NOTE TO USERS

Non-Steroidal Anti-Inflammatory Drugs and the Risk of End Stage Renal Disease in Hypertensive Individuals

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ABSTRACT

Objective: To examine the association between non-steroidal anti-inflammatory drug (NSAID) use and end stage renal disease (ESRD) among hypertensive subjects.

Study Design: We conducted a nested case-control study within a cohort of 77,887 hypertensive adult subjects within the province of Saskatchewan, Canada.

Outcome: The primary outcome was ESRD, defined by chronic dialysis or renal transplantation.

Exposure: NSAID exposure was determined using prescription records, for various time windows up to 10 years preceding the onset of end stage renal disease.

Statistical Analysis: Rate ratios (RR) were estimated with 95% confidence intervals using conditional logistic regression, adjusting for potential confounding variables and stratified for effect modifiers.

Results: We identified 397 cases and 7,399 controls. In subjects followed for at least 10 years continuous NSAID use was observed in 20.8% of cases and 17.9% of controls (RR = 1.18, 95% CI 0.68 – 2.05). Additionally, neither early (RR = 1.10, 95% CI 0.50 – 2.41) nor late (RR = 0.81, 95% CI 0.32 – 2.04) NSAID exposure was associated with ESRD during this time period. Evaluation of other time windows (0 – 2 years, 2 – 5 years and 5 – 10 years) and NSAID dosing provided similar results. Results were not modified by loop diuretic and angiotensin converting enzyme inhibitor use.

Conclusion: Up to 10 years of non-steroidal anti-inflammatory drug use does not appear to influence the development of end stage renal disease. These results however may be influenced by unmeasured co-morbidities and confounding by "contra-indication".

ABRÉGÉ

Objectif : Cette étude a été menée afin d'examiner le lien entre l'usage d'agent anti-inflammatoires non-stéroidiens (NSAIDs) et l'insuffisance rénale terminale (ESRD).

Devis : Nous avons mené une étude cas témoin nichée dans une cohorte de 77,887 sujets adules souffrant d'hypertension, provenant de la province de Saskatchewan au Canada.

Évènement : L'évènement d'intérêt (outcome) primaire est l'insuffisance rénale terminale, définie grâce à l'utilisation de dialyse chronique ou à une greffe rénale.

Exposition : L'exposition aux NSAID a été déterminée à travers l'usage de registres de prescriptions, pour différentes fenêtres de temps jusqu'à 10 ans précédant le début de la et l'insuffisance rénale terminale.

Analyse statistique : Les ratios de taux (RR) ont été estimés, ainsi que leurs intervals de confiance à 95%, par régression logistique, en ajustant pour les variables de confusion potentielles et stratifiant pour les facteurs d'interaction.

Résultats : Nous avons identifié 397 cas et 7,399 témoins. Pour les sujets suivis pendant au moins 10 ans, l'utilisation continue de NSAID a été observée chez 20.8% des cas et 197.9% des témoins (RR=1.18, 95% CI 0.68-2.05). De plus, ni l'utilisation précoce (RR=1.10, 95% CI 0.50-2.41) ni tardive (RR=0.81, 95% CI 0.32-2.04) de NSAIDs a été associée avec l'insuffisance rénale terminale durant cette période. Ces résultats n'ont pas été modifiés par l'utilisation de diurétiques de l'anse ou d'inhibiteurs de l'enzyme de conversion de l'angiotensine. Des résultats similaires ont été obtenus lors de l'évaluation d'effet de dose.

Conclusion : L'utilisation jusqu'à 10 années de médicaments anti-inflammatoires non-stéroidiens n'apparaît pas avoir d'influence sur le développement de l'insuffisance rénale terminale. Cependant. Ces résultats pourraient être influencés par des facteurs de co-morbidités qui n'ont pas été mesurés ou par contre-indication.

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Introduction

Background:

End stage renal disease (ESRD) represents a chronic stage in which the kidney(s) are unable to adequately excrete the body's metabolic waste products and/or balance water and electrolytes. This can lead to uremia and eventually death unless removed by chronic dialysis or a kidney transplant. The development of ESRD thereby leads to a significant decrease in quality of life and is associated with an increase in mortality. Despite various therapies to prevent kidney failure, ESRD is increasing (1). Identification of novel therapies for kidney disease, or conversely avoidance of injurious exposures to the kidneys, is therefore an important goal. Epidemiologic studies of renal failure are complicated by several methodological obstacles including difficulty in disease definition, the relative rarity of disease, its chronicity, and multiple risk factors that interplay in its development and perpetuation (2). The evidence of association between non-steroidal anti-inflammatory drugs (NSAIDs) and renal failure is one particular example. NSAID use is common, its acute renal toxicities are well-known and there is substantial physiologic knowledge of its renal effects. No large-scale clinical or epidemiologic study however has accurately defined an association between NSAIDs and ESRD in high risk individuals. The overall purpose of this study is therefore to evaluate the extent to which NSAID exposure modifies the risk of developing end stage renal disease in a cohort of hypertensive individuals.

Definition of End Stage Renal Disease:

End-stage renal disease (ESRD) occurs when the kidneys are no longer able to excrete wastes, concentrate urine, and regulate electrolytes that are necessary for day to day life. It usually occurs as chronic renal failure progresses to the point where kidney function is less than 10% of baseline, at which point the accumulation of waste products and toxins lead to a variety of symptoms termed uremia. These symptoms can include malnutrition, nausea, general ill feeling and fatigue among many others. If treatment is not initiated in advanced states, coma

and death can result. The only treatment for ESRD is dialysis or kidney transplantation.

Epidemiology of End Stage Renal Disease:

In the United States, there are approximately 276,000 patients with ESRD requiring dialysis, and each year approximately 50,000 new cases arise (1). As well, both the incidence and prevalence of ESRD are increasing and it is expected that by the year 2010, the number of patients on renal replacement therapy will double; making kidney disease a major public health concern. These figures however do not fully represent the burden of kidney disease, as individuals with reduced renal function greatly outnumber incident and prevalent ESRD cases. A 1998 report from the Third National Health and Nutritional Examination Survey - NHANES III (3) conducted from 1988 to 1994 in the United States, estimated that 6.2 million individuals over age 12 years had reduced kidney function defined as a serum creatinine > 132 umol/L, whereas 2.5 million individuals had serum creatinine > 150 umol/L and 800,000 individuals had serum creatinine > 177 umol/L. Additionally, these figures may underestimate the true prevalence of renal disease as the survey did not control for age, gender, ethnicity or body weight; factors which affect the interpretation of serum creatinine measurement. For example, an elderly thin female may have a serum creatinine < 132 umol/L, yet have significantly reduced renal function and be misclassified with preserved kidney function.

Hypertension and End Stage Renal Disease:

Hypertension is a leading cause of end-stage renal disease (1) in both developed and developing countries. Although only a minority of patients with hypertension go on to develop renal insufficiency, both ESRD rates and disease progression in chronic renal failure are directly related to blood pressure control (4,5)

Physiologic Effects of Renal Failure:

The effect of kidney failure on public health care is substantial. Impaired renal function is associated with changes in virtually all organ systems; usually first manifested by elevated blood pressure and abnormalities in laboratory tests, followed by physical symptoms and signs. Among the most common are malnutrition, anemia, decreased physical stamina, bone disease, hypertension, neuropathy and accelerated cardiovascular disease, the major cause of mortality in patients with advanced renal failure or ESRD. Increased cardiovascular risk was emphasized in a 1998 report of the National Kidney Foundation task force on cardiovascular disease and chronic renal disease (6). Drawing on data from the United States Renal Data System (USRDS) and the National Center for Health Statistics (NCHS), the risk ratio of cardiovascular death adjusted for age, gender, ethnicity and presence of diabetes between individuals with ESRD and without, varies from 500:1 in individuals age 25 to 35, to 5:1 in individuals greater than 85 years of age. Patients with renal failure also have reduced physical function such as reduced endurance and muscle strength (3), and tend to suffer from lower employment rates, increased feelings of anxiety, decreased sense of well-being, greater depression and negative health perception (7-11).

Health Care Costs:

Costs attributable to ESRD totaled $10 billion in 1998 in the United States (12). With current trends in prevalence, it is estimated that the ESRD population will exceed 2 million patients by the year 2010, for an annual worldwide cost of 70 to 75 billion dollars (US$) for ESRD support. Unfortunately because of this expense, many countries are unable to provide treatment for ESRD or restrict services to individuals that can afford it.

Factors Influencing Renal Function:

The development of kidney failure follows a well defined, albeit highly variable course in most individuals. Early renal injury from a variety of causes can initiate maladaptive compensation mechanisms, such as renal hyperfiltration which leads

to further injury and a progressive decline in renal function. Disease type, as well as modifiable and non-modifiable risk factors, also influence the initial renal injury and rate of disease progression. In only a few forms of chronic renal disease can renal function be improved by specific therapies. Subsequently a greater emphasis is placed on the preservation of existing renal function, which serves to postpone or avoid renal replacement requirements. Non modifiable risk factors for kidney disease and development of end stage renal disease include ethnicity (African-American, Hispanic and Latino race), male gender, advanced age and previous episodes of renal injury. Modifiable risk factors include reduction of proteinuria, use of the ACE inhibitors or angiotension receptor blockers (ARBs), blood pressure lowering, glycemic control in diabetics and immunosuppressive therapy in inflammatory diseases of the kidney. Other interventions that have been studied but are inconclusive include dietary protein restriction, lipid lowering and correction of anemia. Finally, avoidance of volume depletion and potentially nephrotoxic substances such as radiocontrast material, aminoglycoside antibiotics and amphotericin B are also recommended as they can lead to acute renal injury and potentially cause a more rapid decline in renal function.

Non-Steroidal Anti-Inflammatory Drugs:

In the general public NSAIDs are used widely. They have acknowledged efficacy as non-addicting analgesics and reasonable safety in a wide range of clinical conditions. The majority of healthy subjects who ingest therapeutic doses of NSAIDs for limited duration, tolerate these medications without adverse effects and as such they are one of most frequently used drug classes worldwide. NSAIDs are consumed by more than 30 million people in the United States annually (13). Many physicians and nephrologists advocate avoidance of NSAIDs in patients with renal insufficiency, because of the risk of precipitating acute renal failure as well as concern that chronic NSAID usage could hasten chronic renal injury. It is unknown however whether chronic NSAID use is toxic

to the kidney, either through causing renal injury itself or accelerating the progression of renal failure in already diseased kidneys.

The mechanism of action of NSAIDs, and their inhibition of prostaglandin synthesis was first discovered in 1971 (14-15). Shortly thereafter renal effects of prostaglandin inhibition were described, in particularly the potential for acute renal failure (16-20). The association between NSAID use and chronic renal failure, although methodologically weak, was described in 1986 when Adams et al. reported 17 rheumatology patients with decreased renal function who were being treated with NSAIDs (21). Subsequent studies have drawn associations between NSAID use and renal papillary necrosis, however this latter condition is uncommonly seen in current clinical practice (22, 23).

While the biological effects of NSAIDs are well characterized over short time periods, particularly in acute renal failure, there are no scientifically acceptable data documenting the safety of these drugs on renal structure and function when taken chronically. The predominant physiologic effects of NSAID use relate to reduced prostaglandin synthesis from cyclo-oxygenase inhibition. Prostaglandins synthesized in the renal cortex regulate renal vascular resistance and blood flow. Their inhibition can lead to increased renal vascular resistance, decreased renal blood flow and decreased glomerular filtration rate. In the renal medulla, prostaglandins modulate salt and water handling, and their inhibition can lead to salt and water retention with secondary blood pressure elevation. In the stable, healthy individual baseline prostaglandin synthesis is typically very low and further inhibition of prostaglandin synthesis has minimal effects on renal physiology. Prostaglandin synthesis however, is up-regulated when there is impaired intrarenal hemodynamics, such as intravascular volume depletion, reduced cardiac output or intrinsic renal disease. In these circumstances prostaglandin inhibition can have profound hemodynamic effects, leading to acute renal failure and/or tubular injury from relative hypoperfusion.

There are several potential physiologic methods by which NSAIDs may injure the kidney. By altering intrarenal hemodynamics, NSAID's cause a reduction in renal perfusion and transglomerular filtration pressure, as well as increase salt and water retention with resultant blood pressure elevation. NSAID's can also cause interstitial nephritis from reactive arachidonic acid metabolites, papillary necrosis (analgesic nephropathy) or idiosyncratic reactions including minimal-change and membranous nephropathy. The latter two are usually reversible upon drug removal (24). As well, by altering renal blood flow NSAIDs are well known to precipitate acute renal failure in susceptible individuals. Individuals with pre-existing renal insufficiency appear to be most susceptible (25-29) however renal recovery is the norm with NSAID withdrawal.

Critical Appraisal of Previous NSAID Studies:

Epidemiological studies investigating NSAIDs and ESRD have included case series, case-control and cohort designs *(Appendix 1)*. Although results have varied between individual studies, several methodological concerns and variation between study populations can explain this discordance. The studies will be described according to their chronological appearance in the literature, with a summary of their limitations.

The first epidemiologic study concerning NSAIDs and chronic kidney disease was a case series in 1986 by Adams et al (21). The study reported renal dysfunction (defined as a serum creatinine above the upper limit of gender defined normal values) in 17 rheumatology patients chronically exposed to various NSAID preparations. Despite drug withdrawal 6 patients displayed persistent renal dysfunction, leading to the concern of NSAID induced kidney disease. As a case series, limited evidence is available to implicate NSAIDs and chronic kidney damage. Major concerns include the absence of a comparison group which makes risk ratios impossible to calculate, the time order of exposure and outcome is not ensured, and concurrent health issues are often present in

rheumatology patients which in and of themselves may lead to chronic kidney disease.

The second study, using a case-control design, found no association between ESRD and NSAID (Pyrazolones) use. Performed in 1990 by Morlans et al (30), the investigation examined prevalent hemodialysis patients from Barcelona and compared them to controls obtained from hospital and matched on age and gender. Exposure information was obtained by personal interview, with subjects blinded to the study hypothesis. Overall NSAID use was 15 of 340 cases and 13 of 673 controls (RR 2.16 , 95% CI 0.87 – 5.32). The study however was limited by power, as well as potential recall bias, selection bias, confounding by indication and unclear time-order sequence.

