CARDIOVASCULAR RISK REDUCTION AND PHARMACY: ADVANCING PRACTICE IN PRIMARY CARE

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ABSTRACT

Cardiovascular disease is a leading cause of death and hospitalizations in Canada. Most risk factors for cardiovascular disease are known, and many are modifiable. One such risk factor that often goes unrecognized is non-adherence. Pharmacists are ideally positioned to have an influence on cardiovascular risk reduction, including supporting medication adherence; however it is still unknown whether typical (non-specialist) pharmacists can provide strategies that are effective and sustainable in today's health care system. Thus, the overall objective of this research project was to determine what interventions typical pharmacists can adopt to effectively facilitate cardiovascular risk reduction within the constraints of the current practice environment. This objective was accomplished through 4 related studies: 1) a randomized controlled trial involving a pharmacist-directed cardiovascular risk reduction collaboration within a family physician practice; 2) a systematic review identifying and evaluating published interventions by community pharmacists for cardiovascular disease or diabetes; 3) the design of a pilot study evaluating a novel community pharmacy intervention aimed at cardiovascular risk reduction and; 4) the examination of adherence patterns among antihypertensive medication users to identify associated factors and high-risk periods for non-adherence.

Although the randomized controlled trial did not show a statistically significant benefit of the pharmacist intervention on cardiovascular risk, it did demonstrate the feasibility of incorporating a pharmacist into a collaborative role, without the need for an advanced or specialized degree. Results from the systematic review yielded several studies involving community pharmacists and cardiovascular disease or diabetes. However, the majority of these studies were of poor quality, evaluated complex and intensive interventions, and provided questionable clinical benefits. The design of the pilot study demonstrated the feasibility of developing high quality, robust research involving community pharmacists. Finally, the observational study examining adherence patterns to antihypertensive agents revealed two important findings that can guide the development of future strategies to support adherence: the first year of therapy, and particularly the first dispensation, is a critical time for the development of non-adherence and, contrary to previously published studies, adherence is similar between all classes of antihypertensive medications.

This program of research did not identify one particular pharmacist intervention as being superior for cardiovascular risk reduction in today's practice environment. However, it did highlight the need for improved study quality and the development of interventions that are practical and can be realistically implemented by pharmacists in today's practice environment.

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INTRODUCTION

1.1 Rationale

Chronic diseases are the leading cause of death and disability in Canada.[1] It is estimated that 65% of Canadians have at least one risk factor for the development of a chronic disease, and that over 50% of the population is already living with one.[1] Besides directly affecting individual quality of life, chronic diseases monopolize health care spending. Seventy-seven billion dollars, almost half of the annual cost of illness in Canada, is spent yearly on chronic diseases.[1] Although numerous chronic diseases exist, only five account for 99% of all related deaths: cancer, respiratory illness, diabetes, mental disorders, and cardiovascular disease (CVD).[1]

Cardiovascular disease is an all-encompassing term which includes any disease affecting the heart or blood vessels.[2] Despite well known risk factors and evidence based strategies, it remains the leading cause of death and hospitalization throughout the developed world.[3-5] Also, it is the most expensive chronic disease in Canada, costing just under $20.6 billion in 1998.[6] Cardiovascular disease consumes acute health care services, increases the need for chronic care services including cardiac rehabilitation, outpatient physician visits, medication, and laboratory services, and is associated with indirect costs due to productivity losses and premature mortality.[6]

This humanistic and economic burden is troubling as many CVDs are largely preventable.[7] Widely recognized epidemiological research, started over 50 years ago with the Framingham Study, has identified modifiable predisposing factors to both ischemic heart disease and stroke, which are collectively known as atherosclerotic cardiovascular disease (A-CVD).[8] Risk factors for A-CVD are also important for other cardiovascular diseases; thus risk factor modification has the potential to protect against multiple adverse outcomes.

In clinical practice, it is recommended that all men over 40 years of age and women who are over 50 years of age or post-menopausal should be routinely screened for A-CVD.[9] Canadian guidelines also recommend screening those with: diabetes mellitus; risk factors such as

hypertension, smoking, or abdominal obesity; hyperlipidemia; evidence of atherosclerosis; or a strong family history of premature A-CVD.[9] Despite a wealth of information about risk factors, screening recommendations and effective treatment strategies,[9-11] there is overwhelming evidence that modifications of cardiovascular risk factors, whether behavioural or pharmacological, are not successfully undertaken in the majority of patients at risk.[4, 12-23]

1.2 Non-Adherence to Cardiovascular Medications

Another risk factor for A-CVD that often goes unrecognized is non-adherence.[24] Adherence is defined as the extent to which a person's behaviour, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.[25] The reasons for non-adherence are complex, and it is a major health issue that has been observed worldwide.[25] It is estimated that 50% of patients are non-adherent to chronic medications,[26] and only 10% are adherent to lifestyle or behavioural modifications over the long term.[26] Non-adherence is frequently identified by physicians as a significant barrier to employing guideline-directed preventative care,[27] and has been implicated as a major reason for suboptimal outcomes,[21, 25, 28] decreased patient quality of life, death, and wasted health care resources.[25, 29-31] In Canada, non-adherence costs approximately $8 - 10 billion every year.[32]

Management of A-CVD requires multiple, costly, life-long medications which pose both an inconvenience and financial burden to many patients.[33] Also, patient confidence in prescribers as well as beliefs about the effectiveness, safety or necessity of prescriptions or treatments can affect adherence.[34, 35] Multiple media sources convey negative messages about prescription medications and health care providers appear to have little opportunity to counter them. Not surprisingly, approximately 50% of individuals do not adhere to their cardiovascular medications.[26, 36] Much of this non-adherence occurs within the first two years of therapy,[36-39] and has been specifically associated with increases in morbidity, mortality, cardiovascular-related hospitalizations and coronary revascularization procedures.[21, 31, 40]

1.3 Role of Pharmacy in Cardiovascular Disease Risk Reduction

Because the management of A-CVD is a complex process,[41] multidisciplinary approaches have been recommended to improve the success of risk factor modification.[42] Several organizations

have suggested that pharmacists, especially those in primary care or community settings, should play a more active role in the management of A-CVD[43-46] because of their accessibility,[47] frequent contact with patients, and strong knowledge of pharmacotherapy. Indeed, many studies have examined pharmacist interventions aimed at improving A-CVD management;[18, 47-51] however, few of these research protocols have ever been implemented in real-world settings.[52]

The majority of published pharmacist interventions require close collaborations with physicians and/or frequent and intensive patient follow-up.[18, 51, 53, 54] Unfortunately, the practice environment for most pharmacists in Canada is not conducive to either. Although there has been a recent increase in the number of pharmacists working directly within medical practices, they are typically specialized or hold post-graduate degrees, whereas the majority of baccalaureate trained pharmacists still work in retail or community pharmacy settings.

In community pharmacy settings, remuneration is primarily based on dispensing prescriptions; thus any activities related to non-dispensing activities, however worthwhile, are often not given priority. The current pharmacist shortage is also a factor, as many pharmacists simply do not have the time necessary for program training, or implementation of intensive program protocols. As such, collaborations with physicians are generally limited to brief communications regarding technical issues related to prescription writing, and interactions with patients rarely go beyond basic counselling at prescription dispensations. Similarly, the extent to which pharmacists engage patients for the purpose of supporting adherence is unknown, although, anecdotally, rates appear to be extremely low.

1.4 Summary

Pharmacists in primary care or community pharmacy settings are ideally positioned to have a major influence on cardiovascular risk reduction, including supporting medication adherence. However, it is still unknown whether pharmacists can provide cardiovascular risk-reduction strategies that are effective and sustainable in today's health care system. Given its high prevalence and significant clinical and economic impact, routinely preventing even a fraction of A-CVD, and related non-adherence, may have a major impact. Therefore, further research is needed to identify practical ways that pharmacists can successfully employ cardiovascular risk

reduction strategies that are feasible and sustainable in the current health care system and practice environment.

1.5 Research Question

What strategic interventions can typical (non-specialist) pharmacists in primary care settings adopt to effectively facilitate cardiovascular risk reduction within the constraints of the current health care system and practice environment?

1.6 Research Objectives

The objectives of this program of research were: 1) to evaluate a randomized controlled trial involving a pharmacist-directed cardiovascular risk reduction collaboration within a family physician practice; 2) to systematically review the literature to identify and evaluate published interventions by community pharmacists for the purpose of diabetes or cardiovascular disease risk reduction and/or management; 3) to design a cluster randomized controlled pilot study to objectively evaluate a community pharmacy cardiovascular risk reduction intervention and; 4) to use Saskatchewan Health data to examine adherence patterns among antihypertensive medication users, and to verify and/or identify high-risk periods for non-adherence.

1.7 Program of Research

This thesis is composed of four separate but related studies, each addressing a specific research objective, in an attempt to answer the original research question: *what strategic interventions can typical pharmacists in primary care settings adopt to effectively facilitate cardiovascular risk reduction within the constraints of the current health care system and practice environment?* The first study (Chapter 2) looks at the role of pharmacy in a primary care setting through a randomized controlled trial evaluating a pharmacist-directed cardiovascular risk reduction collaboration within a family physician practice. Chapter 3 looks specifically at community pharmacists, by systematically reviewing published interventions involving community pharmacists aimed at the risk reduction or management of cardiovascular disease or diabetes. Subsequent to the findings of the systematic review, Chapter 4 is the methodology and study design of a pragmatic, province-wide cluster randomized trail to objectively evaluate a community pharmacy intervention aimed at improving adherence to a particular class of

cardiovascular medication (statins). Finally, although a fair amount is known about adherence and utilization patterns of statin medications, little it known about other cardiovascular drugs. Chapter 5 is an observational study of administrative data from Saskatchewan that examines utilization patterns of antihypertensive medications to identify associated factors and high-risk periods for non-adherence.

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- Chapter 2 -

COLLABORATIVE CARDIOVASCULAR RISK-REDUCTION IN PRIMARY CARE: RESULTS OF THE CCARP STUDY

2.1 Abstract

Background: Studies have demonstrated cardiovascular risk reduction success when pharmacists work in collaborative settings. However, these protocols are often complex and may not be easily performed by non-specialized pharmacists.

Objective: To evaluate whether a simple pharmacist protocol can significantly reduce cardiovascular risk in a large family medicine practice in Saskatoon, Saskatchewan, Canada.

Methods: Eligible patients initially met with the pharmacist to receive general counselling about cardiovascular disease. Patients exhibiting a 10-year Framingham risk score ≥15%, or a coronary artery disease equivalent (coronary artery disease, peripheral artery disease, cerebrovascular disease, or diabetes mellitus), were randomized to receive ongoing follow-up (follow-up group) by the pharmacist, or to return to usual care (single contact group), and were followed for a minimum of 6 months. The primary endpoint was the mean reduction in the 10-year risk score. Secondary endpoints included individual modifiable risk factors (systolic and diastolic blood pressure, total cholesterol, LDL-cholesterol, HDL-cholesterol, total cholesterol:HDL-cholesterol, and A1c), statin utilization, initiation and adherence rates.

Results: Baseline characteristics were similar across both groups (n=176). Neither the mean reduction in 10-year risk (-2.68 and -1.25, respectively, one-tailed P=0.098) nor individual risk factors were significantly different between the follow-up and single contact groups. The proportion of patients exhibiting adherence ≥ 80% did not differ at the study end (73.1% [57/78] and 80.0% [52/65] respectively, P=0.333). However, 85.2% (75/88) in the follow-up group remained on statin therapy at the end of the study, compared to 67.0% (59/88) in the single

contact group (P=0.005). Statin initiations in the follow-up group compared to the single contact group were 75.0% [30/40] and 48.9% [22/45], respectively, (P=0.013).

Conclusion: This simple cardiovascular care protocol for non-specialist pharmacists did not result in a clear improvement to cardiovascular risk reduction success among patients in a primary care medical clinic. The intervention did, however, appear to improve statin utilization.

2.2 Introduction

Despite well known risk factors and effective treatment strategies, cardiovascular disease (CVD) remains the leading cause of death in Canada and throughout the developed world.[1, 2] Although multidisciplinary and collaborative protocols involving pharmacists have proven to enhance cardiovascular risk reduction success,[3-5] the complexity and resources required for these strategies likely limits their uptake and sustainability in real-world settings.[6] For example, Carter et al. demonstrated that clinical pharmacists could facilitate blood pressure reduction among patients in primary care clinics; however, the pharmacists and physicians were primarily academic faculty members, focused solely on blood pressure reduction, and managed only a small group of patients (n=77).[7] Likely, the clinical protocol followed in this study would not be easily reproduced by a typical pharmacist without advanced clinical training.

Although protocols such as these provide evidence for the benefits of high-level clinical collaborations, they may be too complex to serve as a general guide for all pharmacists, especially those without previous experience or advanced training. For example, the majority of Canadian pharmacists practice in retail settings with little formal collaborative opportunities. Therefore, we developed a simple strategy for cardiovascular risk reduction that was designed for non-specialist pharmacists who have an opportunity to establish a new practice in primary care settings. The goal of the strategy was to allow a pharmacist to contribute to a collaborative environment quickly without the need for advanced training. We hypothesized that a 'typical' pharmacist could improve the success of cardiovascular risk reduction in most primary care settings by focusing on three specific tasks: screening and risk stratification; identification and reminders about uncontrolled risk factors; and adherence support. The purpose of this pilot study was to evaluate the success of incorporating this strategy into a typical fee-for-service physician practice.

2.3 Methods

Study Setting

This study was a prospective, randomized controlled pilot study that evaluated a pharmacist-led cardiovascular risk reduction strategy among patients attending a single large family medicine practice in Saskatoon, Saskatchewan, Canada. At the time of the study (August 2006 to

December 2007), the family medicine practice was comprised of 12 general practitioners providing care to over 30,000 patients. This practice had not previously employed a clinical pharmacist, and had no previous experience working with a pharmacist in this capacity. Because of budget limitations, all study activities were provided by a single pharmacist who was also the lead investigator (CE). Because this pharmacist was responsible for the development of the study, her training was more extensive than what would be needed to deliver this intervention. However, the intervention was designed so that subsequent pharmacist training would only require a review of cardiovascular risk factors, Framingham risk tools, and risk reduction therapies discussed in Canadian practice guidelines.[8-11] In addition, the investigator was very careful to provide only those activities outlined by the protocol in order to test our hypothesis. Because our collaborative strategy required only basic activities to be performed, we believe the required training could be completed by pharmacists relatively quickly.

Procedures

Prior to its implementation, physicians were given a brief presentation about the proposed study and approved the protocol. Patient recruitment was achieved through physician referral and advertisements placed in patient waiting areas. Physicians were asked to refer all patients who exhibited any cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus, or a previous cardiovascular event) to the study pharmacist. Patients were provided with a written description of the study, including the consent form, and were contacted by the study pharmacist within one week to determine interest in enrollment.

The pharmacist met with all study patients for an initial interview consisting of general counselling about cardiovascular disease. This meeting lasted approximately 1 hour, at which time the pharmacist recorded drug therapies and determined the individual 10-year risk for cardiac death or non-fatal myocardial infarction based on the Framingham Risk Score (FRS) recommended by the Canadian Cardiovascular Society.[8] All data collection was based on medical record review and patient interview; the pharmacist did not personally perform any physical assessment activities such as blood pressure measurement. Basic CVD risk information was provided to all consenting individuals before randomization occurred. All patients received an illustrated booklet that had been previously co-developed by one of the authors (CE). The

booklet contained general information on the cardiovascular disease process, risk factors and emphasized the importance of achieving recommended targets for blood pressure, cholesterol, and A1c. It also contained information about pharmacological management, as outlined by current practice guidelines (Appendix A).[8-11]

Patients were randomly assigned to receive either follow-up with the pharmacist (follow-up group) or usual care (single contact group) if they met one of the following inclusion criteria: a calculated FRS of at least 15%, or a coronary artery disease risk equivalent (coronary artery disease, peripheral artery disease, cerebrovascular disease, or diabetes mellitus).[8] Patients assigned to the single contact (usual care) group received no further contact with the study pharmacist. Once randomization occurred, the pharmacist documented the treatment group assignment and the individual FRS in the medical record. Randomization codes were kept in individually sealed envelopes and opened by the study pharmacist at the end of the initial visit. However, no attempt was made to blind any participant in the study. Randomization lists were stratified by each physician and were created using a table of random numbers in permuted blocks of 4. Patients were excluded if they had severe psychiatric conditions or dementia, symptomatic heart failure (NYHA class III or IV), terminal illness, concurrent participation in an investigational study, or women who were pregnant or breastfeeding.

Study Activities

For patients assigned to the follow-up group, the pharmacist established the following goals: blood pressure less than 130/80 mmHg for individuals with diabetes or chronic kidney disease, and less than 140/90 mmHg for all others;[10] low density lipoprotein cholesterol (LDL) level less than 2.0 mmol/L if FRS was 20% or greater or if a coronary risk equivalent was present, or less than 3.5 mmol/L for all others[8]; a total cholesterol:high density lipoprotein (HDL) cholesterol ratio of less than 4.0 if FRS was 20% or greater or if a coronary risk equivalent was present, and less than 5.0 for all others;[8] and an A1c of 7.0% or less for patients with diabetes.[9] These goals were documented in the medical records of patients in the follow-up group only. When any of these risk factors were uncontrolled, the pharmacist alerted the patient through phone and/or mail, while the physician was notified through the patient chart and in-person when possible. Also, the pharmacist documented the change required to reach the clinical target in the patient's

medical record. No specific recommendations regarding pharmacotherapy were given unless requested.

Patients in the follow-up group received continuous follow-up by the pharmacist at a minimum of every 8 weeks by telephone, mail, electronic mail, or face-to-face appointments. These regular contacts were intended to provide ample opportunities for subjects to ask questions, discuss laboratory results, or convey messages to the clinic staff. Mailed letters were reserved for patients who were successfully controlled or had been recently contacted. Information delivered during follow-ups was patient specific and did not require that a standard content be covered. Although potential reasons for subject follow-up were suggested (Table 2.1), specific study algorithms or protocols were not used. Emphasis was placed on conducting short follow-up contacts that reminded and reinforced the importance of adherence and clinical targets. All subjects were followed for a minimum of 6 months.

Post-Hoc Analysis

In an effort to evaluate the extent to which study patients compared to actual usual care (i.e. patientss with no study involvement), a post-hoc analysis was conducted. Briefly, the medical clinic maintains a roster of patients with a diagnosis of coronary artery disease. From this list, 156 patients who had at least one visit with their physician during the study period and had recorded clinical values (e.g. systolic and diastolic blood pressure, total cholesterol, LDL-cholesterol, HDL-cholesterol, total cholesterol:HDL-cholesterol ratio, and A1c,) were randomly selected by the study pharmacist using a computer-generated list of random numbers between 1 and 1000. The study pharmacist then collected and analyzed baseline and follow-up data for the same time period as the original two study groups. Ethics approval for this post-hoc analysis was obtained from the University of Saskatchewan Biomedical Ethics Board.

Outcome Measures

The primary endpoint was the mean reduction in global cardiovascular risk status as measured by the Framingham risk score.[8] Secondary endpoints included individual modifiable CVD risk factors (systolic and diastolic blood pressure, total cholesterol, LDL-cholesterol, HDL-

cholesterol, total cholesterol:HDL ratio, triglycerides, and A1c in those with diabetes) statin utilization, initiation, and adherence rates.

Statin drugs were chosen as a proxy for overall drug utilization and adherence because they are generally indicated in most high-risk patients.[8] Also, their use can be more easily tracked in an aggregate analysis than antihypertensive medications, which can often be appropriately switched or combined depending upon individual circumstances. For our analyses, statin utilization and adherence were based on prescription dispensations (fills) as recorded by the Saskatchewan Pharmaceutical Information Program database. To be classified as using a statin at the end of the study period, a patient must have filled at least one statin prescription during the study period, and have filled at least one statin prescription within 3 months after the completion of the study (between January 1, 2008 – March 31, 2008). Overall statin utilization was defined as the number of patients who filled at least one prescription during the observation period. Patient adherence to statin therapy was evaluated using the previously validated proportion of days covered (PDC)[12, 13] – that is, the sum of the days' supply for all statin prescription fills during the study period, divided by the number of days between the index date (first statin fill within the study period) and the end of the study period (December 31, 2007). Only those patients who filled their first statin prescription at least three months before the end of the study period were included in the adherence analysis.

Statistical Analysis

Baseline characteristics and study results were compared using chi-square, independent t-tests, and analysis of variance (ANOVA), as appropriate. Before-after mean reductions in FRS were evaluated using paired t-tests. All analyses were conducted using intention-to-treat. For patients lost to follow-up, the group mean was inputted for the missing data to facilitate the intention to treat analysis. For patients who had missing laboratory data at the end of the study period (e.g. laboratory tests not ordered or completed), the last reported results were used, provided that the tests occurred at least six months after randomization. As a sensitivity analysis, we also used a last-observation-carried-forward approach by using baseline values. For analyses that included the post-hoc control group, mean reductions in FRS were performed using analysis of covariance (ANCOVA); logistic regression was used for the proportion of patients exhibiting adherence

≥80%, and statin utilization. All analyses involving the post-hoc control group were adjusted for age, sex, smoking status, and length of time in study.

We estimated that 77 patients would be required in each arm of the study in order to detect a difference of 2 points in the mean FRS between groups, assuming a one-tailed alpha of 0.05 and a beta of 0.80. This effect size [2 (SD 5) point difference] was based on an unpublished clinical intervention previously conducted by the primary investigator (CE), and is comparable to the 35% expected reduction estimate used in the Steno-2 study.[14] A one-tailed alpha was chosen because our intent with this pilot study was to maximize the sensitivity to detect a positive benefit of our intervention with a reasonable sample size.[15] Analyses were carried out using SPSS version 16.0 for Windows (SPSS Inc, Chicago, Ill).

2.4 Results

A total of 252 patients were screened with 176 subsequently randomized to single contact or pharmacist follow-up (Figure 2.1). Mean age of study patients was 60 years and 81% were male. Twenty-one percent of patients had a history of myocardial infarction, 68% had diabetes mellitus. Mean blood pressure was 137/81mmHg and mean LDL-cholesterol was 2.84mmol/L. Overall, the mean duration of follow-up was 380 days (median 392 days) (Table 2.2).

All study patients from both groups (follow-up and single contact) met face-to-face with the pharmacist for the initial screening interview and education session. This session lasted approximately 1 hour in most cases. Subsequently, of 88 patients assigned to follow-up care, 77 (87.5%) received some level of additional individualized support through telephone follow-up (primary method), face-to-face visits, email, personalized letters, or a combination of several methods; face-to-face follow-up visits were arranged for only 13 (14.8%) of these 88 patients. The remaining 11 patients (12.5%) received no individualized attention beyond their initial education and screening encounter; they received only mailed "form" letters every 2 months. In four of these patients, all risk factors were controlled (blood pressure, LDL level, total cholesterol:HDL ratio, and A1c value [if applicable]), and no subjective concerns were communicated to the pharmacist. In the other seven patients, at least one uncontrolled risk factor

was identified; however, four of these patients did not respond to repeated attempts to contact them, and three were missed in the follow-up period for reasons unknown.

