# THE RISK OF GASTROINTESTINAL BLEEDING ASSOCIATED WITH DIURETICS AMONG HYPERTENSIVE PERSONS

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*THIS STUDY IS DEDICATED TO ALL THOSE WHO ARE CONTRIBUTING TO EXISTING KNOWLEDGE IN ORDER TO MAKE THE WORLD A BETTER PLACE FOR GENERATIONS TO COME*

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## ABSTRACT

**Purpose:** There are reports indicating that diuretics may increase the risk of gastrointestinal bleeding. The study was conducted to verify this hypothesis and to assess whether the risk varies with the different types of diuretics.

**Methods:** Using the Saskatchewan health database, a nested case-control design was used, conducted within a population-based cohort of 47,865 new users of antihypertensive medications in Saskatchewan, from 1980 to 1983, and followed up to mid 1987. 753 subjects hospitalized for gastrointestinal bleeding were identified during this period, each of whom was matched with 10 randomly selected controls from a risk set formed at the index date, namely when a case was identified.

**Results:** The rate of hospitalization for gastrointestinal bleeding in this cohort was 2.83 cases per 1,000 subjects per year. The adjusted rate ratio of gastrointestinal bleeding for current use of any diuretic within the 30-day time window prior to the index date was 1.54 (95% confidence interval, CI 1.27 to 1.86) compared with no current use of antihypertensive medications. Among the different classes, potassium-sparing diuretic are associated with the highest adjusted rate ratios (2.64; 95% CI, 1.35 to 5.16), and current use of combination of thiazide diuretics and potassium sparing with the lowest (1.39; 95% CI, 1.11 to 1.73) in the 30-day time window. The adjusted rate ratio of hospitalization for gastrointestinal bleeding for current use of a daily dose of thiazide diuretics less than 50mg was 1.34; 95% CI, 0.37 to 4.90, and for a daily dose equal to 50 to 60 mg the rate ratio was 1.81; 95% CI, 0.93 to 3.54, while for a daily dose greater than 60mg the rate ratio was 2.99; 95% CI, 1.14 to 7.84 within the 30-day time window.

Results were similar when a 60-day exposure time window was used. Higher doses of furosemide (loop diuretic) were positively associated with hospitalization for gastrointestinal bleeding.

**Conclusion:** Diuretic use appears to increase the risk of gastrointestinal bleeding.

# Résumé

**But:** Quelques études ont rapporté que l'usage de diurétiques pourrait augmenter le risque d'hémorragie gastro-intestinale. Cette étude a été menée afin de vérifier cette hypothèse et d'évaluer si ce risque variait entre les différents types de diurétiques.

**Méthodes:** Un devis cas-témoin niché dans une cohorte de 47,865 nouveaux utilisateurs de médicaments hypertenseurs au Satskatchewan entre 1980 et 1983, fut utilisé. Ces patients ont été suivis jusqu'à la mi-1987. 753 sujets hospitalisés pour hémorragies gastro-intestinales furent identifés au cours de cette période. Chaque cas a été apparié à 10 sujets témoins sélectionnés aléatoirement à partir d'un critère de risque au jour indexé de chaque cas, c'est-à-dire le jour où le cas fut identifié.

**Résultats:** Le taux d'hospitalisation pour hémorragie gastro-intestinale dans cette cohorte a été de 2.83 cas par 1,000 sujets par année. Le risque relatif ajusté pour les hémorragies digestives associé à l'utilisation courrante d'un diurétique pour une période de 30 jours précédant le jour indexé était de 1.54 (IC 95%, 1.27 à 1.86) comparé à l'absence d'utilisation concurrente d'antihypertenseurs. Parmi les différentes classes de diurétiques, les diurétiques d'épargne potassique ont montré le risque relatif ajusté le plus élevé (RR 2.64; IC 95%, 1.35 à 5.16), et l'utilisation courante d'une combinaison de diurétiques de type thiazide et ceux d'épargne potassique était associée avec le risque relatif ajusté le plus bas (RR 1.39; IC 95%, 1.11 à 1.73) dans une période d'utilisation de 30 jours. Pour une période de 30 jours, le risque relatif ajusté des hospitalisations pour hémorragies gastro-intestinales associé à l'utilisation courante de diurétiques de type thiazide était de 1.34 (IC 95%, 0.37 à 4.90) pour les posologies quotidiennes inférieures à 50 mg/jour, de

1.81 (IC 95% 0.93 à 3.54) pour une posologie quotidienne de 50-60 mg/jour, et de 2.99 (IC 95%, 1.14 à 7.84) pour les posologies quotidiennes supérieures à 60 mg/jour. Les résultats étaient similaires lorsqu'une période d'exposition de 60 jours fut utilisée. Des doses élevées de furosemide (diurétique de l'ance) étaient positivement associées avec les hospitalisations d'hémorragie gastro-intestinale.

**Conclusion:** L'utilisation de diurétiques semble augmenter le risque d'hémorragie gastro-intestinale.

# 1.0 INTRODUCTION

## 1.1 Background

Technological and scientific advancement have led to more improved and powerful therapeutic drugs than before. These drugs make a vital contribution to health, have become central to any health system, and have helped to provide better medical care, thus reducing human suffering and pain. However, taking drugs is not always without risk. During drug development, preclinical and clinical studies usually provide extensive evidence of the product's effectiveness, but not as much for its safety (WHO, 1997). According to the World Health Organisation (WHO, 1997), normally no more than 3000 patients are treated with the drug during the clinical trial phase, hence making it likely that adverse drug reactions with an incidence of less than one in 10,000 will remain undetected.

Adverse drug reactions can cause severe suffering. They are estimated to cause 3 to 5 percent of all hospital admissions (Davies, 1984), and a survey carried out in 1971 found that they might be responsible for 160,000 deaths each year in US hospitals alone (Shapiro et al., 1971). A more recent study has concluded that adverse drug reactions significantly prolong the length of hospitalisation, which may double the cost, and are associated with an almost two-fold increase in the risk of death (Classen et al., 1997).

In fact, several examples prove that premarketing testing may fail to detect side effects that later manifest themselves as adverse drug reactions (ADRs). Since the early part of

the 1900s, a series of tragic adverse drug reactions has been reported. As far back as 1937, over one hundred children in the US died from renal failure as a result of sulfanilamide (Geiling and Cannon, 1938). In the early 1960s, another catastrophic event occurred when pregnant women used a sleeping pill containing thalidomide. It resulted in the birth of malformed babies, phocomelia- the absence of limbs or parts of limbs, sometimes replaced with the presence of flippers (Lenz, 1966). Recently, tragic events involving diethylene glycol have been reported, claiming the lives of children, and intoxicating many others (Pandya, 1988; Hanif et al., 1995). An important adverse effect of several drugs is damage made to the gastrointestinal mucosa with the resultant complication of bleeding (Pemberton, 1970). These drugs include NSAIDs, corticosteroids (Pahor et al., 1994; Hudson et al., 1995).

### 1.2 Gastrointestinal Bleeding

The passage of blood from either end of the gastrointestinal tract is a common cause of morbidity and mortality (Gilbert, 1990). Gastrointestinal bleeding can be classified as upper (bleeding from upper digestive tract – esophagus, stomach, duodenum) and lower (passage of blood from the area between the duodenum and the anus). Gastrointestinal bleeding (GIB) is regarded as a common problem worldwide and, according to Friedman and Martin (1993), the precise estimates of its frequency are difficult to come by. Population-based studies from the 1960s and 1970s suggested annual rates of upper gastrointestinal bleeding (UGIB) ranging from 48 to 144 episodes per 100,000 population (Greene et al., 1992). The total number of hospital admissions for GIB was estimated to be 150 per 100,000 population, or a total of more than 450,000 admissions per year in US

(Cutler and Mendeloff, 1981). Overall, it is estimated that there are 10,000 to 20,000 deaths per year from UGIB alone in the US (Elta, 1991). Estimated case fatality for UGIB is approximately 10 percent (Gilbert, 1990). Perez Gutthann and colleagues (1997) have reported a 4 percent overall case fatality rate of upper gastrointestinal bleeding, and annual incidence rate of 100 per 100,000 persons in a general population in Canada. Lower gastrointestinal bleeding, specifically colorectal bleeding accounts for approximately 20 percent of all cases of gastrointestinal bleeding (Forde, 1992). The mortality rate for all patients with lower gastrointestinal bleeding (LGIB) has been reported to be as high as 11.4 percent (Forde, 1992). Gastrointestinal bleeding is said to be self-limiting in approximately 80 percent of cases, and in the other 20 percent of patients who have continued bleeding or rebleeding during hospitalization, mortality rates may be as high as 30 to 40 percent (Fleischer, 1983). It is estimated that surgery may be required in 15 to 30 percent of patients presenting with gastrointestinal bleeding, including 10 to 15 percent of patients with bleeding peptic ulcer (Branicki et al., 1991).

Gastrointestinal bleeding is a common reason for hospital admission, and thus imposes a substantial burden on health care resources (Rockall et al., 1995; Longstreth, 1995). In the US, the cost of managing bleeding was estimated to be US$3,180 to US$4,997 per patient (Richter et al., 1991; Jiranek et al., 1995; Quirk et al., 1997). In Canada, the direct medical cost among the elderly who are more prone to gastrointestinal bleeding is estimated to be around Can$6,098 for 8.64 days of inpatient care (Marshall et al., 1999). Gastrointestinal bleeding is one of the most common conditions that precipitate admission to an intensive care unit (Manthous et al., 1997). Significant cardiopulmonary

stress, myocardial ischemia and infarction may accompany gastrointestinal bleeding (Bhatti et al., 1998; Emenike et al., 1999). Anemia is a late manifestation of iron deficiency commonly caused by gastrointestinal blood loss (Joosten et al., 1993).

### 1.2.1 Predictors of Gastrointestinal Bleeding

Clinical and epidemiological studies have described the occurrence of gastrointestinal bleeding and have identified a number of predictors. Although heterogeneous diseases cause gastrointestinal bleeding, common risk factors including age, gender, medications and comorbidity play a role that is independent of the underlying diagnoses (Bordley et al., 1985; McIntosh et al., 1988; Lanas et al., 1992).

The most frequent causes of bleeding from the upper digestive tract are sequelae of peptic ulcer of the duodenum and stomach (Goff, 1993). Results of an international survey in 21 countries showed that peptic ulceration was the most frequent cause of upper gastrointestinal bleeding, accounting for about 36.7 percent (Morgan and Clamp, 1988). Other frequent causes are inflammatory, haemorrhagically erosive changes of the upper gastrointestinal mucosa, ruptured esophageal varices or gastric tumors (Goff, 1993; Friedmann and Martin, 1993). Together, these diseases are estimated to cause about 75 percent of bleeding in patients (Friedmann and Martin, 1993). The expected incidence of bleeding due to ulcer disease is estimated to be 50 patients per 100,000 inhabitants and it is presumed that ulcer disease is the cause of bleeding from the digestive tract in about 35 percent of patients (Friedmann and Martin, 1993).

Over the past decade, older patients, especially those over age 60 year, have made up an increasing proportion of patients with gastrointestinal bleeding, and it is in this group of patients that mortality rates have remained relatively high (Gilbert, 1990; Agrawal, 1991; Gostout et al., 1992). Studies utilizing multivariate analysis have shown that advancing age independently predicts gastrointestinal bleeding after adjusting for other known risk factors (Bordley et al., 1985; Branicki et al., 1992; Lanas et al., 1992). According to Banning et al. (1965), gender may have a significant influence over age distribution. Rockall et al. (1995), have documented that, at all ages, incidence in males was more than double that in females except in elderly patients.

Several drugs, including corticosteroids and NSAIDs, increase the risk of gastrointestinal bleeding (Pemberton, 1970; Pahor et al., 1994; Hudson et al., 1995). By far the most important drugs responsible for gastrointestinal mucosal damage and bleeding are the NSAIDs, both salicylate and non-salicylate in type (Silvoso et al., 1979). Epidemiological studies have shown that NSAIDs increase the risk of peptic ulcer bleeding 3- to 5-fold (Hawkey, 1990; Bollini et al., 1992). Egan and Jensen, in 1991, reported that 60 percent of all ulcer patients admitted with upper gastrointestinal bleeding had ingested aspirin or an NSAID within two weeks of admission. The manifestations of mucosal injury by NSAIDs are submucosal haemorrhage, erosions and ulceration. The major site of injury is the gastric antrum, but the mucosa of the esophagus, duodenum, small bowel and colon may also be affected (Bjarnason et al., 1987). Another type of damage elicited by NSAIDs is caused by a systemic mechanism that involves the inhibition of cyclooxgenase (COX), an enzyme essential to the production of

prostaglandins from arachidonic acid; which has a mucosal protective activity, hence preventing gastric mucosal damage (Vane and Botting, 1995). Alcohol may potentiate the effect of both aspirin and NSAIDs as a cause of acute upper gastrointestinal tract bleeding (Greene et al., 1992). Also, it has been documented that anticoagulants exert a significant effect on the development of ulcer disease and haemorrhage from the digestive tract, and often cause inflammatory and haemorrhagically-erosive changes to the upper and lower gastrointestinal mucosa (Friedmann and Martin, 1993).

A recent study (Garcia Rodriguez et al., 1998) indicated that current users (that is 30 days prior to index date) of antihypertensive drugs had a significantly increased risk of upper gastrointestinal bleeding (1.7; 95% CI, 1.4-2.0) relative to nonusers, and for recent users (31 to 60 days prior to the index date) the risk was 1.5; 95% CI, 1.2 –1.8. Pahor and colleagues (1996) reported that calcium antagonists, an antihypertensive medication, are associated with an increase risk of gastrointestinal bleeding in hypertensive patients over 67 years old. According to Pales et al. (1991), calcium antagonists interfere with blood coagulation by inhibiting platelet aggregation. However, other studies failed to find any association between gastrointestinal bleeding and exposure to calcium antagonists (Suissa et al., 1998; Desboeuf et al., 1998). On the other hand, there are scattered reports, both past (Nordqvist et al., 1959; Gesink and Bradford, 1960; Ball, 1960; Jick and Porter, 1978) and recent (Suissa et al., 1998 and Garcia Rodriguez et al., 1998) indicating a possible association between diuretics, another antihypertensive drug class, and gastrointestinal bleeding.

