ANTIHYPERTENSIVE THERAPY AND RISK OF CARDIOVASCULAR DISEASE IN DIABETIC SUBJECTS

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THESIS ABSTRACT

Objective.– This study was designed to assess the association between cardiovascular disease and the use of antihypertensive drugs in a diabetic population.

Design and Setting.– We conducted a case-control study nested within a cohort of 2499 subjects over 45 years old with diabetes and hypertension in Saskatchewan.

Outcomes.– The main outcome measure was first hospitalization for cardiovascular disease.

Exposure Definition.– The main exposure of interest was current use of antihypertensive drugs, defined as drug dispensing within 90 days of the index date.

Statistical Analysis.– Relative risks were calculated with 95% confidence intervals using conditional logistic regression models. Full multivariate models, adjusting for all potential confounding covariates, were performed.

Results.– Compared with diuretics, current use of calcium antagonists was associated with a 1.90-fold increase in risk of cardiovascular disease (RR 1.90; 95% CI= 1.25-2.91). The current use of β-blockers was not associated with an increase in morbidity. The risk of cardiovascular disease for angiotensin-converting enzyme inhibitors (ACE-I) relative to diuretics was found to be increased only in the subgroup of patients currently exposed to other antihypertensive drugs, including peripheral vasodilators, centrally-

acting α_2-agonists, and α-blockers (RR 1.6; 95% CI= 1.19-2.18).

Conclusion.– Results of this research agree with the findings from several observational studies and clinical trials. However, factors influencing selective prescribing practices could not be completely accounted for and may partially explain our results.

RÉSUMÉ

But de l'étude.– Le but de cette étude était d'évaluer l'association entre les maladies cardio-vasculaires et l'utilisation d'agents anti-hypertenseurs dans une population.

Devis et contexte. – Nous avons utilisé un devis cas-témoin niché dans une cohorte de 2499 sujets de la Saskatchewan, âgés de plus de 45 ans et souffrants de diabète et d'hypertension.

Issue d'intérêt.– L'issue d'intérêt était une première hospitalisation pour cause de maladie cardio-vasculaire.

Définition d'exposition. – La variable d'exposition d'intérêt principal était l'utilisation courante d'agents anti-hypertenseurs, ceci étant défini comme ces agents ayant été servis à l'intérieur d'une période de 90 jours suivant la date "index".

Analyse Statistique.– Les risques relatifs, et leur intervalles de confiance correspondantes, ont été calculés d'après des modèles de régression logistique. Des modèles multi-variés ont été élaborés afin d'ajuster pour toutes les variables potentiellement confondantes.

Résultats.– L'utilisation courante d'antagonistes calciques, comparée à celle de diurétiques, était associée à une augmentation de 90% du risque de maladie cardio-vasculaire (RR 1.90; 95% CI= 1.25-2.91). L'utilisation courante de bloqueurs-β n'était pas associée à une élévation de la morbidité. Nous avons observé que le risque de maladie cardio-vasculaire associé à

l'utilisation des inhibiteurs de l'enzyme de conversion de l'angiotensin (I-ECA), relatif à l'usage de diurétiques, était augmenté seulement pour le sous-groupe de patients concurremment exposés à d'autres médicaments anti-hypertenseurs, dont les agents vasodilatateurs périphériques, ainsi que les agonistes-α_2 et les antagonistes-α ayant une action centrale (RR 1.6; 95% CI= 1.19-2.18).

Conclusion.– Les résultats de cette recherche sont en accord avec les résultats de plusieurs essaies cliniques et études d'observation épidémiologiques. Néanmoins, les facteurs influençant les pratiques de prescription sélective n'ont pu être complètement contrôlés et pourraient expliquer, en partie, nos résultats.

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Chapter One - OBJECTIVES

1.1 Objectives

The general objective of this study was to evaluate the risk of cardiovascular disease associated with the use of antihypertensive medications in diabetic patients with uncomplicated hypertension. This research tested the hypothesis that calcium channel blockers are associated with an excess risk of cardiovascular disease in these patients.

More specifically, this study aims:

- To assess the risk of overall cardiovascular disease among users of diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and other miscellaneous classes of antihypertensive agents in subjects with diabetes and hypertension.

- To assess the risk of myocardial infarction, unstable angina, other ischemic heart disease, congestive heart failure, and stroke among users of the same above-mentioned classes of antihypertensive agents.

- To identify patient characteristics associated with an increased risk of cardiovascular disease.

Chapter Two - LITERATURE REVIEW

2.1 Epidemiology of Diabetes

Diabetes is a public health problem of enormous proportion (1). National surveys in Canada estimate that approximately 1 500 000 people are affected with this disease (1;2). Obesity and aging are independently associated with diabetes. As the population ages and the prevalence of obesity rises, the burden of this chronic disorder will continue to escalate in our society (1;2). It is estimated that approximately 3% of people aged 35 to 64 years have diabetes and this prevalence increases to 10% of individuals over 65 years old (1). It is predicted that by 2010, three million Canadians will be affected with diabetes (2).

2.1.1 Classification of Diabetes

Diabetes mellitus, the most common endocrine disorder (3), is characterized by the body's inability to sufficiently produce and/or properly utilize insulin. Consequently, glucose cannot be efficiently metabolized in the bloodstream. The resulting chronic high levels of blood glucose are associated with the long term complications involving multiple organ systems, namely renal, neurologic, cardiovascular, and ocular systems (1;3;4). For the most part, there are two major classifications of diabetes, type 1 and type 2 diabetes (1;3;4). Approximately 90% of patients belong in the latter classification.

Type 1 Diabetes. Type 1 diabetes generally occurs in younger, lean patients and is characterized by the marked inability of the pancreas to secrete insulin (5). Therefore, these individuals are insulin dependent, since no endogenous insulin is produced (3;5). Among type 1 diabetic patients, the reduction in life expectancy is at least 15 years (3). According to U.S. data, these individuals have a 7-fold excess mortality risk compared with the U.S. population of the same age (6;7). The prevalence of cardiovascular disease in these insulin-dependent diabetics is close to 10%, increasing with age and duration of diabetes (8). Multiple studies have demonstrated up to a 7-fold increase in the prevalence of heart disease (6;8-10).

Type 2 Diabetes. Type 2 diabetes, previously referred to as non-insulin dependent diabetes, typically begins after age 40. The individuals affected usually have a family history of diabetes and are obese (3). The onset of type 2 diabetes is a two-stage process:

- peripheral resistance to the action of insulin, often worsened by obesity, followed by
- the pancreas failing to increase insulin secretion despite the presence of elevated serum glucose levels (1-3).

Life expectancy is reduced by 5-10 years in middle-aged people with type 2 diabetes. This reduction may be greater if the age of onset is younger (1-3;11;12). Overall mortality among type 2 diabetics is approximately twice as high as those of non-diabetic individuals. Mortality is increased at all ages. However, the differences in death rates in comparison to those of the

general population narrows remarkably with advancing age (11).

2.1.2 Treatment of Diabetes

The primary goal of therapy for diabetes is the prevention of acute and chronic complications, that is, the maintenance of the patient's health (3). Improving metabolic control, such that blood glucose level is near-normal, will prevent long term complications for most diabetic patients (1;3;13-15).

Type 1 Diabetes. Multiple daily injections of insulin are required for all patients with type 1 diabetes. Treatment regimen should also include a carefully calculated diet, planned physical activity, and home blood glucose monitoring (3).

Type 2 Diabetes. In addition to diet and exercise, oral medication and/or insulin are typically included in the treatment regimen of a type 2 diabetic patient. Approximately 40% of these individuals require insulin (3).

2.1.3 Chronic Complications of Diabetes

The main long-term complications of diabetes include neuropathy, microvascular disease, including retinopathy and nephropathy , as well as macrovasular disease, such as ischemic heart disease, stroke, and atherosclerotic peripheral vascular disease (1;3).

2.1.3.1 Cardiovascular Morbidity

Although diabetes usually co-exists with other major risk factors of

cardiovascular disease, it has been shown to be an independent contributor to coronary artery disease, stroke, and peripheral vascular disease (3;16). People with diabetes have up to six times the risk of heart disease as do people without diabetes (1). Approximately 21% of the people with diabetes compared with 4% of those without this disease have cardiac disease or are suffering from the effects of a stroke (1).

2.1.3.2 Mortality and Diabetes

Diabetic persons experience very high mortality, especially from vascular disease, compared to the general population (11;17-19). A national survey in the United States estimated that among diabetic men and women, about 75% and 57%, respectively, of the excess mortality was attributable to cardiovascular discase (18). Within the Multiple Risk Factor Intervention Trial (MRFIT) (17), more than 5000 diabetic persons were followed for 12 years and were compared to 350 000 nondiabetic subjects. The risk of cardiovascular death a 12-year followup was almost three times higher in diabetic males compared to nondiabetic controls, regardless of age, ethnic group, blood cholesterol level, systolic blood pressure, or tobacco use. Even when patients had optimal systolic blood pressure control and were nonsmokers, the relative risk of cardiovascular death remained five times higher among diabetic persons than among controls (17;20). From recent statistics, diabetes ranks as the seventh leading cause of death in Canada and the United States (1;18). However, as a result of underreporting on

many death certificates (16;21), the actual number of deaths for which this disease is a contributing factor is probably five times higher than the reported number (1).

2.1.3.3 Economic Burden

In Canada, approximately 25 000 potential years of life lost (PYLL) were lost as a result of diabetes prior to age 75 in 1996 (1). In addition, the direct and indirect health care costs, including lost productivity due to diabetes-related illness and premature death from diabetes and its related complications, is estimated between 5-10 billion dollars annually (1;2).

2.1.4 Risk Factors for Diabetic Complications

There are a number of documented risk factors for diabetic complications, including smoking, dyslipidemia, physical inactivity, and microalbuminuria (1;7;17;22). Hypertension has also been shown to be a strong predictor of morbidity and mortality in persons with diabetes (1;17).

2.2 Hypertension

Arterial hypertension is a disorder characterized by high blood pressure, including a systolic blood pressure consistently greater than 140mmHg and/or a diastolic blood pressure consistently greater than 90mmHg. It is probably the most important health problem in developed countries (1;3). Hypertension may have no identifiable cause, in which case,

it is referred to as *essential* hypertension. An elevated blood pressure may also be an associated manifestation of some other disorder (for example, pheochromocytoma, kidney disease, adrenal tumors, coarctation of the aorta), in which case it is referred to as *secondary* hypertension. Approximately 90% of all hypertensive individuals have the former type of hypertension (3).

2.2.1 Prevalence

According to the 1990 Heart Health Survey that actually measured participants' blood pressure, 26% of men and 18% of women in Canada have hypertension (1;23;24). At ages 18-24 years, 6% of men and 1% of women have high blood pressure. From that age on, there is a steady increase in the prevalence of this disorder (1). After age 65 years, the prevalence of hypertension approaches 50% (1;25). Data from the Framingham study has shown no change in prevalence in four decades (26).

2.2.2 Morbidity and Mortality in Hypertension

As with diabetes, longstanding hypertension affects multiple organ systems, including cardiovascular, renal and ocular (1;23;27;28). The risk of complications is further enhanced when it clusters with other risk factors such as dyslipidemia, obesity, diabetes and insulin resistance (1). The coexistence of these factors may increase the risk of cardiovascular disease up to 10-fold (29).

2.2.3 Management of Hypertension

The Canadian Hypertension Society (23) and the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure in the United States (30) provide North American physicians with guidelines regarding the use of antihypertensive drug therapy. Although the resources for the diagnosis of hypertension are readily available in Canada, this disease remains poorly managed (23-25;31). Only about 50% of Canadians with high blood pressure are aware of their condition and among those with the disease, only one third have adequate blood pressure control (23-25).

2.2.3.1 Non-pharmacologic Management

The control of high blood pressure should initially consist of lifestyle modifications including weight loss, exercise, healthy diet, and avoiding heavy alcohol use. Other recommendations consist of adequate patient education, close blood pressure monitoring by a physician, and self-blood pressure assessment. If the control is inadequate despite non-pharmacologic measures, a medication should be considered (23;24).

2.2.3.2 Pharmacologic Management

It is evident from the available literature that antihypertensive therapy significantly reduces morbidity and mortality from cardiac disease, renal failure, and stroke among hypertensive patients (23;32-38). The classes of antihypertensive drugs available to treat high blood pressure are diuretics,

beta-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin II antagonists, peripheral vasodilators, centrally acting agents, and alpha-blockers (39). The preferred agents for initial drug use in the Canadian guidelines are beta-blockers and diuretics because they have both been shown to consistently reduce morbidity and mortality (23;39;40) If therapy with these drugs fails or is contraindicated, then a second line agent is added or substituted. Therapy should be individualized for all patients, that is, it should be tailored to one's personal profile of risk factors. An attempt should be made to treat high blood pressure and coexisting diseases with a single agent (23). For example, subjects with a history of ischemic heart disease, such as angina or myocardial infarction, beta-blockers or angiotensin-converting enzyme inhibitors (ACE-I) serve as the best therapeutic option (23;41). In the presence of congestive heart failure, ACE-I would be considered the most appropriate choice of medication (23;23;39;40;42). Another associated disease that would modify treatment of hypertension is diabetes (23). However, in recent years there has been much controversy with respect to different classes of agents actually worsening prognosis in this subset of patients by increasing cardiovascular morbidity and mortality.

2.3 Diabetes and Hypertension

2.3.1 Epidemiology of Hypertension in Diabetic Patients.

Hypertension is a common comorbid condition occurring at least twice as frequently in patients with type 1 and type 2 diabetes than in the nondiabetic population (43-47). Among type 2 diabetic adults, approximately 50% also have preexisting hypertension at the time of diagnosis of their diabetes and among those patients without preexisting hypertension, they are more than twice as likely to develop this condition (48).

2.3.2 Morbidity and Mortality due to Hypertension in Diabetic Patients

The coexistence of these two disorders will accelerate the progression of macrovascular disease (44;46;49;50) and microvascular disease, including nephropathy (51) and retinopathy (52) It is estimated that 35-75% of all diabetic complications may be attributed to hypertension (44;46;49;50;53). In addition, mortality secondary to cardiovascular pathology increases by 2.5-7.2-fold in this population (46). Eighty percent of diabetic mortality is thought to be directly related to macrovascular complications (46).

Hypertension in Diabetes Study. The Hypertension in Diabetes Study, embedded within the United Kingdom Prospective Diabetes Study (UKPDS), was one of the first studies that attempted to characterize the incidence of fatal and nonfatal cardiovascular events in newly diagnosed type 2 diabetic patients, according to the presence or absence of hypertension (54). Among

the 3648 diabetic patients, hypertension was present in 35% of women and 46% of men. When compared to normotensive diabetic patients, the mortality risk associated with hypertension was doubled over a median followup period of 4.6 years. Cardiac events, including sudden death, accounted for 58% and stroke accounted for 13% of all causes of death. The risk of stroke was increased 4-fold in diabetic hypertensive subjects and there was a greater than 50% increased risk of myocardial infarction.

The Appropriate Blood Pressure Control (ABCD) Trial. The relation between hypertension and vascular complications among non-insulin dependent diabetic people was also examined among the 950 patients enrolled in the ABCD study (55). Systolic and diastolic hypertension were both identified as strong risk factors for nephropathy, peripheral vascular disease, left ventricular hypertrophy, as well as, coronary artery disease and cerebrovascular disease.

2.3.3 Mechanism for Hypertension in Diabetes

Many pathophysiologic changes are associated with the development of hypertension in diabetes.

Vascular reactivity. Firstly, an increase in total exchangeable body sodium concentration of about 10% and an increase in vascular reactivity to various vasoconstrictors has been described in diabetic patients (48;56). Furthermore, a subgroup of these patients may be "salt-sensitive", as defined by a heightened vasoconstrictive response for a given salt load (an increase

in systolic blood pressure by more than 10mmHg) compared to "salt-resistant" individuals. Therefore, some of the abnormal hemodynamic responses observed in the diabetic state may be due to this altered vascular reactivity (56).

