The Effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) on Blood Pressure in Patients with Hypertension

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ABSTRACT

Hisham S. Aljadhey: The Effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) on Blood Pressure in Patients with Hypertension
(Under the direction of Michael D. Murray, PharmD, MPH)

Dysregulation of blood pressure control in hypertensive patients using nonsteroidal anti-inflammatory drugs (NSAIDs) could increase morbidity, mortality, and health care costs. The aims of this research were to examine the association between NSAIDs and blood pressure in hypertensive patients, compare the effects of various NSAIDs on blood pressure, and determine if NSAIDs were associated with changes in antihypertensive therapy.

This retrospective cohort study included hypertensive patients who received their first prescription for any NSAID and met the inclusion criteria. Patients included in this research received their care from the medicine practice clinics at Wishard Health Services in Indianapolis, Indiana between 1993 and 2006. Patients were followed for one year after the first prescription or 30 days after the last prescription that was dispensed, whichever was less. Patients meeting the same criteria but who were prescribed acetaminophen formed the control group. The primary outcomes were first systolic blood pressure and intensification of antihypertensive therapy. Covariates affecting blood pressure or the prescribing of NSAIDs were included in the statistical models. Propensity score matching techniques were used to balance background characteristics between comparison groups.

A total of 3,928 eligible patients were prescribed NSAIDs or acetaminophen. Compared to acetaminophen, prescription for NSAID was associated with a 2 mmHg increase in systolic blood pressure (P = 0.004), and a 6 mmHg increase in those concurrently prescribed beta-adrenergic blocker (P = 0.008). Ibuprofen was associated with a 3 mmHg increase in systolic blood pressure compared to naproxen (P = 0.015), and a 5 mmHg increase compared to celecoxib (P = 0.035). Ibuprofen was associated with a higher risk of systolic blood pressure increase of ≥ 20 mmHg compared to naproxen (odds ratio, 1.57; 95% confidence interval, 1.10 to 2.25; P = 0.014). Dose effects were not observed for either ibuprofen or naproxen. There was no evidence of intensification in antihypertensive therapy in patients prescribed NSAIDs.

In conclusion, NSAIDs were associated with a small increase in systolic blood pressure in hypertensive patients compared to acetaminophen. The increase in systolic blood pressure from NSAIDs did not increase the risk of intensification of antihypertensive treatment. Confirmatory studies will be needed to affirm these results.

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LIST OF ABBREVIATIONS

NSAIDs: Nonsteroidal anti-inflammatory drugs

ACE-I: Aangiotensin-converting enzyme inhibitor

CCB: Calcium channel blockers

COX: Cyclooxygenase

GFR: Glomerular filtration rate

JNC 7: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

MAR: Missing at random

MCAR: Missing completely at random

MPR: Medication possession ratio

NMAR: Not missing at random

OA: Osteoarthritis

OTC: Over The Counter

PGs: Prostaglandins

RA: Rheumatoid arthritis

RMRS: Regenstrief Medical Record System

I. INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are broadly used for acute and chronic conditions including rheumatoid arthritis and osteoarthritis (1-3). However, it is widely known that NSAIDs are associated with adverse gastrointestinal effects. These adverse effects led to the development of selective cyclooxygenase-2 (COX-2) inhibitors in an attempt to provide safer NSAIDs. However, concerns have arisen that selective COX-2 inhibitors and non-selective NSAIDs cause adverse cardiovascular effects such as myocardial infarction, exacerbation of heart failure, and increase in blood pressure (4-8). These concerns increased following the withdrawal from the market of two selective COX-2 inhibitors, rofecoxib in 2004 and valdecoxib in 2005.

Blood pressure increase in hypertensive patients can lead to deleterious cardiovascular effects. In users of NSAIDs, maintaining or achieving blood pressure control would prevent morbidity and mortality and reduce health care costs (9). Others have estimated that achieving or maintaining blood pressure control in users of selective COX-2 inhibitors would prevent more than 70,000 deaths from stroke and 60,000 others from coronary heart disease; such control would also result in direct health care cost savings of more than 3.8 billion dollars (9).

The effect of NSAIDs on blood pressure in patients prescribed antihypertensive medications has been investigated in clinical trials, but not in

observational studies. These trials have shown that NSAIDs increase blood pressure in patients who were using antihypertensive medications including angiotensin-converting enzyme inhibitors (ACE-I), diuretics, and beta-adrenergic antagonists (10-16). However, clinical trials are susceptible to selection bias since patients enrolled in these trials are different from those in real-world settings (17, 18). In contrast, populations included in observational studies are from clinical practice settings. Few studies have been published on the effect of NSAIDs on blood pressure in patients who are taking more than one antihypertensive medication. This is important since more than two-thirds of hypertensive patients require two or more antihypertensive medications from different drug classes to control their blood pressure (19).

The next section starts with a discussion about the significance of NSAID-induced blood pressure increase, followed by an overview of the main characteristics of NSAIDs that may explain how they affect blood pressure. The biological mechanisms whereby NSAIDs may cause blood pressure increase are discussed. This leads to the specific aims and hypotheses of this research.

Significance of NSAID-induced Blood Pressure Increase

Chronic diseases, especially cardiovascular, are the most common cause of death in the world (20). In the United States about 73 million people, or one in three adults, have high blood pressure. From 1994 to 2004 the death rate from high blood pressure increased by 27 percent, and the actual number of deaths rose by 56 percent (21). Every year, hypertension leads to seven million deaths in the world (19). Hypertension is a major cause of cardiovascular diseases and patients are at higher risk of myocardial infarction, heart failure, stroke, and kidney disease. For

every 20 mmHg systolic or 10 mmHg diastolic increase in blood pressure, the risk of mortality doubles for both ischemic heart disease and stroke (19).

Blood pressure control in hypertensive patients is essential to prevent morbidity and mortality, reduce health care utilization, and ultimately lower health care costs (9). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) sets goals for patients with hypertension to control blood pressure (19). Blood pressure is only controlled in 35% of hypertensive patients (21). It has been estimated that inadequate blood pressure control in hypertensive patients results in about 40,000 cardiovascular events, more than 8,000 cardiovascular deaths, and direct medical expenditure of one billion US dollars per year (22, 23).

Treatment of hypertension is affected by several factors, including medications that increase blood pressure. NSAIDs are frequently used for various types of pain by hypertensive patients. Even a slight increase in blood pressure associated with the use of NSAIDs is considered significant. Decreasing systolic blood pressure by just 2 mmHg lowers stroke mortality by 10% and ischemic heart disease mortality by 7% (24).

The effect of NSAIDs on incident hypertension has been investigated in previous studies (25-30), but little information is available about the magnitude of changes in blood pressure. In 2004, the number of prescriptions for NSAIDs exceeded 100 million (31). Few studies have examined the effect of NSAIDs on blood pressure in patients who are taking antihypertensive medications. In the

United States, more than 20 million patients receive concomitant treatment for arthritis and hypertension (31); often NSAIDs are prescribed to relieve symptoms of arthritis. The association between NSAIDs and blood pressure increase in patients who are taking antihypertensive medications has only been investigated in a meta analysis (10) and short-term clinical trials (3, 12-16, 32-43); it has not been the subject of observational studies where populations are more broadly relevant to most clinical settings. In addition, some of these previous studies did not include the more commonly prescribed NSAIDs.

Previous studies do not indicate whether NSAIDs affect blood pressure in patients who are taking multiple antihypertensive medications. This is important since most patients are prescribed more than one medication to control their blood pressure. In fact, more than two-thirds of hypertensive patients require two or more antihypertensive medications from different classes (19). No previous study has examined changes to antihypertensive therapy made by prescribers after patients started to use NSAIDs.

Prescribers must first decide whether to prescribe NSAIDs for their hypertensive patients, select the NSAID that has the least effect on blood pressure regulation, and choose the dose at which the risk of blood pressure dysregulation is minimal. The results of this research will help practitioners to control blood pressure in hypertensive patients started on NSAIDs. It also will improve health policy decisions regarding the management of the risk of blood pressure increase associated with NSAIDs.

In contrast to previous studies, this research used propensity score matching techniques to balance covariates between compared groups (44) and adopted incident user design to prevent the inclusion of prevalent user bias (45). This research examined the association between NSAIDs and blood pressure in hypertensive patients who were prescribed multiple antihypertensive medications. Also, it investigated the intensification of antihypertensive therapy by prescribers. This research addressed important unanswered questions regarding the use of NSAIDs in hypertensive patients. The results of this study will help practitioners to select NSAIDs with minimal effect on blood pressure for patients with hypertension.

Overview of Non-Steroidal Anti-Inflammatory Drugs

It is important to highlight the characteristics of NSAIDs that are related to their effects on blood pressure. This section provides an overview of NSAIDs that include indications, differences in pharmacokinetics, main adverse effects, and mechanism of action. The most commonly used NSAIDs in practice were included in this research, namely ibuprofen (short-acting NSAID), naproxen (long-acting NSAID), and celecoxib (the only selective COX-2 inhibitor in the market).

Indications

NSAIDs are widely used for chronic conditions including rheumatoid arthritis and osteoarthritis. NSAIDs reduce pain, joint swelling and morning stiffness in rheumatoid arthritis. NSAIDs are recommended for patients with osteoarthritis as a second line treatment, after trying acetaminophen. NSAIDs are also useful for the

relief of mild to moderate pain, acute gout, dysmenorrhea, and headache (1-3, 46-48).

Pharmacokinetics

Non-selective NSAIDs are rapidly and completely absorbed. Because they are highly bound to proteins, they have small volume of distribution. They are metabolized in the liver through cytochrome P450 or by glucuronidation and excreted through the kidney as metabolites. The half-life of NSAIDs varies from one hour up to 50 hours depending on the agent (1, 49). This variation in half-life could explain some of the differences in adverse effects between individual NSAIDs.

Ibuprofen is well absorbed and peak plasma concentrations are achieved within one to two hours after administration. Ibuprofen has short half-life of about 3.5 hours. This short half-life leads to an intermittent effect during the day. Thus, the effect of ibuprofen on blood pressure may not last for a whole day without repeated dosing. It is mainly metabolized in the liver, with less than 10 percent excreted unchanged in the urine and bile (47).

Naproxen has a longer half-life of about 13 hours, thus, it suppresses prostaglandins (PGs) for a longer period. Therefore, naproxen's effect on blood pressure will presumably be of longer duration. It is well absorbed in the upper gastrointestinal tract and is highly bound to plasma proteins. Naproxen is excreted entirely in urine as an inactive glucuronide metabolite (47). Clearance of naproxen is decreased in patients with renal failure because the acyl-glucuronide metabolite of naproxen is retained and hydrolyzed to reform the parent drug (1, 49, 50). This

emphasizes the importance of controlling for renal function when studying the adverse effects of naproxen.

Celecoxib has a bioavailability of about 40% and is highly bound to protein, mainly to albumin. Because of its lipophilicity, celecoxib has a high volume of distribution. The half-life of celecoxib ranges from 11.2 to 15.6 hours. Celecoxib is extensively metabolized in the liver through oxidation by cytochrome P450 2C9, and less than 2% is excreted unchanged in urine (48, 51).

Overview of Adverse Effects

The major adverse effects reported with the use of NSAIDs are gastrointestinal, renal, hepatic, cardiovascular, and hematological. Other adverse effects which occur less frequently include skin reactions and central nervous system reactions such as headache and dizziness.

The most frequent adverse effects with the use of NSAIDs are gastrointestinal. Dyspepsia is the most prevalent, while peptic ulcer and its complications are much less common. PGs have an important role in maintaining normal gastrointestinal physiology. Inhibition of PGs by NSAIDs could lead to gastrointestinal effects that include gastric erosion, peptic ulcer formation and perforation, upper gastrointestinal hemorrhage, and inflammation of the intestine and lower bowel. One study found that the hazard ratio for hospitalization due to adverse gastrointestinal effects in users of NSAIDs is seven times that of patients not treated with NSAIDs (49). As a response to these adverse effects, selective COX-2 inhibitors were developed. In clinical trials, treatment with selective COX-2 inhibitors causes

significantly fewer serious adverse gastrointestinal effects than treatment with nonselective NSAIDs (48).

The risk of adverse cardiovascular effects increases with the use of NSAIDs. These effects include myocardial infarction, stroke, heart failure, and increased blood pressure (4, 8, 52-57). The use of NSAIDs is associated with various renal toxicities, which may lead to acute renal failure and nephropathy (50, 58). Hepatitis and liver function abnormalities can occur with the use of NSAIDs. However, clinical hepatitis and hepatic death are rare adverse effects. Other rare but dangerous adverse hematological effects that could occur include agranulocytosis and aplastic anemia (46).

Mechanism of Action

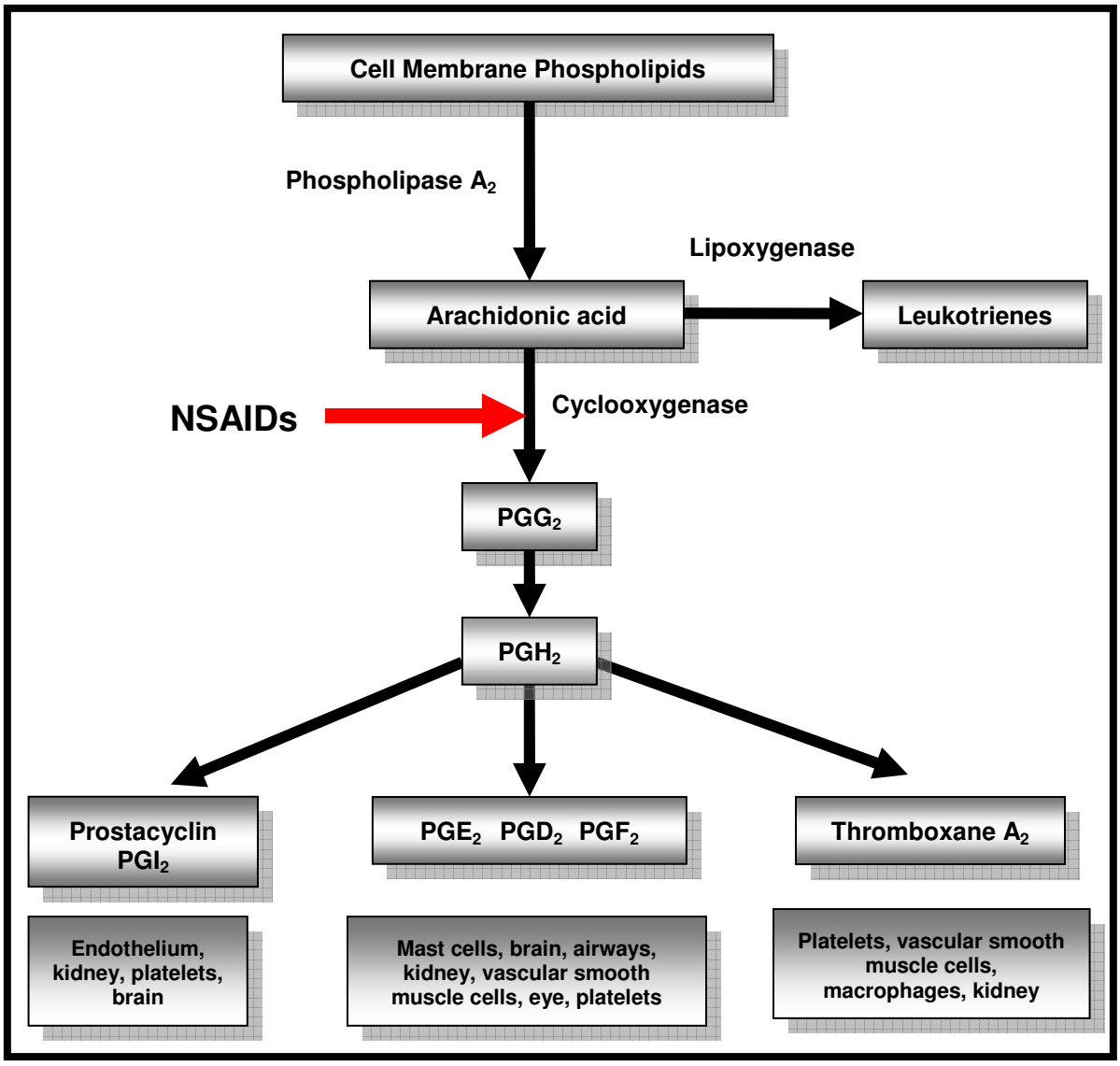
NSAIDs have antipyretic, analgesic, and anti-inflammatory properties. The major mechanism for their effect is the inhibition of an enzyme called cyclooxygenase (COX) (Figure 1). The COX enzyme catalyzes the formation of prostanoids (which include PGs, prostacyclins, and thromboxanes) from arachidonic acid. When NSAIDs inhibit the COX enzyme, the synthesis of PGs will be stopped and inflammation will therefore be reduced.

NSAIDs vary in their selectivity in inhibiting the two isoforms of the COX enzyme, COX-1 and COX-2 (48). Non-selective NSAIDs act by inhibiting both COX-1 and COX-2. COX-1 is found in most normal cells and tissues, including platelets, endothelial cell, cells within the gastrointestinal tract, renal microvasculature, glomerulus, and collecting ducts. Inhibition of COX-1 leads to the adverse

gastrointestinal effects associated with non-selective NSAIDs. However, COX-2 is not expressed in the stomach and is induced during inflammation by cytokines and inflammatory mediators. Therefore, compared to the non-selective NSAIDs, selective COX-2 inhibitors possess similar pharmacological actions but are associated with a lower risk of adverse gastrointestinal effects (48, 52, 53, 59).

The presence of PGE_2 and PGI_2 in the kidney could explain some of the blood pressure increase associated with NSAIDs. PGE_2 is more predominant in the interstitial cells and collecting-duct epithelial cells. While PGI_2 is predominant in the endothelial cells, the thin layer that lines the interior surface of the blood vessels of renal arterioles (60). PGE_2 decreases sodium reabsorption at the loop of Henle (58). PGI_2 is a vasodilator and directly stimulates the renin-angiotensin system (58, 60). The following section discusses the mechanisms for blood pressure increase associated with NSAIDs.

Figure 1. NSAIDs General Mechanism of Action



References: (48, 50, 61). NSAIDs: Non-steriodal anti-inflammatory drugs; PG: Prostaglandin.

Biological Mechanisms of NSAID-induced Blood Pressure Increase

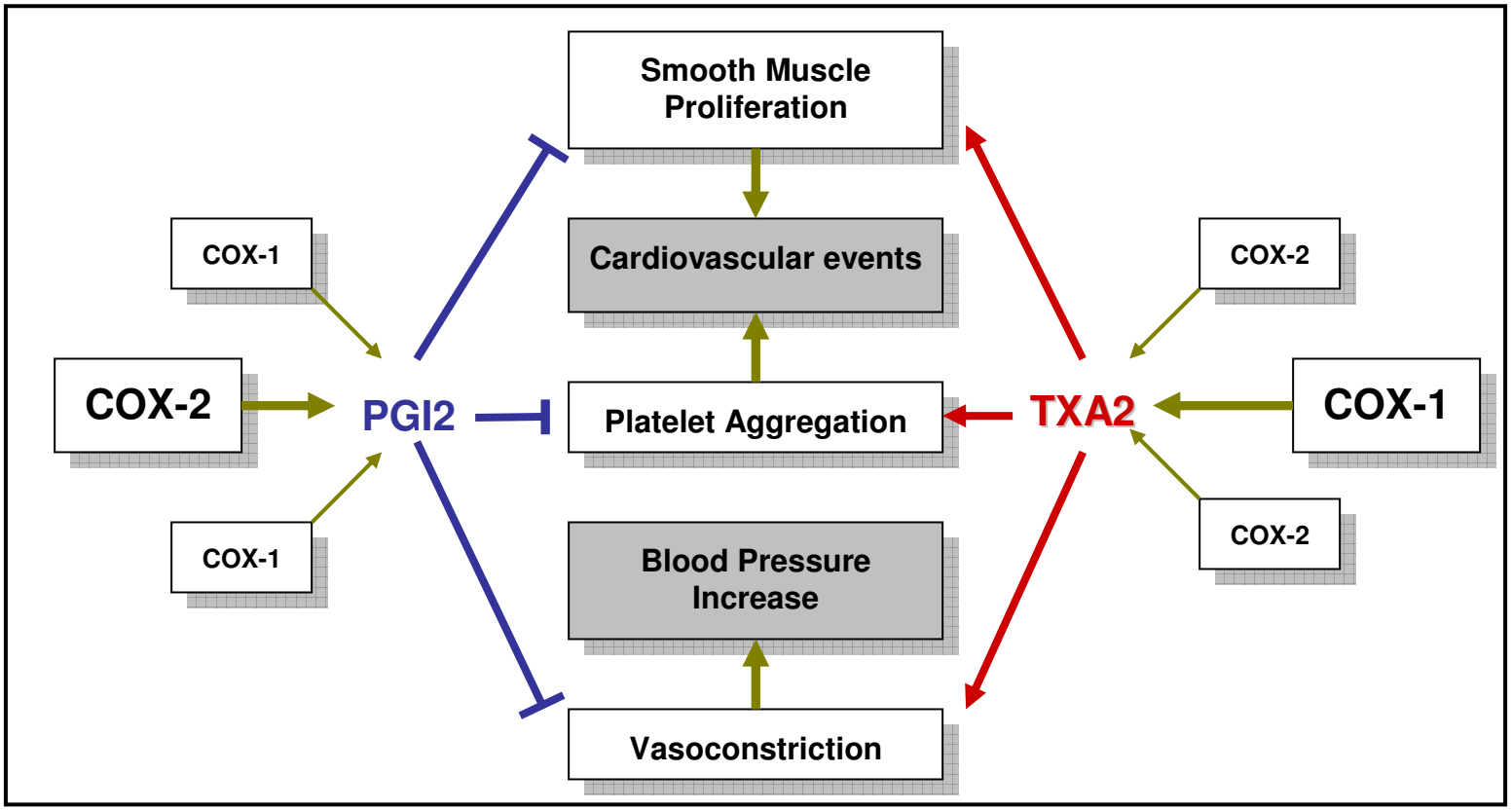
The main mechanisms for the cardiovascular and renal effects of NSAIDs are related to the inhibition of PGs. This section briefly discusses the cardiovascular mechanisms before focusing on the mechanisms that are hypothesized to explain NSAID-induced blood pressure increase. This is followed by a discussion of several

hypotheses that have been put forward to explain the effect of NSAIDs on blood pressure control, when these are taken in conjunction with antihypertensive drugs.

The COX-1 enzyme mediates the production of thromboxane A2. This explains the pro-thrombotic effect of NSAIDs. Thromboxane A2 causes platelet aggregation, vasoconstriction, and smooth muscle proliferation (Figure 2). These effects lead to the formation of a thrombus, resulting in a cardiovascular event. Since aspirin inhibits COX-1 in the platelets irreversibly, it is used as a prophylactic of thromboembolic disease. However, NSAIDs do not sufficiently inhibit COX-1 to suppress the synthesis of thromboxane A2. This explains the lack of cardio-protective effects of NSAIDs.

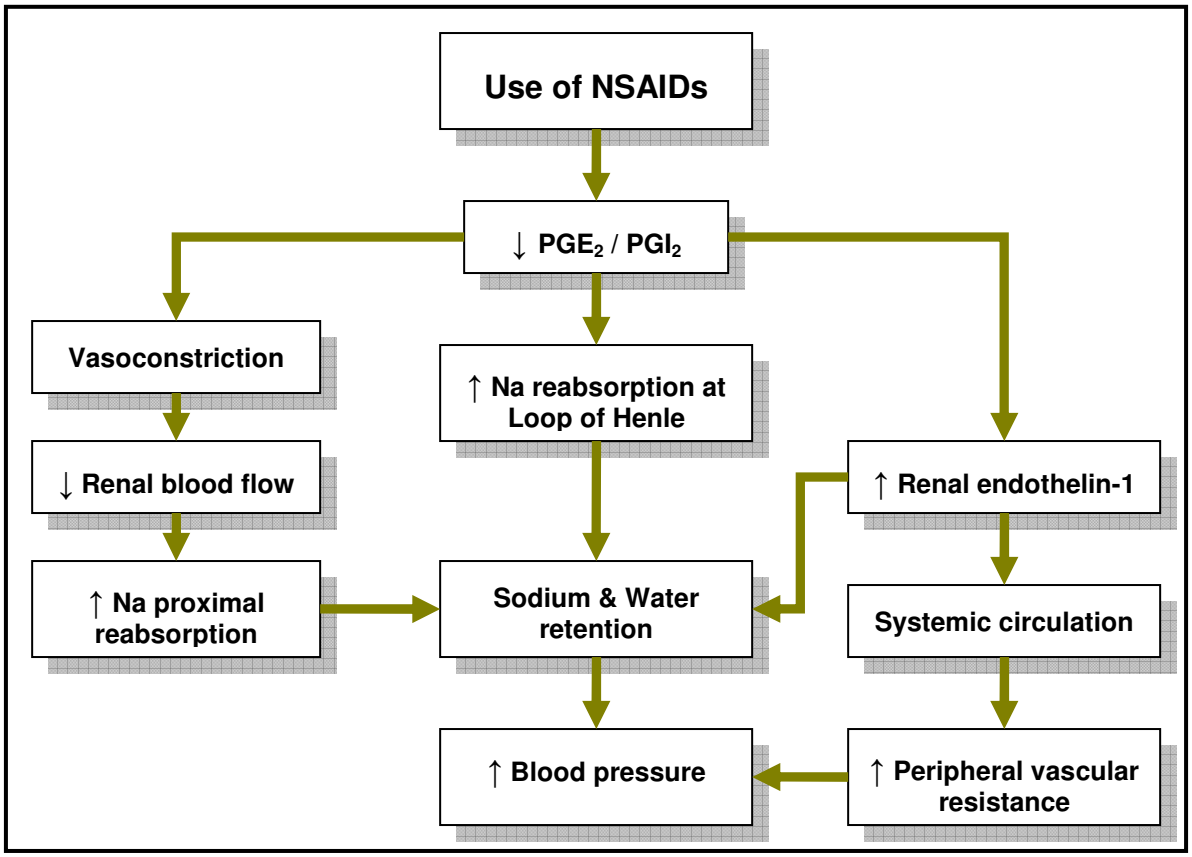
In contrast to COX-1, COX-2 mediates prostacyclin synthesis which causes the inhibition of platelet aggregation, vasodilation, and anti-proliferative effects (62). The COX-2 enzyme will therefore balance the undesirable effects of COX-1 on platelets. Therefore, any NSAID and in particular selective COX-2 inhibitors, by shifting the balance toward a pro-thrombotic effect, are expected to be associated with an increase in the risk of thrombotic cardiovascular events such as myocardial infarction.

Figure 2. Mechanism of Adverse Cardiovascular Effects Mediated by Cyclooxygenase Enzyme



The biological mechanisms that hypothesized to explain NSAID-induced blood pressure increase involve the inhibition of PGs (Figure 3). A direct vasoconstriction effect of NSAIDs might be caused by inhibiting the systemic vasodilation of PGI2. The inhibition of PGs in the kidney by NSAIDs causes sodium and water retention, weight gain, and, ultimately, increases in blood pressure through three main pathways. Firstly, inhibition of prostaglandin E2 (PGE2) enhances the reabsorption of sodium at the thick ascending loop of Henle in the kidney. Secondly, PG inhibition in the kidney causes vasoconstriction in the afferent renal arteriole which leads to a decrease in renal blood flow. Thus, reabsorption of sodium increases in the proximal tubule. Thirdly, PGs inhibition by NSAIDs stimulates the synthesis of a renal peptide called endothelin-1, which causes increased sodium and water reabsorption. In addition, renal endothelin-1 raises blood pressure through an increase in peripheral vascular resistance (31, 50, 57, 58, 63-67).

Figure 3. Mechanisms of Blood Pressure Increase Associated with NSAIDs



PG: Prostaglandin; ↑: Increase; ↓: Decrease. References: (31, 50, 57, 58, 63-67).

Previous studies have suggested that NSAIDs attenuate the effects of antihypertensive drugs including ACE-I, diuretics, and beta-adrenergic antagonists (10, 12-14, 16, 37, 39, 42). The main mechanism explaining the blunting effect of NSAIDs on these antihypertensive medications is related to the inhibition of PGs. It is hypothesized that some of the antihypertensive effects of ACE-I are achieved through polypeptides called kinins, whose vasodilating effect is mediated by PGs. Thus, inhibition of PGs with NSAIDs reduces the antihypertensive effect of ACE-I

(14, 42, 65). Prostacyclin is essential for thiazide diuretics to decrease peripheral vascular resistance. NSAIDs interfere with the antihypertensive effect of thiazides by inhibiting prostacyclin synthesis (49, 68).

Inhibition of PGs by NSAIDs explains the loss of blood pressure control achieved by beta-adrenergic blockers. PG inhibition by NSAIDs increases sensitivity to the vasoconstrictor effects of noradrenaline, angiotensin II, and sympathetic nervous system stimulation (68). By blocking beta-receptors the increased sensitivity to alpha-adrenergic stimulation caused by NSAIDs increases, resulting in loss of the blood pressure lowering effect of beta-adrenergic antagonists (68). Calcium channel blockers (CCBs) exert their antihypertensive effect independently of PGs. CCBs lower blood pressure by causing a direct vasodilation in the peripheral arteries of the vascular smooth muscle. (35, 69).

Based on the fluid retention mechanism of NSAIDs, it is expected that the blood pressure increase associated with NSAIDs is dose dependent. Lower doses of these medications may be a reasonable option for some patients with milder forms of arthritis. However, no observational study has examined the effect of NSAID dose on systolic blood pressure in hypertensive patients. The dose effect of NSAIDs was investigated in this study.

Specific Aims

This research examines changes in blood pressure after starting patients with hypertension on NSAIDs. Previous studies have found a blood pressure increase

within a week of starting NSAIDs (3, 11, 13, 40). In hypertensive patients, adequate blood pressure control is essential to prevent morbidity and mortality and reduce health care costs (9).

