

COLLABORATIVE CARDIOVASCULAR RISK REDUCTION IN PRIMARY CARE II (CCARP II)

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in the Pharmacy Graduate Program
University of Saskatchewan
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ABSTRACT

Cardiovascular disease is the leading cause of death in Canada. Despite improvements in cardiovascular risk factor identification and management over the past couple decades, many patients are still not reaching their guideline-recommended blood pressure, cholesterol, or blood glucose targets. Although numerous studies have demonstrated benefits to incorporating pharmacists onto primary care teams to facilitate cardiovascular risk reduction, such initiatives are not currently being implemented on a widespread basis in Canada. Part of the reason for this may be that most studies have been conducted in specialized, tertiary care clinics, while the majority of Canadians receive care from family physicians.

CCARP II was a prospective, before and after clinical initiative implemented to help bridge this gap between clinical research and current clinical practice. The purpose of CCARP II was to implement and evaluate a pharmacist-led collaboration to identify and manage cardiovascular risk factors in a real-world family medicine setting.

The pharmacist screened 566 patients for uncontrolled cardiovascular risk factors over the 9-month study period. Of all patients screened, 186 (32.9%) were at moderate or high cardiovascular risk with one or more risk factors above target. Of those, 113 patients (60.8%) were referred back to the pharmacist by their physician for ongoing monitoring and follow-up. In this group of patients, statistically significant reductions in systolic blood pressure, LDL cholesterol, and the total cholesterol: HDL ratio were observed over the study period. In patients started on new medications over the study period, a high rate of persistence (87.8%) was observed.

CCARP II demonstrated that there is still a need for systematic screening for unidentified or uncontrolled cardiovascular risk factors in adult patients visiting their physicians; almost one-third of patients in our study had one or more uncontrolled risk factors identified. This initial pilot project was successful in identifying patients with above-target cardiovascular risk factors, and subsequently aiding in the reduction of these risk factors towards target levels.

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DEDICATION

This thesis is dedicated to my family, for their constant love and support. In particular, this thesis is dedicated to my husband Steve and daughter Elodie. Steve: Thank-you for your unwavering faith in me, your never-ending patience, and for the sacrifices you have made so I could pursue this dream. I will love you always. Elodie: May you have the courage to take the road less travelled, and the wisdom to follow your heart.

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LIST OF ABBREVIATIONS

ACEI	Angiotensin Converting Enzyme Inhibitors
ARB	Angiotensin II Receptor Blockers
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAD	Coronary Artery Disease
CCARP II	Collaborative Cardiovascular Risk Reduction in Primary Care II
CHD	Coronary Heart Disease
CrCl	Creatinine Clearance
CRI	Cardiovascular Risk Improvement index
CV	Cardiovascular
CVD	Cardiovascular disease
DHP-CCB	Dihydropyridine Calcium Channel Blocker
EF	Ejection Fraction
HbA1c	Hemoglobin A1c
HCTZ	Hydrochlorothiazide
HDL-C	High Density Lipoprotein Cholesterol
HF	Heart Failure
K	Potassium
LDL-C	Low Density Lipoprotein Cholesterol
MI	Myocardial Infarction
MD	Medical Doctor

PIP	Pharmaceutical Information Program
PVD	Peripheral Vascular Disease
RCT	Randomized Controlled Trial
SBP	Systolic Blood Pressure
SCr	Serum Creatinine
SD	Standard Deviation
Statins	3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors
TC	Total Cholesterol
TG	Triglycerides
TIA	Transient Ischemic Attack

CHAPTER 1

1. Literature Review

1.1 Introduction

Cardiovascular disease is the leading cause of death in Canada (1). Despite improvements in risk factor identification and management over the past several decades, many people are still not reaching their blood pressure, cholesterol, and blood glucose targets (2-5). Numerous studies have demonstrated benefits to incorporating pharmacists onto primary care teams to facilitate cardiovascular risk reduction (6-17); however, these interventions are not currently being implemented on a widespread basis (18-21).

CCARP II was designed to help bridge this gap between clinical research and current clinical practice. Most of the previous pharmacist interventions to reduce cardiovascular risk have taken place in specialty outpatient clinics, often affiliated with tertiary care hospitals (6-8,11,16,17,22-25); however, the majority of Canadians receive their care from family physicians (26). Thus, there is a need to determine whether a collaborative pharmacist-physician protocol designed to reduce cardiovascular risk would be feasible and effective in a real-world primary care family medicine setting. The purpose of CCARP II is to implement and evaluate a pharmacist-led collaboration to identify and manage uncontrolled CV risk factors in a family medicine setting.

1.2 Cardiovascular Disease in Canada

Cardiovascular disease remains the leading cause of death and is the most costly disease in Canada despite declining mortality and hospitalization rates over

the last decade (1,27). The cost of providing healthcare to patients with heart attacks and strokes, as well as the resulting lost productivity, has been estimated at \$22 billion annually or 12% of the national cost of illness (28,29). As the population ages and the prevalence of cardiovascular disease (CVD) increases, these costs are expected to rise substantially (27,28).

