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THE RELATIONSHIP BETWEEN COX-2 INHIBITORS AND CARDIOVASCULAR RISK – A RETROSPECTIVE ANALYSIS USING THE VETERAN AFFAIRS (VA) DATABASE

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by

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DEDICATION

This dissertation is dedicated to my wife, Dianza Motsko, who has patiently stood by my side and provided the support and strength needed to succeed.

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The search for non-steroidal anti-inflammatory drugs (NSAIDs) with less gastrointestinal toxicity, led to the introduction of the selective cyclooxygenase-2 (COX-2) inhibitors. However, with this introduction into the market, there have been concerns regarding their safety, particularly cardiovascular safety.

The purpose of this study was to assess the cardiovascular risk (events included: myocardial infarction, stroke, and myocardial infarction-related deaths) associated with long-term (after 180 days of exposure) and short-term (≤ 180 days exposure) use of nonselective NSAIDs and COX-2 inhibitors.

A retrospective analysis of the Veterans Integrated Service Network 17 Veteran's Affairs (VA) database was conducted. Medicare data and Texas Department of Health mortality data were incorporated to capture events occurring outside the VA healthcare network.

Patients 35 years of age and older receiving celecoxib, rofecoxib, ibuprofen, etodolac, and naproxen from January 1, 1999 through December 31, 2001, were included. Multivariate Cox proportional hazard models were used to analyze the relationship between cardiovascular risk and NSAID/COX-2 inhibitor use while adjusting for various risk factors.

We identified 12,194 exposure periods and 146 cardiovascular events over the entire study period. Compared to long-term ibuprofen use, long-term use of celecoxib (Celebrex®) was associated with a 3.64 fold (95% CI 1.36 – 9.70; $p = 0.01$) increase in cardiovascular risk. Long-term use of rofecoxib (Vioxx ®) was associated with a 6.64 fold (95% CI 2.17 – 20.28; $p \leq 0.01$) increased risk when compared to long-term use of ibuprofen. Short-term use of celecoxib and rofecoxib was not associated with any significant change in cardiovascular risk when compared to ibuprofen use (celecoxib – adjusted risk ratio (aRR) 0.67; 95% CI 0.31 – 1.47; $p = 0.32$ / rofecoxib – aRR 1.40; 95% CI 0.59 – 3.33; $p = 0.44$). Long-term and short-term exposure to naproxen and etodolac was not associated with a cardionegative or cardioprotective effect when compared to ibuprofen use. Additionally, overall exposure (long-term and short-term exposure) to study medications was evaluated; results indicated no significant findings with any COX-2 inhibitor/NSAID.

The findings of this observational study along with recent clinical trial results suggest that long-term exposure to COX-2 inhibitors is associated with an increased cardiovascular risk. In addition, the study results do not support the hypothesis that naproxen provides cardioprotective effects.

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CHAPTER ONE

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CHAPTER OUTLINE

The gastrointestinal (GI) toxicity associated with nonsteroidal anti-inflammatory drugs (NSAIDs) led to the search for and development of the selective cyclooxygenase-2 (COX-2) inhibitors. The introduction of COX-2 inhibitors into the market has raised concerns regarding their safety, particularly cardiovascular safety. Several recent studies and reports have been published addressing these concerns. This chapter will focus on the reports and studies relating to the cardiovascular safety of NSAIDs and COX-2 inhibitors. Information regarding NSAIDs/COX-2 inhibitors' gastrointestinal safety is also included to provide the reader with an overall understanding of the associated risks and benefits.

To obtain an understanding of the complex nature surrounding cardiovascular disease, this chapter will begin with an in-depth look into the epidemiology, etiology, precipitating factors, treatment, and risk factors for cardiovascular disease. Information provided in this section will help explain and support the rationale for and design of the study. The purpose of this study was to assess the cardiovascular risk (events included: myocardial infarction, stroke, and myocardial infarction-related deaths) associated with long-term (after 180 days of exposure) and short-term (≤ 180 days exposure) use of nonselective NSAIDs and COX-2 inhibitors.

SECTION I

CARDIOVASCULAR DISEASE

Note: This section will utilize the American Heart Association, National Center for Health Statistics (CDC/NCHS), and the National Heart, Lung, and Blood Institute (NHLBI) criteria to define cardiovascular disease terminology.[1] A comprehensive list of definitions is provided below along with the corresponding International Classification of Diseases (ICD) 10 codes. The corresponding ICD 10 codes are placed in parentheses.[1]

- "Major cardiovascular diseases" (I00-I78)
- "Congenital cardiovascular defects" (Q20-Q28)
- "Diseases of the heart" – representing roughly three-fourths of "total cardiovascular disease" mortality, indicated with a (*) below
- "Total cardiovascular disease" – comprising all "diseases of the circulatory system" (I00-I99)
    - Acute rheumatic fever/chronic rheumatic heart diseases (I00-I09)*
    - Hypertensive diseases (I10-I15)
    - Hypertensive heart disease (I11)* and hypertensive heart and renal disease (I13)*
    - Ischemic (coronary) heart disease (I20-I25)*
        - Angina pectoris (I20)
        - Acute myocardial infarction (I21-I22)

        - Other acute ischemic coronary heart disease (I24)
        - All other forms of chronic ischemic heart disease (I25.1-I25.9)
    - Pulmonary heart disease and diseases of pulmonary circulation (I26-I28)*
    - Congestive heart failure (I50.0)*
    - Other forms of heart disease (I29-I49, I50.1-I52)*
    - Cerebrovascular disease (stroke) (I60-I69)
    - Atherosclerosis (I70)
    - Other diseases of arteries, arterioles and capillaries (I71-I79)
    - Diseases of veins, lymphatics and lymph nodes, not classified elsewhere (I80-I89)
    - Other and unspecified disorders of the circulatory system (I95-I99)

Total Cardiovascular Disease

Prevalence/Incidence/Mortality – In the United States, one in five Americans is living with some form of cardiovascular disease. There are over 50,000,000 people living with high blood pressure (HBP), 12,900,000 with coronary heart disease, 4,900,000 with congestive heart failure (CHF), and 4,700,000 with stroke (National Health and Nutrition Examination Survey III, CDC/NCHS).[1]

Despite improvements in clinical care and public awareness, coronary heart disease (CHD) remains the leading cause of death for men and women in the United

States. In the United States, heart disease and stroke account for approximately 40% of all deaths.[1,2] Coronary heart disease and stroke account for 72 percent of cardiovascular-related deaths (Appendix A).[1] Mortality resulting from congestive heart failure (CHF), high blood pressure (HBP), diseases of the arteries, rheumatic heart disease, and congenital cardiovascular defects has had a smaller but significant impact on cardiovascular mortality, comprising roughly 15 percent of cardiovascular mortality. Through the years, improvements in cardiovascular care and treatment have been made, resulting in a reduction in morbidity and mortality. From 1950 to 1996, deaths from "diseases of the heart" have declined 56 percent, from 307.4/100,000 to 134.6/100,000.[2] Furthermore, during this same period, stroke rates dropped 70 percent, from 88.8/100,000 to 26.5/100,000.[2]

Age and Cardiovascular Disease – It has been noted that there is an increased prevalence of cardiovascular diseases among older Americans (Appendix B).[3] Likewise, the incidence of cardiovascular events among older Americans is also higher. Based on information obtained from the National Heart, Lung, and Blood Institute's (NHLBI) Framingham Heart Study, the annual rates of a first major cardiovascular event rise from 7 per 1,000 in men age 35-44 to 68 per 1,000 in men age 85-94.[1] Comparable rates for women occur 10 years later in life, narrowing with advancement in age.

Roughly 84 percent of cardiovascular disease-related deaths occur in persons 85 and older. Among the 6,294,000 patients discharged from a short-stay hospital with a

primary diagnosis of cardiovascular disease in the year 2000, 64.5 percent were 65 and older.[3]

Gender and Ethnicity in Cardiovascular Disease – Important differences based on race/ethnicity and gender exist. Since 1984, the number of cardiovascular-related deaths for females has exceeded those of males. In 2000, 440,175 (46.5%) males and 505,661 (53.5%) females died of cardiovascular-related deaths.[4,5] Similar gender differences were noted when broken down into racial categories (Appendix C).[6-8] Even though women have a higher total number of cardiovascular-related deaths, men have a higher overall death rate from cardiovascular disease (CVD). Additionally, black females and males have higher rates of CVD when compared to white males and females. Hispanic males and females had a lower percent of cardiovascular-related deaths in 2000. Gender and racial differences for overall death rates from CVD are as follows:

- Males – 404.0 per 100,000
    - White males – 397.6 per 100,000
    - Black males – 509.6 per 100,000
- Females – 294.3 per 100,000
    - White females – 285.8 per 100,000
    - Black females – 397.1 per 100,000

Among African-American adults, 40.5 percent of men and 39.6 percent of women have some form of cardiovascular disease. Comparatively, cardiovascular disease prevalence is estimated to be lower among whites and Hispanics. (Appendix D).[6-8]

Ischemic/Coronary Heart Disease

Prevalence/Incidence/Mortality – An estimated 650,000 Americans had a new coronary attack in the year 2003 and 450,000 will have a recurrent attack. Coronary heart disease comprises greater than 50 percent of all cardiovascular events in men and women (Appendix A). The lifetime risk of developing CHD after the age of 40 is 49 percent for men and 32 percent for women. Once the age of 70 is reached, the lifetime risk drops to 35 percent for men and 24 percent for women.[1] For total CHD, the incidence of CHD in women lags 10 years behind males and 20 years for events such as acute myocardioal infarction (AMI) and sudden death. Of those who experience a coronary attack in a given year, 47 percent will die and around 80 percent of CHD mortality in people under the age of 65 will occur during their first heart attack.[1]

Age/Gender/Race – As observed in total cardiovascular disease, the Framingham Study found an increasing rate of coronary heart disease and myocardial infarctions with age, in both genders. The crude 24-year incidence rate of coronary heart disease increased from 152 per 1,000 in men aged 30-34 to 383 per 1,000 in men aged 55-59 and from 59 per 1,000 to 294 per 1,000 in women, respectively. Regarding MI, the rate increased from 92

per 1,000 in men aged 30-34 to 252 per 1,000 in men aged 55-59 and from 13 per 1,000 to 117 per 1,000 in women, respectively. Results are displayed in Appendices E and F.[9] Information provided from the Cardiovascular Health Study (CHS) found a similar trend in adults aged 65 and older, with annual rates of new and recurrent myocardial infarctions increasing with age.[1] However, among African American men and women, the annual incidence rate of events declined after the age of 84 (see Appendix G).

In 2000, 50.6 percent of CHD-related deaths were males and 49.4 percent were females. In 2000, the overall coronary heart disease related death rate was 186.9 per 100,000. The gender and racial differences are as follows (gender specific data were available only for whites and African Americans; additionally, 1999 data were used to calculate death rates for Hispanics, American Indians/Alaska Natives and Asian/Pacific Islanders):[1]

- White males – 252.4 per 100,000
- Black males – 262.4 per 100,000
- White females – 145.3 per 100,000
- Black females – 187.5 per 100,000
- Hispanics – 138.4 per 100,000
- American Indians/Alaska Natives – 123.9 per 100,000
- Asian/Pacific Islanders – 115.5 per 100,000

Of those who have experienced a myocardial infarction, nearly 25 percent of men and 38 percent of women will die within one year. Additionally, people with a previous MI have a risk of sudden death 4-6 times higher than in the general population. Around half of men and women under the age of 65 who have had an AMI will die within 8 years.[1] According to the Framingham Heart study, within six years, 18 percent of men and 35 percent of women will have another heart attack; seven percent of men and six percent of women will experience sudden death; and about 22 percent of men and 46 percent of women will develop heart failure. Angina pectoris will develop in 27 percent of men and 14 percent of women within six years after an AMI. "Only 20 percent of coronary attacks are preceded by long-standing angina."[1]

Acute Myocardial Infarction – Etiology and Treatment

Etiology – Coronary artery disease (CAD) is the primary factor leading to a possible AMI. The disease process usually begins early in life, with fatty streaks of deposits developing on the endothelium. These deposits can then, in turn, develop into atherosclerotic plaques, depending on risk factors.[10] Risk factors attributed to the progression of these plaques include: hypertension, diabetes mellitus, smoking, and hyperlipidemia. With the progression of these plaques, narrowing of the arteries and thrombogenic formations occur, causing an AMI. The thrombotic process is a complex process and involves activation of platelets, thrombin, and fibrin.[10] Thrombus formations are believed to be responsible for greater than 85 percent of acute MIs.

Treatment – The primary goals in the management of patients with MI are to: minimize the infarction size, salvage ischemic myocardium, prevent and minimize complications, and improve outcomes.[10] Patients presenting to the emergency room may receive thrombolytic therapy or undergo percutaneous transluminal coronary angioplasty (PTCA). In addition to these procedures, patients may need oxygen and pain management. Pharmaceutical management may include: therapy with nitroglycerin to relieve chest discomfort and salvage ischemic myocardium; lidocaine to manage ventricular tachycardia and ventricular fibrillations; and early administration of β-adrenergic blockers to reduce the incidence of ventricular arrhythmias, recurrent ischemia, reinfarction, and mortality.[10] Post MI management may include the use of β-adrenergic blockers, calcium channel blockers, amiodarone, angiotensin-converting enzyme inhibitors (ACEI), cholesterol medications, aspirin and/or other antiplatelet drugs.[10]

Sudden Cardiac Death

Sudden Cardiac Death – Sudden cardiac death is the unexpected stopping of the heartbeat and is often associated with coronary heart disease. Sudden cardiac death occurs on average around the age of 60, with women lagging 20 years behind men.[1,11] The most common cause of sudden cardiac arrest is a heart attack that results in ventricular fibrillation or pulse-less ventricular tachycardia. Various heart medications

and other drugs (including illicit drugs) can induce abnormal heart rhythms. Additional causes of cardiac arrest include respiratory arrest, electrocution, drowning, choking, trauma, and unknown causes.

Sixty-three percent of women and 50 percent of men who die from sudden cardiac death have had no previous symptoms of the disease.[1] People with a previous heart attack are 4-6 times more likely to experience sudden cardiac death than the general population; with 7 percent of men and 6 percent of women experiencing sudden death six years post myocardial infarction (MI).[11] Roughly 80 percent of all sudden cardiac arrests occur at home, and 60 percent are witnessed by someone. It is estimated that 95 percent of sudden cardiac arrest victims die before reaching the hospital.[1] Survival is directly linked to the amount of time between the onset of sudden cardiac arrest and defibrillation. Victims located in communities with public access defibrillators have an increased survival probability. With immediate CPR and defibrillation within 3-5 minutes, survival rates have been reported as high as 48-74 percent.

No statistical data are available on the exact number of sudden cardiac arrests that occur each year. However, roughly 250,000 people die yearly of coronary heart disease without being hospitalized, equaling about half of all CHD related deaths.[1] The CDC estimates that in 1999, 728,743 people died of heart disease and congenital malformations of the heart in an emergency department (16.5%) or before reaching the hospital (46.9%).[12]

Cerebrovascular Disease

Incidence/Mortality – Stroke is the third leading cause of death; it accounted for roughly 1 of every 14 deaths in the United States in 2000.[1] Of the nearly 700,000 yearly occurrences of new (71%) and recurrent (29%) strokes experienced in the US, roughly 30% will die within one year.[1,13] Approximately 8 – 11% of individuals who experience an AMI will have an ensuing stroke within six years. Fourteen percent of individuals who survive a first stroke or transient ischemic attack (TIA) will experience a subsequent attack within one year. With regards to stroke related mortality, about 50 percent occurred outside the hospital.[1] Age-adjusted stroke incidence rates (per 100,000) for the first occurrence of a stroke are 167 for white males, 138 for white females, 323 for black males, and 260 for black females.[1] There is a steep rise in incidence with age, with 75% of all first stokes occurring after the age of 65 (in the white population).[13]

Etiology/*Treatment* – There are three pathological types of strokes: ischemic (88% of all strokes), intracerebral hemorrhage (9%), and subarachnoid hemorrhage (3%). Not considered a pathological type of stroke, a transient ischemic attack (TIA) differs from an ischemic stroke in three facets, duration (less than 24 hours), differential diagnosis, and ease of diagnosis.[13] Regarding ischemic strokes, roughly 50 percent of occurrences can be attributed to atherothrombotic disease (in the white population), 25 percent to intracranial small vessel disease, and 20 percent from emboli from the heart.[13] In the

event of an ischemic stroke, antiplatelet therapy or anticoagulation therapy are typically the first line agents, followed by risk factor modifications.

Risk Factors - There are a number of modifiable risk factors for ischemic stroke, most of which are associated with atherosclerosis. Factors include: hypertension, hyperlipidemia, smoking, physical activity, obesity, asymptomatic carotid stenosis, alcohol consumption, and atrial fibrillation. Non-modifiable risk factors for stroke include: older age, male sex, nonwhite race, the presence of coronary heart disease or congestive heart failure, and a family history of stroke or TIA.[14]

Congestive Heart Failure

Prevalence/Incidence/Mortality – An estimated 4,900,000 Americans are estimated to have congestive heart failure (CHF).[1] The Framingham study estimates that at the age of 40, the lifetime risk of developing CHF for men is 21.0 percent and 20.3 percent for women. At the age of 80, the lifetime risk drops slightly to 20.2 percent and 19.3 percent, respectively. Of those who have CHF under the age of 65, approximately 80 percent of men and 70 percent of women will die within eight years and fewer than 15 percent of all men and women diagnosed with CHF will live longer than 8-12 years. The one-year mortality rate of people diagnosed with CHF is 20 percent.[1] In the year 2000, the overall death rate for CHF was 18.7 per 100,000, with a rate of 19.5 for white males,

20.4 for black males, 18.1 for white females, and 19.3 for black females. In 2000, there were 990,000 hospital discharges for CHF.[1]

Age/Gender/Race - As seen with the other cardiovascular conditions, the prevalence and incidence rates of CHF increases with age (Appendix H).[1] According to the Cardiovascular Health Study, annual incidence rates of new and recurrent CHF events are as follows:

- Non-black men
    - Age 65-74 – 21.5 per 1,000
    - Age 75-84 – 43.3 per 1,000
    - Age 85 + – 73.1 per 1,000
- Non-black women
    - Age 65-74 – 11.2 per 1,000
    - Age 75-84 – 26.3 per 1,000
    - Age 85 + – 64.9 per 1,000
- Black Men
    - Age 65-74 – 21.1 per 1,000
    - Age 75-84 – 52.0 per 1,000
    - Age 85 + – 66.7 per 1,000
- Black Women
    - Age 65-74 – 18.9 per 1,000
    - Age 75-84 – 33.5 per 1,000
    - Age 85 + – 48.4 per 1,000

Etiology – Congestive heart failure (CHF) is a condition when the heart is unable to provide sufficient amounts of blood to meet the metabolic needs of the body. Congestive heart failure is not a specific disease state, but a clinical syndrome caused by various cardiovascular disorders.[10] According to the Framingham Study, it is estimated that ischemic heart disease is the underlying cause of CHF in 47 percent of females and 59 percent of males.[15] Furthermore, roughly 22 percent of males and 46 percent of female patients who experienced an AMI will develop CHF within six years.[1] Hypertension is implicated as the suspect etiology in 37 percent of females and 30 percent of males.[15] Other etiologies include cardiomyopathies and valvular heart diseases.[10]

Precipitating Factors – Patients with a diagnosis of CHF can be symptom free when they are in a "compensated" state of heart failure. However, there are many factors that can decompensate a patient. A study evaluating 101 patients admitted to the hospital with CHF found that noncompliance with their medications and/or diet was the most common precipitating factor. Uncontrolled hypertension, despite medications, was the second leading cause, followed by arrhythmias.[10]

Treatment – Treatment of acute and severe heart failure will vary depending on the patient's cardiac index and pulmonary capillary wedge pressure. Positive ionotropic agents (e.g., dopamine, dobutamine, amrinone, milrinone) and/or vasodilators (e.g., nitroglycerin, nitroprusside, hydralazine) may be needed to increase cardiac output. In order to decrease intravascular volume and preload, diuretics are usually required. For

the treatment of acute and severe heart failure, intravenous loop diuretics (e.g., furosemide and bumetanide) are usually the drugs of choice.[10]

Regarding the long-term management of chronic heart failure, the first step is to correct any underlying disorders such as anemia or hyperthyroidism. In CHF patients, compensatory mechanisms such as sodium and water retention will occur, leading to systemic and pulmonary congestion. Therefore, diuretics are vital in the prevention of decompensation. Other pharmacological agents include ACEI and β-adrenergic blockers. Digital glycosides are used in the long-term management to increase cardiac index, and to decrease systemic vascular resistance and pulmonary capillary wedge pressure. However, digitalis glycosides have not been shown to reduce CHF-related mortality.[16] In addition to the pharmacological agents, patients should follow recommended exercise and diet requirements (e.g., sodium restriction).[10]

SECTION II

CARDIOVASCULAR RISK FACTORS

Since the 1960s, several intervention studies and clinical trials, demonstrating the beneficial effects of reducing risk factors for cardiovascular disease, have been conducted.[2] Public health efforts to reduce tobacco use, reductions in the consumption of saturated fats and cholesterol, and the increase of hypertensive patients receiving treatment have all contributed to the reduction of morbidity and mortality of cardiovascular diseases and stroke events (Appendix I). Additionally, improvements in detection, medical care, medications, emergency services, and an increase in coronary-care units have contributed to the reduction in cardiovascular events.[2]

Several prospective cohort studies have shown that the risk of developing a cardiovascular disease is directly related to a complex relationship of several factors. [17] Major positive risk factors for the development of CHD are: older age (≥ 45 years of age for men and ≥ 55 years for women), smoking, hypertension, low HDL concentration, hyperlipidemia, and a family history of premature heart disease.[17] Of note, diabetes is no longer a separate risk factor and according to the Adult Treatment Panel III guidelines, diabetes is considered a CHD risk equivalent (risk for major coronary events equal to that in established CHD). Through the use of medications and preventative programs (e.g., smoking cessation), the risk of developing a cardiovascular disease can be reduced.

Tobacco Smoke

"Smoking acts both independently of, and synergistically with, other major risk factors for coronary heart disease."[18] Smoking can disrupt the endothelium and precipitate coronary spasms, thereby possibly contributing to a myocardial infarction in patients with minimal atherosclerosis.[19] The progression of atherosclerosis is directly related to the total pack-years of smoking.[18] Roughly 20 percent of all cardiovascular related deaths are smoking-related.[20] The Centers for Disease Control estimates that 25.0 million adult men (25.7 % of US males) and 22.6 million women (21.5% of US women) were smokers in 2001. Race and gender smoking prevalence rates are detailed in Appendix J.[20]

The smoking prevalence rates are higher among those with 9-11 years of education (35.4%) versus those with greater than 16 years of education (11.6%) and were the highest among those living below the poverty level (33.3%).[20] Even individuals who do not smoke may be at an increased risk from second-hand smoke. Studies have found that exposure to passive smoke may increase the risk of death from CHD by up to 30 percent.[20] Individuals who smoke or are exposed to smoke can return to baseline risk levels over time and become equivalent to non-smokers. The excess risk is decreased by 50 percent one year post smoking cessation and can return to baseline levels within 15-20 years.[18,20] Smoking among people 18 and older has declined about 44 percent since 1965; however, this trend has leveled off in recent years.[20,21]

In addition to cardiovascular disease, smoking has been shown to be a significant risk factor in the development of several medical conditions. Most notable of these conditions are lung cancer, aerodigestive cancer, and chronic obstructive pulmonary disease (COPD). The hazards associated with smoking depend on several factors such as age at onset, number of cigarettes per day, cigarette characteristics, and degree of inhalation.[22] These factors can vary over time, making the determination of smoking prevalence and associated risk very difficult. Therefore, current smoking prevalence alone would be an insufficient indicator for the accumulated risk from smoking.[22] However, "the absolute age-sex-specific lung cancer rates can be used to indicate the approximate proportions of deaths due to tobacco not only from lung cancer itself but also, indirectly, from vascular disease and from various other categories of disease."[23]

Cholesterol

In addition to smoking, high cholesterol has been identified as an independent risk factor for developing coronary heart disease. Clinical trials utilizing lipid lowering agents for the primary and secondary prevention of coronary heart disease related events have found significant reductions in morbidity and mortality.[17] Roughly 105 million Americans age 20 and older have borderline high (200-239 mg/dl) to high (≥ 240 mg/dl) total cholesterol levels and, of those, about 42 million Americans have total cholesterol levels greater than or equal to 240 mg/dl. Similar trends in overall elevated total cholesterol levels in adults aged 20-74 are noted between different racial/ethnic and

gender groups (Appendix K).[24] However, beginning at the age of 50, the number of women with total cholesterol levels greater than or equal to 200 mg/dl will exceed men.

Hypertension

Large population studies have shown hypertension to increase the risk of developing various cardiovascular diseases. Hypertensive patients are shown to have accelerated development of macrovascular lesions, leading to an increased risk/incidence of coronary heart disease, peripheral arterial and cerebrovascular diseases.[25] The risk can be elevated by as much as two to three times (Appendix L).[26] Hypertension has been implicated in 35 percent of all atherosclerotic events and in 49 percent of all cases of heart failure. Several studies have shown that the risk from elevated blood pressure can be partially reversed through appropriate therapies.[26]

Prevalence of high blood pressure is shown to increase with age (Appendix M).[27] Of those with hypertension, 31.6 percent are unaware they have it; 27.4 percent are controlled with antihypertensive medications; 26.2 percent are not controlled with medication; and 14.8 percent are not receiving any hypertensive medication(s). Racial disparities have been noted. For example, African-Americans have a higher prevalence of hypertension (Appendix B, Chart 12); develop hypertension at an earlier age; and have higher levels of blood pressures. In addition to racial/ethnic disparities, people with lower education and income tend to have higher levels of hypertension when compared to the general population.[27]

Diabetes

Diabetes has been shown to increase the risk of cardiovascular morbidity and mortality. The abnormal metabolic conditions accompanying diabetes, chronic hyperglycemia, dyslipidemia, and insulin resistance, lead to an increase risk of macrovascular complications.[28] Diabetic patients have a two to four-fold increase in risk of developing coronary artery disease. Seventy-five percent of diabetics die from some form of heart or blood vessel disease.[29] In one study, the seven-year incidence of developing a first MI was 20 percent in the diabetic population as compared to 3.5 percent in the control group. [28] Post MI diabetic patients, as compared to nondiabetic patients, are at an increased risk of reinfarction, CHF, and death. A previous history of an MI and a diagnosis of diabetes have been associated with a 45 percent recurrence rate as compared to 18.8 percent in nondiabetic patients.[28] Furthermore, diabetic patients without a previous MI are at the same risk for a future MI as nondiabetic patients with a previous MI.[28] For this reason, diabetes is classified as a risk equivalent for CAD.

In addition to the effects on CAD, diabetes adversely affects cerebrovascular arterial circulation. The risk of stroke in diabetic patients is increased by 150 to 400 percent.[28] Patients presenting with stroke are three times more likely to have a diagnosis of diabetes. Diabetes also doubles the risk of recurrence and increases total and stroke related mortality.[28]

An estimated 10.9 million Americans are diagnosed with diabetes and an additional 5.7 million Americans have undiagnosed diabetes. The risk for diabetes for Mexican Americans and African Americans is almost twice that for non-Hispanic whites.[29] For Americans 20 and older, the following have diagnosed and undiagnosed (in parentheses) diabetes:

- Non-Hispanic whites
    - Men – 5.4% (3.0%)
    - Women – 4.7% (2.1%)
- African Americans
    - Men – 7.6% (2.8%)
    - Women – 9.5% (4.7%)
- Mexican Americans
    - Men – 8.1% (5.8%)
    - Women – 11.4% (3.9%)

Obesity

Obesity (defined as a BMI of 30 kg/m^2 or higher) is a condition affecting roughly 20 percent of the US population and 22.7 percent of the Texas population.[30] Obesity has been associated with an increased risk of developing cardiovascular disease and diabetes.[30,31] Obesity has been linked to increased levels of dyslipidemia, higher blood pressures, and glucose intolerance.[32] Clustering of cardiovascular risk factors has been

found in obese men and women. In a study conducted by Kannel et al., 56% of obese men and 62.4% of obese women were found to have ≥ 2 cardiovascular risk factors.[32]

Metabolic Syndrome

Metabolic syndrome is the association of several different risk factors, enhancing the tendency of developing cardiovascular complications. This syndrome is associated with insulin resistance, hypertension, central obesity, and dyslipidemia.[25] Patients with this syndrome are at an increased risk of developing non-insulin dependent diabetes mellitus and at an increased cardiovascular risk.

An estimated 47 million U.S. residents have metabolic syndrome, 21.8 percent of adults. The prevalence of this syndrome increases with age, with a prevalence of 6.7 percent for people aged 20-29; 43.5 percent for ages 60-69; and 42.0 percent for those 70 and older.[1] Men and women and those of different race/ethnicity have a similar prevalence of this syndrome.

Arthritis

With regards to cardiovascular risk, rheumatoid arthritis (RA) has been associated with an increased comorbidity and mortality resulting from cardiovascular disease.[33] Patients with RA have been found to have elevated levels of inflammation and thrombogenic factors, key factors in the development of cardiovascular disease.[33] In a large observational cohort study, RA patients were found to have a significant increase in

mortality (relative risk (RR) 1.60; 95% CI, 1.55-1.63) and thromboembolic events (RR 1.47; 95% CI, 1.41-1.54) when compared with nonarthritic patients. [33] A similar trend was also found when arthritic patients were compared with osteoarthritis patients, mortality (RR 1.72; 95% CI, 1.67-1.78) and thromboembolic events (RR 1.31; 95% CI, 1.25-1.39).[33]

Arthritis and chronic joint symptoms affect nearly 70 million Americans, making arthritis one of the most prevalent diseases and causes of disability in the United States.[34] The prevalence of arthritis or chronic joint symptoms (CJS) among U.S. adults ranges from 19% in adults age 18 – 44 to 58.8% in adults age 65 and older.[34]

Rheumatoid arthritis (RA) and osteoarthritis (OA) are two of the most prevalent joint disorders. Rheumatoid arthritis is a systemic inflammatory disease marked by symmetrical joint involvement. Rheumatoid arthritis patients experience chronic inflammation of the synovial tissue lining the joint, eventually leading to erosion of bone and cartilage.[10] Symptoms of RA develop slowly over several weeks to months. Symptoms include: fatigue, weakness, loss of appetite, joint pain, muscle pain and stiffness. Osteoarthritis is believed to be caused by a combination of abnormal biomechanical stresses on the joint and abnormal biochemical and metabolic changes in the chondrocyte and articular cartilage.[35] Osteoarthritis usually presents with a localized deep aching pain associated with the affected joint. The pain is not related to the destruction of cartilage. Rather, the pain is from stimulation of nerve endings by

mechanical and chemical irritants related to the joint pathology.[10] To alleviate the pain associated with RA and OA, several pharmacological and non-pharmacological treatments are available. Among the pharmacological treatments, nonsteriodal anti-inflammatory drugs are the class of medications most commonly used to treat joint pain and stiffness in patients with RA and OA.[35]

SECTION III

NSAIDs/COX-2 INHIBITORS AND CARDIOVASCULAR RISK

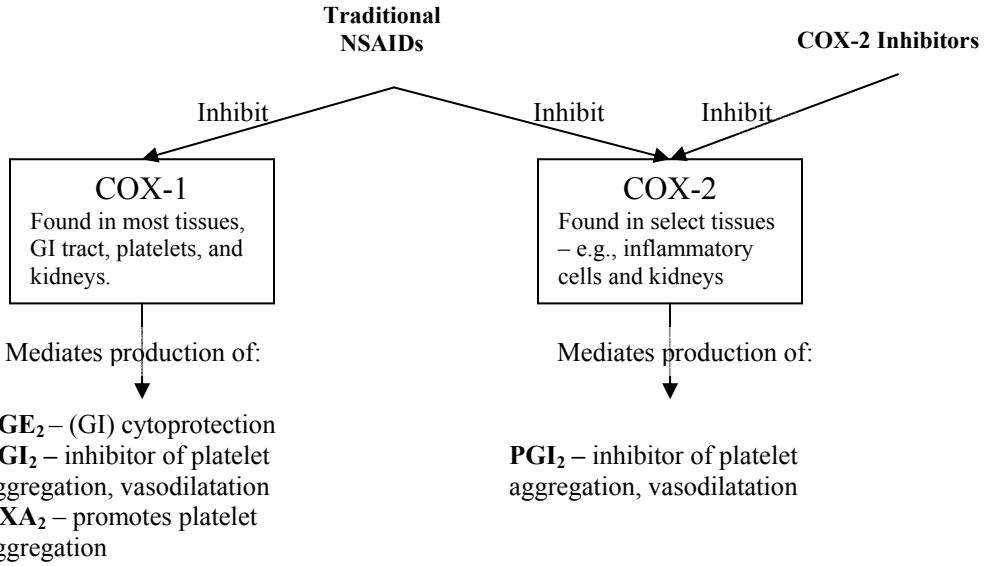
Background

Nonsteroidal anti-inflammatory drugs (NSAIDs) are some of the most commonly prescribed medications in the world. NSAIDs annually account for roughly 70 million prescriptions and 30 billion over-the-counter (OTC) medications sold in the United States (US) yearly.[36] With the ever-increasing age of the US population, utilization of these agents is expected to increase. Since the 1960s, more than 30 NSAIDs have been introduced into the US market.[37] Two of the newest NSAIDs, known as COX-2 inhibitors, were introduced into the market in 1999 under the trade names of Vioxx (rofecoxib) and Celebrex (celecoxib).[38] Today, there are four COX-2 selective inhibitors approved for use in various markets around the world.[39] A fifth COX-2 inhibitor, lumiracoxib, is currently in phase three development. A listing of available NSAID and COX-2 inhibitors is found in Appendix N.

One of the primary limitations regarding the use of traditional NSAIDs is the risk associated with the development of gastrointestinal ulcers. Long-term use of NSAIDs is associated with a two-to-five fold increase in relative risk (RR) and a 30% attributable risk for serious GI-related adverse effects (i.e., ulcer perforation, upper gastrointestinal bleeding, and death).[40] The gastrointestinal toxicity is caused by the inhibition of COX-1 mediated prostaglandin production. Over a decade ago, it was discovered that two isoforms existed of the cyclooxygenase enzyme, COX-1 and COX-2.[41] While COX-1 is

responsible for mediating the integrity of the gastrointestinal mucosa and platelet aggregation, COX-2 is primarily involved in the mediation of inflammation and pain.[42] Traditional NSAIDs (e.g., ibuprofen and naproxen) have been shown to inhibit the activity of COX-1 and COX-2. In an effort to minimize the gastrointestinal toxicity, while providing relief from pain and inflammation, researchers developed anti-inflammatory agents that targeted the COX-2 enzyme while minimizing the inhibition of the COX-1 isoform. Due to this selective targeting, the GI protective prostaglandins (PGE_2) mediated by the COX-1 enzyme are not inhibited. However, by exclusively inhibiting the COX-2 isoform and not the COX-1 isoform, selective COX-2 inhibitors may favor a prothrombotic state.[43] The proposed mechanism of action for this prothrombotic state results from PGI_2 inhibition, an inhibitor of platelet aggregation, and unopposed Thromboxane (TX) A_2 production, a promoter of platelet aggregation. Traditional NSAIDs do not share this same characteristic due to their ability to inhibit COX-1 mediated TXA_2 (see Figure 1). Some researchers have even hypothesized that select NSAIDs (i.e., naproxen) may offer cardioprotective effects.[44-46] Prevention of nonfatal myocardial infarctions by aspirin's ability to inhibit COX-1 mediated thromboxane production lends support to this notion.[47]

Figure 1.1 – Mechanism of Action of Traditional NSAIDs and COX-2 Inhibitors



Note: PG = prostaglandin; TX = thromboxane; COX = cyclooxygenase

Studies that evaluated the impact of COX-2 selective NSAIDs for their cardiovascular and GI safety will be summarized. Results from two major clinical trials, the Vioxx Gastrointestinal Outcomes Research Study (VIGOR) and the Celecoxib Long-Term Arthritis Safety Study (CLASS), two meta-analysis studies, and six retrospective studies (assessing COX-2 cardiovascular risk) will be evaluated. The use of naproxen as a comparator NSAID in the VIGOR trial has been implicated as a possible reason for the significant cardiovascular risk associated with rofecoxib. Therefore, several observational studies assessing naproxen for possible cardioprotective effects will also be evaluated.

Clinical Data

VIGOR Study

Concern regarding the negative cardiovascular effects of this new class of drug became prominent when the VIGOR study was published in November 2000.[42] The trial was designed to assess the gastrointestinal safety of rofecoxib (Vioxx®). The study comprised 8,076 patients diagnosed with rheumatoid arthritis (RA). Patients were at least fifty years of age and were randomly assigned to receive 50 mg of rofecoxib daily or 500 mg of naproxen twice daily. Aspirin use was not allowed in the study; therefore, patients requiring aspirin therapy were excluded. Baseline characteristics were similar in both groups. Over the nine month follow-up period, the rate of GI events was significantly lower for the rofecoxib treatment group (RR, 0.5; 95% CI, 0.3-0.6). However, the

incidence of myocardial infarction was significantly lower in the naproxen group as compared to the rofecoxib treatment group (0.1% vs. 0.4% respectively, RR 0.2; 95% CI, 0.1-0.7).

Due to the excessive cardiovascular events experienced in the VIGOR study, serious cardiovascular events were evaluated by an Independent Adjudication Committee.[48] Ninety-eight events were sent for adjudication, 65 in the rofecoxib group and 33 in the naproxen group. Forty-five patients in the rofecoxib group and 19 patients in the naproxen group met the criteria for a serious thrombotic cardiovascular event. The overall cardiovascular event rate was nearly double in the rofecoxib group (1.67 per 100 patient-years at risk) as compared to the naproxen group (0.70 per 100 patient-years at risk). Separating patients into specific cardiovascular categories (cardiac, cerebrovascular, and peripheral vascular) revealed varying levels of cardiovascular risk between the categories. A higher cardiac event rate was found in the rofecoxib group (1.04 per 100 patient-years at risk) as compared to the naproxen group (0.36 per 100 patient-years at risk). In contrast, a significant difference was not noted between the rofecoxib group and the naproxen group for cerebrovascular and peripheral vascular events. Results are presented in Appendix O.

Four percent of the VIGOR study population met the Food and Drug Administration (FDA) criteria for use of aspirin for secondary cardiovascular prophylaxis. During the study, 33 percent of the myocardial infarctions occurred in this

group. To assess the impact of patients meeting FDA criteria for prophylactic aspirin use, patients were stratified into the following categories: "all patients," "aspirin indicated," and "aspirin not indicated." In the initial analysis of the entire study population, the rate of myocardial infarctions (MI) was significantly lower in the naproxen group as compared to the rofecoxib group (RR 0.20; 95% CI, 0.07-0.58). Patients taking naproxen in the "aspirin indicated" group were significantly less likely to have an MI as compared to the rofecoxib group (RR 0.00; 95% CI, 0.00-0.60). Patients taking rofecoxib in the "aspirin not indicated" group had an insignificant trend towards an increased rate of MIs as compared to the naproxen group (RR 3.03; 95% CI, 0.97 – 9.09). The event rate for cardiovascular deaths and cerebrovascular accidents was also evaluated. No significant results were found in these categories. However, the composite endpoint (cardiovascular deaths, MI, and CVA) in all three groups demonstrated an unfavorable trend for rofecoxib. Results are summarized in Appendix P.

CLASS Study

Contrasting with the VIGOR study, the CLASS study found no significant increase in cardiovascular risk.[49] The CLASS study was a double-blind, randomized controlled trial designed to evaluate the gastrointestinal toxicity associated with celecoxib (800 mg/day) as compared to ibuprofen (2400 mg/day) or diclofenac (150 mg/day).[49] The trial consisted of 8,059 patients who were at least 18 years old and who were diagnosed with osteoarthritis (OA) or rheumatoid arthritis (RA). In this study, as compared to the VIGOR study, patients were permitted to receive ≤ 325 mg/day of

aspirin for cardiovascular prophylaxis. Aspirin users comprised roughly 20% of the study population. Approximately 57% of the patients (n=4,573) were enrolled for the entire six months of the treatment.

The annualized incidence rate of upper GI ulcer complications for celecoxib vs. comparator NSAIDs was 0.76% vs. 1.45% (RR 0.53; 95% CI, 0.26 – 1.11). When symptomatic ulcers were included in the analysis, the annualized incidence rate for celecoxib vs. NSAIDs changed to 2.08% vs. 3.54% (RR 0.59; 95% CI, 0.38-0.94). When patients taking aspirin were factored out, the annualized incidence of upper GI ulcer complications of celecoxib vs. NSAIDs was 0.44% vs. 1.27%, respectively (RR 0.35; 95% CI, 0.14-0.98). In non-aspirin users, when symptomatic ulcers were included in the analysis, the rates changed to 1.40% vs. 2.91% (RR 0.48; 95% CI, 0.28-0.89).

When accounting for simultaneous aspirin administration, the relative risk for developing upper GI complications increased to 4.5 (P = 0.01, a 95% CI was not provided). In contrast, no significant increase in upper GI complications was found among patients taking aspirin and nonselective NSAIDs (RR, 1.7; P = 0.29). Similar GI event rates were noted between patients taking nonselective NSAIDs plus aspirin and patients taking celecoxib plus aspirin. Therefore, patients taking low dose aspirin with celecoxib (or possibly other COX-2 inhibitors) may loose or diminish their GI advantage.

During the study, no significant difference was found regarding the incidence of cardiovascular events between celecoxib and comparator NSAIDs. Since 22 percent of the patients in the CLASS study were on low-dose aspirin, a subgroup analysis was performed to assess the cardiovascular safety of patients not taking aspirin. Results

indicated no significant increase in cardiovascular events among "non-aspirin" patients taking celecoxib versus those taking diclofenac and ibuprofen. Cardiovascular thromboembolic adverse events occurring in the CLASS study are summarized in Appendix Q.

Comments - VIGOR and CLASS

The primary objective of the two major COX-2 clinical trials, CLASS and VIGOR, was to determine if celecoxib or rofecoxib had an improved GI safety profile as compared to traditional NSAIDs. The CLASS study failed to demonstrate a statistically significant difference in complicated GI events between celecoxib and comparator NSAIDs. In contrast, the VIGOR study showed significant reductions in complicated upper GI events when compared to naproxen. Concerning the cardiovascular safety profile, the VIGOR study found a significant increase in cardiovascular events among patients taking rofecoxib as compared to naproxen. In contrast, the CLASS study did not show significant differences in cardiovascular event rates between celecoxib and comparator NSAIDs.

One possible reason for this difference is the varying COX-1/COX-2 selectivity ratio between celecoxib and rofecoxib. Selective COX-2 inhibitors do not exclusively inhibit the COX-2 isoform; they have varying degrees of selectivity for COX-1 and COX-2. As the selectivity for the COX-2 isoform increases, the GI toxicity decreases and the cardiovascular event rate increases. Rofecoxib has been found to be more

specific for the COX-2 enzyme as compared to celecoxib.[50] This speculated mechanism of action could explain the difference found between rofecoxib and celecoxib. Other possible explanations for the difference between the two clinical studies (VIGOR and CLASS) include the use of aspirin in the CLASS study and the use of different comparator NSAIDs.

Meta-analysis Studies

CLASS and VIGOR vs. Placebo group

In an effort to clarify the relationship between the cardiovascular risk associated with COX-2 inhibitors, Mukherjee et al. compared the cardiovascular event rates of the CLASS and VIGOR studies against the combined placebo groups (non-aspirin users) from four aspirin primary prevention trials.[41] The four aspirin studies included: the US Physicians' Health Study, the UK Doctors Study, the Thrombosis Prevention Trial, and the Hypertension Optimal Treatment Trials.[51] The total combined population consisted of 48,540 patients, with 25,133 treated with aspirin and 23,407 in the placebo group. The annualized MI incidence rate for the placebo group (0.52%) was significantly lower than the annualized incidence rates for patients in the VIGOR (0.74%, $p = 0.04$) and CLASS (0.80%, $p = 0.02$) studies.

Major limitations exist when conducting an evaluation of this nature. Of particular concern are the heterogeneous factors between the three groups, VIGOR, CLASS and placebo. For example, the VIGOR study used RA patients exclusively as

compared to the CLASS study which incorporated both RA (27%) and OA (73%) patients. Rheumatoid arthritis patients have been associated with a 32 percent increased risk of developing cardiovascular disease as compared to patients diagnosed with OA.[33,52]

Rofecoxib Clinical Trials

Due to the negative findings from the VIGOR study, Konstam et al. assessed cardiovascular (CV) thrombotic events across 23 phase IIb through V rofecoxib studies.[53] The purpose of the meta-analysis was to determine if there was an excess of cardiovascular thrombotic events (i.e., CV, hemorrhagic, unknown death, nonfatal MI, and nonfatal stroke) in patients treated with rofecoxib versus those treated with placebo or traditional NSAIDs. The analysis consisted of 28,465 patients studied in various patient populations and conditions. Study populations and conditions included: rheumatoid arthritis, osteoarthritis, Alzheimer's, and chronic low back pain. Comparator medications included: naproxen, ibuprofen, nabumetone, and diclofenac. Results from the meta-analysis did not indicate a significant difference in CV thrombotic events between rofecoxib and placebo (RR, 0.84; 95% CI, 0.51-1.38) or between rofecoxib and non-naproxen NSAIDs (RR, 0.79; 95% CI, 0.40-1.55). However, when compared with naproxen, rofecoxib showed a significant increase in risk (RR, 1.69; 95% CI 1.07-2.69). The authors concluded that the difference in cardiovascular events between the rofecoxib and naproxen group may have been due to the antiplatelet effects of naproxen.

As discussed in the previous study, the limitation regarding heterogeneity between study groups can pose significant problems when combining studies. When interpreting the results of the comparison between rofecoxib and placebo, it is important to note that over 50 percent of the patient-years at risk consist of Alzheimer's patients. The large percentage of Alzheimer's patients is due to the long duration of Alzheimer studies and the limited use of placebo groups in RA and OA studies. With regards to the comparison between rofecoxib and non-naproxen NSAIDs, only patients with osteoarthritis were studied. It is important to keep in mind that the negative cardiovascular results found between rofecoxib and naproxen, in this meta-analysis, was primarily driven by the VIGOR study. The VIGOR study was the only rofecoxib clinical trial to show a significant difference in the cardiovascular event rate. Other factors that need to be considered when evaluating this meta-analysis are: study duration; proximity between enrollment and cardiovascular event; and disease specific events (not just the aggregate of CV events). See Appendix R for study results.

Naproxen Use and Cardiovascular Protection

As a result of the VIGOR study, there was a renewed interest in the cardiovascular effects of traditional NSAIDs, with a specific focus on naproxen. Results from the VIGOR study indicated one of three possibilities: (1) rofecoxib increased cardiovascular risk; (2) naproxen offers significant cardioprotective benefits; (3) or a

combination of the two. Four recent studies have been published regarding the relationship between naproxen and cardiovascular events.[44-47]

Study 1

A matched case control study conducted by Raheme et al. evaluated the effect of naproxen vs. other NSAIDs in the prevention of acute myocardial infarction (AMI).[44] The study was comprised of 14,163 subjects taking naproxen and 14,160 patients taking other NSAIDs. Patients were at least 65 years of age and hospitalized for an AMI in Québec between January 1, 1992 and December 31, 1994. An acute myocardial infarction was considered the index date. One control was randomly selected for each case and assigned a corresponding index date. Patients were evaluated one year prior to the index date and were classified into four different categories:

- Concurrent exposure – Prescription with a duration that covered or overlapped the index date
- Chronic exposure – Receiving at least 60 days of medication, consisting of at least one refill and not exceeding a 25% gap in coverage.
- Concurrent-chronic exposure – Patients receiving "chronic exposure" and exposure on the index date.
- Interrupted-chronic exposure – Patients with chronic exposure without exposure on the index date.

