INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

ProQuest Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

UMI®

Antihypertensive drugs: Patterns of use

and biases in the estimation of myocardial infarction risk

Chantal Bourgault

Department of Epidemiology and Biostatistics
McGill University, Montreal

January 2000

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfilment of the requirements for the degree of
Doctor of Philosophy

ABSTRACT

In this thesis, we addressed different issues related to drug exposure as it may bear on the estimates of risk in the context of hypertension treatment. A cohort of 19,501 subjects initiating therapy for uncomplicated hypertension was identified from Saskatchewan Health databases. In a first study aimed at documenting the equivalence of the angiotensin-converting-enzyme (ACE) inhibitors, we found that medical visits and hospitalizations following treatment initiation were lower among patients initially dispensed enalapril and lisinopril relative to captopril. Baseline characteristics could not be ruled out as possible explanations but variability in the outcomes suggest that ACE inhibitors may not be equivalent in all respects. Due to concerns about the appropriateness of using initial treatment as the exposure, patterns of use of antihypertensive were examined longitudinally in the second manuscript using the same cohort. ACE inhibitors, followed by calcium antagonists and β-blockers, were the most commonly prescribed agents to initiate therapy for hypertension. Compliance with therapy was found to decrease over time with only 28% of patients still being compliant after seven years. In addition, 89% of patients underwent at least one modification to therapy, interrupted treatment being the most frequently encountered. Important differences were also found across agents with regard to compliance, type and timing of treatment modifications. The third manuscript reports on a case-control study assessing the association between antihypertensive drug use and the risk of myocardial infarction (MI). Overall, 812 cases of MI were identified using hospital discharge data and death certificates. Four controls were matched to each case on entry date and time at risk of an event. Compared with β-blockers, current use of calcium antagonists was associated with an increased risk of MI (RR=2.3; 95% CI=1.7-3.1). The risk ratio for ACE inhibitors was 1.3 (95% CI=1.0-1.7). Adjustment for markers of cardiovascular risk attenuated both associations and history of drug use was found to modify these associations. In the fourth manuscript, we showed using simulations that the assessment of effect modification in matched case-control studies is steadily more efficient when using a modelling approach, as opposed to a stratified analysis that accounts for the matched design. Overall, these findings show important variability in antihypertensive drug exposure and underline the importance of adequate documentation of the entire drug history and a comprehensive characterization of exposure in the valid estimation of effects in observational studies.

RÉSUMÉ

Cette thèse est consacrée à l'étude de l'utilisation des agents antihypertenseurs et de son impact sur la population. L'importance d'une définition adéquate de l'exposition aux médicaments y est discutée. A partir des données du régime d'assurance-santé de la Saskatchewan, une cohorte de 19,501 patients initiant un traitement pharmacologique pour le traitement de l'hypertension artérielle non compliquée a été identifiée. Une première étude documentant l'équivalence des inhibiteurs de l'enzyme de conversion de l'angiotensine (IECA) a révélé des taux de visites médicales et d'hospitalisations inférieurs chez les utilisateurs d'enalapril et de lisinopril, comparativement à captopril. Ces résultats suggèrent que les IECA ne sont peut-être pas équivalents à tous les points de vue. Doutant de la validité du traitement initial comme mesure d'exposition, les profils d'utilisation des agents antihypertenseurs ont été analysés dans le cadre de la seconde étude. Cette étude a démontré que les IECA, suivis des antagonistes calciques et des β-bloquants, sont les agents les plus fréquemment sélectionnés pour l'initiation d'un traitement. L'observance au traitement, diminuant dans le temps, est très faible: à peine 28% des patients étaient toujours sous thérapie à la fin de la période de suivi. De plus, 89% des patients ont modifié leur régime thérapeutique au moins à une reprise, les interruptions de traitement étant particulièrement fréquentes. D'importantes variations ont également été notées quant à l'observance au traitement, au type et au moment de la première modification au régime thérapeutique selon l'agent initial. Un devis cas-témoin a ensuite été utilisé pour évaluer le risque d'infarctus du myocarde en association avec l'utilisation d'agents antihypertenseurs. 812 cas d'infarctus ont été identifiés à l'aide des données d'hospitalisation et des certificats de décès. Quatre témoins ont été sélectionnés au hasard pour appariement à chacun des cas selon leur date d'entrée dans la cohorte et leur durée de suivi. Cette étude a démontré que comparativement aux β-bloquants, l'utilisation courante d'antagonistes calciques est associée à un risque deux fois plus élevé d'infarctus (RR=2.3; 95% CI=1.7-3.1). Le risque relatif associé à l'utilisation d'IECA est de 1.3 (95% CI=1.0-1.7). L'analyse ajustée pour les facteurs de risque cardiovasculaires montre des risques relatifs moindres. Cette étude a également démontré que l'histoire d'utilisation du médicament peut constituer un modificateur d'effet. Enfin, la quatrième étude compare deux méthodes courantes pour évaluer la présence de modificateurs d'effets dans le cadre d'études cas-témoins appariées. Une efficacité relative supérieure de l'approche par

modélisation, comparativement à l'analyse stratifiée, y est démontrée. En conclusion, ces études montrent de très grandes variations dans les profils d'utilisation des agents antihypertenseurs et souligne l'importance d'une définition adéquate de l'histoire d'utilisation du médicament dans l'évaluation des effets de ceux-ci dans la communauté.

TABLE OF CONTENTS

LIST OF TABLES, FIGURES AND APPENDICES

CHAPTER 1

CHAPTER 2

CHAPTER 6

CHAPTER 7

APPENDICES

PREFACE

This thesis consists of nine chapters, including the introduction (chapter 1), the literature review (chapter 2), a detailed methods section (chapter 3) and four manuscripts (chapters 4-7). The first three manuscripts report the main study findings. The first one investigates the putative equivalence of three agents that belong to the same antihypertensive drug class, the angiotensin-converting-enzyme (ACE) inhibitors, in terms of health services utilization (chapter 4). The second manuscript describes the varying patterns of use of antihypertensive agents (chapter 5) and the third one assesses the relative risk of myocardial infarction in relation to various antihypertensive agents (chapter 6). The fourth manuscript discusses methodological issues that relate to the conduct of the first three studies (chapter 7). The eighth chapter is a recapitulative discussion and critical appraisal of the study findings. Finally, chapter 9 provides an overall summary of the findings reported in the four manuscripts that constitute this thesis. To facilitate reading, references are provided at the end of the thesis whereas Tables and Figures are positioned at the end of each section.

University regulations require that the following paragraphs be integrated into the text of the thesis:

"1. Candidates have the option of including, as part of the thesis, the text of one or more papers submitted or to be submitted for publication, or the clearly-duplicated text (not the reprints) of one or more published papers. These texts must conform to the "Guidelines for Thesis Preparation" with respect to font size, line spacing and margin sizes and must be bound together as an integral part of the thesis. (Reprints of published papers can be included in the appendices at the end of the thesis.)

2. The thesis must be more than a mere collection of manuscripts. All components must be integrated into a cohesive unit with a logical progression from one chapter to the next. In order to ensure that the thesis has continuity, connecting text that provides logical bridges between the different papers are mandatory.

3. The thesis must conform to all other requirements of the "Guidelines for Thesis Preparation" in addition to the manuscripts. The thesis must include the following:

(a) a table of contents;

(b) an abstract in English and French;

(c) an introduction which clearly states the rationale and objectives of the research;

(d) a comprehensive review of the literature (in addition to that covered in the introduction to each paper);

(e) a final conclusion and summary.

4. As manuscripts for publication are frequently very concise documents, where appropriate, additional material must be provided (e.g., in appendices) in sufficient detail to allow clear and precise judgment to be made of the importance and originality of the research reported in the thesis.

5. In general, when coauthored papers are included in a thesis, the candidate must have made a substantial contribution to all papers included in the thesis. In addition, the candidate is required to make an explicit statement in the thesis as to who contributed to such work and to what extent. This statement should appear in a single section entitled "Contributions of Authors" as a preface to the thesis. The supervisors must attest to the accuracy of such statements at the doctoral oral defence. Since the task of the examiners is made more difficult in these cases, it is in the candidate's interest to clearly specify the responsibilities of all the authors of the coauthored papers.

6. When previously published copyright material is presented in a thesis, the candidate must obtain, if necessary, signed waivers from the coauthors and publishers and submit these to the Thesis office with the final deposition.

7. Irrespective of the internal and external examiners reports, if the oral defence committee feels that the thesis has major omissions with regard to the above guidelines, the candidate may be required to resubmit an amended version of the thesis. [...]

8. In no case can a coauthor of any component of such a thesis serve as an examiner for that thesis."

Contributions of Authors

This manuscript-based thesis includes four coauthored papers. In all cases, the candidate was responsible for conceptualizing, designing, analysing and reporting research results. These responsibilities included first all communications and negotiations with Saskatchewan Health to obtain the data. Dr Samy Suissa, the candidate's supervisor, obtained the funds necessary to cover the costs of the data and participated in the study design. These communications were entirely carried out by the

candidate, as were initial data cleaning and summary. The variables used for the purpose of the four studies were entirely defined by the candidate who also carried out all analyses. The programming of the second paper was in most part carried out by a research assistant, Mr. Bruno Rainville, under the direction of the candidate. The programming of the simulation study which is part of the fourth manuscript was performed with the help of two biostatisticians, Dr Michael Edwardes and Mr. Bing Cai. Finally, the four manuscripts composing this thesis were entirely written by the candidate, with revisions by the respective coauthors. Two coauthors of the manuscripts were members of the candidate's thesis supervisory committee (Drs Jacques Le Lorier and Eleanor Elstein). Throughout the process, they provided invaluable methodological and clinical advice as it pertains to the entire research program. The third manuscript is also coauthored by Dr Marc Baltzan, who contributed important information with regard to the clinical management of hypertensive and cardiac disease and who reviewed the death certificates.

The candidate assumes entire responsibility for the scientific quality of the research.

Statement of originality

Several aspects of this study represent original contributions to knowledge. The use of pharmacoepidemiologic methods to document the therapeutic equivalence of prescribed agents in the realm of cost-containment measures is novel. The second manuscript is an original attempt to present in such details a description of the patterns of use of antihypertensive agents in a clinical setting and especially, to document modifications to therapy as they arise in a period of up to seven years. It is also the first study to investigate the determinants of such patterns in the management of hypertension. Although previous studies have examined the use of antihypertensive agents and subsequent risk of myocardial infarction, the third manuscript that composes this thesis is an original attempt to adequately handle potential confounders and modifiers of the association. Indeed, it is the first study to show that not taking the history of antihypertensive and other drug use into account may lead to inaccurate estimates of risk in observational studies of drug effects. The fourth manuscript is the first to our knowledge to present a detailed illustration of the assessment of effect modification in matched case-control studies and to estimate the relative efficiency of two different methods for assessing effect modification.

Disclaimer

This study is based on data provided by the Saskatchewan Department of Health. The interpretations and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan.

REMERCIEMENTS

J'aimerais d'abord exprimer ma plus profonde gratitude et ma reconnaissance à mon directeur de thèse, Samy Suissa, pour son rôle essentiel dans la réalisation de cette thèse. Sa précieuse expertise, son support continuel et sa patience ont fait de cette thèse un projet réalisable et un exercice académique inestimable. Non seulement a-t-il été extrêmement présent et attentif à mes incessants questionnements, mais il m'a également donné la chance d'intégrer un groupe de recherche prolifique et dynamique, d'assister et de présenter mes travaux à des conférences de calibre international et de vivre tous les jours dans un milieu de travail formidable.

J'aimerais également souligner la participation de Jacques Le Lorier et Eleanor Elstein, tous deux membres de mon comité de thèse, pour leurs nombreux conseils et suggestions. Leur expérience clinique, en pharmacoépidemiologie et en cardiologie, m'ont été à plusieurs reprises de grand secours.

Tout au long de ma formation, j'ai également bénéficié des conseils et enseignements de nombreux membres du corps professoral du Département d'Épidémiologie et Biostatistique. Gilles Paradis, qui m'a entraîné dans cette longue aventure. Jean-François Boivin, qui a non seulement facilité mon intégration dans un milieu (et une langue surtout!) qui m'étaient totalement étrangers au sortir du réseau de la santé publique, mais qui m'a également fort bien dirigée lors de la préparation des examens de synthèse. Je suis également extrêmement redevable à Jim Hanley, pour son dévouement et son amour de l'enseignement: personne ne le fait mieux que lui. Merci à Theresa Gyorkos pour ses encouragements constants.

Je remercie également Mme Mary McNutt, du service de recherche de l'assurance-santé de la Saskatchewan, pour sa coopération continuelle lors de l'organisation des bases de données informatisées.

J'en profite également pour exprimer toute ma reconnaissance aux différents organismes qui m'ont offert le support financier essentiel à la réalisation de ce projet. Le Programme National de Recherche et de Développement en santé (NHRDP), de même que le Conseil de Recherche en Sciences Humaines (SSHRC) du Canada, m'ont accordé des bourses de formation doctorale de recherche en santé. Zeneca Pharmaceuticals et Hoescht Marrion Roussel ont subventionné l'achat des données nécessaires à la réalisation de cette recherche. Le Fonds de la Recherche en Santé du Québec a, par la subvention accordée à l'Equipe de Recherche en

Pharmacoépidémiologie, permis la création d'un environnement d'accueil précieux.

Les collègues de travail et compagnons de bureau colorent la vie de tous les jours de diverses façons. Merci à Marc Baltzan, Simone Cowan et Bing Cai pour avoir partagé mes locaux (et subi mes humeurs...) jour après jour lors de la dernière année. Merci à Mario, Lyne, Sophie, Yves et tous ceux que je ne pourrais nommer pour leur compagnie du midi, leurs encouragements constants et leur bonne humeur contagieuse.

Dans tout processus de recherche, le support clérical et administratif est précieux. Mille mercis à Diane Gaudreau, secrétaire, comptable, informaticienne, psychologue (et j'en passe), sans l'aide de qui je n'aurais pu évoluer de la même façon: son professionnalisme et son dévouement sont étonnants. Aussi, le support de Frédérick Gaudreau et de Véronique Désilet pour la mise à jour d'une base de données gigantesque de références m'a épargné bien des soucis. Bruno Rainville a partagé avec moi sa grande expertise de SAS pour la définition des profils d'utilisation des agents antihypertenseurs. Merci Bruno pour tout le temps et l'énergie investis.

Dans la vie comme au travail, l'amitié constitue le don le plus précieux de tous. J'ai la chance d'avoir tout près de moi des amitiés précieuses, certaines ayant même pris naissance nulle autre part que... au travail!!! Serge Benayoun est indéniablement l'un de ceux-là. En plus de sa présence quotidienne pendant plusieurs mois, de ses conseils judicieux et inépuisables et de sa perspicacité, Serge m'a apporté (et m'apporte encore) beaucoup de cette grande joie que nous procure une profonde amitié. Un merci tout particulier pour son dévouement des dernières semaines.

J'ai également eu le bonheur au cours de ces dernières années, de croiser le chemin d'individus remarquables qui m'auront fait grandir et évoluer. Hélène Carabin est sans nul doute la plus grande personne qu'il m'ait été donné de rencontrer. Avec Hélène, on ne peut s'ennuyer, on ne peut rire ni pleurer, on ne peut s'investir ou se désinvestir sans le faire toujours à pleine capacité. Hélène, qui même à Oxford n'est jamais loin, est toujours disponible et étrangement présente, à l'écoute et pleinement engagée dans notre très grande amitié. Merci Hélène, merci mille fois, merci d'être là. (Et... vive le courrier électronique!).

Merci au Petit Prince, pour sa trop courte visite parmi les miens.

Enfin, je ne pourrais trop insister sur le support et les encouragements essentiels des membres de ma famille. Mes parents, Claudette et Gérald, qui n'ont jamais cessé de croire en moi. Mes soeurs, qui sans comprendre vraiment, comprenaient malgré tout

ce que je vivais. Pierre, pour la retraite fermée dans un milieu enchanteur. Et surtout, surtout, mes deux grandes filles qui par leur joie de vivre, les étoiles dans leurs yeux, leurs éclats de rire et l'immensité de leur amour, me donnent constamment envie d'aller plus loin. Mélissa, Valérie, merci d'ensoleiller mon quotidien.

A tous ceux que j'aime, que j'ai aimé et que j'aimerai.

CHAPTER 1 – INTRODUCTION

1.1 Pharmacoepidemiology and drug utilization in the actual practice

Strom[1] has defined pharmacoepidemiology as the study of the use and effects of drugs after their entry into the market. Pharmacoepidemiology can be considered as the last phase of many in the study of drug effects. Following the preclinical stage of drug development, pre-marketing clinical studies aim at investigating drug effects among healthy volunteers (Phase I studies), at documenting drug activity and dose-related effects (Phase II) and finally at establishing drug efficacy using randomized controlled trials (Phase III). Sometimes considered as phase IV studies, drug evaluation conducted in the post-marketing stage includes the assessment of benefits, risks and impact of the drug on the natural history of disease in the society[2]. Through randomized controlled trials, the overall effects of the drugs when used as directed are usually well quantified.

Tightly controlled studies of drug efficacy provide very useful information. However, this information needs to be supplemented with studies that are more applicable to the "real-life" setting[3]. Observational studies may be especially useful to provide information on the long-term effects of drugs in the clinical practice. Even when a drug have been shown to have significant beneficial effects in randomized controlled trials, it may still prove useless (and even harmful) when used inappropriately. Appropriate use of medications is difficult to measure, which have indeed given rise to the emergence of a new field of interest in pharmacoepidemiology where inappropriate prescribing or irrational drug use are investigated. Concerns about the safety, effectiveness and appropriateness of drug use points to the need of carefully conducted pharmacoepidemiologic studies in the clinical setting. Pharmacoepidemiology offers all the necessary tools to show that drugs are often not used at their full potential, in terms of dosage, timing and general indications for use. Observational studies permit to answer questions such as: "How are drugs used in the community and by whom?" and "What are the effects of such use at the population level?".

Carefully conducted observational studies can bridge the gaps between the results arising from experimental studies and document drug effects at the community level. There is no doubt that a well conducted randomized controlled trial provides an accurate demonstration of whether or not a drug can produce the effect claimed for it. The randomized controlled trial may also determine whether two different drugs are equivalent in terms of a specific effect. But the extent of variation in drug taking

behaviours and in the characteristics of subjects using those drugs is believed to be high. Whereas it is not very well documented, drug taking behaviours are sometimes suspected to be somewhat erratic. The randomized controlled trial is usually not designed to examine such issues.

1.2 The use of administrative databases in pharmacoepidemiology

Billing data and computerized pharmacy databases are extremely rich sources of information with regard to the use and effects of prescribed drugs in the context of everyday medical practice. In an era where pharmacepidemiology is not anymore concerned solely with safety issues but has expanded its interest to the domains of drug effectiveness and patterns of use, large administrative databases are increasingly used.

One of the major criticisms of the use of observational designs in the study of intended drug effects is the lack of control over confounding by indication[4-6]. The indication for which a medication is prescribed is hardly measurable and sometimes unknown[7]. Several strategies have been proposed to minimize the role of confounding by indication in observational studies[4,8,9]. Among these strategies, the importance of anchoring the definition of exposure to the onset of therapy has been proposed[10]. However, most observational studies of drug effectiveness are still anchoring exposure at the time of occurrence of the outcome.

Miettinen and Caro showed that not only the timing but also the duration of therapy and prior use of the drug may bear on the estimates of risk[11]. Also, the estimate of risk in case-control studies have been shown to vary in some cases according to the duration of drug use[12]. Hence, knowing to what extent and in what ways exposure to medications may vary during the course of therapy seems crucial.

1.3 Drug utilization in the treatment of hypertension

Hypertension is a chronic disease that may lead to premature cardiovascular disease when untreated. Drug management of hypertension has been shown to be highly effective: considerable evidence indicates that reducing elevated blood pressure is beneficial[13]. The reduction in cardiovascular disease and death attributed to blood pressure reduction has been widely demonstrated[13-17]. A considerable number of randomized controlled trials have also been conducted to test the ability of specific agents to reduce cardiovascular and mortality risk. For instance, the older

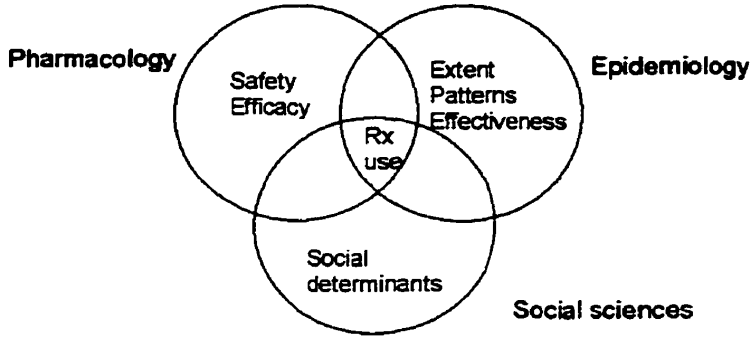
antihypertensive agents β-blockers and diuretics have been shown to have beneficial effects on survival and on the cardiovascular system in general[18,13]. However, the beneficial effects of newer agents, namely the calcium antagonists and the angiotensin-converting-enzyme (ACE) inhibitors, remain controversial. The results of ongoing long-term randomized controlled trials of the effects of ACE inhibitors and calcium antagonists on health outcomes are just emerging[19-22]. These trials were undertaken following the publication of several observational studies suggesting a possible harm of calcium antagonists[23-25]. Mainly due to methodological flaws, these observational studies have however led to contradictory results. We hypothesize that several of these studies were compromised by confounding by indication or noncomparable severity of the underlying disease (or diseases) being treated. If patients with more severe disease or presenting with a comorbidity profile that puts them at higher risk of complications were channelled to receive a specific agent, that could explain some of the increased risk observed in previous studies.

1.4 Study rationale and objectives

Information is lacking at present on characteristics of patients dispensed various drug regimens a long time before they develop heart disease[26]. Drug use is determined by a number of factors. To understand it appropriately, one should make use of the insights of several disciplines such as pharmacology, epidemiology, psychology and social sciences (Figure 1.1). Large prospective studies conducted in a well defined population may throw new light on the natural history of hypertension.

This thesis includes four manuscripts addressing the general topics of antihypertensive drug use and effects. In the first manuscript, we compare within a therapeutic drug class (the angiotensin-converting-enzyme (ACE) inhibitors), the use of health services such as medical visits and hospitalizations following initiation of therapy. An intention-to-treat analysis, where the first dispensed medication defines drug exposure, is used to document the question. The second paper describes the patterns of use of antihypertensive agents in a cohort of patients newly treated for hypertension in the actual clinical practice. The distribution and determinants of initial treatment, compliance to therapy and subsequent modifications to initial therapy are extensively documented for up to seven years of follow-up. The third manuscript constitutes the heart of this study. The paper investigates the risk of myocardial infarction in association

with current use of antihypertensive agents. The definition of exposure to antihypertensive agents is based on the results of the preceding study. Finally, the fourth manuscript addresses methodological issues relating to the assessment of effect modification in matched case-control studies. An empirical illustration is provided.



Modified from Sterky *et al*[27].

Figure 1.1 **Conceptual framework for the study of drug utilization and effects.**

CHAPTER 2 – LITERATURE REVIEW

This chapter provides an extensive review of the literature pertaining to hypertension management, cardiovascular risk and patterns of use of antihypertensive drug therapy. The objective of this review is to provide the information required for a thorough understanding of the numerous factors associated with the treatment of hypertension and the prevention of cardiovascular disease. Cardiovascular disease as a broad group of conditions is first delineated, followed by a short description of each of its components. In this section, emphasis is put on the interrelationship between hypertension and other heart-related conditions and their pharmacologic management. This is an important part of the review as adequate handling of potential confounding by the indication of the drugs in observational studies requires a good understanding of both determinants of risk and prescription practices. The second section presents the prospective studies that have assessed the usefulness of hypertension management and the comparative efficacy of antihypertensive agents at improving blood pressure and other clinical endpoints in hypertension. Randomized controlled trials of the effects of antihypertensive agents on major health outcomes, on which are based the clinical guidelines for the management of hypertension, are also presented. As issues surrounding indications for prescribed drugs constitute an important component of this thesis, attention has been given to the populations under study. Following this, an outline of the controversy on the safety of antihypertensive agents, specifically the calcium antagonists, is presented along with a critical appraisal of the observational studies that gave rise to the debate. Drug utilization studies aimed at characterizing antihypertensive medication use are described in the fourth section. In the last section, methodological issues related to the use of prescription claims in observational studies are briefly discussed.

2.1 Hypertension and other diseases of the heart and circulatory system

Coronary heart disease (CHD) is the major cause of death, disability and illness in industrialized societies[28]. CHD may be defined as a disease process involving the large blood vessels (arteries) supplying blood to the heart muscle. CHD includes two broad groups of conditions, the major components of which are ischemic heart disease (IHD) and cerebrovascular disease (CVD). Other components of cardiovascular disease include congestive heart failure (CHF), arrhythmia, peripheral vascular disease,

atherosclerosis and other miscellaneous diseases of the heart[29]. One of the main risk factor for CHD, hypertension, may also be considered a disease of the vascular system, including the heart. This section will briefly outline the main features of hypertension and cardiovascular disease, emphasizing the relationships between them.

2.1.1 Hypertension

Arterial hypertension may be defined as a sustained elevation of systolic and/or diastolic blood pressure. Blood pressure (BP) is the tension on the walls of the arteries resulting from the action of the heart. BP depends upon the energy of the heart action, the elasticity of the arteries and the volume and viscosity of the blood. It represents the force required by the heart to ensure the circulation of blood through the entire body. A series of interdependent mechanisms, forming a complex system, is responsible for blood pressure regulation[30]. Derangement of only one of these mechanisms is sufficient to induce an elevation of the BP that if sustained, can lead to irreversible organ damage. A simplified approach to the physiology of hypertension indicates that BP is a function of two main hemodynamic factors: 1- the flow of the cardiac output, which depends upon myocardium's contractility, heart rate and blood volume, and 2- peripheral vascular resistance. Other mechanisms involved in the control of blood pressure include the adrenergic nervous system, renin-angiotensin-aldosterone system, renal function and hormonal factors[31]. A defect in any of these mechanisms may lead to hypertension.

Hypertension is usually diagnosed when a high SBP ($\geq$140 mmHg) or DBP ($\geq$90 mmHg) pressure is confirmed at two or more visits[32]. In uncomplicated hypertension, the elevated blood pressure is almost entirely due to peripheral resistance. As the disease process continues, functional changes to the heart occur which slowly lead to impaired left ventricular function and may ultimately lead to a fall in cardiac output: the heart is failing[33]. Hypertension may have no identifiable cause, in which case it is said *essential, idiopathic* or *primary hypertension.* Sustained high BP may also be a consequence of other conditions or diseases (e.g., kidney disease, hormonal disorders, certain drugs), in which case it is denoted as *secondary hypertension.* More than 90 percent of hypertensive patients have primary hypertension[30,31]. Finally, "office" or "white-coat" hypertension is a phenomenon characterized by an increase in BP that arises only during a clinic visit or in the hospital setting[34].

Hypertension is a common condition that affects more than 60 million people in the

United States[31], with an overall estimated prevalence of 15 to 20% among Caucasians and 25 to 30% in the Black population[31,35]. Racial differences in prevalence rates are well known[30,36]. Both the prevalence and the incidence of high BP increase with age and differ across genders[37](Figure 2.1). In people 65 years of age and over, the prevalence of hypertension is more than 50%[38,37]. Whereas the prevalence of hypertension in the elderly is fairly well known, incidence estimates are much less readily available. Several studies suggest annual incidence rates between 2% and 6%[39-42].

Long standing hypertension may affect the vascularization of major end organ systems, such as the heart itself, the brain, the eye and the kidneys. Hypertension is a significant risk factor for coronary heart disease and a major determinant of heart and renal failure and stroke[31,36,43,33,44,45,18,46]. Because it is an asymptomatic condition, a large proportion of hypertensive subjects are either not aware of their condition or are not compliant with therapy[28,31]. The *Canadian Heart Health Surveys* recently estimated that 16% of the overall population have treated and well controlled hypertension. An additional 23% are treated but remain uncontrolled and 19% have untreated hypertension[37]. Similar rates were found in Europe[38]. Untreated hypertension is associated with a 10 to 20 years shortening of life span, usually due to acceleration of atherosclerosis and induction of coronary heart disease. Myocardial infarction (MI) and congestive heart failure (CHF) account for an important number of deaths secondary to hypertension[31]. The Framingham Study showed that the risk of CHF was 2 to 4 times higher for those in the highest quintile of blood pressure, compared to the first[47,48]. Angina pectoris may also occur due to associated coronary artery disease. Hypertension is also a major risk factor for stroke[49] and MI[50]. Uncontrolled hypertension also has negative effects on other systems: neurological and retinal effects may occur, as well as deleterious effects on the central nervous and renal systems.

There does not appear to be a critical level of blood pressure that bears excess risk of cardiovascular events as mortality and morbidity increase with increasing levels of systolic (SBP) and diastolic blood pressure (DBP) in an exponential way[51]. Thus, the cutting lines for a diagnosis of hypertension are somewhat arbitrary[52,31,53]. Even small elevations of blood pressure carry an additional risk[51,54,55,34], especially in the presence of other cardiovascular risk factors. The 1993 US National consensus guidelines established the following categories for blood pressure levels:

Classification of blood pressure for adults aged 18 years or older.

Category	SBP	DBP
Optimal	<120	<80
Normal	120-129	80-84
High normal	130-139	85-89
Hypertension		
Stage I	140-159	90-99
Stage II	160-179	100-109
Stage III	180-209	110-119
Stage IV	≥ 210	≥ 120

Source: *Fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure*[32].

Abbreviations: SBP=Systolic blood pressure; DBP=Diastolic blood pressure.

2.1.2 Ischemic heart disease

Ischemic heart disease (IHD) can be defined as an impairment of the heart muscle by oxygen deprivation as a consequence of reduced blood supply (ischemia) in the heart. IHD results from an imbalance between myocardial oxygen supply and demand as a consequence of a partial or complete obstruction of coronary artery blood flow by atherosclerotic lesions or plaques and its complications. IHD is one of the leading causes of death in industrialized countries[28]. Major clinical manifestations of IHD are angina pectoris and MI.

Angina. Angina is defined as a temporary and often spasmodic chest pain due to transient ischemia. Angina is usually precipitated by effort or excitement. The condition manifests itself when the cardiac blood vessels get very narrow due to atherosclerosis and the heart muscle starts complaining because of a lack of oxygen. Stable angina is the most common form and is often labeled *typical angina. Unstable angina*, which has the worst prognosis, is defined by an increase in frequency, severity and duration of symptoms. A patient not taking medications and presenting with a new onset of symptoms is considered unstable. *Prinzmetal's* or *variant angina* is due to an involuntary contraction of the arteries in which the symptoms usually occur at rest. Nitrates are effective at reducing symptoms and improving exercise tolerance in a majority of patients[56]. Calcium antagonists and ß-blockers may be used as second-line agents to treat both stable and unstable angina[56]. ß-blockers have the ability to lower heart rate, blood pressure and myocardial contractility, thus reducing oxygen requirements. The non-dihydropyridine calcium antagonists verapamil and diltiazem lower heart rates

whereas the dihydropyridine nifedipine, amlodipine, felodipine and nicardipine are also effective vasodilators. Patients with evidence of a thrombus formation or atherosclerotic plaques may also benefit from anticoagulants and antiplatelet therapy[56]. Between 3% and 5% of the population are believed to have angina[57].

Myocardial infarction. Commonly known as "heart attack", myocardial infarction (MI) is defined as a prolonged and irreversible ischemia due to the formation of a thrombus (aggregation of blood factors -mainly platelets-) frequently causing vascular obstruction that produces muscle damage. MI is one of the main manifestations of IHD. It occurs when the artery gets completely or almost completely blocked and the part of the heart muscle supplied by blood from this particular blood vessel dies. This usually presents as an episode of very severe chest discomfort and sweating. The incidence of MI in the US is estimated to be around 10 per 1,000 men per year and 3 per 1,000 women per year in the 45 to 64 age group[58]. For those aged 65 or more, the incidence rates are 19 and 12 per 1,000 men and women respectively[58]. In Canada, more than 10% of all deaths are attributed to myocardial infarction[59]. It is estimated that around one individual in four suffering a heart attack dies before admission to the hospital, often within a few hours of the onset of symptoms[60]. One of the major risk factors for MI is hypertension[50]. MI patients are routinely treated with β-blockers which have been shown to be highly effective in that population.

Other ischemic heart diseases. Sudden cardiac death, defined as death caused by cardiac arrest within a fixed period after the onset of symptoms (varying between 1 and 24 hours according to different definitions), is sometimes presumed to be the result of a severe episode of acute MI. It may also be the result of electrical instability of the heart that manifests under the form of ventricular fibrillation, in which case it is labeled "primary cardiac arrest". It is estimated that up to 40% of coronary heart disease patients die suddenly[61].

2.1.3 Cerebrovascular disease and stroke

Stroke is the cerebral equivalent of MI. In stroke, an area of the brain is damaged either by a sudden decrease in the blood supply of some part of the brain due to atherosclerosis (ischemic stroke) or by a hemorrhage (hemorrhagic stroke) in the

cerebral vessels. Hemorrhagic strokes are much less frequent than ischemic stokes[62,63]. Commonly designated as cerebrovascular accident or cerebral infarction, CVD typically leads to persistent neurological deficits in the affected part of the brain. Known risk factors for stroke includes age, high blood pressure (the risk of stroke is believed to be increased by five in hypertensives compared to normotensives[64]), cigarette smoking, excessive alcohol intake and diabetes. Hypertension is believed to be present in nearly 70% of all strokes[65]. Stroke is the third leading cause of death in the United States, after CHD and cancer[62]. The impact of stroke on public health is mainly as a significant cause of chronic disability[66].

2.1.4 Other diseases of the heart

Heart failure. Congestive heart failure (CHF) denotes the inability of the heart to supply enough oxygen to meet the body's need. Heart failure is physiologically difficult to characterize but as a general rule, a failing heart has a higher than normal left ventricular end-diastolic volume (and pressure) for a given ventricular performance. The failure of cardiac output to increase with effort results in underperfusion of tissues, leading to increased fatigue and dyspnea on exertion. CHF is due to an abnormality of the cardiac function that may result from atherosclerotic coronary artery disease with or without MI. It is usually considered the potential end point of most serious cardiac disease[67]. CHF is usually treated first using restriction of activities and salt intake. Drugs used for the treatment of heart failure include diuretics (to control fluid retention), vasodilators and digitalis to improve myocardial contractility[68,69]. ACE inhibitors have been shown in long-term studies to have beneficial effects in CHF patients not only with regard to symptoms reduction and exercise tolerance, but also with regard to survival[68,70]. Digitalis is more effective in patients with chronic IHD, atrial fibrillation or systemic hypertension but may be toxic in some patients[68]. Myocardial contractility may also be improved using sympathomimetic agents such as epinephrine, isoproterenol, intravenous dopamine and dobutamine[68]. In the US, the incidence of CHF is estimated to be around 10 new cases diagnosed per 1,000 people aged 65 and over. Largely as a result of the aging of the population, both the prevalence and incidence of CHF are increasing[71]. In the Framingham cohort, a vast majority of CHF patients had antecedent hypertension[47]. Survivors of MI and diabetic patients are also at increased risk of developing heart failure[47].

Arrhythmia. Arrhythmia is a generic term denoting any form of disturbance of the heart rhythm. Arrhythmia can result from atherosclerotic disease or from no apparent cardiac disease. Atrial or ventricular fibrillation, ventricular or supraventricular tachycardia and heart block are different forms of arrhythmia with atrial fibrillation being the most common[72]. Atrial fibrillation is seen in 5% to 9% of adults aged 65 or more[73] and is likely caused by the stretching or hypertrophy of the atrial tissue either due to systemic hypertension or to a MI episode that lead to left ventricular dysfunction[72]. Indeed, hypertension is the most common cause of AF, followed by MI[72]. AF is usually treated with digitalis, preferably intravenous, propanolol or other ß-blockers in combination with digitalis or calcium antagonists such as diltiazem or verapamil. Anticoagulant or anti-thrombotic therapy may also be administered in patients at high risk for stroke[72]. Other forms of arrhythmia are managed using disopyramide, procainamide or quinidine. The importance of an individualized approach to an anti-arrhythmic therapy has been underscored[74].

Atherosclerosis. Atherosclerosis is a generalized disease of the arterial tree characterized by thickening and loss of elasticity of the arterial walls in which atheromas (mass or plaque containing lipids such as cholesterol and triglycerides) are formed within the arteries. Atherosclerosis stays asymptomatic until the lesions become large enough to obstruct the circulation, to reduce blood flow and to cause ischemia. In large arteries, plaques are usually of no clinical importance. In relatively small vessels, progressive enlargement of a lesion, caused by high blood pressure, bacterial and viral infections or hypercholesterolemia for instance, may result in either arterial obstruction with subsequent thromboembolism or localized weakness of the vessel wall with formation of an aneurysm. One postulated mechanism leading to atherosclerosis is that high blood pressure, bacterial or viral infections, hypercholesterolemia or other chronic insults result in an injury to the wall of a vessel and contribute to the development of the plaques via an increase in permeability to various plasma constituents[75,76,50]. Complicated lesions may thus lead to hemorrhage, ulcerations or thrombus, and result in myocardial or cerebral infarct, peripheral vascular disease or aortic aneurysm. Prevalence and incidence figures for atherosclerosis are hardly available.

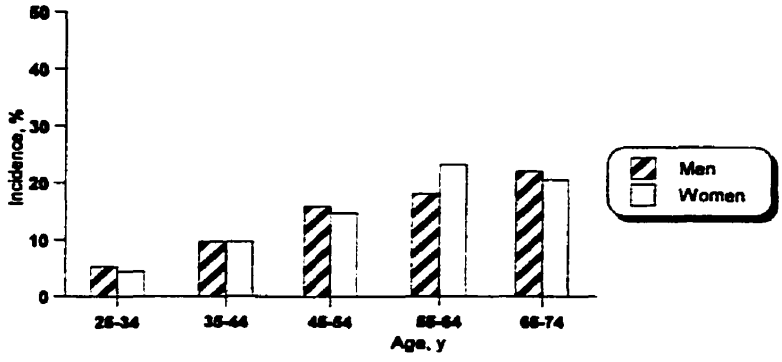
2.1.5 Cardiovascular disease in industrialized countries: Significance of the problem

Both in Canada and in the US in 1990, near 40% of all deaths were due to cardiovascular disease. Of these, 7% were due to stroke and 23% to IHD, more than half of the latter being MI[28]. Canada's rates of cardiovascular mortality in 1987 were 245 per 100,000 men and 134 per 100,000 women[28]. Except for stroke, men experience around two to five fold greater death rates for all CHD[28]. Mortality rates for CHD also increase with age in an exponential way and differ according to social classes: people with lower income and education levels being at higher risk[28]. Both the incidence and case-fatality rates for CHD have declined since the late 1960's and survival rates have significantly increased. This could be explained by the availability of effective interventions and improvements in the management of patients with existing CHD, as well as by changes in lifestyle behaviors[77-80].

CHD has an important impact on population health and utilization of health services. For instance, it is estimated that CHD accounted in 1990 for 12% of all hospital admissions (13% of which were MIs), 20% of hospital-days, 10% of physician visits (nearly half of which for the management of hypertension) and around 17% of all prescriptions dispensed in Canada[28]. Of the 26 million cardiovascular drugs dispensed between 1986 and 1991, around 25% were β-blockers, 23% calcium antagonists, 17% ACE inhibitors, 14% vasodilators, 11% digitalis preparations and 10% other cardiovascular agents[28]. An additional 10 million drugs were likely prescribed for cardiovascular disease, these being diuretics. All direct and indirect costs considered, CHD is believed to represent 21% of the total cost of illness in Canada in 1986[81].

Considerable research has contributed to the identification of risk factors for CHD[82-86,18]. Among those identified, some are modifiable such as smoking, high blood pressure, elevated blood cholesterol, diabetes, physical activity and obesity, and others not (family history of CHD, age and male gender). The presence of multiple risk factors has been reported to have a synergistic effect on overall cardiovascular risk[87]. Along with known risk factors for CHD, high blood pressure is among the most important factors identified by the Framingham study to predict the risk of cardiovascular complications[51] and is an independent risk factor for CHF, renal failure and stroke[30]. Hypertension is also the main cause of left ventricular hypertrophy, which has been shown to be an independent risk factor for coronary heart disease, stroke and CHF[88].

Finally, diabetes mellitus has been shown to increase the incidence of complications in hypertension[89]. All the diseases previously described coexist in a higher proportion than it would be expected by chance alone. They all act in different ways on each others in a complex network of interrelationships.



Extracted from Comoni-Huntley *et al*[40].

Figure 2.1 **Ten-year incidence rates of hypertension according to age and sex in the United States.**

2.2 Drug management of hypertension: Evidence from randomized controlled trials

Figure 2.2 illustrates the conceptual framework that forms the basis for antihypertensive therapy. The risk factors for hypertension (arrow 1) and the relationship of hypertension to cardiovascular outcomes (arrows 2 to 4) have been discussed in section 2.1 of this review. The ability of antihypertensive drug therapy to decrease blood pressure levels (arrow 5) is widely accepted. To gain approval for marketing from the Food and Drug Administration (FDA) in the US, all antihypertensive drugs must have been shown to be effective in reducing blood pressure. The first section will review the prospective controlled studies that investigated the beneficial effects of blood pressure reduction (arrow 4). Mainly, these studies compared an active treatment group with no treatment, usual care or placebo with regard to major health outcomes. In the two following sections, we will present the major randomized placebo-controlled trials that investigated the effects of antihypertensive agents on major health outcomes (arrow 7). The effects of older (diuretics and β-blockers) and newer agents (ACE inhibitors and calcium antagonists) will be outlined in two different sections, the evidence being of different quality. The few trials that have assessed the comparative effects of two or several agents will also be presented. The effects of these agents on surrogate endpoints such as left ventricular hypertrophy (arrow 6) have been extensively documented and will not be addressed here. Finally, the expert recommendations and clinical guidelines on the management of hypertension that mainly arise from systematic evaluation of the evidence from clinical trial data will be briefly presented. Throughout, a critical appraisal of the usefulness and comparability of clinical trial results for the actual medical practice will be highlighted.

2.2.1 Beneficial effects of blood pressure reduction

Numerous large-scale studies have provided evidence of the risks of elevated blood pressure (BP). MacMahon *et al*[18] reported a meta-analysis of nine major observational studies of the risks associated with various diastolic BP levels. They reported steady and incontestable elevated risks for both stroke and cardiovascular disease with increasing diastolic blood pressure (DBP). Indeed, they estimated that a persistent elevation of 5 mmHg in mean DBP is associated with 35-40% and 20-25% increases in stroke and CHD risks respectively[18]. This suggest an important potential for risk

reduction through effective treatment.

Considerable research has shown the benefits of reducing elevated BP. For instance, overviews or meta-analyses of data from randomized controlled trials of the effects of blood pressure reduction have shown reductions of more than 40% for stroke and from 9% to 14% for cardiovascular disease[13-17]. In observational studies, the magnitude of these reductions are estimated to be similar for stroke and even higher (20% to 25%) for CHD[13,18].

Started in 1963, the Veterans Administration trial (VA trial) was stopped after only 18 months due to the overwhelming benefits observed in the actively treated group[90]. The second phase of the same trial[91] was also stopped early due to the high incidence of unwanted effects in the untreated group. The VA studies were the first to provide definitive evidence of the protective effect of antihypertensive therapy. Since then, numerous long-term randomized clinical trials in hypertension have confirmed the beneficial effects of decreasing blood pressure. In the late 70's the Hypertension Detection and Follow-up Program (HDFP) of the National Heart, Lung and Blood Institute provided striking evidence of the efficacy of treatment in patients with DBP of 90-104 mmHg on average[92,93]. Hypertensive patients randomized to aggressive treatment showed five-year mortality rates 17% lower than the "usual care" comparison group. The aggressively treated group also showed significant reductions in stroke and other cardiovascular events. The Multiple Risk Factor Intervention Trial (MRFIT)[94] was a randomized trial comparing mortality rates between two groups of high risk men managed through a special intervention program (SI) consisting of stepped-care treatment for hypertension, counseling for cigarette smoking and dietary advise, or through their usual source of care (UC). Among the subgroup with hypertension at entry, CHD mortality was 24% lower in the SI group compared to UC[95]. Significant reductions in the incidence of cerebrovascular events (including stroke), heart failure and cardiac hypertrophy were also observed in large controlled trials of similar populations such as the Australian therapeutic trial in mild hypertension (ANBP)[96], the Oslo study[97] and the Medical Research Council (MRC) trial[34]. One year after the HDFP did so, the Australian trial[96] also showed important reductions in mortality among treated patients. The main features of these and other studies are presented in Table 2.1 and Figures 2.3 to 2.5 outlines their main results.

From these trials, several systematic overviews and meta-analyses were

published[13-16,52]. For instance, Wilcox and colleagues[52] reviewed nine controlled trials in hypertension[90-92,96-104] to assess the effect of reducing blood pressure on survival and cardiovascular events. Significant reductions in mortality were reported in two of the nine trials[90-92,99] whereas two others tended to suggest a beneficial effect of treatment but lacked statistical significance[96,97,100].

Gifford[105] performed in 1989 an extensive review of eight long-term clinical trials[34,96,99,101,102,106-110] that were carried out among over 40,000 hypertensive subjects to study the usefulness of antihypertensive agents in controlling blood pressure and reducing morbidity and mortality associated with hypertension. Several of these randomized controlled trials have shown a reduction in stroke rates[34,96,99,102,110] following a diuretic- or a β-blocker-based treatment. However, according to Gifford's review, only two of them[99,102] have shown a significant reduction in mortality from myocardial infarction. In 1990, Collins *et al*[13] identified 14 randomized controlled trials of antihypertensive drug therapy. The authors reported that a long-term difference of 5-6 mmHg in usual DBP is associated with about 35-40% less stroke and 20-25% less CHD. Vascular mortality was shown to be significantly reduced whereas non-vascular mortality appeared unchanged. A few years later, Mulrow *et al*[17] identified 12 trials in younger and middle-aged subjects. The summary measures of effect for the 12 trials indicated statistically significant reductions in overall cardiovascular mortality and morbidity from stroke, but not for CHD. However, the combined endpoint of fatal and non-fatal CHD was positively significant.

A number of trials have also been conducted among the elderly to document the effects of hypertension management on major health outcomes in that special population. Mulrow *et al*[17] reviewed 13 large randomized controlled trials lasting at least one year that evaluated the effects of drug treatment on morbidity and mortality outcomes in elderly hypertensives. The six higher quality trials demonstrated the high efficacy of treating healthy older persons with hypertension. All the summary estimates for mortality and combined morbidity and mortality from stroke and CHD were significantly positive. Also, five-year morbidity and mortality benefits derived from these trials were greater than that for younger subjects[17]. From nine trials in the elderly population, Pearce *et al* concluded that antihypertensive therapy in the elderly prevents major coronary events and stroke, and prolongs life[111]. Later, Lindholm *et al*[112] concluded as well in a review of trials in the elderly that drug treatment with β-blockers

and diuretics in hypertensive subjects aged 70 years and above confers highly significant reductions in cardiovascular mortality and morbidity, especially stroke. Finally, another meta-analysis, focussing on the clinical effects of antihypertensive therapy in the very old (>80 years) was published. Treatment was found to prevent 34% of strokes, 22% of cardiovascular events and 39% of heart failure. A relative excess of all-cause mortality of 6% was also reported[445]. Drug treatment have also been shown to be beneficial among patients with isolated systolic hypertension. For instance, the Systolic Hypertension in Elderly Patients (SHEP) study, showed in the early nineties that hypertension control could lead to a reduction in cardiovascular events, although not overall mortality[113]. Figures 2.6 to 2.8 display the main results of the major trials in elderly subjects with hypertension.

All these trials provide strong evidence of a beneficial effect of reducing high blood pressure on major health outcomes. However, these are not without limitations. For instance, the HDFP and MRFIT are not trials of blood pressure reduction *per se* but rather aimed at comparing two forms of hypertension management. Also, the source populations giving rise to these trials differed on a number of factors. For instance, ANBP and MRC patients were free from cardiovascular disease at entry and may be considered as low-risk patients, whereas MRFIT was composed of high-risk men only. Also, all patients in the SHEP and a majority of those in the MRC-elderly trial had isolated systolic hypertension. Systolic hypertension represents a distinct medical entity and the efficacy of treatment in that population could differ from that among patients with essential hypertension. The underlying populations also differed in terms of age and ethnic origin. In addition, as in any other clinical trial, elderly subjects enrolled in these studies were ambulatory and healthy. The study results may therefore be hardly applicable to the usual clinical practice, especially in the case of the elderly population. The "multi-drug approach" that was assessed in several of them (several of which involving a stepped-care approach to therapy as one of the treatment arms) assumes that the beneficial (or even possibly harmful) effect of antihypertensive therapy on the cardiovascular system resides only in its ability to lower blood pressure and no information is provided that pertains to the pharmacodynamic properties of specific agents. Also, unless it is undoubtably proven that an active treatment to decrease blood pressure present a significant advantage over the absence of treatment, a placebo is required. Of the reviewed trials, several[92-94,97] did not have a placebo group. Despite

these limitations, data from these trials prove without any doubt that BP lowering with antihypertensive therapy reduces overall mortality and morbidity from stroke and cardiovascular disease.

2.2.2 Diuretics and β-blockers in hypertension

As stated before, numerous placebo-controlled trials have been completed since the early '70s that showed the efficacy of antihypertensive therapy to reduce blood pressure. Several trials also demonstrated significant benefits of treatment in terms of blood pressure and surrogate endpoints such as reduction of left ventricular mass[44,114-118]. Since most of these trials were confined to first-line treatment with diuretics and, to a lesser extent, β-blockers, their results were also used to gather information on the effect of these specific agents on overall health outcomes. Psaty *et al*[119] reviewed 18 long-term randomized placebo-controlled trials in hypertension. Compared with placebo, β-blocker therapy was effective in preventing stroke and CHF, with similar findings for high-dose diuretics. Low-dose diuretics prevented not only stroke and CHF but also CHD and total mortality. Messerli *et al*[120], in a recent systematic review of β-blockers and diuretics in the elderly, showed that diuretics were superior to β-blockers with regard to all endpoints. Diuretic therapy was effective in preventing cerebrovascular events (OR=0.61; 95% CI= 0.51-0.72), fatal stroke (OR=0.67; 95% CI=0.49-0.90), coronary heart disease (OR=0.74; 95% CI=0.64-0.85), cardiovascular mortality (OR=0.75; 95% CI=0.64-0.87), and all-cause mortality (OR=0.86; 95% CI=0.77-0.96). In contrast, β-blocker therapy only reduced the odds for cerebrovascular events (OR, 0.75; 95% CI, 0.57-0.98) but was ineffective in preventing coronary heart disease, cardiovascular mortality, and all-cause mortality (OR=1.01, 0.98 and 1.05 respectively)[120].

In addition to examining the beneficial effects of β-blockers and diuretics at reducing high blood pressure, several hypertension trials were also aimed at directly compare the effects of these agents[34,103,106,107,121]. These trials are presented in Table 2.2. In secondary analyses of the MRC trial[34], no significant differences were found, except for a lower stroke rate in the diuretics group. In the companion trial in the elderly, stroke rates were the same in both groups whereas the low-dose diuretic group showed less total cardiovascular deaths and coronary endpoints, compared to β-blockers. Two trials in which the comparison of diuretics and β-blockers was a primary objective found no statistically significant difference in cardiovascular disease, total cardiac events and total

mortality[103,106,107]. The Metoprolol Atherosclerosis Prevention in Hypertensives Study (MAPHY)[108], an extended follow-up of the metoprolol and diuretics sub-groups of the Heart Attack Primary Prevention in Hypertension trial (HAPPHY), found significant reductions in total and cardiovascular mortality, fatal stroke and total cardiovascular events at mid follow-up. Except for cardiovascular events, these differences were no longer statistically significant at the end of follow-up. MAPHY is the only trial to have shown a greater benefit from β-blockers (relative to diuretics) with respect to cardiovascular disease. The fact that MAPHY is not an original trial *per se* has however been largely criticized. Several other criticisms have been put forward with regard to these trials. For instance, the two MRC trials were not double blind and only MRC had a placebo group. Also, in one trial[106], half of patients were already receiving antihypertensive therapy when entering the trial whereas in the others, none of them did. Finally, the drugs added to the treatment regimen when target blood pressure was not reached differed in the compared trials, which makes it difficult to disentangle the effects of specific agents. These limitations may have hampered the comparability of these trials.

2.2.3 Newer antihypertensive agents in hypertension

Antihypertensive treatment trials have convincingly demonstrated that diuretics and β-blockers reduce the risk of stroke and coronary heart disease. However, despite their increasing use, the benefits of newer agents such as calcium antagonists and ACE inhibitors on major health outcomes are still debated. Despite some criticisms[122], recent studies suggest that long-acting calcium antagonists are effective compared to placebo, especially among patients with isolated systolic hypertension[19-22].