Hyperinsulinemia. It has been suggested that hyperinsulinemia in subjects with insulin resistance is responsible for blood pressure elevation (57;58). Loss of lean body mass and an increase in adipose tissue, particularly visceral body fat, is generally associated with aging. It is now known that insulin resistance is correlated with these phenomena. This resistance leads to an increased release of free fatty acids by the visceral fat into the portal system, and ultimately leads to an overproduction of triglycerides (56;58). There are two possible ways that insulin may elevate blood pressure. First, hyperinsulinemia has been shown to increase sodium reabsorption and decrease sodium excretion in humans (58;59). It has also been demonstrated that high levels of insulin increase sympathetic nervous system activity by stimulating a rise in circulating levels of catecholamines (58). Another mechanism by which hyperinsulinemia contributes to the development of hypertension is via its effects on vascular remodeling and actually exacerbating the atherosclerotic changes on the endothelium (58). Interestingly, in one recent study (60), troglitazone, an oral hypoglycemic agent which improves insulin resistance was found to lower blood pressure. These results further strengthen the association between hypertension and hyperinsulinemia in subjects with diabetes. However, in some populations,

such as the Pima Indians and the Mexican-Americans, certain epidemiological studies have actually failed to demonstrate the link between plasma insulin concentration and hypertension. Therefore, it is probable that insulin resistance and hyperinsulinemia alone are insufficient for the development of hypertension (58).

2.3.4 Pathogenesis of Atherosclerosis in Diabetes and Hypertension

Several mechanisms acting together play an important role in mediating the pathogenesis of vascular disease in the diabetic hypertensive patient. Some of the more important mechanisms of cardiovascular injury will be outlined briefly in the following section.

Platelet adhesion and aggregation. Platelet adhesion and aggregation are often aggravated in the presence of diabetes and hypertension. It appears that intracellular calcium and magnesium metabolism play an important role in the enhanced platelet reactivity in these patients. Platelet aggregation is associated with an elevated calcium concentration, whereas an increase in magnesium concentration can exert an inhibitory effect on platelet aggregation. It has been demonstrated that in many patients with hypertension and diabetes there exists an imbalance between the relative intracellular concentrations of these cations. More specifically, intracellular concentrations of calcium and magnesium are increased and decreased, respectively, leading to increased platelet aggregation (61-64).

Platelet hyperactivity is also related to the enhanced expression of certain

adhesion molecules, which promote further the attachment of platelets, monocytes, and leukocytes (20;63).

Coagulation abnormalities. Hypercoagulation and disturbances of the fibrinolytic system have been reported to be associated with coexistence of hypertension and diabetes. Higher than normal levels of a number of coagulation factors contribute to a procoagulant state (61;62).

Insulin resistance and lipoprotein abnormalities. As mentioned previously, hyperinsulinemia is believed to be one of the initiating mechanisms for blood pressure elevation in diabetic individuals (57;58). This insulin-resistant state is also associated with an array of lipoprotein abnormalities, such as unusually elevated levels of low-density lipoproteins and diminished levels of high-density lipoproteins (20;57;61-63). This particular derangement of lipoproteins is a well-known risk factor for cardiovascular disease. Likewise, insulin stimulates the production of two other atherogenic factors, endothelin and plasminogen activator inhibitor (61).

Endothelial dysfunction. Dysfunction of the vascular endothelium contributes to the pathogenesis of cardiovascular disease in subjects with coexisting diabetes and hypertension (20;61;62). For example, the production of nitric oxide, a potent vasodilator, is impaired. Patients with decreased nitric oxide levels are predisposed to increased production of certain vasoconstrictors, such as prostaglandins, endothelin, and platelet and vascular growth factors, which synergistically enhance vasomotor tone and vascular remodeling (20;61).

Role of IGF-1. IGF-1 may also participate in the pathogenesis of atherosclerosis in this population through influences on vascular endothelial cells and vascular smooth muscle cells (62).

Hyperglycemia. Chronic hyperglycemia has many direct toxic effects on vascular endothelial cells. This toxicity leads to diminished endothelium-mediated vascular relaxation, increased vasoconstriction, promotion of vascular smooth muscle cell hyperplasia, vascular remodeling, and atherosclerotic changes (61;62).

2.3.5 Management of Hypertension in Diabetic Patients.

2.3.5.1 Blood Pressure Reduction.

According to the current Canadian guidelines (23), hypertension in people with diabetes should be treated aggressively to obtain a target blood pressure below 130/80 mmHg. As previously discussed, drug management of hypertension in nondiabetic subjects significantly reduces cardiovascular disease and death (23;33-38). Findings from the United Kingdom Prospective Diabetes Study (UKPDS) (65;66) and the Hypertension Optimal Treatment (HOT) (67) trial clearly indicate that tight blood pressure control significantly reduces the risk of cardiovascular complications and diabetes-related mortality.

The UKPDS (65) was a randomized control trial designed to compare tight blood pressure control aiming at a blood pressure of less than 150/85

mmHg (with the use of the ACE-I captopril or the β-blocker atenolol as initial treatment) with less tight control aiming at a blood pressure of less than 180/105 mmHg (with the use of the loop diuretic furosemide, the calcium channel blocker nifedipine, methlydopa, or prazosin but avoiding ACE-I and β-blockers). A total of 1148 hypertensive patients with type 2 diabetes were followed for median of 8.4 years. The study achieved a mean difference in systolic blood pressure of 10 mmHg and in diastolic blood pressure of 5 mmHg. Despite this small difference in blood pressure levels between the two groups, the tight control group demonstrated a significant reduction in the risks for most of the endpoints. In the intention-to-treat analysis, intensive management of hypertension significantly reduced the risks of developing any diabetes-related endpoint by 24%, deaths related to diabetes by 32%, strokes by 44%, and microvascular endpoints by 37%.

The HOT trial (67) assessed optimal diastolic blood pressure control by stratifying patients into three treatment groups with goals of less than 90 mmHg, less than 85 mmHg, and less than 80 mmHg. All individuals were initially treated with the long-acting calcium antagonist, felodipine, followed by the addition ACE-I, β-blockers, or diuretics if needed to achieve blood pressure targets. In contrast to the overall study population (n=18790), analysis of data from the diabetic subpopulation(n=1501) found a decrease in major cardiovascular events in relation to target blood pressure. In the group randomly assigned to diastolic blood pressure control of less than 80 mmHg, the risk of these endpoints was 50% lower compared with the group assigned

to diastolic blood pressure control of less than 90 mmHg.

The findings from these two important studies suggest that reducing blood pressure must take precedence in caring for patients with type 2 diabetes. They do not address the issue of prioritizing individual classes of antihypertensive agents (65;68-70).

2.3.5.2 Pharmacotherapy of Hypertension in Diabetic Patients

Several classes of medications are available for the treatment of hypertension in this specific population (39;46): diuretics, β-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin II antagonists, peripheral vasodilators, centrally acting agents, and alpha-blockers (39). The ideal drug for hypertensive patients with diabetes should not only lower blood pressure but should also not adversely affect metabolic control of glucose and lipids. Other important considerations when choosing a specific agent include the prevention or slowed progression of renal disease, as well as, the reduction in long-term cardiovascular complications and mortality (20;46;69;71).

2.3.5.3 Metabolic Issues in Hypertensive Patients with Diabetes

The major metabolic side effects of different classes of antihypertensive agents are summarized in Appendix 1. Please note that *thiazide diuretics* will be referred to as *diuretics* from here on.

Diuretics have been the first-line treatment for hypertension for over 30

years (71), however, they have been an unpopular choice for diabetic people because many studies have indicated they may impair glucose tolerance and actually aggravate control of diabetes. Diuretics potentially increase low-density lipoprotein (LDL) cholesterol concentrations and decrease high-density lipoprotein (HDL) cholesterol concentration, thereby increasing risk of atherogenesis (20;46;58;69;71;72). Of note, these metabolic derangements are most evident at higher doses. Other disadvantages of this class of medication include hypokalemia, hypomagnesemia, and hyperuricemia, but once again these side effects are minimized at the low doses that are currently recommended (58). There are several concerns that limit the usefulness of β-blockers in treating patients with diabetes (58). Chronic administration of these medications is usually accompanied by a rise in insulin resistance (58;71) and a decrease in insulin secretion (72), consequently, adversely affecting glycemic control (20;69). In addition, β-blockers may increase triglyceride and decrease HDL cholesterol levels (46;58;69;72). Although these metabolic alterations are associated mostly with nonselective β-blockers, cardioselective agents may also lead to an increase in triglyceride levels (46). Unfortunately, the risks of hypoglycemia unawareness are increased with β-blockers because these medications prevent the common warning symptoms of hypoglycemia, including tremors and palpitations (46;58). Calcium channel blockers have no apparent adverse effect on carbohydrate and lipid metabolism (20;69;71;72). Although there were initial reports of improvement in glycemic control with

ACE-I (72), it is now believed that they have neutral effects on lipid and glucose control (58;69;72). α-blockers are recognized to improve insulin sensitivity and have a mildly beneficial effect on lipid profile. They have been noted to reduce levels of total cholesterol, triglycerides, and increase HDL cholesterol (20;46;71;72). Centrally acting α_2- receptor agonists and peripheral vasodilators are metabolically neutral with respective to lipid and carbohydrate metabolism. Information on these agents in diabetic patients is scarce because they have not been widely investigated (46).

2.3.5.4 Renoprotection and Antihypertensive Therapy in Diabetic Patients

The results from trials involving β-blockers and diuretics showed no independent renal benefit in hypertensive diabetic patients, other than that associated with the reduction in blood pressure (48;73;74). β-blockers have been shown to reduce albuminuria and to preserve glomerular filtration rate in diabetic hypertensive patients, however their effects appear to be entirely related to the degree of arterial pressure reduction, without any independent effect on preservation of renal function (73). ACE-I prevent microalbuminuria or reduce the progression of the already existing rate of microalbuminuria in diabetic patients (48;75). These effects have been shown to be independent of the blood pressure reduction caused by these agents (46;48;58). The effects of the dihydropyridine calcium antagonists (for example, nifedipine) on renoprotection is controversial (76;77). On the other hand,

nondihydropyridine calcium antagonists (for example diltiazem or verapamil) have been shown to have positive effects on kidney function (46;48;58;62;76). α-adrenergic antagonists and centrally-acting α_2-receptor agonists have never been evaluated in clinical trials with regards to efficacy in slowing renal disease progression (48;73;74).

2.4 Antihypertensive Therapy in Diabetic patients and Risk of Cardiovascular disease

So far, the epidemiology of hypertension in diabetes, as well as the impact of hypertension on the clinical course and development of vascular complications have been discussed. In addition, the benefits of blood pressure reduction have been reviewed. Therefore, treatment must reduce blood pressure, minimize metabolic side effects and protect renal function. Likewise, optimal high blood pressure therapy requires consideration of the cardiovascular and cerebrovascular potentials of the treatment. Over the last decade a number of observational studies and randomized clinical trials have reported variable results with respect to cardiovascular outcomes with different classes of antihypertensive medications. Subsequently, these reports have provided new insight into the role of agents available for blood pressure reduction.

The objective of the following section is to summarize the findings of these recent observational studies and clinical trials.

2.4.1 Review of Evidence from Observational Studies

Many population-based studies analyzing the effects of various antihypertensive drugs on cardiovascular outcome in the general population have been published. These studies reported various adverse effects with certain agents, specifically with calcium channel blockers (49;78;79). A few observational studies have been conducted specifically in the diabetic population. Appendix 2 provides a brief summary of these studies.

Warram et al. (80) observed in a cohort study of 759 diabetic subjects with a median followup of 4.5 years that cardiovascular mortality was 3.8 times higher in patients treated with diuretics alone than in patients with untreated hypertension. After the findings from the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET) (81) were published indicating that patients treated with an ACE-I had a lower rate of major vascular events than patients treated with a calcium antagonist, two other researchers re-analyzed their databases by diabetes status (82;83). In the Established Populations Epidemiologic Studies in the Elderly (EPESE) by Pahor et al. (79;82;84), a cohort of elderly hypertensive patients were followed for five years. Among the diabetic subset of patients, there was a higher mortality rate (risk ratio=3.27) for users of the calcium antagonist nifedipine compared to β-blockers. This finding compares to a risk ratio of 1.36 among the nondiabetic subjects. Similarly, Alderman observed in a case control study of 387 hypertensive patients, that among those with diabetes (n=34), patients treated with calcium antagonists had a 5-fold increased risk

of cardiovascular events as compared to those treated with other antihypertensive agents (49;83). In another case-control study (n=216) (85), the risk of myocardial infarction in hypertensive patients with diabetes treated with calcium channel blockers was twice that of patients treated with ACE-I or diuretics. Another retrospective cohort study of 266 diabetic subjects using either a calcium antagonist or a β-blocker found that the odds ratio for overall mortality was 1.78 in calcium antagonist users relative to β-blocker users (86). Verdacchia et al. (87;88) conducted another retrospective cohort analysis of 164 diabetic hypertensive patients enrolled in the PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) registry. None of the subjects had preexisting cardiovascular morbid events. The analysis revealed that the use of calcium channel blockers was not associated with an excess risk of cardiovascular events.

In summary, only one study found an excess risk associated with diuretics (80). As for the remaining observational studies, in all of them (82;83;85;86) except one (88), there was as excess risk of cardiovascular disease associated with the use of calcium channel antagonists.

2.4.1.1 Critical Appraisal of Observational Studies in Diabetics

The validity of the results of the observational studies have been criticized because of the presence of important methodological flaws (89;90;92). In some studies (80;82;83;85;86), the decision to prescribe calcium channel blockers by the physician for the treatment of hypertension

may have been influenced by factors associated with cardiovascular disease risk. A proportion of the subjects participating had previous history of cardiovascular disease and at the time these studies were conducted, calcium channel blockers were widely used for the treatment of coronary heart disease (91;92). Therefore, confounding by indication may be a possible explanation for the study findings. In addition, in all these population-based studies (80;82;83;85;86;88), prevalent cases of hypertension were used and past history of drug use was not accounted for properly. Therefore, study subjects were at different moments in the course of their disease and patients with more severe disease or more difficult to control hypertension may have been prescribed second line agents, such as calcium antagonists. Another potential concern with the use of prevalent subjects is the depletion of susceptible phenomenon. Noncompliant subjects and those individuals unable to tolerate their medication will not be included in the analysis. Furthermore, underestimation of the true risk may occur because hypertensive individuals with highest risk may have already experienced the study outcome or may have died. Exclusion of these events may bias the true risk toward the null. Finally, exposure was not clearly defined in some studies (83;85;86). For example, in one particular study (86), exposure was measured at the inclusion time only. There was no mention of modifications during the followup time or the exposure at the time of the event. While in other studies only exposure at the time of the event was used, irrespective of prior history of exposure patterns such as switching or

long duration.

2.4.2 Review of the Evidence and Critical Appraisal of Clinical Trials

An outline of the clinical trials evaluating antihypertensive therapy in diabetic subjects is presented in Appendix 3. Only the first three trials were conducted specifically in diabetic populations (55;81;93). For the most part, diabetic subjects are considered in subgroup analyses (94-101).