Adjusting for baseline factors, the AMI incidence rate for interrupted-chronic users of naproxen was not significantly different from patients taking other NSAIDs (adjusted Odds Ratio (OR), 0.98; 95% CI, 0.73-1.33). However, naproxen showed a significant cardioprotective effect when concurrent users (patients taking naproxen at the time of an AMI) of naproxen were compared with other concurrent NSAIDs users (adjusted OR, 0.79; 95% CI, 0.63-0.99). Concurrent-chronic users of naproxen showed a similar trend when compared with other concurrent-chronic users of other NSAIDs (adjusted OR, 0.64; 95% CI 0.48-0.86).

Study 2

Solomon et al. conducted a similar study, evaluating 4,425 cases (17,700 control patients) of AMI in the New Jersey Medicaid or Medicare and Pharmaceutical Assistance for the Aged and Disabled programs.[45] A case control study design was used. Patients were evaluated between January 1, 1991 and December 31, 1995. Twenty-five percent of cases and controls had filled an NSAID prescription six months prior to the AMI index date or the randomly assigned index date for the control group. No relationship was found between (all) NSAID use and AMI risk during the prior six month period (OR, 1.00; 95 % CI, 0.92-1.08) or with concurrent NSAID use on the index date (OR, 1.04; 95% CI, 0.92-1.18). When individual NSAIDs (naproxen, fenoprofen, etodolac, and ibuprofen) were evaluated during the six month period, only naproxen use showed a

significant reduction in AMI risk as compared to control (OR, 0.84; 95% CI, 0.72-0.98). In contrast, fenoprofen was associated with an increased risk of an AMI (OR, 1.95; 95% CI, 1.16-3.30). Ibuprofen and etodolac showed no significant associations with risk of an AMI (OR, 1.02; 95% CI, 0.88-1.18 / OR 1.28; 95% CI, 1.0-1.64, respectively).

Study 3

The third case control study evaluating this issue, conducted by Watson et al., found results similar to the previous two case control studies.[46] The study utilized the British General Practice Research Database and evaluated overall thromboembolic cardiovascular events (myocardial infarction, sudden death, and stroke). Patients aged 40 to 79 years with rheumatoid arthritis were evaluated over a one-year time frame; patients not receiving a prescription for naproxen during the study period were classified as the control group. Three categories of naproxen use were utilized:

- Current – Naproxen use ≤ 30 days from the Index date
- Past – Naproxen use > 30 days but < 365 days
- None – Use ≥ 365 days

Patients were aged 40 to 79 years and had a current diagnosis of rheumatoid arthritis. Risk of acute thromboembolic cardiovascular events for current naproxen use on the index date was significantly lower than the control group (adjusted OR, 0.61; 95% CI,

0.39-0.94), while past naproxen use was not significantly different from control (OR, 0.87; 95% CI, 0.65-1.16).

Study 4

The final study was an observational cohort study consisting of Tennessee Medicaid patients evaluated between January 1, 1987 and December 31, 1998.[47] The purpose of this study was to evaluate NSAIDs and the risk associated with serious coronary heart disease (i.e., acute MI or death from coronary heart disease). The population consisted of 362,882 case and control subjects, matched for age, sex, and date NSAID use began. The control group was randomly drawn from the population and excluded patients taking NSAIDs. Study results found no significant difference between (all) NSAID users and the control group (RR, 1.05; 95% CI, 0.97-1.14). Similar results were found when only naproxen was compared to the control group (RR 0.95; 95% CI, 0.82-1.09). However, when directly comparing naproxen users with ibuprofen users, a significant reduction in coronary heart disease was found (RR, 0.83; 95% CI 0.69-0.98).

All four of these studies lend support to the concept that naproxen may provide some level of cardiovascular protection. However, it is unlikely that the four to five-fold increase in MI risk found in the VIGOR study can be accounted for by this benefit alone.[43,47] One possible reason for the difference in cardiovascular risk between concurrent (patients taking naproxen at the time of cardiovascular event) and non-

concurrent users of naproxen is the limited ability (~ 8 hours) of naproxen to inhibit platelet thromboxane generation for long periods of time.[50,52] The short duration of naproxen's antiplatelet effects suggests that inconsistent naproxen use may not provide prophylactic cardioprotective effects. Limitations among these studies include: the inability to control for OTC products, particularly aspirin; patient differences between case and control groups; and lifestyle factors such as smoking and obesity. Unmeasured potential confounders between NSAID users and nonusers may have been minimized by comparing two different NSAID groups.

Retrospective Studies Evaluating Cardiovascular Risk Associated with COX–2 Inhibitors

Study 1

To address the concern regarding the possible cardiovascular risk associated with COX-2 inhibitors, a retrospective cohort study was conducted among Tennessee Medicaid (TennCare) patients.[54] Patients in the study were between 50-84 years of age and enrolled in TennCare between January 1999 and June 2001. The study evaluated 378,776 patients, of whom 202,916 were control patients; 22,337 were taking celecoxib; 24,132 were taking rofecoxib; and 129,391 patients were taking naproxen or ibuprofen. Patients were classified into four categories:

- Non-User – No NSAID exposure within 365 days of enrollment.

- Current exposure – Use of an NSAID on that day according to days of supply
- Former exposure – No use of an NSAID on that day.
- New User – Patients who began use of an individual NSAID during the follow-up period.

The primary endpoint assessed was serious coronary heart disease. Results were adjusted for age, sex, and comorbidities. Results indicated no associated increased risk of serious CHD from ibuprofen, naproxen, or celecoxib when compared to the control population. Additionally, patients taking less than or equal to 25 mg of rofecoxib where not found to be at an increased risk. However, for patients taking greater than 25 mg of rofecoxib, the risk ratio compared to non-users increased to 1.7 (95 % CI, 0.98-2.95, p = 0.058) and for new users of rofecoxib compared with non-users, the risk ratio increased to 1.93 (95% CI, 1.09-3.43, p = 0.024). Similar results were found when high-dose current and new users of rofecoxib were compared with celecoxib (adjusted RR, 1.78; 95% CI, 0.99-3.21, p = 0.056 / adjusted RR, 2.20; 95% CI, 1.17-4.10, p=0.014, respectively). Of note, only 3,887 patients in the study received doses greater than 25 mg of rofecoxib. Results (for new users) and study variables are provided in Tables 1.1 – 1.2.

Study 2

A second retrospective cohort study was conducted using the administrative health care data from Ontario, Canada, from April 1998 to March 2001.[55] Patients included in the study were 66 years of age and older and were initiated on either celecoxib (n = 15,271), rofecoxib (n = 12,156), naproxen (n = 5,669), or non-naproxen NSAIDs (33,868). Additionally, 100,000 randomly selected control subjects not taking any NSAIDs during the study were selected. Subjects receiving NSAIDs were required to receive continuous exposure of the drug during the study. Information was obtained from pharmacy refill records and a 20 percent grace period was allowed on the previous day supply to refill the next prescription. Also, patients in the nonselective NSAID group were allowed to switch between different nonselective NSAIDs. Patients were followed up to a year after the index date. The primary outcome assessed was the incidence of acute myocardial infarctions. Results were adjusted for age, sex, and cardiovascular risk factors. No significant increase in cardiovascular risk was found in any of the four subgroups when compared with the control group or each other. Additionally, patients taking naproxen did not show a significant reduction in MI incidence as compared to the control group (Adjusted rate ratio – 1.0; 95% CI – 0.6-1.7). Results and study variables are provided in Tables 1.1 – 1.2.

Study 3

The study conducted by Solomon et al. evaluated the association between COX-2 inhibitors and acute myocardial infarctions in older adults.[56] The case-control study was comprised of 54,475 patients 65 years of age and older (mean age ~ 80) enrolled in the New Jersey and Pennsylvania Pharmaceutical Assistance Programs during 1998, 1999, and 2000. The 10,895 AMI cases were matched by age, gender, and month of index date to controls. Confounding factors were controlled for by using logistic regression models; a detailed list of confounding factors can be found in Table 1.1. Study groups consisted of celecoxib and rofecoxib users subdivided by dose (any, high, and low dose) and duration (≤ 30 days; 31-90 days; and > 90 days) of exposure. Rofecoxib and celecoxib were compared to non-NSAID users, each other, ibuprofen, naproxen, and "other" NSAIDs. Results indicated that short term use (< 90 days) of rofecoxib was associated with an increased risk of an AMI compared to similar celecoxib users (results in Table 1.2). Long-term use of rofecoxib (> 90 days) was not associated with an increased risk when compared to celecoxib (adjusted OR, 0.96; 95% CI – 0.72-1.25). High dose rofecoxib (> 25 mg) was associated with a higher cardiovascular risk than low dose rofecoxib users (≤ 25 mg) when compared to high dose and low dose celecoxib users, respectively. No duration category for celecoxib was associated with an increased risk. Results and study variables are provided in Tables 1.1 – 1.2.

Study 4

David Graham and colleagues conducted a nested case-control study among 6 million California Kaiser Permanente members to evaluate the cardiovascular risk associated with NSAIDs and COX-2 inhibitors.[57] The "nested" population was comprised of 1,394,764 men and women 18 - 84 years of age who received a COX-2 inhibitor or non-selective NSAID between 1999 and 2001. There were 8,199 AMI events and 1,524 sudden cardiac deaths. These events were matched to controls based on index date, birth year, gender, and health plan region. The study groups were current users of NSAIDs/COX-2 inhibitors (exposure overlaps index date), recent users (1-60 days prior to index date), and those with remote exposure (> 60 days prior to index date). Covariates were controlled for in the model and are listed in Table 1.1. Study results revealed no cardio-protective effects of naproxen, rather they reveal an increase in cardiovascular risk (Adjusted OR – 1.18; 95% CI – 1.04-1.35). High dose rofecoxib (> 25 mg / daily) was associated with a 3 fold increase in risk. No significant increase in risk was found with low dose rofecoxib when compared to the control group (aOR – 1.29; 95% CI – 0.93 – 1.79). Lastly, a higher cardiovascular risk was found with low dose rofecoxib when compared to celecoxib (results not provided). Study results and study variables are provided in Tables 1.1 – 1.2.

The study also involved a telephone survey of randomly selected controls exposed to celecoxib, ibuprofen, naproxen, rofecoxib, or remotely exposed controls in order to

evaluate the use of low-dose aspirin, OTC-NSAIDs, smoking history, and family history of AMI. Findings suggest no important differences in these factors between the groups.

Study 5

Two articles reported results from a study that used prescription event monitoring data in England to assess the cardiovascular safety of celecoxib and rofecoxib as compared to meloxicam.[58,59] Subjects were identified from prescriptions written by general practitioners between December 1996 – March 1997 for meloxicam; May 2000 – December 2000 for celecoxib; and July 1999 – November 1999 for rofecoxib. General practitioners were sent a questionnaire requesting information about patient factors and events occurring during and after exposure. Endpoint events occurring over nine months were divided into three separate categories, cerebrovascular events, cardiovascular events, and peripheral venous thrombotic events. After adjusting for age and sex, the cerebrovascular event rate was 1.66 times (95% CI, 1.10 – 2.51) higher for celecoxib users and 1.68 times (95% CI 1.15 – 2.46) higher for rofecoxib users, as compared to meloxicam users. No difference in cardiovascular events were found between celecoxib or rofecoxib and meloxicam (RR 1.72; 95 % CI 0.87 – 3.40 / RR 1.38; 95% CI 0.71 – 2.67, respectively). Regarding peripheral venous thrombotic events, no significant difference between celecoxib and meloxicam were found (RR 1.06; 95% CI, 0.51 – 2.19) and a reduced risk (RR 0.29; 95% CI, 0.11 – 0.78) was found with rofecoxib as compared

to meloxicam. Due to methodological concerns (non-responders and only two covariates used, age and sex), results and study variables were **not** provided in Tables 1.1 – 1.2.

Study 6

Kimmel et al. conducted a case-control study evaluating the cardiovascular safety of celecoxib and rofecoxib.[60] Patients (1718) who experienced a myocardial event and control subjects (6800) were evaluated for exposure to study medications via telephone interviews. The study had a 50 percent response rate. When compared to non-NSAID subjects, the study found a cardioprotective effect with celecoxib (aOR, 0.43; 95% CI, 0.23 – 0.79) and traditional NSAIDs (aOR, 0.61; 95% CI 0.52 – 0.71). Naproxen specifically was found to decrease cardiovascular risk by nearly 2 fold (aOR, 2.08; 95% CI, 1.37 – 3.13) Rofecoxib was not associated with an increased risk when compared to non-NSAID subjects (aOR, 1.16; 95% CI, 0.70 – 1.93). However, when compared to naproxen, rofecoxib was associated with an increased risk (aOR, 3.39; 95% CI 1.37 – 8.40). Celecoxib vs. ibuprofen and diclofenac did not reveal a cardioprotective or cardionegative effect (aOR, 0.77; 05% CI, 0.40 – 1.48). Recall bias and low response rate may limit the interpretability of these results. Therefore, results and study variables were **not** provided in Tables 1.1 – 1.2.

Table 1.1 Retrospective COX-2 studies – Study variables.

Study 1 **Ray et al.** [54]	**Study 2** **Mamdani et al.** [55]	**Study 3** **Solomon et al.** [56]	**Study 4** **Graham et al.** [57]
Demographics	**Demographics**	**Demographics**	**Demographics**
Age	Age	Age	Age
Sex	Sex	Sex	Sex
Ethnicity	--	Ethnicity	--
Health care use	**Health care use**	**Health care use**	**Health care use**
Hospital admissions (non-cardiovascular)	Any Hospital visit	No. Physician visits	Hospital admissions (non-cardiovascular)
ER visits	--	Hospitalized past year	Cardiovascular ER
Doctor visits	--	Comorbid conditions	Non-cardiovascular ER
Medical Conditions *Past year*	**Medical Conditions** *Past 5 years*	**Medical Conditions** *Past year*	**Medical Conditions** *Past year*
AMI	Malignancy	AMI	AMI / Revascularization
Stroke	AMI	Angina	Angina
Angina/ Revascularization	Angiography/ Revascularization	Revascularization	Other ischemic heart disease
Heart failure	Heart failure	Heart failure	Heart failure
PVD	Noninfarct CAD	Stroke	Cardiac arrhythmia
RA	Stroke	RA	PVD
--	--	OA	Stroke
Drugs – *past yr.*	**Drugs** – *past 120 dys.*	**Drugs** – *past yr.*	**Drugs** – *past yr.*
Current aspirin use	No. different drugs	No. different drugs	ACE inhibitor
Anti-arrhythmic	Aspirin	Diabetes (? Drug)	ARB
ACE inhibitor	Anti-arrhythmic	Hypertension (? Drug)	Anti-arrhythmic
Anticoagulant	ACE inhibitor	Statin	Anticoagulant
Aspirin	Anticoagulant	Anticoagulant	B-blocker
B-blocker	Nitrate	Hormone replacement	Digitalis glycoside
Calcium-channel blocker	Calcium-channel blocker	Previous nonselective NSAID	Calcium-channel blocker
Digitalis glycoside	B-blocker	--	Hypoglycemic agent
Antidiabetic agent	Digitalis glycoside	--	Lipid-drug
Lipid-drug	Antidiabetic agent	--	Loop diuretic
Loop diuretic	Lipid-drug	--	Nitrate
Nitrate	Loop diuretic	--	Platelet inhibitor
Other Antihypertensive	Other Antihypertensive	--	Thiazide diuretic
Platelet inhibitor	Nonloop diuretics	--	Steroid high dose
Thiazide diuretic	Estrogen	--	HRT
Oestrogen	--	--	--

Abbreviations: IHD – ischemic heart disease; AMI – acute myocardial Infarction; HRT – hormone replacement therapy; No. – number; PVD – peripheral vascular disease; RA – rheumatoid arthritis; CAD – coronary artery disease; ER – emergency room; yr. – year; ACE – Angiotensin-converting Enzyme ; ARB – Angiotensin II Receptor Blockers.

Table 1.1 *Continued* **– Retrospective COX-2 studies – Study variables.**

Study 1 **Ray et al.** [54]	**Study 2** **Mamdani et al.** [55]	**Study 3** **Solomon et al.** [56]	**Study 4** **Graham et al.** [57]
Exclusion Criteria	**Exclusion Criteria**	**Exclusion Criteria**	**Exclusion Criteria**
Cancer	None	Cancer	None
HIV	--	HIV	--
Renal failure	--	Coagulopathy	--
Liver injury	--	--	--
Respiratory failure	--	--	--
Serious immunological disorder	--	--	--
End point(s)	**End point(s)**	**End point(s)**	**End point(s)**
AMI	AMI	AMI	AMI
Death – IHD		--	Sudden cardiac death
Other	**Other**	**Other**	**Other**
--	Long-term care	Nursing home resident	Treated by rheumatologist
--	Low-income status	--	Health plan region
			Smoking-related diagnoses

Abbreviations: IHD – ischemic heart disease; AMI – acute myocardial Infarction; HRT – hormone replacement therapy; No. – number; PVD – peripheral vascular disease; RA – rheumatoid arthritis; CAD – coronary artery disease; ER – emergency room; yr. – year; ACE – Angiotensin-converting Enzyme ; ARB – Angiotensin II Receptor Blockers.

Table 1.2 Summary of results from studies one through four.

Study 1…. Ray et al. [54]	**Person-years**	**Events**	**Adjusted RR**	**95% CI**
Non-users*	237,975	3,085	1.00	--
Ibuprofen	4,319	52	1.01	0.77-1.33
Naproxen	6,489	72	0.92	0.73-1.16
Celecoxib	4,509	55	0.88	0.67-1.16
Rofecoxib ≤ 25 mg	3,430	47	1.02	0.76-1.37
Rofecoxib > 25 mg	500	12	**1.93**	1.09-3.42
Study 2…. Mamdani et al. [55]	**Person-years**	**Events**	**Adjusted RR**	**95% CI**
Non-users*	51,194	419	1.00	--
Non-selective NSAIDs	11,085	134	1.2	0.9-1.4
Naproxen	1,559	15	1.0	0.6-1.7
Celecoxib	7,004	75	0.9	0.7-1.2
Rofecoxib	4,806	58	1.0	0.8-1.4
Study 3….Solomon et al. [56]	**Number**	**Events**	**Adjusted OR**	**95% CI**
Rofecoxib (celecoxib*)	941	225	**1.24**	1.05-1.46
Celecoxib (non-user*)	2,140	425	0.93	0.84-1.02
Rofecoxib (non-user*)	941	225	1.14	1.00-1.31
Celecoxib (naproxen*)	2,140	425	0.95	0.74-1.21
Rofecoxib (naproxen*)	941	225	1.17	0.90-1.52
Celecoxib (ibuprofen*)	2,140	425	0.98	0.76-1.26
Rofecoxib (ibuprofen*)	941	225	1.21	0.92-1.58
Celecoxib (other NSAID*)	2,140	425	0.95	0.82-1.10
Rofecoxib (other NSAID*)	941	225	1.17	0.99-1.38
Rofecoxib ≤ 25 mg (celecoxib ≤ 200 mg*)	--	--	**1.21**	1.01-1.44
Rofecoxib > 25 mg (celecoxib > 200 mg*)	--	--	**1.70**	1.07-2.71
Rofecoxib (celecoxib*) 1 to 30 days	--	--	**1.40**	1.12-1.75
Rofecoxib (celecoxib*) 31 to 90 days	--	--	**1.38**	1.11-1.72
Rofecoxib (celecoxib*) > 90 days	--	--	0.96	0.72-1.25
Study 4….Graham et al. [57]	**Cases**	**Control**	**Adjusted OR**	**95% CI**
Remote use* (> 60 days prior to index)	4,699	19,876	1.00	--
Recent use (1-60 days prior to index)	1,728	6,339	**1.14**	1.06-1.22
***Current use* (overlapped index date)**				
Celecoxib	126	497	0.86	0.69-1.07
Ibuprofen	674	2,606	1.09	0.99-1.21
Naproxen	369	1,416	**1.18**	1.04-1.35
Rofecoxib ≤ 25 mg	58	190	1.29	0.93-1.79
Rofecoxib > 25 mg	10	8	**3.15**	1.14-8.75
Other NSAIDs	1,864	535	**1.16**	1.04-1.30

Abbreviations: PVT – peripheral venous thrombosis; CI – confidence interval; OR – odds ratio; RR – risk ratio

* Comparison group

Rofecoxib Withdrawal

On September 30, 2004 Merck and Co. withdrew rofecoxib from the market due to excess risk of myocardial infarctions and stroke.[61] The decision to remove rofecoxib from the market resulted from negative cardiovascular findings in the APPROVe trial (Adenomatous Polyp Prevention On Vioxx), testing rofecoxib for adenomatous polyposis prevention. The study began in 2000 and consisted of 2,600 individuals with colon polyps. Of note, the study did not allow patients to have any cardiovascular disease.[61] Patients received either 25 mg of rofecoxib or a placebo. Participants were between 40 – 96 years of age, with approximately 62% male and 38% female. Aspirin use < 325 mg per day was permitted during the study.[62] Results indicated that 3.5 percent of individuals assigned to rofecoxib had a myocardial infarction or stroke, as compared to 1.9 percent of individuals assigned to the placebo group.[61] Although some cardiovascular events occurred during the first 18 months of the study, the link was not statistically evident until after 18 months of chronic use.[62]

Celecoxib Cardiovascular Safety

Just ten weeks after rofecoxib was withdrawn from the market, Pfizer announced that patients taking celecoxib in a long-term cancer prevention trial experienced a 2.5-fold increase in risk of experiencing a cardiovascular event compared to those taking a placebo. Patients in the Adenoma Prevention with Celecoxib (APC) trial were taking 400

mg and 800 mg of celecoxib daily. In contrast, a second long-term study, the Prevention of Spontaneous Adenomatopus Polyps (PreSAP) trial, has not revealed an increased risk in patients taking 400 mg daily of celecoxib as compared to those taking placebo. The two studies, comprising 3,600 patients, are following patients over a five-year period. From these two studies, nearly 2,400 patients evaluated in the cardiovascular analysis had completed at least two years of treatment. [63]

Biological Plausibility

Inhibition of the COX-1 enzyme has been shown to increase the risk of upper GI bleeding by inhibition of thromboxane (TX) A_2 mediated platelet function and impairment of prostaglandin (PG) E_2 mediated cytoprotection (see Figure 1).[50] Whereas, "selective COX-2 inhibition blocks PGI_2 [for explanatory purposes, PGI_2 serves to inhibit platelet aggregation and acts as a mediator of inflammation[64]] formation without inhibiting platelet derived TXA_2, thereby increasing platelet activation, adhesion, and aggregation with a resultant possibility for thrombosis and ischemic events."[43] Large clinical trials have demonstrated aspirin's ability to prevent myocardial infarctions and ischemic strokes through inhibition of platelet COX-1.[50] Traditional NSAIDs are also believed to provide varying levels of cardiovascular protection through the inhibition of COX-1. Even though celecoxib and rofecoxib specifically target the COX-2 isoform, they do have varying levels of COX-1 inhibition.[50,65] The biochemical selectivity of rofecoxib for COX-2 as compared to COX-1 has been shown to be up to nine times

greater than celecoxib.[50] Additionally, celecoxib demonstrated a dose-dependent inhibition of platelet COX-1 up to 800 mg.[50,65] In contrast, rofecoxib did not demonstrate a dose response relationship with platelet COX-1 activity up to 1000 mg. The high dose of celecoxib (800 mg) in the CLASS study may have provided sufficient inhibition of COX-1 to prevent a significant number of cardiovascular events.

Results from the CLASS study failed to show a significant difference in rates of complicated GI and cardiovascular events between celecoxib and comparator NSAIDs. Results may reflect the inadequate selectivity of celecoxib for the COX-2 enzyme. In contrast, rofecoxib demonstrated a significantly lower incidence of endoscopic ulcers when compared with naproxen. However, rofecoxib did demonstrate a higher incidence of cardiovascular events as compared to naproxen. Results (GI and cardiovascular) from the VIGOR study may reflect the enhanced selectivity of rofecoxib for the COX-2 isoform.

Further research supporting negative cardiovascular effects of COX-2 inhibition revealed that COX-2 may be a significant factor in late phase ischemic preconditioning (ischemic preconditioning is a process whereby brief episodes of sublethal ischemia render the myocardium resistant to subsequent ischemic stress). The inhibition of COX-2 activity may add to myocardial cell death by obliterating the innate defensive response of the heart against ischemia and reperfusion injury.[66]

Unlike aspirin and traditional NSAIDs, in vitro studies have found that celecoxib and rofecoxib do not inhibit platelet aggregation or prolong bleeding time.[67] Interestingly, one study suggests that ibuprofen and celecoxib may antagonize the COX-1

inhibition produced by aspirin. Celecoxib, with some COX-1 selectivity may compete with aspirin's platelet inhibitory effects. In contrast, rofecoxib was not shown to interfere with aspirin's antiplatelet effects. This could be problematic when evaluating cardiovascular risk among patients taking aspirin for cardiovascular protection. Of note, one study did not demonstrate the same association with celecoxib and aspirin.[67]

One theory explaining the association between rofecoxib and cardiovascular risk, is the effect of rofecoxib on human low density lipoprotein (LDL) oxidation. LDL oxidation is an important contributor to atherosclerosis.[68] This effect is believed to be related to the chemical structure and not related to COX-2 inhibition. Etoricoxib and rofecoxib exhibited prooxidant activity; whereas, celecoxib, valdecoxib and traditional NSAIDs were not associated with changes in lipid peroxidation rates.

Another possible factor explaining the difference in cardiovascular events between rofecoxib and celecoxib is the propensity of these agents to alter blood pressure and cause edema. Even though both agents have been found to affect blood pressure and edema, a randomized double-blind study comparing the two found significantly higher levels of edema and elevated blood pressure in the rofecoxib group.[69] Data also suggest that COX-2 inhibitors may provide significant attenuation of the antihypertensive effects of angiotensin converting enzyme (ACE) inhibitors and diuretics.[51,70-73]

Discussion

The clinical trials to date were not designed to adequately evaluate the cardiovascular risk profiles of the COX-2 inhibitors. The low cardiovascular risk (less than one percent per year) and the short follow-up period in both the VIGOR and CLASS trials (9 and 6 months, respectively), limit the ability to detect moderate differences of major cardiovascular events between COX-2 inhibitors and traditional NSAIDs.[33,50] The negative results of the VIGOR study could be explained by chance, selective inhibition of COX-2, prooxidant activity, effects on hypertension and edema, cardioprotective effects of naproxen, or a combination of these factors.

To date, no prospective studies have been specifically conducted to evaluate the cardiovascular risks associated with COX-2 inhibitors. In addition to celecoxib, rofecoxib, and valdecoxib, several NSAIDs possess some COX-2 selectivity (e.g. diclofenac and etodolac). To date, no study has specifically examined etodolac's or diclofenac's cardiovascular risk.

Several researchers have indicated the need for larger, more rigorous, prospective randomized studies to evaluate the potential cardiovascular effects of selective COX-2 medications. However, large prospective experimental studies can be costly and time consuming. Historical cohort studies and case control studies can be a timely and effective method for evaluating the potential cardiovascular risks associated with COX-2 inhibitors.

Information obtained from epidemiological studies evaluating the possible cardiovascular risk associated with COX-2 inhibitors will help researchers and clinicians determine appropriate therapeutic regimens for the treatment of patients. Additionally, the information obtained will allow evaluation of the potential tradeoffs associated with COX-2 inhibitors in relation to GI and cardiovascular events.

Researchers have advocated the use of aspirin in patients with increased cardiovascular risk taking COX-2 inhibitors. However, it is possible that concomitant use of aspirin may not fully offset the increased risk of selective COX-2 inhibitors. Limited data are available regarding the gastrointestinal effects of combining aspirin with COX-2 inhibitors. The addition of aspirin could negate the gastrointestinal benefits that COX-2 inhibitors provide.

Due to the rising popularity of this new class of medication, future research evaluating the cardiovascular differences between the COX-2 inhibitors and traditional NSAIDs is warranted. Additionally, further research is needed to evaluate the possible cardioprotective effects of naproxen.

SECTION IV

PURPOSE – OBJECTIVES - HYPOTHESES

Purpose of the Study

The purpose of this study was to evaluate the association of cardiovascular events with COX-2 inhibitors. In particular, the study describes and compares cardiovascular events occurring in patients taking traditional NSAIDs and those taking COX-2 inhibitors. Furthermore, cardiovascular risk differences or similarities between naproxen and other traditional NSAIDs/COX-2 inhibitors will be evaluated. In order to obtain a better understanding of the group dynamics, the cardiovascular profiles associated with each study group will be assessed. Prior aspirin use and duration of NSAID therapy will be analyzed and factored into the model.

Study Objectives

The objectives of this study were:

I. To evaluate serious cardiovascular events (AMI, stroke, cardiovascular mortality) associated with use of COX-2 inhibitors;

II. To determine if naproxen offers greater cardioprotective benefits compared to other NSAIDs; and

III. To determine if duration of naproxen/COX-2 inhibitor use has an effect on cardiovascular outcomes (protective for naproxen and cardio-negative for COX-2 inhibitors).

Hypotheses

The hypotheses in this study will take the null form. The following hypotheses were tested:

OBJECTIVE I

H_o1: There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **rofecoxib** versus patients taking a traditional NSAID (i.e., ibuprofen), while controlling for various covariates. Overall use (short-term and long-term use)

H_o2: There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **celecoxib** versus patients taking a traditional NSAID (i.e., ibuprofen), while controlling for various covariates. Overall use

H_o3: There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **etodolac** versus patients taking a traditional NSAID (i.e., ibuprofen), while controlling for various covariates. Overall use

OBJECTIVE II

H_o4: There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **naproxen** versus patients taking another traditional NSAID (i.e., ibuprofen), while controlling for various covariates. Overall use

OBJECTIVE III

Short-term exposure

H_o5: There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **celecoxib** short term (≤ 180 days) and patients taking ibuprofen short-term, while controlling for various covariates.

H_o6: There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **rofecoxib** short term (≤ 180 days) and patients taking ibuprofen short-term, while controlling for various covariates.

H_o7: There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **etodolac** short term (≤ 180 days) and patients taking ibuprofen short-term, while controlling for various covariates.

H_o8: There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **naproxen** short term (≤ 180 days) and patients taking ibuprofen short-term, while controlling for various covariates.

Long-term exposure

H_o9: There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **celecoxib** long-term (> 180 days) and patients taking ibuprofen long-term, while controlling for various covariates.

H_o10: There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **rofecoxib** long-term (> 180 days) and patients taking ibuprofen long-term, while controlling for various covariates.

H_o11: There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **etodolac** long-term (> 180 days) and patients taking ibuprofen long-term, while controlling for various covariates.

H_o12: There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **naproxen** long-term (> 180 days) and patients taking ibuprofen long-term, while controlling for various covariates.

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CHAPTER TWO
Methodology

CHAPTER OUTLINE

Prescription and health care services utilization and mortality data were collected and analyzed to meet the objectives and test the hypotheses outlined in Chapter One. This chapter describes the data sources, study population, study design, study variables, and the statistical procedures used in the study.

Study Overview

The study used a population-based retrospective cohort study design using the VA Heart of Texas Health Care Network databases. Patients selected for the study were 35 years of age or older and dispensed a traditional NSAID or COX-2 inhibitor during the study period. The lower occurrence of cardiovascular events in patients younger than 35 years of age necessitated the removal of these patients from the study population. The study period extended from January 1, 1999 through December 31, 2001. Mortality data provided by the Texas Department of Health and Medicare claims data were used to capture additional outcome measures. Analysis of events in relation to person-time for cardiovascular and cerebrovascular events and cardiovascular-related mortality were analyzed using the Cox regression model.

DATA SOURCES

Veterans Administration

The Department of Veterans Affairs (VA) database offers extensive information concerning health services provided to Veterans. The ability to examine a large number of patients and the availability of clinical laboratory data make the VA database extremely useful for evaluating drug-related adverse events. Other strengths of this database include: the lack of recall and interviewer bias, the capture of prescription claims, the low cost, and the ability to compare similar populations groups. However, there are still weaknesses associated with the database. Weaknesses include: availability of alternative health care coverage, generalizability, compliance issues, inability to capture over-the-counter medications, and the use of a drug formulary.

Medical Insurance

One methodological concern is the ability of Veterans to receive healthcare from sources outside the VA healthcare system. The largest provider of health coverage outside the VA healthcare system is Medicare, providing coverage to roughly 25 percent of Veterans. An additional 15.7 percent of Veterans receive some form of health coverage other than the VA or Medicare. The remaining 56 percent of Veterans do not receive any additional healthcare coverage outside the VA Health Care System.[1] Of note,

only 0.1 percent of Veterans have additional prescription coverage.[1] A detailed listing of health care coverage is provided in Table 2.1.

Table 2.1 – U.S. Veterans Insurance Coverage for Fiscal Year 2000

Type of Insurance*	No. (%)
No Insurance	19,817,247 (56.1)
Medicare	8,950,800 (25.3)
Medicare Supplemental	1,040,101 (2.9)
Major Medical	3,462,186 (9.8)
PPO/HMO	1,438,686 (3.9)
Medicaid	130,215 (0.3)
Prescription	51,759 (0.1)
All Other	381,237 (1.6)
Missing	825 (0.0)

Source: VA Information Resource Center (VIReC)[1]
* Coverage provided by sources outside the VA Health Care System

Generalizability

Utilizing databases can raise concerns regarding the generalizability of the results to other populations. However, using a single database does have advantages. By using the same database for cases and controls, factors such as socioeconomic status may be controlled.[2] One of the primary differences between the Veteran population and other populations is the disproportionate number of men compared to women. Women only comprise roughly 5 percent of the Veteran population.[1] The disproportionate number of men to women may be advantageous because other studies evaluating COX-2 inhibitor related cardiovascular risk consisted primarily of women (COX-2 inhibitor study groups ~ 70% women).[3,4] Furthermore, the level of comorbidities may be higher in the VA population and may the results may not be generalizable to healthier populations.

Pharmacy data

Regarding prescription coverage, even though automated pharmacy claims are one of the best sources of information on drug use, information concerning compliance and use of drugs from outside sources may be lacking.[2] Areas of concern are drugs taken intermittently for symptomatic relief (i.e., NSAIDs), compliance, over-the-counter drugs (OTC), and drugs not on the formulary.[2]

Compliance and duration of therapy

To treat painful symptoms, NSAIDs are often used. These medications are usually provided to patients on an as needed basis or as a scheduled regimen. However, many patients will not utilize this therapeutic option to its maximum potential. For example, compliance rates among arthritis patients taking (traditional) NSAIDs range from 54% to 85%.[5,6] Furthermore, treatment duration may vary between users of traditional NSAIDs and COX-2 inhibitors. A study using the provincial health care database in Quebec, Canada to evaluate new users of NSAIDs and COX-2 inhibitors found a longer duration of treatment with COX-2 inhibitors than traditional NSAIDs. More specifically, the median duration of treatment for patients prescribed celecoxib was 30 days, 23 days for rofecoxib, and 10 days for traditional NSAIDs.[7]

Over-the-counter drug use

Regarding automated pharmacy claims data, one factor that may not be accounted for is the use of OTC medications, particularly aspirin and NSAIDs. One benefit of using the VA pharmacy database is the fact that OTC aspirin and NSAID use is accounted for in their database. However, even though patients have a financial incentive to obtain aspirin and OTC medications through the VA, patients may still obtain these products from other sources.

VA Formulary Criteria for COX-2 inhibitors

One of the primary limitations surrounding the use of prescription claims data obtained from the VA is the restricted formulary. In particular, COX-2 inhibitors are limited to individuals with a high risk of developing NSAID-induced GI injury. Many patients are required to receive prior treatment with traditional NSAIDs or preferential COX-2 inhibitors. (Preferential COX-2 inhibitors are NSAIDs with relative COX-2 selectivity. Drugs included in this category are etodolac, nabumetone, and salsalate.[8]) The requirement of prior NSAID exposure limited the number of individuals with an adequate washout period (period of no NSAID/COX-2 inhibitor use) prior to NSAID/COX-2 inhibitor exposure. A detailed listing of the VA formulary concerning COX-2 inhibitors is provided in Table 2.2.[8]

Table 2.2 – Recommendations for the Use of NSAIDs or COX-2 Inhibitors in Veteran Patients (Formulary):

- **Individuals with a higher risk for NSAID-induced GI injury:**
    - Prior history of a hospital admission for a **serious** gastrointestinal event (gastroduodenal perforation, ulcer or bleed).
    - Concurrent use of warfarin (reinforce to patients to report any signs and symptoms of bleeding. In addition, patients and their INRs should be monitored more closely when any new drug is initiated). Both celecoxib and rofecoxib may increase INR and may increase the risk for bleeding.
    - Additionally, high risk patients with OA must receive a therapeutic trial of acetaminophen 4000 mg qd prior to a COX-2 inhibitor.

- **Other individuals (*Patients not having a history of hospital admission for a significant gastrointestinal event or those not receiving warfarin must have a GI risk score calculated*)**
    - **No risk** (GI score 0-10) **–** Use formulary traditional NSAIDs.
    - **Moderate risk** (GI score 11-15) **–** Use formulary traditional NSAIDs.
    - **Significant risk** (GI score 16-20) **–** Use "preferential COX-2 inhibitors" (e.g. etodolac or diclofenac).
        - If no response or intolerant, then traditional NSAID (ibuprofen, naproxen, etc) plus proton pump inhibitor (PPI) or misoprostol or a COX-2 inhibitor.
        - In patients receiving low dose aspirin for cardiovascular prophylaxis, a non-selective NSAID plus a PPI or misoprostol is preferred since the GI safety of the COX-2 inhibitors is reduced or lost.
    - **Substantial risk** (GI score > 20) – Salsalate, traditional NSAID (ibuprofen, naproxen, etc) plus PPI or misoprostol, or a COX-2 inhibitor.
        - In patients receiving low dose aspirin for cardiovascular prophylaxis, a non-selective NSAID plus a PPI or misoprostol is preferred since the GI safety of the COX-2 inhibitors is reduced or lost.

Texas Department of Health

Mortality data from the Texas Department of Health was required to capture fatal cardiovascular events occurring outside the VA healthcare system. The VA medical databases only capture mortality if someone died at the hospital. Patients meeting the study criteria within the VA database were linked via Social Security Numbers (SSN) to the Texas Department of Health mortality database to extract the required information. Mortality data were collected from the Texas Department of Health from January 1997 through December 2002.

Medicare

Another limitation regarding the use of VA healthcare databases is the ability of Veterans to receive health care coverage outside the VA health care system. Veterans over the age of sixty-five are eligible to receive medical services through Medicare. As previously discussed, roughly 25% of Veterans receive additional coverage from Medicare.[1] In order to minimize missing information due to utilization of outside healthcare coverage, patients over the age of sixty-five meeting the study criteria were evaluated separately in a sensitivity analysis. Medicare data were collected from January 1999 through December 2002.

STUDY POPULATION

The study encompasses patients receiving health care services from the VA Heart of Texas Health Care Network, termed Veterans Integrated Service Network (VISN) 17. VISN 17 serves a population of 1 million veterans living in 134 counties across central Texas. The network consists of seven medical centers and 58 clinic sites.[9] These sites are organized under three health care systems: the VA North Texas Health Care System, the VA Central Texas Health Care System, and the South Texas Veterans Health Care System. A more detailed representation of the VISN 17 health care system profile is provided in Table 2.3 and Figure 2.1.

Table 2.3 – Veterans Integrated Service Network (VISN) 17

VA North Texas Health Care System

- Medical Centers
  - Dallas VA Medical Center (Dallas, TX)
  - Sam Rayburn Memorial Veterans Center (Bonham, TX)
- Fort Worth Outpatient Clinic (Fort Worth, TX)
- Numerous Community-Based Outpatient Clinics

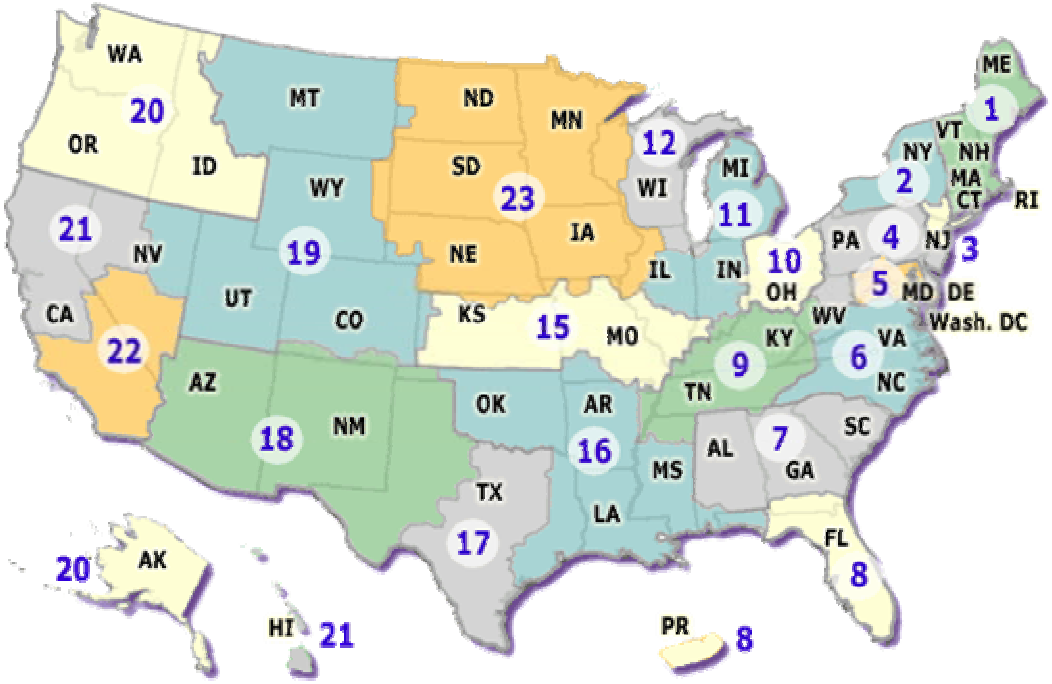
VA Central Texas Health Care System

- Medical Centers
  - Olin E Teague Veterans' Center (Temple, TX)
  - Waco VA Medical Center (Waco, TX)
  - Thomas T. Connally VA Medical Center (Marlin, TX)
- Austin Outpatient Clinic (Austin, TX)
- Numerous Community-Based Outpatient Clinics

VA South Texas Health Care System

- Medical Centers
  - Kerville VA Medical Center (Kerville, TX)
  - Audie L. Murphy Memorial Veterans Hospital (San Antonio, TX)
- Outpatient Clinics
  - Frank M. Tejeda VA Outpatient Clinic (San Antonio, TX)
  - Corpus Christi Clinic (Corpus Christi, TX)
  - McAllen Clinic (McAllen, TX)
  - Laredo Clinic (Laredo, TX)
  - Victoria Clinic (Victoria, TX)
- Numerous Community-Based Outpatient Clinics

Figure 2.1 – United States Map Representing the 23 Veterans Integrated Service Networks.



INVESTIGATIONAL REVIEW BOARD & DATA USE AGREEMENTS

1. University of Texas at Austin - *Approved*
2. University of Texas at San Antonio- *Approved*
3. Veterans Administration – North - *Approved*
4. Veterans Administration – Central - *Approved*
5. Veterans Administration – South - *Approved*
6. Texas Tech University - *Approved*
7. Texas Department of Health – Bureau of Vital Statistics - *Approved*
8. Veterans Administration Medicare Data - *Approved*

RESEARCH DESIGN

The primary study objective was to compare the incidence of cardiovascular events and death from coronary heart disease in Veterans dispensed NSAIDs and COX-2 inhibitors. To meet this objective, a population-based retrospective cohort study design was used (Figure 2.2, page 83).

Cohort Definition

Study period

The administrative health care databases within VISN 17 allowed for cohort identification and selection. The initial selection criterion required the administration and use of any NSAID or COX-2 inhibitor between September 30, 1995 through April 1, 2004. Due to this restrictive criterion, a control group consisting of patients not receiving NSAIDs or COX-2 inhibitors was not available for comparative analyses. From this initial cohort, the sample was further restricted and inclusion and exclusion criteria were applied in order to define the final study cohorts.

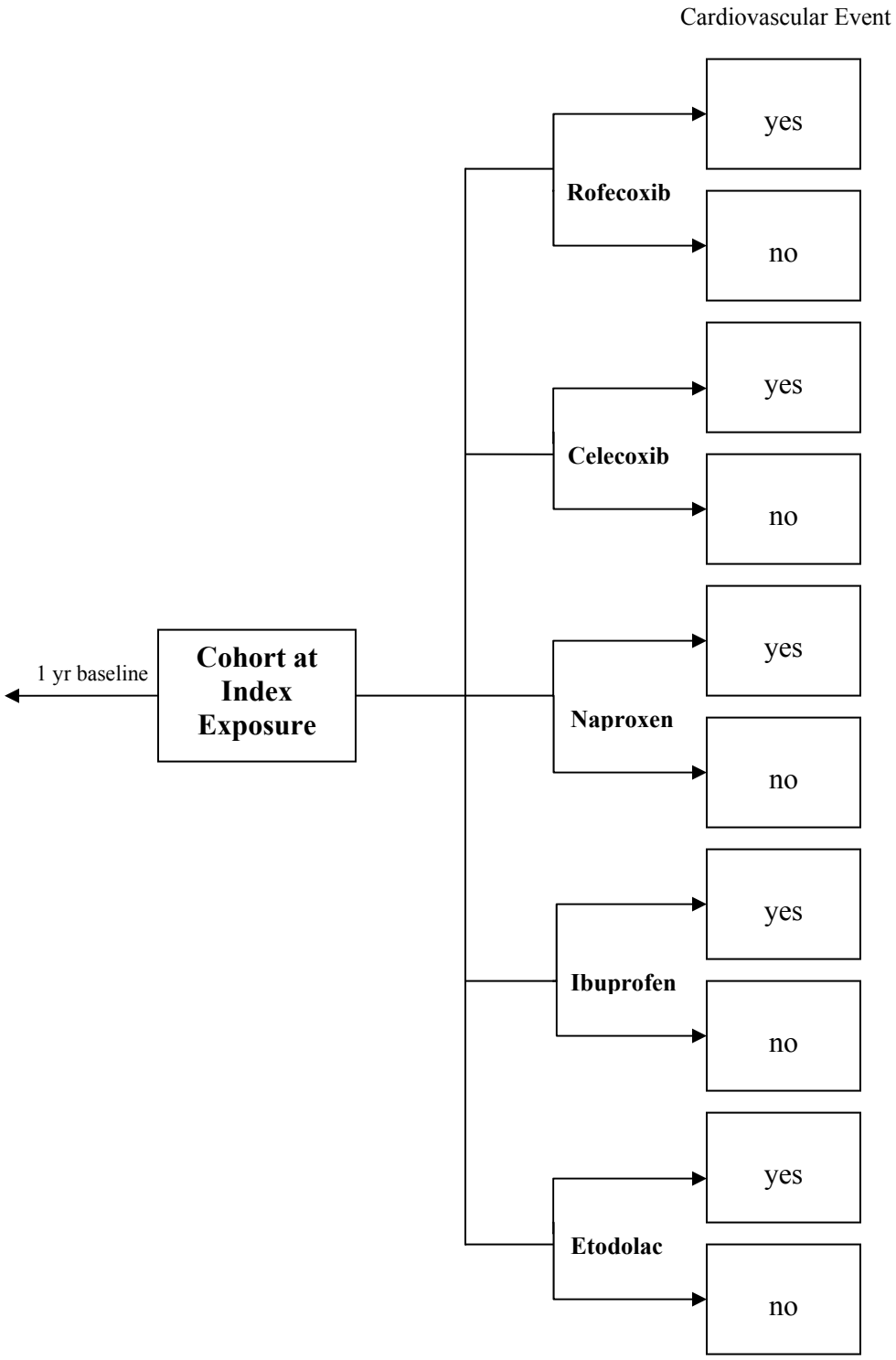
The baseline study period was restricted to January 1, 1999 through December 31, 2001. This time period was chosen to correspond with the approval of the first COX-2 inhibitor introduced into the U.S. market and completeness of available data (Medicare and TDH data). Additionally, reports linking cardiovascular risk to COX-2 inhibitors

became prominent in the years following 2001. This information could cause a channeling effect. Therefore, caution should be used in analyzing data after 2001. Due to the concern of channeling, the 2002 data were only incorporated into the study design as a sensitivity analysis. Celecoxib was approved December 31, 1998 and rofecoxib was approved May 20, 1999.[10] Data from January 1, 1998 to December 31, 1998 were used to evaluate prior cardiovascular conditions, NSAID/COX-2 inhibitor exposure, and confounding factors.