The primary outcome of mean reduction in FRS was not significantly different between the follow-up and single contact groups (-2.68 and -1.25, respectively, one-tailed P=0.098) (Table 2.3). Similarly, none of the individual secondary endpoints (systolic and diastolic blood pressure, total cholesterol, LDL-cholesterol, HDL-cholesterol, total cholesterol/HDL-cholesterol ratio, A1c) were influenced by the pharmacist intervention at the end of the follow up period (Table 2.3). Moreover, for patients utilizing statin therapy, mean statin adherence over the study period was extremely high in both groups: 90.4% (95% CI 83.9% -97.0%) in the follow-up group, and 91.8% (95% CI 85.3% - 98.2%) in the single contact group (P=0.781). The proportion of patients exhibiting adherence ≥80% was 73.1% [57/78] versus 80.0% [52/65] respectively, P=0.333) (Table 2.4).

Before-after comparisons of the FRS within the individual study groups showed a significant reduction in the follow-up group (-2.68, P<0.001) but not in the single contact group (-1.25, P=0.134). More patients in the follow-up group remained on statin therapy at the end of the study period compared to the single contact group (75/88 [85.2%] versus 59/88 [67.0%], respectively, P=0.005). Also, statins appeared to be initiated more frequently in the follow-up group compared to the single contact group (75.0% [30/40] and 48.9% [22/45], respectively, P=0.013) (Table 2.4).

In the post-hoc analysis, the control group (no study involvement) was slightly older, had a lower baseline FRS, and a lower proportion of smokers and males (Table 2.2). Clinical endpoints among these non-study subjects were comparable to subjects in the 2 study groups (FRS, systolic and diastolic blood pressure, total cholesterol, LDL-cholesterol, HDL-cholesterol, total cholesterol:HDL-cholesterol ratio, A1c, and adherence) (Table 2.3 and Table 2.4). Although the change in FRS was numerically higher in the follow up group (-2.68) compared to the single contact group (-1.25) and the post-hoc control group (-0.69) during the same time period, adjustment for prominent baseline differences (age, sex, baseline FRS, smoking status, and length of time in the study) eliminated the statistical significance upon comparing all three

groups (p=0.403, data not shown). However, the proportion of patients filling at least one statin prescription after the study observation period was significantly higher in the follow-up group (75/88 [85.2%]) compared to the natural control group (98/156 [62.8%]). This difference persisted after adjusting for age, sex, baseline FRS, smoking status, and length of time in the study (OR 3.31, 95% CI 1.55 – 7.07, P=0.002, data not shown). Also, new statin initiations were significantly more frequent among patients enrolled in the clinical study (follow-up group 30/40 [75.0%], OR 7.28, 95% CI 2.54 – 20.93, P<0.001, and single contact group 22/45 [48.9%], OR 3.14, 95% CI 1.30 – 7.59, P=0.011) compared to the post-hoc control cohort (14/65 [21.5%]) (Table 2.3), after adjusting for age, sex, baseline FRS, smoking status, and length of time in the study (data not shown).

2.5 Discussion

We conducted a prospective, randomized controlled study evaluating the involvement of non-specialist pharmacist in providing collaborative cardiovascular risk care compared to usual care. At the end of the observation period, our primary endpoint of change in FRS was not significantly different between the two study groups. With respect to our secondary endpoints, no between-group differences were detected for any of the endpoints assessed (systolic and diastolic blood pressure, total cholesterol, LDL-cholesterol, HDL-cholesterol, total cholesterol:HDL, or A1c levels); however, many study patients exhibited controlled risk factors at the baseline assessment. Furthermore, both mean adherence and the proportion of patients with adherence ≥80% were not improved by repeated contact with the study pharmacist. It would seem that our simple hypothesis of communicating uncontrolled risk factor levels was either inadequate, or the study period was too brief to influence these endpoints.

In contrast, we did find evidence suggesting that the pharmacist intervention significantly improved statin medication utilization. Compared to the non-study post-hoc control patients, a higher proportion of the follow-up group were newly initiated on a statin medication and continued to fill a statin medication after the completion of the study period. Overall adherence to statin medications was very high in all groups examined suggesting that this increased use of statins could potentially translate into future lowering of cardiovascular risk.

Interestingly, all patients enrolled in the study appeared to benefit from the pharmacist involvement irrespective of study group assignment. Indeed, even the single contact group exhibited higher rates of statin utilization compared to the non-study post-hoc control cohort of patients. These improvements in the single contact group were most likely a result of contamination because each physician in our study managed patients in both the follow-up as well as the single contact group. It was unavoidable that the single-contact group would receive some benefits as a result of the communication to physicians about their follow-up counterparts. In our view, these findings are important for two reasons. First, our simple pharmacist intervention was associated with objective benefits despite the potential for contamination that favoured a null finding. Second, the benefits observed in the single contact group provide additional evidence for the benefits of reminding physicians about uncontrolled cardiovascular risk factors. Not only did our reminders benefit the intervention group, but they appeared to benefit other similar patients under the physician's care as well. Consequently, we believe pharmacists who have not yet developed the skills or gained the experience in providing pharmacotherapeutic recommendations can still contribute to the care of patients in a collaborative care setting.

Limitations

Given that this was a pilot study, our sample was relatively small, only involved a single center, and the follow-up period was limited. Also, none of the participants were blinded to the treatment assignment. Clinical endpoints such as blood pressure were not standardized and were simply recorded from the medical chart. In addition, twenty patients were lost to follow-up and did not have data available for analysis of the primary endpoint or secondary clinical endpoints. However, all data were analyzed as intent-to-treat, and we were able to evaluate all study patients for the statin utilization and adherence analyses. Our primary endpoint, the FRS, is validated only in primary prevention populations whereas secondary prevention patients were also enrolled in our study. Nevertheless, assessing global risk is considered superior to measuring single risk factors in both primary and secondary prevention populations,[17, 18] and we used the FRS as a composite measure of changes in risk factors, rather than for risk prediction. Finally, the study was comprised of a single intervention pharmacist so we cannot definitively generalize our findings to all non-specialist pharmacists. However, simple reminders systems

may benefit patient care in a similar manner, and we suspect the benefits of involving pharmacists would only increase over time. Obviously, a larger, multi-site trial would be needed to confirm any benefits of this strategy.

Despite these limitations, this is still one of the largest studies to date evaluating the impact of pharmacist involvement on cardiovascular risk reduction,[3, 7, 19] and one of the few that evaluated a practical pharmacist intervention that could likely be carried out by non-specialist pharmacists in typical (i.e. fee-for-service) practice settings. The study focused on simple, frequent contacts with patients and enrolled all high-risk subjects rather than just evaluating those with uncontrolled risk factors. Also, we utilized a global cardiovascular measure as opposed to a single risk factor, which would appear to be a more practical endpoint from the perspective of cardiovascular risk reduction in primary care practice.

2.6 Conclusion

Although the pharmacist involvement did not result in a clear improvement to cardiovascular-risk reduction success among patients attending a primary care medical clinic, it did result in apparent improvements to statin utilization. Considering the wealth of non-specialist pharmacists practicing in Canada and the United States, we believe that researchers should continue to explore potential collaborative care roles that do not involve complex pharmaceutical care models. Ultimately, such a protocol could be much more generalizable to many front-line pharmacists and may even result in additional opportunities for collaborative practice.

Figure 2. 1. Flow of Study Patients

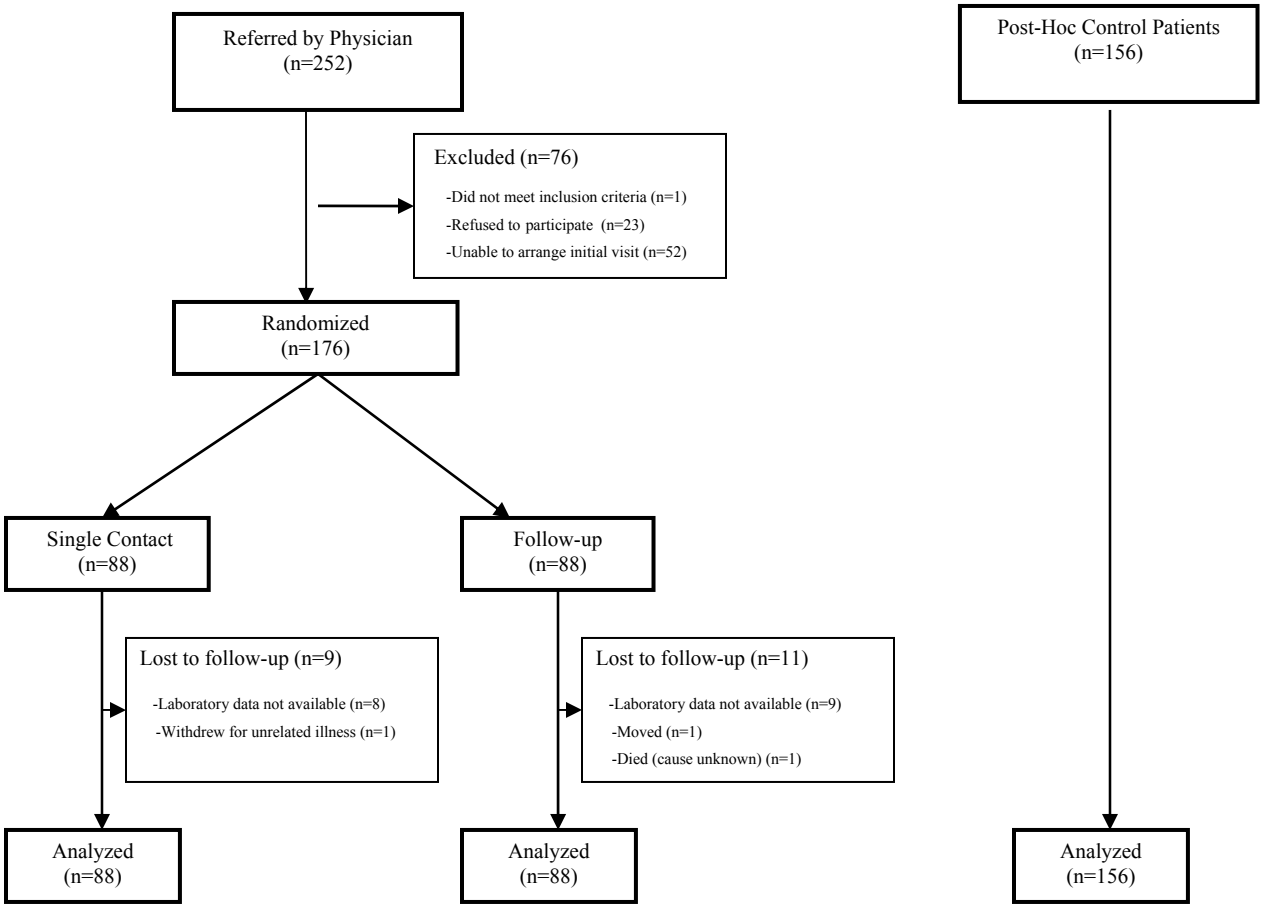

Table 2.1. Potential Reasons for Pharmacist Follow-up with Patients

- Communication of relevant laboratory results, including proximity to individual targets
- Within 7-10 days after the initiation or change of medication
- Within 7-10 days after experiencing an adverse event
- To ensure patient was able to procure necessary follow-up appointments
- Periodic mail outs providing patients with clinical goal reminders, disease specific information, or timely topics

Table 2.2. Patient Baseline Characteristics

	Follow-Up	Single Contact	Post-Hoc Control	P-value[a]	P-value[b]
	n=88	n=88	n=156		
Characteristic					
Age (SD) (years)	60.3 (10.05)	60.2 (10.19)	63.9 (12.42)	0.953	0.013
Male sex (%)	73 (83.0)	69 (78.4)	88 (56.4)	0.445[c]	<0.001[d]
Cigarette Smoker (%)	21 (23.9)	13 (14.8)	8 (5.1)	0.127[c]	<0.001[d]
Cardiovascular History					
Post-MI (%)	19 (21.6)	18 (20.5)	43 (27.6)	0.853[c]	0.374[d]
Post-CVA (%)	4 (4.5)	4 (4.5)	5 (3.2)	1.000[c]	0.821[d]
CAD (%)	13 (14.8)	9 (10.2)	34 (21.8)	0.362[c]	0.057[d]
Diabetes (%)	60 (68.2)	59 (67.0)	103 (66.0)	0.872[c]	0.942[d]
FRS (%)	16.7	15.0	12.4	0.276	0.003
Systolic BP (mmHg)	136.4	136.9	135.1	0.819	0.605
Diastolic BP (mmHg)	80.0	81.3	80.0	0.332	0.503
Total Cholesterol (mmol/L)	4.85	4.67	4.54	0.349	0.142
LDL (mmol/L)	2.88	2.79	2.68	0.605	0.340
HDL (mmol/L)	1.13	1.16	1.15	0.548	0.832
TC:HDL	4.49	4.24	4.19	0.211	0.223
Triglycerides (mmol/L)	2.03	1.81	1.83	0.196	0.344
A1c (%)	7.3[e]	7.0[f]	7.5[g]	0.200	0.064

	Follow-Up	Single Contact	Post-Hoc Control	p-value[a]	p-value[b]
	n=88	n=88	n=156		
Characteristic					
Drug Utilization (%)					
Statin	48 (54.5)	43 (48.9)	91 (58.3)[h]	0.451[c]	0.360[d]
ACEI	70 (79.5)	62 (70.5)		0.164[c]	
Beta Blocker	28 (31.8)	26 (29.5)		0.744[c]	
ASA (or other anticoagulant/ antiplatelet)	68 (77.3)	70 (79.5)		0.714[c]	

a Independent t-test comparing Follow-up and Single Contact (unless indicated)
b ANOVA test comparing Follow-up, Single Contact and Post-Hoc Control (unless indicated)
c Pearson's chi-square comparing Follow-up and Single Contact
d Pearson's chi-square comparing Follow-up, Single Contact and Post-Hoc Control
e n=54
f n=59
g n=100
h Only statin utilization was captured for the Post-Hoc Control group
A1c Glycosolated haemoglobin A1c
ACEI Angiotensin converting enzyme inhibitor
ASA Acetylsalicylic acid
BP Blood pressure
CAD Coronary artery disease
CVA Cerebrovascular accident
FRS Framingham risk score (% 10-year risk)
HDL High density lipoprotein
LDL Low density lipoprotein
MI Myocardial infarction
TC:HDL Total cholesterol:high density lipoprotein

Table 2.3. Results at Study End

	Follow-Up	Single Contact	Post-Hoc Control	P-value[a]	P-value[b]
	n=88	n=88	n=156		
Characteristic					
FRS (%)	14.0	13.7	11.7	0.844	0.071
Mean Reduction in FRS (%)	2.68	1.25	0.69	0.098 (one-tailed)	0.043
Systolic BP (mmHg)	133.3	135.3	135.5	0.304	0.532
Diastolic BP (mmHg)	76.6	77.1	79.1	0.704	0.136
Total Cholesterol (mmol/L)	4.22	4.21	4.32	0.949	0.668
LDL (mmol/L)	2.33	2.33	2.40	0.992	0.791
HDL (mmol/L)	1.15	1.13	1.18	0.544	0.549
TC:HDL	3.82	3.90	3.88	0.614	0.887
Triglycerides (mmol/L)	1.91	1.95	1.78	0.835	0.490
A1c (%)	7.2[c]	6.9[d]	7.4[e]	0.150	0.043
Mean days in study	394	390	367	0.695	0.050

a Independent t-test comparing Follow-up and Single Contact
b ANOVA test comparing Follow-up, Single Contact and Post-Hoc Control
c n=54
d n=58
e n=100
A1c Glycosolated haemoglobin A1c
BP Blood pressure
FRS Framingham risk score (% 10-year risk)
HDL High density lipoprotein
LDL Low density lipoprotein
TC:HDL Total cholesterol:high density lipoprotein

Table 2.4. Statin Utilization and Adherence

Measure			Statin Utilization		
	Follow-Up	**Single Contact**	**Post-Hoc Control**	**P-value[a]**	**P-value[b]**
	n=88	n=88	n=156		
At least one statin fill during study period (%)	78 (88.6)	65 (73.9)	105 (67.3)	0.012	0.001
Statin utilization at study end (%)	75 (85.2)	59 (67.0)	98 (62.8)	0.005	0.001
New statin initiations (%)	30/40 (75.0)	22/45 (48.9)	14/65 (21.5)	0.013	<0.001
			Statin Adherence		
	Follow-Up	**Single Contact**	**Post-Hoc Control**	**P-value[a]**	**P-value[b]**
	n=78	n=65	n=105		
Mean adherence (%) (95% CI)	90.4 (83.9-97.0)	91.8 (85.3-98.2)	92.1 (88.7-98.7)	0.781[c]	0.749[d]
Patients adherent ≥80% (%)	57 (73.1)	52 (80.0)	81 (77.1)	0.333	0.614

a Pearson's chi-square comparing Follow-up and Single Contact
b Pearson's chi-square comparing Follow-up, Single Contact and Post-Hoc Control
c Independent t-test comparing Follow-up and Single Contact
d ANOVA test comparing Follow-up, Single Contact and Post-Hoc Control

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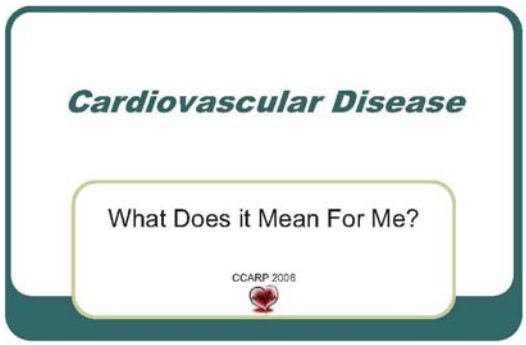
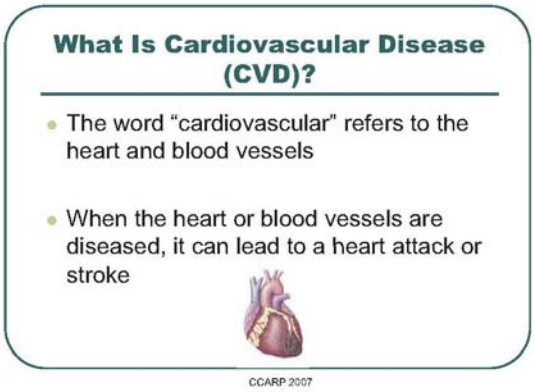
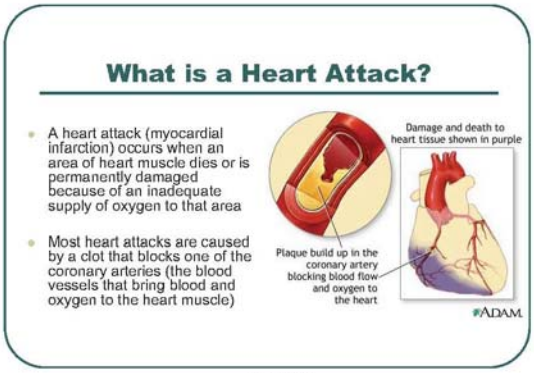
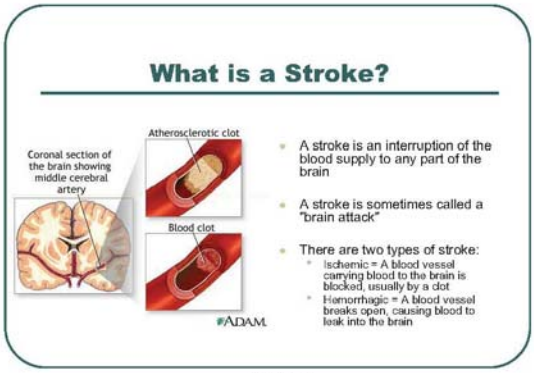
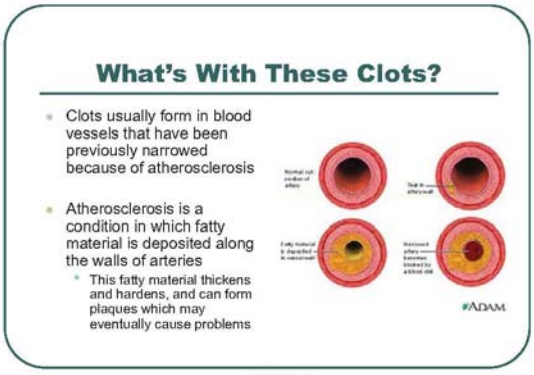
Appendix A. Patient Education Booklet

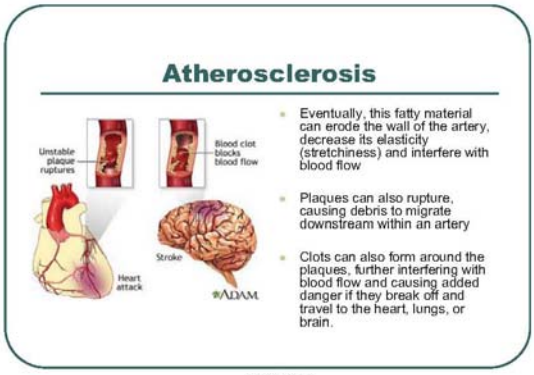












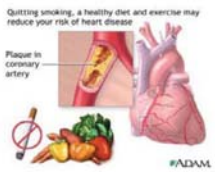
Risk Factors for CVD

- *Non-Modifiable*:
  - Family history of heart attack or stroke
  - Men > 40 years old
  - Women > 50 years old or in menopause
- *Modifiable*:
  - High blood pressure
  - Poor cholesterol levels
  - Being overweight
  - Physical inactivity
  - Smoking
  - Diabetes

CCARP 2007

How Can I Help Lower My Risk?