The Shanghai Trial of Nifedipine in the Elderly (STONE)[19] focused on elderly patients with hypertension. STONE is a single-blind trial conducted in 1,632 subjects aged 60-79 years alternatively allocated to the calcium antagonist nifedipine or placebo. Nifedipine treatment significantly diminished the number of severe clinical outcomes with reductions of 59% for all events and of 62% for combined cardiovascular events. STONE also suggests that outcomes with newer agents like long-acting nifedipine are comparable to outcomes in major clinical trials in the elderly using diuretics and β-blockers[20]. The Systolic Hypertension-Europe study (Syst-Eur) is a multicentre randomized placebo-controlled trial in patients aged at least 60 years old with isolated

systolic hypertension. Its scope was to investigate the effects of modern antihypertensive drug treatment on morbidity and mortality and to assess possible adverse effects of the drugs. Syst-Eur showed that antihypertensive treatment started with nitrendipine led to a 31% reduction in the rate of cardiovascular complications[21]. Antihypertensive therapy was at least as effective in patients with diabetes as in those without diabetes at entry. Active treatment reduced all strokes by 44%, all cardiac endpoints by 26%, and all cardiovascular endpoints by 32%. Total mortality was decreased by 26%, but the similar reduction in cardiovascular mortality did not reach statistical significance. Syst-China is a double-blind placebo-controlled trial investigating whether active treatment could reduce the incidence of stroke and other cardiovascular complications in 2,298 older patients with isolated hypertension[22]. Patients were alternatively attributed therapy with either a placebo or active treatment with nitrendipine, to which captopril (an ACE inhibitor) or the diuretic hydrochlorothiazide (or both) were added as necessary. Antihypertensive treatment was found to lead to significant blood pressure reductions[123,124] and to prevent stroke and other cardiovascular complications[22].

The Hypertension Optimal Treatment (HOT) trial was based on 18,790 hypertensive patients aged 50 to 80 years and treated for hypertension for an average of 3.8 years[125]. The calcium antagonist felodipine was given as baseline therapy with the addition of other agents, according to a five-step regimen. In addition, patients were randomly assigned to aspirin or placebo. Subjects were randomized to be treated with the goal of achieving three different levels of blood pressure. In the HOT trial, a calcium antagonist-based therapy contributed to reduce blood pressure by over 20 mmHg in most patients. Intensive lowering of blood pressure in patients with hypertension was associated with a lower rate of cardiovascular events. Aspirin also significantly reduced major cardiovascular events with the greatest benefit seen in MI. There was no effect on the incidence of stroke or fatal bleeds, but non-fatal major bleeds were twice as common.

MIDAS, the Multicenter Isradipine Diuretic Atherosclerosis Study[126] is a randomized double-blind controlled trial aimed at comparing the rate of atherosclerosis during antihypertensive therapy with isradipine relative to hydrochlorothiazide. There was no difference in the rate of progression of atherosclerosis between isradipine and hydrochlorothiazide over 3 years among the 883 study subjects. There was a 6% higher incidence of major vascular events (e.g., MI, stroke, congestive heart failure, angina,

and sudden death) in the isradipine group and a significant increase in transient ischemic attack, arrhythmia and cardiac procedures in that group.

The Captopril Prevention Project (CAPPP)[127,128] is a randomized intervention trial to compare the effects of ACE inhibitors and conventional therapy on cardiovascular morbidity and mortality in patients with hypertension. CAPPP was conducted among 10,985 patients aged 25-66 years with hypertension. Patients were randomly assigned captopril or conventional antihypertensive treatment (diuretics, β-blockers). Cardiovascular mortality was lower with captopril than with conventional treatment (RR=0.77; 95% CI=0.57-1.04) whereas the rate of fatal and non-fatal myocardial infarction was similar (RR=0.96; 95% CI=0.77-1.19) and stroke was more common with captopril (RR=1.25; 95% CI=1.01-1.55). The authors conclude that captopril and conventional treatment did not differ in efficacy in preventing cardiovascular morbidity and mortality. They interpret the difference in stroke risk as being probably due to the lower levels of blood pressure at baseline.

The Treatment of Mild Hypertension Study (TOMHS)[129] is a randomized placebo-controlled trial carried out among 902 middle-aged patients with hypertension. Patients were randomized to the diuretic chlorthalidone, the β-blocker acebutolol, the α-blocker doxazosin, the calcium antagonist amlodipine, the ACE inhibitor enalapril or a placebo. Over an average of 4.4 years of follow-up, blood pressure reductions were sizable in all six groups and were significantly greater for participants assigned to drug treatment than placebo. A smaller but not significant proportion of participants assigned to the drug-treatment groups died or experienced a major nonfatal cardiovascular event than those assigned to the placebo group (5.1% vs 7.3%). After including other clinical events, the percentage of participants affected was significantly different: 11.1% for those in the drug-treatment groups and 16.2% for those in the placebo group. Differences among the five drug treatments did not consistently favor one group in terms of regression of left ventricular mass, blood lipids and other outcome measures.

Several additional long-term randomized controlled trials are underway that will address further the comparability of newer and older agents over risks and benefits. Published a year ago, Kaplan's textbook on clinical hypertension listed 15 ongoing trials addressing the comparability of newer agents, namely ACE inhibitors and calcium antagonists in reducing mortality and morbidity[130]. More recently, Whelton *et al* listed 32 of them. Most of these trials will compare first-step treatment with conventional therapy

such as diuretics or β-blockers, with one or several of the newer agents. Major long-term randomized-controlled trials of the effects of newer antihypertensive therapy over major health outcomes in hypertension are presented in Table 2.3. The publication of the results of these trials is expected to strengthen the base of knowledge regarding antihypertensive drug effects on morbidity and mortality.

2.2.4 Trials among high risk populations

The effects of calcium antagonists and ACE inhibitors on major disease endpoints have also been evaluated in numerous secondary prevention trials of patients with coronary disease or heart failure for instance, or among hypertensive subjects with diabetes. The results of these studies are briefly summarized below.

Coronary artery disease. There have been numerous randomized controlled trials of calcium antagonists for the treatment of patients with MI, angina or other ischemic cardiac disease. A large number of randomized controlled trials have assessed the effects of calcium antagonists on angina symptoms, postinfarction mortality and reinfarction. The Holland Interuniversity Nifedipine / Metoprolol Trial (HINT) showed in 1986 that calcium antagonists may worsen unstable angina[131]. The trial was stopped early due to an increase rate of MI in the nifedipine group. Two years later, the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT)[132] suggested increased mortality rates in coronary heart disease patients using calcium antagonists. Both the Multicentre Diltiazem Postinfarction Trial Research Goup[133] and the Danish Verapamil Infarction trial (DAVIT-II)[134] showed no increased risk of the calcium antagonists diltiazem and verapamil, against placebo, with regard to mortality or reinfarction. It has been suggested that the fact that they do not increase heart rate such as dihydropyridine agents do, could explain the postulated absence of a deleterious effect of these drugs on cardiovascular outcomes[135].

A large number of overviews arose from these and other trials. Held *et al* assessed the effects of calcium antagonists on reinfarction and mortality in MI and unstable angina using a systematic review of 28 randomized controlled trials[136]. There was no evidence of a beneficial effect of calcium antagonists on the development and size of infarcts or rate of reinfarction, nor was there evidence of heterogeneity among different calcium antagonists in their effects on any endpoint. A trend toward increased mortality

and reinfarction rates with the dihydropyridine calcium antagonists was reported. The authors concluded that calcium antagonists do not reduce the risk of initial or recurrent infarction or death when given routinely to patients with acute MI or unstable angina. Most of these trials were of short duration, however.

Another overview provided no clear evidence of an effect of calcium antagonists on the risk of MI or on overall mortality[137]. This review was updated later in light of a recent trial (DAVIT-II)[138] and earlier results were supported. Also, a meta-analysis in 1995 of 16 randomized controlled trials by Furberg, Psaty and collaborators[24] examined the association of nifedipine and total mortality in patients with coronary artery disease The authors found increased mortality rates among patients dispensed high doses of the short-acting nifedipine (RR=2.8; 95% CI=1.4=5.9). This meta-analysis was however largely criticized, notably due to the fact that the studies included in the analysis were from different source populations.

Overall, calcium antagonists studies in CAD suggested a reduced risk of MI in patients treated with diltiazem and verapamil and an increased risk in patients treated with the short-acting nifedipine[139]. β-blockers have been shown to reduce the risk of reinfarction and cardiovascular death by approximately 25% in patients with MI[140]. Overviews of long-term randomized controlled trials have shown that ACE inhibitors are of proven benefit in post-MI patients, especially with regard to total mortality, hospitalizations for heart failure and reinfarction rates[141].

Heart failure. In 1990, evidence against calcium antagonists was put forward with the publication of the results of another secondary prevention trial, this time among CHF patients, that showed worsening of heart failure following calcium antagonist treatment[142]. Overall, calcium antagonists trials in heart failure have provided no evidence of a beneficial effect of these agents on morbidity and mortality.

Several ACE inhibitor trials in patients with heart failure or left ventricular dysfunction have provided definite evidence of a reduction of about 20% in the risk of MI or sudden death[143,144]. Recent evidence also suggest that whereas β-blockers were previously contraindicated in heart failure, they may reduce hospital admissions and cardiovascular death by approximately 25%[145]. This evidence is however still disputed.

Diabetes. The United Kingdom Prospective Diabetes Study[146] compared an atenolol-based treatment with a captopril-based treatment program with regard to macrovascular, microvascular, renal and cardiovascular complications. In the study of patients with type 2 diabetes, there was no difference in outcomes between the two groups. Two major studies have however recently suggested that calcium antagonists may be unsafe for the management of hypertension in diabetic patients: the ABCD[147] and the FACET[148] studies, which are believed to confirm earlier fears with regard to that hypothesis. The Appropriate Blood pressure Control in Diabetes trial (ABCD)[147] is a prospective, randomized, blinded trial comparing the effects of moderate control of blood pressure with those of intensive control of blood pressure on the incidence and progression of complications of diabetes. The study also compared the calcium antagonist nisoldipine with the ACE inhibitor enalapril as a first-line antihypertensive agent in terms of the prevention and progression of complications of diabetes. In this population of patients with diabetes and hypertension, nisoldipine was associated with a higher incidence of fatal and nonfatal MI (RR=9.5; 95% CI=2.7-33.8) and the trial was stopped early for that reason. Because these findings are based on a secondary endpoints, they will require confirmation.

The Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET)[148] aimed at comparing the effects of fosinopril and amlodipine on serum lipids and diabetes control in NIDDM patients with hypertension. Cardiovascular events were assessed as secondary outcomes. A total of 380 hypertensive diabetics were randomly assigned to fosinopril or amlodipine and followed for up to 3.5 years. If blood pressure was not controlled, the other study drug was added. Both treatments were effective in lowering blood pressure. Patients receiving fosinopril had a significantly lower risk of the combined outcome of MI, stroke or hospitalized angina than those receiving amlodipine (RR=0.49, 95% CI=0.26-0.95). Fosinopril and amlodipine had similar effects on biochemical measures, but the patients randomized to fosinopril had a significantly lower risk of major vascular events, compared to amlodipine.

It is unclear however, in the absence of a placebo group, that one can differentiate between a harmful effect of calcium antagonists or whether ACE inhibitors are clearly preferable to calcium antagonists[149]. As a consequence, these studies were largely criticized[150,149].

2.2.5 Expert recommendations and clinical guidelines on the management of hypertension

The list of medications available for the treatment of hypertension has considerably expanded over the last years. Selecting the most appropriate agent for the treatment of hypertension remains very complex and even sometimes, controversial. The Canadian Hypertension Society and the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure in the United States give on a regular basis indications as to whom may benefit from antihypertensive therapy, when and what type of treatment is better indicated. The presence of risk factors for the development of cardiovascular disease is considered and treatment recommended on that basis. Before 1984, the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC) report on the management of hypertension recommended the stepped care approach to treatment with diuretics as a first step[151]. In 1984, β-blockers were added as first-line agents[54] and in 1988, the ACE inhibitors and calcium antagonists joined the two other drug classes as recommended initial therapy, due to their beneficial effect on blood pressure[152]. Because the ACE inhibitors and calcium antagonists had not been shown to reduce general mortality and cardiovascular morbidity in long-term randomized clinical trials, these two drugs classes were not recommended anymore as first-line agents in the 1993 report, unless there are special indications for their use[32]. Whereas clinical trials of calcium antagonists and ACE inhibitors were underway, the 1997 recommendations for treatment[153] still recommended the use of diuretics and β-blockers as first-line agents for the management of hypertension. Canadian guidelines were more stable over time, recommending monotherapy with either low-dose diuretics or β-blockers as preferred initial therapy both in 1989[154] and in 1993[155].

A succinct description of recommendations for initial drug therapy, based on the 1993 JNC-V guidelines in the US is presented below. The guidelines that were issued in 1993 were retained as these were in effect during most of our study period. One should note however, that with regard to initial therapy in our study, the 1988 guidelines were prevailing. The preferred drugs for initial treatment according to five National guidelines issued in 1993 are also outlined.

Non pharmacological interventions. Dietary and behavioral modifications are strongly recommended before pharmacological treatment is indicated[32,153]. Among those, a low-salt diet, weight reduction, limited alcohol intake, increased physical activity and smoking cessation have been shown to be effective in some patients[156-159]. Adequate potassium, calcium and magnesium intake should also be maintained as they have been shown either to be strong determinants of blood pressure or to have an overall cardioprotective effect[160-163]. However, most patients are believed to be noncompliant with these lifestyle changes and require pharmacologic therapy to attain blood pressure goals.

Lifestyle modifications recommended in treating hypertension and reducing overall cardiovascular risk.

- Weight loss
- Reduced alcohol intake (≤ 1 oz / day)
- Increased aerobic activity
- Reduced sodium intake (< 100 mmol / day)
- Adequate potassium, calcium and magnesium intake
- Smoking cessation
- Reduced dietary saturated fat and cholesterol intake

***Source**: Fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (1993)[32].*

Drug therapy. Drug therapy has been shown to significantly reduce morbidity and mortality from heart and renal failure, stroke and ischemic cardiac events among patients with high blood pressure[90,91,164]. Drugs used to treat hypertension include diuretics, ACE inhibitors, ß-blockers, calcium antagonists, vasodilators and centrally acting agents. Because diuretics and β-blockers have been shown to reduce mortality and morbidity, these two classes are preferred for initial drug therapy both in the Canadian and in the American guidelines[32,155]. If therapy with one of these agents is ineffective in relatively small dose, drug dose may be increased, another drug may be substituted or another agent may be added. A second or third agent may be added again in the case of inadequate response. The stepped care approach in these guidelines assumes that antihypertensive agents have different and gradual

potencies[165].

Some advocate an individualized approach to therapy, which is tailored to personal characteristics and to the other cardiovascular risk profile of the patient[166]. Accordingly, the perceived benefits or contraindications of antihypertensive agents should be balanced in an individualized approach to the treatment of hypertension. However, no general rule guarantees success and for that reason, modern management of hypertension differs from official guidelines and is often based on trial and error[167]. The North American reports noted that in special situations specific drugs should be chosen. In the presence of heart failure or diabetes, for instance, an ACE inhibitor (usually with a diuretic for heart failure) is appropriate. After a recent myocardial infarction (MI) or in angina, β-blockers are preferred; the calcium antagonists verapamil and diltiazem are also recommended in the Canadian guidelines[155]. The role of coexisting conditions such as congestive heart failure or angina is believed to be major in that one drug will often control both the high blood pressure and the other disease[168]. Indeed, hypertension is only one of several indications for antihypertensive agents. For instance, ACE inhibitors and diuretics are indicated both for hypertension and heart failure, and β-blockers and calcium antagonists are indicated for hypertension and angina. Although clinical guidelines based on consensus are readily available, several factors may play a role in the initial choice of antihypertensive therapy and in treatment adjustments. Factors such as disease severity, drug characteristics (side effects, concomitant therapy), comorbidity, patients' characteristics and non-pharmacological therapy may dictate therapeutic choices and lead to selective prescribing. It is estimated that half of the hypertensive patients in the US in the early '90s present with coexisting diseases[169,170]. The most frequent of the conditions are angina, diabetes, hyperlipidemia, heart failure, recent MI, renal impairment, asthma and chronic obstructive pulmonary disease[171]. Appendix 1 presents the main indications and contraindications to antihypertensive medications for hypertensive patients with these coexisting conditions.

Also, medical textbooks do not always recommend the approach to treatment that is advocated in clinical guidelines. For instance, as early as in 1988, a widely used medical textbook[31] recommended ACE inhibitors and calcium antagonists as possible first-line agents, despite the fact that only diuretics and ß-blockers were proposed in the JNC-IV guidelines[54].

Newer medications provide very useful alternatives for patients whose blood

pressure fails to respond to first line agents or for whom diuretics and β-blockers are not acceptable. According to the official guidelines for treatment, these should be reserved for that purpose only, pending additional evidence[172]. In line with clinical guidelines for the treatment of hypertension, this means that switching from a first- to a second-line agent could be considered appropriate if blood pressure is not controlled or in the presence of side effects. We may hypothesize as well that the use of these second-line agents may indicate more severe hypertension or the presence of coexisting conditions.

Preferred drugs for initial therapy according to five current (1993) hypertension guidelines.

Canada[154,155,173]	Monotherapy with either low-dose thiazide diuretic or ß-blockers
New Zealand[174]	Low-dose diuretics and low-dose ß-blockers should be considered as first-line treatment
United Kingdom[175]	Two classes of drugs have been adequately and extensively tested in outcome trials: diuretics (thiazides) and ß-blockers
United States (JNC V)[32]	Because diuretics and ß-blockers have been shown to reduce morbidity and mortality, these two classes are preferred for initial drug therapy
WHO/ISH[176]	Several classes can be recommended as first-line treatment. They may be listed, in order of proven benefit based on morbidity and mortality studies: 1) diuretics, 2) ß-blockers, 3) ACE inhibitors, calcium antagonists, α-adrenoreceptor blockers

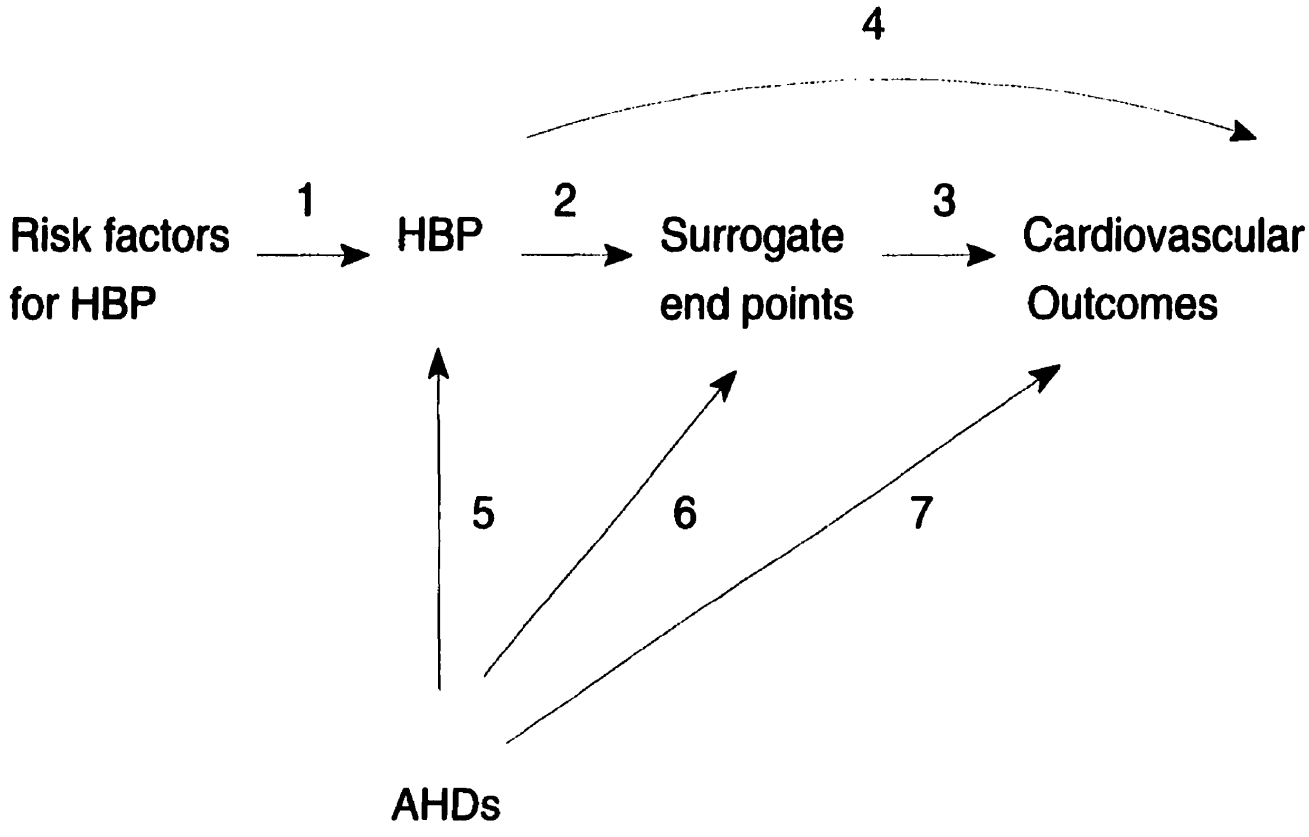
Extracted from Alderman *et al* 1993[177].

2.2.6 Methodological considerations on the usefulness of randomized trials results

The randomized controlled trial, so-called the "gold-standard" for medical research, has its own limitations and is not always perfectly adequate for use as a basis for setting standards with regard to clinical practice. Differences between the results of these numerous trials, for instance, may be explain in terms of design features and study populations. The types of patients enrolled and the varying durations of follow-up markedly differed. Hence, comparing their results may sometimes be inappropriate. The ability of these trials to detect moderate effects such as those expected in cardiovascular disease, may also be limited due to small sample sizes or short duration of follow-up. According to Collins and MacMahon, none of the trials of antihypertensive treatment (up to 1994) recorded enough cardiac events to reliably assess statistically significant reductions in risk of 10 to15%[44]. Often, events that have longer latency or that

will express themselves only after cumulative use of the drugs can not be adequately assessed in short duration trials. Also, sub-group analyses are often performed to identify the specific subsets of the population that showed the most benefits of the intervention[52]. These *post-hoc* subgroup analyses should however be interpreted with caution due to an increased risk of false positive results[178].

In addition, the randomized controlled trial may not be suited for gathering evidence on the use of medication in the clinical ("real-world") setting due to many design-based constraints (strict protocol, selected study populations, close follow-up)[179-182]. For instance, one of the strategies to enhance compliance in randomized controlled trials is to exclude patients not likely to comply with therapy. In the absence of close monitoring, modifications in treatment are likely to be considerably more frequent in a real life setting than it is observed in the experimental realm. Also, treatment with proven efficacy do not necessarily perform as well under conditions of typical practice[183,9]. The scientific rigor and high internal validity of the randomized controlled trial needs to be balanced with the external validity of large observational studies.



Abbreviations: HBP=High blood pressure; AHDs=Antihypertensive drugs.

Figure 2.2 **Conceptual framework for the study of the effects of antihypertensive therapy.**

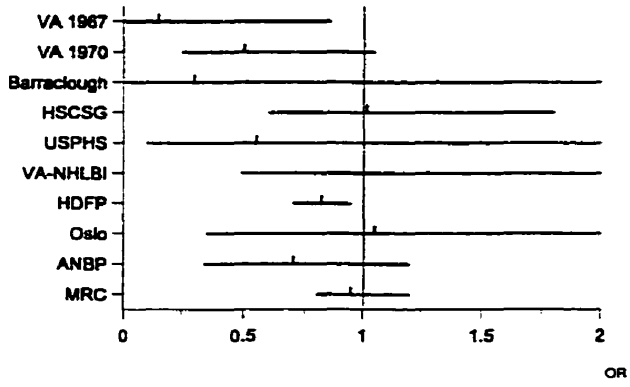


Figure 2.3 **Odds ratios (95% CI) for the effect of blood pressure reduction on all-cause mortality in younger and middle-aged subjects.**

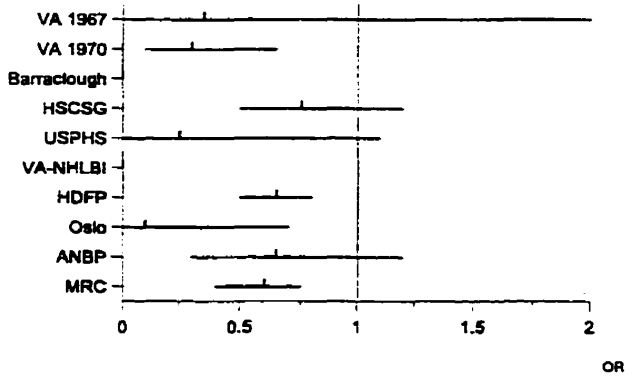


Figure 2.4 **Odds ratios (95% CI) for the effect of blood pressure reduction on stroke in younger and middle-aged subjects.**

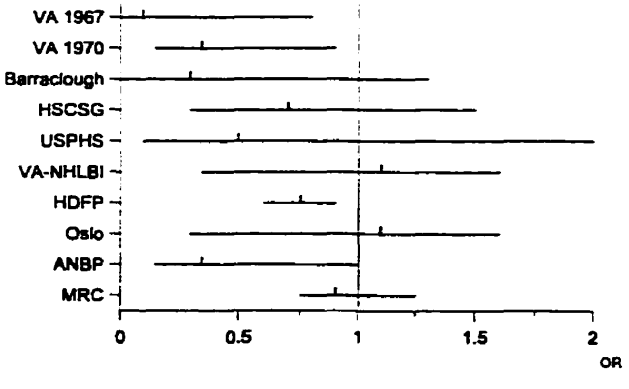


Figure 2.5 **Odds ratios (95% CI) for the effect of blood pressure reduction on cardiovascular disease in younger and middle-aged subjects.**

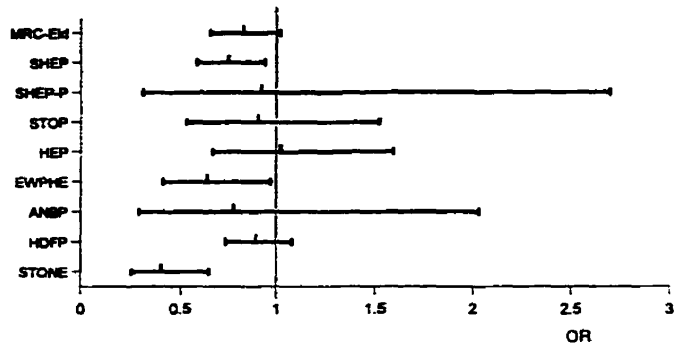
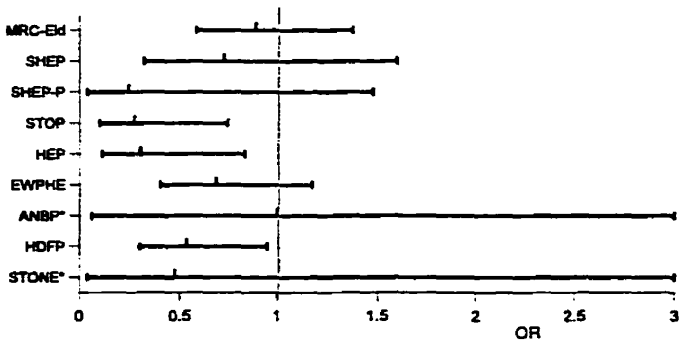


Figure 2.6 **Odds ratios (95% CI) for the effect of blood pressure reduction on major coronary heart disease in the elderly.**



* Upper bound of the CI for the ANBP and STONE studies exceeded 3.0.

Figure 2.7 **Odds ratios (95% CI) for the effect of blood pressure reduction on cardiovascular mortality in the elderly.**

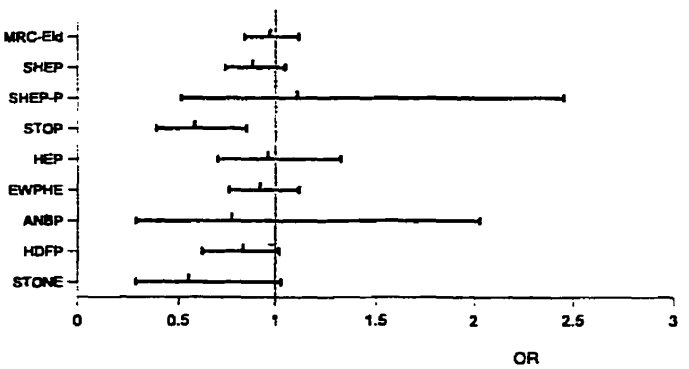


Figure 2.8 **Odds ratios (95% CI) for the effect of blood pressure reduction on all-cause mortality in the elderly.**

Table 2.1 **Major long-term randomized controlled trials of active treatment (against placebo, control or usual care) in hypertension.**

Study (ref)	Year	Duration (y.)	No. Patients	Age (y.)	Active treatment
VA studies[109,110]*					
DBP 90-114 mmHg[91]	1967	3.3	380	51†	Diuretic-based
DBP 115-129 mmHg[90]	1970	1.5	143	51†	
Barraclough[184]	1973	2	116	56†	Diuretic / Methyldopa
USPHS[185]	1977	7	389	21-55	Diuretic-based
VA-NHLBI[186]	1977	1.5	1012	21-50	Diuretics as step 1
HDFP[92,187-193,99]	1979	5	10,940	30-69	Diuretics as step 1
Oslo[97]	1980	5.5	785	40-59	Diuretics as step 1
ANBP[96,194,195]	1980	4	3427	30-69	Diuretics as step 1
EWPHE[102]	1985	4.7	840	>60	Diuretics
MRC[34]	1985	5	17,354	35-60	β-blockers / Diuretics
HEP[79]	1986	4	884	60-79	β-blockers
SHEP-pilot[196]	1989	3.8	551	>60	Diuretics as step 1
SHEP[113]	1991	4.5	4736	>60	Diuretics as step 1
STOP[197]	1991	2	1627	70-84	Diuretics / β-blockers
MRC-elderly[121]	1992	5.8	4396	65-74	Diuretics / β-blockers

Acronyms: VA studies = Veterans Administrations Cooperative Study; USPHS = US Public Health Service Hospitals Cooperative Group Trial; VA-NHLBI = Veterans Administration - National Heart, Lung and Blood Institute Study Group on Antihypertensive therapy; HDFP = Hypertension Detection and Follow-up Program; ANBP = Australian National Blood Pressure trial; EWPHE = European Working Party on High Blood Pressure in the Elderly; MRC = Medical Research Council; HEP = Randomized trial of treatment of Hypertension in Elderly Patients in Primary Care; SHEP = Systolic Hypertension in the Elderly Programme; STOP = Swedish Trial in Older Patients.

* In the VA trials, stratified analysis according to baseline DBP were reported independently by the authors.

† On average.

Table 2.2 **Comparative trials of diuretics and β-blockers in hypertension, with β-blockers as the reference .**

Study (ref.)	No. subjects	Age (y.)	Follow -up (y.)	Treatment contrasts	Difference (%)		
					Stroke	Coronary disease	CV mortality
MRC[34]	17,354	35-64	5	Diuretics vs β-blockers	-58*	17	7
MRC-elderly[121]	4396	65-74	5.8	Diuretics vs β-blockers	-18	-40*	-30*
HAPPHY[107]	6569	40-64	3.8	Diuretics vs β-blockers	30	-11	7
IPPPHS[106,103]	6357	40-64	4	No β-blockers vs β-blockers	3	9	5

Acronyms: MRC = Medical Research Council; HAPPHY = Heart Attack Primary Prevention in Hypertension Trial; MAPHY = Metoprolol Atherosclerosis Prevention in Hypertensives Study; IPPPSH = International Prospective Primary Prevention Study in Hypertension.
Abbreviations: y.=years; CV = Cardiovascular.

* Statistically significant.
Adapted from [198].

Table 2.3 **Long-term randomized-controlled trials of the comparative effects of newer antihypertensive therapy over major health outcomes in hypertension.**

Study (ref.)	No. subjects	Age (y.)	Duration (y.)	Treatment contrasts
ALLHAT[199]	40,000	≥55	6	Amlodipine vs Chlothalidone vs Lisinopril vs Doxazosin
ANBP-II[200]	6000	65-84	5	Ace inhibitor vs Diuretic
ASCOT[201]	18,000	40-80	5	Thiazide ± β-blocker vs Amlodipine ± ACE inhibitor
CAPPP[202]	10,985	25-66	5	Captopril vs Diuretic or β-blocker
CONVINCE[203]	15,000	≥55	7	Verapamil vs HCTZ vs Atenolol
HOT[125]	18,790	50-80	4	Felodipine vs Placebo
HYVET[204]	2100	>80	5	Lisinopril vs Bendrofluazide vs No treatment
INSIGHT[205,206]	6600	≥55	5	Nifedipine vs HCTZ / Amiloride
MIDAS[126]	883	59*	3	Isradipine vs HCTZ
NORDIL[207]	12,000	50-69	7	Diltiazem vs Diuretic or β-blocker
STONE[19]	1632	60-79	2.5	Nifedipine vs Placebo
SHELL[208]	4800	≥60	5	Lacidipine vs Chlorthalidone
STOP-II[197]	6600	70-84	4	Isradipine or Felodipine vs Enalapril or lisinopril vs Moduretic or β-blocker
SYST-China[22,123,124]	3000	≥60	3	Nitrendipine ± Captopril and HCTZ vs Placebo
SYST-Eur [21,209,210]	4695	≥60	7	Nitrendipine (+ enalapril and HCTZ if needed) vs Placebo
TOMHS[129]	902	45-69	4.4	Chlorthalidone vs Atenolol vs Doxazosin vs Amlodipine vs Enalapril vs Placebo

Acronyms: ALLHAT= Antihypertensive and lipid Lowering heart Attack Prevention Trial; ANBP-II=Australian National Blood Pressure Study -II; ASCOT=Anglo-Scandinavian Cardiac Outcomes Trial; CAPPP=Captopril Prevention Project; CONVINCE=Controlled Onset Verapamil Investigation of Cardiovascular Endpoint; HOT= Hypertension optimal Treatment study; HYVET=Hypertension in the Very Elderly Trial; INSIGHT= International Nifedipine Study Intervention as a Goal in Hypertension Treatment; MIDAS=Multicenter Isradipine Diuretic Atherosclerosis Study ;NORDIL = Nordic Diltiazem Study; SHELL=Systolic Hypertension in the Elderly Lacidipine Long-term Study; STONE=Shanghai trial of nifedipine in the elderly; STOP-II=Swedish Trial in old Patients with Hypertension-II; Syst-China=Systolic Hypertension in China; Syst-Eur = Systolic Hypertension in Europe Trial; TOMHS=Treatment of Mild Hypertension Study.

Abbreviations: y.=years; ACE=Angiotensin-converting-enzyme; HCTZ=Hydrochlorothiazide; CD=Capsule dual-release.

* On average.

2.3 The safety of calcium antagonists in the clinical practice: a controversial issue

Calcium antagonists have been widely used for about two decades for the treatment of cardiovascular disease[135]. Despite their occasional side effects, most patients do tolerate these agents very well and as stated in the previous section of this literature review, their efficacy at reducing blood pressure in hypertension and at relieving chest pain in angina has been extensively documented. However, large randomized controlled trials of calcium antagonists that assess the relative long-term value of these agents on the reduction of morbidity and mortality in patients with hypertension are still ongoing with results awaited soon. Recent observational studies of calcium antagonists in hypertension have reported various adverse effects, such as MI[23,25] and other cardiovascular effects[211], cancer[212-214], gastrointestinal and surgical bleeding[215-218], suicide[219] and mortality[25,220]. Data accumulated earlier from secondary prevention trials have also raised concerns as to whether calcium antagonists increase morbidity and mortality in patients with coronary artery disease[24,131,132,136,142].

This section of the thesis will describe the chronology of the controversy on the safety of calcium antagonists and critically examine methodological issues that pertain to the validity of the results of previous observational studies.

2.3.1 Observational studies of the cardiovascular effects of calcium antagonists

In recent years, reports have suggested that hypertensive patients treated with calcium antagonists are at increased risk for a variety of adverse effects[23,25,25,211-220]. Calcium antagonists, and especially the short-acting formulations of them, were suspected of increasing the risk of MI or mortality[23,25,211]. The controversy started with the publication of a population-based case-control study by Psaty *et al* in 1995[23] that suggested an increased risk of MI with calcium antagonists in hypertension (Table 2.4). Psaty *et al*[23] compared 623 hypertensive patients who had sustained a MI with 2023 controls with regard to their current use of antihypertensive agents. The observed risk of MI was 1.6 times higher among current users of calcium antagonists (95% CI=1.12-2.27) compared to β-blockers. The increased risk was higher with increasing dosages and higher for diltiazem and verapamil than for nifedipine.

A cohort study, published the same year by Pahor *et al*[25], showed similar results but higher in magnitude. Pahor *et al* reported on long-term survival in association with the use of antihypertensive agents in the elderly using a cohort design. After adjustment for

potential confounders of the association, the authors found the use of nifedipine to be significantly associated with an increased risk of all-cause mortality (RR=1.7; 95% CI=1.1-2.7), cardiovascular events (RR=3.5; 95% CI=1.6-7.8), CHF (RR=3.5; 95% CI=1.7-7.4) and MI (RR=5.6; 95% CI=1.8-17.5) as compared with β-blockers. Higher doses of nifedipine were associated with higher mortality. Increased risks of CHF (RR=3.3; 95% CI=1.5-6.9) and cardiovascular disease (RR=5.0; 95% CI=2.1-12.3) were also reported for the calcium antagonist diltiazem. No increased risk was found among ACE inhibitors users, relative to β-blockers. Whereas evidence against calcium antagonists was slowly accumulating[221], a number of letters, editorials and commentaries were published and extensively discussed these results[26,221-233].

Yet, a few studies were published that added to the evidence of no harm for calcium antagonists[234-238,211,220]. Surprisingly, a previous case-control study by Aursnes *et al*[234] that showed hypertensive patients treated with calcium antagonists to have a lower but not significant (RR=0.63; 95% CI=0.30-1.35) risk of MI than those receiving conventional therapy (i.e. β-blockers alone or in combination with other agents, and diuretics alone), was not referred to in Psaty's study. Two other case-control studies by Jick *et al*[236,235] concluded that there was no increased risk of MI with calcium antagonists relative to β-blockers. The first of these studies used 210 cases and 793 controls to investigate the relation between different antihypertensive therapies and MI in hypertension[235]. Compared with users of β-blockers alone, the adjusted relative risk (RR) estimate for all calcium antagonists was 0.90 (95% CI=0.5-1.7). In the second study composed of 207 cases of MI and 409 controls, Jick *et al*[236] found that compared with β-blocker users, the matched RR estimates for fatal MI, adjusted for potential confounders including the duration of hypertension and prior use of other antihypertensive drugs, was 0.7 (95% CI=0.4-1.2) for ACE inhibitors and 0.9 (95% CI=0.5-1.5) for calcium antagonists.

A cohort study published in 1996 by Braun *et al*[237] reported no increased risk for mortality between users and non-users of calcium antagonists with coronary artery disease (CAD). After adjustment for concomitant medication use and potential confounders, the RR for mortality was estimated at 0.97 (95% CI=0.84-1.11) relative to users of other antihypertensive medications. Bulpitt *et al*[220] used two existing case-control studies and a cohort to examine mortality in the treatment of hypertension. The authors found the adjusted RR associated with calcium antagonists (relative to diuretics) to be 1.32 (95% CI=0.64-2.70) for ischemic heart disease mortality and 1.05 (95%

CI=0.60-1.84) for cardiovascular mortality. Similar results were observed for methyldopa, β-blockers and ACE inhibitors. Increased 1-year mortality rates were also found in association with calcium antagonist use (RR=1.62; 95% CI=1.06-2.49), relative to other antihypertensive medications.

Alderman *et al*[211] conducted a case-control study to assess the association of any prescribed drug regimen that was being taken on the event date, with cardiovascular outcomes. Compared with those on β-blocker monotherapy, patients taking long-acting calcium antagonists had no increased risk of a cardiovascular event (RR=0.76; 95% CI=0.41-1.43), whereas patients on short-acting calcium antagonists had a significantly elevated risk (RR=3.88; 95% CI=1.15-13.11). A retrospective cohort analysis of newly diagnosed hypertensive subjects without prior coronary heart disease was conducted by Leader *et al*[238] to evaluate the relative risk of acute MI in association with calcium antagonists monotherapy. The authors found no increased risk of calcium antagonists when compared to either β-blockers (RR=0.49; 95% CI=0.11-2.20) or diuretics (RR=0.60; 95% CI=0.16-2.32). Finally, Michels *et al*[239] used the Nurses' Health Cohort to explore the association between calcium antagonists and cardiovascular disease. Single drug users of calcium antagonists had an age-adjusted RR for acute MI of 2.36 (95% CI=1.43-3.91) compared with those prescribed thiazides. Women prescribed calcium antagonists also had a higher prevalence of ischemic heart disease. After adjustment for these and other coronary risk factors, the RR was 1.64 (95% CI=0.97-2.77).

2.3.2 Formal reviews of evidence regarding the controversy

Following the publication of these findings, the need for large prospective randomized controlled trials to evaluate the safety of newer long-acting agents was reinforced[221] and the Food and Drug Administration (FDA) advisory committee was asked to release a statement on this issue. After reviewing all available evidence, the FDA warned the population that the use of short-acting nifedipine could increase the risk of myocardial infraction in some patients while calcium antagonists as a class still remained safe to use[240]. That position was in agreement with that taken by the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH) in September 1996.

In 1997, the World Health Organization (WHO) reviewed the evidence regarding the risks of cardiovascular events[241]. The Committee underlined the fact that evidence for

adverse effects of calcium antagonists was generated from observational studies and small randomized controlled trials, and that long-term large randomized controlled trials were lacking. For that reason, the report stated, in accordance with the United States Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure[32], that whereas diuretics and β-blockers have clearly proven benefits in mortality and morbidity studies, the data on CHD risk from randomized studies of calcium antagonists are limited. However, the available evidence from observational studies does not prove an adverse effect of calcium antagonists on major CHD events including fatal and non fatal MI and other deaths from CHD. Calcium antagonists were consequently considered useful agents for the treatment of hypertension and clinicians were recommended not to change their clinical practice.

2.3.3 Critical appraisal of population-based observational studies of calcium antagonists

The validity of Psaty's conclusions were largely criticized in editorials and letters to the editor[242-253,233] and even, accused of being hampered by important methodological flaws, one of which being the observational nature of the study design. It is indeed likely that the decision to prescribe calcium antagonists for the treatment of high blood pressure was influenced by factors associated with CHD risk. Whereas the authors of several of these studies claimed to have adjusted for potential confounders of the association, confounding by indication was pointed as being the most likely explanation for the study findings. In Psaty's study[23], the medication history of patients using calcium antagonists was not documented. If patients at higher risk for developing a MI were found to be selectively prescribed second-line agents, after uncontrolled hypertension with earlier treatment regimens for instance, indication bias could have explained the results. The finding of a higher risk of CHD after higher doses of calcium antagonists is coherent with the hypothesis of sicker patients receiving calcium antagonists, perhaps for worst blood pressure control or worsened angina. The use of a cohort of patients with long-standing hypertension (12 years on average) may have posed an additional threat to the comparability of the contrasted groups with this regards.

Aursnes *et al*'s study[234] also suffered from several limitations: unknown were the duration of hypertension and prior medication use. Also, the reference category was not homogeneous (including "all other agents") and more than 50% of the cases had

evidence of angina at the beginning of the study. As did Psaty *et al*[23], Aursnes *et al* used a prevalent cohort to fulfill their study objectives. A lack of comparability of the contrasted groups may therefore be highly suspected. The study was however the first to perform stratified analyses according to the presence of angina. Aware of the possibility of differential prescribing of specific agents, Pahor *et al*[25] stratified their analysis for a number of factors known for their association with mortality. However, as in the previous studies, precise information on duration and severity of hypertension before treatment was not available. Indeed, a higher prevalence of CHD at baseline was reported for patients using nifedipine and diltiazem, thus suggesting that confounding by indication may have played a role in the reported associations.

Jick *et al*[236,235] did control in their analyses for earlier use of antihypertensive agents and for the duration of hypertension. However, the use of a prevalent cohort of hypertensive subjects precluded the authors from adequately taking into consideration drug history as study subjects were at different moments in the course of the disease. Hence, the results reported by Jick *et al*[236,235] could be biased by the severity of hypertension. Braun *et al*'s study[237] also used a prevalent cohort of subjects to assess differential mortality rates. In addition, their exposure definition is based on a single report of therapy during screening examination. Finally, the source population is one with coronary artery disease and the study may therefore address a different problem.

Bulpitt *et al*[20] have grouped together the subjects of three different studies: two case-control and a cohort. The source population lacks appropriate definition and identification, Also, they used prevalent users and exposure definition is not clear. In addition to being restricted to a duration of exposure no greater than six months, a prevalent cohort of hypertensive subjects was also used by Alderman *et al*[11] and Michels *et al*[39]. Finally, Leader's study[238] was the first to adequately use a cohort of newly diagnosed hypertensive subjects, therefore increasing the comparability of the contrasted groups. However, a small number of events was observed and the presence of comorbid conditions was not adjusted for. Also, the report did not include deaths occurring outside the hospital, which are fairly common in acute MI.

No deleterious effects of calcium antagonists were suggested among hypertensive subjects, especially those without clinical manifestations of heart disease, before Psaty's case-control study gave rise to an important debate in 1995[23]. Throughout the controversy, a number of epidemiological issues have been emphasized to have had

contributed to nourish the controversy. The points listed below summarize the role of several issues involved in previous observational studies of the effects of calcium antagonists on MI and cardiovascular risks.

Drug-related differences. The discrepancies in these study results may be explained by factors relating to characteristics of the studied drugs. Specific agents differ by their molecular structure, mode of action, dosage and formulation and potentially, by their overall effects[254-257]. One may suggest that all agents from a given therapeutic class should not be assumed to be equivalent. Calcium antagonists for instance, differ in a number of ways[222,258,259]; therefore, adverse effects of the drugs may not be a class effect. For instance, the short-acting dihydropyridines (e.g., nifedipine capsules) have a rapid onset of action and vasodilator effect, whereas long-acting formulations (e.g., nifedipine GITS and amlodipine) have a more consistent duration of action[222]. The case-control study by Psaty *et al*[23] found an increased risk for MI with the calcium antagonists verapamil and diltiazem, but not for the short-acting nifedipine. In contrast, Pahor *et al*[25] found an elevated risk of mortality in association with short-acting nifedipine but not for verapamil and diltiazem. These differences may indicate either that not all calcium antagonists are equal or that different agents from a same therapeutic class are differentially prescribed. Also, the increased risk of cardiovascular events were found in some studies specifically with medium and large doses of calcium antagonists[23,24] or with the short-acting formulations of calcium antagonists only[23-25,211]. Because short-acting agents have to be taken three times a day, compliance with therapy becomes a major issue and accordingly, uncontrolled hypertension may be more frequent. Alderman *et al* [211] for instance, found an increased risk of cardiovascular events associated with the use of short-acting calcium antagonists whereas no increased risk was found for the long-acting formulations. When comparing the two formulations, a relative risk of 8.56 for cardiovascular events was found (95% CI=1.88-38.97). This may suggest a possible heterogeneity of the effects across different agents[260].

Differences in the study populations. A preceding section of this review outlines the results of randomized controlled trials conducted in several populations. These trials suggest that different effects may be observed in different populations. Meta-analysis may be useful when the study populations are homogeneous[261]. In Furberg's meta-

analysis[24], the criteria for inclusion of studies are not clearly stated. The analysis combined the results from 12 trials in post-MI patients, three trials in unstable angina and another that included coronary artery disease patients. As previously discussed, the effects of calcium antagonists may differ according to the studied population and the meta-analysis should have been confined to homogeneous populations with similar risks.

The reference group. In observational studies, the choice of an adequate and clearly defined reference group is crucial. In their case-control study reporting a harmful affect of calcium antagonist on MI risk, Psaty *et al* used current use of β-blockers as a reference group[23]. A few years earlier, the same authors published another case-control study investigating whether β-blockers, used for the treatment of hypertension, were effective at preventing a first event of coronary heart disease[262]. The authors found β-blockers to be particularly useful at preventing a first non-fatal MI in patients with high blood pressure (RR=0.62; 95% CI=0.39-0.99). Given that beneficial effect of β-blockers and unless calcium antagonists are as good as β-blockers, one could expect the risk ratio for calcium antagonists to be high when compared to these agents. In another case-control study, Psaty *et al* reported the risk of incident coronary heart disease to be associated with recently stopping the use of β-blockers (RR=4.5; 95% CI=1.1-18.5)[263]. The withdrawal syndrome associated with β-blockers was not taken into consideration when using these agents as the reference in their latest study[23].

Confounding by indication. Of primary concern when assessing intended drug effects using observational studies is the potential bias introduced by the selective use of antihypertensive therapy. For instance, specific agents or higher doses may be used in patients with more severe disease or at higher risk of an event. In that case, the observed effect of a drug may wrongly be attributed to the drug itself rather than to characteristics of the patients. Contrasted groups not only need comparability with regard to known risk factors for the disease but also with regard to the timing of use of the antihypertensive drug of interest in the course of the disease being treated. Most previous studies have used prevalent cohort and compared different agents without regard to the duration of hypertension and the duration of use of these medications. Medication use was sometimes assessed at baseline only[25] and subsequent changes in

therapy were not considered. In at least two studies, the drug was that used three years earlier[237,25].

Conclusion. Finally, long term safety and efficacy of prescribed drugs are constant issues in medical practice. Randomized controlled trials provide limited insight on scientific evidence with regard to this issue at the population level and for that reason, population-based observational studies do provide useful information with regard to drugs effects in the population. Although previous observational studies were largely criticized for methodological concerns, they raised serious questions and great concern among the medical community with regard to the safety of widely used antihypertensive agents with well proven efficacy and effectiveness.

***Table 2.4* Population-based studies of the effect of calcium antagonists on cardiovascular outcomes.**

Author (ref.)	Study design	Source population	Main CCB exposure	Primary endpoint	Adjusted RR (95% CI)
Aursnes (1995)[234]	Case-control	Prevalent Hypertension	Calcium antagonists	Acute MI	0.63 (0.30-1.35) vs all other Rx
Psaty (1995)[23]	Case-control	Prevalent Hypertension	Current use of calcium antagonists SA	Acute MI	1.58 (1.04-2.39) vs diuretics 1.60 (1.12-2.27) vs ß-blockers
Pahor (1995)[25]	Cohort	Prevalent Hypertension	Nifedipine SA	All-cause mortality Cardiovascular events CHF MI	1.7 (1.1-2.7) vs ß-blockers 1.7 (1.1-2.7) vs ß-blockers 3.5 (1.7-7.4) vs ß-blockers 5.6 (1.8-17.5) vs ß-blockers
			Diltiazem	CHF Cardiovascular disease	3.3(1.5-6.9) vs ß-blockers 5.0 (2.1-12.3) vs ß-blockers
Jick (1996)[235]	Case-control	Prevalent Hypertension	Calcium antagonists	Non fatal acute MI	0.90 (0.5-1.7) vs ß-blockers
Braun (1996)[237]	Cohort	Prevalent CAD	Short-acting nifedipine Diltiazem Verapamil	All-cause mortality	0.97 (0.84-1.11) vs all other Rx
Bulpitt (1997)[220]	Case-control Cohort	Prevalent Hypertension	Calcium antagonists	IHD mortality Cardiovascular mortality One-year mortality	1.32 (0.64-2.70) vs diuretics 1.05 (0.60-1.84) vs diuretics 1.62 (1.06-2.49) vs other Rx
Alderman (1997)[211]	Case-control	Prevalent Hypertension	Calcium antagonists LA Calcium antagonists SA	Cardiovascular events	0.76 (0.41-1.43) vs β-blockers 3.88 (1.15-13.11) vs β-blockers
Jick (1997)[236]	Case-control	Prevalent Hypertension	Calcium antagonists	Fatal MI	0.9 (0.5-1.5) vs ß-blockers
Leader (1997)[238]	Cohort	Newly diagnosed Hypertension	Calcium antagonists	Acute MI	0.49 (0.11-2.20) vs ß-blockers 0.60 (0.16-2.32) vs diuretics
Michels (1998)[239]	Cohort	Prevalent Hypertension	Calcium antagonists SA	MI	1.64 (0.97-2.77) vs diuretics.

Abbreviations: CCB=Calcium antagonists; CI=confidence intervals; MI=myocardial infarction; CAD=coronary artery disease; CVD=cardiovascular disease; SA=Short-acting; LA=Long-acting.

* Unadjusted RR.

2.4 Antihypertensive drug use in the clinical practice

Drug utilization is one of the most important components of overall medical care[264]. The increasing drug expenditures in many countries may be partly due to inappropriate use of newer and more expensive agents. Rational drug use refers to treatment regimens that are safe, effective, appropriate and economical. In the realm of hypertension, inappropriate drug use most often translates into underutilization rather than overutilization of medications. Compliance to therapy for instance, usually defined as the extent to which a patient's behaviour coincides with accepted standards of care or medical advice, has been a major concern over the past decades[265]. Lack of compliance or improper use of drug therapy may lead to failure to produce the desired results. As it is assumed in the experimental paradigm, accurate assessment of drug effects requires evidence that the drug was actually obtained and taken[266]. However, very little is known about drug taking behaviours and the effects of medication use in the clinical practice, where compliance to therapy may not be optimal and patients present with different characteristics that may bear on their drug taking behaviours.