Epidemiologic studies suggest that the improvements in cardiovascular (CV) morbidity and mortality that have been made over the last decade may not be sustained. The incidence of obesity and diabetes, which are major risk factors for CVD, has been increasing at an alarming rate in Canada. Saskatchewan-specific data have shown that the age and sex-adjusted prevalence of diabetes increased 44% from 1993-2001 (30); more recent data from the National Diabetes Surveillance System has shown a 24% increase in the age and sex-adjusted prevalence of diabetes in Canada from 2000-2001 to 2004-2005 (31). Nationally, the adjusted prevalence of hypertension has almost doubled from 8.4% to 14.6% between 1994 and 2005 (32). The increasing prevalence of hypertension, diabetes, and obesity is especially evident among younger adults (32,33), and this portends future increases in CVD unless aggressive preventive measures are instituted.

1.2.1 Management of Cardiovascular Risk Factors

Nine out of every 10 Canadians older than 20 years of age has at least one modifiable risk factor for CVD, and one-third of Canadians have three or more risk factors (including high blood pressure, diabetes, tobacco smoking, overweight or obesity, lack of physical activity, inadequate consumption of fruits and vegetables, and high or extreme stress) (28,31). However, established medical therapies are

consistently under-utilized in patients with cardiovascular disease or its risk factors and the majority of patients are not reaching their cholesterol, blood pressure, and blood glucose goals (2). Using data from two large, prospective Canadian databases, Hackam and colleagues showed that only 50% of patients with known cardiovascular disease had their LDL cholesterol or total-cholesterol to HDL-cholesterol ratio at target (4). A retrospective cohort study from Ontario found that 63.2% of patients with dyslipidemia were untreated, and that women were less likely to be treated than men (5). In terms of hypertension, the study by Hackam and colleagues reported that only 44% of hypertensive patients achieved their target systolic blood pressure (4), while a chart review of primary care patients in North Carolina showed that blood pressure was above target in 52.9% of patients and only 44.3% of these patients had had therapy intensified in the past year (34). Although results from a recent cross-sectional study in Ontario suggest that rates of hypertension control have improved significantly over the past decade, the overall rate of uncontrolled hypertension remains quite high at 34.3% (35). Furthermore, among those patients with concurrent diabetes, uncontrolled hypertension was observed in the majority of patients examined (63.9%) (35). Similar findings have been reported for blood glucose control amongst diabetic patients in Canada where only 64% achieved their fasting targets (3).

Overall, only a small fraction of high risk patients in Canada (21%) appear to have all of their modifiable risk factors under control (3). For moderate risk patients, where the targets for CV control are less strict, the proportion of individuals with optimal control is better, but still far from ideal (66%) (3). These data suggest that a

significant gap exists between guideline-recommended practices and current patient care.

One possible explanation for the treatment gap regarding CV risk reduction targets is the use of inadequate doses of medications (4). One study found that only 25-50% of the target doses of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) and angiotensin-converting enzyme inhibitors (ACEIs) used in clinical trials were prescribed to patients at high risk of cardiovascular events, despite low rates of patients reaching their cholesterol and blood pressure goals (4). It has also been shown that the likelihood that a patient with above-target blood pressure, blood glucose, or cholesterol levels will have drug therapy initiated or titrated at a routine physician office visit is less than 20% (4,36). We believe that opportunities exist to close this treatment gap among patients with uncontrolled cardiovascular risk factors.

1.3 Primary Care and Cardiovascular Disease

Patients with CVD receive a large proportion of their care from family physicians (26). A Nova Scotia study found that 95% of cardiovascular drug prescriptions for seniors are written by family physicians (37). Also, an Ontario study found that 12% of all family physician office visits are for CVD or its risk factors (38). Thus, family physician offices are clearly important settings for the care of patients with CVD.

However, there are limitations to the provision of comprehensive cardiovascular care in family medicine settings. The main issue cited for shortfalls in the treatment of cardiovascular risk factors was time constraints (34). Healthy

patients generally do not book physician appointments, so physicians often must prioritize their time to acute issues rather than asymptomatic risk factor management (34,39). Attempts are currently being made to address this; in Saskatchewan and other provinces, the government has implemented chronic disease management billing codes to facilitate guideline-recommended management of select chronic diseases by fee-for-service family physicians, including diabetes, coronary artery disease, and heart failure (40). However, there are many patients with CVD risk factors who do not have pre-existing CAD, diabetes, or heart failure. For example, approximately 63% of all coronary events occur in patients with no history of CAD (41). The Saskatchewan Ministry of Health is also attempting to develop primary health care clinics across the province that pay physicians on a salary as opposed to the typical fee-for-service structure (42). This alternate payment structure has been adopted to ensure that a physician's income "does not suffer because they spend needed time with a client..." for chronic disease management activities (42). To date, we know of no published study that definitively quantifies the impact of these initiatives.

1.3.1 Pharmacists and Primary Care

Clearly, there exists a treatment gap with respect to the optimal management of cardiovascular risk factors in Canada. It has been proposed that the formation of primary care teams might minimize the care gaps that exist within the current healthcare system, specifically regarding health promotion and disease prevention (43). As medication therapy plays a significant role in the management of CV

disease prevention and management, expanding the presence of pharmacists on primary care teams has been an area of interest for the past several years (18,43).

However, pharmacists appear to be under-utilized and under-represented on primary care teams in Canada (18-21). The slow uptake of pharmacists into these positions may be a result of several factors. First, pharmacists themselves may not be ready to take on an expanded role. A recent survey of practicing pharmacists in Canada found that, while the majority want to provide enhanced clinical services for patients, only 43.5% felt prepared to take on these advanced roles (44). Pharmacists cite a lack of understanding regarding their role on primary care teams as a barrier to wanting to practice in this setting (20,45). Similarly, it has been suggested that other healthcare professionals may be uncertain as to pharmacists' roles on primary care teams (46). Secondly, health system barriers such as lack of remuneration for clinical pharmacy services may also be a hindrance (47,48). The majority of pharmacists practicing in Canada are paid through the dispensing fees associated with filling prescriptions in community pharmacy practice (47,49). However, it would appear that there exists a great opportunity for pharmacists to facilitate CV risk reduction activities in primary care centres in Canada if such barriers can be overcome.