### 1.3 Diuretics

Diuretics are traditionally defined as substances that increase the amount of fluid, excreted by the kidney, and remain drugs of first choice both for treating hypertension and common edematous conditions (Wilcox, 1999). These drugs, in use since the 1950s, are indicated in hypertension accompanied by congestive heart failure and/or renal insufficiency, and are required in all forms of congestive heart failure unless definitely contraindicated (Reyes and Taylor, 1999). Modern diuretics currently used in cardiovascular medicine include three classes of substances, namely, thiazide class, loop diuretics and potassium sparing diuretics (Reyes and Taylor, 1999). Diuretics together with beta blockers represent the first line of treatment for mild to moderate hypertension (Joint National Committee, 1997). Their selection for this purpose is based upon proven ability to control hypertension in patients with mild to moderate elevations of blood pressure, their safety and the information that has developed over time indicating their capacity to reduce cerebrovascular and cardiovascular mortality (Joint National Committee, 1993).

#### 1.3.1 Trends in Diuretic Use

In 1986, over 100 million prescriptions of diuretics had been sold in the United States. As Figure 1 indicates, trends in the sales use of antihypertensive medications between 1986 and 1997 demonstrated declines in the use of diuretics, which had been the most commonly prescribed class of antihypertensive medications since their introduction in the late 1950s (Kaplan, 1999). Proportionate use of diuretics declined from 56 percent in 1982 to only 27 percent in 1993, a relative reduction of 52 percent (Manolio et al., 1995).

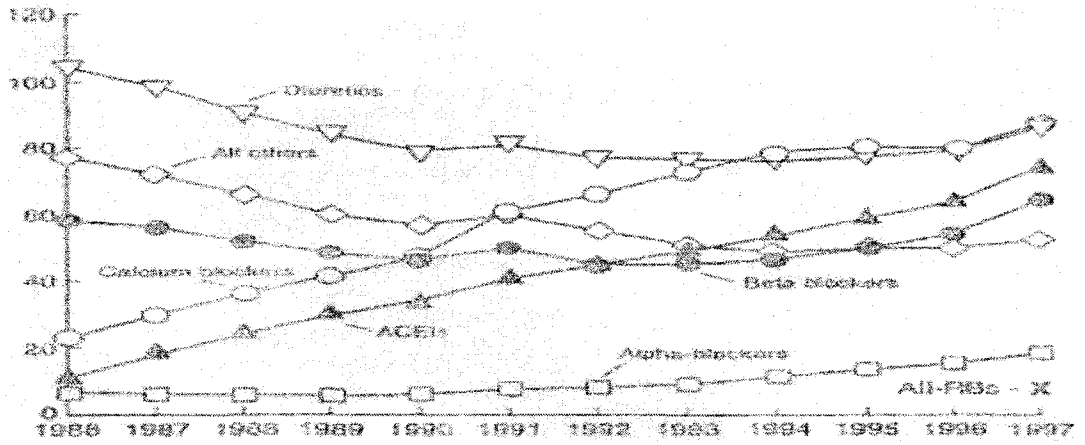


**Figure 1. Sales of antihypertensive drugs (in millions of prescriptions) in the US from 1986 to 1997.**

**Source: Kaplan NM. Clinical hypertension 7th Edition. Williams and Wilkins, Baltimore, 1998, pp 189.**

Siegel and Lopez (1997), reported that in 1992 and also, in 1995, of the 10 most frequently prescribed antihypertensive medications, only one, the combination of triamterene and hydrochlorothiazide, was a diuretic (19.8 million in 1992 and 8.0 million in 1995). Hydrochlorothiazide alone, without any combination was the 14$^{th}$ most commonly prescribed antihypertensive medication in 1995, resulting in 2.4 million prescriptions, down from 3.1 million in 1992. When individual medications were grouped into the major antihypertensive classes, diuretics accounted for 16 percent of prescriptions in 1992 compared to 8 percent in 1995, and during the same period, calcium antagonists went from 33 percent to 38 percent, ACE inhibitors from 25 percent to 33 percent, and beta blockers from 18 percent to 11 percent.

Notwithstanding the reported decline in diuretic use, Messerli and Grossman (1999) have documented that over 24.5 million patients in the United States took diuretics in 1998. A study in Quebec, Canada (Laplante et al., 1998), reported that of 4,049 hypertensive patients seen in 1996, the most frequently prescribed medications were calcium channel

blockers (26.1%), followed by diuretics (25.3%). Also, in a study among subjects, aged 18 to 74 years, from all 10 provinces of Canada, Chockalingam and Fodor (1998) reported that out of a total of 17,965,000 prescriptions of antihypertensive medications in 1994, oral diuretics accounted for 27.90 percent and for diuretic combinations 1.50 percent, while ACE inhibitors was 25.00 percent and calcium channel blockers accounted for 23.60 percent. From the period August 1995 to July 1996, oral diuretics accounted for 25.13 percent and diuretic combination was 1.60 percent out of a total prescription of 119,947,000. In the same period, ACE inhibitors and calcium channel blockers accounted for 27.23 percent and 24.23 percent respectively. Jabary and associates (2000) have also reported that in Spain diuretics remain the most popular antihypertensive medication, whereas the newer drug types are rising rapidly. They have documented that in 1986, diuretics were the most antihypertensive drug consumed, and in 1994, diuretics still remained the most commonly prescribed antihypertensive. Furthermore, another study (Crucitti et al., 2000) in Italy, has reported that, during the period from 1988 to 1995, the most frequently prescribed antihypertensive drugs were calcium channel blockers (47%) followed by diuretics (37%), ACE-inhibitors (33%) and beta-blockers (5.5%).

### 1.3.2 Complications of Diuretic Use

Diuretics are regarded as safe and effective when used to treat edema (Ellison, 1999) and hypertension (Wilcox, 1999). However, there has been increasing awareness of the potentially harmful effects associated with the use of diuretics. Clinical investigations

have disclosed that like many other drugs, diuretics cause significant adverse effects that can complicate therapy (Wilcox, 1999).

The two most common complications of diuretic therapy are volume depletion and hypokalemia (Rivera-Santos and Star, 1997), which are commonly associated with the use of thiazide and loop diuretics. Although there are suggestions of a relationship between thiazide-induced hypokalemia, increased ventricular ectopy, and possible sudden death (Holland et al., 1981; Hollified et al., 1981), only selected subjects who had experienced severe degrees of hypokalemia (<3.0 mmol/L) were included in these studies. A study in nonselected patients did not confirm these observations (Papademetrion et al., 1988). Apart from fluid and electrolyte abnormalities induced by diuretics, there are reports that impaired glucose tolerance and hyperglycemia are associated with the use of several diuretics, particularly the thiazide class diuretics (Nader et al., 1988). It has been shown that the use of thiazide diuretics may have an adverse effect on insulin resistance and insulin release (Pollare et al., 1989). However, in a randomized controlled study, changes in glucose levels were not significantly different with a diuretic compared with other antihypertensive drugs (Neaton et al., 1993). According to Ames (1986), when thiazide diuretics are used for less than one year, serum cholesterol will increase approximately 5 percent to 7 percent. But a review (Moser, 1989) of diuretic-based clinical trials did not find any association between thiazide diuretics and serum cholesterol.

Among other adverse reactions reported with diuretics are impotence, ototoxicity and drug allergy. Deafness has been reported with all commonly used loop diuretics, and the incidence appears to be higher with ethacrynic acid and furosemide (Tuzel, 1981). There is documented evidence indicating that rates of reported impotence were much higher in those receiving a thiazide-diuretic than a placebo or a beta blocker (Greenberg, 1981; Grimm et al., 1997). However, a recent survey of 100 male hypertensive outpatients showed that impotence was related to the severity of hypertension and comorbid cardiovascular disease, but not to the use of diuretics (Jensen et al., 1999). Cumulative evidence, also suggests that the long-term use of diuretics may be associated with renal cell carcinoma (Grossman et al., 1999). In a comprehensive review of published articles between January 1966 and April 1998, Grossman and associates (1999) reported from 9 case control studies, an average odds ratio of 1.55 with a 95% confidence interval of 1.42 to 1.71 ($p < 0.00001$) of renal cell carcinoma occurring in patients treated with diuretics compared with nonusers of diuretics. They also reported that in 3 cohort studies of 1,226,229 patients, diuretic therapy was associated with more than twofold risk of renal cell carcinoma when compared with patients not on diuretics. However, Lee and Hennekens (1999) have argued that the findings from the studies used by Grossman and associates may have resulted from uncontrolled confounding by known or unrecognized risk factors.

Finally, concern has been raised regarding an unexpected association between diuretics and gastrointestinal bleeding. Case reports and epidemiological studies have indicated

this association may exist (Zuckerman and Chazan, 1958; Ball, 1960; Jick and Porter, 1978; Suissa et al., 1998). This relation is the object of the present thesis.

### 1.3.3 Possible Mechanisms of Diuretics on Risk of Gastrointestinal Bleeding

The definite mechanisms responsible for the positive association between diuretics and gastrointestinal bleeding still remain unclear.

#### 1.3.3.1 Biological Plausibility

Documented biological evidence suggests that diuretics can induce gastrointestinal bleeding. One conceivable mechanism for the adverse effects may be related to the sulfonamide content of some diuretics. Sulfonamides may cause aplastic anemia but are much more frequently associated with selective thrombocytopenia (Miescher, 1973). Thrombocytopenia is a platelet disorder that induces mucosal bleeding (Lutcher, 1992). Numerous drugs including furosemide (Duncan et al., 1981) have been associated with immune thrombocytopenia. With drug-induced immune thrombocytopenia, bleeding usually appears abruptly, may be severe, and mucosal membrane bleeding from all sites is common (Duncan et al., 1981). The thiazide diuretics have also been reported as producing thrombocytopenia in an idiosyncratic fashion (Aster 1977). Thiazide-induced thrombocytopenia generally is insidious in onset, and recovery usually occurs gradually, but within several weeks after stopping the drug, and according to Aster (1977). The risk of bleeding in any patient increases progressively as the platelet count falls and at very low counts the risk is quite high. However, Gaydos et al., (1962) have pointed out that thrombocytopenia alone is rarely responsible for bleeding, and that the clinical

observations merely reflect the greater ease with which predisposing lesions give rise to haemorrhage in thrombocytopenic patients as compared to those with normal platelet counts. There are reports that as many as 25 percent of patients who ingest thiazide diuretics develop thrombocytopenia due to suppression of megakaryocyte production (Nader et al., 1988; Lutcher, 1992). It has been reported that in healthy persons, the impairment of platelet function produced by drugs usually is of no clinical significance (Kaneshiro et al., 1969). According to Kaneshiro and associates (1969), on the contrary, in patients with coagulation disorders, in thrombocytopenic or uremic patients, impairment of platelet function by drugs may remove one of the remaining hemostatic defences and result in serious bleeding.

An alternative mechanism could be related to platelet dependent clotting mechanisms, which are inhibited by diuretics, especially furosemide. It has been shown that both nitric oxide and $PGI_2$ can inhibit platelet aggregation and adhesion (Thiemermann, 1991). Furosemide, a loop diuretic, enhances the synthesis and release of endothelium-derived kinins, which act as a potent stimulus for the endothelial formation of nitric oxide and prostaglandin ($PGI_2$) (Wiemer et al., 1994). Furosemide also stimulates the synthesis of endothelial cyclic GMP (Wiemer et al., 1994) that has been well documented as an index of endothelial nitric oxide synthesis (Martin et al., 1988). It has been reported that drugs that release nitric oxide inhibit platelet aggregation and may promote bleeding in patients taking these drugs (Salvemini et al., 1996). Nitric oxide increases blood flow in the gastric mucosa and inhibits the adherence of leukocytes to the endothelium within the gastrointestinal microcirculation (Lanas et al., 2000). Nitric oxide stimulates the soluble

guanylate cyclase (sGC) by interacting with the ferroheme center of the enzyme resulting in the generation of guanosine 3':5'-cyclic monophosphate (cGMP) (Murad, 1986). Increased cGMP levels subsequently lead to inhibition of platelet aggregation (Nishikawa et al., 1982). Besides this well known mechanism of action, Nitric oxide (NO) also release $PGI_2$, and the subsequent release of $PGI_2$ by NO increases at least ten times the ability of nitric oxide to inhibit thrombin-induced human platelet aggregation (Salvemini et al., 1996). According to the authors, these results clearly show that in the presence of $PGI_2$ NO becomes powerful an antiplatelet agent. $PGI_2$ is a potent vasodilator, through a direct relaxation of vascular smooth muscle, and also an inhibitor of platelet aggregation (Schlondorff, 1986). $PGI_2$ acts on platelets through a receptor-mediated activation of membrane-bound adenylate cyclase and a consecutive increase in intracellular $_cAMP$ (Heller and Bevers, 1997).

The possible association between diuretic use and gastrointestinal bleeding has been corroborated by experimental evidence. It has been reported that furosemide enhances the release of endothelial kinins, nitric oxide and $PGI_2$ in animals (Wiemer et al., 1994). Recently, it has been reported that furosemide increases the secretion of $PGI_2$ both in vitro and in vivo in humans (Liguori et al., 1999). Adenosine monophosphate (AMP) is reported to inhibit ADP-induced platelet aggregation in humans, and that it exerts their inhibitory effect on ADP-induced platelet aggregation directly and also by conversion to adenosine (Mustard and Packham, 1970). Inhibition of ADP-induced platelet aggregation by furosemide has been documented in human (Kribben et al., 1988).

It must be noted however, that nitric oxide and postaglandins are reported as having a potential beneficial effect on NSAID-induced gastroduodenal damage (Lanas and Hirschowitz, 1999). Experimental studies in animals (Wallace et al., 1994) and in humans (Lanas, 1999) have suggested that both oral and transdermal NO-releasing drugs reduce the gastroduodenal damage induced by NSAIDs. On the other hand, inhibition of platelet aggregation is seen as a mechanism involved in NSAID-induced gastrointestinal bleeding (Lanas and Hirschowitz, 1999). A case control study reported that drugs that generate nitric oxide are independently associated with a decreased risk of gastrointestinal bleeding (Lanas et al., 2000). According to the authors, this association was evident in patients taking nonsteroidal anti-inflammatory drugs, including low-dose aspirin.

An experimental study was performed in an attempt to show the relationship between thrombocytopenic purpura and the administration of hydrochlorothiazide (Ball, 1960). The effect of hydrochlorothiazide on patient's platelets in the peripheral blood and in vitro was demonstrated, and an abnormality was shown to exist in patient's serum in the presence of the drug. Hydrochlorothiazide has recently been shown to decrease platelet activity in vivo in hypertensive patients (Gleerup et al., 1996).