Study groups

Patients were stratified into five different study groups determined by NSAID and COX-2 inhibitor exposure. The study groups include: naproxen, ibuprofen, etodolac celecoxib, and rofecoxib. Ibuprofen served as the control for the other four study groups. Additionally, naproxen and etodolac also served as a control group in several sensitivity analyses. The initial prescription during the study period was used as the index date. Patients were not allowed to receive the study drug one year prior to the index date. Additionally, patients who received a prescription for other COX-2 inhibitors or NSAIDs in the six months prior to their index date were not allowed in the study (wash-out period).

Figure 2.2 – Historical Cohort Study Design



Duration of Exposure

Duration of cohort involvement started on the index date and lasted until the individual experienced a censorship point: study end-point event, exposure to another NSAID or COX-2 inhibitor, death (non-cardiovascular related death), discontinued study medication, or reached the end of the study (December 31, 2001). Patients were allowed to re-enter the cohort or join a new cohort so long as the patient met the inclusion criteria. Patients who died or experienced a study endpoint were not allowed to re-enter the cohort. Due to the short nature of the study, the follow-up period was not limited, thus allowing patients to be followed the entire duration of the study.

The study groups were restricted to patients being dispensed enough drug for at least 30 days of observation and receiving at least one subsequent prescription. This restriction was used to exclude sporadic users of NSAIDs and to ensure exposure to the study medication. Drug therapy must have begun on or after the start date (January 1, 1999); patients who started therapy prior to this date were not evaluated. Patients who were dispensed more than one study drug on the index date were excluded. Patients were allowed a 20% grace period on the previous days supply to refill the next prescription. Inpatient pharmacy data were available for a portion of the population; patients receiving a study drug while admitted to the hospital were allowed a 10-day grace period to experience a subsequent exposure.

As mentioned in Chapter One, on September 30, 2004, rofecoxib was voluntarily withdrawn from the market due to a recent prospective, randomized, placebo-control trial, the APPROVe (adenomatous Polyp Prevention on VIOXX) trial.[11,12] In this trial involving 2,600 patients with a history of colorectal adenomas (without any cardiovascular disease), an increase in cardiovascular risk was found after 18 months of continuous therapy. Of those taking 25 mg of rofecoxib, 3.5 percent of these patients had a stroke or myocardial infarction, as compared to 1.9 percent of patients in the placebo group. Results from the first 18 months did not show any increased risk of confirmed cardiovascular events.

Therefore, in order to assess the cardiovascular effect of long-term exposure vs. short-term exposure to COX-2 inhibitors, the study sample was first restricted to those receiving greater than 180 days of study medications. During the previous 180 days, if a patient experienced a study endpoint (i.e., AMI, stroke, and/or AMI related death), he or she was excluded from the long-term analysis. Additionally, patients receiving short-term ($\leq$ 180 days) therapy were evaluated separately for an increased cardiovascular risk. The 180 day time period was chosen due to the short duration (less than 6 months) of many of the clinical trials evaluating COX-2 inhibitors. This decision was made prior to the availability of long-term clinical trial information (such as the APPROVe study).

Exclusion Criteria

Age – The lower occurrence of cardiovascular events in patients younger than 35 years of age necessitated the removal of these patients from the study population. Based on national Veterans demographic information, patients under the age of 35 comprise only a small proportion of the total population, roughly 2.5%.[1] Information regarding age-related cardiovascular events can be found in Chapter One.

Exposure – Patient observations with less than 30 days of study medication were excluded. Additionally, only observation periods with two or more prescriptions were considered.

Washout period – Patients who received a study drug one year prior to the index date were excluded. Additionally, patients exposed to other NSAIDs or COX-2 inhibitors within the six months prior to the index date were excluded.

One-year baseline period – Patient observations without at least one year of prior health care use within the VA health care system were excluded.

Study Endpoints

Acute Myocardial Infarction (AMI) – AMI was defined as a patient who received an ICD-9 diagnosis code of 410.xx. Research conducted within the VA healthcare system found a 96.9% positive predictive value of acute myocardial infarction coding in the primary position.[16] Patients discharged alive were required to have a length of stay no less than three days and no greater than 180 days. The results from this study are similar to other studies validating the positive predictive value of MI ICD-9 codes. Of note, duration of stay and position of the ICD-9 code were not available and were not assessed, thus decreasing the positive predictive value of the AMI diagnosis.

Death from AMI – ICD-10 codes: I21 – I22.

Death from "major cardiovascular diseases" – ICD-10 codes: I00 – I78.

*Death from "*ischemic heart disease*"* – ICD-10 codes: I20 – I25.

Cerebrovascular Disease – A study conducted within the VA healthcare system assessing code veracity of stroke-related ICD-9 codes has been conducted. When a high sensitivity model was used, results yielded 89% sensitivity, 57% specificity, 60% positive predictive value, and 88% negative predictive value. When a high specificity algorithm

was used, the results change to: 59% sensitivity, 84% specificity, 72% positive predictive value, and 74% negative predictive value.[17]

ICD-9 codes high sensitivity model (using all fields): 430, 431, 432.0, 432.1, 432.9, 434.00 - 434.01, 434.10-434.11, 436

ICD-9 codes high-specificity model (using all fields): 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00 - 434.01, 434.10-434.11

Confounding Variables

The assessment period was one year prior to enrollment (except age) for all covariates.

Neoplasm[18] – ICD-9 codes: 140.00 – 239.9, 795.0 - 795.1, V10.00 - V10.99, V71.1, V12.72.

Human Immunodeficiency Virus (HIV)[18] – ICD-9 codes: 042.00 - 044.99, V08, 795.71, 79.53, 279.10, 279.19, 795.8.

Renal Failure[18,19] – ICD-9 codes: 584.5 - 585, 586, 792.5, V42.0, V45.1, V56.0-V56.32, V56.8.

Respiratory failure, insufficiency, arrest[18] – ICD-9 codes: 518.5, 518.81 – 518.84, 799.1, V461 – V462

Diabetes[18] – A diagnosis of diabetes required at least one of two criteria: 1) receiving one or more of the following IDC-9 codes:[18] 250.00-250.99, 790.2, 791.5 - 791.6; and/or use of a diabetic medication.

Age[20] – Age was assigned at the time of enrollment. Age was treated as a continuous variable. Participants 35 years of age and older were included. For descriptive purposes age was subdivided into four different categories: < 64 years of age; 65 – 74 years of age; 75 – 84 years of age; and ≥ 85 years of age.

Sex – Male/Female

Race[1] – ***was not included due to missing data***.

Rheumatoid arthritis[18] – The following ICD-9 Codes were used to define RA: 714.0 – 714.9, 720.0

Osteoarthritis arthritis[18] – The following ICD-9 Codes were used to define OA: 715.00 – 715.98, V13.4

Systemic lupus erythematosus and connective tissue disorders[18] – The following ICD-9 Codes were used to define systemic lupus erythematosus and connective tissue disorders: 710.0 – 710.9

Heart Failure[18,21] – Heart failure was defined as one or more health care visits for heart failure - ICD-9 codes: 428.0 – 428.9, 402.01, 402.11, 402.91, 404.01, 404.11, 404.13, 404.91, 404.93.

Previous AMI[21] – The assessment period was one year prior to enrollment into the study. The following ICD-9 Codes were used to define previous AMI: 410.xx.

Previous cerebrovascular disease[17] – The high-specificity model was used to assess prior cerebrovascular disease (with the exception of one sensitivity analysis, in that case the high-sensitivity model was used).

<u>*ICD-9 codes high-specificity model (using all fields):*</u> 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00 - 434.01, 434.10-434.11

Peripheral vascular disease[21,22] – The following ICD-9 codes were used to define peripheral vascular disease: 440.2, 443.1, 443.9, 444.22, 444.81. Additionally, cilostazol, cyclandelate, or pentoxifylline drug use served as an indicator for peripheral vascular disease.

Angina[21] – The following ICD-9 codes were used to define angina: 411 or 413. Additionally, patients dispensed a nitrate were classified as having angina.

Atrial fibrillation – The following ICD-9 code was used to define atrial fibrillation: 427.31

Chronic obstructive pulmonary disease[18,22] – The following ICD-9 codes were used to define COPD: 490 – 492.8, 496

Baseline Laboratory and Patient Vitals Information

Limited baseline laboratory and patient vitals information were available. Not every patient within the VA healthcare system was assessed for hypertension (BP), diabetes (glucose), and dyslipidemia (cholesterol values); subsequently, these factors were not included into the model. Additionally, factors such as height and weight (body mass index (BMI)) were not available for all patients and were not included. If these values were incorporated into the study model, the sample size would be severely reduced. Furthermore, patients for whom this information is available may represent a healthier population (e.g., regular doctor visits) or a sicker population (e.g., required to use medical services). Methods to deal with missing values, such as multiple imputation or list-wise deletion, require the assumption of "missing at random." As described

previously, patients not utilizing VA healthcare services are more than likely not missing at random. Baseline information will be provided for the following factors in order to delineate any major differences between the study groups. The assessment period was 365 days prior to enrollment for all laboratory and patient vitals information.

Hypertension[20] – Multiple readings were averaged to obtain an aggregate score. Patients were placed into five categories (for descriptive purposes) based on Framingham risk stratification and JNC 7 classification.[20,23] The blood pressure categories are presented in Table 2.4.

Table 2.4 – JNC 7 Classification of High Blood Pressure

BP Classification	Group	SBP mmHg	DBP mmHg
Normal	**I**	< 120	and < 80
Prehypertension	**II**	120-129	or 80-84
	III	130-139	or 85-89
Stage 1 Hypertension	**IV**	140-159	or 90-99
Stage 2 Hypertension	**V**	≥ 160	or ≥ 100

Cholesterol[24] – Multiple readings were averaged to obtain an aggregate score. Cholesterol was divided into four different categories. These four categories include: 1) total cholesterol, 2) low density lipoprotein (LDL), 3) high density lipoprotein (HDL), and 4) triglycerides. Categories were further subdivided based on Framingham risk categories and the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report.[20,24] The subcategories (for descriptive purposes) are described in Tables 2.5 – 2.8.

Table 2.5 – ATP III / Framingham Classification of Total Cholesterol (mg/dl)

Classification	Group	Total Cholesterol Level
Desirable	**I**	< 160
	II	160-199
Borderline high	**III**	200-239
High	**IV**	240-279
	V	≥ 280

Table 2.6 – ATP III / Framingham Classification of LDL Cholesterol (mg/dl)

Classification	Group	LDL Cholesterol Level
Optimal	**I**	< 100
Near optimal/above optimal	**II**	100-129
Borderline high	**III**	130-159
High	**IV**	160-189
Very high	**V**	≥ 190

Table 2.7 – ATP III / Framingham Classification of HDL Cholesterol (mg/dl)

Classification	Group	HDL Cholesterol Level
Low£	**I**	< 35
	II	35-44
	III	45-49
	IV	50-59
High	**V**	≥ 60

£ ATP III classifies low HDL Cholesterol as < 40 mg/dl.

Table 2.8 – ATP III Classification of Serum Triglycerides (mg/dl)

Classification	Group	Triglyceride Level
Normal	**I**	< 150
Borderline-high	**II**	150-199
High	**III**	200-499
Very High	**IV**	≥ 500

Body mass index[25] – Multiple readings were averaged to obtain an aggregate score. Height and weight were used to calculate body mass index (BMI). The following formula was used:

BMI = **(**weight in pounds / (height in inches) x (height in inches)**)** x 703

Patients were placed into four different categories based on BMI (for descriptive purposes).

- Underweight – Below 18.5
- Normal – 18.5 – 24.9
- Overweight – 25.0 – 29.9
- Obesity – 30.0 and above

Medications

To further control for differences in baseline risk for cardiovascular disease, prescription drugs were evaluated. The assessment period was 365 days prior to enrollment. The medication categories are detailed in Table 2.9. A more detailed list is provided in Appendix S.

Table 2.9 Baseline Medications

ACE inhibitors / ARBS	Lipid-lowering drugs
Antiarrhythmics	Loop diuretics
Antiplatelets	Methotrexate
Antirheumatics	Nitrates†
Aspirin	Other anticoagulants
β-Blockers	Other antihypertensives
Calcium channel antagonists	Peripheral vascular disease drugs†
Corticosteroids (oral/injectable)	Thiazide diuretics
Digoxin	Warfarin
Estrogen*	
Hypoglycemic agents†	

† Hypoglycemic, nitrates, and peripheral vascular disease drugs were combined with corresponding medical diagnoses.

* Not included in model, only baseline descriptive information.

Statistical Analyses

A historical cohort study design was used to analyze the cardiovascular effects of COX-2 inhibitors. An alpha level of 0.05 was used to test for statistical significance. Analyses were conducted using SPSS and SAS software. Frequency distributions and means for the study variables were examined. Analysis of events in relation to person-time was analyzed via the Cox proportional hazard model. The Wald test was used to determine statistical differences between individual NSAIDs/COX-2 inhibitors. The proportional hazards assumption for each variable was assessed in each analysis for any violations.

Proportional Hazards Assumption

Proportional hazards definition – "the hazard for any individual is a fixed proportion of the hazard for any other individual".[13] In other words, one of the key assumptions for the Cox regression model is that the ratio of the hazards is constant over time. Violation of the proportional hazard assumption is equivalent to the interaction between one or more covariates and time. Several methods are used to assess the proportional hazard assumption. Two of these methods include graphical evaluation and the incorporation of a time-dependent covariate representing the interaction of the original covariate and time. The initial step usually involves assessing the transformed Kaplan-Meier curves. If the hazards are proportional, the survival curves should be parallel. If the graphical results do not look parallel, then one will generate a time

dependent covariate by creating interactions between predictors and survival time. If the results are significant then those predictors are not proportional. Subsequently, "the method of diagnosis is also the cure."[13] Even in the event that the proportional hazard assumption is violated for some variable, the coefficient estimated for the variable will represent an "average" of the effect over the range of times observed in the data. [13]

Multicollinearity

Due the large number of covariates in the model, multicollinearity was checked. Multicollinearity is an unacceptably high level of intercorrelation among independent variables, causing the effects of the independent variables to be inseparable.[14] In the presence of multicollinearity, the estimates are unbiased; however, evaluation of the relative strength of the explanatory variables and their joint effects are unreliable.[14] To assess multicollinearity, correlation matrixes were created for all of the variables. A value above 0.80 was used to indicate a possible problem with multicollinearity.

The Cox proportional hazard equation used to analyze the data can be expressed as the following:

$$\ln h_i(t) = \ln \lambda_o(t) + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \beta_7 x_7 + \beta_8 x_8 + \beta_9 x_9 + \beta_{10} x_{10} + \beta_{11} x_{11} + \beta_{12} x_{12} + \beta_{13} x_{13} + \beta_{14} x_{14} + \beta_{15} x_{15} + \beta_{16} x_{16} + \beta_{17} x_{17} + \beta_{18} x_{18} + \beta_{19} x_{19} + \beta_{20} x_{20} + \beta_{21} x_{21} + \beta_{22} x_{22} + \beta_{23} x_{23} + \beta_{24} x_{24} + \beta_{25} x_{25} + \beta_{26} x_{26} + \beta_{27} x_{27} + \beta_{28} x_{28} + \beta_{29} x_{29} + \beta_{30} x_{30} + \beta_{31} x_{31} + \beta_{32} x_{32} + \beta_{33} x_{33} + \beta_{34} x_{34} + \beta_{35} x_{35} + \beta_{36} x_{36}$$

Where:

$h_i(t)$ = The hazard for individual i at time t;

$\lambda_o(t)$ = baseline hazard function;

x_1 = rofecoxib versus ibuprofen;
$\beta_1 = e^{\beta 1}$ – the ratio of the estimated hazard;

x_2 = celecoxib versus ibuprofen;
$\beta_2 = e^{\beta 2}$ – the ratio of the estimated hazard;

x_3 = naproxen versus ibuprofen;
$\beta_3 = e^{\beta 3}$ – the ratio of the estimated hazard;

x_4 = etodolac versus ibuprofen;
$\beta_4 = e^{\beta 4}$ – the ratio of the estimated hazard;

x_5 = age of the patient;
$\beta_5 = e^{\beta 5}$ – the ratio of the estimated hazard;

x_6 = gender of patient;
$\beta_6 = e^{\beta 6}$ – the ratio of the estimated hazard;

x_7 = renal failure diagnosis;
$\beta_7 = e^{\beta 7}$ – the ratio of the estimated hazard;

x_8 = cancer diagnosis;
$\beta_8 = e^{\beta 8}$ – the ratio of the estimated hazard;

x_9 = chronic obstructive pulmonary disease;
$\beta_9 = e^{\beta 9}$ – the ratio of the estimated hazard;

x_{10} = HIV diagnosis;

$\beta_{10} = e^{\beta 10}$ – the ratio of the estimated hazard;

Cox proportional hazard equation continued

x_{11} = respiratory failure diagnosis;
$\beta_{11} = e^{\beta 11}$ – the ratio of the estimated hazard;

x_{12} = diabetes diagnosis;
$\beta_{12} = e^{\beta 12}$ – the ratio of the estimated hazard;

x_{13} = rheumatoid arthritis diagnosis;
$\beta_{13} = e^{\beta 13}$ – the ratio of the estimated hazard;

x_{14} = osteoarthritis diagnosis;
$\beta_{14} = e^{\beta 14}$ – the ratio of the estimated hazard;

x_{15} = systemic lupus erythematosus and connective tissue disorders diagnosis;
$\beta_{15} = e^{\beta 15}$ – the ratio of the estimated hazard;

x_{16} = heart failure diagnosis;
$\beta_{16} = e^{\beta 16}$ – the ratio of the estimated hazard;

x_{17} = prior myocardial infarction;
$\beta_{17} = e^{\beta 17}$ – the ratio of the estimated hazard;

x_{18} = previous cerebrovascular incident;
$\beta_{18} = e^{\beta 18}$ – the ratio of the estimated hazard;

x_{19} = peripheral vascular disease;
$\beta_{19} = e^{\beta 19}$ – the ratio of the estimated hazard;

x_{20} = angina;
$\beta_{20} = e^{\beta 20}$ – the ratio of the estimated hazard;

x_{21} = atrial fibrillation diagnosis;
$\beta_{21} = e^{\beta 21}$ – the ratio of the estimated hazard;

x_{22} = thiazide diuretic use;
$\beta_{22} = e^{\beta 22}$ – the ratio of the estimated hazard;

x_{23} = angiotensin converting enzyme (ACE) inhibitor use;
$\beta_{23} = e^{\beta 23}$ – the ratio of the estimated hazard;

x_{24} = antiarrhythmic medication use;

$\beta_{24} = e^{\beta 24}$ – the ratio of the estimated hazard;

Cox proportional hazard equation continued

x_{25} = anticoagulant medication use;
$\beta_{25} = e^{\beta 25}$ – the ratio of the estimated hazard;

x_{26} = antiplatelet medication use;
$\beta_{26} = e^{\beta 26}$ – the ratio of the estimated hazard;

x_{27} = antirheumatic medication use;
$\beta_{27} = e^{\beta 27}$ – the ratio of the estimated hazard;

x_{28} = aspirin use;
$\beta_{28} = e^{\beta 28}$ – the ratio of the estimated hazard;

x_{29} = β-blocker use;
$\beta_{29} = e^{\beta 29}$ – the ratio of the estimated hazard;

x_{30} = calcium channel antagonist use;
$\beta_{30} = e^{\beta 30}$ – the ratio of the estimated hazard;

x_{31} = digoxin use;
$\beta_{31} = e^{\beta 31}$ – the ratio of the estimated hazard;

x_{32} = lipid-lowering medication use;
$\beta_{32} = e^{\beta 32}$ – the ratio of the estimated hazard;

x_{33} = loop diuretic use;
$\beta_{33} = e^{\beta 33}$ – the ratio of the estimated hazard;

x_{34} = methotrexate use;
$\beta_{34} = e^{\beta 34}$ – the ratio of the estimated hazard;

x_{35} = corticosteroid use (oral/injectable);
$\beta_{35} = e^{\beta 35}$ – the ratio of the estimated hazard;

x_{36} = other antihypertensive medication use;
$\beta_{36} = e^{\beta 36}$ – the ratio of the estimated hazard;

Sample Size Considerations

The sample size required for a cohort study depends on five factors.[15] The first factor is the *alpha (α) value or type I error* permitted. Type one error is the probability of finding a difference when one does not exist. For sample size estimation, the conventional α value of 0.05 will be used. The second factor to consider is the *beta (β) value or type II error* permitted. Type II error is the probability of finding no difference when a difference does exist. The conventional β value of 0.2 will be used for the sample size calculation. The third variable needed to calculate the sample size is the minimum relative risk one wants to detect. For estimation purposes, the minimum relative risk to be detected will be 1.25 (arbitrarily chosen). The expected incidence of the event in the control group is the fourth variable required. The rarer the event, the larger the sample size required. For estimation purposes (based on annual coronary event rates), the incidence in the control group will be 0.01 and 0.05 (to provide a range). The fifth variable used in estimating the sample size is the ratio of control subjects to exposed subjects. Additional power is obtained when the ratio of control subjects to exposed subjects increases. However, a limit is reached once the ratio reaches a 3:1 to 4:1 ratio. Due to the large number of patients in the control group (ibuprofen), a 4:1 ratio will be used in the sample size calculation. The equation used to estimate the sample size can be expressed as the following:[15]

$$N = \frac{1}{[p(1-R)]^2}\left[Z_{1-\alpha/2}\sqrt{\left(1+\frac{1}{K}\right)U(1-U)} + Z_{1-\beta}\sqrt{pR(1-Rp)+\frac{p(1-p)}{K}} \right]^2$$

Where:

p = the incidence of the disease in the unexposed group;

R = the minimum relative risk to be detected;

α = the type I error rate;

β = the type II error rate;

$Z_{1-\alpha}$ & $Z_{1-\beta}$ = the unit normal derivative corresponding to α and β;

K = the ratio of control subjects to exposed subjects; and

$U = \frac{Kp + pR}{K+1}$.

Using p = 0.01 or 0.05; R = 1.25; α = 0.05; β = 0.2; K = 4:1 the formula indicates that a sample size between **3,247** and **16,990** was needed in the exposed group.

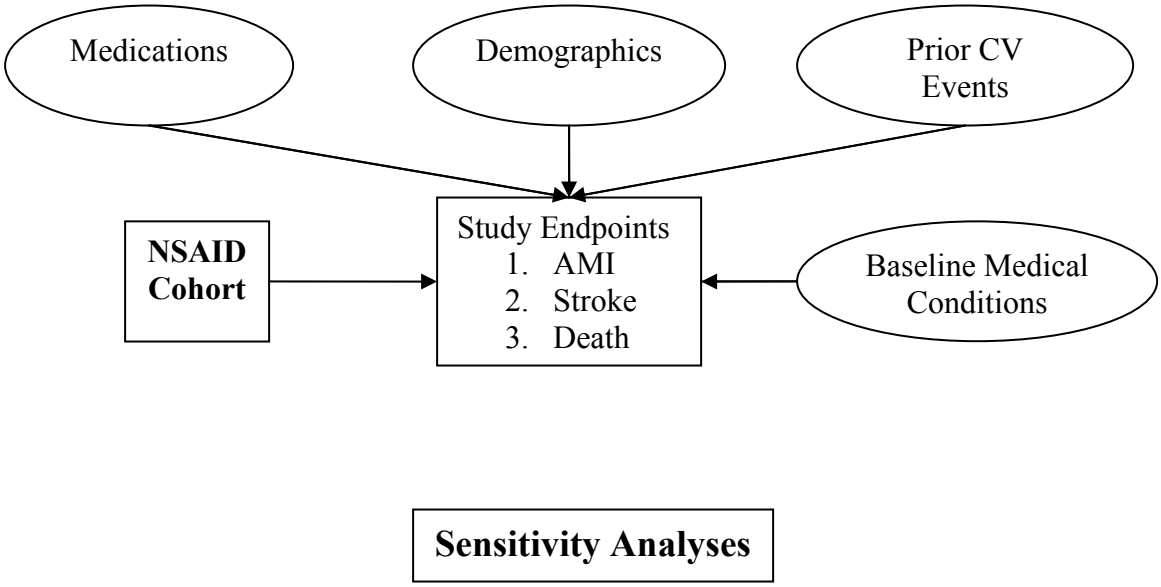
ANALYZING THE DATA / SENSITIVITY ANALYSES

Model I

The first model (Model I) provides an overall evaluation of the relationship between NSAID/COX2 inhibitor use and cardiovascular/cerebrovascular events (Figure 2.3). NSAID users were defined as someone who began taking a traditional NSAID or COX-2 inhibitor during the time they were eligible for the study and had not taken that drug in the prior 365 days. The control group used was ibuprofen users. Study endpoints used were: acute myocardial infarction, death from acute myocardial infarction, and cerebrovascular disease. Sensitivity analyses for Model I include:

1. Expansion of the mortality definition to take account of:
    a) death from major cardiovascular diseases; or
    b) death from ischemic heart disease.
2. Restriction of the population to individuals 65 years of age and older. This allowed for Medicare enrollment and focused on an older population.
3. Assessment of cerebrovascular events using high-specificity and high-sensitivity models (discussed in "study endpoints").
4. Use of naproxen and etodolac as the comparator group for celecoxib and rofecoxib.
5. Incorporation of one additional year of data into the model (2002).

Figure 2.3 – Model I – Historical Cohort Study Design with Confounding Factors

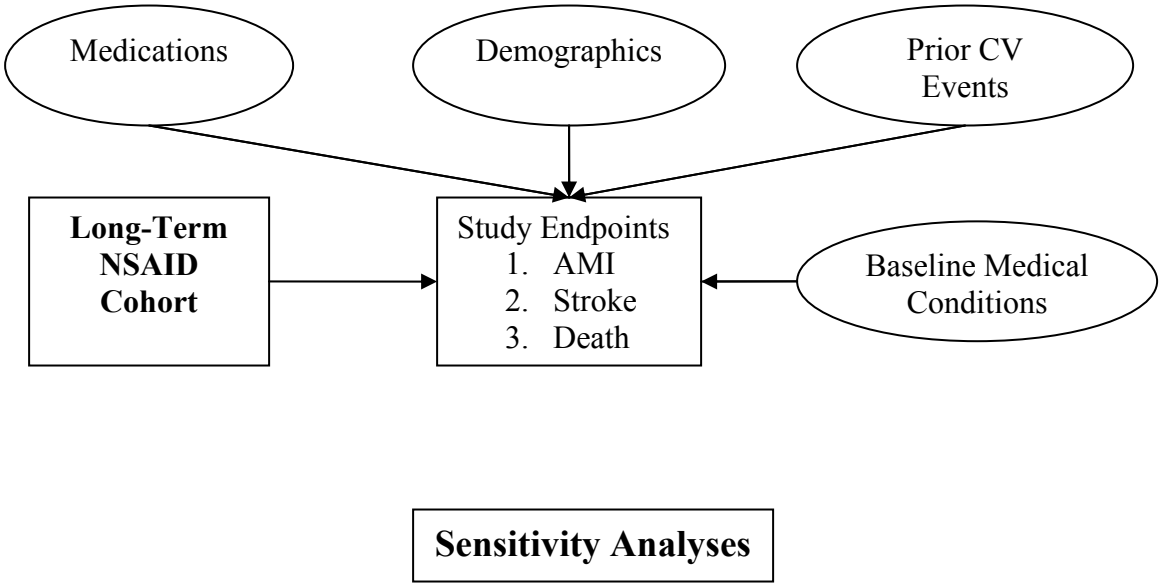


Model II

The second model (Model II) assessed the relationship between long-term use of NSAID/COX2 inhibitor and cardiovascular/cerebrovascular events (Figure 2.4). The interval of continuous NSAID/COX-2 use was extended from 30 days to greater than 180 days of exposure (events may not occur within the prior 180 days). The control group used was ibuprofen users. Study endpoints were: acute myocardial infarction, death from acute myocardial infarction, and cerebrovascular disease. Sensitivity analyses for Model II include:

1. Expansion of the mortality definition to take account of:
    a. death from major cardiovascular diseases; or
    b. death from ischemic heart disease.
2. Restriction of the population to individuals 65 years of age and older. This allowed for Medicare enrollment and focused on an older population.
3. Assessment of cerebrovascular events using high-specificity and high-sensitivity models (discussed in "study endpoints").
4. Use of naproxen and etodolac as the comparator group for celecoxib and rofecoxib.
5. Incorporation one additional year of data into the model (2002).
6. Allowing individuals who had an event in the first 180 days to be included in the model, primarily to further evaluate naproxen's cardioprotective abilities.

Figure 2.4 – Model II – Historical Cohort Study Design with Confounding Factors

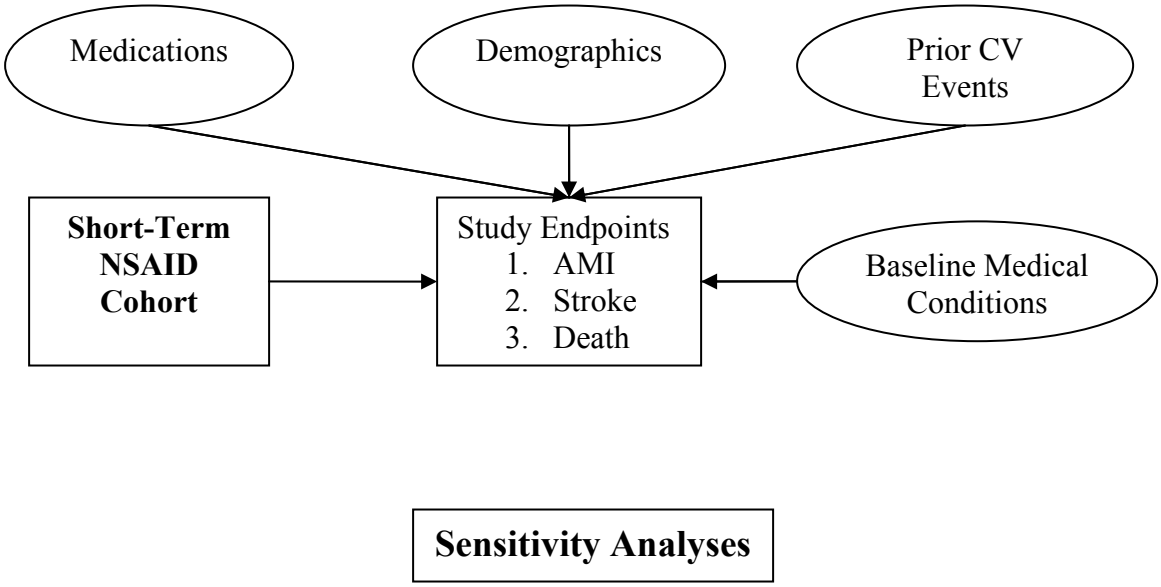


Model III

The third model (Model III) assessed the relationship between short-term use of NSAID/COX2 inhibitor and cardiovascular/cerebrovascular events (Figure 2.5). This analysis restricted the exposure period to the first 180 days of COX-2/NSAID therapy. Additionally, this analysis excluded individuals exposed to > 180 days of study medication. The control group was ibuprofen users. Study endpoints were: acute myocardial infarction, death from acute myocardial infarction, and cerebrovascular disease. Sensitivity analyses for Model III include:

1. Expansion of the mortality definition to take account of:
    a. death from major cardiovascular diseases; or
    b. death from ischemic heart disease.
2. Restriction of the population to individuals 65 years of age and older. This allowed for Medicare enrollment and focused on an older population.
3. Assessment of cerebrovascular events using high specificity and high sensitivity models (discussed in "study endpoints").
4. Use of naproxen and etodolac as the comparator group for celecoxib and rofecoxib.
5. Incorporation of one additional year of data into the model (2002).
6. Allowing individuals with long-term exposure to be incorporated into the model, but analysis limited to their first 180 days of exposure.

Figure 2.5 – Model III – Historical Cohort Study Design with Confounding Factors



Censoring and Drug Use Evaluation Periods

In order to provide the reader with a better understanding of the short-term and long-term models and corresponding sensitivity analyses, a conceptual diagram was created to illustrate the process. Figure 2.6 shows five possible observations occurring in the study. The figure is divided in short-term and long-term use. Overall use (model I) is a combination of long-term and short-term use. The index date is the initial exposure to the study drug. The **X** represents an endpoint event. The end of the line is when the observation was censored for some other reason.

Censoring

There are several reasons an observation was censored from the study. These are as follows:

a. Reached the end of the study;
b. Exposure to another NSAID;
c. Death (not due to a cardiovascular event);
d. Discontinued study medication; and
e. Experienced a study endpoint event.

Model I (overall use/any exposure) – captures all exposure periods and events occurring during the study period, lines **one, two, three, four**, and **five** were evaluated. See Figure 2.6.

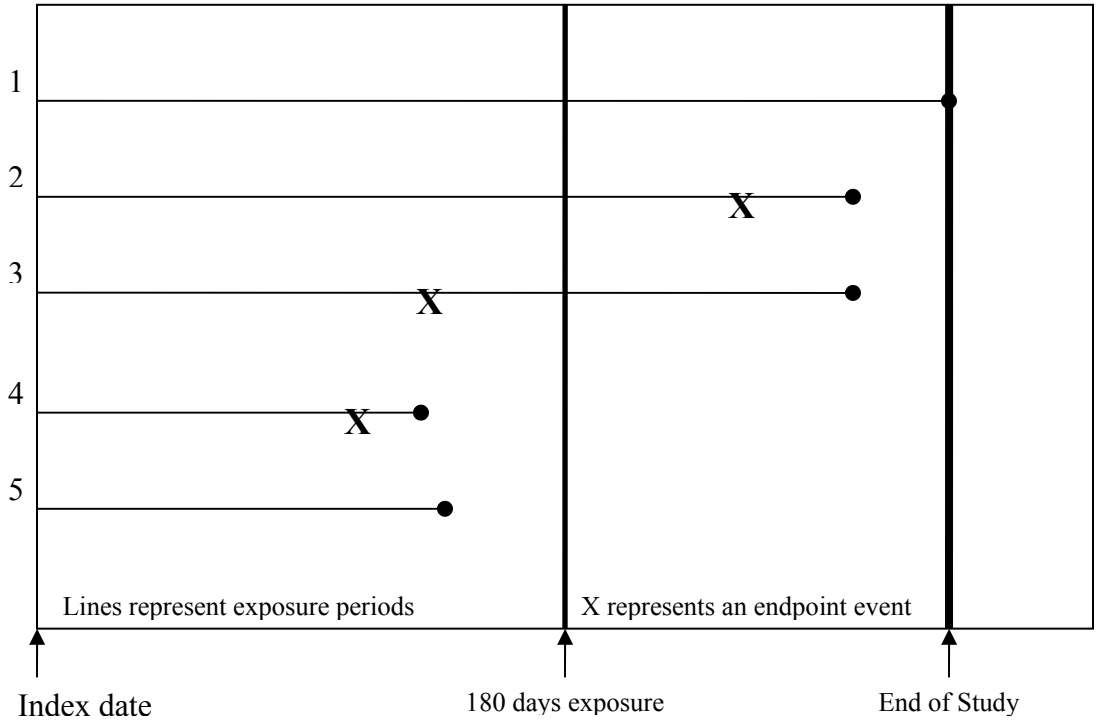
Model II – Limits exposure to long-term use observations, exposure periods greater than 180 days. Additionally, the model only evaluates events that have not occurred during the first 180 day period. Therefore, only lines **one** and **two** were included in the analysis. See Figure 2.6.

Model II – *sensitivity analysis* – Limits exposure to long-term use observations, exposure periods greater than 180 days. However, this model includes events occurring during the first 180 day exposure period. Lines **one**, **two**, and **three** were incorporated into the analysis. See Figure 2.6.

Model III – Limits exposure to short-term use observations, exposure periods less than 180 days. Additionally, the model excludes individuals who are exposed to the study medication for > 180 days. Therefore, only lines **four** and **five** were evaluated. See Figure 2.6.

Model III – *sensitivity analysis* – Limits exposure to short-term use observations, exposure periods less than 180 days. However, this model includes individuals who are exposed to the study medication over long periods of time but analysis is **restricted** to the first 180 days of exposure. Therefore, lines **one**, **two**, **three**, **four**, and **five** were evaluated, but only data from the first 180 days were analyzed. See Figure 2.6.

Figure 2.6 Conceptual model describing the censoring process and drug use evaluation periods



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CHAPTER THREE

Results

CHAPTER OUTLINE

This chapter reports the study findings. The chapter first provides an overview of the criteria used to select the study population and the resulting effect on sample size. Details regarding overall and drug-specific baseline information for medical conditions, medications, and laboratory data will be subsequently provided. Lastly, the study results and sensitivity analyses will be presented.

Study Cohort

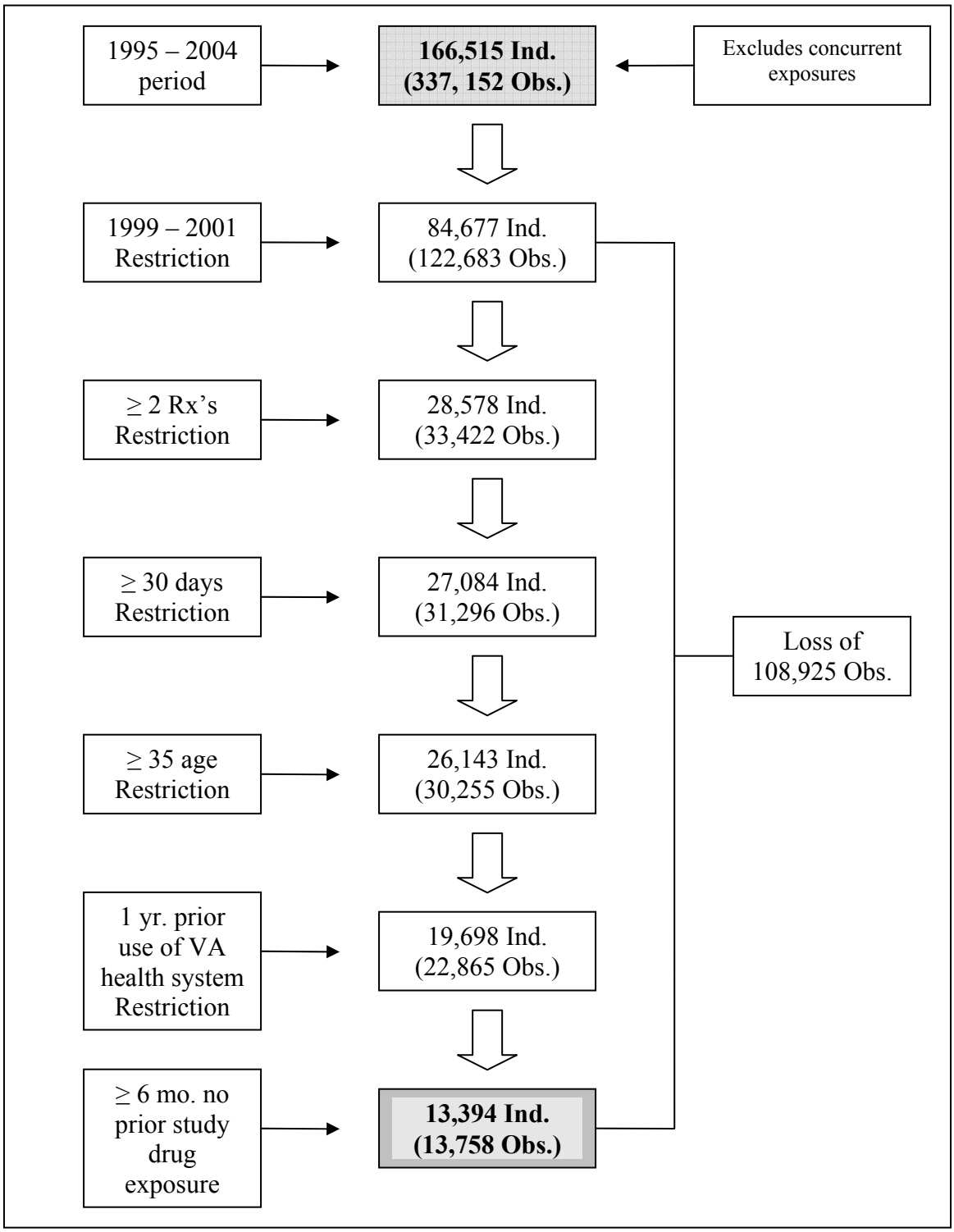
The original cohort encompassed individuals exposed to NSAIDs, COX-2 inhibitors, and salicylic acid drugs (not including aspirin) from September 1995 through May 2004. This cohort consisted of 166,515 unique individuals. Patients in this study were allowed to have multiple exposure periods, consisting of different study drugs along with the same drug multiple times. Therefore, the total number of observations (not unique individuals) for this sample was 337,152. However, due to the limited available data (Medicare & TDH) and concern regarding a channeling effect, the sample was restricted to individuals exposed to these agents from January 1, 1999 through December 31, 2001. This restricted cohort consisted of 84,677 unique individuals and 122,683 observations. When additional study restrictions were applied (age $\geq$ 35, $\geq$ 2

prescriptions, ≥ 30 days of exposure, ≥ 6 months washout period, and ≥ 1 year prior use of VA health care services) the cohort was reduced to 13,394 individuals, and 13,758 observations (Figure 3.1).

Of note, this chart does not include the exclusion criterion – "patients who experience a study endpoint will not re-enter the cohort." This criterion was not included because several endpoints were evaluated and the final number varied with each assessment. For the primary endpoint, (acute myocardial infarction (AMI), stroke, and death from AMI) only nine observations were censored (i.e., did not re-enter cohort). This is the same number of censored patients when death from ischemic heart disease (IHD) or death from a major cardiovascular event was evaluated. For the high stroke sensitivity model, fifteen observations were censored and seven observations were censored for the AMI plus AMI death model.

Medicare data for the year 2002 became available after the preliminary analyses were completed. Reports linking cardiovascular risk to COX-2 inhibitors became prominent in the years following 2001. This information could cause a channeling effect. Therefore, caution should be used in analyzing data after 2001. Due to the concern of channeling, the 2002 data were only incorporated into the study design as a sensitivity analysis.

Figure 3.1 Study restrictions and resulting cohort size.



Abbreviations: Obs. – observations; Ind. – unique individuals; mo. – months; yr. – years; Rx's - prescriptions.

Important – The final cohort of 13,758 observations listed in Figure 3.1 will be used to describe the demographic, study medication use, and baseline characteristics.

Demographic findings

Of the 13,758 eligible observations, 12,888 (93.7%) were men and 870 were women (6.3%). The overall mean age of study subjects was 61.2 years of age (SD - 12.6). The age distribution was bimodal, with peaks in the mid 50s and early 70s (see Figure 3.2). Patients taking celecoxib and rofecoxib were, on average, about seven years older than patients taking ibuprofen, etodolac, and naproxen (Table 3.1).

Race/ethnicity data from the VA were limited; with data available for only 65 percent of subjects. Of this 65 percent, 81.2 percent were white, 13.7 percent were black, and 2.2 percent were Hispanic (see Table 3.2). A majority of the racial/ethnic data were provided by the Medicare data. For subjects 65 years of age and older, race/ethnicity data were available for 98.1 percent of this subgroup. Specific details can be found in Table 3.2. Due to the limited availability, race/ethnicity was not incorporated into the study model.

Study subjects were gathered for three separate regions across Texas; north, south, and central. As seen in Table 3.3, 41.0 percent of the study population was from the north region, 28.8 percent from the central region, and 30.2 percent from the southern region. A few patients used VA healthcare services from more than one region. For these patients, health care profiles were merged together into a single profile and arbitrarily assigned a region.

Figure 3.3 Age distribution of eligible study subjects who received an NSAID, COX-2 inhibitor, or salicylic acid drug during the study period.

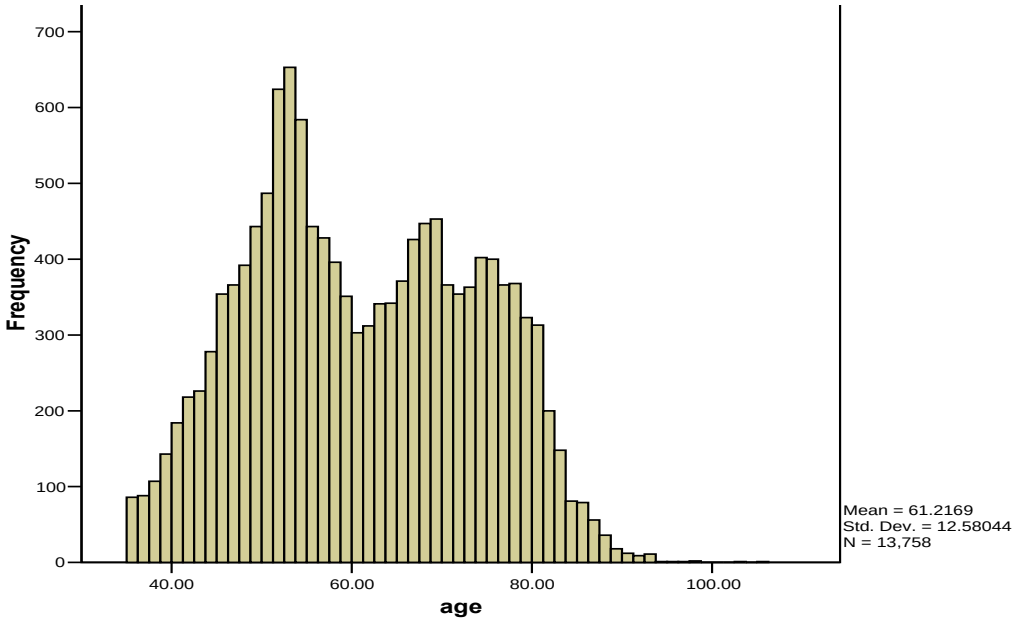


Table 3.1 Baseline age for subjects taking celecoxib, etodolac, ibuprofen, naproxen and rofecoxib.

Categories	Celecoxib	Etodolac	Ibuprofen	Naproxen	Rofecoxib
Mean Age (SD)*	67.5 (11.8)	61.6 (12.5)	58.8 (12.3)	60.3 (12.1)	66.8 (12.4)
< 65	36.7%	58.4%	66.8%	63.1%	40.7%
65 - 74	32.2%	22.9%	20.3%	22.5%	27.2%
75 - 84	27.5%	17.2%	11.7%	13.2%	28.0%
>= 85	3.6%	1.5%	1.1%	1.2%	4.1%
Total (N)	**1530**	**2373**	**4483**	**3241**	**567**

* Units - years

Table 3.2 Racial/Ethnic distribution among eligible study subjects who received an NSAID/COX-2 inhibitor or salicylic acid drug during the study period.

Racial / Ethnic Group	All Study Subjects* N (%)	
White	7,262	(81.2)
Black	1,225	(8.9)
Hispanic	308	(2.2)
Other	148	(1.1)
Total	8,943	(100)
Racial / Ethnic Group	**Study subjects ≥ 65 years of age* N (%)**	
White	4,721	(86.0)
Black	494	(9.0)
Hispanic	223	(4.1)
Other	49	(0.9)
Total	5,487	(100)

* Includes only reported racial/ethnic groups

Table 3.3 Regional distribution of NSAID/COX-2 inhibitor use; north, south, and central VA regions.

Region	No. Study Subjects	(%)
North	5,646	(41.0)
Central	3,959	(28.8)
South	4,153	(30.2)
Total	13,758	(100)

NSAID, COX-2 inhibitor, and salicylic acid drug use

The distribution of subjects obtaining NSAID/COX-2 inhibitors during the study period revealed that a majority of the subjects received either ibuprofen (32.6%) or naproxen (23.6%). The remaining subjects received etodolac (17.2%), celecoxib (11.1%), rofecoxib (4.1%), or other study drugs (other categories < 3% of total each). See Table 3.4 for more details. The original study design involved evaluation of celecoxib, rofecoxib, naproxen, and ibuprofen. The design did allow for additional study groups to be added if sufficient numbers allowed. Etodolac is one of these additional study groups, comprising roughly 17 percent of total drug use.