In 1991 Sandler et al (31) utilized a case-control design to examine NSAID use among individuals with and without renal dysfunction. Cases were obtained from hospitalization records where laboratory testing demonstrated a serum creatinine >130 umol/L. Controls were selected through telephone screening and the Health Care Financing Administration of persons eligible for Medicare matching on age, gender, race and region of residence. 503 of 709 potential cases and 477 of 717 potential controls were subsequently evaluated. Prior NSAID exposure was obtained by telephone interview. Neither the interviewers nor study subjects were blinded to the study hypothesis. The results demonstrated a 2 fold increase in the risk of chronic renal insufficiency with NSAID, and a 10 fold increase in men older than 65 years of age (95% CI 1.2 to 82.7). There was no associated risk in younger men or females. Several potential concerns will be addressed: 1) serum creatinine is an unreliable marker for renal dysfunction thereby leading to potential misclassification of cases and controls, 2) a large non-response rate was evident raising concerns over selection bias, 3) neither group was blinded to study hypothesis thereby leading to misclassification of exposure due to responder bias, 4) other confounders may not have been controlled, 5) potential for confounding by indication and 6) the absolute number of daily NSAID users in either the cases

or controls was small in for men ≥ 65 years (14 and 1 respectively) making the point estimates unstable.

A subsequent case series in 1994 by Sagasothy et al. (32) questioned individuals, admitted to various medical wards and clinics in Malaysia over an 11 year period, on their analgesic consumption. Individuals defined as heavy users (≥ 1 Kg of aspirin, phenazetin or paracetamol, or > 1000 NSAID capsules) had renal ultrasound studies to screen for papillary necrosis and serum creatinine measured to evaluate for renal dysfunction. A total of 69 individuals had radiographic evidence of renal papillary necrosis of which 38 (56%) were NSAID users either alone or in combination with other analgesics, an association previously known. Renal impairment however was present in 26 of the 38 patients (68.4%) with renal papillary necrosis. Although again suggesting a link between chronic NSAID use and renal dysfunction several issues were not addressed. First, a control population was not selected making analysis of prevalence ratios impossible between users and non-users of NSAIDs. Second, heavy users of NSAIDs may be more likely to have other health problems associated with kidney disease. Both of these factors may lead to individuals seeking medical attention more frequently, thereby increasing the apparent prevalence of kidney dysfunction among heavy NSAID users.

A case-control study published in the same year by Perneger et al (33) examined NSAID use among incident ESRD patients, and population based controls matched by geographic area and age. A total of 752 hemodialysis patients (of 978 eligible) and 361 controls (of 402 eligible) were studied. They reported an odds ratio of 8.8 (95% CI 1.1 – 71.8) of end stage renal disease with heavy NSAID use (5000 or more pills), however no appreciable risk increase was evident with other use. This ratio relied on 18 case patients and 2 control patients, thereby having an unstable point estimate. Additional limitations included the potential for recall bias - particularly as individuals were not blinded, as well as selection bias and residual confounding.

The most recent analysis of NSAID use and renal failure used a cohort of 11032 initially healthy men followed in the Physician's Health Study (34), and correlated analgesic exposure using self reported questionnaires to serum creatinine levels. Although limited by problems with recall, no association between analgesic use and renal function was noted. The adjusted risk for high NSAID consumers ($\geq$ 2500 NSAID pills between 1982 and 1997) and reduced creatinine clearance defined as less than 55 ml/min in 1997 was 1.01 (95% CI 0.73 – 1.41). The correlation between the submitted questionnaire and subsequent telephone interview assessment of NSAID consumption was only 0.46. This study also examined only relatively healthy individuals who had a low incidence of renal impairment. These findings may therefore not be applicable to higher risk individuals, particularly those with pre-existing renal failure.

In conclusion, the predominant concerns with methodology used by past studies have included difficulty in establishing the time order of NSAID exposure and renal outcomes, selection bias, potential for confounding by indication, and misclassification bias, particularly through personal recall of drug exposure.

Objectives:

The objective of the study was to evaluate whether NSAID use is associated with an increased risk of ESRD. More specific objectives were to examine NSAID use during time periods both near (i.e. 1 to 5 years) and distant (i.e. 5 to 10 years) to the development of end stage renal disease. The rational of this approach is based on the potential uncertainties of NSAIDs and renal injury. If chronic NSAID use leads to an initial renal injury, which is followed by progressive damage and ESRD (which may or may not be independent of subsequent NSAID exposure) one would expect increased rates of NSAID use among cases distant to ESRD development. Alternatively, if NSAID use influences the rate of renal damage in patients with pre-existing renal failure, one would expect increased rates of NSAID use among cases closer in time to ESRD development. There may of course be a combination of initial injury and accelerated damage from chronic NSAID exposure.

Methods

Overview of the Study Design:

A nested case control analysis of a cohort was used to evaluate the risk of end stage renal disease and NSAID use among patients with newly acquired hypertension. This design was chosen so that individuals would be matched on a characteristic (hypertension) strongly associated with the development of ESRD. Cohort members were recruited from the Health Insurance Databases of the province of Saskatchewan, using drug markers to identify patients with hypertension in the context of actual medical practice. Patients who were dispensed a first prescription for an antihypertensive drug between January 1st, 1980 and December 31st, 1986 were eligible for cohort entry.

Incident cases of end stage renal disease that occurred between cohort entry and follow-up, up to December 31, 1996, were identified. A risk set was created consisting of each case and all potential controls available at the time of case identification. Controls were matched to each case according to the following: date of cohort entry, age, gender and presence or absence of diabetes. Up to 20 controls were randomly chosen from each risk set. Conditional logistic regression was used to calculate crude and adjusted rate ratios for end stage renal disease and NSAID use. Effect modification between NSAID use and other pre selected covariates was also performed.

Sources of Data:

Information was obtained from the computerized databases of the Saskatchewan Health Branch. Although data is collected purely for administrative purposes, it also functions as an excellent source of data for pharmacoepidemiological research (33, 34). This organization is responsible for registering universally insured health-care services to approximately 95 percent of the 1.3 million inhabitants of this Canadian province. Registered Native Canadians, members of the Armed Forces and members of the Royal Canadian Mounted Police, who

together compromise 5 percent of the Saskatchewan population, are recipients of health insurance plans administered by the federal government and are therefore ineligible for provincial coverage. Of note, plan membership is not based on socioeconomic status. Since this is a universal health database it provides information regarding health status of the entire population (36, 37). The Saskatchewan Health Branch consists of several computerized databases, including the Health Insurance Registration file, the Outpatient Prescription Drug Services Branch database, and Hospital Services Branch database.

Overview of the Database:

The Canadian provinces of Saskatchewan has approximately 1 million residents, and is characterized by low annual immigration and emigration rates (<1%). The annual population in fact has remained relatively static since the early 1900s, and from the years 1970 to 2001 total population has only changed from 932,000 to 1,015,000 individuals (38). Of its inhabitants, more than 95 percent of these individuals are entitled to receive benefits through the Saskatchewan Health Branch (36). As a byproduct of providing these health services, the Saskatchewan Health Branch has been accumulating health-care information and computerized databases since 1970 for hospitalizations, 1971 for physician utilization records and 1974 for prescription drug use. This information includes drug prescription data, outpatient and hospital diagnoses, vital statistics, renal replacement therapy, a cancer registry, and services such as mental health, long-term care, children's dental care, and alcohol and drug abuse counseling (see appendix A for individual database information). Most of these databases can be linked by a unique patient identifier number. As a result, a complete and chronological patient profile of drug utilization, patient visits, and hospitalizations is available for all persons under the health plan. Accuracy and validity of the various Saskatchewan Health databases have been previously confirmed, and a series of checks on the completeness and validity of the data are performed routinely by the Saskatchewan Department of Health. The Saskatchewan Department of Health

also carries out random patient verification checks and random pharmacy audits of dispensed medication (37).

Health Insurance Registration File:

The health insurance registration file includes demographic data, such as name, address, sex, date of birth, date of death, social assistant status, as well as dates of effective coverage. This file is updated regularly and is therefore useful for providing valid demographic data. Residents of the province of Saskatchewan are entitled to receive benefits from the health-care system once they have established residency and have registered for a health services card. This card contains a nine digit identification number that is a lifetime number, uniquely identifying each resident. This unique identification number is used to code most health-care services and also serves to link to other health data files (36).

Outpatient Prescription Drug Services Branch Database:

This file includes outpatient prescriptions for all medications listed in the Saskatchewan drug formulary. The formulary is comprehensive and continuously updated. Over 90 percent of all outpatient prescription drugs in the province are contained within the prescription drug plan, representing over 2000 drug products. The addition of newer medications occurs on a regular basis subsequent to continuous review processes by expert committees. On a regular basis, a sample of paid claims is selected and set to the beneficiaries for confirmation that the service paid for had been provided and that all information on the claim was correct (36, 37). There have been changes in data collection over the way for the database. From 1975 to June 30, 1987, and from January 1, 1989 to present, information is collected on an individual basis. Information available for each prescription includes: beneficiaries unique identification number, the drug quantity, strength and dosage, as well as dispensing dates. Information from July 1st, 1987 to December 31st, 1988 is incomplete because consumer-submitted claims are compiled by family unit rather than on an individual basis (36, 37).

Hospital Services Branch Database:

This data file provides hospital discharge information for all beneficiaries, including primary and secondary discharge diagnoses, classified according to the International Classification of Diseases - 9th revision (ICD-9) codes (39), and dates of admission and discharge. Validity studies have shown excellent concordance (99%) between procedures documented in the Hospital Services Branch data file and medical charts. Similar concordance between diagnoses in the hospital file and those in medical charts (of acute myocardial infarction) was extremely high (97%). It is for this reason that the Saskatchewan databases have come to be recognized as a major resource in epidemiologic research. The possibility of outcome misclassification with regard to any of the primary outcomes in this study, namely chronic renal failure, dialysis and renal transplantation is extremely remote. Two of the three outcomes are major procedures while chronic renal failure is a chronic condition easily diagnosed with routine laboratory test. (35, 36, 40).

Ethical consideration:

Although information within the computerized databases of the Saskatchewan health is available for research purposes, strict patient confidentiality is maintained. All data is provided to the researchers in a non nominal basis. A Saskatchewan Health Cross Agency Study Committee must review all requests for data and must provide consent before the release of any information (36, 37). Guidelines for the use of these databases are available and explicitly detailed (37).

Definition of the Cohort:

Prescription codes from the Outpatient Prescription Drug Services Branch Database ***(Appendix 2)*** were used to identify subjects who first received antihypertensive drugs between the years 1980 and 1987, thereby forming a cohort of incident hypertensive cases receiving drug therapy. The first time use of antihypertensive drugs was confirmed by returning to 1978. Since hypertension is a chronic condition, generally requiring lifelong treatment, all subjects receiving three or more prescriptions for antihypertensive drug during one year were considered hypertensive. Individuals less than 18 years of age were identified through date of birth records and excluded.

Subjects were restricted from the cohort if at any time in the year following *time zero* they were dispensed a combination of prescriptions suggesting they were prescribed an antihypertensive for disorders other then hypertension. These combinations of medications ***(Appendix 3)*** and the disease associated with their use include:

1) Concomitant beta-blockers or calcium channel blockers and nitrates (Angina)

2) Concomitant beta-blockers and an anti-arrhythmic agent (Arrhythmia)

3) Concomitant beta-blockers and either antithyroid drugs or radioiodine (Hyperthyroidism)

4) Concomitant beta-blockers and either ergot preparations, sumatriptan or methysergide (migraine headache)

While these patients will be excluded from the primary analyses, secondary analyses will be carried out after stratifying by these indications so as to obtain information within some of these other domains.

Additionally prescription codes were used to identify individuals that received anti-rheumatic drugs at any time before the index date, as diseases such as systemic lupus erythematoses, rheumatoid arthritis, mixed connective tissue disease or scleroderma are associated with both NSAID use and renal disease, and may act as significant confounders ***(Appendix 4)***. Individuals were also excluded if less than 2 years of prescription drug information was available.

Definition of Case Patients:
The outcome is defined as ESRD. Events were identified between January 1st, 1980 and December 31st, 1996 in the discharge diagnoses of the hospital branch database using ICD-9 codes and physician related services. The index date indicates date of the event.

The outcome comprises renal failure requiring dialysis for greater than 6 weeks (ICD-9 code V56), renal transplantation (ICD-9 code V42.0) or death associated with any of these *(Appendix 5)*. The date of first dialysis or date of renal transplantation represents the index date. The requirement of dialysis for greater than 6 weeks was used to exclude individuals with transient renal failure, an event distinct from ESRD which can develop in association with NSAID use. Since ESRD is a chronic disease typically generating multiple physician visits/hospitalizations the possibility of misclassifying this outcome is extremely low.

Selection of Controls:
For each case, a risk set was formed including the case and all cohort members matched according to age, gender, presence or absence of diabetes mellitus and duration in cohort. A random sample of up to 20 controls were chosen for each case among the risk sets.

Controls were selected from the risk set at the time of each incident case, and matched according to:

1) Cohort entry (+/-3 months)
2) Age (+/- 2.5 years)
3) Gender
4) Diabetes (present or absent)

At the time of control selection, the subject was at risk for end stage renal disease, and up to 20 controls were selected for each case. The sampling strategy therefore allows a control to be included in multiple risk sets, as well as, allowing a case to be used as a control before the occurrence of an event. The date of matching was defined as the index data.

Drug Exposure:

The exposure of interest, NSAID use, was measured using computerized files from the Outpatient Prescription Drug Services Branch database. For each subject outpatient prescription drug data for NSAID prescriptions as well as other non-narcotic analgesics (aspirin and acetaminophen) were compiled from 1976, up to the study termination date for each member. Drug exposure was censored for periods between July 1, 1987 and Dec 31, 1988, when individual prescription records were not available. For NSAID use, drug dose was standardized between agents using a defined daily dose (DDD) conversion *(Appendix 6)* (41).

$$\text{Drug Dose} = \frac{\text{Drug Strength x Drug Quantity}}{\text{Defined Daily Dose}}$$

Drug utilization of NSAID, ASA and acetaminophen containing products were then divided into time windows preceding the index date (0 to 1 year, 1 to 2 years, 2 to 5 years, 5 to 10 years and greater than 10 years). This allowed examination of drug use and changing drug patterns over time. Subjects were classified as "Regular Users" of a particular analgesic if the were prescribed an average of 325 mg per week (DDD converted for NSAIDs) during the time window. Individuals

were classified as "Non Users" if they did not receive any prescriptions for the agent, or "Other Users" if they received NSAID prescriptions less than regular users.

Confounders and Effect Modifiers:

Based on prior studies, the following variables were identified as possible confounders or effect modifiers:

Patient Demographics:

Demographic characteristics identified included age at index data, gender and presence or absence of social assistance. These factors have been shown to be associated with ESRD and may additionally influence the prescribing practice of physicians.