It is therefore biologically plausible that diuretic therapy might increase the risk of gastrointestinal bleeding, although whether it does so in practice remains an unanswered question.

### 1.3.3.2 Clinical and Epidemiological Studies

There are few clinical and epidemiological studies lending support to the possibility that diuretic use may be associated with increased risk of gastrointestinal bleeding. There have been scattered reports in the past that have mentioned the development of purpura in patients receiving chlorothiazide or hydrochlorothiazide (Zuckerman and Chazan, 1958; Nordqvist et al., 1959). Gesink and Bradford (1960) described a case of thrombocytopenic purpura in a patient receiving hydrochlorothiazide and demonstrated causality by readministering the drug, with a resultant return of the full clinical picture of purpura and platelet deficiency. In another case-report, four cases developed thrombocytopenic purpura during the administration of chlorothiazide or hydrochlorothiazide, and the conditions cleared after discontinuing therapy (Ball, 1960).

As far back, as 1978, Jick and Porter provided support for the hypothesis that ethacrynic acid, a loop diuretic, may induce gastrointestinal bleeding from data collected on 16646 patients. They reported 4.5 percent (5/111) major gastrointestinal bleeding among patients who used ethacrynic acid alone in comparison with 1.2 percent (7/575) for heparin, 0.5 percent (7/1484) for steroids and 0.3 percent (6/2081) for aspirin. However, another class of diuretic, furosemide, which has similar indications to ethacrynic acid, was not associated with gastrointestinal bleeding. Earlier, Slone et al. (1969) reported a significant association between the administration of ethacrynic acid and the occurrence of gastrointestinal bleeding. In that study, the frequency of gastrointestinal bleeding for the ethacrynic acid group after accounting for other drug use and prior bleeding related diseases was 12 percent and compared to 4 percent for nonusers. When the significance

of the difference between the ethacrynic acid group and the nonusers group was tested using the Mantel Haenszel procedure, with expected values based on the combined distributions of the compared series, they found that the difference was statistically significant, with a p-value less than 0.02. Notwithstanding the positive association reported, the two studies had some important methodological limitations. For example, the study by Slone and colleagues (1969) did not report any exposure time window, while Jick and Porter (1978) used a 7-day exposure time window, which is too short, because it is unlikely for any adverse effect to manifest within this time period of exposure. The study by Jick and Porter (1978) did not control for important factors such as aspirin use and age, and since the studies reported only frequency estimates, these frequencies are not fully comparable in view of the differences between the treatment groups regarding risk factors not properly and/or not controlled for. Also, numbers exposed in the different drug category were small hence the studies lack sufficient power to detect any meaningful effects.

A recent study (Suissa et al., 1998) reported an unexpected elevated risk of gastrointestinal bleeding associated with the use of diuretics. In a nested case-control design within a population-based cohort, they reported an adjusted rate ratio of 1.4 (95% CI 1.0 to 2.0) of gastrointestinal bleeding for current use of diuretics. Garcia Rodriguez and colleagues (1998) also reported that diuretic users had a rate ratio of gastrointestinal bleeding of 1.4 (95% CI, 1.0-1.8) compared with nonusers of antihypertensive medications. The two studies had a weak significantly elevated risk of gastrointestinal bleeding associated with diuretic use judging from the confidence intervals of the

estimates, and more importantly the two studies were designed to evaluate other predictors of gastrointestinal bleeding, but not with a priori hypothesis for diuretics. Furthermore, the association with gastrointestinal bleeding was not studied separately for the various diuretic substances, which differ by their chemical composition. Nevertheless, these studies present clinical and epidemiological evidence, which raises the possibility that diuretic use may be associated with increased risk of gastrointestinal bleeding.

Gastrointestinal bleeding is a significant public health problem that exacts a high cost to society. If the hypothesised association with diuretic were real, the implications would be profound given the large numbers of patients receiving this beneficial drug. The impact in terms of number of affected people, especially the elderly hypertensive patients, provides enough justification for evaluating this conjecture. Prior studies, some of which did not appear to be designed to specifically test the hypothesis, and some with methodological limitations, do not constitute a sufficient body of data upon which to firmly judge association. Hence, the need for more rigorous testing in further studies, to shed more informative light on this subject.

### 1.4 Study Objective

The study examined the relation between exposure to diuretics and risk of gastrointestinal bleeding among hypertensive persons in Saskatchewan, during the period January 1980 to mid-1987.

#### 1.4.1 Specific Objectives

- to identify a historical cohort of patients receiving antihypertensive medication for the first time between 1980 to 1983 using the Saskatchewan prescription database file
- follow this cohort to mid-1987 and identify all incident cases of gastrointestinal bleeding using the Saskatchewan health hospitalisation database file
- to estimate the rate ratios of gastrointestinal bleeding following exposure to any diuretic relative to non-use of any antihypertensive medication within a 30-, 45- and 60-day exposure time window
- to estimate the rate ratios of gastrointestinal bleeding following exposure to loop diuretic, potassium sparing and thiazide-diuretic relative to non-use of any antihypertensive medication within a 30-, 45- and 60-day exposure time window
- to estimate the rate ratios of gastrointestinal bleeding following exposure to other different antihypertensive agents relative to non-use of any antihypertensive medication within a 30-, 45- and 60-day exposure time window
- to adjust all these comparisons for the effects of NSAIDs, antiulcer medications, anticoagulants, glucocorticoids, age, gender and cormorbidity

# 2.0 METHODS

## 2.1 Study Design Overview

A nested case control design was conducted within a population-based cohort of first-time users of diuretics, calcium channel antagonists, beta blockers and ACE (angiotensin-converting enzyme) inhibitors, from 1980 to mid-1987, in the province of Saskatchewan, Canada. The period for cohort entry was chosen to be between January 1, 1980 and December 31, 1983, so that subjects who received their first antihypertensive prescription after this date were excluded from the cohort. This study period was chosen to differ from the period used in the previous Saskatchewan study (Suissa et al., 1998) that spanned the period 1990 to1995. All subjects were followed to June 1987. The range of follow up across the computerized database extended from 3.5 years to 7.5 years. The computerised prescription and hospitalisation databases of the Saskatchewan Prescription Drug Plan were used to assemble the cohort (see Appendix A). Prescription codes for anti-hypertensive drugs were used to identify hypertensive subjects initiating therapy in Saskatchewan between January 1980 and December 1983. Subjects were entered into the cohort at the time they received their first prescription for diuretics or other antihypertensive drugs, hence it was a cohort of incident hypertensives. To confirm the incident nature of the antihypertensive therapy, the process of backtracking for past antihypertensive use was extended for a period of two years prior to the date of the presumed first prescription at issue. The hospitalization database was used to identify subjects who for the past two years prior to initiation of therapy had not been hospitalized for gastrointestinal bleeding or any related diseases. This constituted the study cohort.

From the identified cohort of incident hypertensives, subcohorts of subjects on diuretics and other antihypertensives were followed forward in time so as to identify the outcome of interest that is gastrointestinal bleeding. The outcome information was obtained through the hospitalization database (Hospital Services Branch data file of the Saskatchewan Drug Prescription Plan). Specifying a Type 1 error of 5 percent and a power of 80 percent, an estimated sample size of 275 cases and 2750 controls was needed (see Appendix B) for the diuretic category. A sample of this size will have sufficient power to determine a rate ratio of 1.5 between diuretic use and gastrointestinal bleeding.

**2.2 Data Source**

This study used data from the Saskatchewan Health Database. This database is sufficiently large to provide adequate population size for measuring drug exposure, while also allowing for savings in both cost and time. The database contains information on over 95 percent of the one million residents of the province (Guess et al., 1988). The Province of Saskatchewan maintains complete and accurate computerized records of hospitalizations since 1963 and drug prescriptions since 1975 for the inhabitants of the province (Strand and West, 1992). Two main computerized databases (the prescription drug services branch file and the hospital services branch file) of Saskatchewan Health constituted the primary source of data for the data.

The Prescription Drug Data keeps a record of each prescription dispensed to residents of the province having a Health Service Card. Over 95 percent of the residents are covered by this plan. The information includes the individual's registration beneficiary number,

identity of the drug dispensed using a drug identification number (DIN), the quantity of drug dispensed, the date of dispensing and number of refills. The Saskatchewan Hospital Services Plan (SHSP), which collects data on all hospitalizations contains information such as, the registration beneficiary number, date of birth, gender, date of admission and discharge and services received in the hospital. Discharge diagnostic data are coded for both primary and secondary diagnoses by using the International Classification of Disease 9$^{th}$ edition (ICD-9).

### 2.3 Study Cohort

The study cohort comprised all patients who began antihypertensive therapy for the first time with diuretics, calcium channel blockers, ACE (angiotensin-converting enzyme) inhibitors, beta-blockers or other antihypertensive agents between January 1980 and December 1983. The cohort entry date was the date of first prescription. Cohort members hospitalized for prior diagnoses of gastrointestinal bleeding and other diseases such as peptic ulcer that are specific risk factors for gastrointestinal bleeding, within two years prior to the cohort entry date were excluded from the cohort. Current users of nonsteroidal anti-inflammatory drug (NSAIDs), those under NSAID prescription, and also those under antiulcer, anticoagulant and glucocorticoids prescription within two years prior to the cohort entry date were not excluded but this information was retained for statistical adjustments. Subjects, without valid health identification codes were excluded.

## 2.4 Case Definition

Using the Saskatchewan Hospital Services database, potential cases were first identified as those hospitalised with a primary or secondary discharge diagnosis of bleeding of the gastrointestinal tract. Cases were subjects hospitalised with one of the ICD-9 codes as a primary discharge diagnosis. Both site- and lesion-specific codes and nonspecific codes of the International Classification of Diseases, 9th edition (ICD-9) (WHO, 1977) were used to identify cases from the database by means of the following ICD-9 codes, gastric, duodenal, gastrojejunal, or peptic ulcer with any mention of haemorrhage, haematemesis, melaena and gastrointestinal bleeding not otherwise stated (see Table 1). The reason for using both codes is that, although the positive predictive value (PPV) of the site- and lesion-specific codes is higher than the nonspecific codes (90 percent compared to 70 percent), it has also, been documented that about 50 percent of cases would be missed if nonspecific codes are ignored (Raiford et al., 1996).

**Table 1. International Classification of Diseases, 9th edition (ICD-9)**

| Hospital Discharge Diagnosis | ICD-9 Codes |
|---|---|
| Gastric ulcer | 531.0, 531.4, 531.6 |
| Duodenal ulcer | 532.0, 532.4, 532.6 |
| Peptic ulcer | 533.0, 533.4, 533.6 |
| Gastrojejunal ulcer | 534.0, 534.4, 534.6 |
| Hematemesis | 578.0 |
| Blood in stool-melena | 578.1 |
| Gastrointestinal haemorrhage unspecified | 578.9 |

Also, included as cases were those hospitalised with one of the above (ICD-9) diagnoses as the secondary discharge diagnosis, if the primary diagnosis consisted of:

- esophagus, gastritis and duodenitis
- functional disorders of the stomach and duodenum
- symptoms involving the digestive system
- haemorrhagic conditions, iron deficiency and anemia
- ill-defined and unknown causes of mortality.

Date of the first hospital admission for any of these diagnoses was defined as the index date, and if a cohort member was hospitalised more than once during the study period, only the first event was used.

### 2.5 Controls

For each case, a risk set of all potential controls consisting of all cohort members with the same year and month of cohort entry and follow-up as long or longer than that of the case was formed. To obtain an unbiased estimate of the exposure effect in the nested case-control study, proper control selection is required (Breslow and Day, 1987), and the usual method of selection is to sample controls randomly within risk sets for each case. The risk set is defined as the case and all study subjects who survived past the time of the case's failure and had entered the study before the case's failure (Steenland and Deddens, 1997). Thus, the time during which a cohort member was eligible to be a control was the time in which the subject was also eligible to become a case, if the outcome of interest (GIB) should occur. Hence, future cases can be selected as controls before they become cases, but a cohort member censored after a first event is no longer eligible to be selected

as a control. From this risk set, 10 controls were selected and matched to the case according to the index date. The precision of the estimated effect is improved when more controls are chosen per case (Steenland and Deddens, 1997), and a random sample of 10 controls was chosen for this study based on their findings, because use of 100, 20, and 10 controls yields estimates almost identical to the true parameter estimated from the full cohort (see Table 2).

**Table 2. Relative Efficiency of Case-Control compared to Full Cohort Estimate**

| Number of Controls | Relative Efficiency (%) | MSE | Average Parameter Estimate |
|---|---|---|---|
| 100 | 96.4 | 0.0126 | 1.557 |
| 20 | 85.4 | 0.0145 | 1.537 |
| 10 | 73.9 | 0.0166 | 1.540 |
| 3 | 50.0 | 0.0342 | 1.456 |

**Average Relative Efficiency = variance full cohort parameter for exposure/average variance case-control parameter for exposure. MSE = square of average bias (from full cohort parameter) + average variance of case-control parameter.**

**Source: Steenland and Deddens, Epidemiology 1997;8:238-242.**

### 2.6 Exposure Assessment

All new prescriptions of antihypertensive medications dispensed during the 30-day, 45-day and 60-day exposure time-windows prior to the index date were identified in cases and controls. Prescriptions for all classes of diuretics dispensed during the follow-up period were identified, along with ACE (angiotensin-converting enzyme) inhibitors, beta blockers and calcium channel blockers and other antihypertensives. The information was

extracted from the Saskatchewan Prescription Drug Database. A subject was defined as exposed if diuretics and/or any other class of antihypertensive medication were dispensed in a 60-, 45- and 30-day time window before the index date. A subject was classified as unexposed, when there was no antihypertensive medication use within these time windows before the index date. A 60-, 45- and 30-day exposure time windows were chosen because Saskatchewan Drug Plan reimburses for 30 days of therapy for a single prescription (Guess et al., 1988) and most hypertensive patients would have a refill. Also, it seems clinically reasonable for any adverse effects of the drug to take place within these time windows when considering the aforementioned postulated mechanism of action.