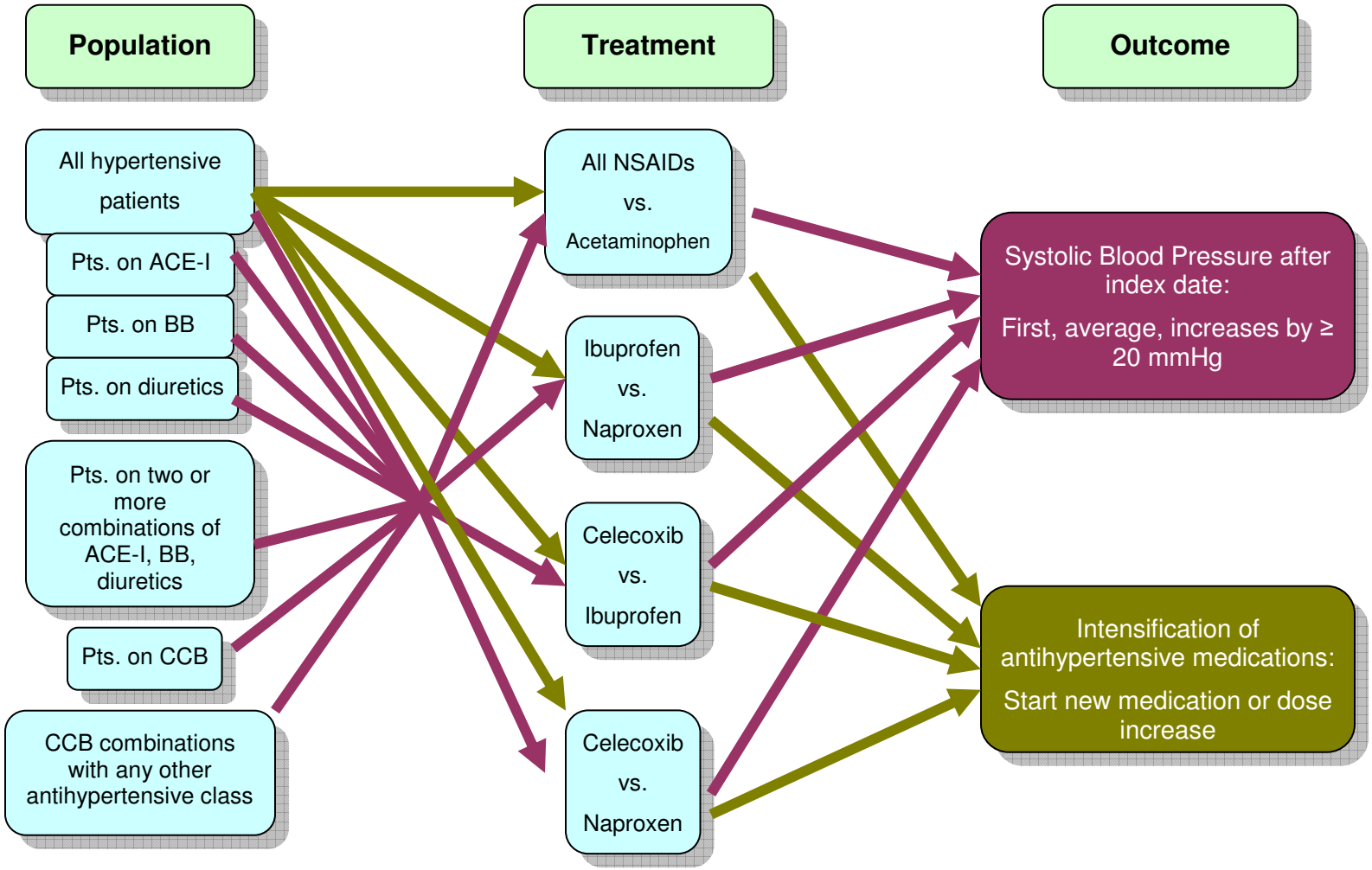
This research addresses important questions that were not answered in previous studies regarding the association between blood pressure and NSAIDs in hypertensive patients who are taking multiple antihypertensive medications. Previous studies that examined the effect of NSAIDs on blood pressure are limited and various aspects of this effect remain unclear. For example, although rofecoxib was associated with increased blood pressure in previous studies, celecoxib did not change blood pressure significantly (2, 3, 15, 29, 40, 43, 70, 71). The effect of NSAIDs on incident hypertension has been investigated, but the magnitude of changes in blood pressure has not been thoroughly examined. Existing observational studies lack the measurement of blood pressure or did not control for important confounding variables. Moreover, these studies did not compare the effects on blood pressure of non-selective NSAIDs and selective COX-2 inhibitors. The effect of NSAIDs on blood pressure in patients using antihypertensive medications was investigated in clinical trials only; it has not been studied in observational studies, where populations are more similar to those in typical clinical settings.

The first aim of this dissertation was to investigate the effects of NSAIDs on blood pressure in hypertensive patients compared to a control group of acetaminophen users. CCBs were analyzed separately, since previous studies have suggested that the blood pressure increase associated with NSAIDs occur more in

patients using any antihypertensive medication except CCB (13, 35, 36, 39). The second aim was to compare the effects of ibuprofen and naproxen on blood pressure. Ibuprofen has a shorter half-life, leading to an intermittent effect during the day; while the half-life of naproxen is longer, leading to continuous PGs suppression. Thus, any effect on blood pressure presumably will last longer with naproxen. Celecoxib's effect on blood pressure was compared to that of naproxen and ibuprofen. Since celecoxib selectively inhibits COX-2, it might present a different risk for blood pressure increase compared to non-selective NSAIDs.

The specific aims of this study were: (1) to examine the association between NSAIDs and blood pressure compared to acetaminophen in patients with hypertension; (2) to compare the effects of various NSAIDs on blood pressure in patients with hypertension; and (3) to examine changes in antihypertensive therapy after starting NSAIDs (Figure 4).

Figure 4. Hypotheses by Population, Treatment, and Outcome of the Study



*ACE-I: Angiotensin converting enzyme inhibitor; BB: Beta-blocker; CCB: Calcium channel blocker.

Aim 1: To examine the association between NSAIDs and blood pressure compared to acetaminophen in patients with hypertension

Hypothesis H1: Compared to acetaminophen, NSAIDs cause a greater increase in systolic blood pressure in patients receiving beta-adrenergic antagonists, diuretics, ACE-I, or a combination of these antihypertensive drugs.

Hypothesis H2: NSAIDs taken in conjunction with CCBs are not associated with a greater increase in systolic blood pressure compared to acetaminophen.

Hypothesis H3: Compared to acetaminophen, NSAIDs are not associated with an increase in systolic blood pressure in patients concomitantly receiving CCBs with drugs from other antihypertensive classes.

This aim compared the effect of NSAIDs on blood pressure to a similar control group of patients who were prescribed acetaminophen. The effect of NSAIDs on blood pressure in patients using antihypertensive medications was examined, as this has not been thoroughly investigated in previous studies. The effect of NSAIDs on blood pressure in patients using diuretics, ACE-I, angiotensin II antagonists, and CCBs was investigated in short-term interventional trials. The results of some of these trials were conflicting (3, 12-14, 16, 33-39, 41, 42, 72, 73). No observational studies were found that explore the effect of NSAIDs on blood pressure in patients taking various antihypertensive medications. In addition, this aim examined the effect of NSAIDs on blood pressure in patients prescribed multiple antihypertensive medications. No prior study has examined this question.

Previous clinical trials show that NSAIDs are not associated with blood pressure increase in patients using CCBs (13, 35, 36, 39). This class of antihypertensive medications could be an alternative option to control blood pressure in patients who need to use NSAID chronically. In this part of the research, the effect of NSAIDs on blood pressure was examined in patients who are using CCB and those who are using CCB with other combinations.

Aim 2: To compare the effects of various NSAIDs on blood pressure in patients with hypertension

H1: Ibuprofen, naproxen, and celecoxib do not differ in their propensity to increase systolic blood pressure.

H2: As the dose of ibuprofen or naproxen increases, patient's systolic blood pressure increases.

H3: In patients taking antihypertensive medications other than CCBs, the use of naproxen or ibuprofen is associated with an increase in systolic blood pressure.

H4: In patients prescribed CCBs, naproxen or ibuprofen is not associated with increases in systolic blood pressure.

H5: In patients concomitantly receiving CCBs and antihypertensives from another class, naproxen or ibuprofen is not associated with increases in systolic blood pressure.

This part of the research compared individual NSAIDs that are commonly used in practice with each other. From the non-selective NSAIDs, the focus was on comparing ibuprofen to naproxen. The effect of naproxen on blood pressure has not been compared to ibuprofen in observational studies. In one short-term interventional trial included patients stabilized on hydrocholorothiazide, differences between naproxen and ibuprofen were suggested since the mean arterial pressure increased with ibuprofen but not with naproxen (12). However, it is unknown if naproxen and ibuprofen differ in their effect on blood pressure for patients using other antihypertensive medications.

Previous observational studies have not compared the effect of selective COX-2 inhibitors on blood pressure to non-selective NSAIDs. Since celecoxib is the only selective COX-2 inhibitor on the market, it was compared to the non-selective NSAIDs included in this study. Unlike previous studies, this research explored the association between the dose of NSAIDs and blood pressure increase.

Aim 3: To examine changes in antihypertensive therapy after starting NSAIDs

H1: Compared to acetaminophen, NSAIDs increase the likelihood of adding a new antihypertensive medication or increasing the dose of a currently prescribed antihypertensive medication.

H2: Ibuprofen, naproxen, and celecoxib do not differ in the need to add a new antihypertensive medication or increase the dose of the current antihypertensive medication.

Prescribers should respond to blood pressure increase in patients by intensifying antihypertensive therapy. They may increase the dose of the current antihypertensive medication or add a new medication from another antihypertensive class. Previous studies have not examined whether intensification in antihypertensive therapy occurs after patients have been prescribed NSAIDs.

II. REVIEW OF RELATED LITERATURE

Investigators have examined the effects of NSAIDs on blood pressure in both healthy and hypertensive patients. Although some studies examined the association between blood pressure increase and selective COX-2 inhibitors, most previous studies have focused on non-selective NSAIDs. Various designs have been used in previous studies. These designs include meta-analyses of published clinical trials, short-term interventional trials, and observational studies.

This chapter discusses those studies that have examined the association between NSAIDs and blood pressure increase. It begins with studies that focus on the effect of NSAIDs on blood pressure in non-hypertensive individuals. Studies involving hypertensive patients will follow. Finally, studies of the effect of NSAIDs on blood pressure in patients using specific antihypertensive medications are discussed.

Effect of NSAIDs on Blood Pressure in Non-hypertensive Patients

Studies have been conducted to examine the effects of non-selective and selective COX-2 inhibitors on blood pressure in non-hypertensive individuals. These studies include meta-analyses of clinical trials, short-term clinical trials, and observational studies. Most observational studies examined the risk of hypertension in non-hypertensive subjects.

A recent meta-analysis examined the association between selective COX-2 inhibitors and the risk of hypertension in 19 clinical trials (2). Compared to non-selective NSAIDs and placebo, the risk of hypertension did not increase significantly in users of selective COX-2 inhibitors. However, the results were significant when the researchers examined each selective COX-2 inhibitor separately. Rofecoxib was associated with a significant increase in the risk of hypertension compared to other non-selective NSAIDs (relative risk, 1.78; 95% confidence interval, 1.17 to 2.69) and placebo (relative risk, 2.63; 95% confidence interval, 1.42 to 4.85). Nonetheless, celecoxib was associated with a non-significant decrease in the risk of hypertension as compared to other non-selective NSAIDs (relative risk, 0.82; 95% confidence interval, 0.68 to 1.00) and placebo (relative risk, 0.81; 95% confidence interval, 0.13 to 5.21) (2). The investigators of this meta-analysis appropriately used the Der Simonian and Laird method (74) to calculate relative risk within the framework of heterogeneous studies. This meta-analysis demonstrates that each selective COX-2 inhibitor needs to be studied separately, as they may have opposite effects on blood pressure.

Conclusions cannot be drawn from this meta-analysis due to several limitations and biases. Most of the blood pressure values were not collected as a primary endpoint, and the definition of hypertension may vary among the trials included. Further, many of the trials lacked information about pre-existing hypertension and the use of antihypertensive medications. Meta-analyses are based on clinical trials, where many participant exclusions are applied, and, as such, patients in these trials do not represent those in real world practices.

To primarily examine the effect of NSAIDs on blood pressure, specific short-term interventional trials have been conducted. Table (1) summarizes the design, sample size and population, drug and dose, duration, and the main results of previous short-term interventional trials. Most of these studies show an increase in blood pressure with NSAIDs. For example, ibuprofen was associated with an increase in blood pressure in a randomized, three-way, crossover study (72). The study included ten young subjects, fourteen elderly subjects, and fourteen further elderly subjects with renal insufficiency. The subjects were randomized to 800 mg ibuprofen three times a day, 20 mg piroxicam, and 200 mg sulindac twice a day. Compared to sulindac, ibuprofen increased the systolic blood pressure by 9.7 mmHg ($P = 0.0002$) and diastolic blood pressure by 6.0 mmHg ($P = 0.005$). In elderly subjects with renal insufficiency, the use of ibuprofen was associated with a significant increase of 15 mmHg in systolic and 6 mmHg in diastolic blood pressure from baseline (72).

Celecoxib was not associated with an increase in blood pressure in clinical trials (75, 76). Twelve young subjects and twelve elderly subjects were randomized to celecoxib or diclofenac for two weeks. The change in blood pressure was not statistically significant in either group (75). A recent randomized study that included 24 healthy volunteers found insignificant changes in blood pressure in users of rofecoxib, celecoxib, or diclofenac (76).

Conducting short-term interventional trials is a good approach to the investigation of particular adverse effect in controlled conditions. These trials are designed to examine the specific adverse effects of medications and compare them

to a control group. When they are designed appropriately, and researchers use the information on the pharmacokinetics and pharmacodynamics of medications, causality can be established between the use of a medication and a particular adverse effect. However, these trials include small numbers of patients (usually less than 20) and many patients are excluded. In contrast, observational studies include patients from real world practices.

Observational studies have been conducted to assess the association between NSAIDs and the risk of hypertension or the frequency of starting antihypertensive medications (Table 2). Increased blood pressure was associated with the current use of NSAIDs in a cross-sectional community based study (77). The researchers interviewed 470 elderly individuals and medication use was recorded from the labels of medication containers. The analysis included only the use of prescription drugs over the preceding two weeks and non-prescription drugs in the past week. Interviewers measured and recorded sitting blood pressure. The investigators controlled for age, gender, body mass index, use of antihypertensive drugs, and the presence of pain. NSAIDs users had an insignificant 4.86 mmHg increase in systolic blood pressure compared to non- NSAIDs users (95% confidence interval, – 0.02 to 9.74). However, NSAID users were more likely to have systolic blood pressure above 140 mmHg (odds ratio, 2.19; 95% confidence interval, 1.33 to 3.61) (77). This study is limited in establishing causality since the investigators used a cross-sectional design and confounders such as cardiovascular and renal diseases were not controlled for in the analysis.

Another cross-sectional community-based study found an increase in the prescription of antihypertensive medications among 2,805 elderly individuals who were using NSAIDs (25). Registered nurses interviewed the subjects, recorded the use of medications, and measured blood pressure. Use of medication was ascertained by either inspection of drugs' containers or lists of drugs provided by subjects. Blood pressure was calculated as the average of two measurements after sitting for 10 minutes. A logistic regression model was used to control for age, gender, body mass index, coronary heart disease, smoking, and alcohol use. The risk of using antihypertensive medications was 1.4 times higher in those who used NSAIDs compared to non-users (95% confidence interval: 1.1 to 1.7). The risk of either using antihypertensive medications or untreated high blood pressure was higher in NSAID users compared to non-users (odds ratio, 1.2; 95% confidence interval, 1.0 to 1.5). However, the use of NSAIDs was not associated with an increase in systolic or diastolic blood pressure (25). A confounding bias could have affected the results of this study as covariates such as diabetes mellitus and renal insufficiency were not included in the analysis. In addition, a cross-sectional study cannot establish causality. Therefore the NSAID's use may not have precipitated the diagnosis of hypertension; rather, patients may coincidently have had hypertension and started using NSAIDs.

A case-control study included elderly subjects from the New Jersey Medicaid Program who were using NSAIDs (78). The study was conducted to determine whether the risk of starting antihypertensive therapy increases in users of NSAIDs. Between November 1981 and February 1990, the investigators identified 9,411

patients who filled a first prescription for an antihypertensive medication. Drug claims were searched for the use of NSAID during the one-year period before the cases. The investigators adjusted for age, gender, race, nursing home residence, number of prescriptions filled, intensity of physician utilization, and days hospitalized. The odds ratio for initiating antihypertensive therapy for recent (less than 60 days) users of NSAIDs compared with nonusers was 1.66 (95% confidence interval, 1.54 to 1.80). The risk of starting antihypertensive therapy was higher for recent compared to former users of NSAIDs (odds ratio, 1.66; 95% confidence interval, 1.54 to 1.80 versus odds ratio, 1.42; 95% confidence interval, 1.30 to 1.55). Also, the risk increased as the daily dose of NSAIDs increased (78). This case-control study did not control for important confounders such as pre-existing heart and renal diseases.

Sub-analyses of large prospective studies show conflicting results on the association between NSAIDs and the risk of hypertension. Two large prospective analyses from the Nurses' Health Study found a significant increase in the risk of hypertension diagnosis among women using NSAIDs and acetaminophen. Bias could be introduced in these studies since self-report was used to ascertain hypertension diagnosis and NSAID use (26, 27). In a prospective study of 8,229 male physicians followed for a mean of 5.8 years, NSAID use did not significantly increase the risk of hypertension (28). Again, self-report was used to ascertain exposure to NSAIDs. The study outcome was self-reported blood pressure of 140/90 mmHg or higher or the use of antihypertensive medication (28). It is unclear whether these conflicting results are because of gender differences or because of limitations in study design. In these studies, the investigators collectively analyzed all NSAIDs.

However, various NSAIDs may differ in their effects on blood pressure. Since self-report was used to ascertain both exposure and outcome, misclassification bias is a major threat to these results.

A recent case-control study found an increase in the risk of hypertension diagnosis in users of rofecoxib, but not celecoxib (29). The study included 3,915 cases of newly diagnosed hypertensive patients aged ≥ 65 years. Exposure to selective COX-2 inhibitors was ascertained during the previous 90 days. A backward selection procedure was used to build a multiple logistic regression model. The investigators adjusted for age, gender, race, hospitalization, number of ambulatory care visits, number of comorbidities, glucocorticoids use, coronary artery disease, diabetes, rheumatoid arthritis, and osteoarthritis. Compared to celecoxib, the odds ratio of developing hypertension in the rofecoxib group was 1.6 (95% confidence interval, 1.2 to 2.1). Compared to non-selective NSAIDs, the risk of hypertension increased significantly in users of rofecoxib (odds ratio, 1.4; 95% confidence interval, 1.1 to 1.9). Compared to celecoxib, the risk of hypertension associated with rofecoxib increased in patients with congestive heart failure, liver disease, or renal disease (odds ratio, 2.1; 95% confidence interval, 1.0 to 4.3) (29). The results of this study revealed that celecoxib is not associated with an increased risk of hypertension. However, modest increases in blood pressure may take a longer time to result in the diagnosis of hypertension. Since investigators of this case-control study ascertained exposure to selective COX-2 inhibitors for only 90 days, they could have missed a modest increase in blood pressure associated with celecoxib. In contrast, the current study was designed to detect small blood pressure increases

with NSAIDs by using systolic blood pressure measurements as the dependent variable.

A recent study examined the effects of switching patients from celecoxib to rofecoxib on the blood pressure of 120 Native American patients (79). The investigators gathered clinical data, including blood pressure, from medical records. Using simple paired t-tests, blood pressure increased when patients switched from celecoxib to rofecoxib (systolic blood pressure increased by 2.9 mmHg, and diastolic blood pressure increased by 1.5 mmHg). This study did not control for covariates likely to affect blood pressure such as changes in antihypertensive medications (79).

The above-mentioned studies show that the risk of hypertension increases in non-hypertensive individuals who are prescribed non-selective NSAIDs or rofecoxib. However, celecoxib was not associated with an increase in the risk of hypertension. The next obvious research question is how NSAIDs affect blood pressure control in patients who already have hypertension. The following section discusses studies that investigate the effect of NSAIDs on blood pressure in hypertensives.

Effect of NSAIDs on Blood Pressure in Hypertensive Patients

In a meta-analysis published in 1993, blood pressure increased in users of indomethacin and naproxen but not in users of other non-selective NSAIDs (57). The authors excluded studies where 20% or more of the participants dropped out and those where antihypertensive treatment was adjusted while patients were taking NSAIDs. Fifty-four clinical trials were included wherein approximately 50% of the patients were taking indomethacin and 92% of them were hypertensive. The results

indicated a significant increase in mean arterial pressure (MAP) in hypertensive patients only, with an increase of 3 mmHg in indomethacin and naproxen users (P <0.001). Ibuprofen, piroxicam, and sulindac did not significantly increase blood pressure (57). Since the average age of patients was 46 years (subjects ranged from 28 to 62 years) and patients with severe hypertension were excluded, the results of this meta-analysis can be generalized to only healthier younger patients. As older patients and those with severe hypertension were excluded, this meta-analysis is likely to have underestimated the effect of NSAIDs on blood pressure.

In short-term interventional clinical trials of hypertensive patients, blood pressure increased with the use of rofecoxib but not with celecoxib (3, 43). In a randomized double-blind clinical trial, 810 hypertensive elderly patients with osteoarthritis were randomized to rofecoxib or celecoxib (3). The investigators excluded patients with renal disease, hepatic diseases, or congestive heart failure. The change from baseline in mean systolic blood pressure was significantly greater for rofecoxib (+ 2.6 mmHg) compared to celecoxib (– 0.5 mmHg) (P = 0.007) (3). A recent randomized double-blind twelve-week trial included 404 patients with osteoarthritis, hypertension, and diabetes mellitus. Patients were randomized to rofecoxib 25 mg, celecoxib 200 mg, or naproxen 1000 mg daily. Blood pressure increased significantly in the rofecoxib group only, where the systolic pressure increased by 4 mmHg and the diastolic increased by 2 mmHg (P <0.01) (43).

Only two observational studies have examined the effect of NSAIDs on blood pressure in hypertensive patients (70, 71). A small retrospective review of medical records included 109 patients who received a new prescription claim for celecoxib or

rofecoxib (70). The investigators included blood pressure values that were available within 90 days before and after the prescription of selective COX-2 inhibitors. They adjusted for age, race, hypertension, number of hypertension medications, cardiovascular disease, hyperlipidemia, and dose of selective COX-2 inhibitor. Systolic blood pressure increased by 5 mmHg after the start of treatment with rofecoxib (P = 0.044). In those 65 years of age and older, systolic blood pressure increased in the rofecoxib group by 7 mmHg (P = 0.02). However, celecoxib use was associated with a non-significant decrease in blood pressure of 1 mmHg (95% confidence interval, – 6.19 to 3.87) (70).

Another retrospective study used electronic medical records to examine the effects of selective COX-2 inhibitors on blood pressure in hypertensive patients (71). The investigators included 960 hypertensive patients older than 55 years, who had received a stable antihypertensive medication dose four months before COX-2 prescription. Patients were followed for 6 months. Patients with a history of heart failure were excluded. The analysis controlled for age, sex, number of comorbid conditions, and number of antihypertensive medications. The use of rofecoxib or celecoxib did not affect the blood pressure or the rate of adding another class of antihypertensive medications. However, this study might have missed moderate changes in blood pressure since the primary outcome was defined as systolic blood pressure increase by more than 20 mmHg, or diastolic pressure by more than 15 mmHg. Compared to celecoxib, the dose of antihypertensive medications increased in rofecoxib users (odds ratio, 1.68; 95% confidence interval, 1.09 to 2.60). Patients who had changes in antihypertensive therapy were included in this study. These

changes could diminish the effect of selective COX-2 inhibitors on blood pressure. In addition, this study did not control for some covariates likely to affect blood pressure. The effect of selective COX-2 inhibitors on blood pressure was not examined by type of antihypertensive medication (71).

In these abovementioned studies, the use of some NSAIDs was associated with blood pressure increase in hypertensive patients. However, analyses did not control for the use of antihypertensive medications. Also, investigators did not examine the specific antihypertensive type. This is important, as the effect of NSAIDs on blood pressure may vary based on the antihypertensive class. The following section discusses studies that included hypertensive patients who were using specific antihypertensive medications.

Effect of NSAIDs on Blood Pressure in Hypertensive Patients by Type of Antihypertensive Medication

Meta-analysis and clinical trials have examined the effects of non-selective and selective COX-2 inhibitors on blood pressure in hypertensive patients using specific types of antihypertensive medications such as ACE-I, angiotensin II receptor antagonists, CCBs, diuretics, and beta-adrenergic antagonists. No observational studies were found that examined the association between NSAIDs and blood pressure increase in hypertensive patients who used any of these antihypertensive medications.

In a meta-analysis of 50 clinical trials examining the effect of NSAIDs on blood pressure, patients who were controlled on beta-adrenergic antagonists had a

significant blood pressure increase (10). Two of the authors independently reviewed each identified trial and decided whether to include it in the meta-analysis. Overall, the use of any non-selective NSAID increased the mean blood pressure by 5 mmHg (95% confidence interval, 1.2 to 8.7). However, NSAIDs did not significantly alter body weight, daily urinary sodium output, creatinine clearance, plasma renin activity, or 24-hour urinary PG E2. Only the use of piroxicam was associated with a significant increase in the mean blood pressure of 6.2 mmHg (95% confidence interval, 0.8 to 11.5 mmHg). In contrast, no changes in blood pressure were observed with the use of ibuprofen or naproxen. Analysis was also performed according to the use of antihypertensives. Patients who were prescribed beta-adrenergic antagonists had a significant increase in blood pressure after using any non-selective NSAID (blood pressure increase, 6.2 mmHg; 95% confidence interval, 1.1 to 11.4 mmHg). There was no significant increase in blood pressure in patients prescribed diuretics or vasodilators (10).

Several short-term clinical trials have investigated the effect of NSAIDs on blood pressure in patients who were taking antihypertensive medications. Ibuprofen use for three weeks was associated with a significant blood pressure increase in 45 subjects who were taking at least two antihypertensive medications (32). Systolic blood pressure increased in the ibuprofen group by 6.8 mmHg, compared to a reduction by 3.7 mmHg in the placebo group ($P = 0.02$). Also, diastolic blood pressure increased by 5.3 mmHg in users of ibuprofen compared to a reduction by 1.1 mmHg in the placebo group ($P = 0.03$) (32). However, this study did not examine

sub-samples of patients who were prescribed various combinations of antihypertensive medications.

A one week trial showed that blood pressure increased in users of ACE-I but not in users of CCBs (13). This randomized-crossover study included 18 patients who responded to four-weeks of treatment with enalapril or nifedipine defined as diastolic blood pressure <90 mmHg or a fall of >10 mmHg from baseline diastolic blood pressure. Patients were started on aspirin (100 mg/day for 2 weeks) followed by indomethacin (75 mg/day for 1 week). Indomethacin increased blood pressure significantly only in the enalapril group (6.8 mmHg increase in systolic blood pressure and 4.6 mmHg increase in diastolic blood pressure) ($P < 0.01$). Since indomethacin reduced the fractional excretion of sodium in both the enalapril and nifedipine groups and blood pressure only increased in the enalapril group, the mechanism of blood pressure increase is not due to decreased renal sodium excretion. Rather, it is presumably due to inhibition of vasodilatory PG production induced by ACE inhibitors (13).

Another study was conducted to investigate the effects of rofecoxib on blood pressure (15). The investigators included twenty hypertensive patients who had stable blood pressure with ACE-I and beta-blockers. Rofecoxib was not associated with an increase in day-time blood pressure, but night-time systolic blood pressure increased by 15.7 mmHg, and diastolic by 8.5 mmHg ($P < 0.05$) (15). Another randomized multi-center trial involved 385 patients who were stable on ACE-I for one month. Patients were randomized to ibuprofen, celecoxib, nabumetone, or a placebo. Systolic and diastolic blood pressure increased significantly only in the

ibuprofen group as compared to the placebo group (P <0.01) (42). However, celecoxib and diclofenac were associated with a 4 mmHg increase in systolic blood pressure in osteoarthritis patients who were treated with ACE-I (P <0.005) (16).

In 178 hypertensive patients whose blood pressure was controlled by lisinopril, the use of celecoxib 400 mg daily did not significantly affect blood pressure (41). This result is consistent with previous studies examining the effect of celecoxib on blood pressure (3, 43, 70, 71). In a six-week trial, mean systolic blood pressure increased significantly in users of rofecoxib (+ 3 mmHg) compared to users of celecoxib (-0.4 mmHg) (P <0.001). Systolic blood pressure increase was greater in users of rofecoxib, who were controlled on ACE-I and beta blockers (approximately 5 mmHg) (P ≤0.04). However, changes in systolic blood pressure were not statistically significant in those controlled on CCBs or diuretics (40). The results of this study support the hypothesis that destabilization of blood pressure depends on the type of antihypertensive medication.

It is unclear if NSAIDs destabilize blood pressure in users of angiotensin II receptor antagonists. In a small clinical trial that included 10 hypertensive patients who were controlled on losartan, the use of indomethacin for one week did not affect blood pressure (38). In contrast, in a larger study of 128 hypertensive patients who were controlled on valsartan or lisinopril, indomethacin increased systolic and diastolic blood pressures significantly by 5.45 mmHg and 3.22 mmHg in users of lisinopril, and by 2.12 mmHg and 1.87 mmHg in users of valsartan (P = 0.01) (14). Changes in blood pressure were not significantly different between the valsartan and lisinopril groups (P = 0.34) (14).

In previous clinical trials, the blood pressure lowering effect of CCBs was not affected by NSAIDs (13, 35, 36, 39). A randomized multi-center double-blind study included 162 hypertensive patients who had their blood pressure controlled with verapamil. Neither ibuprofen nor naproxen significantly affected blood pressure (35). The use of naproxen for four weeks did not change blood pressure significantly in 100 patients who had their blood pressure controlled with nicardipine, a calcium channel blocker (36). Another double-blind crossover study included 61 hypertensive patients who were controlled on amlodipine or enalapril. The use of indomethacin was associated with a 10 mmHg increase in systolic blood pressure when compared to placebo. This increase was observed only in the enalapril group. Diastolic blood pressure did not increase significantly in either group (39). In another trial, indomethacin did not affect blood pressure in users of CCBs (13).

Related literature shows conflicting results on the destabilization of blood pressure associated with the use of NSAIDs in patients on diuretics (12, 33, 34, 37). In two randomized clinical trials, the addition of ibuprofen did not affect blood pressure control in patients receiving thiazide diuretics alone (33, 34). However, another double-blind, randomized, multi-center clinical trial included 97 hypertensive patients who were taking hydochlorothiazide (12). Subjects were randomized to either ibuprofen or naproxen. Ibuprofen use was associated with an increase in diastolic blood pressure by 2.6 mmHg ($P = 0.004$) and mean arterial pressure by 2.7 mmHg ($P = 0.019$). Naproxen was associated only with an increase in diastolic blood pressure by 1.8 mmHg ($P = 0.043$) (12). Another randomized double-blind, crossover study involved 22 elderly patients whose hypertension was controlled on

hydrochlorothiazide. Systolic blood pressure increased significantly by about 4 mmHg in the ibuprofen group as compared to the placebo group. No significant changes in diastolic blood pressure occurred (37).