Appropriate Blood Pressure Control (ABCD) Trial. The ABCD trial (55) was a prospective, randomized blinded trial with type II diabetic subjects. It was conducted to determine the effects of intensive and moderate blood pressure control and to compare the effects of a calcium antagonist nisoldipine and the ACE-I enalapril. The primary outcome measure was glomerular filtration rate. Cardiovascular outcomes were monitored as secondary endpoints. The study included two populations aged 40-74 years: 470 hypertensive patients who had diastolic blood pressure greater than 90 mmHg and 480 normotensive patients. Patients were randomized to receive either intensive antihypertensive drug therapy or moderate antihypertensive therapy. Study subjects were also randomized to double-blinded nisoldipine or enalapril. After a mean followup of 5 years, the Data and Safety Monitoring Board (DSMB) recommended early termination of the hypertensive arm of the trial because of a 5-fold increase in fatal and nonfatal acute myocardial infarction in the nisoldipine group compared to the enalapril group

(25/235 events vs. 5/235 events; RR 5.5: 95% CI 2.2-14.6). This trial has been widely criticized (68;69;92;102-106). The authors of the study also acknowledge that the results should be viewed with caution since the findings are based on secondary endpoints (55). In addition, the study was based at one site only. The ABCD trial had no placebo group; therefore, the differences are possibly due to a beneficial effect of the ACE-I or a deleterious effect of the calcium channel blockers (69;105;106). A comparison of the incidence of myocardial infarction among diabetics randomly assigned to calcium antagonists with other published trials suggests that the rate of myocardial infarction was not significantly different than historical controls (105). Another important factor is that a higher proportion of patients in the ACE-I group were receiving β-blockers concurrently (55) and perhaps these subjects had more cardioprotection (107).

Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET). Another study that contributed to the concern of calcium antagonists was FACET (81). It was an open-label study that randomly assigned 380 hypertensive patients with diabetes to either the ACE-I fosinopril or the calcium antagonist amlodipine and it followed the participants for up to 3.5 years. The primary outcome was the changes in total cholesterol concentration; the secondary outcome was the combined incidence of cardiovascular events. Treatment failures on fosinopril had amlodipine added and vice versa. Patients randomly assigned to fosinopril were approximately

50% less likely to experience major cardiovascular events than patients assigned to calcium antagonists (14/189 [7%] vs. 27/191 [14%]; RR 0.49: 95%CI 0.26-0.95). Once again, these results are based on secondary endpoints and the interpretation of the data is difficult because of the combined use of the study drugs in each group. There was a substantial crossover to combination therapy since amlodipine was added to 37% of fosinopril patients and fosinopril was added to 36% of the amlodipine patients.

As with the ABCD trial (55), FACET (81) was largely criticized (68;104;108-111) mainly for its open-label design and the fact that it was conducted in one health care center, thereby allowing sponsor and investigator bias (108). Furthermore, the higher microalbuminuria levels at baseline in the amlodipine group signify a possible higher cardiovascular risk in these individuals (112;113). Finally, the incidence of events was lowest in patients treated with both fosinopril and amlodipine and, therefore, this may suggest that combination therapy is the preferable choice of treatment (69;108;109).

United Kingdom Prospective Diabetes Study (UKPDS). One of the aims of the UKPDS (93) was to determine whether blood pressure control with the ACE-I captopril or the β-blocker atenolol had specific advantages with respect to macrovascular, microvascular, renal, and cardiovascular complications. Of note, this study was not particularly designed to compare

differing classes of antihypertensive agents, but rather to compare the effects of tight blood pressure control and moderate blood pressure control. In this trial, there was no difference in outcomes between the captopril and atenolol. A trend to fewer sudden deaths with β-blocker than with ACE-I was not significant. Interestingly, 31% of patients in the ACE-I group and 40% in the atenolol group were concurrently on a calcium antagonist by the end of followup.

Multicenter Isradipine Diuretic Atherosclerotic Study (MIDAS). MIDAS (98;99) was a 3-year, randomized trial designed to compare the effect of the calcium antagonist isradipine to the diuretic hydrochlorothiazide on the progression of carotid intimal medial thickness as assessed by carotid ultrasound. Subjects consisted of 883 hypertensive patients with the initial exclusion of diabetic subjects. Cardiovascular outcomes were analyzed as secondary endpoints. Despite the initial exclusion of subjects with diabetes, patients were stratified according to the baseline level of glycosylated hemoglobin (a measure of glucose control). It was found that the relative risk for major events with isradipine compared to hydrochlorothiazide was 2.81 (95% CI 1.09-7.26) among those with poorer glycemic control. Therefore, these findings indicated that hypertensive patients with glucose intolerance responded unfavorably to calcium channel blockers. Of note, these results are based on a total of 21 events over 3 years.

Two other randomized trials that focused on hypertension in the elderly

have also examined their findings in the the diabetic subgroup of patients (95;96;100).

Systolic Hypertension in the Elderly Program (SHEP) Study. SHEP evaluated the efficacy of a diuretic, chlothalidone, with placebo in 4736 elderly hypertensive patients (95). Outcomes included cardiac events, strokes, and mortality. A subgroup analysis of the 583 subjects with diabetes demonstrated that the incidence of cardiovascular events was reduced by 34% with diuretic therapy. Of note, these results contradict the findings in the observational study by Warram (80) that found an increase in cardiovascular mortality in patients receiving a diuretic-based therapy.

Systolic Hypertension in Europe (Sys-Eur) Trial. In the subgroup analysis from Sys-Eur trial (96;100) (n=4203), active treatment with the calcium antagonist nitredipine, alone or in combination with an ACE-I or a diuretic, reduced mortality among diabetic patients (n=492) by 55%, mortality from cardiovascular disease by 76%, stoke by 73%, and cardiac events by 69% compared with placebo.

Although the authors of SHEP (95) and Sys-Eur (96;100) trials both recognize the results are based on post-hoc analysis, they argue these findings are suggestive of the beneficial effects of diuretics and calcium antagonists in the prevention of cardiovascular events in hypertensive subjects with diabetes. However, other experts argue that these two studies

do not address the issue of safety of antihypertensive medications since the comparison groups in both studies were placebo groups (68;84;114). In the Sys-Eur study, along with receiving the calcium antagonist, more than 50% of patients in the active treatment arm were concurrently on ACE-I and diuretics. The authors chose not to provide more details on the effect of calcium antagonists alone. Another limitation of the Sys-Eur study was that a large number a subjects were lost to followup (n=337) compared with the number of primary events (n=124) (96;100).

Captopril Prevention Project Randomized Trial (CAPPP). The CAPPP trial was a randomized open-label trial comparing the effects of an ACE-I and conventional therapy (including diuretics and β-blockers) in 10 985 hypertensive subjects (97). The primary outcome was a composite endpoint of fatal and nonfatal myocardial infarction, stroke, and other cardiovascular deaths. In the post-hoc analysis of 572 patients with diabetes, the primary endpoint was reduced by about 40% in the captopril arm compared to conventional therapy. Some (115) have criticized the post-hoc analysis of such a small group of diabetic patients (n=572) compared to a large number of nondiabetic patients (n=10 393). Also, the authors do not provide any concise information with regards to the number of patients on β-blockers and/or diuretics in the conventional treatment arm (97). These two drug classes have been clearly shown to differ with respect to their effects on hemodynamics, target organs, and cardiovascular outcome (40;116).

Heart Outcomes Prevention Evaluation (HOPE) Study. The HOPE trial (94;101)was a double-blind, 2x2 factorial randomized study evaluating the effects of the ACE-I ramipril and vitamin E in 9541 patients who were at least 55 years old and had a history of coronary artery disease, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor (hypertension, dyslipidemia, smoking). The diabetic subgroup consisted of 3577 patients, of which approximately 56% had hypertension. The primary study endpoint was the composite of myocardial infarction, stroke, or death from cardiovascular causes. Subjects on ramipril had a 25-30% lower risk of major cardiovascular outcomes. The two groups were well matched with respect to medications, including aspirin, lipid-lowering agents, β-blockers, diuretics, and calcium antagonist. The results are not available specifically for the diabetic patients with hypertension alone (n=2003). Ramipril was not given to the treatment arm as an antihypertensive agent. Subjects without hypertension were on this medication if they were randomized to the active treatment arm and those individuals with a history of high blood pressure were already being treated by their physicians with other agents. Worth noting, this study had low power to detect different effects in the subgroups.

2.5 Conclusion

At present, ACE-I are the standard choice of therapy in diabetic patients (41) with proteinuria (75) and CHF (42). Post-myocardial infarction, ACE-I (41) and β-blockers (117) are recommended. Despite evidence from several randomized clinical trials and observational studies, the controversy regarding the best antihypertensive treatment in diabetic subjects without cardiovascular disease remains controversial, especially with respect to the use of calcium antagonists. Several of these studies have found an increased risk associated with calcium antagonists compared to placebo or other agents, while others have obtained conflicting results.

Despite criticisms of the observational studies, they provide valuable information because these studies are conducted in the real world of everyday clinical practice. It is evident that efforts should be made to eliminate or control factors capable of biasing the results. In particular, an observational study should not only rely on prevalent hypertensive patients and should consider exposure throughout the entire followup.

Chapter Three - METHODS

This chapter describes the study design and the methodology employed to assess the risk of cardiovascular disease with the use of antihypertensive drugs in diabetic patients with uncomplicated hypertension.

3.1 Overview of the Study Design

A nested case-control analysis of a cohort was used to evaluate the risk of cardiovascular disease and antihypertensive drug use among diabetic patients with newly acquired, uncomplicated hypertension in the context of actual medical practice. Cohort members were recruited from the health insurance databases of the province of Saskatchewan. Drug markers were used to identify patients with diabetes and hypertension. Patients who were dispensed a first prescription for an antihypertensive drug between January 1, 1980 and December 31, 1986 were eligible for cohort entry. Among these subjects, patients dispensed an antihyperglycemic drug between January 1, 1976 and December 31, 1986 were identified.

Incident cases of cardiovascular disease that occurred between cohort entry and the end of followup were identified. Risk sets were formed consisting of each case and all potential controls matched to the case on the date of cohort entry and time at risk. Ten controls were randomly chosen from each risk set. A current-use time window was measured for all antihypertensive medications. Conditional logistic regression was used to

calculate crude and adjusted rate ratios for cardiovascular disease with the use of each class of antihypertensive drug. Effect modification was also assessed for some covariates.

3.2 Sources of Data

For the purposes of this study, information will be obtained from the computerized databases of the Saskatchewan Health Branch. Although data is collected purely for administrative purposes, it also functions as an excellent source of data for pharmacoepidemiologic research (118;119). This organization is responsible for administering universally insured health care services to approximately 95% of the 1.3 million inhabitants of this Canadian province. Registered Native Canadians, members of the armed forces, and member of the Royal Canadian Mounted Police who altogether compromise 5% of the Saskatchewan population, are recipients of health insurance plans administered by the federal government and are therefore ineligible for provincial coverage. Of note, plan membership is not based on socioeconomic status. Since this is a universal health database, studies carried out using this information provide knowledge regarding the health status of the entire population (119;120).

The Saskatchewan Health Branch consists of several computerized databases, including, the Health Insurance Registration File, the Outpatient Prescription Drug Services Branch Database, and the Hospital Services Branch Database.

3.2.1 Health Insurance Registration File

The Health Insurance Registration File includes demographic data, such as name, address, sex, date of birth, date of death, social assistance status, as well as dates of effective coverage. This file is updated regularly; therefore, it is useful for providing valid denominator data. Residents of the province of Saskatchewan are entitled to receive benefits through the health care system once they have established residence and have registered for a Health Services Card. This card contains a nine-digit identification number that is a lifetime number, uniquely identifying each resident. This unique identification number is used to code almost all health care services and also serves as a link to other health datafiles (119).

3.2.2 Outpatient Prescription Drug Services Branch Database

This file includes outpatient prescriptions for all medications listed in the Saskatchewan Drug Formulary. The prescription of nonformulary medication is believed to be minimal because the formulary is comprehensive and is continuously being updated. Over 90% of all outpatient prescription drugs in the province are contained within the Prescription Drug Plan, representing over 2000 drug products. The addition of newer medications occurs on a regular basis subsequent to continuous review processes by expert committees. On a regular basis, a sample of paid claims is selected and sent to the beneficiaries for confirmation that the service paid for had been provided and that all of the information on the claim was correct

(119;120). There have been changes in data collection over the life of the database. From 1975 to June 1987 and from January 1989 (120) to date, information is collected on an individual basis. The information available for each prescription includes: beneficiary's unique identification number, the drug quantity, strength and dosage, as well as dispensing data. Information from July 1987 to December 1988 is incomplete because consumer-submitted claims were compiled by family unit rather than on an individual basis (119;120).

3.2.3 Hospital Services Branch Database

This datafile provides hospital discharge information for all beneficiaries, including primary and secondary discharge diagnosis, classified according to the International Classification, 9th revision (ICD-9) codes (121), and dates of admission and discharge. Reliability and validity has been evaluated in a number of studies (118;119;122). These datafiles have been shown to be accurate and comprehensive (119).

3.3 Ethical Consideration

Although information within the computerized databases of the Saskatchewan Health is available for research purposes, strict patient confidentiality is maintained. All data is provided to the researchers in a non-nominal basis. Saskatchewan Health Cross Agency Study Committee must review all requests for data and must provide consent before the release of

any information (119;120). Guidelines for the use of these databases are available and are explicitly detailed (120).

3.4 Definition of the Cohort

The first step was to identify all individuals with hypertension. By using the Outpatient Prescription Drug Services Branch Database, all those subjects with one or more prescriptions for an antihypertensive drug (Appendix 5) between January 1, 1980 and December 31,1986 were identified. Once the hypertensive subjects were found, the next goal was to identify individuals with coexisting diabetes. All persons with one or more prescriptions for an antihyperglycemic agent (Appendix 4) between January 1, 1976 and December 31, 1986 remained in the cohort. The next goal was to identify only those individuals with newly diagnosed hypertension. Therefore, only those subjects initiating an antihypertensive drug (Appendix 5) between 1980 and 1986 remained in the cohort. To confirm the incident nature of hypertension, patients who were dispensed at least one antihypertensive medication in the 24 months preceding the onset of the recruitment phase were excluded. Therefore, all diabetic hypertensive subjects identified during the recruitment phase had their drug file reviewed to ensure that hypertension had not been previously diagnosed. Then by using the unique identification number, individuals over 45 years old were identified by date of birth through the Health Registration File. Cohort members were restricted to only those subjects over 45 years of age in order to increase the

likelihood of the outcome event. The *cohort entry date* was the date of the first prescription of an antihypertensive agent. Of note, for the purposes of this study, it was essential to identify a period when agents from all classes were available. Incident cases of hypertension were excluded if their diagnosis was prior to January 1, 1980 because of the unavailability of calcium antagonist and ACE-I. In order to avoid confounding by indication, all subjects receiving antihypertensive medications for indications other than high blood pressure were excluded. Using the Outpatient Prescription Drug Services Branch Database, drug markers were used to identify any concurrent medical illness which would require a patient to take an antihypertensive drug. Subjects prescribed any of the following agents up to 2 years prior to cohort entry were eliminated from the cohort: nitrates (may be used for the treatment of ischemic heart disease), loop diuretics (congestive heart failure), anticoagulants (arrhythmia, ischemic heart disease), and anti-arrhythmic agents (arrhythmia). In addition, files from the Hospital Branch Database were reviewed and subjects were excluded if they were admitted to hospital with cardiac disease and peripheral vascular disease as a primary or secondary diagnosis in the two years preceding cohort entry (Appendix 6).

In conclusion, all cohort members are diabetic subjects over 45 years of age with uncomplicated, newly diagnosed hypertension. All subjects were followed from cohort entry date up to the occurrence of an outcome measure, end of insurance coverage, or December 31, 1996.

3.5 Definition of Case Patients

The outcome is a combined endpoint including first hospitalization for acute myocardial infarction, unstable angina, other ischemic heart disease, heart failure, and stroke (Appendix 7). More specifically, a case is a subject who experienced any of these events requiring hospitalization after cohort entry. Events were identified between January 1, 1980 and December 31, 1996 in the primary and secondary discharge diagnosis of the Hospital Branch Database using ICD-9 codes (121). The index date for the cases is the date of the event.

