instead this association may simply reflect the use of non-ASA NSAIDs as analgesics in the setting of arterial insufficiency.

Two factors may have biased these results toward the null hypothesis. First is the selection bias described in the demographics section. Unlike those receiving non-ASA NSAIDs, everyone in the reference group must have received non-NSAID medications to be included in the database. Therefore, the reference group was more likely to have received cardiovascular medications based on selection and any differences attributable to non-ASA NSAID exposure would be minimized.

Secondly, dichotomizing exposure resulted in the grouping together of those subjects with trivial non-ASA NSAID exposures with those who had maximal exposure to these agents. Previous research has shown that the initiation of an antihypertensive agent among those exposed to non-ASA NSAIDs is exposure dependent.[66] In this study, the first quartile of exposure to non-ASA NSAIDs was 15 days and the median exposure was 40 days. These are relatively short periods of time for new cardiovascular medications to be prescribed. Therefore, it was judged that this statistical methodology is likely to have

underestimated the magnitude the associations under consideration.

The second methodology used in this study utilized linear regression analysis. This technique offers a number of advantages over contingency tables. These include the utilization of continuous variables and the ability to consider co-variables without generating multiple stratified odds ratios. Also, coefficients associated with the variables are more intuitive than odds ratios.

Linear regression analysis of the association between non-ASA NSAID use and cardiovascular medication use revealed a small but clinically significant association between non-ASA NSAIDs and diuretics. For each month of non-ASA NSAID exposure an additional 2.5 days of diuretic therapy was prescribed. Adjusting for age, gender, ASA use or the presence of risk factors for cardiovascular disease was associated with no appreciable effect upon the diuretic prescription. Although previous research had found an association between non-ASA NSAID use and the initiation of agents used to treat hypertension, the results were not stratified by the hypertensive class of anti-hypertensive agent.[66]

The finding of an association from cross sectional data does not confirm causal relationships. However, three possibilities are possible from the diuretic association. First, is the possibility that diuretic use may precipitate non-ASA NSAID prescription. Although diuretics may cause muscle cramps infrequently, most physicians would not be inclined to prescribe a non-ASA NSAID for this adverse effect. The second possibility is that of the scientific hypothesis. Exposure to non-ASA NSAIDs causes conditions for

which diuretics are commonly prescribed. Pulmonary edema, peripheral edema, and hypertension would be likely candidates based previous epidemiological research. Additional evidence comes from reviews of physiological data that shows increased salt and water retention occurs from non-ASA NSAID exposure.[96] Lastly, it is possible that a third factor may cause an increase in both non-ASA NSAID prescription and diuretic prescription. For example, visiting a physician may be an independent risk factor for receiving any prescription. This possibility may be addressed by examining the relationship between non-ASA NSAID use and the use of a unrelated agent such as an antibiotic. In this study, there was no relationship found for the prescription of cephalexin.

The associations found between non-ASA NSAID exposure and the prescription of other cardiovascular agents were very small. The large sample size provided sufficient power to detect an association if it was present. However, statistical power cannot compensate for any selection bias that was present in the study. If such a bias was present as discussed in the demographics section, then clinically meaningful associations may have been missed.

Misclassification bias may have played a role in the analysis of medication use. Although reimbursement for medication under the drug plan is conditional upon prescription and purchase, it does not ensure that the medication was actually consumed. Moreover, ASA and ibuprofen are available over the counter and such purchases may not have been included in the database. Data entry error is another potential source of misclassification. However, studies from other Canadian medication databases have

shown accuracy and validity. A review of Quebec's prescription claims database found the frequency of out of range or missing data to range from 0 to 0.4% of the data fields under consideration.[97] The Drug Programs Information Network in Manitoba also has been found to be valid although it was noted that aboriginal and social assistance recipients were under represented.[98]

It is worthwhile to note that exposure to ASA did not affect any of the associations under consideration to any appreciable extent. At least one physiological study of patients with pulmonary artery catheters in place demonstrated that ASA neutralized the beneficial effects of angiotensin converting enzyme inhibitors.[99] Our data did not demonstrate that ACE inhibitor prescription increased among non-ASA NSAID users.

In summary, of the cardiovascular medications under consideration there was a clinically significant association found between non-ASA NSAID and diuretic prescription. The most plausible explanation for this relationship is that non-ASA NSAIDs cause conditions for which physicians prescribe diuretic therapy.

Non-ASA NSAID Use and Visits to Physicians

The association between non-ASA NSAID and selected cardiovascular conditions was assessed using data generated from ambulatory care visits. Clinically and statistically significant results were noted for edema only. The addition of ASA exposure, age, gender, cardiovascular risk profile or use of cardiovascular medications to the model did not have any appreciable effect upon this relationship. While the odds ratio reported (1.07) may appear close to the null value (1.00), it should be noted that this is the odds

ratio for each additional 30 days of non-ASA NSAID exposure. Therefore, 6 months of non-ASA NSAID exposure would be associated with an odds ratio of 1.50 for developing edema. This finding is compatible with an association between non-ASA NSAID use and diuretic prescription.

A J-curve effect was noted for hypertension and congestive heart failure. This effect may have accounted for a the failure to detect any association between non-ASA NSAID use and these conditions. As discussed in the demographic section, the J-curve may be a marker for selection bias specific to the reference group. Because of the large size of the reference group (64%) of the study population, the bias may have been large.

Another source of bias may have been misclassification of disease status by physicians. Alberta physicians submit diagnostic data to the provincial health department as part of the information required for billing Medicare for services rendered. Although physicians are encouraged to be accurate and comprehensive, there were no processes in place to ensure that diagnostic codes reflect the clinical situation during the period of observation. Therefore, an incorrect diagnostic code could be entered because of physician misdiagnosis, variable interpretation of ICD-9 codes by physicians or their billing staff, or clerical error. Moreover, the number of diagnostic codes that a physician may submit for an ambulatory care visit is limited to three which precludes the ability of physicians to provide a complete patient profile even if the physicians wished to do so for there own purposes. Any misclassification of disease status is likely to be non-differential and as such, the bias would be toward the null hypothesis.