These above studies examined the effect of NSAIDs on blood pressure stabilization in patients who were controlled on one antihypertensive class of medication. However, no study has examined the effect of NSAIDs in patients who are taking more than one antihypertensive medication. This is important since more than two-thirds of hypertensive patients require two or more antihypertensive medications from different drug classes to control their blood pressure (19).

Summary

Previous studies have examined the association between NSAIDs and blood pressure increase in non-hypertensive individuals, hypertensive patients, and patients who were prescribed specific antihypertensive medications. Overall, non-selective NSAIDs have been found to be associated with blood pressure increase in both normotensive and hypertensive patients. In observational studies, NSAIDs were associated with an increased risk of hypertension. Risk factors included age, renal insufficiency, congestive heart failure, and liver and renal diseases. Previous studies have shown conflicting results regarding the effect of selective COX-2 inhibitors on blood pressure. While, in most studies, rofecoxib was associated with an increase in blood pressure, celecoxib was not. NSAIDs increased blood pressure in users of ACE-I and angiotensin II antagonists. However, it is unclear whether NSAIDs affect

the blood pressure in users of beta-adrenergic antagonists or diuretics. Clinical trials have shown that NSAIDs do not attenuate the antihypertensive effect of CCBs.

Several research questions have not been answered by previous studies. The effect of NSAIDs on incident hypertension has been investigated, but the magnitude of change in blood pressure was not thoroughly examined. Observational studies did not compare the effect on blood pressure of individual NSAIDs. This comparison is important since some NSAIDs may lack such effect and be useful for patients with hypertension. Previous observational studies have not studied the effect of NSAIDs on blood pressure in patients using various antihypertensive medications. The dose-effect of NSAIDs was not examined in previous observational studies. Nor did previous studies examine changes in antihypertensive therapy after starting NSAIDs.

Designs used in previous studies included meta-analyses of published clinical trials, short-term interventional trials, and observational studies. The limitations of meta-analyses include combining heterogeneous clinical trials and excluding patients with comorbidities. Short-term interventional trials provide useful information on the association between medications and adverse effects. However, these trials include small numbers of patients (usually less than 20) and many patients are excluded.

Compared to meta-analyses and short-term trials, observational studies include patients from real world practices. However, previous observational studies have been limited in that some were cross-sectional and others did not control for key confounders. In contrast, the current study design avoided several biases and

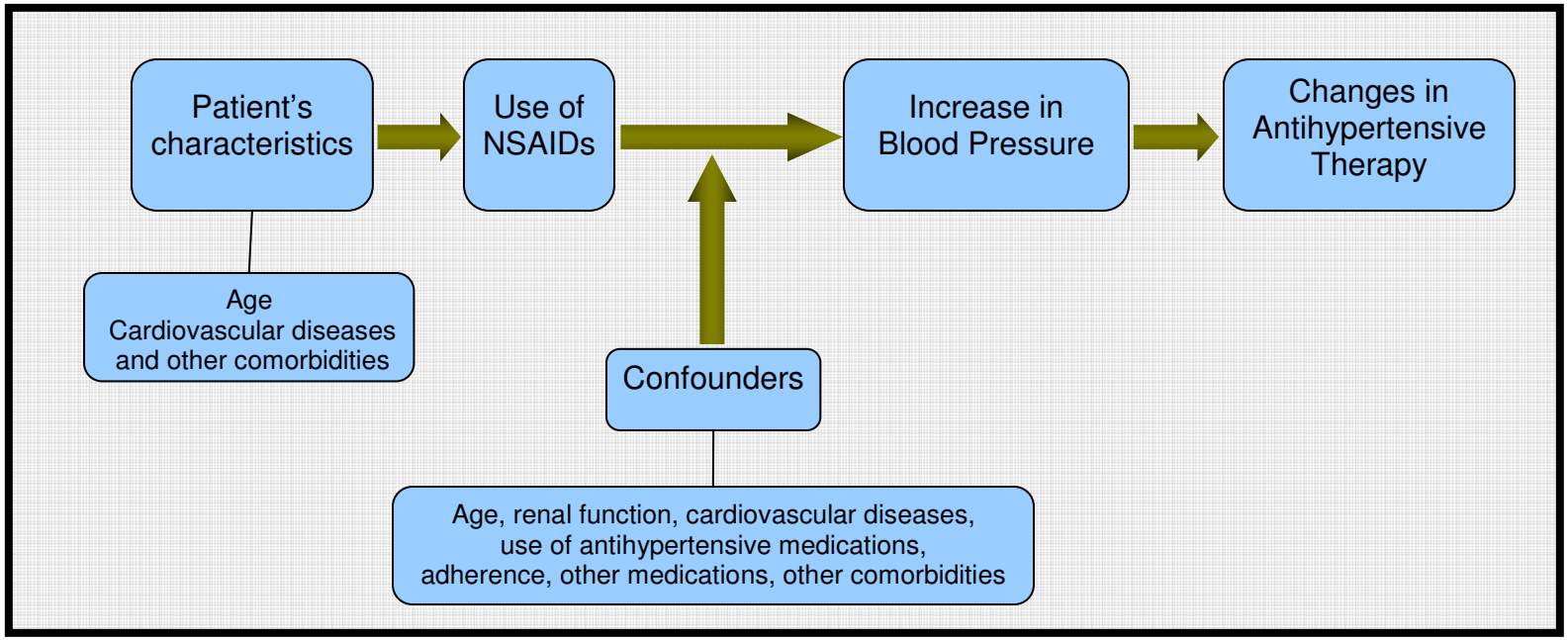
controlled for known confounders using the propensity score method to balance covariates between the compared groups.

Conceptual Framework

Overview

A conceptual framework was created to demonstrate the relationship between the use of NSAIDs, blood pressure increase, and changes in antihypertensive therapy (Figure 5). Several factors could affect the exposure to NSAIDs and the outcomes of interest in this study. Controlling for these factors in the analysis is important. Patients are prescribed NSAIDs according to their individual characteristics. For example, the presence of comorbidities could influence the prescribing of selective COX-2 inhibitors rather than non-selective NSAIDs. Numerous covariates increase blood pressure. An increase in blood pressure could influence the physician's decisions to intensify antihypertensive therapy. This section discusses confounders that affect exposure to NSAIDs or blood pressure. These confounders are classified into demographics, comorbidities, health status, and the use of, and adherence to, antihypertensive medications.

Figure 5. Conceptual Model



Demographics

Studies need to control for demographic covariates such as race, age, and gender when examining the effect of medications on blood pressure. Prevalence and severity of hypertension varies across race in the US population. For example, hypertension is more severe in the African-American than in the white population (19). Age is a risk factor for hypertension and other cardiovascular diseases. Data from previous studies show that older adults are at higher risk of developing hypertension (19). Indeed, the prevalence of hypertension increases in over 60-year-olds to more than fifty percent (19). Several changes in vascular and cardiac physiology due to aging lead to hypertension, congestive heart failure, atherosclerosis, and stroke (80, 81). The increased risk of hypertension with aging is presumably an increase in systolic blood pressure (19). In addition to the increased risk of hypertension, the elderly suffer from multiple chronic conditions, such as rheumatoid arthritis and osteoarthritis, and thus they are prescribed NSAIDs more frequently (82, 83).

Older adults also are more prone to adverse drug effects because of changes in the pharmacokinetics and pharmacodynamics of medications. For many drugs, metabolism and excretion of medications slow in the elderly since kidney and liver functions diminish with aging. This causes greater exposure to medications and can increase the risk of developing adverse effects (84, 85).

Comorbidities

1. Renal insufficiency

Renal insufficiency augments the risk of blood pressure increase. Prescribing selective COX-2 inhibitors increases in patients with renal insufficiency (86). It was found that selective COX-2 inhibitors are 2.5 times more likely to be used by patients with renal insufficiency (86). Since sicker patients, including patients with renal insufficiency, are at a higher risk of gastrointestinal effects, they are often prescribed selective COX-2 inhibitors.

2. Cirrhosis with ascites

Deterioration of renal function associated with cirrhosis may increase blood pressure. Renal synthesis of PGs increases in patients with cirrhosis and ascites. Thus, inhibition of PGs by NSAIDs results in deterioration of renal function because PGs are essential in maintaining both glomerular filtration rate (GFR) and sodium and water excretion. In patients with hepatic cirrhosis and ascites, the use of NSAIDs was associated with a 50% reduction in GFR and a 42% reduction in sodium excretion (50, 87). However, GFR did not change significantly in cirrhotic patients without ascites (87). The number of patients with cirrhosis and ascites is small in the general population and in the database used for the present study, but it is important to consider this disorder in the analysis.

3. Systemic lupus erythematosus

Deterioration of renal function associated with systemic lupus erythematosus may increase blood pressure. The basal renal PG synthesis decreases in systemic lupus erythematosus. Thus, the inhibition of PGs by NSAIDs increases the risk of

renal toxicities in patients with lupus. In one study, the use of NSAIDs in patients with systemic lupus erythematosus was associated with a 60% reduction in GFR (87). Therefore, patients with lupus are at a higher risk for NSAIDs' adverse renal effect, which may result in blood pressure increase. Again, the number of patients with lupus is small.

4. Rheumatoid arthritis and osteoarthritis

NSAIDs are prescribed for the pain and inflammation associated with rheumatoid arthritis and osteoarthritis. Rheumatoid arthritis (RA) affects 1% of the adult population in the US (88). RA is an autoimmune disorder that may result in progressive joint destruction, deformity, and disability. Patients with RA suffer from pain, stiffness, swelling, and limitation in the motion of multiple joints (89). According to the American College of Rheumatology guidelines, NSAIDs are considered one of the first line treatments for RA (88).

Osteoarthritis (OA) affects more people than RA. It has been estimated that about 12% of Americans aged 25 and older suffer from symptoms of OA (90). OA causes pain and swelling of joints in the fingers, hips, knees, feet, and spine (91). Relief of moderate joint pain in patients with OA can be achieved with acetaminophen as effectively as with NSAIDs (92).

5. Diabetes mellitus

Diabetes is a major risk factor for cardiovascular diseases, including hypertension. Blood pressure increase is common in patients with diabetes mellitus. In addition, patients with diabetes are at a higher risk of the blood pressure increase

associated with NSAIDs (19). Treatment of hypertension should be intensified in diabetic patients, to prevent morbidity and mortality (93). The target of blood pressure control for hypertensive patients is to achieve a systolic blood pressure less than 140 mmHg and diastolic less than 90 mmHg. However, for patients with diabetes or renal disease the target is stricter, to levels of less than 130 mmHg systolic blood pressure and less than 80 mmHg diastolic. Hence, most diabetic patients will be on two or more antihypertensive medications to achieve this level of blood pressure control (19, 93).

Health Status

When studying the effect of NSAIDs on blood pressure, controlling for health status could prevent bias resulting from a comparison to healthier or sicker patients. Several studies indicate that sicker patients are prescribed selective COX-2 inhibitors to avoid the gastrointestinal effects associated with non-selective NSAIDs (94-97). An observational study conducted in France included 46,581 patients and found that more users of selective COX-2 inhibitors had gastrointestinal and cardiovascular histories (95). Two studies in the Netherlands have shown that users of selective COX-2 inhibitors were more likely to have cardiovascular comorbidities (96, 97). Another study compared the use of non-selective NSAIDs and selective COX-2 inhibitors between the US and UK populations. In both countries, more users of selective COX-2 inhibitors compared to NSAIDs had cardiovascular and other chronic diseases (94). Therefore, channeling bias is a major threat to the validity of any study that compares non-selective NSAIDs to selective COX-2 inhibitors.

Channeling bias occurs when certain medications are prescribed to patients with major prognostic differences (98).

The Use of Antihypertensive Medications

The use of antihypertensive medications confounds the association between NSAIDs and blood pressure. Patients with hypertension are often started on lifestyle modifications that include diet and exercise to control their blood pressure. When these lifestyle modifications are insufficient to control blood pressure, or if the patient fails to implement them properly, the physician will usually start antihypertensive medications.

JNC 7 recommends starting patients with stage two hypertension (systolic blood pressure of ≥160, or diastolic blood pressure of ≥100) on two antihypertensive medications (19). However, physicians may start patients on a single drug. Then, after maximizing the dose, they may add a second medication from another class to control blood pressure.

Current hypertension guidelines recommend starting patients on thiazide diuretics because they are associated with better clinical outcomes and less mortality than other antihypertensive medications (19). In addition, diuretics are less expensive than other antihypertensive medications. However, the choice of which antihypertensive medication to start depends on several factors. These factors include compelling indications, cost, and patient factors. Patients with compelling indications may start on a different class of antihypertensive medications. For instance, ACE-I might be started in patients diagnosed with both hypertension and

diabetes mellitus. In addition to lowering blood pressure, ACE-I protects renal function (93). After starting any of the antihypertensive medications, the blood pressure response could vary between patients depending on the class used and whether the patient is taking it as prescribed.

Adherence to Antihypertensive Medications

Adherence to antihypertensive medications directly affects blood pressure (99). Adherent patients should have better blood pressure control than those who are non-adherent. In addition, controlling for adherence could work as a proxy for other unmeasured factors, such as adherence to lifestyle modifications and socioeconomic factors. Therefore, adherence to antihypertensive medications needs to be controlled for in the analysis.

It is important to include the above-mentioned covariates in the model when studying the association between NSAIDs and blood pressure. One of the advantages of the source database used in this research is the availability of all these clinical factors, enabling them to be controlled in the analysis. The next chapter discusses the subjects included in this research and the methods employed.

III. RESEARCH DESIGN AND METHODS

Subjects

This research required an appropriate database that contains accurate and complete clinical information. Although several large claim databases exist, they have limitations that make them unsuitable for addressing certain clinical questions. Since many databases have been constructed for non-clinical purposes, the validity of the clinical information, especially diagnosis, is uncertain (100). The main objective of the current study was to examine the magnitude of changes in systolic blood pressure. Claim databases do not collect blood pressure measurements. In contrast, the Regenstrief Medical Record System (RMRS) database contains clinical data including blood pressure measurements that have been collected for clinical purposes.

Patients included in this research received their treatment from a large inner-city medicine practice in Indianapolis, Indiana. RMRS was used to identify eligible patients and collect data on relevant variables. The RMRS is an electronic medical record system that captures patient data from hospitals and outpatient medical practices at the Indiana University Medical Center and from 30 practices in inner-city Indianapolis (101). The RMRS captures prescriptions, laboratory, and other clinical data (101).

The index date was defined as the date of the first NSAID or acetaminophen prescription. The index drug is the NSAID or acetaminophen that was initiated at the index date. The baseline is the time within a year before the index date. Post-index is the time after the index date and before the end date. The study was approved by the Institution Review Boards at the University of North Carolina at Chapel Hill and Indiana University-Purdue University at Indianapolis.

Patients were included in this research if they had received a prescription for any NSAID, were aged 18 years or older, and had a clinical diagnosis of hypertension at baseline. Patients could not have had an active prescription for any NSAID during the year preceding the index date. Included patients must have had at least one sitting systolic blood pressure measurement at baseline. Because these medications could increase blood pressure, patients using cyclosporine, tacrolimus, cisplatin, or carboplatin were excluded.

For the first two aims of this study that examine the association between NSAIDs and systolic blood pressure, included patients must have had at least one post-index measurement of sitting systolic blood pressure. Patients were required to have received the same index drug and had stable antihypertensive therapy until the measurement of blood pressure. Patients were therefore excluded if their antihypertensive therapy had changed, either by increasing the dose or changing antihypertensive medications. Patients meeting the same criteria but who had been prescribed acetaminophen formed the control group.

For the third aim that examines the association between NSAIDs and changes in antihypertensive therapy, the same aforementioned inclusion criteria were used except that patients were not required to have had post-index blood pressure measurement and patients who had changes in antihypertensive therapy were not excluded.

Possible Endogeneity of Changes in Antihypertensive Therapy

Controlling for changes in antihypertensive therapy in the regression analysis is an option when studying the association between NSAIDs and blood pressure. However, the inclusion of changes in antihypertensive therapy in the model as an independent variable may present a problem of endogeneity. Endogeneity occurs when the effect of one independent variable is predicted by other independent variables in the same model. The endogenous variable is correlated with the error term and results in a biased estimate. In this study, changes in antihypertensive therapy were determined by other variables that should be included in the main model.

One option to handle the endogeneity problem is to include an instrumental variable in the model. An instrumental variable is one that is related to the endogenous variable but at the same time is not related to the outcome of interest. In this case, it should be related to the changes in the antihypertensive therapy but not directly related to blood pressure. However, it is difficult to find a variable within this database that exhibits these characteristics. Another way to handle endogeneity is to exclude endogenous variables. This results in an unbiased estimate, but the coefficient on NSAIDs includes the effect of changes in therapy as well as the effect

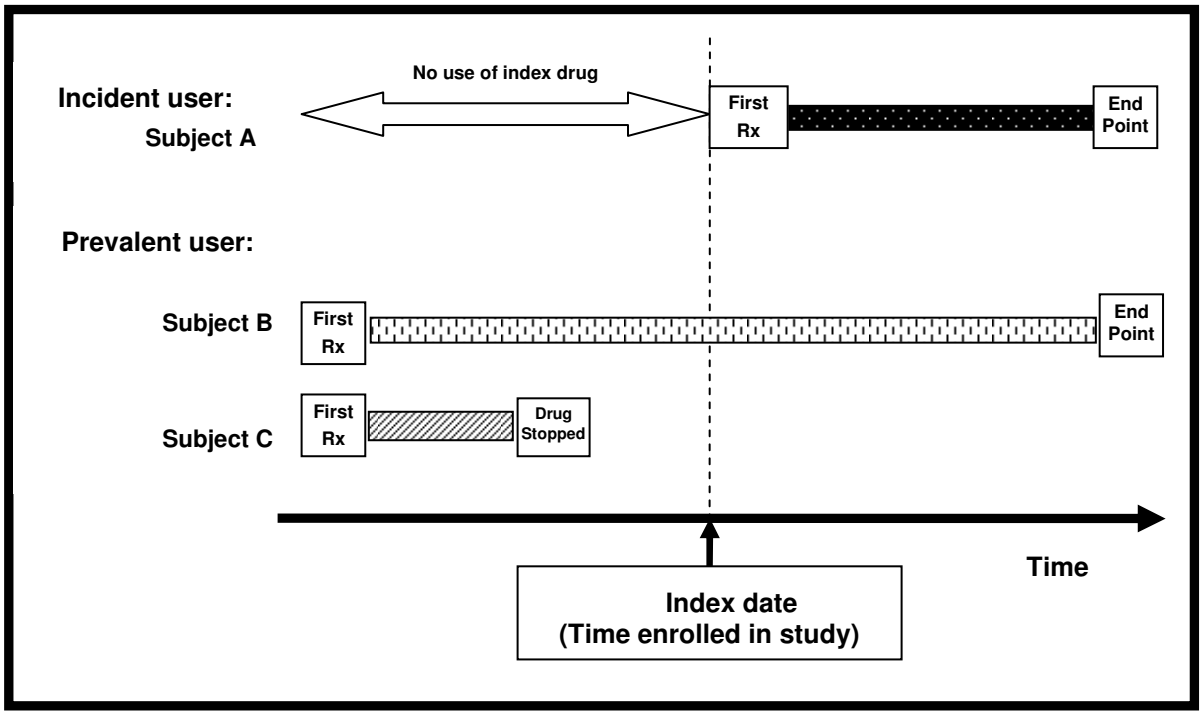
of NSAIDs used. Therefore, caution is required when interpreting the results. A better option is excluding patients who have had changes in antihypertensive therapy. In this study, the latter option was adopted to provide the least biased estimate.

Design

A retrospective design was used to include incident users of NSAIDs (Figure 6). Incident users are those patients who started the medication for the first time after a specific period of non-use. In contrast, prevalent users are those patients who have been taking the drug prior to entry into the study. The inclusion of prevalent users can introduce two types of bias: 1) under-ascertainment of adverse effects that occur early in treatment and 2) the inability to control for some risk factors that may be altered by the study drugs. When the risk of adverse effects is higher at the beginning of drug treatment, the inclusion of prevalent users will underestimate the risk associated with the drug (45). Prior research indicates that blood pressure may increase within a few days after starting NSAIDs. Therefore, studying the effects of NSAIDs on blood pressure is vulnerable to this bias, as patients may stop NSAIDs once they experience adverse effects.

The other bias from including prevalent users is the inability to control for confounders that were affected by the treatment itself. Since NSAIDs affect covariates such as baseline blood pressure and the use of antihypertensive medications, controlling for these covariates will be incomplete in prevalent users leading to a biased estimate.

Figure 6. Comparison between Incident User and Prevalent User Designs



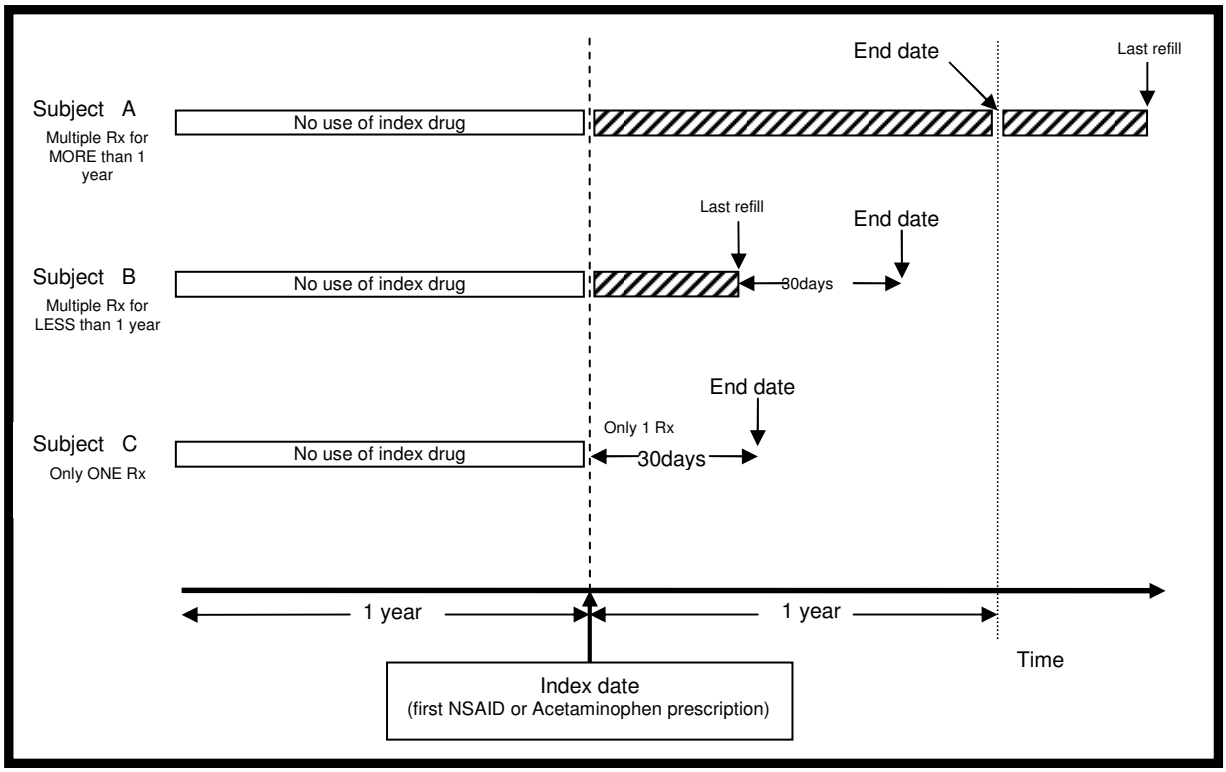
Subject A: In the incident user design all patients will be included and covariates were collected before the drug started. Subject B: Covariates collected at the start of the study might be affected by the drug. Subject C: Subjects who stopped the drug because of adverse effect developed early after starting the drug were not included in the study.

Electronic medical records from the RMRS were used to identify incident users. One year was selected as the period during which patients should not have received NSAID prescription (Figure 7). Information was collected on relevant confounders at baseline. Blood pressures were abstracted at baseline and post-index. The end date of follow-up was defined as one year after the first prescription or 30 days after the last prescription that was dispensed, whichever was less. A thirty-day period was selected because most prescriptions last for one month.

Patients with normal blood pressure may not present to the clinic during the first few months after their index date. And some patients may miss their appointments and not visit the clinic as frequently as scheduled. Considering this

possibility, a one year follow-up was chosen to avoid bias from excluding some hypertensive patients.

Figure 7. Different Scenarios for Patients' Follow-up Periods



Subject A: subjects with multiple prescriptions for more than one year are followed for only one year. Subject B: subjects with multiple prescriptions for less than one year are followed for 30 days after the last prescription. Subject C: subject with only one prescription is followed for only 30 days. Patients were followed to their first blood pressure measurement.

Control Group

Hypertensive patients who were prescribed acetaminophen formed the control group. NSAIDs and acetaminophen are both used for the pain associated with arthritis as well as other types of pain. Acetaminophen is usually prescribed as a first line therapy for patients with osteoarthritis (92). If the patient does not respond to acetaminophen, then the prescriber may switch to a NSAID. Thus, users of acetaminophen are similar to users of NSAIDs in most characteristics and comorbidities.

The use of acetaminophen for the control group may be criticized, as some studies have shown an increase in blood pressure associated with the use of acetaminophen. In one short-term randomized crossover trial of 20 patients, the use of acetaminophen was associated with a 4 mmHg increase in systolic blood pressure (102). However, another randomized trial that included 45 patients found no blood pressure increase in the acetaminophen group (32).

Two analyses of the Nurses' Health Study, which included only women, found an increased risk of hypertension among users of acetaminophen (26, 27). Bias could have been introduced in these studies since self-report was used to ascertain hypertension diagnosis and acetaminophen use. In contrast, acetaminophen did not increase the risk of hypertension in the Physicians' Health Study (28). Again, self-report was used to ascertain exposure to acetaminophen and study outcome. The study outcome was self-reported blood pressure of 140/90 mmHg or higher, or the use of antihypertensive medication (28). Another recent analysis of the Physicians' Health Study that included a larger number of subjects found a relative risk for incident hypertension of 1.34 associated with acetaminophen (95% confidence interval, 1.00 to 1.79) (103).

It is unclear whether these conflicting results are because of gender differences or because of limitations in study design. In the above-mentioned studies, the investigators did not confirm the self-report of hypertension diagnosis. Since self-report was used to ascertain both exposure and outcome, misclassification bias is a major threat to these results. Also, these studies did not sufficiently control for all comorbidities. Furthermore, these studies noted diagnosis

of incident hypertension but did not measure blood pressure. It is important to mention that all these observational studies used similar design and populations. Thus, the evidence that acetaminophen is associated with blood pressure increase remains relatively weak.

In the current study, patients who were prescribed acetaminophen had similar characteristics and comorbidities to NSAID users at baseline (Table 3). Propensity score methods were used to balance covariates between the compared groups. Acetaminophen is used mostly for pain, and pain is independently associated with stress, which could lead to hypertension (104). This confounding by indication was controlled for by using propensity score to balance the diagnosis of RA and OA between the compared groups. The index date for the control group was the date of the first acetaminophen prescription. To be included as a control, the patient should not have had a prescription for acetaminophen during the year before the index date and should meet the same inclusion criteria as for the NSAID group. The ascertainment of the baseline covariates and exposure to acetaminophen was applied in the same way as for users of NSAIDs.

Sample Size

A minimum sample size was calculated for each aim of the study. Based on the dependent variable, multiple linear or logistic regression models were used. For multiple linear regression models, the sample size was calculated using methods proposed by Cohen 1988 (105). To be conservative, alpha was adjusted for the number of hypotheses included in the study to be 0.05/10=0.005. A minimum sample

size of 138 was needed for multiple linear regression to achieve 80% power using alpha of 0.005 (number of predictors=33, effect size=0.35) (105). For logistic regression, the minimum total sample size of 909 (total of both groups) was needed to detect an odds ratio of 2.3 (alpha 0.005, beta 0.80) (106). A sufficient number of patients were identified for each aim (Table 4).

Dependent Variables

Aim 1 and Aim 2: First systolic blood pressure measurement post-index

The systolic blood pressure measurement was included in the model as a continuous variable. This continuous variable enabled this study to examine the magnitude of NSAIDs' effect on blood pressure. The first measurement post-index was selected, as physicians may react to blood pressure increase by changing antihypertensive therapy. Systolic blood pressure was selected because it is associated more with morbidity and mortality than diastolic and should be targeted in the treatment of high blood pressure (19). After age 50, systolic blood pressure presents a more potent cardiovascular risk factor than diastolic. In addition, controlling isolated systolic blood pressure reduces total mortality, cardiovascular mortality, and stroke (19).

According to JNC 7, systolic and diastolic are used to classify blood pressure into four categories, namely: normal, pre-hypertension, stage one hypertension, and stage two hypertension. To be considered normal, blood pressure must be lower than 120/80 mmHg. Pre-hypertension is defined as systolic blood pressure of 120-

139 mmHg or diastolic blood pressure of 80-89 mmHg. Hypertension is considered stage one when systolic blood pressure increases to 140-159 mmHg or diastolic blood pressure to 90-99 mmHg, and stage two if systolic blood pressure is ≥160 mmHg or diastolic blood pressure is ≥100 mmHg (19).

Tierney et al. found in the same study population that one blood pressure reading has significant prognostic value (107). The study included 5,825 hypertensive patients from RMRS who were followed for about 5 years. A 10 mmHg increase in systolic blood pressure from a single clinic visit was associated with a 13% increased risk of renal insufficiency, a 9% increased risk of ischemic heart disease, and a 7% increased risk of stroke. The researchers concluded that, in hypertensive patients, a single blood pressure measurement has an important prognostic effect and physicians need to intervene to lower blood pressure based on a single measurement (107). Thus, the increase in one blood pressure value is clinically important, and using the first measurement is appropriate to study the association between NSAIDs and blood pressure.

Aim 3: Changes in antihypertensive therapy

Blood pressure increase after starting NSAIDs could influence the physician's decision to intensify antihypertensive therapy. Changes in antihypertensive therapy post-index were considered intensified when: (1) the dose of any one of the current antihypertensive medications was increased; or (2) the patient was started on a new antihypertensive medication from another class. A dummy variable was generated with "1" if antihypertensive therapy was intensified and "0" if not.