3.6 Selection of Controls

For each case, risk sets were formed, including the case and all cohort members having initiated antihypertensive therapy in the same calender month and year. A random sample of 10 controls were chosen for each case among the risk sets. At the time of control selection, the subject was still at risk for a cardiovascular event. This sampling strategy allows a control to be included in multiple risk sets, as well as, allowing a case to be used as a control before the occurrence of an event. The date of matching was identified as the index date.

3.7 Drug Exposure

3.7.1 Current Use

For the purposes of this study, the exposure of interest is the current use of any class of antihypertensive drug: diuretics, β-blockers, angiotensin-converting enzyme inhibitors, calcium antagonists, or miscellaneous agents (peripheral vasodilators, centrally-acting α_2-agonists, and alpha-blockers). Patients on multiple medications were considered to be exposed to all prescribed agents. The current use time-window was chosen to be exposure within 90 days prior to the index date. Five variables were created, each one representing current use of one of the classes.

3.7.2 Prior Use

Prior use of an antihypertensive drug use was defined as use between cohort entry and the 90-day current use time window. Five variables were created representing prior use of each category and, as for the current use analysis, these categories were not mutually exclusive.

3.7.3 Any Use

Any use of an antihypertensive medication was defined as use of any medication for high blood pressure between cohort entry and index date.

3.8 Confounders and Effect Modifiers

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

Patients characteristics. Demographic characteristics were identified including age at index date, sex, and whether or not they were receivng social assistance. These factors may influence the prescribing practice of physicians and they also affect a patient's risk for an event.

Prior Use of Antihypertensive Therapy. The history of the use of various and multiple antihypertensive medications was used as a proxy for more severe disease or more difficult to control hypertension. These individuals are possibly at higher risk for an event and their past history may also influence the physician's prescribing practice. In addition to its potential confounding effect, past use was considered as an effect-modifier that is, it may modify the effect of another drug in the current time window.

Duration of Diabetes. This was calculated from the date of the first prescription of an antihyperglycemic agent to the index date. Of note, for subjects initiating therapy for diabetes prior to January 1, 1976, there exists a potential for underestimating the duration of diabetes. Information prior to this date is unavailable. A dichotomous variable was created to indicate if subjects were initiated on antihyperglycemic medication less than 5 years or 5

years and more prior to the index date.

Type of Antihyperglycemic Therapy. Three indicator variables were created to indicate if subjects received oral hypoglycemic agents only, insulin only, or both.

Compliance to Antihypertensive Therapy. Compliance was defined as 9 or more prescriptions of an antihypertensive medication per a 12-month period. As prescription information was not available for hospitalizations, the number of hospitalization days were removed from the denominator. Therefore, the compliance to antihypertensive therapy for each individual was computed using the following equation:

$$\text{Compliance} = \frac{\#\text{ of prescriptions} * 365\text{ days}}{365\text{ days} - \#\text{ days hospitalized}}$$

Therapy for Cardiovascular Disease Initiated During Followup. All cohort members had a diagnosis of uncomplicated hypertension. At the time of recruitment of subjects, it was ensured that no cardiac medications were dispensed in the 24 months prior to cohort entry and no hospitalization occurred for atherosclerotic disease during the same period. As discussed in the literature review, all diabetic, hypertensive patients are at high risk of cardiac disease. The members in this cohort were also at high risk of developing cardiac disease *not* requiring hospitalization during the followup.

Therefore, all prescription files were reviewed between cohort entry and index date and were screened for medications that were deemed to be drug markers for cardiovascular disease including, nitrates (angina), digoxin (arrhythmia, congestive heart failure), loop diuretics (congestive heart failure). Three variables were created- one for each drug marker. These drug markers were considered as confounders, as well as important effect modifiers.

Comorbidity. Certain drugs in a subject's prescription file may indicate the coexistence of another illness(Appendix 8). All cohort members' files were reviewed for such drug markers in the year preceding cohort entry.

3.9 Statistical Analysis

All analyses were performed using SAS statistical package. Odds ratios, as approximations to rate ratios (RR), and 95% confidence intervals (CI) were estimated using conditional logistic regression to account for the effect of matching. The summary outcome was the combined endpoint including first hospitalization for acute myocardial infarction, unstable angina, other ischemic heart disease, heart failure, and stroke. Crude RR were calculated for the risk of cardiovascular disease with the use of β-blockers, diuretics, angiotensin converting enzyme inhibitor, calcium antagonists, and miscellaneous classes (peripheral vasodilators, α_1-blockers, centrally-acting α_2-agonists). For all calculations, current use of diuretics was used as the

reference category. Crude RR were unadjusted for covariates, but were adjusted for current use of other antihypertensive medications. Individuals who discontinued their medication, that is, if there was no prescription in the 90-day current time window, were included in the analysis as a separate category to make sure that diuretic use remained the reference. Univariate analyses of the association between each potential confounder and the risk of cardiovascular disease was conducted.

Full multivariate models, adjusting for all potential confounding covariates, were performed. The following confounders were included in the final model: age, gender, social assistance, type of antihyperglycemic therapy, duration of diabetes, compliance to antihypertensive therapy, prior use of antihypertensive therapy, initiation of therapy during followup for cardiac disease, and comorbid illnesses. To determine whether a covariate was a significant confounder, the change-in-estimate method (a 10% change in OR estimate of current use of antihypertensive) was used. Three effect modifiers were considered in the analysis. First, to test the hypothesis that prior use of medication for high blood pressure may modify the effect of current use interaction terms were created between current use and prior use of antihypertensive therapy. Another effect modifier considered in the analysis was initiation of pharmacologic therapy for the treatment of angina (nitrates), congestive heart failure (loop diuretics, digoxin), and arrhythmia (digoxin) during followup. Finally, potential modification of the risk of one class of medication may exist by current use of another class. Consequently,

ten interaction terms were created among the five current-use variables and tested accordingly.

Crude and adjusted models were also performed for the *individual* cardiovascular endpoints including, acute myocardial infarction, unstable angina, other ischemic heart disease, congestive heart failure, and stroke.

Following the hypothesis that any use of antihypertensive therapy between cohort entry and index date could affect risk of cardiovascular disease, unadjusted and adjusted RRs with 95% CI were calculated using *any use* as the exposure of interest. For this analysis, diuretics were also used as the reference.

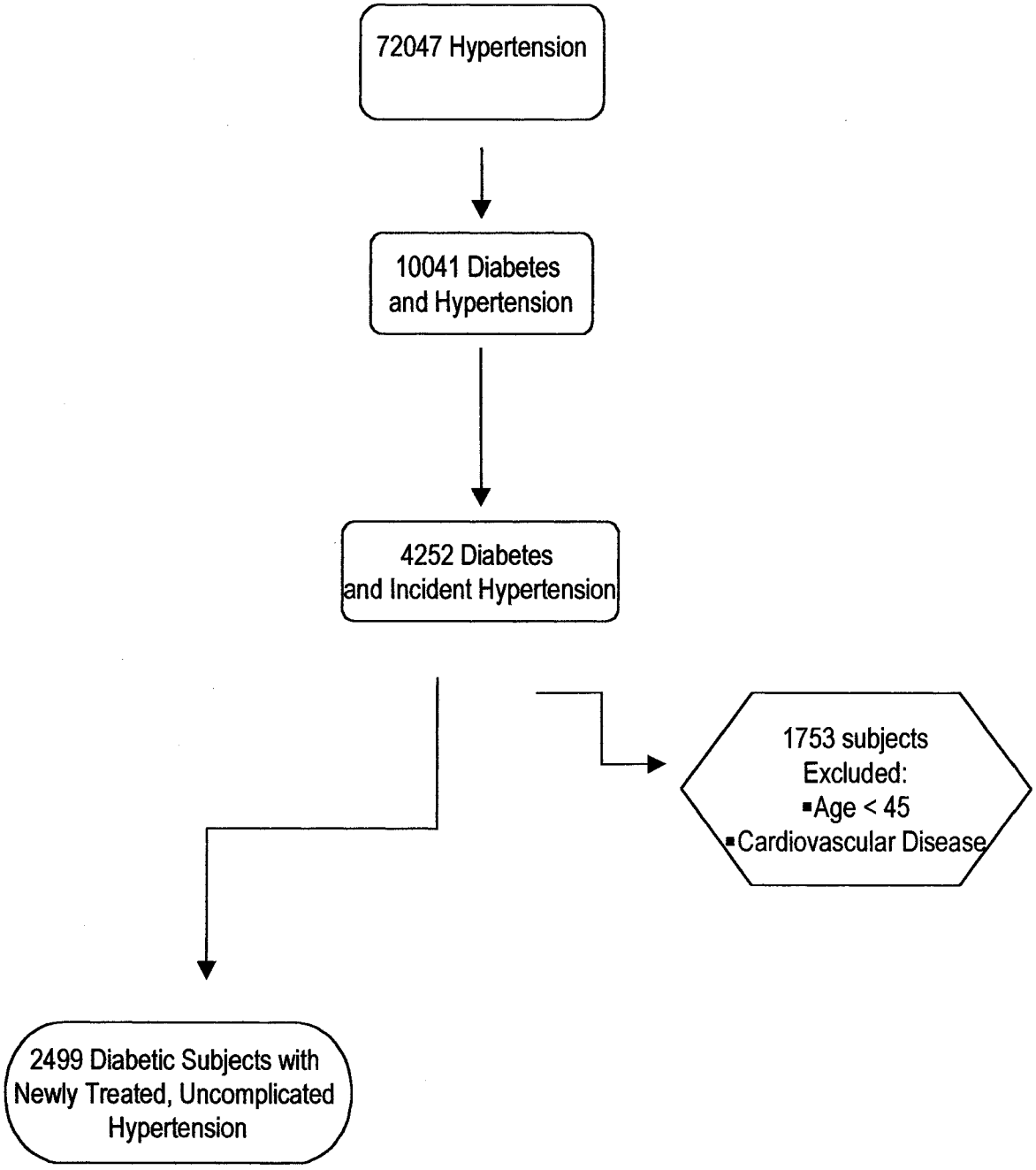
Chapter Four - RESULTS

The findings of this study will be presented in this chapter. First, the enumeration process of the cohort will be described. The next sections will contain the descriptive analysis of the cases and the controls, as well as the analysis of the risk of cardiovascular disease associated with the use of antihypertensive agents in a population of diabetic subjects.

4.1 Selection of the Cohort

The process of cohort selection is displayed in Figure 4.1. Using the Saskatchewan Health Database, 72047 hypertensive patients were identified, among which 10041 had a concurrent diagnosis of diabetes. However, 5789 beneficiaries were excluded because they had a diagnosis of prevalent hypertension, that is, hypertension was diagnosed before cohort entry. Only the 4252 subjects with incident hypertension between January 1, 1980 and December 31, 1987 were kept in the study cohort. Patients were also excluded if they were less than 45 years old (n=331) or if they had a prescription for a medication in the two years preceding cohort entry which served as a marker for any coexistent cardiovascular disease which may necessitate antihypertensive medications (n=1170). Moreover, subjects that were admitted to hospital with cardiovascular disease as a primary or secondary diagnosis were ineligible for entry in the study. Therefore, the final cohort consisted of 2499 diabetic subjects with newly diagnosed, uncomplicated hypertension.

Figure 4.1 Enumeration of the Cohort



4.2 Descriptive Analysis of the Case-Control Set

After cohort entry, 363 cases of cardiovascular disease were identified between January 1, 1980 and December 31 1996. However, 36 cases identified between July 1, 1987 and March 31, 1989 were excluded because, as previously mentioned, the information on outpatient prescriptions is incomplete during this period since consumer-submitted claims were compiled by family unit rather than on an individual basis. The 327 remaining cases are presented in Table 4.1 according to the ICD-9 system of classification. Approximately 28% of patients had a diagnosis of acute myocardial infarction. Coronary heart disease compromised 63% of patients, while only 17.7% and 19.3% of cases received diagnosis of heart failure and stroke, respectively.

Three hundred and twenty seven risk sets were formed. A random sample of 10 controls per case were chosen and matched to the case on the date of cohort entry. Table 4.2 characterizes the cases and controls in terms of demographic factors, duration of diabetes, treatment of diabetes, compliance to antihypertensive therapy, and comorbidity. In comparison to controls, cases were slightly older and a higher proportion were males. More controls were on insulin for the treatment of diabetes, whereas cases tended to be more on oral hypoglycemic agents only. To a small extent, compliance to antihypertensive therapy was superior among cases. The distribution of medication use was similar in the two groups. For duration of diabetes, a

dichotomous variable was created to indicate if pharmacologic therapy was begun more than 5 years prior to index date. As already described in the methods, precise information on prescriptions is unavailable for diabetic subjects that begun therapy before January 1, 1976. For patients with an index date between January 1,1980 and December 31, 1981, calculation of duration of diabetes is problematic. One hundred twenty one subjects with an index date during this period already had a prescription for an antidiabetic agent on January 1, 1976. All of these subjects were assumed to have *at least* 5 years duration of diabetes. This variable was equally distributed among cases and controls. For, example, a subject with an index date on March 1, 1980 AND a prescription for insulin on January 1,1976 may have a duration of diabetes for only 4.5 years. Precisely characterizing the duration of diabetes for this subject is impossible because information on the prescriptions of antihyperglycemic medications prior to 1976 is lacking. Therefore, in this scenario, it would have been assumed that this individual was on antidiabetic medications for at least 5 years.

Table 4.3 presents the distribution of antihypertensive drugs and other drugs in cases and controls. As for therapy with ACE-I, only one case and 19 controls were initiated on this class. More cases than controls begun antihypertensive therapy with β-blockers (20.2% versus 15.6%) and calcium antagonists (6.4% versus 2.9%). However, initial therapy with diuretics and other antihypertensive medications (including peripheral vasodilators, centrally-acting α_2-agonists, and alpha-blockers) was more common among

controls. In terms of current drug use, more controls than cases (28.9% versus 22.6%) were not exposed to any agents in the 90 days prior to index date. On the other hand, cases had a higher tendency to be on multiple classes of antihypertensive medications in the current-use time window. Cases were more likely to be current users of calcium antagonists (15.3% versus 5.5%) and β-blockers (21.7% versus 14.4%). Once again, calcium antagonists were dispensed more frequently to cases (12.2% versus 8.0%) in the prior-use time window. Similarly, overall use of calcium antagonists and β-blockers was higher among cases than controls between cohort entry and index date. As expected, drug markers for cardiovascular disease, including nitrates, digoxin, and loop diuretics, were initiated more frequently in cases during the followup period.