Assessing the use of medications in epidemiological studies is challenging, especially in a chronically ill population such as hypertensive patients: numerous agents are available, treatment regimens, that are generally assumed to be life-long, are highly variable and therapeutic modifications are believed to be highly prevalent. A number of studies have been undertaken to determine the distribution and determinants of use of specific antihypertensive agents in the population. These studies have primarily consisted of cross-sectional samples of antihypertensive drug users to provide a general picture of drug use at a specific point in time[42,267-271]. Others have assessed time trends in the use of medications[272-277] or in drug sales[168,277-281]. Newly diagnosed patients[281] or subjects initiating antihypertensive therapy[42,274,282-285] have also been investigated to describe the physicians' choices in terms of initial therapy, across drug classes. Finally, many studies have been published so far in an attempt to compare the rates of compliance with therapy at the population level for the various drug classes and to document correlates of compliance with therapy[282,284-294,294-296,296-299]. Unfortunately, studies that have examined treatment modifications over the course of therapy are less numerous and a large number of them having examined only one aspect of treatment modifications namely, discontinuation of therapy[42,287,288,290,292,297,300-305].

This part of the review of the literature is divided into four sections. The first section

presents an overview of drug utilization studies, starting with a description of the distribution of antihypertensive drug use in the population, emphasizing secular trends in the management of hypertension and determinants of drug use. In the following section, a review of compliance studies is presented, along with a summary of the factors that have been shown to be associated with compliance or persistence with therapy. The third section presents studies that examined patterns of use such as modifications to therapy and treatment interruptions. The advantages and limitations of drug utilization studies are being discussed in the last section.

2.4.1 Distribution and determinants of antihypertensive drug use

Table 2.5 presents information pertaining to the distribution of use of antihypertensive agents among hypertensive patients. The proportion of patients initiating treatment with a diuretic in the recent years ranges from 10% to 46%. Reported use of ACE inhibitors and calcium antagonists, which entered the market later in time, is much less variable, with prevalence of use ranging from 14% and 34%. Overall, antihypertensive drug utilization have been shown to increase over time in numerous studies. Also, while the prevalence of use of diuretics significantly decreased between 1982 and 1994, ACE inhibitor and calcium antagonist use is steadily growing. It is worth noting also that some of these studies have retained only patients using a single agent, while others covered the entire spectrum of drug classes and allowed overlaps between categories. These variations make comparisons across studies very cumbersome. Discrepancies of prevalence figures in patients with established hypertension are even more pronounced.

Several factors have been identified to be associated with the use of specific agents among patients with hypertension. Among those, women and older patients have been associated with more frequent use of diuretics[267,270-272,281,285] and a lesser use of β-blockers and other antihypertensives[270]. Also, patients with coronary artery disease and heart failure have been shown to be more likely to receive calcium antagonists and β-blockers[267,272,277] whereas diabetes is associated with the use of ACE inhibitors[271,272,277]. A brief description of the studies that have examined the distribution and determinants of antihypertensive treatment follows.

One of the first studies by Ray *et al*[281] showed that patients' characteristics had a definite influence on the choice of initial therapy. Following an initial diagnosis of

hypertension, more than 50% of patients were dispensed a diuretic and 10% a combination of diuretics and β-blockers. Around 15% of patients received a combination of three or more agents. Older patients, women and Caucasians were more likely to receive a diuretic. Psaty *et al*[267] used the baseline examination data of a large cohort study of risk factors for coronary heart disease, the *Cardiovascular Health Study*, to assess the prevalence and distribution of medication use. They found the use of diuretics and, to a lower extent calcium antagonists and β-blockers, to be highly prevalent among patients with cardiovascular disease. Most patients without cardiovascular disease used diuretics. In a following study, Psaty *et al*[42] reported on newly treated hypertension and described the patterns of use of antihypertensive drugs using the second examination of the *Cardiovascular Health Study*. The authors estimated the yearly incidence rate of newly treated subjects to be approximately 5%. When comparing incident to prevalent users, the authors found the probability of using diuretics or β-blocker to be much lower (about half) among new hypertensive (especially males), whereas new users were more likely to use calcium antagonists or ACE inhibitors. The authors concluded that physicians were increasingly prescribing ACE inhibitors and calcium antagonists in place of diuretics and β-blockers for the treatment of hypertension. Knapp *et al*[268] examined drug management of patients for which the main reason for a medical visit was hypertension. The authors found that among all medical visits, 38% lead to a prescription for a diuretic, 24% for a calcium antagonist, 23% for an ACE inhibitor and 19% for a β-blocker. Of the 19,945 visits, 80% led to the prescription of at least one antihypertensive agent, of which 44% were a combination therapy. Among single agents, β-blockers were the least frequent.

In a recent survey of prescribing practices among primary care internists, Mehta *et al*[271] have reported that the use of ACE inhibitors is preferred in patients with diabetes or heart failure. The authors also reported MI patients to be more likely to receive selective β-blockers whereas calcium antagonists and ACE inhibitors would be preferentially prescribed to asthma patients. Diuretics were found to be widely used in older patients.

Using a prescription-based approach (where the prescription is the unit of analysis rather than the patient), Wallenius *et al*[270] analysed prescribing practices in Finland in 1993 among patients with chronic hypertension. Of all prescribed agents, 30% were β-blockers and around 66% were diuretics, calcium antagonists or ACE inhibitors (all equally distributed) in combination or not with a diuretic. Using a patient-based analysis,

the authors found the choice of antihypertensive drugs to depend on age and sex, with fewer women being dispensed β-blockers and antihypertensive agents (including ACE inhibitors and calcium antagonists) and more of them receiving diuretics. Examining prescribing patterns of antihypertensive medications in the primary care setting in Israel, Rotmensch *et al*[69] found that sixty-four per cent of patients with diagnosed hypertension were prescribed a single agent, the most commonly prescribed monotherapy being ACE inhibitors, followed by β-blockers and calcium antagonists. Overall, diuretics were prescribed to 22% of patients, β-blockers and ACE inhibitors to 40% respectively and calcium antagonists to 46% of patients.

Nichol *et al*[73] used a sample of physician-patient encounters between 1989-1991 to investigate factors associated with the management of hypertension. The authors found between 69% and 75% of physician visits including a diagnosis for hypertension to result in a prescription for an antihypertensive agent. The authors also showed combination therapy to be more frequently used among patients aged more than 65 years, having a diagnosis of heart failure or hypertension involving end-organ damage, relative to single drug use. Also, combination therapy was more frequently prescribed by cardiologists. Overall, diuretics, followed by ACE inhibitors and calcium antagonists, were the most frequently dispensed agents.

With the objective of explaining sex differences in antihypertensive drug use, Klungel *et al*[72] examined the use of antihypertensive agents among hypertensive subjects aged 20-59 years. The authors showed that 57% of men and 54% of women were on monotherapy. An important proportion of subjects were prescribed β-blockers both in 1987-90 and in 1991-95 (54% and 49% respectively). Women were much likely to be on a diuretic than any of the three other agents and the differences across gender could not be explained by factors known to influence antihypertensive drug selection. Hypertensive subjects with present or past cardiovascular disease were analysed separately: sex differences in drug use were much smaller among cardiac patients than others. Older age was associated with increased diuretic use, whereas patients with either diabetes or hypercholesterolemia used ACE inhibitors in a higher proportion. Calcium antagonist users were more likely to be smokers and to concomitantly use anti-arrhythmic agents.

Also using a cohort of subjects newly using antihypertensive medications, Monane *et al*[82] found that 50% of first prescriptions were for diuretics. Fewer than 5% of study

subjects started antihypertensive treatment with multiple therapy. Siegel *et al*[277] reported calcium antagonists and ACE inhibitors to be the most commonly used drug classes for all categories of hypertensive patients, with a higher prevalence of use of calcium antagonists in patients with coronary artery disease and of ACE inhibitors in patients with diabetes or heart failure. Confirming previous results, the most recent study by Caro *et al*[285] reported that the likelihood of starting therapy with a diuretic was higher among older patients and women. The factors associated with starting therapy with either a calcium antagonist or a diuretic were increasing amounts of health services utilization prior to initiating treatment (higher number of medical visits, hospital admissions and prescriptions for non-antihypertensive medications).

2.4.1.1 Time trends

The use of antihypertensive medications has tremendously increased over time[275,278,306]. Also, important changes in the patterns of use have arisen in the recent years with numerous new agents entering the market. Several studies have investigated time trends over the use of antihypertensive agents[168,272-281,283,284,307,307]. These studies may be subdivided in two groups. The first group examined trends in the number of prescriptions by drug class in the population at large using published drug use information data[168,278,279] or insurance claims data[277,280,281], with a prescription-based approach. An important weakness of this type of study is the impossibility to perform patient-based analyses and to examine multiple drug use, modifications to therapy and treatment interruptions. A second group of studies, which used the patient as the unit of analysis, have assessed using survey data whether the proportion of patients using antihypertensive agents changed over time[272,275,276,308]; some of these examined specifically trends in initial treatment regimens[274,283,284]. This section provides an overview of drug utilization studies that examined time trends. These studies have all shown that calcium antagonist and ACE inhibitor use is dramatically growing, primarily at the expense of diuretics and β-blockers.

Prescription-based approach. Using published drug use information, Gross *et al*[278] showed a marked increase in the number of prescriptions used for the treatment of hypertension in the United States between 1973 and 1985, especially for the ACE inhibitor captopril which entered the market in the early '80s. Using similar data, Manolio

et al[279] showed an important shift between 1982 and 1993 in proportionate use of antihypertensive agents, with the use of calcium antagonists and ACE inhibitors having dramatically increased whereas diuretic and β-blocker use have continuously declined. The same trends were observed between 1986 and 1995 by Kaplan[168]. Using data from the Pharmaceutical Benefits Scheme, Hurley *et al*[280] examined trends in the prescribing of antihypertensive agents, diuretics and β-blockers in Australia between 1977 and 1987. After computing the number of defined daily doses of each agent per 1,000 inhabitants, the authors showed an increased use of β-blockers and other antihypertensive agents (including calcium antagonists and ACE inhibitors) and a significant decrease in the use of diuretics, especially the thiazides, over time. In a study examining both prescription drug use in a cohort of patients with newly diagnosed hypertension and trends in prescription drug use over time using Pharmacy files data, Ray *et al*[281] showed a moderate decrease in diuretic use, accompanied by a marked increase in the use of ACE inhibitors and calcium antagonists between 1983 and 1986, while β-blocker use seemed relatively stable. Finally, while examining the distribution of antihypertensive treatment-days between 1995 and 1996, Siegel *et al*[277] found the proportionate use of calcium antagonists to slightly decrease (37% to 35%) while that for ACE inhibitors went from 34% to 36%. Again, β-blocker and diuretic use seemed stable in this two-years period.

Patient-based analyses. Drug utilization studies using survey data generally show trends that are consistent with those obtained from sales data. For instance, Hume *et al*[276] published a survey-based study showing a sharp increase in the prevalence of use of calcium antagonists and ACE inhibitors, whereas the use of diuretics and β-blockers tended to decline between 1981 and 1990. Using a similar study design, Glynn[275] showed the overall use of antihypertensive agents to increase over time, with an important decline in the use of diuretics, accompanied by an increased use of ACE inhibitors and calcium antagonists. Whereas the use of cardio-selective β-blocking agents increased across the three study periods (1982-83, 1985-86 and 1988-89), non selective β-blocker use decreased. An examination of secular trends of antihypertensive drug use in The Netherlands between 1987 and 1995[272] showed a dramatic decrease in the use of diuretics and a significant increase in the use of ACE inhibitors and calcium antagonists, whereas the use of β-blockers slightly decreased.

Time trend documentation of new use of antihypertensive drugs is poorer. Monane *et al*[283] reported in 1995 on the evolution and determinants of initial antihypertensive drug choices among elderly patients between 1982 and 1988. At treatment initiation, diuretics accounted for more than 50% of all the prescribed agents, followed by calcium antagonists (14%) and β-blockers (13%). ACE inhibitors were dispensed to 5% of patients initiating therapy. Marked changes were found in the trends of new prescriptions of antihypertensive medications over time. The authors determined that the odds of a subject being prescribed a diuretic, compared with all other antihypertensive agents, significantly decreased over time whereas a fourfold increase in the use of calcium antagonists was observed over the time period[283]. Older patients, women and blacks were more likely to receive a diuretic to initiate treatment. Similar results were obtained when restricting the study population to patients without evidence of congestive heart failure or coronary heart disease.

Psaty *et al*[74] examined in 1995 the changing patterns of antihypertensive medication use on four occasions between 1989 and 1992 using time-series analyses of cohort data (the *Cardiovascular Health Study*). The authors found that among prevalent users, the use of both diuretics and β-blockers significantly declined over time whereas ACE inhibitor and calcium antagonist use increased (data not shown). The most common antihypertensive agents prescribed at treatment initiation were diuretics, followed by calcium antagonists, ACE inhibitors and β-blockers. With the exception of a slight increase in diuretic use among women between 1991 and 1992, no statistically significant trends were found among starters of these agents.

More recently, Caro[284] reported results on the use of antihypertensive medications among newly diagnosed subjects aged 40 years and older in Saskatchewan. From 1989 to 1994, the use of diuretics and β-blockers at treatment initiation decreased whereas that for ACE inhibitors and calcium antagonists slightly increased. The use of other antihypertensive agents to initiate treatment remained stable over time.

2.4.2 Compliance with therapy

Hypertension, like most chronic diseases, generally requires life-long therapy. A major barrier to hypertension management is noncompliance to prescribed drug therapy and lack of persistence (early discontinuation) with treatment[32]. In 1993, it was estimated that approximately 50 millions Americans had elevated blood pressure[32]. Among these,

approximately 70% were aware of their condition, 49% were pharmacologically treated for their condition and only 12% had their blood pressure controlled[309]. In Canada, it is estimated that 16% of adults with hypertension have their hypertension controlled by drug therapy whereas an additional 23% are treated but remain uncontrolled[37]. The silent and asymptomatic nature of hypertension makes noncompliance to therapy even more likely, the patient not feeling the "need" for drug use[297]. Noncompliance to treatment regimens is an important source of failure to control blood pressure, which in turn, may result in an increased risk of complications. Hence, low compliance is believed to be responsible for approximately three-fourths of the failures to achieve blood pressure control[298,299].

This section will first describe the measurement of compliance in observational studies using either pharmacy records or billing data. The prevalence and scope of noncompliance will then be discussed along with an overview of compliance studies, which are summarized in Table 2.6. Studies performed in an experimental setting (mostly using pill counts or electronic devices), aimed at testing the qualities (validity, reliability) of compliance instruments or studies for which the observation period was smaller than six months were excluded. We also restricted our description to the four major antihypertensive drug classes, namely ACE inhibitors, β-blockers, calcium antagonists and diuretics.

2.4.2.1 Measurement of compliance

Computerized database studies can provide useful information with regard to drug utilization patterns and compliance to prescribed drug regimens. Accordingly, several algorithms were developed using pharmacy records[310-313] to measure compliance with therapy. As described in a review paper by Caro[286], most studies that examined prescription refill records to assess adherence to therapy used similar measures to describe compliance[282,291,293-295], persistence with therapy[284-286,292] or discontinuation rates[287,288,290] of antihypertensive treatment. In this section, we will use these terms indistinctly, assuming that they all refer to the extent to which a patient adhere to a given "standard" of treatment, be it the physician's instructions to treatment schedule or general guidelines referring to the management of hypertension.

Most compliance measurements take the form of a percentage of what is considered optimal treatment, whereby drug use is averaged over a given period of

observation. Usually applied to a 365-day period, the most frequently used measure, often labelled the "days supply approach" [291,293,294], the "medication-possession-ratio"[290] or the "days covered approach"[282], consists in a ratio of the number of days for which medications are available to the patient and the number of days of observation. Study subjects are then usually categorized in two groups in terms of the proportion of days for which medications were available: ≥80% versus <80% of the days covered. The cut-off point of 80% for compliance has been used for a few decades[314] based on controlled studies that showed lesser therapeutic efficacy of antihypertensive medications below that level[315]. This widely used measure carries important limitations. For instance, averaging over long periods of time may dilute the actual level of drug taking, which is believed to be highly variable[316]. Another problem with this measure relates to the way overlapping prescriptions are handled: by summing up the duration of use of all prescriptions, one could get compliance rates that would largely exceed 100% and conclude to the presence of overtreatment. On the other hand, one could also decide not to duplicate the duration of use of overlapping prescriptions if another medication was available on that given day, not allowing for possible overtreatment or stockpiling. Steiner[310] have shown that these two variants of the drug availability measure lead to different estimates. Finally, the dichotomous nature of the variable categorizing adherence to therapy is another limitation of this measure, as compliance may rather be seen as a continuous phenomenon[316].

2.4.2.2 Prevalence and scope of noncompliance in the population

Noncompliance is a major barrier to hypertension management, especially premature termination of therapy and erratic drug taking. Long-term hypertension trials generally report fairly high levels of adherence to therapy with few differences across agents[129,317-319]. However, antihypertensive drug compliance in a "real-life setting" is believed to be less than optimal[320]. It has been estimated that 40% to 50% of hypertensive subjects are not compliant to their prescribed treatment regimen in the clinical setting[265,298,299,321-325], noncompliance usually taking the form of underutilization of prescribed medications. Our review shows estimates of noncompliance among hypertensive subjects in the clinical practice to range from 14% to 83% for a one-year period (Table 2.6).

Noncompliance with medications among hypertensive patients could significantly

impact on effective management of hypertension, which may explain the fact that so few patients with hypertension have their disease under control. Much variability in drug taking behaviours may induce variability in clinical and health outcomes. Horwitz and Horwitz[326], for instance, have shown that patients who adhere to therapy have better outcomes than non adherent patients, even when receiving a placebo. The authors suggest that factors other than those attributable to the drugs may interplay with the outcomes of therapy, which has been confirmed in other studies[327]. Unfortunately, few studies have assessed the consequences or long-term effects of noncompliance. Both Maronde *et al*[294] and McCombs *et al*[287] have found that noncompliance could lead to an increased rate of hospital readmission for hypertension-related causes. Psaty *et al*[263] reported earlier a much higher risk of coronary events in hypertensive patients undercompliant with their use of β-blockers. Elliott[296] showed a significant increase in costs when patients using first-line therapy (β-blockers or diuretics) were switched to alternative therapy. Difficult to estimate, the economic impact of noncompliance in the treatment of hypertension is probably also very high[287,290,295,296].

2.4.2.3 Factors associated with noncompliance

Numerous studies have examined correlates of noncompliance in the clinical practice, especially among elderly patients with hypertension. Among those related to drug therapy, initial drug class is probably the factor that have deserved the greater attention with patients using ACE inhibitors or calcium antagonists at treatment initiation being more compliant[282,284,285,287,292,295]. However, other studies have found no significant difference in compliance rates across different drug classes[288,289,291]. Complexity of the treatment regimen has also been proposed as being associated with noncompliance, be it indicated by multiple daily dosing regimens[289,291,297,328], by an increasing number of prescriptions[282] or by the number of changes in therapeutic regimens[285]. Although the use of a combination therapy at treatment initiation was found to be a predictor of good compliance[287], the number of different antihypertensive agents prescribed for treatment was not found to be associated with compliance[291,329]. Also, cohorts of new users of antihypertensive agents have consistently showed compliance rates to decay over time[285,292,295,297-299].

Indicators of health status have also been found to be associated with compliance with therapy. For instance, multiple physician visits[282,289,292], higher prescription rates in

the preceding year[287,292] and the presence of comorbid conditions such as cardiovascular disease[282] or congestive heart failure[295] have been shown to be predictors of good compliance. Finally, older age groups have consistently showed higher compliance rates[287,289,292,293] whereas conflicting results have been reported with regard to gender[289,292,293]. Table 2.6 summarizes the information pertaining to compliance rates across drug classes among patients with hypertension and a review of studies that examined factors associated with compliance follows.

A study by Farmer *et al* in 1994 contrasted prescribed and consumed drugs to obtain an estimate of the compliance ratio for treatment regimens that included calcium antagonists to treat either hypertension or angina[328]. The authors found an overall compliance ratio of 78% which was reported to be higher among patients prescribed once-daily regimens and with shorter length of therapy. No difference was found between patients prescribed nitrates and those who were not. McCombs[287] used a strict definition of compliance: only patients with no interruption of therapy during the observation period, with a 15-day "grace period" allowed for late refills, were considered continuous users. Restricted to new users of antihypertensive drugs, this study found much lower compliance rates than others. Important differences across drug classes were also reported with rates of continuous therapy of 33% for patients newly using ACE inhibitors, as opposed to only 5% for those using diuretics. A study by Jones *et al*[288] showed discontinuation rates to be similar (around 40%) for all four classes of antihypertensive. "Discontinuation of therapy" was defined as changing to a different antihypertensive drug class or failing to refill prescriptions. The study was restricted to new courses of treatment. A year later was published another study examining pharmacy records of both new and established hypertensive subjects[289]. Estimated to lie between 30% and 46%, noncompliance was defined as a failure to refill a prescription within 36 days of the last prescription for that medication. Although they found much higher rates than the two preceding studies[287,288], the authors did not find significant differences in compliance rates across drug classes. Younger age, multiple-daily dosing regimens and fewer provider visits were found to be independent predictors of refill failure, whereas no association was found for gender and regimen complexity.

Also using a cohort of newly treated subjects, Monane *et al*[293] reported the following factors to be associated with better compliance as defined using the "days supply" approach: older age, Caucasian (*vs* blacks) and year of initiation of therapy (later years

leading to better compliance). Overall compliance rate after one year was 49%, for an average of 179 days in the one year follow-up period, with only 23% patients achieving a good level of compliance. Drug-specific factors were not assessed. Rizzo *et al*[295] investigated noncompliance rates and associated costs using medical claims of patients diagnosed with hypertension. Like in many other studies, the highest compliance rates were associated with ACE inhibitors and calcium antagonists (35% each). Short duration of antihypertensive drug use and the presence of heart failure was also shown to be strong predictors of good compliance. Noncompliance was associated with higher health care costs.

Applying the "days supply" approach to a one-year observation period, Okano *et al*[290] found no difference in compliance rates between patients starting therapy with an ACE inhibitors or a calcium antagonist. Overall 52% of patients were considered after one year as being continuous users. Using the same measure of compliance in a cohort of new users of antihypertensive agents, Monane *et al*[282] found the probability of being compliant up to one year to be almost two-fold among subjects starting with an ACE inhibitor or a calcium antagonist and 1.4 times higher among those starting with a β-blocker, as compared with diuretics. Interestingly, Monane *et al*[282] also examined the effect of comorbidity on compliance, showing that the presence of cardiac disease and multiple physician visits increased the likelihood of being compliant with antihypertensive treatment, whereas the overall number of prescribed medications was inversely associated with compliance. Unlike the authors of the two preceding studies, Christensen *et al*[291] computed class-specific measures of compliance. The study found no significant difference in compliance rates for the four drug classes (72% to 86%). Higher rates of noncompliance with therapy were found with increasing doses per day but no association was revealed with the number of different antihypertensive drugs prescribed.

In 1999, Caro *et al* examined persistence to antihypertensive therapy in a cohort of Saskatchewan patients newly diagnosed with hypertension[292]. Patients for which the last prescription filled was sufficient to cover the remainder of the observation period were characterized as persistent with therapy at the end of the period of observation. As the authors have also reported two years earlier[284], persistence with therapy was shown to vary across initial drug classes, with patients using ACE inhibitors having the highest level of persistence after one year (83%), followed by those using calcium antagonists

(81%) and β-blockers (78%). Patients starting on diuretics had the lowest persistence rate (74%). Persistence with therapy was also found to decrease with time, with only 46% of the patients still persistent after 4.5 years. Discontinuation of therapy was shown to arise shortly after treatment initiation, especially among patients using diuretics. In an accompanying report using the same study cohort, Caro *et al*[285] examined more specifically time trends in persistence with therapy in relation to initial drug choice. The authors showed persistence rates to decrease over time across all drug classes. The persistence curves over time were statistically different, with ACE inhibitors always showing higher persistence with therapy. Caro's study was the first to examine persistence with therapy for a period of observation longer than one year.

2.4.3 Modifications to therapy and treatment interruptions

People generally agree that changes to initial therapy are very common. Whereas compliance studies abound, fewer studies have extensively looked at the frequency and types of changes in antihypertensive medications use such as switching across drug classes or drug additions following treatment initiation[288,290,303,305]. Several studies reported only modification rates in general[300,304], proportion of patients switching or interrupting treatment[42,287,296,302] or both[301]. The results of these studies, which are highly variable in content, are outlined below.

Penrose *et al*[302] examined trends in overall antihypertensive medication use between 1991-93 using computerized records. Of the 16,069 patients included in the study, 914 were retained in the analysis because they have been using antihypertensive agents in all 3 years of follow-up. Of these, 63% remained on the same agents during all of the observation period. When examining cost issues, the authors found a 21% increase in costs for patients having changed treatment schedule whereas no increase in cost was found among other patients.

In 1995, a survey regarding the treatment of hypertension in Health Maintenance Organizations (HMOs) was mailed to a small sample of pharmacy directors with the objectives of documenting the prevalence of changes to initial treatment regimens and identifying factors that may impact on the cost of treatment[303]. A majority of respondents (81%) indicated that the average patient undergoes at least one modification to therapy before achieving blood pressure control. Among ACE inhibitors users, the first modification made to the regimen was reported to be dose adjustment (27%). Switching

to another antihypertensive drug class was the next most common step, followed by adding a calcium antagonist and switching to another ACE inhibitor. Among patients initiating treatment with a calcium antagonist, the first modification made to treatment regimen was also dose adjustment (27%) and the next most common modifications to therapy were to add a diuretic, to switch to another calcium antagonist or to add an ACE inhibitor. The authors hypothesized that multiple drug changes and discontinuation of therapy may indicate the need to more effectively manage high blood pressure.

Analysing new users of antihypertensive drugs, McCombs *et al*[287] reported that among patients interrupting treatment, 16% started a new course of therapy later in the year. Also, the authors reported that 34% of patients compliant with therapy had at least one drug added to their treatment regimen, without gaps in therapy. Sasane *et al*[600], presenting the results of a Drug Utilization Evaluation (DUE), showed 58% of subjects using ACE inhibitors and 55% of those using calcium antagonists to have undergone at least one modification to their initial treatment. The maximum number of modifications to therapy was 10 over two years.

Jones *et al*[288] examined treatment modifications and discontinuation rates after new courses of treatment. A "discontinuation" was defined as either changing to a different antihypertensive drug class or failing to take medications. A "new course of treatment" was considered to occur when newly diagnosed patients were starting therapy or when currently treated patients were prescribed a specific agents that had not been used for the previous 4 months. The authors found that changes and discontinuations in initial therapy were very common (between 40% and 50% for all four drug classes). They also reported that after treatment initiation with an ACE inhibitor, a β-blocker or a calcium antagonist, a change in therapy after 6 months was likely to result in a switch to a diuretic (from 47% to 55%). Using the same cohort as Jones *et al*[288], Hughes and McGuire[301] found increases in costs (in terms of medical visits and hospitalisations) arising for patients switching and discontinuing treatment.

In a description of patterns of use of antihypertensive agents among patients newly prescribed an ACE inhibitor or a calcium antagonist, Okano *et al*[290] examined the proportion of continuous users who required no modification to their treatment. Any dose adjustment, switching to a drug from a different therapeutic class or addition of another drug were considered a modification to therapy. The authors also investigated the proportion of patients with more than one change in therapy and the time to occurrence

of a change. Among patients initiated on ACE inhibitors 48% had no change in therapy over the first year, versus 41% of patients started on calcium antagonists. Of those started on ACE inhibitors, 3% were switched to a different drug class (*vs* 5% for calcium antagonists), 4% were added another drug (6% for calcium antagonists) and 25% had multiple changes over the year (33% for patients initiated on calcium antagonists). The shortest time to a first treatment modification among continuous users was 137 days, for dose adjustment. Switches to a different therapeutic drug class and drug additions were shown to arise later on during the year.

In a study of the patterns of antihypertensive drug use in the elderly, Psaty *et al*[42] examined the determinants of having stopped taking antihypertensive drugs after one year. Predictors of drug stopping were a lower level of systolic blood pressure and a smaller number of medications. In that study, "stoppers" were those patients that used antihypertensive drugs at baseline but were not using them anymore at year 1.

In an examination of physician's management of hypertension, characteristics shown to be associated with a modification in antihypertensive drug regimen included lack of control over blood pressure, a previous change in therapy and the presence of coronary artery disease[304]. The authors postulated that this may be due to the fact that antihypertensive therapy is often used to treat both hypertension and other manifestations of coronary disease. Patient's characteristics such as age, cardiovascular risk factors other than hypertension and the presence of late complications of hypertension did not predict modifications to therapy.

Finally, Wilson *et al*[305] showed in patients starting therapy with an ACE inhibitor or a calcium antagonist that among newly diagnosed patients still compliant with therapy after one year, 44% (41% for ACE inhibitors and 46% for calcium antagonists) had at least one modification to therapy. An increase in dose, a drug addition or a switch to another drug class were the most frequent.

2.4.4 Critical appraisal of drug utilization studies

Previous drug utilization studies in the realm of hypertension have been limited by important factors. An important limitation of these studies relates to the fact that they did not use a cohort of newly treated hypertensive subjects but rather included patients at different times in the course of their disease[267-270,272,273,275-277,288,289,291,302,328]. The problem with using prevalent antihypertensive drug users is not trivial: newly diagnosed

hypertensive subjects may present with different characteristics (e.g. severity of hypertension, comorbidity, compliance with therapy) than patients with established hypertension, characteristics that may affect all comparisons. For instance, prevalent users of antihypertensive agents are very likely to represent "survivors", i.e. patients that not only do suffer from hypertension for some time (which makes them at different risk of complications) but have also been deemed to be persistent in their antihypertensive treatment. The use of prevalent users to measure compliance with therapy for instance, would then lead to inflated estimates of compliance because the study group includes only patients that already persisted with their treatment and are therefore likely to further continue[297]. Caro *et al*[292] have reported with this regard that persistence with treatment after one year of observation was 10-fold among patients with established hypertension, as compared with newly diagnosed subjects.

Another important limitation pertains to the wide variety of definitions and study populations that have been used, which makes comparisons across studies highly problematic. For instance, specific studies have focussed on a Department of Defense[290] or a low income population[289] while others have excluded patients with serious comorbidity[284,289,292,293]. The study population also differed in terms of antihypertensive drug exposure. Hence, some were restricted to few drug classes[281,283,290,300,305,328,330] and others have reported patterns of use only among single drug users[272,273,283-286,292,295,328] or continuous users[302]. Also, several of these studies have investigated a limited number of determinants[42,276,281,283].

Very few dimensions of the general concept of "patterns of drug use" have been investigated: the most common was the study of prevalence of antihypertensive drug use at a specific point in time (or several points in time to investigate secular trends), the description of antihypertensive drug classes used to initiate treatment among newly diagnosed subjects and investigations of compliance with therapy. For their three studies of persistence with antihypertensive therapy[284,285,292], Caro *et al* developed a sophisticated algorithm aimed at reconstructing the different treatment regimens using data on drug type, amount and timing. Unfortunately, the authors only used the treatment gap between the last prescription filled and the end of follow-up to identify non persistent patients without considering patterns of drug utilization before that treatment gap. Very few studies have provided an extensive description of modifications to therapy, including switches across drug classes, treatment gaps and interruptions, and

addition or deletion of drugs[288,290,303,305]. The timing of these modification in the course of therapy was also seldom reported.

An accurate picture of drug utilization patterns and compliance with therapy requires non only a longitudinal study of subjects starting antihypertensive treatment, but also measurements at different points after initiation of therapy[297]. In every studies but those by Caro *et al*[284-286,292], even when the study population was adequately composed of new starters of antihypertensive therapy, the period of observation was too short to provide data on the extent of compliance behaviours or patterns of antihypertensive drug use in the long-term.

The experimental setting of randomized controlled trials is not suited to address the question of variability in treatment schedules (e.g. adherence to therapy, erratic drug use, switches across drug classes and treatment interruptions) and, by extension, to address the question of treatment effectiveness in the clinical practice. To address such a question, one needs a better understanding of drug utilization behaviours in the population. Although it presents numerous advantages, the use of administrative data to study medication use and their effects has been largely criticized. One should also bear in mind for instance, that all these studies have used dispensed medications, a measure that may not reflect several dimensions of drug taking behaviours, such as actual intake, patients' versus prescribing physicians' preferences and external factors that may interfere with drug selection such as, marketing of newer agents, drug prices and availability. An outline of the advantages and limitations of using large administrative databases in observational pharmacoepidemiologic studies is presented in the next section.

Finally, drug utilization studies showing differences in compliance or modification rates across drug classes tend to suggest that these differences are due to drug characteristics. Hence, one could be tempted to conclude that hypertension treatment would be optimized by choosing the agents having the best compliance profile[286]. However, the process underlying the decision to start therapy with a given agent is unknown and even the most crucial criteria for causality, namely temporality of events, may not be met. It is in fact possible that specific agents do increase the likelihood of being compliant. But the corollary is also a possibility: patients selected for treatment with a specific agent may be so because of their potential probability of being compliant with therapy which would reverse the "causality" direction. Also unknown are several

characteristics of the patients to start with that may interfere with drug taking behaviours and whether the decision to stop or discontinue therapy came from the treating physician or from the patient himself. Inference to all patients with hypertension is therefore fragile in this context.

With all these limitations in mind, significant gaps in knowledge remain with regard to population-based patterns of use of antihypertensive agents in the realm of hypertension and a better understanding of drug utilization patterns is essential. Further research in this area is needed to accurately document antihypertensive drug use in the clinical setting where a number of factors may interplay with drug taking behaviours.

Table 2.5 **Antihypertensive drug use among pharmacologically treated patients with hypertension.**

Study (ref.)	Location	Years	Antihypertensive drug use (%)					Comments
			ACEI	BBL	CCB	DIU	Other	
Ray[281]	US	1983-86	N/A	5	N/A	56	39	New users
Manolio[279]	US	1982	0.8	20	0.3	56	23	Prescriptions dispensed per year
		1993	2.4	13	27	25	11	
Psaty[267]	US	1990	12	18	9	49	18	Prevalent users without cardiovascular disease
			14	29	31	49	14	Prevalent users with cardiovascular disease
Psaty[42]	US	1990	16	29	22	64	22	Prevalent users
			29	13	26	42	12	New users
Knapp[268]	US	1991	23	19	24	38	11	Physician visits leading to a prescription
			13	7	12	13	3	Physician visits leading to a prescription for a single agent
Wallenius[270]	Finland	1993	20	30	22	24	4	Prescriptions dispensed
Monane[283,282]	US	1982-88	5	13	14	51	11	New single drug users
Psaty[274]	US	1990	26	10	34	45	10	New users
		1992	24	8	28	48	10	
Rotmensch[269]	Israel	1994	40	40	40	22	N/A	Prevalent users
			34	28	27	7	N/A	Prevalent single drug users
Klungel[272]	The Netherlands	1987-90	7	54	3	36	N/A	Prevalent single drug users
		1991-95	23	49	10	18		
Hume[276]	US	1981-82	0	6	0	24	N/A	Prevalent patients with hypertension (incl. untreated)
		1985-86	0	13	0	29	N/A	
		1989-90	7	10	3	21	N/A	
Glynn[275]	US	1988-89	5	15*	11	14	55	Prevalent patients with hypertension (incl. untreated)

Study (ref.)	Location	Years	Antihypertensive drug use (%)					Comments
			ACEI	BBL	CCB	DIU	Other	
Nichol[273]	US	1989-91	21	16	21	29	13	Physician visits leading to a prescription for a single agent
Caro[284,292,285]	Canada	1989	23	12	12	41	10	New users
		1994	32	9	14	36	11	
Siegel[277]	US	1996-97	35	14	39	12	N/A	Prevalent users

Abbreviations: ACEI=Angiotensin-converting-enzyme inhibitors; BBL=β-blockers; CCB=Calcium antagonists; DIU=Diuretics; N/A=Not available.
* 9% cardioselective and 6% non cardio-selective.

***Table 2.6* Compliance and persistence with antihypertensive therapy in the population according to drug classes.**

Study (ref.)	Study population	Measure	Observation period	Compliant patients (%)*				
				DIU	BBL	ACEI	CCB	Overall
McCombs[287]	Incident users	Continuous refills with 15-day "grace periods"	12-18 mths	5	17	33	29	14
Jones[288]	Prevalent users (new courses of Tx)	No treatment modification or interruption	6 mths	41	49	45	41	44
Bailey[289]	Incident & prevalent users	Prescription refill within 36 days	15 mths	54	70	56	61	67
Monane[293]	Incident users	≥80% days with any AHDs available	12 mths	N/A	N/A	N/A	N/A	23
Rizzo[295]	Prevalent users	≥80% days with specific AHDs available	12 mths	15	29	35	35	N/A
Okano[290]	Incident users	≥80% days with any AHDs available	12 mths	N/A	N/A	56	49	52
Monane[262]	Incident users	OR for ≥80% days with any AHDs available	12 mths	Ref.	1.4	1.9	1.7	N/A
Christensen[291]	Incident & prevalent users	≥80% days with specific AHDs available	12 mths	86	83	72	75	83
Caro[292,284,285]	Incident users	Last prescription sufficient to cover the remainder of the observation period	6 mths	80	85	89	86	84
			12 mths	74	78	83	81	78
			54 mths	40	49	53	47	46

Adapted from Caro & Speckman[286].
Abbreviations: Mths=Months; DIU=Diuretics; BBL=β-blockers; ACEI=Angiotensin-converting-enzyme inhibitors; CCB=Calcium antagonists; AHDs=Antihypertensive drugs; OR=Odds ratio; Ref.=Reference group; Tx=Therapy; N/A=Not available.
* Unless otherwise specified.

2.5 Administrative databases in pharmacoepidemiology

There is a wealth of information available in the data routinely collected by medical insurance schemes. For that reason, the use of large administrative databases in pharmacoepidemiology has dramatically increased in the past two decades. Such databases offer significant advantages in epidemiology: they usually are large, often encompassing a million or more people, and allow not only the study of rare events but also the characterization of drug use and effects in the day-to-day clinical practice[331,332]. By avoiding all the data collection phase of usual studies, administrative databases offer the possibility of conducting valuable epidemiologic studies at relatively low cost and in a reasonable time[331]. The information contained in these large databases is precious: not only have they been shown to be accurate and reliable but they also are easy to use and comprehensive[332]. They are widely used for the study of drug effects as the files containing drug information can be linked to other files that contain the outcomes of interest such as hospitalizations, medical visits and death, using a unique identifier. Finally, the drug files permit the reconstruction of the complete history of prescribed medication use in a large number of patients and for a long period of time. The use of administrative databases also permit avoiding information biases such as nondifferential or systematic imprecisions in the recall of some events[331].

Use of large administrative databases in pharmacoepidemiology has however been largely criticized[333-335]. Because they were first created for administrative purposes such as billing of health services, important information is lacking. Lifestyle habits, for instance, or other disease risk factors are not recorded, thus creating a potential for bias in pharmacoepidemiologic studies[336,337]. Confounding by indication is a major issue in pharmacoepidemiology using large administrative databases for the purpose of studying intended drug effects[338]. The absence of information on the actual indications for drug use has to be carefully addressed at the analysis stage. Indeed, diagnoses must be inferred from dispensed drugs or hospital data[331]. Misclassification of exposure may also arise when, for instance, exposure is defined using prescribed medications rather than actual intake[337]. Similarly, misclassification of the outcome of interest, a specific condition for instance, may arise due to recording procedures. Indeed, coding of diagnosis into broad categories of the International Classification of Diseases, Ninth Revision (ICD-9)[339] may not always capture the presence of a specific condition[331]. While validated against medical records, varying degrees of accuracy have been reported[340-

[342]. Usually, diagnoses recorded in administrative databases are believed to be highly specific but less sensitive[343]. Such misclassification, if not related to exposure, can lead to an underestimation of the effects of the drug.

Saskatchewan Health databases are increasingly used as a primary source of data for the study of drug effect. The databases are remarkably complete and as described in a following section (Chapter 3), have demonstrated excellent accuracy[344-348].

CHAPTER 3 – METHODS

This chapter describes the study design and details of the methods employed to examine the patterns of use and effects of antihypertensive drug use. An overview of the computerized databases used as a source of data is first provided. The study population is then defined along with a description of the two specific study designs that were retained to investigate the study questions. A brief outline of the measurement of exposure to antihypertensive and other drugs of interest and the potential confounders of the association is also provided along with a description of the statistical analysis. Methodological details pertaining to the specific study objectives are described within each manuscript.

3.1 Overview of the study design

The study objectives were addressed in two steps. A historical cohort design was first used to examine the patterns of use of antihypertensive medications and their impact on health services utilization, with computerized health databases from Saskatchewan providing the necessary data. A nested case-control study within the initial cohort was then used to evaluate the risk of myocardial infarction (MI) associated with antihypertensive drug use in the context of actual medical practice.

The health insurance databases of the Canadian province of Saskatchewan were used to assemble the cohort. Patients dispensed a first prescription for an antihypertensive agent between the years 1990 and 1993 were eligible for cohort entry. Since information pertaining to the specific diagnostic indications for drug prescribing was not available, drug markers were used to identify patients with hypertension. All antihypertensive agents dispensed up to the end of the observation period were used to gather information on drug exposure. Information on the use of health services and medications during the year preceding cohort entry was used to document patients' comorbidity and other correlates of antihypertensive therapy. Other relevant factors such as age, sex and social assistance at treatment initiation were also documented. Descriptive statistics were used to characterize different patterns of use and compare them across exposure to specific agents.

Incident cases of MI that occurred between cohort entry and the end of follow-up were identified using hospital discharge diagnostic codes and death certificates. Using incidence density sampling strategies, risk sets were formed that consisted of each case

and four controls randomly chosen among treated hypertensive subjects matched on the date of cohort entry and time at risk. Current exposure to antihypertensive agents at the time of the event was measured and contrasted among cases and controls using conditional logistic regression accounting for potential confounders of the association. Effect modification by external factors was also assessed.

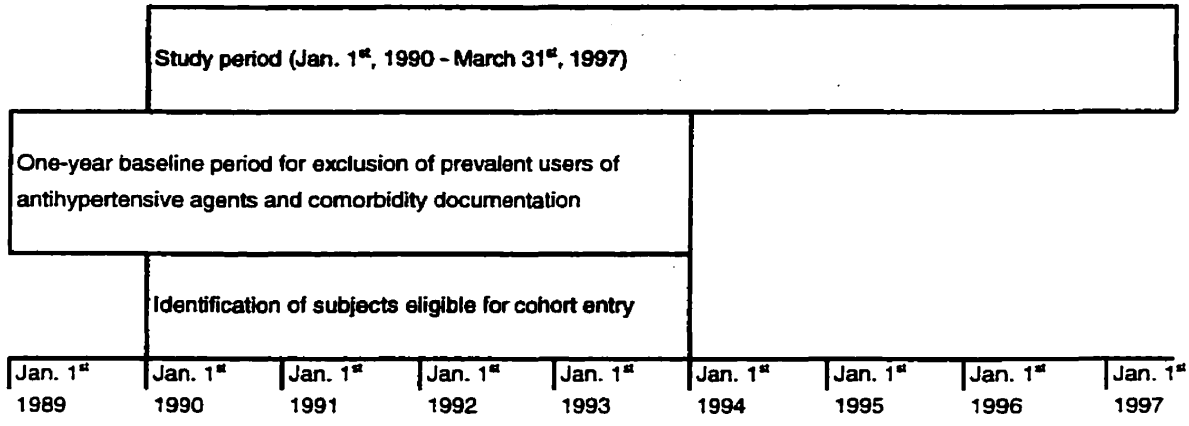


Figure 3.1 **Overview of the study design.**

3.2 Sources of data

The computerized prescription, medical care and hospitalization databases of Saskatchewan, developed as a result of the universal health insurance program provided to most residents of this Canadian province[347,349], were used to assemble the source cohort. All Saskatchewan residents (over 1 million) with a valid Health Services Card are eligible for insurance coverage with the exception of registered Native Canadians, members of the Armed Forces, Royal Canadian Mounted Police (RCMP) and veterans, who totally represent around 7% of the population. Administering the health insurance plan give rise to several computerized databases including the *Health Insurance Registration file*, the *Outpatient Prescription Drug Services file*, the *Medical Care Insurance file* and the *Hospital Services file*, that are increasingly used for research purposes[345,349]. Worth noting, insurance coverage is not discriminating on the basis of socioeconomic status.

Health Insurance Registration file. The Health Insurance Registration file is a central data file containing data on identification and demographic details of all residents eligible for health services in Saskatchewan. Upon enrollment for insurance coverage, all beneficiaries receive a unique health insurance number that serves as a life-long identifier. Among the data systematically recorded in the Registration file are patients' sex, date of birth and death if applicable, receipt of social assistance and insurance coverage dates. Saskatchewan Health may also release upon request the death certificates of all subjects that died during the study period. When released for research purposes, data are provided on a non-nominal basis to disable any patient's identification.

Outpatient Prescription Drug Services file. The Saskatchewan Prescription Drug Services Branch collects data about all prescription drugs listed in the Saskatchewan Drug Formulary and dispensed on an outpatient basis, on a claim-to-claim basis. The frequency of use of prescription drugs not listed on the Formulary is unknown but estimated to be very low given the comprehensiveness of the Formulary and the fact that the list is under continuing review[349]. Information available includes, for each prescription dispensed, the drug identification number (DIN), the active ingredient number (AIN), the drug name, strength, dosage form, and quantity, the dispensing date and cost (including professional fee). These data are available electronically from 1975 onward. Algorithms aiming at the detection of illogical data entries, systematic verification of the claimant's eligibility to the insurance Plan and errors in patient's identification are in use. In addition, random samples of patients' are contacted on a weekly basis for verification regarding reimbursed medications.

Medical Care Insurance file. The Medical Care Insurance Branch file is responsible for administering the Medical Care Insurance Plan. All physician services including medical, surgical, and specialist services are recorded in this file, along with patient's identification data. A unique patient's identifier permits the linkage of this data file with the Health Insurance Registration file.

Hospital Services file. The Saskatchewan Hospital Services Branch data file contains data on all hospitalizations in a general, community or rehabilitation institution in

Saskatchewan. Computerized data include information on primary and secondary discharge diagnoses (coded using the 9th revision of the International Classification of Disease -ICD-9-[339]), dates of admission and discharge, resource use, length of stay and vital status at hospital separation. Again, the health insurance number permits record linkage with all the other data files. Accuracy of recorded data is also checked in a systematic way.

3.3 Cohort definition

Using the Saskatchewan computerized databases, the source population of all 44,020 beneficiaries initiating treatment for hypertension between 1990 and 1993 was selected and tracked for antihypertensive and other drug use and the occurrence of a first event until March 31st, 1997, end of the insurance coverage period, emigration from the province or death, whichever came first. The following procedures were used to select the study cohort. First, all subjects dispensed a β-blocker, a calcium antagonist or an ACE inhibitor between January 1st, 1990 and December 31th, 1993 were identified (see Appendix 2 for a list of included agents). A subject's date of cohort entry was taken to be the date of receipt of the first prescription for any one of these antihypertensive drugs. A number of exclusions were then applied to identify a cohort of patients newly treated for uncomplicated hypertension.

To maximise homogeneity of the study population, both the examination of the patterns of use of antihypertensive agents and the assessment of associated myocardial risk had to be carried out among patients newly using antihypertensive drugs for the treatment of hypertension. To confirm the incident nature of hypertension, patients who were dispensed at least one antihypertensive agent (including diuretics, centrally acting agents and alpha-blockers) in the 12 months preceding cohort entry (n=8,389) were excluded.

Subjects receiving antihypertensive drugs for indications other than hypertension were also identified and excluded based on concurrent prescription of other relevant drugs. Thus, we excluded subjects that used any of the following agents in the preceding year: nitrates (which are likely used for the treatment of angina; n=2,347), digoxin (congestive heart failure; n=1,069), quinidine or quinidine-like agents (arrhythmia; n=266), antithyroid drugs or radio-iodine (hyperthyroidism; n=89), ergot preparations or methysergide (migraine; n=969). Subjects with pre-existing cardiac

disease were also excluded on the basis of their use of anti-coagulants, loop diuretics or other cardiac agents (n=3,532), or if they were admitted to hospital with heart disease as a primary or secondary discharge diagnosis (ICD-9 codes 402, 404, 410-416, 420-429 or 745.4-746.9; n=5,137) in the year preceding cohort entry. Eliminating overlaps, the total number of patients excluded for pre-existing cardiac disease was 7,324. Finally an age criterion was applied to increase the likelihood of restricting the cohort to patients with uncomplicated hypertension, which is more likely to affect middle-aged and older persons[37]. Indeed, we excluded patients aged less than 40 years (n=6,881) and those older than 80 (n=2,793). Thus, the study cohort consisted of 19,501 newly treated patients with uncomplicated hypertension. Cohort selection procedures are displayed in Figure 3.2 and the specific agents used as drug markers are listed in Appendix 3.

3.4 Case-control analysis of the cohort

To address the primary objective of the study, namely to assess the risk of MI in association with antihypertensve drug use, a case-control study nested with the cohort previously defined was conducted.

3.4.1 Case ascertainment

All cases of myocardial infarction (MI) occurring after cohort entry were identified. Cases were all subjects who experienced during follow-up a first episode of MI either requiring hospitalization or leading to death. Using the ICD-9 codes for hospital discharge diagnoses (410-410.9, Appendix 4), each subject was screened for the occurrence of a first diagnosis of MI at hospital discharge between cohort entry and the end of the study period. As a second step, two physicians, a cardiologist and an internist, both blinded to prior exposure to antihypertensive agents or other medication use, independently reviewed all death certificates for deceased subjects. Inter-rater agreement for definite MI was 82% and all discrepancies in the coding of MI as an underlying cause of death were resolved by consensus. Only definite MIs were retained in the analysis. For subjects with multiple MIs, only the first event was used.

3.4.2 Selection of controls

For each case of MI, the risk set composed of all hypertensive subjects having initiated treatment in the same year and month and still at risk for a MI at the case's

event date was formed. Using risk set density sampling[350-352], a random sample of four controls was selected from each risk set and matched to the case accordingly. This approach allows person-years of experience of a case before the occurrence of the event to be used as a control. The incidence sampling approach also permit a control-subject to act as such in multiple risk sets. The *index date* was defined as the event date for the cases and the corresponding matched date for controls.

3.5 Antihypertensive drug exposure

3.5.1 Cohort analysis

The cohort of newly treated hypertensive subjects was used first to document and quantify the frequency of different patterns of use of antihypertensive agents. For that purpose, all antihypertensive drugs dispensed between treatment initiation and the end of the observation period were identified for an analysis restricted to the four major antihypertensive drug classes, namely ß-blocking agents, diuretics, ACE inhibitors and calcium antagonists. Three distinct dimensions of drug taking behaviors were investigated: the drug (or combination of drugs) used at treatment initiation, compliance with antihypertensive therapy and modifications to therapy such as treatment interruptions, discontinuation of therapy, switches across therapeutic drug classes and drug additions.

Initial therapy. Initial antihypertensive regimens were first divided into single drug use (ACE inhibitor, β-blocker or calcium antagonist only) or combination therapy. Combined therapy was defined as the dispensing of medications belonging to more than one drug class or a fixed-combination product containing drugs from different classes (e.g. ACEI-diuretic combination drug) on cohort entry date.

Compliance with therapy. To compute this measure, the number of days a prescription should have lasted was assumed to be 30 days, according to average Saskatchewan prescribing practices. The "days supply" was defined as the cumulative number of days during which one or several antihypertensive medications were available following treatment initiation. If the estimated duration of one prescription fell into that of a subsequent prescription, the days supply was not duplicated thus precluding compliance rates to exceed 100%. However, stockpiling of medications was allowed by

adding to the days supply all prescriptions of a same agent dispensed within a 15-day period. Because the information on drug use during hospital-stay was not available, hospital-days were removed from the denominator in all calculations. Based on controlled studies that showed lesser therapeutic efficacy of antihypertensive medications below that level, a patient was considered to comply with therapy if antihypertensive medications were available for use at least 80% of the days of observation.

Modifications to therapy. Any change in the initial drug regimen, namely interrupting treatment (temporarily or not), switching across drug classes and adding medications belonging to a different therapeutic class, was considered a modification to therapy. For the purpose of identifying treatment interruptions, a period of 90 days or more without using medications was retained. The 90-day cut-off point was based on the ground that with the 80% threshold, 73 days (two and a half months) without using any antihypertensives would be required over a one-year period for a patient to be considered not compliant enough to benefit from therapy. Therefore, a treatment interruption was defined as a failure to fill a prescription for a diuretic, an ACE inhibitor, a β-blocker, a calcium antagonist or any combinations of these, in the 120 days following the last prescription filled. Again, stockpiling of medications was considered by treating all prescriptions of a same agent dispensed in a 15-day time-window as sequential prescriptions. Temporary treatment interruptions (if a new course of treatment was initiated following interruption) and a treatment discontinuation were treated distinctively. Because sequential dispensing of two different agents (or combined drugs) could either mean that an agent was added or that the patient was switched from one drug class to another, differentiating between a switch and the addition of a second or third drug was quite challenging. For that purpose, an algorithm similar to that used by Caro *et al* in a recent study[292] was constructed using for each prescription, information pertaining to the two subsequent dispensing dates. Apart from treatment interruptions and discontinuation of therapy, two types of modifications to therapy were considered: switching from a therapeutic drug class to another and adding a second agent belonging to a different therapeutic drug class. In all of these scenarios, a gap of up to 119 days was allowed between two dispensing dates. Otherwise, the modification was considered to be a treatment interruption.