Independent Variables

Based on previous literature, the models included certain covariates that could affect blood pressure or the use of NSAIDs including age, race, gender, and baseline systolic blood pressure. Baseline systolic blood pressure was defined as the last measurement before the index date. The models controlled for the diagnosis of certain diseases, the use of, and adherence to, antihypertensive medications, the use of medications that are known to be associated with blood pressure increase, time from baseline blood pressure measurement until the index date, and year of the index date. Table 5 lists the variables included in this study, their types, units, and definitions. For these categorical independent variables, a dummy variable was generated with “1” as yes and “0” as no.

The diagnosis of the following conditions at baseline was included in the models: rheumatoid arthritis, osteoarthritis, coronary artery disease or myocardial infarction, stroke (cerebrovascular accident or transient ischemic attack), arrhythmia or ventricular arrhythmia, asthma or chronic obstructive pulmonary disease, renal insufficiency, cirrhosis with ascites, systemic lupus erythematosus, diabetes mellitus, and congestive heart failure. These comorbidities serve to differentiate sicker from healthier patients. For each comorbid condition, a dummy variable was generated that equaled “1” if the condition is present and “0” if not.

The analysis controlled for the use of medications that are known to be associated with increase in blood pressure or incidence of hypertension. Based on previous literature, the use of venlafaxine, a high dose of oral glucocorticoids, and the use of oral contraceptives were included in the models (108-112). Oral

glucocorticoids that were identified in the database were prednisone, cortisone, and dexamethasone. A high dose was defined as 10 mg or higher for prednisonse, 50 mg or higher for cortisone, and a dose of 1.5 mg or higher for dexamethasone.

The patient's age at the index date was included in the model as a continuous variable. For gender, a dummy variable was created that equaled "1" if female and "0" if male. For race, three dummy variables were created, African-American, Caucasian, and other. The Caucasian category was used as the reference group.

Exposure to Index Drug

Including exposure to the index drug (NSAID or acetaminophen) is important to adjust for the variation in the treatment intensity. For example, patients who are using NSAIDs only as needed might have a different blood pressure response from those who are taking NSAIDs daily. The database used does not include a variable to indicate whether the drug was prescribed to be taken as needed. Previous literature did not offer any method that could capture exposure in terms of regular versus as-needed use. Several options were considered to control for variations in exposure to the index drug, including medication gap between refills, medication possession ratio (MPR), and the number of refills per month. Gap between refills does not add any new information to address the as-needed issue beyond that provided by MPR, since it is the opposite of MPR adherence (113). Gap would be more relevant if withdrawal effect of medications were a concern.

Therefore, MPR and the number of refills per month were used to control for variation in exposure to the index drug. The MPR is the refill adherence and was

calculated by dividing the sum of the days between the last refill and the next expected refill (i.e. days supply) by the number of days between the last refill and the next actual refill, then multiplying by 100 to obtain the percent MPR (Equation 1). For each patient, an average MPR was calculated for the index drug.

$$\text{Medication Possession Ratio (MPR)} = \frac{\text{sum of the days' supply obtained}}{\text{total days from first prescription until last fill}} \times 100 \quad (1)$$

The MPR was included as a categorical variable because it had multi-modal distribution. Prior research did not use the MPR to ascertain exposure to NSAIDs or acetaminophen. In the current research, categories with perceived clinical meaningfulness were created for the MPR (<20%, 20% – 80%, >80%). The first category (<20%) will be more likely to include patients who are using the index drug minimally or as needed. The second category (20% – 80%) captures patients using the drug on a regular basis but who are likely to be non-adherent. The third category (>80%) includes adherent patients. A sensitivity analysis was conducted using ±10 around the categories of MPR (10% or 30%, 70% or 90%). For patients prescribed the index drug only once, the MPR was calculated by assuming it lasted for 30 days, the mean quantity supplied duration.

As a proxy for as-needed versus regular use, the number of refills per month was included in the model. Doing so assumes that the patient refills regularly and as such exposed to the drug on a continuous basis (regardless of whether it was prescribed for as-needed or regular use). The number of refills was calculated for each subject. The interval was then calculated by subtracting the index date from the

service date of the last prescription. If a patient had only one prescription, then the interval was calculated by subtracting the index date from the expected finish date. The refills per month were calculated by multiplying the number of refills by 30 and dividing it by the interval. Since refill per month is not normally distributed, a dummy variable was created that equaled “1” if the subject had one refill per month or more, and equaled “0” if the subject had less than one refill per month.

In addition, two sensitivity analyses were conducted. In the first analysis, the model included the extent of exposure as the dose-MPR interaction. In the second, the analysis was restricted to only those patients who had a blood pressure measurement within 30 days of the index date.

The Use of Antihypertensive Medications

Baseline use of antihypertensive medications was included amongst the covariates in the models. Five groups of antihypertensive medications were formed: beta-adrenergic antagonists, CCBs, diuretics, ACE-I or angiotensin II receptor antagonists, and other antihypertensive medications. The frequency distribution of the baseline antihypertensive medications class is listed in Table 3. The regression model included all the dummy variables for the class of antihypertensive medications, and the reference group consisted of those hypertensive patients who were not prescribed any antihypertensive medication.

The effect of NSAIDs on blood pressure was compared across antihypertensive medications using a sub-analysis for each antihypertensive class. A sub-analysis was used instead of interaction terms for several reasons. Compared to

experimental studies, the joint distribution of interacting terms in observational studies might not be optimal, resulting in an incorrect estimate of the effect (114). Another problem is that multi-collinearity created from using interaction terms inflates the variance of the estimate, resulting in wide variations in the estimate from sample to sample. Also, multicollinearity increases the magnitude of the parameter estimate, making it appear to have much stronger effects (114).

Propensity score matching techniques were used to balance background characteristics between compared groups for each class of antihypertensive medications. Four classes of antihypertensive medications were examined: beta-adrenergic antagonists, CCBs, diuretics, and ACE-I. Included patients had to be taking the antihypertensive medication at baseline, had no changes in therapy post-index, and had a prescription during the assessment of systolic blood pressure. This was accomplished by requiring patients to have a prescription filled before or on the day of the systolic blood pressure measurement; and the end date for the same prescription had to be after the day of the measurement. For each antihypertensive class, a dummy variable was created that equaled “1” if the patient was prescribed a medication within the antihypertensive class and “0” if not.

Adherence to Antihypertensive Medications

Adherence to antihypertensive medications was included in the models as it directly affects blood pressure. Compared to variations in exposure to NSAIDs, patients prescribed antihypertensive medications are expected to use it regularly. Previous literature has suggested methods to assess adherence to medications

used for chronic diseases that include use of medications refill, pill count, electronic monitoring, biomarkers, and asking the providers or the patients (113, 115). The database used in the current study, RMRS, includes the pharmacy prescription refill. Patients in this cohort receive their medications at subsidized costs. This makes the prescription database more complete and reflects the medications the patient is actually taking, including OTCs. Therefore, prescription refill adherence was used, by calculating MPR, to assess the level of adherence to antihypertensive medications. The use of MPR to assess medication adherence has been validated in several studies (113). MPR was calculated according to equation 1 above.

Patients were considered adherent if they had an MPR of more than 80%. For each drug, an average MPR was calculated for a period of one year before the index date until the end date. Then the overall average adherence was calculated by dividing the sum of all the MPRs by the number of antihypertensive medications that the patient was taking (116).

Year of Index Date

This study includes patients who started using NSAIDs between 1993 and 2006. During this period, information was evolving about the association between NSAIDs and blood pressure increase. Thus, the physician's decision to prescribe NSAIDs for hypertensive patients could change depending on the year of the index date. In addition, recent clinical trials and guidelines are now recommending more aggressive treatment to control blood pressure. Therefore, the propensity for adjusting antihypertensive therapy may vary by date. To counteract the effect of

these factors on the results, the model included the year of index date. The year variable was divided into three categories: from 1993 through 1996, from 1997 through 2002, and from 2003 onwards. The cut-off points of 1997 and 2003 were selected as JNC 6 was released in 1997 and JNC 7 was released in 2003. The release of an updated version of the JNC report may affect future prescribing practice as the goals of blood pressure control may intensify and recommendations for selection of antihypertensive medications may change.

Time between Baseline Blood Pressure and the Index Date

The time between baseline blood pressure measurement and the index date could vary between the patients included in the study. Many factors could have affected blood pressure in the interval before the patient commenced taking the index drug. Blood pressure could vary for those with a longer period between measurements and the index date; therefore, baseline measurement may not represent the current baseline accurately. Ideally, baseline blood pressure measurement should be closer to the index date and measured at the same time for all patients. Since patients have a clinic visit on the same day as they are prescribed the index drug, it is expected to find many patients with a baseline blood pressure measured at the index date. However, patients do not always pick up their prescription on the same day as they visit the clinic.

To prevent bias introduced by variations in the time from baseline blood pressure measurement until the index date, a variable to indicate this time was included in the model. This variable was constructed by subtracting the date of the

last baseline systolic blood pressure measurement from the index date. Since time was not normally distributed, it was divided into three categories: less than or equal to 7 days, more than 7 days and equal to or less than 30 days, and more than 30 days before the index date.

Dose Analysis

The last dose that the patient was stable on at baseline was selected. Since dose was not normally distributed, patients were stratified into low and high dose groups. Patients who were prescribed less than 75% of the maximum daily dose were included in the low dose category and those prescribed 75% or more were included in the high dose category. The maximum daily dose was obtained from the drug reference Facts and Comparisons (117).

Propensity Score Analysis

Several studies indicate that comorbidities could influence the prescribing of selective COX-2 inhibitors compared to non-selective NSAIDs (94-97, 118). This emphasizes the importance of controlling for these factors in the analysis. In observational studies, different analytical techniques can be used to control for covariates when assessing treatment effects. The most commonly used are model-based techniques. This approach of using modeling is limited, in that it runs statistical analysis and display results without warning when compared groups are not balanced on covariates. In contrast, the propensity score method warns the investigator of inadequate overlapping of covariates.

The propensity score is mainly used to balance covariates between compared groups in observational studies. It is the estimated probability for each subject of being exposed to treatment A versus treatment B, based on the person's covariates. It combines all confounding covariates into a single composite factor. For each comparison, a different propensity score needs to be estimated (44, 119, 120). Rosenbaum and Rubin introduced the propensity score as the conditional probability of the assignment to treatment given the subject's covariates, assuming that Z is independent given x (121):

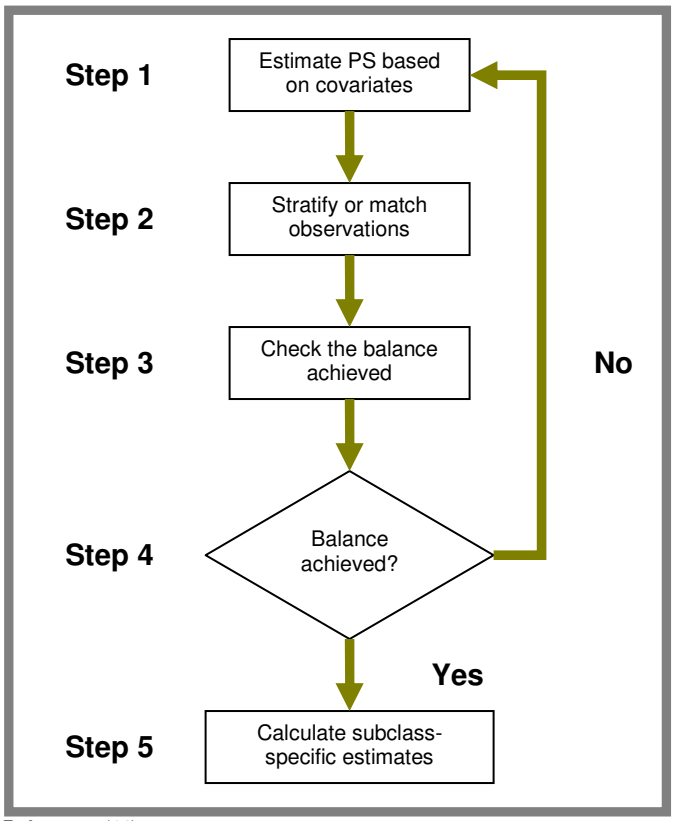
$$e(x) = pr(z=1 \mid x) \qquad (2)$$

General steps to conduct the propensity score are suggested in the literature (Figure 8) (44). The first step is to estimate the propensity score for each patient based on the observed covariates. The most common method for propensity score

estimation is to conduct a logistic regression, where the treatment is the dependent variable regressed over other covariates. Then the logit is calculated from probabilities as in the equation (3).

$$\log it = \left[\frac{p}{1-p} \right] \qquad (3)$$

Figure 8. General Steps to Conduct Propensity Score



Reference: (44)

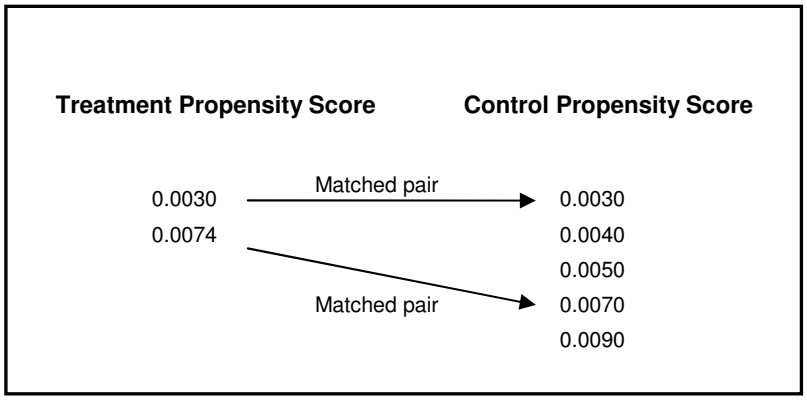
Variables that predict exposure to treatment are included in the propensity score model. Excluding variables that predict outcome will increase variance and result in a less optimal propensity score model. (122) Therefore, in addition to including covariates that are predictive of the exposure to treatment, variables that

are related to the outcome of interest should be included when predicting the propensity score.

After calculating the propensity score, the score can be used in three different ways to balance covariates among compared groups: (1) matching samples of exposed and control patients who have a similar propensity score; (2) stratifying patients based on their propensity score, usually in five balanced groups; (3) including the propensity score as a covariate in a multivariable model (i.e. regression adjustment) (119, 123, 124). Covariate adjustment is biased if the covariance matrices in the treated and control groups are unequal. Therefore, matching and stratification are considered superior to covariance adjustment (123). The current study used the propensity score matching method because matching is sometimes superior to sub-classification in providing more comparable groups.

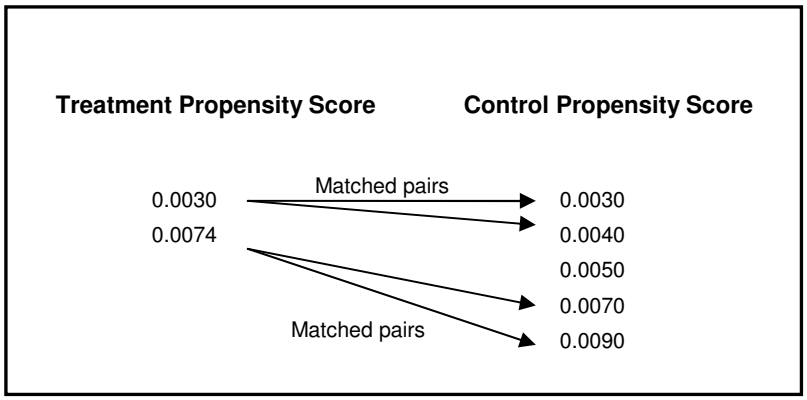
Matching can be applied using different methods including nearest neighbor and 1 to 2 matching, radius matching, kernel matching, and Mahalanobis metric matching. In the nearest neighbor method the treatment and control subjects are randomly ordered, then the first treatment is selected and matched with one (two for 1 to 2 matching) control with the closest propensity score (Figures 9 and 10). This method could result in unbalanced matches if the caliper is not used (125).

Figure 9. Nearest Neighbor Matching Method (1 to 1)



* Each treated subject is matched with one control subject with the same or closest propensity score.

Figure 10. Nearest Neighbor Matching Method (1 to 2)



* Each treated subject is matched with two control subjects with the same or closest propensity score.

In radius matching, each treated subject is matched only to a control whose propensity score falls in a predefined radius of the treated propensity score. This will result in more balanced groups since matching within this radius will occur with a similar control. However, it is difficult to decide which radius to use (125).

Kernel matching involves assigning weight to control. This weight is inversely proportional to the distance between the propensity scores of treated and control subjects. Then, treated subjects are matched with a weighted average of all the controls. A lower distance between propensity scores means a higher weight and this results in a good match (125).

Matching using the Mahalanobis metric is another popular method which has been used before for bias reduction in observational studies (126). The Mahalanobis metric works by randomly ordering subjects and then calculating the distance between the first treated subject and all controls. The distance is defined as:

$$d(i, j) = (u - v)^T C^{-1} (u - v) \qquad (4)$$

Where u and v are the values for the matching variables for treated and control subject (i, j), and C is the sample covariance matrix of matching variables from the full set of control subjects (123). Each treatment subject will be matched to a control subject within a predetermined range of the treated subject's estimated propensity score (125, 127).

Lack of overlap in propensity score between treatment groups means that they are not comparable, and thus the use of propensity score matching may not be helpful (Figures 11 and 12). The use of a caliper with any of the above-mentioned methods can restrict the matching of treatment subjects to control subjects with a common support region. Caliper is a predefined range of the subject's predicted propensity score. By using the caliper the matching of treated subjects can be restricted to controls with a common support region. After defining the caliper a random treated subject is matched with a control based on a propensity score within this caliper. When using a caliper, some subjects will be unmatched resulting in a smaller sample, but a between-group balance will be achieved. It is important to note that subject loss occurs when using a caliper when the treatment and control groups do not have a good overlap in covariates. Where overlap exists, comparisons are

valid. It was suggested to use one-fourth standard deviation of the estimated propensity score (128). After defining the caliper, one treated subject is randomly selected and matched with a control based on the propensity score within this caliper (125).

Figure 11. Lack of Overlap in Propensity Scores between Treatment and Control

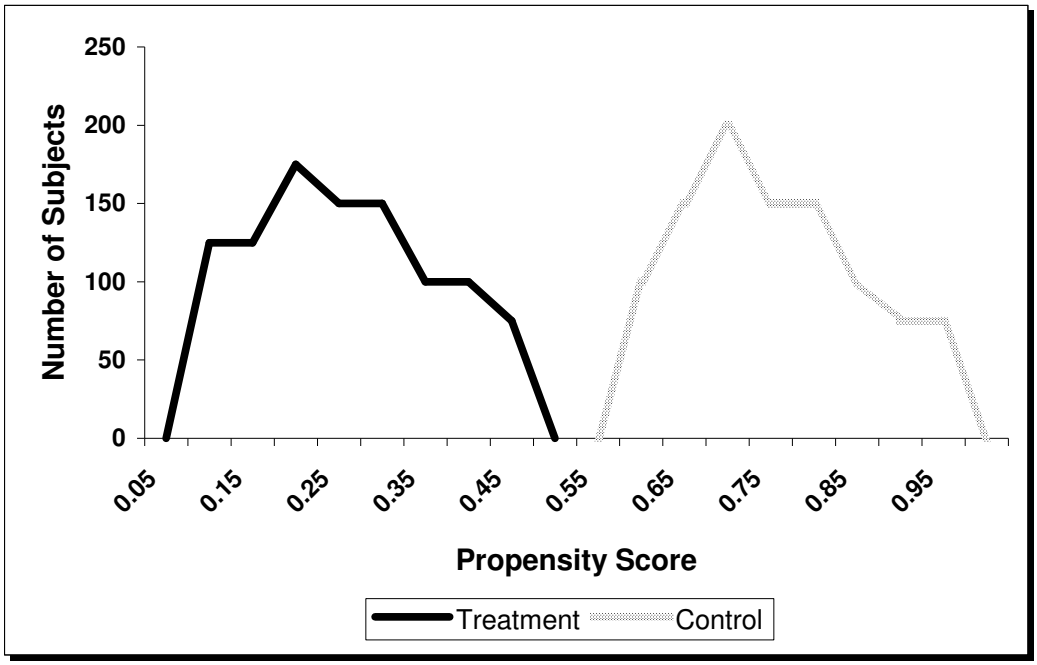
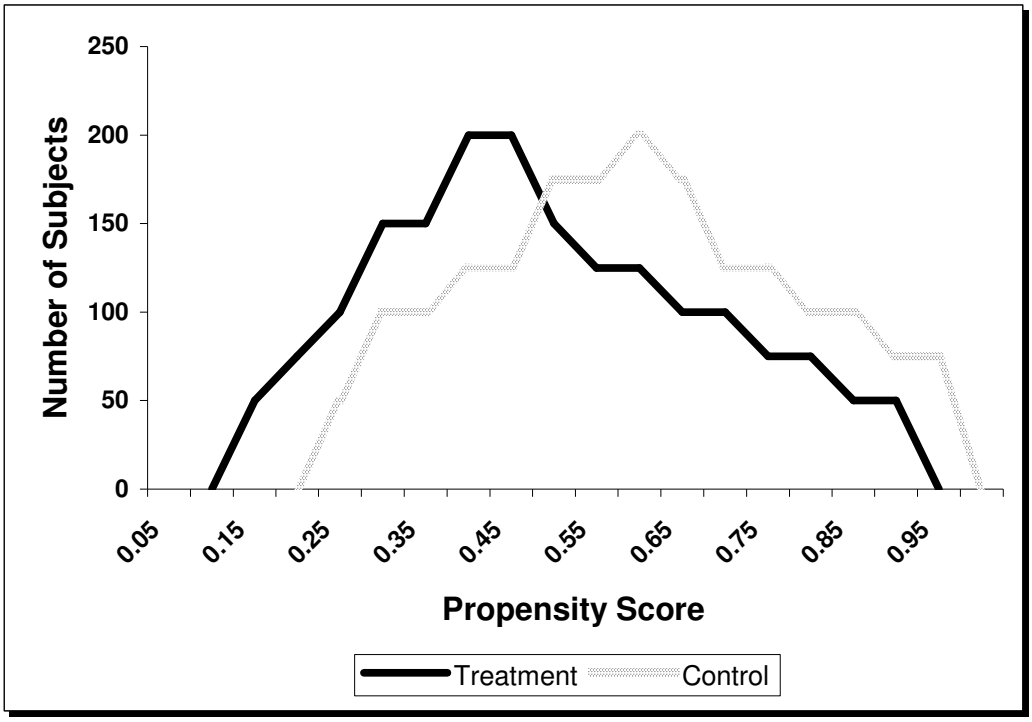
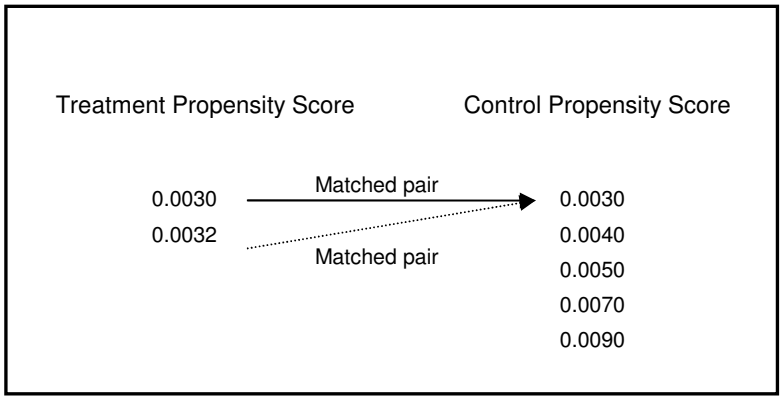


Figure 12. Overlap in Propensity Scores between Treatment and Control



All matching methods can be used with or without replacement. In matching without replacement, control subjects are dropped from consideration once they were matched to treated subjects. Thus, each control is used only once in the final dataset. When overlap between treated and control subjects does not exist, matching without replacement could lead to poor matches. To solve this, it was suggested that matching with replacement be used to improve the matching process. With replacement, a control subject could be matched to more than one treated subject (Figure 13). Allowing replacement increases the balance of covariates between the matches. However, replacement reduces the number of distinct control subjects included, thus increasing the variance of the estimator (129). In addition, replacement may not improve the balance of covariates between the treatment and control groups.

Figure 13. Nearest Neighbor Matching Method with Replacement



* In matching with replacement a control subject could be matched to more than one treated subject.

In a recent sensitivity analysis, the Mahalanobis matching method yielded better results than all other matching methods (125). The matching methods compared included: nearest neighbor, 2 to 1 matching, Mahalanobis, Mahalanobis with caliper, radius matching, kernel matching, and stratification. The author used criteria from five tests to compare the balance of covariates between various methods of matching. First, two sample t-statistics tests were used to compare the variables' means between the treatment and control groups (chi-square was used for categorical variables). Second, the mean difference was compared as a percentage of the average standard deviation. Third, the percentage reduction of bias in the means of variables was compared between various matching methods. Fourth, the Kalmogorov-Smirnov test was used to compare the density estimates of the explanatory variables between treated and control subjects. Fifth, the author compared the density estimates of the propensity scores between treated and control subjects (125). Mahalanobis with caliper was found to have the best matching on variables. The outcome was estimated by examining the difference in means between treated and control groups. Also, standard errors were decreased by threefold when a regression analysis was conducted after propensity score matching

(125). Therefore, applying a regression analysis after propensity scores matching may improve the precision of the estimate.

Mahalanobis metric matching without replacement method was used in the current study since it produces a better balance between the covariates in the treated and control groups (123, 125). This research included variables in the model based on a theoretical framework and knowledge of the disease and medications, before examining the balance between covariates.

The choice of the statistical software affects the covariates balance and ultimately the study's results. PSMATCH2 in STATA software for propensity score matching was not used because the Mahalanobis matching is conducted only with replacement. To match without replacement, all matching duplicates need to be deleted after matching; however, this is inappropriate as some treated subjects would be lost in this process. Therefore, this study used a macro code within SAS software to implement Mahalanobis matching without replacement from the beginning. Propensity scores were predicted using the PROC LOGISTIC procedure in SAS/STAT software. The logit was calculated and then the subjects were matched based on their propensity score using the Mahalanobis matching method without replacement. A caliper of one quarter of the standard deviation of the propensity score was used (± 0.25 * standard deviation).

The next step after matching subjects is to assess the balance of covariates across the two groups. A chi-square test for categorical variables and Student's t-test for continuous variables were used to assess the covariate balance. Another method

to assess balance is standardized difference. The standardized difference is the mean difference between the two groups as a percentage of the average standard deviation (123, 127) (Equation 5).

$$\text{Standardized difference} = \frac{100\left(\bar{x}_{exposed} - \bar{x}_{unexposed}\right)}{\sqrt{\frac{s^2_{exposed} + s^2_{unexposed}}{2}}} \quad (5)$$

The goal is to keep this difference as small as possible. Also, the percentage of bias reduction achieved by the estimated propensity score can be calculated using Equation 6. The percent bias reduction is the bias reduced for each variable by using the propensity scores method. It is calculated as the absolute value of the standardized difference in means for the matched divided by the absolute value of the standardized difference in means for the unmatched, which is then subtracted from one and multiplied by 100 to obtain the percentage of bias reduction.

$$\text{\% Bias Reduction} = 1 - \left(\frac{\left|\text{Standardized Difference}_{\text{matched}}\right|}{\left|\text{Standardized Difference}_{\text{unmatched}}\right|} \right) \quad (6)$$

In the current study, the balance of covariates between the groups was examined using the chi-square test for categorical variables and Student's t-test for continuous variables. Also, the standardized difference and the percentage of bias reduction were calculated. After satisfied with covariate balance, a multiple linear regression model was used to study the effect of NSAIDs on systolic blood pressure and changes in antihypertensive therapy. The key independent variable was the use of NSAIDs. Covariates that were not balanced by propensity score matching were included in the regression model. Also, the model included the time from index date

until blood pressure measurement, since this time occurred after the index date it could not be included in the propensity score matching. Another advantage of using a regression model is that it reduces the standard error and, hence, improves the precision of the estimate (125).

Adjustment for Multiple Comparisons

The term ‘multiple comparisons’ refers to the comparison of the mean values when multiple treatments are involved (130), while ‘multiple testing’ refers to all tests and hypotheses included in a study. When a number of hypotheses are tested, the chance of making a Type I error increases. This would result in a false significant difference. For this reason, some researchers have recommended adjusting the p-values for the number of hypotheses tested in a study (130, 131). In contrast, other researchers argue that this adjustment might lead to inaccurate decision and an increase in the likelihood of a Type II error (132, 133).

Adjusting the p-value for multiple comparisons is undertaken because multiple testing increases the chance of finding statistically significant results. To prevent this from occurring a smaller p-value is used to ensure that the error for all tests remain at 0.05. One method to adjust for multiple comparisons is the Bonferrroni adjustment. However, compared to other methods this is considered by most researchers to be more conservative. Alternatively, other methods such as confidence intervals, Bernoulli, Hochberg, and Tukey are used to adjust for multiple comparisons (132, 134-136). The selection of adjustment method depends on the type of comparison. For example, Tukey can be used in a one-way unbalanced

analysis of variance. However, when covariates are included in the general linear model, a simulation method is recommended, because other methods do not fully exploit the correlation structure (130, 131).

Several reasons for not adjusting the p-value are discussed in the literature (132, 133). By reducing the chance of making a type I error, the chance of making a type II error of not finding a difference when there is one increases. As a result, important differences could be missed. In addition, adjusting the p-value increases the sample size needed in a given study. Also, current methods used for adjustment have limitations, and some may not adjust the p-value appropriately. Other ways to handle the multiple comparisons issue include the use of a composite endpoint to limit the number of tests and the selection of one primary endpoint and several secondary endpoints (132).

In the current study, simulation was used to adjust for multiple comparisons; because in the general linear model other methods such as Tukey-Kramer do not fully exploit the correlation structure (130, 131). The simulation works by drawing a random sample from the standard normal distribution to compute the test statistics for all pairwise comparisons. This process is repeated multiple times to estimate the simulation-consistent estimate and calculate the adjusted confidence interval and *P* value (130). In this study, confidence intervals and *P* values were adjusted for multiple comparisons by simulation using the ADJUST=SIMULATE option in SAS GLM procedure. Multiple comparisons were adjusted for only when more than two treatment levels were compared in the same regression model. An alpha of 0.05 was used in the analysis. When adjusting for multiple comparisons, the value of

alpha will be smaller, based on the adjustment. Since the number of hypotheses to be tested in this study is not large and the study is exploratory, no adjustment was made for multiple testing.