Severity of Hypertension:

The requirement for multiple antihypertensive medications was used as a proxy for hypertension severity, as hypertension severity is a clear risk factor for ESRD. During the first year of cohort entry, patients were examined for different antihypertensive drug classes, dispensed on the same date. Patients were classified as having mild hypertension if they received only one class of antihypertensive drug prescription at a time, moderate hypertension if they received two antihypertensive drugs from different classes on the same day or severe hypertension, defined as greater than or equal to three drugs on the same date. Combination agents that contain 2 or antihypertensive medications were considered as a single drug.

Duration of Diabetes:

Duration of diabetes was calculated from the date of first prescription for an anti-hyperglycemic agent and index date. A dichotomous variable was created to indicate if subjects started antihyperglycemic medications less than 7.5 years (median value) or 7.5 years and more prior to the index data. For subjects

initiating therapy for diabetes prior to January 1st, 1976, there is the potential for underestimating diabetes duration as prescription drug information is unavailable prior to this date. A second variable was therefore created indicating the receipt of an anti-hyperglycemic agent during the first year of the database.

Type of Antihyperglycemic Therapy:

Three variables were created to indicate if subjects received insulin therapy only, oral hypoglycemic agents only, or both.

Type of Antihypertensive Therapy:

Individuals were considered to be exposed to a particular antihypertensive agent if they received 3 or more prescriptions for that class of anti-hypertensive agent during the follow up period.

Comorbidities:

Certain medications in the drug prescription database file can represent coexistence of other illnesses. All cohort members were therefore reviewed for such drug markers during the time between cohort entry and index data (Appendix 7). Individuals prescribed at least three agents during follow up were considered to be exposed. Physician diagnostic and hospital discharge codes were also reviewed for a diagnosis of peripheral vascular disease, heart failure, heart disease, stroke and arterial aneurysm (indicating vascular disease) during the same time period (Appendix 8). A single physician or hospital discharge diagnosis served to represent existence of the condition.

Social Economic Status:

Individuals were considered to be receiving social assistance if any drug prescription during the first year of cohort entry had a positive social assistance plan indicator.

Statistical Analysis:

All analyses were performed using SAS statistical software version 8.02 (SAS Institute Inc. Cary NC, USA). Odds ratios were used as an estimator of rate ratios. Both rate ratios and 95 percent confidence intervals were estimated using conditional logistic regression to account for matching. The outcome was ESRD as determined by physician procedure fees. Crude rate ratios were calculated for the risk of end stage renal disease with non-steroidal anti-inflammatory, as well as aspirin and acetaminophen drug use. For all calculations, no exposure to the drug class under study was used as the reference category. Univariate analysis of the association between each potential confounder and the risk of and stage renal disease was conducted, using the changing estimate method, and crude rate ratios were adjusted for covariates.

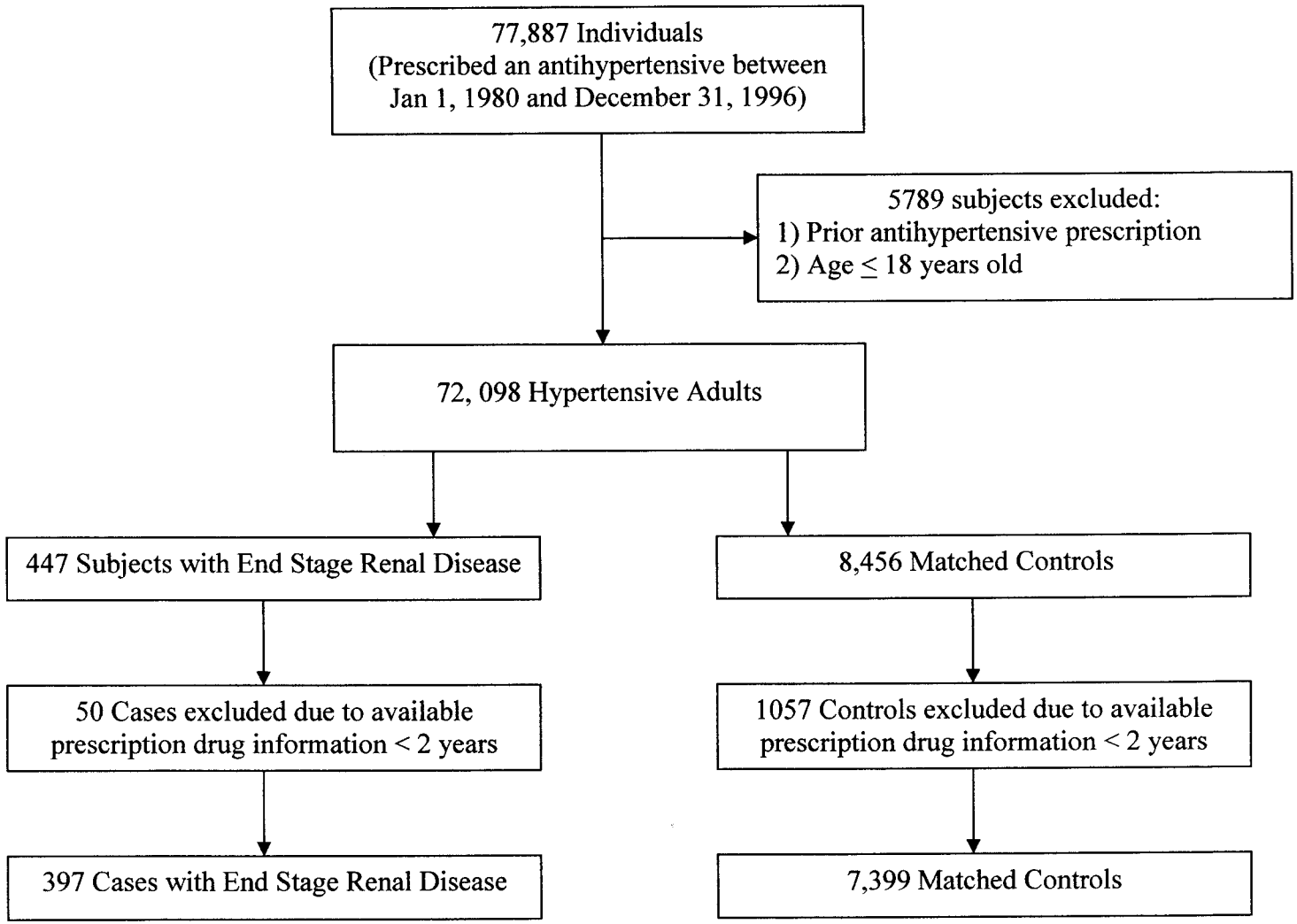
Multivariate models, adjusted for all potential confounding variables and effect modifiers were performed. The following confounders were included in the final model: socio-economic status indicator, type of antihypertensive exposure, type of antihyperglycemic therapy, duration of diabetes, other non-narcotic analgesic use and comorbidities. To determine whether covariates were a significant confounder, the changing estimate method (a $\geq$10 percent change in odds ratio estimates) was used. The following effect modifiers were considered in the analysis: loop diuretics, ACE inhibitors, diabetic therapy (insulin only, oral hypoglycemic agent only or both), aspirin, acetaminophen, and each of the matching variables (age, gender, calendar time of cohort entry).

Results

Selection of the Cohort:

The process of cohort selection is displayed in figure 1. Using the Saskatchewan Health Database 77,887 hypertensive patients were identified between January 1, 1980 and December 31, 1996. 5789 beneficiaries were excluded because they received an anti-hypertensive drug prescription in the 2 years prior to cohort entry or were less than 18 years of age at cohort entry. A total of 72,098 subjects with incident hypertension between January 1st, 1980 and December 31st, 1987 were therefore kept in the study cohort.

Figure 1. Cohort Selection



Descriptive Analysis of the Case Controls Set:

After cohort entry, 397 cases of end stage renal disease were identified between January 1st, 1980 and December 31st, 1996, and 397 risk sets formed. A random sample of up to 20 controls for each case were chosen and matched on the following variables: age, entry date into cohort, gender, and presence or absence of diabetes mellitus. For duration of diabetes, a dichotomous variable was created to indicate if pharmacologic therapy was begun more than 7.5 years prior to index date. As already described in the methods, precise information on prescriptions is unavailable for diabetic subjects that began therapy before January 1, 1976. A second variable was therefore created to indicate whether an anti-hyperglycemic agent was prescribed during the first year of the Outpatient Prescription Drug Services Branch database.

Table 1 and 2 provide demographic information, as well as comorbidities and anti-hypertensive therapy among cases and controls. As expected by the matching protocol, one sees a similar age and gender distribution, as well as duration of hypertension between cases and controls. Duration of drug information (not matched) was also similar between cases and controls. Mean age of cases and controls was 62.9 and 64.2 years respectively, with an age range of 22.8 - 86.6 and 19.4 - 87.3. The majority of individuals were male (63.5% of cases and 61.6% of controls), consistent with the higher prevalence of renal disease among males. Duration of hypertension prior to the index date averaged (mean) 6.1 years for cases and 6.2 years for controls, with a range up to 14.4 years for both.

Although individuals were matched according to the presence or absence of diabetes mellitus, a higher proportion of cases with ESRD utilized insulin only (17.9% versus 9.0%). This mirrors clinical findings where the incidence of type 1 diabetes mellitus (where insulin only serves as a proxy) is much lower then that of type 2, but the risk of kidney failure is more common. These rates often balance

each other so that a similar number of individuals with type 1 and 2 diabetes mellitus develop ESRD.

The prevalence of cardiovascular co-morbidities was high among both cases and controls. Using physician diagnostic codes peripheral vascular disease was present among cases in 10.3% of patients, heart disease in 35.8%, heart failure in 21.7%, arterial aneurysms in 4.0% and stroke in 5.5%. These were between 1.8 (stroke) and 4.8 (heart failure) times higher than controls. Although individuals with kidney disease tend to require multiple visits to physicians and as such be prone to detection bias, these findings are not unexpected. Individuals with kidney failure have much higher rates of cardiovascular disease and other co-morbidities than the general population, even when matched by age, gender and presence of hypertension. The increased use of anti-gout therapy among cases (16.1% versus 7.3% in controls) is an example where a condition (gout) is well known to be associated with renal dysfunction.

Each of the six classes of antihypertensive medication was used more frequently among cases then controls. It is not unusual to see multiple anti-hypertensive agents being used in patients with kidney disease, as renal disease often leads to difficult to control hypertension. The largest difference in drug use was seen in loop diuretics; used by 35% of cases but only 13.5% of controls. As renal function declines, there is a tendency to retain salt and water with subsequent development of edema. Other diuretics tend to lose their efficacy as renal failure develops, making loop diuretics the preferred agent. ACE inhibitors, which are often preferentially used in patients with kidney disease were used by 29.2% of cases compared to 14.3% of controls, while other anti-hypertensives (often 3rd line agents – see table 1 for listing) were used by 32.3% and 16.2% of individuals respectively.

NSAID use, standardized according to defined daily dose, as well as aspirin and acetaminophen exposures at various time intervals prior to the index date for

cases and controls is displayed in **table 3**. For all intervals (0 to 1, 1 to 2, 2 to 5 and 5 to 10 years), no significant difference existed in either the proportion of NSAID users or the distribution of NSAID dose dispensed between cases and controls. Between 5 and 10 years prior to index date 45.9% of cases and 42.9% of controls received no prescription for NSAID products. A cumulative dose of 500 to 1000 grams of NSAIDs was dispensed to 6% of cases and 5.3% of controls, while 2.73% of cases and 1.97% of controls received greater than 1000 grams during this period. Similar results are seen with ASA and acetaminophen prescriptions. For very high users defined as greater than or equal to 500 grams of drug consumption per year, no significant difference was evident for each time period.

Table 1. Distribution of Characteristics Among Cases and Controls

Characteristics	Cases, No. (%) (n=397)	Controls, No. (%) (n = 7399)
Age at index date, year		
<30	10 (2.5)	141 (1.9)
30 – 39	33 (8.3)	449 (6.1)
40 – 49	39 (9.8)	679 (9.2)
50 – 59	55 (13.9)	1006 (13.6)
60 – 69	95 (23.9)	1897 (25.6)
70 – 79	143 (36.0)	2851 (38.5)
≥80	22 (5.5)	376 (5.1)
Age (Years)		
Mean (+/- SD)	62.9 (14.6)	64.2 (13.6)
Range	22.8 – 86.6	19.4 – 87.3
Drug Duration (Years)		
Mean (+/- SD)	9.3 (4.2)	8.5 (3.9)
Range	2.1 – 19.8	2.0 – 20.9
Follow up (Years)		
Mean (+/- SD)	6.1 (3.7)	6.2 (3.7)
Range	0.01 – 14.4	0.0 – 14.4
Gender – Male	252 (63.5)	4556 (61.6)

Table 2. Distribution of Co-Morbidities and Anti-Hypertensive Therapy Among Cases and Controls

Characteristics	Cases, No. (%) (n=397)	Controls, No. (%) (n = 7399)	Crude RR[1]	Adjusted[2] RR (95% CI)
Anti-Diabetic Therapy				
Insulin only	71 (17.9)	669 (9.0)	8.86	6.94 (2.64 – 18.30)
Oral hypoglycemic only	19 (4.8)	408 (5.5)	1.38	1.23 (0.47 – 3.22)
Both	14 (3.51)	289 (3.9)	4.94	3.85 (1.20 – 12.39)
Cardiovascular Medication Use				
Lipid Lowering	30 (7.6)	389 (5.3)	1.48	1.17 (0.76 – 1.80)
Nitrates	61 (15.4)	1057 (14.3)	1.10	0.55 (0.38 – 0.78)
Diagnostic Codes				
Peripheral Vascular Disease	41 (10.3)	160 (2.2)	4.19	3.73 (2.44 – 5.70)
Heart Disease	142 (35.8)	1340 (18.1)	1.34	1.49 (1.03 – 2.14)
Heart Failure	86 (21.7)	336 (4.5)	4.78	3.10 (2.03 – 4.74)
Arterial Aneurysm	16 (4.0)	53 (0.7)	3.77	3.58 (1.78 – 7.18)
Stroke	22 (5.5)	228 (3.1)	1.20	1.00 (0.59 – 1.67)
Anti-HTN Medication Use				
Ace Inhibitor	116 (29.2)	1055 (14.3)	2.04	1.69 (1.27 – 2.23)
Beta Blocker	170 (42.8)	2775 (37.5)	1.40	1.45 (1.15 – 1.84)
Calcium Channel Blocker	121 (30.5)	1578 (21.3)	1.51	1.39 (1.06 – 1.83)
Diuretic	248 (62.5)	3964 (53.6)	1.50	1.37 (1.09 – 1.73)
Loop Diuretic	139 (35.0)	996 (13.5)	3.26	2.12 (1.61 – 2.79)
Other	129 (32.3)	1207 (16.2)	0.69	1.16 (0.45 – 3.03)
Medication Use				
Central Nervous System	123 (31.0)	2130 (28.8)	1.08	0.98 (0.77 – 1.26)
Anti-Parkinsonian	6 (1.5)	56 (0.8)	2.01	2.43 (0.97 – 6.12)
Inhaled Corticosteroids	39 (9.6)	450 (6.1)	1.83	1.65 (1.06 – 2.55)
Other Respiratory Agents	35 (8.8)	634 (8.6)	0.76	0.53 (0.34 – 0.82)
Anticonvulsant	14 (3.5)	226 (3.1)	1.04	0.89 (0.49 – 1.63)
Anti-Ulcer	90 (22.7)	1381 (18.7)	1.24	1.04 (0.79 – 1.38)
Anti-Gout	64 (16.1)	539 (7.3)	2.64	2.16 (1.56 – 2.98)