1.3.2 Pharmacist Interventions to Improve Cardiovascular Risk Indicators in Primary Care

There are numerous studies of pharmacist interventions to improve specific CVD risk factors, including blood pressure (50-52) and cholesterol levels (53-55). Additionally, a meta-analysis has found benefit to pharmacist interventions in

hypertension, dyslipidemia, and diabetes (56). However, there are fewer examples of pharmacist programs targeting global CV risk reduction (Table 1.1). Because cardiovascular risk factors tend to cluster within patients, and because they tend to have a synergistic impact on overall cardiovascular risk, addressing risk factors in isolation may be missing an important opportunity. Of the studies that have reported benefits of pharmacists working collaboratively with physicians and other healthcare providers to address global CV risk in primary care (6-10,12-17,22,57), issues relating to internal and external validity hinder these studies from providing robust evidence for the optimal activities of a primary care pharmacist in this setting. This is likely partially responsible for the currently limited utilization of clinical pharmacists in real-world primary care settings.

The internal validity of available global CV risk reduction studies is frequently low. Of the 21 studies described in Table 1.1, only six were randomized controlled trials (15,17,25,57-59). One of these studies did not achieve their target patient recruitment, thus reducing their power to detect a difference between groups (58). Two studies (6,10) randomly assigned patients to pharmacist intervention or usual care groups; however, no between-group comparisons were made, eliminating the benefit of the randomly assigned control group.

In 2009, members of our research group conducted a randomized controlled trial examining a global CV risk reduction intervention within a family medicine practice in Saskatoon (59). Although the study was designed to maximize internal validity, several questions remained unanswered at the completion of the trial. First, physician referral of at-risk patients was slow throughout the trial period. Thus,

would the identification of at-risk patients improve if the pharmacist was responsible for patient screening? Secondly, data from a post-hoc analysis conducted after the study suggested that participating physicians were influenced by the Hawthorne effect because they were caring for patients in both the usual care groups and intervention groups simultaneously. The Hawthorne effect is an alteration in a study participant's behaviour or study outcomes due to the participant's awareness that they are being observed (60). Would the impact of the intervention have been more pronounced without this confounding influence? Third, all patients in this trial were required to sign informed consent prior to enrolment, and only 70% of those referred were subsequently enrolled. Would the ability of the pharmacist to facilitate CV risk improvement be different if applied to all patients within a clinic rather than just those volunteering for a study? Fourth, the intervention was applied to all patients at high risk for CV disease, reducing our ability to detect an impact of the intervention for those patients that were already well controlled. What would be the benefits if we restricted our intervention to those with uncontrolled risk factors only? Finally, if the option of pharmacist prescribing was offered to physicians for the purposes of titrating medications to target, to what extent would they refer patients for this service?

The majority of these questions were a result of the poor external validity of our study due to the strict requirements of the RCT study design. Indeed, external validity of many published studies in this area is also quite low. Many of the studies were conducted in specialized hospital or outpatient clinic settings (6-8,11,16,17,22-25), while the majority of Canadian patients receive care from general family

medicine clinics (26). It is likely that the practitioners who work in specialty practices are not representative of the doctors and pharmacists that work in family medicine settings. One of the greatest barriers to collaboration in family physician practices is the time required for these initiatives (61).

Many of the pharmacist interventions previously described in the literature involved time-intensive pharmacist interventions and had low sample sizes (23,24,62,63). Considering the high volume of patients seen in family physician clinics along with the high prevalence of CV risk factors among Canadian adults, time-consuming pharmacist interventions that enrol small numbers of patients are likely inadequate to address the needs of this population. Additionally, protocols relying on physician referral for patient recruitment (7,12,16,23,24,57,59) are limited by the potential for missing patients with unidentified CV risk factors.

Previous CV risk reduction initiatives led by pharmacists have been varied in scope and focus of the intervention, making it difficult to ascertain which factors are associated with CV risk reduction success. Many involved assessment and communication of patients' CV risk (8,9,13,16,59). Most of the interventions have involved patient education and counselling to some extent (6,7,10,12,14,16,17,22,59). However, it is often difficult to determine the amount of time spent on these activities. Additionally, most of the interventions have involved assessments of patients' drug therapies, ongoing monitoring for target achievement, and recommended or implemented alterations to facilitate CV risk reduction (6,7,9-17,22,57,59).

Collaborative prescribing agreements, which enable pharmacists to titrate and adjust select medications, have been used in several studies to facilitate CV risk reduction success (7,12,13,16,57). It has been suggested that collaborative prescribing by pharmacists may produce greater improvements in clinical parameters than those in which the pharmacist makes recommendations to the physician (64,65). Of the 17 studies reviewed here, five utilized collaborative prescribing agreements, and all found positive results of the pharmacist intervention (7,12,13,16,57). Of the 12 studies that relied on pharmacists making recommendations for drug therapy changes to the physician, nine found a positive result of the pharmacist intervention (6,8-10,14,15,17,22), while three found no difference (25,58,59). Thus, it is still unclear if pharmacist-prescribing protocols facilitate success to a greater extent. In addition, the extent to which participating physicians would choose the option of pharmacist prescribing on a case-by-case basis has only been examined in one other study (7); it would be interesting to corroborate these findings.