Missing Data on Dose

Missing data on dose was encountered in this database. Missing data on some variables is a common problem in observational studies and clinical trials. Several mechanisms explain the relationship between missing data and variables included in the study. A typical mechanism is “missing completely at random” (MCAR). MCAR means that missing data on a variable is unrelated to the value of any variables in the model, including its own true value (137, 138). This is the strongest assumption and it is not possible to see whether missing data are correlated with the value of the variable itself. “Missing at random” (MAR) is another mechanism in which missing values may depend on observed variables, but conditional on those values data are missing randomly. For example, data on Y are said to be MAR if these data are not related to the value of Y after controlling for other observed variables in the analysis. Thus, in MAR, missing values do not depend on the values of unobserved variables. The last mechanism is “not missing at random” (NMAR) in which missing values do depend on unobserved values (137, 138).

There are several approaches to handling missing data including the use of dummy variable adjustment, imputation by substituting the mean or conditional mean imputation, and complete case analysis. In the dummy variable adjustment

method, missing data are recoded to zero and a dummy variable is included to indicate which observations were missing. The major limitation of this method is that it can introduce bias (137).

Imputation is another method to handle missing data and can be done by either substituting the mean or substituting the mean that was regressed on other covariates. When data are MCAR, imputation may not bias the results. It is a more efficient approach but the standard errors are incorrect (137).

The complete case analysis method is the most commonly used and most statistical packages apply this automatically when a regression model is run. In this method, observations with missing values are dropped. One limitation of this method compared to other techniques is that the standard error is higher. However, this method is not biased with MCAR data and the standard errors and test statistics are correct. Also, this method is not biased if data are MAR and missing data depends only on independent variables (not dependent variable). Therefore, complete case analysis will not introduce bias in most situations, and thus is recommended over the other techniques discussed (137). In this study, complete case analysis was used for missing data on dose by dropping those particular observations.

Over The Counter NSAIDs

Some NSAIDs are available over the counter (OTC) in addition to by prescription and this database captures only the use of prescription NSAIDs. Bias could be introduced if patients were classified as non-users while they are using OTC NSAIDs. However, because patients included in this study were provided with

their medications through a prescription assistance program, it is less likely that they would have purchased OTC NSAIDs.

Bias from not accounting for OTC NSAIDs is not likely to affect the results of the current study, as a recent sensitivity analysis was conducted that found that missing OTC drug exposure is not a significant source of bias even if the exposure is as high as 80% (139). This sensitivity analysis was conducted using published estimates of the association between NSAIDs and colorectal cancer. The investigators varied the overall prevalence of NSAID exposure (from 1% to 99%), the proportion of NSAIDs exposure due to OTC use alone, and the true risk ratio (0.25, 0.5, 0.75, and 0.9). They assumed that the proportion of NSAID exposure due to OTC use was the same between diseased and non-diseased individuals (non-differential misclassification of exposure); and that the relative true risk used in the sensitivity analysis reflected the effect of NSAIDs on colorectal cancer. Also, they assumed that unexposed subjects were correctly classified as unexposed (139).

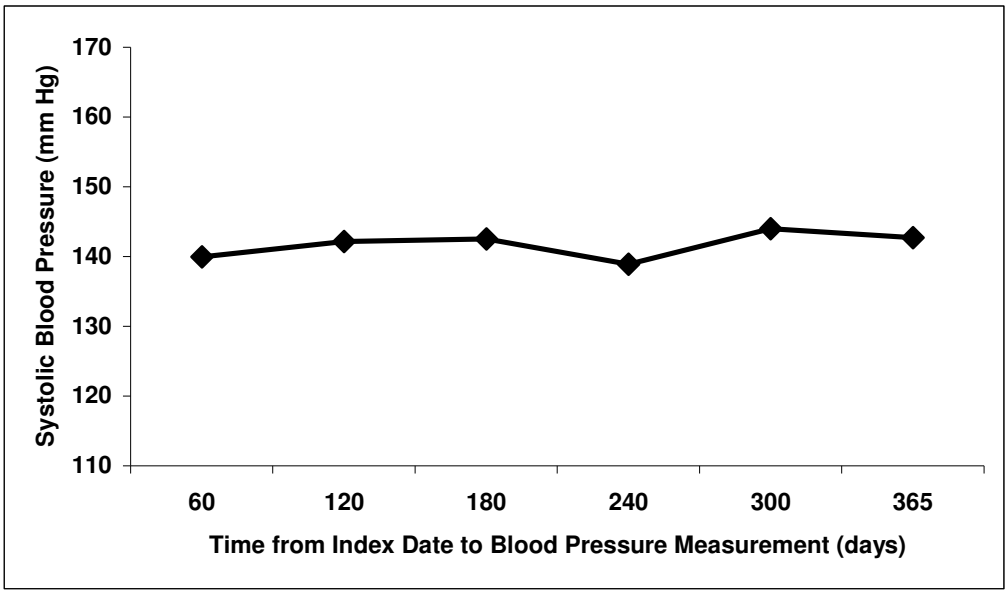
The investigators concluded that, in many circumstances, prescription data may be sufficient for epidemiological research even though some of the drugs are available OTC (139). Even if 35% of the population uses NSAIDs and 80% of the NSAIDs used are OTC, the results will not be biased. As long as the proportion of exposure is similar between diseased and non-diseased people, misclassifying as unexposed will bias the effect estimate toward the null. In this study sample of subjects, it is less likely that OTC NSAIDs use would differ for the various groups under consideration.

Time to Blood Pressure Measurement

The period of time from the index date until the measurement of blood pressure will vary between patients. Those who come to the clinic earlier could differ from other patients in certain respects, including the severity of diseases. To prevent bias caused by variations in time, patients could be stratified into several groups based on their time from the index date until the measurement of blood pressure, and several rounds of propensity score matching could then be conducted for each group. This option is appropriate if those patients who present earlier are strongly believed to have increased blood pressure. To explore whether patients with high blood pressure present to clinic earlier than those with normal blood pressure, the database was examined. No correlation was found between the time elapsing before blood pressure measurement and the value of systolic blood pressure (Figure 14).

Another approach, to prevent bias caused by variations in time, is to include a covariate indicating the time from the index date until blood pressure measurement in the final model. Therefore, this study included the value for this time period as a covariate in the regression model after matching for propensity score.

Figure 14. Systolic Blood Pressure by Time from Index Date until Blood Pressure Measurement



Average of Systolic Blood Pressure Measurements

As discussed earlier, the use of a single blood pressure measurement is a reliable predictor of morbidity based on the work by Tierney et al. using the same database (107). To investigate this issue further, the results were compared when using an average of all blood pressure measurements to the results when using only a single measurement.

Following the first prescription of NSAIDs, if the patient experienced an increase in blood pressure, detected at a clinic visit, physicians might increase the dose or start new antihypertensive medication. Thus, to prevent any potential effect of changing antihypertensive therapy on blood pressure, blood pressure measurements were included only until the date when the antihypertensive regimen

was changed. In the final regression model, the average systolic blood pressure was included as a dependent variable.

Clinically Significant Increase in Systolic Blood Pressure

Another analysis was conducted to investigate whether the increase in systolic blood pressure associated with NSAIDs is clinically important. Clinically important increase was defined as systolic blood pressure increase from baseline by at least 20 mmHg. The use of 20 mmHg was based on a previous study that investigated the effect of selective COX-2 inhibitors on blood pressure (71). A dummy variable was created that equaled “1” if systolic blood pressure increased by 20 mmHg or more, and equaled “0” if not.

IV. RESULTS

Baseline Characteristics

A total of 3,928 patients were prescribed NSAIDs (n=2,181) or acetaminophen (n=1,747) and met the inclusion criteria (Figure 15). As shown in Figure 16, baseline blood pressure measurements were within 30 days before the index date for most patients. Fifty percent (n=1,961) of patients included in the study had their baseline systolic blood pressure measurement on the index date (and more than 70% (n=2,788) within 30 days before the index date). Blood pressure measurements near the index date reflect the baseline in the ideal situation. However, more patients in the acetaminophen group had baseline blood pressure measurements closer to the index date compared to the NSAID group ($P<0.001$) (Figure 16).

Figure 15. Derivation of Cohort Size

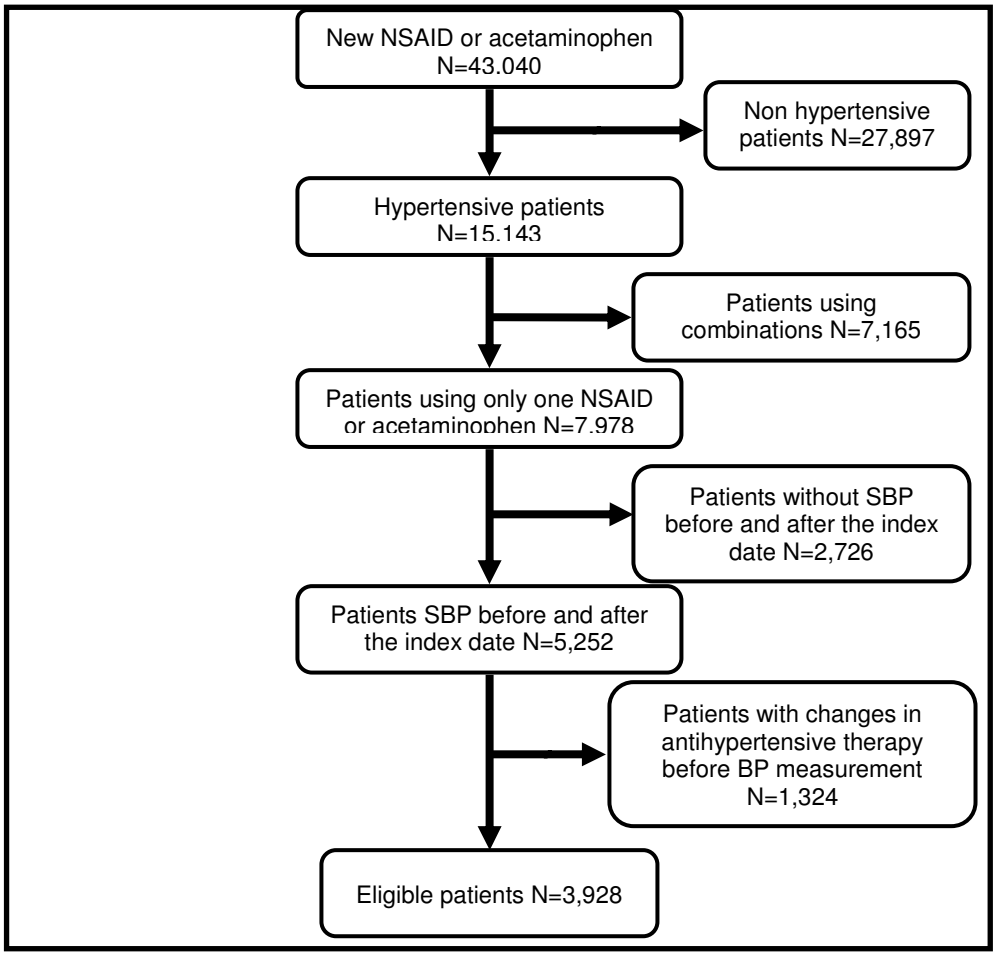
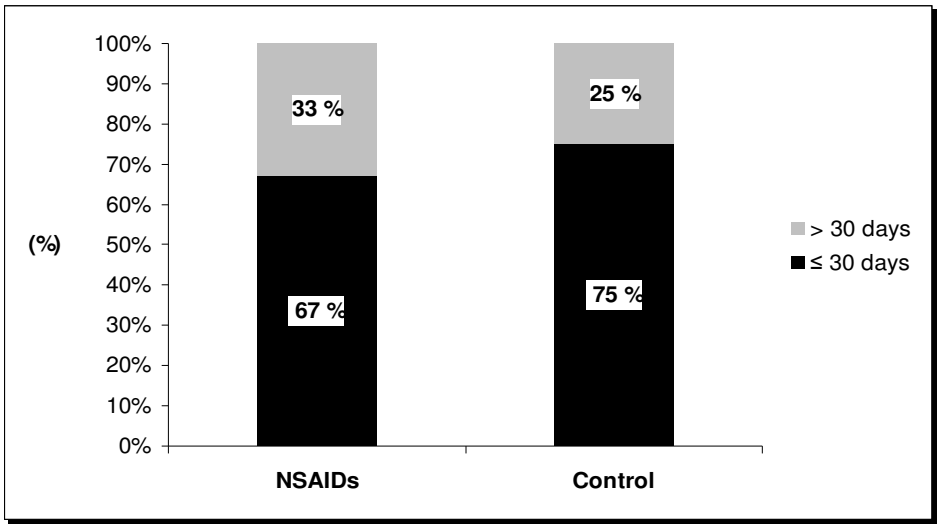


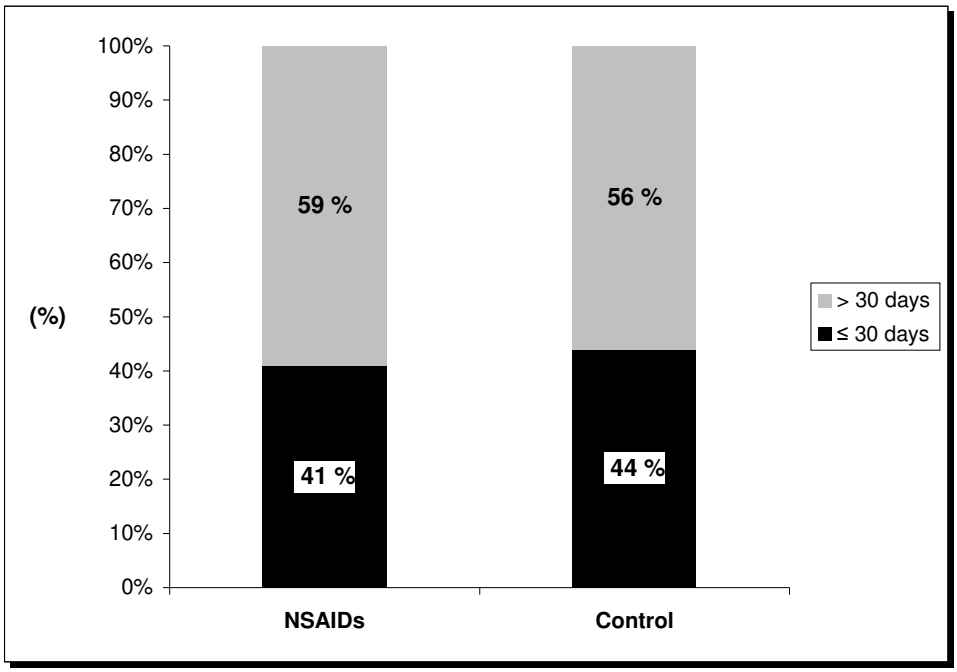
Figure 16. Percentage of Subjects in each Category of Time from Baseline Systolic Blood Pressure Measurement to Index Date by Index Drug



*** P-value <0.001 for comparison of frequency between NSAIDs and Control (N=3,928).**

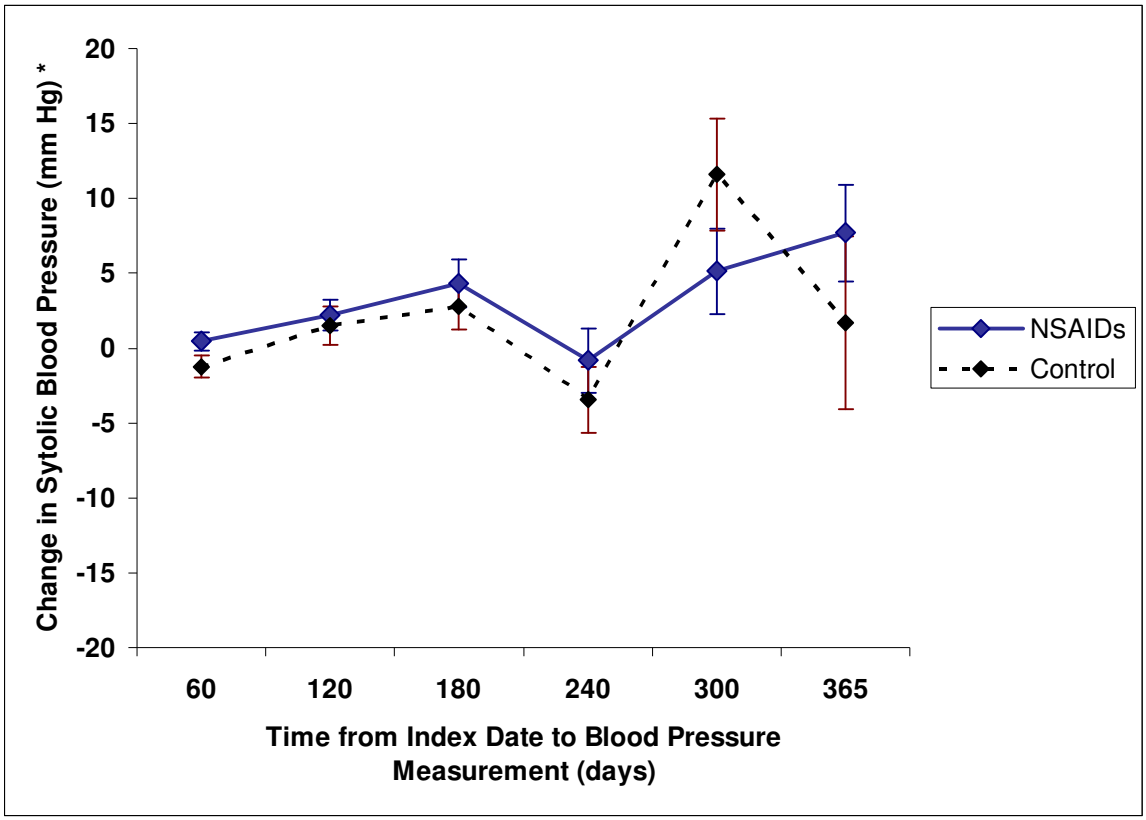
Time to blood pressure measurements was similar between NSAIDs and acetaminophen groups (P = 0.0773) (Figure 17). Forty two percent (n=1,650) of all subjects included in the study had their first systolic blood pressure measurement within 30 days after the index date. Changes in systolic blood pressure over time were similar between groups (Figure 18). The spikes in blood pressure at the end of the figure are due to the smaller sample sizes at later time points, which created greater fluctuation in the mean systolic blood pressure.

Figure 17. Percentage of Subjects in each Category of Time from Index Date to First Systolic Blood Pressure Measurement by Index Drug



*** P-value= 0.0773 for comparison of frequency between NSAIDs and Control (N=3,928).**

Figure 18. Mean Change in Systolic Blood Pressure by Time to First Blood Pressure Measurement



*** Change in systolic blood pressure = systolic blood pressure after index date – systolic blood pressure before index date (N=3,928).**
**** Each line connects between means of change in systolic blood pressure for each treatment group (error bar: ± standard error). P-value was ≥ 0.1 for comparison between NSAIDs and acetaminophen at each time point.**

Most baseline characteristics differed between the NSAIDs and acetaminophen groups (Table 6). Patients in the acetaminophen group were older and had higher baseline systolic blood pressure. Also, more patients in the acetaminophen group had renal insufficiency, congestive heart failure, and other comorbidities. It is therefore important to balance these covariates between the two groups before estimating the changes in blood pressure. In the first aim of this dissertation the association between NSAIDs and systolic blood pressure was compared to those who were prescribed acetaminophen.

Results for Aim 1

The association between NSAIDs and Blood Pressure Compared to Acetaminophen in Patients with Hypertension

A total of 2,680 patients using NSAIDs or acetaminophen were matched (1,340 patients from each group). Matching on propensity scores resulted in balanced covariates between the two groups (Table 7). The standardized difference and bias were reduced in 33 of the 37 variables. Although four variables had an increase in bias after matching, none of the variables were statistically different between the two groups.

Systolic blood pressure rose by 2 mmHg in patients who were prescribed NSAIDs compared to acetaminophen (95% confidence interval, 0.7 to 3.3; P = 0.004; N=2,680) (Table 8). The results were similar when using the first or the average systolic blood pressure as the dependent variable. Since several blood pressure measurements were used to calculate the average blood pressure, the standard error was smaller and as such, the estimate was more accurate. Compared to acetaminophen, a prescription for NSAID was not associated with clinically important increase in systolic blood pressure (defined as increase by at least 20 mmHg) (odds ratio, 1.17; 95% confidence interval, 0.96 to 1.43; P = 0.127). Patients who were prescribed an ACE-I, beta-adrenergic blocker, or a CCB had an increase in blood pressure associated with NSAID prescription. Compared to acetaminophen, a prescription for NSAID was associated with a 2.8 mmHg increase in average systolic blood pressure in patients who were prescribed an ACE-I (95% confidence interval, 0.2 to 5.4; P = 0.035; N=768), and a 5.5 mmHg increase in those prescribed

a beta-adrenergic blocker (95% confidence interval, 1.4 to 9.6; P = 0.008; N=340), and a 3.2 mmHg increase in those prescribed a CCB (95% confidence interval, 0.6 to 5.7; P = 0.014; N=804). However, the increase in systolic blood pressure associated with NSAIDs in patients prescribed ACE-I or CCB was observed only in the average but not in the first systolic blood pressure analysis (Table 8). There were no statistically significant changes in systolic blood pressure associated with a prescription for NSAIDs in those prescribed a diuretic.

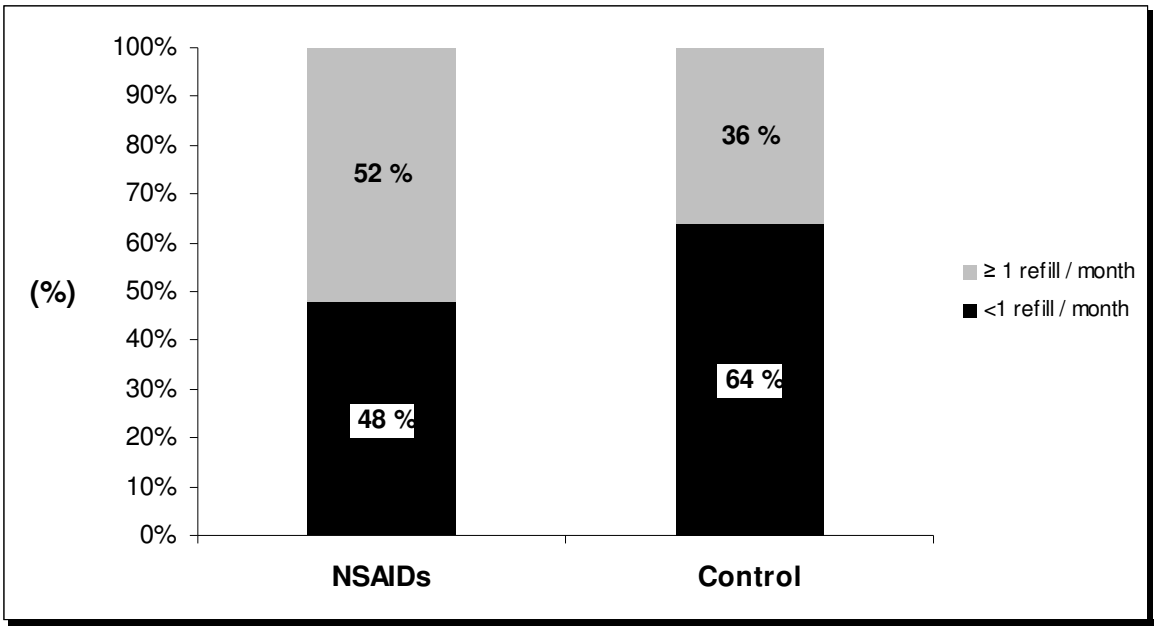
A prescription for NSAIDs in patients who were prescribed combinations of antihypertensive medications was not associated with statistically significant changes in systolic blood pressure (Table 9). However, there was an increase in systolic blood pressure at alpha less than 0.1 in the combination of BB and ACE-I. Compared to acetaminophen, a prescription for NSAID was associated with a 7.5 mmHg increase in systolic blood pressure in patients who were prescribed both BB and ACE-I (95% confidence interval, – 1.0 to 16.0; P = 0.084; N=108).

Sensitivity Analysis of Exposure to the Index Drug

Patients prescribed acetaminophen were more likely to have less than one refill per month compared to the NSAIDs group (P <0.001) and they were also more likely to have a MPR less than 20% (P <0.001) (Figures 19 and 20). Table 10 shows the result of the sensitivity analysis for the MPR and refills per month. The estimate of change in systolic blood pressure was not altered appreciably by changing the definitions of the MPR categories or refills per month. Therefore, the MPR was

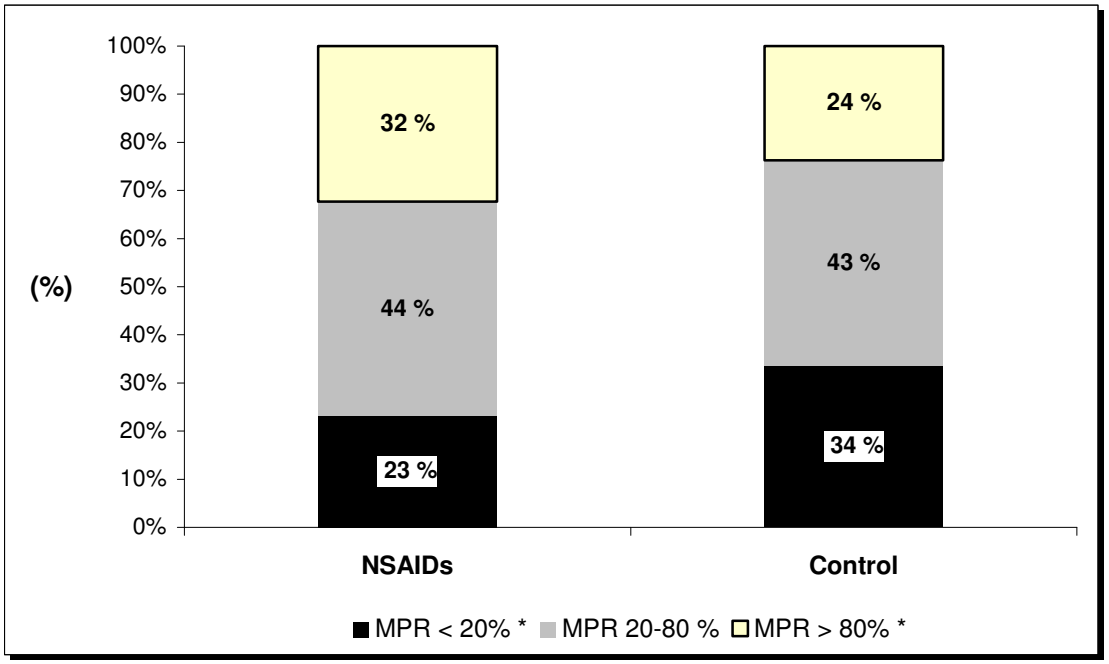
included in the same three categories (<20%, 20% – 80%, >80%) and the refills per month in one category of one or more refills per month.

Figure 19. Percentage of Subjects in each Refill per Month Category by Index Drug



*** P-value <0.001 for comparison of frequency between NSAIDs and Control. N=3,928.**

Figure 20. Percentage of Subjects in each Medication Possession Ratio (MPR) Category by Index Drug



*** P-value <0.001 for comparison of frequency between NSAIDs and Control. N=3,928.**

In addition to the above two variables included to control for drug exposure, another sensitivity analysis was conducted that included only those patients who had a blood pressure measurement within 30 days after the index date. Forty two percent of patients had blood pressure measurements within 30 days after the index date. After propensity score matching, the result remained significant (systolic blood pressure estimate, 2.7 mmHg; 95% confidence interval, 0.55 to 4.89; P = 0.01).

Summary

Compared to acetaminophen, NSAID prescription was associated with a moderate increase in systolic blood pressure of 2 mmHg in patients with hypertension. Also, a prescription for NSAID was associated with a 3 mmHg increase in systolic blood pressure in patients who were prescribed ACE-I or CCB, and a 6 mmHg increase in those prescribed beta-adrenergic blockers. However, no statistically significant change in blood pressure was associated with NSAIDs in patients prescribed various combinations of two or more antihypertensive medications. In conclusion, prescribing NSAIDs was associated with a small increase in blood pressure in hypertensive patients compared to acetaminophen.

Results for Aim 2

Effects of Specific NSAIDs on Blood Pressure

A. Ibuprofen compared to naproxen:

A total of 1,808 patients prescribed ibuprofen (n=1,313) or naproxen (n=495) met the inclusion criteria and had at least one blood pressure measurement before and after the index date. Most baseline characteristics were similar between patients in the ibuprofen and naproxen groups (Table 11). However, some baseline variables were imbalanced, including race, baseline blood pressure, time from baseline blood pressure to the index date, year of the index date, diagnosis of renal insufficiency, adherence to antihypertensive medications, and exposure to the index drug. More than 95% (n=472) of patients prescribed naproxen were matched to patients prescribed ibuprofen. Matching on propensity scores resulted in balanced covariates between the two treatment groups (Table 11).

Compared to naproxen, a prescription for ibuprofen was associated with a 2.5 mmHg increase in average systolic blood pressure (95% confidence interval, 0.5 to 4.6; P = 0.015). Compared to naproxen, ibuprofen was associated with clinically important increase in systolic blood pressure (defined as increase by at least 20 mmHg) (odds ratio, 1.57; 95% confidence interval, 1.10 to 2.25; P = 0.014). The absolute risk in the ibuprofen group was 20.6% and in the naproxen was 14.6% and the calculated number needed to harm was twelve patients. Compared to naproxen, a prescription for ibuprofen was associated with a 5.9 mmHg increase in average systolic blood pressure in patients who were prescribed a beta-adrenergic blocker

(95% confidence interval, 0.0 to 11.7; P = 0.049; N=130) (Table 12). A prescription for ibuprofen in patients who were prescribed various combinations of two or more antihypertensive medications was not associated with significant changes in systolic blood pressure (Table 13).

B. Ibuprofen compared to celecoxib:

A total of 1,456 patients were using celecoxib (n=143) or ibuprofen (n=1,313) and were included to compare changes in blood pressure between the two treatment groups. Twenty-four covariates at baseline were imbalanced between the celecoxib and ibuprofen groups (Table 14). Based on their propensity scores, 113 patients from the celecoxib group were matched to the same number of patients from the ibuprofen group. Table 14 shows that propensity score matching resulted in similar covariate distributions between the two treatment groups. A prescription for ibuprofen was associated with a 5.2 mmHg increase in average systolic blood pressure compared to celecoxib (95% confidence interval, 0.4 to 10.0; P = 0.035) (Table 15). Compared to celecoxib, ibuprofen was associated with a clinically important increase in systolic blood pressure (defined as increase by at least 20 mmHg) (odds ratio, 1.92; 95% confidence interval, 1.00 to 3.71; P = 0.050). The absolute risk in the ibuprofen group was 26.5% and in the celecoxib was 15.9% and the calculated number needed to harm was seven patients.