1. Adjusted for other covariates in category

2. Adjusted for other covariates in table

Table 3. NSAID, Aspirin and Acetaminophen use prior to index

	0 to 1 Year Prior to Index		1 to 2 Years Prior to Index	
	(Cases = 397)	(Controls = 7399)	(Cases = 397)	(Controls = 7399)
Nsaid				
No Use	302 (76.1)	5557 (75.1)	299 (75.3)	5462 (73.8)
<100 grams/year	63 (15.9)	1136 (15.4)	66 (16.6)	1165 (15.8)
100–200 grams/year	13 (3.3)	317 (4.3)	15 (3.8)	361 (4.9)
>200 grams/year	19 (4.8)	389 (5.3)	17 (4.3)	411 (5.6)
> 500 grams/year	2 (0.5)	34 (0.5)	3 (0.8)	45 (0.6)
Mean +/- SD of Users	115 +/- 137	119 +/- 134	116 +/- 169	123 +/- 137
Median (Range) of Users	60.0 (3.0 – 644.8)	64.0 (1.0 – 1020.0)	48.0 (5.0 – 957.7)	66.7 (2.3 – 822.9)
ASA				
No Use	353 (88.9)	6734 (91.0)	352 (88.7)	6688 (90.4)
<100 grams/year	28 (7.1)	371 (5.0)	28 (7.1)	394 (5.3)
100–200 grams/year	9 (2.3)	156 (2.1)	7 (1.8)	157 (2.1)
>200 grams/year	7 (1.7)	138 (1.9)	10 (2.5)	160 (2.2)
> 500 grams/year	0 (0)	31 (0.4)	1 (0.3)	33 (0.5)
Mean +/- SD of Users	106 +/- 112	142 +/- 169	126 +/- 157	148 +/- 168
Median (Range) of Users	77.4 (7.5 – 497.3)	88.4 (4.6 – 131.8)	66.3 (2.3 – 877.5)	88.4 (3.8 – 1040.0)
Acetaminophen				
No Use	354 (89.2)	6899 (93.2)	368 (92.7)	6853 (92.6)
<50 grams/year	42 (10.6)	454 (6.1)	27 (6.8)	494 (6.7)
50-100 grams/year	1 (0.3)	25 (0.3)	2 (0.5)	34 (0.5)
>100 grams/year	0 (0)	21 (0.3)	0 (0)	18 (0.24)
Mean +/- SD of Users	25 +/- 31	41 +/- 87	31 +/- 36	39 +/- 82
Median (Range) of Users	15.0 (3.6 – 180.0)	15.0 (2.4 – 1080.0)	15.0 (3.6 – 138.0)	14.9 (0.6 – 816.0)

	2 to 5 Years Prior to Index		5 to 10 Years Prior to Index	
	(Cases = 316)	(Controls = 5726)	(Cases = 183)	(Controls =2792)
Nsaid				
No Use	182 (57.6)	3123 (54.5)	84 (45.9)	1198 (42.9)
<100 grams/year	99 (31.3)	2006 (35.0)	64 (35.0)	1074 (38.5)
100–200 grams/year	13 (4.1)	301 (5.3)	11 (6.0)	149 (5.3)
>200 grams/year	22 (7.0)	296 (5.2)	5 (2.73)	55 (1.97)
> 500 grams/year	2 (0.6)	18 (0.3)	5 (2.7)	55 (2.0)
Mean +/- SD of Users	281 +/- 393	216 +/-313	329 +/- 534	251 +/- 413
Median (Range) of Users	101.0 (5.0 – 2402)	75.0 (25.0 – 2400)	105.0 (6.0 – 3916)	83.4 (2.7 – 4266)
ASA				
No Use	248 (78.5)	4657 (81.3)	132 (72.1)	2041 (73.1)
<100 grams/year	57 (18.0)	843 (14.8)	33 (18.0)	455 (16.3)
100–200 grams/year	6 (1.9)	120 (2.1)	3 (1.64)	44 (1.6)
>200 grams/year	5 (1.6)	106 (1.9)	1 (0.6)	13 (0.5)
> 500 grams/year	3 (1.0)	20 (0.4)	1 (0.6)	13 (0.5)
Mean +/- SD of Users	224 +/- 457	222 +/- 372	215 +/- 415	227 +/- 473
Median (Range) of Users	76.2 (7.5 – 2712)	78.0 (3.8 – 3452)	65.0 (2.3 – 2400)	65.0 (3.0 – 4583)
Acetaminophen				
No Use	256 (81.0)	4802 (83.9)	134 (73.2)	2092 (74.9)
<50 grams/year	58 (18.4)	894 (15.6)	32 (17.5)	390 (14.0)
50-100 grams/year	2 (0.6)	18 (0.3)	1 (0.6)	6 (0.2)
>100 grams/year	0 (0)	12 (0.2)	0 (0)	2 (0.1)
Mean +/- SD of Users	48 +/- 132	46 +/- 95	47 +/- 866	51 +/- 159
Median (Range) of Users	12.0 (3.6 – 512)	15.0 (2.4 – 1614)	12.0 (3.0 – 4272)	15.0 (0.9 – 2682)

Unadjusted Rate Ratios for NSAID use and ESRD:

Table 4 presents the results of the unadjusted analysis of NSAID use and ESRD for three time periods (within 2 years, 2 to 5 years and 5 to 10 years) divided between early and late exposure for each window. No exposure in the specified time window was used as the reference group. Regular use was defined as individuals receiving an averaged dose of at least 325 mg per week of any NSAID formulation during the respective time period. Individuals that received NSAID prescriptions but were not regular users were classified as irregular users. Rate ratios were adjusted for other use patterns (i.e. continuous, late, early, etc) but not potential confounders. Prescriptions for aspirin and acetaminophen were included and treated similarly.

For each time period, NSAIDs were not associated with ESRD regardless of use pattern. The unadjusted rate ratio for continuous use varied between 0.78 (95% CI 0.55 – 1.10) for the period 2 years prior to index date, up to 1.24 (95% CI 0.79 – 1.97) in the analysis 10 years prior to index date. Rate ratios for early, late and irregular use also crossed 1.0 for each of the time periods, suggesting no association between NSAID use and ESRD in an unadjusted analysis. Similar results were seen in individuals receiving aspirin. For individuals classified as continuous acetaminophen users in the 10 year analysis, the unadjusted rate ratio was 3.10. Increased risk was not seen in early, late or irregular acetaminophen use, suggesting a possible anomaly with multiple windows of exposure.

Table 4. Unadjusted Rate Ratio of Analgesic Use and End Stage Renal Disease Based on Time Period of Exposure

	NSAID		Aspirin		Acetaminophen	
Time Periods Prior to Index Date	Unadjusted Rate Ratio	95 % CI	Unadjusted Rate Ratio	95 % CI	Unadjusted Rate Ratio	95 % CI
0 to 1 and 1 to 2 years						
No Use	1.00	---	1.00	---	1.00	---
Continuous Use	0.78	0.55 – 1.1	0.99	0.61 – 1.62	1.34	0.58 – 3.11
Early Use	0.97	0.67 – 1.39	1.44	0.89 – 2.34	1.05	0.46 – 2.40
Late Use	1.22	0.85 – 1.74	1.34	0.79 – 2.26	2.23	1.21 – 4.12
Irregular Use	0.52	0.07 – 3.83	5.24	1.04 – 26.5	0.62	0.08 – 4.57
0 to 2 and 2 to 5 years						
No Use	1.00	---	1.00	---	1.00	---
Continuous Use	0.86	0.61 – 1.22	1.42	0.89 – 2.25	1.70	0.76 – 3.78
Early Use	0.99	0.66 – 1.50	0.97	0.58 – 1.61	0.28	0.04 – 2.05
Late Use	0.80	0.47 – 1.37	1.11	0.61 – 2.04	1.57	0.56 – 4.45
Irregular Use	1.17	0.62 – 2.21	1.25	0.29 – 5.36	0.96	0.44 – 2.11
0 to 5 and 5 to 10 years						
No Use	1.00	---	1.00	---	1.00	---
Continuous Use	1.24	0.79 – 1.97	1.29	0.68 – 2.42	3.10	1.04 – 9.25
Early Use	1.00	0.50 – 2.01	1.20	0.60 – 2.38	0.57	0.07 – 4.41
Late Use	0.60	0.26 – 1.39	1.73	0.96 – 3.09	1.01	0.13 – 7.71
Irregular Use	0.76	0.52 – 1.12	0.92	0.62 – 1.37	1.23	0.89 – 1.71

Regular use: Defined as an average exposure of ≥ 325 mg per week (dose adjusted) during the time window, **Continuous use:** Defined as regular use between both time windows prior to index, **Early use:** Defined as regular use during the earlier time window prior to index, **Late use:** Defined as regular use in later time window prior to index. **Irregular use:** Defined as "Other Exposure" not classified as above.

Predictors of ESRD:

Covariates were compared between cases and controls as shown in **Table 2**. For crude odds ratios, each variable was evaluated individually in the model.

As discussed in the descriptive analysis of cases and controls, individuals with diabetes mellitus treated with insulin only served as a predictor of ESRD despite diabetes being a matching variable. Using physician diagnostic codes, several cardiovascular markers including peripheral vascular disease (adjusted RR 3.73, 2.44 – 5.70), heart disease (adjusted RR 1.49, 1.03 – 2.14), heart failure (adjusted RR 3.10, 2.03 – 4.74) and arterial aneurysms (adjusted RR 3.58, 1.78 – 7.18) were associated with ESRD. Concerning exposure to specific anti-hypertensive agents, the odds ratio of each drug category use was increased among cases with the exception of other anti-hypertensive drug use. This ranged from a low of 1.37 for diuretics (95% CI 1.09 – 1.73) to a high of 2.12 for loop diuretics (95% CI 1.61 – 2.79). Other drug markers for associated conditions revealed a crude association between inhaled corticosteroids (adjusted RR 1.65, 95% CI 1.06 – 2.55) and anti-gout therapy (adjusted RR 2.16, 95% CI 1.56 – 2.98).

Assessment of Confounding:

Confounding was assessed by comparing the crude and adjusted rate ratio for the association between NSAID use and ESRD for each potential variable. If an adjusted rate ratio differed from the crude odds ratio by more than 10% than confounding was considered to be present. Two separate time windows, the period 0 to 2 and 2 to 5 years **(Table 6)** as well as the period 0 to 5 and 5 to 10 **(Table 7)**, were used for the analysis.

The only variable that changed by more than 10% in the up to 5 year analysis **(Table 7)** was the use of loop diuretics. The addition of this covariate decreased the rate ratio for continuous NSAID use from 0.86 to 0.75 and irregular use from 1.17 to 1.07. In the up to 10 year analysis **(Table 7)** the largest change between crude and adjusted rate ratio was again noted among individuals receiving loop diuretics, with continuous use changing from 1.19 to 1.02. Anti-ulcer and anti-gout therapy produced a change just under 10%. Both reduced the rate ratio of continuous use from 1.19 to 1.09.

Table 5. Distribution of Confounding Variables Among Controls (Up to 5 Years)

	No Use Reference (n = 2478)	Continuous Use (n = 908)	Early Use (n = 507)	Late Use (n = 330)	Other Use (n = 171)
Age at index date, year					
<30	57 (2.3)	6 (0.7)	4 (0.8)	2 (0.6)	4 (2.3)
30 – 39	168 (6.8)	21 (2.3)	18 (3.6)	20 (6.1)	19 (11.1)
40 – 49	200 (8.1)	57 (6.3)	31 (6.1)	23 (7.0)	20 (11.7)
50 – 59	312 (12.6)	123 (13.6)	57 (11.2)	41 (12.4)	24 (14.0)
60 – 69	587 (23.7)	256 (28.2)	156 (30.8)	82 (24.9)	41 (24.0)
70 – 79	1028 (41.5)	391 (43.1)	194 (38.3)	147 (44.6)	58 (33.9)
≥80	126 (5.1)	54 (6.0)	47 (9.3)	15 (4.55)	5 (2.9)
Gender – Male	1589 (64.1)	435 (47.9)	292 (57.6)	129 (39.1)	83 (51.5)
Anti-Diabetic Therapy					
Insulin only	266 (10.7)	104 (11.5)	52 (10.3)	43 (13.0)	15 (8.8)
Oral hypoglycemic only	149 (6.0)	68 (7.5)	35 (6.9)	28 (8.5)	9 (5.3)
Both	96 (3.9)	60 (6.6)	28 (5.5)	20 (6.1)	5 (2.9)
Cardiovascular Medication Use					
Lipid Lowering	150 (6.1)	62 (6.8)	30 (5.9)	24 (7.3)	14 (8.2)
Nitrates	367 (14.8)	151 (16.6)	102 (20.1)	64 (19.4)	21 (12.3)
Diagnostic Codes					
Peripheral Vascular Disease	58 (2.3)	20 (2.2)	12 (2.4)	6 (1.8)	4 (2.3)
Heart Disease	477 (19.3)	193 (21.3)	116 (22.9)	67 (20.3)	31 (18.1)
Heart Failure	117 (4.7)	60 (6.6)	34 (6.7)	20 (6.1)	8 (4.7)
Arterial Aneurysm	27 (1.1)	4 (0.44)	4 (0.8)	2 (0.6)	2 (1.2)
Stroke	87 (3.5)	39 (4.3)	19 (3.8)	15 (4.6)	7 (4.1)
Anti-HTN Medication Use					
Ace Inhibitor	429 (17.3)	172 (18.9)	82 (16.2)	53 (16.1)	31 (18.1)
Beta Blocker	969 (39.1)	339 (37.3)	192 (37.9)	131 (39.7)	67 (39.2)
Calcium Channel Blocker	568 (22.9)	225 (24.8)	136 (26.8)	77 (23.3)	38 (22.2)
Diuretic	1363 (55.0)	540 (59.5)	291 (57.4)	182 (55.2)	97 (56.7)
Loop Diuretic	293 (11.8)	211 (23.2)	82 (16.2)	50 (15.2)	29 (17.0)
Other	451 (18.2)	172 (18.9)	84 (16.6)	51 (15.5)	27 (15.8)