Many pharmacist intervention studies have been published over the past several years; however, a definitive conclusion about the role of pharmacists in CV risk reduction in primary care remains elusive. Not all of the studies have been positive (25,58,59) and interventions have varied widely in terms of the focus and scope of the activities conducted by the pharmacist. Also, the generalizability of many studies is limited due to their specialized practice setting (6-8,11,16,17,22-25). The majority of the studies relied on referrals for patient recruitment, potentially missing patients with unidentified CV risk factors (7,12,16,23,24,57,59).

Table 1.1: Summary of Pharmacist Interventions to Reduce Global Cardiovascular Risk

Study	Design	Patients	Intervention	Outcomes
MEDMAN (58)	Randomized controlled trial	n = 1493 patients with established CHD (Did not achieve target patient recruitment)	Pharmacist assessment and follow-up; recommendations sent to family physician.	No significant between- group differences in proportion of patients receiving appropriate treatment for CHD (per the National Service Framework).
Simpson et al. (15)	Randomized controlled trial	n = 260 patients with T2DM	Pharmacist assessment and follow-up; recommendations discussed with primary care physician.	Primary Outcome: Intervention group had a significantly greater decrease in SBP (-7.4mmHg) than control group (-2.5mmHg) over 1 year (4.9mmHg difference in favor of the intervention; p=0.01). Trend towards improved glycemic and lipid control, not statistically significant.
Rothman et al. (57)	Randomized controlled trial	n = 217 patients with poorly controlled T2DM (A1c > 8%)	Patient education, cardiovascular risk assessments, medication initiation and titration (per algorithms), ongoing monitoring and follow-up of clinical parameters versus one-time pharmacist education session followed by usual care.	Intervention group had significantly lower systolic blood pressure (-9 mmHg) and A1c levels (-0.8%) compared to the usual care group. In the intervention group, 91% of patients were on aspirin therapy versus 58% of control patients (p<0.001). No significant between-group differences in total cholesterol levels were

Study	Design	Patients	Intervention	Outcomes
				observed.
CCARP (59)	Randomized controlled trial	n = 176 patients in a large family medicine practice in Saskatoon, SK, with a Framingham risk score of $\geq 15\%$ or a CAD equivalent	Pharmacist met with each patient to review medications, calculate their Framingham Risk Score, and provide patient education. Patients were then randomly assigned to pharmacist follow-up or return to usual care. Pharmacist determined blood pressure, cholesterol, and blood glucose targets for patients in the intervention group, and notified the patient and the physician of risk factors not at target. The pharmacist followed-up with patients in the intervention arm every eight weeks to assess target achievement, provide education and promote adherence.	There was no significant difference in mean reductions in Framingham risk score between groups (-2.68 in the intervention and -1.25 in the single-contact group, $p=0.098$). There were no significant between-group differences in BP, LDL-C, TC: HDL-C ratio, or A1c. Statin utilization was significantly higher in the pharmacist follow-up group (85.2% vs. 67%).
VA-MEDIC (17)	Randomized controlled trial	n = 109 patients with uncontrolled diabetes	Group education sessions by pharmacists, nurses, physical therapists and dietitians, followed by pharmacist intervention sessions.	A significantly greater proportion of patients in the intervention group achieved their target A1c and BP levels compared to the usual care group; no significant between-group differences were seen in cholesterol levels or smoking rates.
Phumipamorn et al. (25)	Randomized controlled trial	n = 135 Muslim patients with diabetes in Thailand	Patient education, adherence assessments.	No significant between-group differences in A1c before or after the intervention. Significant reductions in TC and LDL-C

Study	Design	Patients	Intervention	Outcomes
				were observed in the intervention group compared to the control group.
Al Mazroui (6)	Randomized before/after trial with concurrent control group	n = 240 patients with T2DM in the United Arab Emirates	Medication review, drug and disease-state counselling, adherence support. Recommendations discussed with family doctor.	Significant reduction in A1c in intervention group (from 8.5 to 6.9%). Also reduced Framingham risk score, systolic, and diastolic blood pressure in the intervention group; no change in the control group from baseline.
Freemantle Diabetes Study (10)	Randomized before/after trial with concurrent control group	n = 198 patients with diabetes in Australia	Baseline, 6, and 12-month lifestyle and medication counselling as well as follow-ups every 6 weeks by a pharmacist. Recommendations sent to family physician.	A1c was reduced by 0.5% from baseline in the intervention group; no change in the control group. Estimated 10-year risk of CV events (per UKPDS risk engine) decreased from 25.1 to 20.3% in the intervention group, while no change was seen in the control group.
Asheville Project (8)	Before/ after study	n = 565 patients employed by the City of Asheville or Mission Hospitals with hypertension or dyslipidemia	Patient education, medication reviews, monitoring. Recommendations sent to family physician.	Significant improvement in systolic BP post-intervention (137 to 126 mmHg). Proportion of patients achieving target BP improved from 40.2 to 67.4%. Significant reduction in LDL-C, TC, and TG; proportion of patients achieving LDL-C targets increased from 49.9 to 74.6%.