- Lifestyle changes:
  - Quitting smoking
  - Healthy diet
  - Regular exercise
- Medications for:
  - Blood clot prevention
  - High blood pressure
  - Poor cholesterol levels



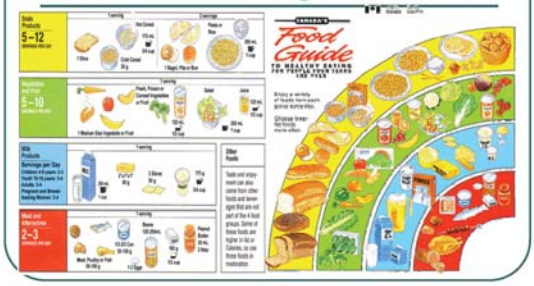
CCARP 2007

Diet

- A well controlled diet is very important in helping reduce your CVD risk
- A dietitian is a valuable source of important dietary information
- Canada's Food Guide to Healthy Eating is another excellent resource for making dietary decisions

CCARP 2007

Canada's Food Guide to Healthy Eating



CCARP 2007

Exercise

- Talk with your doctor first, before starting any exercise program
- Start slowly, gradually build up to at least 30 -60 minutes, five days a week

CCARP 2007

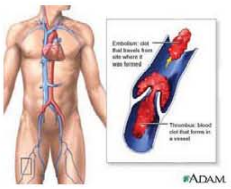
Quitting Smoking

- Quitting smoking is essential for helping control blood pressure, cholesterol, and blood sugar, and for preventing some forms of cancer

CCARP 2007

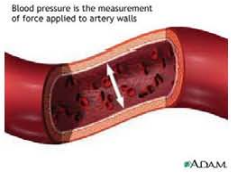
Blood Clot Prevention

- By preventing the formation of blood clots, you can help reduce your risk for having a heart attack or stroke
- There are several medications used for preventing clot formation – the most common is ASA (Aspirin)



CCARP 2007

High Blood Pressure (Hypertension)

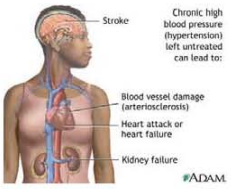


- Blood pressure is the force applied against the walls of the arteries as the heart pumps blood through the body
- The pressure is determined by the force and amount of blood pumped and the size and flexibility of the arteries

CCARP 2007

The Problem with Hypertension

- When high blood pressure is left untreated, damage to organs throughout the body can occur



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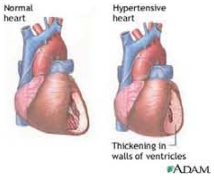
Hypertension Measurement



- The top number of your blood pressure measurement (systolic) represents the pressure generated when the heart beats, while the bottom number (diastolic) is the pressure when the heart is at rest.

CCARP 2007

Hypertension Targets

- There are different targets for blood pressure depending on your other medical conditions:
  - With diabetes: <130/80 mmHg
  - Without diabetes: <140/90 mmHg
  - Chronic kidney disease: <130/80 mmHg

CCARP 2007

Managing Hypertension

- Blood pressure can be controlled by diet, exercise, and quitting smoking
- Usually, medications are also needed

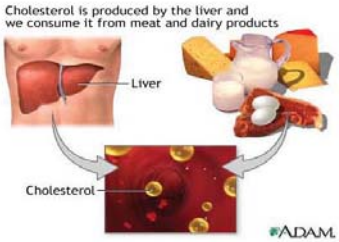
CCARP 2007

Cholesterol

- A soft, waxy substance that is present in all parts of the body including the nervous system, skin, muscle, liver, intestines, and heart
- Made by the body and obtained from animal products in the diet
- Cholesterol is manufactured in the liver for normal body functions including the production of hormones, bile acid, and Vitamin D
  - It is transported in the blood to be used by all parts of the body

CCARP 2007

Where Does Cholesterol Come From?



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The Problem With Cholesterol

- Excessive cholesterol contributes to atherosclerosis and heart disease
- There are 3 major types of cholesterol:
  - HDL (Good Cholesterol)
  - LDL (Bad Cholesterol)
  - Triglycerides
- The problems start when there is too much bad cholesterol and not enough good cholesterol

CCARP 2007

Cholesterol Targets

- Cholesterol targets for people who are at high risk for CVD are:
  - LDL < 2.0 mmol/L
  - TC:HDL < 4.0

    A ratio of all the cholesterol in your body compared to the good cholesterol

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Managing Cholesterol

- Low fat, high fibre diet
- Regular exercise
- Medications that:
  - Reduce the amount of cholesterol made by the body
  - Decrease how much cholesterol is absorbed from the food we eat

CCARP 2007

The Good News...

- YOU can help lower your risk for a heart attack or stroke with good blood pressure, cholesterol, and blood sugar (if you have diabetes) control
  - Lifestyle changes
    - Healthy diet
    - Regular exercise
    - Quitting smoking
  - Proper medication use
    - Blood pressure
    - Cholesterol
    - Blood clot prevention

CCARP 2007

- Chapter 3 -

DIABETES AND CARDIOVASCULAR DISEASE INTERVENTIONS BY COMMUNITY PHARMACISTS: A SYSTEMATIC REVIEW

3.1 Abstract

Objective: To systematically review and summarize community pharmacist interventions for preventing or managing diabetes or cardiovascular disease and/or its major risk factors.

Data Sources: A comprehensive literature search was performed using Medline, Embase, International Pharmaceutical Abstracts (IPA), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Cochrane Central Register of Controlled Trials. The "grey" literature was searched using the ProQuest Dissertations and Theses, Theses Canada, and OAlster databases.

Study Selection: Articles published in English or French and with any study design were considered for the review. Studies were included if they contained interventions designed to reduce the incidence, risk, or mortality of cardiovascular (CVD) or diabetes; affect clinical indicators of CVD or diabetes mellitus (including hypertension, dyslipidemia, or A1c); and/or improve adherence to treatment strategies. Only those studies involving interventions carried out primarily by pharmacists in community pharmacy settings were included. Study quality was assessed using a checklist validated for both randomized and non-randomized studies.

Data Synthesis: A total of 3361 studies were initially identified with 37 meeting our inclusion criteria. Ten studies were randomized controlled trials, 4 were cluster randomized trials, and 2 studies had randomized before-after designs. The remaining studies were controlled before-after (n=2), cohort (n=3), and uncontrolled before-after (n=16). Interventions focused on diabetes (n=11), hypertension (n=8), medication adherence (n=8), lipids (n=5), evidence based medication initiation or optimization (n=3), risk factor prediction scores (n=1), and body mass index (n=1). All studies contained interventions focused at the patient level and the majority of studies (32/37) involved interventions directed at both the physician and patient. No specific

intervention(s) emerged as being superior, and study quality was generally poor, making it difficult to determine the true effect of the intervention(s).

Conclusions: The majority of community pharmacy studies reviewed appeared to show benefit in the reduction or management of diabetes or CVD. However, poor study quality, time-intensive interventions, and unproven clinical significance warrant the need for further high quality studies.

3.2 Introduction

Community pharmacists have been involved in activities related to the prevention and management of cardiovascular disease (CVD) and diabetes for many years, with research dating back to the late 1970's. Over the past decade, the number of community pharmacy practice publications has increased substantially. This increase is likely driven by several factors: recommendations that pharmacists should play a more active role in disease management[1-6], a push from within the profession to broaden the role of community pharmacists beyond the traditional dispensing and distribution functions[7], and an increasing need to generate objective evidence supporting these expanded roles.

There have been numerous studies reporting clinically significant benefits of community pharmacist interventions in diabetes and CVD. Some would argue, however that major advancements in real-world practice have not followed suit.[8] It has been suggested that this may be due to a lack of knowledge synthesis (e.g. systematic reviews) or ineffective dissemination of the results.[8] It is also possible that the published pharmacy research used as evidence for practice change has lacked the quality and/or generalizability necessary to successfully guide and support this change.

Although previous reviews have looked at community pharmacist interventions involving CVD or diabetes, they had a limited search strategy,[5, 9-11] were focused on a single risk factor,[5, 9, 11, 12] were not specific to community pharmacists (e.g. hospital or clinic-based),[5, 10, 11, 13] or are now dated.[14] Thus, we aimed to systematically review and summarize community pharmacist interventions directed at the prevention or management of diabetes or CVD and/or their major risk factors.

3.3 Methods

Search Strategy

A comprehensive literature search was performed by a librarian (EW) using the databases Medline (1950-), Embase (1980-), International Pharmaceutical Abstracts (IPA) (1970-) and Cochrane Central Register of Controlled Trials (1898-) from date indicated to November 2009 (Appendix B). Searches were initially carried out in June 2007 and then re-run to find additional,

new articles in December 2007. Database e-mail alerts from Medline, Embase, and IPA were used to notify the authors of any articles published after December 2007; these alerts were monitored until the end of November 2009. In addition, the Cumulative Index to Nursing and Allied Health Literature [CINAHL (1982-)] was also searched initially; however, partway through the project, the database provider changed, limiting search access and therefore it was not included after June 2007. The "grey" literature was searched using the ProQuest Dissertations and Theses, Theses Canada, and OAlster databases; searches were done in August 2009. Systematic review articles and bibliographies from original studies were also hand searched for potentially relevant studies; experts and/or authors were not contacted. No publication date limits were used in the searches.

Inclusion and Exclusion Criteria

To maximize the inventory of pharmacy-practice interventions that have been evaluated over the years, all studies published in English or French were considered for the review without regard for study design. However, only full text articles were included. Interventions must have been intended to reduce the incidence, risk, or mortality of CVD or diabetes; affect clinical indicators of CVD or diabetes mellitus (including hypertension, dyslipidemia, body weight, or A1c); and/or improve adherence to cardiovascular or diabetes therapies. Only those studies involving interventions carried out by pharmacists in community pharmacy settings were included. Interventions that focused solely on patient screening, and those that did not report measured outcomes, were excluded.

Review Methods

All duplicate records were removed electronically (RefWorks software) and the remaining identified abstracts were screened by the reviewers (CE, DB, EW, DL) to assess their eligibility. Full copies of the potentially eligible studies were obtained, and each study was reviewed independently by 2 of 4 possible reviewers (CE, DB, EW, DL) to determine whether they should be included. Studies were evenly distributed between the 4 reviewers. Discrepancies were resolved by one of the reviewers who was not involved in the original review. Data was initially extracted by 2 of 4 possible reviewers (CE, DB, EW, DL), and included author, year of publication, study design, patient population, sample size, study outcomes, intervention(s),

length of intervention(s) and results. Results specific to the primary outcome, and conclusions made by the authors were further extracted by CE. If a primary outcome was not specified, the first outcome reported in the results section was used unless another outcome was specified in a power calculation.

Methodological quality of the selected studies was assessed independently by two authors (CE, EY) using a quality checklist validated for both randomized and non-randomized studies.[15] Only studies with a control group were scored, as uncontrolled studies are already known to be of low quality.[16, 17] The maximum score on the checklist is 32, and those studies with a score of less than 18 were considered to be of low quality.[18] Any scoring discrepancies were resolved by a third author (DB). Given the disparity of the studies, a meta analysis was not performed.

3.4 Results

Our search initially resulted in 3361 citations, and 37 studies met the inclusion criteria (Figure 3.1). Inter-observer agreement was κ=0.8753 for study inclusion among reviewers, indicating excellent agreement. Ten studies were randomized controlled trials (RCTs), 4 were cluster randomized (randomized by community pharmacy or district rather than individual subjects). Two studies[19, 20] that were labelled by the authors as RCTs have been categorized as a randomized before-after design, given the fact that no between-group comparisons were made. In each of the four cluster randomized studies identified, the authors inappropriately failed to account for the clustering effect in the analyses.[21, 22] The remaining studies were cohort (n=3), controlled before-after (n=2), and uncontrolled before-after (n=16).

Studies were published between 1978 and 2009, with the majority published after 1999 (Table 3.1). Based on the primary endpoint, interventions focused on diabetes (n=11),[23-34] hypertension (n=8),[20, 35-41] medication adherence (n=8),[42-49] and lipids (n=5).[19, 50, 51] The remaining studies focused on evidence based medication initiation or optimization (n=3),[52-57] risk factor prediction scores (n=1),[58] and body mass index (n=1).[59] Study lengths were variable and ranged from 2 to 57 months.

Interventions

Based on the descriptions provided by the authors, interventions were classified as either patient-directed (pharmacist activities directed primarily towards patients) or physician-directed (pharmacist activities directed primarily towards physicians) (Table 3.2). All studies contained interventions involving patients and the majority of studies (32/37) involved interventions directed at both the physician and patient. Overall, we found few differences between the types of interventions tested in the last decade compared to those in the 1970's and 1980's (Figure 3.2).

Patient-directed interventions were most commonly in the form of regular follow-up (35/37 [94.6%]) or education (35/37 [94.6%]), with only a few using reminders (e.g. reminders to refill prescriptions) (4/37 [10.8%]). Education was provided by the pharmacist either verbally or through written materials, and typically included information relating to the patient's disease state and medications (e.g. mechanism of action, adverse effects). Appropriate lifestyle management (diet, exercise, and smoking cessation) was frequently discussed, as was the importance of medication adherence. Follow-ups were conducted in person, by telephone, or mail, and generally occurred at pre-determined intervals ranging from 2 weeks[25] to 3 months.[23, 24, 32, 43, 55] However, some interventions allowed for individualized impromptu follow-ups based on the perceived need by either the patient or pharmacist.[28, 52] Patient reminders included methods to remind patients to take or refill their medications, or "compliance packaging" of medications.[47]

The identification of drug related problems (DRPs) and subsequent therapeutic recommendations was a key component of many physician-directed interventions (25/37 [67.6%]). Recommendations to physicians included therapy initiation, dosage adjustments, and the ordering of laboratory tests. Several interventions (14/73 [37.8%]) included notifying physicians of their patients' involvement in, or progress with, the study through various means (e.g. fax, telephone). Finally, 8/37 (21.6%) interventions required the pharmacist to refer patients back to their physician for appropriate follow-up.

Interventions were typically time intensive, often requiring individual patient interviews, follow-up, and extensive collaboration with physicians. Out of 16 studies with available data, the median time per patient activity (typically patient interviews or consultations) was 27 minutes, with some lasting up to 65 minutes.[49, 59] However, only three studies commented on the complexity of their interventions: one study reported the adjustments that had to be made to "accommodate the increased time commitment needed for the project";[55] one utilized pharmacists who were not involved in dispensing activities;[33] and only one considered the feasibility and practical implications of implementing the intervention into community pharmacy practice.[41]

Overall, favourable results were reported or concluded by the authors in 29/37 (78%) studies with more favourable results reported in studies without a control group [85% (17/20)] compared to 71% (12/17) in those with a control group (Table 1). Accurately evaluating the impact of the specific interventions was difficult as many authors did not specify a primary endpoint or incompletely reported the results.[20, 30, 33, 34, 36, 46] Regardless, the 3 most commonly tested interventions (patient education, patient follow-up, and the identification of drug related problems and subsequent physician recommendations) were deemed effective in producing a "significant" difference in the primary outcome in the majority of the studies; however, it was impossible to determine whether any intervention type was superior. While these results are promising, it is important to note that the authors' favourable conclusions were not supported by any reported data in at least 2 of the reviewed studies.[27, 48] In addition, none of the studies demonstrated any benefits to major health outcomes and were mainly restricted to relatively small differences in drug utilization, laboratory outcomes, or medication adherence. Therefore, the clinical importance of these interventions remains unclear.

Study Quality

Quality scores for those studies evaluated (only those studies with a control group were assigned a quality score) were poor, as only 6/21 (28.6%) studies received a score of 18/32 (56%) or greater.[15] All 6 studies were published in the last decade. Studies published from 2004-2009 scored relatively higher on items assessing reporting quality than did studies published before

2004. In most cases, poorly reported studies lacked an adequate description and/or comparison of subjects at baseline, and did not report p-values (or confidence intervals) for the study results.

Randomized studies scored relatively better than the non-randomized designs, as expected, but only six (out of 16) achieved a score of 18/32 or higher. Of the 16 randomized design studies, only one study reported blinding of the personnel involved in data collection and analysis, and only 3 reported blinding of the intervention allocation. Intention to treat (ITT) analysis was explicitly mentioned in 8/16 (46.6%) randomized studies,[20, 35, 38, 42, 43, 47, 52, 54] however only 5 of these studies performed an appropriate ITT analysis.

Overall, only 12/37 (32.4%) studies described an *a priori* power calculation, and only 4 of these actually achieved adequate power for analysis of the primary endpoint. Identification of pre-determined outcomes was poor, particularly in the uncontrolled before-after studies, where only 9/16 (56.2%) of these studies clearly specified a primary endpoint.

3.5 Discussion

To the best of our knowledge, this is the first systematic review that has summarized interventions specific to community pharmacists that focus on both diabetes and CVD and all major related risk factors. All identified studies involved patient-directed interventions such as education and follow-up. Most studies also involved physician-directed interventions, the most common of which was the identification of drug related problems and provision of therapeutic recommendations. The majority of studies were published in the last 10 years, although the interventions have remained similar over the past 30 years. Studies were generally of poor quality and evaluated interventions that typically appeared to be time intensive.

Poor study quality has plagued pharmacy practice research for years,[60-62] and problems range from poor design to poor reporting. Although RCTs are considered the gold standard for the evaluation of treatment efficacy/effectiveness, the majority of studies in this review used a non-randomized design. In fact, 16 of the studies did not use a control group at all, and 2 studies with a control group made no between-group comparisons. Without a control group, it is difficult to

conclude a causal relationship between the intervention being evaluated and the subsequent outcome(s).[63]

Based on the studies examined in this review, reporting of results seems to have improved over time, and is likely due to the development of guidelines for the reporting of both randomized and observational studies.[64, 65] However, poor reporting was still an issue even in more recent publications especially in the non-randomized studies. The lack of a clearly identified primary outcome, and appropriate statistical comparisons (i.e. p-values and confidence intervals) were common, and made it difficult to evaluate and interpret the results. In some cases the authors suggested favourable outcomes that were either inconsistent with the results reported,[27, 48] or not supported by statistical evidence.[34, 36, 46]

A major challenge when designing pharmacy research is the matter of blinding. In most cases, it is difficult for either the patients or study researchers to be blinded, especially if the intervention involves direct patient care. However, because blinding is a factor in most quality assessment scores, some argue that the quality of pharmacy practice studies will always be underestimated.[8] Blinding those responsible for the data collection and analysis, and the concealment of intervention allocation in RCTs, can reduce bias and improve study quality; however, these strategies were rarely undertaken in these studies.

Study quality was likely influenced by several factors. First, contemporary techniques to minimize bias and confounding may have been unknown to many investigators who conducted their research before the 1990's. Indeed, we found that studies published since 2000 were generally of higher quality compared to all others. Interestingly, we could not identify major differences in the types of interventions used in lower-quality studies versus high-quality studies. Similarly, we could not find any notable differences in the types of pharmacist interventions tested throughout the years. For example, in 1978, McKenney et al evaluated a pharmacist intervention that was comparable to more recent interventions published in the pharmaceutical care era.

The majority of interventions involved in-depth consultations with individual patients (and subsequently physicians or other health care professionals) for the purpose of identifying and resolving actual and potential drug related problems.[66, 67] In general, these strategies appeared to be time-intensive, and their impact on patient outcomes remains unproven. Also, the extent to which these strategies could be integrated into current community pharmacy settings is not clear. Only three studies commented on the impact the intervention had on staffing and time requirement of employees. Even highly successful interventions[51] will have little benefit if they cannot be implemented in real world settings.[68-71] We believe that more research is needed to evaluate strategies that can be implemented into current community pharmacy practice.

Limitations

A limitation of our search strategy is that we only included full text articles published in English or French. Although 5 studies were excluded based on language, it is unlikely that the intervention(s) being evaluated in those studies differed significantly from the included studies. Categorization of interventions and quality assessments were based on what was reported in the published studies, and we did not contact authors for extra details. As with any systematic review, there is the potential for publication bias. The quality checklist used has its own limitations. The lack of a reference standard for the total quality score forces reviewers to make a judgement call on what they consider to be an acceptable level of quality.[72] We chose a score of 18/32 or higher based on a previously published review,[18] although much lower acceptable levels of quality have also been used.[72] The checklist also required subjective judgements which were often made more difficult by the poor reporting of some studies. However, by using two independent reviewers and a third to resolve any discrepancies, we can have confidence in our assessments.

3.6 Conclusion

The majority of community pharmacy studies reviewed from the past 30 years appear to show benefit in the reduction, or management, of diabetes or CVD and its risk factors. However, study quality was generally poor, interventions were time intensive, and none of the studies demonstrated any benefits to major health outcomes. Therefore, the clinical importance of these

interventions remains unclear, and further well-designed, well-conducted studies are needed to guide community pharmacists in this important area of practice.

Figure 3.1. Diagram of Literature Search

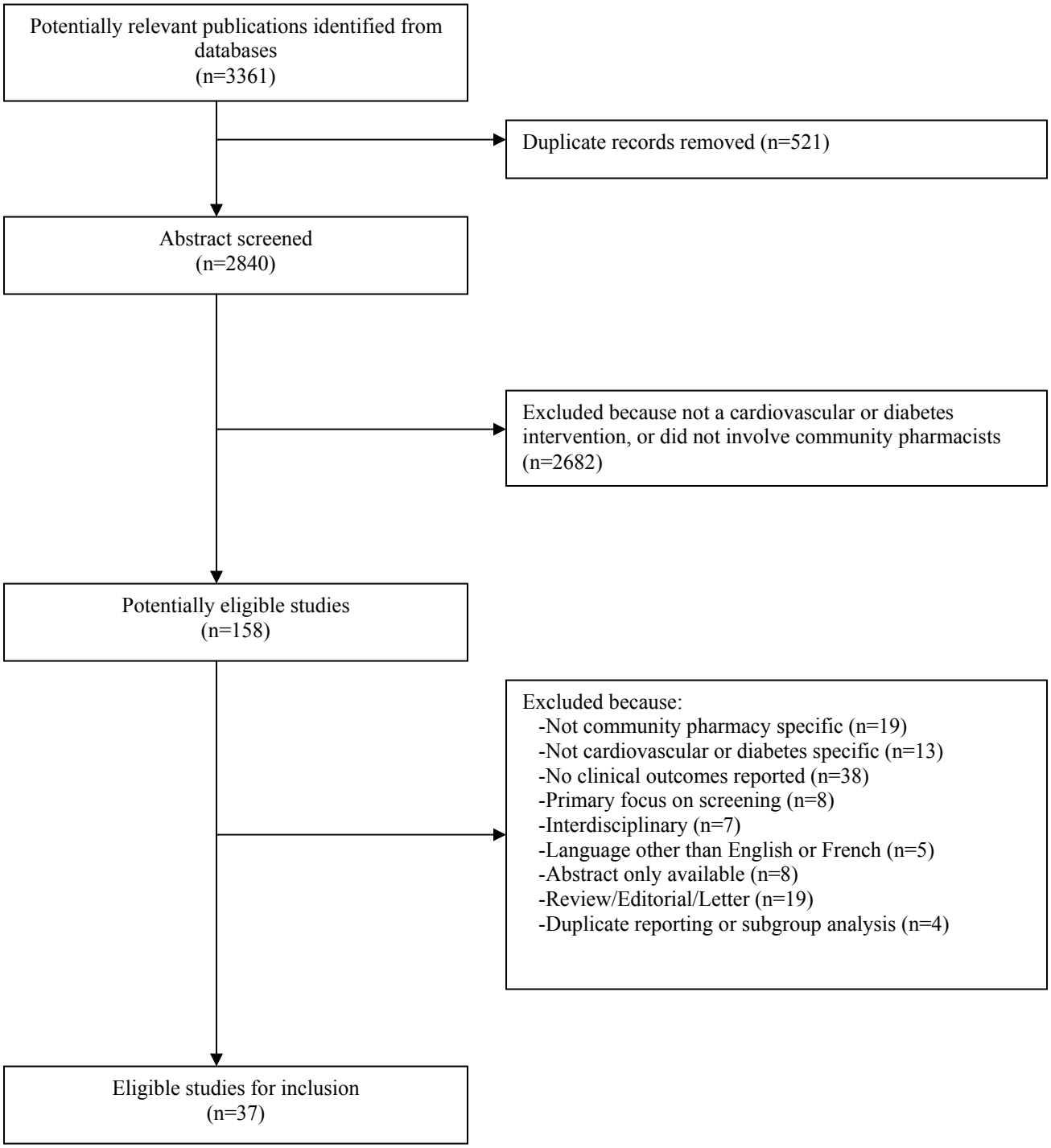
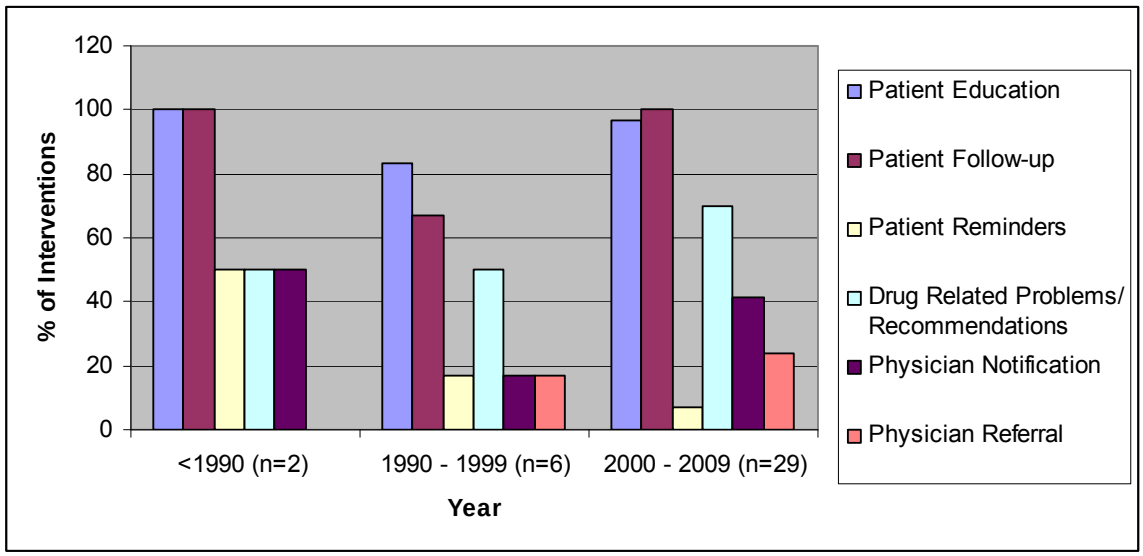