Regional contributions for the top five drugs (ibuprofen, naproxen, etodolac, celecoxib, and rofecoxib) were evaluated. Similar percentages were found with regards to the amount of ibuprofen and naproxen, with each region contributing between 28 to 40 percent. Disproportionate contributions were found with etodolac, celecoxib, and rofecoxib. North Texas contributed the largest percent of etodolac (~ 73%) to the study, followed by central (~ 25%), and south Texas (~ 2%). The southern region contributed the largest percentage of celecoxib and rofecoxib observations (51% and 62%, respectively), followed by central, and north Texas. See Table 3.5 for more details. Regional prescribing patterns are presented in Table 3.6. Ibuprofen was the most commonly prescribed study drug within all three regions. Following ibuprofen, naproxen was the second most prescribed study drug in the central and south regions; whereas,

etodolac was the second most prescribed drug in the north. Etodolac was infrequently prescribed in the south region.

One of the study objectives was to evaluate the association between cardiovascular events and long-term (> 180 days) and short-term (≤ 180 days) exposure to NSAIDs and COX-2 inhibitors. A majority of subjects for the five study groups are short-term users. Roughly, 25 – 40 percent of subjects used these drugs long-term. See Table 3.7 for more details. Of note, this includes all exposure times and does not censor observations with end-point events occurring during the first 180 days. Person-years were also calculated for each study drug and are provided in Table 3.7.

Table 3.4 Frequency and Percent of NSAID, COX-2 inhibitors, and salicylic acid medications prescribed to eligible subjects during the study period.

Drug	Frequency	Percent
Ibuprofen	4,483	32.6
Naproxen	3,241	23.6
Etodolac	2,373	17.2
Celecoxib	1,530	11.1
Rofecoxib	567	4.1
Piroxicam	414	3.0
Indomethacin	389	2.8
Salicylic Acid Drugs	388	2.8
Sulindac	300	2.2
Other NSAIDs	42	0.3
Diclofenac	21	0.2
Nabumentone	6	0.0
Meloxicam	4	0.0
Total	13,758	100

Table 3.5 Percent of study drug (celecoxib, etodolac, ibuprofen, naproxen, and rofecoxib) from each region.

Region	Celecoxib	Etodolac	Ibuprofen	Naproxen	Rofecoxib
North	17%	73%	40%	38%	17%
Central	32%	25%	30%	28%	21%
South	51%	2%	30%	34%	62%
Total (%)*	1,530 (100)	2,373 (100)	4,483 (100)	3,241 (100)	567 (100)

*Total N = 12,194

Table 3.6 Percent of study drugs (celecoxib, rofecoxib, etodolac, ibuprofen, and naproxen) within each region.

Region	Celecoxib	Etodolac	Ibuprofen	Naproxen	Rofecoxib	Total (%)*
North	5%	34%	35%	24%	2%	5,091 (100)
Central	14%	17%	39%	26%	3%	3,479 (100)
South	21%	1%	37%	31%	10%	3,624 (100)

*Total N = 12,194

Table 3.7 Duration of therapy patterns for celecoxib, rofecoxib, etodolac, ibuprofen, and naproxen.

Exposure	Celecoxib	Etodolac	Ibuprofen	Naproxen	Rofecoxib
0 - 90 days	29.9 %	41.4 %	51.1 %	46.7 %	32.6 %
> 90 – 180 days	29.5 %	30.5 %	24.4 %	26.7 %	30.7 %
> 180 – 365 days	20.5 %	20.0 %	16.6 %	17.3 %	24.9 %
≥ 365 days	20.1 %	8.1 %	7.9 %	9.4 %	11.8 %
Mean (SD)	234.3 (213)	159.0 (130)	152.2 (154)	164.2 (164)	188.6 (149)
Person-Years	964.1	1021.5	1850.7	1438.8	285.5
Events*	39	23	38	29	17
Total (N)	1,530	2,373	4,483	3,241	567

* Number of primary endpoint events (acute myocardial infarction, death from acute myocardial infarction, and cerebrovascular event).

Baseline medical conditions

Entire study cohort

The following baseline medical conditions were derived from VA and Medicare ICD-9 billing codes. The assessment period was one year prior to the index date (start of study medication). Exact codes used to delineate the medical conditions can be found in Chapter Two. Sixteen baseline medical conditions were evaluated, ranging from prior cardiovascular events through terminal conditions. The predominant medical conditions were: osteoarthritis (13.2%), cancer (12.8%), and diabetes (11%). Very few patients had a diagnosis for HIV or "systemic lupus erythematosus and connective tissue disorders." The percent and frequency of baseline medical conditions can be found in Table 3.8.

A study within the VA healthcare system assessing code veracity of stroke-related ICD-9 codes has been conducted. When a high-sensitivity model was used, results yielded 89% sensitivity, 57% specificity, 60% positive predictive value, and 88% negative predictive value. When a high-specificity algorithm was used, the results change to: 59% sensitivity, 84% specificity, 72% positive predictive value, and 74% negative predictive value.[1] When using the high-sensitivity model, 157 prior stroke cases were found. The high-specificity model restricted the 157 stroke cases found in the high-sensitivity model to 40 events.

Table 3.8 Frequency and percent of subjects with a baseline medical diagnosis in the year prior to the index date. N = 13,758

Medical Condition	Frequency	Percent
Atrial fibrillation	310	2.3
Angina	625	4.5
Cancer	1,763	12.8
COPD	894	6.5
Diabetes	1,509	11.0
Heart failure	577	4.2
HIV	18	0.1
Lupus*	27	0.2
Osteoarthritis	1,815	13.2
PVD	392	2.8
Renal failure	85	0.6
Respiratory failure	73	0.5
Rheumatoid arthritis	186	1.4
Prior AMI	139	1.0
Prior stroke sensitivity	157	1.1
Prior stroke specificity	40	0.3

Abbreviations: COPD – chronic obstructive pulmonary disease; HIV - human immunodeficiency virus; PVD – peripheral vascular disease; AMI – acute myocardial infarction.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

A post-hoc analysis was conducted to evaluate the different types of cancer represented in the cancer category. Cancer diagnoses were subdivided into 25 different categories based on an algorithm developed by the Agency for Health Care Research and Quality.[2] Of the 1,763 observations with a cancer diagnosis in the year prior to the index date, 751 (43 %) had multiple classifications of cancer. Nearly 26 percent of the cases were benign neoplasms, followed by unspecified cancers (~ 16%), skin cancer (~ 14%), prostate cancer (~ 10%), lung cancer (~ 4%), head and neck cancer (3.9%), and colon cancer (3.4%). See Table 3.9 for more details.

Table 3.9 Frequency and percent of cancer categories for study subjects diagnosed in the year prior to the index date.

Cancer category	Frequency	Percent
Head and neck cancer	98	3.9
Esophageal cancer	12	0.5
Stomach cancer	7	0.3
Colon cancer	86	3.4
Rectum/anus cancer	44	1.8
Liver and intrahepatic bile duct cancer	8	0.3
Pancreas cancer	4	0.2
GI/peritoneal cancer	16	0.6
Bronchial/lung cancer	93	3.7
Other respiratory cancer	9	0.4
Bone and connective tissue cancer	23	0.9
Melanomas of skin cancer	44	1.8
Other skin cancer	355	14.2
Female cancers*	41	1.6
Prostate cancer	260	10.4
Testicular cancer	4	0.2
Other male genital cancers	8	0.3
Bladder cancer	56	2.2
Kidney/renal pelvis cancer	15	0.6
Other urinary organ cancer	4	0.2
Brain/nervous system cancer	12	0.5
Thyroid cancer	1	0.0
Hodgkins disease	15	0.6
Non-Hodgkins lymphoma	48	1.9
Leukemias	28	1.1
Multiple myeloma	12	0.5
Cancer; other and unspecified malignancy	76	3.0
Secondary malignancies	43	1.7
Malignant neoplasm without site specification	33	1.3
Neoplasms of unspecified nature or uncertain behavior	398	15.8
Benign neoplasm of uterus	5	0.2
Other and unspecified benign neoplasm	650	25.9
Total [ξ]	2508	100

* Breast, uterus, cervical, ovarian, and other female cancers

[ξ] "Total" represents the number of classifications, one subject allowed to represent multiple categories.

Baseline medical conditions by study drug

In order to obtain a better understanding of the study groups, demographic and baseline information was subdivided by study medication. The following drugs were evaluated: celecoxib, rofecoxib, naproxen, ibuprofen, and etodolac. In every category (except HIV) detailed in Table 3.10, a higher percentage of subjects with prior medical conditions were found in the celecoxib and rofecoxib groups as compared to the ibuprofen, naproxen, and etodolac groups. Patients taking celecoxib and rofecoxib had higher percentages of cancer, diabetes, arthritis, and cardiovascular conditions.

One of the study objectives required subjects to be exposed to the study medication for greater than 180 days without an endpoint event occurring during the initial 180 day period. Table 3.11 details the baseline medical conditions for long-term users. No major differences were found in this restricted sample as compared to the entire study population. Similar to the "any exposure" model, long-term users of celecoxib and rofecoxib were found to have higher percentages of baseline values as compared to ibuprofen, naproxen, and etodolac for most medical conditions.

Table 3.10 Percent of subjects classified with a baseline medical condition in the year prior to their index date by study drug.

	CELECOXIB N = 1530	ETODOLAC N = 2373	IBUPROFEN N = 4483	NAPROXEN N = 3241	ROFECOXIB N = 567
Atrial fibrillation	6.7%	2.1%	1.0%	1.4%	5.6%
Angina	8.0%	5.2%	2.8%	4.0%	8.5%
Cancer	19.5%	13.8%	10.2%	11.2%	20.5%
COPD	9.9%	7.1%	5.1%	5.4%	13.2%
Diabetes	15.6%	11.3%	8.9%	10.2%	17.5%
Heart Failure	8.3%	4.1%	3.0%	3.1%	9.0%
HIV	0.0%	0.0%	0.2%	0.1%	0.4%
Lupus*	0.5%	0.1%	0.1%	0.1%	1.1%
Osteoarthritis	24.7%	13.8%	8.5%	11.0%	24.0%
PVD	5.2%	2.4%	2.1%	2.6%	5.3%
Renal failure	1.1%	0.7%	0.3%	0.3%	2.5%
Respiratory Failure	1.0%	0.6%	0.4%	0.3%	1.2%
Rheumatoid arthritis	3.1%	1.6%	0.7%	0.8%	2.6%
Prior AMI	1.6%	1.1%	0.8%	0.8%	1.9%
Prior Stroke Sensitivity	2.5%	1.3%	0.7%	0.7%	2.6%
Prior Stroke Specificity	0.6%	0.3%	0.3%	0.2%	0.5%

* Systemic lupus erythematosus and connective tissue disorders diagnosis

Table 3.11 Long-term NSAID/COX-2 inhibitor users classified with a baseline medical condition in the year prior to the index date by study drug.

	CELECOXIB N = 611	ETODOLAC N = 656	IBUPROFEN N = 1085	NAPROXEN N = 849	ROFECOXIB N = 206
Atrial fibrillation	6.6%	1.5%	1.0%	1.9%	3.4%
Angina	6.9%	5.6%	3.7%	4.6%	6.3%
Cancer	20.6%	13.2%	10.0%	12.9%	20.4%
COPD	10.2%	7.0%	5.5%	6.2%	10.7%
Diabetes	16.2%	12.8%	8.1%	12.4%	15.5%
Heart Failure	8.2%	4.4%	3.8%	3.6%	5.3%
HIV	0%	0%	0%	0.1%	0%
Lupus*	0.01%	0.5%	0.2%	0.1%	1.0%
Osteoarthritis	24.1%	16.4%	10.6%	13.5%	22.8%
PVD	5.6%	1.7%	1.7%	2.6%	6.8%
Renal	1.5%	0.5%	0.2%	0.4%	2.4%
Respiratory Failure	0.01%	0.3%	0.5%	0.1%	0.5%
Rheumatoid arthritis	4.4%	1.8%	1.1%	0.9%	1.9%
Prior AMI	1.6%	0.9%	0.5%	0.8%	2.4%
Prior Stroke Sensitivity	2.1%	1.1%	0.8%	1.1%	2.9%
Prior Stroke Specificity	0.2%	0.3%	0.3%	0.4%	1.0%

* Systemic lupus erythematosus and connective tissue disorders diagnosis

Baseline medications

Subjects were assessed one year prior to the index date for exposure to twenty different categories of medications (Table 3.12). Many of the subjects received antihypertensive medications, with roughly 20 percent of subjects receiving beta-blockers, 25 percent receiving calcium channel blockers, 30 percent receiving ACE inhibitors/ARBs, 27 percent receiving a diuretic (two categories combined), and 18.3 percent receiving some other form of antihypertensive drug. Of the 13,758 observations, 40 percent received at least one antihypertensive medication. Of this 40 percent, nearly 60 percent received more than one type of antihypertensive therapy in the year prior to their index date. This number could be higher if subjects received multiple medications from the same category. Other pertinent categories include aspirin, cholesterol medications, diabetes medications, and nitrates. Roughly, 28 percent of subjects received aspirin therapy in the year prior to their index date, 30.8 percent received a cholesterol medication, 18.3 received a diabetic medication, and 16.1 percent received a nitrate. Evaluation of concurrent aspirin therapy was considered post hoc; however, when assessed very few patients received concurrent therapy. Therefore, concurrent aspirin therapy was not included in the model.

Table 3.12 Frequency and percent of subjects who received a baseline medication in the year prior to the index date. N = 13,758

Medication	Frequency	Percent
Antiarrhythmic	191	1.4
Aspirin	3,886	28.2
ß - Blocker	2,692	19.6
Calcium channel blocker	3,461	25.2
Diabetes drug	2,523	18.3
Digoxin	732	5.3
Estrogen*	383	2.8
Other HTN drugs	2,516	18.3
Loop diuretic	1,522	11.1
Methotrexate	71	0.5
Nitrate	2,219	16.1
PVD drug	108	0.8
Warfarin	591	4.3
ACE inhibitor/ARBS	4,077	29.6
Antiplatelet	464	3.4
Antirheumatic	38	0.3
Steroid	855	6.2
Cholesterol drug	4,234	30.8
Diuretic other	2,220	16.1
Other anticoagulant	120	0.9

* Not in model, for descriptive purposes only

Baseline medications by study drug

Baseline medications were subdivided by study medication (ibuprofen, naproxen, etodolac, celecoxib, and rofecoxib) for evaluation. A similar trend to the baseline medical conditions was found with the baseline study medications (Table 3.13). Celecoxib and rofecoxib subgroups were found to have a higher percentage of patients receiving baseline medications as compared to etodolac, ibuprofen, and naproxen subjects. One interesting finding is the disproportionate number of patients taking warfarin in the celecoxib and rofecoxib study groups as compared to ibuprofen, naproxen, and etodolac study groups (Table 3.13). When the cohort was restricted to long-term users of study medications, no major differences were found between overall users (Table 3.13) and long-term users of study medications (Table 3.14).

Table 3.13 Percent of subjects who received baseline medications in the year prior to their index date by study drug.

	CELECOXIB N = 1530	ETODOLAC N = 2373	IBUPROFEN N = 4483	NAPROXEN N = 3241	ROFECOXIB N = 567
Antiarrhythmics	3.7%	1.2%	0.8%	1.3%	3.2%
Aspirin	31.8%	27.6%	26.5%	28.5%	31.6%
B-Blocker	23.9%	20.7%	16.9%	18.4%	28.0%
Ca-Blocker	32.4%	25.6%	21.9%	24.4%	29.8%
Diabetes Drug	20.0%	18.3%	16.8%	19.0%	22.6%
Digoxin	12.2%	5.3%	3.5%	4.1%	9.5%
Estrogen	2.6%	2.8%	2.8%	3.0%	3.7%
Other HTN Drugs	24.2%	20.9%	15.0%	16.9%	22.9%
Loop Diuretics	18.1%	11.6%	8.9%	8.8%	16.8%
Methotrexate	1.3%	0.5%	0.3%	0.4%	0.9%
Nitrate	22.4%	16.8%	14.1%	14.4%	22.6%
PVD drug	1.2%	0.7%	0.6%	0.8%	1.6%
Warfarin	14.1%	3.6%	1.9%	2.4%	13.1%
ACE/ARBs	33.7%	31.2%	26.3%	29.7%	33.3%
Antiplatelet	5.9%	3.0%	2.7%	2.9%	6.5%
Antirheumatic	0.7%	0.3%	0.2%	0.2%	0.2%
Steroid	9.3%	5.9%	5.6%	5.0%	8.1%
Cholesterol drug	37.6%	33.3%	25.9%	31.6%	37.9%
Diuretic Other	17.5%	18.6%	14.3%	15.5%	16.8%
Other Anticoagulant	1.4%	0.5%	0.9%	0.6%	2.3%

Table 3.14 Long-term NSAID/COX-2 inhibitor users who received a baseline medication in the year prior to their index date by study drug.

	CELECOXIB N = 611	ETODOLAC N = 656	IBUPROFEN N = 1085	NAPROXEN N = 849	ROFECOXIB N = 206
Antiarrhythmics	3.4%	1.4%	0.8%	1.6%	1.5%
Aspirin	30.6%	30.9%	30.3%	32.4%	33.0%
B-Blocker	22.6%	20.2%	18.9%	18.4%	28.6%
Ca-Blocker	34.9%	26.3%	26.2%	28.7%	22.8%
Diabetes Drug	19.8%	21.0%	18.3%	20.9%	21.4%
Digoxin	12.9%	5.9%	4.2%	5.4%	7.8%
Estrogen	1.6%	2.7%	2.3%	3.2%	2.4%
Other HTN Drugs	25.5%	26.6%	16.8%	21.6%	20.9%
Loop Diuretics	17.5%	12.9%	9.4%	10.4%	14.6%
Methotrexate	0.0%	1.1%	0.6%	0.8%	0.0%
Nitrate	21.9%	17.8%	17.0%	16.6%	21.4%
PVD drug	1.5%	0.9%	0.9%	1.4%	1.0%
Warfarin	15.9%	4.0%	1.4%	2.1%	16.0%
ACE/ARBS	32.2%	34.4%	30.6%	35.3%	34.5%
Antiplatelet	6.4%	4.0%	2.9%	2.1%	7.8%
Antirheumatic	0.0%	0.3%	0.2%	0.2%	0.5%
Steroid	8.0%	4.9%	4.9%	4.7%	6.8%
Cholesterol drug	40.6%	38.1%	31.6%	37.3%	40.8%
Diuretic Other	19.0%	20.5%	16.0%	17.2%	20.4%
Other Anticoagulant	1.3%	0.6%	0.2%	0.2%	2.4%

Combined medical condition and medication

For three conditions (diabetes, angina, and peripheral vascular disease), the medical diagnoses and use of a related medication were merged together into a single category. Regarding diabetes, when using only hypoglycemic medications for classification purposes, 18.3 percent of the observations received a diagnosis for diabetes. When classification of diabetes via medication use was merged with a medical diagnosis for diabetes, 21.5 percent of the observations were subsequently classified as diabetic (a difference of 3.2%). Elevated serum glucose (≥ 200 mg/dl) was also considered as a classification criteria for diabetes. However, this did not yield a significant increase in classification (~ 1% increase) and therefore was not used. With respect to angina, 16.1 percent of the study subjects received a nitrate medication. When use of a nitrate was merged with a diagnosis of angina, 17.7 percent of the observations were classified with angina (~ 1.6% increase). The final category, peripheral vascular disease, comprised a small percentage of the population. When "PVD medications" (0.8%) were merged with a diagnosis of PVD (2.8%), a resulting 3.5 percent of observations were classified with this condition.

Patient vitals & laboratory data

In the original study design, laboratory values and patient vitals were to be used as covariates in the study model. However, due to the limited availability of readings and small sample size, they were excluded from the model. If the patient vitals and laboratory values were used, the study population would be reduced by 64 percent and an insufficient number of subjects would be available to conduct the study. Additionally, subjects with available vital and laboratory data may not be representative of the entire population. Despite these limitations, the laboratory data were assessed to determine if clinically significant differences were found between the study medications (e.g., to determine if celecoxib and rofecoxib subjects had higher cholesterol, blood pressure, and body mass index values as compared to the other study groups).

Laboratory values and patient vitals were assessed and analyzed for outlying values. Laboratory values and patient vitals from the original cohort of 166,515 individuals were evaluated. Values outside the plausible range were removed from analysis. Systolic blood pressure (SBP) values less than 50 millimeters of mercury (mmHg) and diastolic blood pressure (DBP) values less than 30 mmHg were removed. Values in this range represent a small proportion of the values, less than 0.1 percent of diastolic readings and less than 0.1 percent of systolic readings. Height values less than 47 inches (3.9 feet) were deleted, representing less than 0.1 percent of values. Weight

values less than 70 pounds and greater than 900 pounds were deleted, representing less than 0.1 percent of readings. Body mass index (BMI) was assessed; values less than 6.5 units were deleted, representing less than 0.1 percent of readings. Extreme height, weight, and BMI values were then assessed individually and records were assessed for consistent values across time. Values with improbable deviations over time were removed (e.g., weight varying by 100 lbs from one month to the next). Lastly, cholesterol readings were assessed for outlying values. Total cholesterol values less than 40 mg/dl and greater than 750 mg/dl were deleted (< 1% of values). High density lipoprotein (HDL) values greater than 150 mg/dl were deleted (< 1% of values). Low density lipoprotein (LDL) values less than 22 mg/dl and greater than 260 mg/dl were deleted (< 1% of values). Triglyceride values less than 10 mg/dl and greater than 3000 mg/dl were deleted (< 1% of values).

Patient vital and laboratory readings occurring in the year prior to the index date were averaged into a single value. Median values along with the lowest and highest reading were also obtained. The range of values in Table 3.15 detail the lowest and highest value assigned to any observation. No clinically significant differences were found between mean and median measurements. Therefore, only mean values will be used and presented in this paper. Only a single measurement of height was available for each subject.

Blood pressure (BP) readings were available for approximately 60 percent of the observations. Of these observations, the average SBP was 139 mmHg (SD, 17.9) and the average DBP value was 76 mmHg (SD, 18.1). Based on JNC-7 criteria, the average blood pressure reading is in the prehypertension stage (SBP, 120 – 139; DBP, 80 – 89). Cholesterol values were available for roughly 45 to 57 percent of the observations (exact percent depends on the type of cholesterol evaluated). The average total cholesterol value is in the desirable range according to ATP III guidelines, at 192 mg/dl (SD, 39.7). The average HDL value is low (< 45 mg/dl) according to ATP III guidelines. The average LDL value is in the "near optimal/ above optimal" range, at 112 mg/dl (SD, 32.9). According to ATP III guidelines, the average triglyceride value is in the borderline-high category, at 191 mg/dl (SD, 145.2). The average subject within the study cohort was overweight, with a BMI of 29.2 (SD, 5.9). Calculated BMI values were available for 57% of the population. Further details are available in Table 3.15.

Baseline laboratory and patient vitals by study drug

Baseline laboratory data and patient vitals were assessed by study drug. When comparing values across the study groups, similar values were found. Blood pressure, cholesterol, and body mass index values only varied by a few points between the categories. However, slightly lower total cholesterol and LDL values were found with celecoxib and rofecoxib as compared to the other study groups. Results can be found in Tables 3.16 – 3.21.

In addition to segmenting laboratory values and patient vitals by study drug, values were restricted to patients receiving greater than 180 days of study medication (long-term users). This was done to evaluate if long-term users were comparable (in terms of baseline laboratory and vitals) to the population as a whole. Results are not shown; however, no clinically significant differences were found between the restricted sample and the principle study population. The subset of patients receiving short-term therapy was not assessed.

Table 3.15 Baseline patient vitals and laboratory data.

Category	N*	Mean	SD	Min	Max
SBP mean	8219	139.0	17.9	56	267
DBP mean	8219	75.7	10.4	30	177
Total Cholesterol mean	7852	191.7	39.7	40	667
HDL mean	6434	44.9	13.1	5	136
LDL mean	6229	112.1	32.9	22	259
TG mean	7102	191.1	145.2	20	2800
Weight mean (lbs)	7929	201.1	44.0	77.5	633
BMI mean	7867	29.2	5.9	.	.
Height (inches)[§]	7870	69.5	3.2	.	.

Abbreviations: SBP – systolic blood pressure; DBP – diastolic blood pressure; HDL – high density Lipoprotein; LDL – low density lipoprotein; TG – triglyceride; BMI – body mass index.

* Numbers based on available data

§ Only one value available per person

Table 3.16 Baseline blood pressure values for subjects taking celecoxib, etodolac, ibuprofen, naproxen and rofecoxib.

Categories[ξ]	Celecoxib	Etodolac	Ibuprofen	Naproxen	Rofecoxib
SBP mean (SD)	139.6 (18.3)	139.0 (17.8)	138.5 (18.1)	139.2 (17.2)	139.9 (18.0)
DBP mean (SD)	73.7 (9.8)	75.6 (10.5)	76.6 (10.4)	76.1 (10.2)	73.5 (10.3)
I Normal	17.1%	14.6%	15.5%	13.8%	13.5%
II Pre-HTN	15.1%	17.4%	17.2%	17.5%	14.4%
III Pre-HTN	20.3%	21.6%	21.9%	21.3%	22.6%
IIII Stage 1 HTN	34.8%	33.9%	33.0%	35.7%	35.6%
IV Stage 2 HTN	12.7%	12.5%	12.5%	11.7%	13.8%
Total (N)*	929	1683	2523	1874	340

Abbreviations: SBP – systolic blood pressure; DBP – diastolic blood pressure; SD – standard deviation
* Number of subjects with available readings.
[ξ] BP values for categories I – IV can be found in Table 2.4

Table 3.17 Baseline total cholesterol values for subjects taking celecoxib, etodolac, ibuprofen, naproxen and rofecoxib.

Categories	Celecoxib	Etodolac	Ibuprofen	Naproxen	Rofecoxib
Total Cholesterol mean (SD)	187.3 (36.9)	192.3 (39.6)	192.3 (40.0)	193.8 (40.6)	187.4 (44.7)
< 160	22.7%	19.2%	20.3%	19.0%	24.2%
160 - 199	43.2%	40.9%	39.7%	39.3%	42.7%
200 - 239	26.1%	29.1%	29.6%	30.2%	23.7%
240 - 279	6.6%	7.9%	7.8%	8.7%	7.4%
≥ 280	1.4%	2.9%	2.7%	2.7%	1.9%
Total (N)*	1075	1298	2326	1864	417

* Number of subjects with available readings.

Table 3.18 Baseline high density lipoprotein (HDL) values for subjects taking celecoxib, etodolac, ibuprofen, naproxen and rofecoxib.

Categories	Celecoxib	Etodolac	Ibuprofen	Naproxen	Rofecoxib
HDL mean (SD)	45.5 (13.2)	43.7 (12.8)	45.2 (13.4)	45.2 (13.2)	45.4 (12.5)
< 35	18.7%	22.7%	19.5%	18.3%	18.7%
35 - 44	35.7%	37.5%	37.0%	39.4%	34.9%
45 - 49	15.6%	15.5%	14.6%	14.8%	13.1%
50 - 59	18.7%	15.1%	16.7%	16.1%	21.1%
≥ 60	11.3%	9.2%	12.3%	11.5%	12.2%
Total (N)*	886	1180	1825	1528	327

* Number of subjects with available readings.

Table 3.19 Baseline low density lipoprotein (LDL) values for subjects taking celecoxib, etodolac, ibuprofen, naproxen and rofecoxib.

Categories	Celecoxib	Etodolac	Ibuprofen	Naproxen	Rofecoxib
LDL mean (SD)	106.5 (31.8)	112.4 (32.4)	113.6 (33.3)	114.2 (33.5)	108.1 (32.4)
< 100	44.2%	35.4%	35.1%	35.1%	41.9%
100 - 129	35.1%	36.7%	35.3%	35.1%	35.7%
130 - 159	15.6%	20.7%	21.3%	20.8%	16.8%
160 - 189	3.3%	5.6%	6.3%	6.5%	4.7%
≥ 190	1.7%	1.6%	2.0%	2.5%	0.9%
Total (N)*	886	1138	1767	1468	322

* Number of subjects with available readings.

Table 3.20 Baseline triglyceride values for subjects taking celecoxib, etodolac, ibuprofen, naproxen and rofecoxib.

Categories	Celecoxib	Etodolac	Ibuprofen	Naproxen	Rofecoxib
TG mean (SD)	190.0 (130.9)	193.9 (143.7)	189.9 (151.2)	189.2 (140.2)	188.3 (197.0)
< 150	48.4%	45.3%	50.7%	48.2%	52.2%
150 - 199	17.2%	20.5%	16.6%	19.0%	17.5%
200 - 499	31.6%	31.3%	29.2%	29.6%	28.3%
≥ 500	2.8%	2.9%	3.5%	3.2%	1.9%
Total (N)*	955	1261	2075	1675	360

* Number of subjects with available readings.

Table 3.21 Baseline body mass index (BMI) for subjects taking celecoxib, etodolac, ibuprofen, naproxen and rofecoxib.

Categories	Celecoxib	Etodolac	Ibuprofen	Naproxen	Rofecoxib
BMI mean (SD)	29.2 (5.5)	29.5 (6.0)	28.9 (6.0)	29.3 (5.7)	29.0 (5.9)
< 18.5	0.7%	1.3%	1.6%	0.8%	1.5%
18.5 - 24.9	19.1%	21.2%	24.6%	22.2%	24.4%
25 - 29.9	42.5%	35.0%	36.4%	36.7%	37.7%
> 30	37.7%	42.4%	37.4%	40.3%	36.4%
Total (N)*	899	1633	2379	1795	332

* Number of subjects with available readings.

ANALYTICAL RESULTS

OBJECTIVE I – *To evaluate serious cardiovascular events (AMI, stroke, or cardiovascular mortality) associated with use of COX-2 inhibitors.*

Study Hypotheses	Description	Fail to Reject /Reject Null Hypotheses
H_o1	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **rofecoxib** versus patients taking a traditional NSAID (i.e., ibuprofen), while controlling for various covariates. Overall use (short-term and long-term use)	**Fail to Reject**
H_o2	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **celecoxib** versus patients taking a traditional NSAID (i.e., ibuprofen), while controlling for various covariates. Overall use	**Fail to Reject**
H_o3	There is no difference in the overall risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **etodolac** versus patients taking a traditional NSAID (i.e., ibuprofen). "any exposure" model	**Fail to Reject**

OBJECTIVE II – *To determine if naproxen offers greater cardioprotective benefits compared to other NSAIDs.*

Study Hypotheses	Description	Fail to Reject /Reject Null Hypotheses
H_o4	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **naproxen** versus patients taking another traditional NSAID (i.e., ibuprofen), while controlling for various covariates. Overall use	**Fail to Reject**

Regarding objective one, the unadjusted model found an associated risk for serious cardiovascular events with celecoxib and rofecoxib when compared to ibuprofen (RR, 2.04; 95% CI, 1.30 – 3.20; $p < 0.01$ / RR, 2.88; 95% CI, 1.63 – 5.11; $p < 0.01$, respectively). However, there were no significant differences found with naproxen or etodolac. See Table 3.22 for further details.

When adjusting for various covariates, the Cox regression model revealed that overall, recipients of etodolac, celecoxib, and rofecoxib were not associated with an increased risk of serious cardiovascular events when compared to ibuprofen users (See Table 3.23). With regards to the study medications, all results were not statistically significant. Results yielded an adjusted risk ratio (aRR) of 1.13 (95% CI, 0.70 – 1.83; p = 0.61) for celecoxib users; 1.59 (95% CI, 0.87 – 2.90; p = 0.13) for rofecoxib users, and 0.82 (95% CI, 0.48 – 1.40; p = 0.47) for etodolac users. When compared to ibuprofen, naproxen was not found to be cardioprotective (or cardionegative) in the all-inclusive model (aRR, 0.86; 95% CI, 0.53 – 1.40; p = 0.54).

Several covariates in the model were statistically significant. These included: COPD, osteoarthritis, prior AMI and stroke, ß-blocker, loop diuretic, methotrexate, antiplatelet, and age. Other covariates were not statically significant; however, they may have contributed to the overall fit of the model. Some variables had little to no contribution to the model (HIV, lupus, and antirheumatics). This is primarily due to the low numbers of subjects in these categories.

Table 3.22 Un-adjusted association between exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) – Ibuprofen Comparison.

		(95% CI)		
Exposure (reference group)	**Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Any exposure				
Celecoxib (ibuprofen)	2.04	1.30	3.20	< 0.01
Etodolac (ibuprofen)	1.08	0.64	1.81	0.78
Rofecoxib (ibuprofen)	2.88	1.62	5.11	< 0.01
Naproxen (ibuprofen)	0.99	0.61	1.60	0.96

Total population: 12,188; Ibuprofen – 4,481; Naproxen – 3,240; Celecoxib – 1,530; Etodolac – 2,371; Rofecoxib – 566. . Endpoint events – 146; censored 12,042.

Table 3.23 Adjusted association between exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) – Ibuprofen Comparison.

Exposure (reference group)	Adjusted Risk Ratio	(95% CI)	Sig. (p)
Celecoxib (ibuprofen)	1.13	(0.70 – 1.83)	0.61
Etodolac (ibuprofen)	0.82	(0.48 – 1.40)	0.47
Rofecoxib (ibuprofen)	1.59	(0.87 – 2.90)	0.13
Naproxen (ibuprofen)	0.86	(0.53 – 1.40)	0.54
Covariates			
Diabetes	1.32	(0.92 – 1.90)	0.13
Angina	1.16	(0.76 – 1.78)	0.48
PVD	1.48	(0.87 – 2.49)	0.15
Atrial Fibrillation	1.29	(0.66 – 2.52)	0.45
Cancer	0.89	(0.58 – 1.37)	0.60
COPD	1.98	(1.27 – 3.10)	**< 0.01**
Heart failure	1.27	(0.75 – 2.16)	0.38
HIV	0	.	.
Lupus*	0	.	.
Osteoarthritis	1.85	(1.27 – 2.68)	**< 0.01**
Renal failure	0.56	(0.15 – 2.05)	0.38
Respiratory failure	0.74	(0.20 – 2.78)	0.65
Rheumatoid arthritis	0.84	(0.29 – 2.37)	0.74
Prior AMI	3.98	(2.10 – 7.60)	**< 0.01**
Prior Stroke (specificity model)	4.07	(1.42 – 11.67)	**0.01**
Antiarrhythmic	1.41	(0.67 – 2.94)	0.37
Aspirin	1.07	(0.74 – 1.56)	0.72
B-blocker	1.51	(1.03 – 2.22)	**0.03**
Ca-blocker	0.96	(0.67 – 1.37)	0.80
Digoxin	1.03	(0.60 – 1.75)	0.92
Other HTN Meds	0.69	(0.45 – 1.04)	0.08
Loop diuretic	1.58	(1.03 – 2.41)	**0.03**
Methotrexate	5.90	(1.72 – 20.22)	**< 0.01**
Warfarin	0.99	(0.54 – 1.79)	0.96
ACE/ARBS	1.21	(0.84 – 1.73)	0.31
Antiplatelet	1.79	(1.07 – 2.99)	**0.03**
Antirheumatic	0	.	.
Steroid	0.47	(0.21 – 1.06)	0.07
Cholesterol drug	0.91	(0.63 – 1.31)	0.62
Diuretic other	0.74	(0.47 – 1.18)	0.20
Anticoagulant	0.34	(0.05 – 2.50)	0.29
Sex (male)	0.69	(0.25 – 1.89)	0.47
Age	1.04	(1.02 – 1.05)	**< 0.01**

Total population: 12,188; Ibuprofen – 4,481; Naproxen – 3,240; Celecoxib – 1,530; Etodolac – 2,371; Rofecoxib – 566. Endpoint events – 146; censored 12,042.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

OBJECTIVE III – *To determine if duration of naproxen/COX-2 inhibitor use has an effect on cardiovascular outcomes (protective for naproxen and cardio-negative for COX-2 inhibitors). Compared to ibuprofen*

Study Hypotheses	Description	Fail to Reject /Reject Null Hypotheses
Long-term exposure		
H_o9	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **celecoxib** long-term (> 180 days) and patients taking ibuprofen long-term, while controlling for various covariates.	Reject
H_o10	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **rofecoxib** long-term (> 180 days) and patients taking ibuprofen long-term, while controlling for various covariates.	Reject
H_o11	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **etodolac** long-term (> 180 days) and patients taking ibuprofen long-term, while controlling for various covariates.	Fail to Reject
H_o12	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **naproxen** long-term (> 180 days) and patients taking ibuprofen long-term, while controlling for various covariates.	Fail to Reject

Important reminder to the reader - in this analysis patients are excluded if an endpoint event occurred during the first 180 days.

The following analysis evaluates the cardiovascular risk associated with long-term exposure to study medications. The unadjusted model revealed a 3.72-fold (95% CI, 1.47 – 9.39; p = 0.01) increased risk of serious cardiovascular events in subjects using celecoxib long-term as compared to long-term ibuprofen users. Similarly, long-term users of rofecoxib were found to be 7.46 times (95% CI, 2.59 – 21.54; p = < 0.01) more likely to experience a serious cardiovascular event when compared to long-term users of ibuprofen. Results for the unadjusted model are listed in Table 3.24.

After controlling for confounders, long-term use of celecoxib was associated with an increased risk of serious cardiovascular events when compared to persons taking ibuprofen long-term (aRR, 3.64; 95% CI, 1.36 – 9.70; p = 0.01). See Table 3.25 Furthermore, long-term rofecoxib use was found to have roughly twice the magnitude of risk (aRR, 6.64; 95% CI, 2.17 – 20.28; p = < 0.01). After long-term exposure, subjects taking etodolac were not associated with an increased or decreased risk of serious cardiovascular events when compared to ibuprofen users (aRR, 1.26, 95% CI, 0.35 – 4.56; p = 0.73). Similarly, after long-term use, naproxen was not found to be cardioprotective or cardionegative (aRR, 1.15, 95% CI, 0.35 – 3.77; p = 0.81). Information regarding the study covariates can be found in Table 3.25.

Table 3.24 Un-adjusted association between long-term exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) – Ibuprofen Comparison. [ξ]

		(95% CI)		
Exposure (reference group)	**Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Any exposure				
Celecoxib (ibuprofen)	3.72	1.47	9.39	0.01
Etodolac (ibuprofen)	1.25	0.35	4.44	0.73
Rofecoxib (ibuprofen)	7.46	2.59	21.54	< 0.01
Naproxen (ibuprofen)	1.18	0.38	3.66	0.77

Total population: 3,407; Ibuprofen – 1,085; Naproxen – 849; Celecoxib – 611; Etodolac – 656; Rofecoxib – 206. Endpoint events – 42; censored 3,275.

[ξ] Long-term exposure defined as > 180 days (with no events during the first 180 days).

Table 3.25 Adjusted association between long-term exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) – Ibuprofen comparison.[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	3.64	1.36	9.70	**0.01**
Etodolac (ibuprofen)	1.26	0.35	4.56	0.73
Rofecoxib (ibuprofen)	6.64	2.17	20.28	**< 0.01**
Naproxen (ibuprofen)	1.15	0.35	3.77	0.81
Covariates				
Diabetes	1.38	0.67	2.83	0.39
Angina	0.58	0.23	1.45	0.25
PVD	0.24	0.03	1.97	0.18
Atrial Fibrillation	3.27	0.93	11.45	0.06
Cancer	0.50	0.19	1.28	0.15
COPD	1.85	0.73	4.72	0.20
Heart failure	3.11	1.12	8.65	**0.03**
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	0.93	0.41	2.12	0.86
Renal failure	0.34	0.03	3.50	0.36
Respiratory failure	0	.	.	.
Rheumatoid arthritis	1.98	0.43	9.13	0.38
Prior AMI	9.65	2.39	38.95	**< 0.01**
Prior Stroke (specificity model)	0	.	.	.
Antiarrhythmic	0.43	0.06	3.24	0.41
Aspirin	0.71	0.32	1.54	0.38
B-blocker	0.79	0.34	1.87	0.60
Ca-blocker	0.73	0.36	1.50	0.39
digoxin	0.91	0.31	2.68	0.87
other HTN Meds	0.47	0.20	1.10	0.08
loop diuretic	4.13	1.95	8.76	**< 0.01**
methotrexate	0	.	.	.
warfarin	0.21	0.05	0.87	**0.03**
ACE/ARBS	0.96	0.47	1.98	0.91
Antiplatelet	2.78	1.08	7.15	**0.03**
Antirheumatic	0	.	.	.
Steroid	0.76	0.17	3.43	0.72
cholesterol drug	1.12	0.57	2.21	0.74
diuretic other	1.22	0.54	2.77	0.63
Anticoagulant	0	.	.	.
Sex (male)	0.54	0.07	4.06	0.55
Age	1.03	1.00	1.06	0.09

Total population: 3,407; Ibuprofen – 1,085; Naproxen – 849; Celecoxib – 611; Etodolac – 656; Rofecoxib – 206. Endpoint events – 42; censored 3,275.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Long-term exposure defined as > 180 days (with no events during the first 180 days).

OBJECTIVE III – *short-term use*

Study Hypotheses	Description	Fail to Reject /Reject Null Hypotheses
Short-term exposure		
H_o5	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **celecoxib** short term (≤ 180 days) and patients taking ibuprofen short-term, while controlling for various covariates.	**Fail to Reject**
H_o6	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **rofecoxib** short term (≤ 180 days) and patients taking ibuprofen short-term, while controlling for various covariates.	**Fail to Reject**
H_o7	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **etodolac** short term (≤ 180 days) and patients taking ibuprofen short-term, while controlling for various covariates.	**Fail to Reject**
H_o8	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **naproxen** short term (≤ 180 days) and patients taking ibuprofen short-term, while controlling for various covariates.	**Fail to Reject**

To further delineate the temporal relationship between NSAID and COX-2 inhibitor use and cardiovascular risk, observations with less than or equal to 180 days of exposure were evaluated. Observations exceeding 180 days of exposure were not evaluated. The unadjusted model found a significant increase in serious cardiovascular risk among short-term users of rofecoxib as compared to short-term users of ibuprofen. All other comparisons were not statistically significant. Results for the unadjusted model are listed in Table 3.26. With regards to the adjusted model, short-term use of <u>any</u> NSAID or COX-2 inhibitor was not associated with an increase or decreased risk of serious cardiovascular events (Table 3.27). All results were statistically non-significant.

Table 3.26 Un-Adjusted association between short-term exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) – Ibuprofen Comparison.[ξ]

		(95% CI)		
Exposure (reference group)	**Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Any exposure				
Celecoxib (ibuprofen)	1.80	0.88	3.67	0.10
Etodolac (ibuprofen)	0.93	0.45	1.93	0.85
Rofecoxib (ibuprofen)	3.03	1.34	6.85	**0.01**
Naproxen (ibuprofen)	0.71	0.34	1.48	0.36

Total population: 8,730; Ibuprofen – 3,383; Naproxen – 2,376; Celecoxib – 908; Etodolac – 1,705; Rofecoxib – 358. Endpoint events – 63; censored 8,667.

[ξ] Short term exposure defined as ≤ 180 days; **does not include long-term use observations**.

Table 3.27 Adjusted association between short-term exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) – Ibuprofen Comparison.[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	0.67	0.31	1.47	0.32
Etodolac (ibuprofen)	0.63	0.30	1.34	0.23
Rofecoxib (ibuprofen)	1.40	0.59	3.33	0.44
Naproxen (ibuprofen)	0.60	0.29	1.26	0.18
Covariates				
Diabetes	0.89	0.50	1.58	0.68
Angina	1.08	0.56	2.09	0.82
PVD	1.82	0.86	3.85	0.12
Atrial Fibrillation	1.40	0.54	3.63	0.49
Cancer	1.22	0.67	2.25	0.51
COPD	2.43	1.24	4.75	**0.01**
Heart failure	1.44	0.64	3.22	0.37
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	2.35	1.33	4.14	**< 0.01**
Renal failure	1.33	0.24	7.20	0.74
Respiratory failure	1.67	0.37	7.66	0.51
Rheumatoid arthritis	0.37	0.04	3.11	0.36
Prior AMI	1.99	0.65	6.06	0.23
Prior Stroke (specificity model)	4.35	0.93	20.45	0.06
Antiarrhythmic	1.93	0.70	5.33	0.20
Aspirin	1.59	0.90	2.83	0.11
B-blocker	1.92	1.06	3.45	**0.03**
Ca-blocker	0.76	0.43	1.35	0.35
digoxin	0.80	0.33	1.96	0.63
other HTN Meds	0.51	0.24	1.05	0.07
loop diuretic	0.66	0.32	1.34	0.25
methotrexate	10.38	2.10	51.26	**< 0.01**
warfarin	1.74	0.73	4.14	0.21
ACE/ARBS	1.89	1.08	3.32	**0.03**
Antiplatelet	1.46	0.63	3.39	0.37
Antirheumatic	0	.	.	.
Steroid	0.38	0.11	1.34	0.13
cholesterol drug	0.93	0.53	1.64	0.81
diuretic other	0.70	0.35	1.41	0.32
Anticoagulant	0.99	0.13	7.70	0.99
Sex (male)	0.83	0.20	3.46	0.79
Age	1.03	1.01	1.06	**0.01**

Total population: 8,730; Ibuprofen – 3,383; Naproxen – 2,376; Celecoxib – 908; Etodolac – 1,705; Rofecoxib – 358. Endpoint events – 63; censored 8,667.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Short term exposure defined as ≤ 180 days; **does not include long-term use observations**.

A summary of the previous analyses can be found in Table 3.28.

Table 3.28 Summary – Adjusted association between NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) – ibuprofen, comparison group.

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Any exposure				
Celecoxib (ibuprofen)	1.13	0.70	1.83	0.61
Etodolac (ibuprofen)	0.82	0.48	1.40	0.47
Rofecoxib (ibuprofen)	1.59	0.87	2.90	0.13
Naproxen (ibuprofen)	0.86	0.53	1.40	0.54
> 180 days exposure [ξ] **-** *excludes observations with events during the first 180 days*				
Celecoxib (ibuprofen)	3.64	1.36	9.70	**0.01**
Etodolac (ibuprofen)	1.26	0.35	4.56	0.73
Rofecoxib (ibuprofen)	6.64	2.17	20.28	**< 0.01**
Naproxen (ibuprofen)	1.15	0.35	3.77	0.81
≤ 180 days exposure[σ] **–** *excludes long-term use observations*				
Celecoxib (ibuprofen)	0.67	0.31	1.47	0.32
Etodolac (ibuprofen)	0.63	0.30	1.34	0.23
Rofecoxib (ibuprofen)	1.40	0.59	3.33	0.44
Naproxen (ibuprofen)	0.60	0.29	1.26	0.18

[ξ] Long-term exposure defined as > 180 days (with no events during the first 180 days).
[σ] Excludes long-term use observations, exposures greater than 180 days.

SENSITIVITY ANALYSES

Several sensitivity analyses were conducted. These include:

1) allowing events to occur during the first 180 days of exposure – long-term model;
2) including long-term use observations into the short-term model (limited to the first 180 days);
3) use of different comparator groups (i.e., naproxen and etodolac);
4) evaluating only AMI and AMI-related deaths (excludes stroke cases);
5) expanding the stroke definition (stroke sensitivity model);
6) broadening the mortality definition to include deaths from ischemic heart disease;
7) broadening the mortality definition to include deaths from major cardiovascular diseases;
8) restricting the age groups to subjects 65 years of age and older; and
9) including one additional year of data (2002).