C. Celecoxib compared to naproxen:

Six hundred and thirty eight patients who were using celecoxib (n=143) or naproxen (n=495) were included in this analysis. One hundred and two patients from

the celecoxib group were matched to the same number of patients in the naproxen group. Matching on propensity scores resulted in balanced covariates between the two treatment groups (Table 16). A prescription for celecoxib was not associated with changes in systolic blood pressure compared to naproxen (change in systolic blood pressure, – 0.3; 95% confidence interval, – 5.1 to 4.5; P = 0.897) (Table 15). Compared to naproxen, celecoxib was not associated with a clinically important increase in systolic blood pressure (defined as increase by at least 20 mmHg) (odds ratio, 1.07; 95% confidence interval, 0.52 to 2.18; P = 0.855).

D. Dose of NSAID:

After propensity score matching, dose data were available for 54% (n=709) of patients who were prescribed ibuprofen and for 52% (n=258) of patients who were prescribed naproxen. The mean dose for ibuprofen was 2,053 mg (median was 2400 mg) and the mean dose for naproxen was 908 mg (median was 1000 mg). Since dose was not normally distributed, patients were stratified in low and high dose groups. Patients who were prescribed less than 75% of the maximum daily dose were included in the low dose category and those prescribed 75% or more were included in the high dose category. Prescription of a high dose of ibuprofen was not associated with significant changes in systolic blood pressure compared to a low dose (change in average systolic blood pressure, 2.3; 95% confidence interval, – 1.3 to 5.1; P = 0.3). Also, no significant change in blood pressure was associated with the prescription of naproxen in a high dose compared to a low dose (change in average systolic blood pressure, – 3.3; 95% confidence interval, – 9.6 to 3.1; P = 0.4).

E. Dose and adherence of NSAIDs:

The results did not change when a sensitivity analysis was conducted when the dose interaction with the MPR adherence was included in the model as a covariate. Similar to section “D” above, prescription of a high dose of ibuprofen was not associated with significant changes in systolic blood pressure compared to a low dose (change in average systolic blood pressure, 1.1; 95% confidence interval, – 2.1 to 4.4; P = 0.7). Also, prescribing a high dose of naproxen was not associated with significant changes in systolic blood pressure compared to a low dose (change in average systolic blood pressure, – 2.4; 95% confidence interval, – 9.0 to 4.2; P = 0.7).

Summary

Compared to naproxen, ibuprofen was associated with an increase in systolic blood pressure by approximately 3 mmHg. Also, a prescription for ibuprofen was associated with a 6 mmHg increase in systolic blood pressure in patients who were prescribed beta-adrenergic blockers. In addition, ibuprofen was associated with clinically important increase in systolic blood pressure compared to naproxen. The use of combinations of two or more antihypertensive medications was not associated with significant changes in blood pressure between naproxen and ibuprofen. Compared to celecoxib, ibuprofen was associated with a systolic blood pressure increase of 5 mmHg. No significant changes in blood pressure were found when comparing patients prescribed celecoxib to those prescribed naproxen. Neither ibuprofen nor naproxen demonstrated a dose effect. In conclusion, naproxen and

celecoxib were associated with a lower blood pressure increase compared to ibuprofen.

Results for Aim 3

The association between NSAIDs and Changes in Antihypertensive Therapy

More patients were eligible for this aim since they were not required to have had a blood pressure measurement after the index date. A total of 6,849 patients prescribed NSAIDs (n=3,740) or acetaminophen (n=3,109) were eligible for inclusion in the analysis. Propensity scores were computed and 2,494 patients in the NSAID group were matched to the same number of patients in the acetaminophen group. Twenty nine of the 37 variables were imbalanced between the two groups before matching. After matching on propensity score, all variables were similar between the two groups except age (P = 0.008) and the diagnosis of coronary artery disease or history of myocardial infarction (P = 0.025) (Table 17). Therefore, these two imbalanced variables were included in the logistic regression model after propensity score matching.

Change in antihypertensive therapy was defined as adding new antihypertensive medication from another class or increasing the dose of a current antihypertensive medication. Compared to acetaminophen, the prescribing of NSAIDs was not associated with a change in antihypertensive therapy (odds ratio, 0.95; 95% confidence interval, 0.84 to 1.08; P = 0.4).

The association with change in antihypertensive therapy was compared between ibuprofen and naproxen. Eight hundred and seventy seven patients were prescribed naproxen and 2,227 were prescribed ibuprofen. More than 92% (n=805) of those in the naproxen group were matched based on their propensity scores to the same number of patients in the ibuprofen group. All covariates were balanced after matching (Table 18). A prescription for naproxen was not associated with statistically significant changes in antihypertensive therapy compared to ibuprofen (odds ratio, 1.06; 95% confidence interval, 0.84 to 1.33; P = 0.7).

The effect of celecoxib on change in antihypertensive therapy was compared to ibuprofen and naproxen. One hundred sixty eight patients in celecoxib group were matched based on their propensity scores to the same number of patients in the ibuprofen group. A prescription for ibuprofen was not associated with statistically significant changes in antihypertensive therapy compared to celecoxib (odds ratio, 1.44; 95% confidence interval, 0.74 to 2.82; P = 0.3). One hundred sixty seven patients in celecoxib group were matched based on their propensity scores to the same number of patients in the naproxen group. A prescription for naproxen was not associated with statistically significant changes in antihypertensive therapy compared to celecoxib (odds ratio, 1.56; 95% confidence interval, 0.79 to 3.11; P = 0.2). Thus, prescription for NSAID was not associated with changes in antihypertensive therapy.

V. DISCUSSION

Summary of the Results

This research examined changes in blood pressure after starting NSAIDs in patients with hypertension. Compared to acetaminophen, a prescription for an NSAID was associated with a small increase (2 mmHg) in systolic blood pressure in patients with hypertension. However, a prescription for an NSAID was not associated with clinically important increase in systolic blood pressure compared to acetaminophen (odds ratio, 1.17; 95% confidence interval, 0.96 to 1.43; P = 0.127). A prescription for NSAID was associated with a 3 mmHg increase in average systolic blood pressure in patients who were also prescribed ACE-I or CCB, and a 6 mmHg increase in those prescribed a beta-adrenergic blocker. The change in blood pressure was not statistically significant in patients prescribed diuretics or most combinations of multiple antihypertensive medications. A large increase in systolic blood pressure (7 mmHg) was observed in the combinations of beta-adrenergic blockers with other antihypertensive medications; however this increase was not statistically significant.

For the second aim, ibuprofen was found to be associated with a 3 mmHg increase in systolic blood pressure compared to naproxen. Also, ibuprofen was associated with a 6 mmHg increase in systolic blood pressure in patients who were prescribed beta-adrenergic blockers. The use of various combinations of two or

more antihypertensive medications was not associated with significant changes in blood pressure between naproxen and ibuprofen. Compared to celecoxib, prescription for ibuprofen was associated with a 5 mmHg increase in systolic blood pressure (P = 0.035). A prescription for ibuprofen was associated with a clinically important increase in systolic blood pressure compared to naproxen or celecoxib (odds ratio, 1.57, P = 0.014; and odds ratio, 1.92, P = 0.050, respectively). The difference in blood pressure for patients prescribed celecoxib was not significantly different from those prescribed naproxen. There was no evidence of a dose-response effect with ibuprofen or naproxen.

For the third aim, prescription of NSAIDs was not associated with changes in antihypertensive therapy compared to acetaminophen. Patients prescribed ibuprofen, naproxen, and celecoxib had a similar probability of change in antihypertensive treatment.

Interpretation of the Results

Studies of medication safety often seek causal relationships between a drug and an adverse effect. Observational studies designed to investigate adverse drug effects demonstrate association, not causation. Several covariates other than prescription of the medication could explain a particular adverse effect. Investigators attempt to control for these covariates in the design and analysis stages; however, some important covariates are unknown or data are unavailable.

Bradford Hill's criteria remain among the best general guidelines for causal inference (140). When interpreting the results of this study the causality criteria need

to be considered. The cohort design of this study satisfies temporal relationship criterion, as blood pressure was measured after patients were started on NSAIDs. In contrast, some previous studies investigating the association between NSAIDs and the incidence of hypertension were conducted using a cross-sectional design. A problem with that design is that it might not satisfy the temporal criterion because a patient might have started the medication after the outcome had already occurred. It is more convincing that the association is causal when a biological mechanism exists for the adverse effect. Biological mechanisms explain most of the adverse effects observed in this study. For example, NSAIDs' inhibition of PGs can explain some of their effects on blood pressure in patients prescribed a beta-adrenergic antagonist.

This current research shows that NSAIDs are associated with increased blood pressure compared to acetaminophen in patients with hypertension. Although results were conflicting, previous studies suggested that acetaminophen was associated with blood pressure increase (26, 27, 102, 103). If blood pressure truly increases with acetaminophen, then the blood pressure increases observed in this research with NSAIDs is underestimated.

The blood pressure increase associated with NSAIDs was greater in patients prescribed a beta-adrenergic antagonist than other antihypertensive medications. The reason for this variation in blood pressure among antihypertensives could be related to the degree of PGs inhibition and the differences among these medications in the antihypertensive mechanism. The blood pressure increase in patients taking NSAIDs and beta-adrenergic antagonists is consistent with the findings of two other

studies (10, 11). Similar to the current results, one meta-analysis reported a 6 mmHg increase in blood pressure in patients who were stable on beta-adrenergic antagonists and started NSAIDs (10). Another short-term clinical trial included patients who were taking propranolol and found that NSAIDs were associated with a 7 mmHg increase in diastolic blood pressure (11). A proposed mechanism to explain this effect with beta-adrenergic antagonists is that inhibition of PGs by NSAIDs could increase sensitivity to the vasoconstrictor effects of sympathetic nervous system stimulation. Blocking beta receptors increases this sensitivity to the sympathetic nervous system, resulting in abolishment of the blood pressure lowering effect of beta-adrenergic antagonists (68). In addition, some beta- adrenergic antagonists reduce GFR and thus renal function (141). In the long-term, this could increase the sensitivity to blood pressure increase by NSAIDs.

The blood pressure increase with NSAIDs in ACE-I users agrees with previous studies that reported a 5 to 10 mmHg increase in systolic blood pressure (13, 14, 16, 39). NSAIDs' inhibition of PGs is the mechanism proposed explaining the loss of blood pressure lowering effect of ACE-I. Because PGs may mediate a component of the antihypertensive effect for ACE-I, NSAIDs' inhibition of PGs could disrupt the blood pressure control achieved by ACE-I (14, 42, 65). Patients with diabetes mellitus who are diagnosed with hypertension are more likely to use ACE-I than other antihypertensive medications to preserve their kidneys and prevent nephropathy. Treatment of hypertension should intensify if a patient has diabetes mellitus (93); therefore, it is important to monitor blood pressure closely in diabetic patients who are prescribed NSAIDs to ensure adequate blood pressure control.

This study found an increase in blood pressure with NSAIDs in patients who were taking CCBs. In previous studies, blood pressure did not increase with NSAIDs in those who were stable on CCBs (13, 35, 36, 39). One explanation for this contradicting result is that previous studies did not detect this effect because of small study sample size. Another explanation is variability in the estimated true difference as this increase was observed only with the average but not first systolic blood pressure.

The current study found no significant changes in blood pressure in those patients who were stable on diuretics. In two randomized clinical trials, the addition of ibuprofen did not affect blood pressure control with thiazides (33, 34). Current hypertension guidelines recommend starting patients on thiazide diuretics because they are associated with better clinical outcomes and fewer mortalities than other antihypertensive medications (19). In addition, diuretics are less expensive than other antihypertensive medications. Thus, diuretics are recommended to control blood pressure in hypertensive patients who need to be started on NSAIDs.

No statistically significant changes in systolic blood pressure were associated with a prescription for NSAID in patients who were prescribed multiple antihypertensive medications. However, insignificant increases were found with combinations with beta blockers and ACE-I. Previous studies did not examine the combination of antihypertensive medications. In the current study, a minimum sample size of 138 was needed to detect large effect size difference (105). Because some of the combinations with beta-adrenergic blockers involved only small number

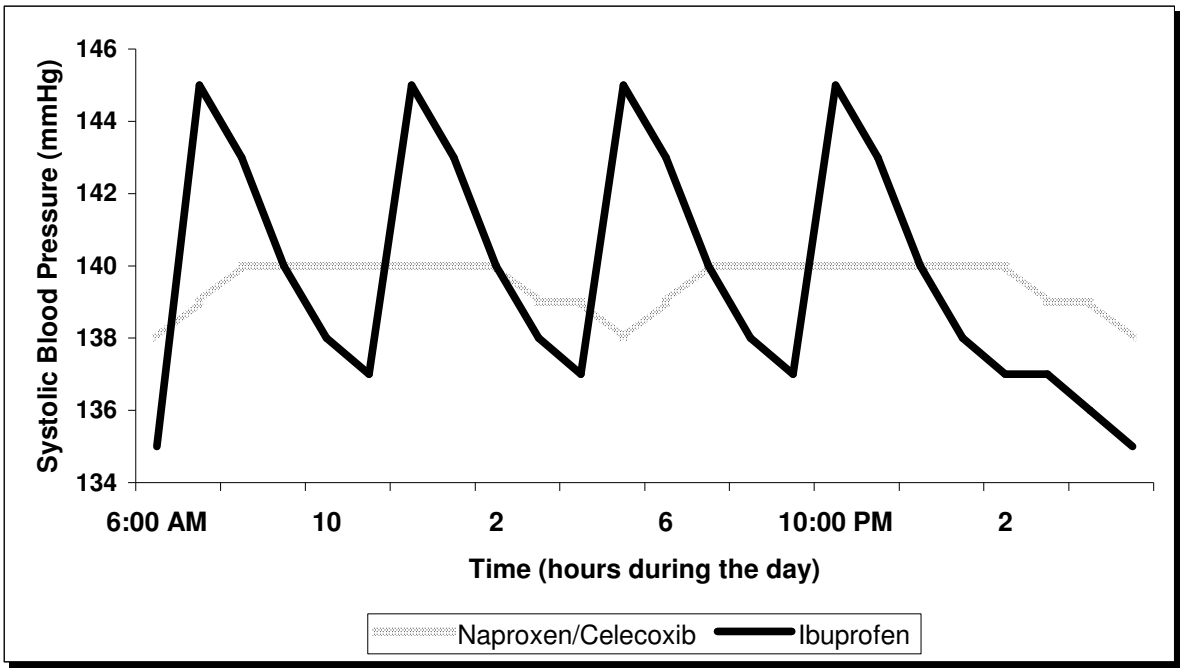
of patients, it is possible that this study was not statistically powered to detect small effects.

The results of this study show that ibuprofen was associated with blood pressure increase compared to naproxen and celecoxib. A clinical trial that included 97 hypertensive patients who were taking hydrochlorothiazide observed a smaller increase in diastolic blood pressure in naproxen users (1.8 mmHg) compared to ibuprofen users (2.6 mmHg) (12). Previous studies have shown that celecoxib was not associated with an increased risk of hypertension (29, 70, 71, 79) or increased blood pressure (3, 40-43, 75, 76).

The difference between ibuprofen and naproxen could be due to the fact that a lower concentration of ibuprofen than naproxen is needed to inhibit COX-1 and COX-2 (142). Thus, doses are not likely comparable between naproxen and ibuprofen relative to COX enzyme inhibition. An explanation for the blood pressure increase with ibuprofen compared to naproxen or celecoxib is related to the frequency of dosing. Naproxen and celecoxib is often taken only twice daily while ibuprofen is taken four times daily; assuming that patients take their NSAIDs during the day (e.g. from 6 am to 9 pm) this may lead to greater spikes in blood pressure during the day with ibuprofen (Figure 21). These spikes in blood pressure would more likely be captured with clinic measurement of blood pressures such as those used in this study. Thus, blood pressure will be higher if it is measured at times during the day when the concentration of ibuprofen is high. A study reported that ibuprofen (short-acting NSAID) was associated with systolic and diastolic blood

pressure increase while piroxicam (long-acting NSAID) was not associated with changes in blood pressure (72).

Figure 21. Blood Pressure Fluctuation Over 24 Hours Based on Dosing Frequency of NSAIDs



*** Peaks are more likely with four times daily dosing of naproxen and celecoxib (at 6 am, 11 am, 4 pm, and 9 pm) compared to twice daily dosing of ibuprofen (at 6 am and 6 pm).**

No dose effects were found for ibuprofen or naproxen. This may be explained by a lack of NSAID dose effect on blood pressure, the prescribed dose differed from the dose patients actually took, or patients prescribed a high dose experienced adverse effects, and could have stopped taking the drug temporarily or permanently. This study shows that the prescription of NSAIDs was not associated with an increased risk of changes in antihypertensive therapy. One explanation is that it may take a long time for these small effects to be clinically significant before physicians adjust the antihypertensive therapy.

Clinical Significance and Implications

Hypertension is a prevalent cardiovascular disease. In the United States about 73 million people, or one in three, have high blood pressure (21). Blood pressure is only controlled in 35% of hypertensive patients (21). Poor blood pressure control increases morbidity and mortality, utilization of healthcare resources, and, ultimately, health care costs. In addition to other factors, the use of medications such as NSAIDs increases the risk of uncontrolled blood pressure.

This research examined changes in blood pressure after starting an NSAID in patients with hypertension. The blood pressure increase associated with NSAIDs found in this study was small. In the long-term, small changes in blood pressure have important clinical and public health impacts. For example, decreasing systolic blood pressure by just 2 mmHg reduces stroke mortality by 10% and ischemic heart disease mortality by 7% (24). It stands to reason that a similar increment in blood pressure could result in the same percentage increase in adverse events. However, in the short-term this research found that a prescription for an NSAID was not associated with clinically important systolic blood pressure increase (defined as increase by at least 20 mmHg) or changes in antihypertensive therapy compared to acetaminophen. This should be interpreted in the light of possible increase in blood pressure with acetaminophen. Although results were conflicting, previous studies suggested that acetaminophen was associated with blood pressure increase (26, 27, 102, 103). If blood pressure truly increases with acetaminophen, then blood pressure increase observed in this research with NSAIDs would be underestimated.

In the current research, ibuprofen was associated with an increase in blood pressure, but naproxen and celecoxib were not. This increase with ibuprofen was clinically important (systolic blood pressure increase by at least 20 mmHg). Patients prescribed ibuprofen, naproxen, and celecoxib had similar probability of change in antihypertensive treatment. Therefore, naproxen is a good option for patients who need NSAIDs and celecoxib for those at higher risk for adverse gastrointestinal effects. Before prescribing any new medication, it is important to consider both the benefits and adverse effects. Risks associated with NSAIDs need to be considered, including blood pressure increase, adverse cardiovascular effects, and gastrointestinal effects. For each patient, these adverse effects need to be balanced against the benefits of using these medications. To reduce adverse events, patient may participate in the decision to initiate treatment with NSAIDs so that they understand their risks. Patients should not take over the counter NSAIDs without consulting a health care provider. In addition, patients started on NSAIDs may need to self-monitor their blood pressure.

Limitations

This study has limitations that should be considered when interpreting the results. Patients included in this study came from a single health system and may not represent other practices. Hence, this study should be replicated in other settings and with different patients. Since this study used propensity score matching, risk factors for the increased blood pressure associated with NSAIDs were controlled and, as such, not investigated.

This research did not control for factors such as dietary sodium intake, physical activity, or alcohol consumption. These factors could affect blood pressure by 2 to 9 mmHg (19). This research captured adherence to medications by using refill adherence. Although the use of MPR refill adherence was validated in previous studies, it measures possession of medications by the patient and may not reflect what the patient is actually taking.

In this study, controlling for as-needed versus regular use of medications was challenging. Patients may use NSAIDs regularly or as needed, depending on the severity of their symptoms. Thus, it was difficult to know how the patients were actually taking their medications, even if physicians' instructions were collected. Nonetheless, the goal of this study was to determine whether blood pressure increase is associated with NSAIDs in patients from a general practice, who might use these medications as needed, regularly, or both. However, variation in drug exposure was controlled by including in the model both the MPR and the number of refills per month. In addition, the results did not change when sensitivity analysis was conducted that included only patients whose blood pressure was measured within 30 days after the index date.

Clustering of physicians was not considered in this study. Clustering occurs when the intervention is delivered similarly to subjects who are treated by the same health care professional (143). Not adjusting for clustering inflates the standard error, thus reducing the power of the study. Cluster adjustment is only needed when the intervention depends on the skills of the health care professional and the time spent in patient education, which could vary from one provider to another. When the

intervention involves the use of medications, the outcome of the study depends mainly on the medication used and patient factors (143). Hence, clustering is unlikely to have affected the results of this study as patients from similar general internal medicine clinics were included. Also, no specialty clinics such as hypertension or pain clinics were used. This ensured that patients received similar follow-up and blood pressure monitoring. In addition, blood pressure measurements were those performed at scheduled clinic visits as opposed to walk-in or urgent visits wherein other factors such as stress could affect blood pressure.

Propensity score matching was used to balance covariates at baseline. However, propensity score only balances the observed variables. Hence, the benefit gained from using the propensity score is dependent upon how well the relevant covariates were identified. In randomized studies, both observed and unobserved covariates have a greater likelihood of balance. The current research controlled for known covariates that affect the use of NSAIDs or blood pressure.

Suggestions for Future Research

Further studies are needed to confirm the results of this study and to answer questions related to the association between NSAIDs and blood pressure. Larger studies are needed to confirm the results of NSAIDs' effect on blood pressure in patients using combinations of antihypertensive medications. Future studies may compare the effects of NSAIDs to both a control group of non-users and acetaminophen group. Mechanisms explaining variations in the loss of the blood pressure lowering effect among antihypertensive medications need to be explored.

The effect of NSAIDs on blood pressure depends on the individual NSAIDs used. The mechanisms for these differences among NSAIDs are not clear.

It is unknown if the doses of antihypertensive medications affect the association between NSAIDs and blood pressure. Since the mechanism of NSAIDs' blood pressure increase is related to PG inhibition, those who are taking high doses of antihypertensive medications might be more sensitive to the blood pressure increase associated with NSAIDs. For example, one study found that the effect of NSAIDs on the diuretic response of furosemide depends on the dose of the diuretics (144).

Summary and Conclusions

The first aim of the current research was to compare the effect of NSAIDs on blood pressure to acetaminophen in hypertensive patients. NSAIDs, compared to acetaminophen, were associated with a 2 mmHg increase in systolic blood pressure. The systolic blood pressure increase was 3 mmHg in a sub-sample of those who were prescribed ACE-I or CCB and 6 mmHg in those prescribed a beta-adrenergic blocker. No statistically significant change in blood pressure was associated with NSAIDs in patients prescribed diuretics or combinations of multiple antihypertensive medications.

In the second aim of comparing the effect of various NSAIDs on blood pressure, ibuprofen was associated with a systolic blood pressure increase, compared to both naproxen and celecoxib, of 3 and 5 mmHg, respectively. Compared to naproxen, ibuprofen was associated with a systolic blood pressure

increase in those prescribed beta-adrenergic blockers by 6 mmHg. The third aim of this research was to examine changes in antihypertensive therapy after starting NSAIDs. No statistically significant changes in antihypertensive therapy were found in NSAIDs users.

The increase in systolic blood pressure associated with NSAIDs is small when compared to acetaminophen and may not affect a physician's decision to change antihypertensive therapy from one visit to another. However, ibuprofen was associated with a greater risk for systolic blood pressure increase by at least 20 mmHg compared to naproxen. In the long term this change could be associated with significant comorbid consequences. For example, one study found that decreasing systolic blood pressure by just 2 mmHg lowers stroke mortality by 10% and ischemic heart disease mortality by 7% (24). For hypertensive patients who need NSAIDs, diuretics could be used to control blood pressure. Further studies are needed to confirm the results of this study.

APPENDICES

Appendix A. Tables

Table 1 . Summary of Short-term Trials Examining the Effect of NSAIDs on Blood Pressure

Author	Year	NSAID/Dose	Antihypertensive	Sample size & population	Design	Duration	Main results	
							SBP (mmHg)	DBP or MAP* (mmHg)
Lopez-ovejero JA(11)	1978	IND 200mg	Chlorthalidone/ HCTZ or Propranolol	N=26 with HTN	---	1 week	---	IND ↑ 7.3 in Propranolol
Koopmans PP (145)	1984	IND 50mg, NAP 250mg, or SUL 200mg	HCTZ 50mg	N=10 with HTN	CO.	4 weeks	↔	↔
Cinquegrani MP(73)	1986	IND 200 mg or Placebo	Intravenous hydralazine	N=9. Healthy volunteers.	R. DB. CO.	24 hours	↔	MAP: IND ↓ 4 vs. placebo ↓9
Koopmans PP(146)	1987	IBU 400mg x3, DIC 25mg x3, SUL 200mg x2	HCTZ 50mg	N=8 with HTN	CO.	28 weeks	↔	↔
Radack KL(32)	1987	IBU 400 mg x3, Acetaminophen 1 gm x3, or Placebo	Controlled with at least 2 antihypertensives	N= 45 with HTN.	R. DB.	3 wks	IBU ↑ 6.8 Placebo ↓ 3.7	IBU ↑ 5.3 Placebo ↓ 1.1
Davies JG(33)	1988	IBU 400 mg x4	Propranolol or Bendrofluazide	N=10 with HTN.	R. DB. CO.	4 weeks	↔	↔
Wright JT(34)	1989	IBU 800 mg x4, or placebo	HCTZ	N=12 African American women with HTN.	R. DB. CO.	8 days	↔	↔
Klassen D(12)	1993	IBU 800 mg x3 NAP 375mg x2	HCTZ	N=97 with HTN.	R. DB. MC.	4 wks	↔	IBU ↑ 2.6 NAP ↑ 1.8
Polonia J(13)	1995	IND 25 mg x3	Enalapril or Nifedipine	N=18 with HTN.	R. CO.	1 week	IND ↑ 6.8 in Enalapril group.	IND ↑ 4.6 in Enalapril group.
Houston MC(35)	1995	IBU 400 mg x3. NAP 250 mg x2. Or placebo	Verapamil.	N=162 with HTN	R. MC. DB.	3 weeks	↔	↔
Klassen DK(36)	1995	NAP 375 mg x2 Or Placebo	Nicardipine	N=100 with HTN	R. MC. DB	4 weeks	↔	↔
Gurwitz JH(37)	1996	IBU 600 mg x3 Or placebo	HCTZ	N=22, >60 yrs. With HTN.	R. DB. CO.	4 weeks	IBU ↑ 5	↔
Murray MD(72)	1997	IBU 800 mg x3, PIR 20mg, SUL 200 mg x2.	None	10 young, 14 elderly, and 14 elderly with renal insufficiency	R, three-way, CO.	36 days	IBU vs. SUL ↑ by 10	IBU vs. SUL ↑ by 6.0
Olsen ME(38)	1999	IND 50 mg x2 Or placebo	Losartan	N=10 with HTN.	R. CB. CO.	1 week	↔	↔
Morgan TO(39)	2000	IND 50 mg x2 Or placebo	Amlodipine or Enalapril	N=61 with HTN.	DB. CO.	3 weeks	IND ↑ 10 in Enalapril	↔
Whelton A(3)	2001	CEL 200 mg or ROF 25 mg	Various	N=810 ≥65yrs. With OA & HTN.	R, DB.	6 weeks	ROF ↑ 2.6 CEL ↓ 0.5	↔
Fogari R(14)	2002	IND 50mg x3 or placebo	Valsartan or Lisinopril	N=128 with uncontrolled HTN (DBP>100 mmHg)	R, CO, DB, MC.	2 weeks	IND ↑ in Lisinopril 5.45 ↑ 2.12 in Valsartan	IND ↑ in Lisinopril 3.22 ↑ in Valsartan 1.87
Whelton A(40)	2002	CEL 200 mg or ROF 25 mg	ACE-I, B-B, CCB, Diuretic.	N=1,092. > 65. With OA & HTN.	R. DB.	6 weeks	ROF ↑ 3 CEL ↓ 0.4	↔
Dilger K(75)	2002	CEL 200 mg x2 DIC 75 mg x2	None	N=24. 12 young and 12 elderly.	R. DB. CO.	2 weeks	↔	↔
Reitblat T(15)	2002	ROF 25 mg Namebutone 2000 mg for 1 wk then 1000 mg	ACE-I, B-B.	N=20. With OA & HTN.		4 weeks	ROF ↑ 15.7	ROF ↑ 8.5
White WB(41)	2002	CEL 200 mg x2 Or placebo	Lisinopril	N=178. With HTN	R. DB	4 weeks	↔	↔
Palmer R(42)	2003	IBU 800 mg x3, CEL 200 mg x2, nabumetone 1000 mg x2, or placebo	ACE-I	N=385. With HTN	R. MC.	4 weeks	↔	↔
Izhar M(16)	2004	CEL 200 mg Or DIC 75 mg x2	ACE-I	N=25. African American & Hispanic with OA & HTN	R. CO.	4 weeks	CEL ↑ 4 DIC ↑ 4	CEL ↑ 4 DIC ↑ 2
Sowers JR(43)	2005	CEL 200 mg ROF 25 mg NAP 500 mgx2	Various	N=404. With OA, HTN, and DM.	R. DB.	12 weeks	ROF ↑ 4	ROF ↑ 2
Hinz B(76)	2006	CEL 200 mg ROF 25 mg x2 DIC 75 mg x2	None	N=24. Healthy volunteers	R.	8 days	↔	↔

* DBP used unless otherwise stated. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial pressure; CEL: Celecoxib; ROF: Rofecoxib; IBU: Ibuprofen, DIC: Diclofenac; NAP: Naproxen; SUL: Sulindac; IND: Indomethacin; HTN: Hypertension, R: Randomized. DB: double-blind. MC: Multi-center CO: Crossover; OA: Osteoarthritis; DM: Diabetes mellitus; ACE-I: Angiotensin converting enzyme inhibitor; B-B: Beta-blocker; CCB: Calcium channel blocker; HCTZ: Hydrochlorothiazide; ↔ : No changes; ↑: Increase; ↓: Decrease.