3.5.2 Case-control analysis

In the nested case-control study, patients on combination therapy were considered to be concurrently exposed to all prescribed agents. The exposure of interest was current use of ACE inhibitors, β-blockers and calcium antagonists. As in the cohort analysis of the patterns of use of antihypertensive agents, drug exposure was measured at the level of therapeutic classes only in order to ensure sufficient numbers.

Current use. Several of the prior observational studies of the cardiovascular effects of antihypertensive drug use have assessed whether the use of antihypertensive agents at the time or around the time the event occurred increased the risk of MI. Accordingly, current use of an antihypertensive agents was deemed to be a relevant way of measuring exposure in the third manuscript. The current use time-window was chosen to be 90 days prior to index date. Hence, exposure to an antihypertensive agents was considered to have occurred if such an agent was dispensed in the 90 days preceding the index date. One indicator variable for current use of each of the four major antihypertensive drug classes was created.

History of use. History of antihypertensive drug use was defined as any use between cohort entry and the 90-day current use time window. Hence, no overlap was permitted to occur between the current use and the prior use time-windows. Four indicator variables for prior use of ACE inhibitors, calcium antagonists, β-blockers and diuretics (not exclusive) were constructed on that basis.

3.6 Confounders and effect modifiers

Based on prior studies, the following factors were found to be potential confounders of the association of current use of antihypertensive drugs and the risk of MI, and were consequently adjusted for in all models:

Patients' characteristics. Patients' characteristics such as age at treatment initiation, sex and whether or not they were receiving social assistance, may potentially influence both the selection of a specific agent and the baseline risk of experiencing a myocardial infarction. Also, calendar year of initiation of therapy may also be a confounder if, for instance, both prescription patterns and rates of myocardial infarction vary over time.

These were accounted for in all analyses.

Drug use and health services utilization prior to cohort entry. Drug use in the year preceding cohort entry was treated as an indicator of each patient's health status prior to initiation of antihypertensive therapy. Drug markers were defined as one or several agents whose primary indications for prescribing may indicate the presence of a disease. Thus, it is inferred that the condition is being measured by the presence of the drug. A list of the drugs used to proxy for the presence of chronic conditions prior to cohort entry is available in Appendix 5. Briefly, we adjusted for the use of anti-diabetic agents, non-steroidal anti-inflammatory drugs (NSAIDs), anti-ulcer agents, neurotropic agents, hypolipemic drugs, anti-asthma and oral corticosteroids in the year prior to treatment initiation. Health services utilization may represent an indicator of both the patients' general health status and their propensity to use health services, including medication use. Hence, hospital admissions and medical visits, especially those made to cardiologists or internists in the year prior antihypertensive treatment initiation, were adjusted for.

History of use of antihypertensive agents. History of drug use has been shown to bear on the intended effect of a drug[11]. In the evaluation of whether current use of antihypertensive agents was associated with the risk of myocardial infarction, documenting history of drug use was therefore deemed to be extremely relevant to ensure the comparability of the contrasted groups. Most studies that accounted for prior exposure to the drug of interest have treated history of drug use as a potential confounder of the association. As such, authors of previous studies have included in multivariate models an indicator for prior use of the drug of interest. We did so both for comparability purposes and to measure the effect of accounting for the entire history of medication use when assessing drug effects. Hence, history of use of each antihypertensive agent was adjusted for as a proxy measure of the severity of hypertension by including indicator variables for prior use of each of the four antihypertensive drug classes in the models. However, because each specific antihypertensive agent has its own indications for treatment, drug use history and concomitant cardiac conditions should be considered not only as potential markers of subsequent cardiovascular risk, but also as potential modifiers of the drug effects[11].

Indeed, long-term users of a drug may be very different in terms of susceptibility to experience an adverse effect from patients having discontinued treatment. We therefore treated prior use of antihypertensive agents also as a potential modifier of effect.

Regular use of antihypertensive agents. For all chronic diseases, continuity of drug use is mandatory for the beneficial effect to arise. An indicator of "compliance with therapy" was constructed to account for differences in continuity of use across agents. A regular antihypertensive drug user was defined as one for which at least 12 prescriptions per year were dispensed on average. As such, the duration of each prescription was assumed to be 30 days.

Initiation of therapy for cardiovascular disease or diabetes during the course of antihypertensive therapy. All patients were assumed to initiate therapy for the treatment of uncomplicated hypertension. As such, we ensured that all the patients included in the cohort were not dispensed cardiac or anti-diabetic agents before initiating treatment for hypertension. That hypertensive patients develop heart failure, angina or diabetes during the course of their hypertensive disease is very common and part of the disease process (see section 2.1). Besides, it increases their risk of experiencing negative cardiac outcomes. For these reasons, we included in the models three indicator variables for the onset of nitrates therapy (angina), digoxin therapy (congestive heart failure) or anti-diabetic therapy with insulin or hypoglycemic agents, which are deemed to be drug markers for MI risk. Use of these agents could have arisen concomitantly or prior to the current use time-window.

3.7 Statistical analyses

In the first manuscript, Poisson regression models for rates, accounting for between-subject variation[353], were used to contrast three different ACE inhibitors with respect to subsequent use of health services. These regression techniques permitted adjustment for potential confounders of the association at treatment initiation such as age, sex and social assistance, as well as medical visits, drug use and hospitalizations in the preceding year. In the second manuscript, simple contingency tables for proportions were used to present descriptive data on the patterns of use of antihypertensive agents. No statistical testing was used to compare the figures at the crude level. Associations

between various patterns of antihypertensive drug use (initial treatment, compliance, time to first modification to therapy) and patient's characteristics were assessed using multivariate logistic regression and Cox proportional hazards models.

All analyses for the third manuscript were performed using conditional logistic regression to account for the effect of matching. Matching factors were not included in the models to assess the presence of residual confounding because the strata used for matching were considered sufficiently fine (year and month of cohort entry). As it is customary to do so, univariate examination of the association between each of the potential confounders and MI risk was carried out. Also, the crude relative risk of MI was computed for each of the antihypertensive drug exposure categories. In this crude analysis, the relative risks were not adjusted for comorbidity but were adjusted for current use of other antihypertensive agents and matching was accounted for.

Finally, full multivariate models including all potential confounders were presented. The complete history of use of antihypertensive agents was adjusted for as a proxy measure of the severity of hypertension by including indicator variables for regular use, and both current and prior use of each of the four antihypertensive drug classes in the models. Multivariate analyses were conducted using conditional logistic regression. Potential modification of the effects of current use of ACE inhibitors and calcium antagonists by history of use of these agents was examined by including interaction terms for prior use of each studied agent in the regression models. Interaction terms were also included to verify the hypothesis that the onset of angina, congestive heart failure or diabetes during the course of the hypertensive disease could modify the cardiac effects of antihypertensive agents. The final equation used to relate current use of specific antihypertensive agents and the occurrence of an MI was the following:

$$\text{Log(rate[MI])} = \beta\textbf{\textit{currAHD}} + \beta\textbf{\textit{priorAHD}} + \beta\textbf{\textit{reguse}} + \beta\textbf{\textit{CVD}} + \beta\textbf{\textit{demogr}} + \beta\textbf{\textit{comorb}} + \beta\textbf{\textit{currAHD*priorAHD}} + \beta\textbf{\textit{currAHD*CVD}}$$

where ***currAHD*** is a vector reflecting current use of calcium antagonists, ACE inhibitors and diuretics (with β-blockers as the reference), ***priorAHD*** is a vector of four binary variables indicating prior use of ACE inhibitors, calcium antagonists, β-blockers and diuretics, ***reguse*** is an indicator of regular use, ***CVD*** represents the onset of angina, CHF or diabetes during follow-up and ***demogr*** and ***comorb*** are two vectors of the

subjects demographic characteristics and comorbid conditions. Finally, each of the two binary variables for current use of ACE inhibitors and calcium antagonists was multiplied by prior use of each of the four studied antihypertensives (***currAHD*priorAHD***) as well as with the three indicators of cardiovascular disease (***currAHD*CVD***).

To avoid overfitting and collinearity problems, two separate models were used to estimate the independent effects of current use of the two newer antihypertensive agents (calcium antagonists and ACE inhibitors) relative to β-blockers as potentially modified by prior use and drug markers for MI risk. However, interaction terms were retained in the final model providing that the p-value for the estimate was ≤ 0.15. Throughout, the linearity of the logit for each continuous variable used in the models was verified. In all cases, 95% confidence intervals were computed for point estimates, both crude and adjusted.

3.8 Simulation study

In the process of the previous analyses, we noted that effect modification in matched case-control studies could be assessed in two ways that produced results of differing precision. Therefore, we used Monte Carlo simulation analyses to assess the relative efficiency of the estimators for the odds ratios when assessing effect modification in matched case-control studies according to two different techniques: a stratified analysis and a modelling approach. The simulations were performed using SAS language to compare the relative efficiency of the stratified analysis for matched data as opposed to the multivariate modelling approach where an interaction term is actually fitted as an independent parameter. Only situations where the outcome, the exposure and the modifier are all binary variables were considered.

A macro was first created to generate data sets using pre-defined parameters. A number of these parameters were held fixed namely:

- a 1: 1 matching ratio;
- Intra-class correlation for the exposure = 0.5;
- Intra-class correlation for the modifier = 0.5;
- Modifier is assumed not to be a confounder of the association;
- Sample size = 1,000 pairs.

The following factors were varied in order to permit the estimation of the relative

efficiency in several scenarios:

- Probability of exposure:

Stratum 1	Stratum 0
0.5	0.5
0.2	0.8
0.8	0.2

- True odds ratio:

Stratum 1	Stratum 0
1.5	0.3
0.8	0.2
5.7	2.1
0.7	12
0.5	0.5
1	1
3	3

- Probability of belonging to a given stratum of the modifier (equal for cases and controls):

Stratum 1	Stratum 0
0.5	0.5
0.2	0.8

For each of the 42 different scenarios (3 probabilities of exposure * 7 stratum-specific ORs * 2 probabilities of belonging to stratum 1 of the modifier), a thousand hypothetical samples were created in which the estimated odds ratios (OR_0 & OR_1), their natural logarithm ($LogOR_0$ & $LogOR_1$), and their respective variance ($varLogOR_0$ & $varLogOR_1$) were estimated using the two contrasted approaches. For each of the two approaches, the variance of the lof of the true odds ratio was computed from the empirical distribution of the estimated odds ratios again, for each of the 42 simulations. The relative efficiency (RE) was calculated as the ratio of the true variances obtained from each specific approach and is reported as such. The RE can be simply interpreted as the proportion of the sample size needed in one approach relative to the other, for the two variances to be equal, that is to estimate the odds ratio with the same precision.

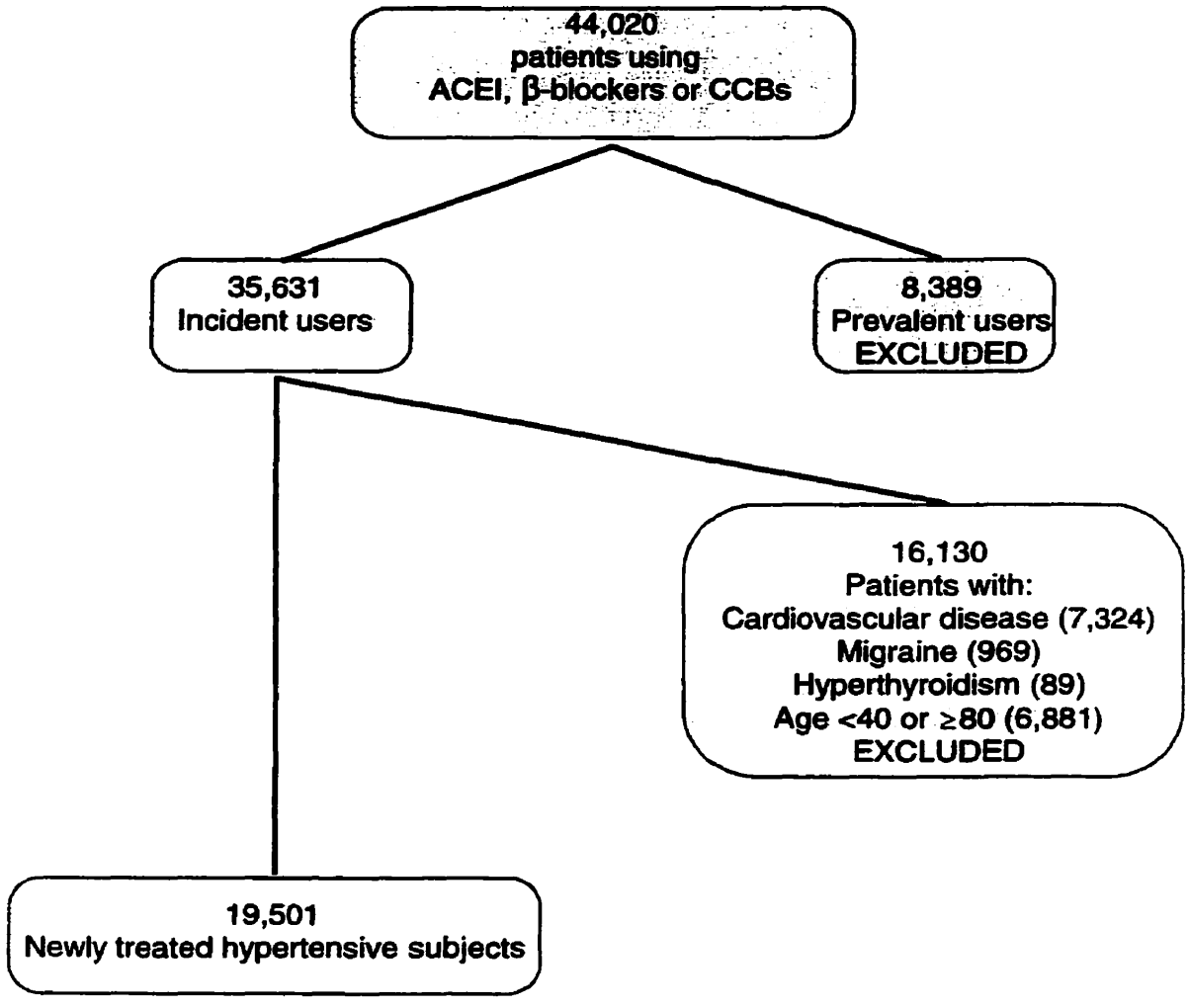


Figure 3.2 **Selection of the study cohort.**

CHAPTER 4 – THERAPEUTIC EQUIVALENCE WITHIN DRUG CLASSES

4.1 Preface to the first manuscript

This manuscript presents the first part of a study examining antihypertensive drug use and its effects on health outcomes. Reference-based pricing is a cost-sharing measure by which the amount reimbursed for a group of drugs is determined by reference to an interchangeable drug, any excess cost being borne by the patient. Implemented in several countries, such policy has however been subject to many criticisms, especially with regard to the concept of *interchangeability* of drugs. Indeed, whereas many products within a therapeutic drug class have been shown in randomized controlled trials to be equally efficacious and safe on average, this may differ in the context of the actual practice. This study is an attempt to document the equivalence of different agents within a drug class (the angiotensin-converting-enzyme (ACE) inhibitors) with respect to subsequent use of health services at the population level, as it is assumed in a reference-based pricing policy. We hypothesize that potential differences in the effectiveness, levels of compliance or side effect profile of the drugs, for instance, could lead to different use of health services. In the realm of health policies, the burden of increasing costs of prescribed drugs should be offset by improvements in health outcomes and decreased use of health services.

We thought that the use of ACE inhibitors in the treatment of hypertension would be a good example to assess the potential impact of reference-based pricing. Hypertension is highly prevalent, new agents are being introduced on a regular basis and there is a wide variation in the costs of ACE inhibitors. There is therefore a need for balancing higher costs of newer agents with a possibly greater effectiveness, relative to older and often cheaper agents.

The general objective being addressed is the following:

- To examine the potential impact of a cost-containment measure namely, reference-based pricing of pharmaceuticals, on the use of health resources.

The specific objective is:

- To assess whether hypertensive patients initially prescribed three specific agents belonging to the ACE inhibitors class (captopril, enalapril and lisinopril) differ in their use of health services and hence, whether ACE inhibitors may be considered

equivalent.

This manuscript, which has recently been published, should be quoted as follows:

Bourgault C, Elstein E, Le Lorier J, Suissa S. Reference-based pricing of prescription drugs: Exploring the equivalence of angiotensin-converting-enzyme inhibitors. *CMAJ* 1999;161:255-60.

4.2 *Manuscript 1.* Reference-based pricing of prescription drugs: Exploring the equivalence of angiotensin-converting-enzyme inhibitors

Chantal Bourgault, MSc[*,†]; Eleanor Elstein, MD[†]; Jacques Le Lorier, MD, PhD[‡]; Samy Suissa, PhD[*,†]

[*] Department of Epidemiology and Biostatistics, McGill University, Montréal, Québec, Canada.

[†] Pharmacoepidemiology Research Unit, Division of Clinical Epidemiology, Royal Victoria Hospital, Montréal, Québec, Canada.

[‡] Centre de recherche de l'Hôtel-Dieu de Montréal, Université de Montréal, Montréal, Québec, Canada.

ABSTRACT

Background: Reference-based pricing (RBP) is a cost-containment policy for drugs that are chemically different but deemed to be therapeutically equivalent. Recent RBP measures have targeted several drug classes, including angiotensin-converting-enzyme (ACE) inhibitors. The objective of this study is to assess whether ACE inhibitors differ in their impact on health services utilization and hence, whether they can reasonably be considered as therapeutically equivalent.

Methods: A retrospective cohort was formed from all 4,709 Saskatchewan residents aged 40 to 79 years who initiated antihypertensive therapy with one of the ACE inhibitors captopril, enalapril or lisinopril between January 1, 1991 and December 31, 1993. Outcome measures, also obtained from the universal insurance databases, included physician visits and hospital admissions during a follow-up of up to four years.

Results: The adjusted rate ratio of visits to a general practitioner associated with enalapril treatment was 0.84 (95% CI: 0.80-0.88) and 0.79 (95% CI: 0.74-0.83) for lisinopril, relative to captopril. Visits to a specialist showed similar but lower rate ratios. Adjusted rate ratios of hospital admissions were slightly lower: 0.82 for subjects initiated on enalapril (95% CI: 0.73-0.93) and 0.65 (95% CI: 0.56-0.75) for lisinopril. Stratified analyses showed that healthier subjects had less benefit from enalapril and lisinopril than the sicker ones, relative to captopril.

Interpretation: Medical visits and hospital admissions are consistently higher in subjects initiating treatment with captopril compared to enalapril or lisinopril. Although baseline differences between groups cannot be ruled out as alternative explanations, sufficient variability in outcomes exist to recommend that RBP policies be evaluated before and after implementation with respect to their impact on overall health spending.

INTRODUCTION

In response to growing expenditures for prescription drugs[264], many cost-containment measures have been proposed[354-356]. Reference-based pricing (RBP) is a direct cost-sharing measure by which the amount reimbursed for a group of drugs is determined by reference to an *interchangeable* agent, any excess cost being borne by the patient. Many products within a therapeutic class have been shown to be equally efficacious and safe on average when evaluated in randomized clinical trials. The reasoning underlying RBP policies is that if all of these products are deemed to be equally effective and to have similar side effect profiles, the most cost-effective product could be insured as the drug of choice[357]. Implemented in several countries, claims have been made that such policies are insensitive to the clinical differences among drugs[358] and promote drug substitution without adequate scientific evaluation[359,360]. Whether the prescription drug-related savings induced by a RBP policy are being offset by increased health expenditures is unknown[358,359,361-363].

Among other classes of drugs, angiotensin-converting-enzyme inhibitors (ACEI) have been the target of RBP. Numerous randomized clinical trials have demonstrated the safety and efficacy of ACEI in reducing blood pressure[364-376]. Consequently, ACEI are generally considered to be a homogeneous drug class[377,378]. However, these agents have been shown to differ with regard to potency, duration and site of action, dosage form, drug interactions, side effect profile and even, efficacy[373-392]. If these differences lead to a rise in health services utilization such as prescription drug use and physician and hospital visits, the assumption of equivalence underlying RBP would be violated. No study has yet compared the impact of different ACEI on the use of health services.

In this study, we examined the potential impact of implementing a reference-based pricing policy on the use of health services. Specifically, we assessed whether the three most commonly prescribed ACEI captopril, enalapril and lisinopril differ in their impact on health services utilization and hence, if they can reasonably be considered as equivalent.

METHODS

Sources of data

We used the computerized prescription, medical care and hospitalization databases of Saskatchewan to construct a cohort of newly treated hypertensive subjects. These databases were developed in the context of the universal health insurance program provided to over 1 million residents of this Canadian province[344-347]. Drug-related information includes, for each prescription dispensed on an out-patient basis, the nature of the drug, strength and dosage form, dispensing date, quantity dispensed and cost. Data were also available on all physician visits and hospitalizations, with information on the date of each visit and the specialty of the physician seen. Hospitalization data contain information on primary and secondary discharge diagnoses (coded using the 9th revision of the International Classification of Diseases[339]), admission and discharge dates and vital status at discharge. Demographic data (date of birth, gender, date of death if applicable, and social assistance status at treatment initiation) were also obtained.

Cohort definition

All subjects aged 40 to 79 years, initiating therapy with an ACEI for the treatment of hypertension between January 1, 1991 and December 31, 1993, were selected. To identify subjects initiating therapy, we excluded those dispensed any antihypertensive agent in the 12 months preceding treatment initiation. Several measures were used to attempt to rule out subjects receiving antihypertensive therapy for indications other than uncomplicated hypertension. First, subjects initiating therapy with an ACEI for the treatment of chronic heart failure or renal scleroderma were excluded based on their use of digoxin, oral corticosteroids or pencillamine in the year prior to treatment initiation. Subjects having used anti-coagulants, hemostatic, loop diuretics or other cardiac agents, or admitted to hospital with heart disease (ICD-9 codes 402, 404, 410, 420.9-429.9 or 745.4-746.9) in the same period were also excluded on the ground that they may have had pre-existing cardiac disease at treatment initiation. Finally, subjects possibly presenting with transient hypertension were excluded by retaining only those dispensed three or more prescriptions for an antihypertensive medication in the first year.

To ensure that a sufficient number of observations was available, only subjects dispensed the three most frequently prescribed ACEI (captopril, enalapril and lisinopril)

were retained. Cohort entry was taken to be the date of receipt of the first prescription for one of these drugs and the specific agent initially prescribed defined the exposure group in which a subject was categorized. Although subjects did have to pay deductibles and co-payments, no RBP policy was in force in Saskatchewan during the study period. Subjects were followed until December 31, 1994, death, emigration from the province or end of coverage of the insurance plan, whichever came first.

Statistical analysis

Poisson regression models for rates accounting for extra-Poisson between-subject variation[353] were used to contrast the three agents. These regression techniques permitted adjustment for potential confounding by age, sex, socioeconomic status as measured by the receipt of social assistance at treatment initiation and year of treatment initiation. Differences in comorbidity were accounted for by statistically adjusting for medical and hospital visits and drug use (NSAIDs, psychotropic agents and medications used for the treatment of respiratory illnesses, diabetes, rheumatism, ulcers, epilepsy and hyperlipidemia) in the year preceding treatment initiation. Crude and fully adjusted models with 95% confidence intervals are presented.

Use of health services after initiation of therapy was measured by the occurrence of visits to general practitioners (GP), to specialists and to hospital. These outcomes were compared across subjects according to the ACEI first prescribed, with captopril as the reference, as this is the cheaper and came on the market first. Medical and hospital visits were computed as incidence-density rates using outpatient time as the denominator (number of events per person per year) in order to account for the differing amount of follow-up across contrasted groups. Analyses encompassed all health services utilization, including those that arose secondary to hypertension control (such as dose adjustment, drug switching or stopping) or on account of drug side effects.

RESULTS

Among the 27,710 subjects treated with an antihypertensive agent between January 1, 1991 and December 31, 1993, 529 subjects initiated therapy with captopril, 2,939 with enalapril and 1,241 with lisinopril. Table 4.1 presents characteristics of these subjects at treatment initiation and in the preceding year. Subjects initiated on captopril were older, included more males and a greater proportion received social assistance at treatment initiation than subjects initiated with enalapril or lisinopril. They also started treatment earlier in time, particularly when compared with subjects initiated on lisinopril, which was not available in Saskatchewan before July 1991. Health services utilization and drug dispensing at baseline also differed between subjects using the three agents. Subjects initiated on captopril were more likely to have received prescription drugs for diabetes or respiratory illnesses whereas a smaller proportion of them received anti-ulcer, anti-asthma or anti-rheumatism drugs, NSAIDs, psychotropic agents, anticonvulsants and antilipemics. Despite the fact that they had more hospital admissions in the preceding year than subjects initiated on enalapril or lisinopril, subjects starting treatment with captopril had less physician visits in that same period.

Health services utilization after treatment initiation

Table 4.2 shows that subjects initiated on captopril were dispensed more medications after treatment initiation, with an overall rate of 18.6 prescriptions per subject per year (vs 16.4 and 14.7 for enalapril and lisinopril users respectively). While they received fewer ACEI, captopril users were dispensed more β-blockers and calcium antagonists, and almost twice the number of prescriptions for diuretics per year. Subjects initiated on captopril also had more hospital admissions and visits to a physician after treatment initiation.

After adjustment for potential confounders, the rates of visits to a GP, a specialist or to hospital were significantly higher in subjects initiated on captopril than those initiated on enalapril or lisinopril (Table 4.3). To test the consistency of study results across different levels of comorbidity, a stratified analysis according to the baseline rates of hospital admissions was performed (Table 4.4). This analysis shows some modification of the effects of the drugs by hospitalization rates at baseline. For instance, the rates of visits to a GP remained higher in captopril users than in enalapril or lisinopril users only among subjects with less hospital admissions at baseline and were otherwise similar.

This suggests that subjects prescribed enalapril and lisinopril subsequently visited a GP to a lesser extent only if they were healthier to start with. Interestingly, the increased risk of visits to a specialist associated with the use of captopril was attenuated for patients hospitalized only once whereas both among subjects hospitalized twice or more and with those having no hospital admissions at baseline, enalapril and lisinopril still showed a "protective" effect over captopril. This variability, similar to that observed with regard to hospital admissions, could be due to random error, as indicated by the overlapping confidence intervals or to incomplete adjustment for comorbidity.

To address the comparability of the groups and the role of potential confounders, additional analyses were carried out (data not shown). First, we stratified the comparisons according to patient's health status at baseline, with two strata defined by the presence or absence of dispensed drugs or hospital admissions in the year preceding treatment initiation. The results of these analyses were similar to that of the main analyses, indicating that compared with starting antihypertensive therapy with captopril, treatment initiation with lisinopril or enalapril was associated with lower rates of GP, specialist and hospital visits. We also restricted the analyses to the 1,580 subjects initiated on monotherapy, who did not switch to another antihypertensive agent during the course of their treatment and who had not been hospitalized in the year preceding treatment initiation with most decreased risks previously observed among all subjects being attenuated. The lack of statistical significance of the measures of effect could however be due to the reduced sample size.

DISCUSSION

We showed that hypertensive subjects initiating treatment with enalapril or lisinopril visit a physician less frequently and appear to have a lower risk of being hospitalized than subjects initiating treatment with captopril. This suggests that ACE inhibitors may not be equivalent in all respects as previously discussed[373-392]. This is contrary to the fundamental assumption behind reference-based pricing. It could also mean that the anticipated savings from such a policy may be offset by the subsequent costs arising from increased use of health services[393,394].

The usefulness of non-experimental studies in evaluating the population effects of drug treatments is well known[395,396]. Without randomization, these studies are however susceptible to confounding by indication that arises from selective prescribing of drugs as a function of disease status, comorbidity or other characteristics pertaining to the patients and prescribers. This may not be a major problem since official guidelines and medical textbooks do not discriminate between specific ACEI regarding treatment initiation. Moreover, we adjusted for factors believed to be determinants of the use of health services[5], excluded subjects with suspected cardiovascular disease other than hypertension and performed sensitivity analyses. Nevertheless, differences may have remained between the contrasted drugs that could have biased the results.

Another limitation of this study stems from the use of computerized databases of drug dispensing. Dispensed medications may not represent actual intake of these drugs, which could have diluted the measures of effect. Furthermore, the definition of exposure did not take into account the different patterns of use and the assumed treatment may not have held true for all subjects. This may have distorted the results, especially if non-adherence to initial treatment was systematically associated with the use of health services.

Several concerns have been raised about RBP of pharmaceuticals and the potential impact such a policy may have on patient's care and overall expenditures[358-362]. A few uncontrolled studies in hypertensive subjects have observed substantial cost savings with equal efficacy when substituting benazepril to enalapril[397], lisinopril to captopril[398] or quinapril to either captopril, enalapril or lisinopril[399]. However, most of these clinical studies suffer from a number of weaknesses such as small sample size, short follow-up and above all, lack of control over potential confounders. No randomized controlled trial has demonstrated the differential impact of ACEI on overall health outcomes, and their

effects beyond those on pharmaceutical expenditures are still unknown[393,394].

This study illustrates the complexities behind the evaluation of RBP of pharmaceuticals and confirms the need for more data to address the efficiency of such an appealing policy. For optimal drug use, the burden of increasing costs of prescribed drugs should be offset by improvements in health outcomes and the short-term effects of RBP should be weighted against its long-term impact. These could be different in other drug classes and the effect could vary as a function of the outcome under study as well. The questions of whether RBP really achieves its objectives of controlling overall drug expenditures and to what extent, as well as its implications in terms of access to care, efficiency and quality of care, remains to be answered. Rigorous outcomes studies are needed to evaluate the impact of cost-containment measures such as RBP of pharmaceuticals on the health system as well as on individual patients.

Acknowledgments

This study used data provided by the Saskatchewan Department of Health. The statements contained hereby do not necessarily represent those of the Saskatchewan government. The authors would like to thank Mrs. Mary McNutt of the Saskatchewan Research Services, Population Health Branch, for assistance with the data. We also thank Dr. Marc Baltzan for useful comments on the manuscript.

This study was funded by a grant from Zeneca Pharmaceuticals Canada, Ltd. Chantal Bourgault is the recipient of doctoral fellowships from the National Health Research and Development Program of Canada (NHRDP) and the Social Sciences and Humanities Research Council of Canada (SSHRC). Samy Suissa is a Senior Scientist from the Medical Research Council (MRC) of Canada. The Pharmacoepidemiology Research Unit is funded by an *Équipe* grant from the *Fonds de la Recherche en Santé du Québec* (FRSQ).

The authors of this research were fully independent in conception, design, analysis and interpretation.

Table 4.1 **Characteristics of study subjects at treatment initiation and in the preceding year, by study group.**

Characteristics	Initial treatment; no. subjects (%)*		
	Captopril n=529	Enalapril n=2939	Lisinopril n=1241
Characteristics at treatment initiation			
Age, mean (SD)†	62.7 (10.7)	60.9 (10.6)	59.9 (10.4)
Males	273 (51.6)	1413 (48.1)	630 (50.1)
Social assistance	28 (5.3)	119 (4.1)	49 (4.0)
Length of follow-up‡, mean no. months (SD)†	36.3 (11.1)	34.4 (10.6)	29.3 (8.5)
Prescription drug use in the year preceding treatment initiation			
Respiratory agents	32 (6.1)	143 (4.9)	64 (5.2)
Anti-diabetics	48 (9.1)	244 (8.3)	77 (6.2)
Anti-asthma, rheumatism	20 (3.8)	142 (4.8)	51 (4.1)
Anti-ulcers	43 (8.1)	263 (9.0)	129 (10.4)
Anticonvulsants	2 (0.4)	46 (1.6)	20 (1.6)
Antilipemics	9 (1.7)	50 (1.7)	45 (3.6)
NSAIDs§	130 (24.6)	779 (26.5)	345 (27.8)
Psychotropic agents	70 (13.2)	498 (16.9)	209 (16.8)
Any medication	262 (49.5)	1481 (50.4)	631 (50.9)
Use of health services in the year preceding treatment initiation			
Hospital admissions, mean no. (range)‖	0.43 (0-6)	0.32 (0-7)	0.22 (1-10)
0	380 (71.8)	2280 (77.6)	1041 (83.9)
1	106 (20.0)	488 (16.6)	161 (13.0)
2 or more	43 (8.1)	171 (5.8)	39 (3.1)
Visits to GP, mean no. (range)‖	6.9 (0-96)	7.2 (0-104)	8.1 (0-105)
Visits to specialist, mean no. (range)‖	3.2 (0-62)	3.7 (0-113)	3.2 (0-64)

* Unless otherwise specified.
† SD = standard deviation.
‡ Follow-up time at risk only (excluding hospital-days).
§ NSAIDs = Non-steroidal anti-inflammatory drugs.
‖ Ranges of values are provided rather than standard deviations because these distributions are skewed.

Table 4.2 **Yearly rates of health resources consumption after treatment initiation, by study group.***

Health resources consumption	Initial treatment; no. events per subject per year		
	Captopril n=529	Enalapril n=2939	Lisinopril n=1241
Prescription drug use			
ACE inhibitors	6.4	6.8	6.8
β-blockers	0.8	0.6	0.5
Calcium antagonists	1.4	1.1	0.9
Diuretics	3.0	1.9	1.4
Any antihypertensive	11.6	10.4	9.6
Any agent†	18.6	16.4	14.7
Health services utilization			
Hospital admissions	0.56	0.44	0.27
Visits to GP	11.5	9.5	9.1
Visits to specialist	5.2	4.3	3.3

* Yearly rates of health resources were computed as the number of events per subject per year using outpatient time as the denominator.

† All prescribed agents, including antihypertensive medications.

Table 4.3 **Crude and adjusted rate ratios of health services utilization after treatment initiation.**

	Crude	Adjusted*	
	RR	RR	(95% CI)
Visits to GP			
Captopril	1.00	1.00	Ref.
Enalapril	0.83	0.84	(0.80-0.88)
Lisinopril	0.82	0.79	(0.74-0.83)
Visits to specialist			
Captopril	1.00	1.00	Ref.
Enalapril	0.84	0.82	(0.75-0.90)
Lisinopril	0.69	0.73	(0.65-0.82)
Hospital admissions, any cause			
Captopril	1.00	1.00	Ref.
Enalapril	0.78	0.82	(0.73-0.93)
Lisinopril	0.57	0.65	(0.56-0.75)

* Adjusted for gender, age (years), social assistance at treatment initiation, year of treatment initiation and comorbidity at baseline as measured by the use of prescribed drugs (NSAIDs, psychotropic agents, drugs dispensed for the treatment of diabetes, ulcers, respiratory diseases, epilepsy and hyperlipidemia) and the number of physician visits, hospital admissions and dispensed medications at baseline.

Table 4.4 **Adjusted rate ratios of health services utilization after treatment initiation, stratified by the rates of hospital admissions in the year preceding treatment initiation.**

	Rates of hospital admissions at baseline					
	None (n=3701)		1 (n=755)		≥2 (n=253)	
	$RR_{adj.}$	(95% CI)	$RR_{adj.}$	(95% CI)	$RR_{adj.}$	(95% CI)
Visits to GP						
Captopril	1.00	Ref.	1.00	Ref.	1.00	Ref.
Enalapril	0.84	(0.79-0.88)	0.84	(0.75-0.95)	0.94	(0.77-1.14)
Lisinopril	0.79	(0.74-0.85)	0.78	(0.67-0.91)	0.83	(0.64-1.08)
Visits to specialist						
Captopril	1.00	Ref.	1.00	Ref.	1.00	Ref.
Enalapril	0.84	(0.75-0.93)	1.14	(0.89-1.45)	0.58	(0.41-0.81)
Lisinopril	0.77	(0.68-0.87)	0.93	(0.68-1.28)	0.38	(0.22-0.67)
Hospital admissions, any cause						
Captopril	1.00	Ref.	1.00	Ref.	1.00	Ref.
Enalapril	0.76	(0.66-0.88)	0.99	(0.75-1.32)	0.93	(0.63-1.38)
Lisinopril	0.63	(0.53-0.75)	0.79	(0.54-1.15)	0.54	(0.30-0.98)

* Adjusted for gender, age (years), social assistance at treatment initiation, year of treatment initiation and comorbidity at baseline as measured by the use of prescribed drugs (NSAIDs, psychotropic agents, drugs dispensed for the treatment of diabetes, ulcers, respiratory diseases, epilepsy and hyperlipidemia) and the number of physician visits, hospital admissions and dispensed medications at baseline.

4.3 Additional discussion

In the context of abundant therapeutic choices and wide variation in the acquisition costs of drugs, cost-containment measures such as reference-based pricing of pharmaceuticals may seem appealing[356]. For optimal drug use, the burden of increasing costs of prescribed drugs should be offset by improvements in health outcomes. However cost-containment policies may shift part of the drug expenditures to the consumers or to other components of the health care system. Our study shows that patients using three different agents belonging to the same therapeutic class, and that would thus be assumed to be therapeutically equivalent under a reference-based pricing scheme, showed different rates of physician and hospital visits following treatment initiation. This suggests that reference-based pricing, if implemented as such, may have negative impacts both on patients and the health care system.

Our study however, has important limitations. First, the study design emulates the clinical trial paradigm but subjects were not randomized to treatment. They may consequently have been different at treatment initiation with respect to their disease status, degree of comorbidity, socioeconomic status or other unmeasured confounders. Despite their usefulness in evaluating the population effects of drug treatments, non-experimental studies are susceptible to biases arising from confounding by the indication for the prescribed drug, whereby selective prescribing of a specific agent may lead to a lack of comparability between the contrasted groups with regard to the outcomes under study. In our analysis, blood pressure levels and the presence of comorbid conditions are likely to constitute indications for the selection of a specific agent. Having no access to clinical or physiological measures of the severity of hypertension, potential confounding by indication had to be addressed using solely prescription and health services utilization data. We found the groups to be different at baseline and consequently controlled for factors believed to be determinants of the use of health services. We also selected the cohort so as to exclude subjects for whom the main indication for treatment initiation with ACE inhibitors was not hypertension, thus maximizing the homogeneity of the study population. Moreover, analyses restricted to homogeneous groups of subjects were performed and produced similar results. Despite these adjustments, differences may have remained between the contrasted subjects, and the results may still be biased by undocumented factors.

Another limitation of this study stems from the use of computerized databases of

drug dispensing. Although we don't think it's of great concern, dispensed medications may not represent actual intake of these drugs, which could have diluted the measures of effect. Furthermore, the definition of exposure did not take into account the different patterns of use and the assumed treatment may not have held true for all subjects, which may have distorted the results. A bias would have been introduced especially if non-adherence to initial treatment was systematically associated with the use of health services.

This study was not designed to evaluate reference-based pricing policies; nor was it designed to compare the cost-effectiveness of different agents belonging to a given therapeutic class. Further rigorous outcome studies are needed to fully understand the impact of cost-containment measures such as reference-based pricing of prescription drugs on the health system as well as on individual patients.

CHAPTER 5 – PATTERNS OF ANTIHYPERTENSIVE DRUG USE

5.1 Preface to the second manuscript

This manuscript presents a study examining the patterns of use of antihypertensive drugs and their effects on health outcomes. The first manuscript was based on an intention-to-treat analysis of the cohort: the agent dispensed at treatment initiation was assumed to represent that for the entire study period. Following a review of drug utilization studies (see Chapter 2, section 2.4), we had important reservations with regard to the definition of exposure used in our reference-based pricing manuscript: drug taking behaviours are believed to be highly variable if not, erratic.

As underlined in the review, prior drug utilization studies suffered from a number of limitations. Among those, the use of prevalent cohorts of antihypertensive drug users was emphasized and its effect on the validity of the results underlined. Furthermore, it is worth noting that no study has so far examined in detail various patterns of use over a period of observation longer than a year. We therefore felt the need to extensively document the patterns of antihypertensive drug use from initiation of treatment to the end of the study period using a cohort of newly treated hypertensive subjects. This is the aim of the second manuscript.

This study is a complement to that of Caro *et al*[285,292] which happens to have used the same Saskatchewan databases and a very similar study population and period. The main differences between our study cohort and that of Caro *et al* are the following: Caro *et al* excluded patients starting treatment with a combination therapy whereas we thought it is an important group to characterize. Caro's group included patients initiating therapy with diuretics; we unfortunately did not have access to these data. Whereas they presented an interesting algorithm aimed at characterizing drug taking behaviours in the cohort, Caro *et al* actually did not describe the patterns of use of antihypertensive agents. Also, their main interest was on rates of persistence with therapy at the end of the period of observation whereas we documented compliance over the entire period of observation. By showing an early decrease in persistence rates as measured using the last prescription dispensed at the end of the study period, Caro *et al*[285] implicitly suggested that switches, drug additions and interruptions of treatment were rather frequent. Our study examines these patterns of use in detail.

The general objective being addressed is the following:

- To characterize the therapeutic choices made by physicians and their patients in the management of uncomplicated hypertension by examining the distribution and determinants of selected patterns of antihypertensive drug use over a long period.

The specific objectives of this study are:

- To examine the choice of initial therapy from 1990 to 1993 in a population of adult subjects with uncomplicated hypertension and identify factors associated with such a choice.
- To determine the extent of compliance with therapy in that population and whether noncompliance was associated with patient's characteristics, comorbidity and health services utilization.
- To estimate the incidence and timing of treatment modifications during the course of therapy and document their correlates.

This manuscript, which will be submitted for publication, should be quoted as follows:

Bourgault C, Rainville B, Suissa S. Patterns of antihypertensive drug use among a population-based cohort of adult patients newly treated for hypertension. Unpublished manuscript. Montreal: Department of Epidemiology and Biostatistics, McGill University, 1999.

5.2 *Manuscript 2.* Patterns of antihypertensive drug use among a population-based cohort of adult patients with newly treated hypertension

Chantal Bourgault, PhD candidate; Bruno Rainville, MSc; Samy Suissa, PhD

Department of Epidemiology and Biostatistics, McGill University, Montréal, Canada.
Pharmacoepidemiology Research Unit, Division of Clinical Epidemiology, Royal Victoria Hospital, McGill University Health Center, Montréal, Canada.

ABSTRACT

Background: The benefits of consistently using antihypertensive agents for the treatment of hypertension have been extensively documented in long-term randomized controlled trials. However clinical trial results may not reflect actual clinical practice and information about how these drugs are used in the general population is scarse.

Objectives: To examine longitudinally the patterns of use of antihypertensive agents and their determinants in the first seven years of treatment among patients initiating antihypertensive therapy.

Methods: Information on patterns of antihypertensive drug use, compliance and modifications to therapy were derived from a careful examination of medication use in a cohort of 19,501 subjects aged 40 to 79 years, without prior cardiac disease and initiating antihypertensive therapy with an angiotensin-converting-enzyme (ACE) inhibitor, a calcium antagonist or a β-blocker (1990-93). Data on antihypertensive drug therapy and other prescription drugs were extracted from the Saskatchewan Health computerized databases (Canada).

Measures of antihypertensive drug use: Initial drug use was defined as the agent(s) dispensed at cohort entry. Compliance to therapy was measured in terms of the proportion of days during which antihypertensive medications were available to the patient. Modifications to therapy were described in terms of treatment interruptions, discontinuation of therapy, switches across drug classes and drug additions.

Results: ACE inhibitors, followed by calcium antagonists and β-blockers, were the most commonly prescribed agents to initiate treatment. Patients with prior evidence of diabetes were less likely to be dispensed β-blockers, as were younger and female patients. Visits to a cardiologist decreased the likelihood of receiving a combination therapy or ACE inhibitors but increased that of being dispensed a calcium antagonist. Only 28% of patients were found to be compliant to their antihypertensive treatment over a period averaging five years. Factors associated with noncompliance included initiating therapy with a β-blocker, younger age, male gender and the absence of hospital admissions in the year preceding cohort entry. Also, compliance rates were found to decrease over time. Over 89% of study subjects underwent at least one modification to their initial regimen, treatment interruptions and discontinuation of therapy being the most frequent. Relative to β-blockers, patients initiated on combination therapy were

more likely to keep on with their initial treatment schedule and less likely to discontinue therapy. Users of ACE inhibitors at treatment initiation, and to a lesser extent those using calcium antagonists, were more likely to add or switch twice in a row or to add or switch first and interrupt treatment thereafter. One year after starting treatment, only 33.8% of patients were still using the drug they were dispensed at treatment initiation, with a median time to the first modification of 134 days. A rapid early decrease in the proportion of patients continuing on initial therapy was noted, especially among those initiated on β-blockers. Timing of treatment modifications also differed according to the type of modification, with discontinuation of therapy and treatment interruptions occurring earlier in time than drug switches and additions.

Conclusion: Substantial noncompliance to therapy and erratic drug taking behaviours were found in this population. Prescribing practices and drug taking behaviours do not seem to be in accordance with National guidelines.

INTRODUCTION

Preventing cardiovascular disease and death is the primary goal of hypertension management. Long term randomized controlled trials have shown that consistent drug therapy both decreases the complications of hypertension and improve survival[92,97,113,187,400-402]. Sub-optimal treatment of high blood pressure constitutes a major barrier to the effectiveness of hypertension therapy. For instance, poor compliance with therapy, early discontinuation and erratic drug use manifested by frequent interruptions and switches to other treatment regimens have been shown to be associated with the progression of coronary artery, renal disease and congestive heart failure, and to increase the risk of a readmission to hospital[263,287,294-296,302,305,330].

In randomized controlled trials, the frequency of treatment discontinuation after 6 to 12 months has been estimated to be around 15% for patients randomized to angiotensin-converting-enzyme (ACE) inhibitors, 20-25% for β-blockers and 20% for calcium antagonists[129,317-319]. The Medical Research Council (MRC) trial reported withdrawal rates after five years of 43% for a group of patients on diuretics and 42% for β-blockers[34]. These changes to treatment regimens are believed to be mainly due to side effects of the drugs and the decision to stop was coming from the patient. However, the randomized controlled trial may not be suited for evidence gathering on the use of medication in the clinical setting due to many design-based constraints.

Several attempts have been made to document patterns of medication use for the treatment of hypertension in the population. Most of these studies have reported the distribution and determinants of drug use[42,267-270,272-277,281-285], often in relation to official guidelines on the management of hypertension. Numerous are those that examined compliance[282,291,293-295], persistence with therapy[284-286,292] or discontinuation rates[287,288,290]. Such studies were however hampered by some limitations such as a short follow-up, undocumented comorbidity and reports where patients initiating therapy were mixed with those having established hypertension. Also, several of them were restricted to patients on monotherapy or using newer drugs only.

Few studies have examined longitudinally, from treatment initiation onward, the patterns of antihypertensive drug use, including treatment interruptions, modifications in treatment regimens and continuity of use among patients initiating therapy. Jones *et al*[288] documented treatment modifications in currently treated patients starting a new course of therapy. Bobal *et al*[303] studied changes in treatment following treatment initiation

based on an opinion survey conducted on a small sample of Pharmacy directors. Okano *et al*[290] examined the patterns of antihypertensive drug use during the first year following initial treatment in a military population and their family considered compliant with therapy. Wilson *et al*[305] examined the determinants of modifications to therapy among newly treated patients compliant with antihypertensive therapy. Other studies reported only on modification rates in general[300,304] or on the proportion of patients switching or interrupting treatment[302,296,287,42]. Four recent publications, all based on the same study, focused on persistence with antihypertensive treatment in the actual clinical practice[284,292,285,286]. Although the authors present an interesting algorithm to identify changes in treatment such as additions, switches and drug deletions, they do not report on them other than by controlling in their analyzes for "turbulence" in the treatment regimen (number of changes). Despite these previous studies, an important information gap exists with regard to the patterns of use of antihypertensive agents in the population. Most of these studies suffered from the limitations stated above and others were not extensive in their description of patterns of use. Indeed, although recent studies have suggested considerable variability in the patterns of antihypertensive drug use in the clinical setting, little is known about the patterns of use of antihypertensive therapy at the population level.

Our study analyzed prescriptions for newly treated patients with hypertension. More specifically, we examined patterns of antihypertensive medication use among patients initiating pharmacological treatment for hypertension with an ACE inhibitor, a ß-blocker or a calcium antagonist. The general objective was to describe the therapeutic choices made by physicians and their patients in the management of uncomplicated hypertension by examining the distribution and determinants of selected patterns of antihypertensive drug use over a long period.

To fulfill these objectives, we 1) examined the choice of initial therapy from 1990 to 1993 in a population of adult subjects with uncomplicated hypertension and identified factors associated with such a choice; 2) determined the extent of compliance with therapy in that population and whether noncompliance with therapy was associated with patient's characteristics, comorbidity and health services utilization and 3) estimated the incidence and timing of treatment modifications during the course of therapy and documented their correlates.

MATERIALS AND METHODS

Source of data

Data were obtained from the Saskatchewan computerized drug data files developed in the context of the universal health insurance program provided to approximately 95% of all residents of this Canadian province[344-347,349]. These data files provided us with drug-related information including drug type and dispensing date, demographic data (date of birth, gender, coverage initiation and termination dates, date of death if applicable and receipt of social assistance at treatment initiation) and information related to hospital admissions and medical visits. The accuracy of these data for use in a research setting has been documented[345,346].

Study population

A cohort of 35,631 subjects initiating therapy with at least one of the ACE inhibitors, ß-blockers or calcium antagonists between January 1st, 1990 and December 31, 1993 was first identified. *Treatment initiation* was taken to be the date of receipt of the first prescription of one or several of these agents. To ensure that study subjects were initiating treatment, those dispensed any antihypertensive agent in the year preceding treatment initiation (including diuretics, α-blockers or centrally acting agents) were excluded from the cohort. Several criteria were used to identify subjects for which the most likely indication for antihypertensive treatment was uncomplicated essential hypertension. Because incidence rates of hypertension are lower in these age groups, we first excluded 9,674 subjects aged less than 40 years or 80 years and over. We further restricted the cohort to subjects without evidence of cardiovascular disease as indicated by medication use prior to treatment initiation. Cardiovascular therapy was defined as the dispensing of a prescription for quinidine or any anti-arrhythmic drugs, nitrates, digoxin, anti-coagulants, loop diuretics or other cardiac agents during the year preceding cohort entry. Also subjects admitted to hospital in the preceding year with heart disease as a discharge diagnosis (ICD-9 codes 402, 404, 410-416, 420-429 or 745.4-746.9) were excluded. Overall, 7,324 subjects were excluded from the initial cohort due to prior cardiovascular disease. Finally, 89 subjects that used antithyroid drugs or radio-iodine and 969 subjects that used ergot preparations or methysergide were excluded because antihypertensive medications are also indicated for the treatment of hyperthyroidism and migraine. The 19,501 study subjects left were followed

for antihypertensive drug use documentation until the earliest of March 31, 1997, date of death, emigration from the province or end of coverage of the insurance plan.

Antihypertensive drug use

All antihypertensive drugs dispensed between treatment initiation and the end of the observation period were identified. Our analysis of patterns of use was limited to the following four major antihypertensive drug classes: ß-blocking agents, diuretics, ACE inhibitors and calcium antagonists. Three dimensions of antihypertensive drug patterns of use were examined: the choice of an initial agent or group of agents, compliance with therapy and modifications to therapy during the course of the disease.

Initial therapy. Initial antihypertensive drug was defined as the agent or group of agents dispensed on the very first day of therapy. Initial antihypertensive regimens were first divided into single drug use (ACE inhibitor, β-blocker or calcium antagonist only) or combination therapy. Combination therapy was defined as the dispensing of medications belonging to more than one drug class or a fixed-combination product containing drugs from different classes (e.g. ACE inhibitor-diuretic combination drug) at treatment initiation. Table 5.1 lists the agents included in this classification scheme. Specific agents that belong to each drug class were regrouped to ensure sufficient numbers in each category.

Compliance with therapy. A standard measure was used to assess patient's compliance with antihypertensive therapy. The "days supply" was defined as the cumulative number of days during which one or several antihypertensive medications were available for use following treatment initiation. To compute this measure, the number of days a prescription should have lasted was assumed to be 30 days, according to average Saskatchewan prescribing practices. If the duration of one prescription fell into that of a subsequent prescription, the days supply were not duplicated thus precluding compliance rates to exceed 100%. However, stockpiling of medications was allowed by adding to the days supply all prescriptions of a same agent dispensed in a 15-days time window. In all calculations, hospital-days were removed from the denominator since information on in-patient use of medications is not available. Based on controlled studies that showed lesser therapeutic efficacy of antihypertensive

medications below that level, a patient was considered to comply with therapy if any antihypertensive medications was available for use at least 80% of the days of observation. Compliance rates were reported yearly for the entire period of observation.

Modifications to therapy. Any change in the initial drug regimen, namely interrupting treatment (temporarily or not), switching across drug classes and adding medications belonging to a different therapeutic class was considered a modification to therapy. For the purpose of identifying treatment interruptions, a period of 90 days or more without using medications was retained. The 90-day cut-off point was based on the ground that with the 80% threshold for compliance, 2.5 months without using any antihypertensive drugs would be required over a one-year period for a patient to be considered not compliant enough to benefit from therapy. Therefore, an antihypertensive treatment interruption was defined as a failure to fill a prescription for any of the studied agents in the 120 days following the filling date of the last prescription. When the last treatment regimen included more than one agent from the same drug class, possible stockpiling of medications was considered by treating them as sequential prescriptions and assuming continuing therapy, providing the prescriptions were dispensed no later than in the last 15 days. A temporary treatment interruption (when a new course of treatment was initiated following an interruption) and a treatment discontinuation were treated distinctively as they may identify different sub-populations.