Diuretics were also stratified into loop diuretics, thiazides, potassium-sparing and thiazides combined with potassium sparing to assess the associated risk of gastrointestinal bleeding separately for each class of diuretic. Likewise, beta blockers were also stratified into selective and non-selective substances (see Appendix C for drug definition). Furthermore, cumulative prescribed dosage during this period for furosemide, the only loop diuretic available, was determined to estimate the average daily-prescribed dosage (ratio=cumulative dosage/30 day). The subjects were then categorized into 3 different estimated daily dosages (below 40mg/day, 40mg/day and above 40mg/day), based on the recommended defined daily dose (DDD) for furosemide (WHO, 1993). Estimated daily dosages were not assessed for potassium sparing or thiazide-diuretics because of the small number of users in this study cohort.

## 2.7 Covariates

Besides age at index date and gender, other variables potentially associated with gastrointestinal bleeding were assessed at the baseline and during the follow-up period, from the database. In particular, number of hospital admissions as a marker for chronic illnesses, as well as the use of NSAIDs, antiulcer medications, anticoagulants and glucocorticoids all during the year prior to the index date were considered as potential confounders.

## 2.8 Analysis

First, an analysis of the entire cohort was performed to estimate rates of gastrointestinal bleeding. The main outcome of the analysis is a binary measure of occurrence of gastrointestinal bleeding. The first occurrence of gastrointestinal bleeding was considered in the data analysis. Participants with no events of interest (gastrointestinal bleeding) were censored at the end of the follow-up period or at the time of death, whichever occurred first. Cumulative person-time was used to estimate the rate of gastrointestinal bleeding in the entire cohort as well as according to several co-factors.

With respect to the case-control sample, subjects were defined as currently exposed to diuretics and/or any other antihypertensive drug class if it was dispensed in a 60-, 45- and 30-day time window before the index date. Participants who received more than one antihypertensive drug were considered as currently exposed to each of them. Nonuse of diuretics and any other main antihypertensive drug class within these time windows were the reference category.

Conditional logistic regression models were used to estimate the unadjusted and adjusted rate ratios and 95% confidence interval (CI) for the association of diuretics and other classes of antihypertensive drugs of interest with gastrointestinal bleeding. Variables adjusted for in the model included concurrent use of other antihypertensive drugs, age at index date and gender. The use of NSAIDs, anti-ulcer medications, anti-coagulants and glucocorticoids and number of hospital admissions as a marker for chronic illnesses all during the year prior to index date, were also adjusted for. For diuretics, risk for gastrointestinal bleeding was also assessed separately for loop diuretics, thiazide diuretic, potassium sparing diuretics and thiazide-diuretic combined with potassium sparing. For beta blockers the risk for gastrointestinal bleeding was also assessed separately after dichotomizing the exposure to beta blockers into selective and non-selective substances. Because of the small number of ACE inhibitor users, it was grouped with other types of antihypertensives, which excluded diuretics, beta blockers and calcium channel blockers (see Appendix C). Different classes of antihypertensives mixed with thiazide were grouped together with thiazide diuretics as one variable in the later part of the analysis, since none of them showed any significant association with the risk of gastrointestinal bleeding.

Furthermore, a separate logistic model was fitted after categorizing the exposure to loop diuretic (furosemide) into three groups with an estimated prescribed daily dosage below, above, or equal to the defined daily dose (DDD) for furosemide, which is 40mg/day (WHO, 1993). In addition, a model was fitted after categorizing the exposure to thiazide diuretics into three groups with an estimated prescribed daily dosage below 50mg/day,

50mg-60mg per day and above 60mg/day. The crude daily dosages were estimated based on the quantity supplied divided by 30 days, and the ratio multiplied by the given strength. It was assumed that quantity of drugs supplied were for a 30-day period. This was based on the fact that nearly all prescriptions are about 30 days of therapy because the Saskatchewan Drug Plan reimburses for 30 days of therapy on a single prescription, and a refill is treated as a new prescription (Guess et al., 1988). The statistical analysis was performed using SAS version 8.1.

### 3.0 Expected Contribution

Since any drug therapy has inherent yet unknown risks, it is essential to obtain the necessary information on the safety of a drug. Hence, this study is expected to give insight supporting or refuting the previously hypothesized risk of gastrointestinal bleeding associated with diuretics and provides an estimate for the association of interest. Physician awareness of these risk factors is crucial so that the benefit and hazards of diuretic therapy in high-risk patients can be properly weighed. If a drug is really responsible for gastrointestinal bleeding, it should be used carefully in patients at higher risk. On the other hand, erroneously attributing an adverse effect to a drug would discard a possible beneficial drug from the therapeutic arsenal.

### 4.0 Ethical Consideration

The study is embedded within a larger study, which has been approved by the McGill university ethics committee. Further, the protocol of this study was prepared in accordance with the regulation of Saskatchewan Health, which has specific ethical guidelines for the use of data from their computerized databases. These guidelines have

been formulated with a view to maintaining confidentiality of each individual's information. A patient's identity was unknown, and results of the study are based on aggregate data only, and any publication from this study will also be based on aggregate data.

# 5.0 RESULTS

## 5.1 Characteristics of the Study Cohort

The initial cohort comprised of 47,865 subjects, and 245 were excluded because of a hospitalisation for gastrointestinal bleeding (GIB) two years prior to cohort entry, leaving 47,620 eligible subjects. During the follow-up period, 753 cases were identified, of whom 734 (97.5%) were hospitalised with a primary diagnosed of GIB, and additional 19 (2.5%) had GIB as the secondary discharge diagnosis. Unspecified haemorrhage of gastrointestinal bleeding was the most common (48.7%) diagnosis (Table 3). Out of the 753 cases, 41.4 percent were females, and 31.3 percent were less than 65 years of age.

**Table 3. Distribution of hospital discharge diagnoses of cases of gastrointestinal bleeding**

| Hospital Discharge Diagnosis | ICD-9 Codes | Number (%) |
|---|---|---|
| Gastric ulcer | 531.0, 531.4, 531.6 | 103 (13.7) |
| Duodenal ulcer | 532.0, 532.4, 532.6 | 113 (15.0) |
| Peptic ulcer | 533.0, 533.4, 533.6 | 42 (5.6) |
| Gastrojejunal ulcer | 534.0, 534.4, 534.6 | 3 (0.4) |
| Hematemesis | 578.0 | 58 (7.7) |
| Melena | 578.1 | 67 (8.9) |
| Haemorrhage of gastrointestinal tract, Unspecified | 578.9 | 367 (48.7) |

ICD-9 = International classification of diseases 9th edition

At cohort entry the mean age in years was 60.6 ± 14.1, with a range of 30 to 85 years, and 58.0 percent were below 65 years old. The cohort includes 54.9 percent females, and 56.4 percent of the cohort members were initially treated with diuretics (thiazide class, potassium sparing agents and thaizide combined with potassium sparings) and 11.6 percent with loop diuretics (Table 4).

**Table 4. Characteristics of the Cohort at Cohort Entry (n=47620)**

| Characteristics of the Cohort | |
|---|---|
| Age in years (mean ± SD) | |
| - Total cohort | 60.6 ± 14.1 |
| - Females | 59.6 +14.5 |
| - Males | 61.7 +13.5 |
| Age range (in years) | 30 – 85 |
| Gender (females %) | 54.9 |
| Use of Anti-hypertensive drug at cohort entry (%, n): | |
| - ACE* inhibitors | 0.00 (2) |
| - Beta blockers (non-selective) | 17.78 (8465) |
| - Beta blockers (selective) | 1.77 (842) |
| - Calcium channel blockers | 1.57 (747) |
| - Diuretics† | 56.36 (26839) |
| - Loop diuretic (furosemide) | 11.59 (5521) |
| - Other anti-hypertensives | 10.93 (5204) |

***ACE = angiotensin-converting enzyme inhibitors; SD = standard deviation**

**†Diuretics = thaizide-diuretic, potassium sparing and thiazide combined with potassium sparings**

As Table 5 shows, the rate of hospitalization for gastrointestinal bleeding for the study cohort was 2.83 cases per 1000 subjects per year, and the mean total person-years of follow-up was 265719.6. The rate was 6.03 cases per 1000 subjects per year for those who were over 74 years old, while for those below 65 years the rate was 1.53 cases per 1000 subjects per year. The rate for gastrointestinal bleeding among males was 3.70 cases per 1000 subjects per year, and that for females was 2.13 cases per 1000 subjects per year.

**Table 5. Incidence of hospitalization for gastrointestinal bleeding in the study cohort**

| Characteristics | Person-Years | Cases | Rates (cases per 1000 person-years) |
|---|---|---|---|
| Total cohort | 265719.6 | 753 | 2.83 |
| Female | 146729.6 | 312 | 2.13 |
| Males | 119130.8 | 441 | 3.70 |
| Age group in years: | | | |
| <65 | 154429.3 | 236 | 1.53 |
| 65-74 | 64016.0 | 232 | 3.62 |
| >74 | 47265.6 | 285 | 6.03 |

Females were more likely to use diuretics, and a greater proportion of the males used calcium channel blockers and both selective and non-selective beta-blockers.

### 5.2 Characteristics of Cases and Controls

Table 6 shows the characteristics of cases and controls in the nested case-control sample. Cases were about 8 years older than controls and less likely to be females. The mean age in years, at index date for the total nested case control sample was 64.38 (±14.2), and 55.1 percent were below 65 years old. Compared with subjects less than 65 years of age, those older than 74 years had a rate ratio of 3.92 (95% CI, 3.25 – 4.72) of hospitalization for gastrointestinal bleeding, while the rate ratio for subjects 65 to 74 years old was 2.17 (95% CI, 1.77 – 2.66). In this nested case control sample, males were at a higher risk (rate ratio 1.74; 95% CI, 1.48 – 2.04) of hospitalization for gastrointestinal bleeding compared with females. The majority of subjects, both cases and controls, reported less than 2 hospital admissions during the year prior to the index date, and only 14.74 percent of the cases and 2.06 percent of the controls were hospitalized more than 3 times during the same time period. After adjusting for gender and age at index date, the number of hospitalisation (a marker for comorbidity) was significantly associated with hospitalization for gastrointestinal bleeding. The cases used more medications than the controls during the 90 days prior to the index date. Among the medications that were investigated as potential predictors of gastrointestinal bleeding during 90 days prior to the index date, NSAIDs were the most frequently taken (43.7% of the cases and 19.2% of the controls). Compared to nonusers, after adjusting for concurrent use of other drugs, age at index date and gender, the rate ratios were, for NSAIDs 3.13; 95% CI, 2.65 – 3.70, for antiulcer medications, 3.74; 95% CI, 2.99 – 4.67, for anticoagulants, 6.29; 95% CI, 3.90 – 10.16, and for glucocorticoids the rate ratio was 1.55; 95% CI, 1.07 – 2.25.

**Table 6. Distribution of characteristics for cases and controls**

| Characteristics | Cases (n = 753) | Controls (n = 7530) | Rate Ratio (95% CI) |
|---|---|---|---|
| Age at index date (years): | | | |
| Mean ± SD | 71.7 ± 12.6 | 63.7 ± 14.2 | |
| < 65 years old (%) | 26.3 | 51.3 | 1.0 |
| 65 – 74 years old (%) | 27.5 | 25.1 | 2.17 (1.77 - 2.66) |
| > 74 years old (%) | 46.2 | 23.7 | 3.92 (3.25 - 4.72) |
| Females (%) | 41.4 | 54.7 | 1.0 |
| Males (%) | 58.6 | 45.3 | 1.74 (1.48 - 2.04) |
| Medication used during the 90 days prior to index date (%): | | | |
| NSAIDs | 43.7 | 19.2 | 3.13 (2.65 - 3.70)* |
| Anti-ulcer drugs | 19.3 | 5.4 | 3.74 (2.99 - 4.67)* |
| Anti-coagulants | 4.3 | 0.8 | 6.29 (3.90 - 10.16)* |
| Glucocorticoids | 5.8 | 2.4 | 1.55 (1.07 - 2.25)* |
| Number of hospital admissions during the year prior to index date (%): | | | |
| Less than 2 | 48.21 | 90.31 | 1.00 |
| 2 - 3 | 37.05 | 7.04 | 7.58 (6.28 – 9.13)† |
| >3 | 14.74 | 2.06 | 10.22 (7.70-13.56)† |

***Adjusted rate ratios for other medications, gender and age at index date; NSAIDs = nonsteriodal anti-inflammatory drugs; Glucocorticoids = glucocorticoids (injection, oral, inhalation); SD = standard deviation;**

**†Adjusted for gender and age at index date**

### 5.3 Antihypertensive Medications and Risk of Gastrointestinal Bleeding

In the analyses, ACE inhibitors were added to the "other antihypertensive" category because of the small number of users as shown in Table 4. For definition of antihypertensive medication categories see Appendix C. Table 7a and Table 7b present the rate ratio of current use of each antihypertensive drug class in the three different time-windows (30 days, 45 days and 60 days) before the index date. In crude analyses, current use of diuretics, relative to no use of antihypertensive medications within each of the three time-windows, was associated with an increased risk of gastrointestinal bleeding (30-day time-window: RR 1.70, 95% CI, 1.45 - 1.99; 45-day time-window: RR 1.80, 95% CI, 1.55 - 2.10; 60-day time-window: RR 1.77 95% CI, 1.52 - 2.06). However, current use of both selective and non-selective beta blockers were associated with lower risk.

Adjustment for concurrent use of antihypertensive medications did not lead to appreciable reduction in these rate ratios. Diuretics and calcium channel blockers were both associated with an increased risk of hospitalization for gastrointestinal bleeding, in all the three time-windows. The rate ratios for diuretics in the different time-windows were as follows, 30-day: 1.68, 95% CI, 1.43 - 1.98; 45-day: 1.77, 95% CI, 1.52 - 2.07; 60-day: 1.73, 95% CI, 1.48 - 2.02, and for calcium channel blockers the rate ratios were, 30-day: 1.56, 95% CI, 1.01 - 2.39; 45-day: 1.54, 95% CI, 1.04 - 2.28; 60-day: 1.50, 95% CI, 1.01 - 2.20. On the other hand both selective and non-selective beta blockers showed a reduced risk, with the non-selective showing a much lower risk compared to the selective beta blockers.