Figure 3.2. Proportion of Interventions Published by Decade



Patient Education - Initial education and/or counselling session provided directly to patient
Patient Follow-up - Regular contact with patients (in-person, phone, mail)
Patient Reminders - Medication reminders and/or compliance packaging (no patient education provided)
Drug Related Problems / Recommendations - Identification of actual or potential drug related problems and/or therapeutic recommendations made to physician by the pharmacist in response to identified drug related problems
Physician Notification - Physician notified about patient's study involvement and/or progress (no specific recommendations made)
Physician Referral - Patient referred to physician by pharmacist

Table 3.1. Characteristics of Included Studies

Author (year)	Study Design	Study Population	Sample Size		Primary Outcome[a]	Intervention Category[b]		Intervention Length	Results[c]	Quality Score[d]
			Intervention	Comparator		Intervention	Comparator			
Doucette[23] (2009)	RCT	Type 2 diabetes	n=36	n=42	Change in mean A1c	PT-ED PT-FU MD-DRP MD-NOT	Usual care	12 months	Unfavourable	Low
Nietert[42] (2009)	RCT	Patients at least 7 days overdue for a diabetes, hypertension, lipid, depression or psychosis medication	Phone group n=1018 Fax group n=1016	n=1014	Time to refill (days)	Phone group PT-FU PT-RE Fax group MD-NOT (patient late for refills)	Usual care	7 months	Unfavourable	High
Planas[35] (2009)	RCT	Diabetes with hypertension	n=32	n=20	Change in mean systolic BP	PT-ED PT-FU MD-DRP MD-NOT	Usual care	9 months	Favourable	Low
Fera[24] (2008)	Uncontrolled before-after	Diabetes	n=914	N/A	Change in mean A1c from baseline	PT-ED PT-FU MD-NOT	N/A	Minimum 3 months	Favourable	N/A
Krass[25] (2007)	CRT	Type 2 diabetes	n=28 pharmacies	n=28 pharmacies	Change in mean A1c	PT-ED PT-FU MD-DRP MD-REF	Usual care	6 months	Favourable	Low
Lai[36] (2007)	Uncontrolled before-after	Hypertension	n=103	N/A	Change in mean BP from baseline	PT-ED PT-FU MD-DRP	N/A	9 months	Favourable	N/A

Author (year)	Study Design	Study Population	Sample Size		Primary Outcome[a]	Intervention Category[b]		Intervention Length	Results[c]	Quality Score[d]
			Intervention	Comparator		Intervention	Comparator			
MEDMAN[52] (2007)	RCT	CHD	n=980	n=513	Proportion of patients receiving secondary prevention treatment for CHD	PT-ED PT-FU MD-DRP	Usual care	12 months	Unfavourable	High
Semchuk[53] (2007)	Uncontrolled before-after	High risk for CV events	n=217	N/A	Proportion of patients with a dose increase or addition of any CV risk-lowering med compared to baseline	PT-ED PT-FU MD-DRP MD-NOT MD-REF	N/A	24 weeks	Favourable	N/A
Fornos[26] (2006)	RCT	Type 2 diabetes	n=58	n=56	Change in mean A1c	PT-ED PT-FU MD-DRP	Usual care	13 months	Favourable	High
Krass[27] (2006)	Cohort	Type 2 diabetes	n=39	n=79	Change in mean A1c	PT-ED PT-FU MD-DRP MD-NOT	PT-ED MD-DRP	6 months	Favourable	Low
Oparah[37] (2006)	Uncontrolled before-after	Hypertension	n=42	N/A	Change in mean BP from baseline	PT-ED PT-FU MD-DRP	N/A	6 months	Favourable	N/A
Vrijens[43] (2006)	CRT	Patients taking atorvastatin for at least 3 months	n=194	n=198	Proportion of days that the pill bottle (MEMS) was opened	PT-ED PT-FU PT-RE	Usual care	12 months	Favourable	High
Garrett[28] (2005)	Uncontrolled before-after	Diabetes	n=256	N/A	Change in mean A1c from baseline	PT-ED PT-FU MD-DRP MD-NOT MD-REF	N/A	Minimum 3 months	Favourable	N/A

Author (year)	Study Design	Study Population	Sample Size		Primary Outcome[a]	Intervention Category[b]		Intervention Length	Results[c]	Quality Score[d]
			Intervention	Comparator		Intervention	Comparator			
Paulos[19] (2005)	Randomized Before-after	Dyslipidemia	n=23	n=19	Change in mean TC from baseline	PT-ED PT-FU MD-DRP MD-REF	Usual care	16 weeks	Favourable	Low
Taylor[29] (2005)	Controlled Before-after	Type 2 diabetes	n=128	n=111	Change in mean A1c from baseline	PT-ED PT-FU	Usual care	9 months	Favourable	Low
Zillich[38] (2005)	CRT	Hypertension	n=6 pharmacies	n=6 pharmacies	Change in mean systolic and diastolic BP	PT-ED PT-FU MD-DRP	PT-FU	3 months	Unfavourable for systolic BP Favourable for diastolic BP	Low
SCRIP-plus Tsyuyki[50] (2004) Yamada[51] (2005)	Uncontrolled before-after	Very high risk for CV events	n=419	N/A	Change in mean LDL from baseline Change in LDL one year after completion of intervention	PT-ED PT-FU MD-DRP	N/A	6 months	Favourable (Maintained 12 months after completion of intervention)	N/A
Ali[44] (2003)	Uncontrolled before-after	Non-adherent to cholesterol meds in previous 3 months	n=149	N/A	Change in medication compliance (prescription refill rate) from baseline	PT-ED PT-FU MD-NOT	N/A	6 months	Favourable	N/A
Ashville Project[31] Cranor (2003) Cranor[30] (2003)	Uncontrolled before-after	Diabetes	n=85	N/A	Change in proportion of patients with A1c ≤7.0% from baseline	PT-ED PT-FU MD-REF	N/A	7-9 months Up to 5 years	Favourable	N/A

Author (year)	Study Design	Study Population	Sample Size		Primary Outcome[a]	Intervention Category[b]		Intervention Length	Results[c]	Quality Score[d]
			Intervention	Comparator		Intervention	Comparator			
Bouvy[45] (2003)	RCT	Heart failure and taking a loop diuretic	n=74	n=78	Medication non-compliance (days without medication as identified by MEMS)	PT-ED PT-FU MD-NOT	Usual care	6 months	Favourable	Low
Chabot[39] (2003)	Cohort	Hypertension	n=41	n=59	Change in mean BP	PT-ED (based on computerized decision aid tool) PT-FU MD-DRP	Usual care	9 months	Unfavourable (Only favourable for SBP in subjects with a high income)	Low
Krass[59] 2 (2003)	Uncontrolled before-after	Not being treated for dyslipidemia or hypertension	n=282	N/A	Change in mean BMI from baseline	PT-ED PT-FU MD-REF	N/A	3 months	Unfavourable	N/A
Taylor[46] (2003)	Uncontrolled before-after	Elderly African Americans with hypertension	n=8	N/A	Change in medication compliance (“variant of tablet count”)from baseline	PT-ED PT-FU MD-DRP	N/A	3 months	Favourable	N/A
Garcao[40] (2002)	RCT	Hypertension	n=50	n=50	Proportion of patients with controlled BP	PT-ED PT-FU MD-DRP	Usual care	6 months	Favourable	High
Nau[32] (2002)	Uncontrolled before-after	Type 2 diabetes	n=47	N/A	Change in mean A1c from baseline	PT-ED PT-FU MD-DRP MD-NOT	N/A	9 months (median)	Unfavourable	N/A

Author (year)	Study Design	Study Population	Sample Size		Primary Outcome[a]	Intervention Category[b]		Intervention Length	Results[c]	Quality Score[d]
			Intervention	Comparator		Intervention	Comparator			
Tsuyuki[54] (2002)	RCT	High risk for CV events	n=344	n=331	Composite: physician ordered fasting lipid panel, initiates a new cholesterol lowering drug, or increases the dose of a current cholesterol drug	PT-ED PT-FU MD-DRP MD-NOT	PT-ED PT-FU	16 weeks	Favourable	High
Blenkinsopp[41] (2000)	CRT	Hypertension	n=11 pharmacies	n=9 pharmacies	Proportion of patients with controlled BP	PT-ED PT-FU MD-DRP MD-REF	Usual care	6 months	Favourable	Low
Bluml[55] (2000)	Uncontrolled before-after	Dyslipidemia	n=397	N/A	Change in mean TC from baseline	PT-ED PT-FU MD-DRP MD-NOT	N/A	24.6 months (mean)	Favourable	N/A
McMillan-Nola[58] (2000)	Controlled Before-after	Known CAD or lipid levels requiring treatment	n=25	n=26	Change in risk factor prediction scores from baseline	PT-ED PT-FU MD-DRP	Usual care	6 months	Unfavourable	Low
Berringer[33] (1999)	Uncontrolled before-after	Diabetes	n=82	N/A	Change in mean SBGM from baseline	PT-ED PT-FU MD-DRP	N/A	12 months	Favourable	N/A
Fincham[34] (1998)	Uncontrolled before-after	Diabetes	n=51	N/A	Proportion of patients having a foot exam performed compared to baseline	PT-ED	N/A	2 months	Favourable	N/A
Shibley[56] (1997)	Uncontrolled before-after	Hyperlipidemia	n=25	N/A	Change in mean TC from baseline	PT-ED PT-FU MD-DPR MD-NOT	N/A	12 months	Favourable	N/A

Author (year)	Study Design	Study Population	Sample Size		Primary Outcome[a]	Intervention Category[b]		Intervention Length	Results[c]	Quality Score[d]
			Intervention	Comparator		Intervention	Comparator			
Park[20] (1996)	Randomized before-after	Hypertension	n=32	n=32	Mean systolic and diastolic BP	PT-ED PT-FU MD-DRP	Usual care	4 months	Favourable	Low
Skaer[47] (1993)	RCT	Newly diagnosed Type 2 diabetes receiving a first prescription for glyburide 5mg BID	Mail reminder n=79 Compliance packaging n=53 Reminder + packaging n=48	n=78	Adherence (MPR)	PT-RE	Usual care	360 days	Favourable	Low
Ibrahim[57] (1990)	Uncontrolled before-after	Not previously diagnosed with dyslipidemia	n=57	N/A	Change in mean TC from baseline	PT-ED PT-FU MD-REF	N/A	6 months	Favourable	N/A
Ascione[48] (1985)	RCT	Taking at least one CV medication	n=52	n=50	Proportion of patients refilling prescriptions late	PT-ED PT-FU PT-RE	Usual care	4 months	Favourable	Low
McKenney[49] (1978)	Cohort	Hypertension	n=70	n=66	Proportion of compliant patients (receiving +/-15% of prescribed dose)	PT-ED PT-FU MD-DRP MD-NOT	Usual care	4 months	Favourable	Low

RCT Randomized controlled trial
BP Blood pressure
N/A Not applicable
CRT Cluster randomized trial

CHD Coronary heart disease
CV Cardiovascular
MEMS Medication event monitoring system
TC Total cholesterol
LDL Low density lipoprotein
BID Twice daily
MPR Medication possession ratio
a. If no primary outcome specified, we used the first outcome reported in the Results section, or outcome used in power calculation (if done).
b. Intervention categories:
PT-ED = Patient-directed education
PT-FU = Regular patient follow-up
PT-RE = Medication reminders or compliance packaging
MD-DRP = Identification and reporting of drug related problems and subsequent recommendations made to patient's physician
MD-NOT = Notification to the physician about patient's participation or progress in the study
MD-REF = Patients were referred to their physician by the pharmacist
c. Based on authors' conclusions
d. Based on Downs and Black Checklist;[15] High ≥18/32 (56%); Low <18/32[18]

54

Table 3.2. Categorization of Interventions

Categories	Description
Patient-directed	
Education	Initial education and/or counselling session provided directly to patient
Follow-up	Regular contact with patients (in-person, phone, mail)
Reminders	Medication reminders and/or compliance packaging (no patient education provided)
Physician-directed	
Drug related problems - Recommendations	Identification of actual or potential drug related problems and/or therapeutic recommendations made to physician by the pharmacist in response to identified drug related problems
Notification	Physician notified about patient's study involvement and/or progress (no specific recommendations made)
Referral	Patient referred to physician by pharmacist

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Appendix B. List of Search Terms Used

The focus of this review was community pharmacy interventions, therefore in each database, a series of terms was used to identify articles about pharmacists, and another series of terms was used to identify those which took place in the community. These were combined with AND so that each article would contain a term describing each of these concepts. In databases which permitted use of more complicated search strategies (i.e., CINAHL, CENTRAL, EMBASE, IPA, and MEDLINE), additional terms were used to specify that articles include terms relating to at least one of hypertension, dyslipidemia, diabetes, cardiovascular disease, or adherence to drugs for treatment of one of the conditions listed above. No language restrictions were applied to the searches.

Wiley Cochrane Central Controlled Trials Registry (CENTRAL)
Searched December 2007

1 (pharmacist*):ti,ab,kw or (druggist*):ti,ab,kw or (chemist*):ti,ab,kw or (pharmacy):ti,ab,kw or (pharmacies):ti,ab,kw
2 (drugstore*):ti,ab,kw or (pharmaceutical NEXT care):ti,ab,kw or (pharmaceutical NEXT service*):ti,ab,kw
3 (#1 OR #2)
4 (community):ti,ab,kw or (retail):ti,ab,kw or (chain):ti,ab,kw or (neighborhood):ti,ab,kw or (neighbourhood):ti,ab,kw
5 (#4 AND #3)
6 (hypertens*):ti,ab,kw or (blood NEXT pressure):ti,ab,kw or (systolic):ti,ab,kw or (diastolic):ti,ab,kw
7 (cholesterol) or (hdl):ti or (ldl):au or (vldl):ab or (lipoprotein*):kw
8 (dyslipid*em*):ti,ab,kw or (hyperlipid*em*):ti,ab,kw or (hyperlip*em*):ti,ab,kw or (hypercholesterol*em*):ti,ab,kw or (hypertriglycerid*em*):ti,ab,kw
9 (hyperlipoprotein*em*):ti,ab,kw or (hypolipoprotein*em*):ti,ab,kw or (dyslipoprotein*em*):ti,ab,kw or (lip*em*):ti,ab,kw or (dyslip*em*):ti,ab,kw
10 (cholesterol*em*):ti,ab,kw or (lipid*):ti,ab,kw or (lipoprotein*em*):ti,ab,kw or (triglyceride*):ti,ab,kw
11 (#7 OR #8 OR #9 OR #10)
12 (blood NEXT glucose):ti,ab,kw or (blood NEXT sugar):ti,ab,kw or (hyperglyc*em*):ti,ab,kw or (hypergluc*em*):ti,ab,kw or (glucose NEXT intoleran*):ti,ab,kw
13 (hypoinsulin*em*):ti,ab,kw or (insulin NEXT deficien*):ti,ab,kw or (insulin NEXT dependen*):ti,ab,kw or (insulinop*en*):ti,ab,kw or (Insulin NEXT insufficien*):ti,ab,kw
14 (insulin*em*):ti,ab,kw or (glycosylated NEXT hemoglobin NEXT a):ti,ab,kw or (glycosylated NEXT haemoglobin NEXT a):ti,ab,kw or (a1c near/1 hemoglobin):ti,ab,kw or (a1c near/1 haemoglobin):ti,ab,kw
15 (hb NEXT a1c):ti,ab,kw or (hba1c):ti,ab,kw or (dysglyc*em*):ti,ab,kw or (dysgluc*em*):ti,ab,kw or (dysinsulin*em*):ti,ab,kw
16 (insulin NEXT resistan*):ti,ab,kw or (metabolic NEXT syndrome):ti,ab,kw or (syndrome NEXT x):ti,ab,kw or (diabet*):ti,ab,kw or (prediabet*):ti,ab,kw
17 (niddm):ti,ab,kw
18 (#12 OR #13 OR #14 OR #15 OR #16 OR #17)
19 (cardio*):ti,ab,kw or (vascular):ti,ab,kw or (heart):ti,ab,kw or (cardiac):ti,ab,kw or (coronary):ti,ab,kw
20 (stroke):ti,ab,kw or (apople*):ti,ab,kw or (infarct*):ti,ab,kw or (brain NEXT attack*):ti,ab,kw or (cerebrovascular):ti,ab,kw

21 (thrombo*):ti,ab,kw or (embol*):ti,ab,kw or (isch*em*):ti,ab,kw or (myocard*):ti,ab,kw or (pericard*):ti,ab,kw
22 (aort*):ti,ab,kw or (aneurysm*):ti,ab,kw or (angina*):ti,ab,kw or (arrhythm*):ti,ab,kw or (sick NEXT sinus):ti,ab,kw
23 (ventricular NEXT fibrill*):ti,ab,kw or (atrial NEXT fibrill*):ti,ab,kw or (atherosclero*):ti,ab,kw or (arteriosclero*):ti,ab,kw
24 (#19 OR #20 OR #21 OR #22 OR #23)
25 (adheren*):ti,ab,kw or (complian*):ti,ab,kw or (concord*):ti,ab,kw
26 (statin*):ti,ab,kw or (hydroxymethylglutaryl NEXT coa NEXT reductase NEXT inhibitor*):ti,ab,kw or (hydroxymethylglutaryl NEXT coenzyme NEXT a NEXT reductase NEXT inhibitor):ti,ab,kw or (hmg NEXT coa NEXT reductase NEXT inhibitor*):ti,ab,kw or (ace NEXT inhibitor*):ti,ab,kw
27 (angiotensin-converting NEXT enzyme NEXT inhibitor*):ti,ab,kw or (calcium NEXT channel NEXT block*):ti,ab,kw or (hypotensive*):ti,ab,kw or (cholesterol NEXT absorption NEXT inhibitor*):ti,ab,kw or (bile NEXT acid NEXT sequestrant*):ti,ab,kw
28 (alpha NEXT adrenergic NEAR/1 inhibitor*):ti,ab,kw or (alpha NEXT adrenergic NEAR/1 block*):ti,ab,kw or (alpha NEXT adrenergic NEAR/1 antagonist*):ti,ab,kw
29 (anti-arrhythm*):ti,ab,kw or (cardiotonic*):ti,ab,kw or (anti-anginal*):ti,ab,kw or (vasodilator*):ti,ab,kw or (lower NEAR/3 cholesterol):ti,ab,kw
30 (lower* NEAR/3 cholesterol):ti,ab,kw or (lower* NEAR/3 blood NEXT pressure):ti,ab,kw or (lower* NEAR/3 blood NEXT sugar):ti,ab,kw or (antihypertensive*):ti,ab,kw or (anti-hypertensive*):ti,ab,kw
31 (oral NEXT hypoglyc*emic*):ti,ab,kw or (antidiabetic*):ti,ab,kw or (anti-diabetic*):ti,ab,kw or (anticoagulant*):ti,ab,kw or (anti-coagulant*):ti,ab,kw
32 (antiplatelet*):ti,ab,kw or (anti-platelet*):ti,ab,kw or (antilipid*emic*):ti,ab,kw or (anti-lipid*emic*):ti,ab,kw or (antilip*emic*):ti,ab,kw
33 (anti-lip*emic*):ti,ab,kw or (hypolip*emic*):ti,ab,kw or (hypolipid*emic*):ti,ab,kw or (hypocholesterol*emic*):ti,ab,kw or (anticholesterol*emic*):ti,ab,kw
34 (anti-cholesterol*emic*):ti,ab,kw or (angiotensin NEXT ii NEXT receptor NEXT antagonist*):ti,ab,kw or (arb*):ti,ab,kw or (mineralcorticoid receptor antagonist*):ti,ab,kw or (aldosterone antagonist*):ti,ab,kw
35 (beta-adrenergic NEAR/2 block*):ti,ab,kw or (beta-adrenergic NEAR/2 inhibitor*):ti,ab,kw or (beta-adrenergic NEAR/2 antagonist*):ti,ab,kw
36 (#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35)
37 (#25 AND #36)
38 (#6 OR #11 OR #18 OR #24 OR #37)
39 (#5 AND #38)

OVID Embase (1980-present)
Searched December 2007; notification alerts monitored until November 2009