Because sequential dispensing of two different agents (or combined drugs) could either mean that an agent was added or that the patient was switched from one drug class to another, differentiating between a switch and the addition of a second or third drug was quite challenging. For that purpose, an algorithm similar to that used by Caro *et al* in a recent study[292] was constructed using for each prescription, information pertaining to the subsequent dispensing dates. Apart from treatment interruptions and discontinuation of therapy, two types of modifications to therapy were considered: switching from a therapeutic drug class to another (if at least one prescription that belonged to a different therapeutic class was encountered in the following trimester), and adding a second agent belonging to a different therapeutic drug class (if at least one of such agents was encountered in the following trimester). Dropping one or several drugs from treatment was not considered in the algorithm. In all of these scenarios, a gap of up to 119 days was allowed between two dispensing dates. Otherwise, the

modification was considered to be a treatment interruption.

Statistical analysis

Simple contingency tables for proportions were used to present descriptive data on the patterns of use of antihypertensive agents. Logistic regressions were used to examine the correlates of initial drug use (with β-blockers as the reference) and compliance with therapy. Time to the first modification to therapy was assessed using multivariate Cox proportional hazards models and the rates of various types of modifications to therapy (treatment interruptions, switches and drug additions) were modeled using Poisson regression for rates accounting for between-subjects variation. Potential factors associated with any of these patterns of use included patient's characteristics (age, sex and social assistance at treatment initiation), drug markers for comorbid conditions during the year prior to treatment initiation (prescriptions for NSAIDs, glucocorticoids, neurotropic and lipid lowering agents, as well as drugs used for the treatment of respiratory illness and ulcers) and health services utilization (hospitalizations and visits to a cardiologist or to an internist) prior to treatment initiation. The year of initiation of treatment and when applicable, the duration of follow-up, were also controlled for to account for possible time trends and exposure opportunity.

The development of diabetes and cardiac disease such as angina and congestive heart failure was also considered by including them as predictors of treatment modifications, along with antihypertensive drugs (ACE inhibitor, β-blocker, calcium antagonist or combination therapy) used at treatment initiation.

RESULTS

Patients' characteristics

Table 5.2 shows the demographic and health-related characteristics of the 19,501 patients that initiated antihypertensive therapy and met the age and probable indication inclusion criteria. The subjects were 60 years of age on average and 49% were males. Slightly more than 4% were receiving social assistance at initiation of antihypertensive therapy. More patients were included in the cohort at the beginning of the study period (27% in 1990) than at the end (22% in 1993).

Initial antihypertensive therapy

Proportionate use of antihypertensive drugs at treatment initiation. The proportion of patients dispensed various antihypertensive medications at treatment initiation is shown in Figure 5.1. An ACE inhibitor was the most commonly dispensed agent in patients initiating antihypertensive therapy with 37.4% of patients starting treatment with such agents. A calcium antagonist was the initial agent for 27.5% of patients and 26.4% initiated their treatment with a β-blocker. Of the 1,708 patients starting on combination therapy (8.8%), 86.4% received one or several of the three main agents in combination with a diuretic. Only 64 patients received more than two different agents at treatment initiation.

Time trends. Examination of the rates of use of these agents at treatment initiation over time showed the proportionate use of ACE inhibitors to have significantly increased between 1990 and 1993, whereas the use of calcium antagonists and β-blockers as single agents seemed more stable (Figure 5.2). With the exception of ACE inhibitors in combination with a diuretic, which showed an important increase in use, the overall choice of initiating treatment with multiple drug therapy was rather stable over time.

Factors associated with initial therapy. Factors associated with the choice of one or the other of these specific agents when initiating a treatment for hypertension are displayed in Table 5.3. These analyses show a higher likelihood of using calcium antagonists at treatment initiation, relative to β-blockers, among patients dispensed anti-diabetic or respiratory agents in the preceding year and those having visited a cardiologist. Males and older patients were also more likely to be dispensed calcium

antagonists at treatment initiation relative to β-blockers. Prior use of neurotropic drugs was negatively associated with calcium antagonists. Correlates of ACE inhibitor use at treatment initiation are similar to that of calcium antagonists: older age, male gender and prior use of agents to treat diabetes and respiratory illness have all been shown to increase the likelihood of being dispensed ACE inhibitors. However, prior use of anti-ulcer or neurotropic agents and prior visits to a cardiologist were negatively associated with ACE inhibitor use relative to β-blockers. The factors associated with the use of combined drugs when starting therapy differ slightly from that of ACE inhibitors and calcium antagonists. For instance, prior use of NSAIDs, neurotropic or anti-ulcer agents, as well as prior visits to a cardiologist decreased the risk of starting antihypertensive treatment with multiple agents, whereas respiratory illness and diabetes were positively associated with that initial choice. Older age and male gender also increased the likelihood of using multiple agents at treatment initiation.

Compliance with therapy

Overall, only 27.8% of the study population were dispensed enough antihypertensive drugs over the entire period of observation to have daily medications available at least 80% of the time. These subjects may be considered compliant with antihypertensive therapy.

Predisposing factors. Patients dispensed β-blockers at treatment initiation had poorer compliance with an overall proportion of compliant patients of 18.2% (data not shown). Multivariate analyzes show that relative to β-blocker users, patients using ACE inhibitors and combination therapy at treatment initiation were twice more likely to be compliant ($RR_{adj.}$=2.3; 95% CI=2.1-2.5 and $RR_{adj.}$=2.4; 95% CI=2.1-2.8 respectively), whereas calcium antagonist users were 40% more likely to be compliant ($RR_{adj.}$=1.4; 95% CI=1.2-1.5) (Table 5.4). Other predictors of good compliance were older age, female gender and hospital admissions in the prior year. A significant decay in compliance rates in the first year of therapy was also observed in each of the four treatment regimens used at treatment initiation (Figure 5.3). The rates were stable thereafter.

Modifications to therapy

Incidence of modifications to therapy. During the entire period of observation, 11.5%

of patients continuously used one or several agents from the same therapeutic class without any modification or interruption in treatment. The overall modification rate was found to be 58.1 modifications per 100 subjects per year with variations across the types of modification. Treatment interruptions and additions of one or several agents to the actual treatment regimen were the most frequently encountered (30.1 and 27.9 modifications per 100 subjects per year respectively) whereas the rate of switches across therapeutic classes was rather low (5 per 100 subjects per year). Predictors of the frequency of switching across drug classes or adding a drug to the actual treatment regimen were found to be older age, male gender and the presence of heart failure or angina during the course of therapy. The rates of such modifications to therapy were also significantly higher among subjects started on ACE inhibitors ($RR_{adj.}$=1.29; 95% CI=1.24-1.34), calcium antagonists ($RR_{adj.}$=1.1; 95% CI=1.1-1.2) and combination therapy ($RR_{adj.}$=1.5; 95% CI=1.4-1.5) as compared with β-blockers. None of the factors included in multivariate models were significantly and clinically important predictors of treatment interruptions in Poisson regressions.

Types of modifications. Figure 5.4 displays the frequency and type of the first two modifications to therapy to occur. Overall, 88.5% of the subjects underwent at least one modification to their initial antihypertensive therapy during the entire period of follow-up. Of the first episodes of modification to therapy, the most common were treatment interruption (31.5%) and discontinuation of therapy (22.6%). Agents belonging to a different drug class were added for 20.1% of the study subjects whereas 14.3% switched to another therapeutic drug class. An examination of the patterns of antihypertensive drug use following a first modification shows that of those who added a drug to their treatment regimen first, 47.6% did not subsequently modified their treatment whereas 20.9% underwent another drug addition or switch. Of those who switched first, these figures were 24.4% and 36% respectively. Half of the stoppers came back to their initial treatment following the interruption. For 6940 subjects (35.6%), the first modification was the only one to occur during the entire period of observation.

Summarizing the type and frequency of the first two treatment modifications according to initial treatment led to eight different patterns which are outlined in Table 5.5. Important differences exist with regard to the types of modification across drug classes. Patients initiated on combination therapy were more likely than others to keep

on with their initial treatment schedule or to interrupt treatment a first time and start a new course of therapy using a different treatment schedule. Subjects using β-blockers at treatment initiation, and to a lesser extent those dispensed calcium antagonists, were more likely to discontinue therapy or to interrupt treatment a first time and come back to their initial treatment thereafter. Patients using ACE inhibitors at treatment initiation, and those using calcium antagonists to a lesser extent, were more likely to add or switch twice in a row or to add or switch first and interrupt treatment thereafter. Stratification beyond the second modification to therapy resulted in numbers too small to draw conclusions from.

Timing and predictors of the first modification to therapy. One year after starting treatment, only 33.8% of patients were still using the drug they were dispensed at treatment initiation. Overall, the median time to a first modification was found to be 134 days. Figure 5.5 shows a rapid early decrease in the proportion of patients continuing on initial therapy. The first modification to therapy arose considerably later for patients initiated on combination therapy or ACE inhibitors, with median times to the first modification of 202 and 208 days respectively, compared to 75 days for patients initiated on β-blockers and 105 days for calcium antagonists. Timing of treatment modifications also differed according to the type of modification, with discontinuation of therapy and treatment interruptions occurring earlier in time than drug switches and additions (Figure 5.6). Overall, 50% of subjects discontinuing therapy did so within 37 days of initiation of therapy. Median time for treatment interruptions was 86 days whereas these figures are 146 and 218 days for drug switches and additions respectively.

Predictors of a first modification to therapy were not found to differ in a clinically important way across modification types, all relative risks lying between 0.85 and 1.2 (data not shown). As a general rule, younger subjects were found to be more likely to experience any modification to therapy, as were males. Patients initiating therapy with a β-blocker were also found to have higher rates of modifications than others, even after statistical adjustment for other potential predictors. Finally, subjects starting treatment with a combination therapy were less likely to experience any modification to therapy.

DISCUSSION

This study represents one of the first attempts to describe over a long period of observation the patterns of use of antihypertensive agents in a population initiating therapy for uncomplicated hypertension. Our study confirms that the patterns of use of antihypertensive agents are highly variable, with a high frequency of treatment interruptions and modifications to therapy. Three main findings are worth mentioning. First, it appears that ACE inhibitors, calcium antagonists and combination drugs are widely and increasingly used as initial therapy, especially among males and older patients. Second, compliance with therapy was found to be very low, especially among subjects using β-blockers. Younger patients, men and subjects that were not hospitalized in the prior year were also found to be less compliant with therapy. Finally, we found that only 11.5% of study subjects continuously used the agent they were initiated on. Caro *et al*[285] reported earlier that a surprisingly high number of patients discontinued therapy early after treatment initiation. Our study confirms their finding but we found this to be more of a problem among β-blocker users who seemed to differ from the others. These subjects showed a higher rate of modifications, most of those being discontinuation of therapy that occurred early in time. It is interesting to note that patients on combination therapy were less likely to modify their treatment regimen and if so, the modification arose later in time. A number of potential predictors of the rates of modification across drug classes were statistically significant when tested in multivariate regressions but the low magnitude of the relative risks rendered them of minimal interest.

When this study was undertaken, ß-blockers and diuretics were the only drugs shown in randomized controlled trials to reduce the incidence of hypertension complications and to decrease mortality in the long term[18,13], and therefore to be recommended in the treatment of hypertension as first-line agents [32,154,175,155]. Yet, ACE inhibitors and calcium antagonists are extensively used in the treatment of hypertension. Adherence to guidelines is not believed to be very high in general[271], which is confirmed by our results. Official guidelines are based on the results of long-term randomized controlled trials as a scientific evidence for drug efficacy and safety. The amount of uncertainty over the cardiovascular effects of newer agents and their potential role as first line agents is such that several long-term randomized controlled trials are either underway or very recently published their first results[403]. However, these trials are not

without limitations and their applicability in the real-world is doubtful. The way medications are used in clinical trials does not reflect everyday practice. For that reason, randomized controlled trials' results are hardly comparable to what actually happens at the population level, despite efforts to include modifications to therapy, treatment interruptions and general adherence to treatment regimens in effectiveness and sub-group analyzes. It is assumed however that medical practitioners would translate the positive results of large-scale randomized controlled trials in hypertension into effective treatment regimens for their patients. Our study shows that this may not be the case.

The decision whether to prescribe and what agent to prescribe entirely relies on the practicing physician who has complete freedom of choice. Commercial influences in a lucrative pharmaceutical marketplace may have contributed to decrease the use of "older" agents such as ß-blockers and diuretics[404,405]. These campaigns may have contributed to the increased use of calcium antagonists and ACE inhibitors, despite the lack of evidence of their beneficial effect on cardiovascular morbidity and mortality. Characteristics of the patients such as age, gender and the presence of risk factors or markers of complicated hypertension could also influence hypertension management. Such factors did emerge in our study as predictors or correlates of both initial drug choice and compliance rates. Surprisingly, none of them did emerge as predictors of the rates of treatment modification. Further studies should investigate the role of other potential determinants of medication use in hypertension.

We found that patients initiated on β-blockers were less compliant with therapy, had higher discontinuation rates, which occurred earlier in time. Several factors, other than the characteristics of the drugs *per se*, could explain these results. One likely hypothesis is that patients with less severe hypertension or without specific concomitant conditions that puts them at higher risk of complications were more likely to receive these agents at treatment initiation, which would be consistent with clinical guidelines. If sicker patients are more compliant with therapy for instance, the observed differences in compliance rates to specific agents could be a result of differing indications for use. Our finding that compliance with therapy was better with the newer ACE inhibitors and calcium antagonists than with older agents such as β-blockers and diuretics is similar to those reported earlier[287,292,285,295].

We may assume as well that the presence of modifications to therapy may be indicative of poor blood pressure control, lack of tolerance to the drug or of the onset of

concomitant conditions for which antihypertensive medications are also indicated. The corollary, the absence of a modification to therapy, may suggest a satisfactory outcome of antihypertensive treatment. Failure to achieve blood pressure control or the presence of concomitant diseases may prompt the treating physician to "step-up" the treatment regimen by either 1- prescribing a higher dose of the same agent, 2- substituting a more potent medication, or 3- adding another antihypertensive agent. Such escalation in the treatment regimen has been labeled "stepped-care therapy" and has been proposed as the privileged approach to hypertension management for several years [32,154,175,155]. Not surprisingly, variability in treatment regimens may carry subsequent variability in clinical and cardiovascular health outcomes. Possible explanations for the fact that β-blocker users are more likely to discontinue therapy and to be noncompliant is that they may suffer from the mildest form of the disease. For instance, the treatment may have been interrupted due to goal attainment of blood pressure levels using solely non pharmacologic interventions. Side effects of the drugs is also a possible reason for stopping treatment but this hypothesis would need to be investigated further. Patients initiating therapy using combination drugs are probably considerably different from the other new hypertensives. First, it is contrary to every clinical guidelines to initiate therapy using multiple drugs. These "atypical" patients are not numerous: they represent 8.8% of out study population; which would represent around 3.5% of new hypertensives if patients starting treatment with diuretics were included. We hypothesize that they probably represent sicker patients, more prone to use health services (including drugs) and consequently more compliant with therapy. Finally, diuretics are believed to have an additive (if not synergistic) effect with all of the other antihypertensive drug classes[168]. Addition of a diuretic to any treatment regimen, which was very common in our study, could therefore be an indicator of the lack of control over blood pressure.

Computerized databases of prescription claims offer major advantages for drug utilization studies, including the possibility of documenting the entire history of drug use, starting from the very first prescription being dispensed. Records of dispensed medications offer the possibility to document patterns and timing of drug exposure, to describe the levels of adherence to therapy and to assess determinants and consequences of different patterns of use. Also, the large number of study subjects allows us to describe in detail the frequency of patterns of drug use such as treatment interruptions, drug additions and switches to different therapeutic drug classes.

The degree of detail with regard to drug dispensing and a seven year period of observation constitute major strengths of this study. Modifications and compliance to therapy are hard to measure with accuracy[316]. Previous drug utilization studies and examination of drug taking behaviors have mostly focused on measures of compliance averaged over a short period (usually 12 months), thus masking important variations in adherence to therapy. Our study shows compliance rates to decrease over time. Also, 22% of the study subjects have modified their treatment regimens for the first time after the first year of observation. Hence, limiting the latter to one year would results in a considerable loss of information. In addition, we increased the accuracy of our measure of compliance by insuring that the durations of use of overlapping prescriptions of a same agent were not duplicated in the measurement of compliance and time spent in hospital was removed from all denominators. These measures lead to a more accurate and conservative estimate of compliance.

The use of such databases also carries some limitations. A major limitation pertains to the lack of information about the indication and the specific directions for use of the prescribed agents in computerized records. In some study subjects, antihypertensive agents may have been used to treat other conditions such as coronary artery disease or congestive heart failure rather than hypertension, introducing heterogeneity in our study population. Drug markers have however been used previously with good correlations with the diagnosis of hypertension[275]. Also, actual duration of use for a given prescription was not available and the average duration of an antihypertensive drug prescription in Saskatchewan had to be used as a proxy. Finally, drug data represents dispensed medications and actual drug taking behaviors remains unknown. We may suggest however that the likelihood of a patient not actually taking medications that have been filled continuously is probably low.

As discussed by Christensen[291], the use of a period of follow-up that spans several months may introduce a "smoothing effect", whereby undercompliance during a short period is masked by the overall average. Enlund[325] suggested that 3 months of follow-up with four dispensing dates is sufficient to assess compliance to antihypertensive medications. Not having the information pertaining to the actual use of dispensed agents, we could not measure compliance in such detail. However, we computed yearly rates of compliance as an attempt to overcome possible dilution of effect. Also related to this issue is the fact that patients may obtain refills before depleting their actual supply.

This would inflate overcompliance rates computed using short follow-up periods. Stockpiling of medications was considered in all our estimates of compliance.

The major limitation of our study pertains to the definition of the cohort. Whereas they may represent a considerable proportion of the hypertensive population newly starting therapy, subjects initiating treatment with a diuretic were not included in the study. This considerably limits the generalizability of our study findings. Also, increasing or decreasing drug doses was not included in our definition of a modification of therapy while it has been shown to be quite frequent. Finally, and due the way we constructed the algorithm contributing to identify treatment modifications, we could not document drug dropping. This means that our reported rates of modification to therapy are probably conservative.

Convincing evidence has shown that antihypertensive treatment reduces the risk of fatal and non fatal cardiovascular disease, especially stroke, myocardial infarction and heart failure[13,406,407], thereby reducing the risk of mortality. The number of different medications that may be prescribed for the treatment of hypertension is large, which reflects a continuous need for more effective treatment at the population level. Despite the progress in the field of hypertension management, selecting the most appropriate agent for the individual patient remains a challenge. Because of the very wide variety of choices, clinical guidelines are periodically updated as a guidance to physicians. However, these guidelines are based on efficacy results obtained from randomized controlled trials which may not reflect the actual population that will use these agents. Also, the relative value of antihypertensive agents should not be measured solely by their ability to lower blood pressure or by their beneficial effect on intermediate variables such as left ventricular hypertrophy. Evidence of their ability to deliver better cardiovascular protection and to improve survival should be available for the entire population of potential users, not only for highly selected groups of subjects such as those participating in randomized controlled trials. Hence, noncompliance or high degrees of variability in drug taking behaviors should be taken into account when assessing drug effects at the population level.

Sound decisions have to be made by treating physicians in clinical practice, decisions that have enormous medical, societal and costs implications. Additional studies are needed to further examine the patterns of use of antihypertensive agents, their determinants and above all, consequences at the population level. In particular,

studies are needed that quantify the effects of such changes on health outcomes and costs. Observational studies of drug utilization at the population level are well suited to fulfill these objectives.

Acknowledgments

Ms Bourgault is the recipient of doctoral fellowships from the National Health Research and Development Program (NHRDP) of Canada and from the Social Sciences and Humanities Research Council of Canada (SSHRC). Dr Suissa is a Senior Scientist from the Medical Research Council (MRC) of Canada. The Pharmacoepidemiology Research Unit is funded by an *Équipe* grant from the *Fonds de la Recherche en Santé du Québec* (FRSQ).

This study used data provided by the Saskatchewan Department of Health. The statements contained hereby do not necessarily represent those of the Saskatchewan government. The authors would like to thank Ms. Mary McNutt of the Saskatchewan Research Services, Population Health Branch, for her expertise and assistance with the data. Funded by Zeneca Pharmaceuticals, the authors of this research were fully independent in conception, design, analysis and interpretation.

Table 5.1 **Specific antihypertensive agents used at treatment initiation, by drug class.**

Antihypertensive drug class		
ACE inhibitors	Captopril Enalapril Lisinopril Fosinopril	Quinapril Benzapril Cilazapril Ramipril
Calcium antagonists	Nifedipine Diltiazem Verapamil Nicardipine Felodipine	Amlodipine Nifedipine PA Diltiazem SR Verapamil SR
β-blockers	Acebutolol Atenolol Propranolol Pindolol Metoprolol Nadolol	Labetolol Oxprenolol Timolol Propranolol SR Metoprolol SR Oxprenolol SR
Combination drugs	Any drug class combinations ACEI+diuretic β-blocker + diuretic CCB + diuretic ACEI + β-blocker* ACEI + CCB* β-blocker + CCB* ACEI + β-blocker + CCB*	Fixed ACE inhibitor / diuretic combinations Enalapril / HCTZ Lisinopril / HCTZ Fixed β-blocker / diuretic combinations Pindolol / HCTZ Timolol / HCTZ Propranolol / HCTZ Metoprolol / HCTZ Atenolol / Chlorthalidone

ACEI=Angiotensin-converting-enzyme inhibitors; CCB=Calcium antagonists; PA=Prolonged action; SR=Sustained release; HCTZ=Hydrochlorothiazide.
* With or without diuretics.

Table 5.2 Characteristics of the study population.

	%	(N)
SOCIODEMOGRAPHIC FACTORS		
Age (years)		
40-49	23.3	(4541)
50-59	25.7	(5017)
60-69	28.9	(5636)
70-79	22.1	(4307)
Mean (s.d.)	**59.9**	**(11.0)**
Males	49	(9563)
Social assistance at treatment initiation	4.1	(798)
Year of treatment initiation		
1990	27.4	(5343)
1991	26.6	(5184)
1992	23.9	(4665)
1993	22.1	(4309)
INITIAL ANTIHYPERTENSIVE AGENT		
Single agent	**91.2**	**(17793)**
ACE inhibitor	37.4	(7291)
Calcium antagonist	27.5	(5355)
β-blocker	26.4	(5147)
Multiple agents	**8.8**	**(1708)**
Diuretic-based combination	7.6	(1483)
Other drug combination	1.2	(225)

Table 5.3 **Baseline characteristics of study subjects in association with initial drug (*vs* β-blockers).**

Characteristic	Prevalence (%)				Adjusted RR*		
	BBL (n=5147)	ACEI (n=7291)	CCB (n=5355)	Multitx (n=1708)	ACEI	CCB	MultiTx
Year of treatment initiation							
1990	30.4	24.1	28.0	30.3	1.00 (reference)	1.00 (reference)	1.00 (reference)
1991	26.3	25.5	28.0	27.7	1.25 (1.13-1.38)	1.19 (1.07-1.32)	1.09 (0.93-1.27)
1992	21.7	26.4	23.4	21.8	1.57 (1.41-1.74)	1.18 (1.06-1.32)	1.01 (0.86-1.18)
1993	21.5	24.0	20.6	20.2	1.46 (1.31-1.62)	1.05 (0.93-1.17)	0.96 (0.81-1.13)
Age, mean (years)							
40-49	34.1	20.2	18.6	18.4	1.00 (reference)	1.00 (reference)	1.00 (reference)
50-59	26.3	27.0	24.4	22.6	1.74 (1.57-1.92)	1.62 (1.45-1.81)	1.61 (1.36-1.91)
60-69	24.0	30.1	31.2	31.2	2.11 (1.91-2.33)	2.15 (1.93-2.40)	2.33 (1.98-2.74)
70-79	15.6	22.7	25.8	27.7	2.53 (2.26-2.84)	2.83 (2.51-3.19)	3.20 (2.69-3.81)
Mean	**56.4**	**60.5**	**61.4**	**62.0**			
Social assistance	4.7	3.8	3.6	5.2	0.95 (0.79-1.14)	0.95 (0.77-1.16)	1.49 (1.13-1.94)
Male gender	43.3	50.7	51.4	52.1	1.29 (1.19-1.39)	1.30 (1.20-1.41)	1.26 (1.12-1.42)
Respiratory illness	3.0	5.1	6.5	5.7	1.88 (1.52-2.31)	2.02 (1.64-2.50)	2.11 (1.58-2.82)
Ulcer disease	12.8	9.7	13.4	9.3	0.78 (0.69-0.88)	0.98 (0.87-1.11)	0.71 (0.58-0.86)
NSAIDs	27.9	26.7	28.6	21.4	1.04 (0.95-1.13)	1.07 (0.98-1.18)	0.74 (0.64-0.85)
Hyperlipidemics	1.9	2.0	2.5	1.2	1.04 (0.79-1.36)	1.16 (0.88-1.53)	0.68 (0.40-1.09)
Diabetes	1.9	7.9	5.8	5.4	4.27 (3.40-5.34)	2.70 (2.13-3.45)	2.37 (1.74-3.22)
Glucocorticoids	4.0	4.5	6.2	3.8	1.03 (0.85-1.26)	1.20 (0.98-1.46)	0.74 (0.53-1.01)
Neurotropics	27.7	16.0	19.5	14.9	0.52 (0.47-0.57)	0.61 (0.55-0.67)	0.45 (0.38-0.52)
Visits to cardiologist	27.7	31.9	44.7	34.4	0.75 (0.69-0.82)	1.58 (1.45-1.72)	0.85 (0.75-0.97)
Hospital admissions	18.6	18.9	23.9	34,3	1.10 (1.00-1.22)	1.11 (1.00-1.23)	2.47 (2.15-2.83)

Abbreviations: ACEI=Angiotensin-converting-enzyme inhibitors; CCB=Calcium antagonists; BBL=β-blockers; Multitx=Multitherapy; NSAIDs=Non-steroidal anti-inflammatory agents;

* Adjusted RR: All risk ratios are adjusted simultaneously for every potential confounder. Separate models were ran for each agent with β-blockers as the reference.

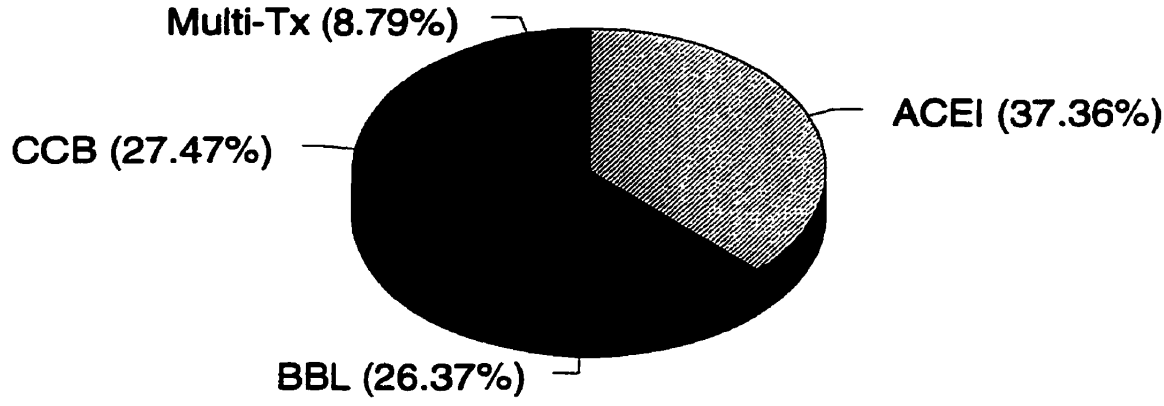
Table 5.4 **Predictors of compliance with antihypertensive therapy over entire follow-up.**

	Compliant (n=5420)	Not compliant (n=14081)	Crude RR (95% CI)	Adjusted RR‡ (95% CI)
Year of treatment initiation				
1990	25.4	28.2	1.00 (reference)	1.00 (reference)
1991	26.8	26.5	1.13 (1.03-1.23)	1.04 (0.95-1.14)
1992	24.7	23.6	1.16 (1.06-1.27)	0.98 (0.88-1.07)
1993	23.2	21.7	1.19 (1.09-1.30)	0.95 (0.84-1.06)
Age, yr				
40-49	17.6	25.5	1.00 (reference)	1.00 (reference)
50-59	25.1	25.0	1.40 (1.27-1.54)	1.31 (1.19-1.44)
60-69	31.1	28.1	1.61 (1.47-1.76)	1.45 (1.32-1.59)
70-79	26.2	20.5	1.85 (1.68-2.03)	1.57 (1.42-1.73)
Medication use in the year preceding treatment initiation				
Ulcers	10.9	11.7	0.92 (0.84-1.02)	0.95 (0.86-1.06)
Respiratory illnesses	5.1	5.0	1.01 (0.88-1.17)	0.96 (0.82-1.13)
NSAIDs	26.4	27.4	0.95 (0.88-1.02)	0.95 (0.88-1.03)
Hyperlipidemia	2.1	2.1	1.00 (0.81-1.26)	1.00 (0.80-1.25)
Diabetes	7.2	4.9	1.50 (1.32-1.71)	1.25 (1.10-1.43)
Asthma / rhumatism	4.6	4.9	0.94 (0.81-1.09)	0.91 (0.77-1.07)
Psychotropic agents	18.8	20.4	0.90 (0.83-0.98)	0.96 (0.88-1.05)
Social assistance at treatment initiation	3.8	4.2	0.89 (0.76-1.04)	0.95 (0.80-1.12)
Male gender	46.0	50.2	0.85 (0.80-0.90)	0.80 (0.75-0.86)
Hospital admission† (year preceding treatment initiation)	24.1	20.6	1.23 (1.14-1.32)	1.17 (1.08-1.27)
Visit to a cardiologist / internist† (year preceding treatment initiation)	34,1	24.1	1.00 (0.94-1.07)	0.99 (0.92-1.07)
Initial antihypertensive therapy				
β-blocker	17.3	29.9	1.00 (reference)	1.00 (reference)
ACE inhibitor	46.9	33.7	2.41 (2.21-2.63)	2.27 (2.08-2.48)
Calcium antagonist	24.1	28.8	1.45 (1.32-1.59)	1.35 (1.22-1.48)
Combination therapy	11.8	7.6	2.69 (2.39-3.04)	2.43 (2.14-2.75)
Duration of follow-up, yr				
Mean (SD)	4.8 (1.6)	5.0 (1.5)	0.92 (0.90-0.94)*	0.92 (0.90-0.95)*

* Per year of follow-up.
† An indicator variable was used for the presence of at least one visits or hospital admission.
‡ Adjusted RR: All risk ratios are adjusted simultaneously for every potential confounder.

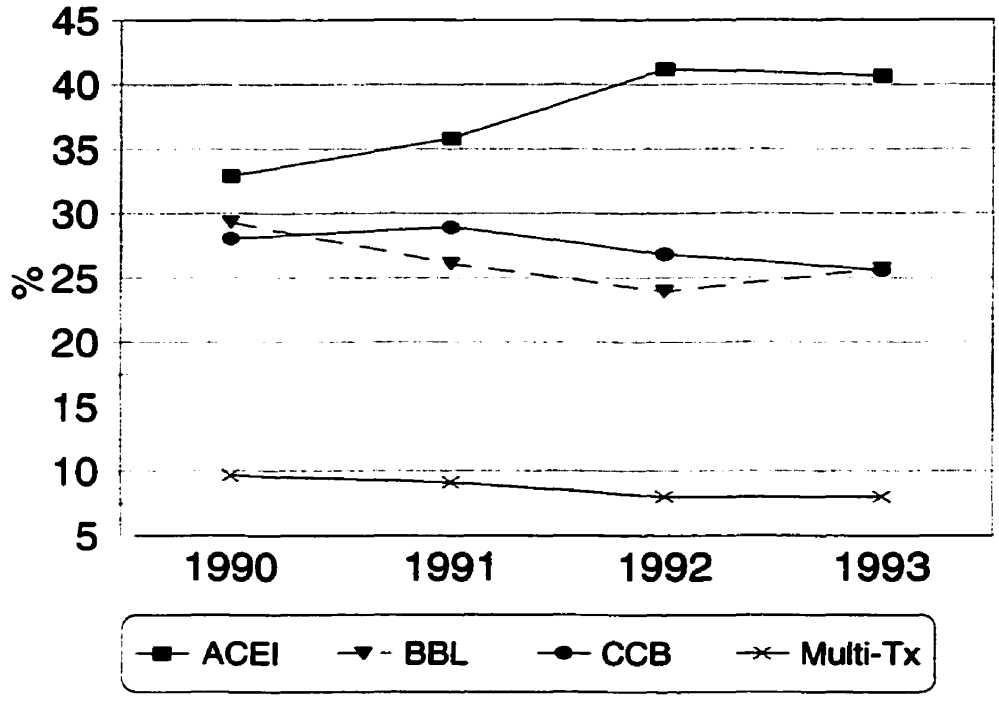
Table 5.5 **Types and frequency of the first two modifications to therapy.**

Patterns	Initial treatment, % (n)			
	ACEI (n=7291)	BBL (n=5147)	CCB (n=5355)	Multitx (n=1708)
Did not modify therapy	13.1 (955)	7.9 (408)	9.3 (500)	22.3 (380)
Discontinued therapy without having modified before	14.8 (1078)	31.8 (1638)	25.6 (1369)	18.7 (319)
Added or switched once and did not modified afterward	17.5 (1279)	8.9 (458)	11.5 (617)	10.7 (182)
Added or switched once and then discontinued	3.5 (254)	4.1 (210)	4.9 (260)	2.0 (35)
Added or switched twice	12.0 (876)	7.4 (383)	8.5 (456)	6.4 (109)
Added or switched, interrupted and started a new course of therapy later on	9.9 (719)	6.8 (352)	8.3 (442)	4.6 (79)
Interrupted treatment and came back to initial treatment	17.7 (1293)	18.7 (960)	17.0 (910)	13.3 (228)
Interrupted treatment and started a new course of therapy using different agents	11.5 (837)	14.3 (738)	15.0 (801)	22.0 (376)



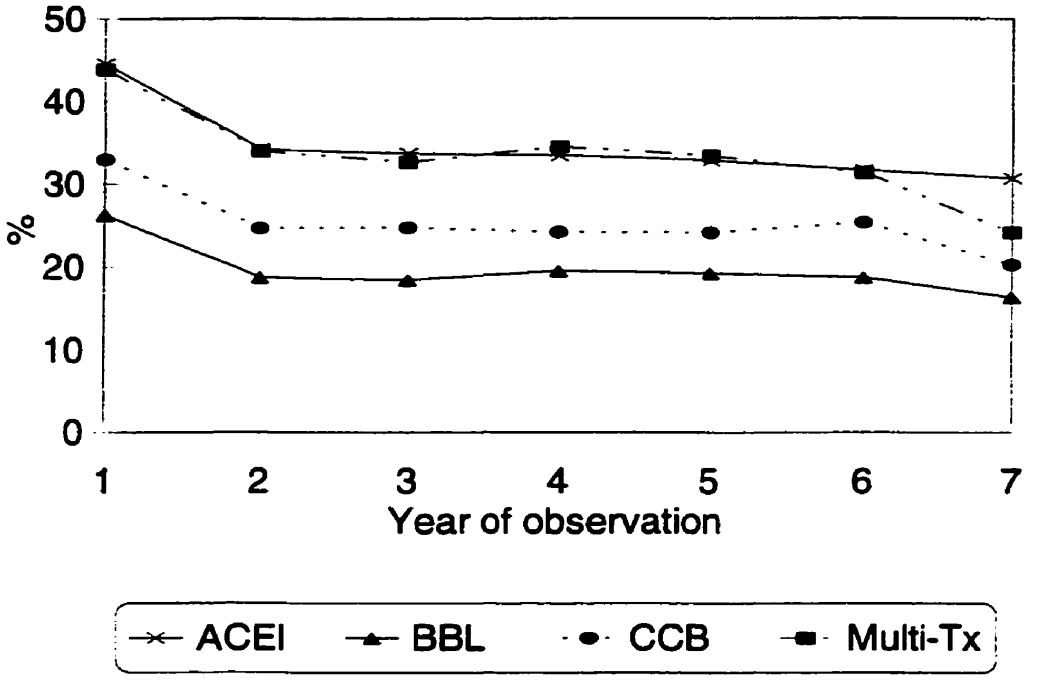
Abbreviations: ACEI=Angiotensin-converting-enzyme inhibitors; CCB=Calcium antagonists; BBL=β-blockers; Multi-Tx=Multitherapy.

Figure 5.1 **Patients initiating antihypertensive drug therapy.**



Abbreviations: ACEI=Angiotensin-converting-enzyme inhibitors; CCB=Calcium antagonists; BBL=β-blockers; Multi-tx=Multitherapy.

Figure 5.2 **Time trends in initial treatment according to drug class.**



Abbreviations: ACEI=Angiotensin-converting-enzyme inhibitors; CCB=Calcium antagonists; BBL=β-blockers; Multi-Tx=Multitherapy.

Figure 5.3 **Yearly compliance rates according to initial treatment.**

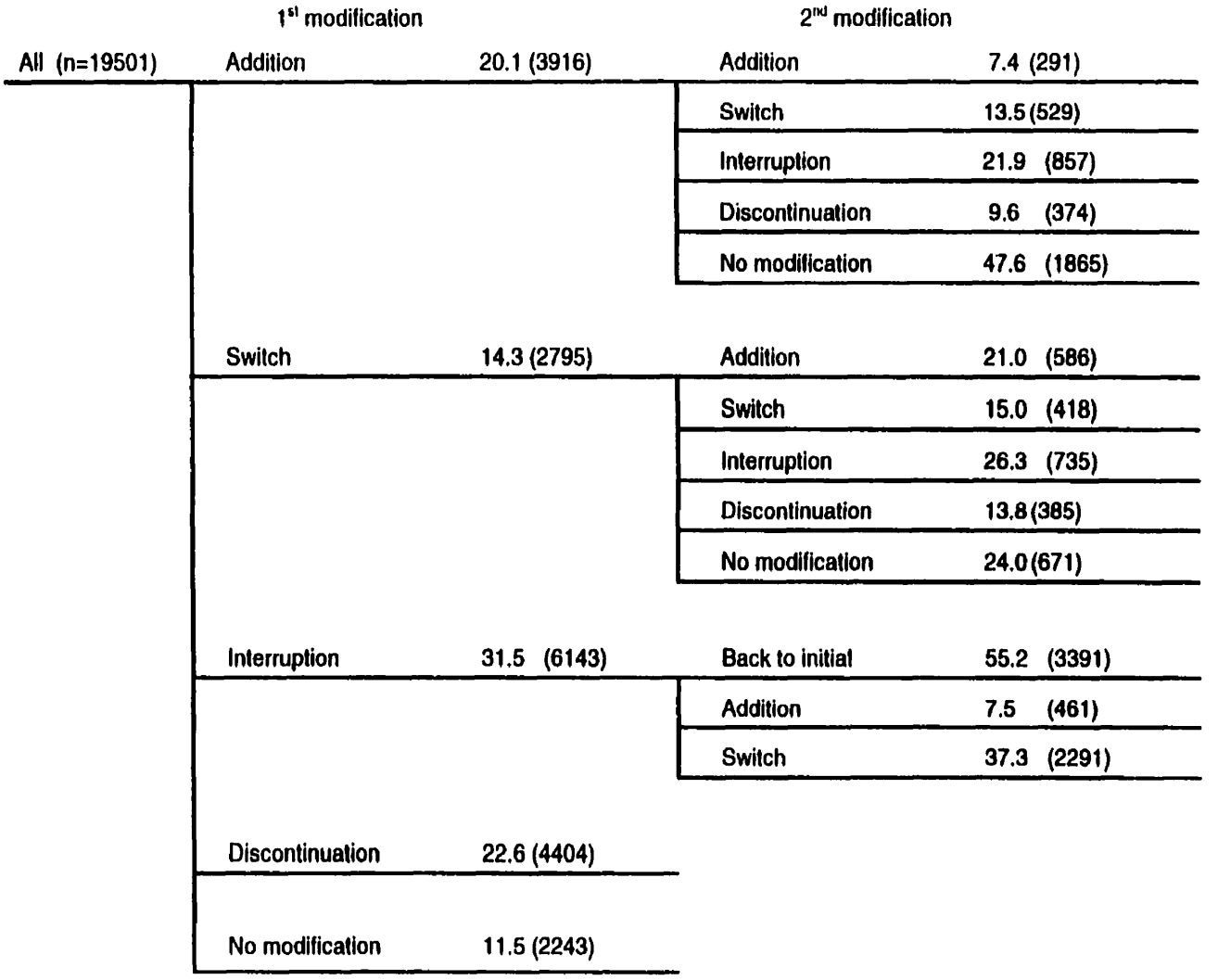
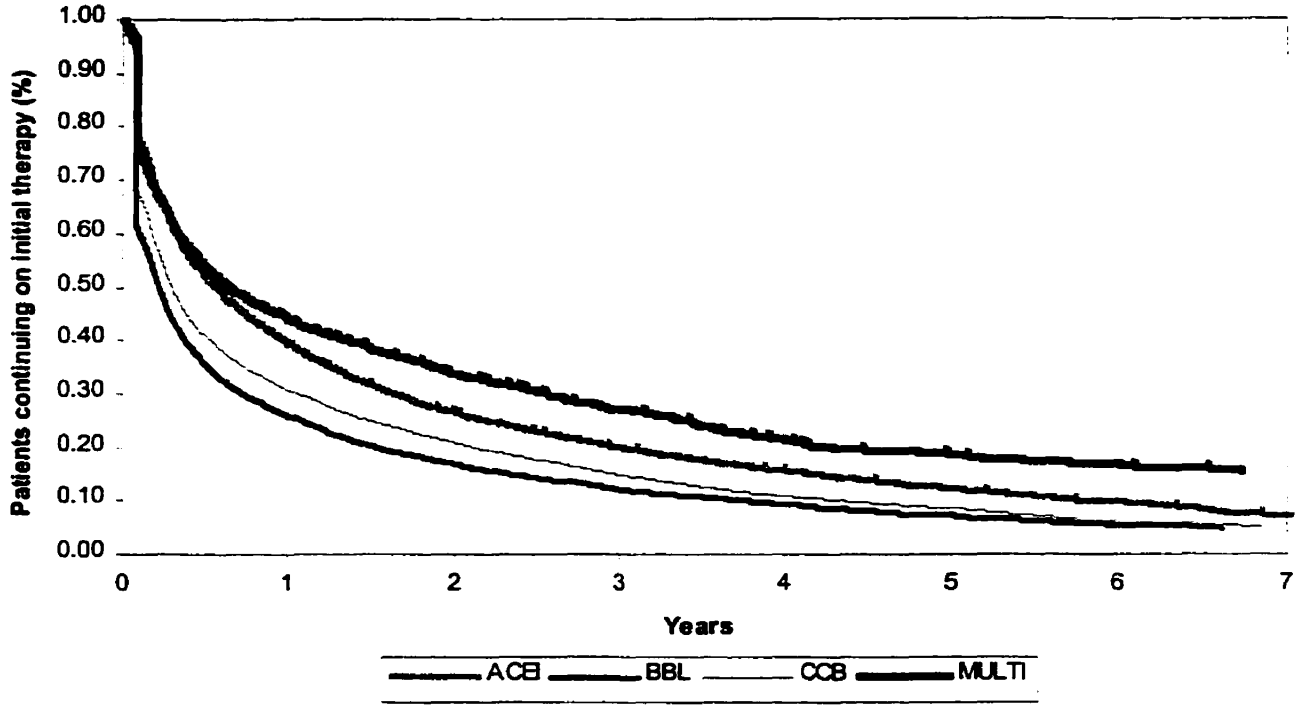


Figure 5.4 **Types and frequency of the first two treatment modifications.**

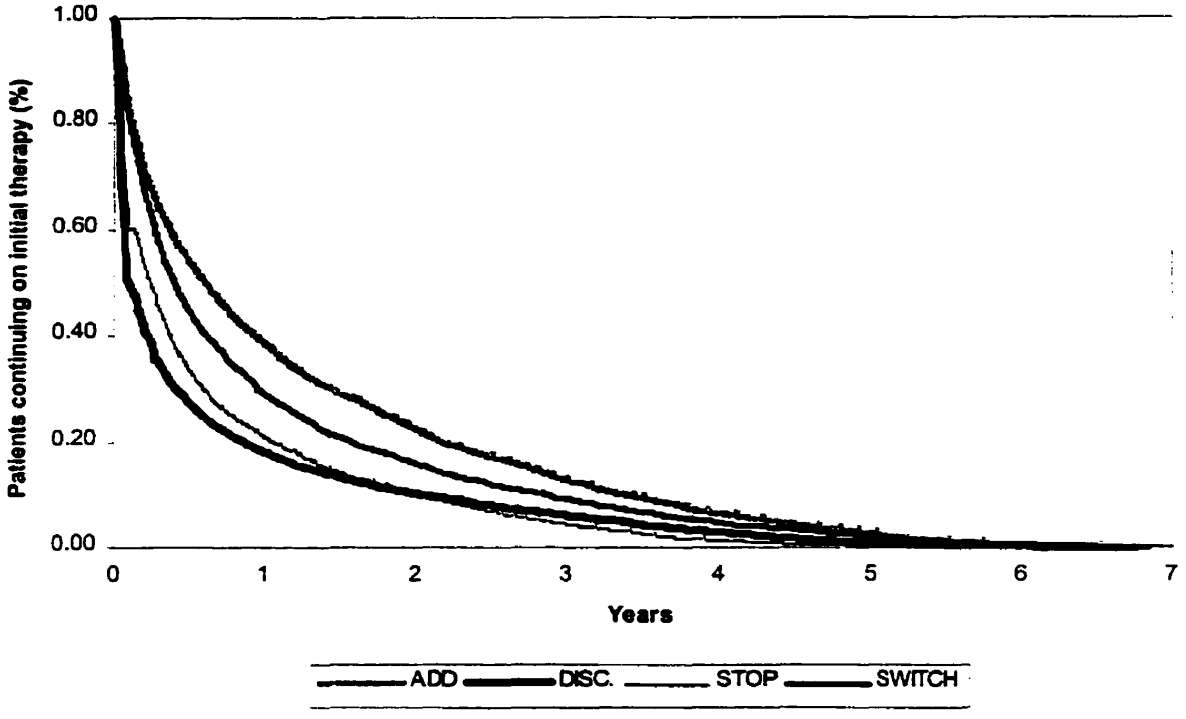


Initial Therapy	Year									
	Q1	Q2	Q3	Q4	2	3	4	5	6	7
ACEI	65.2	52.4	44.9	39.3	26.6	20.2	15.8	12.4	9.9	6.1
BBL	47.7	35.7	29.8	25.8	16.9	12.1	9.3	7.2	5.5	0.0
CCB	53.8	41.0	34.8	30.6	20.8	14.9	10.9	8.5	6.0	0.0
Multi-Tx	65.3	54.0	48.2	44.0	33.8	27.4	21.5	18.5	17.0	0.0
Overall	57.4	45.0	38.4	33.8	23.1	17.2	13.2	10.5	91.7	0.0

* Figures are proportions (%) of patients continuing on initial therapy, per quarter and year, according to initial therapy.

Abbreviations: ACEI=Angiotensin-converting-enzyme inhibitors; BBL=β-blockers; CCB=Calcium antagonists; Multitx=Combination therapy; Q1-Q4: Quarters one to four of the first year.

***Figure 5.5* Cumulative proportion of patients continuing on initial therapy, per quarter and year of follow-up, according to initial agent.**



First modification to therapy	Year									
	Q1	Q2	Q3	Q4	2	3	4	5	6	7
Addition	66.5	53.6	45.1	38.7	22.4	12.7	6.5	3.0	0.7	0.0
Switch	61.4	44.4	35.7	29.1	15.9	9.1	4.8	2.2	0.6	0.0
Interruption	60.4	48.8	33.4	25.8	21.1	10.2	4.6	1.5	0.5	0.1
Discontinuation	50.4	37.9	27.1	21.9	18.1	10.2	6.1	2.9	1.1	0.2
Overall	57.0	45.0	38.0	34.0	23.0	17.0	13.0	10.0	8.0	6.0

* Figures are proportions (%) of patients continuing on initial therapy, per quarters and year, according to the type of a first modification to initial treatment.

Abbreviations: Q1-Q4: Quarters one to four of the first year.

Figure 5.6 **Cumulative proportion of patients continuing on initial therapy, per quarter and year of follow-up, according to the type of a first modification.**

CHAPTER 6 – ANTIHYPERTENSIVES AND MYOCARDIAL INFARCTION RISK

6.1 Preface to the third manuscript

This manuscript presents the results of a study that investigates the risk of myocardial infarction in association with antihypertensive drug use. In the previous chapters of this thesis, we have seen that prior observational studies have pointed to a possible deleterious effect of calcium antagonists on MI risk. We have seen as well that patterns of antihypertensive drug use are highly variable with patients not being fully compliant with therapy and switches across drug classes, treatment interruptions and modifications to treatment regimens being very frequent.

Long-term users of a drug may be very different in terms of susceptibility to experience an adverse effect from patients having switched or discontinued therapy. Indeed, and because each specific antihypertensive agent has its own indications for treatment, drug use history and co-existing conditions should be considered not only as potential markers of cardiovascular risk but also as potential modifiers of the drug effects[11]. We addressed these methodological concerns by conducting a case-control study nested within the cohort described earlier.

The objective of this study was:

- To investigate the risk of MI associated with the use of antihypertensive agents in the treatment of uncomplicated hypertension.

This manuscript, which will be submitted for publication, should be quoted as follows:

Bourgault C, Elstein E, Baltzan M, Le Lorier J, Suissa S. Myocardial infarction in relation to antihypertensive agents: History of drug use as a modifier of risk. Unpublished manuscript. Montreal: Department of Epidemiology and Biostatistics, McGill University, 1999.

6.2 *Manuscript 3.* Myocardial infarction in relation to antihypertensive agents: History of drug use as a modifier of risk

Chantal Bourgault, PhD candidate[1,2]
Eleanor Elstein, MD[3]
Marc Baltzan, MD, MSc[1,2]
Jacques Le Lorier, MD, PhD[4]
Samy Suissa, PhD[1,2]

1. Department of Epidemiology and Biostatistics, McGill University, Montréal, Canada.
2. Pharmacoepidemiology Research Unit, Division of Clinical Epidemiology, Royal Victoria Hospital, McGill University Health Centre, Montréal, Canada.
3. Department of Medicine, Royal Victoria Hospital, McGill University Health Centre, Montréal, Canada.
4. Centre de recherche de l'Hôtel-Dieu de Montréal, Centre Hospitalier de l'Université de Montréal, Montréal, Canada.

ABSTRACT

Background: Previous observational studies have reported conflicting results with regard to the coronary risk associated with calcium antagonists use. Emerging clinical trial data tend to show a beneficial effect of calcium antagonists in hypertension whereas angiotensin-converting-enzyme (ACE) inhibitors have been shown to be the preferred agent for managing hypertension in diabetic patients. However, results from experimental studies may not be applicable to the clinical setting.

Objective: To assess the risk of experiencing a first myocardial infarction (MI) in relation to antihypertensive drug use.

Design and setting: Case-control study nested within a cohort of 19,501 subjects aged 40 to 79 years and initiating antihypertensive therapy with an ACE inhibitor, a calcium antagonist or a β-blocker in Saskatchewan during the period 1990-93. Data on prescription drug use, medical visits and hospital admissions were extracted from the Saskatchewan Health computerized databases in Canada. Death certificates were independently reviewed to document the cause of death.

Outcome: Cases were hospitalizations for MI between 1990 and 1997 identified using discharge diagnoses (ICD-9 codes 410-410.9) or death with MI as a contributing cause. Controls were a random sample of hypertensive subjects from the cohort, matched to each case on cohort entry date and duration of follow-up.

Exposure definition and statistical analysis: Current use of antihypertensive agents was defined as drug dispensing within 90 days of index date. Risk ratios for current use were estimated with 95% confidence intervals using conditional logistic regression models. Adjustment was made for age, sex, social assistance, medication use and comorbidity prior to antihypertensive treatment initiation. The effect of drug use during the course of therapy was also assessed.

Results: 812 cases of MI were identified, 26% of which were fatal. Compared with β-blockers, current use of calcium antagonists was associated with a two-fold increase in the risk of MI (RR=2.2; 95% CI=1.8-2.7). The risk ratio for current use of ACE inhibitors was 1.3 (95% CI=1.0-1.6). Adjustment for comorbidity and history of drug use attenuated both associations. In addition, history of drug use was found to modify these associations. The risk ratio of MI comparing current use of ACE inhibitors to β-blockers was found to be especially high among patients using digoxin. Decreasing risk ratios for calcium antagonists were found with increasing number of drug markers such as prior

use of ACE inhibitors, calcium antagonists or nitrates.

Conclusion: The risk of experiencing a MI in hypertensive patients using calcium antagonists or ACE inhibitors was found to differ across sub-populations. The results of previous observational studies based on current drug utilization that ignored history of drug use were likely incomplete. These findings underline the importance of adequate documentation of the entire drug history and a comprehensive characterization of exposure in the valid estimation of effects in observational studies.

INTRODUCTION

Preventing cardiovascular disease and death is the primary goal of hypertension management. In hypertension, ß-blockers and diuretics have been shown to reduce the incidence of myocardial infarction, stroke and death in the long term[18,13]. Until very recently, no randomized controlled trial had been completed with regard to the cardiovascular effects of angiotensin-converting-enzyme (ACE) inhibitors and calcium antagonists in hypertension. Results of recent clinical trials of calcium antagonists tend to suggest that calcium antagonists are safe and effective in hypertension[19-22] but that ACE inhibitors may be preferable for managing hypertension in patients with diabetes[147-148]. Until the results of ongoing prospective trials comparing newer agents to diuretics and β-blockers are available, ACE inhibitors and calcium antagonists are still recommended in the treatment of hypertension only as second-line or "alternative" agents[153,175,155]. Yet, these drugs are extensively used as first-line agents in the treatment of hypertension, probably based on the surrogate endpoint of lowering blood pressure[279,42].