**Table 7a. Use of antihypertensive medications and rate ratios for hospitalization for gastrointestinal bleeding associated with current exposure at index date**

| Antihypertensive Medication | Cases n=753 % | Controls n=7530 % | Unadjusted Rate Ratio | *Adjusted Rate Ratio | †Fully Adjusted Rate Ratio (95% CI) |
|---|---|---|---|---|---|
| **30-day Time Window** | | | | | |
| Reference (none) | 53.52 | 60.44 | 1.00 | 1.00 | **1.00** |
| Diuretics | 36.65 | 25.56 | 1.70 | 1.68 | **1.54** (1.27 – 1.86) |
| Thiazide combine‡ | 2.26 | 3.08 | 0.73 | 0.83 | **1.06** (0.60 – 1.85) |
| Beta blockers-ns | 7.17 | 9.67 | 0.72 | 0.67 | **0.68** (0.32 – 1.03) |
| Beta blockers-s | 1.20 | 2.43 | 0.49 | 0.44 | **0.93** (0.56 – 1.42) |
| CC blockers | 3.32 | 2.24 | 1.50 | 1.56 | **0.90** (0.65 – 1.27) |
| Others§ | 6.24 | 4.13 | 1.54 | 1.39 | **1.63** (1.13 – 2.36) |
| **45-day Time Window** | | | | | |
| Reference (none) | 43.96 | 52.15 | 1.00 | 1.00 | **1.00** |
| Diuretics | 45.02 | 31.41 | 1.80 | 1.77 | **1.63** (1.36 – 1.96) |
| Thiazide combine‡ | 2.66 | 3.76 | 0.70 | 0.82 | **1.02** (0.61 – 1.71) |
| Beta blockers-ns | 7.70 | 11.99 | 0.61 | 0.59 | **0.74** (0.54 – 1.02) |
| Beta blockers-s | 1.99 | 2.72 | 0.72 | 0.65 | **0.95** (0.59 - 1.52) |
| CC blockers | 4.12 | 2.92 | 1.43 | 1.54 | **0.99** (0.55 - 1.79) |
| Others§ | 7.57 | 5.06 | 1.53 | 1.38 | **1.73** (1.24 – 2.42) |

***Adjusted for concurrent use of different types of antihypertensives;**

**†Adjusted for concurrent use of different types of antihypertensives and other covariates**

**‡Thiazide combine=any antihypertensives excluding diuretics mixed with thiazide**

**§Others =antihypertensives excluding diuretics, beta blockers and calcium channel blockers**

**none = no use of antihypertensive medications during the time window**

**ns = nonselective; s = selective; CC = calcium channel**

**Table 7b. Use of antihypertensive medications and rate ratios for hospitalization for gastrointestinal bleeding associated with current exposure at index date**

| Antihypertensive Medication | Cases n=753 % | Controls n=7530 % | Unadjusted Rate Ratio | *Adjusted Rate Ratio | †Fully Adjusted Rate Ratio (95% CI) |
|---|---|---|---|---|---|
| **60-day Time Window** | | | | | |
| Reference (none) | 39.84 | 47.37 | 1.00 | 1.00 | **1.00** |
| Diuretics | 48.47 | 34.93 | 1.77 | 1.73 | **1.52** (1.27 – 1.82) |
| Thiazide combine‡ | 3.19 | 4.26 | 0.74 | 0.87 | **1.05** (0.66 – 1.69) |
| Beta blockers-ns | 8.90 | 13.13 | 0.64 | 0.63 | **0.77** (0.57 – 1.05) |
| Beta blockers-s | 2.39 | 2.92 | 0.81 | 0.74 | **0.91** (0.57 – 1.44) |
| CC blockers | 4.25 | 3.09 | 1.40 | 1.50 | **1.16** (0.67 – 2.00) |
| Others§ | 8.50 | 5.55 | 1.57 | 1.43 | **1.64** (1.21 – 2.22) |

***Adjusted for concurrent use of different types of antihypertensives;**

**†Adjusted for concurrent use of different types of antihypertensives and other covariates**

**‡Thiazide combine=any antihypertensives excluding diuretics mixed with thiazide**

**§Others = antihypertensives excluding diuretics, beta blockers and calcium channel blockers**

**none = no use of antihypertensive medications during the time window**

**ns = nonselective; s = selective; CC = calcium channel**

The rate ratios for the combined effect of selective and non-selective beta blockers after adjusting for concurrent use of other antihypertensive medications in the different time-windows are, 30-day: 0.62, 95% CI, 0.46 - 0.83; 45-day: 0.60, 95% CI, 0.46 - 0.78; 60-day: 0.65, 95% CI, 0.55 - 0.89 (see Table 8).

Models that also adjusted for other covariates factors, such as NSAIDs and anti-ulcer drug use, anticoagulants, glucocorticoids, age at index date, gender and number of

hospitalization as a marker for comorbidity showed that use of diuretics was associated with an increased risk of gastrointestinal bleeding in all the three different exposure time-windows. For diuretics the rate ratio for the 30-day time window was 1.54; 95% CI, 1.27 – 1.86; for the 45-day time window the rate ratio was 1.63; 95% CI, 1.36 – 1.96; and that for the 60-day time window was 1.52; 95% CI, 1.27 – 1.82. Use of calcium channel blockers did not show any meaningful association with hospitalization for gastrointestinal bleeding in all three different time-windows. However, both beta blockers, especially the non-selective was associated with a reduced risk in all the three different time-windows (30-day: 0.68; 95% CI, 0.32 – 1.03; 45-day: 0.74; 95% CI, 0.54 – 1.02; 60-day: 0.77; 95% CI, 0.57 – 1.05). According to Table 8, the combined effect of both selective and non-selective beta blockers disclosed a lower rate ratio of gastrointestinal bleeding in all the time windows (30-day: 0.86; 95% CI, 0.63 – 1.17; 45-day: 0.79; 95% CI, 0.59 – 1.05; 60-day: 0.84; 95% CI, 0.64 – 1.11).

Current use of "other antihypertensive" was associated with a higher risk within all the 3 different exposure time windows (30-day: RR 1.63, 95% CI, 1.13 – 2.36; 45-day: RR 1.73, 95% CI, 1.24 – 2.42; 60-day: RR 1.64, 95% CI, 1.21 – 2.22). However, models that also adjusted for other confounding factors, such as age at index date, gender and NSIADs use, disclosed that there was no association between use of combination of thiazide and other antihypertensive medications excluding diuretics and hospitalization for gastrointestinal bleeding (30-day: RR 1.06, 95% CI, 0.60 – 1.85; 45-day: RR 1.02, 95% CI, 0.61 – 1.71; 60-day: RR 1.05, 95% CI, 0.66 – 1.69).

**Table 8. Rate ratios for hospitalization for gastrointestinal bleeding associated with current exposure to antihypertensive drugs at index date after combining selective and non-selective beta blockers**

| Antihypertensive Medication | Cases n=753 % | Controls n=7530 % | Unadjusted Rate Ratio | *Adjusted Rate Ratio | †Fully Adjusted Rate Ratio (95% CI) |
|---|---|---|---|---|---|
| **30-day Time window** | | | | | |
| Reference (none) | 53.52 | 60.44 | 1.00 | 1.00 | **1.00** |
| Diuretics | 36.65 | 25.56 | 1.70 | 1.68 | **1.54** (1.27 – 1.86) |
| Beta blockers | 8.37 | 12.10 | 0.66 | 0.62 | **0.86** (0.63 – 1.17) |
| CC blockers | 3.32 | 2.24 | 1.50 | 1.55 | **0.93** (0.56 – 1.56) |
| **45-day Time window** | | | | | |
| Reference (none) | 43.96 | 52.15 | 1.00 | 1.00 | **1.00** |
| Diuretics | 45.02 | 31.41 | 1.80 | 1.77 | **1.63** (1.36 – 1.96) |
| Beta blockers | 9.69 | 14.69 | 0.62 | 0.60 | **0.79** (0.59 – 1.05) |
| CC blockers | 4.12 | 2.92 | 1.43 | 1.53 | **0.94** (0.59 – 1.51) |
| **60-day Time window** | | | | | |
| Reference (none) | 39.84 | 47.37 | 1.00 | 1.00 | **1.00** |
| Diuretics | 48.47 | 34.93 | 1.77 | 1.73 | **1.52** (1.27 – 1.83) |
| Beta blockers | 11.29 | 15.99 | 0.67 | 0.65 | **0.84** (0.64 – 1.11) |
| CC blockers | 4.25 | 3.09 | 1.40 | 1.50 | **0.91** (0.57 – 1.44) |

***Adjusted for concurrent use of different types of antihypertensives;**

**†Adjusted for concurrent use of different types of antihypertensives and other covariate**

**none = no use of antihypertensive medications during the time window**

**CC = calcium channel**

### 5.4 Risk of Gastrointestinal Bleeding among Users of Different Classes of Diuretics

To further evaluate the risk of hospitalization for gastrointestinal bleeding and the different classes of diuretics, analyses were performed categorizing diuretics into loop diuretics, thiazide diuretics, and potassium sparing diuretics (see Appendix C for definition of drug categories). There were important differences in the risk of gastrointestinal bleeding associated with the individual class of diuretics. Potassium sparing and thiazide diuretics had the highest risk of gastrointestinal bleeding. Tables 9a and 9b show the rate ratios for individual diuretics within the time windows. In the crude analyses, current use of loop diuretics, relative to no use of antihypertensive medications within the different time windows, was associated with an increased risk of hospitalization for gastrointestinal bleeding, the rate ratios were (30-day: 3.78; 95% CI, 2.97 – 4.84; 45-day: 3.84; 95% CI, 3.07 – 4.79; 60-day: 3.59; 95% CI, 2.89 – 4.45). For current use of potassium sparing diuretics the rate ratios were (30-day: 5.59; 95% CI, 3.33 – 9.37; 45-day: 5.82; 95% CI, 3.63 – 9.32; 60-day: 5.89; 95% CI, 3.72 – 9.32), while for the thiazide diuretics, the rate ratios (95% CI) were 30-day: 1.33 (0.86 – 2.06); 45-day: 1.25 (0.85 – 1.84); 60-day: 1.13 (0.76 – 1.66). After adjusting for concurrent use of other antihypertensive medications, the rate ratios for loop diuretics did not change appreciable within the different time windows (30-day: 3.37, 95% CI, 2.94 – 4.78; 45-day: 3.49, 95% CI, 3.08 – 4.83; 60-day: 3.27, 95% CI, 2.93 – 4.54). However, the rate ratios for current use of potassium sparing diuretics decreased appreciable (30-day: 3.42; 95% CI, 1.96 – 5.97; 45-day: 3.82; 95% CI, 2.30 – 6.34; 60-day: 3.98; 95% CI, 2.44 – 6.51), and the rate ratios for thiazide diuretics increased slightly

(30-day: 1.47, 95% CI, 1.00- 2.41; 45-day: 1.44, 95% CI, 1.01 – 2.23; 60-day: 1.32, 95% CI, 0.93 – 2.04).

**Table 9a. Rate ratios of hospitalization for gastrointestinal bleeding associated with individual diuretic classes within the 30-day and 45-day time windows**

| Antihypertensive Medication | Cases n=753 % | Controls n=7530 % | Unadjusted Rate Ratio | *Adjusted Rate Ratio | †Fully Adjusted Rate Ratio (95% CI) |
|---|---|---|---|---|---|
| **30-day Time Window** | | | | | |
| Reference (none) | 53.52 | 60.44 | 1.00 | 1.00 | **1.00** |
| Loop diuretics | 13.01 | 3.75 | 3.78 | 3.37 | **1.52** (1.11 – 2.07) |
| Potassium sparing | 3.05 | 0.57 | 5.59 | 3.42 | **2.64** (1.35 – 5.16) |
| Thiazide diuretics | 3.19 | 2.42 | 1.33 | 1.47 | **1.95** (1.17 – 3.27) |
| Pot Spar/Thiazide‡ | 20.85 | 19.43 | 1.09 | 1.20 | **1.39** (1.11 – 3.27) |
| Thiazide combine§ | 2.26 | 3.08 | 0.73 | 0.81 | **1.06** (0.61 – 1.86) |
| Beta blockers | 8.37 | 12.10 | 0.66 | 0.67 | **0.87** (0.64 – 1.19) |
| CC blockers | 3.32 | 2.24 | 1.50 | 1.42 | **0.93** (0.55 – 1.56) |
| Others¶ | 6.24 | 4.13 | 1.54 | 1.46 | **1.65** (1.14 – 2.39) |

***Adjusted for concurrent use of different antihypertensive drugs**

**†Adjusted for concurrent use of different antihypertensive drugs and other covariates**

**‡Pot Spar/Thiazide=Hydrochlorothiazide combined with Potassium sparing**

**§Thiazide combine= antihypertensives excluding diuretics combined with thiazide**

**¶Others=antihypertensives excluding diuretics, beta blockers and calcium channel blockers**

**CC blockers = calcium channel blockers**

**Table 9b. Rate ratio of hospitalization for gastrointestinal bleeding associated with individual diuretic classes within the 60-day time window**

| Antihypertensive Medication | Cases n=753 % | Controls n=7530 % | Unadjusted Rate Ratio | *Adjusted Rate Ratio | †Fully Adjusted Rate Ratio |
|---|---|---|---|---|---|
| **45-day Time Window** | | | | | |
| Reference (none) | 43.96 | 52.15 | 1.00 | 1.00 | **1.00** |
| Loop diuretics | 15.80 | 4.59 | 3.84 | 3.49 | **1.64** (1.23 – 2.19) |
| Potassium sparing | 3.72 | 0.66 | 5.82 | 3.82 | **2.84** (1.55 – 5.20) |
| Thiazide diuretics | 3.98 | 3.21 | 1.25 | 1.44 | **1.89** (1.20 – 2.98) |
| Pot Spar/Thiazide‡ | 26.69 | 23.73 | 1.17 | 1.31 | **1.50** (1.22 – 1.85) |
| Thiazide combine§ | 2.66 | 3.76 | 0.70 | 0.80 | **1.04** (0.62 – 1.74) |
| Beta blockers | 9.69 | 14.69 | 0.62 | 0.65 | **0.80** (0.60 – 1.01) |
| CC blockers | 4.12 | 2.92 | 1.43 | 1.44 | **0.95** (0.64 – 1.62) |
| Others¶ | 7.57 | 5.06 | 1.53 | 1.43 | **1.74** (1.24 – 2.43) |
| **60-day Time Window** | | | | | |
| Reference (none) | 39.84 | 47.37 | 1.00 | 1.00 | **1.00** |
| Loop diuretics | 16.73 | 5.23 | 3.59 | 3.27 | **1.44** (1.09 – 1.90) |
| Potassium sparring | 3.98 | 0.72 | 5.89 | 3.98 | **2.99** (1.67 – 5.36) |
| Thiazide diuretics | 3.98 | 3.55 | 1.13 | 1.32 | **1.60** (1.01 – 2.54) |
| Pot Spar/Thiazide‡ | 29.22 | 26.40 | 1.15 | 1.30 | **1.44** (1.17 – 1.76) |
| Thiazide combine§ | 3.19 | 4.26 | 0.74 | 0.85 | **1.07** (0.67 – 1.73) |
| Beta blockers | 11.29 | 15.99 | 0.67 | 0.71 | **0.85** (0.65 – 1.12) |
| CC blockers | 4.25 | 3.09 | 1.40 | 1.41 | **0.92** (0.58 – 1.46) |
| Others¶ | 8.50 | 5.55 | 1.57 | 1.45 | **1.62** (1.17 – 2.25) |