Table 4.1 Hospital Discharge Diagnosis of the Cases

Cardiovascular Disease	ICD-9 Codes	n	Percent
Ischemic Heart Disease:			
Myocardial Infarction	410	91	27.8
Angina	413	43	13.2
Other	411,412,414	72	22.0
Heart failure	428	58	17.7
Stroke	433-437	63	19.3
		327	100

Table 4.2 Characteristics of Cases and Controls

Characteristics	Cases (n=327)	Controls (n=3270)
Age in years (mean ± SD) ¶	70.9 ± 9.8	67.6 ± 10.3
Male (%)	62.7	49.8
Social Assistance (%)*	8.3	7.7
Duration of followup (mean in years) §	2.6	2.6
Anti-diabetic Therapy (%) †		
Insulin only	18.4	23.8
Oral hypoglycemic only	62.7	55.0
Both	19.0	21.3
Duration of diabetes (%)‡		
Less than 5 years	54.4	56.6
5 years or greater	45.6	43.4
Compliance to antihypertensive therapy (%)	28.8	25.0
Medication use £		
Respiratory	8.3	8.0
Lipid-lowering	3.7	2.4
Glucocorticoids	4.0	4.6
Neurotropic	27.5	26.9
Anti-parkinsonian	0.3	1.0
NSAIDs	35.2	39.0
Anticonvulsant	3.1	3.3
Anti-ulcer	12.8	11.9

¶ Age at index date
§ Followup defined: (index date - cohort entry date)
* At cohort entry
† Anti-diabetic therapy evaluated from the first prescription of an antihyperglycemic agent to the index date
£ Prior to cohort entry
‡ Duration of diabetes calculated in years from the first prescription of an antidiabetic agent to index date

Table 4.3 Patterns of Drug Use Among Cases And Controls

	Cases (n=327)	Controls (3270)
Antihypertensive Medications		
Initial Therapy (%)*		
ACE-I	0.003	0.006
β-Blocker	20.2	15.6
Calcium antogonist	6.4	2.9
Diuretics	59.9	64.1
Other£	13.2	16.7
Current Use (%)§		
ACE-I	4.6	4.4
β-Blocker	21.7	14.4
Calcium antagonist	15.3	5.5
Diuretics	42.8	44.3
Other£	14.4	15.9
None	22.6	28.9
Single class ¶	59.0	59.4
Multiple class †	18.3	11.7
Prior Use (%) ‡		
ACE-I	5.2	5.4
β-Blocker	22.6	22.7
Calcium antagonist	12.2	8.0
Diuretics	57.5	61.3
Other£	17.7	23.7
Any Use ¥		
ACE-I	6.4	6.3
β-Blocker	31.8	27.4
Calcium antagonist	17.7	9.3
Diuretics	70.3	75.0
Other£	22.9	28.7
Other Medications (%) [a]		
Nitrates	23.6	6.0
Digoxin	8.9	5.1
Loop diuretics	14.4	7.2

* Initial drug use refers to the antihypertensive agent at cohort entry
§ Current use refers to the drug availability in the 90 days prior to index date
¶ Single class refers to exposure to a only one class of an antihypertensive drug during the 90-day current time window
† Multiple class refers to exposure to a more than one class of an antihypertensive drug during the 90-day current time window
‡ Prior use defined as dispensing on an antihypertensive agent between cohort entry and the 90-day current time window
¥ Any use defined as dispensing on an antihypertensive agent between cohort entry and the index date
[a] Drug markers for cardiovascular disease: nitrates (ischemic heart disease), digoxin (heart failure, arrhythmia), loop diuretics (heart failure) initiated between cohort entry and index date
£ Other includes peripheral vasodilators, centrally-acting α_2-agonists, and α-blockers

4.3 Analysis of Risk

4.3.1 Unadjusted RR for Cardiovascular Disease

4.3.1.1 Current Use Analysis

Table 4.4 presents the results of the unadjusted analysis. Throughout, current use of diuretics was used as the reference group. In this analysis, the risk ratio was adjusted for other antihypertensive medications, but was not adjusted for potential confounders. Current use of calcium antagonists showed a statistically significant increase risk of cardiovascular disease (RR=3.25; 95% CI 2.23-4.71). Although lower in magnitude, users of β-blockers had a 60% increase in risk relative to diuretic users (RR=1.60; CI 1.18-2.18). Current exposure to ACE-I and other antihypertensive medications, including peripheral vasodilators, centrally-acting α_2-agonists, and alpha-blockers, was not associated with cardiovascular disease.

4.3.1.2 Any Use Analysis

One hypothesis of this study was that use of an antihypertensive drug any time between cohort entry and index may potentially affect cardiovascular risk. As shown in Table 4.4, any use of calcium antagonists increased risk by more than 2-fold (RR=2.30: CI 1.64-3.23). There was also a 19% risk increase with β-blockers and 25% risk reduction with other antihypertensive drugs, however, the confidence intervals for both estimates included the null value (RR=1.19; CI 0.93-1.54 and RR= 0.75; CI 0.57-0.98, respectively).

Table 4.4 Unadjusted Risk Ratios for Cardiovascular Disease Associated with Antihypertensive Drugs

Antihypertensive Drug*	Unadjusted Risk Ratio§	95% CI
Current Use Analysis:		
Diuretics‡	---	---
β-Blockers	1.60	1.18 - 2.18
ACE-I	0.96	0.53 - 1.76
Calcium Antagonists	3.25	2.23 - 4.71
Other†	0.96	0.68 - 1.35
Any Use Analysis:		
Diuretics‡	---	---
β-Blockers	1.19	0.93 – 1.54
ACE-I	0.96	0.56 - 1.63
Calcium Antagonists	2.30	1.64 - 3.23
Other†	0.75	0.57 - 0.98

* Current-use time window defined as use within 90 days prior to index date
§ Case and controls matched on the month and year of cohort entry
‡ Current use of diuretics served as the reference group
† Other includes peripheral vasodilators, centrally-acting α_2-agonists, and α-blockers

4.3.2 Predictors of Cardiovascular Disease

Each predictor was evaluated individually in the model. Gender and the use of oral hypoglycemic agents only were predictors of outcome (Table 4.5). Age was notably associated with risk of cardiovascular disease, with the risk increasing by 3% for each 1-year increase in age. Moreover, initiation of pharmacologic therapy for the treatment of angina, arrhythmia, and congestive failure between cohort entry and the index date was strongly associated with cardiovascular disease. There was 4.8-fold increase in risk with nitrate use, a 2.2-fold increase with loop diuretics, and a 1.8-fold increase with digoxin.

Table 4.5 Evaluation of Predictors of Cardiovascular Events

Variable	Unadjusted Rate Ratio[§]	95% CI
Gender	1.69	1.34 - 2.14
Age at index date, years	1.03	1.02 - 1.05
Social assistance	1.09	0.72 - 1.64
Duration of diabetes over 5 years	1.09	0.87 - 1.38
Anti-diabetic therapy		
Insulin only	0.72	0.54 - 0.97
Oral hypoglycemic only	1.38	1.09 - 1.75
Both	0.87	0.65 - 1.16
Compliance to antihypertensive therapy	1.27	0.95 - 1.68
Cardiovascular Medication Use[¶]		
Nitrates	4.78	3.60 - 6.44
Loop diuretics	2.24	1.59 - 3.17
Digoxin	1.81	1.20 - 2.73
Medication use[£]		
Respiratory	1.06	0.68 - 1.63
Lipid-lowering	1.61	0.85 - 3.03
Glucocorticoids	0.87	0.48 - 1.58
Neurotropic	1.07	0.82 - 1.34
Anti-parkinsonian	0.30	0.04 - 2.22
NSAIDs	0.83	0.65 - 1.06
Anticonvulsant	0.92	0.47 - 1.78
Anti-ulcer	1.12	0.79 - 1.59

[§] Case and controls matched on the month and year of cohort entry
[¶] Drug markers for cardiovascular disease: nitrates (ischemic heart disease), digoxin (heart failure, arrhythmia), loop diuretics (heart failure) initiated between cohort entry and index date.
[£] Prior to cohort entry

4.3.3 Distribution of Potential Confounders among Controls According to Current Antihypertensive Drug Exposure

In a case-control study, a preliminary assessment of confounding is made by determining the association between the potential confounder and the exposure variable of interest among controls. The results of this analysis are presented in Table 4.6. If the association between current exposure to an antihypertensive drug and the covariate differs from the association between the reference group and the covariate, then this discrepancy is suggestive of confounding.

As with the reference category, the proportion of controls with a current exposure to an antihypertensive medication was remarkably higher in the older age category, with the exception of other antihypertensive drugs. A higher proportion of controls currently exposed to peripheral vasodilators, centrally-acting α_2-agonists, and α-blockers were in the younger age category. Among controls that were users of calcium antagonists, a higher percent were older as compared with the reference group (85.6% versus 75.2%). In comparison to the controls currently exposed to diuretics, females were slightly less well-represented among users of β-blockers, ACE-I, and calcium antagonists. A greater proportion of controls on diuretics were receiving social assistance at the time of cohort entry.

Antidiabetic medications were differentially distributed among the reference group and the antihypertensive drug exposure categories. Among users of ACE-I and calcium antagonists, approximately 43% and 38% of

controls, respectively, were prescribed both insulin and oral hypoglycemic agents during the course of their disease, as compared to the reference group, where only 19% of controls were exposed to both agents. Relative to users of diuretics, fewer controls currently exposed to ACE-I and calcium antagonists were users of oral hypoglycemic drugs. Insulin was more likely to be the drug of choice for current users of other antihypertensive medications.

Compliance to antihypertensive therapy was markedly greater among patients on ACE-I or calcium antagonists than those on diuretics. Among controls, drugs for the treatment of high blood pressure were not differentially prescribed to subjects with different duration of diabetes, nor among subjects with different comorbidities.

As expected, a correlation was found between current use of an antihypertensive medication and past use of the same drug. Relative to the reference group, more current users of ACE-I and calcium antagonists were previous users of β-blockers and other antihypertensive drugs. Prior use of ACE-I was higher among controls with current exposure to calcium antagonists than those with current exposure to diuretics. Similarly, previous prescription of calcium antagonists occurred more frequently among controls with current use of ACE-I. As well, prior use of diuretics was notably higher among users of ACE-I.

Initiation of medications used as drug markers for cardiovascular disease was heterogeneous among the reference group and the current users of β-blockers, ACE-I, calcium antagonists, and other antihypertensive

drugs. The proportion of controls on nitrates was remarkably higher in subjects with current exposure to calcium antagonists (32.2%), ACE-I (13.1%), and β-blockers (14.7%), than in subjects on diuretics (4.0%). Initiation of digoxin also occurred more commonly among patients currently using calcium antagonists. Once again, loop diuretics were differentially prescribed among current users of antihypertensive drugs. The highest percent of controls taking loop diuretics was found among current users of ACE-I, while the lowest proportion was found among the reference group.

The following conclusions are derived from the bivariate analysis:

- Current exposure to β-blockers was associated with gender and nitrate use
- Current exposure to ACE-I was associated with gender, antihyperglycemic medications, compliance to antihypertensive therapy, prior use of antihypertensive medications, including β-blockers, calcium antagonists, and other antihypertensive drugs, as well as the initiation of therapy for cardiovascular disease, namely the use of nitrates, digoxin, and loop diuretics.
- Current exposure to calcium antagonists was associated with age, gender, antihyperglycemic medications, compliance to antihypertensive therapy, prior use of antihypertensive medications, including ACE-I, β-blockers, and other antihypertensive drugs, as well as the initiation of therapy for cardiovascular disease, namely the use of nitrates and loop diuretics.

- Current exposure to other antihypertensive drugs was associated with age and antihyperglycemic medications.

Table 4.6 Distribution of Confounding Variables among Controls According to Current Antihypertensive Drug Exposure*

	Diuretics (Reference)	β-Blockers	ACE-I	Calcium Antagonists	Others
	%	%	%	%	%
Age, at index date					
• < 60 years	24.8	37.0	24.1	14.4	77.7
• ≥ 60 years	75.2	62.9	75.9	85.6	22.3
Age in years (mean ± SD) ¶	67.6	64.0 ±9.9	67.3 ±9.4	69.8 ±9.4	67.1 ±9.3
Gender (% male)	45.9	60.4	56.6	58.3	48.2
Social Assistance ‡	8.2	7.2	4.8	5.6	6.2
Anti-diabetic Therapy †					
• Insulin only	24.5	24.7	24.8	18.9	41.0
• Oral hypoglycemic	56.2	58.7	33.1	43.3	59.0
• Both	19.3	16.6	42.7	37.8	22.0
Duration of diabetes §					
• Less than 5 years	54.6	61.3	62.8	58.9	55.7
• 5 years or greater	45.4	38.7	37.2	41.1	44.3
Compliance to antihypertensive therapy	33.0	43.8	62.8	54.4	43.0
Medication use £					
• Respiratory	7.9	7.9	7.6	5.6	7.9
• Lipid-lowering	2.3	3.2	6.9	6.1	2.5
• Glucocorticoids	4.8	4.0	4.8	5.0	3.3
• Neurotropic	29.2	26.6	23.5	30.0	21.2
• Anti-parkinsonian	0.9	0.9	0.0	0.6	.8
• NSAIDs	41.6	40.0	35.9	46.1	37.8
• Anticonvulsant	3.2	3.2	2.8	6.7	3.3
• Anti-ulcer	10.4	12.6	16.2	18.9	9.83

Table 4.6 Distribution of Confounding Variables among Controls According to Current Drug Exposure*

	Diuretics (Reference)	β-Blockers	ACE-I	Calcium Antagonists	Others
	%	%	%	%	%
Prior Use ¥					
• ACE-I	3.2	3.2	80.7	18.9	2.1
• β-Blocker	13.3	67.5	50.3	37.2	14.6
• Calcium antagonist	3.5	8.1	31.7	76.1	3.9
• Diuretics	68.7	39.4	74.5	55.0	40.1
• Other	14.1	16.7	35.2	27.8	68.6
Cardiovascular medication use [a]					
• Nitrates	4.0	14.7	13.1	32.2	2.1
• Digoxin	6.1	2.3	12.4	7.8	3.5
• Loop diuretics	5.5	6.0	22.1	16.1	5.8

* Current-use time window defined as use within 90 days prior to index date
¶ Age at index date
‡ At cohort entry
† Anti-diabetic therapy evaluated from the first prescription of an antihyperglycemic agent to the index date
§ Duration of diabetes calculated in years from the first prescription of an antidiabetic agent to index date
£ Prior to cohort entry
¥ Prior use defined as dispensing of an antihypertensive agent between cohort entry and the 90-day current time window
[a] Drug markers for cardiovascular disease: nitrates (ischemic heart disease), digoxin (heart failure, arrhythmia), loop diuretics (heart failure) initiated between cohort entry and index date

4.3.4 Assessment of Confounding: *Current Use Analysis*

One of the methods by which confounding may be appreciated is by comparing the crude and adjusted estimates of the association. If a discrepancy exists between the unadjusted risk estimate and the adjusted risk estimate, then the variable of interest is a possible confounder. For the purposes of this analysis, a change in risk estimate by 10% or more was considered to be indicative of confounding. Table 4.7 and Table 4.8 present the crude risk ratio for current calcium antagonist use and current β-blocker use, as well as the risk ratio when the individual potential confounding variables were included in the model.

With regards to current calcium antagonist use, the only variable that changed the risk estimate by more than 10% was nitrate use. Specifically, with the addition of this covariate, the risk ratio decreased from 3.25 (95% CI 2.23-4.71) to 1.91 (95% CI 1.27-2.88). All other variables were not found to change the estimate in risk. As for current use of β-blockers, the risk of cardiovascular disease increased from 1.60 (95% CI 1.19-2.19) to 1.92 (95% CI 1.40-2.62) when age at index date was considered in the model. Also, nitrate use decreased the risk ratio to 1.22 (95% CI 0.88-1.69). Once again, all other potential confounders were not believed to be important as they did not notably modify the risk ratio. Of note, gender did change the risk of cardiovascular disease with current use of β-blockers, however, the risk ratio only decreased by approximately 5%. This degree of change in the risk estimate was not considered to be significant. The analysis did not reveal

any important confounders in the association of current use of ACE-I and current use of other antihypertensive drugs and the risk of cardiovascular disease.