Recent observational studies of the effect of newer antihypertensive drugs on major health outcomes such as cardiovascular morbidity and mortality have shown conflicting results. Whereas some of them suggested the possibility of cardiovascular harm associated with the use of calcium antagonists[23-25], others could not confirm these findings[234-238]. The observational nature of these studies has been largely criticized, mostly on the ground of a lack of comparability between contrasted groups. Indeed, uncontrolled confounding by indication[26,231,246] and the use of inadequate exposure definitions[408] were specifically pointed out. In accordance with the stepped-care approach to the management of hypertension suggested in consensus guidelines[153,175,155], the duration and severity of hypertension and the presence of co-existing conditions may be important determinants of selective prescribing. As recommended, second-line agents such as calcium antagonists and ACE inhibitors should be prescribed when first-line agents (β-blockers and diuretics) have been ineffective at decreasing blood pressure, have not been well tolerated, or when the disease has worsened. Calcium antagonists and ACE inhibitors should also be preferentially prescribed in the presence of certain associated conditions or clear contraindications to first-line agents. As such, patients treated with calcium antagonists would in all likelihood be at higher risk of a cardiovascular event.

Patterns of antihypertensive drug use in the population are complex and variable: drug switches are common and gaps in treatment are frequent[238,409], which makes the results of randomized controlled trials hardly generalizable to the clinical setting. These modifications to therapy may be due to drug side effects, to uncontrolled hypertension or to the onset of complications of the disease. Indeed, and because each specific antihypertensive agent has its own indications for treatment, drug use history and co-existing cardiac conditions should be considered not only as potential markers of subsequent cardiovascular risk, but also as potential modifiers of the drug effects[11]. Long-term users of a drug may be very different in terms of susceptibility to experience an adverse effect from patients having discontinued treatment. None of the previous observational studies of the effects of calcium antagonists have investigated the potential modifying effect of history of drug use while simultaneously adjusting for comorbidity.

To address these methodological concerns, we conducted a population-based study investigating the risk of fatal and non-fatal myocardial infarction (MI) associated with the use of antihypertensive drugs in the treatment of uncomplicated hypertension. The role of history of drug use and co-existing conditions on the estimates of risk of antihypertensive agents was addressed.

METHODS

Sources of data

The data for this study were obtained from the prescription, medical care and hospitalization databases of Saskatchewan Health. These databases were developed in the context of the universal health insurance program provided to 93% of all residents of this Canadian province, with a population of over one million[344-347]. Computerized drug-related information includes, for each prescription dispensed on an out-patient basis, the drug quantity, strength and dosage form as well as dispensing date. Data on all hospitalizations in Saskatchewan provide information on primary and secondary discharge diagnoses (coded using the 9th revision of the International Classification of Diseases -ICD-9[339]), admission and discharge dates and vital status at hospital separation. Demographic data (date of birth, gender, coverage initiation and termination dates, date of death if applicable and receipt of social assistance at treatment initiation) are also available. The accuracy of these data for use in research settings has been extensively documented[345,346].

Study population

A cohort of all subjects aged 40 to 79 years, initiating therapy with an ACE inhibitor, a ß-blocker or a calcium antagonist between January 1st, 1990 and December 31th, 1993 was identified. *Cohort entry* was taken to be the date of receipt of the first prescription of one of these three agents. To ensure that study subjects were initiating treatment, those dispensed any of ACE inhibitors, β-blockers, calcium antagonists, diuretics, α-blockers or centrally acting agents in the year preceding cohort entry were excluded. Study subjects were followed until the earliest of March 31th, 1997, date of death, date of the first myocardial infarction (MI), emigration from the province or end of coverage of the insurance plan. Drug markers were used to exclude from the cohort those subjects for which the most likely indication for antihypertensive treatment was not uncomplicated essential hypertension. For instance, those initiating pharmacologic therapy for heart failure and renal scleroderma were identified and excluded based on their use of digoxin, oral corticosteroids or pencillamine in the year prior to cohort entry. We also excluded subjects that used any of the following agents in the preceding year: nitrates (angina), quinidine or quinidine-like agents (arrhythmia), antithyroid drugs or radio-iodine (hyperthyroidism), ergot preparations or methysergide (migraine). Subjects with pre-

existing cardiac disease were also excluded on the basis of their use of anti-coagulants, loop diuretics or other cardiac agents, or if they were admitted to hospital with heart disease as the primary or secondary discharge diagnosis (ICD-9 codes 402, 404, 410-416, 420-429 or 745.4-746.9) in the year preceding cohort entry.

Study design

All cases of myocardial infarction (MI) occurring after cohort entry were identified. Non-fatal cases were defined as a first hospitalization with a primary or secondary discharge diagnosis of MI (ICD-9 codes 410-410.9). Fatal cases were defined as death with MI as a contributing cause. Death certificates, obtained from Saskatchewan Health, were blindly and independently reviewed by two physicians to determine the primary cause of death. Inter-rater agreement for definite MI was 82% and all discrepancies were resolved by consensus. For subjects with multiple MI, only the first event was used for analysis.

A nested case-control approach to the analysis of cohorts was used[350-352]. For each case, the risk set composed of all hypertensive subjects having initiated treatment in the same year and month and still at risk for a MI at the case's event date was formed. A random sample of four controls was selected from each risk set and matched to the case accordingly. The *index date* was defined as the event date for the cases and the corresponding matched date for controls.

Drug exposure

All antihypertensive drugs dispensed from cohort entry to the index date were identified. To measure comorbidity at baseline, we also identified other medications dispensed in the year preceding cohort entry. Subjects were considered to be currently exposed to ACE inhibitors, ß-blockers, calcium antagonists or diuretics if at least one prescription was dispensed within 90 days of the index date, without regard to the quantity. Different agents from each drug class were grouped together to ensure sufficient statistical power. History of antihypertensive drug use was defined as any use prior to the beginning of the 90-day current use time window. Since the average duration of an antihypertensive drug prescription is 30 days in Saskatchewan, regular use was defined as the dispensing of at least one prescription for an antihypertensive agent per month for the entire period of observation.

Statistical analysis

Cases of MI were contrasted with controls with regard to current use of antihypertensive agents, with a special attention given to ACE inhibitors and calcium antagonists. As antihypertensive drug stoppers may represent a different population, only subjects currently exposed to at least one antihypertensive agent were retained in the analyses. Current users of ß-blockers formed the reference category. Odds ratio approximations to the risk ratios and 95% confidence intervals (CI) were estimated using conditional logistic regression to account for the effect of matching[410-411]. These risk ratios were adjusted for potential confounding by age, sex and social assistance at treatment initiation. Hospital admissions and medication use (NSAIDs, glucocorticoids, neurotropic agents and drugs used for the treatment of diabetes, respiratory illness, ulcers and hypercholesterolemia) during the year prior to initiation of antihypertensive therapy were used for further adjustment.

Initiation of pharmacologic therapy for the treatment of diabetes, angina or congestive heart failure (CHF) during the course of hypertensive disease was identified using drug markers. These important risk factors for MI were first considered as potential confounders and adjusted for. However, following the hypothesis that these risk factors could modify the cardiac effects of antihypertensive agents, possible effect modifications were tested accordingly. History of antihypertensive drug use as a proxy measure of the severity of hypertension was adjusted for by including indicator variables for regular, current and prior use of each of the four antihypertensive drug classes in the models. Also, potential modification of the effects of current use of ACE inhibitors and calcium antagonists by history of use of these agents was tested by including interaction terms for prior use of each studied agent in the regression models.

To avoid overfitting and collinearity problems, two separate models were used to estimate the independent effects of current use of calcium antagonists and ACE inhibitors relative to β-blockers, as potentially modified by prior use and cardiovascular risk. Fully adjusted models are presented as no important gain in precision were obtained using the "most parsimonious model" approach. However, interaction terms were retained in the final model providing that the p-value for the estimate was ≤ 0.15.

RESULTS

35,631 patients initiated therapy with an ACE inhibitor, a β-blocker or a calcium antagonist during the inclusion period. After applying the age eligibility criteria and excluding patients with prior cardiac disease or other potential indications for antihypertensive drug treatment, the cohort included 19,501 subjects followed for an average of five years. From this cohort, 812 subjects experienced at least one episode of myocardial infarction (MI). Of the first events, 211 (26%) were fatal. The overall rate of MI for the entire cohort was 8.3 cases per 1,000 subjects per year.

Table 6.1 presents characteristics of the 812 cases and their 3,248 matched controls. Cases were on average five years older than controls, 66.4% were males (48.7% for controls) and slightly fewer of them were receiving social assistance at treatment initiation. Before initiation of antihypertensive treatment, cases were dispensed more NSAIDs, glucocorticoids and medications used to treat respiratory illnesses, diabetes, ulcers and hypercholesterolemia, but were less likely to have been dispensed neurotropic agents. Also, cases were hospitalized more often in the year preceding treatment initiation, with a yearly average of 44 admissions per 100 subjects, as opposed to 32 among controls.

The distribution of antihypertensive and other drug use is presented in Table 6.2. More cases than controls initiated their antihypertensive treatment with a calcium antagonist (37.8% *vs* 27.9%) or an ACE inhibitor (41.0% *vs* 38.8%). However, controls were more likely (38.6% *vs* 23.3% respectively) not to be using any antihypertensive agents in the 90 days preceding index date. Especially prior to the current use time window, β-blocker use (our reference category) was systematically lower among cases than among controls. Also, more cases were dispensed diuretics, often used in combination with another agent. With the exception of those using calcium antagonists, fewer cases (8.9% *vs* 21.1% for β-blockers; 16.4% *vs* 20.7% for ACE inhibitors), stayed on the same agent during the entire follow-up without using any of the other antihypertensive drugs. Regular use of antihypertensive medications also differed markedly with cases more likely to be regular users. As expected, there was a marked difference in the distribution of drug markers for MI risk, with more cases than controls having initiated nitrates (34.5% *vs* 13.2%), digoxin (7.4% *vs* 2.9%) or anti–diabetic therapy (20.1% *vs* 7.8%) following cohort entry.

Table 6.3 presents the distribution of current use of β-blockers, ACE inhibitors and

calcium antagonists, as well as the risk ratios of experiencing a MI across these exposure categories. Throughout, current use of ß-blockers is used as the reference category. At the crude level, current users of calcium antagonists showed a significant increased risk of MI (RR=2.2; 95% CI=1.8-2.7) whereas only a slight elevated risk was found for ACE inhibitors (RR=1.3; 95% CI=1.0-1.6). After adjusting for demographics and comorbidity before treatment initiation, current users of calcium antagonists still showed a statistically significant increased risk of MI but lower in magnitude (RR=1.8; 95% CI=1.4-2.3). Adjustment for history of drug use (cardiovascular risk factors, regular antihypertensive therapy and prior use of ACE inhibitors, ß-blockers, calcium antagonists and diuretics) further reduced the risk ratio to 1.6 (95% CI=1.1-2.2). Overall, only age, male gender, use of antidiabetic agents prior to cohort entry and cardiovascular drug use during the course of antihypertensive therapy were found to be confounders of the association of calcium antagonist with MI risk. Statistical adjustment did not significantly alter the results for the effect of current use of ACE inhibitors relative to ß-blockers (RR=1.0; 95% CI=0.7-1.4).

Figure 6.1 shows that the relative effect of current use of ACE inhibitors, compared to β-blockers, was not constant across sub-groups of patients. Indeed, the risk ratio was higher in patients who initiated therapy with nitrates (RR=1.3; 95% CI=0.76-2.2), digoxin (RR=7.4; 95% CI=2.4-22.6) or both (RR=12.2; 95% CI=3.9-37.6) than it was among subjects without therapeutic evidence of heart failure or angina (RR=0.79; 95% CI=0.56-1.1). No modification of effect was found in relation to diabetes or prior antihypertensive drug use.

Figure 6.2 shows a different picture for the effect of calcium antagonists relative to β-blockers. Surprisingly, the risk ratio of MI increases as the number of indicators for MI risk decreases. For instance, the risk of MI for current use of calcium antagonists compared to β-blockers was three-fold among subjects without prior use of ACE inhibitors, calcium antagonists and nitrates during the course of antihypertensive therapy (RR=3.1; 95% CI=1.9-5.1). A two-fold increased risk was found among patients with either one or the other of these drug markers whereas patients using all of those had no significantly increased risk of MI if they used calcium antagonists relative to β-blockers.

DISCUSSION

Our study shows that in the early years of treatment for hypertension, the overall risk of myocardial infarction (MI) is slightly higher among current users of calcium antagonists and ACE inhibitors, compared to β-blocking agents. Although the crude estimates were elevated, adjustment for confounding factors such as comorbidity, concomitant antihypertensive drug use and drug history attenuated and even eliminated these associations. These results agree with those reported in two previous observational studies. Psaty *et al* found a risk ratio for MI of 1.6 (95% CI=1.1-2.3) for current use of calcium antagonists relative to β-blockers[23]. Another case-control study among elderly patients with hypertension showed similar relative risks higher in magnitude. Pahor *et al* reported MI risk to be increasing in patients using nifedipine (RR=5.6; 95% CI=1.8-17.5)[25]. Yet, three other case-control[234-236] and two cohort studies[238,239] found no elevated risk for MI.

The discrepancies in the results of these observational studies may be explained by the baseline differences in the contrasted groups. Selective prescribing of a specific agent to patients at higher risk for a MI could easily result in elevations of the risk ratios as high as those reported in these studies. For instance, all of them but one[238] were based on prevalent users of antihypertensive agents. In such studies, markers of cardiovascular risk such as duration of hypertension, history of drug use as a proxy for disease severity and coexisting conditions were not accounted for. Also, "current use" of a drug anchored at the time of the event has no clinical meaning if not also anchored at the time the treatment was initiated. Not accounting for the timing of antihypertensive drug use with regard to the natural course of the disease is the most likely reason for the discrepancies in these results.

Our finding that the association of newer agents with MI varies among different sub-groups of patients may also explain part of the discrepancies. For instance, among patients who used digoxin during the course of antihypertensive therapy, current users of ACE inhibitors were found to be at much higher risk of MI than those using β-blockers. To our knowledge, no heart failure trial has directly compared the relative cardiovascular effects of β-blockers and ACE inhibitors. However, ACE inhibitors have been shown in placebo-controlled trials to improve symptoms, quality of life and survival[68] and to lessen MI risk[70] in CHF patients. As such, they are considered a well accepted therapy for the treatment of this condition. Although the results of several β-

blocker trials in heart failure indicate a benefit on morbidity and mortality[412-415], the survival effect of β-blocking agents remains controversial among sub-groups of patients with severe heart failure[416-420]. Indeed, β-blocker use was contraindicated in heart failure until quite recently and long-term trials are currently underway to assess whether β-blockers exacerbate heart failure in severe patients. Given their documented efficacy in heart failure, we would have expected a beneficial effect of ACE inhibitors relative to β-blockers among heart failure patients rather than the observed increased risk. A likely explanation for this is confounding by indication, whereby characteristics of subjects (disease severity, co-existing conditions and concurrent therapies), rather than the drug itself, explain the results. Indeed, it is current practice for severe CHF patients to be prescribed ACE inhibitors in addition to digoxin. ACE inhibitor use in that case may therefore be a marker for heart failure due to advanced coronary artery disease, which inherently carries a higher risk of MI.

In spite of their susceptibility to biases related to selective prescribing, observational studies are a very useful source of information with regard to the population effects of specific agents. Because they can be conducted at the population level, most of what we learn about drug side effects and adverse events comes from observational studies[421]. Considered by most researchers as the gold standard for the study of drug effects, randomized controlled trials are both time and resource intensive. For that reason, proper evaluation of the relative effects of several antihypertensive agents is seldom done in large clinical trials of health outcomes[422]. Also, the highly selected populations of randomized controlled trials do not represent the population encountered by most practitioners in the real-life setting of a clinical practice. Finally, and because antihypertensive agents are likely to be used for many years, short-term trials may fail to detect adverse or beneficial effects. As a consequence, information obtained from clinical trials may be hardly generalizable to the population at large.

Controlled studies of so-called surrogate endpoints (reductions in blood pressure and left ventricular hypertrophy for instance) are also widely used to document the effects of medications. However, surrogate efficacy and health effectiveness are distinct entities[423] and these endpoints may not always be reliable indicators of drug effectiveness[424,423,254]. Indeed, the ultimate goal of antihypertensive treatment is the prevention of cardiovascular complications of hypertension. Lowering blood pressure is one of several measures of effectiveness; many antihypertensive agents have actions

other than blood pressure lowering which could influence the effectiveness of these drugs on health outcomes[254].

The risk of MI associated with current use of calcium antagonists was also shown to vary across sub-groups as identified by prior use of nitrates, ACE inhibitors and calcium antagonists: lower risk ratios were found among patients using several of these drugs following cohort entry. It seems as if the increased risk of MI associated with calcium antagonists use was limited to milder disease, e.g. those without prior use of second-line agents, and without angina. The beneficial effects of β-blockers in patients with coronary artery disease (CAD) is well established[140] while calcium antagonist trials in that population have shown inconsistent results[16]. For instance, two studies compared long-acting calcium antagonists with β-blockers among patients with angina: the Angina Prognosis Study in Stockholm (APSIS)[447] and the Total Ischaemic Burden European Trial (TIBET)[446] studies. In both studies, clinical equivalence on hard endpoints was found between the two groups. The lack of homogeneity characterizing our group of patients without prior use of ACE inhibitor, calcium antagonists and nitrates could partly explain the results. Among current users of calcium antagonists, a number of patients were newly starting antihypertensive therapy whereas others have used β-blockers in the past. We may hypothesize that these two groups of patients (patients who were recently initiated on calcium antagonists and those who were switched to (or were added) a calcium antagonist after a β-blocking agent) were more severe in their hypertension. They would as a consequence be at higher risk of a MI, compared with long-term and new users of β-blockers. Another, even more likely explanation for the observed gradient in the estimates is that relative risks are sensitive to the prevalence of the disease in the population. Because of the higher baseline rate of MI among so-called "sicker" patients (those having used both second-line agents and nitrates), a small risk ratio may be equivalent in terms of excess risk to a large risk ratio among milder patients with a lower baseline risk.

Our study has several strengths and weaknesses. The lack of information with regard to important clinical data such as the indication for the drug, blood pressure and lipid levels, smoking habits and other potential determinants of MI risk constitutes an important limitation of our study. Whereas we believe that calcium antagonists are generally prescribed to patients which are at higher risk for a MI, this hypothesis could not be confirmed with the data at hand. Although we attempted to control for indicators

of severity and comorbidity, confounding by indication could still pose a threat to the validity of our results. Misclassification of the exposure may also be problematic in our study. First, some subjects may have been continuously exposed within the current use time-window whereas others may only have been exposed a few days. If the relative risk was found to vary over time, our estimates could be biased. Also, in an era where specific calcium antagonists have been shown to present very different properties[425,426], not having distinguished short- and long-acting formulations precludes one to determine whether these present different risks of adverse events. Hence, the study findings about one calcium antagonist may not apply to all others and lumping all specific agents together may have masked some of the drug effects. Finally, our algorithm that uses drug markers to identify coexisting conditions possibly induced misclassification of some of the study subjects.

In addition to using population-based data that have been validated and shown to have excellent accuracy[345,346], our study has several strengths. Numerous measures were used to address the problem of confounding by indication. We excluded subjects who received a prescription for an antihypertensive agent in the year preceding cohort entry, who already had evidence of cardiovascular disease at treatment initiation or whose prescription for an antihypertensive medication was likely to be for another indication than hypertension. Restricting the study population to subjects without evidence of complicated hypertension to start with contributed to minimizing biases related to selective prescribing. Also, cases and controls were closely matched for the date of treatment initiation, so that time trends in prescribing practice and duration of treated hypertension were inherently accounted for, thus rendering exposure opportunity similar in the comparison group. Despite this however, we believe our study results to be affected at least in part, by confounding by indication.

A number of methodological issues were also addressed at the analysis stage of the study. We were able to estimate the independent effect of each antihypertensive drug class during a short period preceding the event while documenting previous use of these agents. Miettinen and Caro[11] suggested that the duration and timing of drug utilization, as well as previous use of the drug, may bear on the estimates of risk. Non-response to first-line therapy or a sudden manifestation of cardiac symptoms, both being likely to put the patient at higher risk for an adverse cardiovascular event, may lead either to a switch to a different agent or to treatment discontinuation. This is the underlying reasoning of

the stepped-care approach to the management of hypertension. Ignoring the subject's history of antihypertensive drug use in such a case would falsely lead one to attribute the excess frequency of adverse effects in the exposed group to a specific agent. However, with accurate measurement and statistical control over these factors, observational studies of drug effects using incident cohorts may still be reliable. In our study, indicators of comorbidity and markers of the severity of hypertension were included in all analyses to characterize cardiovascular risk. To our knowledge, this is the first attempt to consider history of drug use as a modifier of risk in the realm of hypertension. As such, this study underlines the importance of documenting the entire drug history when studying the intended effects of drugs.

A number of long-term randomized controlled trials of calcium antagonists are currently underway to examine the effects of treatment with calcium antagonists on cardiovascular morbidity and mortality, with results awaited soon. In the few trials that have already published results, outcomes with newer agents like long-acting nifedipine were comparable to those of diuretics and β-blockers. For instance, the Shanghai Trial of Nifedipine in the Elderly (STONE) showed striking benefits of nifedipine over placebo[20]. The Systolic Hypertension-Europe (Syst-Eur) randomized trial showed important reduction in stroke rates with lesser undesirable effects with the calcium antagonist nitrendipine[21]. The Syst-China trial showed that significant blood pressure reduction can be achieved and maintained in older Chinese patients treated with a calcium antagonist, associated with a converting-enzyme inhibitor and a thiazide diuretic. The authors concluded that antihypertensive treatment prevents stroke and other cardiovascular complications in older Chinese patients with isolated systolic hypertension. Along with the STONE, this trial was not truly randomized. Finally, the Hypertension Optimal Treatment (HOT) trial revealed clearly lower cardiovascular mortality rates in the actively treated group in which 78% of the patients used long-acting dihydropyridine calcium antagonists[125]. The practical dilemma faced by clinicians on how and to whom to prescribe antihypertensive agents is likely to end only with the results of accumulating evidence from different sources.

Acknowledgments

Ms Bourgault is the recipient of doctoral fellowships from the National Health Research and Development Program (NHRDP) and from the Social Sciences and Humanities Research Council of Canada (SSHRC). Dr Suissa is a Senior Scientist from the Medical Research Council (MRC) of Canada. The Pharmacoepidemiology Research Unit is funded by an *Équipe* grant from the *Fonds de la Recherche en Santé du Québec* (FRSQ).

This study used data provided by the Saskatchewan Department of Health. The statements contained hereby do not necessarily represent those of the Saskatchewan government. The authors would like to thank Ms. Mary McNutt of the Saskatchewan Research Services, Population Health Branch, for her expertise and assistance with the data.

Table 6.1 **Characteristics of cases and controls in the year preceding initiation of antihypertensive therapy.**

Characteristics	Cases (n=812)	Controls (n=3,248)
Age, yrs (mean±SD)	65.3±9.9	59.5±11.0
Male (%)	66.4	48.7
Social assistance (%)	3.5	4.3
Medication use (%)		
Respiratory illness*	10.0	7.9
Diabetes	14.5	5.4
Anti-ulcer	14.0	10.3
Hypercholesterolemia	3.1	1.7
NSAIDs	30.7	27.2
Neurotropic drugs†	19.2	21.7
Glucocorticoids	6.0	4.7
Hospital admissions (% for ≥1)	27.8	21.5
no. per subject per year‡ (mean±SD)	0.44±0.90	0.32±0.78

Abbreviations: yrs=years, SD=standard deviation, NSAIDs=Non-steroidal anti-inflammatory drugs.

* Includes isoproterenol, β_2-adrenergic agents, xanthines, epinephrine, respiratory products including bronchodilators and mucolytics, glucocorticoids and cromolyn.

† Includes benzodiazepines, antidepressants, L-Dopa, anticonvulsants, ergot derivatives, lithium and major tranquillizers.

‡ Hospital admissions include all-cause hospitalizations.

Table 6.2 **Patterns of drug use among cases and controls.**

	Cases (n=812)	Controls (n=3,248)
Antihypertensive drugs		
Initial therapy* (%)		
β-blocker	21.2	33.3
ACE inhibitor	41.0	38.8
Calcium antagonist	37.8	27.9
Current use† (%)		
β-blocker	16.4	16.0
ACE inhibitor	34.1	28.8
Calcium antagonist	35.6	18.6
Diuretic	23.3	14.6
None	23.3	38.6
Prior use‡ (%)		
β-blocker	29.4	38.2
ACE inhibitor	52.6	44.6
Calcium antagonist	49.1	36.9
Diuretic	36.7	26.5
None	9.6	9.5
Single-drug use§ (%)		
β-blocker	8.9	21.1
ACE inhibitor	16.4	20.7
Calcium antagonist	18.2	15.4
Regular use‖ (%)	34.0	24.1
Other drugs¶(%)		
Congestive heart failure	7.4	2.9
Angina	34.5	13.2
Diabetes	20.1	7.8

Abbreviations: ACE=Angiotensin-converting-enzyme.

* By design, subjects used ACE inhibitors, β-blockers or calcium antagonists as initial therapy; diuretics was not an entry criteria.

† Current use refers to drug dispensing within 90 days of index date.

‡ Prior use refers to drug dispensing at any time before the "current use" time-window.

§ Single drug use defined as being on monotherapy (no drug combination at any time) and not having switched across antihypertensive drug classes during follow-up.

‖ Regular use defined as dispensing of at least one antihypertensive drug prescription per month on average from cohort entry to index date.

¶ Other drugs include digoxin (congestive heart failure), nitrates (angina) and insulin or hypoglycemic agents (diabetes).

Table 6.3 **Crude and adjusted risk ratios of MI for current use of calcium antagonists and ACE inhibitors.***

Antihypertensive drug class	Exposed Cases (no.)	Exposed Controls (no.)	Unexposed Cases (no.)	Unexposed Controls (no.)	Crude	Adjusted for comorbidity at baseline†	Adjusted for history of drug use‡
β-blockers	133	520	490	1474	1.0 (reference)	1.0 (reference)	1.0 (reference)
ACE inhibitors	277	936	346	1058	1.3 (1.0-1.6)	1.1 (0.9-1.8)	1.0 (0.7-1.4)
Calcium antagonists	289	605	334	1389	2.2 (1.8-2.7)	1.8 (1.4-2.3)	1.6 (1.1-2.2)

Abbreviations: CI=confidence intervals; AHDs=Antihypertensive drugs; CHF=congestive heart failure.

* Current use of antihypertensive agents was defined as drug dispensing in the 90-day time window preceding index date, regardless of prior exposure to these agents. Drug categories are not mutually exclusive and a subject may have used several agents in that period. Subjects with no current use were excluded.

† Risk ratios of antihypertensive agents adjusted for one another, for gender, age (years) and social assistance at treatment initiation and for medication use for the treatment of asthma, diabetes, ulcers, hypercholesterolemia and respiratory illness, NSAIDs, neurotropic agents and hospital admissions in the year preceding treatment initiation.

‡ History of drug use includes regular use of antihypertensives, drug use for the treatment of diabetes (insulin or hypoglycemic agents), angina (nitrates) and heart failure (digoxin) after treatment initiation as well as antihypertensive drug dispensing (ACE inhibitors, β-blockers, calcium antagonists and diuretics) between cohort entry and the current use time window.

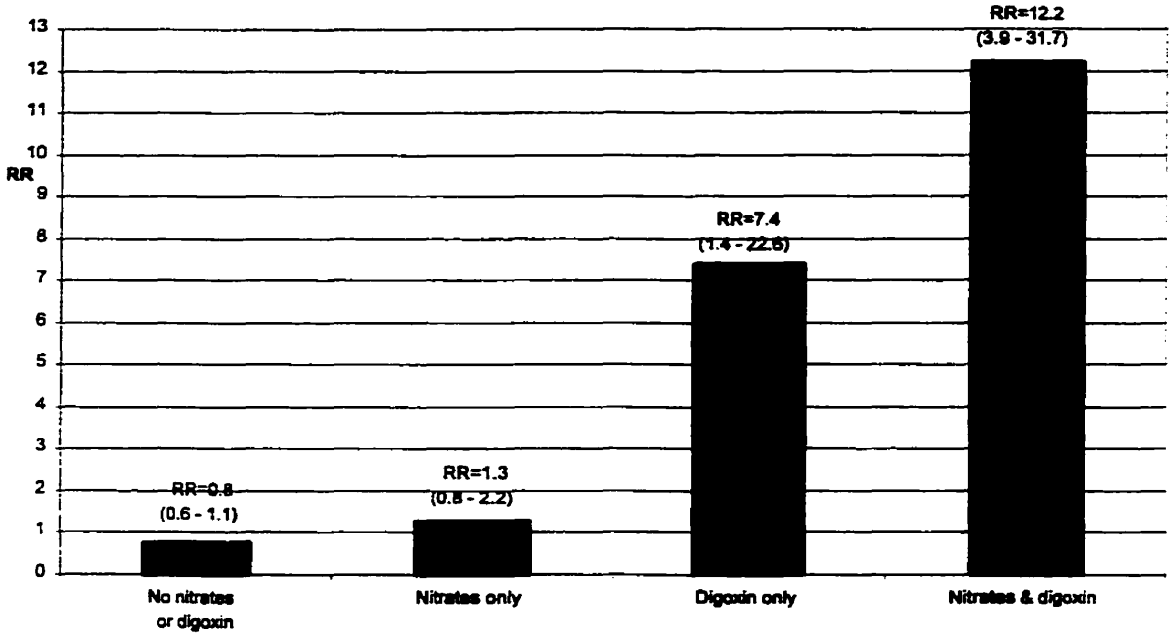
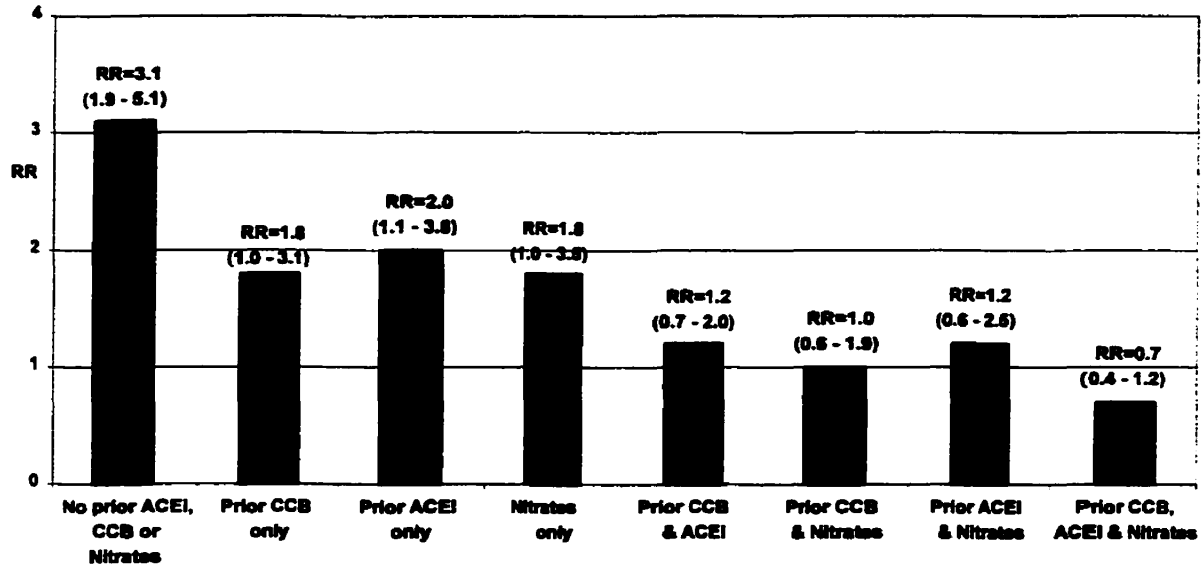


Figure 6.1 **Adjusted risk ratios (95% confidence intervals) for current use of ACE inhibitors relative to β-blockers, by drug markers for MI risk.**



Abbreviations: ACEI=Angiotensin-converting-enzyme inhibitors; BBL=β-blockers; CCB=Calcium antagonists; Multitx=Combination therapy

Figure 6.2 **Adjusted risk ratios (95% confidence intervals) for current use of calcium antagonists relative to β-blockers, by drug markers for MI risk.**

CHAPTER 7 – EFFECT MODIFICATION IN MATCHED CASE-CONTROL STUDIES

7.1 Preface to the fourth manuscript

The last manuscript is a methodological paper that arose from analyses performed in the previous manuscripts. The third paper lead us to consider the presence of effect modification in the assessment of MI risk in association with antihypertensive drug use. While performing the analyses, we were confronted to different alternatives with respect to the best strategy of data analysis for matched case-control studies: Can matching be ignored in the analysis? How to ensure having the proper comparison group without breaking the matching features of the sample? May we use simple stratified analyses or is it more appropriate to use a multivariate modelling approach that includes interaction terms? A search of the literature with this respect was unfortunately disappointing, as surprising as it may seem given the widespread use of matched case-control studies in epidemiology. It then became obvious that an empirical illustration addressing at least some of the points mentioned above would be more than relevant for use in epidemiology.

We did so in three parts. We first described the computation procedures that lead to the stratum-specific odds ratios in matched case-control studies. Throughout, we emphasized the fact that in a matched analysis, not all data are used to compute the odds ratio, which may reduce efficiency. The second part of the manuscript consisted in a simulation study comparing two approaches in their relative efficiency: a stratified analysis and a modelling approach. Using 1,000 replications of a 1:1 matched case-control sample, we estimated the efficiency of one approach relative to the other by comparing the variance of the odds ratio obtained under each approach. This comparison was performed for 42 different scenarios where the sample size, the probability of exposure, the stratum-specific odds ratios and the distribution of the effect modifier were varied. This manuscript is the first attempt to quantify the magnitude of the relative efficiency of two approaches to analysing matched case-control studies and to provide an empirical illustration of the assessment of effect modification in such studies. Lastly, we used the same nested case-control sample that was used in the third manuscript investigating MI risk to illustrate a simple case of effect modification. Results obtained from a stratified analysis were compared with those obtained by including an interaction term in a multivariate conditional logistic regression model. In all cases, matching was accounted for.

This manuscript, which will be submitted for publication, should be quoted as follows:

Bourgault C, Edwardes M, Cai B, Suissa S. Assessing effect modification in matched case-control studies. Unpublished manuscript. Montreal: Department of Epidemiology and Biostatistics, McGill University, 1999.

7.2 *Manuscript 4.* Assessing effect modification in matched case-control studies

Chantal Bourgault, PhD candidate
Michael Edwardes, PhD
Bing Cai, MSc
Samy Suissa, PhD

Department of Epidemiology and Biostatistics, McGill University.
Division of Clinical Epidemiology, Royal Victoria Hospital, Montreal, Canada.

ABSTRACT

Background. The usefulness of matching in case-control studies derives from the enhanced efficiency that it affords for the control of confounding. While confounding is a constant source of concern in observational studies, effect modification is seldom reported even though it can lead to important information with regard to population risks. Two methods exist to assess effect modification in matched case-control studies but their relative efficiencies are not known.

Objective. The objective of this paper is to describe the methods used to assess effect modification in matched case-control studies, namely the stratified analysis and the modelling approach, and to estimate their relative efficiencies.

Methods. A Monte Carlo simulation study was used to compare the variance of the odds ratio obtained under the two methods using 1,000 replications of a pair-matched case-control sample. Such comparisons were performed for 42 different scenarios where the sample size, the probability of exposure, the stratum-specific odds ratios and the distribution of the modifier were varied. A matched case-control study of 812 cases of myocardial infarction and as many controls, nested within a cohort of subjects initiating therapy for the treatment of hypertension, is used to illustrate these findings.

Results. In every scenario, the stratum-specific odds ratios estimated by the modelling strategy were more precise than those obtained by a stratified analysis. The modelling approach resulted in relative efficiencies ranging between 8% and 76%. When the matched sets are evenly distributed in the two strata of the modifier, the relative efficiencies of the modelling strategy are the highest, ranging from 10 to 40%.

Conclusion. Due to the higher efficiency of this approach, we recommend the use of a modelling strategy where an interaction term is included in the model to assess effect modification in matched case-control studies.

INTRODUCTION

Instances in epidemiology in which we may want to assess the differential risks of an event associated with a given exposure in specific sub-groups of subjects are increasingly frequent. Whereas confounding is a threat in pharmacoepidemiologic studies, effect modification can lead to important information with regard to drug effects[427]. With the wide use of computerized databases that include a large number of subjects, it is becoming easier to identify high-risk groups that can later be targeted for public health or clinical interventions. Yet, effect modification is seldom reported in observational studies.

When we assessed the effect of antihypertensive agents on the risk of myocardial infarction using a matched case-control design for instance[428], we hypothesized that prior exposure to these and other medications could bear on the relative risk associated with current use of these agents, as previously suggested[11]. In such a case, one could perform a stratified analysis by running separate models for each sub-group, while accounting for the matching of controls to cases. Alternatively, one could choose to introduce an interaction term in multivariate models and run a matched (conditional) logistic regression on the entire case-control sample. Whereas the stratified analyses appears simpler and easier to interpret, the modelling approach is believed to be more efficient.

An extensive discussion of the rationale for matched case-control studies may be found in epidemiology textbooks[411,429-432]. However, very few published manuscripts have addressed the analysis of matched case-control studies in the specific case of effect modification. Breslow and Day suggest in their discussion of the analysis of case-control studies, that the modelling approach, which assumes a given structure for the joint effects of the two factors in each matched set, allows a more efficient use of the data when assessing effect modification, compared to a stratified analysis[411]. They do not provide however, an estimate of the relative efficiencies of the two methods.

In this paper, we propose to describe the two different methods suggested to assess effect modification in matched case-control studies and to assess their relative efficiencies. We illustrate these techniques with data from a case-control study nested within a cohort of subjects initiating drug therapy for the treatment of uncomplicated hypertension.

STUDY SETTING

For simplicity, we only consider situations where the exposure, the outcome and the effect modifier are binary variables. Matching was performed in a ratio of one control per case (1:1 or pair matching) for factors assumed to be confounders of the association. The modifier is on the other hand assumed not to be a confounder of the association. As was shown previously[433], matching alone in case-control studies does not automatically control for confounding. The statistical analysis must account for the matching scheme to obtain valid estimates of effect. Accordingly, the matching was considered in all analyses.

Table 7.1 presents the typical layout for a binary exposure variable in a pair-matched case-control study. In this type of study, each matched set (or pair) can only be of four possible types:

A. Both the case and the control are exposed;

B. Only the case is exposed;

C. Only the control is exposed;

D. Neither the case nor the control are exposed.

Scenarios A and D includes pairs that are concordant with respect to exposure. The computation of an odds ratio assumes that the marginal totals of each pair-specific 2X2 table are fixed and the conditional probability of exposed cases in each matched set is calculated accordingly. As no variability is induced by concordant pairs, these provide no information with regard to the exposure distribution. As such, they do not contribute to the calculation of the odds ratio (OR) and are discarded from the analysis. Indeed, for a crude analysis when only the matching factors are controlled for, the maximum likelihood estimator for the OR is expressed as the ratio of discordant pairs, i.e. the number of pairs in which the case is exposed but not the control (B) to the number of pairs in which the control is exposed but not the case (C). Hence, the maximum likelihood estimator of the natural logarithm of the OR is obtained by the following formulae:

$$\ln OR = \ln(B / C)$$

The 95% confidence intervals (CI) for the natural logarithm of the odds ratio may be calculated as follows:

$$\ln(B/C) \pm 1.96 * SE(\ln(B/C))$$

where SE(ln(B/C)) is the standard error for the natural logarithm of the OR, which may be calculated as follows:

$SE(\ln(B/C)) = (1/B+1/C)^{1/2}$.

An odds ratio that equals one means that the probabilities of the two different types of discordant pairs are the same and hence, that there is no association between the exposure and the outcome. Similar methods are available for case-control studies with multiple controls per case[434,435].

ASSESSING EFFECT MODIFICATION

In the absence of effect modification, the overall odds ratio is assumed to be constant across all matching factors and those included in the regression model. For example, when the risk of experiencing a myocardial infarction (MI) in association with age is reported to be adjusted for sex, it is assumed that the relative risk of MI associated with age is the same for males as it is for females. However, heterogeneity of the odds ratio across strata can not be always assumed and one would want in some cases to assess the presence of effect modification by a third factor.

Indeed, in addition to control for potential confounding, matched case-control studies entail the need to assess the presence of effect modification by an external factor if one assumes that there may be variation in the magnitude and/or direction of effect across the levels of a third factor. The absence of effect modification means that the effect is constant across all strata of this third factor. When one does not assess the presence of effect modification and it is actually present, the resulting odds ratio is a weighted average of the stratum-specific ones. It may therefore be advisable, when the presence of an effect modifier is suspected, to statistically assess whether such an effect is present or not.

Assessment of effect modification calls for either a stratified analysis in which the data set is divided into two or several strata and stratum-specific odds ratios are calculated, or for a multivariate modelling procedure such as conditional logistic regression, whether or not confounders other than the matching variable have to be accounted for[411]. A major problem with stratified analyses is the difficulty to control confounding and effect modification by several factors simultaneously. Indeed in matched case-control studies, the data are spread over a new dimension where the number of strata becomes extremely large as the number of stratification variables increases. The use of conditional logistic regression allows the estimation of the exposure OR adjusted for all potential confounders of the association. As in regular unmatched studies, conditional logistic regression also permits the assessment of potential modification of the effect by external factors.

Modelling procedures in matched studies are the same as those for unmatched data. However, when a matched analysis is performed, each matched set is typically treated as a distinct stratum. In multivariate models, each matching stratum (i.e. each k unique combination of matching factors) has its own intercept. The crude logistic model

may be represented as such:

$$\ln(\text{odds}) = \alpha_k + \beta_1 X_1 + \beta_j X_j$$

where α_k represents the intercepts for the k^{th} stratum of the matching factor, $\beta_1 X_1$ represents the magnitude of the effect of the main exposure variable and $\beta_j X_j$ represents a vector of covariates. When the presence of effect modification is suspected, one could either run such a model for each independent strata of the putative modifier or include in the model an interaction term. In the latter case, the model would read as follows:

$$\ln(\text{odds}) = \alpha_k + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_j X_j$$

where α_k represents the intercepts for the k different strata of the matching factor, $\beta_1 X_1$ represents the magnitude of the effect of the main exposure variable, $\beta_2 X_2$ represents the effect of the potential modifier and $\beta_3 X_1 X_2$ represents the effect for the interaction term expressed as the product of X_1 and X_2 and $\beta_j X_j$ represents a vector of covariates. The estimate of the OR for stratum 0 of the modifier would therefore be given by:

$$\ln(\text{odds}_0) = \alpha_k + \beta_1 X_1$$

with usual standard error, whereas that for stratum 1 of the modifier would be given by:

$$\ln(\text{odds}_1) = \alpha_k + \beta_1 X_1 + \beta_3 X_1 X_2$$

with variance for the odds ratio:

$$\text{Var}(\ln(B/C)_1) = (\text{Var}\beta_1) + (\text{Var}\beta_3) + 2^*(\text{cov}(\beta_1.\beta_3)).$$

EFFICIENCY OF THE ESTIMATION OF THE ODDS RATIOS

In the process of previous analyses, we noted that effect modification in matched case-control studies could be assessed in two ways that produced results of differing precision. Therefore, we used Monte Carlo simulation analyses to assess the relative efficiencies (RE) of the estimators for the odds ratios when assessing effect modification in matched case-control studies according to two different techniques. The simulations were performed using SAS language to compare the RE of a stratified analysis for matched data as opposed to a multivariate modelling approach where an interaction term is actually fitted as an independent parameter. Only situations where the outcome, the exposure and the modifier are all binary variables were considered.

A macro command was first created to generate data sets using pre-defined parameters. A number of these parameters were held fixed namely: a 1:1 matching ratio, intra-class correlations for the exposure = 0.5, intra-class correlation for the modifier = 0.5 and a sample size of 1,000 pairs. Throughout, the modifier is assumed not to be a confounder of the association. The following factors were varied in order to permit the estimation of the RE in several scenarios: the probabilities of exposure in the two strata composing the modifier (0.5 and 0.5; 0.2 and 0.8 or 0.8 and 0.2), the true stratum-specific odds ratios (1.5 and 0.3; 0.8 and 0.2; 5.7 and 2.1; 0.7 and 12.0; 0.5 and 0.5; 1.0 and 1.0 or 3.0 and 3.0) and the probability of belonging to a given stratum of the modifier, which is equal for cases and controls given the assumption of no confounding (0.5 and 0.5 or 0.2 and 0.8).

For each of the 42 different scenarios (3 probabilities of exposure * 7 stratum-specific ORs * 2 probabilities of belonging to stratum 1 of the modifier), a thousand hypothetical samples were created in which the estimated odds ratios (OR_0 and OR_1), their natural logarithm ($LogOR_0$ and $LogOR_1$), and their respective variance ($varLogOR_0$ and $varLogOR_1$) were estimated using the two approaches being compared. For each of the two approaches, the variance of the log of the true odds ratio was computed from the empirical distribution of the estimated odds ratios again, for each of the 42 simulations. The RE was calculated as the ratio of the true variances obtained from each specific approach and is reported as such. The RE can be simply interpreted as the proportion of the sample size needed in one approach relative to the other, for the two variances to be equal, that is to estimate the odds ratio with the same precision.

Tables 7.2 and 7.3 show the results of the simulations. From the comparison of the

RE of the multivariate modelling approach, compared to a simple stratified analysis, we may conclude the following: In all circumstances, the multivariate approach led to estimates for the odds ratios that were more stable, as indicated by smaller variances. The modelling method resulted in RE varying between 8% and 76%. The relative efficiencies of the modelling strategies, compared to the stratified analysis, considerably vary according to the distribution of the matched sets into the two strata of the modifier. For instance, when the matched sets were evenly distributed in the two strata of the modifier (Table 7.2), most of the RE lies between 10% and 40%. In the case of an uneven distribution of the matched in the modifier's strata, we observe a much better RE in the stratum containing sparse data (20% of the matched pairs), relative to that which contains 80% of the matched pairs. The relative efficiencies does not seem to vary in a systematic way according to the magnitude of the odds ratios or according to the extent of effect modification. In two occasions, one of the approaches could not fit the simulated sample due to sparse data in one stratum (or the two of them).

EMPIRICAL ILLUSTRATION

Table 7.4 illustrates 2X2 Tables of the distribution of the matched sets overall and across the two levels of a modifier. For the benefits of the illustration, we used data from a previous study of MI risk in association with antihypertensive agents[428]. In the actual illustration, we used age as the main exposure, categorized into younger (less than 60 years) and older (60 years or more) subjects. The event under study is the occurrence of a first myocardial infarction (MI) and the modifier is gender. Theoretically, the overall estimate of the OR and the stratum-specific OR are displayed, as obtained using a standard stratified analysis.

Even without considering effect modification, the loss of information due to matching is considerable as pairs which are discordant with respect to exposure do not contribute useful information for the computation of the overall matched odds ratio. Table 7.5 illustrates the number of pairs that were found to be unused for the computation of the stratum-specific odds ratios using a stratified analysis. As previously mentioned, only discordant pairs with respect to exposure and homogeneous strata with respect to the modifier are being used for the calculation of the matched OR. Concordant pairs are not contributing useful information and matched sets that include subjects presenting with a different level of the modifier can not be used in the "stratified" analysis. In this example, 418 matched sets (50% of the entire sample) are not contributing information for the matched analysis, and an additional 200 matched sets (almost 25% of the sample) are not used if we perform a stratified analysis.

Table 7.6 shows the stratum-specific odds ratio obtained from the two compared techniques. The odds ratios were 2.07 (95% CI=1.43-3.01) and 4.15 (95% CI=2.27-7.61) for males and females respectively using the stratified analysis. The overall OR of 2.49 represents a weighted average of the stratum-specific odds ratios of 2.07 for men and 4.15 for women. When an interaction term was included in a conditional logistic regression model, the OR were 2.25 (95% CI=2.02-2.52) for males and 4.66 (95% CI=3.09-7.04) for females. This may be interpreted as age being a stronger risk factor for MI in females than it is in males. As expected, the odds ratios obtained from the modelling procedure are more stable, the confidence intervals being tighter in both strata. The model used to obtain stratum-specific odds ratios by conditional logistic regression is displayed in Table 7.7.

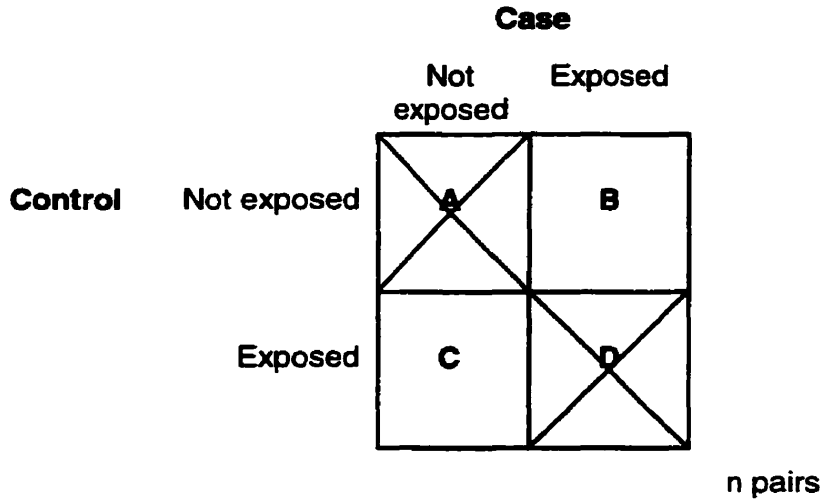
The estimate of the OR of MI for older age among women is directly obtained by

exponentiating the parameter estimate i.e., $OR_W = \exp(\beta_1 X_1)$ whereas that for men is given by $OR_M = \exp(\beta_1 X_1 + \beta_3 X_1 X_2)$.

CONCLUSION

Instances where one would want to test for the presence of effect modification are relatively common in epidemiology. As it was illustrated in our example, multivariate modelling procedures may be very useful not only for the assessment of confounding but also to increase precision. It seems to be particularly the case in matched case-control studies where the main utility for matching derives from the enhanced precision that it affords for the control of confounding. We showed that using modelling strategies to assess for the presence of effect modification in matched case-control studies is highly efficient, especially when dealing with sparse data. No clear patterns arose from the simulation data with respects to the different scenarios that we investigated. However, the odds ratios were steadily more precise when using the modelling strategy, compared to the stratified analysis. Since most epidemiological studies deal with relatively small samples, we recommend the use of the modelling procedure to assess effect modification in matched case-control studies.