The usefulness of using administrative databases has been the subject of numerous articles. The American College of Physicians has published a thorough review of the use of large databases.[100] Briefly, administrative databases offer numerous advantages including their relatively low cost, ability to obtain population based numbers of subjects, potential for linkage with other data sources, and ability to obtain anonymous data thereby avoiding the need for individual informed consent. Disadvantages include the inability to retrieve missing data, inability to improve the precision of the data collected (e.g. linking medication prescription to indication or obtaining details of actual prescribed doses), limitations in the scope of the data collected (e.g. only problems severe enough to bring to the attention of the physician are included) and difficulty in accessing the validity of information collected for other purposes other than research.

The issue of validity is particularly problematic. While missing data fields or linkage difficulties can be quantified or described, users of administrative databases may not be able to assess the validity of the data collected by others. Most of the articles regarding the validity of administrative data consider Medicare and Medicaid hospital discharges. These will be discussed in the next section.

A Medline Search from 1966 to present combining the words - billing and codes - and administrative and databases found only two studies that considered the validity of diagnostic codes submitted by physicians in ambulatory care settings. For example, a study of dermatologist visits in the United States found a 43% overlap of 10 clinical diagnoses among the 8 ICD-9 CM codes that could have been used.[101] A study which compared chart data and billing codes for 20 communicable diseases at the University of

Arizona found 33% of the billing codes to be inaccurate.[102] There were no published articles from Canadian sources.

With respect to our data assessing the validity by reviewing the patient record cannot be carried out, as the data is anonymous. However, some comparisons can be made. For example, the prevalence of the cardiovascular conditions under consideration generally agreed with reports from Statistics Canada.[49] Hypertension was the most prevalent disorder followed by coronary artery disease and congestive heart failure. Cerebrovascular disease, peripheral vascular disease and edema were the least prevalent of the conditions under consideration.

Although 38% of study population received at least one non-ASA NSAID only 19% of the population had degenerative or inflammatory conditions of the musculoskeletal system as defined in Appendix 2. However, this difference is likely due to subjects receiving non-ASA NSAIDs for control of pain associated with other conditions such as neoplasia, headache, trauma, or neuralgia. It was reassuring to see that the J-curve effect was not present when the indications for non-ASA NSAIDs was graphed to non-ASA NSAID exposure.

In summary, of the ambulatory visit data an association was seen only for non-ASA NSAID exposure and edema. The association between non-ASA NSAID use and other cardiovascular conditions were not clinically significant. There may have been biases that prevented certain relationships from being detected.

Non-ASA NSAID Use and Hospitalization

The association between non-ASA NSAID exposure and hospitalization for selected conditions was assessed using hospital separation data. Because these conditions were acute relative to those studied for ambulatory care visits, it was possible to use case control methodology to assess for a relationship between cases and exposures. This type of analysis provides ancillary evidence for a cause and effect relationship, which is an advantage over cross sectional techniques.

Exposure to non-ASA NSAIDs was shown to be a risk factor for hospitalization for congestive heart failure. Adjusting for exposure to ASA, cardiovascular medication, demographic variables and risk factors for cardiovascular disease did not significantly change the magnitude of this association. Although the absolute value of the odds ratio was small, it should be noted that the period of exposure used for this analysis was 90 days. This may explain why the magnitude of the association was larger in a pharmacoepidemiological study from the Netherlands where the period of observation was 7 years.

In most cases there is a direct relationship between the period of risk factor exposure and frequency of disease. The length of time required for non-ASA NSAIDs to become relevant from an etiological perspective is not known. It required less than 24 hours for a study to demonstrate that ASA attenuated the beneficial hemodynamic effects of captopril.[71] This period of time is consistent with the pharmacokinetics of ASA. If non-ASA NSAIDs contribute to salt and water retention by inhibiting renal prostaglandin synthesis, then it is likely that changes to renal hemodynamics also occur within hours to

days of exposure. All persons exposed to non-ASA NSAIDs did not develop congestive heart failure. Therefore, it could be proposed that patients vary with respect to the sensitivity they have to the effects of this agent. If this is the case, there may be no minimum period of exposure required to non-ASA NSAIDs to be a relevant risk factor.

Co-exposure of the subjects to ASA and non-ASA NSAIDs did not influence the risk of developing congestive heart failure in this analysis. This has not been reported elsewhere. A priori, there was evidence to support the hypothesis that ASA is both a risk and protective factor for congestive heart failure among users of non-ASA NSAIDs. That ASA may aggravate hypertension and counter the beneficial hemodynamic effects of captopril supports the possibility that this agent would have increased the risk of congestive heart failure. Alternatively, ASA is known to prevent myocardial infarction, which is a major risk factor for congestive heart failure. In this sense, ASA could be protective against congestive heart failure. Irrespective of the underlying dynamics, this analysis does not suggest that physicians need be particularly concerned about the cardiovascular effects of ASA and non-ASA NSAID prescription.