Table 4.7 Potential Confounding Variables on the Association of Current Calcium Antagonist Use and Cardiovascular Events

Variable	Risk Ratio[§]	95% CI
Current calcium antagonists[*] (unadjusted)	3.25	2.23 - 4.71
Adjusted individually for the following:		
Gender	3.08	2.11 - 4.49
Age at index date, years	3.22	2.21 - 4.70
Social assistance	3.26	2.24 - 4.74
Duration of diabetes over 5 years	3.24	2.23 - 4.71
Anti-diabetic therapy		
Insulin only	3.19	2.19 - 4.64
Oral hypoglycemic only	3.36	2.31 - 4.89
Both	3.36	2.31 - 4.90
Compliance to antihypertensive therapy	3.27	2.24 - 4.76
Cardiovascular Medication Use[¶]		
Nitrates	1.91	1.27 - 2.88
Loop diuretics	3.05	2.09 - 4.45
Digoxin	3.20	2.20 - 4.66
Medication use[£]		
Respiratory	3.27	2.21 - 4.35
Lipid-lowering	3.21	2.19 - 4.88
Glucocorticoids	3.22	2.30 - 4.98
Neurotropic	3.20	2.23 - 4.68
Anti-parkinsonian	3.20	2.18 - 4.46
NSAIDs	3.23	2.20 - 4.70
Anticonvulsant	3.29	2.25 - 4.99
Anti-ulcer	3.24	2.22 - 4.75

[*] Current-use time window defined as use within 90 days prior to index date
[§] Case and controls matched on the month and year of cohort entry
[¶] Drug markers for cardiovascular disease: nitrates (ischemic heart disease), digoxin (heart failure, arrhythmia), loop diuretics (heart failure) initiated between cohort entry and index date.
[£] Prior to cohort entry

Table 4.8 Potential Confounding Variables on the Association of Current β-Blocker Use and Cardiovascular Events

Variable	Risk Ratio[§]	95% CI
Current β-Blocker use [*] (unadjusted)	1.60	1.18 - 2.18
Adjusted individually for the following:		
Gender	1.51	1.11 - 2.05
Age at index date, years	1.92	1.40 - 2.62
Social assistance	1.61	1.18 - 2.18
Duration of diabetes over 5 years	1.61	1.19 - 2.19
Anti-diabetic therapy		
Insulin only	1.60	1.18 - 2.17
Oral hypoglycemic only	1.60	1.17 - 2.16
Both	1.60	1.18 - 2.17
Compliance to antihypertensive therapy	1.62	1.19 - 2.20
Cardiovascular medication Use[¶]		
Nitrates	1.22	0.88 - 1.69
Loop diuretics	1.62	1.19 - 2.20
Digoxin	1.66	1.22 - 2.25
Medication use[£]		
Respiratory	1.58	1.17 - 2.15
Lipid-lowering	1.57	1.12 - 2.20
Glucocorticoids	1.62	1.19 - 2.16
Neurotropic	1.60	1.17 - 2.24
Anti-parkinsonian	1.62	1.20 - 2.20
NSAIDs	1.56	1.19 - 2.22
Anticonvulsant	1.63	1.12 - 2.25
Anti-ulcer	1.60	1.20 - 2.19

[*] Current-use time window defined as use within 90 days prior to index date
[§] Case and controls matched on the month and year of cohort entry
[¶] Drug markers for cardiovascular disease: nitrates (ischemic heart disease), digoxin (heart failure, arrhythmia), loop diuretics (heart failure) initiated between cohort entry and index date.
[£] Prior to cohort entry

4.3.5 Assessment of Confounding: *Any Use Analysis*

The confounders in the association between the risk of cardiovascular disease and any use of antihypertensive drugs (table 4.9 and Table 4.10) were found to be similar to those covariates identified in the previous section. After adjusting for nitrate therapy, the risk ratio for current use of calcium antagonists decreased remarkably from 2.30 (95% CI 0.92-1.94) to 1.34 (95% CI 0.92-1.94). None of the other variables were found to confound the association between calcium antagonist use and cardiovascular disease.

In the model assessing any use of β-blockers and risk of cardiovascular disease, there were marked alterations in the risk ratio only when age and nitrate therapy were considered. The risk ratio increased from 1.19 (95% CI 0.93-1.54) to 1.35 (95% CI 1.04-1.74) when adjusted for age at index date. Likewise, when nitrate therapy was considered in the model, the risk ratio decreased to 0.96 (95% CI 0.74-1.25). However, as with the unadjusted risk ratio, the confidence interval for the estimate included the null value. Regarding the association between cardiovascular outcomes and any use of ACE-I and other antihypertensive agents, no significant confounders were identified.

Table 4.9 Potential Confounding Variables on the Association of Any Calcium Antagonist Use and Cardiovascular Events

Variable	Risk Ratio[§]	95% CI
Any calcium antagonists	2.30	1.64 - 3.23
Adjusted individually for the following:		
Gender	2.19	1.56 - 3.08
Age at index date, years	2.26	1.60 - 3.17
Social assistance	2.31	1.65 - 3.24
Duration of diabetes over 5 years	2.30	1.64 - 3.22
Anti-diabetic therapy		
Insulin only	2.28	1.62 - 3.20
Oral hypoglycemic only	2.40	1.71 - 3.37
Both	2.37	1.69 - 3.34
Compliance to antihypertensive therapy	2.25	1.60 - 3.16
Cardiovascular medication Use[¶]		
Nitrates	1.34	0.92 - 1.94
Loop diuretics	2.17	1.54 - 3.05
Digoxin	2.27	1.62 - 3.19
Medication use[£]		
Respiratory	2.30	1.64 - 3.23
Lipid-lowering	2.27	1.62 - 3.19
Glucocorticoids	2.30	1.64 - 3.22
Neurotropic	2.30	1.64 - 3.23
Anti-parkinsonian	2.29	1.63 - 3.21
NSAIDs	2.32	1.65 - 3.25
Anticonvulsant	2.31	1.64 - 3.24
Anti-ulcer	2.29	1.63 - 3.22

* Any-use time window defined as use between cohort entry and index date
§ Case and controls matched on the month and year of cohort entry
¶ Drug markers for cardiovascular disease: nitrates (ischemic heart disease), digoxin (heart failure, arrhythmia), loop diuretics (heart failure) initiated between cohort entry and index date.
£ Prior to cohort entry

Table 4.10 Potential Confounding Variables on the Association of Any β-Blocker Use and Cardiovascular Events

Variable	Risk Ratio[§]	95% CI
Any β-Blocker use[*] (unadjusted)	1.19	0.93 - 1.54
Adjusted individually for the following:		
Gender	1.14	0.88 - 1.46
Age at index date, years	1.35	1.04 - 1.74
Social assistance	1.20	0.93 - 1.54
Duration of diabetes over 5 years	1.19	0.93 - 1.54
Anti-diabetic therapy		
Insulin only	1.19	0.93 - 1.53
Oral hypoglycemic only	1.19	0.93 - 1.53
Both	1.19	0.93 - 1.54
Compliance to antihypertensive therapy	1.17	0.91 - 1.51
Cardiovascular medication use[¶]		
Nitrates	0.96	0.74 - 1.25
Loop diuretics	1.21	0.94 - 1.55
Digoxin	1.21	0.94 - 1.56
Medication use[£]		
Respiratory	1.19	0.93 - 1.54
Lipid-lowering	1.19	0.93 - 1.53
Glucocorticoids	1.19	0.93 - 1.53
Neurotropic	1.19	0.93 - 1.54
Anti-parkinsonian	1.19	0.93 - 1.53
NSAIDs	1.19	0.93 - 1.53
Anticonvulsant	1.19	0.93 - 1.53
Anti-ulcer	1.19	0.93 - 1.54

[*] Any-use time window defined as use between cohort entry and index date
[§] Case and controls matched on the month and year of cohort entry
[¶] Drug markers for cardiovascular disease: nitrates (ischemic heart disease), digoxin (heart failure, arrhythmia), loop diuretics (heart failure) initiated between cohort entry and index date.
[£] Prior to cohort entry

4.3.6 Assessment of Effect Modification

It was hypothesized that certain variables could modify the effect of current antihypertensive drug use on cardiovascular risk. The effect modifiers considered were prior antihypertensive drug use and initiation of therapy for treatment of angina (nitrate), congestive heart failure (loop diuretics, digoxin), and arrhythmia (digoxin). As well, the risk of an outcome associated with the current use of one class of medication may be altered by the concurrent use of another class of high blood pressure medication. No modification was found in relation to prior use of antihypertensive drugs or with the use of cardiovascular medication. However, the interaction term created between current use of ACE-I and other antihypertensive drugs was significant (p-value=0.0003). Therefore, the risk associated with the current use of ACE-I was modified, depending on whether or not a subject was concurrently receiving a drug in the *other* category. Similarly, the risk associated with current use of other antihypertensive medications was altered if a subject was also prescribed an ACE-I.

4.3.7 Multivariate Analysis

The current exposure categories of antihypertensive drugs, potential confounders, predictors of cardiovascular disease, and clinically relevant variables were considered in the final model.

4.3.7.1 Final Model: *Current Use Analysis*

The results of multivariate analysis are detailed in Table 4.11. The risk ratios for each category of current antihypertensive drug exposure, with adjustment for effect modification for ACE-I are included in the table. The current use of β-blockers was not found to be associated with the risk of cardiovascular disease (RR=1.35; 95% CI 0.96-1.90). However, current calcium antagonist use increased risk by 90% (RR=1.90; 95% CI 1.25-2.91) relative to diuretic use. Similarly, current users of ACE-I that were also current users of other antihypertensive drugs had a 7.8-fold increase in the risk of disease (RR=7.86; 95% CI 2.25-27.43). The risk ratio for current use of ACE-I without this other class of drugs may be suggestive of a protective effect, however, the confidence interval of the risk estimate includes the null value (RR=0.61; 95% 0.29-1.28).

Gender and age at index date continued to be predictors of cardiovascular disease to a similar magnitude in the adjusted analysis. Initiation of digoxin therapy was no longer a predictor of outcome. This finding contrasted the effects of nitrates and loop diuretics, which continued to be important predictors of cardiovascular disease in the adjusted analysis.

4.3.7.2 Multivariate Analysis: *Any Use Analysis*

Table 4.12 presents the result of risk ratios for any use of antihypertensive drugs and risk of cardiovascular disease adjusted for gender, social assistance at cohort entry, age at index date, compliance to antihypertensive therapy, duration of diabetes, antidiabetic therapy, drug use for the treatment of angina (nitrates), congestive heart failure (loop diuretics, digoxin), arrhythmia (digoxin), as well as medication use for the treatment of dyslipidemia, seizure disorder, respiratory illness, Parkinson's disease, ulcers, arthritides, mental disease, and use of NSAIDs.

None of the exposure categories were shown to be significant. All of the confidence intervals for each risk estimate included the null value.

Table 4.11 Multivariate Analysis: Final Model for the Current Use of Antihypertensive Drugs and Risk of Cardiovascular Events

Antihypertensive Drug*	Adjusted Risk Ratio§	95% CI
Current use* of:		
Diuretics‡	—	—
β-Blockers	1.35	0.96 - 1.90
Calcium Antagonists	1.90	1.25 - 2.91
ACE-I		
With other antihypertensives	7.86	2.25 - 27.4
Without other antihypertensives	0.61	0.29 - 1.28
Gender	1.53	1.19 - 1.96
Age at index date, years	1.03	1.02 - 1.05
Social assistance	1.14	0.74 - 1.76
Duration of diabetes over 5 years	1.10	0.86 - 1.41
Anti-diabetic therapy ¥		
Insulin only	0.77	0.57 - 1.06
Both	0.62	0.44 - 0.86
Compliance to antihypertensive therapy	0.96	0.67 - 1.37
Cardiovascular Medication Use¶		
Nitrates	3.57	2.53 - 5.05
Loop diuretics	1.85	1.26 - 2.72
Digoxin	1.08	0.68 - 1.72
Medication use£		
Respiratory	0.88	0.56 - 1.37
Lipid-lowering	1.71	0.86 - 3.64
Glucocorticoids	0.92	0.49 - 1.70
Neurotropic	1.02	0.77 - 1.35
Anti-parkinsonian	0.27	0.04 - 2.03
NSAIDs	0.77	0.59 - 0.99
Anticonvulsant	1.08	0.54 - 2.16
Anti-ulcer	1.01	0.69 - 1.47

* Current-use time window defined as use within 90 days prior to index date

§ Adjusted for gender, social assistance at cohort entry, age (years) at index date, compliance to antihypertensive therapy, duration of diabetes, antidiabetic therapy, drug use for the treatment of angina (nitrates), congestive heart failure (loop diuretics, digoxin), arrhythmia (digoxin), as well as medication use for the treatment of dyslipidemia, seizure disorder, respiratory illness, Parkinson's disease, ulcers, arthritides, mental disease, and use of NSAIDs. Final model includes interaction term for current use of ACE-I and other antihypertensive drugs

‡ Current use of diuretics served as the reference group

† Other includes peripheral vasodilators, centrally-acting α_2-agonists, and α-blockers

¶ Drug markers for cardiovascular disease: nitrates (ischemic heart disease), digoxin (heart failure, arrhythmia), loop diuretics (heart failure) initiated between cohort entry and index date.

£ Prior to cohort entry

¥ Comparison group was use of oral hypoglycemic agents only

Table 4.12 Multivariate Analysis: *Any Use Analysis*

Antihypertensive Drug*	Adjusted Risk Ratio§	95% CI
Diuretics‡	---	---
β-Blockers	1.01	0.77 - 1.33
ACE-I	0.79	0.44 - 1.41
Calcium Antagonists	1.27	0.56 - 1.86
Other†	0.74	0.55 - 0.98

* Any-use time window defined as use between cohort entry and index date
§ Adjusted for gender, social assistance at cohort entry, age (years) at index date, compliance to antihypertensive therapy, duration of diabetes, antidiabetic therapy, drug use for the treatment of angina (nitrates), congestive heart failure (loop diuretics, digoxin), arrhythmia (digoxin), as well as medication use for the treatment of dyslipidemia, seizure disorder, respiratory illness, Parkinson's disease, ulcers, arthritides, mental disease, and use of NSAIDs
‡ Any of diuretics served as the reference group
† Other includes peripheral vasodilators, centrally-acting α_2-agonists, and α-blockers

4.3.8 Assessment of Risk for Individual Cardiovascular Outcomes with Antihypertensive Therapy

4.3.8.1 Current Use Analysis

In addition to evaluating the risk of overall cardiovascular disease with various classes of antihypertensive therapy, risk assessment for individual cardiovascular outcomes was determined. The actual number of cases per classification are presented in Table 4.1. Table 4.13 presents these results for the current use analysis. With regards to the outcome *angina,* estimates could not be obtained for current use of ACE-I because of insufficient numbers.

All ischemic heart disease was assessed by combining cases of myocardial infarction, angina, and other ischemic heart disease. The multivariate analysis revealed that risk of this outcome was increased by 69% with current use of β-blockers (RR=1.69; 95% CI 1.11-2.59)and by 2.8-fold with current use of calcium antagonists (RR=2.82; 95% CI 1.68-4.74).

In terms of myocardial infarction and angina, the unadjusted risk ratios for current use of β-blockers and calcium antagonists showed an increased risk for outcome, however, these risk ratios were no longer significant when adjusted for potential confounders. Multivariate analysis showed that only current users of calcium antagonists were at a greater risk for other ischemic heart disease (RR=5.58; 95% CI 2.41-12.90). With regards to heart failure and stroke, no current exposure category were found to be associated with an

increased risk.

4.3.8.2 Any Use Analysis

Table 4.14 details the results of the risk assessment for individual cardiovascular outcomes with *any* antihypertensive exposure categories. Once again, the risk of angina associated with any use of ACE-I could not be obtained because of insufficient numbers. For all ischemic heart disease, there was 1.7-fold increase with β-blockers (RR=1.69; 95% CI 1.11-2.59) and a 2.8-fold increase with calcium antagonists (RR=2.82; 95% CI 1.68-4.74). With regards to angina, only the crude risk ratios were significant for any use of β-blockers and calcium antagonists. Any calcium antagonist use also increased the risk of ischemic heart disease by 2.5-fold (RR=2.5; 95% CI 1.20-5.20). In contrast, no significant results were found for the analysis of risk of myocardial infarction, heart failure, and stroke.