	No Use Reference (n = 2478)	Continuous Use (n = 908)	Early Use (n = 507)	Late Use (n = 330)	Other Use (n = 171)
Medication Use					
Central Nervous System	614 (24.8)	394 (43.4)	176 (34.7)	100 (30.3)	66 (38.6)
Anti-Parkinsonian	20 (0.8)	3 (0.3)	10 (2.0)	4 (1.2)	0 (0)
Inhaled Corticosteroids	141 (5.7)	95 (10.5)	42 (8.3)	16 (4.9)	12 (7.0)
Other Respiratory Agents	212 (8.6)	98 (10.8)	45 (8.9)	24 (7.3)	16 (9.4)
Anticonvulsant	76 (3.1)	38 (4.2)	22 (4.3)	9 (2.7)	4 (2.3)
Anti-Ulcer	353 (14.3)	319 (35.1)	138 (27.2)	81 (24.6)	54 (31.6)
Anti-Gout	155 (6.3)	110 (12.1)	48 (9.5)	22 (6.7)	15 (8.8)
ASA					
No Use	2045 (82.5)	589 (64.9)	352 (69.4)	229 (69.4)	133 (77.8)
Continuous Use	96 (3.9)	71 (7.8)	33 (6.5)	21 (6.4)	7 (4.1)
Early Use	93 (3.8)	92 (10.1)	58 (11.4)	19 (5.8)	9 (5.3)
Late Use	64 (2.6)	50 (5.5)	17 (3.4)	20 (6.1)	4 (2.3)
Other Use	6 (0.2)	4 (0.4)	3 (0.6)	2 (0.6)	1 (0.6)
Acetaminophen					
No Use	2154 (86.9)	586 (64.5)	353 (69.6)	269 (81.5)	106 (62.0)
Continuous Use	14 (0.6)	20 (2.2)	18 (3.6)	2 (0.6)	6 (3.5)
Early Use	12 (0.5)	18 (2.0)	15 (3.0)	2 (0.6)	1 (0.6)
Late Use	9 (0.4)	17 (1.9)	3 (0.6)	6 (1.8)	3 (1.8)
Other Use	16 (0.7)	33 (3.6)	16 (3.2)	9 (2.7)	8 (4.7)

Continuous use: Defined as regular use (average exposure of $\geq$ 325 mg per week - dose adjusted) between 2 and 5 years prior to index and in the 2 years prior to index. **Early use:** Defined as regular use between 2 and 5 years prior to index, but no exposure during the 2 years prior to index. **Late use:** Defined as regular use in the 2 years prior to index, but no exposure before. **Irregular use:** Defined as "Other Exposure" not classified as above.

Table 6. Potential Confounding Variables on the Association of NSAID Use and ESRD: 0 to 2 and 2 to 5 year time windows.

	NSAID USERS PRIOR TO INDEX DATE			
	Continuous Use 43 (13.6) vs 908 (15.9)	**Early Use** 28 (8.9) vs. 507 (8.9)	**Late Use** 15 (4.8) vs. 330 (5.8)	**Irregular Use** 11 (3.5) vs. 171 (3.0)
Crude OR	**0.86 (0.61-1.22)**	**0.99 (0.66-1.49)**	**0.80 (0.47-1.37)**	**1.17 (0.62-2.21)**
Adjusted Individually For The Following:				
Anti-Diabetic Therapy				
Insulin only	0.87 (0.62-1.24)	1.02 (0.67-1.53)	0.80 (0.46-1.38)	1.17 (0.62-2.20)
Oral hypoglycemic only	0.86 (0.61-1.22)	0.99 (0.66-1.49)	0.80 (0.47-1.38)	1.18 (0.63-2.21)
Both	0.87 (0.62-1.22)	0.99 (0.66-1.49)	0.81 (0.47-1.39)	1.17 (0.62-2.20)
Cardiovascular Medication Use				
Lipid Lowering	0.86 (0.61-1.21)	0.98 (0.65-1.48)	0.79 (0.46-1.35)	1.16 (0.62-2.18)
Nitrates	0.86 (0.61-1.22)	0.99 (0.65-1.49)	0.80 (0.46-1.37)	1.17 (0.63-2.21)
Diagnostic Codes				
Peripheral Vascular Disease	0.87 (0.61-1.23)	0.99 (0.65-1.50)	0.83 (0.48-1.43)	1.13 (0.60-2.15)
Heart Disease	0.85 (0.60-1.20)	0.96 (0.63-1.45)	0.80 (0.46-1.38)	1.17 (0.62-2.22)
Heart Failure	0.85 (0.60-1.21)	0.94 (0.61-1.42)	0.78 (0.45-1.36)	1.14 (0.60-2.17)
Arterial Aneurysm	0.87 (0.62-1.23)	0.99 (0.66-1.50)	0.81 (0.47-1.40)	1.15 (0.61-2.16)
Stroke	0.86 (0.61-1.21)	0.99 (0.66-1.49)	0.79 (0.46-1.36)	1.16 (0.62-2.18)
Anti-HTN Medication Use				
Ace Inhibitor	0.85 (0.60-1.21)	1.02 (0.67-1.54)	0.81 (0.47-1.39)	1.17 (0.62-2.21)
Beta Blocker	0.87 (0.62-1.22)	0.99 (0.65-1.49)	0.79 (0.46-1.36)	1.17 (0.62-2.20)
Calcium Channel Blocker	0.85 (0.60-1.20)	0.97 (0.64-1.46)	0.79 (0.46-1.36)	1.17 (0.62-2.21)
Diuretic	0.86 (0.61-1.21)	0.98 (0.65-1.48)	0.81 (0.47-1.40)	1.17 (0.62-2.20)
Loop Diuretic	0.75 (0.53-1.07)	0.91 (0.60-1.38)	0.78 (0.45-1.34)	1.07 (0.56-2.02)
Other	0.85 (0.60-1.20)	0.98 (0.65-1.48)	0.81 (0.47-1.40)	1.23 (0.65-2.32)

Medication Use				
Central Nervous System	0.85 (0.60-1.20)	0.98 (0.65-1.48)	0.80 (0.46-1.37)	1.16 (0.62-2.18)
Anti-Parkinsonian	0.87 (0.62-1.22)	0.98 (0.65-1.48)	0.80 (0.46-1.37)	1.18 (0.63-2.22)
Inhaled Corticosteroids	0.84 (0.59-1.18)	0.97 (0.64-1.46)	0.80 (0.46-1.37)	1.17 (0.62-2.20)
Other Respiratory Agents	0.86 (0.61-1.22)	0.99 (0.65-1.49)	0.80 (0.47-1.37)	1.17 (0.62-2.21)
Anticonvulsant	0.86 (0.61-1.22)	0.99 (0.65-1.49)	0.80 (0.47-1.37)	1.18 (0.63-2.21)
Anti-Ulcer	0.80 (0.57-1.13)	0.95 (0.63-1.43)	0.76 (0.44-1.32)	1.11 (0.59-2.09)
Anti-Gout	0.81 (0.57-1.14)	0.95 (0.63-1.44)	0.80 (0.47-1.38)	1.12 (0.59-2.11)
Other Analgesic Use				
ASA	0.83 (0.59-1.18)	0.96 (0.63-1.45)	0.78 (0.45-1.34)	1.15 (0.61-2.17)
Acetaminophen	0.83 (0.59-1.19)	0.97 (0.64-1.47)	0.79 (0.46-1.36)	1.14 (0.61-2.15)

Continuous use: Defined as regular use (average exposure of $\geq$ 325 mg per week - dose adjusted) between 2 and 5 years prior to index and in the 2 years prior to index. **Early use:** Defined as regular use between 2 and 5 years prior to index, but no exposure during the 2 years prior to index. **Late use:** Defined as regular use in the 2 years prior to index, but no exposure before. **Irregular use:** Defined as "Other Exposure" not classified as above.

Table 7. Potential Confounding Variables on the Association of NSAID Use and End Stage Renal Disease: 0 to 5 and 5 to 10 year time windows.

	NSAID USERS PRIOR TO INDEX DATE			
	Continuous Use	**Early Use**	**Late Use**	**Irregular Use**
Crude OR	**1.19 (0.85-1.66)**	**1.07 (0.63-1.81)**	**0.48 (0.25-0.94)**	**0.78 (0.59-1.03)**
Adjusted Individually For The Following:				
Anti-Diabetic Therapy				
Insulin only	1.20 (0.85-1.68)	1.05 (0.62-1.79)	0.49 (0.25-0.96)	0.80 (0.60-1.05)
Oral hypoglycemic only	1.19 (0.85-1.66)	1.07 (0.63-1.81)	0.48 (0.25-0.94)	0.78 (0.59-1.03)
Both	1.19 (0.85-1.66)	1.06 (0.63-1.80)	0.49 (0.25-0.95)	0.78 (0.59-1.03)
Cardiovascular Medication Use				
Lipid Lowering	1.18 (0.84-1.65)	1.08 (0.64-1.83)	0.48 (0.25-0.94)	0.78 (0.59-1.04)
Nitrates	1.18 (0.84-1.66)	1.07 (0.63-1.81)	0.48 (0.25-0.94)	0.78 (0.59-1.03)
Diagnostic Codes				
Peripheral Vascular Disease	1.20 (0.86-1.70)	1.03 (0.60-1.77)	0.50 (0.26-0.98)	0.78 (0.60-1.04)
Heart Disease	1.13 (0.80-1.58)	1.06 (0.62-1.80)	0.49 (0.25-0.96)	0.76 (0.57-1.00)
Heart Failure	1.13 (0.80-1.59)	0.98 (0.57-1.70)	0.51 (0.26-1.00)	0.75 (0.57-1.00)
Arterial Aneurysm	1.22 (0.87-1.71)	1.10 (0.65-1.86)	0.50 (0.26-0.97)	0.79 (0.60-1.05)
Stroke	1.19 (0.85-1.67)	1.06 (0.62-1.79)	0.48 (0.24-0.93)	0.78 (0.59-1.03)
Anti-HTN Medication Use				
Ace Inhibitor	1.17 (0.84-1.65)	1.06 (0.62-1.81)	0.50 (0.25-0.97)	0.80 (0.60-1.06)
Beta Blocker	1.19 (0.85-1.66)	1.08 (0.64-1.83)	0.48 (0.25-0.94)	0.78 (0.59-1.03)
Calcium Channel Blocker	1.17 (0.83-1.64)	1.08 (0.64-1.84)	0.48 (0.25-0.94)	0.79 (0.59-1.04)
Diuretic	1.16 (0.83-1.63)	1.07 (0.63-1.81)	0.47 (0.24-.092)	0.78 (0.59-1.03)
Loop Diuretic	1.02 (0.72-1.44)	1.06 (0.62-1.82)	0.47 (0.24-0.91)	0.76 (0.57-1.01)
Other	1.19 (0.85-1.67)	1.13 (0.66-1.92)	0.48 (0.24-0.93)	0.80 (0.60-1.06)

Medication Use				
Central Nervous System	1.16 (0.82-1.63)	1.05 (0.62-1.78)	0.48 (0.25-0.93)	0.77 (0.59-1.02)
Anti-Parkinsonian	1.19 (0.85-1.66)	1.05 (0.62-1.79)	0.48 (0.25-0.94)	0.78 (0.59-1.03)
Inhaled Corticosteroids	1.14 (0.81-1.60)	1.04 (0.61-1.76)	0.48 (0.25-0.94)	0.78 (0.59-1.02)
Other Respiratory Agents	1.19 (0.85-1.66)	1.07 (0.63-1.81)	.048 (0.25-0.94)	0.78 (0.59-1.03)
Anticonvulsant	1.19 (0.85-1.66)	1.07 (0.63-1.81)	0.48 (0.25-0.94)	0.78 (0.59-1.03)
Anti-Ulcer	1.09 (0.77-1.54)	1.03 (0.61-1.75)	0.46 (0.24-0.90)	0.76 (0.57-1.00)
Anti-Gout	1.09 (0.78-1.54)	1.02 (0.60-1.74)	0.46 (0.23-0.89)	0.75 (0.56-0.99)
Other Analgesic Use				
ASA	1.12 (0.79-1.58)	1.05 (0.62-1.77)	0.47 (0.24-0.91)	0.76 (0.57-1.00)
Acetaminophen	1.13 (0.80-1.60)	1.03 (0.61-1.75)	0.47 (0.24-0.92)	0.76 (0.57-1.01)

Continuous use: Defined as regular use (average exposure of $\geq$ 325 mg per week - dose adjusted) between 5 and 10 years prior to index and in the 5 years prior to index. **Early use:** Defined as regular use between 5 and 10 years prior to index, but no exposure during the 5 years prior to index. **Late use:** Defined as regular use in the 5 years prior to index, but no exposure before. **Irregular use:** Defined as "Other Exposure" not classified as above.

Assessment of Effect Modifiers:

It was hypothesized that certain variables could modify the effect of NSAID use and ESRD. The effect modifiers considered were use of loop diuretics, ACE inhibitors, diabetic therapy (insulin only, oral hypoglycemic agent only or both), aspirin, acetaminophen, and each of the matching variables; age, gender, calendar time of cohort entry.

In the time period of zero to two years and two to five years, significant effect modification was observed with continuous NSAID use and loop diuretics (RR 0.47 with loop diuretic vs. 1.03 without, p-value 0.03), ACE inhibitors (RR 0.41 with ACE inhibitor vs. 1.12 without, p-value 0.02) and insulin only therapy (RR 0.15 with insulin only vs. 1.18 without, p-value 0.01). In the time period of zero to five years and five to ten years, effect modification was found between continuous NSAID use and gender (RR 0.49 for females vs. 2.34 for males, p-value 0.02) as well as insulin only therapy (RR 0.30 with insulin vs. 1.63 without, p-value 0.02).

Multivariate Analysis:

The various time windows of regular NSAID drug use, exposure to aspirin and acetaminophen, potential confounders, effect modifiers and clinically relevant variables were considered in the final model.

Model results are displayed in **tables 8** (drug use 2 years prior to ESRD), **9** (drug use 5 years prior to ESRD) and **10** (drug use 10 years prior to ESRD). For drug use 10 years prior to ESRD the adjusted rate ratio was 1.18 (95% CI 0.68 – 2.05) for continuous NSAID use, 1.10 (95% CI 0.50 – 2.41) for exposure 5 to 10 years prior to index date, 0.81 (95% CI 0.32 – 2.04) for exposure only during the 5 years preceding ESRD and 0.75 (95% CI 0.48 – 1.17) for other NSAID use. For other models, there was no significant association between NSAID use and the development of ESRD. A slight association was noted between late acetaminophen use and ESRD (RR 2.23, 95% CI 1.21 – 4.12) for drug use up to 2

years prior to ESRD. This result was not consistent in other time windows and was marginally significant, possible due to multiple comparisons.