The relationships between non-ASA NSAID exposure and stroke, thromboembolic disease, and acute myocardial infarction were not statistically significant. It is possible that selection or non-differential misclassification biased the results toward the null hypothesis. Selection bias in this data has been discussed in previous sections. Misclassification of disease status may have occurred for a number of reasons. Health records personnel based on their interpretation of the medical record enter diagnosis codes. Therefore, an additional interpretation occurs when compared to codes submitted

directly by physicians. Another problem can occur when diagnoses are not confirmed. Therapies such as bed-rest or the administration of oxygen are non-specific. Symptoms caused by congestive heart failure, myocardial infarction, or even stroke can be alleviated with these measures. It is possible for physicians to incorrectly attribute symptoms to infection, dementia, or pulmonary disease and observe improvements in clinical status owing to non-specific therapies. This is particularly true in the elderly where presentations are often atypical.[103]

The validity of hospital derived diagnostic data has been a significant issue for the Medicare program in the United States. Under that program a determinant of hospital reimbursement was the diagnosis-related groups. Studies done for audit purposes found that 15% – 20% of diagnosis codes contained errors of which often magnified the severity of illness which would translate into fiscal benefit for the hospitals.[104] The Canadian experience appears to be similar according to a review authored by the Institute for Clinical Evaluative Sciences.[105] Reabstraction studies have been done for Ontario and Newfoundland hospital data, which showed the primary diagnosis and primary procedure codes to be accurate in 88% and 74% of charts respectively. In a study where cardiologists reviewed the charts of those coded for myocardial infarction in an Ontario academic center. It was found that only 20.6% of subjects did not meet the World Health Organization Criteria for this diagnosis. In general, secondary diagnoses and procedures are coded with less reproducibility.

In summary, non-ASA NSAID exposure was found to be a risk factor for the development of congestive heart failure. Co-prescription of ASA did not influence this

relationship. Associations between non-ASA NSAID exposure was not found for myocardial infarction, stroke or thromboembolic disease although bias toward the null hypothesis may have occurred.

Non-ASA NSAID Use and Mortality

The association of non-ASA NSAID exposure and mortality was assessed using cross sectional methodology. The results showed a small but clinically and statistically significant mortality benefit from each additional month of non-ASA NSAID use. The magnitude of mortality reduction did not change if ASA co-prescription, age, sex, and risks for cardiovascular disease (smoking, diabetes, or hypercholesterolemia) were considered in the model. This finding has not been reported elsewhere. Although the adverse effects of non-ASA NSAIDs are emphasized in the medical literature, the finding of an overall mortality benefit is not entirely unexpected.

It is possible to speculate on how non-ASA NSAIDs may protect against mortality. Given that adverse effects are known, for non-ASA NSAIDs to provide a net benefit, they must have an impact on the most common causes of death which are cardiovascular disease and cancer.

The data in support of a cardiovascular benefit is not compelling at this point. This analysis showed an increase in admission for congestive heart failure among those using non-ASA NSAIDs and the protective effect of non-ASA NSAIDs on myocardial infarction did not achieve statistical significance. However, biases in the data tended to be toward the null hypothesis and protection against ischemic heart disease may have

been underestimated. In support of a protective effect of non-ASA NSAIDs is a large body of research that considers the atherosclerotic plaque to be dynamic with a significant inflammatory component. Similar research into dementia also considers the possibility that low levels of vascular inflammation may be contributive. Therefore, the possibility that non-ASA NSAIDs may have a net beneficial effect on cardiovascular disease cannot be excluded at this point.

Cancer is the second leading cause of death in Canada. Studies have documented reduction in incident cancer among users of aspirin and non-ASA NSAIDs. A study of 12,668 adults who were followed for an average of 12.4 years found that users of ASA had incidence rate ratios of 0.68 (95% CI: 0.49 – 0.95) for lung cancer, 0.35 (95% CI: 0.17 – 0.73) for colorectal cancer in men, and 0.70 (0.50 – 0.96) for breast cancer in women.[106] A smaller case-control trial of 147 cases of colorectal adenoma found that both ASA and non-ASA NSAID use were associated with a relative risk of 0.49 (95% CI: 0.3 – 0.8).[107]

Confounding may also explain the low mortality rate associated with non-ASA NSAIDs. For example, it is possible that the prescription of non-ASA NSAIDs is associated with relatively good health (lack of frailty) and that good health is responsible for low mortality. The analysis did consider the effects of age, gender, and risk factors for cardiovascular disease such as diabetes, evidence of smoking, and hypercholesterolemia. None of these factors changed the relationship between non-ASA NSAID use and mortality which makes confounding on these variables unlikely.

Another explanation may relate to the unavoidable situation where death precludes risk factor exposure. The cross-sectional methodology compared total (12 month) non-ASA NSAID exposure between the deceased and survivor groups. Deaths are distributed throughout the year. Therefore, survivors would be expected to have more exposure to non-ASA NSAIDs or any other risk factor under consideration relative to the deceased.

Conclusions

This study evaluated the association of non-ASA NSAID use and the use of cardiovascular medications and frequencies of selected cardiovascular conditions in elderly persons. The utilization of this class of medication was also described. It was found that non-ASA NSAID prescription was associated with an increased diuretic use, an increase in the prevalence of edema, and increase in incidence of congestive heart failure. Associations between non-ASA NSAIDs and other medications and conditions were either not clinically relevant or statistically significant. Non-ASA NSAIDs account for a large volume of prescriptions to the elderly and its associated with a significant cost to the ABC-DP. There appears to be no relationship between the use of particular agents and medical efficacy, frequency of adverse effects, or cost as reported in the scientific literature.

Appendix 1

Medications of interest and applicable maximum daily dose (MDD).

Medication Class	Medication Name	MDD (mg)
ACE inhibitors	benazepril	40
	captopril	150
	cilazapril	10
	enalapril	40
	fosinopril	40
	lisinopril	40
	quinapril	40
	ramipril	20
Beta receptor antagonists	acebutolol	800
	atenolol	100
	labetalol	800
	metoprolol	400
	nadolol	240
	oxprenolol	480
	pindolol	45
	propranolol	320
	timolol	60
Calcium channel blockers	amlodipine	10
	diltiazem	360
	felodipine	20
	nicardipine	120
	nifedipine (PA)	80
	nifedipine (other)	120
	verapamil	480
Digoxin	digoxin	0.25
Diuretics	amiloride	20
	bendroflumethiazide	20
	chlorothiazide	2000
	chlorthalidone	100
	ethacrynic acid	100
	furosemide	80
	hydrochlorothiazide	100
	indapamide	2.5
	methyclothiazide	5
	metolazone	10