1) Including events that occur during the first 180 days of exposure - Long-term model

This sensitivity analysis was primarily conducted to further evaluate the possible cardioprotective effects of naproxen. The sample was expanded to evaluate long-term use observations (> 180 days exposure) with events occurring during the first 180 days. In doing so, 13 excluded ibuprofen observations; 11 excluded celecoxib observations; 10 excluded etodolac observations; 2 excluded rofecoxib observations; and 15 excluded naproxen observations were added to the model (when compared to the long-term model that excluded endpoint events during the first 180 days). However, even with this modification, long-term naproxen use was still not associated with a cardioprotective effect (aRR, 1.11; 95% CI, 0.56 – 2.18; p = 0.77). See Table 3.29

Table 3.29 Summary – Adjusted association between long-term exposure to NSAIDs & COX-2 inhibitors and cardiovascular events (including events occurring during the first 180 days) – including events during first 180 days.[ξ]

Exposure (reference group)	Adjusted Risk Ratio	(95% CI) Lower	Upper	Sig. (p)
Celecoxib (ibuprofen)	1.63	0.85	3.13	0.14
Etodolac (ibuprofen)	1.02	0.48	2.19	0.95
Rofecoxib (ibuprofen)	2.00	0.86	4.68	0.11
Naproxen (ibuprofen)	1.11	0.56	2.18	0.77

See **Appendix T** for full model

[ξ] Long-term exposure defined as > 180 days (**events may occur during the first 180 days**).

[σ] End point - defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event.

2) *Including long-term observations into the short-term model (limited to the first 180 days).*

To further evaluate the short-term association between cardiovascular events and drug exposure, all observation periods were limited to the first 180 days. In making this modification, the sample size was increased by 3,464 observations. This modification did not find an association between serious cardiovascular events and short-term use of NSAIDs/COX-2 inhibitors. All results were statistically nonsignificant. See Table 3.30 for further details.

Table 3.30 Adjusted association between short-term exposure (limiting long-term exposure periods to the first 180 days) to NSAIDS & COX-2 inhibitors and serious cardiovascular events – all observations. [ξ]

Exposure (reference group)	Adjusted Risk Ratio	(95% CI) Lower	Upper	Sig. (p)
Celecoxib (ibuprofen)	0.77	0.43	1.39	0.39
Etodolac (ibuprofen)	0.74	0.41	1.32	0.31
Rofecoxib (ibuprofen)	0.87	0.40	1.88	0.72
Naproxen (ibuprofen)	0.85	0.49	1.46	0.55

See **Appendix U** for full model

[ξ] Short term exposure defined as ≤ 180 days; includes long-term use observations with exposure periods limited to the first 180 days.

3) Use of different comparator groups (i.e. naproxen and etodolac)

The following sensitivity analysis evaluated the use of different comparator groups, i.e., naproxen and etodolac. Compared to ibuprofen, naproxen yielded similar adjusted risk ratios in all categories. Regarding long-term use, celecoxib users were found to be 3.16 (95% CI, 1.16 – 8.57; p = 0.02) times more likely to experience a serious cardiovascular event and rofecoxib users were 5.76 (95% CI, 1.82 – 18.21; p = < 0.01) times more likely to experience an event than naproxen users. Ibuprofen and etodolac yielded non-significant results. Additionally, overall general use and short-term use of study medications were not associated with cardiovascular risk. With regards to using etodolac as a comparator group, two of the results differed from the models using ibuprofen as a comparator. Long-term users of celecoxib were not statistically different from long-term users of etodolac in terms of cardiovascular risk (aRR, 2.89, 95% CI, 0.95 – 8.80; p = 0.06). Additionally, overall use of rofecoxib (long-term and short-term use) was associated with a statistically significant increase in cardiovascular risk compared to etodolac (aRR, 1.93; 95% CI, 1.02 – 3.67; p = 0.04). All other results were comparable to results with models using ibuprofen as the control group. See Table 3.31 for more details.

Table 3.31 Summary – Adjusted association between NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) naproxen, and etodolac comparison groups.

Exposure (reference group)	Adjusted Risk Ratio	(95% CI) Lower	Upper	Sig. (p)
Any exposure [a]				
Ibuprofen (naproxen)	1.17	0.72	1.90	0.54
Celecoxib (naproxen)	1.32	0.80	2.20	0.28
Etodolac (naproxen)	0.96	0.55	1.67	0.88
Rofecoxib (naproxen)	1.85	*0.99*	3.45	0.05
> 180 days exposure [b, ξ]				
Ibuprofen (naproxen)	0.87	0.27	2.84	0.81
Celecoxib (naproxen)	3.16	1.16	8.57	**0.02**
Etodolac (naproxen)	1.09	0.29	4.05	0.90
Rofecoxib (naproxen)	5.76	1.82	18.21	**< 0.01**
≤ 180 days exposure [c, σ]				
Ibuprofen (naproxen)	1.66	0.79	3.47	0.18
Celecoxib (naproxen)	1.12	0.46	2.67	0.81
Etodolac (naproxen)	1.05	0.45	2.47	0.91
Rofecoxib (naproxen)	2.33	0.90	6.04	0.08
Any exposure [d]				
Ibuprofen (etodolac)	1.22	0.72	2.07	0.47
Celecoxib (etodolac)	1.38	0.81	2.35	0.24
Rofecoxib (etodolac)	1.93	1.02	3.67	**0.04**
Naproxen (etodolac)	1.04	0.60	1.82	0.88
> 180 days exposure [e, ξ]				
Ibuprofen (etodolac)	0.80	0.22	2.89	0.73
Celecoxib (etodolac)	2.89	0.95	8.80	0.06
Rofecoxib (etodolac)	5.28	1.51	18.44	**0.01**
Naproxen (etodolac)	0.92	0.25	3.40	0.90
≤ 180 days exposure [f, σ]				
Ibuprofen (etodolac)	1.58	0.74	3.34	0.23
Celecoxib (etodolac)	1.06	0.45	2.49	0.90
Rofecoxib (etodolac)	2.21	0.86	5.71	0.10
Naproxen (etodolac)	0.95	0.40	2.23	0.91

[ξ] Long-term exposure defined as > 180 days (with no events during the first 180 days).
[σ] Excludes long-term use observations.
[a] See **Appendix V** for full model
[b] See **Appendix W** for full model
[c] See **Appendix X** for full model
[d] See **Appendix Y** for full model
[e] See **Appendix Z** for full model
[f] See **Appendix AA** for full model

4) Evaluating only AMI and AMI-related deaths (excludes stroke cases)

The next sensitivity analysis removes stroke from the endpoint classification and evaluates just acute myocardial infarctions and acute myocardial infarction-related deaths. No statistically significant differences were found in the "any exposure" category. Similar results to the primary model (the model containing stroke) were found in the evaluation of long-term users. Long-term users of celecoxib and rofecoxib were 3.59 times (95% CI, 1.03 – 12.56; p = 0.05) and 7.07 times (95% CI, 1.57 – 31.95; p = 0.01) more likely to experience a serious coronary event as compared to long-term ibuprofen users, respectively. No statically significant differences were found with short-term use and overall general use. See Table 3.32.

Table 3.32 Summary – Adjusted association between NSAIDS & COX-2 inhibitors and serious coronary events (defined as acute myocardial infarction or death from coronary heart disease)

Exposure (reference group)	Adjusted Risk Ratio	(95% CI) Lower	Upper	Sig. (p)
Any exposure [a]				
Celecoxib (ibuprofen)	0.90	0.50	1.60	0.71
Etodolac (ibuprofen)	0.76	0.41	1.41	0.39
Rofecoxib (ibuprofen)	1.02	0.46	2.26	0.96
Naproxen (ibuprofen)	1.01	0.60	1.71	0.98
> 180 days exposure [b, ξ]				
Celecoxib (ibuprofen)	3.59	1.03	12.56	**0.05**
Etodolac (ibuprofen)	1.13	0.20	6.49	0.89
Rofecoxib (ibuprofen)	7.07	1.57	31.95	**0.01**
Naproxen (ibuprofen)	1.86	0.48	7.27	0.37
≤ 180 days exposure [c, σ]				
Celecoxib (ibuprofen)	0.58	0.23	1.48	0.26
Etodolac (ibuprofen)	0.51	0.21	1.27	0.15
Rofecoxib (ibuprofen)	0.89	0.28	2.81	0.84
Naproxen (ibuprofen)	0.68	0.31	1.50	0.34

[ξ] Long-term exposure defined as > 180 days (with no events during the first 180 days).
[σ] Excludes long-term use observations.
[a] See **Appendix BB** for full model
[b] See **Appendix CC** for full model
[c] See **Appendix DD** for full model

5) Expanding the stroke definition (stroke sensitivity model)

This sensitivity analysis modifies the endpoint definition by expanding the stroke definition (stroke sensitivity). Using this model, all results were found to be statically non-significant. However, a non-significant trend towards increased cardiovascular risk was found with long-term use of celecoxib and rofecoxib when compared to ibuprofen use. Further details are available in Table 3.33

Table 3.33 Summary – Adjusted association between NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) - high sensitivity stroke model.[*]

Exposure (reference group)	Adjusted Risk Ratio	(95% CI) Lower	Upper	Sig. (p)
Any exposure [a]				
Celecoxib (ibuprofen)	0.90	0.60	1.33	0.59
Etodolac (ibuprofen)	0.68	0.44	1.05	0.08
Rofecoxib (ibuprofen)	1.03	0.60	1.76	0.92
Naproxen (ibuprofen)	0.85	0.58	1.26	0.42
> 180 days exposure [b, ξ]				
Celecoxib (ibuprofen)	1.53	0.71	3.31	0.28
Etodolac (ibuprofen)	0.75	0.26	2.16	0.59
Rofecoxib (ibuprofen)	2.16	0.81	5.77	0.12
Naproxen (ibuprofen)	0.76	0.32	1.83	0.54
≤ 180 days exposure [c, σ]				
Celecoxib (ibuprofen)	0.63	0.33	1.19	0.15
Etodolac (ibuprofen)	0.54	0.28	1.02	0.06
Rofecoxib (ibuprofen)	0.81	0.34	1.91	0.63
Naproxen (ibuprofen)	0.77	0.44	1.36	0.37

[*] Note: uses stroke sensitivity model for prior stroke covariate
[ξ] Long-term exposure defined as > 180 days (with no events during the first 180 days).
[σ] Excludes long-term use observations.
[a] See **Appendix EE** for full model
[b] See **Appendix FF** for full model
[c] See **Appendix GG** for full model

6) Broadening the mortality definition to include deaths from ischemic heart disease

The following two sensitivity analyses adjust the mortality definition of the primary model to evaluate deaths for ischemic heart diseases (not just AMI) and total cardiovascular disease. As a reminder, death from ischemic heart disease encompasses angina pectoris, acute myocardial infarction, "other acute ischemic coronary heart disease," and all other forms of chronic ischemic heart disease. This modification did not find any different results from the primary model. Further details are available in Table 3.34.

Table 3.34 Summary – Adjusted association between NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from ischemic heart disease, or cerebrovascular event).*

Exposure (reference group)	Adjusted Risk Ratio	(95% CI) Lower	Upper	Sig. (p)
Any exposure [a]				
Celecoxib (ibuprofen)	1.14	0.71	1.82	0.59
Etodolac (ibuprofen)	0.82	0.49	1.37	0.45
Rofecoxib (ibuprofen)	1.53	0.85	2.78	0.16
Naproxen (ibuprofen)	0.96	0.61	1.53	0.87
> 180 days exposure [b, ξ]				
Celecoxib (ibuprofen)	3.03	1.20	7.63	**0.02**
Etodolac (ibuprofen)	1.02	0.29	3.54	0.98
Rofecoxib (ibuprofen)	5.59	1.93	16.24	**< 0.01**
Naproxen (ibuprofen)	1.49	0.53	4.15	0.45
≤ 180 days exposure [c, σ]				
Celecoxib (ibuprofen)	0.78	0.37	1.63	0.50
Etodolac (ibuprofen)	0.66	0.32	1.36	0.26
Rofecoxib (ibuprofen)	1.41	0.60	3.31	0.43
Naproxen (ibuprofen)	0.64	0.31	1.30	0.21

* Using the high specificity stroke model
ξ Long-term exposure defined as > 180 days (with no events during the first 180 days).
σ Excludes long-term use observations.
[a] See **Appendix HH** for full model
[b] See **Appendix II** for full model
[c] See **Appendix JJ** for full model

7) Broadening the mortality definition to include deaths from major cardiovascular diseases

The second analysis expands the mortality definition a little further and evaluates all cardiovascular related deaths. The precise definition for "total cardiovascular disease" can be found in Chapter One, page 16. Using this broad definition, all study results were the same as the primary model except for long-term celecoxib use. Long-term use celecoxib was associated with a non-significant increase in cardiovascular events as compared to ibuprofen (aRR, 2.17; 95% CI, 0.94 – 5.03; p = 0.07). See Table 3.35 for more details.

Table 3.35 Summary – Adjusted association between NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from major cardiovascular disease, or cerebrovascular event).*

Exposure (reference group)	Adjusted Risk Ratio	(95% CI) Lower	Upper	Sig. (p)
Any exposure [a]				
Celecoxib (ibuprofen)	1.14	0.73	1.79	0.55
Etodolac (ibuprofen)	0.87	0.53	1.42	0.58
Rofecoxib (ibuprofen)	1.58	0.90	2.77	0.11
Naproxen (ibuprofen)	1.01	0.65	1.56	0.98
> 180 days exposure [b, ξ]				
Celecoxib (ibuprofen)	2.17	0.94	5.03	0.07
Etodolac (ibuprofen)	0.96	0.31	2.91	0.94
Rofecoxib (ibuprofen)	3.90	1.43	10.62	**0.01**
Naproxen (ibuprofen)	1.14	0.45	2.91	0.78
≤ 180 days exposure [c, σ]				
Celecoxib (ibuprofen)	0.86	0.43	1.74	0.67
Etodolac (ibuprofen)	0.64	0.31	1.32	0.23
Rofecoxib (ibuprofen)	1.72	0.78	3.76	0.18
Naproxen (ibuprofen)	0.77	0.40	1.49	0.44

* Using the high specificity stroke model
ξ Long-term exposure defined as > 180 days (with no events during the first 180 days).
σ Excludes long-term use observations.
[a] See **Appendix KK** for full model
[b] See **Appendix LL** for full model
[c] See **Appendix MM** for full model

8) Restricting the age groups to subjects 65 years of age and older

Subjects were restricted to those aged 65 and older in order to assess an older population more at risk for cardiovascular disease. When restricted to subjects 65 years of age and older, the risk associated with long-term celecoxib and rofecoxib use nearly doubles. In this age group, celecoxib long-term users were 7.36 times (95% CI, 1.62 – 33.48; p = 0.01) more likely to experience a serious cardiovascular event and rofecoxib long-term users were 13.24 times (95% CI, 2.59 – 67.68; p = < 0.01) more likely to experience a serious cardiovascular event when compared to ibuprofen users. One additional difference from the primary model is the significant association between general use rofecoxib and serious cardiovascular events (aRR, 2.14; 95% CI, 1.09 – 4.19; p = 0.03). All other results were not statistically significant. See Table 3.36 for more details.

Table 3.36 Summary – Adjusted association between NSAIDS & COX-2 inhibitors and serious cardiovascular events[γ] in VA subjects ≥ 65 years of age.[*]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Any exposure [a]				
Celecoxib (ibuprofen)	1.52	0.87	2.67	0.14
Etodolac (ibuprofen)	1.10	0.58	2.10	0.77
Rofecoxib (ibuprofen)	2.14	1.09	4.19	**0.03**
Naproxen (ibuprofen)	1.08	0.59	1.97	0.81
> 180 days exposure [b, ξ]				
Celecoxib (ibuprofen)	7.36	1.62	33.48	**0.01**
Etodolac (ibuprofen)	3.54	0.62	20.13	0.15
Rofecoxib (ibuprofen)	13.24	2.59	67.68	**< 0.01**
Naproxen (ibuprofen)	1.72	0.28	10.50	0.55
≤ 180 days exposure [c, σ]				
Celecoxib (ibuprofen)	0.84	0.36	1.95	0.68
Etodolac (ibuprofen)	0.78	0.32	1.89	0.59
Rofecoxib (ibuprofen)	1.60	0.62	4.16	0.33
Naproxen (ibuprofen)	0.52	0.20	1.33	0.17

[γ] Defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event
[*] Using the high specificity stroke model
[ξ] Long-term exposure defined as > 180 days (with no events during the first 180 days).
[σ] Excludes long-term use observations.
[a] See **Appendix NN** for full model
[b] See **Appendix OO** for full model
[c] See **Appendix PP** for full model

9) Including one additional year of data (2002)

The final sensitivity analysis incorporates one more year of data to the overall analysis, the 2002 data. The inclusion of the 2002 data increased the sample size to 16,488, an increase of 4,300 observations. Of note, the sample size refers to naproxen, ibuprofen, celecoxib, rofecoxib and etodolac users. Drug specific increases are as follows:

- Ibuprofen 4,481 → 5,699;
- Naproxen 3,240 → 4,385;
- Celecoxib 1,530 → 1,980;
- Etodolac 2,371 → 3,615 and;
- Rofecoxib 566 → 809.

The number of endpoints increased from 146 to 238. Study findings were similar to the model using data from 1999 – 2001; with non-significant findings for the "any exposure" and short-term use categories. Long-term celecoxib and rofecoxib use was associated with an increase in cardiovascular risk when compared to long-term ibuprofen users. However, the magnitude of association was less. Celecoxib use were 2.05 times (95% CI, 1.03 – 4.07; p = 0.04) more likely to experience a serious cardiovascular event when compared to long-term ibuprofen use and rofecoxib users were 2.59 times (95% CI,

1.10 – 6.10; p = 0.03) more likely to experience a serious cardiovascular event when compared to long-term ibuprofen use. See Table 3.37 for more details.

Table 3.37 Summary – Adjusted association between NSAIDS & COX-2 inhibitors and serious cardiovascular events – 1999 through 2002.[γ, *]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Any exposure				
Celecoxib (ibuprofen)	1.14	0.77	1.70	0.51
Etodolac (ibuprofen)	0.99	0.67	1.47	0.97
Rofecoxib (ibuprofen)	1.56	0.96	2.54	0.07
Naproxen (ibuprofen)	1.03	0.70	1.52	0.87
> 180 days exposure				
Celecoxib (ibuprofen)	2.05	1.03	4.07	**0.04**
Etodolac (ibuprofen)	1.83	0.90	3.70	0.09
Rofecoxib (ibuprofen)	2.59	1.10	6.10	**0.03**
Naproxen (ibuprofen)	1.39	0.68	2.88	0.37
≤ 180 days exposure				
Celecoxib (ibuprofen)	0.69	0.35	1.37	0.29
Etodolac (ibuprofen)	0.65	0.34	1.23	0.19
Rofecoxib (ibuprofen)	1.70	0.84	3.44	0.14
Naproxen (ibuprofen)	0.79	0.44	1.44	0.44

[γ] Defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event
[*] Using the high specificity stroke model
[ξ] Long-term exposure defined as > 180 days (with no events during the first 180 days).
[σ] Excludes long-term use observations.
[a] See **Appendix QQ** for full model
[b] See **Appendix RR** for full model
[c] See **Appendix SS** for full model

ASSESSING THE STABILITY OF THE MODEL

Proportional Hazard Assessment

1) *Graphical Assessment* – The first step was to evaluate the overall model evaluating serious cardiovascular disease between NSAIDs/COX-2 inhibitors and ibuprofen (Figures 3.4 – 3.5). The observational assessment looked as though the hazards are close to proportional; however, it is difficult to determine graphically. Of note, it is highly unlikely that the proportional hazard assumption is ever exactly satisfied. [3]
2) *Time dependent covariate* – To test the proportional hazard assumption, a time dependent variable was created evaluating the interaction between drug categories and time. In the overall model assessing serious cardiovascular risk between NSAIDs/COX-2 inhibitors, no statistically significant interaction was found ($p = 0.68$) between study drugs and time, suggesting proportional hazards. However, when comparing only celecoxib and rofecoxib to ibuprofen, the interaction term approaches significance ($p = 0.053$), possibly indicating the violation of the proportional hazard assumption.

   One of the *a priori* hypotheses was that the risk of a cardiovascular event may not be proportional. Specifically, long-term use of COX-2 inhibitors was hypothesized to have a different association between risk of a cardiovascular

event compared to short term use. One method described by Therneau and Grambsch to allow for non-proportional hazards is to partition the follow-up time, creating multiple models.[4] This was done *a priori* and exposure times were partitioned into two groups, long-term exposure and short-term exposure. It is important to remember that the long-term model differs from the short-term and "any exposure" models by not allowing events to occur during the first 180 days. Furthermore, to control for nonproportional hazards, only observations still at risk after 180 days should be evaluated.[4] Both the short-term model and the long-term models were assessed for proportional hazards via the graphical assessment method and incorporation of a time dependent covariate assessment method.

1) *Graphical Assessment, long/short term models* – When visually evaluating the long-term and short-term models, the models do appear to violate the proportion hazard assumption. See Figures 3.6 – 3.9.
2) *Time dependent covariate, long/short term models* – Both models were evaluated with a time dependent interaction term between study drugs and time. The long-term model incorporating the time dependent variable resulted in a nonsignificant finding ($p = 0.45$), suggesting proportional hazards. Additionally, the short-term model with the incorporated time dependent variable yielded nonsignificant results ($p = 0.31$). The assessment of proportional hazards was also conducted for the short-term model and the long-term model using a study drug covariate

containing only ibuprofen, celecoxib, rofecoxib, and exposure time (the time dependent variable approaching significance in the "any exposure" model). The long-term model with the limited study drug covariate revealed a non-significant interaction term (p = 0.98), indicating proportional hazards. The short-term model yielded similar results with a non-significant interaction term between time and study medications (p= 0.81).

Figure 3.4 Kaplan-Meier curves – Serious cardiovascular disease – all exposures

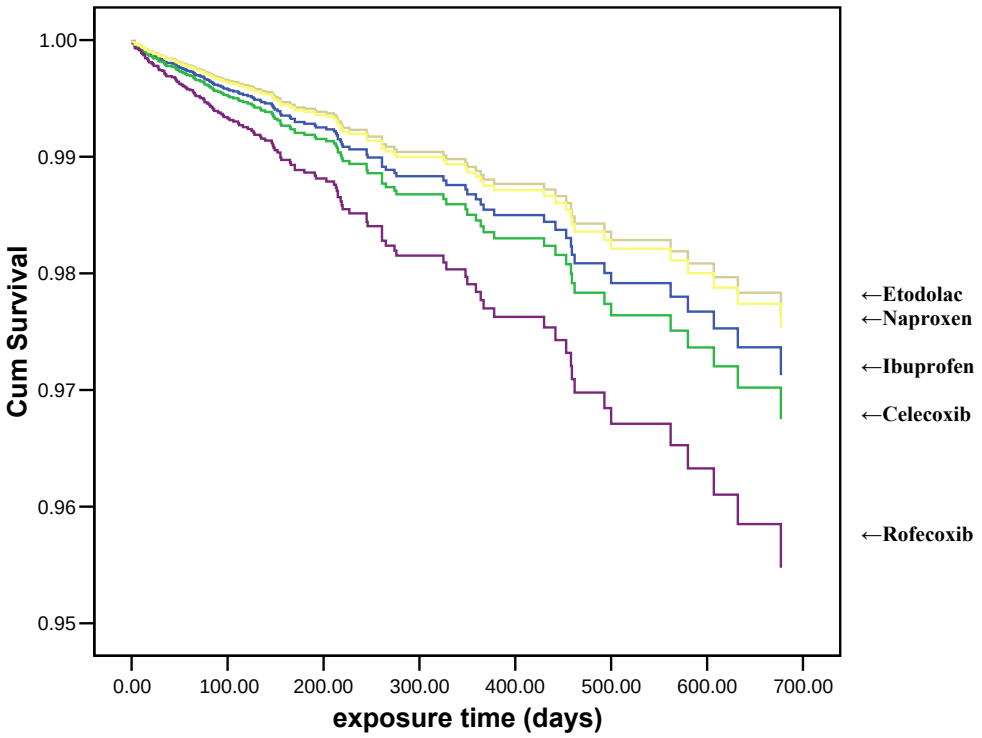
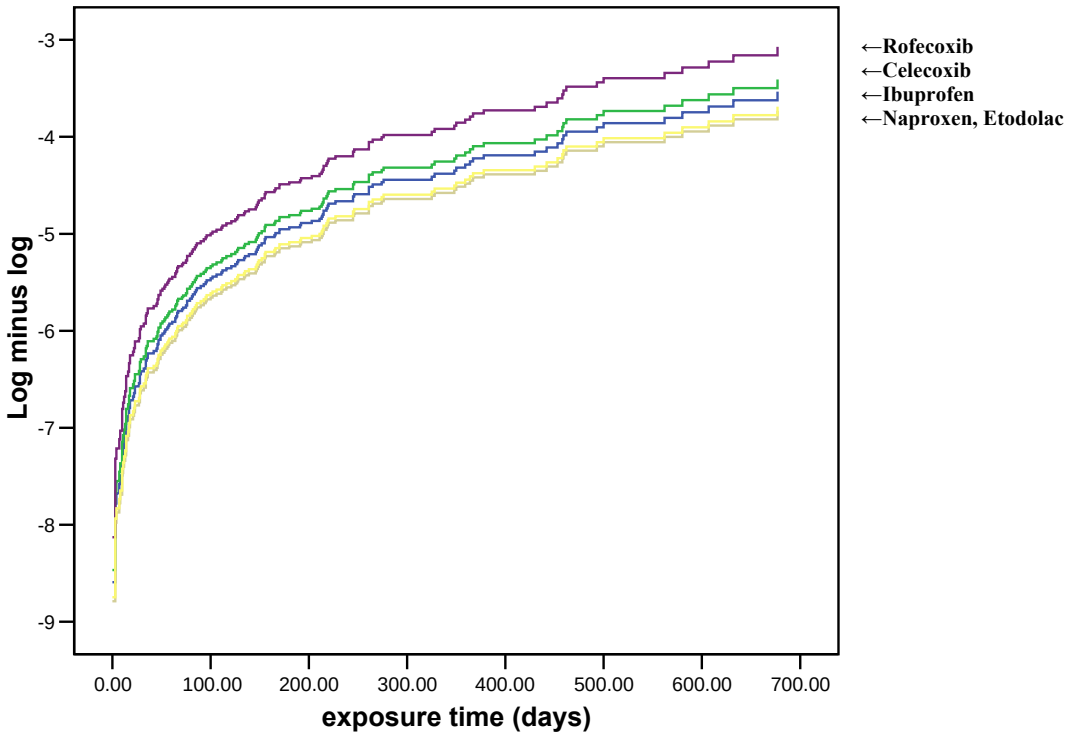


Figure 3.5 Transformed Kaplan-Meier curves – Serious cardiovascular disease – all exposures



The log-minus-log plots are used to test the proportional hazard assumption, plotting the log-scale on the x-axis; approximately parallel lines would indicate a proportional hazard between x–y.

Figure 3.6 Kaplan-Meier curves – Serious cardiovascular disease – > 180 days exposure

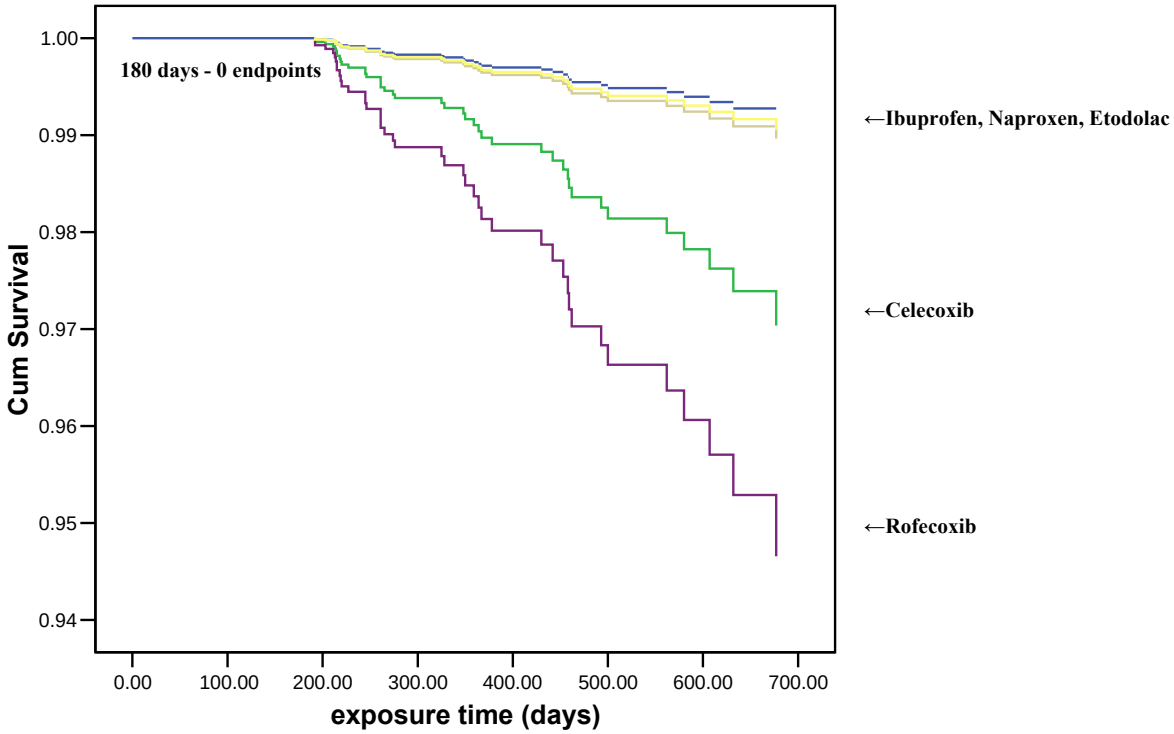


Figure 3.7 Transformed Kaplan-Meier curves – Serious cardiovascular disease – > 180 days exposure

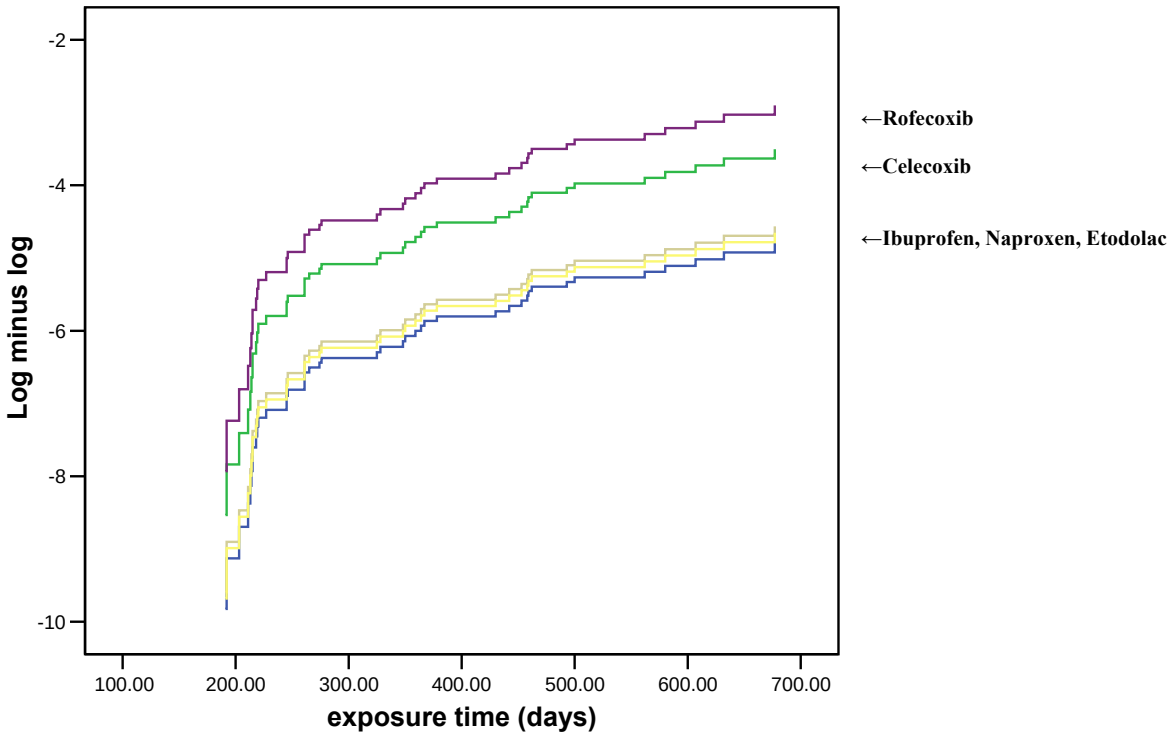


Figure 3.8 Kaplan-Meier curves – Serious cardiovascular disease – ≤ 180 days exposure

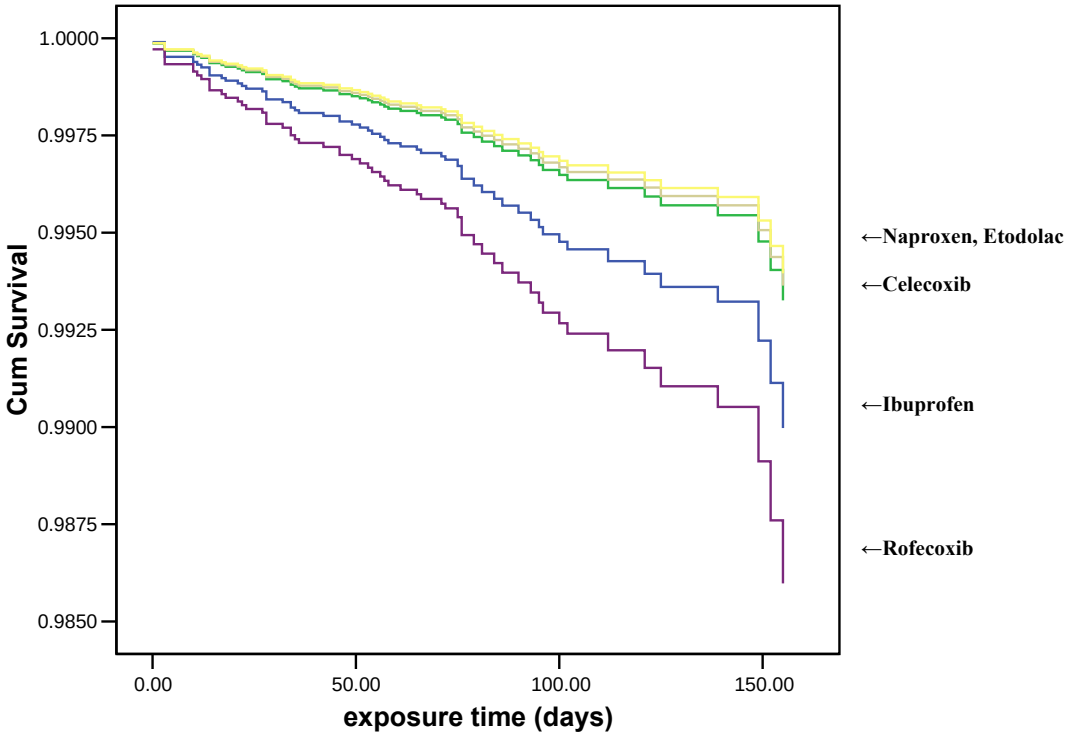
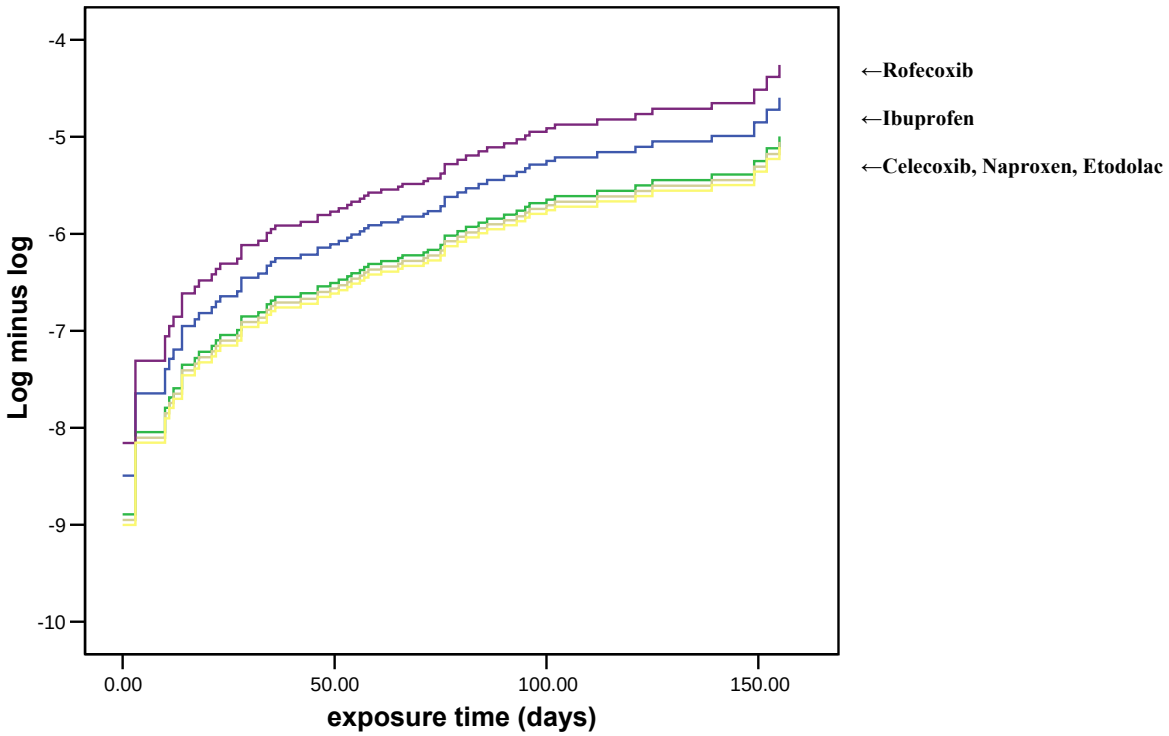


Figure 3.9 Transformed Kaplan-Meier curves – Serious cardiovascular disease – ≤ 180 days exposure



Multicollinearity

To assess multicollinearity, correlation matrixes were created for all of the variables. This was done for the "any exposure", short-term, and long-term models (1999 – 2001 data, serious cardiovascular events). Intercorrelation among independent variables above 0.80 indicates a possible problem with multicollinearity.[5] Several methods exist to handle multicollinearity. However, upon assessment of the correlation matrixes, none of the covariates in any of the models were found to have problematic correlations. Correlation matrixes not shown.

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CHAPTER FOUR

Discussion and Conclusion

CHAPTER OVERVIEW

COX-2 inhibitors were developed with the belief that their use would reduce adverse reactions caused by the inhibition of the COX-1 enzyme. However, clinical, epidemiological, and other studies provide evidence that the use of COX-2 inhibitors is associated with an increased risk of cardiovascular events. This study investigated the association between COX-2 inhibitor and NSAID use, and cardiovascular risk among Texas veterans. In addition, this study evaluated naproxen's cardioprotective capability. This chapter: summarizes and discusses the results of the study; provides possible biological explanations for the study findings; compares and contrasts study results with previous research findings; discusses the sensitivity analyses; addresses study limitations; describes possible implications of this study; and provides concluding remarks.

HYPOTHESES – ACCEPT / REJECT

The results of the hypotheses tests are presented in Table 4.1.

Table 4.1 Results of study hypotheses by study objective.

Study Hypotheses	Description	Fail to Reject /Reject Null Hypotheses
Objective I - To evaluate serious cardiovascular events (AMI, stroke, cardiovascular mortality) associated with COX-2 inhibitors.		
H_o1	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **rofecoxib** versus patients taking a traditional NSAID (i.e., ibuprofen), while controlling for various covariates. Overall use (short-term and long-term use)	Fail to Reject
H_o2	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **celecoxib** versus patients taking a traditional NSAID (i.e., ibuprofen), while controlling for various covariates. Overall use	Fail to Reject
H_o3	There is no difference in the overall risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **etodolac** versus patients taking a traditional NSAID (i.e., ibuprofen). "any exposure" model	Fail to Reject
Objective II - To determine if naproxen offers greater cardioprotective benefits compared to other NSAIDs.		
H_o4	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **naproxen** versus patients taking another traditional NSAID (i.e., ibuprofen), while controlling for various covariates. Overall use	Fail to Reject

Table 4.1 – *Continued* – **Results of study hypotheses by study objective.**

Study Hypotheses	Description	Fail to Reject /Reject Null Hypotheses
Objective III - To determine if duration of naproxen/COX-2 inhibitor use has an effect on cardiovascular outcomes (protective for naproxen and cardio-negative for COX-2 inhibitors).		
Short-term exposure		
H_o5	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **celecoxib** short term (≤ 180 days) and patients taking ibuprofen short-term, while controlling for various covariates.	Fail to Reject
H_o6	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **rofecoxib** short term (≤ 180 days) and patients taking ibuprofen short-term, while controlling for various covariates.	Fail to Reject
H_o7	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **etodolac** short term (≤ 180 days) and patients taking ibuprofen short-term, while controlling for various covariates.	Fail to Reject
H_o8	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **naproxen** short term (≤ 180 days) and patients taking ibuprofen short-term, while controlling for various covariates.	Fail to Reject
Long-term exposure		
H_o9	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **celecoxib** long-term (> 180 days) and patients taking ibuprofen long-term, while controlling for various covariates.	**Reject**
H_o10	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **rofecoxib** long-term (> 180 days) and patients taking ibuprofen long-term, while controlling for various covariates.	**Reject**
H_o11	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **etodolac** long-term (> 180 days) and patients taking ibuprofen long-term, while controlling for various covariates.	Fail to Reject
H_o12	There is no difference in the risk of experiencing a serious cardiovascular event (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) between patients taking **naproxen** long-term (> 180 days) and patients taking ibuprofen long-term, while controlling for various covariates.	Fail to Reject

SUMMARY OF PRIMARY STUDY RESULTS

"Any exposure model"

The unadjusted model, allowing long-term and short-term exposure ("any exposure"), found a significant increase in cardiovascular risk associated with celecoxib and rofecoxib. However, when the model was adjusted for various covariates the results were no longer significant. No significant increase or decrease in risk was found with etodolac or naproxen in the unadjusted or adjusted "any exposure" models.

"Short-term model"

Compared to ibuprofen, a cardiovascular risk was not found with short-term exposure (< 180 days) to etodolac, naproxen, or celecoxib (unadjusted and adjusted models). Rofecoxib, in the unadjusted short-term model showed a significant increase in cardiovascular risk; however, when adjusting for various covariates the risk became nonsignificant.

"Long-term model"

Long-term use of celecoxib and rofecoxib was associated with an increased risk of cardiovascular disease in the adjusted (aRR, 3.64 / aRR, 6.64, respectively) and unadjusted models (RR, 3.72 / RR, 7.46, respectively).

DISCUSSION OF SENSITIVITY ANALYSES

Several sensitivity analyses were conducted. The same outline used in Chapter Three will be adopted in this section. Most of the sensitivity analyses found similar results to the primary models.

Sensitivity analyses include:

1) Allowing events to occur during the first 180 days of exposure – long-term model

The long-term model excluded events occurring during the first 180 days to control for nonproportional hazards and to demonstrate the cardiovascular ramifications after long-term use. According to Therneau and Grambsch, to control for nonproportional hazards, only observations still at risk after x days (180 days in this study) should be evaluated.[1] This analysis allowed events to occur during the first 180 days of long-term exposure. The primary purpose of this sensitivity analysis was to evaluate the long-term protective effects of naproxen. However, this analysis did not reveal any cardioprotective properties with naproxen. Additionally, rofecoxib and celecoxib were not associated with a statistically significant increase in cardiovascular risk as compared to ibuprofen, contrasting with the primary long-term model.

2) *Including long-term use observations into the short-term model (limited to the first 180 days).*

The original study design divided the sample into two mutually exclusive portions, individuals receiving long-term therapy and individuals receiving short-term therapy. This was done to help control for any unmeasured variables in the study; patients receiving long-term therapy may have different characteristics than individuals receiving short-term therapy. To further evaluate the short-term effects, long-term use observations were included in the analysis; however, the duration of assessment was limited to the first 180 days of exposure. This analysis did not yield any significant changes in the results.

3) *Use of different comparator groups (i.e. naproxen and etodolac).*

This sensitivity analysis evaluated different comparator groups. Each NSAID/COX-2 inhibitor has unique properties that may detract from or contribute to cardiovascular risk. A brief overview will be provided regarding a few differences among the comparator groups. Ibuprofen was chosen because it has not been associated with an increase or decrease in cardiovascular risk. One important factor to keep in mind is that ibuprofen has been found to interfere with aspirin's antiplatelet effects which may result in an increased number of cardiovascular events in this group. The exact ramifications associated with concomitant use of ibuprofen and aspirin is yet to be determined.[2] Naproxen has not been associated with this effect and has the opposite problem, providing possible cardioprotective effects (discussed previously). Etodolac is an NSAID possessing some level of COX-2 specificity; the exact level is currently under debate. Similar results in all models were found with naproxen as compared to ibuprofen. Etodolac yielded similar results; however, the increased risk associated with long-term celecoxib use was no longer statistically significant (aRR 2.89; 95% CI, 0.95 – 8.80; p = 0.06). This could be attributed to etodolac's COX-2 selectivity or smaller sample size (~ 25% < naproxen and ~ 60 % < ibuprofen).

4) *Evaluating only AMI and AMI related deaths (excludes stroke cases)*

Due to the difficulty in evaluating stroke cases from ICD-9 codes, only AMI and AMI-related deaths were evaluated. Additionally, many of the published observational studies evaluated just AMI cases (± AMI death). This sensitivity analysis did not result in any significant changes in any of the results.

5) *Expanding the stroke definition (stroke sensitivity model)*

As discussed previously, a study conducted within the VA healthcare system assessing code veracity of stroke related ICD-9 codes has been conducted. When a high-sensitivity model was used, results yielded 89% sensitivity, 57% specificity, 60% positive predictive value, and 88% negative predictive value. When a high-specificity algorithm was used, the results change to: 59% sensitivity, 84% specificity, 72% positive predictive value, and 74% negative predictive value.[3] In order to evaluate the full range of possibilities, the endpoint was changed to capture additional stroke cases. However, in doing so, many of the additional cases (nearly 40 %) are false positive. This alteration resulted in nonsignificant results in all analyses, even long-term therapy. However, this can be explained by the high number of false positives. Furthermore, the sensitivity analysis evaluating only AMI and AMI-related deaths found a significant trend with long-term use of rofecoxib and celecoxib.

6) *Broadening the mortality definition to include deaths from ischemic heart disease.*
7) *Broadening the mortality definition to include deaths from major cardiovascular diseases.*

The next two sensitivity analyses broaden the mortality definition by evaluating death from ischemic heart disease / total cardiovascular disease (definition found in Chapter One, page 16). When expanding the definition to include death from ischemic heart disease, no significant changes in any of the models were found. Similar results were found when total cardiovascular disease-related deaths was assessed; however, the increased risk associated with long-term use of celecoxib was no longer statistically significant (aRR, 2.17; 95% CI, 0.94 – 5.03; p = 0.07). The nonsignificant result may be explained by the broad scope of conditions found in the "total cardiovascular disease" category, ranging from hypertensive diseases through heart failure.

8) *Restricting the age groups to subjects 65 years of age and older.*

This sensitivity analysis served two purposes: the first was to evaluate the cardiovascular risk in elderly individuals at increased risk for cardiovascular disease; and secondly to utilize the most complete set of data available (Medicare data). This sensitivity analysis resulted in a dramatic change in the results. In this analysis, overall use of rofecoxib was associated with an increased risk of cardiovascular events (aRR, 2.14; 95% CI 1.09 – 4.19; p = 0.03). Additionally, the magnitude of risk nearly doubles for long-term use of celecoxib (aRR, 7.36 vs. aRR, 3.64) and rofecoxib (aRR, 13.24 vs. aRR, 6.64).

9) *Including one additional year of data (2002).*

The last sensitivity analysis incorporated one additional year of data into the model. This sensitivity analysis was conducted to allow for a larger sample. The principal concern with using the 2002 data is a possible channeling effect. Several reports linking cardiovascular risk to COX-2 inhibitors became prominent in 2002. This information could cause physicians to alter prescribing patterns and place high risk patients on alternative forms of medication (e.g., ibuprofen). Results from this analysis yielded results similar to the original model. However, the magnitude of risk associated with long-term celecoxib (3.64 vs. 2.05) and rofecoxib (6.64 vs. 2.59) use was lower.