Study	Design	Patients	Intervention	Outcomes
Taveira et al. (16)	Retrospective cohort study (before/ after intervention)	n = 355 patients at high-risk of CVD at a Veteran Affairs Medical Centre in the United States	Pharmacists provided patient education, assessed patient adherence, monitored laboratory values, and developed a drug therapy regimen to achieve CV risk reduction targets using medication titration algorithms for hypertension, diabetes, cholesterol, and smoking cessation.	10-year CV risk (as assessed by Framingham) decreased from 16% to 12% post-intervention. TC, LDL-C, A1c, and SBP were all significantly reduced post-intervention. Smoking rates were also significantly reduced from baseline.
Carson et al. (9)	Before/after study	n = 324 patients with established CHD or at high risk for CV events in a primary care setting in New York	Pharmacist screened patient profiles to determine if they were candidates for aspirin therapy or lipid-lowering treatment. Recommendations for treatment alterations made to family physicians.	Aspirin utilization in secondary prevention patients increased from 45% at baseline to 81% post-intervention. LDL-C was significantly reduced by 26%.
Reid et al. (13)	Before and after study	n = 206 patients with hypertension in the United Kingdom	Blood pressure assessments and medication titrations by pharmacists; also CV risk assessments and cholesterol medication recommended to family doctor if indicated.	Proportion of patients achieving target BP increased significantly post-clinic (from 36% at baseline to 85% at follow-up). Proportion of patients receiving aspirin and statin therapy also increased significantly post-clinic.
McCord (12)	Before/after study	n = 155 patients with diabetes	Education, medication initiation or titration (collaborative prescribing agreements), monitoring by pharmacist.	Significant reduction in A1c post-intervention (from 9.1% to 7.49%). Significant reductions in LDL-C and TG were also observed. No significant changes in blood pressure.
Geber (11)	Retrospective chart review	n = 146 patients with documented	Pharmacist medication assessment or control group.	LDL-C targets reached by 85% of patients in the intervention

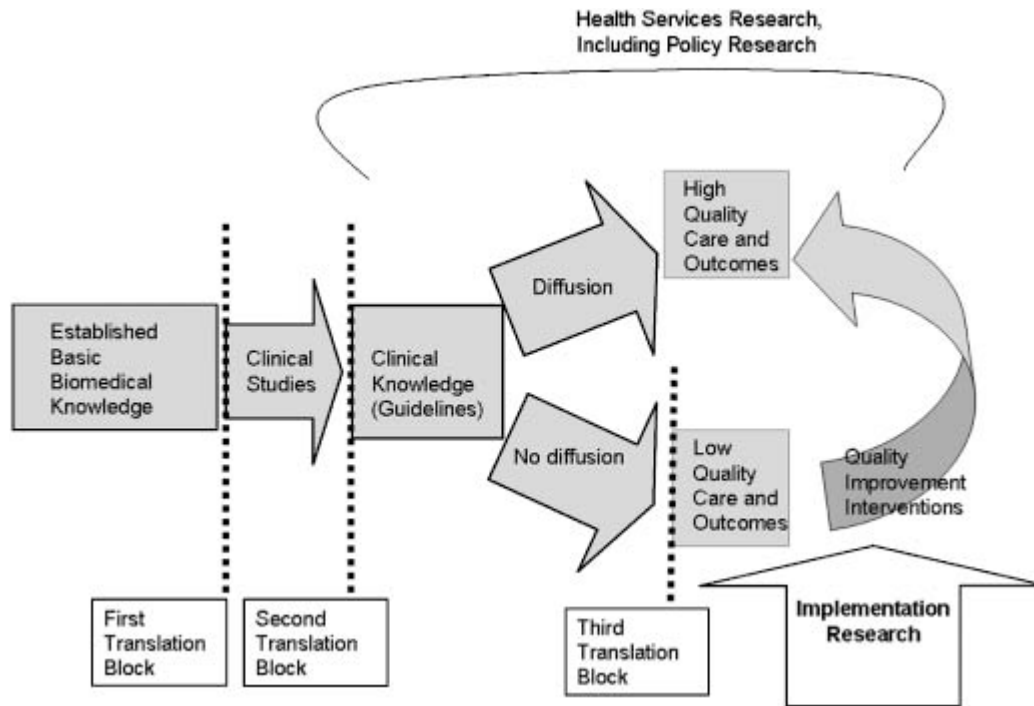
Study	Design	Patients	Intervention	Outcomes
	(non-randomized clinical trial)	CAD		group vs 50% of control patients (p<0.01). Rates of aspirin utilization were not different between groups (97% vs 92%).
Anaya et al. (7)	Retrospective cohort analysis (before/after intervention)	n = 110 patients with diabetes	Disease/drug information; initiation, titration, and monitoring of drug therapy for diabetes, hypertension, and dyslipidemia.	Significant reduction in A1c from baseline (8.9 to 8.2%). No significant change in cholesterol levels or blood pressure post-intervention.
DiabetesCARE (22)	Before/after analysis	n = 101 employees of the University of Kentucky with diabetes	Group education sessions and individual assessments by a pharmacist.	A1c was significantly reduced from 7.55% to 7.02% post-intervention. Significant reductions in LDL, TC, and TG. No significant change in blood pressure.
Reilly et al. (14)	Before and after study	n = 100 patients with established CHD in Scotland	Medication reviews, patient education, ongoing monitoring of CV risk factors; recommendations for drug therapy alterations made to GP.	Proportion of patients receiving aspirin increased significantly from 39% to 92%; proportion of patients achieving their SBP and total cholesterol targets also increased significantly post-intervention.