	spironolactone	200
	triamterene	300
Hypoglycemics	acetohexamide	
	chlorpropamide	
	gliclazide	
	glyburide	
	insulin	
	metformin	
	tolbutamide	
Other antihypertensives	clonidine	1.2
	hydralazine	200
	methyldopa	3000
	minoxidil	40
	prazosin	20
	reserpine	0.25
	terazosine	20
	yohimbine	18
Cephalexin	cephalexin	4000
Anti-hyperlipidemics	cholestyramine resin	
	clofibrate	
	colestipol	
	fenofibrate	
	fluvastatin	
	gemfibrozil	
	lovastatin	
	pravastatin	
	probucol	
	simvastatin	
	xanthinol niacinate	
Non-ASA NSAIDs	diclofenac sodium	150
	diflunisal	1000
	fenoprofen	3000
	floctafenine	1200
	flurbiprofen	300
	ibuprofen	1200
	indomethacin	200
	ketoprofen	200
	ketorolac	40
	mefenamic acid	1000
	naproxen	1000

	phenylbutazone	400
	piroxicam	20
	sulindac	400
	tenoxicam	20
	tiaprofenic acid	600
	tolmetin	1600
Nitrates	isosorbide dinitrate	
	nitroglycerin	
	nitroglycerin disc	
	nitroglycerin oral	
	nitroglycerin paste	
	nitroglycerin sl	
	pentaerythritol tetranitrate	
Agents for peripheral vascular disease		
	cyclandelate	
	isoxsuprine	
	pentoxifylline	
	tolazoline	
Anti-platelet agent	acetylsalicylic acid	1300
Vitamin K antagonists	acenocoumarol	
	warfarin	
Nicotine replacement	nicotine	

Appendix 2

ICD-9 CM codes for conditions of interest, selected cardiovascular risk factors and indications for NSAID therapy.

Section I: Conditions of Interest

Acute myocardial infarction

410 Acute myocardial infarction
410.0 Acute myocardial infarction of anterolateral wall
410.1 Acute myocardial infarction of other anterior wall
410.2 Acute myocardial infarction of inferolateral wall
410.3 Acute myocardial infarction of inferoposterior wall
410.4 Acute myocardial infarction of other inferior wall
410.5 Acute myocardial infarction of other lateral wall
410.6 True posterior wall infarction
410.7 Subendocardial infarction
410.8 Acute myocardial infarction of other specified sites
410.9 Acute myocardial infarction of unspecified site
411.0 Postmyocardial infarction syndrome

Coronary artery disease

411 Other acute & subacute forms of ischemic heart disease
411.1 Intermediate coronary syndrome
411.8 Other acute & subacute forms of ischemic heart disease
412 Old myocardial infarction
413 Angina pectoris
413.0 Angina decubitus
413.1 Prinzmetal angina
413.9 Other & unspecified angina pectoris
414 Other forms of chronic ischemic heart disease
414.0 Coronary atherosclerosis
414.1 Aneurysm of heart
414.8 Other specified forms of chronic ischemic heart disease
414.9 Chronic ischemic heart disease, unspecified

Congestive heart failure

276.6 Fluid overload disorder
428 Heart failure
428.0 Congestive heart failure
428.1 Left heart failure
428.9 Heart failure, unspecified

Cerebrovascular disease

- 431 Intracerebral hemorrhage
- 433 Occlusion & stenosis of precerebral arteries
- 433.0 Occlusion & stenosis of basilar artery
- 433.1 Occlusion & stenosis of carotid artery
- 433.2 Occlusion & stenosis of vertebral artery
- 433.3 Occlusion & stenosis of multiple & bilateral precerebral arteries
- 433.8 Occlusion & stenosis of other specified precerebral artery
- 433.9 Occlusion & stenosis of unspecified precerebral artery
- 434 Occlusion of cerebral arteries
- 434.0 Cerebral thrombosis
- 434.1 Cerebral embolism
- 434.9 Cerebral artery occlusion, unspecified
- 435 Transient cerebral ischemia
- 435.0 Basilar artery syndrome
- 435.1 Vertebral artery syndrome
- 435.8 Other specified transient cerebral ischemias
- 435.9 Unspecified transient cerebral ischemia
- 436 Acute, but ill-defined, cerebrovascular disease
- 437 Other & ill-defined cerebrovascular disease
- 437.0 Cerebral atherosclerosis
- 437.1 Other generalized ischemic cerebrovascular disease

Hypertension

- 401 Essential hypertension
- 401.0 Malignant essential hypertension
- 401.1 Benign essential hypertension
- 401.9 Unspecified essential hypertension
- 402 Hypertensive heart disease
- 402.0 Malignant hypertensive heart disease
- 402.1 Benign hypertensive heart disease
- 402.9 Unspecified hypertensive heart disease
- 403 Hypertensive renal disease
- 403.0 Malignant hypertensive renal disease
- 403.1 Benign hypertensive renal disease
- 403.9 Unspecified hypertensive renal disease
- 404 Hypertensive heart & renal disease
- 404.0 Malignant hypertensive heart & renal disease
- 404.1 Benign hypertensive heart & renal disease
- 404.9 Unspecified hypertensive heart & renal disease
- 405 Secondary hypertension
- 405.0 Malignant secondary hypertension
- 405.1 Benign secondary hypertension

405.9 Unspecified secondary hypertension
437.2 Hypertensive encephalopathy
796.2 Elevated blood pressure reading without diagnosis of hypertension