Table 2 . Summary of Observational Studies Examining the Effect of NSAIDs on Blood Pressure

First author	Year	Drug	Sample size & population	Design/Methods	Main results
Chrischilles EA(77)	1993	NSAIDs	N=470. >65yrs.	Cross-sectional. Community based. Medication use recorded from label.	NSAIDs users were more likely to have SBP>140 mmHg (OR, 2.19; 95% CI, 1.33 - 3.61).
Johnson AG(25)	1993	NSAIDs	N=2,805. >60yrs. In Australia.	Cross-sectional. Community based.	Risk of HTN was higher in NSAIDs users (OR, 1.4; 95% CI, 1.1-1.7).
Gurwitz JH(78)	1994	NSAIDs	N=9,411 cases. New Jersey Medicaid.	Case-control. Adjusted for: age, gender, race, nursing home residence, number of prescriptions, intensity of physician utilization, and days hospitalized.	Risk of antihypertensive medications initiation was higher in NSAIDs users (OR, 1.66; 95% CI, 1.54-1.80).
Curhan GC(26)	2002	NSAIDs Aspirin Acetaminophen	N=80,020. Women who participated in Nurses' Health Study II. Age: 31-50yrs. No HTN.	Prospective. Drug use & diagnosis of HTN were self-reported.	HTN risk increased in NSAIDs users (RR, 1.86; 95% CI, 1.51-2.28) and acetaminophen users (RR, 2.0; 95% CI, 1.52-2.62)
Dedier J(27)	2002	NSAIDs Aspirin Acetaminophen	N=51,630. Women who participated in Nurses' Health Study. Age: 44-69yrs. No HTN.	Prospective. Drug use & diagnosis of HTN were self-reported.	HTN risk increased in aspirin users (RR, 1.21; 95% CI, 1.13-1.30), NSAIDs users (RR, 1.35; 95% CI, 1.25-1.46), and acetaminophen users (RR, 1.20; 95% CI, 1.08-1.33).
Kurth T(28)	2005	NSAIDs Aspirin Acetaminophen	N=8,229 healthy men physicians. Age 40-84 yrs.	Prospective. Drug use & diagnosis of HTN were self-reported.	No significant increase in HTN risk in users of, NSAIDs, aspirin, or acetaminophen groups
Cho J(70)	2003	ROF CEL	N=109.	Retrospective. Medical record review. Outcome: change in SBP after start of drugs.	ROF increased SBP by 4.76 mmHg compared to baseline (P = 0.04). CEL did not affect BP.
Nietert PJ(71)	2003	ROF CEL	N=960. >55yrs. With HTN	Retrospective. Using electronic medical record. Followed for 6 months.	No change in BP (defined: SBP>20, or DBP>15), or new class of HTN drugs.
Solomon DH(29)	2004	ROF CEL	N=3,915 cases. ≥65. Medicare.	Case control. 90 days exposure to COX-2 before HTN diagnosis.	Risk of HTN increased: ROF vs. CEL (OR, 1.6; 95% CI, 1.2-2.1) ROF vs. NSAIDs (OR, 1.4; 95% CI, 1.1-1.9)
Fredy J(79)	2005	ROF CEL	N=120. Native American from Indian Health Service.	Medical record review for patients switched from CEL to ROF. Simple paired t-test.	BP increased when switched from CEL to ROF: SBP: 2.9 mmHg (P = 0.02) & DBP: 1.5 mmHg (P = 0.04)
Yood MU(147)	2006	NSAIDs ROF CEL	N=23,562 cases.	Case control. Cases: started antihypertensive therapy. Recent users: prescription within 60 days.	Risk of starting antihypertensive therapy in recent users: NSAIDs: (OR=1.6, 95% CI 1.5-1.7) COX-2 inhibitors: (OR=1.8, 95% CI 1.6-2.1)
Wang J(30)	2007	NSAIDs CEL	N=54,444. Non-hypertensives.	Retrospective cohort. Using electronic medical record.	No changes in risk of HTN between CEL and NSAIDs (HR, 1.01; 95% CI, 0.86-1.19)

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CEL: Celecoxib; ROF: Rofecoxib; HR: Hazard Ratio; HTN: Hypertension; OR: Odds Ratio; RR: Relative Risk. CI: Confidence Interval.

Table 3. Baseline Characteristics by Treatment Group

Variable	NSAIDs (n=2,181) N (%)*	Acetaminophen (n=1,747) N (%)*
Age (yrs) mean (SD)	55 (13)	60 (14)
Gender:		
Female	1, 531 (70)	1,216 (70)
Male	650 (30)	531 (30)
Race:		
African American	1,264 (58)	1,093 (63)
White	817 (37)	599 (34)
Others	100 (5)	55 (3)
Baseline Systolic blood pressure (mmHg) mean (SD)	139 (22)	141 (24)
Diagnosis of:		
Osteoarthritis	487 (22)	397 (23)
Rheumatoid Arthritis	65 (3)	44 (3)
Renal insufficiency	60 (3)	145 (8)
Cirrhosis with Ascites	8 (0.4)	10 (1)
Systemic Lupus Erythematosus	19 (1)	10 (1)
Diabetes	611 (28)	603 (35)
Congestive Heart Failure	244 (11)	325 (19)
Coronary Artery Disease or Past History of Myocardial Infarction	288 (13)	333 (19)
Stroke	166 (8)	213 (12)
Arrhythmia	25 (1)	33 (2)
Asthma or Chronic Obstructive Pulmonary Disease	380 (17)	338 (19)
Medications:		
ACE-I or Angiotensin II blocker	779 (36)	758 (43)
Beta - Blocker	399 (18)	296 (17)
Calcium Channel Blocker	735 (34)	670 (38)
Diuretic	952 (44)	841 (48)
Other antihypertensive medications	157 (7)	203 (12)

* Total N=3,928. N (%) unless indicated as mean (Standard Deviation). Because of rounding it may not add to 100 %.

ACE-I: Angiotensin converting enzyme inhibitor;

Table 4. Number of Eligible Subjects at Baseline by Study Aim and Hypothesis

Aim	Hypotheses	Groups to compare (number of patients)
Aim 1 To examine the association between NSAIDs and blood pressure compared to acetaminophen group in patients with hypertension.	H1: Compared to acetaminophen, NSAIDs cause a greater increase in systolic blood pressure in patients receiving beta-adrenergic antagonists, diuretics, ACE-I or angiotensin II receptor antagonists, or combination of these antihypertensive drugs.	NSAIDs (N=2,181) vs. Acetaminophen (N=1,747) Number of antihypertensive medications used in both NSAIDs and acetaminophen: ACE-I/AIIA: 1,324; B-Blockers: 544 CCB: 1,193; Diuretics: 1,516
	H2: NSAIDs are not associated with an increase in systolic blood pressure in patients receiving CCBs compared to acetaminophen.	
	H3: Compared to acetaminophen, NSAIDs are not associated with an increase in systolic blood pressure in patients concomitantly receiving CCBs with drugs from other antihypertensive classes.	
Aim 2 To compare the effects of various NSAIDs on blood pressure in patients with hypertension.	H1: Ibuprofen, naproxen, and celecoxib do not differ in their propensity to increase systolic blood pressure.	Celecoxib (N=143) vs. Ibuprofen (N=1,313) OR Naproxen (N=495)
	H2: As the dose of ibuprofen or naproxen increases, the systolic blood pressure increases.	Dose: Ibuprofen (N=709), Naproxen (N=258)
	H3: In patients taking antihypertensive medications other than CCBs, the use of naproxen or ibuprofen is associated with an increase in systolic blood pressure.	Ibuprofen (N=1,313) vs. Naproxen (N=495) Number of antihypertensive medications used in both ibuprofen and naproxen: ACE-I/AIIA: 528; B-Blockers: 244 CCB: 515; Diuretics: 642
	H4: In patients prescribed CCBs, naproxen or ibuprofen will not be associated with increases in systolic blood pressure.	
	H5: In patients concomitantly receiving CCBs and antihypertensives from another class, naproxen or ibuprofen will not be associated with increases in systolic blood pressure.	
Aim 3 To examine the changes in antihypertensive therapy after starting NSAIDs.	H1: Compared to acetaminophen, NSAIDs increase the likelihood of adding a new antihypertensive medication or increasing the dose of a currently prescribed antihypertensive medication.	NSAIDs (N=3,740) vs. Acetaminophen (N=3,109)
	H2: Ibuprofen, naproxen, and celecoxib do not differ in the need to add a new antihypertensive medication or increase the dose of the current antihypertensive medication.	Celecoxib (N=193) vs. Ibuprofen (N=2,227) OR Naproxen (N=877)

ACE-I: Angiotensin converting enzyme inhibitor; AIIA: Angiotensin II antagonist; CCB: Calcium channel blocker; NSAIDs: Non-steroidal anti-inflammatory drugs;

Table 5. Type, Unit and Definition of Variables Included in the Statistical Models

Variable	Type	Unit	Definition
Dependent: Systolic blood pressure	Continuous	mmHg	The first systolic blood pressure value after the index date
Changes in antihypertensive therapy	Dichotomous	---	Increase in dose or starting of another antihypertensive medication
Independent: Age	Continuous	Years	Age at index date
Index drug	Dichotomous	---	NSAID or acetaminophen prescribed to patient
Gender	Dichotomous	---	Gender
Race	Categorical	---	Race categorized as African American, white, and others.
Medication adherence	Categorical	---	Calculated MPR = sum of the days' supply obtained / total days from first prescription until last fill.
Time to measurement of blood pressure	Categorical	Days	Number of days between index date and BP measurement
Time prior index date	Categorical	Days	Number of days from BP measurement until index date
Year	Categorical	Years	Year of index date
Systolic Blood Pressure before	Continuous	mmHg	Last systolic blood pressure value before the index date
Diagnosis of: Rheumatoid Arthritis Osteoarthritis Arrhythmia Myocardial Infarction Coronary artery disease Stroke Congestive heart failure Diabetes Asthma Chronic Obstructive Pulmonary Disease Renal insufficiency	Dichotomous	---	Clinical diagnoses before index date
Use of Medications: ACE-I Angiotensin II blocker Beta- Blocker CCB Diuretic Other antihypertensive medication Venlafaxine Oral contraceptive Oral high dose glucocorticoid*	Dichotomous	---	The use of each drug or drug class before index date

ACE-I: Angiotensin converting enzyme inhibitor; MPR: Medication Possession Ratio; BP: Blood pressure.
* High dose was defined as ≥10mg for prednisonse, ≥50mg for cortisone, and ≥1.5 mg for dexamethasone.

Table 6. Baseline Characteristics by Treatment Group

Variable	NSAIDs (n=2,181) N (%)*	Acetaminophen (n=1,747) N (%)*	P Value **
Age (yrs) mean (SD)	55 (13)	60 (14)	<.001
Gender:			
Female	1, 531 (70)	1,216 (70)	0.687
Male	650 (30)	531 (30)	0.687
Race:			
African American	1,264 (58)	1,093 (63)	0.003
White	817 (37)	599 (34)	0.040
Others	100 (5)	55 (3)	0.007
Baseline Systolic blood pressure (mmHg) mean (SD)	139 (22)	141 (24)	0.006
Time from baseline SBP to index date:			
≤ 7 days	1,166 (53)	1,137 (65)	<.001
> 7 days and ≤ 30 days	306 (14)	179 (10)	<.001
> 30 days	709 (33)	431 (25)	<.001
Year of index date:			
1993 - 1996	1,084 (50)	1,017 (58)	<.001
1997-2002	857 (39)	706 (40)	0.477
2002 - 2006	240 (11)	24 (1)	<.001
Diagnosis of:			
Osteoarthritis	487 (22)	397 (23)	0.768
Rheumatoid Arthritis	65 (3)	44 (3)	0.381
Renal insufficiency	60 (3)	145 (8)	<.001
Cirrhosis with Ascites	8 (0.4)	10 (1)	0.343
Systemic Lupus Erythematosus	19 (1)	10 (1)	0.277
Diabetes	611 (28)	603 (35)	<.001
Congestive Heart Failure	244 (11)	325 (19)	<.001
Coronary Artery Disease or Past History of Myocardial Infarction	288 (13)	333 (19)	<.001
Stroke	166 (8)	213 (12)	<.001
Arrhythmia	25 (1)	33 (2)	0.055
Asthma or Chronic Obstructive Pulmonary Disease	380 (17)	338 (19)	0.121
Medications:			
ACE-I or Angiotensin II blocker	779 (36)	758 (43)	<.001
Beta - Blocker	399 (18)	296 (17)	0.270
Calcium Channel Blocker	735 (34)	670 (38)	0.003
Diuretic	952 (44)	841 (48)	0.005

Variable	NSAIDs (n=2,181) N (%)*	Acetaminophen (n=1,747) N (%)*	P Value **
Other antihypertensive medications	157 (7)	203 (12)	<.001
Oral high dose glucocorticoid ***	17 (1)	24 (1)	0.068
Oral Contraceptive	16 (1)	16 (1)	0.528
Venlafaxine	17 (1)	6 (0.3)	0.075
Adherence to antihypertensive medications:			
MPR > 80%	1,510 (69)	1,293 (74)	0.001
MPR < 80%	287 (13)	209 (12)	0.262
Not using antihypertensive medications (reference)	384 (18)	245 (14)	0.002
Exposure to index drug:			
MPR > 80%	706 (32)	413 (24)	<.001
MPR 20-80 %	964 (44)	742 (43)	0.278
MPR < 20%	511 (23)	592 (34)	<.001
Number of refills per month:			
< 1	1,056 (48)	1,110 (64)	<.001
≥ 1	1,125 (52)	637 (36)	<.001

* Total N=3,928. N (%) unless indicated as mean (Standard Deviation). Because of rounding it may not add to 100 %.

** P-value of t-tests for continuous variables and chi-square tests for categorical variables.

*** High dose was defined as ≥10mg for prednisonse, ≥50mg for cortisone, and ≥1.5 mg for dexamethasone.

ACE-I: Angiotensin converting enzyme inhibitor; MPR: Medication Possession Ratio; SBP: Systolic blood pressure.

Table 7. Comparison of Covariate Balance between NSAIDs and Acetaminophen before and after Propensity Score Matching

Variable	Sample	NSAIDs*	Acetaminophen*	P Value**	Standardized Difference	Bias Reduction (%)
Age (yrs) mean	Unmatched	55	60	<.001	-42.0	
	Matched	56	57	0.119	-6.0	86%
Gender:						
Female	Unmatched	70	70	0.687	1.3	
	Matched	72	70	0.157	5.5	-323%
Race:						
African American	Unmatched	58	63	0.003	-9.4	
	Matched	63	61	0.353	3.6	62%
Others	Unmatched	5	3	0.007	7.5	
	Matched	4	3	0.837	0.8	89%
Baseline Systolic blood pressure (mmHg) mean	Unmatched	139	141	0.006	-8.8	
	Matched	140	140	0.949	-0.2	97%
Time from baseline SBP to index:						
≤ 7 days	Unmatched	53	65	<.001	-23.8	
	Matched	62	61	0.596	2.0	91%
> 7 days and ≤ 30 days	Unmatched	14	10	<.001	11.6	
	Matched	10	11	0.380	-3.4	71%
> 30 days	Unmatched	33	25	<.001	17.4	
	Matched	28	28	0.975	0.1	99%
Year of index date:						
1993 - 1996	Unmatched	50	58	<.001	-17.1	
	Matched	57	56	0.713	1.4	92%
1997-2002	Unmatched	39	40	0.477	-2.3	
	Matched	41	42	0.741	-1.3	44%
2002 - 2006	Unmatched	11	1	<.001	40.8	
	Matched	2	2	0.881	-0.6	99%
Diagnosis of:						
Osteoarthritis	Unmatched	22	23	0.768	-0.9	
	Matched	21	22	0.295	-4.0	-327%
Rheumatoid Arthritis	Unmatched	3	3	0.381	2.8	
	Matched	3	3	0.819	0.9	69%
Renal insufficiency	Unmatched	3	8	<.001	-24.5	
	Matched	4	4	0.922	0.4	98%
Cirrhosis with Ascites	Unmatched	0.4	1	0.343	-3.0	
	Matched	1	1	0.807	-0.9	69%

Variable	Sample	NSAIDs*	Acetaminophen*	P Value**	Standardized Difference	Bias Reduction (%)
Systemic Lupus Erythematosus	Unmatched	1	1	0.277	3.5	
	Matched	1	1	0.465	-2.8	20%
Diabetes	Unmatched	28	35	<.001	-14	
	Matched	28	31	0.124	-5.9	58%
Congestive Heart Failure	Unmatched	11	19	<.001	-20.9	
	Matched	14	14	0.651	-1.7	92%
Coronary Artery Disease or History of Myocardial Infarction	Unmatched	13	19	<.001	-16.0	
	Matched	14	15	0.266	-4.3	73%
Stroke	Unmatched	8	12	<.001	-15.4	
	Matched	9	9	0.784	-1.1	93%
Arrhythmia	Unmatched	1	2	0.055	-6.1	
	Matched	1	1	0.489	-2.7	56%
Asthma or Chronic Obstructive Pulmonary Disease	Unmatched	17	19	0.121	-5.0	
	Matched	18	19	0.420	-3.1	37%
Medications:						
ACE-I or Angiotensin II blocker	Unmatched	36	43	<.001	-15.7	
	Matched	37	38	0.594	-2.1	87%
Beta- Blocker	Unmatched	18	17	0.270	3.5	
	Matched	15	17	0.338	-3.7	-4%
Calcium Channel Blocker	Unmatched	34	38	0.003	-9.7	
	Matched	36	36	0.829	-0.8	91%
Diuretic	Unmatched	44	48	0.005	-9.0	
	Matched	46	45	0.921	0.4	96%
Other BP medications	Unmatched	7	12	<.001	-15.2	
	Matched	9	9	0.835	-0.8	95%
Oral high dose glucocorticoid***	Unmatched	1	1	0.068	-5.8	
	Matched	1	1	0.850	-0.7	87%
Oral Contraceptives	Unmatched	1	1	0.528	-2.0	
	Matched	1	1	0.998	0.0	100%
Venlafaxine	Unmatched	1	0.3	0.075	5.8	
	Matched	1	0.4	0.782	1.1	82%
Adherence to antihypertensive medications:						
MPR > 80%	Unmatched	69	74	<.001	-10.6	
	Matched	72	70	0.320	3.8	64%
MPR < 80%	Unmatched	13	12	0.262	3.6	
	Matched	12	13	0.159	-5.4	-51%

Variable	Sample	NSAIDs*	Acetaminophen*	P Value**	Standardized Difference	Bias Reduction (%)
Not using antihypertensives (reference group)	Unmatched	18	14	0.002	9.8	
	Matched	16	16	0.965	0.2	98%
Exposure to index drug:						
MPR > 80%	Unmatched	32	24	<.001	19.5	
	Matched	26	27	0.750	-1.2	94%
MPR 20-80 %	Unmatched	44	43	0.278	3.5	
	Matched	44	43	0.859	0.7	80%
MPR < 20%	Unmatched	23	34	<.001	-23.3	
	Matched	30	30	0.909	0.4	98%
Number of refills per month:						
≥ 1 refills	Unmatched	52	36	<.001	30.8	
	Matched	44	43	0.301	4.0	87%

* % unless indicated as mean. Because of rounding it may not add to 100 %.

** P-value of t-tests for continuous variables and chi-square tests for categorical variables.

*** High dose was defined as ≥10mg for prednisonse, ≥50mg for cortisone, and ≥1.5 mg for dexamethasone.

Standardized difference: 100 ($\overline{\chi}_{\text{treated}} - \overline{\chi}_{\text{control}}$)/$\sqrt{}$ {($s^2_{\text{treated}} + s^2_{\text{control}}$)/2}. A positive value means the treated group is higher in % (or mean) compared to the control group and negative value means the control is higher than the treated.

Bias reduction (%) =1- {|Standardized difference $_{\text{matched}}$| / | Standardized difference $_{\text{unmatched}}$ |} x 100. A positive value means bias is reduced by propensity score matching and negative means bias increased.

ACE-I: Angiotensin converting enzyme inhibitor; MPR: Medication Possession Ratio; SBP: Systolic blood pressure. Unmatched: all patients before propensity score matching, N=3,928 (2,181 NSAIDs and 1,747 acetaminophen). Matched: only matched patients, N=2,680 (1,340 in each group).

Table 8. Difference in Systolic Blood Pressure between NSAIDs and Acetaminophen after Propensity Score Matching

Sample	Dependent Variable*	Estimate of SBP (mmHg)**	95% Confidence Interval	P Value
All Patients (n=2,680)	First SBP	1.8	0.3 to 3.3	0.022
	Average SBP	2.0	0.7 to 3.3	0.004
ACE-I (n=768)	First SBP	2.8	-0.2 to 5.8	0.067
	Average SBP	2.8	0.2 to 5.4	0.035
CCB (n=804)	First SBP	2.5	-0.4 to 5.4	0.089
	Average SBP	3.2	0.6 to 5.7	0.014
BB (n=340)	First SBP	6.3	1.7 to 10.8	0.007
	Average SBP	5.5	1.4 to 9.6	0.008
Diuretics (n=1,022)	First SBP	0.2	-2.3 to 2.8	0.859
	Average SBP	1.3	-0.8 to 3.4	0.236

ACE-I: Angiotensin converting enzyme inhibitor; BB: Beta-blocker; CCB: Calcium channel blocker; SBP: Systolic blood pressure.

* First SBP is the first systolic blood pressure measurement after the index date. Average SBP is the average of all systolic blood pressure measurements after the index date and prior to any changes in the antihypertensive therapy.

** Estimate of SBP is the estimate difference between NSAIDs and acetaminophen after controlling for baseline SBP. A higher value means NSAIDs is associated with higher increase in systolic blood pressure compared to acetaminophen.

Table 9 . Difference in Systolic Blood Pressure between NSAIDs and Acetaminophen in Patients Using Combinations of Antihypertensive Medications after Propensity Score Matching

Sample	Dependent Variable*	Estimate of SBP (mmHg)**	95% Confidence Interval	P Value
CCB & ACE-I (n=202)	First SBP	1.1	-5.6 to 7.8	0.748
	Average SBP	3.1	-2.8 to 8.9	0.302
CCB & BB (n=104)	First SBP	4.0	-5.0 to 13.0	0.382
	Average SBP	6.0	-2.0 to 14.1	0.141
CCB & diuretics (n=328)	First SBP	1.6	-3.3 to 6.5	0.517
	Average SBP	3.5	-0.8 to 7.9	0.110
ACE-I & BB (n=108)	First SBP	7.5	-1.0 to 16.0	0.084
	Average SBP	6.7	-1.1 to 14.5	0.091
ACE-I & diuretics (n=366)	First SBP	1.0	-3.4 to 5.5	0.647
	Average SBP	1.2	-2.7 to 5.1	0.553
BB & diuretics (n=156)	First SBP	3.8	-3.9 to 11.5	0.330
	Average SBP	4.2	-2.8 to 11.3	0.237
CCB & ACE-I & diuretics (n=100)	First SBP	1.5	-7.9 to 10.8	0.757
	Average SBP	3.8	-4.9 to 12.4	0.391
BB & ACE-I & diuretics (n=42)	First SBP	6.8	-9.4 to 22.9	0.402
	Average SBP	5.4	-10.3 to 21.1	0.487

ACE-I: Angiotensin converting enzyme inhibitor; BB: Beta-blocker; CCB: Calcium channel blocker; SBP: Systolic blood pressure.

* First SBP is the first systolic blood pressure measurement after the index date. Average SBP is the average of all systolic blood pressure measurements after the index date and prior to any changes in the antihypertensive therapy.

** Estimate of SBP is the estimate difference between NSAIDs and acetaminophen after controlling for baseline SBP. A higher value means NSAIDs is associated with higher increase in systolic blood pressure compared to acetaminophen.

Table 10. Difference in Systolic Blood Pressure between NSAIDs and Acetaminophen in Sensitivity Analysis of Medication Possession Ratio and Refills per Month for Index Drug after Propensity Score Matching

MPR categories (%)*	Refills per month**	Estimate of SBP (mmHg)***	Standard Error	95% Confidence Interval	P Value
<20, 20 – 80, >80	----	1.8	0.783	0.3 to 3.3	0.02
<10, 10 – 80, >80	----	1.8	0.783	0.3 to 3.3	0.02
<30, 30 – 80, >80	----	1.8	0.784	0.3 to 3.4	0.02
<20, 20 – 70, >70	----	1.8	0.783	0.3 to 3.3	0.02
<20, 20 – 90, >90	----	1.8	0.783	0.2 to 3.3	0.02
<10, 10 – 70, >70	----	1.8	0.783	0.3 to 3.3	0.02
<10, 10 – 90, >90	----	1.8	0.783	0.2 to 3.3	0.02
<30, 30 – 70, >70	----	1.8	0.784	0.3 to 3.4	0.02
<30, 30 – 90, >90	----	1.8	0.785	0.3 to 3.3	0.02
<20, 20 – 80, >80	≥ 1, <1	1.7	0.783	0.2 to 3.3	0.03
<20, 20 – 80, >80	≥ .5, <.5	1.8	0.783	0.2 to 3.3	0.02
<20, 20 – 80, >80	≥ 2, <2	1.8	0.783	0.3 to 3.4	0.02
<20, 20 – 80, >80	≥ 3, <3	1.8	0.783	0.3 to 3.4	0.02

N=2,680. MPR: Medication Possession Ratio; SBP: Systolic blood pressure.

* MPR categories are the categorical variables for the MPR of the index drug. For example, in the first row patients were classified in the first MPR category if MPR for the index drug is less than 20%, in the second category if MPR is between 20% and 80%, and in the third if MPR is more than 80%.

** Number of refills per month from the index date until the end of follow up period. A categorical variable was created to equal one if the number of refills satisfy the first value (i.e. ≥1, ≥ .5, ≥ 2, or ≥ 3) and equal zero if not.

*** Estimate of SBP is the estimate difference between NSAIDs and acetaminophen after controlling for baseline SBP. A higher value means NSAIDs is associated with higher increase in systolic blood pressure compared to acetaminophen.

Table 11. Comparison of Covariate Balance between Naproxen and Ibuprofen before and after Propensity Score Matching

Variable	Sample	Naproxen*	Ibuprofen*	P Value**	Standardized Difference	Bias Reduction (%)
Age (yrs) age	Unmatched	54	53	0.215	6.5	
	Matched	54	54	0.994	0.0	99
Gender:						
Female	Unmatched	73	68	0.053	10.3	
	Matched	72	73	0.853	-1.2	88
Race:						
African American	Unmatched	51	62	<.001	-22.4	
	Matched	52	55	0.517	-4.2	81
Others	Unmatched	6	4	0.067	9.2	
	Matched	6	5	0.649	3.0	68
Baseline Systolic blood pressure (mmHg) mean	Unmatched	141	139	0.040	10.9	
	Matched	141	141	0.968	-0.3	98
Time from baseline SBP to index:						
≤ 7 days	Unmatched	57	51	0.023	12.0	
	Matched	57	58	0.851	-1.2	90
> 7 days and ≤ 30 days	Unmatched	13	14	0.678	-2.2	
	Matched	13	12	0.750	2.1	6
> 30 days	Unmatched	30	35	0.035	-11.2	
	Matched	30	30	0.977	-0.2	98
Year of index date:						
1993 - 1996	Unmatched	41	58	<.001	-35.4	
	Matched	43	43	0.836	-1.3	96
1997-2002	Unmatched	43	34	<.001	18.9	
	Matched	43	43	0.941	-0.5	97
2002 - 2006	Unmatched	16	8	<.001	25.8	
	Matched	14	14	0.688	2.6	90
Diagnosis of:						
Osteoarthritis	Unmatched	21	18	0.092	8.8	
	Matched	21	20	0.721	2.3	73
Rheumatoid Arthritis	Unmatched	2	2	0.989	-0.1	
	Matched	2	3	0.371	-5.8	-7938
Renal insufficiency	Unmatched	1	3	0.032	-12.3	
	Matched	1	2	0.596	-3.5	72
Cirrhosis with Ascites	Unmatched	0.4	0.3	0.743	1.7	
	Matched	0.2	0.2	0.998	0.0	99

Variable	Sample	Naproxen*	Ibuprofen*	P Value**	Standardized Difference	Bias Reduction (%)
Systemic Lupus Erythematosus	Unmatched	0.4	0.5	0.728	-1.9	
	Matched	0.4	0.6	0.657	-2.9	-53
Diabetes	Unmatched	29	26	0.165	7.3	
	Matched	29	29	0.919	-0.7	91
Congestive Heart Failure	Unmatched	10	10	0.987	-0.1	
	Matched	9	10	0.754	-2.0	-2269
Coronary Artery Disease or History of Myocardial Infarction	Unmatched	14	12	0.194	6.7	
	Matched	13	15	0.412	-5.3	21
Stroke	Unmatched	7	7	0.757	-1.6	
	Matched	7	6	0.576	3.6	-121
Arrhythmia	Unmatched	2	1	0.042	9.6	
	Matched	1	2	0.566	-3.7	61
Asthma or Chronic Obstructive Pulmonary Disease	Unmatched	16	16	0.975	-0.2	
	Matched	16	17	0.814	-1.5	-826
Medications:						
ACE-I or Angiotensin II blocker	Unmatched	38	33	0.055	10.0	
	Matched	37	40	0.375	-5.8	43
Beta- Blocker	Unmatched	20	16	0.066	9.5	
	Matched	19	21	0.436	-5.1	47
Calcium Channel Blocker	Unmatched	32	34	0.365	-4.8	
	Matched	32	35	0.359	-5.9	-25
Diuretic	Unmatched	40	42	0.438	-4.1	
	Matched	40	44	0.317	-6.5	-59
Other BP medications	Unmatched	5	8	0.034	-11.7	
	Matched	5	5	0.988	0.1	99
Oral high dose glucocorticoid***	Unmatched	0.8	0.8	0.951	-0.3	
	Matched	0.8	0.6	0.700	2.5	-662
Oral Contraceptives	Unmatched	0.6	0.8	0.727	-1.9	
	Matched	0.4	0.6	0.657	-2.9	-53
Venlafaxine	Unmatched	1	0.4	0.043	9.4	
	Matched	0.8	0.8	0.995	0.0	100
Adherence to antihypertensive medications:						
MPR > 80%	Unmatched	72	67	0.048	10.5	
	Matched	72	74	0.485	-4.5	57
MPR < 80%	Unmatched	12	14	0.261	-6.0	
	Matched	12	11	0.821	1.5	76

Variable	Sample	Naproxen*	Ibuprofen*	P Value**	Standardized Difference	Bias Reduction (%)
Not using antihypertensives (reference group)	Unmatched	16	19	0.166	-7.4	
	Matched	16	15	0.512	4.3	42
Exposure to index drug:						
MPR > 80%	Unmatched	41	21	<.001	44.1	
	Matched	39	36	0.430	5.1	88
MPR 20-80 %	Unmatched	45	48	0.234	-6.3	
	Matched	47	49	0.433	-5.1	19
MPR < 20%	Unmatched	14	31	<.001	-41.5	
	Matched	14	14	0.979	0.2	100
Number of refills per month:						
≥ 1 refills	Unmatched	52	54	0.419	-4.3	
	Matched	52	52	0.796	-1.7	61

* % unless indicated as mean. Because of rounding it may not add to 100 %.