Table 8. Patterns of Drug Use 2 Years Prior to End Stage Renal Disease:

	Cases (n = 397)	Controls (n = 7399)	Crude RR (95% CI)	Adjusted[1] RR (95% CI)	Adjusted[2] RR (95% CI)	Adjusted[3] RR (95% CI)
NSAIDs, No (%)						
No use	284 (71.5)	5182 (70.0)	Reference	Reference	Reference	Reference
Continuous	40 (10.1)	950 (12.8)	0.78 (0.55 – 1.10)	0.72 (0.50 – 1.05)	0.73 (0.50 – 1.06)	0.71 (0.49 – 1.03)
Early (use between 1 -2 years)	35 (8.8)	669 (9.0)	0.97 (0.67 – 1.39)	0.93 (0.63 – 1.36)	0.94 (0.64 – 1.38)	0.91 (0.62 – 1.35)
Late (use between 0 – 1 years)	37 (9.3)	564 (7.6)	1.22 (0.85 – 1.74)	1.30 (0.88 – 1.90)	1.31 (0.90 – 1.92)	1.30 (0.88 – 1.90)
Irregular	1 (0.25)	34 (0.46)	0.52 (0.07 – 3.83)	0.41 (0.47 – 3.54)	0.40 (0.05 – 3.53)	0.41 (0.05 – 3.64)
ASA, No (%)						
No use	342 (86.1)	6547 (88.5)	Reference	Reference	Reference	Reference
Continuous	18 (4.5)	362 (4.9)	0.99 (0.61 – 1.62)	0.80 (0.47 – 1.36)	0.79 (0.46 – 1.36)	0.80 (0.47 – 1.37)
Early (use between 1 -2 years)	19 (4.8)	259 (3.5)	1.44 (0.89 – 2.34)	1.18 (0.70 – 2.01)	1.19 (0.70 – 2.03)	1.22 (0.72 – 2.09)
Late (use between 0 – 1 years)	16 (4.0)	225 (3.0)	1.34 (0.79 – 2.26)	0.88 (0.49 – 1.58)	0.89 (0.50 – 1.59)	0.87 (0.48 – 1.55)
Irregular	2 (0.5)	6 (0.1)	5.24 (1.04 – 26.5)	7.73 (1.36 – 44.15)	8.19 (1.43 – 46.90)	8.01 (1.40 – 45.92)
Acetaminophen, No (%)						
No use	372 (93.7)	7062 (95.4)	Reference	Reference	Reference	Reference
Continuous	6 (1.5)	84 (1.1)	1.34 (0.58 – 3.11)	1.34 (0.55 – 3.28)	1.41 (0.58 – 3.48)	1.38 (0.56 – 3.41)
Early (use between 1 -2 years)	6 (1.5)	112 (1.5)	1.05 (0.46 – 2.40)	0.80 (0.33 – 1.96)	0.84 (0.34 – 2.05)	0.83 (0.33 – 2.05)
Late (use between 0 – 1 years)	12 (3.0)	108 (1.5)	2.23 (1.21 – 4.12)	2.00 (1.01 – 3.94)	2.04 (1.03 – 4.03)	2.09 (1.05 – 4.14)
Irregular	1 (0.25)	33 (0.45)	0.62 (0.08 – 4.57)	0.53 (0.07 – 4.13)	0.56 (0.07 – 4.39)	0.55 (0.07 – 4.35)

Regular use: Defined as an average exposure of ≥ 325 mg per week (dose adjusted) during the time window. **Continuous use:** Defined as regular use between 1 to 2 years prior to index and in the year prior to index. **Early use:** Defined as regular use between 1 to 2 years prior to index, but no exposure during the year prior to index. **Late use:** Defined as regular use in the year prior to index, but no exposure before. **Irregular use:** Defined as "Other Exposure" not classified as above. **Adjusted Rate Ratio:** Model adjusted for the presence of peripheral vascular disease, heart disease, heart failure, arterial aneurysm, stroke, diabetes mellitus (coded as insulin use only, oral hypoglycemic use only or both), and the use of CNS, anti-parkisonian, inhaled corticosteroids, other respiratory agents, anticonvulsants, anti-ulcer and gout medication. **Adjusted Rate Ratio[2]:** Model adjusted for previous analgesic use [defined as ≥ 9.75 grams at any time] and above variables in model 1. **Adjusted Rate Ratio[3]:** Model adjusted for other analgesic use and above variables in model 1

Table 9. Patterns of Drug Use 5 Years Prior to End Stage Renal Disease

	Cases (n = 316)	Controls (n = 5726)	Crude RR (95% CI)	Adjusted[1] RR (95% CI)	Adjusted[2] RR (95% CI)	Adjusted[3] RR (95% CI)
NSAIDs, No (%)						
No use	219 (69.3)	3810 (66.5)	Reference	Reference	Reference	Reference
Continuous	43 (13.6)	908 (15.9)	0.86 (0.61 – 1.22)	0.74 (0.51 – 1.08)	0.75 (0.51 – 1.08)	0.75 (0.51 – 1.09)
Early (use between 2 - 5 years)	28 (8.9)	507 (8.9)	0.99 (0.66 – 1.50)	0.85 (0.55 – 1.32)	0.85 (0.55 – 1.33)	0.87 (0.56 – 1.36)
Late (use between 0 - 2 years)	15 (4.8)	330 (5.8)	0.80 (0.47 – 1.37)	0.84 (0.47 – 1.50)	0.85 (0.47 – 1.51)	0.84 (0.47 – 1.51)
Irregular	11 (3.5)	171 (3.0)	1.17 (0.62 – 2.21)	1.12 (0.58 – 2.20)	1.12 (0.57 – 2.19)	1.10 (0.56 – 2.16)
ASA, No (%)						
No use	263 (83.2)	4856 (84.8)	Reference	Reference	Reference	Reference
Continuous	22 (7.0)	295 (5.2)	1.42 (0.89 – 2.25)	1.11 (0.66 – 1.87)	1.10 (0.65 – 1.86)	1.10 (0.65 – 1.85)
Early (use between 2 - 5 years)	17 (5.4)	344 (6.0)	0.97 (0.58 – 1.61)	0.62 (0.35 – 1.08)	0.64 (0.36 – 1.11)	0.65 (0.37 – 1.13)
Late (use between 0 - 2 years)	12 (3.8)	203 (3.6)	1.11 (0.61 – 2.04)	0.75 (0.38 – 1.46)	0.74 (0.38 – 1.46)	0.77 (0.39 – 1.50)
Irregular	2 (0.6)	28 (0.5)	1.25 (0.29 – 5.36)	1.23 (0.24 – 6.43)	1.27 (0.24 – 6.81)	1.24 (0.23 – 6.58)
Acetaminophen, No (%)						
No use	296 (93.7)	5420 (94.7)	Reference	Reference	Reference	Reference
Continuous	7 (2.2)	70 (1.2)	1.70 (0.76 – 3.78)	1.54 (0.65 – 3.65)	1.63 (0.68 – 3.87)	1.59 (0.66 – 3.82)
Early (use between 2 - 5 years)	1 (0.3)	61 (1.1)	0.28 (0.04 – 2.05)	0.13 (0.02 – 1.16)	0.14 (0.02 – 1.23)	0.14 (0.02 – 1.23)
Late (use between 0 - 2 years)	4 (1.3)	49 (0.9)	1.57 (0.56 – 4.45)	1.91 (0.63 – 5.82)	2.02 (0.66 – 6.17)	1.93 (0.62 – 5.96)
Irregular	8 (2.5)	126 (2.2)	0.96 (0.44 – 2.11)	0.81 (0.35 – 1.91)	0.87 (0.37 – 2.06)	0.85 (0.36 – 2.00)

Regular use: Defined as an average exposure of ≥ 325 mg per week (dose adjusted) during the time window. **Continuous use:** Defined as regular use between 2 and 5 years prior to index and in the 2 years prior to index. **Early use:** Defined as regular use between 2 and 5 years prior to index, but no exposure during the 2 years prior to index. **Late use:** Defined as regular use in the 2 years prior to index, but no exposure before. **Irregular use:** Defined as "Other Exposure" not classified as above.
Adjusted Rate Ratio: Model adjusted for the presence of peripheral vascular disease, heart disease, heart failure, arterial aneurysm, stroke, diabetes mellitus (coded as insulin use only, oral hypoglycemic use only or both), and the use of CNS, anti-parkisonian, inhaled corticosteroids, other respiratory agents, anticonvulsants, anti-ulcer and gout medication. **Adjusted Rate Ratio[2]:** Model adjusted for previous analgesic use [defined as ≥ 9.75 grams at any time] and above variables in model 1
Adjusted Rate Ratio[3]: Model adjusted for other analgesic use and above variables in model 1

Table 10: Patterns of Drug Use 10 Years Prior to End Stage Renal Disease (0 to 5 year and 5 to 10 year windows)

	Cases (n = 183)	Controls (n = 2792)	Crude RR (95% CI)	Adjusted[1] RR (95% CI)	Adjusted[2] RR (95% CI)	Adjusted[3] RR (95% CI)
NSAIDs, No (%)						
No use	57 (31.1)	740 (26.5)	Reference	Reference	Reference	Reference
Continuous	38 (20.77)	500 (17.91)	1.24 (0.79 – 1.97)	1.17 (0.68 – 2.00)	1.24 (0.72 – 2.13)	1.18 (0.68 – 2.05)
Early (use between 5 - 10 years)	12 (6.6)	167 (6.0)	1.00 (0.50 – 2.01)	1.10 (0.50 – 2.40)	1.14 (0.52 – 2.51)	1.10 (0.50 – 2.41)
Late (use between 0 - 5 years)	7 (3.8)	143 (5.1)	0.60 (0.26 – 1.39)	0.86 (0.35 – 2.11)	0.91 (0.37 – 2.24)	0.81 (0.32 – 2.04)
Irregular	69 (37.7)	1242 (44.48)	0.76 (0.52 – 1.12)	0.74 (0.48 – 1.14)	0.77 (0.50 – 1.21)	0.75 (0.48 – 1.17)
ASA, No (%)						
No use	105 (57.4)	1703 (61.0)	Reference	Reference	Reference	Reference
Continuous	12 (6.6)	173 (6.2)	1.29 (0.68 – 2.42)	0.60 (0.27 – 1.31)	0.61 (0.28 – 1.35)	0.55 (0.25 – 1.25)
Early (use between 5 - 10 years)	11 (6.0)	140 (5.0)	1.20 (0.60 – 2.38)	1.23 (0.58 – 2.60)	1.28 (0.60 – 2.73)	1.14 (0.53 – 2.47)
Late (use between 0 - 5 years)	15 (8.2)	153 (5.5)	1.73 (0.96 – 3.09)	1.06 (0.54 – 2.05)	1.07 (0.55 – 2.08)	1.09 (0.56 – 2.11)
Irregular	40 (21.9)	623 (22.3)	0.92 (0.62 – 1.37)	0.74 (0.48 – 1.16)	0.76 (0.49 – 1.20)	0.74 (0.47 – 1.16)
Acetaminophen, No (%)						
No use	100 (54.6)	1757 (62.9)	Reference	Reference	Reference	Reference
Continuous	4 (2.2)	30 (1.1)	3.10 (1.04 – 9.25)	2.85 (0.79 – 10.32)	3.22 (0.89 – 11.64)	3.03 (0.81 – 11.27)
Early (use between 5 - 10 years)	1 (0.6)	31 (1.1)	0.57 (0.07 – 4.41)	0.41 (0.04 – 3.74)	0.43 (0.05 – 3.91)	0.46 (0.05 – 3.98)
Late (use between 0 - 5 years)	1 (0.6)	20 (0.7)	1.01 (0.13 – 7.71)	1.22 (0.15 – 10.00)	1.32 (0.16 – 11.08)	1.33 (0.16 – 11.06)
Irregular	77 (42.1)	954 (34.2)	1.23 (0.89 – 1.71)	1.11 (0.76 – 1.63)	1.19 (0.81 – 1.75)	1.17 (0.79 – 1.73)

Regular use: Defined as an average exposure of ≥ 325 mg per week (dose adjusted) during the time window. **Continuous use:** Defined as regular use between 5 and 10 years prior to index and in the 5 years prior to index. **Early use:** Defined as regular use between 5 and 10 years prior to index, but no exposure during the 5 years prior to index. **Late use:** Defined as regular use in the 5 years prior to index, but no exposure before.
Irregular use: Defined as "Other Exposure" not classified as above. **Adjusted Rate Ratio[1]:** Model adjusted for the presence of peripheral vascular disease, heart disease, heart failure, arterial aneurysm, stroke, diabetes mellitus (coded as insulin use only, oral hypoglycemic use only or both), and the use of CNS, anti-parkisonian, inhaled corticosteroids, other respiratory agents, anticonvulsants, anti-ulcer and gout medication. **Adjusted Rate Ratio[2]:** Model adjusted for previous analgesic use [defined as ≥ 9.75 grams at any time] and above variables in model 1 **Adjusted Rate Ratio[3]:** Model adjusted for other analgesic use and above variables in model 1

Other Use Analysis:

To investigate the possible effect of confounding by "contra-indication", individuals that were prescribed at least 30 grams of NSAID products at anytime, who then had no exposure for at least 1 year prior to index date, were compared to non-users. The purpose of this design is to represent individuals that are NSAID exposed, but reach a time point where they avoid subsequent NSAID products. This serves to model the potential scenario in which a physician directs a patient to avoidance NSAIDs because of concern with renal impairment. To provide a broader time window, analysis was restricted to individuals with at least 10 years of prescription drug information. A similar analysis was performed for ASA and acetaminophen. The results are displayed in **table 11**. For NSAIDs, all confidence intervals of the adjusted rate ratios crossed 1.0. The crude rate ratio for past NSAID exposure was 0.84 (95% CI 0.57 – 1.24) and adjusted rate ratio 0.83 (95% CI 0.52 – 1.31). Over a third of cases and controls (35.0 and 38.3% respectively) were past NSAID users. Similar results were seen among ASA and acetaminophen use, as well as when a cutoff of 100 grams of analgesic consumption was used.

Dose Effect:

Table 12 displays the association between analgesic consumption over a 10 year period and risk of end stage renal disease. Compared to nonusers, the adjusted rate ratio for individuals prescribed less than 66 grams of NSAIDs was 0.71 (95% CI 0.43 – 1.19), 0.92 (95% CI 0.55 – 1.53) for individuals prescribed between 66 and 300 grams and 1.05 (95% CI 0.63 – 1.74) for individuals prescribed more than 300 grams. The p-value for trend was non-significant. No association between analgesic dose and risk for end stage renal disease was present for aspirin or acetaminophen.