Table 7.1 **Computation of the odds ratio in a pair matched case-control study.**



Odds ratio (OR) = B/C

Table 7.2 **Relative efficiency of two methods for the assessment of effect modification in 1:1 matched case-control studies, for n=1,000 pairs and even distribution of strata for the modifier.**

Prob. of exposure		Overall			Stratum 1 (prob. = 0.5)								Stratum 0 (prob. = 0.5)							
					True	Stratified analysis			Modelling strategy				True	Stratified analysis			Modelling strategy			
Stratum 1	Stratum 0	LogOR	Var LogOR	Mean Var LogOR	OR	LogOR	LogOR	Var LogOR	Mean Var LogOR	LogOR	Var LogOR	Mean Var LogOR	Relative efficiency	OR	LogOR	LogOR	Var LogOR	Mean Var LogOR	LogOR	Var LogOR	Mean var LogOR	Relative efficiency
0.5	0.5	-0.3490	0.0335	0.0325	1.5	0.4055	0.4221	0.1427	0.1458	0.9745	0.0467	0.0451	0.31	0.3	-1.2040	-1.2642	0.2137	0.2495	-1.2293	0.0621	0.0634	0.25
0.2	0.8	-0.3832	0.0337	0.0348			0.4063	0.2037	0.2137	-0.0506	0.0434	0.0438	0.21			-1.2486	0.2239	0.2593	-0.4538	0.0518	0.0485	0.19
0.8	0.2	-0.1417	0.0328	0.0309			0.4629	0.2742	0.2843	1.9373	0.1073	0.1108	0.39			-1.2725	0.4781	0.4102	-2.0630	0.1308	0.1436	0.35
0.5	0.5	-0.8317	0.0385	0.0364	0.8	-0.2231	-0.2331	0.1380	0.1420	1.0041	0.0615	0.0591	0.42	0.2	-1.6094	-1.6837	0.2817	0.2789	-1.6426	0.0751	0.0729	0.26
0.2	0.8	-0.8448	0.0388	0.0400			-0.2652	0.2490	0.2759	-0.3293	0.0613	0.0635	0.23			-1.6772	0.2646	0.3016	-0.8731	0.0540	0.0493	0.16
0.8	0.2	-0.3844	0.0338	0.0317			-0.2197	0.2105	0.2230	2.2028	0.1565	0.1599	0.72			-1.6247	0.6186	0.4173	-2.5354	0.1807	0.1978	0.47
0.5	0.5	1.1898	0.0458	0.0457	5.7	1.7405	1.8491	0.3239	0.3156	0.2338	0.0248	0.0247	0.08	2.1	0.7419	0.7845	0.1624	0.1715	0.7520	0.0628	0.0627	0.37
0.2	0.8	1.0547	0.0427	0.0434			1.8044	0.2762	0.2768	0.1092	0.0263	0.0258	0.09			0.8170	0.3446	0.3771	1.6129	0.1085	0.1280	0.34
0.8	0.2	0.6325	0.0359	0.0350			1.7384	0.6557	0.3880	0.4745	0.0327	0.0313	0.08			0.7920	0.2053	0.2199	0.0651	0.0572	0.0616	0.28
0.5	0.5	0.6984	0.0366	0.0353	0.7	-0.3567	-0.3686	0.1408	0.1420	-0.8135	0.0315	0.0293	0.21	12.0	2.4849	2.5521	0.5604	0.3490	2.5418	0.1270	0.1303	0.37
0.2	0.8	0.2449	0.0330	0.0329			-0.4147	0.2677	0.2995	-1.3180	0.0567	0.0582	0.19			2.0928	0.8486	0.3142	3.8244	***	***	***
0.8	0.2	1.0734	0.0430	0.0439			-0.3667	0.2042	0.2101	-0.5440	0.0269	0.0271	0.13			2.5624	0.4385	0.3434	1.6572	0.0644	0.0601	0.17
0.5	0.5	-0.7082	0.0368	0.0363	0.5	-0.6931	-0.7143	0.1553	0.1525	0.0070	0.0456	0.0443	0.29	0.5	-0.6931	-0.7213	0.1600	0.1834	-0.7155	0.0553	0.0570	0.31
0.2	0.8	-0.4681	0.0344	0.0356			-0.7700	0.3328	0.3520	-1.1753	0.0728	0.0773	0.22			-0.7185	0.2041	0.2254	0.0122	0.0556	0.0554	0.25
0.8	0.2	-0.4540	0.0342	0.0313			-0.7138	0.1995	0.2018	1.1706	0.0726	0.0739	0.37			-0.7480	0.3350	0.3640	-1.5504	0.0947	0.1043	0.29
0.5	0.5	-0.0035	0.0325	0.0341	1.0	0.0000	0.0015	0.1361	0.1413	0.0030	0.0326	0.0305	0.22	1.0	0.0000	0.0115	0.1372	0.1485	-0.0047	0.0490	0.0521	0.36
0.2	0.8	-0.0110	0.0324	0.0327			-0.0251	0.2252	0.2447	-0.7827	0.0459	0.0458	0.19			0.0061	0.2237	0.2371	0.7715	0.0664	0.0710	0.30
0.8	0.2	0.0014	0.0326	0.0305			0.0243	0.2253	0.2331	0.7879	0.0461	0.0467	0.20			0.0021	0.2283	0.2409	-0.7651	0.0667	0.0758	0.31
0.5	0.5	1.1059	0.0437	0.0434	3.0	1.0986	1.1543	0.1977	0.2214	0.0008	0.0247	0.0246	0.11	3.0	1.0986	1.1425	0.1932	0.1898	1.1144	0.0650	0.0664	0.35
0.2	0.8	0.7351	0.0372	0.0353			1.1290	0.2122	0.2303	-0.2169	0.0294	0.0286	0.12			1.1978	0.4468	0.3979	2.0159	0.1265	0.1332	0.33
0.8	0.2	0.7453	0.0373	0.0385			1.1940	0.4428	0.4125	0.2214	0.0295	0.0286	0.07			1.1590	0.2170	0.2364	0.4049	0.0546	0.0590	0.25

*** Could not be estimated.

Table 7.3 **Relative efficiency of two methods for the assessment of effect modification in 1:1 matched case-control studies. for n=1,000 pairs and uneven distribution of strata for the modifier.**

Prob. of exposure		Overall			Stratum 1 (prob. = 0.2)								Stratum 0 (prob. = 0.8)							
					True		Stratified analysis			Modelling strategy				True		Stratified analysis			Modelling strategy			
Stratum 1	Stratum 0	LogOR	Var LogOR	Mean Var LogOR	OR	LogOR	LogOR	Var LogOR	Mean Var LogOR	LogOR	Var LogOR	Mean Var LogOR	Relative efficiency	OR	LogOR	LogOR	Var LogOR	Mean Var LogOR	LogOR	Var LogOR	Mean var LogOR	Relative efficiency
0.5	0.5	-0.8432	0.0388	0.0404	1.5	0.4055	0.3007	1.0165	0.5949	0.9795	0.0674	0.0679	0.11	0.3	-1.2040	-1.2398	0.0749	0.0809	-1.2350	0.0498	0.0536	0.66
0.2	0.8	-0.8060	0.0379	0.0384			0.2210	1.2171	0.5747	-0.1440	0.0788	0.0845	0.15			-1.2311	0.0787	0.0847	-0.8731	0.0447	0.0434	0.51
0.8	0.2	-0.4742	0.0431	0.0435			0.1945	1.3196	0.4917	1.7193	0.1053	0.1061	0.22			-1.2595	0.1649	0.1665	-1.6736	0.1079	0.1230	0.74
0.5	0.5	-1.2752	0.0480	0.0474	0.8	-0.2231	-0.1712	0.9822	0.6008	1.0154	0.0882	0.0939	0.16	0.2	-1.6094	-1.6548	0.0982	0.1030	-1.6526	0.0629	0.0643	0.62
0.2	0.8	-0.4679	0.0344	0.0340			-0.2245	0.7065	0.6325	-1.7601	0.1128	0.1149	0.18			-1.6680	0.1544	0.1780	-1.1147	0.0570	0.0491	0.28
0.8	0.2	-0.6981	0.0476	0.0478			-0.0967	1.2440	0.5497	1.9674	0.1455	0.1469	0.27			-1.6800	0.2372	0.2414	-2.1176	0.1491	0.1692	0.70
0.5	0.5	0.9117	0.0399	0.0399	5.7	1.7405	1.0647	1.1236	0.4287	0.2346	0.0380	0.0385	0.09	2.1	0.7419	0.7452	0.0589	0.0587	0.7497	0.0441	0.0444	0.76
0.2	0.8	0.6569	0.0515	0.0522			1.1805	1.0661	0.4294	0.0561	0.0437	0.0430	0.10			0.7673	0.1162	0.1256	1.1360	0.0822	0.0950	0.76
0.8	0.2	0.6240	0.0367	0.0374			0.5385	1.4980	0.3689	0.3502	0.0431	0.0448	0.12			0.7504	0.0736	0.0836	0.4161	0.0454	0.0491	0.59
0.5	0.5	1.5438	0.0567	0.0571	0.7	-0.3567	-0.2696	0.9779	0.6041	-0.8164	0.0536	0.0534	0.09	12.0	2.4849	2.5836	0.2146	0.2141	2.5569	0.1166	0.1267	0.59
0.2	0.8	0.7167	0.0480	0.0462			-0.2223	1.3706	0.4690	-1.4446	0.1101	0.1117	0.24			2.5276	0.5134	0.3679	3.2958	***	***	***
0.8	0.2	1.8629	0.0603	0.0621			-0.1783	1.2159	0.5758	-0.5729	0.0420	0.0461	0.08			2.5301	0.1545	0.1656	2.0993	0.0678	0.0639	0.39
0.5	0.5	-0.7082	0.0368	0.0363	0.5	-0.6931	-0.5325	1.0104	0.5759	0.0049	0.0719	0.0756	0.13	0.5	-0.6931	-0.7112	0.0584	0.0597	-0.7121	0.0416	0.0417	0.70
0.2	0.8	-0.5463	0.0365	0.0366			-0.3414	1.4133	0.4384	-1.3061	0.1450	0.1637	0.37			-0.7156	0.0736	0.0778	-0.3745	0.0452	0.0458	0.59
0.8	0.2	-0.5062	0.0436	0.0419			-0.4026	1.1723	0.5732	0.9942	0.0789	0.0801	0.14			-0.7201	0.1137	0.1145	-1.1159	0.0764	0.0829	0.72
0.5	0.5	-0.0035	0.0325	0.0341	1.0	0.0000	-0.0106	0.9823	0.6022	0.0061	0.0513	0.0518	0.09	1.0	0.0000	-0.0018	0.0512	0.0502	-0.0046	0.0368	0.0381	0.76
0.2	0.8	-0.0082	0.0374	0.0369			-0.0227	1.2894	0.5673	-0.6901	0.0857	0.0853	0.15			-0.0060	0.0812	0.0845	0.3546	0.0531	0.0574	0.68
0.8	0.2	-0.0037	0.0376	0.0361			0.0038	1.2662	0.5248	0.6398	0.0557	0.0591	0.11			-0.0097	0.0821	0.0864	-0.3735	0.0536	0.0575	0.67
0.5	0.5	1.1059	0.0437	0.0434	3.0	1.0986	0.7598	1.0648	0.5256	0.0002	0.0388	0.0394	0.08	3.0	1.0986	1.1085	0.0692	0.0678	1.1129	0.0493	0.0489	0.72
0.2	0.8	0.8014	0.0501	0.0496			0.7501	1.1060	0.5370	-0.2919	0.0508	0.0502	0.09			1.1543	0.1505	0.1543	1.5575	0.1018	0.1150	0.75
0.8	0.2	0.8701	0.0384	0.0408			0.4659	1.4301	0.4313	0.1202	0.0410	0.0437	0.10			1.1170	0.0769	0.0889	0.7742	0.0451	0.0491	0.55

*** Could not be estimated.

Table 7.4 **Illustration of a matched analysis of the effect of age on the risk of myocardial infarction (MI), stratified for gender.**

		MI cases: Young	MI cases: Old
Controls	Young	117	281
	Old	113	301

Overall OR = 281 / 113
2.49

Men

		MI cases: Young	MI cases: Old
Controls	Young	51	85
	Old	41	79

OR = 85 / 41
2.07

Women

		MI cases: Young	MI cases: Old
Controls	Young	8	54
	Old	13	71

OR = 54 / 13
4.15

Table 7.5 **Distribution of the matched sets in an age-stratified analysis .**

Exposed cases	Exposed controls	Male cases (Stratum1)	Male controls (Stratum 2)	No. of matched sets	
0	0	0	0	8	Concordant pairs: not used
0	0	0	1	9	Concordant pairs and Heterogeneity of the modifier: not used
0	0	1	0	49	Concordant pairs and Heterogeneity of the modifier: not used
0	0	1	1	51	Concordant pairs: not used
0	1	0	0	13	
0	1	0	1	8	Heterogeneity of the modifier: not used
0	1	1	0	50	Heterogeneity of the modifier: not used
0	1	1	1	41	
1	0	0	0	54	
1	0	0	1	63	Heterogeneity of the modifier: not used
1	0	1	0	79	Heterogeneity of the modifier: not used
1	0	1	1	85	
1	1	0	0	71	Concordant pairs: not used
1	1	0	1	46	Concordant pairs and Heterogeneity of the modifier: not used
1	1	1	0	105	Concordant pairs and Heterogeneity of the modifier: not used
1	1	1	1	79	Concordant pairs: not used

Table 7.6 **Gender-specific odds ratios (95% CI) for the effect of age on MI risk obtained from a stratified analysis *vs* a modelling strategy.**

	Stratified analysis		Modelling strategy	
Men	2.07	(1.43 - 3.01)	2.25	(2.02 - 2.52)
Women	4.15	(2.27 - 7.61)	4.66	(3.09 - 7.04)

Table 7.7 **Statistical model used to obtain stratum-specific odds ratio in conditional logistic regression.**

	Parameter estimate (β)	Standard error (SE_β)	Risk ratio $\exp(\beta)$
Old age (X_1).	1.5398	0.2103	4.66
Male (X_2).	1.4589	0.2133	4.3
Old*Male (X_1X_2)	-0.7272	0.2526	0.48

Note: $Cov(\beta_1,\beta_2) = -0.0432$

CHAPTER 8 – DISCUSSION

This chapter features the interpretation of the main results and provides a critical appraisal of our research. The strengths and limitations of this study are discussed and weighed against existing knowledge on the subject matter. Directions for future research resulting from this thesis are also outlined.

A cohort of 19,501 patients initiating treatment with an ACE inhibitor, a β-blocker or a calcium antagonist between 1990 and 1993 was used to study antihypertensive drug use and effects at the population level. Throughout, the role that medication use - antihypertensive and others- during the course of antihypertensive therapy plays in the assessment of subsequent risk is highlighted.

8.1 Equivalence of ACE inhibitors

The first manuscript aimed at exploring the equivalence of three agents belonging to the same drug class namely the ACE inhibitors captopril, enalapril and lisinopril, with respect to the use of health services following treatment initiation. The study design was that of a cohort with exposure defined as the first dispensed agent. After adjustment for baseline differences across groups, we found medical visits and hospital admissions following initiation of antihypertensive therapy to differ. More specifically, the rate ratios of visits to a general practitioner, those made to a specialist and hospital admissions were higher in the captopril group compared to the two others. In addition, stratified analyses showed that healthier subjects had less benefit from enalapril and lisinopril than the sicker ones. This suggests that different agents that belong to the same drug class may no be therapeutically equivalent in all respect. A number of limitations characterize this study however. These are discussed further in the following sections of this chapter.

8.2 Patterns of use of antihypertensive drugs

Following the completion of the first study, we were interested in documenting the accuracy of exposure definition. The second manuscript involved the characterizing of patterns of use of antihypertensive agents following initiation of treatment using the same cohort of subjects with uncomplicated hypertension. We found newer agents to be more frequently prescribed than β-blockers at initiation of therapy. The patterns of use of antihypertensive agents were also found to be highly variable with very high rates of

noncompliance and of modifications to treatment regimens. In addition, these varying patterns of use were found to be different according to the agents being used, with patients initiated on combination therapy being more likely to remain on their initial treatment regimen and less likely to discontinue overall therapy. Users of newer agents such as ACE inhibitors and calcium antagonists were more likely to add or switch treatment regimen and interrupt therapy. Finally a rapid early decrease in the proportion of patients continuing on initial therapy was noted, especially among those initiated on β-blockers.

This study was the first to examine longitudinally the patterns of use of antihypertensive agents in a cohort of subjects initiating treatment for uncomplicated hypertension. It was also the only one that reported on utilization patterns over a period of observation exceeding one year and that did not exclude patients initiating therapy with a drug combination. This constitutes a major strength since patients initiating therapy with combined agents are believed to be different from the others.

8.3 Antihypertensive agents and MI risk

Recent observational studies suggesting that calcium antagonists increase the rate of myocardial infarction (MI)[23-25] have lead to a major debate over the safety of these agents. Yet, a number of other similar studies have found no elevated risk for calcium antagonists[234-238]. The issue at stake is whether calcium antagonists are safe and whether all antihypertensive agents are equivalent in protecting hypertensive subjects from cardiovascular events.

In a population-based matched case-control study nested within the cohort, we found MI risk to differ across antihypertensive agents with current users of calcium antagonists and, to a lesser extent ACE inhibitors, being at higher risk of MI relative to β-blockers. These results points to the same direction as those of two previous studies. Psaty *et al* found a risk ratio of 1.6 (95% CI=1.1-2.3) for current use of calcium antagonists relative to β-blockers[23]. Another case-control study by Pahor *et al* conducted among the elderly population with hypertension showed similar results but higher in magnitude[25]. In our study, control for factors such as personal characteristics of the study subjects, coexisting conditions and history of antihypertensive drug use attenuated the crude association, thus suggesting a potential role of confounding by the indication for the drug.

A significant finding of our study is that of the association of current use of antihypertensive agents to differ across sub-groups defined by drug markers for MI risk. For instance, among users of digoxin during the course of antihypertensive therapy, current users of ACE inhibitors were found to be at very high risk of an event, compared with β-blockers. Also, the relative risk of calcium antagonists on MI was found to be elevated in milder patients, as defined by the absence of prior use of ACE inhibitors and calcium antagonists and by the absence of use of nitrates during the course of therapy. No elevated risk of MI in association with calcium antagonist use was found among users of drugs believed to be markers for MI risk. On the other hand, the initiation of therapy for the treatment of diabetes was not found to increase the risk of MI. These findings suggest that careful documentation of coexisting conditions and prior use of the studied agents is warranted. The processes involved in the selection of a specific agent in hypertension should be studied further so as to increase the validity of observational studies of intended drug effects. Also, further research is needed to confirm the novel finding of a differential effect of antihypertensive drugs on MI in different risk groups.

This is the first population-based study that quantified the risk of MI in association with antihypertensive agents in a cohort of patients newly treated for hypertension while taking into account history of use of antihypertensive agents and medications used to treat coexisting conditions known to bear on MI risk. This is also the first study to provide an extensive analysis of the patterns of use of antihypertensive agents at the population level in such a cohort, several previous studies having used prevalent cohorts. Previous studies have been compromised by one or more of the following limitations: small sample size, inconsistent criteria for exposure definition, failure to control for factors believed to be confounders of the association and most of all, having used exposure measure of current use independently of history of drug use. Emerging clinical trials such as the Shanghai Trial of Nifedipine in the Elderly (STONE), the Systolic Hypertension - Europe trial (Syst-Eur) and the Syst-China tend to show a beneficial effect of calcium antagonists in hypertension[19-22]. This suggests that their use in this setting is safe and effective. The results of randomized controlled may not be applicable however to the every day clinical setting. Two studies have also recently suggested that calcium antagonists may be unsafe for the management of hypertension in diabetic patients. In the Appropriate Blood pressure Control in Diabetes (ABCD) study, patients taking calcium antagonists had significantly more MI than ACE inhibitor users[147]. In the

Fosinopril versus Amlodipine Cardiovascular Events randomized Trial (FACET), patients using the ACE inhibitor fosinopril, relative to the calcium antagonist amlodipine, had a significantly lower risk of the combined endpoint defined by MI, stroke or angina[148]. Our results do not confirm these findings. Methodological considerations that may help explaining these discrepancies are outlined below.

8.4 Methodological considerations

The presents section addresses the strengths and limitations of our research and considers the potential for bias.

8.4.1 Selection bias

All Saskatchewan residents initiating treatment with an ACE inhibitor, a β-blocker or a calcium antagonist were included in the study. Subjects initiating treatment for hypertensive disease with a diuretic, a centrally acting agent, a vasodilator or any other drugs used to treat hypertension were excluded by study design. There is no reason to believe that these subjects may have been different from the participating subjects with regard to the exposure-disease relationship as it would only be the case if their risk of experiencing an acute MI following calcium antagonist use was different from that of subjects having initiated antihypertensive therapy on other agents. However, this feature of our study limits the external validity of our findings.

An important strength of our study is the selection of new users of antihypertensive drugs, that is only patients initiating treatment with these drugs formed the source cohort. This feature permitted the documentation of the entire history of use for these drugs, which constitutes an important strength of the study. In contrast, previous studies on the patterns of use of antihypertensive drugs included prevalent users, which may introduce a selection bias. It has been suggested in the late '80s that past experience with a drug may influence the risk of an adverse event in association with current treatment[10,11]. This means that in epidemiological studies of unwanted effects of a drug, past use of that very same drug may modify the risk of current use, the risk not being constant over time. In the depletion of susceptibles phenomenon, patients who continuously use a drug may be seen as "survivors", i.e. those who can tolerate it, while those who are susceptibles select themselves out of the population at risk[436]. Including these subjects as unexposed subjects in the analysis would lead to an underestimate of

the risk ratio. This also means that compared to long-term users, first-time users may be at higher risk of experiencing an event. Therefore, adequate handling of past exposure to document the entire history of use appears essential to prevent selection bias. This bias is believed to have influenced the estimates of risk of previous observational studies that reported no elevated risk for MI in association with calcium antagonists[234-236,238,239]. Also, this bias is likely to have lead to an underestimation of compliance rates in prior drug utilization studies, given that treatment adherence tends to decrease over time[409].

A selection bias would also be introduced if an underlying cardiovascular disease was already present but not diagnosed at the time the exposure was defined. In that case, a protopathic bias[437] may have been introduced in our third study whereby treatment with calcium antagonists was initiated BECAUSE symptoms of cardiovascular became apparent, as opposed to these agents having induced coronary heart disease, thus leading to wrong conclusions regarding the temporal features of the events. The exact date of onset of cardiovascular disease is almost impossible to ascertain. For instance, markers of atherosclerosis and silent ischemia may be present in hypertensive patients without any evidence in our data. Then, our attempts to exclude subjects with markers of underlying cardiovascular disease using prescribed drugs in the year preceding antihypertensive treatment initiation and to stratify for the presence of cardiovascular treatment initiation during the course of antihypertensive therapy may be insufficient to eliminate bias.

8.4.2 Information bias

In epidemiological studies, misclassification of the outcome and exposure may lead to information bias[432]. We think the use of Saskatchewan Health databases to gather information on drug use and occurrence of MI has contributed to minimizing this type of bias. Numerous validation procedures are in force to ensure the accuracy of data[347,345,349,332]. For instance, the eligibility of the claimant is reviewed at the time of each reimbursement claim. A sample of paid claims is also periodically verified through direct contact with the claimant. Diagnoses in the Hospitalization database have generally shown a good agreement when compared to medical charts[340-342], especially that for MI[346]. In addition, overall, Saskatchewan Health databases have shown excellent accuracy[344-348]. Finally, the use of administrative databases also permit avoiding information biases such as nondifferential or systematic imprecisions in the recall of

some events[331].

A limitation of using these large databases is the lack of information pertaining to actual intake of the drug. No information is available with regard to the duration of use of these drugs, nor is there any information on whether the patient did actually take the medication or not. Assumptions made regarding the duration of use of antihypertensive drugs -average duration of 30 days in our case- may lead to errors in exposure classification which, if differentially distributed in the contrasted groups, could have lead to biases in the estimates of risk. For instance, all the estimates of compliance would be biased if some of the compared agents were used for periods of time longer than 30 days whereas others would be used for less than 30 days. Similarly, study subjects who have not actually taken their medications for the full assumed duration of use could have been randomly misclassified, with the effect of attenuating the risk ratios toward the null. A bias would have been introduced if some of the compared groups were more prone to not actually taking the drug as prescribed. There is no reason to think however that such a systematic misclassification would occur.

We are very cautious when interpreting the results of the first study now that patterns of use of antihypertensive agents have been extensively investigated. Indeed, exposure characterization using solely the first dispensed agents is highly susceptible to misclassification errors. Drug exposure is a highly variable phenomenon, which makes it difficult to delineate[427]. Having shown in the second study that compliance with therapy and subsequent modifications to treatment regimens is depending upon initial treatment, reinforces this position.

Misclassification of the outcomes could also have occurred in our study. In the case of the first manuscript, differential and even random misclassification of the health services utilization is unlikely since recording of medical visit and hospitalizations is believed to be very accurate in these databases. In addition, not having documented the reasons underlying health services use contributes to minimizing the presence of bias. In the case-control analysis of the occurrence of MI, misclassification bias related to case ascertainment is possible. However, myocardial infarction is a well-defined entity and may be less subject to misclassification. For instance, variation of death certificates coding over time and geographic regions has not been shown to contribute to the observed decline in MI mortality rates[438]. However, identification of incident cases of MI using hospital discharge data and death certificates was found in two studies to be less

efficient than when community registries are used[439-440]. Of the MI cases identified using community registries, approximately 80% were also identified using hospital data. The sensitivity of death certificates data was found to be high in three studies(80% to 90%)[440-442]. The lower sensitivity of hospital data to capture MI cases could bias the incidence rates of the disease. However, as long as this sensitivity do not differ between the contrasted groups, the estimates of the rate ratios should not be biased. Whereas there may have been missed cases, notably those few which were not severe enough to require hospital admission, systematic differences in MI ascertainment is unlikely. MI is a hard endpoint and in addition to the fact that most of the study period occurred before the publication of Psaty's study[23] and the beginning of the debate over the safety of calcium antagonists, an overascertainment of MI cases among calcium antagonist users is unlikely. Also, coding for the cause of death was undertaken without regard to antihypertensive drug use.

8.4.3 Confounding

The major drawback of administrative databases is the lack of information on the indications for prescribed drugs. Because the severity of the disease, the presence of coexisting conditions and personal characteristics of the patients may all bear on the risk of an event, this lack of information poses a serious threat to the validity of observational studies of intended drug effects. The underlying mechanism is that because the medications are dispensed to prevent a disease, the reason for prescription could, if independently related to both the exposure and the event one attempts to prevent, distort the results. In our study, several factors such as comorbidity and disease severity, could explain the observed association between antihypertensive drug use and the risk of MI. In addition to unknown factors, risk factors for coronary artery disease such as blood pressure, smoking, cholesterol and lipids levels, are also likely to have influenced the results. However, in several case-control studies[262,443,23] patient characteristics such as smoking, diabetes and cholesterol levels were only weakly associated with the choice of therapy. Also, several approaches have been proposed when using large databases for population-based observational studies[444]. To minimize the presence of confounding by indication, we underwent several measures. We first took a careful handling of the use of duration of hypertension in all studies. One could assume that the longer the duration of hypertension, the greater the potential hazards of inadequate treatment,

hence the need to account for duration of therapy when assessing adverse effects of specific agents. In the cohort analyses, we controlled for the duration of follow-up. In the case-control study, we matched every case to four randomly chosen controls that not only initiated therapy the same month and calendar year than the case but also who were still at risk for an event at the case's event date. This design feature presents two main advantages. First, all compared groups are equivalent in terms of duration of treated hypertension. This can therefore be ruled out as an explanation for the observed results. The second advantage of this approach is that the opportunity for the exposure, namely for switching or adding other drug classes, is made similar in the contrasted groups. The approach used by Psaty and his group[23] to match cases and controls on the date of the event does not control for the duration of hypertension, nor does it allow the same opportunity for exposure among the cases and the controls. This could also have induced biases in their study results.

We adjusted in all analyses for factors thought to be associated with the general health status of the subjects which may bear on selective prescribing of the drugs. For instance, the number of hospital admissions and medical visits in the year preceding therapy as well as drug use for several chronic conditions at baseline were adjusted for. We also excluded from the cohort all subjects with prior evidence of cardiovascular disease or for which the most likely indication for antihypertensive treatment was not hypertension. These exclusions should have increased the homogeneity of the cohort. Despite these efforts however, confounding by the indication for the drug may still be a likely explanation for the results.

An inherent weakness of our study was the inability to control for blood pressure levels and severity of hypertension, since no clinical measures are available in the Saskatchewan databases. If we assume, in addition to the fact that matching ensured us that the compared group were similar in terms of duration of hypertension, that all antihypertensive agents are equivalent in their ability to lower blood pressure, unavailability of information regarding blood pressure control should not be a major threat to the validity of the results. However, it appears reasonable to think that people with uncontrolled blood pressure may have been prescribed a second-line agent such as the newer calcium antagonists and ACE inhibitors whereas well controlled patients are initiated, and maybe tend to stay, on β-blockers. Similarly in the first study, sicker patients may have been channelled to the use of the ACE inhibitor captopril, in which

case the likelihood of subsequently using health services would have been higher. This hypothesis needs confirmation however. If it was shown to be true, we could conclude in the presence of confounding by indication in our study results.

As stated earlier by Collet, Boivin and Spitzer[427], one of the major challenges of pharmacoepidemiology is the recognition and prevention of potential biases as possible alternative explanations for the observed study results. Well thought and carefully designed observational studies of drug safety should have more credibility as they contribute meaningful data and key information about the usefulness of drug therapy which has important implications for clinicians, health administrators and regulators. Careful examination of potential confounding biases and assessment of effect modification however appears mandatory.

CHAPTER 9 – SUMMARY AND CONCLUSION

Our study of the patterns of use and effects of antihypertensive medications at the population level revealed a number of interesting results. This final chapters provides a summary of the results and draws the following conclusions:

- Medical visits and hospital admissions following initiation of antihypertensive therapy with the ACE inhibitors captopril, enalapril and lisinopril differed, thus suggesting that different agents that belong to the same drug class may no be therapeutically equivalent in all respect. The definition of exposure in this study was however highly prone to misclassification and one should interpret these results with caution.

- A very high variability in the patterns of antihypertensive drug use was observed with very high rates of noncompliance to therapy and modification to treatment regimens.

- Myocardial infarction risk was found to differ across antihypertensive agents with current users of calcium antagonists and, to a lower extent ACE inhibitors, being at higher risk relative to β-blockers. Control for factors such as personal characteristics of the study subjects, coexisting conditions and history of antihypertensive drug use attenuated these associations, thus suggesting a potential role of confounding by indication.

- Relative risks of MI in association with current use of antihypertensive agents were found to differ across sub-groups defined by drug markers for MI risk. For instance, among subjects who had used digoxin during the course of antihypertensive therapy, current users of ACE inhibitors were found to be at very high risk of an event, compared with β-blockers. Also, relative risks of calcium antagonists were found to be elevated in milder patients as defined by the absence of prior use of ACE inhibitors and calcium antagonists and by the absence of use of nitrates during the course of therapy. In the more severe group of patients, i.e. those who have used at least two of these three drug markers for MI risk, no increased risk of MI was found for calcium antagonist users relative to β-blockers.

- Initiation of drug therapy for the treatment of diabetes was not found to modify the

relative risks of MI.

This is the first population-based study that quantified the risk of MI in association with antihypertensive agents in a cohort of patients newly treated for hypertension while taking into account history of use of antihypertensive agents and medications used to treat coexisting conditions known to bear on MI risk. This is also the first study to provide an extensive analysis of the patterns of use of antihypertensive agents at the population level in such a cohort, most previous studies having used prevalent cohorts. The results of this study suggest that careful documentation of coexisting conditions and prior use of the studied agents is warranted. Pharmacoepidemiologic studies present the advantage of allowing the assessment of drug use and effects in the context of everyday clinical practice. The wealth of available data also permit detailed characterizing of patterns of use of medications from the very beginning of treatment. However, these are subject to confounding by the indication for the prescribed drugs and to biases by other undocumented factors. The processes involved in the selection of a specific agent in hypertension should be studied further so as to increase the validity of observational studies of intended drug effects. Further research is also needed to confirm the novel finding of differential relative effects of antihypertensive drugs on MI according to risk groups.

REFERENCES

1. Strom BL. What is Pharmacoepidemiology? In: Strom BL, editor. Pharmacoepidemiology. 2nd edition ed. 1994:3-13.

2. Dukes MN. Drug utilization studies. Methods and uses. Introduction. WHO Regional Publications 1993;European Series. 45:1-4.

3. Strom BL, Melmon KL. Can postmarketing surveillance help to affect optimal drug therapy?. JAMA 1979;242:2420-2422.

4. Horwitz RI, Feinstein AR. The application of therapeutic-trial principles to improve the design of epidemiologic research: a case-control study suggesting that anticoagulants reduce mortality in patients with myocardial infarction. Journal of Chronic Disease 1981;34:575-583.

5. Strom BL, Melmon KL, Miettinen OS. Postmarketing studies of drug efficacy: when must they be randomized? Clinical Pharmacology & Therapeutics 1983;34:1-7.

6. Slone D, Shapiro S, Miettinen OS, Finkle WD, Stolley PD. Drug evaluation after marketing. Annals of Internal Medicine 1979;90:257-261.

7. Miettinen OS. The need for randomization in the study of intended effects. Statistics in Medicine 1983;2:267-271.

8. Horwitz RI. Complexity and contradiction in clinical trial research. American Journal of Medicine 1987;82:498-510.

9. Horwitz RI, Viscoli CM, Clemens JD, Sadock RT. Developing improved observational methods for evaluating therapeutic effectiveness. American Journal of Medicine 1990;89:630-638.

10. Kramer MS, Lane DA, Hutchinson TA. Analgesic use, blood dyscrasias, and case-control pharmacoepidemiology. Journal of Chronic Disease 1987;40:1073-1081.

11. Miettinen OS, Caro JJ. Principles of nonexperimental assessment of excess risk, with special reference to adverse drug reactions. Journal of Clinical Epidemiology 1989;42:325-331.

12. Guess HA. Behavior of the exposure odds ratio in a case-control study when the hazard function in not constant over time. Journal of Clinical Epidemiology 1989;42:1179-1184.

13. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990;335:827-838.

14. Cutler JA, Furberg CD. Drug treatment trials in hypertension: a review . Preventive Medicine 1985;14:499-518.

15. Hebert PR, Fiebach NH, Eberlein KA, et al. The community-based randomized trials of pharmacologic treatment of mild-to-moderate hypertension. American Journal of Epidemiology 1988;127:581-590.

16. Yusuf S, Lessem J, Jha P, Lonn E. Primary and secondary prevention of myocardial infarction and strokes: an update of randomly allocated, controlled trials. Journal of Hypertension - Supplement 1993;11:S61-S73.

17. Mulrow CD, Cornell JA, Herrera CR, Kadri A, Farnett L, Aguilar C. Hypertension in the elderly. Implications and generalizability of randomized trials. JAMA 1994;272:1932-1938.

18. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990;335:765-774.

19. Gong L, Zhang W, Zhu Y, Zhu J, Kong D, Page V, et al. Shanghai trial of nifedipine in the elderly (STONE). J Hypertens. 1996;14:1237-1245.

20. Hamet P, Gong L. Antihypertensive therapy debate: contribution from the Shanghai Trial Of Nifedipine in the Elderly (STONE). J Hypertens. 1996;14:9-14.

21. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet 1997;350:757-764.

22. Liu L, Wang JG, Gong L, Liu G, Staessen JA. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. Systolic Hypertension in China (Syst-China) Collaborative Group. J Hypertens. 1998;16:1823-1829.

23. Psaty BM, Heckbert SR, Koepsell TD, Siscovick DS, Raghunathan TE, Weiss NS, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. JAMA 1995;274:620-625.

24. Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. Circulation 1995;92:1326-1331.

25. Pahor M, Guralnik JM, Corti MC, Foley DJ, Carbonin P, Havlik RJ. Long-term survival and use of antihypertensive medications in older persons. Journal of the American Geriatrics Society 1995;43:1191-1197.

26. Buring JE, Glynn RJ, Hennekens CH. Calcium channel blockers and myocardial infarction. A hypothesis formulated but not yet tested. JAMA 1995;274:654-655.

27. Anonymous. Sterky G, editor. Medicines and society: a challenge in health development. 1988;Stockholm: Karolinska Institute, Departments of International Health Care Research (IHCAR) and Clinical Pharmacology, Huddinge University Hospital.

28. Heart and Stroke Foundation. Cardiovascular disease in Canada. 1993;Ottawa, Canada.

29. Potter JF. Hypertension and the elderly. British Medical Bulletin 1994;50:408-419.

30. McCarron DA, Haber E, Slater EE. High blood pressure. In: Dale DC, Federman DD, editors. Scientific American Medicine. New York: Scientific American, Inc., 1993:1-32.

31. Wiser T, Young L. Essential hypertension. In: Young L&K-KM, editor. Applied Therapeutics. The clinical use of drugs. Fourth ed. Vancouver: Applied therapeutics Inc., 1988:123-159.

32. Anonymous. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Archives of Internal Medicine 1993;153:154-183.

33. Lip G, Gammage M, Beevers DG. Hypertension and the heart. British Medical Bulletin 1994;50:299-321.

34. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. BMJ 1985;291:97-104.

35. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. Hypertension 1995;25:305-313.

36. Whelton PK. Epidemiology of hypertension. Lancet 1994;344:101-106.

37. Joffres MR, Ghadirian P, Fodor JG, Petrasovits A, Chockalingam A, Hamet P. Awareness, treatment, and control of hypertension in Canada. American Journal of Hypertension 1997;10:1097-1102.

38. Trenkwalder P, Ruland D, Stender M, Gebhard J, Trenkwalder C, Lydtin H, et al. Prevalence, awareness, treatment and control of hypertension in a population over the age of 65 years: results from the Starnberg Study on Epidemiology of Parkinsonism and Hypertension in the Elderly (STEPHY). J Hypertens. 1994;12:709-716.

39. Davidson RA, Hale WE, Moore MT, May FE, Marks RG, Stewart RB. Incidence of hypertension in an ambulatory elderly population. Journal of the American Geriatrics Society 1989;37:861-866.

40. Cornoni-Huntley J, LaCroix AZ, Havlik RJ. Race and sex differentials in the impact of hypertension in the United States. The National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Archives of Internal Medicine 1989;149:780-788.

41. Dannenberg AL, Garrison RJ, Kannel WB. Incidence of hypertension in the Framingham Study. American Journal of Public Health 1988;78:676-679.

42. Psaty BM, Savage PJ, Tell GS, Polak JF, Hirsch CH, Gardin JM, et al. Temporal Patterns of antihypertensive medication use among elderly patients. The Cardiovascular Health Study. JAMA 1993;270:(15)1837-1841. Drug utilization.

43. Reid J. Hypertension and the brain. British Medical Bulletin 1994;50:371-380.

44. Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. British Medical Bulletin 1994;50:272-298.

45. Barnett AH. Diabetes and hypertension. British Medical Bulletin 1994;50:397-407.

46. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. Archives of Internal Medicine 1993;153:598-615.

47. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA 1996;275:1557-1562.

48. Kannel WB, Belanger AJ. Epidemiology of heart failure. American Heart Journal 1991;121:951-957.

49. Hawkins D, Bussey H, Prisant L. Hypertension. 1991:139-159.

50. Rakugi H, Yu H, Kamitani A, Nakamura Y, Ohishi M, Kamide K, et al. Links between hypertension and myocardial infarction. American Heart Journal 1996;132:213-221.

51. Kannel WB. Some lessons in cardiovascular epidemiology from Framingham. American Journal of Cardiology 1976;37:269.

52. Wilcox RG, Mitchell JR, Hampton JR. Treatment of high blood pressure: should clinical practice be based on results of clinical trials?. BMJ 1986;293:433-437.

53. Alderman MH. Quantifying cardiovascular risk in hypertension. Cardiology Clinics 1995;13:519-527.

54. Anonymous. The 1984 report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. Archives of Internal Medicine 1984;144:1045

55. Anonymous. Guidelines for the treatment of hypertension. WHO. Lancet 1983;I:457.

56. Parker J, Parker J. Angina pectoris. In: Jean Gray, editor. Therapeutic choices. Premier ed. Ottawa: Canadian Pharmaceutical Association, 1990:194-205.

57. Gill D, Mayou R, Dawes M, Mant D. Presentation, management and course of angina and suspected angina in primary care. Journal of Psychosomatic Research 1999;46:349-358.

58. Gillum RF, Feinleib M. Cardiovascular disease in the United States: Mortality, prevalence and incidence. In: Kapoor AS and Singh BN, editor. New York: Churchill Livingstone, 1993:49-59.

59. Heart and Stroke Foundation of Canada. Reeder BA, editor. Heart disease and stroke in Canada. 1997;Ottawa, Canada: Statistics Canada.

60. Eisenberg MS, Bergner EL, Hallstrom AP, Cummins RO. Sudden cardiac death. Scientific American 1986;254:37-43.

61. Dagenais GR, Cantin B, Dagenais F, et al. Importance of outside hospital mortality as a first acute ischemic event: The Quebec Cardiovascular Study. Canadian Journal of Cardiology 1996;12:914-918.

62. Bronner LL, Kanter DS, Manson JE. Primary prevention of stroke. New England Journal of Medicine 1995;333:1392-1400.

63. Ostfeld AM. A review of stroke epidemiology. Epidemiologic Reviews 1980;2:136-152.

64. Kannel WB, et al. Epidemiologic assessment of the role of blood pressure in stroke, the Framingham study. JAMA 1970;214:301

65. Dunbabin DW, Sandercock PA. Preventing stroke by the modification of risk factors. Stroke 1990;21:IV36-IV39

66. Warlow CP. Epidemiology of stroke. Lancet 1998;352 Suppl 3:SIII1-SIII4.

67. Anonymous. Ramzi S.Cotran VK&SLR, editor. Robbins Pathologic basis of disease. 1988;Fourth ed., 13, Philadelphia: W.B. Saunders Company.

68. Anonymous. Treatment of heart failure. In: Anonymous1998:894-900.

69. Cohn JN. The management of chronic heart failure. New England Journal of Medicine 1996;335:(7)490-498.

70. Cleland JG, Swedberg K, Poole-Wilson PA. Successes and failures of current treatment of heart failure. Lancet 1998;352 Suppl 1:SI19-SI28.

71. Brophy JM. Epidemiology of congestive heart failure: Canadian data from 1970 to 1989. Canadian Journal of Cardiology 1992;8:495-498.

72. Curnew G. Arrhythmic patients at risk. Perspectives in Cardiology 1999;39-49.

73. Turpie AG, et al. Antithrombotic therapy in atrial fibrillation. Canadian Family Physician 1996;42:1341-1345.

74. Kowey PR. Pharmacological effects of antiarrhythmic drugs. Review and update. Archives of Internal Medicine 1998;158:325-332.

75. Hutchinson RG. Coronary prevention, a clinical guide. Chicago: 1985.

76. Fraser GE. Preventive cardiology. New York: Oxford University press, 1986.

77. McGovern PG, Pankow JS, Shahar E, Doliszny KM, Folsom AR, Blackburn JL, et al. Recent trends in acute coronary heart disease -Mortality, morbidity, medical care, and risk factors. The Minnesota Heart Survey Investigators. New England Journal of Medicine 1996;334:884-890.

78. Levy D, Thom TJ. Death rates from coronary disease -Progress and a puzzling paradox. New England Journal of Medicine 1999;339:915-917.

79. Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. BMJ 1986;293:1145-1151.

80. Rosamund WD, Chambless LE, Folsom AR, Cooper LS, Conwill DE, Clegg L, et al. Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. New England Journal of Medicine 1998;339:861-867.

81. Wigle DT, Mao Y, Wong T, Lane R. Health and Welfare Canada, editor. Economic burden if illness in Canada, 1986. 1990;Ottawa, Ontario:

82. Dawber TR. The Framingham Study: The epidemiology of atherosclerotic disease. Cambridge, Mass.: Harvard University Press, 1980.

83. National Institutes of Health. Epidemiology and prevention of cardiovascular disease. 1994;National institutes of Health: US Department of Health and Human Services.

84. Barrett-Connor E. Sex differential in ischemic heart disease mortality in diabetics: a prospective population-based study. American Journal of Epidemiology 1983;118:489-496.

85. Anonymous. American Heart Association: The Committee on exercise and cardiac rehabilitation of the Council on Clinical Cardiology. Benefits and recommendations for physical activity programs for all Americans. Circulation 1983;86:340-344.

86. Stampfer MJ, Willett WC, et al. A prospective study of postmenopausal estrogen therapy and coronary heart disease. New England Journal of Medicine 1985;313:1044-1049.

87. Wilhelmsen L. Synergistic effects of risk factors. Clinical & Experimental Hypertension 1990;12:845-863.

88. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Left ventricular mass and incidence of coronary heart disease in an elderly cohort. The Framingham Heart Study. Annals of Internal Medicine 1989;110:101-107.

89. Leren P. The cardiovascular effects of alpha-receptor blocking agents. J Hypertens. 1992;10:S11-S15.

90. Freis ED, Arias LA, Armstrong ML, et al. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressures averaging 115 through 129 mmHg. Veterans Administration Cooperative Study Group. JAMA 1967;202:1028.

91. Anonymous. Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressures averaging 90 through 114 mmHg. Veterans Administration Cooperative Study Group. JAMA 1970;213:1143.

92. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA 1979;242:2562-2571.

93. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program. II. Mortality by race-sex and age. JAMA 1979;242:2572-2577.

94. Zukel WJ, Paul O, Schnaper HW. The multiple risk factor intervention trial (MRFIT). I. Historical perspective. Preventive Medicine 1981;10:387-401.

95. Cutler JA, Neaton JD, Hulley SB, Kuller L, Paul O, Stamler J. Coronary heart disease and all-causes mortality in the Multiple Risk Factor Intervention Trial: subgroup findings and comparisons with other trials. Preventive Medicine 1985;14:293-311.

96. Anonymous. The Australian therapeutic trial in mild hypertension. Report by the Management Committee. Lancet 1980;1:1261-1267.

97. Helgeland A. Treatment of mild hypertension: a five-year controlled drug trial. American Journal of Medicine 1980;69:725.

98. Berglund G, Wilhelmsen L, Sannersted R, et al. Coronary heart disease after treatment of hypertension. Lancet 1978;Suppl.i:1-5.

99. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program. III. Reduction in stroke incidence among persons with high blood pressure. JAMA 1982;247:633-638.

100. Anonymous. Prognostic factors in the treatment of mild hypertension. The Management Committee of the Australian National Blood Pressure Study. Circulation 1984;69:668-676.

101. Anonymous. Multiple risk factor intervention trial. Risk factor changes and mortality results. Multiple Risk Factor Intervention Trial Research Group. JAMA 1982;248:1465-1477.

102. Amery A, Birkenhager W, Brixko P, Bulpitt C, Clement D, Deruyttere M, et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet 1985;1:1349-1354.

103. Anonymous. Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: the International Prospective Primary Prevention Study in Hypertension (IPPPSH). The IPPPSH Collaborative Group. J Hypertens. 1985;3:379-392.

104. Johnston D, Steptoe A. MRC trial of treatment of mild hypertension. BMJ 1985;291:346-347.

105. Gifford RW, Jr. Review of the long-term controlled trials of usefulness of therapy for systemic hypertension. American Journal of Cardiology 1989;63:8B-16B.

106. Furberg CD, Cutler JA. Diuretic agents versus beta-blockers. Comparison of effects on mortality, stroke, and coronary events. Hypertension 1989;13:I57-I61.

107. Wilhelmsen L, Berglund G, Elmfeldt D, Fitzsimons T, Holzgreve H, Hosie J, et al. Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. J Hypertens. 1987;5:561-572.

108. Johannesson M, Wikstrand J, Jönsson B, Berglund G, Tuomilehto J. Cost-effectiveness of antihypertensive treatment: Metroprolol versus thiazide diuretics. PharmacoEconomics 1993;3:36-44.

109. Anonymous. Effects of treatment on morbidity in hypertension. Veterans Administrative Cooperative Study Group on antihypertensive agents. Circulation 1972;45:991-1004.

110. Freis ED. The Veterans Administration Cooperative Study on antihypertensive agents. Implications for stroke prevention. Stroke 1974;5:76-77.

111. Pearce KA, Furberg CD, Rushing J. Does antihypertensive treatment of the elderly prevent cardiovascular events or prolong life? A meta-analysis of hypertension treatment trials. Archives of Family Medicine 1995;4:943-949.

112. Lindholm LH. Antihypertensive treatment in the elderly. Clinical & Experimental Hypertension 1996;18:435-447.

113. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255-3264.

114. Dzau VJ. Angiotensin converting enzyme inhibitors and the cardiovascular system. J Hypertens. 1992;10:S3-S10.

115. Eichstadt H, Mertens D, Schroeder R, Tichter W, Kreuz D. Left ventricular hypertrophy - Regression in response to lisinopril therapy in patients with mild to medium-severe hypertension. Perfusion 1991;4:338-343.

116. Eselin JA, Carter BL. Hypertension and left ventricular hypertrophy: Is drug therapy beneficial? Pharmacotherapy 1994;14:60-88.

117. Gottdiener JS, Reda DJ, Massie BM, Materson BJ, Williams, DW, et al. Effect of single-drug therapy on reduction of left ventricular mass in mild to moderate hypertension: comparison of six antihypertensive agents. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Circulation 1997;95:2007-2014.

118. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program. Prevention and reversal of left ventricular hypertrophy with antihypertensive drug therapy. Hypertension 1985;7:105-112.

119. Psaty BM, Smith NL, Siscovick DS, Koepsell TD, Weiss NS, Heckbert SR, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. JAMA 1997;277:739-745.

120. Messerli FH, Grossman E, Goldbourt U. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. JAMA 1998;279:1903-1907.

121. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. BMJ 1992;304:405-412.

122. Sukkari SR, Sasich LD. Trials of CCBs. CMAJ 1998;158:21-23.

123. Wang JG, Liu G, Wang X, Zhang S, Sun M, Pan X, et al. Long-term blood pressure control in older Chinese patients with isolated systolic hypertension: a progress report on the Syst-China trial. Journal of Human Hypertension 1996;10:735-742.

124. Lisheng L. Effects of hypertension control on stroke incidence and fatality: report from Syst.-China and post-stroke antihypertensive treatment. Journal of Human Hypertension 1996;10 Suppl 1:S9-11.

125. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998;351:1755-1762.

126. Borhani NO, Mercuri M, Borhani PA, Buckalew VM, Canossa-Terris M, Carr AA, et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). A randomized controlled trial. JAMA 1996;276:785-791.

127. Hansson L, Hedner T, Lindholm L, Niklason A, Luomanmaki K, Niskanen L, et al. The Captopril Prevention Project (CAPPP) in hypertension--baseline data and current status. Blood Pressure 1997;6:365-367.

128. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999;353:611-616.

129. Neaton JD, Grimm RHJ, Prineas RJ, Stamler J, Grandits GA, Elmer PJ, et al. Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. JAMA 1993;270:713-724.

130. Kaplan NM, with a chapter by Lieberman E. Williams & Wilkins, editor. Clinical Hypertension. 1998;Seventh ed., Baltimore.

131. Anonymous. Early treatment of unstable angina in the coronary care unit: a randomised, double blind, placebo controlled comparison of recurrent ischemia in patients treated with nifedipine or metoprolol or both. Hollan Interuniversity Nifedipine / Metoprolol Trial (HINT). British Heart Journal 1986;56:400-413.

132. SPRINT I Study. A randomized intervention trial of nifedipine in patients with acute myocardial infarction. Secondary prevention reinfarction Israeli Nifedipine Trial. European Heart Journal 1988;9:354-364.

133. Multicenter Diltiazem PostInfarction Trial Research Group. The effect of Diltiazem on mortality and reinfarction after myocardial infarction. New England Journal of Medicine 1988;319:385-392.

134. Fisher Hansen J. Treatment with Verapamil after an acute myocardial infarction (Davit I and II). Danish Study Group on Verapamil in Myocardial Infarction. Drugs 1991;42(Suppl.2):42-53.

135. Yusuf S. Calcium antagonists in coronary artery disease and hypertension. Time for reevaluation? Circulation 1995;92:1079-1082.

136. Held PH, Yusuf S, Furberg CD. Calcium channel blockers in acute myocardial infarction and unstable angina: an overview. BMJ 1989;299:1187-1192.

137. Yusuf S, Held P, Furberg CD. Update of effects of calcium antagonists in myocardial infarction or angina in light of the second Danish Verapamil Infarction Trial (DAVIT-II) and other recent studies. American Journal of Cardiology 1991;67:1295-1297.

138. DAVIT-II Study. The effects of verapamil on mortality and major events after myocardial infarction. Danish Study group of Verapamil in Myocardial Infarction. American Journal of Cardiology 1990;66:779-785.

139. Anonymous. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Journal of Human Hypertension 1997;11:331-342.

140. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Progress in Cardiovascular Diseases 1985;27:335-371.

141. Anonymous. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. Circulation 1998;97:2202-2212.

142. Elkayam U, Amin J, Mehra A, Vasquez J, Weber L, Rahimtoola SH. A prospective, randomized, double blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with tha of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. Circulation 1990;82:1954-1961.

143. Lonn EM, Yusuf S, Jha P, Montague P, Teo KK, Benedict CR, et al. Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection. Circulation 1994;90:2056-2069.

144. Mancia G, Seravalle G, Vailati S, Grassi G. Benefit versus risk of calcium antagonists in hypertensive patients with concomitant risk factors. J Hypertens. 1996;14:S33-S38

145. Doughty RN, Rodgers A, Sharpe N, MacMahon S. Effects of beta-blocker therapy on mortality in patients with heart failure. A systematic overview of randomized controlled trials. European Heart Journal 1997;18:560-565.

146. Anonymous. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UK Prospective Diabetes Study group (UKPDS). BMJ 1998;317:713-720.

147. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL , Gifford N, Schrier, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. New England Journal of Medicine 1998;338:645-652.

148. Tatti P, Pahor M, Byington RP, Dimauro P, Guarisco R, Strollo G, et al. Outcome results of the fosinopril versus amlodipine cardiovascular events randomized trial (FACET) in patients with hypertension and NIDDM. Diabetes Care 1998;21:597-603.

149. Poulter NR. Calcium antagonists and the diabetic patient: a response to recent controversies. American Journal of Cardiology 1998;82:40R-41R.

150. Parving HH. Calcium antagonists and cardiovascular risk in diabetes. American Journal of Cardiology 1998;82:42R-44R.

151. Anonymous. Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blodd Pressure. JAMA 1977;237:255-261.

152. Anonymous. The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. 1988 Joint National Committee. Archives of Internal Medicine 1988;148:1023-1038.

153. Anonymous. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Archives of Internal Medicine 1997;157:2413-2446.

154. Myers MG, Carruthers SG, Leenen FH, Haynes RB. Recommendations from the Canadian Hypertension Society Consensus Conference on the Pharmacologic Treatment of Hypertension. CMAJ 1989;140:1141-1146.

155. Ogilvie RI, Burgess ED, Cusson JR, Feldman RD, Leiter, LA, et al. Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of essential hypertension. CMAJ 1993;149:575-584.

156. MacMahon SW, Wilcken DEL, MacDonald GJ. The effect of weight reduction on left ventricular mass: a randomised controlled trial in young, overweight hypertensive patients. New England Journal of Medicine 1986;314:334.

157. Maheswaran R, Gill JS, Davies P, et al. High blood pressure due to alcohol: a rapidly reversible effect. Hypertension 1991;17:87.

158. Nelson L, Jennings GL, Esler MD, et al. Effect of changing levels of physical activity on blood-pressure and haemodynamics in essential hypertension. Lancet 1986;2:473.

159. Blair SN, Goodyear NN, Gibbons LW, et al. Physical fitness and incidence of hypertension in healthy normotensive men and women. JAMA 1984;252:487.