Peripheral vascular disease
440 Atherosclerosis
440.0 Atherosclerosis of aorta
440.1 Atherosclerosis of renal artery
440.2 Atherosclerosis of arteries of the extremities
440.8 Atherosclerosis of other specified arteries
440.9 Generalized & unspecified atherosclerosis
441 Aortic aneurysm
441.0 Dissecting aneurysm [any part]
441.1 Thoracic aneurysm, ruptured
441.2 Thoracic aneurysm without mention of rupture
441.3 Abdominal aneurysm, ruptured
441.4 Abdominal aneurysm without mention of rupture
441.5 Aortic aneurysm of unspecified site, ruptured
441.9 Aortic aneurysm of unspecified site without mention of rupture
442 Other aneurysm
442.0 Aneurysm of artery of upper extremity
442.1 Aneurysm of renal artery
442.2 Aneurysm of iliac artery
442.3 Aneurysm of artery of lower extremity
442.8 Aneurysm of other specified artery
442.9 Aneurysm of unspecified site

Thromboembolic disease
415.1 Pulmonary embolism & infarction
451.1 Phlebitis & thrombophlebitis of deep vessels of lower extremities

Section II: Selected Risk Factors for Cardiovascular Disease

Chronic renal failure
585 Chronic renal failure
587 Renal sclerosis, unspecified
589.1 Bilateral small kidneys

Diabetes mellitus
250 Diabetes mellitus
250.0 Diabetes mellitus without mention of complication
250.1 Diabetes with ketoacidosis
250.2 Diabetes with hyperosmolar coma

250.3 Diabetes with other coma
250.4 Diabetes with renal manifestations
250.5 Diabetes with ophthalmic manifestations
250.6 Diabetes with neurological manifestations
250.7 Diabetes with peripheral circulatory disorders
250.8 Diabetes with other specified manifestations
250.9 Diabetes with unspecified complication
251.3 Postsurgical hypoinsulinemia
362.0 Diabetic retinopathy

Hyperlipidemia

272.0 Pure hypercholesterolemia
272.2 Mixed hyperlipidemia

Smoker

305.1 Tobacco use disorder
491 Chronic bronchitis
491.0 Simple chronic bronchitis
491.1 Mucopurulent chronic bronchitis
491.2 Obstructive chronic bronchitis
491.8 Other chronic bronchitis
491.9 Unspecified chronic bronchitis
492 Emphysema
492.0 Emphysematous bleb
493.2 Chronic obstructive asthma (with obstructive pulmonary disease)
496 Chronic airway obstruction, not elsewhere classified

Section III. Selected Indications for NSAID Therapy

710.0 Systemic lupus erythematosus
712.0 Crystal arthropathies
712.1 Chondrocalcinosis due to dicalcium phosphate crystals
712.2 Chondrocalcinosis due to pyrophosphate crystals
712.3 Chondrocalcinosis, cause unspecified
712.8 Other specified crystal arthropathies
712.9 Unspecified crystal arthropathy
714 Rheumatoid arthritis & other inflammatory polyarthropathies
714.0 Rheumatoid arthritis
714.1 Feltys syndrome
714.2 Other rheumatoid arthritis with visceral or systemic involvement
714.4 Chronic postrheumatic arthropathy
714.8 Other specified inflammatory polyarthropathies
714.9 Unspecified inflammatory polyarthropathy

715 Osteoarthrosis & allied disorders
715.0 Osteoarthrosis, generalized
715.1 Osteoarthrosis, localized, primary
715.2 Osteoarthrosis, localized, secondary
715.3 Osteoarthrosis, localized, not specified whether primary or secondary
715.8 Osteoarthrosis involving or more than one site, not generalized
715.9 Osteoarthrosis, unspecified whether generalized or localized
720 Ankylosing spondylitis & other inflammatory spondylopathies
720.0 Ankylosing spondylitis
720.1 Spinal enthesopathy
720.2 Sacroiliitis, not elsewhere classified
720.8 Other inflammatory spondylopathies
720.9 Unspecified inflammatory spondylopathy
721 Spondylosis & allied disorders
721.0 Cervical spondylosis without myelopathy
721.1 Cervical spondylosis with myelopathy
721.2 Thoracic spondylosis without myelopathy
721.3 Lumbosacral spondylosis without myelopathy
721.4 Thoracic or lumbar spondylosis with myelopathy
721.5 Kissing spine
721.6 Ankylosing vertebral hyperostosis
721.7 Traumatic spondylopathy
721.8 Other allied disorders of spine
721.9 Spondylosis of unspecified site
722 Intervertebral disc disorders
722.0 Displacement of cervical intervertebral disc without myelopathy
722.1 Displacement of thoracic or lumbar intervertebral disc without myelopathy
722.2 Displacement of intervertebral disc, site unspecified, without myelopathy
722.4 Degeneration of cervical intervertebral disc
722.5 Degeneration of thoracic or lumbar intervertebral disc
722.6 Degeneration of intervertebral disc, site unspecified
722.7 Intervertebral disc disorder with myelopathy
722.8 Postlaminectomy syndrome
722.9 Other & unspecified disc disorder
723.0 Spinal stenosis in cervical region
724.0 Spinal stenosis, other than cervical

References

[1] Moncada S, Vane JR. Pharmacology and endogenous roles of prostaglandin endoperoxides, thromboxane A2, and prostacyclin. Pharmacol Rev 1978;30:293-331.

[2] Popma JJ, Weitz J, Bittl JA, Ohman EM, Kuntz RE, Lansky AJ, King SB 3rd. Antithrombotic therapy in patients undergoing coronary angioplasty. Chest 1998;114 Suppl 5:728S-741S.

[3] Matchar DB, McCrory DC, Barnett HJ, Feussner JR. Medical treatment for stroke prevention [published erratum appears in Ann Intern Med 1994;121:470 and 1995;122:885]. Ann Intern Med 1994;121:41-53.

[4] Hogan DB, Campbell NR, Crutcher R, Jennett P, MacLeod N. Prescription of nonsteroidal anti-inflammatory drugs for elderly people in Alberta. CMAJ 1994;151:315-322.

[5] Shearn MA. Non-steroidal anti-inflammatory agents; nonopiate analgesics; drugs used in gout. In: Katzung BG, editor. Basic and Clinical Pharmacology, Third Ed. Los Altos: Appleton & Lange; 1987. p. 401-4.