Table 11. Past Users (≥ 30 grams) That Stop
Restricted to Individuals with greater than 10 years of drug exposure information

	Cases (n = 183)	Controls (n = 2792)	Crude RR (95% CI)	Adjusted[1] RR (95% CI)	Adjusted[2] RR (95% CI)
NSAIDs, No (%)					
Non User	57 (31.2)	740 (26.5)	Reference	Reference	Reference
Past User	64 (35.0)	1068 (38.3)	0.84 (0.57 – 1.24)	0.81 (0.52 – 1.27)	0.83 (0.52 – 1.31)
Other	62 (33.9)	984 (35.2)	0.89 (0.60 – 1.32)	0.89 (0.57 – 1.40)	0.90 (0.57 – 1.43)
ASA, No (%)					
Non User	105 (57.4)	1703 (61.0)	Reference	Reference	Reference
Past User	39 (21.3)	595 (21.3)	1.10 (0.73 – 1.64)	0.84 (0.53 – 1.34)	0.85 (0.53 – 1.37)
Other	39 (21.3)	494 (17.7)	1.13 (0.76 – 1.69)	0.85 (0.54 – 1.33)	0.86 (0.54 – 1.36)
Acetaminophen, No (%)					
Non User	100 (54.6)	1757 (62.9)	Reference	Reference	Reference
Past User	13 (7.1)	261 (9.4)	0.82 (0.44 – 1.53)	0.63 (0.30 – 1.31)	0.67 (0.31 – 1.41)
Other	70 (38.3)	774 (27.7)	1.39 (0.99 – 1.94)	1.25 (0.85 – 1.83)	1.30 (0.88 – 1.92)

Adjusted Rate Ratio[1]: Model adjusted for the presence of peripheral vascular disease, heart disease, heart failure, arterial aneurysm, stroke, diabetes mellitus (coded as insulin use only, oral hypoglycemic use only or both), and the use of CNS, anti-parkisonian, inhaled corticosteroids, other respiratory agents, anticonvulsants, anti-ulcer and gout medication
Adjusted Rate Ratio[2]: Model adjusted for other analgesic use and above variables in model 1

Table 12: Analgesic dose over 10 years and risk of End Stage Renal Disease:

Drug Category	Cases (n=183)	Controls (n=2792)	Crude RR (95% CI)	Adjusted[1] RR (95% CI)	Adjusted[2] RR (95% CI)
Nsaids					
Quartile 1 (No Use)	57 (31.1)	740 (26.5)	Reference	Reference	Reference
Quartile 2 (<66 gms)	37 (20.2)	683 (24.5)	0.72 (0.46 – 1.14)	0.72 (0.43 – 1.18)	0.71 (0.43 – 1.19)
Quartile 3 (66–300 gms)	41 (22.4)	686 (24.6)	0.83 (0.54 – 1.28)	0.87 (0.53 – 1.42)	0.92 (0.55 – 1.53)
Quartile 3 (> 300 gms)	48 (26.2)	683 (24.5)	1.06 (0.69 – 1.63)	1.01 (0.61 – 1.65)	1.05 (0.63 – 1.74)
ASA					
Quartile 1 (No Use)	95 (51.9)	1703 (61.0)	Reference	Reference	Reference
Quartile 2 (<45 gms)	22 (12.0)	364 (13.0)	0.79 (0.47 – 1.30)	0.69 (0.40 – 1.19)	0.67 (0.38 – 1.18)
Quartile 3 (45–240 gms)	30 (16.4)	362 (13.0)	1.45 (0.93 – 2.25)	1.07 (0.64 – 1.77)	1.05 (0.53 – 1.75)
Quartile 4 (>240 gms)	26 (14.2)	363 (13.0)	1.19 (0.75 – 1.90)	0.82 (0.47 – 1.42)	0.81 (0.46 – 1.42)
Acetaminophen					
Quartile 1 (No Use)	100 (54.6)	1757 (62.9)	Reference	Reference	Reference
Quartile 2 (<10.8 gms)	29 (15.9)	314 (11.3)	1.45 (0.93 – 2.27)	1.43 (0.87 – 2.35)	1.46 (0.88 – 2.42)
Quartile 3 (10.8–30 gms)	29 (15.9)	348 (12.5)	1.27 (0.80 – 2.00)	1.05 (0.62 – 1.76)	1.12 (0.66 – 1.89)
Quartile 4 (>30 gms)	25 (13.7)	373 (13.4)	1.05 (0.65 – 1.71)	0.87 (0.49 – 1.54)	0.88 (0.49 – 1.58)

Adjusted Rate Ratio[1]: Model adjusted for the presence of peripheral vascular disease, heart disease, heart failure, arterial aneurysm, stroke, diabetes mellitus (coded as insulin use only, oral hypoglycemic use only or both), and the use of CNS, anti-parkisonian, inhaled corticosteroids, other respiratory agents, anticonvulsants, anti-ulcer and gout medication

Adjusted Rate Ratio[2]: Model adjusted for other analgesic use and above variables in model 1

Power Calculations:

In circumstances where the exposure of interest is uncommon in cases and controls, one may not find a statistical difference between groups because of issues with power. To evaluate this issue, power was calculated for several of the primary study windows and for past exposure measurements. Results are displayed in table 20. A greater than 80% power to detect a 50% risk difference was present in no use and continuous use for both the 2 and 5 year time windows.

Table 20. Power Calculations for NSAID Exposure

	Proportion in Control Population (%)	Power for Risk Ratio of 1.5 (%)	Power for Risk Ratioof 2.0 (%)
Up to 2 Years			
No use	70.0	96.4	99.9
Continuous	12.8	88.2	99.9
Early[1]	9.0	78.8	99.7
Late[2]	7.6	73.4	99.3
Irregular	0.46	56.5	95.1
(Cases: 397, Controls: 7399)			
Up to 5 Years			
No use	66.5	93.8	99.9
Continuous	15.9	86.3	99.9
Early[3]	8.9	69.9	98.9
Late[4]	5.8	55.9	94.7
Irregular	3.0	37.2	77.8
(Cases: 316, Controls: 5726)			
Up to 10 Years			
No use	26.5	78.9	99.6
Continuous	17.9	69.9	98.6
Early[5] (use between 5 – 10	6.0	39.5	80.6
Late[6] between 0 – 5 years)	5.1	35.8	75.4
Irregular	44.5	84.3	99.8
(Cases: 183, Controls 2792)			
Past Use			
None	26.5	78.9	99.6
Past Use	38.3	83.7	99.8
Other Use	35.2	83.0	99.8
(Cases: 183, Controls 2792)			

Where the one-sided p-value = 0.05.

1. Use between 1-2 years, but not between 0-1 years preceding index date
2. Use between 0-1 years, but not between 1-2 years preceding index date
3. Use between 2-5 years, but not between 0-2 years preceding index date
4. Use between 0-2 years, but not between 2-5 years preceding index date
5. Use between 5-10 years, but not between 0-5 years preceding index date
6. Use between 0-5 years, but not between 5-10 years preceding index date

Discussion

In this chapter, all findings described in the previous chapter are summarized and, whenever possible, compared to findings in previous studies. For some of these findings, biological or epidemiological explanations are addressed immediately, while for others, explanations are deferred to the last section of this chapter, "limitations", where various potential biases of the study are discussed.

Summary of Findings:

The overall risk of end stage renal disease was found to be a similar between users and non-users of NSAIDs. Although power differed between various time windows, duration, dose or pattern of NSAID did not affect results even in NSAID users of up to 10 years duration. Several medications were statistically significant effect modifiers (loop diuretics, ACE inhibitors, gender and insulin only therapy), but did not influence this association.

These findings are in agreement with two prior studies (30, 34). Morlans et al (30) found no association with NSAID use (Pyrazolones) in hemodialysis patients, although was limited in statistical power. In the current analysis, power to detect a 50% relative risk difference exceeding 95% in certain time windows. The Physician's Health Study (34), which comprised relatively healthy males, also found no link between analgesic use and renal function. The current findings extend this information to high risk individuals.

Although other studies have found an increased risk of ESRD / chronic renal failure with NSAID use, this discrepancy can be explained from several methodological shortcomings. Results may be influenced by selection or information bias, particularly with regard to recall of past exposures, as well as inconsistent outcome definition; ranging from end stage renal disease requiring dialysis to an elevation in serum creatinine representing a cut point for renal dysfunction. The findings by Sandler et al (31) relied on patient recall of

exposures, which is prone to misclassification bias. As well, there was a large proportion of individuals that did not participate leading to potential for selection bias. Similar issues were evident in the case-control study by Perneger et al (32).

There was statistically significant effect modification between NSAIDs and the following variables; loop diuretic therapy, ACE inhibitors, insulin only therapy (a marker for type 1 diabetes mellitus), and gender. The lower risk of ESRD with NSAIDs and the first three variables likely reflects prescription behaviors among physicians in terms of patients at high risk for ESRD. The design of the current study however was not established to fully explore this issue. A higher risk of ESRD with NSAID use was also noted in males (for the 10 year time window), similar to findings reported by Sandler et al (31). The clinical reason for this however is unclear, as variation in risk across other time windows was not observed. Further research in this area is warranted.

Methodological Considerations:

Several important methodologic issues were addressed in the study. The strengths and weaknesses of our research will be reviewed in the following section.

Selection Bias:

Selection bias is defined as a distortion in the estimate of effect resulting from the manner in which subjects are selected from the study population, and/or the presence of selective losses from the study population prior to data analysis. These lead to an effect estimate from the available study subjects that is different from the one that would have been obtained had all subjects (or their representative sample) theoretically eligible to participate had been included in the analysis (42, 43).

One of the major limitations of previous observational studies has been the operational definition of the study base and selection of appropriate controls. By use of a cohort of incident hypertensive individuals from a population based

database, one has the opportunity to select cases and controls that are matched on known and unknown variables (43-45). For example, although hypertension is a common disease, many individuals are not diagnosed or treated. It has been estimated that less than 25% of all hypertensive individuals receive medical therapy. Therefore, those individuals that visit a physician and are prescribed an anti-hypertensive medication, are potentially different than other hypertensive individuals not receiving therapy. It is possible that these other individuals may be less compliant with therapy, refuse medications, be less likely to see a physician and may be associated with higher rates of smoking and alcohol use. The cohort therefore creates a more representative study base from which to draw cases and controls. It is unlikely that this study base would affect generalizability, as the biologic effects of NSAIDs should not differ between different subpopulations. Selection bias is also limited as individuals are matched to those that have hypertension. This matches not only on hypertension, but also the requirement for physician visits which may be associated with other confounders (medical compliance, healthy behaviors, etc). Additionally, the matching was time-dependant on cohort entry, reducing the risk of bias from changing medical or prescription practices. Additionally, the Saskatchewan database tracts all prescriptions, physician visits and hospitalizations once an individual is entered into the Health Branch Database. Since the population of Saskatchewan is relatively static, the potential for losses to follow-up are minimized.

Another limitation of other observational studies has been the selection of prevalent cases of ESRD or chronic kidney disease. Disease prevalence is related both to the incidence, as well as duration of the disease investigated. If the exposure of interest is associated with either disease progression or its duration, then risk estimate will be affected

One potential bias of the study is that it is not possible to identify all cases of ESRD. Since case definition relies on service codes for dialysis and transplantation, there is the possibility that individuals with ESRD refuse or are

not offered renal replacement therapy. In studies in the United Kingdom, it has been estimated that roughly 25% of individuals refuse dialysis, either because of other comorbidities, quality of life issues or their beliefs regarding renal replacement therapy. If these individuals differ from the identified cases in terms of increased NSAID utilization, one would expect to see results biased towards the null.

Information Bias:

Errors in risk estimates may occur if misclassification of the exposure or outcome occurs (46 - 48). In any case control study, when classification of the exposure varies according to disease status, then differential information bias is present. In contrast, non differential information bias is induced when the measurement of exposure does not vary among cases and controls. Pharmacoepidemiology is especially sensitive to non differential information bias, since drug exposure is related to many factors which are difficult to measure and this limitation is equally distributed among cases and controls (49, 50).

Measure of Exposure:

A significant strength of this study over others is that misclassification was minimized by avoiding non differential recall of drug exposure, as a commonly seen in other studies. Exposure was measured equally for cases and controls. In the physician health survey, recall correlation was 0.46.

One major limitation of using administrative databases is the drug dispensed does not automatically imply drug consumption. Therefore, misclassification of exposure may have occurred if patients were not actually taking the medication. Also, some subjects may have been exposed continuously for the study windows, whereas other individuals may have been exposed for only short durations. In the study, there is no reason to believe that measurement of exposure was depended on the cases status of the subject. However non differential misclassification may have provided an altered estimate of the risk.

Additional concern is with contamination by non-prescription analgesic consumption. This is not a factor for NSAIDs up until 1998 when NSAIDs became over the counter. For aspirin and acetaminophen however, the database records only these drugs that are prescribed by a physician. Therefore consumption of other over the counter medications is possible.

Measure of Outcome:

Misclassification bias is felt to be minimized in the study by using data from the Saskatchewan Health Branch. With each paid claim submitted to the outpatient prescription drug service database, information of the claimant is verified. A sample of the claims is also sent directly to the beneficiary to ensure that the information is correct. In addition, validation of the accuracy of the hospital services branch database is also undertaken and illogical entries are automatically recognized by computer programs. In addition, excellent agreement has been observed in several validation studies between medical charts and information hospital services branch database.

The possibility of outcome misclassification with regard to any of the primary outcomes in this study, namely end stage renal disease, dialysis and renal transplantation are extremely remote. Two of the three outcomes are major procedures while end stage renal disease is a chronic condition easily diagnosed with routine laboratory test.

Although ESRD comprises only a small proportion of individuals with chronic renal failure, ESRD was chosen as the case definition. Detection of chronic renal failure by serum creatinine requires frequent laboratory testing, not available from the Saskatchewan Health Database files and creatinine on its own correlates poorly with other gold standards for measuring renal function, such as inulin clearance, as it is affected by age, muscle mass and gender. Also serum levels of creatinine may fluctuate over time, creating difficulty in setting a specific value as

a cut off. These difficulties with outcome definition can lead to misclassification which may obscure true associations between risk factors and renal disease. Additionally, use of a laboratory based measurement may provide a biased estimate of both exposure and outcome as individuals that have blood tests are not representative of the general population. ESRD overcomes most of these issues as it provides a hard outcome with a readily identifiable time of occurrence.

Measurement of Confounders:

A confounder is any variable that is associated with the exposure in question independent of its association with the disease in question. A variable that is an intermediate step in the causal path between exposure in question and disease under study is not a confounding variable. Neither is a variable that is the result of the disease.