BP = blood pressure, CAD = coronary artery disease, CHD = coronary heart disease, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, T2DM = Type 2 Diabetes Mellitus, TC = total cholesterol, TG = triglycerides

1.4 Implementation Research and CCARP II

Overall, we believe sufficient evidence exists to show benefit of pharmacist-led interventions to reduce global cardiovascular risk factors in primary care despite the fact that internal validity of certain studies has been inconsistent (6-16,57,66). However, due to the issues with the external validity of these studies as described above, important gaps in knowledge exist with respect to implementation of collaborative CV risk reduction interventions in real-world primary care settings, where the majority of Canadians receive their care. For example, there is virtually no information available to determine the number of patients that could benefit from a CV risk reduction intervention because the majority of clinical intervention studies do not perform systematic screening, nor do they include all eligible patients due to the requirement for informed consent. Thus, we aimed to conduct a project falling under the category of ‘implementation research’, which is translational research that seeks to bridge the gap between clinical science and actual clinical practice (Figure 1.1) (67).

Figure 1.1: Implementation Research (67)



We believe that real-world collaborative initiatives that target identification and management of CV risk factors must consist of several key characteristics. First, the collaborative initiative must be applicable to primary care settings. Since the majority of patients in Canada receive screening, treatment, monitoring, and follow-up for CV risk factors from family physicians (26), it is important to develop collaborative initiatives that are effective and feasible in this setting. Second, we believe that patients must be enrolled as a result of a systematic screening process for uncontrolled CV risk factors in addition to being enrolled by physician referral. Targeting only patients with previously recognized and documented CV risk factors may miss a significant proportion of individuals at risk. Third, comprehensive CV risk factor reduction is important to reduce overall cardiovascular risk. Therefore,

the pharmacist needs to address all risk factors including hypertension, diabetes, dyslipidemia, and appropriate drug utilization. Fourth, ongoing support for patient adherence to drug therapy for CV risk factor reduction is important. One study estimated that 50% of patients discontinue antihypertensive therapy within 6-12 months of its initiation (68). Similarly, it has been found that approximately half of patients become non-adherent to statin therapy within one year of starting (69). Regular patient follow-ups that include assessment of adherence and regular feedback regarding treatment progress are important factors in long-term adherence (70). Such follow-ups are especially important when patients are first starting new medications and at high risk of nonadherence (69). Finally, effective pharmacist-led initiatives must focus on maximizing efficiency in order to make a significant impact on the treatment gap in CV care.

CHAPTER 2

2. Purpose of Project

2.1 Purpose of CCARP II

The purpose of our study is to implement a pharmacist-led collaboration to identify and manage uncontrolled CV risk factors in a family medicine setting. We hope to build on the successes of previous work by our research team (CCARP) (59) as well as other pharmacist-led programs while addressing some of the limitations related to external validity as described above, specifically the setting of the intervention and the method of patient identification.

2.2 Objectives

2.2.1 Objective 1

To apply a systematic screening procedure within an existing family medicine practice to identify patients with uncontrolled CV risk factors.

2.2.1.1 Specific Aim 1

To determine the proportion of patients at moderate or high CV risk with one or more uncontrolled risk factors presenting to a typical primary care clinic.

2.2.1.2 Specific Aim 2

To determine the proportion of patients at moderate or high risk for CV events with one or more risk factors not at target that were referred for ongoing pharmacist assessment and monitoring. These patients are referred to as the

“enrolled patients.”

2.2.1.3 Specific Aim 3

To determine the proportion of enrolled patients with previously unidentified CV risk factors.

2.2.2 Objective 2

To reduce above-target CV risk factors in enrolled patients.

2.2.2.1 Specific Aim 1

To measure changes in blood pressure, cholesterol levels, HbA1c in the enrolled patients.

2.2.2.2 Specific Aim 2

To determine the proportion of enrolled patients who achieve a novel endpoint for global CV risk reduction – the Cardiovascular Risk Improvement index (CRI)-20 (see Endpoints, section 3.4.2.1 for description) after the intervention.

2.2.2.3 Specific Aim 3

To determine the proportion of enrolled patients who receive treatment with evidence-based therapies (ACEI/ARBs, beta-blockers, antiplatelet agents) before and after the intervention.

2.2.2.4 Specific Aim 4

To determine the proportion of enrolled patients that achieve their predetermined targets in CV risk factors after the intervention in CV risk factors that

were uncontrolled at baseline.

2.2.2.5 Specific Aim 5

To determine the proportion of enrolled patients prescribed new CV medications over the study period that are persistent with these new drug therapies at the end of the study period.

2.2.3 Objective 3

To evaluate the acceptability of collaborative prescribing by pharmacists in this setting.

2.2.3.1 Specific Aim 1

To determine the proportion of enrolled patients referred to pharmacist for medication initiation or titration (per collaborative prescribing agreement).

2.2.3.2 Specific Aim 2

To record the number of prescriptions written by the pharmacist over the study period.

2.2.4 Objective 4

To evaluate the human resource requirements of the program.

2.2.4.1 Specific Aim 1

To record all pharmacist consults and interventions to estimate the time required for this role.

2.3 Hypothesis

A collaborative, pharmacist-led intervention will aid in the identification of patients with uncontrolled risk factors for CVD, and subsequently help reduce these cardiovascular risk factors to facilitate target achievement.