[6] Carson JL, Willett LR. Toxicity of nonsteroidal anti-inflammatory drugs. An overview of the epidemiological evidence. Drugs 1993;46 Suppl 1:243-8.

[7] Tannenbaum H, Davis P, Russell AS. Atkinson MH, Maksymowych W, Huang SH, et al. An evidence-based approach to prescribing NSAIDs in musculoskeletal disease: a Canadian consensus. CMAJ 1996;155:77-88.

[8] Hobson M. Medications in older patients. West J Med 1992;157:539-43.

[9] Haught WH, Mansour M, Rothlein R, Kishimoto TK, Mainolfi EA, Hendricks JB, et al. Alterations in circulating intercellular adhesion molecule-1 and L-selectin: further evidence for chronic inflammation in ischemic heart disease. Am Heart J 1996;132:1-8.

[10] DeGraba TJ. Expression of inflammatory mediators and adhesion molecules in human atherosclerotic plaque. Neurology 1997;49 Suppl 4:S15-9.

[11] Shah PK. Pathophysiology of plaque rupture and the concept of plaque stabilization. Cardiol Clin 1996;14:17-29.

[12] Abdelmouttaleb I, Danchin N, Ilardo C, Aimone-Gastin I, Angioi M, Lozniewski A, et al. C-Reactive protein and coronary artery disease: additional evidence of the implication of an inflammatory process in acute coronary syndromes. Am Heart J 1999;137:346-51.

[13] Eriksson LO, Beermann B, Kallner M. Renal function and tubular transport effects of sulindac and naproxen in chronic heart failure. Clin Pharmacol Ther 1987;42:646-54.

[14] Vane JR, Botting RM. Mechanism of action of nonsteroidal anti-inflammatory drug. Am J Med 1998;104 Suppl 3A:2S-8S

[15] Masferrer JL, Zweifel BS, Manning PT, Hauser SD, Leahy KM, Smith WG, et al. Selective inhibition of inducible cyclooxygenase 2 in vivo is antiinflammatory and nonulcerogenic. Proc Natl Acad Sci USA 1994;91:3228-32.

[16] Bianchi Porro G, Caruso I, Petrillo M, Montrone F, Ardizzone S. A double-blind gastroscopic evaluation of the effects of etodolac and naproxen on the gastrointestinal mucosa of rheumatic patients. J Intern Med 1991;229:5-8.

[17] Robbins SL, Cotran RS, Kumar V. Pathologic basis of disease. 3rd ed. Toronto: W.B. Saunders Company; 1984. p. 55.

[18] Bayer Corporation Consumer Care Division. The Full Story. Available from: URL: http://www.bayerus.com/aspirin/index.html

[19] Massotti G, Galanti G, Poggesi L, Abbate R, Neri Serneri GG. Differential inhibition of prostacyclin production and platelet aggregation by aspirin. Lancet 1979;2(8154):1213-7.

[20] Alberta Blue Cross Drug Benefit Guide. Edmonton: Alberta Blue Cross; 1995.

[21] Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet 1988;2(8607):349-60.

[22] Cairns JA, Gent M, Singer J, Finnie KJ, Froggatt GM, Holder DA, et al. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. N Engl J Med 1985;313:1369-75.

[23] Lewis HD Jr, Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE 3d, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. N Engl J Med 1983;309:396-403.

[24] Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. N Engl J Med 1989;321:129-35.

[25] Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, et al. Randomised trial of prophylactic daily aspirin in British male doctors. BMJ 1988;296(6618):313-6.

[26] The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet 1997;349(9065):1569-81.

[27] CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet. 1997;349(9066):1641-9.

[28] Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration [published erratum appears in BMJ 1994;308:1540]. BMJ 1994;308:81-106.

[29] Laupacis A, Albers G, Dalen J, Dunn MI, Jacobson AK, Singer DE. Antithrombotic therapy in atrial fibrillation. Chest 1998;114 Suppl 5:579S-589S.

[30] Hess H, Mietaschk A, Deichsel G. Drug-induced inhibition of platelet function delays progression of peripheral occlusive arterial disease. A prospective double-blind arteriographically controlled trial. Lancet 1985;1(8426):415-9.

[31] Goldhaber SZ, Manson JE, Stampfer MJ, LaMotte F, Rosner B, Buring JE, et al. Low-dose aspirin and subsequent peripheral arterial surgery in the Physicians' Health Study. Lancet 1992;340(8812):143-5.

[32] A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348(9038):1329-39.

[33] Collaborative overview of randomised trials of antiplatelet therapy--III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. Antiplatelet Trialists' Collaboration. BMJ 1994;308(6923):235-46.

[34] Raskin JB, White RH, Jaszewski R, Korsten MA, Schubert TT, Fort JG. Misoprostol and ranitidine in the prevention of NSAID-induced ulcers: a prospective, double-blind, multicenter study. Am J Gastroenterol 1996;91:223-7.

[35] Lindsley CB. Uses of nonsteroidal anti-inflammatory drugs in pediatrics. Am J Dis Child 1993;147:229-36.

[36] Should We Be Using NSAIDs for the Treatment of Osteoarthritis and "Rheumatism"? Therapeutics Letter 1995;(4)

[37] Tannenbaum H, Davis P, Russell AS, Atkinson MH, Maksymowych W, Huang SH, et al. An evidence-based approach to prescribing NSAIDs in musculoskeletal disease: a Canadian consensus. CMAJ 1996;155:77-88.

[38] Nishihara KK, Furst DE. Aspirin and other nonsteroidal anti-inflammatory drugs. In: Pine JW, editor. Koopman: Arthritis and Allied Conditions, 13th ed. Baltimore: Williams & Wilkins; 1997. p. 611-54.

[39] Gillis MC, editor-in-chief. Compendium of Pharmaceuticals and Specialties, 34th ed. Ottawa: Canadian Pharmaceutical Association; 1999.