*Adjusted for concurrent use of different antihypertensive drugs

†Adjusted for concurrent use of different antihypertensive drugs and other covariates

‡Pot Spar/Thiazide=Hydrochlorothiazide combined with Potassium sparing

§Thiazide combine= antihypertensives excluding diuretics combined with thiazide

¶Others=antihypertensives excluding diuretics, beta blockers and calcium channel blockers

CC blockers = calcium channel blockers

Adjustment for concurrent use of other antihypertensive medications, gender, age at index date, number of hospitalization as a marker for comorbidity, NSAIDs, antiulcer medications, anticoagulants and glucocorticoids led to a reduction in the rate ratios for potassium sparing and loop diuretics within the three exposure time windows, while the rate ratios for thiazide diuretics did increase appreciably (Table 9a and Table 9b). The rate ratios for loop diuretics were almost constant across the different time windows (30-day: 1.52; 95% CI, 1.11 – 2.07; 45-day: 1.64; 95% CI, 1.23 – 2.19; 60-day: 1.44; 95% CI, 1.09 – 1.90) and showed increased risk of hospitalization for gastrointestinal bleeding. Higher rate ratios (30-day: 2.64; 95% CI, 1.35 – 5.16; 45-day: 2.84; 95% CI, 1.55 – 5.20; 60-day: 2.99; 95% CI, 1.67 – 5.36) were observed for current use of potassium sparing. Also, significant rate ratios (30-day: 1.95; 95% CI, 1.17 – 3.27; 45-day: 1.89; 95% CI, 1.20 – 2.98; 60-day: 1.60; 95% CI, 1.01 – 2.54) were observed with the current use of thiazide diuretics.

As shown in Table 10a, higher doses of furosemide were positively associated with hospitalization for gastrointestinal bleeding. The rate ratios for current use of less than 40mg/day of furosemide daily after adjustments for concurrent use of other antihypertensive medications and other covariates were (30-day: 1.37; 95% CI, 0.90 – 2.08; 45-day: 1.44; 95% CI, 0.93 – 2.24; 60-day: 1.08; 95% CI, 0.71 – 1.66). The rate ratios for a daily dose equal to 40mg/day (30-day: 1.47; 95% CI, 0.91 – 2.36; 45-day: 1.49; 95% CI, 0.96 – 2.17; 60-day: 1.40; 95% CI, 0.98 – 2.00), and for a daily dose greater than 40mg/day the rate ratios (95% CI) were 30-day: 1.96 (1.14 – 5.03); 45-day: 2.19 (0.99 – 5.31); 60-day: 1.93 (1.08 – 4.45).

**Table 10a. Rate ratio of hospitalization for gastrointestinal bleeding associated with estimated daily dose of furosemide within the 30-day and 45-day time windows**

| Antihypertensive Medication | Cases n=753 % | Controls n=7530 % | Unadjusted Rate Ratio | *Adjusted Rate Ratio | †Fully Adjusted Rate Ratio (95% CI) |
|---|---|---|---|---|---|
| **30-Day Time Window** | | | | | |
| Reference (none) | 53.52 | 60.44 | 1.00 | 1.00 | **1.00** |
| Furosemide dosage | | | | | |
| • <40mg/day | 7.30 | 2.06 | 4.06 | 1.63 | **1.37** (0.90 – 2.08) |
| • 40mg/day | 4.78 | 1.46 | 3.24 | 2.62 | **1.47** (0.91 – 2.36) |
| • >40mg/day | 1.20 | 0.29 | 4.89 | 4.38 | **1.96** (1.14 – 5.03) |
| **45-Day Time Window** | | | | | |
| Reference (none) | 43.96 | 52.15 | 1.00 | 1.00 | **1.00** |
| Furosemide dosage | | | | | |
| • <40mg/day | 9.03 | 2.56 | 4.04 | 1.62 | **1.44** (0.93 –2.24) |
| • 40mg/day | 5.84 | 1.82 | 3.44 | 2.83 | **1.49** (0.96 – 2.17) |
| • >40mg/day | 1.33 | 0.37 | 4.35 | 3.66 | **2.19** (0.99 – 5.31) |
| **60-Day Time Window** | | | | | |
| Reference (none) | 39.84 | 47.37 | 1.00 | 1.00 | |
| Furosemide dosage | | | | | |
| • <40mg/day | 9.96 | 2.82 | 3.58 | 1.63 | **1.08** (0.71 – 1.66) |
| • 40mg/day | 6.11 | 2.23 | 3.18 | 2.55 | **1.40** (0.98 – 2.00) |
| • >40mg/day | 1.46 | 0.46 | 3.11 | 3.51 | **1.93** (1.08 – 4.45) |

***Adjusted for concurrent use of different antihypertensive drugs**

**†Adjusted for concurrent use of different antihypertensive drugs and other covariates**

There was a significant dose-response relationship when the model was fitted using the continuous form of the dosage (Table 10b).

**Table 10b. Daily Dosage (continuous form) of Furosemide and occurrence of Gastrointestinal Bleeding**

| Antihypertensive Medication | Cases n=753 | Controls n=7530 | *Fully Adjusted Rate Ratio (95% CI) |
|---|---|---|---|
| **30-day Time Window** | | | |
| Furosemide† (mean±SD) | 0.638±0.315 | 0.615±0.257 | **1.19** (1.06 – 1.57) |
| **45-day Time Window** | | | |
| Furosemide† (mean±SD) | 0.638±0.310 | 0.625±0.274 | **1.17** (1.09 – 1.58) |
| **60-day Time Window** | | | |
| Furosemide† (mean±SD) | 0.647±0.312 | 0.613±0.272 | **1.18** (1.10 – 1.62) |

***Adjusted for concurrent use of different antihypertensive drugs and other covariates**

**†Daily dose in units of 100mg**

**SD=standard deviation**

Thiazide combined with potassium sparing was categorized into three (3) groups, namely, thiazide/amiloride, thiazide/spironolactone and thiazide/triamterene to assess the associated risk of gastrointestinal bleeding separately for all 3 groups. After adjustment for all covariates and fitting a model with all three-drug groups, only thiazide combined with amiloride was significantly associated with an increased risk of hospitalization for gastrointestinal bleeding within all three exposure time windows (Table 11). For the 30-day exposure time-window, the rate ratio was 1.96 (95% CI, 1.34-2.85), for the 45-day time-window the rate ratio was 2.11 (95% CI, 1.50-2.98), and the rate ratio was 1.94 (95% CI, 1.39-2.73) for the 60-day exposure time window.

**Table 11. Use of thiazide-diuretic combined with potassium sparing and rate ratios of hospitalization for gastrointestinal bleeding associated with current exposure at index date**

| Antihypertensive Medication | Cases n=753 % | Controls n=7530 % | Unadjusted Rate Ratio | *Adjusted Rate Ratio | †Fully Adjusted Rate Ratio (95% CI) |
|---|---|---|---|---|---|
| **30-day Time Window** | | | | | |
| Reference (none) | 53.52 | 60.44 | 1.00 | 1.00 | **1.00** |
| HCTZ+Amiloride | 6.37 | 4.82 | 1.35 | 1.50 | **1.96** (1.34-2.85) |
| HCTZ+Spironolact | 0.53 | 0.56 | 0.95 | 1.02 | **0.71** (0.21-2.42) |
| HCTZ+Triamterene | 13.94 | 14.08 | 0.99 | 1.10 | **1.26** (0.97-1.62) |
| **45-day Time Window** | | | | | |
| Reference (none) | 43.96 | 52.15 | 1.00 | 1.00 | **1.00** |
| HCTZ+Amiloride | 7.97 | 5.83 | 1.41 | 1.66 | **2.11** (1.50-2.98) |
| HCTZ+Spironolact | 0.66 | 0.65 | 1.02 | 1.14 | **0.57** (0.18-1.76) |
| HCTZ+Triamterene | 18.06 | 17.33 | 1.05 | 1.20 | **1.38** (1.09-1.74) |
| **60-day Time Window** | | | | | |
| Reference (none) | 39.84 | 47.37 | 1.00 | 1.00 | **1.00** |
| HCTZ+Amiloride | 8.23 | 6.35 | 1.34 | 1.58 | **1.94** (1.39-2.73) |
| HCTZ+Spironolact | 0.93 | 0.70 | 1.32 | 1.54 | **0.94** (0.35-2.48) |
| HCTZ+Triamterene | 20.05 | 19.47 | 1.04 | 1.19 | **1.31** (1.04-1.64) |

***Adjusted = adjusted for concurrent use of any antihypertensive medications**

**†Fully Adjusted = adjusted for concurrent use of any antihypertensive medications and other covariates**

**none = no use of any antihypertensive during the time-window**

**HCTZ = Hydrochlorothiazide**

**Spironolact = Spironolactone**

In addition, an analysis was performed to assess whether there was a dose-response relationship regarding exposure to thiazide. The first model was fitted including three indicator variables (estimated daily prescribed dosage: <50mg, equal to 50-60mg and

above 50mg) and all other covariates, and for the second model the continuous form of the dosage was used to fit the model (Tables 12a, 12b). As shown in the tables, there was significant dose-response relationship, but the analyses indicate that the risk was higher within the 30-day exposure time-window.

**Table 12a. Daily dosage of Thiazide and occurrence of gastrointestinal bleeding**

| Antihypertensive Medication | Cases n=753 % | Controls n=7530 % | *Fully Adjusted Rate Ratio (95% CI) |
|---|---|---|---|
| **30-day Time Window** | | | |
| Reference (none) | 53.52 | 60.44 | **1.00** |
| <50mg/day | 0.53 | 0.50 | **1.34** (0.37 – 4.90) |
| 50-60mg/day | 1.73 | 1.42 | **1.81** (0.93 – 3.54) |
| >60mg/day | 0.93 | 0.50 | **2.99** (1.14 – 7.84) |
| **45-day Time Window** | | | |
| Reference (none) | 43.96 | 52.15 | **1.00** |
| <50mg/day | 0.53 | 0.66 | **1.10** (0.32 – 3.85) |
| 50-60mg/day | 2.52 | 1.98 | **1.93** (0.99 – 3.39) |
| >60mg/day | 0.93 | 0.60 | **2.53** (1.12 – 6.48) |
| **60-day Time Window** | | | |
| Reference (none) | 39.84 | 47.37 | **1.00** |
| <50mg/day | 0.53 | 0.73 | **0.86** (0.25 – 2.96) |
| 50-60mg/day | 2.52 | 2.24 | **1.60** (0.91 – 2.81) |
| >60mg/day | 0.93 | 0.65 | **2.42** (1.01 – 6.17) |

***Fully Adjusted = adjusted for concurrent use of any antihypertensive medications and use of NSAIDs, antiulcer drugs, anticoagulants, glucocorticoids, age at index date, gender and number of hospital admissions at baseline**

**none = no use of any antihypertensive during the time-window**

**Table 12b. Daily Dosage (continuous form) of Thiazide and occurrence of Gastrointestinal Bleeding**

| Antihypertensive Medication | Cases n=753 | Controls n=7530 | *Fully Adjusted Rate Ratio (95% CI) |
|---|---|---|---|
| **30-day Time Window** | | | |
| Thiazide† (mean±SD) | 0.622±0.465 | 0.565±0.396 | **1.20** (1.09 – 1.76) |
| **45-day Time Window** | | | |
| Thiazide† (mean±SD) | 0.608±0.429 | 0.533±0.340 | **1.19** (1.08 – 1.59) |
| **60-day Time Window** | | | |
| Thiazide† (mean±SD) | 0.592±0.404 | 0.520±0.338 | **1.19** (1.09 – 1.64) |

***Fully Adjusted = adjusted for concurrent use of any antihypertensive medications and other covariates**

**†Daily dose in units of 100mg**

**SD=standard deviation**

# 6.0 DISCUSSION

In this nested case-control study, we found that the use of diuretics is independently associated with an elevated risk of hospitalization for gastrointestinal bleeding. This association, however, is mainly evident in subjects taking potassium sparing and thiazide diuretics. Also, a significantly increased risk was observed in furosemide (loop diuretic) users. This study confirms previous findings that calcium channel blocker use is not associated with hospitalization for gastrointestinal bleeding and that beta blocker use is independently associated with a reduction of this risk. An interesting observation is that this reduction appears to stem from non-selective beta blockers and not selective beta blockers.

## 6.1 Antihypertensive Medications and Occurrence of Gastrointestinal Bleeding

In this study, exposure to diuretics was associated with an increased risk of admission to the hospital for gastrointestinal bleeding (GIB), and calcium channel blocker was not positively associated with GIB. The risk of current exposure to all diuretics combined was about 1.5-fold increased compared with nonusers of antihypertensive medications within the 30-day exposure time windown, and are close to the estimates from previously published studies. In a previous study, Suissa and colleagues (1998) reported a rate ratio of hospitalization for gastrointestinal bleeding of 1.42 (95% CI, 1.00 – 2.01) for users of diuretics compared with nonusers of antihypertensives. The present study showed a rate ratio of 1.54 (95% CI, 1.27 – 1.86) for diuretic users compared with nonusers of any antihypertensives within the 30-day time window, and approximately a 1.5-fold higher

risk was observed within the 45- and 60-day time windows. Although the previous study looked at a 90-day exposure time window, these analyses suggest that the present results might be consistent with the previous study, as Garcia Rodriguez and colleagues (1998), also reported that diuretic users had a rate ratio of gastrointestinal bleeding of 1.4 (95% CI, 1.0-1.8) compared with nonusers of antihypertensive medications in a 30-day exposure time window, a result identical to that of Suissa and colleagues regarding the rate ratio and the confidence interval. These two previous studies observed weak association probably because of the small number of diuretic users in the study population as these studies were design to evaluate different issues, hence did not have the necessary power to address this hypothesis. Moreover, these studies did not investigate different diuretics.