CHAPTER 3

3. Methods and Procedures

3.1 Clinical Intervention

The clinical intervention consisted of both protocol-driven activities (i.e., provided in a standardized way to all patients), as well as variable activities that were provided in response to a patients' clinical situation (i.e. at the pharmacist's discretion). Protocol-driven activities are important in clinical research to ensure high internal validity; however, a certain degree of clinical flexibility is also necessary to ensure external validity of professional interventions (71). In this intervention, the patient screening and preparation of the CV risk assessment form (see description below in 3.1.1) by the pharmacist was systematic and protocol-driven, while follow-up activities were tailored to each patient's clinical situation.

3.1.1 Patient Screening

All patients who receive their primary medical care under Drs. Bettin, Dosman, Rajakumar, and Wu (all family physicians) at the Saskatoon Community Clinic were eligible for screening. Screening was performed by the pharmacist on all male patients ≥ 40 years of age and female patients ≥ 50 years of age prior to a physician appointment for any reason. Patients requiring screening were identified using HEALTHSuite, the electronic appointment scheduling software at the Clinic, the day prior to their physician appointment. The pharmacist kept a master list of

patients already screened and compared this to the upcoming day-lists to ensure patients were screened only once over the study period.

Screening involved calculation of a 10-year Framingham risk score (Appendix 1) (72), which requires the following patient information: Age, sex, blood pressure, total cholesterol, HDL cholesterol, and smoking status. If any of these data were unavailable, the pharmacist notified the physician and arranged for the information to be collected. Patients with a coronary risk equivalent (angina, revascularization procedures, acute coronary syndromes, ischemic stroke or TIA, or known atherosclerosis or PVD) were automatically designated as high risk ($\geq 20\%$ - 10 year risk). As per the Canadian Diabetes Association (73), all men ≥ 45 years and women ≥ 50 years with diabetes were also automatically considered at high risk. As recommended in the 2009 Canadian Dyslipidemia Guidelines, patients with a family history of premature CVD (i.e. in a first-degree relative prior to 60 years of age) had their Framingham scores adjusted by a factor of 1.7 (women) and 2.0 (men) (72).

Patients at moderate (10-19%) or high ($\geq 20\%$) risk of cardiovascular events were eligible for pharmacist follow-up if they had at least one CV risk factor not at guideline-recommended targets. This included patients with hypertension and the last recorded chart BP $> 140/90$ mmHg (non-diabetics) or patients with diabetes or chronic kidney disease and BP $> 130/80$ mmHg; patients at moderate CV risk and LDL-C > 3.5 mmol/L or TC: HDL ratio > 5 or patients at high CV risk and LDL-C > 2 mmol/L or TC: HDL ratio > 4 ; or patients with diabetes and HbA1c $> 7\%$. Cholesterol and HbA1c measurements used were the most recent values recorded in

the chart. Cholesterol values measured within the year prior to screening were used; HbA1c levels had to be done within six months prior to screening. If the last-available values were older than this, these tests were reordered. Patients did not receive pharmacist follow-up if they had been diagnosed with a terminal illness or dementia.

Once target patients were identified, the pharmacist prepared the CV Risk Profile Form (Appendix 2) for the physician to review. The CV risk profile form informed the physician of the patient's 10-year CV risk, the patient's current and target levels for blood pressure, cholesterol, and HbA1c, and pharmacist recommendations to facilitate target achievement. Recommendations were primarily based on algorithms that were developed by the clinical pharmacist (E.Y.) and pre-approved by all participating physicians prior to commencement of the study.

At the patient's scheduled appointment with the physician that prompted the screening, the patient received a letter notifying them of the pharmacist's involvement in their CV care (Appendix 3). The physician reviewed the CV Risk Profile Form prepared by the pharmacist, assessed the patient, and implemented the recommendations if appropriate. The physician then indicated on the CV Risk Profile Form what kind of pharmacist follow-up was required. Follow up options (specific pharmacist follow up activities described below in 3.1.2) included: a) clinical pharmacist follow-up with all drug therapy recommendations to be implemented by the physician (i.e. no collaborative prescribing); b) clinical pharmacist follow-up with collaborative prescribing (i.e., pharmacist implemented