Errors in the measurement of confounding variables is another potential limitation of this research. The Saskatchewan Health Data files do not contain much direct information on potential confounders other than age and sex (34), however datafiles can be used indirectly to obtain information on potential confounders. For example, for chronic conditions that do not necessarily lead to hospitalization but do require medical therapy, information on outpatient dispensing of medications can be obtained. Subjects dispensed drugs that are used specifically for one condition can be assumed to have developed that condition (i.e. Diabetes). The Rate ratios can be adjusted for these potential confounders. The hospitalization, procedure database and physician diagnosis can also be used to identify co-morbidities with specific ICD-9 code. Unfortunately misclassification of some study subjects may have occurred because coexisting co-morbidities were identified using drug markers only. Some potential confounders such as smoking and ethnic background are not available from the database. Adjustment for the use of loop diuretics, other antihypertensive agents and hypertension severity did not alter the risk difference, suggesting that confounding did not play a significant role in our findings.

Duration of hypertension, gender and presence or absence of diabetes mellitus was accounted for in the design and cannot explain the results of this study. Each case was matched up to 20 randomly selected controls that initiated antihypertensive treatment in the same calendar month and year as the cases and were still at risk for an event of the time of matching. Furthermore, temporal factors influence prescribing and dialysis practices are inherently controlled for by this matching. Many other unmeasured confounders are correlated with age and gender.

Despite our efforts, we believe that the results may have been affected by confounding to some extent due to unknown factors unaccounted for in the analysis.

Confounding by Indication:

One of the major concerns with pharmacoepidemiology research is the potential for confounding by indication. Confounding by indication occurs when a medication is selectively prescribed to an individual when thought to be indicated by the physician (49, 51). In the case of NSAIDs, it is generally felt that these medications are contradicted in individuals with chronic kidney disease. Therefore when renal disease is discovered by a physician, they will be less inclined to prescribe nonsteroidal anti-inflammatory drugs, thereby creating a confounding by "contraindication". In this hypothetical situation, NSAIDs are avoided in individuals at high-risk for event (ESRD), and consequently the risk estimates associated with this medication appear protective.

Information on patient characteristics that may suggest confounding by contraindication such as measures of kidney disease including urinalysis, protein quantification and serum creatinine are not available in the Health Data Files. To evaluate this possibility, we examined individuals that were initially treated with NSAIDs then stopped. This analysis serves to emulate the discovery of chronic

kidney disease and the recommendation to avoid further NSAIDs. Even with this analysis, no attributable risk could be demonstrated with NSAID use and ESRD.

Latency Period:

One of the concerns with studying ESRD is that the duration of time between initial renal injury and outcome (dialysis or transplantation) can take many years to develop. As a result, a large proportion of NSAID users are likely to have pre-existing renal disease. In this analysis, if the results pointed to a detrimental affect with NSAIDs, it would not be possible to differentiate whether NSAID use causes or accelerates renal injury.

Power:

Whenever one obtains a null result, it is important to keep in mind that this may be a result of study power. Although the study had adequate power (>90% to detect a odds ratio of 1.5 for continuous NSAID use, p=0.05) when examining ESRD risk from NSAID utilization within 5 years of case identification, the study power to detect a similar difference up to 10 years was lower (78.9% for continuous NSAID use).

Missing Data:

During administrative changes, prescription drug information between the periods July 1st, 1987 and December 31st, 1988 is not available on an individual basis. Extrapolating drug use is therefore difficult as the index date for subjects may be before, during or after this lapse in information. Additionally, it removes the ability to analyze changes in drug patterns. For these reasons it was elected to consider all subjects as unexposed during the black out period. Additionally since the proportion of NSAID users among cases and controls is small and the expected bias non-differential, one would predict a limited bias towards the null hypothesis. Lastly, matching by cohort entry time and hypertension also matches the black out periods between cases and controls.

Conclusion

The following conclusions can be drawn from the study:

1. The duration and pattern of NSAID use, up to 10 years prior to the development of end stage renal disease does not appear to be associated with an increased risk of ESRD.

2. The cumulative dose of NSAID use 10 years prior to case definition is not statistically associated with end stage renal disease.

The results of the study provide evidence that NSAIDs do not increase the risk of end stage renal disease. These results however are limited to individuals only up to 10 years duration and cannot be extrapolated for earlier use, as the study could not test the hypothesis that exposure more than 10 years is associated with a risk of end stage renal disease. This is a potential concern, as kidney disease is often a slowly progressive disorder that can take many years before the initiation of dialysis. However if this were the case, and nonsteroidal anti-inflammatory drugs were detrimental one would expect to see an acceleration in disease progression and associated risk with drug utilization in shorter time window's prior to index date. The study may also be affected by confounding by indication. Although evaluated by looking at prescription behaviors among physicians, residual confounding may remain.

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Appendix 1: Observational Studies Examining NSAID use and Kidney Disease

Author (Year)	Study Design	Exposure	Measures	Cases	Controls	Findings	Possible Limitations
Adams et al.[19] (1986)	Case Series	NSAID		Elevated serum creatinine (n = 17)	N/A	6 - persistent renal impairment despite NSAID withdrawal	Un-controlled study Confounding
Morlans et al.[28] (1990)	Case Control	ASA Acetaminophen NSAID Phenacetin	Personal Interview (Subjects blinded to study hypothesis)	Hemodialysis patients (n = 340)	Hospital controls matched for age and sex (n = 673)	ASA RR: 2.54 (1.24 – 5.2) Acetaminophen – n/s NSAID - n/s Phenacitin RR: 19.1 (2.3 – 157)	Recall Bias Selection Bias Confounding by Indication. Time – Order Sequence
Sandler et al.[29] (1991)	Case control	NSAID	Telephone Interview (un-blinded)	Chronic renal failure on hospital discharge (n = 503 of 709)	Age, sex, race and region matched (n = 477 of 717)	NSAID OR: 4.6 (1.5 – 14) for daily NSAID use in males, 16.6 (2.1 – 129) for males older than 65 Other subgroup analysis no association	Recall bias Selection bias Confounding by Indication Time-Order Sequence
Segasothy et al.[30] (1994)	Case Series	ASA Acetaminophen NSAIDs Phenacetin	Personal Interview	n = 259 of 308 with > 1 Kg of lifetime analgesic exposure	N/A	26.6% - radiographic evidence of renal papillary necrosis 38 consumed NSAIDs exclusively	Un-controlled study Confounding
Perneger et al.[31] (1994)	Case Series	ASA Acetaminophen NSAID	Telephone Interview (un-blinded)	Hemodialysis patients (n = 752 of 978)	Age and sex matched (n = 361 of 402)	ASA – n/s Acetaminophen OR: 2.0 (1-5K pills), 2.4 (> 5K pills) NSAIDS OR: 8.8 (> 5K pills) NB: Based on 2 cases	Recall Bias Observer Bias Time-Order Sequence Selection Bias

Appendix 2. Antihypertensive Medications Available by Prescription

ACE Inhibitors	Beta-Blockers	Calcium Channel Blockers
Captopril Enalapril Lisinopril Fosinopril Quinapril Enalapril / HCTZ Linsinopril / HCTZ Benazepril Ramapril Cilazapril Perindopril	Acebutolol Atenolol Propranolol Pindolol Metoprolol Nadolol Labetalol Oxprenolol Timolol Pindolol/HCTZ Timolol/HCTZ Propranolol/HCTZ Atenolol/HCTZ Metoprolol/HCTZ	Nifedipine Diltiazem Verapamil Nicardipine Felodipine Amilodipine
Diuretics	**Loop Diuretics**	**Other Agents**
HCTZ Amiloride Amiloride/HCTZ Chlorthalidone Indapamide Metalazone Spironolactone Spironolactone/HCTZ Triamterene Triameterene/HCTZ	Furosemide Torsemide Ethacrynic Acid	Methyldopa Methyldopa/HCTZ Clonidine Hydralazine Minoxidil Reserpine Doxazosin Guanethidine Losartan Bethanidine Debrisoquine Rauwolfia Prazosin Methyldopa/Chlorthiazide Guanethidine/HCTZ Reserpine/HCTZ Pargyline Diazoxide Terazosin Methyclothiazide/Deserpidine Reserpine/Hydralazine//HCTZ Chlorthalidone/Resperpine Hydroflumethiazide/Reserpine/ Protoveratrines

Appendix 3. Cohort Restriction Criteria

Exclusion	Definition	Relevant Codes
Angina	Concomitant beta-blockers or calcium channel blockers and nitrates within the first year of cohort entry	Beta-blockers (001-009) or Calcium Channel Blockers (016-021) and - 078 Isosorbide Dinitrate - 079 Isosorbide-5 Mononitrate - 080 Nitroglycerin - 081 Erythrityl tetranitrate
Arrhythmias	Concomitant beta-blockers and an anti-arrhythmic agent within the first year of cohort entry	Beta-blockers (001-009) and - 058 Amiodarone - 059 Digoxin - 060 Disopyramide - 061 Flexainide - 062 Procainamide - 063 Propafenone - 065 Quinide Bisulfate - 066 Quinide Polygalacturonate - 067 Quinide Sulfate - 068 Tocainide
Hyperthyroidism	Concomitant beta-blockers and either antithyroid drugs or radioiodine within the first year of cohort entry	Beta-blockers(001-009) and - 109 Methimazole - 110 Propylthiouracil
Migraine headache	Concomitant beta-blockers and either ergot preparations, sumatriptan or methysergide within the first year of cohort entry	Beta-blockers (001-009) and - 100 Dihydroergotamine Mesylate - 101 Ergotamine Tartrate - 102 Ergotamine Tartrate / Caggeine - 103 Ergotamine Tartrate / Cyclizine - 105 Methysergide - 107 Sumatriptan - 108 Ergotamine Tartrate / Caffeine

Appendix 4. Exclusion of Subjects

Exclusion	Definition	Relevant Codes
Connective tissue disease	Prescription codes for anti-rheumatic drugs, at any time prior to index date.	Prescription Codes: - 092 Penicillamine - 116 Auranofin - 116 Aurothioglucose - 116 Cyclophosphamide - 116 Methotrexate - 116 Sodium Aurothiomalate - 116 Hydroxychloroquine

Appendix 5:
Fee-For Service Codes of Interest

Peritoneal dialysis – each 24 hour period	D0121
Hemodialysis – initial	D0122
Hemodialysis – second to fifth	D0123
Hemodialysis – sixth and subsequent	D0124
Hemodialysis – cut down artery and vein	D0125, L0660
Hemodialysis – Schribner (or similar) shunt – initial or repeat	D0126, L0661
A.V. fistula for hemodialysis	D0127, L0662
Hemodialysis and training in dialysis centre	D0128
Any subsequent hemodialysis in the centre	D0129
Supervision of hemodialysis at home, per week	D0130
Supervision of peritoneal dialysis at home, per week	D0131
Any subsequent peritoneal dialysis in the centre	D0134
Renal surgery – A.V fistula with graft – prosthetic or venous	L0663
Renal surgery – ligation of fistula	L0666
Peritoneal dialysis – chronic dialysis catheter – insertion	D0118, L0667
Peritoneal dialysis – chronic dialysis catheter – removal	D0117, L0669
Acute dialysis catheter insertion includes first 24 hours of dialysis	D0119, L0670

Appendix 6. NSAIDs Available in the Saskatchewan Drug Formulary During the Study Period

Drug Name	DDD[1]	Maximal Daily Dose[3]
Diclofenac	0.1	200 mg
Diclofenac / Misoprostol	0.1	200 mg
Diflunisal	0.75	1500 mg
Fenoprofen	1.2	3000 mg
Floctafenine	0.6[2]	1200 mg
Flurbiprofen	0.2	300 mg
Ibuprofen	1.2	3200 mg
Indomethacin	0.1	200 mg
Ketoprofen	0.15	200 mg
Mefenamic Acid	1.0	1500 mg
Nabumatone	1.0	2000 mg
Naproxen	0.5	1500 mg
Phenylbutazone	0.3	600 mg
Phenylbutazone / Antacid	0.3	600 mg
Piroxicam	0.02	20 mg
Sulindac	0.4	400 mg
Tiaprofenic Acid	0.6	-
Tolmetin	0.7	2000 mg
Zomepiraz	0.3	-

1. Defined Daily Dose – Anatomical Therapeutic Chemical (ATC) classification index – WHO Collaboarting Centre for Drug Statistics Methodology
2. Estimated according to maximal daily dose

Appendix 7. Co-morbidities Identified by Prescription Drug Use

Agent	Definition
Hyper-cholesterolemia	Prescription for cholesterol lowering agents
Gout	Prescription for uric acid agents
Insulin requiring diabetes mellitus	Prescription for insulin agents
Mental Illness	Prescription for mental illness or anxiety
Other anti-hypertensive	Prescription for other anti-HTN medication
Oral hypoglycemics	Prescription for oral hypoglycemic agents
Parkinson's Disease	Prescription for anti-Parkinson medication
Inhaled Corticosteroids	Prescription for respiratory steroids
Respiratory Illness	Prescription for other respiratory agents
Seizure Disorder	Prescription for anticonvulsants
Ulcer Therapy	Prescription for upper GI therapy

NB: at least three prescription received between cohort entry and index date.

Appendix 8. Co-morbidities by Physician Diagnosis or Discharge Diagnosis from Hospital

Name	Definition
Stroke	ICD-9: 431 = "Intracerebral hemorrhage" 432 = "Other and unspecified intracranial hemorrhage" 433 = "Occlusion and stenosis of precerebral arteries" 434 = "Occlusion of cerebral arteries" 436 = "Acute, but ill-defined, cerebrovascular disease"
Peripheral Vascular Disease	ICD-9: 440 = "Atherosclerosis" 444 = "Arterial embolism and thrombosis" * Excludes 443.0 Raynaud's syndrome 443.1 Thromboangiitis obliterans 443.8 Other specified peripheral vascular diseases 443.81 Peripheral angiopathy in diseases classified elsewhere 443.89 Other
Heart Disease	ICD-9: 410.0 = "Acute Myocardial Infarction" 411.0 = "alt. Acute & Subacute Form of Ischemic Heart Disease" 412.0 = "Old Myocardial Infarction" 413.0 = "Angina Pectoris" 414.0 = "alt. Forms of Chronic Ischemic Heart Disease" 414.1 = "Aneurysm of Heart" 414.8 = "alt. Ischeamic, Myocardial" 414.9 = "unspec. Ischaemic Heart Disease NOS"
Heart Failure	ICD-9: 428.0 = "Heart Failure" 428.1 = "Left Heart Failure" 428.9 = "Unspecified Cardiac, Heart or Myocardial Failure"
Arterial Aneurysm	ICD-9: 441 = "Aortic aneurysm and dissection" 442 = "Other aneurysm"