In the current study the risk was substantially greater in potassium sparing and thiazide diuretic users. The risk associated with diuretic in this present study is largely accounted for by the estimate of risk in the thiazide and thiazide combined with potassium sparing diuretics categories, where most of the use (approximately 80 percent) occurred in this study population (see Appendix C). The underlying mechanism for the gastrointestinal bleeding observed with diuretic use in this study, is not apparent. This is more so, because diuretic is made-up of different substances, and their effect on the gastrointestinal tract may differ. Of possible relevance, is that some diuretics release prostaglandins and nitric oxide (Wiemer et al., 1994), which inhibit platelet aggregation (Salvemini et al., 1996), and in addition, nitric oxide is said to increase blood flow in the

gastric mucosa (Lanas et al., 2000). It must be noted that this biological mechanism is still quite speculative.

The use of calcium channel blockers was not associated with an elevated risk of hospitalization for gastrointestinal bleeding in this study. Although the crude rate ratios were elevated within all the 3 different exposure time-windows, adjustment for confounding factors abolished the effect within all the 3 exposure time-windows. In contrast another population-based study (Pahor et al., 1996), suggested that the use of calcium channel blockers might have an adverse effect on the risk of gastrointestinal bleeding. In that study, users of calcium channel blockers had an RR of hospitalization for fatal upper or lower gastrointestinal bleeding of 1.86 (95% CI, 1.22 – 2.82) compared with users of beta-blockers. A recent study (Kaplan et al., 2000) has also reported that the RR associated with calcium channel blocker use was 2.05 (95% CI, 1.33 – 3.17) compared with beta blocker users, after adjustment for confounding factors. There are some animal and in vitro studies, which support a biologically plausible mechanism by which calcium channel blockers may predispose to bleeding (Pietraszek et al., 1988, Blache and Ojeda, 1992), however, available human studies are conflicting (Feinberg and Bruck, 1993, Wagenknecht et al., 1995, Grimm and Shaheen, 1996). The studies reporting positive findings looked at a 90-day exposure time window, whereas the present study examined 30-, 45- and 60-day exposure time windows. More importantly, however, is the fact that the two previous studies used beta blocker users as their reference group, while the present study used nonusers of any antihypertensive medications. It has been documented that beta blockers are protective factors for

bleeding (Poynard et al., 1991; Bernard et al., 1997), and this might have accounted for the increased risk in the previous studies. Nevertheless, the present results are consistent with other observational studies that examined a 90-day exposure time window. Suissa and others (1998) reported a rate ratio of hospitalization for gastrointestinal bleeding of 1.06 (95% CI, 0.78 – 1.43) for users of calcium channel blockers compared with nonusers, while Kelly and others (1999) reported 1.2 (95% CI, 0.9 –1.6). Also, Smalley et al., (1998) reported 1.1 (95% CI, 0.7 – 1.7) for calcium channel blocker users compared with nonusers.

The results of the current population-based study support the hypothesis that beta blockers may prevent nonvariceal gastrointestinal bleeding (Gordon, 1996), and is consistent with other studies (Suissa et al., 1998). The current findings further suggest less gastrointestinal bleeding in non-selective beta blocker users than with users of selective beta blockers, when compared with nonusers of antihypertensive medications. It has been reported that non-selective beta blockers without intrinsic sympathomimetic activity increase platelet aggregability and that the fibrinolytic system can be reduced by the same drugs (Winther, 1987; Winther and Trap-Jensen, 1988). Documented evidence indicates that propranolol, a non-selective beta blocker exert a protective effect against ethanol-induced gastric haemorrhagic lesions in animals (Bhandare et al., 1990), and this effect may be mediated by prostaglandins and nitric oxide, or a membrane stabilizing action (Daly, 1984). Also, propanolol has been shown to block isoproterenol stimulated gastrin production (Daly, 1984).

It was observed that treatment with "other antihypertensive" category in this study (see Appendix C) was significantly associated with an increased risk of gastrointestinal bleeding. The risk was about 1.6-fold increased compared with nonusers of antihypertensive medications, and this risk was similar in all 3-exposure time windows, even after adjustment for various covariates. Notwithstanding the fact that the majority of patients in this group used methyldopa, the different chemical structures of agents in this category, makes it difficult to give any meaningful interpretation to this association. There are documented reports that methyldopa, hydralazine and reserpine could cause thrombocytopenia with purpura (Krogh, et al., 1993), and also that capoten, an ACE inhibitor can cause gastric irritation (Krogh et al., 1993). These could be the plausible explanation for the observed association. However, epidemiological studies based on more recent data (Suissa et al., 1998; Garcia Rodriguez et al., 1998) found no association between ACE inhibitors and gastrointestinal bleeding.

### 6.2 Individual Diuretics and Occurrence of Gastrointestinal Bleeding

The current study showed that there are substantial differences in the risk of gastrointestinal bleeding among users of different diuretic classes. These differences persisted after adjusting for potential confounding factors. Potassium sparing diuretics were associated with the highest gastrointestinal bleeding rate ratio and combination of thiazide diuretics and potassium sparing diuretics, with the lowest. However, we did not assess whether there were any clinical features among users of the different classes of diuretics that could have accounted for these differences.

In this observational study, hypertensive patients who were current users of loop diuretics (furosemide) had approximately a 1.5-fold higher risk of hospitalized gastrointestinal bleeding than hypertensive patients who did not use any antihypertensive medications, and this was constant across all the 3 different exposure time windows. The findings suggest that furosemide use increases the risk of gastrointestinal bleeding. This positive association was unexpected, since furosemide has not been under general suspicion as a possible cause of gastrointestinal bleeding. This result is in contrast to a previous study (Jick and Porter, 1978) evaluating the association between loop diuretics (ethacrynic acid and furosemide) and gastrointestinal bleeding, which reported that there was no association between furosemide and gastrointestinal bleeding. However, the authors found a positive association with ethacrynic acid, a loop diuretic, which has similar indications and action as furosemide. Such discordance may reflect differences in either drug exposure or methodological differences between this study and the previous studies. Previous studies (Jick and Porter, 1978; Slone et al., 1969) had methodological limitations, and the inherent biases are likely to have weakened the strength of any true association. Also, the brief exposure time window (7 days) in the previous study (Jick and Porter, 1978) probably did not allow assessment of the full incidence of adverse events that might be caused by this substance. The association we have detected could have arisen by chance in multiple comparative analyses, but this is unlikely because the rate ratios are reasonably substantial, and because the numbers on which estimates are based are large. This is the first epidemiological study to show that furosemide use is associated with an increased risk of hospitalization for gastrointestinal bleeding. However, there is some biological credibility for an association. Furosemide prevents

platelet aggregation and inhibits several platelet-activating factors (Kribben et al., 1988). In addition, furosemide stimulates synthesis of nitric oxide and postaglandins ($PGI_2$), a potent vasodilator, and an endogenous inhibitor of platelet aggregation and adherence to the vessel wall (Schlonderff, 1986). It has been documented that furosemide, in addition to $PGI_2$, also enhance secretion of thromboxane, the physiological antagonist of $PGI_2$ (Wilson et al., 1993; Liguori et al., 1999), which is said to cause cell cytolysis (Peterson, 1989). Vasodilation in conjunction with inhibition of platelet aggregation may increase the risk of bleeding, or at least prevent the normal vasoconstrictive response to bleeding. These antiplatelet properties may justify the increased risk of bleeding that has been observed among furosemide users in this study. However, no experimental evidence is currently available about any deleterious effect of furosemide on the gastrointestinal mucosa. It is therefore unlikely that this substance might cause gastrointestinal bleeding in the absence of pre-existing lesions. Furthermore, furosemide is more likely to be prescribed for persons with more severe diseases, such as heart failure and renal failure, who in turn, have a greater probability of hospitalization for gastrointestinal bleeding. The current investigation had no independent measure of disease severity, and since the number of hospital admission measure is unlikely to compensate completely for disease severity among recipients of furosemide, residual confounding could be the possible explanation for this increased risk observed.

Users of potassium sparing diuretics had approximately a 2.9-fold higher risk of hospitalization for gastrointestinal bleeding within the 45- and 60-day exposure time windows, and about 2.6-fold higher within the 30-day time window when compared with

nonusers of antihypertensives. There was strong evidence in this study, that current use of potassium sparing diuretics had a markedly elevated risk of gastrointestinal bleeding. The number of subjects available for these analyses was small to assess with confidence a dose-effect response. Spironolactone, a potassium sparing diuretic, is reported to cause ulceration, gastritis and gastric bleeding (Facts and Comparison, 2000). Also, according to Touyz and Schiffrin (1995) amiloride, another potassium sparing diuretic, significantly inhibits thrombin-stimulated platelet response and suppresses the inhibiting effect of endothelin-1 on thrombin-induced platelet aggregation and intracellular free calcium concentration. The small number of potassium sparing users did not permit evaluation of individual drugs of potassium sparing diuretics.

In a study evaluating the mucosal irritant potential of a potassium sparing diuretic and wax-matrix potassium chloride, Ryan and colleagues (1984) reported that a combination of potassium sparing and thiazide diuretic, even when given with an anticholinergic drugs, appearsed not to irritate the gastrointestinal mucosal. They did not look at the effect of potassium sparing alone. In the present study, we found that a combination of potassium sparing and thiazide diuretic was significantly associated with the risk of hospitalization for gastrointestinal bleeding than patients who did not use any antihypertensive medication. The disparate risk observed between users of potassium sparing diuretics and users of potassium sparing combined with thiazide diuretics in this study, could possibly be explained by the difference in dosage. However, we found that treatment with hydrochlorothiazide combined with amiloride was independently associated with an increased risk of hospitalization for gastrointestinal bleeding.

Hypertensive patients who were current users of hydrochlorothiazide combined with amiloride had approximately a 2-fold higher risk of hospitalized gastrointestinal bleeding than hypertensive patients who did not use any antihypertensive medications, and this was evident in all the 3 different exposure time windows. This may be due to the fact that documented evidence suggests that amiloride can activate pre-existing peptic ulcers, and also cause gastric irritation, thrombocytopenia, purpura, aplastic and haemolytic anemia (Krogh et al., 1993). Surprisingly, in contrast with documented evidence that spironolactone can cause gastric bleeding, gastritis and ulceration (Kogh et al., 1993; Facts and Comparisons, 2000), we found that a combination of spironolactone and hydrochlorothiazide was associated with a decreased risk of hospitalization for gastrointestinal bleeding.

This study shows that, compared with none users of any antihypertensive medication during the exposure time windows, use of thiazide diuretics was associated with an increased risk of hospitalization for gastrointestinal bleeding. The association was consistent in all three exposure time windows after adjustment for other risk factors. Thiazide diuretics produce thrombocytopenia (Aster 1977), which is a platelet disorder that induces mucosal bleeding (Lutcher, 1992). The findings of the current study are consistent with previous case report studies (Ball, 1960; Gesink and Bradford, 1960), which suggested a link between thiazide diuretics and bleeding.

### 6.3 Risk of Gastrointestinal Bleeding associated with Furosemide and Thiazide diuretics by Daily Dose

Prior studies did not examine the dose-response relationship between thiazide diuretics and gastrointestinal bleeding. As anticipated, given the strong relationship between thiazide use and gastrointestinal bleeding, the risk of bleeding in patients taking thiazide was higher with high doses than with low doses, across all the three different exposure time-windows. Increasing thiazide diuretic use was associated with increasing risk of hospitalization for gastrointestinal bleeding, with approximately a 2-fold risk among users of more than 60mg/day thiazide relative to none users of any antihypertensive medication during the exposure time window.

In this study, current exposure with a daily dose above 40 mg/day of furosemide was associated with a two-fold increase in risk compared with nonusers of antihypertensive medication. The risk of hospitalization for gastrointestinal bleeding was increased in every dispensing category in each exposure time window. However, lower dispensing rates of furosemide were not significantly associated with hospitalization for gastrointestinal bleeding. This relationship was observed in each of the three exposure time windows.

Estimated daily dosage (based on the quantity supplied divided by 30 days, and the ratio multiplied by the given strength) was used as a surrogate for the actual prescribed daily dose, since the actual prescribed daily dose was not available in the data set. This surrogate measure might not reflect the actual prescribed daily dose. In addition, the dose

of these drugs, especially furosemide, varies depending on different indications, which could not be assessed in the study subjects. Hence the estimated daily dosage can only be regarded as crude estimate.

### 6.4 Strengths and Limitations of the Study

Because of the nature of the study design and the secondary sources used in the analysis, some alternative explanations of results cannot be ruled out, and need to be mentioned.

In a long-term follow-up study, individual prescribed dosages and drug regimens of antihypertensive treatment are highly variable (time-dependent), therefore, the calculation of person-time at risk in a pharmacoepidemiological cohort study may yield only crude estimates of drug exposure, and also, because of the large size of the cohort, a nested case-control design was used for this study, which is more efficient (Suissa, 2000; Rothman and Greenland, 1998). Whereas reliance on data from computerized databases has inherent weaknesses and the use of non-experimental design can be problematic, the strengths of such studies are being increasingly recognized. Besides the obvious advantage of large sample size, there is the added merit of a large and extended follow up at a relatively inexpensive price. If the non-experimental study is well designed and properly analysed, it can produce useful information at a minimal fraction of the time and cost needed by the experimental design. An additional methodological advantage of database studies is that, being set in the context of actual medical practice, they provide information of greater relevance than what is obtained within the artificial confines of a clinical trial. However, the use of drug prescription as a marker for exposure to a

particular medication might not reflect the actual medication intake, since it is known that compliance with drug regimens is never complete, and this is an important methodological limitation of this study.

The essence of any epidemiological study within a population is whether or not sampling leads to a biased study population. In this study, subjects were selected from the entire population without restriction, thus eliminating potential selection bias. Given that the Saskatchewan database contains information on 95 percent of the population (Guess et al., 1988), selection bias into the study is highly unlikely. Furthermore, because subjects in the cohort were identified without regard to disease status, there is little risk of the selection biases that may occur in a purely retrospective case-control study (Langholz and Clayton, 1994). Since the study design restricts cohort entry to the time of beginning antihypertensive treatment, confounding by severity of gastrointestinal complications of hypertension treatment will not be expected to affect study validity. Specifically, we believe the status of all antihypertensive medications with regard to the risk of gastrointestinal bleeding will be identical during the period 1980-1983 (period of cohort entry), and allocation of hypertensive subjects to the various drugs during this period would have been random as far as gastrointestinal bleeding was concerned.