** P-value of t-tests for continuous variables and chi-square tests for categorical variables.

*** High dose was defined as ≥10mg for prednisonse, ≥50mg for cortisone, and ≥1.5 mg for dexamethasone.

Standardized difference: 100 ($\overline{\chi}_{\text{treated}} - \overline{\chi}_{\text{control}}$)/$\sqrt{}$ {($s^2_{\text{treated}} + s^2_{\text{control}}$)/2}. A positive value means the treated group is higher in % (or mean) compared to the control group and negative value means the control is higher than the treated.

Bias reduction (%) =1- {|Standardized difference $_{\text{matched}}$| / | Standardized difference $_{\text{unmatched}}$ |} x 100. A positive value means bias is reduced by propensity score matching and negative means bias increased.

ACE-I: Angiotensin converting enzyme inhibitor; MPR: Medication Possession Ratio; SBP: Systolic blood pressure. Unmatched: all patients before propensity score matching, N=1,808 (1,313 ibuprofen and 495 naproxen). Matched: only matched patients, N=944 (472 in each group).

Table 12. Difference in Systolic Blood Pressure between Naproxen and Ibuprofen after Propensity Score Matching

Sample	Dependent Variable*	Estimate of SBP (mmHg)**	95% Confidence Interval	P Value
All Patients (n=944)	First SBP	-2.0	-4.4 to 0.4	0.108
	Average SBP	-2.5	-4.6 to -0.5	0.015
ACE-I (n=276)	First SBP	0.7	-4.1 to 5.4	0.786
	Average SBP	-1.1	-5.3 to 3.0	0.593
CCB (n=268)	First SBP	-2.3	-6.8 to 2.2	0.320
	Average SBP	-2.2	-6.1 to 1.7	0.261
BB (n=130)	First SBP	-4.3	-10.6 to 2.0	0.187
	Average SBP	-5.9	-11.7 to -0.0	0.049
Diuretics (n=340)	First SBP	-3.2	-7.6 to 1.2	0.158
	Average SBP	-3.3	-7.0 to 0.5	0.085

ACE-I: Angiotensin converting enzyme inhibitor; BB: Beta-blocker; CCB: Calcium channel blocker; SBP: Systolic blood pressure.

* First SBP is the first systolic blood pressure measurement after the index date. Average SBP is the average of all systolic blood pressure measurements after the index date and prior to any changes in the antihypertensive therapy.

** Estimate of SBP is the estimate difference between naproxen and ibuprofen after controlling for baseline SBP. A positive value means naproxen is associated with higher increase in systolic blood pressure compared to ibuprofen. A negative value means ibuprofen is associated with higher increase in systolic blood pressure compared to naproxen.

Table 13. Difference in Systolic Blood Pressure between Naproxen and Ibuprofen in Patients Using Combinations of Antihypertensive Medications after Propensity Score Matching

Sample	Dependent Variable*	Estimate of SBP (mmHg)**	95% Confidence Interval	P Value
CCB & ACE-I (n=60)	First SBP	0.4	-11.9 to 12.7	0.953
	Average SBP	-0.8	-11.7 to 10.1	0.886
CCB & BB (n=34)	First SBP	-4.5	-18.8 to 9.7	0.521
	Average SBP	-4.4	-18.3 to 9.6	0.528
CCB & diuretics (n=118)	First SBP	-3.2	-11.3 to 5.0	0.447
	Average SBP	-3.2	-9.5 to 3.2	0.326
ACE-I & BB (n=40)	First SBP	-5.8	-19.1 to 7.5	0.379
	Average SBP	-10.1	-23.0 to 2.8	0.120
ACE-I & diuretics (n=124)	First SBP	-3.3	-10.5 to 4.0	0.373
	Average SBP	-4.3	-11.0 to 2.5	0.216
BB & diuretics (n=70)	First SBP	-7.0	-16.3 to 2.4	0.143
	Average SBP	-5.4	-14.0 to 3.2	0.217
CCB & ACE-I & diuretics (n=28)	First SBP	-4.6	-22.9 to 13.8	0.610
	Average SBP	-0.5	-16.5 to 15.6	0.951
BB & ACE-I & diuretics (n=22)	First SBP	-7.4	-29.2 to 14.4	0.483
	Average SBP	-8.9	-30.8 to 13.0	0.404

ACE-I: Angiotensin converting enzyme inhibitor; BB: Beta-blocker; CCB: Calcium channel blocker; SBP: Systolic blood pressure.

* First SBP is the first systolic blood pressure measurement after the index date. Average SBP is the average of all systolic blood pressure measurements after the index date and prior to any changes in the antihypertensive therapy.

** Estimate of SBP is the estimate difference between naproxen and ibuprofen after controlling for baseline SBP. A positive value means naproxen is associated with higher increase in systolic blood pressure compared to ibuprofen. A negative value means ibuprofen is associated with higher increase in systolic blood pressure compared to naproxen.

Table 14. Comparison of Covariate Balance between Celecoxib and Ibuprofen before and after Propensity Score Matching

Variable	Sample	Celecoxib*	Ibuprofen*	P Value**	Standardized Difference	Bias Reduction (%)
Age (yrs) mean	Unmatched	62	53	<.001	67.9	
	Matched	60	61	0.631	-6.4	91
Gender:						
Female	Unmatched	89	68	<.001	51.7	
	Matched	89	85	0.433	10.4	80
Race:						
African American	Unmatched	48	62	0.001	-28.2	
	Matched	50	49	0.790	3.5	87
Others	Unmatched	5	4	0.624	4.1	
	Matched	4	3	0.701	5.1	-22.6
Baseline Systolic blood pressure (mmHg) mean	Unmatched	138	139	0.893	-1.2	
	Matched	140	137	0.247	15.4	-1171
Time from baseline SBP to index:						
≤ 7 days	Unmatched	50	51	0.850	-1.7	
	Matched	52	54	0.790	-3.5	-113
> 7 days and ≤ 30 days	Unmatched	20	14	0.047	16.4	
	Matched	20	17	0.605	6.9	58
> 30 days	Unmatched	29	35	0.200	-11.5	
	Matched	28	29	0.883	-1.9	83
Year of index date:						
1993 - 2002	Unmatched	78	92	<.001	-41.9	
	Matched	84	80	0.388	11.5	73
2002 - 2006	Unmatched	22	8	<.001	41.9	
	Matched	16	20	0.388	-11.5	73
Diagnosis of:						
Osteoarthritis	Unmatched	58	18	<.001	91.1	
	Matched	50	38	0.061	25.0	73
Rheumatoid Arthritis	Unmatched	15	2	<.001	49.7	
	Matched	14	11	0.419	10.7	78
Renal insufficiency	Unmatched	4	3	0.421	6.6	
	Matched	4	4	1.000	0.0	100
Systemic Lupus Erythematosus	Unmatched	6	0.5	<.001	29.6	
	Matched	3	3	1.000	0.0	100
Diabetes	Unmatched	39	26	0.002	26.7	
	Matched	36	36	1.000	0.0	100

Variable	Sample	Celecoxib*	Ibuprofen*	P Value**	Standardized Difference	Bias Reduction (%)
Congestive Heart Failure	Unmatched	25	10	<.001	40.5	
	Matched	19	20	0.865	-2.2	94
Coronary Artery Disease or History of Myocardial Infarction	Unmatched	25	12	<.001	34	
	Matched	17	22	0.313	-13.4	61
Stroke	Unmatched	17	7	<.001	30.2	
	Matched	13	10	0.404	11.1	63
Arrhythmia	Unmatched	3	0.6	0.006	16.9	
	Matched	3	3	1.000	0.0	100
Asthma or Chronic Obstructive Pulmonary Disease	Unmatched	31	16	<.001	34.7	
	Matched	28	30	0.770	-3.9	89
Medications:						
ACE-I or Angiotensin II blocker	Unmatched	45	33	0.005	24.3	
	Matched	39	47	0.227	-16.1	34
Beta- Blocker	Unmatched	34	16	<.001	42.6	
	Matched	27	29	0.656	-5.9	86
Calcium Channel Blocker	Unmatched	36	34	0.685	3.6	
	Matched	34	39	0.407	-11.0	-210
Diuretic	Unmatched	65	42	<.001	47.8	
	Matched	62	63	0.981	-1.8	96
Other BP medications	Unmatched	6	8	0.548	-5.5	
	Matched	6	8	0.604	-6.9	-26
Venlafaxine	Unmatched	2	0.4	0.008	15.5	
	Matched	1	2	0.561	-7.7	50
Adherence to antihypertensive medications:						
MPR > 80%	Unmatched	83	67	<.001	38.4	
	Matched	83	86	0.581	-7.3	81
MPR < 80%	Unmatched	9	14	0.107	-15.2	
	Matched	7	10	0.472	-9.5	37
Not using antihypertensives (reference group)	Unmatched	8	19	<.001	-34.2	
	Matched	10	4	0.120	20.7	39
Exposure to index drug:						
MPR > 80%	Unmatched	76	21	<.001	130.9	
	Matched	73	71	0.768	3.9	97
MPR 20-80 %	Unmatched	22	48	<.001	-55.6	
	Matched	26	27	0.880	-2.0	96
MPR < 20%	Unmatched	1	31	<.001	-86.8	
	Matched	2	3	0.651	-6.0	93

Variable	Sample	Celecoxib*	Ibuprofen*	P Value**	Standardized Difference	Bias Reduction (%)
Number of refills per month:						
≥ 1 refills	Unmatched	34	54	<.001	-41.7	
	Matched	37	36	0.890	1.8	96

* % unless indicated as mean. Because of rounding it may not add to 100 %.

** P-value of t-tests for continuous variables and chi-square tests for categorical variables.

Standardized difference: 100 ($\overline{\chi}_{\text{treated}} - \overline{\chi}_{\text{control}}$)/√ {($s^2_{\text{treated}} + s^2_{\text{control}}$)/2}. A positive value means the treated group is higher in % (or mean) compared to the control group and negative value means the control is higher than the treated.

Bias reduction (%) =1- {|Standardized difference $_{\text{matched}}$| / | Standardized difference $_{\text{unmatched}}$ |} x 100. A positive value means bias is reduced by propensity score matching and negative means bias increased.

ACE-I: Angiotensin converting enzyme inhibitor; MPR: Medication Possession Ratio; SBP: Systolic blood pressure. Unmatched: all patients before propensity score matching, N=1,456 (143 celecoxib and 1,313 ibuprofen). Matched: only matched patients, N=226 (113 in each group).

Table 15 . Difference in Systolic Blood Pressure between Celecoxib and Ibuprofen or Naproxen after Propensity Score Matching

Comparison	Dependent Variable*	Estimate of SBP(mmHg)**	95% Confidence Interval	P Value
Celecoxib vs. Ibuprofen (n=226)	First SBP	-5.4	-10.8 to 0.0	0.051
	Average SBP	-5.2	-10.0 to -0.4	0.035
Celecoxib vs. Naproxen (n=204)	First SBP	-0.3	-5.5 to 4.9	0.913
	Average SBP	-0.3	-5.1 to 4.5	0.897

SBP: Systolic blood pressure.

* First SBP is the first systolic blood pressure measurement after the index date. Average SBP is the average of all systolic blood pressure measurements after the index date and prior to any changes in the antihypertensive therapy.

** Estimate of SBP is the estimate difference between celecoxib and the comparator drug (ibuprofen or naproxen) after controlling for baseline SBP. A positive value means celecoxib is associated with higher increase in systolic blood pressure compared to the comparator drug. A negative value means the comparator drug is associated with higher increase in systolic blood pressure compared to celecoxib.

Table 16. Comparison of Covariate Balance between Celecoxib and Naproxen before and after Propensity Score Matching

Variable	Sample	Celecoxib*	Naproxen*	P Value**	Standardized Difference	Bias Reduction (%)
Age (yrs) mean	Unmatched	62	54	<.001	60.6	
	Matched	60	59	0.805	3.5	94
Gender:						
Female	Unmatched	89	73	<.001	41.2	
	Matched	87	81	0.248	16.1	61
Race:						
African American	Unmatched	48	51	0.547	-5.7	
	Matched	48	44	0.574	7.8	-37
Others	Unmatched	5	6	0.599	-5.1	
	Matched	6	7	0.774	-4.0	22
Baseline Systolic blood pressure (mmHg) mean	Unmatched	138	141	0.190	-12.5	
	Matched	139	141	0.387	-12.1	3
Time from baseline SBP to index:						
≤ 7 days	Unmatched	50	57	0.148	-13.7	
	Matched	52	52	1.000	0.0	100
> 7 days and ≤ 30 days	Unmatched	20	13	0.040	18.6	
	Matched	20	19	0.859	2.5	87
> 30 days	Unmatched	29	30	0.977	-0.3	
	Matched	28	29	0.877	-2.2	-691
Year of index date:						
1993 - 2002	Unmatched	78	84	0.075	-16.3	
	Matched	80	78	0.729	4.8	70
2002 - 2006	Unmatched	22	16	0.075	16.3	
	Matched	20	22	0.729	-4.8	70
Diagnosis of:						
Osteoarthritis	Unmatched	58	21	<.001	81.0	
	Matched	49	43	0.399	11.8	85
Rheumatoid Arthritis	Unmatched	15	2	<.001	49.7	
	Matched	5	6	0.757	-4.3	91
Renal insufficiency	Unmatched	4	1	0.021	18.4	
	Matched	1	3	0.313	-14.1	23
Diabetes	Unmatched	39	29	0.037	19.4	
	Matched	37	36	0.885	2.0	90
Congestive Heart Failure	Unmatched	25	10	<.001	40.6	
	Matched	21	20	0.861	2.4	94

Variable	Sample	Celecoxib*	Naproxen*	P Value**	Standardized Difference	Bias Reduction (%)
Coronary Artery Disease or History of Myocardial Infarction	Unmatched	25	14	0.002	27.5	
	Matched	20	19	0.859	2.5	91
Stroke	Unmatched	17	7	<.001	32	
	Matched	13	14	0.836	-2.9	91
Arrhythmia	Unmatched	3	2	0.360	8.0	
	Matched	3	4	0.701	-5.4	33
Asthma or Chronic Obstructive Pulmonary Disease	Unmatched	31	16	<.001	34.9	
	Matched	24	27	0.628	-6.8	81
Medications:						
ACE-I or Angiotensin II blocker	Unmatched	45	38	0.133	14.2	
	Matched	43	45	0.778	-3.9	72
Beta- Blocker	Unmatched	34	20	<.001	32.9	
	Matched	30	33	0.652	-6.3	81
Calcium Channel Blocker	Unmatched	36	32	0.375	8.3	
	Matched	35	40	0.470	-10.1	-21
Diuretic	Unmatched	65	40	<.001	52.1	
	Matched	57	56	0.888	2.0	96
Other BP medications	Unmatched	6	5	0.492	6.3	
	Matched	5	5	1.000	0.0	100
Venlafaxine	Unmatched	2	1	0.429	6.9	
	Matched	1	1	1.000	0.0	100
Adherence to antihypertensive medications:						
MPR > 80%	Unmatched	83	72	0.006	27.7	
	Matched	82	86	0.441	-10.7	61
MPR < 80%	Unmatched	9	12	0.346	-9.2	
	Matched	9	6	0.421	11.2	-22
Not using antihypertensives (reference group)	Unmatched	8	16	0.009	-26.8	
	Matched	9	8	0.800	3.5	87
Exposure to index drug:						
MPR > 80%	Unmatched	76	41	<.001	75	
	Matched	75	73	0.751	4.4	94
MPR 20-80 %	Unmatched	22	45	<.001	-48.9	
	Matched	24	26	0.745	-4.5	91
MPR < 20%	Unmatched	1	14	<.001	-47.9	
	Matched	2	2	1.000	0.0	100

Variable	Sample	Celecoxib*	Naproxen*	P Value**	Standardized Difference	Bias Reduction (%)
Number of refills per month:						
≥ 1 refills	Unmatched	34	52	<.001	-37.3	
	Matched	34	39	0.468	-10.1	73

* % unless indicated as mean. Because of rounding it may not add to 100 %.

** P-value of t-tests for continuous variables and chi-square tests for categorical variables.

Standardized difference: 100 ($\overline{\chi}_{\text{treated}} - \overline{\chi}_{\text{control}}$)/√ {($s^2_{\text{treated}} + s^2_{\text{control}}$)/2}. A positive value means the treated group is higher in % (or mean) compared to the control group and negative value means the control is higher than the treated.

Bias reduction (%) =1- {|Standardized difference $_{\text{matched}}$| / | Standardized difference $_{\text{unmatched}}$ |} x 100. A positive value means bias is reduced by propensity score matching and negative means bias increased.

ACE-I: Angiotensin converting enzyme inhibitor; MPR: Medication Possession Ratio; SBP: Systolic blood pressure. Unmatched: all patients before propensity score matching, N=638 (143 celecoxib and 495 naproxen). Matched: only matched patients, N=204 (102 in each group).

Table 17. Comparison of Covariate Balance between NSAIDs and Acetaminophen before and after Propensity Score Matching

Variable	Sample	NSAIDs*	Acetaminophen*	P Value**	Standardized Difference	Bias Reduction (%)
Age (yrs) mean	Unmatched	55	60	<.001	-39.0	
	Matched	56	57	0.008	-7.5	81
Gender:						
Female	Unmatched	68	69	0.348	-2.3	
	Matched	69	68	0.362	2.6	-13
Race:						
African American	Unmatched	59	64	<.001	-8.9	
	Matched	63	61	0.145	4.1	53
Others	Unmatched	4	3	0.162	3.4	
	Matched	3	4	0.588	-1.5	55
Baseline Systolic blood pressure (mmHg) mean	Unmatched	141	143	0.001	-3.5	
	Matched	141	142	0.223	-7.9	56
Time from baseline SBP to index:						
≤ 7 days	Unmatched	55	65	<.001	-21.6	
	Matched	61	61	0.931	-0.2	99
> 7 days and ≤ 30 days	Unmatched	12	9	<.001	9.4	
	Matched	8	10	0.101	-4.6	51
> 30 days	Unmatched	34	26	<.001	16.8	
	Matched	31	29	0.267	3.1	81
Year of index date:						
1993 - 1996	Unmatched	52	59	<.001	-14.2	
	Matched	58	58	0.774	0.8	94
1997-2002	Unmatched	35	39	<.001	-8.6	
	Matched	40	40	0.795	-0.7	91
2002 - 2006	Unmatched	13	2	<.001	43.7	
	Matched	2	2	0.924	-0.3	99
Diagnosis of:						
Osteoarthritis	Unmatched	23	24	0.070	-4.4	
	Matched	21	23	0.095	-4.7	-8
Rheumatoid Arthritis	Unmatched	3	3	0.562	1.4	
	Matched	2	2	0.588	-1.5	-9
Renal insufficiency	Unmatched	3	9	<.001	-23.0	
	Matched	5	5	1.000	0.0	100
Cirrhosis with Ascites	Unmatched	0.4	0.5	0.479	-1.7	
	Matched	0.6	0.5	0.705	1.1	37

Variable	Sample	NSAIDs*	Acetaminophen*	P Value**	Standardized Difference	Bias Reduction (%)
Systemic Lupus Erythematosus	Unmatched	0.7	0.5	0.185	3.2	
	Matched	0.5	0.5	1.000	0.0	100
Diabetes	Unmatched	27	34	<.001	-15.1	
	Matched	28	30	0.052	-5.5	64
Congestive Heart Failure	Unmatched	11	19	<.001	-21.2	
	Matched	13	14	0.459	-2.1	90
Coronary Artery Disease or History of Myocardial Infarction	Unmatched	13	18	<.001	-13.4	
	Matched	13	16	0.025	-6.4	52
Stroke	Unmatched	8	11	<.001	-12.5	
	Matched	9	9	0.398	-2.4	81
Arrhythmia	Unmatched	1	2	0.019	-5.6	
	Matched	1	1	0.716	-1.0	82
Asthma or Chronic Obstructive Pulmonary Disease	Unmatched	17	18	0.049	-4.8	
	Matched	16	17	0.119	-4.4	7
Medications:						
ACE-I or Angiotensin II blocker	Unmatched	31	34	0.003	-7.2	
	Matched	30	31	0.157	-4.0	44
Beta- Blocker	Unmatched	16	14	0.030	5.3	
	Matched	13	14	0.231	-3.4	36
Calcium Channel Blocker	Unmatched	28	31	0.012	-6.1	
	Matched	29	29	0.553	-1.7	72
Diuretic	Unmatched	36	39	0.018	-5.7	
	Matched	37	37	0.860	-0.5	91
Other BP medications	Unmatched	7	10	<.001	-10.1	
	Matched	8	8	0.715	-1.0	90
Oral high dose glucocorticoid***	Unmatched	0.7	1	0.045	-4.8	
	Matched	0.9	0.9	0.881	-0.4	91
Oral Contraceptives	Unmatched	0.5	0.8	0.221	-2.9	
	Matched	0.7	0.8	0.869	-0.5	84
Venlafaxine	Unmatched	0.7	0.3	0.024	5.6	
	Matched	0.4	0.4	0.818	-0.7	88
Adherence to antihypertensive medications:						
MPR > 80%	Unmatched	68	74	<.001	-12.2	
	Matched	72	71	0.661	1.2	90
MPR < 80%	Unmatched	16	13	0.014	6.0	
	Matched	13	14	0.282	-3.0	49

Variable	Sample	NSAIDs*	Acetaminophen*	P Value**	Standardized Difference	Bias Reduction (%)
Not using antihypertensives (reference group)	Unmatched	16	13	<.001	9.7	
	Matched	15	15	0.634	1.3	86
Exposure to index drug:						
MPR > 80%	Unmatched	38	29	<.001	18.5	
	Matched	32	32	1.000	0.0	100
MPR 20-80 %	Unmatched	43	43	0.507	-1.6	
	Matched	44	44	0.887	-0.4	75
MPR < 20%	Unmatched	20	28	<.001	-18.7	
	Matched	25	24	0.869	0.5	98
Number of refills per month:						
≥ 1 refills	Unmatched	57	46	<.001	21	
	Matched	53	51	0.148	4.1	80

* % unless indicated as mean. Because of rounding it may not add to 100 %.

** P-value of t-tests for continuous variables and chi-square tests for categorical variables.

*** High dose was defined as ≥10mg for prednisonse, ≥50mg for cortisone, and ≥1.5 mg for dexamethasone.

Standardized difference: 100 ($\overline{\chi}_{\text{treated}} - \overline{\chi}_{\text{control}}$)/√ {($s^2_{\text{treated}} + s^2_{\text{control}}$)/2}. A positive value means the treated group is higher in % (or mean) compared to the control group and negative value means the control is higher than the treated.

Bias reduction (%) =1- {|Standardized difference $_{\text{matched}}$| / | Standardized difference $_{\text{unmatched}}$ |} x 100. A positive value means bias is reduced by propensity score matching and negative means bias increased.

ACE-I: Angiotensin converting enzyme inhibitor; MPR: Medication Possession Ratio; SBP: Systolic blood pressure. Unmatched: all patients before propensity score matching, N=6,849 (3,740 NSAIDs and 3,109 acetaminophen). Matched: only matched patients, N=4,988 (2,494 in each group).

Table 18. Comparison of Covariate Balance between Naproxen and Ibuprofen before and after Propensity Score Matching

Variable	Sample	Naproxen*	Ibuprofen*	P Value**	Standardized Difference	Bias Reduction (%)
Age (yrs) mean	Unmatched	54	54	0.832	-0.9	
	Matched	54	54	0.600	-2.6	-206
Gender:						
Female	Unmatched	70	66	0.055	7.7	
	Matched	69	70	0.828	-1.1	86
Race:						
African American	Unmatched	53	64	<.001	-22.5	
	Matched	55	54	0.726	1.7	92
Others	Unmatched	5	4	0.116	6.1	
	Matched	5	5	0.638	-2.3	61
Baseline Systolic blood pressure (mmHg) mean	Unmatched	142	141	0.450	3.0	
	Matched	142	141	0.801	1.3	59
Time from baseline SBP to index:						
≤ 7 days	Unmatched	59	52	<.001	15.1	
	Matched	58	60	0.511	-3.3	78
> 7 days and ≤ 30 days	Unmatched	10	12	0.157	-5.7	
	Matched	10	10	0.805	1.2	79
> 30 days	Unmatched	31	36	0.003	-12.1	
	Matched	32	30	0.590	2.7	78
Year of index date:						
1993 - 1996	Unmatched	40	60	<.001	-41.2	
	Matched	43	46	0.229	-6.0	85
1997-2002	Unmatched	41	31	<.001	21.2	
	Matched	42	39	0.155	7.1	67
2002 - 2006	Unmatched	19	9	<.001	28.9	
	Matched	15	15	0.781	-1.4	95
Diagnosis of:						
Osteoarthritis	Unmatched	21	19	0.240	4.6	
	Matched	19	21	0.453	-3.7	19
Rheumatoid Arthritis	Unmatched	2	2	0.702	-1.5	
	Matched	2	2	0.574	-2.8	-81
Renal insufficiency	Unmatched	3	3	0.259	-4.6	
	Matched	3	3	0.874	-0.8	83
Cirrhosis with Ascites	Unmatched	0.6	0.4	0.556	2.4	
	Matched	0.6	0.6	1.000	0.0	100

Variable	Sample	Naproxen*	Ibuprofen*	P Value**	Standardized Difference	Bias Reduction (%)
Systemic Lupus Erythematosus	Unmatched	0.3	0.4	1.000	-1.7	
	Matched	0.4	0.9	0.205	-6.3	-271
Diabetes	Unmatched	27	25	0.270	4.4	
	Matched	27	28	0.737	-1.7	62
Congestive Heart Failure	Unmatched	10	10	0.895	0.5	
	Matched	10	10	1.000	0.0	100
Coronary Artery Disease or History of Myocardial Infarction	Unmatched	14	13	0.486	2.8	
	Matched	13	14	0.515	-3.2	-18
Stroke	Unmatched	6	8	0.279	-4.4	
	Matched	7	7	0.693	-2.0	55
Arrhythmia	Unmatched	1	1	0.793	1.0	
	Matched	1	1	0.807	1.2	-17
Asthma or Chronic Obstructive Pulmonary Disease	Unmatched	16	15	0.686	1.6	
	Matched	15	14	0.436	3.9	-142
Medications:						
ACE-I or Angiotensin II blocker	Unmatched	33	29	0.017	9.4	
	Matched	32	31	0.830	1.1	89
Beta- Blocker	Unmatched	16	14	0.140	5.8	
	Matched	16	17	0.313	-5.0	14
Calcium Channel Blocker	Unmatched	27	29	0.315	-4.0	
	Matched	28	28	1.000	0.0	100
Diuretic	Unmatched	34	35	0.511	-2.6	
	Matched	34	35	0.753	-1.6	40
Other BP medications	Unmatched	6	7	0.249	-4.7	
	Matched	6	6	1.000	0.0	100
Oral high dose glucocorticoid***	Unmatched	0.8	0.8	0.921	0.4	
	Matched	0.9	0.7	0.781	1.4	-251
Oral Contraceptives	Unmatched	0.5	0.6	0.792	-1.8	
	Matched	0.4	0.7	0.507	-5.0	-181
Venlafaxine	Unmatched	1	0.3	<.001	11.6	
	Matched	0.5	0.7	0.526	-3.2	73
Adherence to antihypertensive medications:						
MPR > 80%	Unmatched	70	66	0.069	7.3	
	Matched	70	70	0.744	-1.6	78
MPR < 80%	Unmatched	14	16	0.144	-5.9	
	Matched	14	15	0.478	-3.5	40

Variable	Sample	Naproxen*	Ibuprofen*	P Value**	Standardized Difference	Bias Reduction (%)
Not using antihypertensives (reference group)	Unmatched	16	18	0.389	-3.5	
	Matched	17	15	0.272	5.5	-58
Exposure to index drug:						
MPR > 80%	Unmatched	48	27	<.001	45	
	Matched	44	43	0.841	1.0	98
MPR 20-80 %	Unmatched	40	48	<.001	-15.1	
	Matched	44	43	0.880	0.8	95
MPR < 20%	Unmatched	12	25	<.001	-36.3	
	Matched	13	13	0.604	-2.6	93
Number of refills per month:						
≥ 1 refills	Unmatched	60	58	0.276	4.4	
	Matched	59	59	0.960	0.3	94

* % unless indicated as mean. Because of rounding it may not add to 100 %.

** P-value of t-tests for continuous variables and chi-square tests for categorical variables.

*** High dose was defined as ≥10mg for prednisonse, ≥50mg for cortisone, and ≥1.5 mg for dexamethasone.

Standardized difference: 100 ($\overline{\chi}_{\text{treated}} - \overline{\chi}_{\text{control}}$)/$\sqrt{}$ {($s^2_{\text{treated}} + s^2_{\text{control}}$)/2}. A positive value means the treated group is higher in % (or mean) compared to the control group and negative value means the control is higher than the treated.

Bias reduction (%) =1- {|Standardized difference $_{\text{matched}}$| / | Standardized difference $_{\text{unmatched}}$ |} x 100. A positive value means bias is reduced by propensity score matching and negative means bias increased.

ACE-I: Angiotensin converting enzyme inhibitor; MPR: Medication Possession Ratio; SBP: Systolic blood pressure. Unmatched: all patients before propensity score matching, N=3,104 (2,227 ibuprofen and 877 naproxen). Matched: only matched patients, N=1,610 (805 in each group).

Appendix B. Categories of Antihypertensive Medications

Category	Sub-category	Drug name
Diuretics	Thiazide	chlorothiazide
		chlorthalidone
		hydrochlorothiazide
		polythiazide
		indapamide
		metolazone
	Loop	bumetanide
		furosemide
		torsemide
	K-sparing	amiloride
		triamterene
	Aldesterone blocker	eplerenone
		spironolactone
Beta blockers		atenolol
		betaxolol
		bisoprolol
		metoprolol
		nadolol
		propranolol
		timolol
	BB with ISA	acebutolol
		penbutolol
		pindolol
	Combined alpha and BB	carvedilol
		labetalol
Angiotensin converting enzyme inhibitors (ACE-I)		benazepril
		captopril
		enalapril
		fosinopril
		lisinopril
		moexipril
		perindopril
		quinapril
		ramipril
		trandolapri
Angiotensin II antagonists		candesartan
		eprosartan
		irbesartan
		losartan
		olmesartan
		telmisartan
		valsartan
Calcium Channel Blockers (CCB)		diltiazem
		verapamil
		amlodipine
		felodipine

Category	Sub-category	Drug name
		isradipine
		nicardipine
		nifedipine
		nisoldipine
Vasodilators		hydralazine
		minoxidil
Other blood pressure medications	alpha 1 blcokers	doxazosin
		prazosin
		terazosin
	Centrally acting drugs	clonidine
		methyldopa
		reserpine
		guanfacine

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