BIOLOGICAL PLAUSABILITY

Several biological mechanisms of actions have been reported, ranging from changes in blood pressure, effects on LDL oxidation, and effects on the prostanoid synthetic pathways. COX-1 inhibition blocks TXA_2 production, a prostanoid that induces platelet activation, aggregation, and adhesion.[4] In contrast, COX-2 inhibition blocks PGI_2 production, a beneficial prostanoid possessing vasodilating and platelet anti-aggregating properties. By selectively inhibiting the COX-2 enzyme, the protective effects of PGI_2 are removed and allow the production of TXA_2 (a platelet aggregator); thereby, possibly causing elevations in blood pressure, hardening of arteries, and increasing the risk for heart attacks and strokes.[5] Atherosclerosis is a slow, progressive disease, beginning with damage of the innermost layer of the vessel wall and progressing to possible occlusion or rupture.[6] COX-2 and COX-1 have both been found to be elevated in atherosclerotic plaques, contributing to elevations in TXA_2 and PGI_2.[7] Inversely, COX-2 was not found in normal blood vessels. This information suggests that COX-2 inhibition without COX-1 inhibition may be more problematic in individuals with atherosclerosis, possibly explaining why a cardiovascular signal was not found in short-term studies or in longer-term studies that typically exclude high risk individuals.[5,8] To obtain an overall estimate of cardiovascular risk in the study population, several cardiovascular comorbidities will be discussed/assessed. Smoking, elevated cholesterol, diabetes, obesity, and high blood pressure are five factors associated with atherosclerosis.[6] These conditions are common in this population.

Smoking

Smoking can disrupt the endothelium and precipitate coronary spasms; thereby, possibly contributing to a myocardial infarction in patients with minimal atherosclerosis.[9] The progression of atherosclerosis is directly related to the total pack-years of smoking, and may be cumulative and irreversable.[10] The prevalence of smoking within the VA has been shown to be significantly higher than in the general population (33 percent vs. 23 percent, respectively).[11] Additionally, veterans receiving healthcare within the VA were 52 percent more likely to be current smokers than other veterans.[12] In addition to cardiovascular disease, smokers are at a higher risk of developing COPD and lung cancer. Information regarding smoking was not available for this study; however, baseline diagnoses for COPD and lung cancer were available. When comparing study groups, celecoxib and rofecoxib were found to have higher percentages of COPD compared to etodolac, ibuprofen, and naproxen. Furthermore, celecoxib and rofecoxib were found to have higher percentages of lung cancer than ibuprofen and naproxen. See Table 4.2 for more details. The higher percentage of these conditions could indicate larger numbers of past or current smokers among users of COX-2 inhibitors.

Table 4.2 Baseline percentages of COPD and lung cancer by study medication

	CELECOXIB	ETODOLAC	IBUPROFEN	NAPROXEN	ROFECOXIB
COPD	9.9%	7.1%	5.1%	5.4%	13.2%
Lung Cancer	0.8%	0.8%	0.6%	0.6%	0.7%
Total (N)	**1530**	**2373**	**4483**	**3241**	**567**

Elevated Cholesterol

In addition to smoking, high cholesterol has been identified as an independent risk factor for developing coronary heart disease. Amongst the study groups, borderline to high total cholesterol readings were found in roughly 33 to 40 percent of the observations (using available readings – see Table 3.17, page 154). A similar percentage of cholesterol medication use was found in the study population (30.8 %), ranging from 25.9 percent to 37.9 percent between the study groups. Higher percentages of cholesterol medication use were found in celecoxib (37.6%) and rofecoxib (37.9%) users as compared to ibuprofen (25.9%), etodolac (33.3%), and naproxen (31.6%) users. Inversely, a lower percentage of borderline to high total cholesterol readings were found in celecoxib (34.1%) and rofecoxib (33.0%) observations as compared to ibuprofen (40.1%), etodolac (39.9%), and naproxen (41.6%) observations.

High Blood Pressure

Hypertensive patients are shown to have accelerated development of macrovascular lesions, leading to an increased risk/incidence of coronary heart disease, peripheral arterial and cerebrovascular diseases.[13] Additionally, hypertension has been implicated in 35 percent of all atherosclerotic events.[14] Roughly 45 percent of the study population was classified with stage one or stage two hypertension (average SBP readings above 140 mmHg or average DBP reading above 90 mmHg). When factoring in

prehypertension (SBP reading ≥ 120 mmHg or DBP ≥ 80), percentages rose to roughly 85 percent. Negligible differences were found between the study medication groups. See Table 3.16 for further details.

Diabetes

Diabetic patients have a two to four fold increase in the risk of developing coronary artery disease, and seventy-five percent of diabetics die from some form of heart or blood vessel disease.[15] Roughly 21.5 percent of the study population was found to have diabetes (based on ICD-9 codes and diabetes medications). Celecoxib (24.8%) and rofecoxib (27.9%) observations were found to have higher percentages of diabetes as compared to ibuprofen (19.4%), etodolac (21.5%), and naproxen (21.6%).

Overweight and Obesity

Obese individuals have been associated with an increase risk of developing cardiovascular disease and diabetes.[16,17] Obesity has been linked to increased levels of dyslipidemia, higher blood pressures, and glucose intolerance.[18] Obesity (defined as a BMI of 30 kg/m^2 or higher) is a condition affecting roughly 20 percent of the US population and 22.7 percent of the Texas population.[16] Close to 40 percent of the study population was found to be obese, nearly double the US average. When factoring in overweight individuals, this number rises to nearly 80 percent. The mean BMI for all five study drugs was approximately 29 units. See Table 3.21 for more details.

Overall Comorbidity

A brief assessment was conducted evaluating the coexistence of the previous conditions (with the exception of smoking) in the study population. This was done to provide an overall assessment of cardiovascular risk in this population.

The following criteria were used to classify subjects:

a) Hypertension – stage 1 or stage 2 hypertension (SBP > 140 mmHg or DBP > 90 mmHg) or use of a hypertensive medication
b) Hyperlipidemia – average total cholesterol reading above 240 mg/dl or use of a cholesterol medication.
c) Diabetes – use of a diabetic medication or diabetes related ICD-9 code
d) Obesity – BMI > 30 kg/m^2

Using these criteria, 77.5 percent of the study population was found to have at least one cardiovascular risk factor. Forty-nine percent of the observations possessed two or more risk factors and three or more factors were found in 21.4 percent of the population. This is only a crude estimate; many of the observations did not have laboratory and patient vitals. However, this only means that the numbers provided are an underestimate of the true risk in this population. Additionally, this assessment does not include all cardiovascular risk factors (e.g., prior stroke, MI, etc…). Of note: a covariate representing this information was added to the model (post-hoc), and no significant changes were found in the results.

BIOLOGICAL PLAUSABILITY – *continued*

Based on the cardiovascular comorbidity assessment, nearly 80 percent of the population may be at risk for thrombosis. Therefore, if the theory holds that only individuals at risk for thrombosis are at risk from COX-2 inhibitors, then an overwhelming majority of individuals using COX-2 inhibitors in this population are at risk.

COX-2 inhibitors differ with regards to their potency as an inhibitor of the COX-2 enzyme. Etoricoxib, rofecoxib, and valdecoxib have been consistently shown to be more COX-2 selective than celecoxib (etoricoxib > rofecoxib ≈ valdecoxib > celecoxib). There is conflicting information with regard to etodolac's COX-2 selectivity. Several studies show celecoxib to be more COX-2 selective than etodolac; however, others do not.[19-25] The selectivity and potency of COX-2 inhibitors may differ in different tissues or even different types of cells from the same tissue.[26] Furthermore, even though rofecoxib is a more selective COX-2 inhibitor than celecoxib, it is used in correspondingly lower doses.[26] Information regarding whether or not therapeutic equivalence equates to similar reductions in PGI_2 is unavailable. As discussed in Chapter One, COX-2 selectivity is lost at higher doses for celecoxib. Celecoxib demonstrated a dose-dependent inhibition of COX-1 up to 800 mg.[27,28] In contrast, rofecoxib did not demonstrate a dose-response relationship with platelet COX-1 activity up to 1000 mg. The high dose of celecoxib (800 mg) in the CLASS study may have provided sufficient

inhibition of COX-1 to prevent a significant number of cardiovascular events. On the other hand, the high dose of rofecoxib use in the VIGOR study may have contributed to the increased number of cardiovascular events. This factor is important to this study dissertation because a majority of celecoxib use was under 300 mg (74.2%). High dose rofecoxib (> 25 mg) comprised 12.6 percent of rofecoxib use. Due to the low percentage of high-dose celecoxib and rofecoxib use found in the VA population and the small sample size, the relationship between cardiovascular risk and dose was not evaluated. However, this study provides an excellent opportunity to evaluate the cardiovascular risk associated with routine celecoxib and rofecoxib prescribing.

Another postulated mechanism for the increased cardiovascular risk associated with COX-2 inhibitors, is their effect on blood pressure. Short-term studies of COX-2 inhibitors and NSAIDs show little to no effects on blood pressure in normotensive individuals.[29] However, for individuals treated for hypertension, these medications have been associated with elevated levels of blood pressure. Therefore, nearly 40 percent of this population is at risk for NSAID/COX-2 inhibitor-associated blood pressure elevations. In a study comparing celecoxib to rofecoxib in hypertensive patients over a 6-week period, elevated SBP readings (> 20 mmHg plus SBP ≥ 140 mmHg) were found among 14.9 percent of elderly patients given rofecoxib 25 mg/day as compared to 6.9 percent of patients receiving celecoxib 200 mg/day.[30] However, there is no evidence that celecoxib increases blood pressure more than traditional NSAIDs. [29]

One of the latest theories explaining the association between rofecoxib and cardiovascular risk is the effect of rofecoxib on human low density lipoprotein (LDL) oxidation. LDL oxidation is an important contributor to atherosclerosis.[31] This effect is believed to be related to the chemical structure and not related to COX-2 inhibition. Etoricoxib and rofecoxib exhibited prooxidant activity; whereas, celecoxib, valdecoxib and traditional NSAIDs were not associated with changes in lipid peroxidation rates.

Biological Assessment

Atherosclerosis can be a slow process, and multiple cardiovascular-related processes can be occurring as a result of COX-2 inhibition. COX-2 inhibition could be causing minute amounts of damage to the cardiovascular system over time. With regards to celecoxib, this drug has been shown to be less selective for the COX-2 enzyme, exhibit lower changes in blood pressure as compared to rofecoxib, and is not associated with lipid peroxidation rates. Therefore, compared to rofecoxib, celecoxib may take longer to show signs of cardiovascular toxicity and present a lower risk to patients. This biological hypothesis may explain why a cardiovascular risk was not found with short-term use (≤ 180 days) and overall use. Additionally, this may explain why the cardiovascular risk with long-term use (> 180 days) was nearly double in the rofecoxib group as compared to the celecoxib group (aRR – 6.64 vs. aRR – 3.64, respectively). Etodolac was not found to be associated with a cardiovascular risk in any analyses. This can explained by a

decreased selectivity for COX-2 or variations in tissue penetration, pharmacokinetics and other factors.[26] The next section will discuss naproxen's "cardioprotective" abilities.

Naproxen was the NSAID being evaluated in this study for possible cardioprotective effects. Traditional NSAIDs have not been found to inhibit platelet Tx (aspirin-like properties) throughout their dosing intervals, thereby not providing cardioprotection. However, some studies indicate that naproxen may provide sustained platelet Tx inhibition throughout normal dosing intervals (~ 8 hours).[32] One of the original hypotheses explaining the increased risk associated with rofecoxib in the VIGOR trial was that the comparator, naproxen, was cardioprotective. This explanation has since been discounted as the sole reason for the elevated cardiovascular risk found with rofecoxib. Nevertheless, naproxen was evaluated in this dissertation study to determine if it possessed cardioprotective properties. Results from this study revealed that for these VA patients, naproxen was not associated with a cardioprotective effect when compared to ibuprofen users. Of note, one reason a cardioprotective effect may be found in clinical trials and not in observational studies is that persistent use of naproxen is more likely to occur in clinical trials. The next two sections will discuss observational and clinical trials evaluating COX-2 inhibitors and naproxen.

OBSERVATIONAL STUDIES – *review*

Study 1- Ray et al.

The study conducted by Ray et al. did not find an associated risk of serious coronary heart disease with ibuprofen, naproxen, celecoxib, or low dose rofecoxib (≤ 25 mg) when compared to non-NSAID users.[33] However, the study did show an associated risk with high dose rofecoxib (> 25 mg) when compared to celecoxib and non-NSAID users.

Study 2 – Mamdani et al.

The second retrospective cohort study evaluated elderly patients 66 years of age and older.[34] In this analysis, no significant association between cardiovascular risk and NSAID/COX-2 inhibitor exposure was found when compared to control or other drug groups (exposure < 1 year). Additionally, patients taking naproxen did not show a significant reduction in AMI events as compared to the control group.

Study 3 – Solomon et al.

Similarly, this study evaluated elderly patients exposed to COX-2 inhibitors and NSAIDs.[35] This study evaluated duration of exposure and associated cardiovascular risk.

The study evaluated overall, short-term (< 30 days), intermediate (30 – 90 days), and long-term use (> 90 days). In the overall model and for the time dependent models, celecoxib was not associated with an increased risk of acute myocardial infarctions. Overall use of rofecoxib was associated with an elevated cardiovascular risk when compared to celecoxib or the control group. No increased risk was found between rofecoxib and naproxen/ibuprofen. When duration of exposure was evaluated, short-term and intermediate exposure to rofecoxib was found to have the highest risk when compared to celecoxib. No significant risk was associated with long-term use of rofecoxib (> 90 days). Lastly, as seen with study 1, high dose rofecoxib was associated with a higher adjusted relative risk than low dose rofecoxib. Naproxen's cardioprotective effects were not evaluated in this study.

Study 4 – Graham et al.

Graham and colleagues conducted a nested case-control study among 6 million California Kaiser Permanente members to evaluate the cardiovascular risk associated with NSAIDs and COX-2 inhibitors.[36] Study findings revealed an increased risk associated with high-dose rofecoxib when compared to remote users (no use of NSAIDs > 60 days prior to index date). Evaluation of low-dose rofecoxib did not reveal an increased cardiovascular risk when compared to "remote users." However, an increased risk was found with low-dose rofecoxib as compared to celecoxib. Paradoxically, naproxen was found to have an <u>increased</u> risk of cardiovascular events in this population.

Study 5 – Layton et al.

Two articles reported results from a study that used prescription event monitoring data in England to assess the cardiovascular safety of celecoxib and rofecoxib as compared to meloxicam.[37,38] The studies showed an increase rate of cerebrovascular events in rofecoxib and celecoxib users as compared to meloxicam users. No significant difference was found in the rate of cardiovascular events in rofecoxib and celecoxib users as compared to meloxicam users. A decrease in peripheral venous thrombotic events was found in rofecoxib users as compared to meloxicam users. Regarding celecoxib use, no significant difference was found.

Study 6 – Kimmel et al.

Kimmel et al. conducted a case-control study evaluating the cardiovascular safety of celecoxib and rofecoxib.[39] Patients who experienced a myocardial event and control subjects were evaluated for exposure to study medications via telephone interviews. The study had a 50 percent response rate. When compared to non-NSAID subjects, the study found a cardioprotective effect with celecoxib and traditional NSAIDs. Rofecoxib was not associated with an increased risk when compared to non-NSAID subjects. However, when compared to naproxen, rofecoxib was associated with an increased risk. Celecoxib vs. ibuprofen and diclofenac did not reveal a cardioprotective or cardionegative effect.

Observational Studies – *Assessment*

A wide range of results regarding rofecoxib's and celecoxib's cardiovascular safety have been reported. One consistent theme across the studies is that celecoxib has not been found to increase cardiovascular risk. One study even found a cardioprotective effect among celecoxib users. However, this study had several limitations and when compared to NSAIDs, the protective effect was not found. Another anomaly is the study that found an increased cerebrovascular risk associated with celecoxib (this same study failed to detect a difference in cardiovascular risk).

In reference to the observational studies discussed, similar results were found in this dissertation study with regards to short-term and overall use of celecoxib. Short-term use of celecoxib and overall use of celecoxib was not found to be associated with an increased (or decreased) risk of cardiovascular events. Unlike other studies, this study segmented the population into two time periods to evaluate the cardiovascular risk after long-term exposure (> 180 days). The long-term use of celecoxib was found to be associated with an increased cardiovascular risk as compared to long-term ibuprofen use. Only one study (*study 3*) evaluated the duration of use and associated risk. That study failed to show any increased risk in any time period for celecoxib. However, that study defined long-term use as receiving celecoxib for greater than 90 days as opposed to the 180 days in the dissertation study. For study 3, the number of patients exposed for greater than 180 days is unclear. Furthermore, patients using celecoxib spanning 90 – 180 days may not have incurred enough cardiovascular damage to translate into a

significant increase in risk. The study used rofecoxib as a comparator group for analyses involving duration of therapy; therefore, if celecoxib starts to increase the risk after several months of exposure and rofecoxib does as well, then a difference may not be found.

The cardiovascular signal for rofecoxib seems to be much stronger than for celecoxib, especially at high doses. Due to the low percentage of high dose celecoxib (≥ 300 mg) and rofecoxib (> 25 mg) users, this dissertation study was unable to examine a dose-response relationship. Across the observational studies, results varied as to the associated risk with rofecoxib. Some studies revealed no risk with low doses of rofecoxib, whereas others did.(REF) All of the studies evaluating high-dose rofecoxib found a significant link between cardiovascular risk and rofecoxib. For our study, when evaluating overall use and short-term use, no association between rofecoxib use and cardiovascular risk was found. This result was not unexpected, especially since several of the studies failed to find a significant increase in risk with low-dose rofecoxib or overall use (low-dose and high-dose combined). As discussed above, one study (*study 3*) evaluated the temporal relationship between exposure and risk. The study revealed significantly higher rates of cardiovascular events among low-dose and high-dose rofecoxib use when compared to celecoxib. When evaluated over time, the risk dissipated after 90 days, either implying that the risk associated with rofecoxib is short-term or that long-term exposure to celecoxib is associated with an increased risk. Another important factor to keep in mind is that overall use (high-dose and low-dose use

over the entire study period) of rofecoxib was not associated with an increased cardiovascular risk when compared to ibuprofen or naproxen (*study 3 – Solomon et al*).

CLINICAL TRIALS

There are several limitations when evaluating the cardiovascular safety in clinical trials. While they are considered the gold standard for determining safety and efficacy, they usually involve a small number of patients and may not be powered to detect unexpected side effects (such as cardiovascular disease). Additionally, in attempts to obtain "clean" results, many of these studies exclude individuals with various risk factors (i.e., cardiovascular risk factors). Therefore, many of the studies conducted evaluating COX-2 inhibitors may not be representative of the population actually receiving the drug. Furthermore, risk factors may differ between clinical trials and may make comparisons difficult. One prime example is the different populations in the CLASS (celecoxib) and VIGOR (rofecoxib) studies.[40-42] The VIGOR study was comprised primarily of rheumatoid arthritis patients, whereas the CLASS trial was comprised primarily of osteoarthritis patients. Rheumatoid arthritis patients have been shown to be at higher risk for cardiovascular events than osteoarthritis patients. As discussed in the biological plausibility section, persons at risk for cardiovascular disease may be susceptible to the negative effects of COX-2 inhibitors. Additionally, the CLASS trial allowed high-risk patients to take aspirin, thereby possibly nullifying any COX-2 associated risk. Another flaw limiting the generalizability of these clinical trials results from the use of super-

therapeutic doses. Both of these clinical trials used nearly double the standard dose in their studies. Therefore, patients receiving 800 mg of celecoxib (a dose found to inhibit COX-1) may be at less risk for cardiovascular events than normal doses and patients receiving 50 mg of rofecoxib may be at an elevated risk (does not lose COX-2 selectivity at this dose).

An interesting finding about valdecoxib (a COX-2 inhibitor not evaluated in this study) was recently released. Two randomized, placebo-controlled studies in patients immediately after coronary-artery bypass grafting showed valdecoxib to increase cardiovascular risk by three-fold.[43] This adds to the hypothesis that individuals at risk are more susceptible to the negative cardiovascular effects of COX-2 inhibitors. As a reminder, valdecoxib is believed to have a similar COX-2 selectivity as rofecoxib.

Two clinical trials providing the most credence for the results found in this dissertation study are the APPROVe trial (Adenomatous Polyp Prevention On Vioxx) and the Adenoma Prevention with Celecoxib (APC) trial.[44,45] In both of these trials, a significant cardiovascular risk was found with rofecoxib and celecoxib as compared to a placebo group. In the APPROVe trial, it took nearly 18 months before a significant increase in cardiovascular risk was found. This was a population on low-dose rofecoxib with few cardiovascular risk factors. All the details are not known at this time regarding patient characteristics (↑ or ↓ cardiovascular risk) in the APC trial. However, it is known that after a two-year period, a 2.5-fold increased risk was found in long-term users of celecoxib.

LIMITATIONS

With any observational study several limitations exist. One of the principal limitations to almost any observational study is the inability to control for various factors not found in the database. In this study, several important variables were not available. These include: proximity to a VA hospital, smoking status, over-the-counter use of aspirin and NSAIDs, family history of cardiovascular events, persistent use of study medication, and others.

Events occurring outside the VA medical system

With regards to hospital proximity, VA patients not living near a VA hospital may have limited ability to receive health care services from a VA facility in the event of a major cardiovascular event. To control for this factor, Medicare data were obtained to capture events occurring outside the VA health care system. A study was conducted evaluating point of care for acute myocardial infarctions among elderly veterans (≥ 65 years). This study found that more than half (54%) of veterans with prior use of the VA medical system were initially hospitalized in a Medicare hospital when they suffered an AMI.[46] While the Medicare data will help capture events occurring outside the VA medical system in patients enrolled in Medicare, data for individuals not enrolled who experience an event may not be captured. The sensitivity analysis restricting the population to individuals 65 years of age and older helped to control for this limitation.

Baseline assessment

At baseline, individuals receiving celecoxib and rofecoxib were found to have higher percentages of baseline risk factors when compared to ibuprofen, etodolac, and naproxen. However, this could be explained by the larger percentage of individuals over the age of 65 receiving celecoxib (63.3%) and rofecoxib (59.3%) as compared to ibuprofen (33.2%), etodolac (38.4%), and naproxen (36.9%). Additionally, the adjusted model helps to control for these factors.

Laboratory values and patient vitals

In the original study design, laboratory values and patient vitals were to be used as covariates in the study model. However, due to the limited availability of readings and small sample size, they were excluded from the model. In an attempt to account for this shortfall, an assessment was conducted to evaluate if systematic differences occurred between the study groups. Blood pressure, cholesterol levels, and body mass index values were not found to be significantly different between the study groups.

VA Formulary

One of the primary limitations surrounding the use of prescription claims data obtained from the VA is the restricted formulary. In particular, COX-2 inhibitors are limited to individuals with a high risk of developing NSAID-induced GI injury. Many patients were required to receive prior treatment with traditional NSAIDs or preferential COX-2 inhibitors. (Preferential COX-2 inhibitors are NSAIDs with relative COX-2 selectivity. Drugs included in this category are etodolac, nabumetone, and salsalate.[47]) The requirement could result in a selection bias.

OTC use and other confounding factors

Regarding prescription coverage, even though automated pharmacy claims are one of the best sources of information on drug use, information concerning compliance and use of drugs from outside sources may be lacking.[48] Concurrent use of aspirin was available in this study; however, very few patients were found to have overlapping use. Therefore, many patients were probably taking over-the-counter aspirin. However, this would only be a problem if use differed across the study groups. Comparable percentages of baseline aspirin use were found between all five study groups (~30%). Furthermore, other studies evaluating this issue have not shown a difference in aspirin use between NSAIDs/COX-2 inhibitors. [35,36] Furthermore, these same studies did not

find any clinically significant differences between NSAIDs/COX-2 inhibitors for smoking history or family history of coronary heart disease.

Comorbidity and medical use

Several analyses evaluating the association between cardiovascular risk and COX-2 inhibitor use had covariates measuring number of medical visits, number of comorbid conditions, and different types of medication. These variables were not available in this study. Only select medications and ICD-9 codes were available for analysis, thereby limiting the ability to determine overall disease burden or determine the frequency of medical care. It is unknown if these variables would significantly contribute to this study.

Code validity

Research conducted within the VA healthcare system found a 96.9 percent positive predictive value of acute myocardial infarction coding in the primary position.[49] Patients discharged alive were required to have a length of stay no less than three days and no greater than 180 days. Code position or length of stay was not available in this study. Due to this, the positive predictive value for an AMI diagnosis may be reduced. A recent study in Medicare recipients evaluated the validity of acute myocardial infarction ICD-9 codes. That study found a 92.3 percent positive predictive value for an AMI

coded in the primary or secondary position without a length of stay restriction.[50] That study provides some flexibility with regards to field position and length of stay requirement. However, it is unknown if other fields were used in that study.

Diagnostic code validity for cerebrovascular disease has been previously discussed. This algorithm does not have a length of stay or code position requirement. Information regarding the code validity for mortality data was not available for this population.

Generalizability

Utilizing databases can raise concerns regarding the generalizability of the results to other populations. One of the primary differences between this population and other populations is the disproportionate number of men compared to women. Women comprised roughly 6% of the study population. The disproportionate number of men to women may be advantageous because most (if not all) of the observationsal studies evaluating COX-2 inhibitor related cardiovascular risk consisted primarily of women (COX-2 inhibitor study groups ~ 70 - 80% women).[33,35,36,39] Additionally, a large proportion of this population was estimated to be at risk for cardiovascular disease and results may not be generalizable to healthier populations.

Sample Size

It should be noted that this study comprised only 12,194 observation periods between the five study drugs. Sample size and number of endpoint events by drug is provided: 1,530 celecoxib observations with 39 events; 2,373 etodolac observations with 23 events; 4,483 ibuprofen observations with 38 events; 3,241 naproxen observations with 29 events; and 567 rofecoxib observations with 17 events. This number was reduced further when the sample was split into long-term and short-term use. Due to the small numbers, this study may not have had sufficient power to detect a difference in short-term drug use (or in overall drug use). Even with the addition of the 2002 data, this study may still be under-powered. Additionally, due to the small number of observations and events, the significant findings from the long-term exposure model should be interpreted cautiously.

Censoring

Two forms of censoring occurred in this study, Type I and random censoring. Type I censoring occurs when censoring is under the control of the investigator (i.e., study termination); whereas, random censoring is not under the control of the investigator.[51] There are two types of random censoring, informative and noninformative. The later of the two could possibly lead to severe biases in the study. Informative censoring occurs when an individual is censored due to the effects of

treatment or other nonrandom event. Therefore, bias can occur if censored cases tend to be at high risk for a future event or when censored cases would have had longer times to an event. The censored case should be representative of all those subjects with the same values of the explanatory variables who survive to that point in time. It is plausible that informative censoring may occur in this study. For example, patients who are taking NSAIDs/COX-2 inhibitors experiencing elevated blood pressure or edema may discontinue therapy prior to an event. However, it is more likely that patients were censored due to: discontinuation of medication due to dissatisfaction with pain relief; self modification of treatment therapy (e.g., taking one tablet daily in place of two tablets daily); experiencing noncardiovascular related side-effects (e.g., stomach discomfort); or other factors. Nevertheless, knowledge regarding the exact reason an observation was censored is unavailable and is considered a study limitation.

CONCLUSION

After long-term exposure to celecoxib and rofecoxib, an increased risk of serious cardiovascular disease (defined as acute myocardial infarction, death from an acute myocardial infarction, or cerebrovascular event) was found. Compared to ibuprofen. long-term exposure to celecoxib increased the risk for a serious cardiovascular event by 3.64 fold and long-term exposure to rofecoxib increased risk by 6.64 fold. This study failed to find an increased risk associated with short-term use of celecoxib and rofecoxib. Although etodolac has been found to possess some affinity for the COX-2 enzyme over the COX-1 enzyme, an elevated cardiovascular risk was not found with this drug. Similar to other studies, no cardioprotective effects were found with naproxen use. Therefore, the explanation that naproxen's "cardioprotective" ability was the cause for the 5-fold increase in cardiovascular events in the VIGOR study is highly unlikely.

NSAIDs and COX-2 inhibitors are some of the most widely prescribed medications in the world. Due to this factor, the findings of this study have wide reaching implications. Two prospective clinical trials now support the findings of this study. However, additional studies are needed to examine this issue in celecoxib and other COX-2 inhibitors currently on the market, especially in a population at risk for cardiovascular disease. Due to the findings of this study and the two prospective clinical trials, caution is advised in the use of long-term celecoxib. Rofecoxib has been voluntarily removed from the market.

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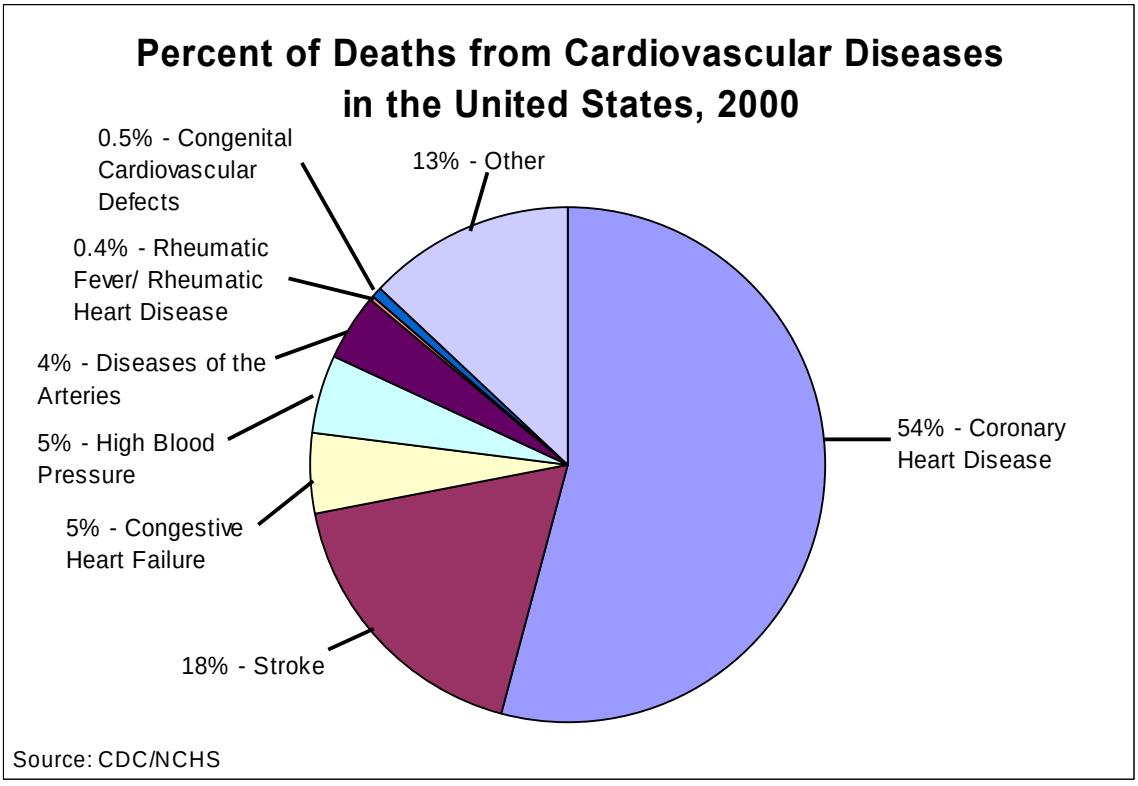
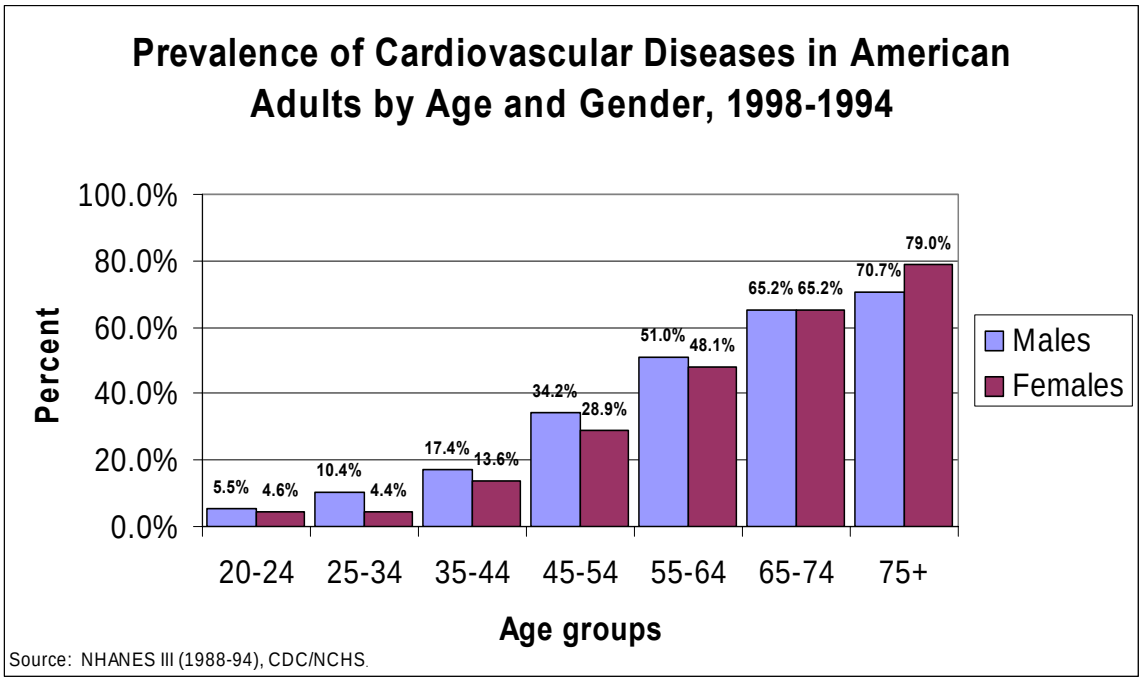
APPENDICIES

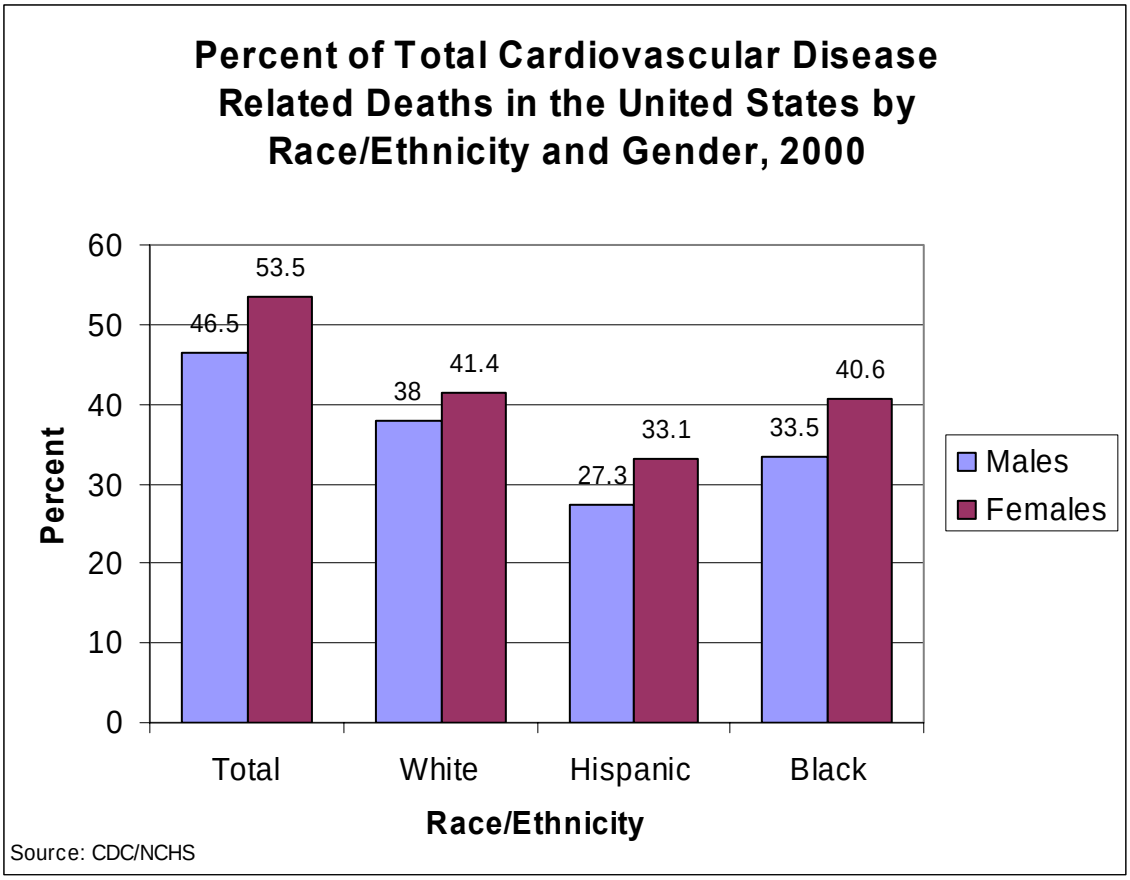
Appendix A:



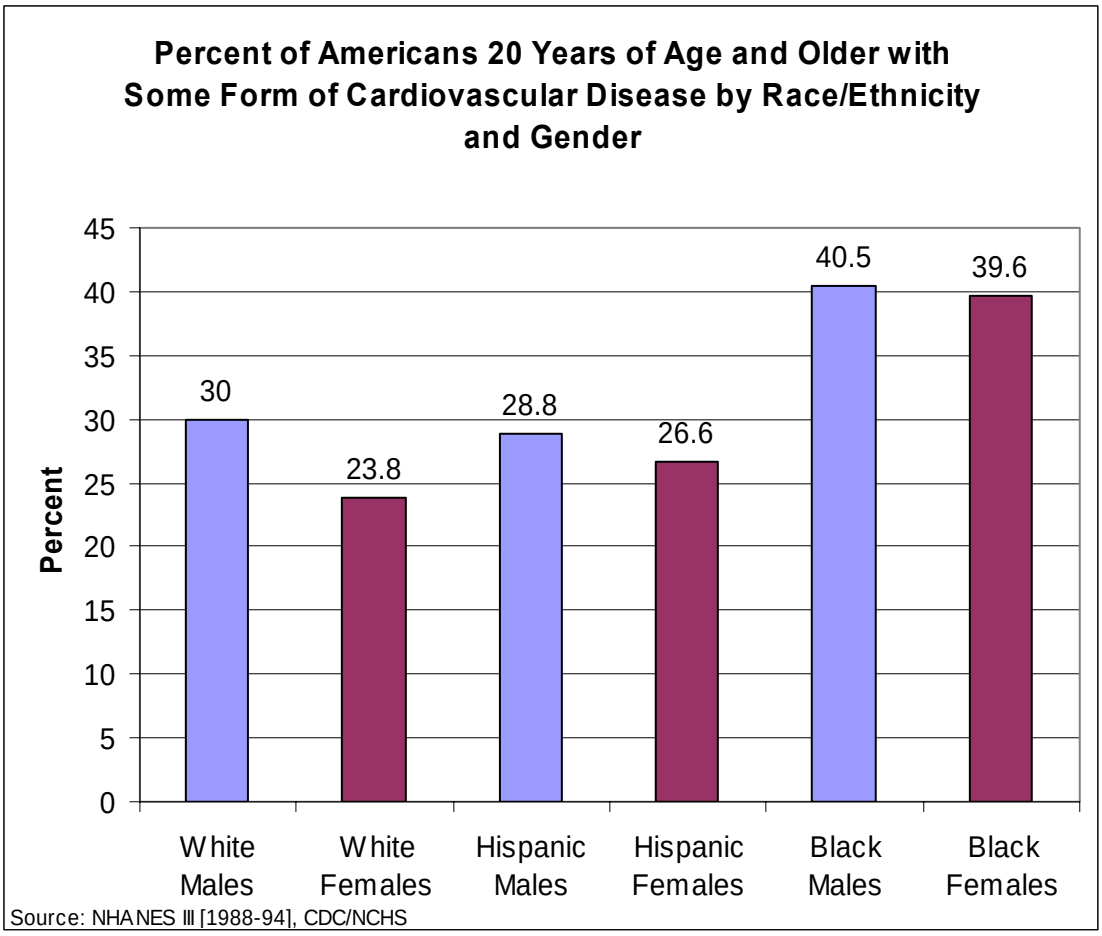
Appendix B:


Prevalence of Cardiovascular Diseases in American Adults by Age and Gender, 1998-1994
100.0%
80.0%
60.0%
40.0%
20.0%
0.0%
Percent
5.5%
4.6%
10.4%
4.4%
17.4%
13.6%
34.2%
28.9%
51.0%
48.1%
65.2%
65.2%
70.7%
79.0%
20-24
25-34
35-44
45-54
55-64
65-74
75+
Age groups
Males
Females
Source: NHANES III (1988-94), CDC/NCHS.

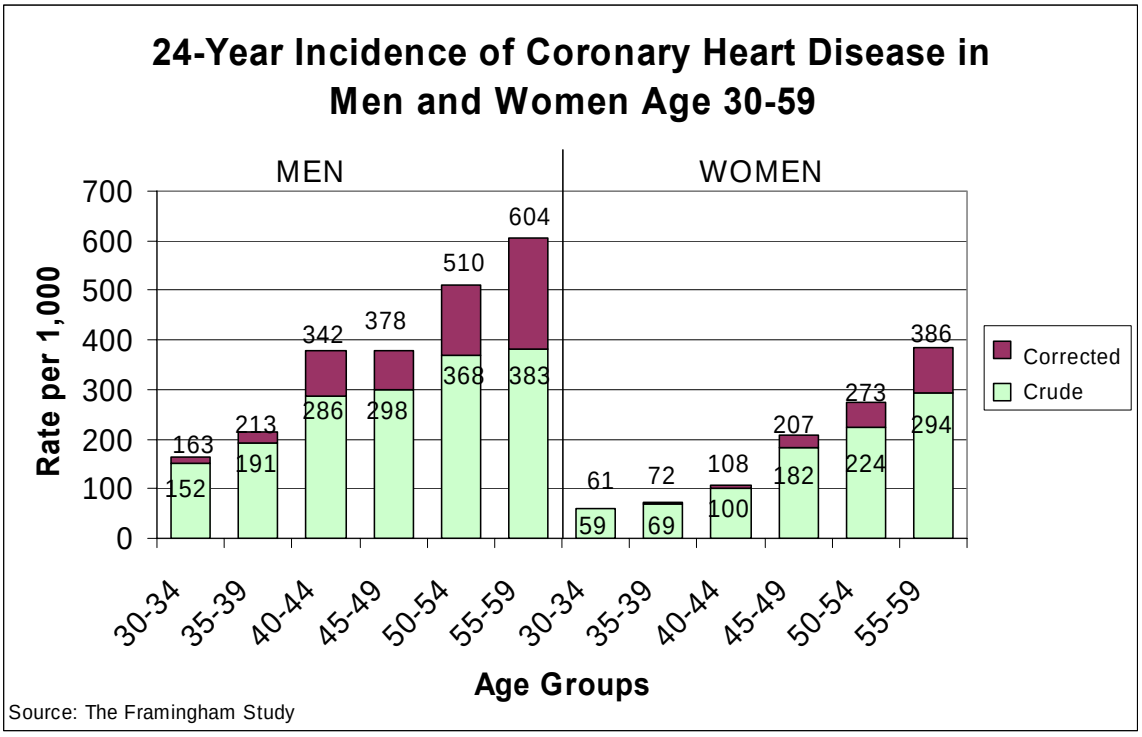
Appendix C:


Percent of Total Cardiovascular Disease Related Deaths in the United States by Race/Ethnicity and Gender, 2000
60
50
40
30
20
10
0
Percent
53.5
46.5
41.4
38
33.1
27.3
40.6
33.5
Total
White
Hispanic
Black
Race/Ethnicity
Males
Females
Source: CDC/NCHS

Appendix D:


Percent of Americans 20 Years of Age and Older with Some Form of Cardiovascular Disease by Race/Ethnicity and Gender
Percent
45
40
35
30
25
20
15
10
5
0
30
23.8
28.8
26.6
40.5
39.6
White Males
White Females
Hispanic Males
Hispanic Females
Black Males
Black Females
Source: NHANES III [1988-94], CDC/NCHS

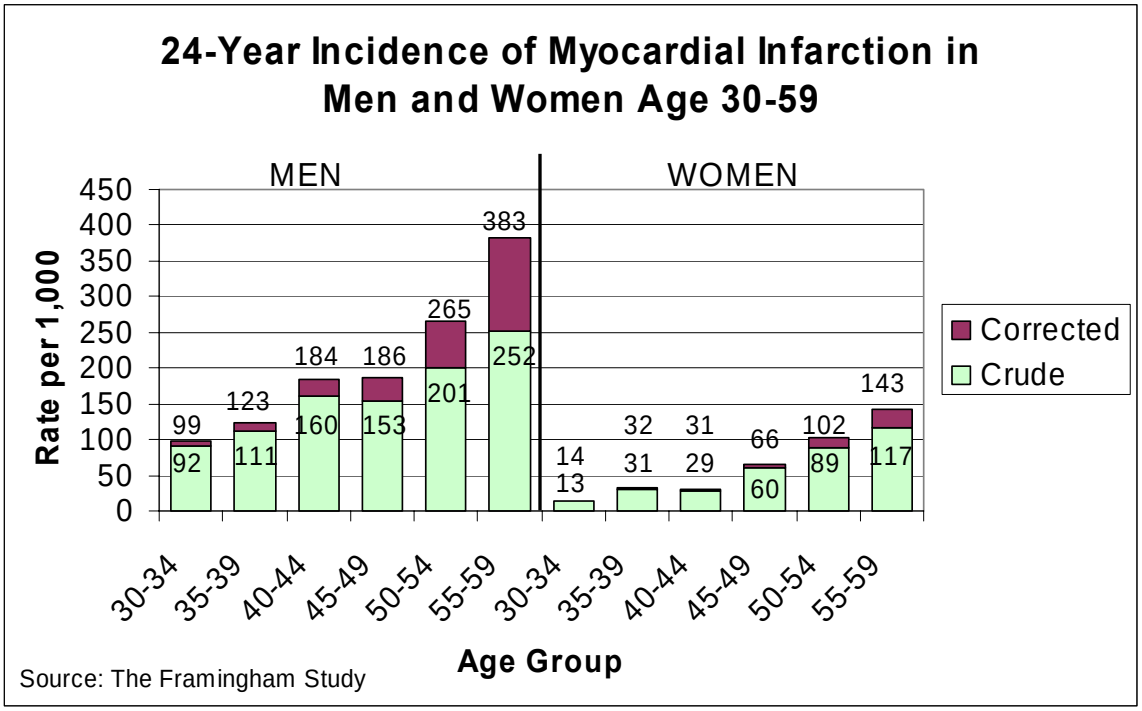
Appendix E:



Source: The Framingham Study

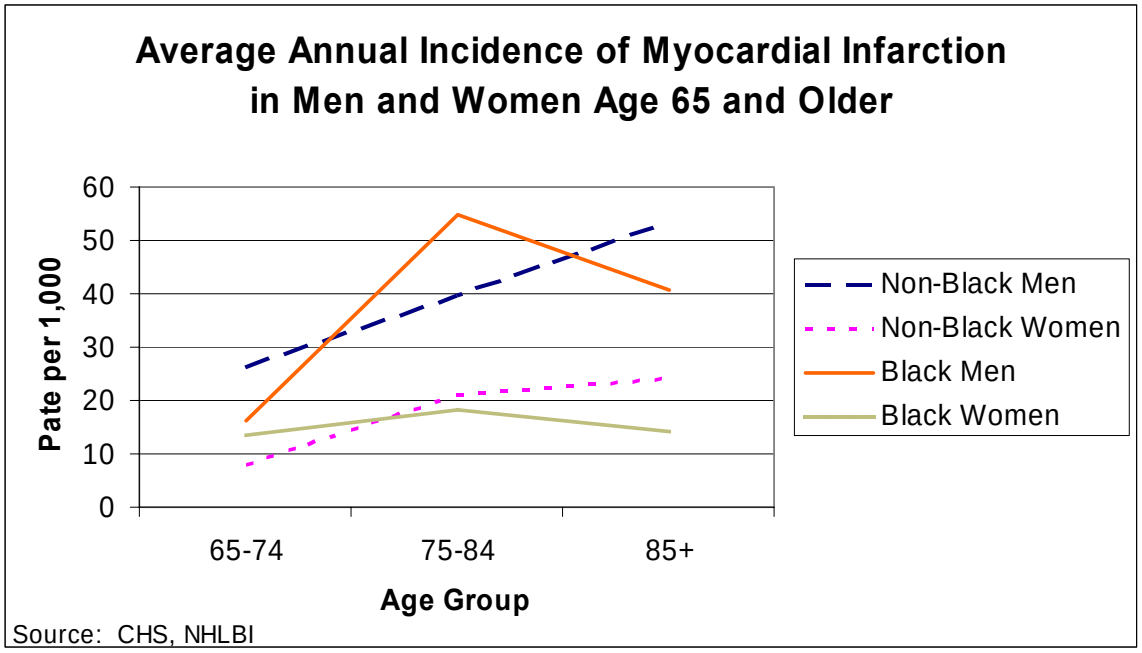
Note: Corrected rates provide an estimate of the risk if no other disorders intervened.