1 pharmacist/
2 pharmacist?.mp.
3 druggist?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
4 chemist?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
5 pharmacy/
6 pharmacy.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7 pharmacies.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
8 pharmaceutical care/
9 pharmaceutical
care.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
10 drugstore?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device

manufacturer, drug manufacturer name]
11 pharmaceutical service?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13 community.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
14 retail.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
15 neighbo?rhood.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer nam
e]
16 chain.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
17 13 or 14 or 15 or 16
18 17 and 12
19 exp hypertension/
20 hypertens$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
21 exp blood pressure/
22 blood pressure.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
23 systolic.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
24 diastolic.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
25 19 or 20 or 21 or 22 or 23 or 24
26 exp cholesterol/
27 cholesterol.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
28 high density lipoprotein/
29 low density lipoprotein/
30 very low density lipoprotein/
31 hdl.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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36 dyslipid?em$.mp. [mp=title, abstract, subject he
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37 exp hyperlipidemia/
38 hyperlipid?em$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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47 dyslip?em$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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50 lipoprotein?em$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
51 exp triacylglycerol/
52 triglyceride?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
53 lipid?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
54 exp disorders of lipoprotein metabolism/
55 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56 glucose blood level/
57 blood glucose.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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59 hyperglycemia/
60 hyperglyc?em$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
61 hypergluc?em$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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63 hypoinsulin?em$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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70 hypoinsulinemia/
71 insulin deficiency/
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91 niddm.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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94 exp cardiovascular disease/
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98 cardiac.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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114 sick sinus.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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120 patient compliance/
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124 120 or 121 or 122 or 123
125 exp cardiovascular agent/
126 exp antidiabetic agent/
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128 hydroxymethylglutaryl coa reductase inhibitor?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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131 exp dipeptidyl carboxypeptidase inhibitor/
132 ace inhibitor?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
133 angiotensin-converting enzyme inhibitor?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
134 exp calcium channel blocking agent/
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136 hypotensive?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
137 cholesterol absorption inhibitor?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
138 bile acid sequestrant?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
139 exp adrenergic receptor blocking agent/
140 ((alpha-adrenergic or beta-adrenergic) adj1 (inhibitor? or block$ or antagonist?)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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152 antiplatelet?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
153 anti-platelet?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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160 hypocholesterol?emic?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
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163 exp aldosterone antagonist/

164 aldosterone antagonist?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
165 angiotensin 2 receptor antagonist/
166 angiotensin ii receptor antagonist?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
167 angiotensin ii receptor block$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
168 arb?.mp.
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172 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171
173 124 and 172
174 25 or 55 or 92 or 119 or 173
175 18 and 174

OVID International Pharmaceutical Abstracts (1970-present)
Searched December 2007; notification alerts monitored until November 2009

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2 druggist?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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8 pharmaceutical service?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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17 blood pressure.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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21 cholesterol.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
22 hdl.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
23 ldl.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
24 vldl.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
25 lipoprotein?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
26 dyslipid?em$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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28 hyperlip?em$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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31 hyperlipoprotein?em$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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33 dyslipoprotein?em$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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39 lipoprotein?em$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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41 lipid?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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44 blood sugar.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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46 hypergluc?em$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
47 glucose intoleran$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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51 insulinop?en$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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62 dysinsulin?em$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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71 vascular.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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78 brain attack?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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80 thrombo$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]

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89 sick sinus.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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96 complian$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
97 concord$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
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102 hmg coa reductase inhibitor?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
103 ace inhibitor?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
104 angiotensin-converting enzyme inhibitor?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
105 calcium channel block$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
106 hypotensive?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
107 cholesterol absorption inhibitor?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
108 bile acid sequestrant?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
109 (alpha adrenergic adj1 (inhibitor? or block$ or antagonist?)).mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
110 anti-arrhythm$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
111 cardiotonic?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
112 anti-anginal?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
113 vasodilator$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
114 (lower adj3 cholesterol).mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
115 (lower? adj3 cholesterol).mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
116 (lower? adj3 blood pressure).mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
117 (lower? adj3 blood sugar).mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
118 antihypertensive?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
119 anti-hypertensive?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
120 oral hypoglyc?emic?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
121 antidiabetic?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
122 anti-diabetic?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
123 anticoagulant?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]

124 anti-coagulant?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
125 antiplatelet?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
126 anti-platelet?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
127 antilipid?emic?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
128 anti-lipid?emic?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
129 antilip?emic?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
130 anti-lip?emic?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
131 hypolip?emic?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
132 hypolipid?emic?.mp. [mp=title, subject heading word, registry word, abstract, trade name/g
eneric name]
133 hypocholesterol?emic?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic
name]
134 anticholesterol?emic?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
135 anti-cholesterol?emic?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic
name]
136 angiotensin ii receptor antagonist?.mp. [mp=title, subject heading word, registry word, abstract, trade
name/generic name]
137 arb?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
138 mineralcorticoid receptor antagonist?.mp. [mp=title, subject heading word, registry word, abstract, trade
name/generic name]
139 aldosterone antagonist?.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic
name]
140 (beta-adrenergic adj2 (block$ or inhibitor? or antagonist?)).mp. [mp=title, subject heading word, registry
word, abstract, trade name/generic name]
141 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114
or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or
131 or 132 or 133 or 134 or 136 or 137 or 139 or 140
142 98 and 141
143 20 or 42 or 69 or 94 or 142
144 15 and 143

OVID MEDLINE (1950-present)
Searched December 2007; notification alerts monitored until November 2009

1 pharmacists/
2 pharmacist?.mp.
3 druggist?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique
identifier]
4 chemist?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique
identifier]
5 pharmacies/
6 pharmacy.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique
identifier]
7 pharmacies.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique
identifier]
8 drugstore?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique
identifier]
9 pharmaceutical care.mp. [mp=title, original title, abstract, name of substance word, subject heading word,
unique identifier]
10 pharmaceutical service?.mp. [mp=title, original title, abstract, name of substance word, subject heading word,
unique identifier]
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12 community.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique
identifier]

13 retail.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
14 chain.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
15 neighbo?rhood.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
16 12 or 13 or 14 or 15
17 16 and 11
18 community pharmacy services/
19 17 or 18
20 exp hypertension/
21 hypertens$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
22 exp blood pressure/
23 blood pressure.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
24 systolic.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
25 diastolic.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
26 20 or 21 or 22 or 23 or 24 or 25
27 exp cholesterol/
28 cholesterol.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
29 exp lipoproteins hdl/
30 exp lipoproteins ldl/
31 exp lipoproteins vldl/
32 hdl.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
33 ldl.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
34 vldl.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
35 exp dyslipidemias/
36 lipoprotein?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
37 dyslipid?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
38 hyperlipid?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
39 hyperlip?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
40 hypercholesterol?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
41 hypertriglycerid?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
42 hyperlipoprotein?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
43 hypolipoprotein?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
44 dyslipoprotein?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
45 lip?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
46 lipid?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
47 dyslip?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
48 cholesterol?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

49 triglycerid?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
50 lipoprotein?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
51 exp triglycerides/
52 triglyceride?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
53 lipid?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
54 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
55 blood glucose/
56 blood glucose.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
57 blood sugar.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
58 exp hyperglycemia/
59 hyperglyc?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
60 hypergluc?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
61 glucose intoleran$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
62 hypoinsulin?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
63 insulin deficien$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
64 insulin dependen$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
65 insulinop?en$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
66 insulin insufficien$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
67 insulin?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
68 hemoglobin a glycosylated/
69 glycosylated hemoglobin a.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
70 glycosylated haemoglobin a.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
71 (a1c adj1 hemoglobin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
72 (a1c adj1 haemoglobin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
73 hb a1c.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
74 hba1c.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
75 dysglyc?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
76 dysgluc?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
77 dysinsulin?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
78 insulin resistan$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
79 metabolic syndrome.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

80 syndrome x.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
81 exp diabetes mellitus/
82 diabet$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
83 diabet$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
84 prediabet$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
85 niddm.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
86 exp hyperinsulinism/
87 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86
88 exp cerebrovascular disorders/
89 exp cardiovascular diseases/
90 cardio$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
91 vascular.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
92 heart.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
93 cardiac.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
94 coronary.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
95 stroke.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
96 apople$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
97 infarct$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
98 brain attack?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
99 cerebrovascular.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
100 thrombo$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
101 embol$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
102 isch?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
103 myocard$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
104 pericard$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
105 aort$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
106 aneurysm$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
107 angina$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
108 arrhythm$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
109 sick sinus.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
110 ventricular fibrill$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
111 atrial fibrill$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
112 atherosclero$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
113 arteriosclero$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique

identifier]
114 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or
98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113
115 patient compliance/
116 adheren$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
117 complian$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
118 concord$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
119 115 or 116 or 117 or 118
120 exp antilipemic agents/
121 exp cardiovascular agents/
122 exp hypoglycemic agents/
123 statin?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
124 hydroxymethylglutaryl coa reductase inhibitor?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
125 hydroxymethylglutaryl coenzyme a reductase inhibitor?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
126 hmg coa reductase inhibitor?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
127 exp angiotensin-converting enzyme inhibitors/
128 ace inhibitor?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
129 angiotensin-converting enzyme inhibitor?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
130 exp calcium channel blockers/
131 calcium channel block$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
132 hypotensive?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
133 cholesterol absorption inhibitor?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
134 bile acid sequestrant?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
135 exp adrenergic alpha-antagonists/
136 (alpha adrenergic adj1 (inhibitor? or block$ or antagonist?)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
137 anti-arrhythm$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
138 cardiotonic?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
139 anti-anginal?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
140 vasodilator$.mp. [mp=title, original title, abstract, name of substance w
ord, subject heading word, unique identifier]
141 (lower$ adj3 cholesterol).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
142 antihypertensive?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
143 anti-hypertensive?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
144 oral hypoglyc?emic?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

145 antidiabetic?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
146 anti-diabetic?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
147 anticoagulant?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
148 anti-coagulant?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
149 antiplatelet?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
150 anti-platelet?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
151 antilipid?emic?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
152 anti-lipid?emic?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
153 antilip?emic?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
154 anti-lip?emic?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
155 hypolip?emic?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
156 hypolipid?emic?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
157 hypocholesterol?emic?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
158 anticholesterol?emic?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
159 anti-cholesterol?emic?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
160 angiotensin ii receptor antagonist?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
161 exp angiotensin ii type 1 receptor blockers/
162 arb?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
163 mineralcorticoid receptor antagonist?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
164 exp aldosterone antagonists/
165 aldosterone antagonist?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
166 exp adrenergic beta-antagonists/
167 (beta-adrenergic adj2 (block$ or inhibitor? or antagonist?)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
168 (lower$ adj3 blood pressure).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
169 (lower$ adj3 blood sugar).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
170 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 1
43 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169
171 119 and 170
172 26 or 54 or 87 or 114 or 171
173 19 and 172

CINAHL search strategy (1982-present)
Searched June 2007

1 Pharmacists/
2 pharmacist?.mp.
3 druggist?.mp.
4 chemist?.mp.
5 Pharmacy, Retail/
6 pharmacy.mp.
7 pharmacies.mp.
8 drugstore?.mp.
9 pharmaceutical care.mp.
10 pharmaceutical service.mp.
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12 community.mp.
13 (retail or chain or neighbo?rhood).mp.
14 12 or 13
15 exp Hypertension/
16 hypertens$.mp.
17 exp Blood Pressure/
18 systolic.mp.
19 diastolic.mp.
20 blood pressure.mp.
21 15 or 16 or 17 or 18 or 19 or 20
22 Cholesterol/
23 cholesterol.mp.
24 exp Lipoproteins, HDL/
25 exp Lipoproteins, LDL/
26 hdl.mp.
27 ldl.mp. [mp=title, original title, abstract, name of substance, word, subject heading word, unique identifier]
28 vldl.mp. [mp=title, original title, abstract, name of substance, word, subject heading word, unique identifier]
29 exp Hyperlipidemia/
30 lipoprotein?.mp.
31 dyslipid?em$.mp.
32 hyperlipid?em$.mp.
33 hyperlip?em$.mp.
34 hypercholesterol?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
35 hypertriglycerid?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
36 hyperlipoprotein?em$.mp.
37 hypolipoprotein?em$.mp.
38 dyslipoprotein?em$.mp.
39 lip?em$.mp.
40 lipid?em$ mp.
41 dyslip?em$.mp.
42 cholesterol?em$.mp.
43 triglycerid?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
44 lipoproteinem$.mp.
45 triglycerides/
46 triglyceride?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
47 lipid?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
48 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or

41 or 42 or 43 or 44 or 45 or 46 or 47
49 blood glucose/
50 blood glucose.mp.
51 blood sugar.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
52 hyperglycemia/
53 hyperglyc?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
54 hypergluc?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
55 glucose intoleran$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
56 hypoinsulin?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
57 insulin deficien$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
58 insulin dependen$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
59 insulinop?en$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
60 insulin insufficien$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
61 insulin?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
62 hemoglobin a, glycosylated/
63 glycosylated hemoglobin a.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
64 glycosylated haemoglobin a.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
65 (a1c adj1 hemoglobin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
66 (a1c adj1 haemoglobin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
67 hb a1c.mp. [mp=title, original title, abstract, name of substance, word subject heading word, unique identifier]
68 hba1c.mp. [mp=title, original title, abstract, name of substance, word subject heading word, unique identifier]
69 dysglyc?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
70 dysgluc?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
71 dysinsulin?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
72 insulin resistan$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
73 metabolic syndrome.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
74 syndrome x.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
75 exp diabetes mellitus/
76 glucose intolerance/
77 exp insulin resistance/
78 diabet$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
79 prediabet$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
80 niddm.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
81 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or

68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80
82 exp cerebrovascular disorders/
83 exp cardiovascular diseases/
84 cardio$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
85 heart.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
86 cardiac.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
87 coronary.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
88 stroke.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
89 apople$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
90 infarct$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
91 brain attack?.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
92 cerebrovascular.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
93 thrombo$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
94 embol$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
95 isch?em$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
96 myocard$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
97 pericard$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
98 aort$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
99 aneurysm$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
100 angina$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
101 arrythm$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
102 sick sinus.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
103 ventricular fibrill$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
104 atrial fibrill$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
105 atherosclero$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
106 arteriosclero$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
107 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106
108 exp patient compliance/
109 adheren$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
110 complian$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
111 concord$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
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- Chapter 4 -

A PRAGMATIC CLUSTER RANDOMIZED TRIAL EVALUATING THE IMPACT OF A COMMUNITY PHARMACY INTERVENTION ON STATIN ADHERENCE: RATIONALE AND DESIGN OF THE COMMUNITY PHARMACY ASSISTING IN TOTAL CARDIOVASCULAR HEALTH (CPATCH) STUDY

4.1 Abstract

Background: Traditional randomized controlled trials are considered the gold standard for evaluating the efficacy of a treatment. However, in adherence research, limitations to this study design exist, especially when evaluating real-world applicability of an intervention. Although adherence interventions by community pharmacists have been tested, problems with internal and external validity have limited the usefulness of these studies, and further well-designed and well-conducted research is needed. We aimed to determine the real-world effectiveness of a community pharmacy adherence intervention using a robust study design. This novel design integrates cluster randomization and an outcome evaluation of medication adherence using a population-based administrative data source in the province of Saskatchewan, Canada.

Methods: Community pharmacies from across the province of Saskatchewan, Canada were randomized to deliver an adherence intervention to their patients or usual care. Intervention pharmacies were trained to employ a practical adherence strategy targeted at new users of statin medications. While randomization and implementation of the intervention occurred at the community pharmacy level, the outcome analysis will occur at the level of the individual patients. The primary outcome is the mean statin adherence among all eligible new users of statin medications. Secondary outcomes include the proportion of new statin users who exhibit adherence ≥80%, and persistence with statin use.

Conclusion: This novels study design was developed to combine the rigor of a randomized trial with a pragmatic approach to implementing and capturing the results in a real-world fashion. We

believe this approach can serve as an example for future study designs evaluating practice-based adherence interventions.

4.2 Introduction

Randomized controlled trials (RCT) are considered the gold standard design for the evaluation of treatment efficacy,[1] and are increasingly being used for evaluating interventions aimed at improving medication adherence.[2] However, in adherence research, limitations to this study design exist. First, traditional RCTs require that all study participants are informed and consenting volunteers. This requirement likely pre-selects individuals who are at a lower risk for non-adherence, particularly for RCTs of behavioural interventions. Indeed, patients enrolling in clinical trials may be systematically different from those declining to participate.[2,3] In addition, when traditional RCT designs are used, the same health care professional is often forced to provide the adherence intervention and 'usual care' concurrently.[4,5] Clearly, contamination is unavoidable when the same health practitioner is providing the control and experimental conditions simultaneously.[3]

Because of their accessibility and frequent interactions with patients, community pharmacists are considered ideally situated to deliver interventions aimed at improving medication adherence.[3] However, adherence interventions by community pharmacists have not consistently shown benefits.[3,6] One of the reasons may be that these studies are often plagued with methodological problems. Many studies do not report a power calculation, do not utilize proper randomization techniques or allocation concealment, and most do not provide adequate details of the intervention when reporting the results.[7] Furthermore, generalizability of successful interventions is often low because most health care professionals do not have the time or resources to implement complex study protocols.[8-11] As a result, little is known about the extent to which community pharmacists can influence adherence in real world settings.

We describe the design of a study aimed at evaluating the real-world effectiveness of an adherence intervention provided by community pharmacies; the Community Pharmacy Assisting in Total Cardiovascular Health (CPATCH) study. This prospective study employs a novel design that integrates cluster randomization with an evaluation of *all* at-risk patients using an administrative database. The design presented herein was developed to strengthen the external validity of research studies that examine adherence interventions while maintaining the high standards required for prospective clinical trials. Although the general CPATCH strategy is

intended to be employable with all cardiovascular medications, this study is focused on the prevention of non-adherence among new users of statin medications. Statin medications were chosen for this initial study, as it is well known that 40% to 50% of all new statin users become non-adherent within the first year,[12,13] and a sizeable proportion discontinue the medication after only one dispensation.[14]

4.3 Methods

Recruitment of Community Pharmacies

In the Fall 2009, all community pharmacies across the province of Saskatchewan (n=357) were invited to enrol in the CPATCH study. Advertisements were placed in bulletins and newsletters distributed by provincial pharmacy organizations. Also, individual letters were mailed to all pharmacy owners/managers in the province and the study investigators advertised in person at various local pharmacy conferences and events.

Community pharmacies interested in enrolling were directed to the study coordinating centre at the University of Saskatchewan to determine their eligibility. Pharmacies were eligible for enrollment if: i) they filled at least 85 total statin prescriptions during a consecutive 6 week period; ii) the owner/manager indicated that this adherence intervention would be given priority over all other study initiatives offered by the pharmacy staff; and iii) all members of the pharmacy (dispensary) staff provided informed consent.

Randomization

The CPATCH study employed a clustered randomized trial design whereby community (retail) pharmacies were randomized into one of two groups: an intervention group that received training to provide the CPATCH adherence strategy to their patients; and a usual care group that did not receive any specialized adherence training and will provide their patients with standard care.
A computer generated randomization list, in permuted blocks of 6, was created by an employee at the Drug Information centre at the University of Saskatchewan who is not an investigator in this study. Each randomly allocated group assignment (intervention or usual care) was individually sealed in sequential, opaque envelopes and kept in the office of the Drug Information Centre. Given the nature of the intervention, it was impossible for the study

investigators and pharmacy researchers (i.e. participating pharmacies) to be blinded to the group assignments; however, all study researchers were blinded to the sequence generation, and all allocations were concealed until the study group was assigned. Furthermore, randomization was carried out in multiples of 6 (i.e., six pharmacies were randomized at a time) to ensure that the investigators had no opportunity to anticipate which group a pharmacy would be allocated to.

The Intervention

Pharmacies (i.e. pharmacists and pharmacy technicians) randomized to the intervention group received training on how to implement the CPATCH support program within their store; the control pharmacies did not receive any training, and were intentionally not given any indication of the focus of the study intervention (adherence of new statin users). Training on the CPATCH strategy was provided through a 2.5 hour workshop delivered in a setting outside the dispensary. Briefly, the training program introduced a simple and coordinated strategy to consistently identify and support patients at high risk for statin non-adherence. The criteria used to identify individuals at high-risk for non-adherence were based on epidemiologic observations of statin use. Specifically, individuals receiving their first dispensation for a statin medication have a 40%-50% risk of becoming non-adherent in the first year of therapy.[12,13] Further, many patients will discontinue after only one dispensation.[14] These dispensation patterns were used to provide objective evidence regarding the risk for non-adherence associated with new prescriptions of these medications. Also, these data were used to justify our hypothesis that initial statin dispensation encounters are critical to the prevention of non-adherence.

The CPATCH strategy was designed specifically to be implemented into real-world community pharmacy practice without the need for additional resources or significant changes to existing workflow procedures. As a result, the program is flexible to each specific pharmacy. The consistent elements of the overall CPATCH training strategy are: i) routine identification of new users (those in their first year of therapy) of statin medications as they present for each dispensation; ii) consistent assessment for barriers to non-adherence at every dispensation for at-risk patients (new users); iii) a paradigm shift from traditional counselling to an approach that focuses on patient preparation and reassurance; preparation for the negative messages about statins they will likely hear in the coming months and reassurance that this medication is backed

by objective evidence, and iv) a commitment by pharmacy staff to actively respond to identified adherence barriers such as cost, intolerance, lack of knowledge, or beliefs about the medication. The focus of this strategy is to lower the incidence of non-adherence rather than remedy those patients with already established non-adherence.

Subjects

Intervention pharmacies will identify patients within the first year of statin therapy through dispensation records and face-to-face encounters. Although intervention pharmacies will target all statin users within their first year of therapy, data will only be collected on those patients who: i) receive a new statin prescription from a study pharmacy (intervention or control) during the observation period; ii) have no statin fills recorded during the year prior to the index prescription (first fill for a statin medication during the study observation period); and iii) have been continuously enrolled as a Saskatchewan Drug Plan beneficiary for at least 365 days prior to the index prescription. These study patients will be identified independently by personnel from the Saskatchewan Ministry of Health and all outcome data will be collected at the administrative database level (see "Follow-up").

The observation period for each pharmacy will begin two weeks after their training session. This two week lag period will be used to allow each staff to implement the strategy and resolve any issues with the help of the CPATCH investigators. To ensure consistency between groups, usual care pharmacies were assigned a start date that matched the date of an intervention pharmacy falling most closely in the order of randomization. As a result, in each permuted block of six randomized pharmacies, three pairs (one control and one intervention) of stores will share the same start date.

Follow-up

All patient information and outcome data will be collected from administrative databases maintained by the Saskatchewan Ministry of Health (Sask Heath). Sask Health maintains a registry and several databases containing health services records such as prescription drug data, hospital services data, and physician services data (Table 4.1). Health services information captured by distinct databases can be linked at the patient level through a unique identification

number for each individual. These databases have served as the basis for many observational studies because they capture data on the vast majority of Saskatchewan residents.[15-18] For this study, the databases will be used to capture health services utilization (prescriptions, physician visits and hospitalizations) including diagnoses on all eligible subjects.

All Saskatchewan residents are eligible for provincial health insurance coverage, except inmates of federal penitentiaries and members of the Royal Canadian Mounted Police and Canadian Forces (less than 1% of the Saskatchewan population). All health insurance beneficiaries are eligible for Saskatchewan Drug Plan benefits except those who receive these benefits from another government agency, primarily registered Indians (about 9% of the population). Therefore about 10% of the Saskatchewan population is ineligible for the study because of no or incomplete capture of health services information.