[40] Fries JF, Williams CA, Ramey D, Bloch DA. The relative toxicity of disease-modifying antirheumatic drugs. Arthritis Rheum 1993;36:297-306.

[41] Langman MJ, Weil J, Wainwright P, Lawson DH, Rawlins MD, Logan RF, et al. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs [published erratum appears in Lancet 1994;343(8908):1302]. Lancet 1994;343(8905):1075-8.

[42] Misra NP. A comparative study of flurbiprofen and piroxicam in osteoarthritis. J Postgrad Med 1992;38:164-6.

[43] Eversmeyer W, Poland M, DeLapp RE, Jensen CP. Safety experience with nabumetone versus diclofenac, naproxen, ibuprofen, and piroxicam in osteoarthritis and rheumatoid arthritis. Am J Med 1993;95 Suppl 2A:10S-18S.

[44] Kovar PA, Allegrante JP, MacKenzie CR, Peterson MG, Gutin B, Charlson ME. Supervised fitness walking in patients with osteoarthritis of the knee. Ann Intern Med 1992;116:529-34.

[45] Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. N Engl J Med 1991;325:87-91.

[46] Deal CL, Schnitzer TJ, Lipstein E, Seibold JR, Stevens RM, Levy MD, et al. Treatment of arthritis with topical capsaicin: a double-blind trial. Clin Ther 1991;13:383-95.

[47] Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group. J Rheumatol 1998;25:2203-12.

[48] Kephart G, Sketris I, Smith M, Maheu A, Brown M. Coprescribing of nonsteroidal anti-inflammatory drugs and cytoprotective and antiulcer drugs in Nova Scotia's senior population. Clin Ther 1995;17:1159-73.

[49] Births and deaths. Ottawa; Statistics Canada: May 1997. Catalogue No. 84-210-XIB.

[50] Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993;22 Suppl 4A:6A-13A.

[51] Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation 1993;88:107-15.

[52] Hulley SB, Furberg CD, Gurland B, McDonald R, Perry HM, Schnaper HW, et al. Systolic Hypertension in the Elderly Program (SHEP): antihypertensive efficacy of chlorthalidone. Am J Cardiol 1985;56:913-20.

[53] Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. Hypertension 1995;25:305-13.

[54] Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Arch Intern Med 1993;153:154-83.

[55] Goldberg RJ, Gore JM, Gurwitz JH, Alpert JS, Brady P, Strohsnitter W, et al. The impact of age on the incidence and prognosis of initial acute myocardial infarction: the Worcester Heart Attack Study. Am Heart J 1989;117:543-9.

[56] McCormick D, Gurwitz JH, Lessard D, Yarzebski J, Gore JM, Goldberg RJ. Use of aspirin, beta-blockers, and lipid-lowering medications before recurrent acute myocardial infarction: missed opportunities for prevention? Arch Intern Med 1999;159:561-7.

[57] Goroll AH. Evaluation of leg edema. In: Goroll AH, May LA, Mulley AG Jr, editors. Goroll: Primary Care Medicine, 3rd ed. Philadelphia: J.B. Lippincott Company; 1995. p. 105-6.

[58] Benvenuti F, Ferrucci L, Guralnik JM, Gangemi S, Baroni A. Foot pain and disability in older persons: an epidemiologic survey. J Am Geriatr Soc 1995;43:479-84.

[59] van Kraaij DJ, Jansen RW, de Gier JJ, Gribnau FW, Hoefnagels WH. Prescription patterns of diuretics in Dutch community-dwelling elderly patients. Br J Clin Pharmacol 1998;46:403-7.

[60] Whisnant JP, Wiebers DO, O'Fallon WM, Sicks JD, Frye RL. A population-based model of risk factors for ischemic stroke: Rochester, Minnesota. Neurology 1996;47:1420-8.

[61] Sacco RL. Pathogenesis, classification, and epidemiology of cerebrovascular disease. In: Rowland LP, editor. Rowland: Merritt's Textbook of Neurology, 9th ed. Baltimore; Williams & Wilkins: 1995. p. 227-43.

[62] Jackson MR, Clagett GP. Antithrombotic therapy in peripheral arterial occlusive disease. Chest 114 1998;Suppl 5:666S-682S.

[63] Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. Arch Intern Med 1993;153:477-84.

[64] Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 1994;121:289-300.

[65] Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical epidemiology. A basic science for clinical medicine. 2nd ed. Boston; Little, Brown and Company: 1991. p. 379-91.

[66] Gurwitz JH, Avorn J, Bohn RL, Glynn RJ, Monane M, Mogun H. Initiation of antihypertensive treatment during nonsteroidal anti-inflammatory drug therapy. JAMA 1994;272:781-6.

[67] Johnson AG. NSAIDs and blood pressure. Clinical importance for older patients. Drugs Aging 1998;12:17-27.

[68] Haynes RB, Lacourciere Y, Rabkin SW, Leenen FH, Logan AG, Wright N, et al. Report of the Canadian Hypertension Society Consensus Conference: 2. Diagnosis of hypertension in adults. CMAJ 1993;149:409-18.

[69] Hogan DB, Campbell NR, Jennett P, MacLeod N, Brant R. Increased use of cardiovascular medications in seniors prescribed non-ASA non-steroidal anti-inflammatory drugs. Clin Invest Med 1996;19:46-54.

[70] Muller FO, Middle MV, Schall R, Terblanche J, Hundt HK, Groenewoud G. An evaluation of the interaction of meloxicam with frusemide in patients with compensated chronic cardiac failure. Br J Clin Pharmacol 1997;44:393-8.

[71] Townend JN, Doran J, Lote CJ, Davies MK. Peripheral haemodynamic effects of inhibition of prostaglandin synthesis in congestive heart failure and interactions with captopril. Br Heart J 1995;73:434-41.

[72] Heerdink ER, Leufkens HG, Herings RM, Ottervanger JP, Stricker BH, Bakker A. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. Arch Intern Med 1998;158:1108-12.