Appendix F:

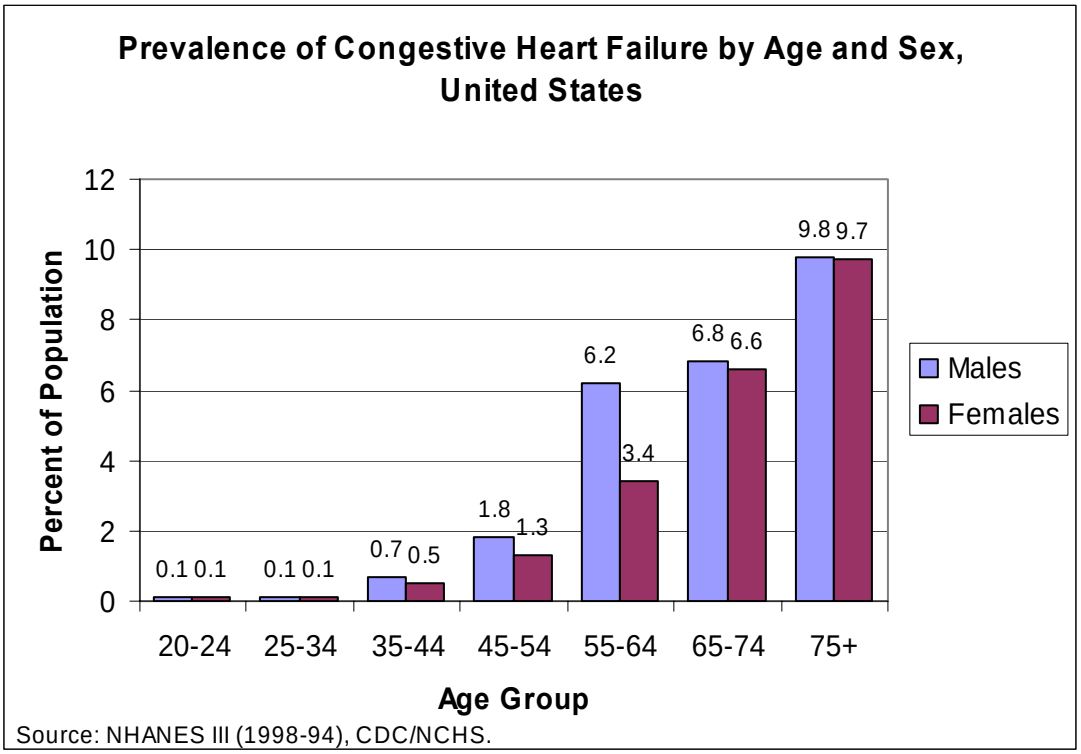


Note: Corrected rates provide an estimate of the risk if no other disorders intervened.

Appendix G:


Average Annual Incidence of Myocardial Infarction
in Men and Women Age 65 and Older
Pate per 1,000
60
50
40
30
20
10
0
65-74
75-84
85+
Age Group
Non-Black Men
Non-Black Women
Black Men
Black Women
Source: CHS, NHLBI

Appendix H:


Prevalence of Congestive Heart Failure by Age and Sex, United States
Percent of Population
12
10
8
6
4
2
0
0.1 0.1
0.1 0.1
0.7 0.5
1.8 1.3
6.2 3.4
6.8 6.6
9.8 9.7
20-24
25-34
35-44
45-54
55-64
65-74
75+
Age Group
Males
Females
Source: NHANES III (1998-94), CDC/NCHS.

Appendix I:

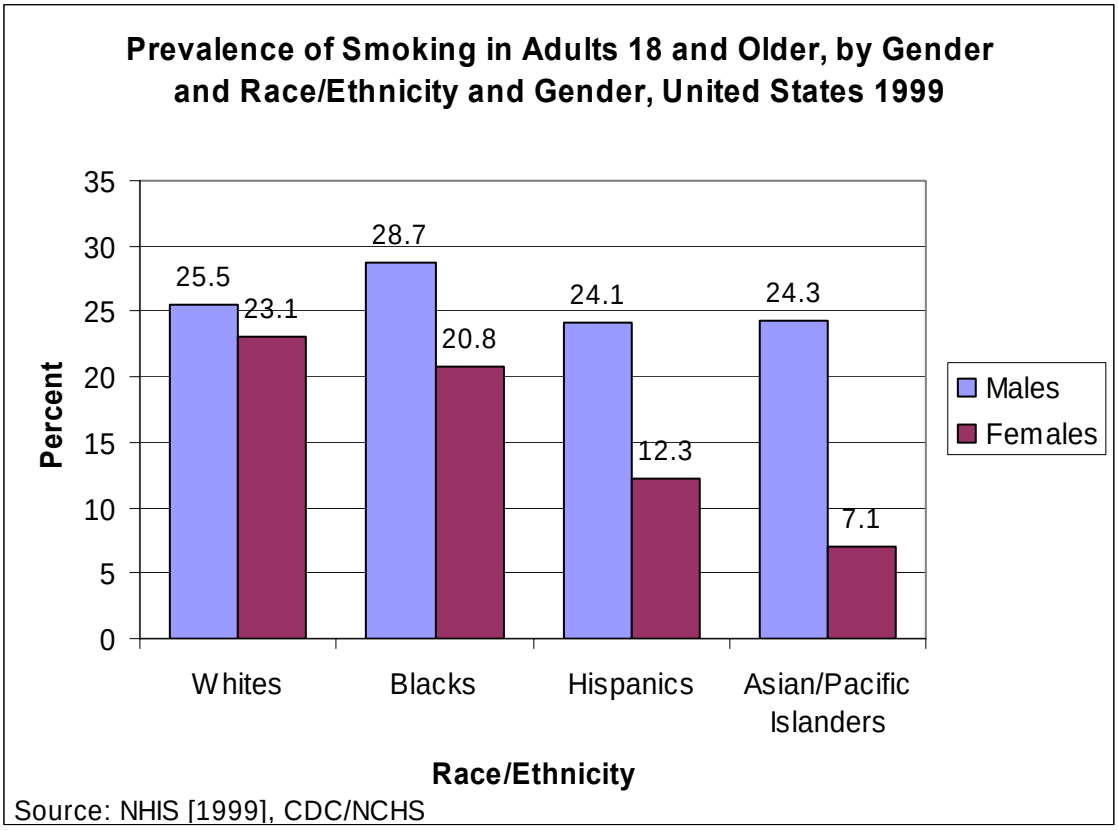
Estimated Change in Risk Factors and Correlates for Heart Disease and Stroke – United States

Characteristics	Baseline Year	Baseline Estimate	Follow-up Year(s)	Follow-up Estimate	Change
Adults aged 20-74 years with hypertension *¥	1960-1962	37%	1988-1994	23%	14%
Hypertensive patients taking action to control their blood pressure (e.g., medications, diet, reductions in sodium, and exercise.	1985	79%	1990	90%	11%
Controlled hypertensive patients	1976-1980	11%	1988-1991	29%	18%
Adults aged 20-74 years with high cholesterol levels ¥€	1960-1962	32%	1988-1994	29%	3%
Mean serum cholesterol levels of adults (mg/dl) ¥	1960-1962	220	1988-1994	203	17
Adults aged ≥ 18 who are current smokers ¥	1965	42%	1995	25%	17%
Persons who are overweight ¥£	1960-1962	24%	1988-1994	35%	11%
Percentage of calories in the diet from fat **	1976-1980	36%	1988-1994	12%	24%
Percentage of calories in the diet from saturated fat **	1976-1980	13%	1988-1994	12%	1%
Number of physicians indicating cardiovascular disease as their primary area of practice	1975	5,046	1996	14,304	9,258

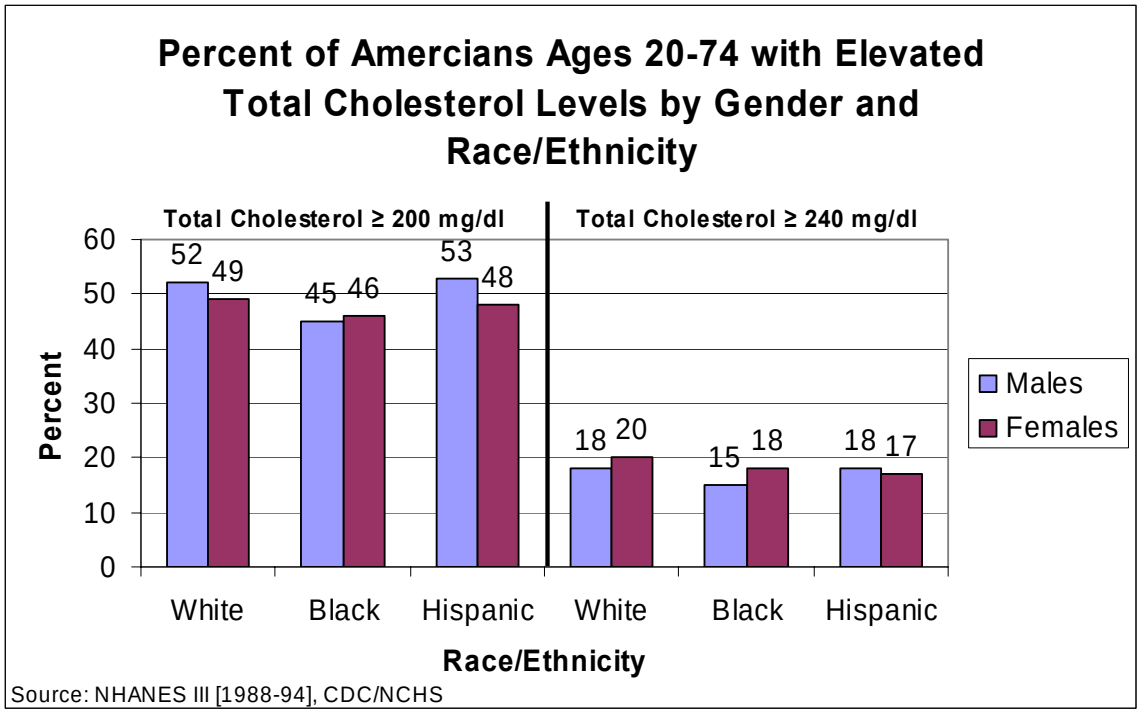
* Systolic pressure ≥ 140 mm hg, diastolic pressure ≥ 90 mm hg, or taking hypertensive medications.
¥ Estimate is age-adjusted to the 1940 U.S. population.
€ Serum cholesterol level ≥ 240 mg/dl.
£ Defined as body mass index ≥ 27.8 kg/m^2 among men and 27.2 kg/m^2 among women
** Based on 1-day dietary recall.

Source: Cardiovascular Health Br, Div of Adult and Community Health, National Center for Chronic Disease Prevention and Health Promotion, CDC. Achievements in Public Health, 1900-1999: Decline in Deaths from Heart Disease and Stroke – United States, 1900-1999. *MMWR*. 48(30):649-656, 1999.[2,3,4,5]

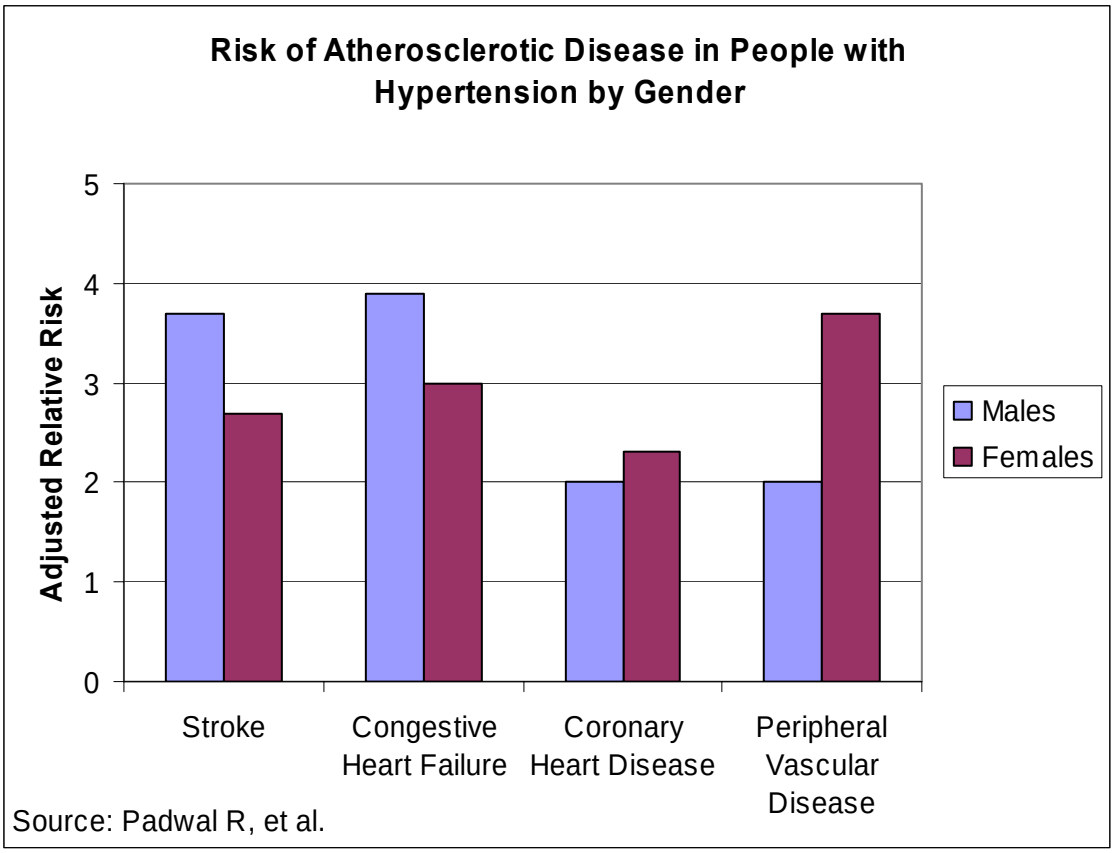
Appendix J:


Prevalence of Smoking in Adults 18 and Older, by Gender and Race/Ethnicity and Gender, United States 1999
Percent
35
30
25
20
15
10
5
0
25.5
23.1
28.7
20.8
24.1
12.3
24.3
7.1
Whites
Blacks
Hispanics
Asian/Pacific Islanders
Race/Ethnicity
Males
Females
Source: NHIS [1999], CDC/NCHS

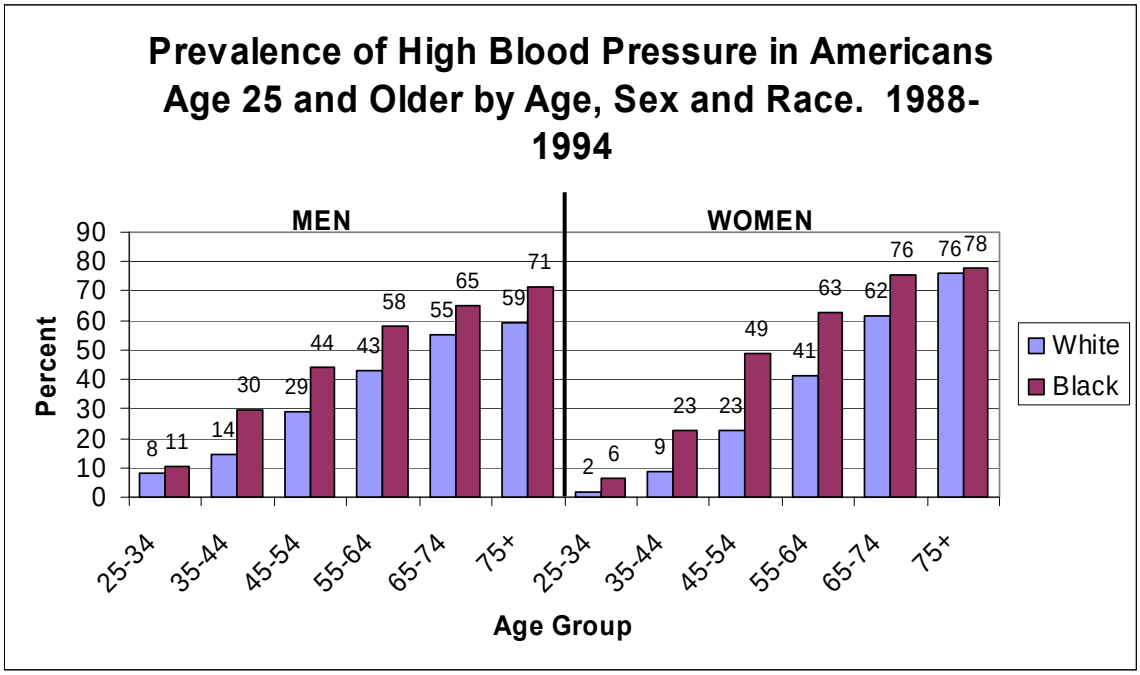
Appendix K:


Percent of Amercians Ages 20-74 with Elevated Total Cholesterol Levels by Gender and Race/Ethnicity
Total Cholesterol ≥ 200 mg/dl
Total Cholesterol ≥ 240 mg/dl
Percent
60
50
40
30
20
10
0
52
49
45
46
53
48
18
20
15
18
18
17
White
Black
Hispanic
White
Black
Hispanic
Race/Ethnicity
Males
Females
Source: NHANES III [1988-94], CDC/NCHS

Appendix L:


Risk of Atherosclerotic Disease in People with Hypertension by Gender
Adjusted Relative Risk
0
1
2
3
4
5
Stroke
Congestive Heart Failure
Coronary Heart Disease
Peripheral Vascular Disease
Males
Females
Source: Padwal R, et al.

Appendix M:



Source: Wolz M, et al. Statement from the National High Blood Pressure Education Program: Prevalence of Hypertension. *American Journal of Hypertension*. 13:103-104, 2000.[22]

Appendix N:

Nonsteriodal Anti-inflammatory Drugs / COX-2 Inhibitors

Non-Selective (Traditional) NSAID	
Generic	Brand
Ibuprofen	Motrin, Advil, Nuprin, Rufen
Naproxen	Naprosyn, Aleve, Anaprox, EC-Naprosyn, Naprelan
Diclofenac	Voltaren, Voltaren XR, Cataflam, Arthrotec*
Etodolac	Lodine, Lodine XL
Flurbiprofen	Ansaid
Indomethacin	Indocin, Indocin SR, Indocid, Indotec
Ketoprofen	Orudis, Actron, Oruvail, Orafen
Ketorolac	Toradol
Meclofenamate	
Meloxicam	Mobic
Nabumetone	Relafen
Oxaprozin	Daypro
Piroxicam	Feldene, Fexicam
Sulindac	Clinoril
Tolmetin	Tolectin
Salicylic Acid Derivatives	
Generic	Brand
Aspirin	Ecotrin, Empirin, Bayer
Choline magnesium trisalicylate	Trilisate
Diflunisal	Dolobid
Salsalate	Salflex, Disalcid
COX-2 Inhibitors	
Generic	Brand
Celecoxib	Celebrex
Rofecoxib	Vioxx
Valdecoxib	Bextra
Etoricoxib	Arcoxia

*diclofenac + misoprostol

Appendix O:

Summary of the Analysis of Confirmed Adjudicated Serious Thrombotic Cardiovascular Adverse Events, Occurring in the VIGOR Study†

Event Category	Treatment Group	N	Number of Patients With Events	PYR†	Rates‡	Relative Risk§ Estimate	95% CI
All thrombotic events	rofecoxib	4047	45	2697	1.67		
	naproxen	4029	19	2698	0.70	0.42	(0.25, 0.72)
All cardiac events	rofecoxib	4047	28	2698	1.04		
	naproxen	4029	10	2698	0.37	0.36	(0.17, 0.74)
All cerebrovascular events	rofecoxib	4047	11	2699	0.41		
	naproxen	4029	8	2699	0.30	0.73	(0.29, 1.80)
All peripheral vascular events	rofecoxib	4047	6	2699	0.22		
	naproxen	4029	1	2699	0.04	0.17	(0.00, 1.37)

† In keeping with the data analysis section of the Adjudication standard operating procedures (SOP), this table does not include events determined by adjudication to be hemorrhagic cerebrovascular accidents.
Data source: Adapted - FDA Advisory Committee. Cardiovascular Safety Review of Rofecoxib.

‡ Per 100 patient-years at risk (PYR).

§ Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.

Appendix P:

Analysis of Cardiovascular Events in the VIGOR Study Using Endpoint Definitions Standard in Large Antiplatelet Trials[ξ]

Event Category	Treatment Group	N	Number of Patients With Events	PYR†	Rates‡	Relative Risk§ Estimate	95% CI
All Patients							
Cardiovascular deaths[%], MI, CVA	Rofecoxib	4047	35	2698	1.30		
	Naproxen	4029	18	2700	0.67	0.51	(0.29,0.91)
Cardiovascular deaths[%]	Rofecoxib	4047	7	2700	0.26		
	Naproxen	4029	7	2699	0.26	1.00	(0.35, 2.85)
MI	Rofecoxib	4047	20	2699	0.74		
	Naproxen	4029	4	2699	0.15	0.20	(0.07,0.58)
Stroke*	Rofecoxib	4047	11	2699	0.41		
	Naproxen	4029	9	2699	0.33	0.82	(0.34,1.97)
Aspirin Indicated							
Cardiovascular deaths[%], MI, CVA	Rofecoxib	170	12	105	11.42		
	Naproxen	151	3	102	2.94	0.26	(0.07, 0.91)
Cardiovascular deaths[%]	Rofecoxib	170	1	106	0.95		
	Naproxen	151	2	102	1.96	2.07	(0.11, 122.10)
MI	Rofecoxib	170	8	105	7.60		
	Naproxen	151	0	102	0.00	0.00	(0.00, 0.60)
Stroke*	Rofecoxib	170	3	106	2.84		
	Naproxen	151	2	102	1.96	0.69	(0.06, 6.02)
Aspirin Not Indicated							
Cardiovascular deaths[%], MI, CVA	Rofecoxib	3877	23	2593	0.89		
	Naproxen	3878	15	2596	0.58	0.65	(0.34, 1.25)
Cardiovascular deaths[%]	Rofecoxib	3877	6	2594	0.23		
	Naproxen	3878	5	2597	0.19	0.83	(0.25, 2.73)
MI	Rofecoxib	3877	12	2593	0.46		
	Naproxen	3878	4	2597	0.15	0.33	(0.11, 1.03)
Stroke*	Rofecoxib	3877	8	2593	0.31		
	Naproxen	3878	7	2597	0.27	0.87	(0.32, 2.40)

ξ Data source: Adapted - FDA Advisory Committee. Cardiovascular Safety Review of Rofecoxib.
† Patient-years at risk.
‡ Per 100 PYR.
§ Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.
% Includes sudden death, unknown cause of death, fatal myocardial infarction, fatal stroke (hemorrhagic or ischemic), fatal subarachnoid hemorrhage, fatal primary intracranial hemorrhage, fatal gastrointestinal bleeding episode.
¶ Includes fatal and nonfatal ischemic strokes, and fatal or nonfatal hemorrhagic strokes.
§ Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.
* Includes fatal or nonfatal ischemic strokes, and fatal or nonfatal hemorrhagic strokes.

“Aspirin Indicated” patients are patients with past medical histories of cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, angina pectoris, coronary artery bypass graft surgery, or percutaneous coronary interventions). [84] “Aspirin Not Indicated” patients are patients without a past medical history of these conditions.

Appendix Q:

Serious Cardiovascular Thromboembolic Events among CLASS Study Patients*

All Patients	Celecoxib N=3987	NSAIDs N=3981	Diclofenac N=1996	Ibuprofen N=1985
Total Event (Crude Rate, %)	52(1.3)	49(1.2)	28(1.4)	21(1.1)
Cardiac Events (fatal/nonfatal)				
MI	19(0.5)	13(0.3)	4(0.2)	9(0.5)
Myocardial Ischemia	1(<0.1)	2(<0.1)	2(0.1)	0(0.0)
Unstable Angina	8(0.2)	4(0.1)	4(0.2)	0(0.0)
Fatal Acute MI	7(0.2)	2(<0.1)	0(0.0)	2(0.1)
Other Cardiac Death	1(<0.1)	2(<0.1)	1(<0.1)	1(<0.1)
Cardiac Arrest/Sudden Cardiac Death	2(<0.1)	6(0.2)	5(0.3)†	1(<0.1)
Cerebrovascular Events (Fatal/Nonfatal) ‡				
Stroke	4(0.1)	12(0.3)†	6(0.3)	6(0.3)
Peripheral Vascular Events (Fatal/Nonfatal)**				
Arterial	3(<0.1)	1(<0.1)	0(0.0)	1(<0.1)
Venous	11(0.3)	9(0.2)	6(0.3)	3(0.2)
Non-aspirin Patients	Celecoxib N=3105	NSAIDs N=3124	Diclofenac N=1551	Ibuprofen N=1573
Total Event (Crude Rate, %)	25(0.8)	23(0.7)	16(1.0)	7(0.4)
Cardiac Events (fatal/nonfatal)				
MI	6(0.2)	4(0.1)	2(0.1)	2(0.1)
Unstable Angina	2(<0.1)	0(0.0)	0(0.0)	0(0.0)
Fatal Acute MI	4(0.1)	1(<0.1)	0(0.0)	1(<0.1)
Other Cardiac Death	0(0.0)	1(<0.1)	1(<0.1)	0(0.0)
Cardiac Arrest/Sudden Cardiac Death	2(<0.1)	5(0.2)	5(0.3)†	0(0.0)
Cerebrovascular Events (Fatal/Nonfatal) ‡				
Stroke	2(<0.1)	6(0.2)	4(0.3)	2(0.1)
Peripheral Vascular Events (Fatal/Nonfatal)**				
Arterial	1(<0.1)	1(<0.1)	0(0.0)	1(<0.1)
Venous	10(0.3)	6(0.2)	4(0.3)	2(0.1)

* Data is provided as No. (%). Unpublished data –adapted from information provided by Pharmacia/Pfizer. (Events during the 6 month treatment period).

† $p < 0.05$ vs. celecoxib

‡ All strokes were ischemic except for 1 event on diclofenac. No cerebrovascular events were fatal.

** No peripheral vascular events were fatal.

Appendix R:

Meta-Analysis Results from 23 Phase IIb to V Rofecoxib Studies[§]

Indication for Treatment	No. of Patients	APTC Events* / Patient-Years at Risk (Rate)[£]	No. of Patients	APTC Events* / Patient-Years at Risk (Rate)[£]	Relative Risk (95% CI)
	Rofecoxib		**Placebo**		
Rheumatoid arthritis	1622	3/337 (0.89)	989	1/201 (0.50)	1.78 (0.14, 9.37)
Osteoarthritis	3165	12/655 (1.83)	1215	3/232 (1.30)	1.53 (0.43, 5.44)
Alzheimer's / low back pain	1503	18/1197 (1.50)	1278	28/1246(2.25)	0.68 (0.37, 1.23)
Total	6290	33/2189 (1.51)	3482	32/1678 (1.91)	0.84 (0.51, 1.38)
	Rofecoxib		**Non-Naproxen NSAIDs**		
Rheumatoid arthritis	0	…	0	…	…
Osteoarthritis	4549	21/1934 (1.09)	2755	14/984 (1.42)	0.79 (0.40, 1.55)
Alzheimer's / low back pain	0	…	0	…	…
Total	4549	21/1934 (1.09)	2755	14/984 (1.42)	0.79 (0.40, 1.55)
	Rofecoxib		**Naproxen**		
Rheumatoid arthritis	6057	46/3947 (1.17)	4859	20/3078 (0.65)	1.74 (1.02, 2.96)
Osteoarthritis	3026	11/675 (1.63)	3011	7/665 (1.05)	1.55 (0.60, 4.00)
Alzheimer's / low back pain	0	…	0	…	…
Total	9083	57/4622 (1.23)	7870	27/3742 (0.72)	1.69 (1.07, 2.69)

* Antiplatelet Trialists' Collaboration (APTC) defined events consisting of the culmination of (1) CV, hemorrhagic, and unknown death; (2) nonfatal MI; and (3) nonfatal stroke.

£ Rate = APTC events per 100 patient-years at risk

§ Data source: Konstam M, et al. Cardiovascular Thrombotic Events in Controlled, Clinical Trials of Rofecoxib. *Circulation*. 104:2280-2288, 2001.

Appendix S:

Baseline Medication Categories

Antiarrhythmic	Aspirin	Beta Blockers	Calcium Channel Blocker
ADENOSINE	ASPIRIN	ACEBUTOLOL	AMLODIPINE
AMIODARONE		ATENOLOL	BEPRIDIL
DISOPYRAMIDE		BETAXOLOL	DILTIAZEM
FLECAINIDE		BISOPROLOL	FELODIPINE
IBUTILIDE FUMARATE		CARVEDILOL	ISRADIPINE
LIDOCAINE		ESMOLOL	MIBEFRADIL
MEXILETINE		LABETALOL	NICARDIPINE
MORICIZINE		METOPROLOL	NIFEDIPINE
PROCAINAMIDE		NADOLOL	NISOLDIPINE
PROPAFENONE HCL		PENBUTOLOL	VERAPAMIL
QUINIDINE		PINDOLOL	
SOTALOL		PROPRANOLOL	
TOCAINIDE		TIMOLOL	

Diuretic Other	Diabetes Drugs	Digoxin	Estrogen
HYDROCHLOROTHIAZIDE	ACARBOSE	DIGOXIN	CHLOROTRIANISENE
SPIRONOLACTONE	CHLORPROPAMIDE		ESTRADIOL
AMILORIDE	GLIMEPIRIDE		ESTROGEN
CHLORTHALIDONE	GLIPIZIDE		ESTROPIPATE
TRIAMTERENE	GLYBURIDE		RALOXIFENE
INDAPAMIDE	INSULIN		CONTRACEPTIVES
METHYCLOTHIAZIDE	METFORMIN		
METOLAZONE	MIGLITOL		
	NATEGLINIDE		
	PIOGLITAZONE		
	REPAGLINIDE		
	ROSIGLITAZONE		
	TOLAZAMIDE		
	TOLBUTAMIDE		
	TROGLITAZONE		

Appendix S cont.:

Hypertension Other	Loop Diuretic	Methotrexate	Nitrate
CLONIDINE	FUROSEMIDE	METHOTREXATE	ISOSORBIDE DINITRATE
HYDRALAZINE	BUMETANIDE		ISOSORBIDE MONONITRATE
TERAZOSIN	ETHACRYNIC ACID		NITROGLYCERIN
ALFUZOSIN	TORSEMIDE		
BOSENTAN			
DOXAZOSIN			
EPLERENONE			
GUANABENZ			
GUANADREL			
GUANETHIDINE			
GUANFACINE			
METHYLDOPA			
MINOXIDIL			
PROZOSIN			
RESERPINE			

PVD drugs	Other Anticoagulant	Warfarin	ACE/ARB
CILOSTAZOL	DALTEPARIN	WARFARIN	CAPTOPRIL
CYCLANDELATE	ENOXAPARIN		FOSINOPRIL
PENTOXIFYLLINE	HEPARIN		LISINOPRIL
			BENAZEPRIL
			CANDESARTAN
			ENALAPRIL
			VALSARTAN
			LOSARTAN
			IRBESARTAN
			MOEXIPRIL
			OLMESARTAN
			QUINAPRIL
			RAMIPRIL
			TELMISARTAN
			TRANDOLAPRIL

Appendix S cont.:

Antiplatelet	AntiRheumatic	Steroid	Cholesterol
ANAGRELIDE	ADALIMUMAB	METHYLPREDNISOLONE	ATORVASTATIN
DIPYRIDAMOLE / ASPIRIN (25 MG)	ANAKINRA	PREDNISONE	CHOLESTYRAMINE
CLOPIDOGREL	AURANOFIN	BETAMETHASONE	CLOFIBRATE
DIPYRIDAMOLE	AUROTHIOGLUCOSE	BUDESONIDE	COLESEVELAM
TICLOPIDINE	AZATHIOPRINE	CORTISONE	COLESTIPOL
	CYCLOSPORINE (ONLY NEORAL)	DEXAMETHASONE	EZETIMIBE
	ETANERCEPT	HYDROCORTISONE	FENOFIBRATE
	INFLIXIMAB	TRIAMCINOLONE	FLUVASTATIN
	LEFLUNOMIDE		GEMFIBROZIL
	PENICILLAMINE		LOVASTATIN
	GOLD THIOMALATE		NIACIN
			PRAVASTATIN
			ROSUVASTATIN
			SIMVASTATIN
			CIRIVASTATIN

Appendix T:

Adjusted association between long-term naproxen use (including events occurring during the first 180 days) and serious cardiovascular events [σ, ξ]

Exposure (reference group)	Adjusted Risk Ratio	(95% CI) Lower	Upper	Sig. (p)
Celecoxib (ibuprofen)	1.63	0.85	3.13	0.14
Etodolac (ibuprofen)	1.02	0.48	2.19	0.95
Rofecoxib (ibuprofen)	2.00	0.86	4.68	0.11
Naproxen (ibuprofen)	1.11	0.56	2.18	0.77
Covariates				
Diabetes	1.83	1.13	2.96	**0.01**
Angina	1.33	0.75	2.34	0.33
PVD	1.31	0.61	2.80	0.49
Atrial Fibrillation	1.39	0.53	3.63	0.50
Cancer	0.66	0.35	1.23	0.19
COPD	1.70	0.92	3.13	0.09
Heart failure	1.46	0.73	2.92	0.29
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	1.64	**0.99**	2.71	0.05
Renal failure	0.19	0.02	1.81	0.15
Respiratory failure	0	.	.	.
Rheumatoid arthritis	1.17	0.34	4.08	0.80
Prior AMI	9.56	4.25	21.52	**< 0.01**
Prior Stroke (specificity model)	3.74	0.80	17.44	0.09
Antiarrhythmic	0.81	0.24	2.75	0.74
Aspirin	0.74	0.44	1.24	0.26
B-blocker	1.14	0.67	1.93	0.64
Ca-blocker	1.14	0.70	1.83	0.60
Digoxin	1.16	0.59	2.30	0.67
Other HTN Meds	0.80	0.48	1.35	0.41
Loop diuretic	3.02	1.78	5.14	**< 0.01**
Methotrexate	3.84	0.47	31.28	0.21
Warfarin	0.48	0.20	1.16	0.10
ACE/ARBS	0.91	0.55	1.49	0.70
Antiplatelet	1.88	0.95	3.75	0.07
Antirheumatic	0	.	.	.
Steroid	0.57	0.19	1.71	0.31
Cholesterol drug	0.86	0.53	1.40	0.55
Diuretic other	0.81	0.43	1.52	0.51
Other Anticoagulant	0	.	.	.
Sex (male)	0.67	0.16	2.80	0.59
Age	1.04	1.01	1.06	**< 0.01**

Total population: 3,894; Ibuprofen – 1,098; Celecoxib – 622; Etodolac – 666; Rofecoxib – 208; Naproxen – 864. Endpoint events – 83; censored – 3,375.

***** Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Long-term exposure defined as > 180 days (**events may occur during the first 180 days**).

[σ] Defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event

Appendix U:

Adjusted association between short-term exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events[σ] – all observations.[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	0.77	0.43	1.39	0.39
Etodolac (ibuprofen)	0.74	0.41	1.32	0.31
Rofecoxib (ibuprofen)	0.87	0.40	1.88	0.72
Naproxen (ibuprofen)	0.85	0.49	1.46	0.55
Covariates				
Diabetes	1.27	0.83	1.94	0.28
Angina	1.52	0.92	2.50	0.10
PVD	1.95	1.11	3.42	**0.02**
Atrial Fibrillation	0.92	0.41	2.06	0.84
Cancer	0.98	0.60	1.60	0.94
COPD	2.18	1.30	3.68	**< 0.01**
Heart failure	1.03	0.54	1.96	0.94
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	2.52	1.65	3.87	**< 0.01**
Renal failure	0.68	0.16	2.94	0.61
Respiratory failure	1.34	0.36	5.03	0.66
Rheumatoid arthritis	0.55	0.13	2.36	0.42
Prior AMI	3.31	1.59	6.89	**< 0.01**
Prior Stroke (specificity model)	5.14	1.94	13.64	**< 0.01**
Antiarrhythmic	1.64	0.72	3.75	0.24
Aspirin	1.19	0.76	1.84	0.44
B-blocker	1.92	1.22	3.02	**< 0.01**
Ca-blocker	0.99	0.65	1.52	0.98
Digoxin	1.14	0.60	2.14	0.69
Other HTN Meds	0.74	0.45	1.22	0.24
Loop diuretic	1.04	0.62	1.75	0.88
Methotrexate	9.86	2.79	34.80	**< 0.01**
Warfarin	1.42	0.71	2.81	0.32
ACE/ARBS	1.35	0.88	2.08	0.17
Antiplatelet	1.37	0.73	2.56	0.32
Antirheumatic	0	.	.	.
Steroid	0.44	0.17	1.15	0.09
Cholesterol drug	0.84	0.55	1.30	0.45
Diuretic other	0.63	0.36	1.11	0.11
Other Anticoagulant	0.51	0.07	3.81	0.51
Sex (male)	0.82	0.26	2.64	0.75
Age	1.03	1.01	1.06	**< 0.01**

Total population: 12,194; Ibuprofen – 4,483; Naproxen – 3,241; Celecoxib – 1,530; Etodolac – 2,373; Rofecoxib – 567. Endpoint events – 104; censored 12,090.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Short term exposure defined as ≤ 180 days; includes long-term use observations with exposure periods limited to the first 180 days.

[σ] Defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event.

Appendix V:

Adjusted association between exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) – Naproxen Comparison

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Ibuprofen (naproxen)	1.17	0.72	1.90	0.54
Celecoxib (naproxen)	1.32	0.80	2.20	0.28
Etodolac (naproxen)	0.96	0.55	1.67	0.88
Rofecoxib (naproxen)	1.85	**0.99**	3.45	0.05
Covariates				
Diabetes	1.32	0.92	1.90	0.13
Angina	1.16	0.76	1.78	0.48
PVD	1.48	0.87	2.49	0.15
Atrial Fibrillation	1.29	0.66	2.52	0.45
Cancer	0.89	0.58	1.37	0.60
COPD	1.98	1.26	3.09	**< 0.01**
Heart failure	1.27	0.74	2.16	0.38
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	1.85	1.27	2.68	**< 0.01**
Renal failure	0.56	0.15	2.05	0.38
Respiratory failure	0.74	0.20	2.78	0.65
Rheumatoid arthritis	0.84	0.29	2.37	0.74
Prior AMI	3.98	2.10	7.55	**< 0.01**
Prior Stroke (specificity model)	4.07	1.42	11.67	**0.01**
Antiarrhythmic	1.40	0.67	2.94	0.37
Aspirin	1.07	0.74	1.56	0.72
B-blocker	1.51	1.03	2.22	**0.03**
Ca-blocker	0.95	0.67	1.37	0.80
Digoxin	1.03	0.60	1.75	0.92
Other HTN Meds	0.69	0.45	1.04	0.08
Loop diuretic	1.58	1.03	2.41	**0.03**
Methotrexate	5.90	1.72	20.22	**< 0.01**
Warfarin	0.98	0.54	1.79	0.96
ACE/ARBS	1.21	0.84	1.73	0.31
Antiplatelet	1.79	1.07	2.99	**0.03**
Antirheumatic	0	.	.	.
Steroid	0.47	0.21	1.06	0.07
Cholesterol drug	0.91	0.63	1.31	0.62
Diuretic other	0.74	0.47	1.18	0.20
Other Anticoagulant	0.33	0.04	2.49	0.29
Sex (male)	0.69	0.25	1.89	0.47
Age	1.04	1.02	1.05	**< 0.01**

Total population: 12,188; Ibuprofen – 4,481; Naproxen – 3,240; Celecoxib – 1,530; Etodolac – 2,371; Rofecoxib – 566. Endpoint events – 146; censored 12,042.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

Appendix W:

Adjusted association between long-term exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) – Naproxen Comparison [ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Ibuprofen (naproxen)	0.87	0.27	2.84	0.81
Celecoxib (naproxen)	3.16	1.16	8.57	**0.02**
Etodolac (naproxen)	1.09	0.29	4.05	0.90
Rofecoxib (naproxen)	5.76	1.82	18.21	**< 0.01**
Covariates				
Diabetes	1.38	0.67	2.83	0.39
Angina	0.58	0.23	1.45	0.25
PVD	0.24	0.03	1.97	0.18
Atrial Fibrillation	3.27	0.93	11.45	0.06
Cancer	0.50	0.19	1.28	0.15
COPD	1.85	0.73	4.72	0.20
Heart failure	3.11	1.12	8.65	**0.03**
HIV	0	.	.	.
Lupus*	0.00	.	.	.
Osteoarthritis	0.93	0.41	2.12	0.86
Renal failure	0.34	0.03	3.50	0.36
Respiratory failure	0	.	.	.
Rheumatoid arthritis	1.98	0.43	9.13	0.38
Prior AMI	9.65	2.39	38.95	**< 0.01**
Prior Stroke (specificity model)	0.00	.	.	.
Antiarrhythmic	0.43	0.06	3.24	0.41
Aspirin	0.71	0.32	1.54	0.38
B-blocker	0.79	0.34	1.87	0.60
Ca-blocker	0.73	0.36	1.50	0.39
Digoxin	0.91	0.31	2.68	0.87
Other HTN Meds	0.47	0.20	1.10	0.08
Loop diuretic	4.13	1.95	8.76	**< 0.01**
Methotrexate	0	.	.	.
Warfarin	0.21	0.05	0.87	**0.03**
ACE/ARBS	0.96	0.47	1.98	0.91
Antiplatelet	2.78	1.08	7.15	**0.03**
Antirheumatic	0	.	.	.
Steroid	0.76	0.17	3.43	0.72
Cholesterol drug	1.12	0.57	2.21	0.74
Diuretic other	1.22	0.54	2.77	0.63
Other Anticoagulant	0.00	.	.	.
Sex (male)	0.54	0.07	4.06	0.55
Age	1.03	1.00	1.06	0.09

Total population: 3,317; Ibuprofen – 1,085; Naproxen – 849; Celecoxib – 611; Etodolac – 656; Rofecoxib – 206. Endpoint events – 42; censored 3,275.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Long-term exposure defined as > 180 days.

Appendix X:

Adjusted association between <u>short-term</u> exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) – Naproxen Comparison.[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Ibuprofen (naproxen)	1.66	0.79	3.47	0.18
Celecoxib (naproxen)	1.12	0.46	2.67	0.81
Etodolac (naproxen)	1.05	0.45	2.47	0.91
Rofecoxib (naproxen)	2.33	0.90	6.04	0.08
Covariates				
Diabetes	1.38	0.67	2.83	0.39
Angina	0.58	0.23	1.45	0.25
PVD	0.24	0.03	1.97	0.18
Atrial Fibrillation	3.27	0.93	11.45	0.06
Cancer	0.50	0.19	1.28	0.15
COPD	1.85	0.73	4.72	0.20
Heart failure	3.11	1.12	8.65	0.03
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	0.93	0.41	2.12	0.86
Renal failure	0.34	0.03	3.50	0.36
Respiratory failure	0	0.00	.	0.99
Rheumatoid arthritis	1.98	0.43	9.13	0.38
Prior AMI	9.65	2.39	38.95	**< 0.01**
Prior Stroke (specificity model)	0	.	.	.
Antiarrhythmic	0.43	0.06	3.24	0.41
Aspirin	0.71	0.32	1.54	0.38
B-blocker	0.79	0.34	1.87	0.60
Ca-blocker	0.73	0.36	1.50	0.39
Digoxin	0.91	0.31	2.68	0.87
Other HTN Meds	0.47	0.20	1.10	0.08
Loop diuretic	4.13	1.95	8.76	**< 0.01**
Methotrexate	0	.	.	.
Warfarin	0.21	0.05	0.87	**0.03**
ACE/ARBS	0.96	0.47	1.98	0.91
Antiplatelet	2.78	1.08	7.15	0.03
Antirheumatic	0.00	.	.	.
Steroid	0.76	0.17	3.43	0.72
Cholesterol drug	1.12	0.57	2.21	0.74
Diuretic other	1.22	0.54	2.77	0.63
Other Anticoagulant	0	.	.	.
Sex (male)	0.54	0.07	4.06	0.55
Age	1.03	1.00	1.06	0.09

Total population: 8,730; Ibuprofen – 3,383; Naproxen – 2,376; Celecoxib – 908; Etodolac – 1,705; Rofecoxib – 358.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Short term exposure defined as ≤ 180 days.

Appendix Y:

Adjusted association between exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) – Etodolac Comparison.

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Ibuprofen (etodolac)	1.22	0.72	2.07	0.47
Celecoxib (etodolac)	1.38	0.81	2.35	0.24
Etodolac (etodolac)	1.93	1.02	3.67	**0.04**
Rofecoxib (etodolac)	1.04	0.60	1.82	0.88
Covariates				
Diabetes	1.32	0.92	1.90	0.13
Angina	1.16	0.76	1.78	0.48
PVD	1.48	0.87	2.49	0.15
Atrial Fibrillation	1.29	0.66	2.52	0.45
Cancer	0.89	0.58	1.37	0.60
COPD	1.98	1.26	3.09	**< 0.01**
Heart failure	1.27	0.74	2.16	0.38
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	1.85	1.27	2.68	**< 0.01**
Renal failure	0.56	0.15	2.05	0.38
Respiratory failure	0.74	0.20	2.78	0.65
Rheumatoid arthritis	0.84	0.29	2.37	0.74
Prior AMI	3.98	2.10	7.55	**< 0.01**
Prior Stroke (specificity model)	4.07	1.42	11.67	**0.01**
Antiarrhythmic	1.40	0.67	2.94	0.37
Aspirin	1.07	0.74	1.56	0.72
B-blocker	1.51	1.03	2.22	**0.03**
Ca-blocker	0.95	0.67	1.37	0.80
Digoxin	1.03	0.60	1.75	0.92
Other HTN Meds	0.69	0.45	1.04	0.08
Loop diuretic	1.58	1.03	2.41	**0.03**
Methotrexate	5.90	1.72	20.22	**< 0.01**
Warfarin	0.98	0.54	1.79	0.96
ACE/ARBS	1.21	0.84	1.73	0.31
Antiplatelet	1.79	1.07	2.99	**0.03**
Antirheumatic	0	.	.	.
Steroid	0.47	0.21	1.06	0.07
Cholesterol drug	0.91	0.63	1.31	0.62
Diuretic other	0.74	0.47	1.18	0.20
Other Anticoagulant	0.33	0.04	2.49	0.29
Sex (male)	0.69	0.25	1.89	0.47
Age	1.04	1.02	1.05	**< 0.01**

Total population: 12,188; Ibuprofen – 4,481; Naproxen – 3,240; Celecoxib – 1,530; Etodolac – 2,371; Rofecoxib – 566. Endpoint events – 146; censored 12,042.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

Appendix Z:

Adjusted association between long-term exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) – Etodolac Comparison.[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Ibuprofen (etodolac)	0.80	0.22	2.89	0.73
Celecoxib (etodolac)	2.89	0.95	8.80	0.06
Etodolac (etodolac)	5.28	1.51	18.44	**0.01**
Rofecoxib (etodolac)	0.92	0.25	3.40	0.90
Covariates				
Diabetes	1.38	0.67	2.83	0.39
Angina	0.58	0.23	1.45	0.25
PVD	0.24	0.03	1.97	0.18
Atrial Fibrillation	3.27	0.93	11.45	0.06
Cancer	0.50	0.19	1.28	0.15
COPD	1.85	0.73	4.72	0.20
Heart failure	3.11	1.12	8.65	**0.03**
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	0.93	0.41	2.12	0.86
Renal failure	0.34	0.03	3.50	0.36
Respiratory failure	0.00	0.00	.	0.99
Rheumatoid arthritis	9.65	2.39	38.95	**< 0.01**
Prior AMI	1.98	0.43	9.13	0.38
Prior Stroke (specificity model)	0	.	.	.
Antiarrhythmic	0.43	0.06	3.24	0.41
Aspirin	0.71	0.32	1.54	0.38
B-blocker	0.79	0.34	1.87	0.60
Ca-blocker	0.73	0.36	1.50	0.39
Digoxin	0.91	0.31	2.68	0.87
Other HTN Meds	0.47	0.20	1.10	0.08
Loop diuretic	4.13	1.95	8.76	**< 0.01**
Methotrexate	0	.	.	.
Warfarin	0.21	0.05	0.87	**0.03**
ACE/ARBS	0.96	0.47	1.98	0.91
Antiplatelet	2.78	1.08	7.15	**0.03**
Antirheumatic	0	.	.	.
Steroid	0.76	0.17	3.43	0.72
Cholesterol drug	1.12	0.57	2.21	0.74
Diuretic other	1.22	0.54	2.77	0.63
Other Anticoagulant	0	.	.	.
Sex (male)	0.54	0.07	4.06	0.55
Age	1.03	1.00	1.06	0.09

Total population: 3,317; Ibuprofen – 1,085; Naproxen – 849; Celecoxib – 611; Etodolac – 656; Rofecoxib – 206. . Endpoint events – 42; censored 3,275.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Long-term exposure defined as > 180 days.