160. Cappucio FP, MacGregor GA. Does potassium supplementation lower blood pressure? A meta-analysis of published trials. J Hypertens. 1991;9:465-465.

161. Cutler JA, Brittain E. Calcium and blood pressure: an epidemiologic perspective. American Journal of Hypertension 1990;3:1375.

162. Altura BT, Altura BM. Cardiovascular actions of magnesium: importance in etiology and treatement of high blood pressure. Magnesium Bulletin 1987;9:6.

163. Ascherio A, Rimm EB, Giovannucci EL, et al. A prospective study of nutritional factors and hypertension among US men. Circulation 1992;86:1475.

164. Taguchi J, Freis ED. Partial reduction of blood pressure and prevention of complications in hypertension. New England Journal of Medicine 1980;291:329.

165. Pardell H. Antihypertensive strategy: a current and prospective review. American Journal of Cardiology 1990;65:2H-5H.

166. Meredith PA. Implications of the links between hypertension and myocardial infarction for choice of drug therapy in patients with hypertension. American Heart Journal 1996;132:222-228.

167. Tobian L, Brunner HR, Cohn JN, Gavras H, Laragh JH, Materson BJ, et al. Modern strategies to prevent coronary sequelae and stroke in hypertensive patients differ from the JNC V consensus guidelines. American Journal of Hypertension 1994;7:859-872.

168. Kaplan NM, Gifford RW, Jr. Choice of initial therapy for hypertension. JAMA 1996;275:1577-1580.

169. Materson BJ, Preston RA. Newer principles of patient profiling for antihypertensive therapy. Circulation 1989;80:IV128-IV135.

170. Hollenberg NK. Evolution of the treatment of hypertension: what really matters in the 1990s?. American Journal of Medicine 1992;93:4S-10S.

171. Forette F, Bert P, Rigaud AS. Are calcium antagonists the best option in elderly hypertensives? J Hypertens. 1994;12:S19-S23.

172. Alderman MH. Which antihypertensive drugs first--and why!. JAMA 1992;267:2786-2787.

173. Reeves RA, Fodor JG, Gryfe CI, Patterson C, Spence JD. Report of the Canadian Hypertension Society Consensus Conference: 4. Hypertension in the elderly. CMAJ 1993;149:815-820.

174. Jackson R, Barham P, Bills J, Birch T, McLennan L, MacMahon S, et al. Management of raised blood pressure in New Zealand: a discussion document. BMJ 1993;307:107-110.

175. Sever P, Beevers G, Bulpitt C, Lever A, Ramsay L, Reid, et al. Management guidelines in essential hypertension: report of the second working party of the British Hypertension Society. BMJ 1993;306:983-987.

176. Anonymous. 1993 guidelines for the management of mild hypertension. Memorandum from a World Health Organization/International Society of Hypertension meeting. Guidelines Subcommittee of the WHO/ISH Mild Hypertension Liaison Committee. Hypertension 1993;22:392-403.

177. Alderman MH, Cushman WC, Hill MN, Krakoff LR, Pecker MS. International roundtable discussion of national guidelines for the detection, evaluation, and treatment of hypertension. American Journal of Hypertension 1993;6:974-981.

178. Zanchetti A. The calcium channel blocker controversy in perspective. Cardiology 1997;88:66-70.

179. Rosser WW. Application of evidence from randomised controlled trials to general practice. Lancet 1999;353:661-664.

180. Goldbourt U. Evaluating the association between drug use and outcome--should the information from observational studies affect therapeutic use? Cardiology 1997;88:63-67.

181. Psaty BM, Siscovick DS, Weiss NS, Koepsell TD, Rosendaal FR, Lin D, et al. Hypertension and outcomes research. From clinical trials to clinical epidemiology. American Journal of Hypertension 1996;9:178-183.

182. Gambassi G, Lapane K, Hume AL, Carbonin P, Bernabei R. Antihypertensive therapy in the elderly: Evidence-based guidelines and reality. Author's reply. Archives of Internal Medicine 1999;159:1622-1622.

183. Epstein RS, Sherwood LM. From outcomes research to disease management: a guide for the perplexed. Annals of Internal Medicine 1996;124:832-837.

184. Barraclough M, Bainton D, Joy MDeal. Control of moderately raised blood pressure: Report of a co-operative randomized controlled trial. BMJ 1973;3:434-436.

185. Smith WM. Treatment of mild hypertension: results of a ten-year intervention trial. US Public Health Service Hospitals Cooperative Study Group. Circulation Research 1977;40:98-105.

186. Perry HM, Goldman Al, Lavin MA, et al. Evaluation of drug treatment in mild hypertension: VA-NHLBI feasibility trial. Annals of New York Academy of Science 1978;304:267-288.

187. Hypertension Detection and Follow-up Program Cooperative Group. The effect of treatment on mortality in "mild" hypertension: results of the Hypertension Detection and Follow-up Program. New England Journal of Medicine 1982;307:976-980.

188. Hypertension Detection and Follow-up Program Cooperative Group. Persistence of reduction in blood pressure and mortality of participants in the Hypertension Detection and Follow-up Program. JAMA 1988;259:2113-2122.

189. Frishman WH. Multifactorial actions of beta-adrenergic blocking drugs in ischemic heart disease: current concepts. Circulation 1983;67:I11-I18.

190. Cressman MD, Gifford RW, Jr. Clinicians' interpretation of the results and implications of the Hypertension Detection and Follow-up Program. Progress in Cardiovascular Diseases 1986;29:89-97.

191. Daugherty S, Berman R, Entwisle G, Haerer A. Cerebrovascular events in the Hypertension Detection and Follow-up Program. Progress in Cardiovascular Diseases 1986;29:63-72.

192. Stamler J. Risk factor modification trials: implications for the elderly. European Heart Journal 1988;9:9-53.

193. Maxwell MH, Ford CE. Cardiovascular morbidity and mortality in HDFP patients 50-69 years old at entry. Journal of Cardiovascular Pharmacology 1985;7:S5-S9.

194. Anonymous. Treatment of mild hypertension in the elderly: a study initiated and administered by the National Heart Foundation of Australia. Medical Journal of Australia 1999;2:398-402.

195. Anonymous. Treatment of mild hypertension in the elderly. The management Committee. Medical Journal of Australia 1981;2:398-402.

196. Perry HMJ, Smith WM, McDonald RH, et al. Mortality and morbidity in the Systolic Hypertension in the Elderly Program (SHEP) pilot study. Stroke 1989;20:4-13.

197. Dahlof B, Lindholm LH, Hansson L, et al. Morbidity and mortality in the Swedish trial in old patients with hypertension STOP-Hypertension. Lancet 1991;338:1281-1285.

198. Ramsay LE, Hag IU, Yeo WW, Jackson PR. Interpretation of prospective trias in hypertension;Do treatment guidelines accurately reflect current evidence? J Hypertens. 1996;14:S187-S194.

199. Davis BR, Cutler JA, Gordon DJ, Furberg CD, Wright JT, Jr, et al. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT Research Group. American Journal of Hypertension 1996;9:342-360.

200. Hansson L. The benefits of lowering elevated blood pressure: A critical review of studies of cardiovascular morbidity and mortality in hypertension. J Hypertens. 1996;14:537-544.

201. Sever P, Mackay JA. The hypertension trials. J Hypertens. 1996;14:S29-S34.

202. Anonymous. The Captopril Prevention project: A prospective intervention trial of angiotensin converting enzyme inhibition in the treatment of hypertension. CAPP group. J Hypertens. 1990;8:985-990.

203. Black HR, Elliott WJ, Neaton JD, Grandits G, Grambsch P, Grimm RH, Jr., et al. Rationale and design for the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) Trial. Controlled Clinical Trials 1998;19:370-390.

204. Bulpitt C, Fletcher AE, Amery A. The hypertension in the very elderly trial (HYVET). Journal of Human Hypertension 1994;8:631-632.

205. Brown MJ, Castaigne A, Ruilope LM, Mancia G, Rosenthal T, de LP, et al. INSIGHT: international nifedipine GITS study intervention as a goal in hypertension treatment. Journal of Human Hypertension 1996;10 Suppl 3:S157-S160.

206. Brown MJ, Castaigne A, de LP, Mancia G, Rosenthal T, Ruilope LM. Study population and treatment titration in the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT). J Hypertens. 1998;16:2113-2116.

207. Anonymous. The Nordic Diltiazem Study (NORDIL). A prospective intervention trial of calcium antagonist therapy in hypertension. Blood Pressure 1993;2:312-321.

208. Malacco E, Gnemmi AE, Romagnoli A, et al. Systolic Hypertension in the Elderly: Long-term lacidipine treatment (SHELL). The SHELL Study group. Journal of Cardiovascular Pharmacology 1994;23:S62-S66

209. Slovick D, Staessen J, Bert P, Bulpitt C, de CP, Fagard R, et al. Nitrendipine in older patients with isolated systolic hypertension: second progress report on the SYST-EUR trial. Journal of Human Hypertension 1993;7:411-412.

210. Staessen J, Bert P, Bulpitt C, De Cort P., Fagard R, Fletcher A, et al. Nitrendipine in older patients with isolated systolic hypertension: second progress report on the SYST-EUR trial. Journal of Human Hypertension 1993;7:265-271.

211. Alderman MH, Cohen H, Roque R, Madhavan S. Effect of long-acting and short-acting calcium antagonists on cardiovascular outcomes in hypertensive patients. Lancet 1997;349:594-598.

212. Pahor M, Guralnik JM, Ferrucci L, Corti MC, Salive ME, Cerhan JR, et al. Calcium-channel blockade and incidence of cancer in aged populations. Lancet 1996;348:493-497.

213. Jick H, Jick S, Derby LE, Vasilakis C, Myers MW, Meier CR. Calcium-channel blockers and risk of cancer. Lancet 1997;349:525-528.

214. Fitzpatrick AL, Daling JR, Furberg CD, Kronmal RA, Weissfeld JL. Use of calcium channel blockers and breast carcinoma risk in postmenopausal women. Cancer 1997;80:1438-1447.

215. Pahor M, Guralnik JM, Furberg CD, Carbonin P, Havlik R. Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. Lancet 1996;347:1061-1065.

216. Garcia-Rodriguez LA, Cattaruzzi C, Troncon MG, Agostinis L. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. Archives of Internal Medicine 1998;158:33-39.

217. Wagenknecht LE, Furberg CD, Hammon JW, Legault C , Troost BT. Surgical bleeding: unexpected effect of a calcium antagonist. BMJ 1995;310:776-777.

218. Legault C, Furberg CD, Wagenknecht LE, Rogers AT , Stump, DA, et al. Nimodipine neuroprotection in cardiac valve replacement: report of an early terminated trial. Stroke 1996;27:593-598.

219. Lindberg G, Bingefors K, Ranstam J, Rastam L, Melander A. Use of calcium channel blockers and risk of suicide: ecological findings confirmed in population based cohort study. BMJ 1998;316:741-745.

220. Bulpitt CJ, Palmer AJ, Beevers DG, Coles EC, Ledingham, JG, et al. Calcium channel blockers and cardiac mortality in the treatment of hypertension: a report from the Department of Health Hypertension Care Computing Project (DHCCP). Journal of Human Hypertension 1997;11:205-211.

221. Horton R. Spinning the risks and benefits of calcium antagonists. Lancet 1995;346:586-587.

222. Elliott HL, Epstein M, Haller H, Mancia G. Safety of calcium antagonists. Lancet 1995;346:1421-1421.

223. Lichtlen PR. Risks and benefits of calcium antagonists. Lancet 1995;346:962-962.

224. Schubert T. Risks and benefits of calcium antagonists. Lancet 1995;346:961-961.

225. Cooper RS. Risks and benefits of calcium antagonists. Lancet 1995;346:961-961.

226. Opie LH. Risks and benefits of calcium antagonists. Lancet 1995;346:961-961.

227. Messerli FH. Are calcium antagonists safe? Lancet 1995;346:767-768.

228. Collins R, Peto R. Risks and benefits of calcium antagonists. Lancet 1995;346:962-962.

229. Poole-Wilson PA. Are calcium antagonists safe? Lancet 1995;346:769-770.

230. Brown MJ. Are calcium antagonists safe? Lancet 1995;346:768-769.

231. Macdonald G. Are calcium antagonists safe? Lancet 1995;346:768-768.

232. Horton R. Are calcium antagonists safe? Lancet 1995;346:770-770.

233. Lenfant C. The calcium channel blocker scare. Lessons for the future. Circulation 1995;91:2855-2856.

234. Aursnes I, Litleskare I, Froyland H, Abdelnoor M . Association between various drugs used for hypertension and risk of acute myocardial infarction. Blood Pressure 1995;4:157-163.

235. Jick H, Derby LE, Gurewich V, Vasilakis C. The risk of myocardial infarction associated with antihypertensive drug treatment in persons with uncomplicated essential hypertension. Pharmacotherapy 1996;16:321-326.

236. Jick H, Vasilakis C, Derby LE. Antihypertensive drugs and fatal myocardial infarction in persons with uncomplicated hypertension. Epidemiology 1997;8:446-448.

237. Braun S, Boyko V, Behar S, Reicher-Reiss H, Shotan A, Schlesinger Z, et al. Calcium antagonists and mortality in patients with coronary artery disease: a cohort study of 11,575 patients. Journal of the American College of Cardiology 1996;28:7-11.

238. Leader SG, Mallick R, Briggs NC. Myocardial infarction in newly diagnosed hypertensive Medicaid patients free of coronary heart disease and treated with calcium channel blockers. American Journal of Medicine 1997;102:150-157.

239. Michels KB, Rosner BA, Manson JE, Stampfer MJ, Walker AM, Willett WC, et al. Prospective study of calcium channel blocker use, cardiovascular disease, and total mortality among hypertensive women - the Nurses Health study. Circulation 1998;97:1540-1548.

240. Marwick C. FDA gives calcium channel blockers clean bill of health but warns of short-acting nifedipine hazards. JAMA 1996;275:423-424.

241. Anonymous. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Hypertension Research 1997;20:61-73.

242. Opie LH, Messerli FH. Nifedipine and mortality. Grave defects in the dossier. Circulation 1995;92:1068-1073.

243. Messerli FH. Case-control study, meta-analysis, and bouillabaisse: Putting the calcium antagonist scare into context. Annals of Internal Medicine 1996;123:888-889.

244. Kloner RA. Nifedipine in ischemic heart disease. Circulation 1995;92:1074-1078.

245. Kaplan N. Do calcium antagonists cause myocardial infarction? American Journal of Cardiology 1996;77:81-82.

246. Tijssen JG, Hugenholtz PG. Critical appraisal of recent studies on nifedipine and other calcium channel blockers in coronary artery disease and hypertension. European Heart Journal 1996;17:1152-1157.

247. Feeman WE, Jr. Myocardial infarction associated with antihypertensive drug therapy. JAMA 1996;275:515-517.

248. Cooper RS, Freeman V. Myocardial infarction associated with antihypertensive drug therapy. JAMA 1996;275:515-516.

249. Blandino DA. Myocardial infarction associated with antihypertensive drug therapy. JAMA 1996;275:516-516.

250. Stryer DB, Lurie P, Bero LA. Dear doctor ... regarding calcium channel blockers. JAMA 1996;275:517-519.

251. Kaplan NM. Dear doctor ... regarding calcium channel blockers. JAMA 1996;275:518-518.

252. MacCarthy EP. Dear doctor ... regarding calcium channel blockers. JAMA 1996;275:518-518.

253. Alderman MH. Hypertension and how to treat it: studies good and bad and a strategic suggestion. American Journal of Hypertension 1996;9:715-717.

254. Furberg CD, Pahor M, Psaty BM. The unnecessary controversy. European Heart Journal 1996;17:1142-1147.

255. Grossman E, Messerli FH. Calcium antagonists in cardiovascular disease: a necessary controversy but an unnecessary panic. American Journal of Medicine 1997;102:147-149.

256. Epstein M. Calcium channel blockers and hypertension: evolving perspective--1996. Cardiovascular Drugs & Therapy 1997;10 Suppl 3:883-891.

257. McMurray J, Murdoch D. Calcium-antagonist controversy: the long and short of it? Lancet 1997;349:585-586.

258. Messerli FH. "Cardioprotection"--not all calcium antagonists are created equal. American Journal of Cardiology 1990;66:855-856.

259. Braun S. Safety of calcium channel blockers: perspective on the controversy. Cardiology 1997;88:1-2.

260. Epstein M. The calcium antagonist controversy: the emerging importance of drug formulation as a determinant of risk. American Journal of Cardiology 1997;79:9-19.

261. Gambhir DS. The nifedipine scare in hypertension: Fact or fiction?. Indian Heart Journal 1996;48:227-229.

262. Psaty BM, Koepsell TD, LoGerfo JP, Wagner EH, Inui TS. Beta-blockers and primary prevention of coronary heart disease in patients with high blood pressure. JAMA 1989;261:2087-2094.

263. Psaty BM, Koepsell TD, Wagner EH, LoGerfo JP, Inui TS. The relative risk of incident coronary heart disease associated with recently stopping the use of beta-blockers. JAMA 1990;263:1653-1657.

264. Health Canada. National health expenditures in Canada. 1975-1996. 1997;Ottawa.

265. Anonymous. Sackett DL, Haynes RB, editors. Compliance with therapeutic regimens. 1976;Baltimore: Johns Hopkins University Press.

266. Feinstein AR. "Compliance bias" and the interpretation of therapeutic trials. In: Haynes RB, Taylor DW, Sackett DL, editors. Compliance in health care. Baltimore: Johns Hopkins University Press, 1979:309-322.

267. Psaty BM, Lee M, Savage PJ, Rutan GH, German PS, Lyles M. Assessing the use of medications in the elderly: methods and initial experience in the Cardiovascular Health Study. Journal of Clinical Epidemiology 1992;45:(6)683-692. Drug utilization.

268. Knapp DA, Michocki RJ, Richardson JP. An evaluation of antihypertensive prescribing practices. PharmacoEconomics 1994;5:408-418.

269. Rotmensch HH, Mendelevitch L, Silverberg DS, Liron M. Prescribing pattern of antihypertensive drugs in the community. Journal of Human Hypertension 1996;10 Suppl 3:S169-S172

270. Wallenius S, Peura S, Klaukka T, Enlund H. Who is using antihypertensive drugs? A prescription analysis from Finland. Scandinavian Journal of Primary Health Care 1996;14:54-61.

271. Mehta SS, Wilcox CS, Schulman KA. Treatment of hypertension in patients with comorbidities: Results from the study of hypertensive prescribing practices (SHyPP). American Journal of Hypertension 1999;12:333-340.

272. Klungel OH, de Boer A, Paes AH, Seidell JC, Bakker A. Sex differences in antihypertensive drug use: determinants of the choice of medication for hypertension. J Hypertens. 1998;16:1545-1553.

273. Nichol MB, Margolies JE, Gill MA. Factors associated with antihypertensive prescribing. Annals of Pharmacotherapy 1997;31:154-159.

274. Psaty BM, Koepsell TD, Yanez ND, Smith NL, Manolio TA, Heckbert SR, et al. Temporal patterns of antihypertensive medication use among older adults, 1989 through 1992. An effect of the major clinical trials on clinical practice? JAMA 1995;273:1436-1438.

275. Glynn RJ, Brock DB, Harris T, Havlik RJ, Chrischilles, EA, et al. Use of antihypertensive drugs and trends in blood pressure in the elderly. Archives of Internal Medicine 1995;155:1855-1860.

276. Hume AL, Barbour MM, Willey CJ, Assaf AR, Lapane KL, Carleton RA. Changing trends in antihypertensive therapy in two New England communities during the 1980s. Pharmacotherapy 1993;13:244-251.

277. Siegel D, Lopez J, Meier CR. Pharmacologic treatment of hypertension in the Department of Veterans Affairs during 1995 and 1996. American Journal of Hypertension 1900;11:1271-1278.

278. Gross TP, Wise RP, Knapp DE. Antihypertensive drug use. Trends in the United States from 1973 to 1985. Hypertension 1989;13:I113-I118.

279. Manolio TA, Cutler JA, Furberg CD, Psaty BM, Whelton PK, Applegate WB. Trends in pharmacologic management of hypertension in the United States. Archives of Internal Medicine 1995;155:829-837.

280. Hurley SF, Williams SL, McNeil JJ. Trends in prescribing of antihypertensive drugs in Australia, 1977-1987. Medical Journal of Australia 1900;152:259-260.

281. Ray WA, Schaffner W, Oates JA. Therapeutic choice in the treatment of hypertension. Initial treatment of newly diagnosed hypertension and secular trends in the prescribing of antihypertensive medications for Medicaid patients. American Journal of Medicine 1986;81:9-16.

282. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R, Avorn J. The effects of initial drug choice and comorbidity on antihypertensive therapy compliance: results from a population-based study in the elderly. American Journal of Hypertension 1997;10:697-704.

283. Monane M, Glynn RJ, Gurwitz JH, Bohn RL, Levin R, Avorn J. Trends in medication choices for hypertension in the elderly. The decline of the thiazides. Hypertension 1995;25:1045-1051.

284. Caro JJ. Stepped care for hypertension: are the assumptions valid?. Journal of Hypertension - Supplement 1997;15:S35-S39.

285. Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD. Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. CMAJ 1999;160:41-46.

286. Caro JJ, Speckman JL. Existing treatment strategies: does noncompliance make a difference?. Journal of Hypertension - Supplement 1998;16:S31-S34.

287. McCombs JS, Nichol MB, Newman CM, Sclar DA. The costs of interrupting antihypertensive drug therapy in a Medicaid population. Medical Care 1994;32:214-226.

288. Jones JK, Gorkin L, Lian JF, Staffa JA, Fletcher AP. Discontinuation of and changes in treatment after start of new courses of antihypertensive drugs: a study of a United Kingdom population. BMJ 1995;311:293-295.

289. Bailey JE, Lee MD, Somes GW, Graham RL. Risk factors for antihypertensive medication refill failure by patients under Medicare Managed Care. Clin.Ther. 1996;18:1252-1262.

290. Okano GJ, Rascati KL, Wilson JP, Remund DD, Grabenstein JD, Brixner DI. Patterns of antihypertensive use among patients in the US Department of Defense database initially prescribed an angiotensin-converting enzyme inhibitor or calcium channel blocker. Clin.Ther. 1997;19:1433-1445.

291. Christensen DB, Williams B, Goldberg HI, Martin DP, Engelberg R, LoGerfo, et al. Assessing compliance to antihypertensive medications using computer-based pharmacy records. Medical Care 1997;35:1164-1170.

292. Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. CMAJ 1999;160:31-37.

293. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R, Avorn J. Compliance with antihypertensive therapy among elderly Medicaid enrollees: the roles of age, gender, and race. American Journal of Public Health 1996;86:1805-1808.

294. Maronde RF, Chan LS, Larsen FJ, Strandberg LR, Laventurier MF, Sullivan, et al. Underutilization of antihypertensive drugs and associated hospitalization. Medical Care 1989;27:1159-1166.

295. Rizzo JA, Simons WR, Meier J. Variations in compliance among hypertensive patients by drug class: implications for health care costs. Clin.Ther. 1997;19:1446-1457.

296. Elliott WJ. Costs associated with changing antihypertensive drug monotherapy: 'preferred' vs 'alternative' therapy.[Abstract]. American Journal of Hypertension 1995;8:80A.

297. Taylor DW, Sackett DL, Haynes RB, Johnson AL, Gibson ES, Roberts RS. Compliance with antihypertensive drug therapy. Annals of the New York Academy of Sciences 1978;304:390-403.

298. Sackett DL. Hypertension V. Compliance with antihypertensive therapy. Canadian Journal of Public Health 1980;71:153-160.

299. Sackett DL. The hypertensive patient: 5. Compliance with therapy. Canadian Medical Association Journal 1979;121:259-261.

300. Sasane R, Brixner D, Goodwin W. Antihypertensive drug utilization review - A step approach. Journal of Managed Care Pharmacy 1997;3:299-300.

301. Hughes D, McGuire A. The direct costs to the NHS of discontinuing and switching prescriptions for hypertension. Journal of Human Hypertension 1998;12:533-537.

302. Penrose A, Dovey S, Tilyard M. Trends in antihypertensive prescribing. New Zealand Medical Journal 1996;109:4-7.

303. Bobal E, O'Connor DL, Keefe J. Trends in the treatment of hypertension within managed care organizations: anational survey of HMO pharmacy directors. Journal of Managed Care Pharmacy 1997;3:317-322.

304. Berlowitz DR, Ash AS, Hickey EC, Friedman RH, Glickman M, Kader B, et al. Inadequate management of blood pressure in a hypertensive population. New England Journal of Medicine 1998;339:1957-1963.

305. Wilson M, Patwell J, Shoheiber O, Brixner D, Kalmanowicz J, Eicher J. The clinical and economic implications of drug utilization patterns in the treatment of hypertension with ACE inhibitors and calcium channel blockers in a managed care setting. Journal of Management Care Pharmacy 1998;4:194-202.

306. Anonymous. Pricing authority notes changes in cardiovascular disease prescribing. Pharmaceutical Journal 1996;257:791-791.

307. Siegel D, Lopez J. Trends in antihypertensive drug use in the United States: Do the JNC V recommendations affect prescribing? Fifth Joint National Commission on the Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 1997;278:1745-1748.

308. Vuadens P, Bogousslavsky J. Diagnosis as a guide to stroke therapy. Lancet 1998;352 Suppl 3:SIII5-SIII9.

309. Stockwell DH, Madhavan S, Cohen H, Gibson G, Alderman MH. The determinants of hypertension awareness, treatment, and control in an insured population. American Journal of Public Health 1994;84:1768-1774.

310. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. Journal of Clinical Epidemiology 1997;50:105-116.

311. Steiner JF, Koepsell TD, Fihn SD, Inui TS. A general method of compliance assessment using centralized pharmacy records. Description and validation. Medical Care 1988;26:814-823.

312. Inui TS, Carter WB, Pecoraro RE, Pearlman RA, Dohan JJ. Variations in patient compliance with common long-term drugs. Medical Care 1980;18:986-993.

313. Hamilton RA, Briceland LL. Use of prescription refill records to assess patient compliance. American Journal of Public Health 1992;49:1691-1691.

314. Haynes RB, Gibson ES, Taylor DW, Bernholz CD, Sackett DL. Process versus outcome in hypertension: a positive result. Circulation 1982;65:28-33.

315. Sackett DL, Haynes RB, Gibson ES, Hackett BC, Taylor DW, Roberts RS, et al. Randomized clinical trials of strategies for improving medication compliance in primary hypertension. Lancet 1975;i:1205-107.

316. Rudd P. Partial compliance: implications for clinical practice. Journal of Cardiovascular Pharmacology 1993;22:S1-S5.

317. Black DM, Brand RJ, Greenlick M, Hughes G, Smith J. Compliance to treatment for hypertension in elderly patients: the SHEP pilot study. Systolic Hypertension in the Elderly Program. Journal of Gerontology 1987;42:552-557.

318. Croog SH, Levine S, Testa MA, Brown B, Bulpitt CJ, Jenkins CD, et al. The effects of antihypertensive therapy on the quality of life. New England Journal of Medicine 1986;314:1657-1664.

319. Shulman N, Cutter G, Daugherty R, Sexton M, Pauk G, Taylor MJ, et al. Correlates of attendance and compliance in the hypertension detection and follow-up program. Controlled Clinical Trials 1982;3:13-27.

320. Furberg CD, Berglund G, Manolio TA, Psaty BM. Overtreatment and undertreatment of hypertension. Journal of Internal Medicine 1994;235:387-397.

321. Eraker SA, Kirscht JP, Becker MH. Understanding and improving patient compliance. Annals of Internal Medicine 1984;100:258-268.

322. Clark LT. Improving compliance and increasing control of hypertension: needs of special hypertensive populations. American Heart Journal 1991;121:664-669.

323. Sackett DL, Snow JC. The magnitude of compliance and noncompliance. In: Haynes RB, Taylor DW, Sackett DL, editors. Compliance in health care. Baltimore: Johns Hopkins University Press, 1979:11-22.

324. Sackett DL. Hypertension VI. Follow-up of the treated hypertensive patient. Canadian Journal of Public Health 1980;71:225-230.

325. Enlund H. Measuring patient compliance in antihypertensive therapy--some methodological aspects. Journal of Clinical & Hospital Pharmacy 1982;7:43-51.

326. Horwitz RI, Horwitz SM. Adherence to treatment and health outcomes. Archives of Internal Medicine 1993;153:1863-1868.

327. Petitti DB. Coronary heart disease and estrogen replacement therapy. Can compliance bias explain the results of observational studies? Annals of Epidemiology 1994;4:115-118.

328. Farmer KC, Jacobs EW, Phillips CR. Long-term patient compliance with prescribed regimens of calcium channel blockers. Clin.Ther. 1994;16:316-326.

329. Goldberg Arnold RJ. The pros & cons of large databases to evaluate cost-effective therapy. Managed Healthcare 1997;38-39.

330. Simons WR, Rizzo JA, Stoddard M, Smith ME. The costs and effects of switching calcium channel blockers: Evidence from Medicaid claims data. Clin.Ther. 1995;17:154-173.

331. Lewis NJW, Patwell JT, Briesacher BA. The role of insurance claims databases in drug therapy outcomes research. PharmacoEconomics 1993;4:323-330.

332. Strom BL, Carson JL. Use of automated databases for pharmacoepidemiology research. Epidemiologic Review 1990;12:87-107.

333. Moses LE. Innovative methodologies for research using data bases. Statistics in Medicine 1991;10:629-633.

334. Byar DP. Problems with using observational databases to compare treatments. Statistics in Medicine 1991;10:663-666.

335. McDonald CJ, Hui SL. The analysis of humongous databases: problems and promises. Statistics in Medicine 1991;10:511-518.

336. Feinstein AR. Para-analysis, *faute de mieux*, and the perils of riding on a data barge. Journal of Clinical Epidemiology 1989;42:929-935.

337. Shapiro S. The role of automated record linkage in the postmarketing surveillance of drug safety: A critique. Clinical Pharmacology & Therapeutics 1989;46:371-386.

338. Petri H, Urquhart J. Channeling bias in the interpretation of drug effects. Statistics in Medicine 1991;10:577-581.

339. World Health Organization. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. 9th ed. Geneva: 1977.

340. Rawson NS, Malcolm E. Validity of the recording of ischaemic heart disease and chronic obstructive pulmonary disease in the Saskatchewan health care datafiles. Statistics in Medicine 1995;14:2627-2643.

341. Rawson NS, Malcolm E. Validity of the recording of cholecystectomy and hysterectomy in the Saskatchewan health care datafiles. 1995;Report #3, 1-17. Saskatchewan.

342. Rawson NS, Rawson. Reliability of the recording of hysterectomy in the Saskatchewan health care system. British Journal of Obstetrics & Gynaecology 1996;103:891-897.

343. Patten SB. Integrating administrative and research data in pharmacoepidemiological research . Canadian Journal of Clinical Pharmacology 1998;5:92-97.

344. West R. Saskatchewan health data bases: a developing resource. American Journal of Preventive Medicine 1987;6:25-27.

345. Strand LM, Downey W. Health databases in Saskatchewan. In: Strom BL, editor. Pharmacoepidemiology. 2nd edition ed. 1994:217-229.

346. Rawson N. Aspects of the validity of the Saskatchewan administrative health care utilization datafiles. Pharmacoepidemiology and drug safety 1994;3:S3.

347. Malcolm E., Downey W, Strand LM, McNutt M, West R. Saskatchewan Health's linkable data bases and pharmacoepidemiology. Post Marketing Surveillance 1993;6:175-264.

348. West SL, Strom BL. Validity of pharmacoepidemiology drug and diagnosis data. In: Strom BL, editor. Pharmacoepidemiology. 2nd edition ed. Philadelphia: 1994:549-580.

349. Rawson NSB, D'Arcy C, Blackburn JL, Wallace SM, Downey W, Senft D. Epidemiological research using linked computerized datafiles in Saskatchewan, Canada. 1992;Saskatoon: Psychiatric Pharmacoepidemiology Research Consortium. Report #2: 1 p. Technical reports series.

350. Lubin JH, Gail MH. Biased selection of controls for case-control analyses of cohort studies. Biometrics 1984;40:63-75.

351. Robins JM, Prentice RL, Blevins D. Designs for synthetic case-control studies in open cohorts. Biometrics 1989;45:1103-1116.

352. Suissa S. Novel approaches to pharmacoepidemiology study design and statistical analysis. In: Strom BL, editor. Pharmacoepidemiology. 2nd edition ed. 1994:629-645.

353. McCullagh P, Nelder JA. Generalized linear models. 1989;Second ed., 37, London.

354. McLaughlin PR. Reference based pricing for provincial drug benefit programs. Canadian Journal of Cardiology 1996;12:(1)25-26.

355. Woollard RF. Opportunity lost: A frontline view of reference-based pricing. Canadian Medical Association Journal 1996;154:(8)1185-1188.

356. Strom BL. Generic drug substitution revisited. New England Journal of Medicine 1987;316:1456-1462.

357. McGregor M. Coverage of drug costs: reference-based pricing. Canadian Journal of Cardiology 1998;14:666-668.

358. Rigter H. Recent public policies in the Netherlands to control pharmaceutical pricing and reimbursement. PharmacoEconomics 1994;6:(Suppl. 1)15-21.

359. Anonymous. A position paper on drug-pricing strategies for prescription pharmaceuticals in Canada. Canadian Cardiovascular Society. Canadian Journal of Cardiology 1997;13:33-45.

360. MacLeod SM. Improving physician prescribing practices: bridge over troubled waters. Canadian Medical Association Journal 1996;154:675-677.

361. Rubin RJ, Mendelson DN. A framework for cost-sharing policy analysis. PharmacoEconomics 1996;10:(Suppl. 2)56-67. Cost-containment.

362. Boulet AP, Tessier G. Reference-based pricing in British Columbia: implications for cardiologists- an analysis. Canadian Journal of Cardiology 1997;13:46-51.

363. Olley PM, McLaughlin PR. The Canadian Cardiovascular Society and reference-based drug pricing. Canadian Journal of Cardiology 1998;14:669-670.

364. Rush JE, Merrill DD. The safety and tolerability of lisinopril in clinical trials. Journal of Cardiovascular Pharmacology 1987;9:S99-S107.

365. Inman WH, Rawson NS, Wilton LV, Pearce GL, Speirs CJ. Postmarketing surveillance of enalapril. I: Results of prescription-event monitoring. BMJ 1988;297:826-829.

366. Herpin D, Conte D. Assessment of the antihypertensive effect of lisinopril using 24-hour ambulatory monitoring. Journal of Human Hypertension 1989;3 Suppl 1:11-15.

367. Rush JE, Lyle PA. Safety and tolerability of lisinopril in older hypertensive patients. American Journal of Medicine 1988;85:55-59.

368. Murray NH. Duration of angiotensin-converting enzyme inhibition: implications for tolerability. Cardiology 1991;79 Suppl 1:22-29.

369. Espinel CH, Williams JL, Coughlin SS. Enalapril and lisinopril in the treatment of mild to moderate essential hypertension. Clin.Ther. 1990;12:181-190.

370. Moyses C, Higgins TJ. Safety of long-term use of lisinopril for congestive heart failure. American Journal of Cardiology 1992;70:91C-97C.

371. Parish RC, Miller LJ. Adverse effects of angiotensin converting enzyme (ACE) inhibitors. An update. Drug Safety 1992;7:14-31.

372. Howes LG. Critical assessment of ACE inhibitors. Part 2 . Australian Family Physician 1995;24:639-3.

373. Jenkins AC, Dreslinski GR, Tadros SS, Groel JT, Fand R, Herczeg SA. Captopril in hypertension: seven years later. Journal of Cardiovascular Pharmacology 1985;7:S96-S101.

374. Waeber B, Gavras I, Brunner HR, Gavras H. Safety and efficacy of chronic therapy with captopril in hypertensive patients: an update. Journal of Clinical Pharmacology 1981;21:508-516.

375. Wiser T, Young L. Essential hypertension. In: Young L&K-KM, editor. Applied Therapeutics. Fourth ed. Vancouver: 1988:123-159.

376. McAreavey D, Robertson JI. Angiotensin converting enzyme inhibitors and moderate hypertension. Drugs 1990;40:326-345.

377. Gavras H, Gavras I. Angiotensin converting enzyme inhibitors. Properties and side effects. Hypertension 1988;11:II37-II41.

378. Gerbrandt KR, Yedinak KC. Formulary Management of ACE Inhibitors. PharmacoEconomics 1996;10:594-613.

379. Lancaster SG, Todd PA. Lisinopril. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and congestive heart failure. Drugs 1988;35:646-669.

380. Edwards CR, Padfield PL. Angiotensin-converting enzyme inhibitors: past, present, and bright future. Lancet 1985;1:30-34.

381. Riley LJJ, Vlasses PH, Ferguson RK. Clinical pharmacology and therapeutic applications of the new oral converting enzyme inhibitor, enalapril. American Heart Journal 1985;109:1085-1089.

382. Irvin JD, Viau JM. Safety profiles of the angiotensin converting enzyme inhibitors captopril and enalapril. American Journal of Medicine 1986;81:46-50.

383. Case DB. Angiotensin-converting enzyme inhibitors: are they all alike?. Journal of Clinical Hypertension 1987;3:243-256.

384. Gavras I, Gavras H. Captopril and enalapril. Annals of Internal Medicine 1983;98:556-557.

385. Rotmensch HH, Vlasses PH, Ferguson RK. Resolution of captopril-induced rash after substitution of enalapril. Pharmacotherapy 1983;3:131-133.

386. Conway J, Coats AJ, Bird R. Lisinopril and enalapril in hypertension: a comparative study using ambulatory monitoring. Journal of Human Hypertension 1990;4:235-239.

387. Gosse P, Dallocchio M, Gourgon R. ACE inhibitors in mild to moderate hypertension: comparison of lisinopril and captopril administered once daily. French Cooperative Study Group. Journal of Human Hypertension 1989;3:23-28.

388. Gourlay S, McNeil J, Forbes A, McGrath B. Differences in the acute and chronic antihypertensive effects of lisinopril and enalapril assessed by ambulatory blood pressure monitoring. Clinical & Experimental Hypertension 1993;15:71-89.

389. Plotquin Y, Barmat R, Bolanos R, Kirszner T, Saggese O, Bedrossian P, et al. Comparative study of the efficacy and duration of action of enalapril and lisinopril using 48 hour ambulatory blood pressure monitoring in patients with mild to moderate hypertension. Acta Therapeutica 1993;19:229-240.

390. Siche JP, de Gaudemarie R, De Lorraine A, Jalbert M, Mansour P, Madonna O, et al. Comparative trial of lisinopril and captopril (once daily) in mild to moderate essential hypertension: benefit of 24-hour ambulatory blood pressure monitoring. In: Keane WF, editor. A focus on the clinical effects of a long-acting ACE inhibitor / Hypertension. New York: Raven Press Ltd., 1990:31-39.

391. Whelton A, Miller WE, Dunne B, Jr., Hait HI, Tresznewsky ON. Once-daily lisinopril compared with twice-daily captopril in the treatment of mild to moderate hypertension: assessment of office and ambulatory blood pressures. Journal of Clinical Pharmacology 1990;30:1074-1080.

392. Whelton A, Dunne B, Jr., Glazer N, Kostis JB, Miller WE, Rector DJ, et al. Twenty-four hour blood pressure effect of once-daily lisinopril, enalapril, and placebo in patients with mild to moderate hypertension. Journal of Human Hypertension 1992;6:325-331.

393. Reeder CE, Lingle EW, Schulz RM, Mauch RP, Jr., Nightengale BS, Pedersen CA, et al. Economic impact of cost-containment strategies in third party programmes in the US (part I). PharmacoEconomics 1993;4:92-103.

394. Kozma CM, Schulz RM, Dickson M, Dye JT, Cox ER, Holdford DA, et al. Economic impact of cost-containment strategies in third party programmes in the US (Part II). PharmacoEconomics 1993;4:187-202.

395. Borden EK. Pharmacoepidemiology in Canada in the '90s - Where is the role in treatment decision - making? Canadian Journal of Clinical Pharmacology 1996;3:165-166.

396. Strom BL, Melmon KL. The use of pharmacoepidemiology to study beneficial drug effects. Pharmacoepidemiology 1994;449-467.

397. Briscoe TA, Dearing CJ. Clinical and economic effects of replacing enalapril with benazepril in hypertensive patients. American Journal of Health-System Pharmacy 1996;53:2191-2193.

398. Gill TH, Hauter F, Pelter MA. Conversions from captopril to lisinopril at a dosage ratio of 5:1 result in comparable control of hypertension. Annals of Pharmacotherapy 1996;30:7-11.

399. Hilleman DE, Mohiuddin SM, Wurdeman RL, Wadibia EC. Outcomes and cost savings of an ACE inhibitor therapeutic interchange. Journal of Management Care Pharmacy 1997;3:219-223.

400. Doyle AE. Cardiovascular morbidity and mortality in mild hypertension: the Australian Trial. Journal of Cardiovascular Pharmacology 1985;7:S10-S13.

401. Grimm RH, Jr., Cohen JD, Smith WM, Falvo-Gerard L, Neaton JD. Hypertension management in the Multiple Risk Factor Intervention Trial (MRFIT). Six-year intervention results for men in special intervention and usual care groups. Archives of Internal Medicine 1985;145:1191-1199.

402. Cohen JD, Grimm RH, Jr., Smith WM. Multiple risk factor intervention trial (MRFIT). VI. Intervention on blood pressure. Preventive Medicine 1981;10:501-518.

403. MacMahon S, Neal B, Rodgers A. Overview of trials completed or in progress: what's resolved and what's not?. American Journal of Hypertension 1996;9:189A-189A.

404. Kennedy HL, Rosenson RS. Physician use of beta-adrenergic blocking therapy: a changing perspective. Journal of the American College of Cardiology 1995;26:547-552.

405. Wang TJ, Ausiello JC, Stafford RS. Trends in antihypertensive drug advertising, 1985-1996. Circulation 1999;99:2055-2057.

406. MacMahon SW, Cutler JA, Neaton JD, Furberg CD, Cohen JD, Kuller LH, et al. Relationship of blood pressure to coronary and stroke morbidity and mortality in clinical trials and epidemiological studies. Journal of Hypertension - Supplement 1986;4:S14-7.

407. MacMahon SW, Cutler JA, Furberg CD, Payne GH. The effects of drug treatment for hypertension on morbidity and mortality from cardiovascular disease: a review of randomized controlled trials. Progress in Cardiovascular Diseases 1986;29:99-118.

408. Leader S, Mallick R. Potential biases in assessing the risks of pharmacotherapy due to mismeasurement of drug exposure. Clin.Ther. 1998;20:160-168.

409. Bourgault C, Rainville.B., Suissa S. Patterns of antihypertensive drug utilization among adult patients newly treated for hypertension. In preparation 1999.

410. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons, 1989.

411. Breslow NE, Day NE. Statistical methods in cancer research. The analysis of case-control studies. 1980;1, Lyon: World Health Organization. International Agency for Research on Cancer.

412. Cohn JN, Fowler MB, Bristow MR, Colucci WS, Gilbert EM, Kinhal V, et al. Safety and efficacy of carvedilol in severe heart failure. The U.S. Carvedilol Heart Failure Study Group. Journal of Cardiac Failure 1997;3:173-179.

413. Packer M, Colucci WS, Sackner-Bernstein JD, Liang CS, Goldscher DA, Freeman I, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. Circulation 1996;94:2793-2799.

414. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. New England Journal of Medicine 1996;334:1349-1355.

415. Anonymous. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9-13.

416. Packer M. Do beta-blockers prolong survival in chronic heart failure? A review of the experimental and clinical evidence. European Heart Journal 1998;19 Suppl B:B40-B46.

417. Avezum A, Tsuyuki RT, Pogue J, Yusuf S. Beta-blocker therapy for congestive heart failure: a systemic overview and critical appraisal of the published trials. Canadian Journal of Cardiology 1998;14:1045-1053.

418. Packer M. Effects of beta-adrenergic blockade on survival of patients with chronic heart failure. American Journal of Cardiology 1997;80:46L-54L.

419. Packer M. Beta-adrenergic blockade in chronic heart failure: principles, progress, and practice. Progress in Cardiovascular Diseases 1998;48:39-52.

420. Packer M. Beta-blockade in heart failure. Basic concepts and clinical results. American Journal of Hypertension 1998;11:23S-37S.

421. Walker AM, Stampfer MJ. Observational studies of drug safety. Lancet 1996;348:489-489.

422. Psaty BM, Heckbert SR, Koepsell TD, Weiss NS, Siscovick DS, Lemaitre RN, et al. Myocardial infarction associated with antihypertensive drug therapy. Author's reply. JAMA 1996;275:516-517.

423. Alderman MH. More news about calcium antagonists. American Journal of Hypertension 1996;9:710-712.

424. Furberg CD, Psaty BM. Should calcium antagonists be first-line agents in the treatment of cardiovascular disease? The public health perspective. Cardiovascular Drugs & Therapy 1996;10:463-466.

425. Lip GY, Beevers DG. Are calcium antagonists safe in hypertension?. Postgraduate Medical Journal 1996;72:193-194.

426. Materson BJ. Calcium channel blockers. Is it time to split the lump?. American Journal of Hypertension 1995;8:325-329.

427. Collet JP, Boivin JF, Spitzer WO. Bias and confounding in pharmacoepidemiology. In: Strom BL, editor. Pharmacoepidemiology. 2nd edition ed. 1994:609-627.

428. Bourgault C, Elstein E, Baltzan M, LeLorier J, Suissa S. Myocardial infarction in relation to antihypertensive agents: History of drug use as a modifier of risk. In preparation 1999.

429. Kleinbaum DG, Kupper LL, Morgenstern H. Van Norstrand Reinhold, editor. Epidemiological research. Principles and quantitative methods. 1982;New York:

430. Schlesselman JJ. Oxford University Press, editor. Case-control studies. Design, conduct, analysis. 1982;Oxford:

431. Kelsey JL, Thompson WD, Evans AS. Abraham M.Lilienfeld, editor. Methods in observational epidemiology. 1986;10, Oxford University Press.

432. Rothman KJ, Greenland S. Modern Epidemiology. 1998;2nd edition ed., Philadelphia: Lippincott - Raven publishers.

433. Costanza MC. Matching. Preventive Medicine 1995;24:425-433.

434. Miettinen OS. Estimation of relative risk for individually matched series. Biometrics 1970;26:75-86.

435. Walter SD. Matched case-control studies with a variable number of controls per case. Biometrika 1979;66:181-183.

436. Yola M, Lucien A. Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. Journal of Clinical Epidemiology 1994;47:731-737.

437. Feinstein AR. Clinical epidemiology. The architecture of clinical research. 1985;Philadelphia: W.B. Saunders Company.

438. Guibert RL, Wigle DT, Williams JI. Decline of acute myocardial infarction death rates not due to cause of death coding. Canadian Journal of Public Health 1989;80:418-422.

439. Hammar N, Nerbrand C, Ahlmark G, Tibblin G, Tsipogianni A, Johansson, et al. Identification of cases of myocardial infarction: hospital discharge data and mortality data compared to myocardial infarction community registers. International Journal of Epidemiology 1991;20:114-120.

440. Boyle CA, Dobson AJ. The accuracy of hospital records and death certificates for acute myocardial infarction. Australian & New Zealand Journal of Medicine 1995;25:316-323.

441. Dobson AJ, Gibberd RW, Leeder SR. Death certification and coding for ischemic heart disease in Australia. American Journal of Epidemiology 1983;117:397-405.

442. Lloyd-Jones DM, Martin DO, Larson MG, Levy D. Accuracy of death certificates for coding coronary heart disease as the cause of death. Annals of Internal Medicine 1998;129:1020-1026.

443. Siscovick DS, Raghunathan TE, Psaty BM, Koepsell TD, Wicklund KG, Lin, et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. New England Journal of Medicine 1994;330:1852-1857.

444. Psaty BM, Koepsell TD, Siscovick DS, et al. An approach to several problems in using large databases for population-based case-control studies of the therapeutic efficacy and safety of antihypertensive medicines. Statistics in Medicine 1991;10:653-662.

445. Gueyffier F, Bulpitt C, Boissel J-P, Schron E, Ekbom T, Fagard R et al. Antihypertensive drugs in very old people: a sub-group meta-analysis of randomised controlled trials. INDANA Group. Lancet 1999; 353:793-796.

446. Dargie HJ, Ford I, Fox KM. Effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. Total Ischaemic Burden European Trial (TIBET). European Heart Journal 1996; 17:104-112.

447. Rehnqvist N, Hjemdahl P, Billing E, Bjorkander I, Eriksson SV, Forslund L et al. Effects of metoprolol vs verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS). European Heart Journal 1996; 17(1):76-81.

APPENDICES

Appendix 1 – Main indications and contraindications to the major antihypertensive medications for hypertension with coexisting conditions.

Coexisting conditions	Recommended	Alternative	Not recommended
Angina	β-blockers	Non-dihydropyridine CCB β-blockers + dihydr. CCB	Dihydropyridine CCB
Recent MI	β-blockers	Non-dihydropyridine CCB	Dihydropyridine CCB
CHF	Diuretics ACE inhibitors	Vasodilator hydralazine	β-blockers CCB
Peripheral vascular disease	Vasodilators	β-blockers	
Dyslipidemia	α-blockers ACE inhibitors β-blockers with ISA CCB	Low dose thiazides	High dose thiazides β-blockers without ISA
Diabetes	Centrally acting agents	β-blockers Thiazides Centrally acting agents Vasodilators	High dose thiazides β-blockers without ISA
Asthma, COPD	Potassium sparing diuretics		β-blockers
Renal failure	ACE inhibitors α-blockers Centrally acting agents CCB Diuretics		β-blockers Thiazides

Abbreviations: CCB=Calcium antagonists; MI=myocardial infarction; COPD=Chronic obstructive pulmonary disease; ISA=Intrinsic sympathomimetic activity.
Extracted from 1993 Canadian guidelines[155].

Appendix 2 – Antihypertensive drugs used for inclusion in the cohort.

Drug class	Drug names
Ace inhibitors	Captopril
	Enalapril
	Lisinopril
	Fosinopril
	Quinapril
	Enalapril / HCTZ
	Lisinopril / HCTZ
	Benzapril
	Cilazapril
	Ramipril
Calcium antagonists	Nifedipine
	Diltiazem
	Verapamil
	Nicardipine
	Felodipine
	Amilodipine
	Nifedipine PA
	Diltiazem SR
	Verapamil SR
β-blockers	Acebutalol
	Atenolol
	Propanolol
	Pindolol
	Metoprolol
	Nadolol
	Labetolol
	Oxprenolol
	Timolol
	Propanolol SR
	Pindolol / HCTZ
	Timolol / HCTZ
	Propanolol / HCTZ
	Atenolol / chlorthalidone
	Metoprolol / HCTZ
	Metoprolol SR
	Oxprenolol SR

Abbreviations: HCTZ=Hydrochlorothiazide; PA=Prolonged action; SR=Sustained release.

Appendix 3 – Drug markers and ICD-9 codes used for exclusion criteria.

Exclusion criteria	Indicator
Cardiac hospitalization	ICD-9 codes for primary or secondary discharge diagnosis: -402-402.9 (hypertensive heart disease) -404-404.9 (hypertensive heart and renal disease) -410-414.9 (ischemic heart disease, including myocardial infarction and angina) -415-416.9 (acute and chronic pulmonary heart disease) -420-429.9 (pericarditis, endocarditis, other disease of the pericardium or of the endocardium, cardiomyopathy, conduction disorders, dyrhythmias heart failure and other complications of the heart) -745.4-746.9 (ventricular, septal or endocardial defects and others anomalies of the heart)
Congestive heart failure	Digoxin
Angina	Nitroglycerin, isosorbide dinitrate
Arrhythmia	Quinidine bisulfate, quinidine polygalacturonate, quinidine sulfate, procainamide, propafenone Hcl, sotalol
Hypertyroidism	Methimazole, propylthiouracil
Migraine	Dihydroergotamine, ergotamine, pizotyline, ergotamine combination products, flunarizine HCl
Cardiac or antihypertensive agents	Anti-coagulants, hemostatics, loop diuretics, thiazide diuretics, alpha-blockers, β-blockers, calcium antagonists, centrally-acting agents

Appendix 4 – ICD-9 for hospital discharge diagnosis used to identify non-fatal cases of myocardial infarction.

ICD-9 codes	Specific cardiac condition
410	Acute myocardial infarction
411	Other acute and subacute forms of ischemic heart disease
412	Old myocardial infarction
413	Angina pectoris
414	Other forms of chronic ischemic heart disease
414.0	Coronary atherosclerosis
414.1	Aneurysm of the heart
414.8	Other (chronic myocardial ischemia)
414.9	Ischemic heart disease not otherwise specified

Appendix 5 – Drugs markers used to measure comorbidity in the year preceding cohort entry.

Condition	Specific agents
Respiratory illness	Isoproterenol ß-adrenergic agents Xanthines products Respiratory products, including bronchodilators and mucolytics (but excluding cromolyn) Epinephrine
Asthma, rheumatism	Glucocorticoids
Diabetes	Insulin or oral hypoglycemic agents
Anti-ulcers	Cimetidines
Hyperlipidemia	Antilipemics
Neurotropic agents	Lithium, benzodiazepines, antidepressants, major tranquilisers
NSAIDs	Ibuprofen, diclofenac, naproxen, indomethacin, mefenamic acid, diflunisal, sulindac, tolmetin, flubiprofen, piroxicam, ketoprofen, tiaprofenic acid, ASA, fenoprofen, ASA/codeine