[73] Blackwell E, Loughlin K, Dumler F, Smythe M. Nabumetone-associated interstitial nephritis. Pharmacotherapy 1995;15:669-72.

[74] Schooley RT, Wagley PF, Lietman PS. Edema associated with ibuprofen therapy. JAMA 1977;237:1716-7.

[75] Brochier ML. Evaluation of flurbiprofen for prevention of reinfarction and reocclusion after successful thrombolysis or angioplasty in acute myocardial infarction. The Flurbiprofen French Trial. Eur Heart J 1993;14:951-7.

[76] Nielsen HK, Husted SE, Krusell LR, Fasting H, Charles P, Hansen HH, et al. Anticoagulant therapy in deep venous thrombosis. A randomized controlled study. Thromb Res 1994;73:215-26.

[77] Kajanoja P, Forss M. Prevention of venous thrombosis by dipyridamole-naproxen and low-dose heparin in patients undergoing hysterectomy. Ann Clin Res 1981;13:392-5.

[78] The Nation: 1996 Census of Population. Ottawa; Statistics Canada: 1997 July. Catalogue No. 93F0021XDB96000.

[79] PASS: Power and sample size calculator [computer program]. Indiana (IN): Methodist Hospital of Indiana, Inc.; 1987.

[80] Pagano M, Gauvreau K. Principles of biostatistics. Belmont: Duxbury Press:1993. p. 35-58.

[81] Stata [computer program]. Version 5.0. College Station (TX) Stat Corporation; 1997.

[82] Health Care '97 A Guide to Health Care in Alberta. Edmonton: Alberta Health: 1997.

[83] Greene JM, Winickoff RN. Cost-conscious prescribing of nonsteroidal anti-inflammatory drugs for adults with arthritis. A review and suggestions. Arch Intern Med 1992;152:1995-2002.

[84] Ettinger WH Jr, Burns R, Messier SP, Applegate W, Rejeski WJ, Morgan T, et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The Fitness Arthritis and Seniors Trial (FAST). JAMA 1997;277:25-31.

[85] Wobig M, Dickhut A, Maier R, Vetter G. Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. Clin Ther 1998;20:410-23.

[86] Morreale P, Manopulo R, Galati M, Boccanera L, Saponati G, Bocchi L. Comparison of the antiinflammatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis. J Rheumatol 1996;23:1385-91.

[87] Furst DE. Are there differences among nonsteroidal antiinflammatory drugs? Comparing acetylated salicylates, nonacetylated salicylates, and nonacetylated nonsteroidal antiinflammatory drugs. Arthritis Rheum 1994;37:1-9.

[88] Henry D, Lim LL, Garcia Rodriguez LA, Perez Gutthann S, Carson JL, Griffin M, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. BMJ 1996;312:1563-6.

[89] Guidelines for the management of rheumatoid arthritis. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Arthritis Rheum 1996;39:713-22.

[90] Risks of agranulocytosis and aplastic anemia. A first report of their relation to drug use with special reference to analgesics. The International Agranulocytosis and Aplastic Anemia Study. JAMA 1986;256:1749-57.

[91] Shrestha M, Morgan DL, Moreden JM, Singh R, Nelson M, Hayes JE. Randomized double-blind comparison of the analgesic efficacy of intramuscular ketorolac and oral indomethacin in the treatment of acute gouty arthritis. Ann Emerg Med 1995;26:682-6.

[92] Altman RD, Honig S, Levin JM, Lightfoot RW. Ketoprofen versus indomethacin in patients with acute gouty arthritis: a multicenter, double blind comparative study. J Rheumatol 1988;15:1422-6.

[93] Eberl R, Dunky A. Meclofenamate sodium in the treatment of acute gout. Results of a double-blind study. Arzneimittelforschung 1983;33:641-3.

[94] Ruotsi A, Vainio U. Treatment of acute gouty arthritis with proquazone and indomethacin. A comparative, double-blind trial. Scand J Rheumatol 1978;(21):15-7.

[95] Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995;123:241-9.

[96] Clive DM, Stoff JS. Renal syndromes associated with nonsteroidal antiinflammatory drugs. N Engl J Med 1984;310:563-72.

[97] Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol 1995;48:999-1009.

[98] Kozyrskyj AL, Mustard CA. Validation of an electronic, population-based prescription database. Ann Pharmacother 1998;32:1152-7.

[99] Guazzi MD, Campodonico J, Celeste F, Guazzi M, Santambrogio G, Rossi M, et al. Antihypertensive efficacy of angiotensin converting enzyme inhibition and aspirin counteraction. Clin Pharmacol Ther 1998;63:79-86.

[100] Weinberger M, Laine C, editors. Measuring quality, outcomes, and cost of care using large databases. Perspectives from the sixth Regenstrief conference. Ann Int Med 1997;127:665-774.

[101] Shenefelt PD. Limits of ICD-9-CM code usefulness in epidemiological studies of contact and other types of dermatitis. Am J Contact Dermat 1998;9:176-8.

[102] Campos-Outcalt DE. Accuracy of ICD-9-CM codes in identifying reportable communicable diseases. Qual Assur Util Rev 1990;5:86-9.

[103] Chew WM, Birnbaumer DM. Evaluation of the elderly patient with weakness: an evidence based approach. Emerg Med Clin North Am 1999;17:265-78.

[104] Iezzoni LI. Assessing quality using administrative data. Ann Int Med 1997;127:666-674.

[105] Williams JI, Young W. Accuracy of Canadian health administrative databases. North York: ICES Publications; 1996. Publication # 96-03-WP.

[106] Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology 1994;5:138-46.

[107] Logan RF, Little J, Hawtin PG, Hardcastle JD. Effect of aspirin and non-steroidal anti-inflammatory drugs on colorectal adenomas: case-control study of subjects participating in the Nottingham faecal occult blood screening programme. BMJ 1993;307:285-9.