The researchers will provide Sask Health with the list of participating pharmacies and their specific Saskatchewan Drug Plan identifiers (i.e., provider identifier), and enrolment dates. Sask Health personnel will extract all statin prescriptions dispensed from the participating pharmacies during the 18 months following the pharmacy's enrolment date. The individuals receiving these prescriptions will form the pool of potential new statin-users. The prescription histories of the potential pool members will be reviewed to determine which subjects are new statin-users. Hospital, physician and prescription information for eligible new statin-users will be compiled and de-identified prior to release to the researchers for analysis.

It is estimated that each pharmacy will need six months to accrue their sample size of new statin users, thereby allowing 12 months for follow up. However, because it will not be possible to determine when each pharmacy's sample size has been met, data will be collected on all new-users presenting to each pharmacy throughout the observation period. Patients will be followed from one year prior to their index prescription until the end of the pharmacy's observation period, death, or loss of beneficiary status, whichever is sooner.

Outcomes

Although community pharmacies are the unit of randomization, our primary outcome is the mean adherence among all eligible new users of statin medications who have been followed up for at least 12 months past their index prescription. This primary outcome will be measured at the individual level. All statin dispensations for each subject will be captured by the prescription drug plan database and mean adherence will be measured using the proportion of days covered (PDC),[19,20] adjusted for any days that a subject may be hospitalized during the observation period. The PDC is calculated by taking the sum of the days' supply for all statin prescription fills during the study period, divided by the number of days of observation. Study participants who have statin dispensations from non-study pharmacies will be captured and accounted for using methods previously published.[21] Secondary outcomes include the proportion of new statin users who exhibit adherence (PDC) ≥80%, and the persistence with statin use among patients with a minimum of 12 months of follow up. Persistence is defined as the number of days from the index prescription to the earliest occurrence of study end date or date of discontinuation (assumed when a refill is not obtained within 102 days of finishing the estimated supply).[22,23] Only those subjects with a minimum of 6 months of follow-up will be included in the secondary analyses.

Sample Size

Using data from a previous observational study evaluating one-year statin adherence of new users at 34 different community pharmacies in Saskatchewan,[21] we were able to estimate an intracluster (or intraclass) correlation coefficient (ICC) of 0.0143, and determine that mean statin adherence in this population was 0.71 (SD 0.13). Thus, in order to detect a 15% improvement in mean adherence, considered to be clinically important,[24,25] with 80% power at a $p < 0.05$, 270 subjects would be required in each group. The community pharmacies enrolled in CPATCH are expected to accrue a minimum of 25 subjects over a 6 month period. As a result, 22 clusters (pharmacies) are needed, but 30 will actually be enrolled as the planned statistical analysis requires a minimum of 15 clusters within each group.[26]

Statistical Methods

Baseline characteristics will be compared between groups using both cluster and individual-level variables (Table 4.2). To determine the effect of the intervention, mean adherence will be measured at one year using generalized estimating equations (GEE) with an exchangeable correlation matrix and robust standard errors, with individuals as the analytical unit.[27] Both univariate and multivariable models will be developed based on individual and pharmacy-level variables considered statistically significant ($P<0.10$), or clinically important (e.g. age, sex) (Tables 4.2). To estimate the extent to which the intervention was implemented in each pharmacy, pharmacy team staff members will record the names of all new users identified during the course of their day-to-day practice. At the end of each month, a pharmacy staff member will compare the number of identified patients recorded on the list to the total number of new users who received a statin prescription based on their electronic dispensation records. These "screening rates" will be reported to the investigators monthly, and will be adjusted for in the final models. All first order interactions will be tested.

Two secondary endpoints, the proportion of new statin users who exhibit optimal adherence (≥80%) at one-year, and mean persistence will be measured on an individual level and analyzed using GEE with an exchangeable correlation matrix and robust standard errors. All analyses will be intention-to-treat, and will include any pharmacies that have withdrawn, as well as any individual subjects who are no longer beneficiaries of the Saskatchewan Drug Plan (due to death or coverage termination). Mean imputation will be used for subjects or pharmacies lost-to-follow-up.

Ethics approval for the study protocol was obtained from the University of Saskatchewan Biomedical Ethics Board (09-135). The study is registered at ClinicalTrials.gov no. NCT00971412.

4.4 Discussion

Medication non-adherence is a global problem[28] that consumes substantial financial health care resources,[29] and has been recognized as a predictor of negative patient outcomes.[17,30] Non-adherence is complicated and multifactorial,[31] and health interventions that are aimed at

improving it are often not evaluated using pragmatic study designs. Recognizing this, we have utilized a novel study design evaluating an intervention involving community pharmacies, aimed at improving medication adherence.

A CRT design was selected for this study for two reasons. First, the intervention is intended for implementation at the community pharmacy level, so it is logical that community pharmacies would be the unit of randomization. Second, this design will lessen the risk for experimental contamination because pharmacists will not be forced to provide intervention and usual care activities at the same time.[32] We can not rule out the potential for the Hawthorne effect[33] within the usual care pharmacies; however, the effect is likely minimal as this group was intentionally not given any indication of the focus of the study intervention (adherence of new statin users). Also, this design will eliminate the need to recruit, obtain consent, and randomize individual patients, which is often impractical in typical community pharmacy settings.

We were prudent in following the guidelines for cluster randomized trials outlined in the CONSORT statement,[34] ensuring that the risk of contamination between groups will be minimized, while maintaining the integrity of the experimental group comparison. Because the intervention will be evaluated in all new statin users presenting to each pharmacy, it will enhance the external validity of this study. Also, by ensuring all patient data are collected at arms length (by the Saskatchewan Ministry of Health), pharmacists can implement the adherence support strategy on all patients without the administrative burden of obtaining patient consent and collecting study specific information.

In addition, we have also provided the ICC used in estimating our sample size. To our knowledge, this ICC is the first one to be published in this particular field of research. We hope this value will prove useful in the design of future studies as well as encourage other researchers, especially in the area of medication adherence, to share their ICCs or cluster specific event rates.

4.5 Conclusion

We have presented, in detail, the design of the CPATCH study. Our approach combines the rigor of a randomized trial with a pragmatic approach to implementing and recording the results

in a real-world fashion. We believe this approach can serve as an example of study design for the evaluation of future practice-based adherence interventions in large randomized trials.

Table 4.1. Relevant Data Elements Available from Saskatchewan Health Databases[18]

Database	Available Data
Prescription drug	Patient information Drug information Prescriber information Dispensing pharmacy information Cost information
Hospital services	Patient information Diagnostic and procedure information (based on ICD-10-CA[a] and CCI[b]) Admission and discharge dates Length of hospital stay
Physician services	Patient information Physician information Diagnostic information (3 digit ICD-9[c] code) Billing information
Insurance registry	Beneficiary information (effective date, end date, sex, age, residence)

a. International Statistical Classification of Disease and Related Health Problems, Tenth Revision, Canada[35]
b. Canadian Classification of Health Interventions[36]
c. International Classification of Disease, Ninth Revision

Table 4.2. Individual and Pharmacy Level Variables Available for Multivariable Analysis

Variable	Description	Database Source
Individual Level		
Sex	Sex of patient	Insurance registry
Age	Age of patient at index date (calculated using date of birth)	Insurance registry
Income security benefits	Patient receives income security benefit (a proxy for socioeconomic status)	Prescription drug
Concurrent medications	Concurrent medications use during one year prior to patient's index date, and for the first 6 months of the study observation period. Beta blockers Angiotensin converting enzyme inhibitors ASA Oral hypoglycemics	Prescription drug
Prior cardiovascular event	Cardiovascular event(s) in one year prior to patient's index date (Based in ICD-10-CA classifications) Myocardial infarction (I21. – I23.) Stroke (all causes) (I60. – I64.) Transient ischemic attack (G45.0) Unstable angina (I20.0) Other ischemic heart disease (I24. – I25.) Revascularization procedures PTCA (1.IJ.50, 1.IJ.57.GQ, 1.IL.35), CABG (1.IJ.76) Coronary Angiography (3.IP.10)	Hospital services
Study cardiovascular event	Cardiovascular event(s) in during study observation period (Based in ICD-10-CA classifications) Myocardial infarction (I21. – I23.) Stroke (all causes) (I60. – I64.) Transient ischemic attack (G45.0) Unstable angina (I20.0) Other ischemic heart disease (I24. – I25.) Revascularization procedures PTCA (1.IJ.50, 1.IJ.57.GQ, 1.IL.35), CABG (1.IJ.76) Coronary Angiography (3.IP.10)	Hospital services
Chronic disease score	Chronic disease score (measure of chronic disease status derived from population-based automated pharmacy data)[37]	Prescription drug
Prior hospitalizations	Number of hospitalizations in one year prior to patient's index date	Hospital services
Study hospitalizations	Number of hospitalizations during study observation period	Hospital services
Physician visits	Number of physician visits during and prior to observation	Physician services

Variable	Description	Database Source
Pharmacy Level		
Pharmacy type	Indicates the type of pharmacy (mass merchandise, chain/grocery, independent)[38]	Investigators to categorize
Pharmacy location	Rural (population<10,000) Regional (population 10,000 – 100,000) Urban (population >100,000)	Investigators to categorize
Prescription volume	Mean number of new statin prescriptions filled monthly (proxy measure for prescription volume)	Prescription drug
Pharmacist coverage	Pharmacist overlap or single pharmacist	Pharmacy survey
Technician support	Pharmacy technician support	Pharmacy survey
Monthly screening rates	Proportion of new users identified by pharmacy staff (proxy measure of the extent that the identification component of the intervention was performed)	Pharmacy staff

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- Chapter 5 -

PATTERNS OF ADHERENCE IN THE FIRST YEAR OF ANTIHYPERTENSIVE THERAPY: AN OBSERVATIONAL STUDY

5.1 Abstract

Background: Adherence to chronic medications is poor. The first year of therapy has been associated with the highest probability for non-adherence, and studies of statin medications have suggested that a significant proportion of first year non-adherence is due to discontinuation after only a single dispensation (first-fill discontinuations). Studies examining utilization of antihypertensive (AHT) medications rarely report patterns of adherence specific to the first year of therapy. Also, the majority of studies report that adherence is significantly better with angiotensin-receptor blockers (ARBs) compared to other categories of AHT agents. The purpose of this study was to address two specific questions: 1) what proportion of non-adherence in the first year of AHT therapy is due to first-fill discontinuations? and 2) are ARBs associated with improved adherence compared to other AHT agents?

Methods: This retrospective cohort study utilized data from linked administrative databases in the province of Saskatchewan. Eligible subjects were 40 years of age or older and had received a new AHT prescription between 1994 and 2002. The primary endpoint for the first study question was the proportion of non-adherent subjects who discontinued their AHT after the first dispensation (i.e. first-fill discontinuation). For the second research question, the cohort was restricted to a subgroup of individuals receiving monotherapy. The primary endpoint for the second research question was the proportion of subjects achieving optimal adherence at one year stratified by AHT category. Further analyses specifically compared adherence between ARBs, angiotensin converting enzyme inhibitors (ACEIs) and non-dihydropyridine calcium channel blockers (Non-DHP), and between ARBs and ARB + hydrochlorothiazide combinations. Adherence was estimated using the cumulative mean gap ratio measure.

Results: A total of 52,125 subjects were eligible. The proportion of subjects with optimal adherence (≥80%) at one year was 50.4% (26,285/52,125). First fill discontinuations occurred in 38.9% (10,054/25,840) of non-adherent subjects. In subjects receiving monotherapy only, adherence varied between the different AHT categories. Optimal adherence (≥80%) was observed in 59.9%, 67.2%, and 53.0% of subjects initiating ARBs (losartan) [245/409], ACEI (ramipril) [1097/1632], and non-DHP (amlodipine) [473/893] respectively. Compared to losartan, the adjusted odds for achieving optimal adherence was not significantly different for users of ramipril (adjusted OR 1.28, 95% CI 0.99 – 1.643, p=0.05) or amlodipine (adjusted OR 0.81, 95% CI 0.63 – 1.05, p=0.12). Adherence was high in both the ARB (1013/1600 [63.3%]) and ARB + HCTZ (305/453 [67.3%]) categories, and no significant difference was found between them (adjusted OR 1.16, 95% CI 0.92 – 1.46, p=0.20).

Conclusion: A substantial proportion of non-adherence to AHT medications can be attributed to subjects who discontinue after only a single fill of medication. Adherence to AHT medications is poor across all categories and it is unlikely that specific agents, such as ARBs, are independently associated with optimal adherence.

5.2 Introduction

It is well known that adherence to chronic medications is poor,[1] and the first year of therapy has been consistently associated with the highest probability for non-adherence.[2-5] Studies of adherence to statin medications have indicated that non-adherence in the first year of therapy can be frequently attributed to individuals who discontinue after only a single dispensation ("first-fill discontinuations").[3, 6] However, it is not clear whether these observations reflect a statin-specific non-adherence pattern or a pattern of non-adherence related to cardiovascular, or chronic disease, medications in general. Typically, studies of antihypertensive (AHT) medications have reported discontinuation rates after one year of therapy, with results ranging from 28%[7] to 43%.[8] Few studies have specifically examined whether first-fill discontinuations contribute to non-adherence in the first year in other widely prescribed cardiovascular medications, like AHT therapy.

Available studies suggest AHT medications are associated with varying levels of non-adherence depending on the category prescribed. Specifically, several investigators have reported that subjects taking angiotensin-receptor blockers (ARBs) are significantly more likely to demonstrate good adherence and/or persistence compared to those taking other AHT agents.[7-15] Previously, authors have speculated that improved adherence is likely due to the more favourable side effect profile of ARBs.[7, 12] As the determinants of adherence are complex and multifactorial,[1, 2] we hypothesized that the association between ARB use and good adherence is likely due to confounding or bias overlooked in the previous studies rather than any specific characteristics of a single AHT medication category.

The purpose of this study was to address two specific questions: 1) what proportion of non-adherence in the first year of AHT therapy is due to first-fill discontinuations? and 2) is ARB use independently associated with improved adherence compared to other AHT medications?

5.3 Methods

We created a cohort of subjects who were new users of AHT therapy between January 1, 1994 and December 31, 2002 using the linked administrative databases from the province of Saskatchewan, Canada. The Saskatchewan Ministry of Health maintains several health services

databases including prescription drug data, physician services utilization, hospital services utilization, and vital statistics. Health services information captured by these distinct databases can be linked electronically at the individual level through a unique identification number. All Saskatchewan residents are eligible for provincial health insurance coverage, except inmates of federal penitentiaries and members of the Royal Canadian Mounted Police and Canadian Forces (less than 1% of the Saskatchewan population); approximately 90% of the Saskatchewan population is eligible for prescription drug coverage. Residents ineligible for coverage under the drug plan are primarily Registered Indians who have their prescription costs paid for by another government agency.[16] These databases have served as the basis for many observational studies of medication adherence and are considered to be of high quality.[4, 17-19]

To be eligible, subjects must have been at least 40 years of age and filled a new AHT prescription in one of the following pre-specified categories: beta blockers, angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), non-dihydropyridine calcium channel blocker (Non-DHP CCB), dihydropyridine calcium channel blocker (DHP CCB), thiazide diuretic, potassium-sparing diuretic; or one of the following combination products: ACEI + hydrochlorothiazide (HCTZ), ARB + HCTZ, beta blocker + diuretic, and potassium-sparing diuretic + HCTZ (Appendix C). A new prescription was defined as having no dispensations for any AHT agent in the 5 years prior to the first AHT prescription (index date).

In an attempt to ensure that the AHT was being prescribed for uncomplicated hypertension (i.e., without significant comorbidities), we excluded all subjects who had a history of hospitalization or outpatient physician services in the previous 5 years for any of the following: cardiovascular events (e.g. myocardial infarction, unstable angina, congestive heart failure), diabetes, HIV/AIDS, renal or liver disease, esophageal varices, or solid organ transplant. The observation period began on the first AHT prescription dispensation (i.e., index date) and continued for 1 year (365 days). Because medication use during hospital stays is not captured by the Saskatchewan Drug Plan, subjects who were hospitalized for any reason during the observation period were excluded. To ensure reliable estimates of adherence for all patients, only subjects with a full 365 days of follow-up (i.e. still receiving Saskatchewan Health and prescription benefits) were included in the analysis.

First Fill Discontinuations:

The primary endpoint for the first study question was the proportion of non-adherent subjects who discontinued their AHT after the first dispensation (i.e. first-fill discontinuation). Because many individuals receiving AHT therapy require concurrent combinations from multiple AHT categories, accurately determining non-adherence can be complex. For example, it is not clear how to classify patients that are selectively adherent to one AHT medication but not another.[20, 21] Therefore, we defined non-adherence as the failure to obtain enough AHT medication to cover ≥ 80% of the observation period (365 days) with at least one AHT medication, regardless of the total number of different AHT categories prescribed during that period.[20] For example, a subject who initially filled an ACE inhibitor and then subsequently switched to a beta-blocker would be considered adherent if sufficient medication was available between the agents to cover 80% of the observational period. The 80% threshold is easily defined and is commonly used in studies measuring adherence.[5, 17, 22]

Adherence was estimated with the cumulative mean gap ratio (the number of days when medication was unavailable in relation to the total number of days of the observation period).[23] This was calculated by dividing the number of days that any AHT medication was unavailable (due to a delayed refill or discontinuation) by the number of days in the observation period, then subtracting that number from 1 to obtain an adherence value.[23, 24] In Saskatchewan, AHT prescriptions are primarily dispensed on a monthly (34 day) basis, so we calculated the number of days medication was unavailable by subtracting the expected gap (34 days) from the actual gap (number of days between AHT dispensation dates). Although Saskatchewan pharmacies may dispense diuretic prescriptions in larger quantities (100-day supplies), the majority of all diuretic dispensations (89.6%) were dispensed in quantities not exceeding 34 tablets. Negative values indicated early refills, and therefore a surplus of medication; positive values indicated late refills, and a period of days when medication was not available. To account for oversupply, we subtracted the total number of days of surplus medications from the total days of unavailable medication (assuming that all dispensed medications would be consumed in their entirety). For individuals taking only a single medication, this cumulative gap calculation is mathematically identical to the "fill frequency" measure that has been previously used with Saskatchewan data.[4, 17, 25]

Adherence Associated with ARBs versus Other AHT Categories

For the second research question, we restricted the overall cohort of all AHT users to a subgroup of individuals receiving monotherapy only. These subjects were identified by excluding all those who filled medications from >1 AHT category during the one-year follow-up period (i.e., if they switched to a different category of AHT, or had an AHT medication added); however, switching medications within the same category was allowed. The primary endpoint was the proportion of subjects achieving optimal adherence at one year stratified by AHT category (Appendix C).

In a secondary analysis, we repeated the adherence analysis by restricting the cohort to those who were prescribed either losartan (ARB), ramipril (ACEI), or amlodipine (DHP CCB) as their initial therapy. Losartan was chosen as a comparator because it was the first ARB released into the Canadian market (1995), and was the most frequently (25.6%) prescribed ARB in our cohort. Ramipril and amlodipine were selected as comparators because they shared the closest Canadian release date to losartan (ramipril 1997, amlodipine 1992), and they were only available as brand name formulations throughout the entire study period. Therefore, these cohorts were composed of subjects receiving "newly" marketed AHT medications where no generic substitute was available. The final analysis compared adherence rates between subjects receiving any ARB medication and those receiving ARB + HCTZ combination products to evaluate the influence of a diuretic on the adherence of these medications (Appendix C).

Sensitivity Analyses

We performed a number of sensitivity analyses to evaluate the robustness of our results. First, to ensure inclusion of medication oversupply was not influencing our study results, we excluded medication oversupply from our adherence calculation by setting all surplus medication values to 0, and then summed all days where medication was unavailable (i.e., assuming all previously dispensed medications were discarded or not taken). Second, we re-calculated adherence after modifying the "days supply" variable to 30 and 40 days in place of 34. Third, because the Saskatchewan Drug Plan did not collect a "days supply" variable during the study period, we conducted a sensitivity analysis using 2 alternate adherence measures. First, we calculated the "tablets per day" by dividing the total number of tablets dispensed during the observation period by the number of days in the observation period (365 days).[3] Second, we employed a modified

proportion of days covered (PDC) in which we used the individual drug monographs of the most commonly prescribed AHT in each category (Appendix 1) to estimate a days supply variable by dividing the quantity of tablets/capsules in each dispensation by the recommended daily regimen.[25] The estimated days supply variable was then divided by the number of days in the observation period. Finally, we compared adherence of other ARBs (candesartan, irbesartan, telmisartan, and valsartan) to ramipril and amlodipine.

Statistical Analysis

Baseline characteristics were compared using ANOVA and chi-square, where appropriate. Crude proportions for optimal adherence between the individual AHT categories were compared using chi-square. Multivariate logistic regression was used to adjust for confounding factors that may have influenced the proportion of subjects exhibiting optimal adherence or discontinuing after the first fill. The following covariates were either statistically significant ($p<0.1$) or considered to be clinically relevant for both models: sex, age at index, Von Korff chronic disease score[26] (a well validated measure of comorbidity derived from medication usage) at index, income security benefits at index (a proxy measure for socioeconomic status), year that the index prescription was dispensed, and number of physician visits during the observation year, as adherence may be higher in subjects receiving regular follow-up.[27] We also adjusted for concurrent dispensations of the following medications during the observation year: oral diabetes medications and/or insulin, nitrates, statins, ASA, warfarin, and antidepressants. Additionally, we estimated the overall prescription burden by totalling the number of selected non-AHT prescription medication classes filled (Appendix C) during the observation year. All first order interactions were tested, with none being clinically significant ($p>0.1$). All analyses were carried out using SPSS version 16.0 for Windows (SPSS Inc, Chicago, IL), and Stata SE, version 10 (Stata, College Station, Texas). Because all data were de-identified by Saskatchewan Ministry of Health personnel prior to being sent to the investigators, the study protocol was granted a letter of exemption by the University of Saskatchewan Biomedical Research Ethics Board.

5.4 Results

First Fill Discontinuations

We identified 67,939 subjects who were newly initiated on AHT therapy between January 1994 and December 2002 with 52,125 (the overall cohort) having a minimum follow-up of 365 days without being hospitalized (Figure 5.1). The mean age of this cohort was 59.4 (SD 12.6) years, mean chronic disease score was 2.9 (SD 1.8),[26] and 42% were male (Table 5.1). Of the overall cohort, 15,911 (30.5%) subjects filled more than one category of AHT during the first year of therapy (Figure 5.1). The proportion of subjects with optimal adherence (≥80%) at one year was 50.4% (26,285/52,125) when accounting for oversupply with any type of AHT medication. Of the 25,840 subjects who were non-adherent at one year, 10,054 (38.9%) discontinued after the first dispensation (first fill discontinuation). First fill discontinuations were associated with younger age, female gender, and use of an antidepressant medication during the observation period. In contrast, subjects who filled their index prescription from 1996 onwards, and those who visited their physician more often were less likely to discontinue their AHT after the first fill. Also, concurrent use of ASA, statins, and diabetes therapy in the observation year were associated with fewer discontinuations after the first AHT fill (Table 5.2).