Table 4.13 Risk of Individual Cardiovascular Disease Outcomes with Antihypertensive Medications: Current-Use Analysis *

	ACE-I	β-Blockers	CCB	Others †
All ischemic heart disease ¶				
Unadjusted RR	0.76 (0.32-1.84)	2.22 (1.53-3.22)	5.15 (3.27-8.11)	0.77 (0.47-1.25)
Adjusted RR §	0.76 (0.29-1.98)	1.69 (1.11-2.59)	2.82 (1.68-4.74)	0.81 (0.49-1.34)
Myocardial infarction				
Unadjusted RR	1.03 (0.36-2.96)	1.81 (1.00-3.27)	2.84 (1.32-6.12)	0.96 (0.54-1.71)
Adjusted RR §	1.00 (0.32-3.16)	1.42 (0.73-2.79)	1.50 (0.60-3.75)	0.69 (0.32-1.50)
Angina				
Unadjusted RR	—	3.45 (1.55-7.71)	5.62 (1.88-16.8)	1.32 (0.51-3.42)
Adjusted RR §	—	2.20 (0.79-6.09)	1.83 (0.47-7.07)	0.87 (0.29-2.59)
Other				
Unadjusted RR	0.65 (0.12-3.55)	2.15 (1.17-3.97)	9.25 (4.45-19.2)	0.66 (0.26-1.65)
Adjusted RR §	1.04 (0.16-6.90)	1.84 (0.88-3.87)	5.58 (2.41-12.9)	0.92 (0.34-2.47)
Congestive heart failure				
Unadjusted RR	1.62 (0.53-4.98)	0.85 (0.38-1.94)	1.84 (0.71-4.75)	0.89 (0.39-2.02)
Adjusted RR §	1.32 (0.34-5.11)	1.07 (0.38-3.00)	0.89 (0.27-2.94)	0.62 (0.23-1.72)
Stroke				
Unadjusted RR	1.6 (0.53-4.98)	0.85 (0.38-1.94)	1.84 (0.71-4.75)	0.89 (0.39-2.02)
Adjusted RR §	1.03 (0.24-4.48)	0.80 (0.32-2.00)	0.48 (0.12-1.89)	1.80 (0.89-3.65)

*Current-use time window defined as use within 90 days prior to index date. For all current-use analysis, the reference group was current use of diuretics

§ Adjusted for gender, social assistance at cohort entry, age (years) at index date, compliance to antihypertensive therapy, duration of diabetes, antidiabetic therapy, drug use for the treatment of angina (nitrates), congestive heart failure (loop diuretics, digoxin), arrhythmia (digoxin), as well as medication use for the treatment of dyslipidemia, seizure disorder, respiratory illness, Parkinson's disease, ulcers, arthritides, mental disease, and use of NSAIDs

† Other includes peripheral vasodilators, centrally-acting α_2-agonists, and α-blockers

¶ Includes myocardial infarction, angina, and other ischemic heart disease

Abbreviations: RR=Risk Ratio, CCB=Calcium Antagonists

Table 4.14 Risk of Individual Cardiovascular Disease Outcomes with Antihypertensive Medications: Any-Use Analysis *

	ACE-I	β-Blockers	CCB	Others †
All ischemic heart disease ¶				
Unadjusted RR	0.67 (0.30-1.49)	1.62 (1.19-2.21)	3.32 (2.21-4.99)	0.65 (0.45-0.94)
Adjusted RR §	0.57 (0.24-1.35)	1.24 (0.88-1.75)	1.70 (1.06-2.73)	0.64 (0.44-0.94)
Myocardial infarction				
Unadjusted RR	1.12 (0.44-2.86)	1.33 (0.83-2.13)	1.94 (0.96-3.87)	0.68 (0.41-1.14)
Adjusted RR §	0.91 (0.32-2.54)	1.15 (0.68-1.94)	0.93 (0.39-2.20)	0.71 (0.41-1.22)
Angina				
Unadjusted RR	—	1.07 (1.07-4.00)	4.28 (1.73-10.6)	0.88 (0.39-1.93)
Adjusted RR §	—	1.12 (0.49-2.58)	1.83 (0.59-5.72)	0.69 (2.29-1.65)
Other				
Unadjusted RR	0.46 (0.09-2.37)	1.82 (1.09-3.06)	4.84 (2.53-9.27)	0.55 (0.27-1.10)
Adjusted RR §	0.45 (0.07-2.86)	1.35 (0.73-2.51)	2.50 (1.20-5.20)	0.55 (0.27-1.15)
Congestive heart failure				
Unadjusted RR	1.94 (0.75-4.98)	0.66 (0.34-1.26)	1.33 (0.58-3.04)	0.81 (0.43-1.52)
Adjusted RR §	1.63 (0.56-4.74)	0.76 (0.35-1.65)	0.80 (0.29-2.21)	0.63 (0.30-1.33)
Stroke				
Unadjusted RR	0.87 (0.26-2.90)	0.63 (0.33-1.19)	0.64 (0.22-1.94)	1.10 (0.62-1.95)
Adjusted RR §	0.97 (0.27-3.49)	0.66 (0.33-1.31)	0.43 (0.13-1.47)	1.11 (0.60-2.06)

*Any-use time window defined as use between cohort entry and index date. For all any-use analysis, the reference group was any use of diuretics

§ Adjusted for gender, social assistance at cohort entry, age (years) at index date, compliance to antihypertensive therapy, duration of diabetes, antidiabetic therapy, drug use for the treatment of angina (nitrates), congestive heart failure (loop diuretics, digoxin), arrhythmia (digoxin), as well as medication use for the treatment of dyslipidemia, seizure disorder, respiratory illness, Parkinson's disease, ulcers, arthritides, mental disease, and use of NSAIDs

† Other includes peripheral vasodilators, centrally-acting α_2-agonists, and α-blockers

¶ Includes myocardial infarction, angina, and other ischemic heart disease

Abbreviations: RR=Risk Ratio, CCB=Calcium Antagonists

4.4 Summary of Study Results

A population-based nested case-control study was conducted to determine the association between the use of antihypertensive drug use and the risk of cardiovascular disease. The main study findings are as follows:

1. Current calcium antagonist use was associated with a 90% increase in overall risk of cardiovascular disease relative to diuretic use. In contrast, use of these agents at any time during followup was not associated with an increased risk of cardiovascular disease.

2. The risk of cardiovascular disease for ACE-I relative to diuretics was found to vary across subgroups of patients. For patients not currently exposed to other antihypertensive drugs, including peripheral vasodilators, centrally-acting α_2-agonists, and α-blockers, there was no increased risk of cardiovascular disease. On the other hand, if current users of ACE-I were concurrently exposed to other antihypertensive drugs, the risk of outcome was increased by 7.8-fold.

3. Current use of β-blockers was not associated with an increased risk of cardiovascular disease.

4. Current use of calcium antagonists relative to diuretics was also associated with a 5.6-fold increase in the risk of other ischemic heart

disease. However, use of calcium antagonists at anytime during followup increased the risk of this outcome by 2.5-fold.

5. For all ischemic heart disease, current use of β-blockers relative to diuretics was associated with a 69% increase in risk, whereas current use of calcium antagonists relative to diuretics was associated with a 2.8-fold increase in risk. There was a 1.7-fold increase in the risk of all ischemic heart disease with the use of calcium antagonists at anytime during followup.

6. Independent predictors of cardiovascular disease in this study include age, gender, and the initiation of pharmacologic treatment for angina (nitrates) and heart failure (loop diuretics).

Chapter Five - DISCUSSION

The interpretation of the study findings, as well as a review of the methodological issues in this research are reviewed in the following chapter. A population-based nested case-control study was conducted in diabetic subjects with newly-diagnosed, uncomplicated hypertension in order to determine the association between the use of antihypertensive therapy and the occurrence of cardiovascular disease.

5.1 Risk of Cardiovascular Disease and the Use of Antihypertensive Therapy

The overall risk of cardiovascular disease was found to be higher among current users of calcium antagonists compared to current users of diuretics in this study. Although the magnitude of the risk estimates vary, the results of this research are in agreement with findings from several observational studies. However, a few studies did not show elevated risks of disease with calcium antagonists. The discrepancies among the studies may be related to differences in baseline characteristics of the participants. Pahor et al. (79;82;84) found that in a population of hypertensive subjects, the relative risk of mortality was 3.27 for use of the short-acting calcium antagonist, nifedipine, versus β-blocker use in a subset of diabetic patients. Yet, among the nondiabetic subpopulation, the relative risk of mortality was 1.36. Similarly, Alderman et al. (49;83) showed that the risk of

cardiovascular events was increased by almost 7-fold among diabetic patients using calcium antagonists compared to all other classes of antihypertensive medications. In another observational study, Heckbert et al.(85) showed that ACE-I relative to calcium antagonists were protective against fatal and nonfatal myocardial infarctions. Lastly, an 80% increase in the risk of all-cause mortality was found among calcium antagonist users relative to ACE-I users in another retrospective cohort study (86). Only one observational study (88), revealed that the use of calcium antagonists was not associated with an excess risk of cardiovascular events. However, these findings were based on a cohort of only 164 subjects.

The characteristics of the participants in the observational studies conducted in diabetic patients differ from our study subjects in several important aspects. Firstly, all of the previous studies used cohorts of prevalent cases of hypertension. Duration of hypertension and past exposure to antihypertensive medications were not accounted for in the analysis in previous studies. When considering current use of a drug as the exposure of interest, it is essential to consider past use of the same agent, as it may alter the magnitude of the risk estimate (123). Also, duration of hypertension may have biased the results in previous studies since it is a possible confounder. Duration of hypertension is directly related to overall risk of cardiovascular complications, as well, the prescribing practices of physicians may vary over time.

In the other studies, confounding by indication may have partially

explained the results since subjects with a previous history of cardiovascular disease were not excluded. Confounding occurs when the indication for the antihypertensive therapy, that is, previous history of cardiovascular disease, is associated with future risk of another cardiovascular outcome. It is also associated with the exposure, since physicians tend to prescribe antihypertensive therapy that has been shown to be effective in coronary heart disease. The discrepancy of results in previous observational studies, may also be explained by inconsistent outcome definition, ranging from all-cause mortality to the more specific outcome of myocardial infarction.

Exposure definition for cases and controls was also heterogeneous in prior research and in some studies, measurement of exposure was ambiguous. Current exposure was defined as the use of the agent within 2 weeks of the outcome or up to 6 months prior to the index date. In the study by Lindberg (86), exposure was defined as the drug prescribed at cohort entry and it is not evident if use just prior to the event was accounted for in the analysis. In one other study (79;82), exposure was defined as the use of the calcium antagonist, nifedipine, at any time during followup.

In our study, the main exposure of interest was the current exposure to an antihypertensive agent. Use of a drug at the time or around the time of an event is essential if the risk of an acute outcome to an antihypertensive drug is being studied. As with previous studies, we also attempted to determine if use of an agent at anytime during followup increased risk of disease. For current users of calcium antagonists, the risk of cardiovascular disease was

increased by 1.9-fold (RR=1.90; 95% CI 1.25-2.91), whereas, use of these same medications at anytime between cohort entry and the index date did not increase the risk of outcome (RR=1.27; 95% CI 0.56 1.86). This latter finding probably underestimates the true measure of risk in this study. Exposure measurement as *any use* is not sufficiently precise in the analysis of risk. For example, a subject in our database may have had dispensations of two prescriptions for a calcium antagonist 3 years prior to the event. However, it is almost impossible to believe that an agent taken a few years prior to the index date is actually responsible for the event. On the other hand, the risk of cardiovascular disease may be overestimated for current users of calcium antagonists. Current use was defined as exposure to an antihypertensive medication within 90 days of the index date. This group includes subjects that were recently initiated on the medication (less than or equal to 90 days), as well as subjects that were taking the medication for a longer period of time (greater than 90 days). It is possible that individuals recently given calcium antagonists were patients with more severe hypertension or perhaps patients manifesting early symptoms of ischemic heart disease. Therefore, it is possible to assume that the true estimate of risk in this study lies between 1.3 and 1.9.

Prior use of antihypertensive drugs was considered to be an important modifier of current use. However, due to negative findings in the multivariate analysis, this variable was excluded in the final model. Significant findings were probably not obtained because of an insufficient sample of patients.

The increased risk of cardiovascular disease with current use of calcium antagonists is biologically plausible. According to one explanation, diabetes results in changes in the composition of cellular membranes, and consequently, these alterations increase the affinity of lipophilic drugs such as calcium antagonists (40;84). However, others in this field have criticized this hypothesis on an experimental basis (124-126). In addition, calcium antagonists cause excessive sympathetic stimulation, and, thereby, may increase risk of myocardial infarction and mortality (78;79).

Contrary to many of the randomized trials (55;81;94;97;101) and two observational studies (85;86), protective effects of current ACE-I use was not demonstrated in our study. The cohort members were accrued between 1980 and 1986, during which time ACE-I were the newest agent on the market. Also, even though followup continued until December 31, 1996, only 25% of the subjects had index dates after January 1, 1987. The results are also difficult to interpret because there were only 15 cases and 144 controls that were current users of ACE-I, and consequently, the absolute numbers are too small to draw a conclusion. Current use of other antihypertensive drugs, including peripheral vasodilators, centrally-acting α_2-agonists, and α-blockers, was identified as an effect modifier of current use of ACE-I. In total, 14 subjects were found to be concurrently exposed to both of these classes of medications. The small number of patients precludes a final conclusion on this interaction. However, for all subjects, the ACE-I was added after the initiation of prazosin, methyldopa, clonidine, or hydralazine. Therefore, we

believe this group of individuals had more severe hypertension or more difficult to control disease and subsequently, were channeled into receiving this newer, second-line agent.

The crude estimates also showed an increased risk with the current use of β-blockers. However, this association was eliminated once adjustments were made for the various confounding variables, including demographic characteristics, antihyperglycemic therapy, compliance to antihypertensive therapy, duration of diabetes, comorbidities, and the initiation of other cardiovascular medications. This finding is consistent with the results of the randomized control trial, the United Kingdom Prospective Diabetes Study (UKPDS) (65), in which β-blockers were found to be equivalent to ACE-I.

A significant increase in risk with current use of calcium antagonists was only found for overall ischemic heart disease and other ischemic heart disease in the analysis of risk for individual cardiovascular outcomes. There was no association between calcium antagonist use and the risk of myocardial infarction, angina, congestive heart failure, and stroke. However, the number of subjects in each group was small and this may explain the negative findings.

Although the randomized clinical trial is the preferred method of evaluating the benefits and adverse effects of drug therapies, observational studies can also provide useful information. Controlled trials are usually conducted under special circumstances with strict protocol and a select group

of subjects. Entry criteria frequently exclude patients less likely to comply. Also, close monitoring during followup ensures that the subjects take the medications properly. Because of financial restraints, randomized clinical trials are at times limited by small sample size and short duration of followup. Despite the benefits of certain drugs in trials, the same medications sometimes prove to be ineffective after they are marketed in a population. Finally, the results of a clinical trial should be interpreted with caution if based on post hoc analysis (127). Of all the trials assessing risk of cardiovascular disease in association with antihypertensive agents in diabetic subjects, only three were not based on subgroup analysis, including FACET (81), ABCD (55), and UKPDS (93). On the other hand, observational studies provide information on subjects in a real life clinical setting. In our study, subjects were followed for a prolonged period of time, the longest duration of followup being over 15 years. Moreover, it was possible to study the effects of all the classes of antihypertensive medications simultaneously.

5.2 Methodologic Considerations

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

5.2.1 Selection Bias

One major limitation regarding previous observational studies evaluating the risk of cardiovascular disease and antihypertensive medication is that prevalent cohorts of hypertensive subjects were used. The prevalence of disease is related to the incidence, as well as the duration of disease. Consequently, prevalent patients may be characterized by some known or unknown prognostic factor that will bear on their risk of disease. When using prevalent cases of hypertension, results may be biased because subjects who experienced the outcome prior to cohort entry will not be included in the analysis. Consequently, with the inclusion of only the remaining "survivors" in the analysis, the true risk estimate may be biased toward the null. Therefore, new users may appear to be at higher risk than chronic users of medications. In our study, cohort members were diabetic subjects with newly diagnosed hypertension. Saskatchewan Outpatient Prescription Drug files were reviewed up to 24 months prior to cohort entry to ensure that prevalent cases were excluded from the source cohort. Only new users of antihypertensive drugs were included and the entire history of the drug profile was documented and adjusted for in the analysis. However, as discussed, prior

use was eliminated from the final model because it was not found to be a modifier of current antihypertensive drug use.