Notwithstanding the fact that the cohort consisted of incident hypertensive persons, the use of the number of hospitalizations as a marker for chronic disease status might not reflect the true picture, and this is an important limitation of the present analysis, taking into consideration the importance of comorbidity in gastrointestinal bleeding. Even after adjusting for comorbidity, there might be residual confounding. However, the likelihood

of misclassification of subjects with respect to comorbidity was the same for cases and controls, and also uniform for all antihypertensive medication groups. Controlling for drugs that are independently important risk factors, and also markers for conditions that are known to be risk factors of gastrointestinal bleeding might somehow address this possible confounding. Another important issue is that of confounding by indication, which generally tends to bias the results of non-experimental studies on intended effects (Miettinen, 1983). The cohort inception period was such that confounding by indication will be absent because exposure allocation to any particular antihypertensive medication class during that period was made based on considerations other than gastrointestinal tract conditions, because during that period, and as of now there are no clear cut clinical recommendations regarding the risk or beneficial effect of diuretics on gastrointestinal bleeding. Although it cannot be ruled out entirely that the earlier scattered reports of the association between thiazide-diuretics and thrombocytopenia could influence prescription patterns during that period. Nevertheless, it is believed that potential gastrointestinal effects of the antihypertensive medications prescribed to cohort members were, in fact, unintended. Thus, allocation to a particular antihypertensive medication was analogous to randomization with respect to the outcome of interest, which is gastrointestinal bleeding.

The primary outcome considered for analysis was hospitalization for gastrointestinal bleeding. Since both specific and non-specific sites were used, the possibility of misclassifying this outcome is extremely unlikely. The validity of information contained in the health care utilization databases of Saskatchewan Health has been assessed in

different ways. Validity studies have shown excellent concordance (99%) between procedures documented in the Hospital Service Branch data file and medical charts (Rawson, 1995). Similarly, concordance between diagnoses in the hospital file and those in medical charts (of acute myocardial infarction) was extremely high (97%) (Rawson, 1995). Nevertheless, a nondifferential outcome misclassification of fatal gastrointestinal events of 20-30 percent has been reported in the Saskatchewan Hospital service Plan (Guess et al, 1988). However, any unexpected outcome misclassification is not expected to be differential across the classes of antihypertensive medications. Thus, any non-differential misclassification of gastrointestinal bleeding would bias the rate ratios in the direction of the null and provide a conservative estimate of effect (Rothman and Greenland, 1998).

Drug exposure in this administrative database is recorded prospectively at the time a person fills the prescription in the pharmacy, which is dispensed by a pharmacist hence misclassification is extremely remote. Data on over-the counter use of NSAIDs, and also information on alcohol use as a possible confounder were not available; hence the likelihood of a residual confounding cannot be ruled out. This would not affect the results of the study, unless over-the counter use of NSAIDs and alcohol consumption varied by class of antihypertensive medication. However, there is no reason to believe that over-the-counter use of NSAIDs occurred more often among one class of antihypertensive users than the others or more among users of antihypertensives than nonusers. Since the study design permitted analysis of drug exposure at or near the time of hospitalization for gastrointestinal bleeding, it was possible to estimate the

independent effects of different antihypertensive medications, as compared with non-users of antihypertensives during the 30-day, 45-day and 60-day periods before the index date. Date of prescription was a marker for exposure to a particular medication. While we are certain that those classified as exposed are actually exposed, we cannot say so for the unexposed group, because an individual classified as unexposed within the specified time window, may be exposed to a particular medication if it was prescribed a few days before the exposure time window. Nevertheless, such a situation will tend to make the exposed and unexposed groups similar with regard to the exposure of interest, and would bias the rate ratios in the direction of the null, and provide a conservative estimate. Another drawback with regard to drug exposure was that, the estimated daily dosages for furosemide could only be regarded as crude estimates.

It is worth mentioning that in certain subjects both exposure and outcome may have been misclassified, since drug use was assessed only as date of prescription. Some subjects may have discontinued therapy or switched to different drugs during the follow-up period. Furthermore, the diagnoses in the Saskatchewan Hospital files may not be very accurate, as already indicated (Guess et al., 1988), and some gastrointestinal bleeding events may have been missed. However, such potential misclassifications would probably weaken any association and introduce a conservative bias, leading us to underestimate the extent to which diuretic is independently associated with gastrointestinal bleeding.

## 7.0 Conclusion and Policy Implications

In this study we were able to show that use of diuretics was independently associated with gastrointestinal bleeding, and this association was mainly observed in users of potassium sparing, thiazide diuretics and furosemide (loop diuretic). Taken together with other studies the current study reinforces the concern about the possible association between diuretics and gastrointestinal bleeding. The rate ratios for furosemide and thiazide diuretics suggest an unfavourable risk-benefit assessment for users, but the data also support use of low doses to reduce the burden of gastrointestinal bleeding. The finding of an elevated risk of furosemide was unexpected and requires further investigation.

The question of whether certain diuretic agents are associated with a significantly higher risk of gastrointestinal bleeding than others cannot be answered definitively by any single study, and needs further investigation. Furthermore, the important question of whether diuretic-induced gastrointestinal bleeding partially or wholly offset the benefit of the blood lowering effects in patients with hypertension remains to be answered. Until such substantial information becomes available, alarming health care providers and patients that diuretic use will increase the risk of gastrointestinal bleeding is premature. However, our data suggest a need for continued vigilance to assess the risk-benefit ratio of diuretic use.

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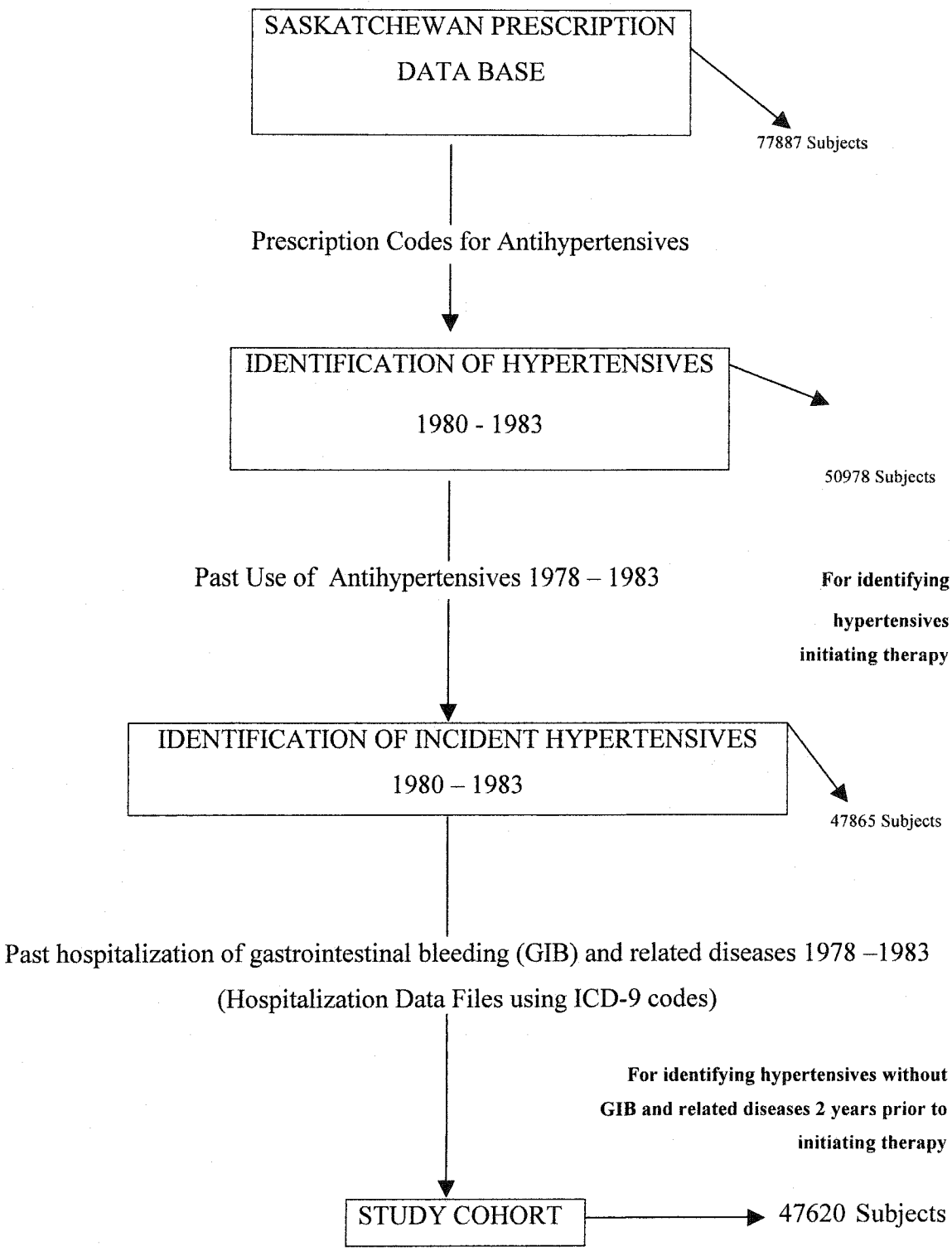
**Appendix A** **Flow Diagram of Cohort Assembly**



## Appendix B

### Sample Size Estimation

Estimating the relative risk with specified relative precision among those exposed to diuretic:

- Anticipated probability of exposure given disease ?
- Anticipated probability of exposure given no disease (approximated by overall exposure rate) 30%
- Anticipated RR based on previous study 1.5
- Confidence level 95%
- Relative precision 20%
- Case control ratio 1:10

Estimated sample size of 275 would be needed in the case group and 2750 in the control group (Lwanga SK Lemeshow S. Sample size determination in health studies. A practical manual. World Health Organization, Geneva, 1991).

**Appendix C**

**Definition and Frequency Distribution of Drugs in each Drug Category within the Exposure Time-Windows**

| DRUG CATEGORY | FREQUENCY DISTRIBUTION WITHIN THE EXPOSURE TIME WINDOW | | |
|---|---|---|---|
| | 30-Day (%) | 45-Day (%) | 60-Day (%) |
| DIURETICS | | | |
| Thiazide Class | | | |
| - hydrochlorothiazide | 172 (6.86) | 255 (6.97) | 337 (6.97) |
| - chlorthalidone | 53 (2.11) | 83 (2.27) | 98 (2.03) |
| Loop Diuretic | | | |
| - furosemide | 424 (16.91) | 610 (16.66) | 800 (16.56) |
| Potassium Sparing | | | |
| - amiloride | 1 (0.04) | 2 (0.05) | 2 (0.04) |
| - spironolactone | 66 (2.63) | 87 (2.38) | 110 (2.28) |
| - triamterene | 5 (0.20) | 8 (0.22) | 9 (0.19) |
| Potassium Sparing/Thiazide | | | |
| - amiloride/HCTZ | 459 (18.30) | 649 (17.73) | 854 (17.67) |
| - spironolactone/HCTZ | 51 (2.03) | 69 (1.88) | 91 (1.88) |
| - triamterene/HCTZ | 1277 (50.92) | 1897 (51.82) | 2530 (52.36) |

| | | | |
|---|---|---|---|
| THIAZIDE MIXED WITH OTHER ANTIHYPERTENSIVES | | | |
| - pindolol/HCTZ | 13 (4.63) | 21 (5.25) | 25 (4.69) |
| - timolol/HCTZ | 11 (3.91) | 14 (3.50) | 18 (3.38) |
| - propranolol/HCTZ | 38 (13.52) | 55 (13.75) | 73 (13.70) |
| - methyldopa/HCTZ | 162 (57.65) | 231 (57.75) | 310 (58.16) |
| - methyldopa/chlorthiazide | 39 (13.88) | 55 (13.75) | 69 (12.95) |
| - reserpine/hydralazine/HCTZ | 17 (6.05) | 23 (5.75) | 35 (6.57) |
| - reserpine/chlorthalidone | 1 (0.36) | 1 (0.25) | 3 (0.56) |
| BETA BLOCKERS | | | |
| Selective | | | |
| - atenolol | 61 (5.55) | 96 (6.00) | 116 (5.56) |
| - metoprolol | 161 (14.65) | 215 (13.45) | 280 (13.42) |
| Non-selective | | | |
| - propranolol | 557 (50.68) | 823 (51.47) | 1077 (51.63) |
| - pindolol | 121 (11.01) | 176 (11.01) | 243 (11.65) |
| - nadolol | 57 (5.19) | 83 (5.19) | 102 (4.89) |
| - labetolol | 8 (0.73) | 11 (0.69) | 17 (0.81) |
| - oxprenolol | 30 (2.73) | 45 (2.81) | 59 (2.83) |
| - timolol | 104 (9.46) | 150 (9.20) | 192 (9.20) |

| | | | |
|---|---|---|---|
| CALCIUM CHANNEL BLOCKERS | | | |
| - nifedipine | 112 (49.56) | 162 (48.65) | 208 (48.71) |
| - diltiazem | 71 (31.42) | 107 (32.13) | 129 (30.21) |
| - verapamil | 43 (19.03) | 64 (19.22) | 90 (21.08) |
| OTHER ANTIHYPERTENSIVES | | | |
| - capoten (ACE inhibitor) | 27 (6.68) | 43 (7.23) | 54 (7.01) |
| - methyldopa | 165 (40.84) | 245 (41.18) | 322 (41.82) |
| - clonidine | 49 (12.13) | 76 (12.77) | 99 (12.86) |
| - hydralazine | 81 (20.05) | 113 (18.99) | 145 (18.83) |
| - reserpine | 5 (1.24) | 6 (1.01) | 7 (0.91) |
| - guanethidine | 4 (0.99) | 5 (0.84) | 5 (0.65) |
| - debrisoquine sulfate | 4 (0.99) | 6 (1.01) | 7 (0.91) |
| - rauwolfia serpentina | 2 (0.50) | 3 (0.50) | 3 (0.39) |
| - prazosin | 67 (16.58) | 98 (16.47) | 128 (16.62) |

HCTZ = hydrochlorothiazide

ACE = angiotensin-converting enzyme