Adherence Associated with ARBs versus Other AHT Categories

A total of 36,214 subjects filled one AHT category exclusively throughout the first year; these individuals were termed the "monotherapy" cohort (Figure 5.1). The mean age at the index date was 59 years (SD 12.7), and 40% of subjects were male (Table 5.3). Subjects were relatively healthy, with a mean chronic disease score of 2.9 (SD 1.8).[26] Compared to the overall cohort, the monotherapy cohort had slightly fewer males; mean age and CDS at index were similar. Statistically significant differences between AHT monotherapy categories were observed for all baseline characteristics; however, few clinically important differences could be identified, except for a lower proportion of men in the thiazide and potassium-sparing + HCTZ groups (Table 5.3).

Optimal adherence was observed in 39.8% (14,405/36,214) of the monotherapy subjects, and significant differences were observed between the 10 medication categories (Figure 5.2). The highest rates of optimal adherence (≥80%) were associated with use of ARB + HCTZ (64.2%), ACEI + HCTZ (61.9%), ARB (61.1%) and ACEI (58.3%). Female subjects, those who were

older, and had a lower chronic disease score at index were more likely to have optimal adherence, as were those with concurrent use of statin and ASA therapy during the observation year. Subjects who visited their physician more frequently and those with an index date after 1996 were also more likely to exhibit optimal adherence (Table 5.4).

When comparing the ARB category (represented by losartan) specifically to the ACEI (represented by ramipril) and DHP CCB (represented by amlodipine) categories, optimal adherence (≥80%) was observed in 59.9% (245/409), 67.2% (1097/1632), and 53.0% 473/893), respectively, which clearly contrasted the pooled rate of 39.8%. Compared to losartan, the adjusted odds for achieving optimal adherence was not significantly different for users of ramipril (adjusted OR 1.28, 95% CI 0.99 – 1.64, p=0.05) or amlodipine (adjusted OR 0.81, 95% CI 0.63 – 1.05, p=0.12). Similarly, no significant difference was found between the proportion of subjects achieving optimal adherence on the combination of an ARB + HCTZ (305/453 [67.3%]) compared to those on an ARB (1013/1600 [63.3%]; adjusted OR 1.16, 95% CI 0.92 – 1.46, p=0.20).

Interestingly, a pattern seemed to emerge when AHT categories were arranged chronologically by their release year into the Canadian market. Subjects in the most recently released AHT categories appear to exhibit better adherence compared to those receiving AHT medications released earlier (Figure 5.3). To further examine this trend, we compared only drugs within the ACEI class and found an almost identical pattern; those drugs released most recently had better adherence than did those drugs released earlier (data not shown).

Sensitivity results

First, analyses that excluded medication oversupply from our adherence calculation (i.e., setting all surplus medication values to 0) yielded comparable results to our main findings, except that only 38.2% (19,886/52,125) of subjects in the overall cohort were classified as adherent (≥80%) at one year. Furthermore, the proportion of non-adherent subjects discontinuing after the first fill was also comparable at 31.2% (10,054 / 32,239). Second, when adherence was calculated using an expected gap of 30 days and 40 days adherence rates were similar at 45.4% (26,663/52,125) and 54.5% (28,529/52,125) to the overall cohort findings. Both alternative methods of

calculating adherence provided similar results for the monotherapy cohort using either the tablets per day method (13,967/36,214 [38.6%]) or the modified PDC (16,036/36,214 [44.3%]). Finally, when compared to ramipril and amlodipine, candesartan, irbesartan, telmisartan, and valsartan all showed similar results to when losartan was used (data not shown).

5.5 Discussion

In this retrospective cohort study nearly half (49.6%) of subjects who were newly initiated on AHT medications were classified as non-adherent (<80%) after one year. Of these non-adherent subjects, 40% failed to obtain any further AHT medication after the first dispensation. When comparing the various AHT categories, the proportion of monotherapy subjects with optimal adherence ranged from 64.2% (ARB + HCTZ) to 22.9% (potassium-sparing diuretic + HCTZ). However, our findings strongly suggest that the association between adherence and specific AHT agents may be influenced by factors that are unrelated to pharmacologic differences.

To the best of our knowledge, this is the first paper to specifically examine the prevalence of first-fill discontinuations on non-adherence to AHT medications. Two previous publications have briefly commented on discontinuations after only a single fill, and reported almost identical rates of 18%[28] and 19%.[29] However, neither study was specifically evaluating this outcome and presented rates that were not specific to non-adherent subjects;[28, 29] also, we could not be certain that their study population consisted only of new users.[29]

Our findings are worrisome as non-adherence to AHT therapy has been identified as a major cause of inadequate blood pressure control, leaving patients at significant risk for complications related to hypertension.[30] Given the significant impact that first-fill discontinuations have on non-adherence to AHT therapy, we believe that interventions aimed at improving adherence should be focused on those subjects presenting with a first ever prescription. Also, we find it extremely interesting that this pattern of non-adherence is virtually identical to that of statins, which exhibit completely different biologic and adverse effects than AHT medications.

Similar to previous studies, the initial comparison of adherence rates between the individual AHT classes appear to suggest that adherence is best with ARBs and poorest with diuretics.[11, 13,

[14] However, we further compared adherence between only those subjects receiving a representative drug from each of the ARB (losartan), ACEI (ramipril) and DHP CCB (amlodipine) groups. By doing so, we attempted to minimize selection bias as all 3 drugs were marketed at relatively the same time, and were only available as brand name formulations throughout the entire study period. After covariate adjustment, neither the ACEI (ramipril) nor DHP CCB (amlodipine) groups differed significantly from the ARB (losartan) group. Indeed, it appeared that adherence was better in the AHT categories that were most recently released on the Canadian market. Interestingly, we found an almost identical pattern when comparing drugs within the ACEI category only; subjects receiving ACEIs that were released most recently had a better adherence than did those who received drugs released earlier.

In an attempt to test the idea that the tolerability and adverse effect profiles of different AHT classes (especially diuretics) may be responsible for non-adherence,[31, 32] we compared adherence and for subjects in the ARB and ARB + HCTZ categories. Despite containing a diuretic, which has been associated with poor adherence[11, 14, 15, 28] presumably caused by troublesome side effects,[32] adherence was not appreciably different between the categories.

Our findings suggest that external factors may be more strongly linked to adherence than the pharmacologic properties of certain AHT medications. For example, newer medications may be perceived as "better", and therefore they may be prescribed for patients who demonstrate a strong motivation to control/treat their hypertension; or, they may be prescribed disproportionately to patients who seem to be able to afford them. Regardless of the cause, it does appear that those patients receiving ARBs are different from those typically receiving drugs from other AHT categories. Bourgault et al found that subjects initiated on ARBs were more likely to initiate a new course of AHT therapy (any category) if they discontinued their initial ARB compared to those initiated on other AHT agents.[10] Certainly, more research in this area is warranted, especially now that ARBs are no longer the newest AHT category available.

There are several limitations which must be considered when examining the results. First, we only evaluated subjects after one year of therapy, and therefore can not comment on adherence past the first year. However, as the first year of therapy has been identified as the highest risk

period for non-adherence,[2-5] we believe these results are still important. Second, we restricted part of our analyses to subjects who only received one AHT category in the first year. Because of this we cannot be sure if these patterns are influenced by concurrent AHT therapy. Despite this, our study sample was large and we had representation from all different categories of AHTs. Also, we did include all new users of AHT therapy to evaluate the proportion of subjects who discontinued after the first fill. Third, it is possible that not all subjects were prescribed an AHT for hypertension. Specifically, certain subjects may have been receiving treatment for conditions that were more acute and periodic, such as transient edema, or migraine prophylaxis. However, we did employ a hypertension definition comparable to similar observational studies using administrative data,[7, 33] and attempted to ensure that the AHT agent had been prescribed solely for uncomplicated hypertension by excluding all subjects who were previously hospitalized for any complicating reason in the previous 5 years. Fourth, as with all administrative database studies, we assumed that filling a prescription meant the medication was actually taken. Although this assumption would appear to be realistic,[24] we cannot say with complete certainty that the medication was consumed. Also, administrative databases inherently lack detailed patient-level clinical information so we were unable to assess the reasons for non-adherence. Further, we can not be certain that systematic differences in blood pressure or other clinical characteristics were equally distributed amongst our cohorts. However, baseline comparisons appear to indicate that subjects were indeed similar. Fifth, because days supply was not captured by Saskatchewan Health and Extended Benefits Branch during the period of this study, we had to estimate it. However, the majority of the drugs in the analysis were dispensed on a monthly (34 days) basis, and we performed two sensitivity analyses which demonstrated similar results. Finally, although the first ARB (losartan) was released into the Canadian market on December 31, 1995, it did not receive an unrestricted listing on the Saskatchewan Formulary until July 1, 1997.[13] Because of this, we are unable to say with complete certainty that all subjects in the ARB category were new users. However, only a small proportion (5.3%) of the 1600 subjects in the ARB category had an index date before July 1, 1998, and therefore could not be verified as a new user by at least one previous year of no AHT use.

5.6 Conclusion

The results from the present study confirm that a substantial proportion of non-adherence to AHT medications can be attributed to patients who discontinue after only a single dispensation. Also, adherence to AHT medications is poor across all categories and it is unlikely that specific categories, such as ARBs, are independently associated with optimal adherence. Given that non-adherence to AHT medications is not only associated with an increase in blood pressure, but also an increase in vascular events, hospitalizations, and healthcare costs,[33, 34] adherence strategies aimed at patients presenting with their first ever AHT prescription for any AHT category will likely have a significant impact.

Figure 5.1. Selection of Study Subjects

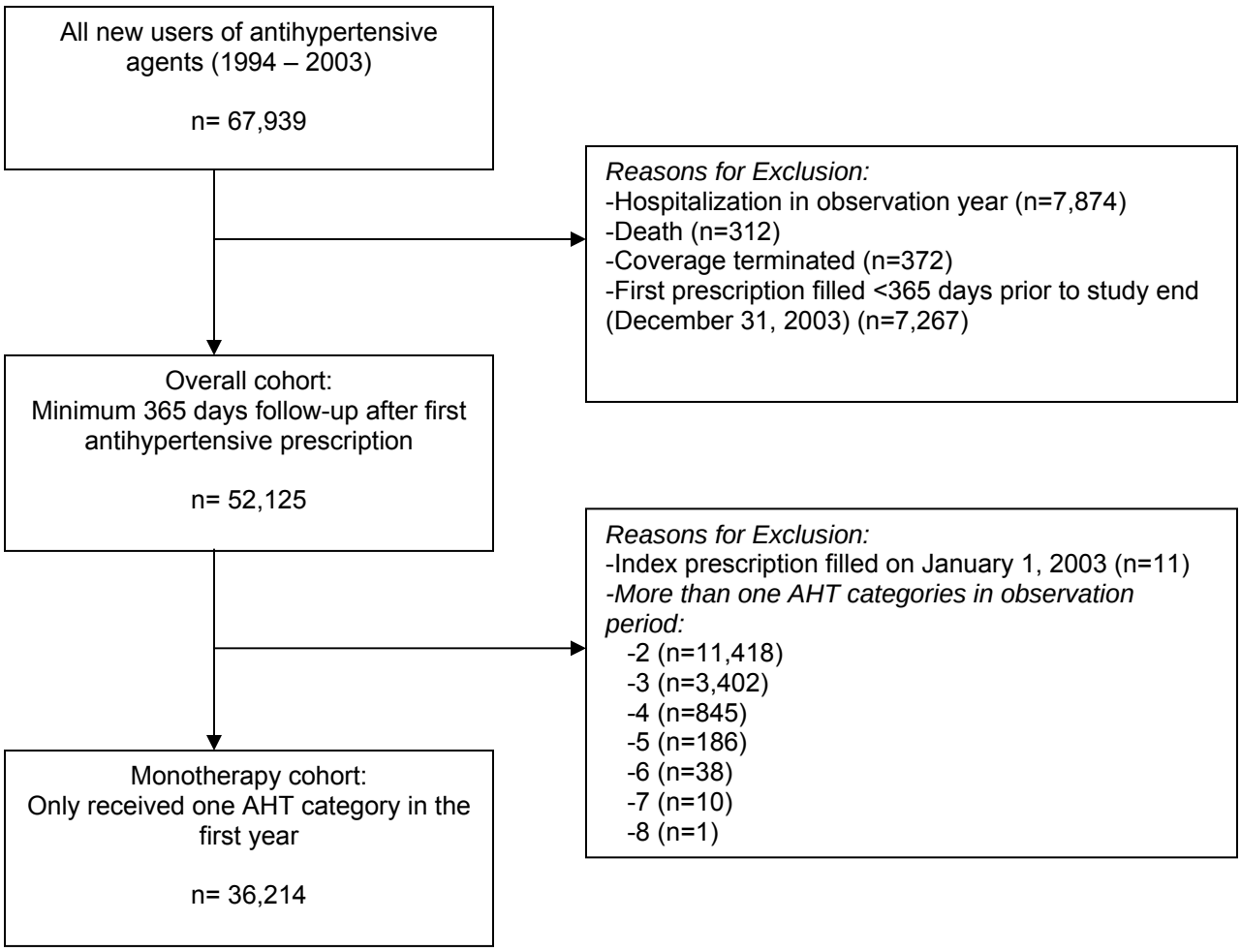
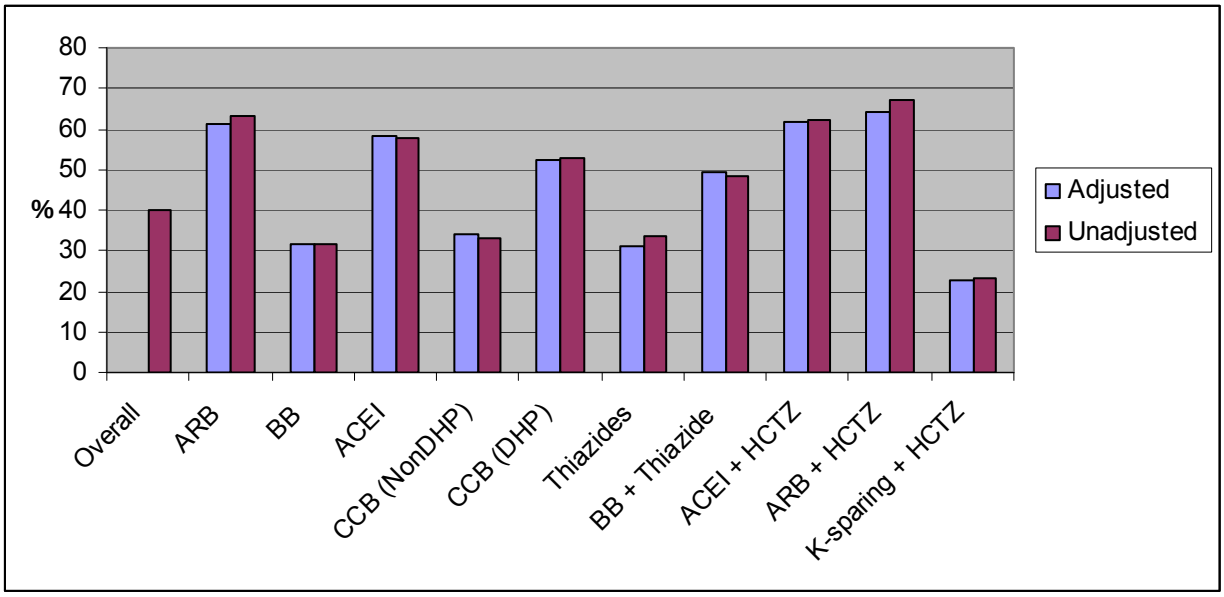
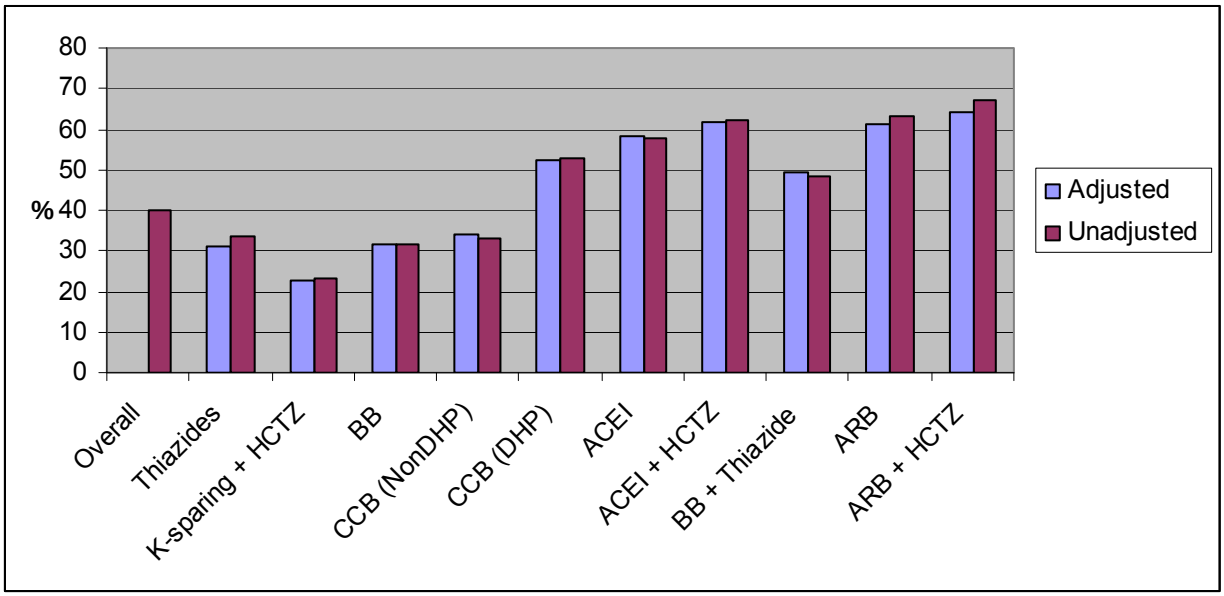


Figure 5.2. Proportion of Monotherapy Cohort with Adherence[a] ≥80% (n=36,214)



a. Cumulative gap measure
ARB Angiontensin receptor blocker
BB Beta blocker
ACEI Angiotensin converting enzyme inhibitor
CCB Calcium channel blocker
DHP Dihyrdopyridine
HCTZ Hydrochlorothiazide
K Potassium

Figure 5.3. Proportion of Monotherapy Cohort with Adherence[a] ≥80%:Drug Categories Arranged Chronologically[b] [left to right] According to Release Date into Canadian Market



a. Cumulative gap measure
b. Although captopril (ACEI) was released prior to CCB (Non DPH), it only accounted for 0.1% of our study cohort. Therefore, we placed the ACEI chronologically based on when the utilized ACEI were marketed in Canada.
K Potassium
HCTZ Hydrochlorothiazide
BB Beta blockers
CCB Calcium channel blockers
DHP Dihydropyridine
ARB Angiotensin receptor blockers

Table 5.1. Baseline Characteristics of Overall Cohort (n=52,125)

Characteristic	n
Subjects	52,125
Mean age (years) at index (SD)	59.4 (12.5)
Male (%)	21623 (41.5)
Mean CDS at index (SD)	2.9 (1.8)
Index year (%)	
1994	4249 (8.2)
1995	4666 (9.0)
1996	4615 (8.9)
1997	5539 (10.6)
1998	5600 (10.7)
1999	6296 (12.1)
2000	6905 (13.2)
2001	7147 (13.7)
2002	7063 (13.6)
Physician visits[a] in observation year (%)	
0	391 (0.8)
1-3	4907 (9.4)
4-11	28017 (53.7)
12+	18810 (36.1)
Total concurrent non-AHT medications in observation year (%)	21355 (41.0)
0	25072 (48.1)
1-2	5029 (9.6)
3-4	669 (1.3)
5+	
Concurrent non-AHT medication in observation year (%)	802 (1.5)
Diabetes / Insulin	2035 (3.9)
Nitrates	4301 (8.3)
Statins	1059 (2.0)
ASA	571 (1.1)
Warfarin	6951(13.3)
Antidepressants	
Income security benefits[b] (%)	
None	41242 (79.1)
SAP	1371 (2.6)
Family-based	557 (1.1)
Senior-based	8955 (17.2)

a. Number of distinct days where at least 1 service was provided to an individual subject by as Saskatchewan physician
b. None, no income security benefits; SAP, a program of last resort for families and individuals who, for various reasons, including disability, illness, low income or unemployment, cannot meet basic living costs; Family-based, supplements the financial resources of low-income families with dependent children – eligibility based on annual family income and assets; Senior-based, supplementary income for subjects ≥65 years who have little or no income other than the federal Old Age Security pension and Guaranteed Income Supplement

SD Standard deviation
CDS Chronic disease score (Von Korff)[26]
AHT Antihypertensive
SAP Saskatchewan Assistance Program

Table 5.2. Predictors of Discontinuation After First Fill for Overall Cohort Subjects with Adherence[a] <80%

Predictor	n	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P* Value
Sex				
Male	10462	-	-	
Female	15378	1.318 (0.1252 – 1.387)	1.319 (1.250 – 1.391)	<0.0001
Age	25840	0.9897 (0.985 – 0.989)	0.990 (0.998 – 0.992)	<0.0001
Income Security Benefit[b]				
None	20348	-	-	
Saskatchewan Assistance Program	773	1.319 (1.142 – 1.524)	1.209 (1.042 – 1.402)	0.012
Family-based	345	1.399 (1.130 – 1.731)	1.250 (1.004 – 1.555)	0.046
Senior-based	4374	0.899 (0.840 – 0.960)	1.041 (0.963 – 1.125)	0.313
Number of physician visits during observation year				
None	328	-	-	
1-3	3654	0.892 (0.711 – 1.121)	0.863 (0.685 – 1.086)	0.207
4-11	13656	0.459 (0.368 – 0.573)	0.424 (0.339 – 0.531)	<0.0001
12+	8202	0.407 (0.325 – 0.508)	0.355 (0.283 – 0.446)	<0.0001
Index Year				
1994	2547	-	-	
1995	2744	0.964 (0.864 – 1.075)	0.958 (0.857 – 1.070)	0.445
1996	2678	0.927 (0.831 – 1.035)	0.935 (0.836 – 1.045)	0.238
1997	3028	0.848 (0.762 – 0.944)	0.872 (0.781 – 0.972)	0.014
1998	2902	0.870 (0.781 – 0.970)	0.884 (0.792 – 0.987)	0.028
1999	2947	0.741 (0.665 – 0.827)	0.763 (0.683 – 0.853)	<0.0001
2000	3045	0.832 (0.723 – 0.897)	0.862 (0.772 – 0.961)	0.008
2001	2972	0.805 (0.723 – 0.897)	0.835 (0.748 – 0.933)	0.001
2002	2977	0.686 (0.615 – 0.765)	0.711 (0.636 – 0.795)	<0.0001
Concurrent non-AHT medications during observation year				
None	10712	-	-	
1-2	12446	1.031 (0.978 – 1.088)	1.216 (1.144 – 1.292)	<0.0001
3-4	2374	1.036 (0.946 – 1.135)	1.405 (1.253 – 1.575)	<0.0001
5+	308	0.825(0.649 – 1.047)	1.281 (0.983 – 1.670)	0.067