Another potential selection bias that affects pharmacoepidemiology is protopathic bias (128). This bias occurs if a medication is begun after the onset of clinical manifestations of the disease. For example, a calcium antagonist may be initiated in a subject after the onset of chest pain, which may be his first symptom of ischemic heart disease. If the subject later develops a myocardial infarction, an inaccurate positive association between the drug and the outcome would occur. A strength of our study is that all patients with markers for cardiovascular disease in the 24 months prior to cohort entry were excluded. However, in spite of this rigorous exclusion criteria, selection bias may still not have been completely eliminated since identification of subjects with silent ischemia was impossible in our database. Moreover, as mentioned in the previous section, it is possible that some subjects in our database experienced symptoms of ischemic heart disease (for example, chest pain) just prior to the initiation of a calcium antagonist. Unfortunately, identification of these individuals was impossible with the information available. New-onset angina during followup of the cohort was probably occurring since we found an association between nitrate use and cardiovascular disease. In fact, the risk of cardiovascular disease with calcium antagonist use decreased significantly once nitrate use was accounted for in the analysis. However, we do not believe that protopathic bias explains all of the effect seen in this study since, despite adjusting for

nitrate use in the final analysis, the positive association between calcium antagonists and risk of cardiovascular disease remained.

5.2.2 Information Bias

Errors in risk estimates may occur in epidemiologic research if misclassification of the exposure and outcome occur. In a case-control study, when classification of the exposure varies according to disease status, then differential information bias is present. In contrast, non-differential information bias is induced if errors in the measurement of exposure do not vary among case and controls (129). Pharmacoepidemiology is especially sensitive to non-differential information bias, since drug exposure is related to many factors that are difficult to measure and this limitation is equally distributed among cases and controls (128).

Misclassification bias was minimized in this study by using data from the Saskatchewan Health Branch. With each paid claim submitted to the Outpatient Prescription Drug Services database, information of the claimant is verified. A sample of paid claims is also sent directly to the beneficiary to ensure that the information is correct (119;120). In addition, validation of the accuracy of the Hospital Services Branch Database has been undertaken. Illogical entries are automatically recognized by the computer programs (120). In addition, excellent agreement has been observed in several validation studies between medical charts and the information in the Hospital Services Branch Database (118;122;130;131). Overall, the Saskatchewan

Health databases have shown to be accurate and comprehensive (119;120;122). Finally, misclassification was minimized by avoiding nondifferential recall of drug exposure. Exposure was measured equally for cases and controls.

One major limitation of using administrative databases is that drug dispensation does not automatically imply drug consumption. Current exposure in this study was defined as dispensation of at least one prescription of an antihypertensive agent within 90 days of the index date. In addition, no information is available on the duration of use or the quantity of medication dispensed. It was assumed that each prescription lasted for 30 days. Therefore, misclassification of exposure may have occurred if patients were not actually taking the medication. Also, some subjects may have been exposed continuously for the entire period, whereas other individuals may have been exposed only for a very short time. If risk estimates are believed to have a temporal association over the current-use time window, then the risk estimates could be distorted. Moreover, miscalculation of compliance may have occurred because of this lack of precise information on the number of days supplied with each prescription. Assuming a 30-day supply of medications with each prescription, subjects dispensed 9 or more prescriptions per year were considered compliant. However, the potential for error is evident if duration of each prescription was for a longer duration than the assumed 30-day time period. In this study, there is no reason to believe measurement of exposure was dependent on the case status of a subject.

However, nondifferential misclassification may have provided a conservative estimate of the risk.

Errors in measurement of outcome may have occurred, but as already outlined, information in this administrative database has proven to be accurate. With respect to myocardial infarction, 97% concordance was found between diagnoses in medical charts and data in the hospital computer files (118). The concordance varied between 79% and 94% for angina and other ischemic heart disease. The validity of heart failure and stroke has not been evaluated. However, all of the cardiovascular diseases used in the definition of the outcome are well-defined and well-recognized entities by physicians and therefore, we believe misclassification of the outcome is minimal. There has been much debate over the last few years on the use of calcium antagonist and myocardial infarction, and consequently, cases of cardiovascular disease may have been inappropriately diagnosed among users of calcium antagonists. However, ascertainment of disease was probably not systematically different among subjects exposed to different classes of antihypertensive agents since most of the study period occurred before the controversy.

Errors in the measurement of the confounding variables is another potential limitation of this research. Misclassification of some study subjects could have occurred because coexisting comorbidities prior to cohort entry and cardiovascular disease developing during followup were identified using drug markers only.

5.2.3 Confounding

Confounding by indication is probably the most important bias influencing pharmacoepidemiologic research (128;132). This bias occurs when a medication is selectively prescribed to an individual when thought to be indicated by the physician. Calcium antagonists are indicated not only for the treatment of hypertension, but also for ischemic heart disease. Therefore, if subclinical angina is suspected in a patient with high blood pressure, a physician will specifically prescribe a calcium channel blocker for this individual who is already at high risk of progressing to an acute myocardial infarction. In this hypothetical situation, calcium antagonists are given to a patient at high risk for an event, and consequently, the risk estimate associated with this class of medication will reflect the use of these drugs in response to subclinical disease.

Information on patient characteristics that may lead to confounding by indication such as, disease severity and presence of coexisting medical conditions, is not available in the administrative database of Saskatchewan. Also, there is a lack of information on other risk factors for cardiovascular disease, such as blood pressure values, glucose and cholesterol levels, and smoking. However, Psaty et al. (78) found there was no association between antihypertensive drug use and smoking.

In our study, considerable efforts were undertaken to minimize confounding by indication. First, strict inclusion criteria created a homogenous cohort of subjects with uncomplicated hypertension. Subjects

were not eligible for recruitment if coexisting cardiovascular disease was suspected based on their prescription profile and hospitalization data in the 2 years preceding cohort entry. Use of medications for several chronic pathologies was also adjusted for in the analysis. Furthermore, patients were stratified for the presence of cardiovascular pharmacologic treatment during the course of antihypertensive therapy. Adjustments for the use of nitrates, digoxin, and loop diuretics did attenuate the magnitude of the risk difference, thereby, implying that confounding by indication may have played a role in our findings.

Duration of hypertension was also accounted for in the design and cannot explain the results of this study. Each case was matched to ten randomly selected controls that initiated antihypertensive treatment in the same calender month and year as the case and were still at risk for an event at the time of matching. Furthermore, temporal factors that influence prescribing practices and hospitalizations for cardiovascular disease are inherently controlled for by this matching. Many unmeasured confounders are correlated with age and sex. However, cases and controls were not matched on these variables since we were interested in measuring their effects specifically in the analysis. In fact, these two variables were not found to be confounders in this study and consequently, it would have been unnecessary to match on these factors.

Despite our efforts, we believe that our results may be affected by confounding by indication to some extent due to unknown factors

unaccounted for in the analysis. Also, residual confounding may be present in this study since duration of diabetes was measured as a dichotomous variable instead of a continuous one. This bias occurs because there probably exists a difference in risk of disease within the categories created for duration of diabetes.

Chapter Six - CONCLUSIONS

The following conclusions may be drawn from this study:

- The current use of calcium antagonists relative to diuretics was associated with a clinically important risk of cardiovascular disease. There was no variability in risk according to prior use of antihypertensive treatment or the use of drug markers for cardiovascular disease.
- There was no association between cardiovascular disease and the use of β-blockers relative to diuretics. A significant increase in cardiovascular disease was associated with the use of ACE-I and other antihypertensive medications only if subjects were concurrently taking both.
- Independent prognostic factors for cardiovascular disease included age, gender, and the initiation of pharmacologic treatment of angina (nitrates) and heart failure (loop diuretics).

The results of this study further supports the fact that calcium antagonists are associated with an increased risk of cardiovascular disease. According to the recent Canadian guidelines for the management of hypertension (23), first- line therapy should include an ACE-I or a cardioselective β-blocker for patients with diabetes. These

recommendations are based on the findings of two recent trials, namely, UKPDS (93) and HOPE (94;101). We agree that on the basis of the available evidence, ACE-I, followed by a β-blocker and a diuretic should be the preferred agents of choice.

Perhaps the controversy pertaining to the use of calcium antagonists in the treatment of high blood pressure in subjects with diabetes will end with the findings of a number of ongoing trials. For instance, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT), is a randomized clinical trial comparing the effects of individual antihypertensive agents in the prevention of cardiovascular events in a population of high risk subjects with hypertension older than 55 years old (133). For the purposes of this study, 40 000 patients, 14 000 of whom have diabetes, have been randomized to a calcium antagonist (amlodipine), an ACE-I (lisinopril), an α-blocker (doxazosin), or a thiazide diuretic (chlorthalidone). The results should be available by 2002.

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APPENDICES

APPENDIX 1

Metabolic Profiles of Different Classes of Antihypertensive Therapy

	Thiazide-like	β-Blockers	Calcium Antagonist	ACE-Inhibitors	α_1-blockers	Others
Glycemia	↑	↑	-	-	-	-
Insulin Resistance	-↑	↑	-	-↓	↓	-
Lipid Metabolism:						
HDL	↓	↓	-	-	↑	-
LDL	↑	-	-	-	-	-
TG	-	↑	-	-	↓	-

Notes:

HDL = High-density lipoprotein cholesterol
LDL = Low-density lipoprotein cholesterol
TG = Triglycerides
↑ = Increase
↓ = Decrease
- = Neutral

APPENDIX 2

Observational Studies on the Association of Cardiovascular Disease and Antihypertensive Therapy in Diabetic Subjects

	Study Design	Cohort Definition	Study Population	Main Exposure	Primary Endpoint	Adjusted RR/OR
Warram et al.{927}	Cohort	Prevalent hypertension	759 subjects	Diuretics at cohort entry	Cardiovascular mortality	5.1 p<0.0001 Diuretics vs none
Pahor et al.{851}{984}	Cohort	Prevalent hypertension	N/A	Nifedipine at any time during f/u	Cardiovascular/non-cardiovascular events §	3.27 vs 1.36 Diabetic vs nondiabetic
Alderman et al.{985}{943}	Case-control	Prevalent hypertension	34 cases	Current use of CCB	Cardiovascular events †	6.85 (1.5-31.3) CCB vs other
Heckbert et al.{986}	Case-control	Prevalent hypertension	216 case 34 controls	Current use of ACE-I	Fatal or nonfatal myocardial infarct	0.48 (0.23-0.97) ACE-I vs CCB
Lindberg et al.{987}	Retrospective cohort	Prevalent hypertension	366 subjects	CCB or BB at cohort entry	All-cause mortality	1.78 (1.17-2.71) CCB vs ACE-I
Verdacchia et al.{37}	Retrospective cohort	Prevalent hypertension	164 subjects	Current use CCB	Cardiovascular events ‡	0.88 (0.47-1.67) CCB vs nonusers CCB

§ All-cause mortality, incident cancer, severe gastrointestinal bleeding, peri-operative blood transfusion
† Nonfatal MI, stroke, revascularization, congestive heart failure, ischemic heart disease, death due to cardiovascular disease
‡ Coronary artery disease, stroke, transient ischemic attacks, congestive heart failure, renal failure, aorto-iliac occlusion
Abbreviations: CCB=calcium channel blockers, BB=β-blockers, ACE-I-angiotensin converting enzyme inhibitor

APPENDIX 3
Randomized clinical trials of antihypertensive therapy in diabetic patients

	# of diabetic subjects	Diabetes as subgroup	Years of followup	Main treatment comparisons	Cardiovascular endpoints (primary or secondary)	RR/RRR: first drug to second drug (95%CI)
ABCD{923}	470	No	2	Nisoldipine vs Enalapril	Fatal or nonfatal MI	9.5 (2.3-21.4)
FACET{924}	380	No	2	Fosinopril vs Amlodipine	Combined MI, stroke, or angina	0.49 (0.26-0.95)
UKPDS{396}	758	No	9	Captopril vs Atenolol	Diabetes-related endpoints Diabetes-related death Strokes	-24% 8 - -38%) -32% (6 - -51%) -44% (11 - -65)
MIDAS{992}{928}	415	Yes	3	Isradipine vs Hydrochlorothiazide	Cardiovascular events or death	2.71 (1.07-6.86)
SHEP{816}	583	Yes	4.5	Chlorthalidone vs Placebo	Major cardiovascular events Major coronary heart disease	0.66 (0.46-0.94) 0.44 (0.25-0.77)
Sys-Eur {993}{850}	492	Yes	2	Nitredipine vs Placebo	Cardiovascular mortality Cardiovascular events Cardiac events	-70% (19 - -89%) -62% (19 - -80%) -57% (-6 - -82%)
CAPPP{921}	572	Yes	6	Captopril vs β-blockers or Thiazide-like diuretics	Fatal and nonfatal MI	0.34 (0.17-0.67)
HOPE{994}{443}	3577	Yes	4.5	Ramipril and Vitamin E vs Placebo	Myocardial infarct, stroke, or cardiovascular death	-25% (-12 - -36)

Abbreviations: RR=relative risk RRR= relative risk reduction

APPENDIX 4

Antihyperglycemic Drugs Used to Identify Diabetic Subjects

Insulin Preparations	Sulfonylureas	Biguanides
Regular	Acetohexamide	Phenformin
Lente	Chlorpropamide	Metformin
Semilente	Glyburide	
Ultralente	Tolbutamide	
Isophane		
Zinc Crystalline		
Premixed		
Sulfated		
Protamine Zinc		

APPENDIX 5

Antihypertensive Drugs Used to Identify Hypertensive Subjects

Thiazide-like	β-Blockers	Calcium	ACE-Inhibitors	Other
Hydrochloro-	Acebutolol	Nifedipine	Captopril	Methyldopa
Amiloride	Atenolol	Diltiazem	Enalapril	Clonidine
Chlorthalidone	Propanolol	Verapamil	Lisinopril	Hydralazine
Indapamide	Metoprolol	Nicardipine	Fosinopril	Minoxidil
Metolazone	Nadolol	Felodipine	Quinapril	Reserpine
Spironolactone	Labetolol	Amlodipine	Benazepril	Doxazosin
Triamterene	Oxprenolol		Ramipril	Guanethidine
	Timolol		Cilazapril	Bethanidine
	Sotolol		Perindopril	Debrisoquine
				Rauwolfia
				Prazosin
				Paragyline
				Diazoxide
				Terazosin

APPENDIX 6

List of Diagnosis Used to Exclude Cohort Members with Atherosclerotic Disease Prior to Cohort Entry

Hospital Discharge Diagnosis	ICD-9 Codes
Acute Myocardial Infarction	410
Other acute and subacute form of ischemic heart	411
Old myocardial infarction	412
Angina pectoris	413
Other forms of chronic ischemic heart disease	414
Heart failure	428
Stroke	433-437
Atherosclerosis	440

APPENDIX 7

ICD-9 Codes Used for the Identification of Case Patients

Cardiovascular Disease	ICD-9 Codes
Myocardial Infarction	410
Angina	413
Other ischemic heart disease	411,412,414
Heart failure	428
Stroke	433-437

APPENDIX 8

Drug Markers Used for Comorbidity Assessment in the Year Preceding Cohort Entry

Comorbidity	Medication
Dyslipidemia	Cholestyramine, Clofibrate, Colestipol, Fluvastin,
Seizure Disorder	Anticonvulsants
Respiratory Illness	β-adrenergic agents, Xanthines, Epinephrine,
Parkinson's Disease	Anti-Parkinsonian Agents
Ulcers	Histamine$_2$ blockers, Proton pump inhibitors
Respiratory	Glucocorticoids
Mental Disease/Anxiety	Major tranquilizers, Benzodiazepines, Anti-depressants,
NSAIDs	Diclofenac, Naprosyn, Indomethacin, Sulindac, Ibuprofen,