Appendix AA:

Adjusted association between short-term exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) – Etodolac Comparison.[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Ibuprofen (etodolac)	1.58	0.74	3.34	0.23
Celecoxib (etodolac)	1.06	0.45	2.49	0.90
Etodolac (etodolac)	2.21	0.86	5.71	0.10
Rofecoxib (etodolac)	0.95	0.40	2.23	0.91
Covariates				
Diabetes	0.89	0.50	1.58	0.68
Angina	1.08	0.56	2.09	0.82
PVD	1.82	0.86	3.85	0.12
Atrial Fibrillation	1.40	0.54	3.63	0.49
Cancer	1.22	0.67	2.25	0.51
COPD	2.43	1.24	4.75	**0.01**
Heart failure	1.44	0.64	3.22	0.37
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	2.35	1.33	4.14	**< 0.01**
Renal failure	1.33	0.24	7.20	0.74
Respiratory failure	1.67	0.37	7.66	0.51
Rheumatoid arthritis	1.99	0.65	6.06	0.23
Prior AMI	0.37	0.04	3.11	0.36
Prior Stroke (specificity model)	4.35	0.93	20.45	0.06
Antiarrhythmic	1.93	0.70	5.33	0.20
Aspirin	1.59	0.90	2.83	0.11
B-blocker	1.92	1.06	3.45	**0.03**
Ca-blocker	0.76	0.43	1.35	0.35
Digoxin	0.80	0.33	1.96	0.63
Other HTN Meds	0.51	0.24	1.05	0.07
Loop diuretic	0.66	0.32	1.34	0.25
Methotrexate	10.38	2.10	51.26	**< 0.01**
Warfarin	1.74	0.73	4.14	0.21
ACE/ARBS	1.89	1.08	3.32	**0.03**
Antiplatelet	1.46	0.63	3.39	0.37
Antirheumatic	0	.	.	.
Steroid	0.38	0.11	1.34	0.13
Cholesterol drug	0.93	0.53	1.64	0.81
Diuretic other	0.70	0.35	1.41	0.32
Other Anticoagulant	0.99	0.13	7.70	0.99
Sex (male)	0.83	0.20	3.46	0.79
Age	1.03	1.01	1.06	**0.01**

Total population: 8,730; Ibuprofen – 3,383; Naproxen – 2,376; Celecoxib – 908; Etodolac – 1,705; Rofecoxib – 358. Endpoint events – 63; censored 8,667.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Short term exposure defined as ≤ 180 days.

Appendix BB:

Adjusted association between exposure to NSAIDS & COX-2 inhibitors and serious coronary events (defined as acute myocardial infarction or death from coronary heart disease) – Ibuprofen Comparison.

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	0.90	0.50	1.60	0.71
Etodolac (ibuprofen)	0.76	0.41	1.41	0.39
Rofecoxib (ibuprofen)	1.02	0.46	2.26	0.96
Naproxen (ibuprofen)	1.01	0.60	1.71	0.98
Covariates				
Diabetes	1.42	0.92	2.17	0.11
Angina	2.01	1.22	3.31	**0.01**
PVD	1.42	0.76	2.67	0.27
Atrial Fibrillation	0.81	0.33	1.98	0.65
Cancer	0.83	0.49	1.39	0.48
COPD	1.80	1.05	3.11	**0.03**
Heart failure	1.03	0.53	1.99	0.94
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	1.69	1.07	2.66	**0.02**
Renal failure	0.95	0.23	3.88	0.94
Respiratory failure	1.21	0.29	5.10	0.80
Rheumatoid arthritis	0.94	0.28	3.15	0.92
Prior AMI	5.93	3.03	11.62	< **0.01**
Prior Stroke (specificity model)	1.16	0.16	8.58	0.88
Antiarrhythmic	1.32	0.53	3.28	0.55
Aspirin	0.95	0.61	1.47	0.80
B-blocker	1.43	0.91	2.26	0.12
Ca-blocker	1.00	0.66	1.52	1.00
Digoxin	1.37	0.74	2.51	0.31
Other HTN Meds	0.56	0.33	0.95	**0.03**
Loop diuretic	1.21	0.72	2.03	0.46
Methotrexate	5.49	1.23	24.63	**0.03**
Warfarin	0.82	0.38	1.78	0.61
ACE/ARBS	1.15	0.75	1.77	0.52
Antiplatelet	1.93	1.07	3.51	**0.03**
Antirheumatic	0	.	.	.
Steroid	0.55	0.23	1.34	0.19
Cholesterol drug	0.78	0.51	1.21	0.27
Diuretic other	0.70	0.40	1.23	0.22
Other Anticoagulant	0.62	0.08	4.68	0.64
Sex (male)	0.46	0.11	1.88	0.28
Age	1.04	1.02	1.06	< **0.01**

Total population: 12,189; Ibuprofen – 4,482; Naproxen – 3,240; Celecoxib – 1,530; Etodolac – 2,371; Rofecoxib – 566. Endpoint events – 106; censored 12,083.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

Appendix CC:

Adjusted association between long-term exposure to NSAIDS & COX-2 inhibitors and serious coronary events (defined as acute myocardial infarction or death from coronary heart disease) – Ibuprofen comparison.[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	3.59	1.03	12.56	**0.05**
Etodolac (ibuprofen)	1.13	0.20	6.49	0.89
Rofecoxib (ibuprofen)	7.07	1.57	31.95	**0.01**
Naproxen (ibuprofen)	1.86	0.48	7.27	0.37
Covariates				
Diabetes	0.87	0.32	2.37	0.79
Angina	1.10	0.37	3.25	0.86
PVD	0	0	.	0.99
Atrial Fibrillation	2.27	0.39	13.09	0.36
Cancer	0.48	0.13	1.79	0.28
COPD	2.73	0.81	9.22	0.11
Heart failure	2.35	0.59	9.39	0.23
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	0.48	0.13	1.83	0.28
Renal failure	1.26	0.08	18.80	0.87
Respiratory failure	0.00	0.00	.	1.00
Rheumatoid arthritis	1.73	0.20	15.04	0.62
Prior AMI	18.05	3.50	93.05	**< 0.01**
Prior Stroke (specificity model)	0	.	.	.
Antiarrhythmic	0.29	0.02	3.98	0.36
Aspirin	0.62	0.22	1.72	0.36
B-blocker	0.55	0.18	1.73	0.31
Ca-blocker	1.01	0.42	2.46	0.98
Digoxin	1.43	0.36	5.72	0.61
Other HTN Meds	0.43	0.14	1.38	0.16
Loop diuretic	3.54	1.33	9.45	**0.01**
Methotrexate	0	.	.	.
Warfarin	0.28	0.05	1.49	0.14
ACE/ARBS	0.78	0.30	2.02	0.61
Antiplatelet	3.73	1.13	12.33	**0.03**
Antirheumatic	0	.	.	.
Steroid	0.38	0.04	3.39	0.38
Cholesterol drug	1.15	0.48	2.73	0.76
Diuretic other	1.34	0.47	3.81	0.58
Other Anticoagulant	0	.	.	.
Sex (male)	0	.	.	.
Age	1.01	0.97	1.05	0.74

Total population: 3,241; Ibuprofen – 1,088; Naproxen – 850; Celecoxib – 615; Etodolac – 657; Rofecoxib – 206. Endpoint events – 27; censored 3,214.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Long-term exposure defined as > 180 days.

Appendix DD:

Adjusted association between short-term exposure to NSAIDS & COX-2 inhibitors and serious coronary events (defined as acute myocardial infarction or death from coronary heart disease) – Ibuprofen comparison.[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	0.58	0.23	1.48	0.26
Etodolac (ibuprofen)	0.51	0.21	1.27	0.15
Rofecoxib (ibuprofen)	0.89	0.28	2.81	0.84
Naproxen (ibuprofen)	0.68	0.31	1.50	0.34
Covariates				
Diabetes	1.05	0.55	2.03	0.87
Angina	1.57	0.73	3.40	0.25
PVD	2.09	0.89	4.91	0.09
Atrial Fibrillation	0.70	0.19	2.60	0.59
Cancer	0.98	0.46	2.09	0.96
COPD	1.63	0.70	3.81	0.26
Heart failure	1.24	0.46	3.37	0.67
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	2.85	1.47	5.54	**< 0.01**
Renal failure	1.96	0.32	11.89	0.47
Respiratory failure	3.48	0.66	18.24	0.14
Rheumatoid arthritis	0.74	0.09	6.48	0.79
Prior AMI	2.79	0.89	8.77	0.08
Prior Stroke (specificity model)	3.49	0.43	28.66	0.24
Antiarrhythmic	1.83	0.51	6.56	0.35
Aspirin	1.35	0.68	2.68	0.39
B-blocker	2.29	1.15	4.55	**0.02**
Ca-blocker	0.95	0.49	1.82	0.87
Digoxin	1.20	0.43	3.30	0.73
Other HTN Meds	0.30	0.10	0.84	0.02
Loop diuretic	0.50	0.21	1.19	0.12
Methotrexate	4.77	0.51	45.10	0.17
Warfarin	1.28	0.44	3.76	0.65
ACE/ARBS	2.18	1.13	4.21	**0.02**
Antiplatelet	1.48	0.58	3.78	0.42
Antirheumatic	0	.	.	.
Steroid	0.65	0.18	2.31	0.51
Cholesterol drug	0.77	0.39	1.50	0.44
Diuretic other	0.56	0.23	1.34	0.19
Other Anticoagulant	1.78	0.23	13.73	0.58
Sex (male)	0.57	0.08	4.26	0.59
Age	1.03	1.00	1.06	**0.04**

Total population: 8,730; Ibuprofen – 3,383; Naproxen – 2,376; Celecoxib – 908; Etodolac – 1,705; Rofecoxib – 358. Endpoint events – 46; censored 8,684.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Short term exposure defined as ≤ 180 days.

Appendix EE:

Adjusted association between exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) - high sensitivity stroke model.[§]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	0.90	0.60	1.33	0.59
Etodolac (ibuprofen)	0.68	0.44	1.05	0.08
Rofecoxib (ibuprofen)	1.03	0.60	1.76	0.92
Naproxen (ibuprofen)	0.85	0.58	1.26	0.42
Covariates				
Diabetes	1.18	0.87	1.61	0.28
Angina	1.24	0.88	1.74	0.22
PVD	1.30	0.83	2.03	0.25
Atrial Fibrillation	1.48	0.88	2.51	0.14
Cancer	0.98	0.70	1.39	0.93
COPD	1.65	1.12	2.43	**0.01**
Heart failure	1.13	0.72	1.78	0.59
HIV	0	.	.	.
Lupus*	1.05	0.14	7.67	0.96
Osteoarthritis	1.52	1.10	2.08	**0.01**
Renal failure	0.52	0.19	1.41	0.20
Respiratory failure	1.41	0.60	3.32	0.43
Rheumatoid arthritis	1.42	0.68	2.95	0.35
Prior AMI	3.38	1.90	6.00	**< 0.01**
Prior Stroke (sensitivity model)	6.33	4.13	9.71	**< 0.01**
Antiarrhythmic	1.01	0.50	2.03	0.98
Aspirin	1.25	0.92	1.69	0.16
B-blocker	1.15	0.83	1.60	0.40
Ca-blocker	0.96	0.71	1.30	0.79
Digoxin	1.21	0.78	1.86	0.40
Other HTN Meds	0.71	0.50	**1.00**	0.05
Loop diuretic	1.24	0.86	1.80	0.25
Methotrexate	1.98	0.52	7.52	0.32
Warfarin	1.10	0.68	1.79	0.69
ACE/ARBS	1.20	0.89	1.62	0.23
Antiplatelet	2.21	1.48	3.28	**< 0.01**
Antirheumatic	3.79	0.75	19.14	0.11
Steroid	0.57	0.30	1.09	0.09
Cholesterol drug	0.75	0.55	1.02	0.07
Diuretic other	0.77	0.52	1.13	0.18
Other Anticoagulant	0.26	0.04	1.87	0.18
Sex (male)	0.70	0.29	1.73	0.44
Age	1.05	1.03	1.06	**< 0.01**

Total population: 12,182; Ibuprofen – 4,481; Naproxen – 3,239; Celecoxib – 1,528; Etodolac – 2,369; Rofecoxib – 565. Endpoint events – 212; censored 11,970.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[§] Note: uses stroke sensitivity model for prior stroke covariate

Appendix FF:

Adjusted association between <u>long-term</u> exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) - high sensitivity stroke model.[ξ, §]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	1.53	0.71	3.31	0.28
Etodolac (ibuprofen)	0.75	0.26	2.16	0.59
Rofecoxib (ibuprofen)	2.16	0.81	5.77	0.12
Naproxen (ibuprofen)	0.76	0.32	1.83	0.54
Covariates				
Diabetes	0.95	0.48	1.87	0.88
Angina	0.84	0.40	1.76	0.64
PVD	1.21	0.42	3.50	0.73
Atrial Fibrillation	2.85	**0.98**	8.24	0.05
Cancer	1.07	0.53	2.18	0.85
COPD	1.52	0.63	3.65	0.35
Heart failure	1.11	0.42	2.92	0.83
HIV	0	.	.	.
Lupus*	1.96	0.21	18.23	0.56
Osteoarthritis	0.79	0.37	1.68	0.54
Renal failure	0.54	0.05	5.39	0.60
Respiratory failure	0	.	.	.
Rheumatoid arthritis	1.47	0.40	5.45	0.56
Prior AMI	5.04	1.36	18.69	**0.02**
Prior Stroke (sensitivity model)	3.42	1.01	11.62	**0.05**
Antiarrhythmic	1.06	0.24	4.66	0.94
Aspirin	1.08	0.57	2.04	0.82
B-blocker	0.62	0.29	1.34	0.23
Ca-blocker	0.78	0.42	1.45	0.43
Digoxin	1.83	0.80	4.19	0.15
Other HTN Meds	0.50	0.24	1.04	0.06
Loop diuretic	2.33	1.15	4.72	**0.02**
Methotrexate	0	.	.	.
Warfarin	0.31	0.09	1.00	0.05
ACE/ARBS	1.11	0.58	2.13	0.74
Antiplatelet	3.10	1.41	6.82	**< 0.01**
Antirheumatic	0.00	.	.	.
Steroid	1.45	0.52	4.03	0.47
Cholesterol drug	0.80	0.43	1.48	0.47
Diuretic other	1.05	0.50	2.18	0.91
Other Anticoagulant	0	.	.	.
Sex (male)	0.48	0.07	3.61	0.48
Age	1.05	1.02	1.08	**< 0.01**

Total population: 3,295; Ibuprofen – 1,080; Naproxen – 846; Celecoxib – 604; Etodolac – 652; Rofecoxib – 202. Endpoint events – 55; censored 3,240.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Long-term exposure defined as > 180 days.

[§] Note: uses stroke sensitivity model for prior stroke covariate

Appendix GG:

Adjusted association between <u>short-term</u> exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) - high sensitivity stroke model.[ξ, §]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	0.63	0.33	1.19	0.15
Etodolac (ibuprofen)	0.54	0.28	1.02	0.06
Rofecoxib (ibuprofen)	0.81	0.34	1.91	0.63
Naproxen (ibuprofen)	0.77	0.44	1.36	0.37
Covariates				
Diabetes	1.27	0.80	2.02	0.30
Angina	1.20	0.69	2.08	0.51
PVD	1.43	0.74	2.76	0.29
Atrial Fibrillation	1.95	0.91	4.17	0.09
Cancer	1.14	0.68	1.92	0.61
COPD	1.63	0.89	3.00	0.11
Heart failure	1.39	0.69	2.79	0.36
HIV	0	.		.
Lupus*	0	.	.	.
Osteoarthritis	1.87	1.15	3.05	**0.01**
Renal failure	0.88	0.22	3.52	0.86
Respiratory failure	1.95	0.61	6.19	0.26
Rheumatoid arthritis	0.24	0.03	1.96	0.18
Prior AMI	1.76	0.60	5.16	0.30
Prior Stroke (sensitivity model)	4.86	2.32	10.18	**< 0.01**
Antiarrhythmic	1.18	0.43	3.23	0.75
Aspirin	1.41	0.88	2.26	0.15
B-blocker	1.27	0.76	2.12	0.36
Ca-blocker	0.95	0.60	1.51	0.83
digoxin	0.86	0.41	1.82	0.69
other HTN Meds	0.71	0.40	1.24	0.22
loop diuretic	0.61	0.33	1.13	0.12
methotrexate	7.53	1.59	35.77	**0.01**
warfarin	1.63	0.79	3.37	0.19
ACE/ARBS	1.90	1.20	3.00	**0.01**
Antiplatelet	1.61	0.83	3.13	0.16
Antirheumatic	7.01	0.70	70.01	0.10
Steroid	0.41	0.14	1.22	0.11
cholesterol drug	0.88	0.55	1.41	0.59
diuretic other	0.67	0.37	1.21	0.18
Other Anticoagulant	0.47	0.05	4.48	0.51
Sex (male)	0.96	0.30	3.11	0.95
Age	1.04	1.02	1.06	**< 0.01**

Total population: 8,725; Ibuprofen – 3,383; Naproxen – 2,376; Celecoxib – 906; Etodolac – 1,703; Rofecoxib – 357. Endpoint events – 92; censored 8,633.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Short term exposure defined as ≤ 180 days.

[§] Note: uses stroke sensitivity model for prior stroke covariate

Appendix HH:

Adjusted association between exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from ischemic heart disease, or cerebrovascular event).[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	1.14	0.71	1.82	0.59
Etodolac (ibuprofen)	0.82	0.49	1.37	0.45
Rofecoxib (ibuprofen)	1.53	0.85	2.78	0.16
Naproxen (ibuprofen)	0.96	0.61	1.53	0.87
Covariates				
Diabetes	1.28	0.90	1.82	0.17
Angina	1.18	0.79	1.77	0.42
PVD	1.36	0.81	2.28	0.25
Atrial Fibrillation	1.28	0.67	2.43	0.46
Cancer	0.90	0.60	1.36	0.62
COPD	1.84	1.19	2.85	**0.01**
Heart failure	1.32	0.79	2.19	0.28
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	1.88	1.31	2.70	**< 0.01**
Renal failure	0.77	0.25	2.40	0.65
Respiratory failure	0.69	0.19	2.55	0.58
Rheumatoid arthritis	0.82	0.29	2.32	0.71
Prior AMI	3.73	1.97	7.04	**< 0.01**
Prior Stroke (specificity model)	4.21	1.48	12.00	**0.01**
Antiarrhythmic	1.27	0.61	2.64	0.52
Aspirin	1.11	0.77	1.59	0.57
B-blocker	1.57	1.09	2.28	0.02
Ca-blocker	0.91	0.64	1.29	0.60
Digoxin	1.27	0.78	2.08	0.33
Other HTN Meds	0.72	0.48	1.07	0.11
Loop diuretic	1.68	1.12	2.52	**0.01**
Methotrexate	5.41	1.59	18.44	**0.01**
Warfarin	0.93	0.52	1.66	0.80
ACE/ARBS	1.24	0.87	1.76	0.23
Antiplatelet	1.67	1.00	2.76	**0.05**
Antirheumatic	0	.	.	.
Steroid	0.54	0.25	1.14	0.11
Cholesterol drug	0.99	0.70	1.40	0.95
Diuretic other	0.70	0.45	1.10	0.13
Other Anticoagulant	0.29	0.04	2.19	0.23
Sex (male)	0.65	0.24	1.77	0.40
Age	1.03	1.02	1.05	**< 0.01**

Total population: 12,188; Ibuprofen – 4,481; Naproxen – 3,240; Celecoxib – 1,530; Etodolac – 2,371; Rofecoxib – 566. Endpoint events – 156; censored 12,032.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

Appendix II:

Adjusted association between long-term exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from ischemic heart disease, or cerebrovascular event).[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	3.03	1.20	7.63	**0.02**
Etodolac (ibuprofen)	1.02	0.29	3.54	0.98
Rofecoxib (ibuprofen)	5.59	1.93	16.24	**< 0.01**
Naproxen (ibuprofen)	1.49	0.53	4.15	0.45
Covariates				
Diabetes	1.37	0.69	2.73	0.36
Angina	0.61	0.27	1.40	0.24
PVD	0.23	0.03	1.80	0.16
Atrial Fibrillation	2.75	0.82	9.26	0.10
Cancer	0.55	0.23	1.31	0.18
COPD	1.45	0.58	3.65	0.43
Heart failure	3.00	1.17	7.67	**0.02**
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	1.20	0.57	2.53	0.63
Renal failure	0.39	0.04	4.02	0.43
Respiratory failure	0.00	.	.	.
Rheumatoid arthritis	1.93	0.43	8.66	0.39
Prior AMI	8.72	2.24	33.99	**< 0.01**
Prior Stroke (specificity model)	0.00	0.00	.	0.99
Antiarrhythmic	0.40	0.06	2.82	0.35
Aspirin	0.86	0.42	1.75	0.67
B-blocker	1.03	0.48	2.19	0.94
Ca-blocker	0.71	0.36	1.39	0.32
Digoxin	1.25	0.49	3.19	0.63
Other HTN Meds	0.53	0.24	1.16	0.11
Loop diuretic	3.89	1.88	8.05	**< 0.01**
Methotrexate	0	.	.	.
Warfarin	0.23	0.06	0.88	**0.03**
ACE/ARBS	0.90	0.45	1.79	0.77
Antiplatelet	2.55	1.02	6.37	**0.05**
Antirheumatic	0	.	.	.
Steroid	0.70	0.16	3.10	0.63
Cholesterol drug	1.25	0.66	2.36	0.50
Diuretic other	1.23	0.57	2.66	0.60
Other Anticoagulant	0	.	.	.
Sex (male)	0.49	0.07	3.70	0.49
Age	1.03	0.99	1.06	0.11

Total population: 3,317; Ibuprofen – 1,085; Naproxen – 849; Celecoxib – 611; Etodolac – 656; Rofecoxib – 206. Endpoint events – 46; censored 3,271.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Long-term exposure defined as > 180 days.

Appendix JJ:

Adjusted association between short-term exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from ischemic heart disease, or cerebrovascular event).[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	0.78	0.37	1.63	0.50
Etodolac (ibuprofen)	0.66	0.32	1.36	0.26
Rofecoxib (ibuprofen)	1.41	0.60	3.31	0.43
Naproxen (ibuprofen)	0.64	0.31	1.30	0.21
Covariates				
Diabetes	0.82	0.47	1.43	0.49
Angina	1.11	0.59	2.08	0.74
PVD	1.70	0.82	3.55	0.16
Atrial Fibrillation	1.43	0.58	3.49	0.44
Cancer	1.18	0.65	2.13	0.58
COPD	2.32	1.21	4.44	**0.01**
Heart failure	1.61	0.76	3.42	0.21
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	2.26	1.31	3.91	**< 0.01**
Renal failure	1.27	0.24	6.69	0.78
Respiratory failure	1.42	0.32	6.26	0.65
Rheumatoid arthritis	0.36	0.04	2.90	0.34
Prior AMI	1.90	0.63	5.69	0.25
Prior Stroke (specificity model)	4.39	0.94	20.48	0.06
Antiarrhythmic	1.63	0.60	4.42	0.33
Aspirin	1.45	0.83	2.53	0.19
B-blocker	1.97	1.11	3.47	**0.02**
Ca-blocker	0.74	0.43	1.30	0.30
Digoxin	1.01	0.46	2.24	0.98
Other HTN Meds	0.53	0.27	1.07	0.08
Loop diuretic	0.82	0.43	1.58	0.56
Methotrexate	8.40	1.74	40.40	**0.01**
Warfarin	1.59	0.70	3.63	0.27
ACE/ARBS	1.99	1.16	3.43	**0.01**
Antiplatelet	1.33	0.58	3.03	0.50
Antirheumatic	0	.	.	.
Steroid	0.52	0.17	1.55	0.24
Cholesterol drug	1.06	0.62	1.82	0.84
Diuretic other	0.62	0.31	1.24	0.18
Other Anticoagulant	0.89	0.12	6.81	0.91
Sex (male)	0.73	0.17	3.04	0.66
Age	1.03	1.00	1.05	**0.02**

Total population: 8,730; Ibuprofen – 3,383; Naproxen – 2,376; Celecoxib – 908; Etodolac – 1,705; Rofecoxib – 358. Endpoint events – 68; censored 8,662.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Short term exposure defined as ≤ 180 days.

Appendix KK:

Adjusted association between exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from major cardiovascular disease, or cerebrovascular event).[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	1.14	0.73	1.79	0.55
Etodolac (ibuprofen)	0.87	0.53	1.42	0.58
Rofecoxib (ibuprofen)	1.58	0.90	2.77	0.11
Naproxen (ibuprofen)	1.01	0.65	1.56	0.98
Covariates				
Diabetes	1.16	0.83	1.63	0.39
Angina	1.14	0.78	1.68	0.49
PVD	1.24	0.74	2.07	0.41
Atrial Fibrillation	1.52	0.83	2.76	0.17
Cancer	0.99	0.67	1.45	0.94
COPD	1.64	1.06	2.52	**0.02**
Heart failure	1.16	0.71	1.90	0.56
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	1.70	1.20	2.41	**< 0.01**
Renal failure	0.75	0.25	2.31	0.62
Respiratory failure	1.02	0.32	3.18	0.98
Rheumatoid arthritis	1.01	0.40	2.56	0.99
Prior AMI	3.21	1.71	6.02	**< 0.01**
Prior Stroke (specificity model)	3.77	1.32	10.73	**0.01**
Antiarrhythmic	1.10	0.53	2.28	0.79
Aspirin	1.14	0.81	1.60	0.46
B-blocker	1.73	1.22	2.46	**< 0.01**
Ca-blocker	0.90	0.64	1.25	0.53
Digoxin	1.31	0.83	2.08	0.24
Other HTN Meds	0.73	0.50	1.06	0.10
Loop diuretic	1.74	1.18	2.56	**0.01**
Methotrexate	4.15	1.22	14.10	**0.02**
Warfarin	0.89	0.51	1.55	0.68
ACE/ARBS	1.20	0.86	1.68	0.28
Antiplatelet	1.78	1.10	2.87	**0.02**
Antirheumatic	0	.	.	.
Steroid	0.64	0.32	1.26	0.19
Cholesterol drug	1.00	0.71	1.39	0.99
Diuretic other	0.70	0.46	1.08	0.11
Other Anticoagulant	0.58	0.14	2.42	0.45
Sex (male)	0.59	0.22	1.62	0.31
Age	1.04	1.02	1.05	**< 0.01**

Total population: 12,188; Ibuprofen – 4,481; Naproxen – 3,240; Celecoxib – 1,530; Etodolac – 2,371; Rofecoxib – 566. Endpoint events – 172; censored 12,016.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

Appendix LL:

Adjusted association between long-term exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from major cardiovascular disease, or cerebrovascular event).[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	2.17	0.94	5.03	0.07
Etodolac (ibuprofen)	0.96	0.31	2.91	0.94
Rofecoxib (ibuprofen)	3.90	1.43	10.62	**0.01**
Naproxen (ibuprofen)	1.14	0.45	2.91	0.78
Covariates				
Diabetes	1.23	0.64	2.38	0.53
Angina	0.65	0.30	1.38	0.26
PVD	0.21	0.03	1.62	0.13
Atrial Fibrillation	3.76	1.22	11.58	0.02
Cancer	0.70	0.32	1.54	0.38
COPD	1.19	0.48	2.95	0.71
Heart failure	2.45	0.99	6.08	0.05
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	1.03	0.49	2.15	0.94
Renal failure	0.60	0.06	5.76	0.66
Respiratory failure	0	.	.	0.99
Rheumatoid arthritis	2.94	0.86	10.08	0.09
Prior AMI	6.75	1.78	25.60	**< 0.01**
Prior Stroke (specificity model)	0	.	.	.
Antiarrhythmic	0.36	0.05	2.61	0.31
Aspirin	1.08	0.56	2.09	0.82
B-blocker	1.27	0.63	2.55	0.50
Ca-blocker	0.84	0.45	1.57	0.58
Digoxin	1.21	0.50	2.92	0.67
Other HTN Meds	0.53	0.25	1.12	0.10
Loop diuretic	2.95	1.46	5.98	**< 0.01**
Methotrexate	0	.	.	.
Warfarin	0.22	0.06	0.82	**0.02**
ACE/ARBS	0.96	0.50	1.84	0.90
Antiplatelet	2.17	0.90	5.21	0.08
Antirheumatic	0	.	.	.
Steroid	1.03	0.30	3.53	0.96
Cholesterol drug	1.21	0.66	2.21	0.54
Diuretic other	0.98	0.46	2.07	0.95
Other Anticoagulant	0	.	.	.
Sex (male)	0.46	0.06	3.40	0.44
Age	1.04	1.01	1.07	**0.02**

Total population: 3,317; Ibuprofen – 1,085; Naproxen – 849; Celecoxib – 611; Etodolac – 656; Rofecoxib – 206. Endpoint events – 51; censored 3,317.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Long-term exposure defined as > 180 days.

Appendix MM:

Adjusted association between short-term exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from major cardiovascular disease, or cerebrovascular event).[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	0.86	0.43	1.74	0.67
Etodolac (ibuprofen)	0.64	0.31	1.32	0.23
Rofecoxib (ibuprofen)	1.72	0.78	3.76	0.18
Naproxen (ibuprofen)	0.77	0.40	1.49	0.44
Covariates				
Diabetes	0.81	0.47	1.37	0.42
Angina	1.06	0.59	1.92	0.84
PVD	1.52	0.74	3.11	0.25
Atrial Fibrillation	1.34	0.58	3.14	0.49
Cancer	1.26	0.73	2.18	0.41
COPD	2.07	1.10	3.87	**0.02**
Heart failure	1.33	0.64	2.77	0.44
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	2.11	1.26	3.55	**< 0.01**
Renal failure	0.99	0.20	5.00	0.99
Respiratory failure	2.24	0.62	8.15	0.22
Rheumatoid arthritis	0.37	0.05	2.96	0.35
Prior AMI	1.82	0.61	5.39	0.28
Prior Stroke (specificity model)	3.70	0.80	17.02	0.09
Antiarrhythmic	1.42	0.53	3.77	0.49
Aspirin	1.39	0.83	2.35	0.21
B-blocker	1.95	1.14	3.34	**0.01**
Ca-blocker	0.71	0.42	1.21	0.20
Digoxin	1.19	0.58	2.44	0.64
Other HTN Meds	0.57	0.30	1.08	0.09
Loop diuretic	1.08	0.59	1.99	0.80
Methotrexate	6.96	1.48	32.58	**0.01**
Warfarin	1.39	0.64	3.02	0.40
ACE/ARBS	1.72	1.04	2.87	**0.04**
Antiplatelet	1.72	0.82	3.61	0.15
Antirheumatic	0	.	.	.
Steroid	0.45	0.15	1.31	0.14
Cholesterol drug	1.12	0.67	1.86	0.67
Diuretic other	0.69	0.36	1.30	0.25
Other Anticoagulant	1.59	0.37	6.96	0.54
Sex (male)	0.64	0.16	2.68	0.55
Age	1.03	1.01	1.05	**0.01**

Total population: 8,730; Ibuprofen – 3,383; Naproxen – 2,376; Celecoxib – 908; Etodolac – 1,705; Rofecoxib – 358. Endpoint events – 76; censored 8,654.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Short term exposure defined as ≤ 180 days.

Appendix NN:

Adjusted association between NSAIDS & COX-2 inhibitors and serious cardiovascular events[σ] in VA subjects ≥ 65 years of age.[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	1.52	0.87	2.67	0.14
Etodolac (ibuprofen)	1.10	0.58	2.10	0.77
Rofecoxib (ibuprofen)	2.14	1.09	4.19	**0.03**
Naproxen (ibuprofen)	1.08	0.59	1.97	0.81
Covariates				
Diabetes	1.20	0.79	1.81	0.39
Angina	0.94	0.59	1.52	0.81
PVD	1.68	0.97	2.91	0.06
Atrial Fibrillation	1.37	0.68	2.78	0.38
Cancer	0.87	0.56	1.37	0.55
COPD	2.13	1.33	3.40	**< 0.01**
Heart failure	1.41	0.80	2.50	0.23
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	1.69	1.13	2.55	**0.01**
Renal failure	0.61	0.17	2.25	0.46
Respiratory failure	0.74	0.19	2.84	0.66
Rheumatoid arthritis	0.87	0.30	2.54	0.80
Prior AMI	3.12	1.46	6.67	**< 0.01**
Prior Stroke (specificity model)	4.58	1.55	13.54	0.01
Antiarrhythmic	1.54	0.69	3.42	0.29
Aspirin	0.96	0.63	1.45	0.84
B-blocker	1.59	1.04	2.44	**0.03**
Ca-blocker	1.04	0.70	1.55	0.85
Digoxin	1.00	0.55	1.80	0.99
Other HTN Meds	0.54	0.33	0.87	**0.01**
Loop diuretic	1.54	0.96	2.49	0.08
Methotrexate	5.90	1.69	20.55	**0.01**
Warfarin	0.86	0.44	1.67	0.65
ACE/ARBS	0.96	0.63	1.44	0.83
Antiplatelet	1.90	1.09	3.32	**0.02**
Antirheumatic	0	.	.	.
Steroid	0.49	0.20	1.18	0.11
Cholesterol drug	0.80	0.53	1.21	0.30
Diuretic other	1.01	0.62	1.64	0.97
Other Anticoagulant	0.43	0.06	3.29	0.42
Sex (male)	1.00	0.31	3.20	1.00
Age	0.99	0.96	1.03	0.62

Total population: 4,971; Ibuprofen – 1,486; Naproxen – 1,196; Celecoxib – 968; Etodolac – 986; Rofecoxib – 335. Endpoint events – 114; censored 4,857.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[σ] Defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event

Appendix OO:

Adjusted association between NSAIDS & COX-2 inhibitors and serious cardiovascular events[σ] in VA subjects ≥ 65 years of age – long-term exposure.[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	7.36	1.62	33.48	**0.01**
Etodolac (ibuprofen)	3.54	0.62	20.13	0.15
Rofecoxib (ibuprofen)	13.24	2.59	67.68	**< 0.01**
Naproxen (ibuprofen)	1.72	0.28	10.50	0.55
Covariates				
Diabetes	1.12	0.49	2.55	0.78
Angina	0.34	0.11	1.03	0.06
PVD	0.34	0.04	2.74	0.31
Atrial Fibrillation	3.21	0.81	12.72	0.10
Cancer	0.47	0.18	1.25	0.13
COPD	2.14	0.80	5.68	0.13
Heart failure	4.23	1.40	12.83	**0.01**
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	1.08	0.45	2.58	0.86
Renal failure	0.38	0.04	3.87	0.41
Respiratory failure	0.00	0.00	.	0.99
Rheumatoid arthritis	2.33	0.48	11.43	0.30
Prior AMI	6.41	1.16	35.33	**0.03**
Prior Stroke (specificity model)	0	.	.	.
Antiarrhythmic	0.85	0.10	7.52	0.88
Aspirin	0.64	0.27	1.54	0.32
B-blocker	1.13	0.46	2.83	0.79
Ca-blocker	0.83	0.37	1.82	0.64
Digoxin	0.95	0.29	3.06	0.93
Other HTN Meds	0.27	0.10	0.77	**0.01**
Loop diuretic	4.31	1.89	9.82	**< 0.01**
Methotrexate	0	.	.	.
Warfarin	0.21	0.05	0.93	**0.04**
ACE/ARBS	0.70	0.30	1.65	0.41
Antiplatelet	3.02	1.06	8.64	**0.04**
Antirheumatic	0.00	0.00	.	0.99
Steroid	0.87	0.18	4.11	0.86
Cholesterol drug	1.10	0.50	2.39	0.82
Diuretic other	1.56	0.63	3.84	0.33
Other Anticoagulant	0	.	.	.
Sex (male)	0.95	0.12	7.35	0.96
Age	0.97	0.91	1.03	0.31

Total population: 1,610; Ibuprofen – 413; Naproxen – 381; Celecoxib – 411; Etodolac – 315; Rofecoxib – 127. Endpoint events – 34; censored 1,576.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Long-term exposure defined as > 180 days.

[σ] Defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event

Appendix PP:

Adjusted association between NSAIDS & COX-2 inhibitors and serious cardiovascular events[σ] in VA subjects ≥ 65 years of age – short-term exposure.[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	0.84	0.36	1.95	0.68
Etodolac (ibuprofen)	0.78	0.32	1.89	0.59
Rofecoxib (ibuprofen)	1.60	0.62	4.16	0.33
Naproxen (ibuprofen)	0.52	0.20	1.33	0.17
Covariates				
Diabetes	1.00	0.53	1.92	0.99
Angina	0.75	0.36	1.59	0.46
PVD	1.98	0.91	4.32	0.09
Atrial Fibrillation	1.69	0.64	4.45	0.29
Cancer	1.01	0.52	1.95	0.99
COPD	2.82	1.39	5.74	**< 0.01**
Heart failure	1.58	0.66	3.76	0.30
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	2.33	1.26	4.33	**0.01**
Renal failure	1.61	0.32	8.21	0.57
Respiratory failure	1.37	0.30	6.32	0.69
Rheumatoid arthritis	0.20	0.02	2.38	0.20
Prior AMI	2.16	0.60	7.78	0.24
Prior Stroke (specificity model)	4.13	0.82	20.80	0.09
Antiarrhythmic	1.55	0.49	4.95	0.45
Aspirin	1.31	0.69	2.47	0.40
B-blocker	1.66	0.85	3.26	0.14
Ca-blocker	0.83	0.44	1.57	0.56
Digoxin	0.55	0.20	1.54	0.26
Other HTN Meds	0.40	0.17	0.92	**0.03**
Loop diuretic	0.73	0.33	1.62	0.44
Methotrexate	11.80	2.10	66.29	**0.01**
Warfarin	1.83	0.72	4.67	0.21
ACE/ARBS	1.52	0.80	2.89	0.20
Antiplatelet	2.08	0.85	5.13	0.11
Antirheumatic	0	.	.	.
Steroid	0.45	0.12	1.67	0.23
Cholesterol drug	0.74	0.38	1.42	0.36
Diuretic other	0.89	0.42	1.87	0.76
Other Anticoagulant	2.16	0.27	17.58	0.47
Sex (male)	0.71	0.09	5.37	0.74
Age	0.97	0.92	1.02	0.26

Total population: 3,283; Ibuprofen – 1,065; Naproxen – 801; Celecoxib – 547; Etodolac – 664; Rofecoxib – 206. Endpoint events – 49; censored 3,234.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Short term exposure defined as ≤ 180 days.

[σ] Defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event

Appendix QQ: *Data - Years 1999 – 2002 – all observations*

Adjusted association between exposure to NSAIDS & COX-2 inhibitors and serious cardiovascular events (defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event) – Ibuprofen Comparison, 1999 - 2002.

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	1.14	0.77	1.70	0.51
Etodolac (ibuprofen)	0.99	0.67	1.47	0.97
Rofecoxib (ibuprofen)	1.56	0.96	2.54	0.07
Naproxen (ibuprofen)	1.03	0.70	1.52	0.87
Covariates				
Diabetes	1.60	1.21	2.12	**< 0.01**
Angina	1.27	0.91	1.76	0.16
PVD	1.44	0.95	2.19	0.08
Atrial Fibrillation	1.06	0.63	1.81	0.82
Cancer	0.97	0.70	1.34	0.83
COPD	1.75	1.23	2.47	**< 0.01**
Heart failure	1.45	0.97	2.18	0.07
HIV	0.99	0.12	8.48	1.00
Lupus*	0	.	.	.
Osteoarthritis	1.63	1.21	2.20	**< 0.01**
Renal failure	0.80	0.31	2.11	0.66
Respiratory failure	0.82	0.32	2.10	0.68
Rheumatoid arthritis	0.74	0.29	1.91	0.54
Prior AMI	2.90	1.73	4.86	**< 0.01**
Prior Stroke (specificity model)	2.67	1.02	6.98	**0.05**
Antiarrhythmic	1.63	0.91	2.90	0.10
Aspirin	1.04	0.78	1.40	0.78
B-blocker	1.46	1.08	1.97	**0.01**
Ca-blocker	0.95	0.71	1.26	0.70
Digoxin	1.23	0.82	1.85	0.32
Other HTN Meds	0.86	0.63	1.17	0.33
Loop diuretic	1.47	1.05	2.05	**0.02**
Methotrexate	2.33	0.64	8.44	0.20
Warfarin	0.72	0.43	1.19	0.20
ACE/ARBS	0.98	0.74	1.30	0.89
Antiplatelet	1.78	1.19	2.66	**< 0.01**
Antirheumatic	1.18	0.14	10.08	0.88
Steroid	0.79	0.44	1.39	0.41
Cholesterol drug	0.85	0.64	1.13	0.26
Diuretic other	0.87	0.62	1.22	0.41
Other Anticoagulant	0.59	0.18	1.88	0.37
Sex (male)	0.84	0.39	1.79	0.64
Age	1.04	1.02	1.05	**< 0.01**

Total population: 16,488; Ibuprofen – 5,699; Naproxen – 4,385; Celecoxib – 1,980; Etodolac – 3,615; Rofecoxib – 809. Endpoint events – 238; censored 16,250.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

Appendix RR:

Adjusted association between long-term NSAIDS & COX-2 inhibitor use and serious cardiovascular events [σ] – 1999 through 2002.[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	2.05	1.03	4.07	**0.04**
Etodolac (ibuprofen)	1.83	0.90	3.70	0.09
Rofecoxib (ibuprofen)	2.59	1.10	6.10	**0.03**
Naproxen (ibuprofen)	1.39	0.68	2.88	0.37
Covariates				
Diabetes	1.74	1.09	2.76	**0.02**
Angina	1.19	0.69	2.06	0.54
PVD	0.90	0.39	2.11	0.81
Atrial Fibrillation	1.52	0.59	3.94	0.38
Cancer	0.78	0.44	1.38	0.39
COPD	1.81	1.01	3.28	**0.05**
Heart failure	2.28	1.17	4.46	**0.02**
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	1.14	0.67	1.94	0.62
Renal failure	0.65	0.12	3.56	0.62
Respiratory failure	1.34	0.24	7.55	0.74
Rheumatoid arthritis	1.67	0.51	5.47	0.40
Prior AMI	2.75	0.91	8.28	0.07
Prior Stroke (specificity model)	0	.	.	0.98
Antiarrhythmic	0.78	0.21	2.81	0.70
Aspirin	0.72	0.44	1.20	0.21
B-blocker	1.29	0.77	2.14	0.33
Ca-blocker	0.79	0.49	1.27	0.33
Digoxin	1.33	0.66	2.66	0.43
Other HTN Meds	0.77	0.46	1.30	0.33
Loop diuretic	2.00	1.16	3.44	**0.01**
Methotrexate	0	.	.	.
Warfarin	0.38	0.15	0.98	**0.04**
ACE/ARBS	0.75	0.46	1.21	0.24
Antiplatelet	2.42	1.26	4.64	**0.01**
Antirheumatic	9.28	1.12	76.72	**0.04**
Steroid	0.74	0.28	1.97	0.54
Cholesterol drug	1.01	0.63	1.60	0.98
Diuretic other	1.25	0.74	2.11	0.41
Other Anticoagulant	0	.	.	.
Sex (male)	0.84	0.25	2.74	0.77
Age	1.03	1.01	1.05	**0.02**

Total population: 5,112; Ibuprofen – 1,535; Naproxen – 1,316; Celecoxib – 814; Etodolac – 1,238; Rofecoxib – 310. Endpoint events – 88; censored 5,024.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Long-term exposure defined as > 180 days.

[σ] Defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event

Appendix SS:

Adjusted association between short-term NSAIDS & COX-2 inhibitor use and serious cardiovascular events [σ] – 1999 through 2002.[ξ]

		(95% CI)		
Exposure (reference group)	**Adjusted Risk Ratio**	**Lower**	**Upper**	**Sig. (p)**
Celecoxib (ibuprofen)	0.69	0.35	1.37	0.29
Etodolac (ibuprofen)	0.65	0.34	1.23	0.19
Rofecoxib (ibuprofen)	1.70	0.84	3.44	0.14
Naproxen (ibuprofen)	0.79	0.44	1.44	0.44
Covariates				
Diabetes	1.03	0.64	1.66	0.90
Angina	1.17	0.68	2.01	0.57
PVD	1.74	0.93	3.28	0.08
Atrial Fibrillation	1.06	0.46	2.42	0.90
Cancer	1.16	0.70	1.94	0.56
COPD	2.56	1.49	4.42	**< 0.01**
Heart failure	1.32	0.68	2.54	0.41
HIV	0	.	.	.
Lupus*	0	.	.	.
Osteoarthritis	2.10	1.30	3.41	**< 0.01**
Renal failure	1.29	0.37	4.44	0.69
Respiratory failure	0.75	0.16	3.47	0.71
Rheumatoid arthritis	0	.	.	.
Prior AMI	3.09	1.32	7.25	**0.01**
Prior Stroke (specificity model)	4.78	1.38	16.55	**0.01**
Antiarrhythmic	1.92	0.82	4.46	0.13
Aspirin	1.48	0.91	2.40	0.11
B-blocker	1.52	0.92	2.50	0.10
Ca-blocker	0.88	0.55	1.42	0.61
Digoxin	0.89	0.43	1.82	0.74
Other HTN Meds	0.67	0.38	1.16	0.15
Loop diuretic	1.04	0.59	1.84	0.90
Methotrexate	4.96	0.63	38.87	0.13
Warfarin	1.38	0.66	2.91	0.39
ACE/ARBS	1.56	0.97	2.51	0.07
Antiplatelet	1.47	0.74	2.92	0.27
Antirheumatic	0	.	.	.
Steroid	0.58	0.23	1.51	0.27
Cholesterol drug	0.79	0.49	1.26	0.32
Diuretic other	0.71	0.40	1.27	0.25
Other Anticoagulant	1.27	0.38	4.19	0.70
Sex (male)	0.84	0.26	2.73	0.78
Age	1.03	1.01	1.06	**< 0.01**

Total population: 11,198; Ibuprofen – 4,149; Naproxen – 3,051; Celecoxib – 1,149; Etodolac – 2,354; Rofecoxib – 495. Endpoint events – 89; censored 11,109.

* Systemic lupus erythematosus and connective tissue disorders diagnosis

[ξ] Short term exposure defined as ≤ 180 days.

[σ] Defined as acute myocardial infarction, death from coronary heart disease, or cerebrovascular event

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