Predictor	n	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P* Value
Specific therapies during observation year				
Oral hypoglycemic or insulin				
No	25546	-	-	
Yes	294	0.515 (0.395 – 0.671)	0.532 (0.405 – 0.699)	<0.0001
Nitrates				
No	24844	-	-	
Yes	996	0.810 (0.709 – 0.926)	0.950 (0.824 – 1.094)	0.473
Statin				
No	24398	-	-	
Yes	1442	0.548 (0.486 – 0.618)	0.579 (0.511 – 0.656)	<0.0001
ASA				
No	25412	-	-	
Yes	428	0.735 (0.599 – 0.902)	0.779 (0.629 – 0.966)	0.023
Warfarin				
No	25579	-	-	
Yes	261	0.618 (0.472 – 0.810)	0.776 (0.588 – 1.024)	0.073
Antidepressant				
No	22139	-	-	
Yes	3701	1.230 (1.147 – 1.320)	1.142 (1.051 – 1.240)	0.002
Chronic disease score	25840	0.970 (0.956 – 0.983)	0.99 (0.98 – 1.00)	<0.0001

a. Cumulative gap measure
b. None, no income security benefits; SAP, a program of last resort for families and individuals who, for various reasons, including disability, illness, low income or unemployment, cannot meet basic living costs; Family-based, supplements the financial resources of low-income families with dependent children – eligibility based on annual family income and assets; Senior-based, supplementary income for subjects ≥65 years who have little or no income other than the federal Old Age Security pension and Guaranteed Income Supplement

AHT Antihypertensive

Table 5.3 Baseline Characteristics of Monotherapy Cohort (n=36,214)

	Overall	BB	ACEI	ARB	CCB (Non-DHP)	CCB (DHP)	Thiazides	BB + Thiazide	ACEI + HCTZ	ARB + HCTZ	K-sparing + HCTZ	P-Value[a]
Subjects (%)	36214	6907 (19.1)	8623 (23.8)	1600 (4.4)	1170 (3.2)	2111 (5.8)	5690 (15.7)	126 (0.4)	553 (1.5)	453 (1.3)	8980 (24.8)	
Mean age (years) at index (SD)	59.1 (12.7)	55.9 (11.8)	59.2 (12.1)	58.0 (11.4)	60.0 (12.4)	61.9 (12.6)	61.1 (13.5)	58.2 (10.8)	58.4 (10.8)	59.8 (11.9)	59.0 (13.6)	<0.0001
Male (%)	14576 (40.2)	2842 (41.1)	4566 (53.0)	849 (53.1)	544 (46.5)	995 (47.2)	1692 (29.7)	67 (53.2)	302 (54.5)	23 (51.9)	2477 (27.6)	<0.0001
Mean CDS at index (SD)	2.9 (1.8)	2.1 (1.6)	3.9 (1.6)	3.0 (1.7)	3.8 (2.2)	3.0 (1.8)	1.9 (1.7)	1.6 (1.3)	3.8 (1.5)	2.8 (1.4)	2.9 (1.7)	<0.0001
Index year (%)												
1994	3313 (9.1)	551 (8.0)	746 (8.7)	0 (0)	187 (16.0)	271 (12.8)	400 (7.0)	12 (9.5)	20 (3.6)	0 (0)	1126(12.5)	<0.0001
1995	3583 (9.9)	673 (9.7)	928 (10.8)	0 (0)	199 (17.0)	242 (11.5)	386 (6.8)	17 (13.5)	24 (4.3)	0 (0)	1114(12.4)	
1996	3476 (9.6)	729 (10.6)	842 (9.8)	2 (0.1)	130 (11.1)	168 (8.0)	403 (7.1)	22 (17.5)	31 (5.6)	0 (0)	1149(12.8)	
1997	4029(11.1)	807 (11.7)	1001(11.6)	50 (3.1)	122 (10.4)	223 (10.6)	524 (9.2)	13 (10.3)	65 (11.7)	8 (1.8)	1216(13.5)	
1998	3888(10.7)	863 (12.5)	800 (9.3)	122 (7.6)	127 (10.9)	242 (11.5)	608 (10.7)	11 (8.7)	54 (9.7)	26 (5.7)	1035(11.5)	
1999	4221(11.7)	888 (12.9)	951 (11.0)	258 (16.1)	113 (9.7)	208 (9.9)	744 (13.1)	13 (10.3)	76 (13.7)	38 (8.4)	932(10.4)	
2000	4507(12.4)	845 (12.2)	1023(11.9)	328 (20.5)	104 (8.9)	258 (12.2)	849 (14.9)	13 (10.5)	110 (19.9)	64 (14.1)	913(11.5)	
2001	4566(12.6)	776 (11.2)	1103(12.8)	407 (25.4)	98 (8.4)	279 (13.2)	861 (15.1)	19 (15.1)	95 (17.1)	104(23.0)	824(10.2)	
2002	4631(12.8)	775 (11.2)	1229(14.3)	433 (27.1)	90 (7.7)	220 (10.4)	915 (16.1)	6 (4.8)	79 (14.3)	213(47.0)	671(9.2)	
Physician visits[b] in observation year (%)												
0	349 (1.0)	66 (1.0)	100 (1.2)	18 (1.1)	10 (0.9)	26 (1.2)	49 (0.1)	0 (0)	7 (1.3)	6 (1.3)	67 (0.7)	<0.0001
1-3	4496(12.4)	781 (11.3)	1076(12.5)	180 (11.2)	107 (9.1)	278 (13.2)	745 (13.1)	23 (18.3)	71 (12.8)	52 (11.5)	1183(12.4)	
4-11	20423(56.4)	3617 (52.4)	5092(59.1)	1010(63.1)	596 (51.0)	1150(54.5)	3265 (57.4)	67 (53.2)	357 (64.4)	295(65.0)	4974(55.4)	
12+	10946(30.2)	2443 (35.4)	2355(27.3)	392 (24.5)	457 (39.0)	657 (31.1)	1631 (28.7)	36 (28.6)	119 (21.5)	100(22.2)	2756(30.7)	
Total concurrent non-AHT medications in observation year (%)												
0	15077(41.6)	2606 (37.7)	3794(44.0)	728 (45.5)	321 (27.4)	913 (43.2)	2458 (43.2)	58 (46.0)	278 (50.2)	221(48.7)	3700(41.2)	<0.0001
1-2	16334 (45.1)	3220 (46.6)	3782(43.9)	711 (44.4)	589 (50.4)	950 (45.0)	2521 (44.3)	51 (40.5)	231 (41.7)	191(42.3)	4088(25.0)	
3-4	4051 (11.2)	911 913.2)	899 (10.4)	137 (8.5)	202 (17.3)	194 (9.2)	612 (10.8)	14 (11.1)	39 (7.0)	38 (8.4)	1006(11.2)	
5+	752 (2.1)	170 (2.5)	148 (1.7)	24 (1.5)	58 (5.0)	54 (2.6)	100 (1.8)	3 (2.4)	6 (1.1)	3 (0.7)	186 (2.1)	

Concurrent non-AHT medication in observation year (%)												
Diabetes / Insulin	451 (1.2)	33 (0.5)	246 (2.9)	22 (1.4)	18 (1.5)	15 (0.7)	41 (0.7)	4 (3.2)	11 (2.0)	8 (1.8)	53 (0.6)	<0.0001
Nitrates	1232 (3.4)	609 (8.8)	137 (1.6)	10 (0.6)	272 (23.2)	82 (3.9)	42 (0.7)	1 (0.8)	10 (1.8)	3 (0.7)	66 (0.7)	
Statins	2624 (7.2)	430 (6.2)	928 (10.8)	196 (12.2)	85 (7.3)	164 (7.8)	319 (5.6)	5 (4.0)	50 (9.0)	70 (15.5)	377 (4.2)	
ASA	648 (1.8)	200 (2.9)	127 (1.5)	13 (0.8)	55 (4.7)	48 (2.3)	74 (1.3)	3 (2.4)	12 (2.2)	5 (1.1)	111 (1.2)	
Warfarin	358 (1.0)	89 (1.3)	102 (1.2)	10 (0.6)	34 (2.9)	15 (0.7)	39 (0.7)	0 (0)	4 (0.7)	2 (0.4)	63 (0.7)	
Antidepressants	4958 (13.7)	1460 (21.1)	819 (9.5)	162 (10.1)	211 (18.0)	219 (0.4)	745 (13.1)	12 (9.5)	62 (11.2)	43 (9.5)	1225(13.6)	
Income security benefits[c] (%)												
None	28554 (78.8)	5665 (82.0)	6905(80.1)	1365(85.3)	924 (79.0)	1594(75.5)	4437 (78.0)	94 (74.6)	436 (78.7)	362(84.3)	6752(75.2)	<0.0001
SAP	1045 (2.9)	262 (3.8)	219 (2.5)	22 (1.4)	38 (3.9)	57 (2.7)	123 (2.2)	5 (4.0)	15 (2.7)	4 (0.9)	300 (3.3)	
Family-based	400 (1.1)	105 (1.5)	93 (1.1)	25 (1.6)	13 (1.1)	13 (0.6)	59 (1.0)	6 (4.8)	4 (0.7)	6 (1.3)	76 (0.8)	
Senior-based	6215 (17.2)	875 (12.7)	1406(16.3)	188 (11.8)	195 (16.7)	447 (21.2)	1071 (18.8)	21 (16.7)	99 (17.9)	61 (13.5)	1852(20.6)	

a. Overall test of significance that all 10 treatment groups are similar (ANOVA and Chi-square)

b. A single visit includes all services delivered to a single subject by a single physician for the same diagnosis on the same day at the same clinic/location

None, no income security benefits; SAP, a program of last resort for families and individuals who, for various reasons, including disability, illness, low income or unemployment, cannot meet basic living costs; Family-based, supplements the financial resources of low-income families with dependent children – eligibility based on annual family income and assets; Senior-based, supplementary income for subjects ≥65 years who have little or no income other than the federal Old Age Security pension and Guaranteed Income Supplement

BB Beta blockers
ACEI Angiotensin converting enzyme inhibitors
ARB Angiotensin receptor blockers
CCB Calcium channel blockers
DHP Dihydropyridine
K Potassium
HCTZ Hydrochlorothiazide
SD Standard deviation
CDS Chronic disease score (Von Korff)[26]
AHT Antihypertensive
SAP Saskatchewan Assistance Program

Table 5.4. Predictors of Adherence[a] (≥80%) for Monotherapy Cohort

Predictor	n	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P* Value
Sex				
Male	14569	-	-	
Female	21645	0.922 (0.884 – 0.963)	1.175 (1.120 – 1.233)	<0.0001
Age	36214	1.013 (1.011 – 1.014)	1.011 (1.009 – 1.013)	<0.0001
Income Security Benefit[b]				
None	26472	-	-	
Saskatchewan Assistance Program	1240	0.773 (0.685 – 0.872)	0.962 (0.845 – 1.096)	0.562
Family-based	905	0.670 (0.581 – 0.774)	0.770 (0.660 – 0.899)	0.001
Senior-based	7597	1.109 (1.053 – 1.168)	1.011 (0.949 – 1.077)	0.727
AHT Category				
ARB	1600	-	-	
Beta Blocker	6907	0.267 (0.238 – 0.299)	0.295 (0.262 – 0.333)	<0.0001
ACEI	8623	0.795 (0.712 – 0.887)	0.903 (0.805 – 1.014)	0.084
CCB (Non-DHP)	1170	0.284 (0.242 – 0.333)	0.323 (0.273 – 0.381)	<0.0001
CCB (DHP)	2111	0.644 (0.564 – 0.735)	0.709 (0.617 – 0.813)	<0.0001
Thiazides	5690	0.296 (0.263 – 0.332)	0.293 (0.260 – 0.331)	<0.0001
Beta Blocker + Thiazide	126	0.544 (0.378 – 0.782)	0.653 (0.450 – 0.949)	0.025
ACEI + HCTZ	554	0.949 (0.778 – 1.159)	1.052 (0.857 – 1.292)	0.627
ARB + HCTZ	453	1.194 (0.957 – 1.490)	1.150 (0.916 – 1.443)	0.228
K-sparing + HCTZ	8980	0.177 (0.158 – 0.198)	0.192 (0.170 – 0.216)	<0.0001
Number of physician visits during observation year				
None	349	-	-	
1-3	4496	1.894 (1.386 – 2.589)	2.177 (1.579 – 3.003)	<0.0001
4-11	20423	4.712 (3.470 – 6.398)	5.522 (4.030 – 7.567)	<0.0001
12+	10946	4.464 (3.284 – 6.068)	5.552 (4.043 – 7.624)	<0.0001

Predictor	n	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P* Value
Index Year				
1994	3313	-	-	
1995	3583	1.028 (0.929 – 1.136)	1.003 (0.902 – 1.116)	0.953
1996	3476	1.014 (0.916 – 1.122)	1.015 (0.912 – 1.116)	0.782
1997	4029	1.180 (1.071 – 1.300)	1.117 (1.007 – 1.238)	0.036
1998	3888	1.235 (1.120 – 1.361)	1.186 (1.070 – 1.316)	0.001
1999	4221	1.519 (1.382 – 1.670)	1.371 (1.239 – 1.518)	<0.0001
2000	4507	1.584 (1.443 – 1.740)	1.365 (1.235 – 1.510)	<0.0001
2001	4566	1.766 (1.609 – 1.938)	1.439 (1.302 – 1.591)	<0.0001
2002	4631	1.822 (1.660 – 1.999)	1.403 (1.268 – 1.551)	<0.0001
Concurrent non-AHT medications during observation year				
None	15077	-	-	
1-2	16334	1.047 (1.001 – 1.096)	0.936 (0.887 – 0.988)	0.017
3-4	4051	1.082 (1.008 – 1.161)	0.909 (0.830 – 0.996)	0.040
5+	752	1.072 (0.923 – 1.244)	0.886 (0.742 – 1.058)	0.182
Specific therapies during observation year				
Diabetes or insulin				
No	35763	-	-	
Yes	451	1.515 (1.258 – 1.825)	0.995 (0.814 – 1.216)	0.959
Nitrates				
No	34982	-	-	
Yes	1232	0.899 (0.799 – 1.011)	0.894 (0.783 – 1.019)	0.094
Statin				
No	33590	-	-	
Yes	2624	2.089 (1.928 – 2.264)	1.607 (1.469 – 1.758)	<0.0001
ASA				
No	35566	-	-	
Yes	648	1.460 (1.250 – 1.706)	1.524 (1.285 – 1.806)	<0.0001
Warfarin				
No	35856	-	-	
Yes	358	1.185 (0.960 – 1.461)	1.003 (0.801 – 1.256)	0.979
Antidepressant				
No	31256	-	-	
Yes	4958	0.843 (0.793 – 0.897)	0.931 (0.865 – 1.003)	0.059
Chronic disease score	36214	1.092 (1.080 – 1.105)	0.985 (0.970 – 0.999)	0.040

a. Cumulative gap measure
b. None, no income security benefits; SAP, a program of last resort for families and individuals who, for various reasons, including disability, illness, low income or unemployment, cannot meet basic living costs; Family-based, supplements the financial resources of low-income families with dependent children – eligibility based on annual family income and assets; Senior-based, supplementary income for subjects ≥65 years who have little or no income other than the federal Old Age Security pension and Guaranteed Income Supplement

ACEI – Angiotensin converting enzyme inhibitors ARB – Angiotensin receptor blockers CCB – Calcium channel blockers DHP – Dihydropyridine AHT – Antihypertensive

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Appendix C. Drugs Available for Inclusion in Analyses

Antihypertensive Agents		Non-Antihypertensive Drug Categories [a]
Single Entity Agents	**Combination Agents**	
Beta Blockers	Beta Blocker + Thiazide	Cardiac agents
Acebutolol	Atenolol / Chlorthalidone*	Statins
Atenolol*	Propanolol / HCTZ	Other lipid agents
Metoprolol	Timolol / HCTZ	Anticoagulants
Nadolol		Antiplatelets
Propanolol	ACEI + HCTZ	Insulin
Timolol	Cilazepril / HCTZ	Oral diabetes agents
	Enalapril / HCTZ	Glucose testing agents
ACEI	Lisinopril / HCTZ*	Antidepressants
Benazepril	Quinapril / HCTZ	Older antipsychotics
Captopril		Newer antipsychotics
Cilazepril	ARB + HCTZ	Glucocorticosteroids
Enalapril	Candesartan / HCTZ	Oral
Fosinopril	Irbesartan / HCTZ	Inhaled
Lisinopril*	Losartan / HCTZ*	Parenteral
Perindopril	Telmisartan / HCTZ	Bisphosphonates
Quinapril	Valsartan / HCTZ	HRT
Ramipril		Uric acid agents
	K-sparing diuretic + HCTZ	Migraine agents
ARB	Amiloride / HCTZ	NSAIDs
Candesartan	Spironolactone / HCTZ	Proton pump inhibitors
Eprosartan	Triamterene / HCTZ*	H2 antagonists
Irbesartan		Misoprostol
Losartan*		Other gastrointestinal agents
Telmisartan		Transplant
Valsartan		
CCB (Non-DHP)		
Diltiazem*		
Verapamil		
CCB (DHP)		
Amlodipine		
Felodipine		
Nifedipine SR*		
Thiazides		
Chlorthalidone		
HCTZ*		
Indapamide		
Metolazone		

*Used for the Modified Proportion of Days Covered calculation

a. Drug class categorization determined by Saskatchewan Drug Plan personnel

ACEI Angiotensin converting enzyme
ARB Angiotensin receptor blocker
CCB Calcium channel blocker
DHP Dihydropyridine
SR Slow release
HCTZ Hydrochlorothiazide
K Potassium
HRT Hormone replacement therapy
NSAID Non-steroidal anti-inflammatory drug

- Chapter 6 -

SUMMARY

6.1 Summary of Research

Given its enormous economic and clinical impact, it is not surprising that a significant amount of research continues to be directed towards cardiovascular disease (CVD) risk-reduction. Recognizing the negative impact that non-adherence can have on the prevention and management of CVD, it is also understandable that a part of this research focuses on strategies to improve adherence. Accessibility, frequent patient contact, and strong pharmacotherapy knowledge make pharmacists, especially those in primary care settings, an obvious choice to be involved in interventions aimed at CVD risk-reduction.

Although studies have examined interventions involving pharmacists in CVD risk-reduction,[1-6] few have been implemented into practice.[7] Challenges within the current practice environment including pharmacist shortages, lack of time, and remuneration models based on technical dispensing activities are possible reasons for this lack of uptake into real-world settings. As such, it is still unknown what impact *typical* pharmacists can really have on cardiovascular risk-reduction in today's health care system. Recognizing the challenges of today's practice environment for pharmacists, the objective of this research program was to investigate strategies that typical pharmacists in primary care settings can implement to effectively facilitate cardiovascular risk reduction within the constraints of the current health care system. This objective was achieved through four separate, but related studies, involving both interventional and observational research.

Clinical pharmacy positions within medical clinics have traditionally been reserved for pharmacists who are specialized or hold post-graduate degrees. Considering the majority of Canadian pharmacists hold baccalaureate degrees, the intent of the Collaborative Cardiovascular Risk-Reduction in Primary Care (CCARP) pilot study was to evaluate an intervention specifically designed for typical, non-specialist pharmacists who have the opportunity to work in a family physician practice. The intervention, aimed at lowering global cardiovascular risk, was

purposely designed so that no significant extra training or specialization would be required of the pharmacist.

Despite being a pilot study, CCARP is still one of the largest studies to date evaluating the impact of pharmacist involvement on cardiovascular risk reduction,[3, 7, 21] and one of the few that evaluated a practical pharmacist intervention intended to be carried out by non-specialist pharmacists in typical (i.e. fee-for-service) practice settings. Although a statistical difference was not shown in the primary endpoint, the intervention did appear to improve evidence-based drug utilization. Furthermore, the study was able to demonstrate the feasibility of incorporating a non-specialist pharmacist into a busy family physician practice.

To build on the lessons learned from the CCARP study, future studies are needed to clarify the effects of this approach. In addition, certain study design modifications should be considered. First, subsequent studies should use a cluster-randomized approach, grouping patients by clinic, or at a minimum, by physician. This would minimize the potential for contamination and allow researchers to draw more definite conclusions. Also, although all patients enrolled in CCARP were classified as moderate-high risk for a cardiovascular event, many had good control of their risk factors at the time of entry into the study. In order to increase the efficiency of future studies, we would recommend only enrolling those with uncontrolled risk factors. Finally, to ensure that small, yet clinically significant improvements are detected, a composite primary endpoint, rather than a less sensitive risk score, like the Framingham score used in the CCARP study, would be more appropriate.

Research into pharmacist involvement in CVD risk reduction has often focused on pharmacists in clinical settings. However, since approximately 70% of Canadian pharmacists practice in community pharmacies, we were interested in identifying CVD research conducted in these settings. Our systematic review of the literature demonstrated that CVD research has been occurring in community pharmacy settings for over 30 years. Unfortunately, although the majority of the studies reviewed claimed to show a benefit, much of the research was of poor quality and did not demonstrate any clinically relevant benefit, making it difficult to determine the true impact of the pharmacist interventions.

The majority of community pharmacy interventions studied in the systematic review were complex and time-intensive, with a median contact time of 27 minutes. Given the current pharmacist shortage, few community pharmacists would be able to devote that much time to a single patient while still managing the rest of their daily duties and responsibilities. This issue of time commitment has frequently been ignored by investigators as only 3 of the 37 studies commented on the complexity and feasibility of their intervention. Considering that time intensiveness appears to be a major barrier to the implementation of research findings into real world practice, further research is needed to develop high quality, efficient and effective strategies that can be implemented in today's practice environment.

Recognizing this, we designed the Community Pharmacy Assisting in Total Cardiovascular Health (CPATCH) study. By doing so, we not only demonstrated the feasibility of designing a high quality, robust study involving community pharmacists, but also focused on an area known to have a significant impact on patient outcomes: medication adherence.[8, 9] To optimize the efficiency of the CPATCH intervention, patients were objectively targeted at a time when they were most likely to become non-adherent. Previous research suggests this critical time occurs during the first year, and at the first dispensation of therapy.[10-13] The intervention was also specifically designed to not require any major time commitment or changes to existing workflow patterns, thereby maximizing its external validity to current community pharmacy environments.

Although the CPATCH study design focuses on statin medications, the intervention and methodology is intended to be transferable to other medication classes. For instance, the final study in this research program demonstrated that the patterns of first year non-adherence with antihypertensive medications are almost identical to those of statins. Further observational studies examining adherence to other cardiovascular medication classes are needed to determine if these patterns are indeed consistent. If so, it supports the application of the CPATCH strategy to a broader range of subjects and medications.

Throughout this program of research, we demonstrated that non-specialist pharmacists in primary care settings can be involved in CVD risk reduction interventions; however, one specific

strategy did not emerge as superior. What is apparent is the need for further high quality research, especially in the area of community pharmacy interventions. It is also evident that additional research is required to determine how to maximize the uptake of research protocols into current practice. This 'baby-step' approach to facilitating pharmacy practice change is complimentary to many current research programs that investigate activities in typical practice environments. Finally, utilization and adherence to chronic medications are an obvious area where the profession of pharmacy can contribute significantly to advancing the quality of Canada's health care system.

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