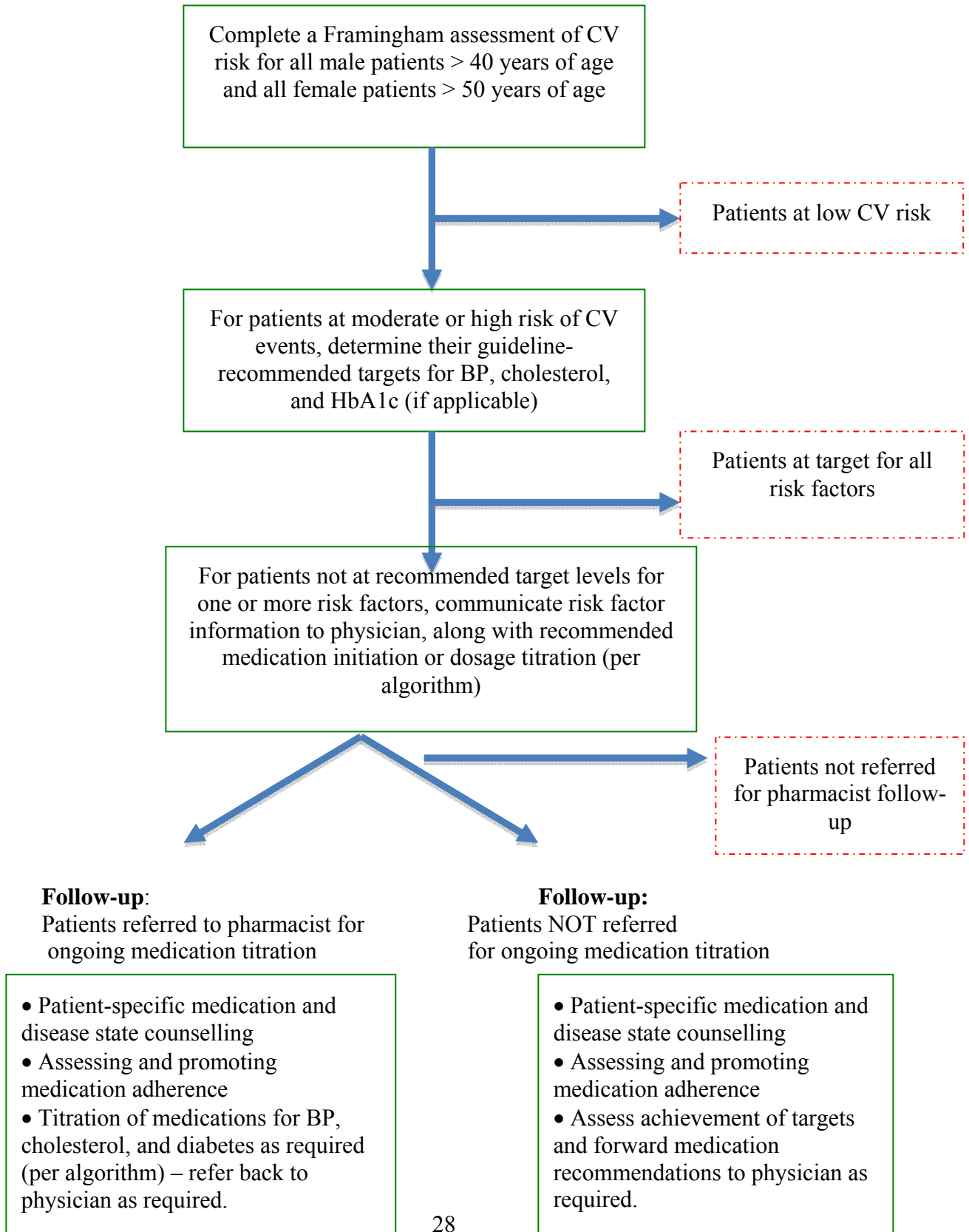
drug therapy recommendations); or c) no pharmacist follow-up. The Cardiovascular Risk Profile form was then returned to the pharmacist so she could determine what kind of patient follow-up (if any) was needed.

3.1.2 Patient Follow-up by the Pharmacist

Pharmacist follow-up activities included counselling the patient on their CV risk and the importance of controlling risk factors, providing medication information, assessing and promoting medication adherence, monitoring for target achievement, and making additional recommendations regarding drug therapy changes to the patient's physician (as needed). To improve the efficiency of this intervention compared with previous, time-intensive pharmacist interventions (23,24,62), the intensity and frequency of patient follow-ups was determined by the pharmacist on a case-by-case basis by perceived need. Patient education and counselling was primarily provided to patients started on new medications, as these are the patients at highest risk of nonadherence (69), and those with known or suspected adherence issues (as noted by the patient's family physician, patient self-report, or as suspected from the Pharmaceutical Information Program (PIP), Saskatchewan's electronic prescription monitoring database). Reminders were sent out to patients overdue for follow-up blood pressure or laboratory assessments (cholesterol or HbA1c levels). At subsequent clinic appointments, an updated CV Risk Profile Form was provided to the physician along with any recommendations for drug therapy changes. If urgent medication problems were identified between appointments (such as tolerability issues), the pharmacist discussed them with the patient's physician.

For patients referred to the pharmacist for collaborative prescribing, the pharmacist was also able to initiate or adjust CV medications according to pre-approved algorithms (see Appendices 4-10) to facilitate target achievement. However, due to delays in the approval of pharmacist prescribing legislation in Saskatchewan, collaborative prescribing was only an option for patients enrolled after March 4, 2011.

Figure 2.1: Patient Pathway



3.2 Study Duration

The total study duration was 9 months. The pharmacist began patient screening October 21, 2010 and continued until May 13, 2011, to ensure all patients had at least one month of pharmacist follow-up. Patient follow-ups continued until June 17, 2011 (study end date).

3.3 Ethical Considerations

One of the major ethical considerations with this project related to the privacy of patients' medical records, and whether they could be accessed by the pharmacist prior to the physician appointment to facilitate cardiovascular risk screening. Several steps were taken to ensure study protocol complied with ethical requirements. First of all, the investigators spoke with a privacy officer at the Saskatchewan Privacy Commission on three separate occasions to discuss this issue. Secondly, the investigators met with the Chair of Biomedical Ethics at the University of Saskatchewan (Dr. M. Desautels, August 2010) to discuss the project. Finally, the study protocol was submitted to the Biomedical Research Ethics board for review and approved on ethical grounds. One of the main considerations was that the collaboration was to be implemented on all patients within the medical clinic and the pharmacist would be undertaking activities that were facilitating the care that was provided by the most responsible physician in every case. We took all steps reasonable to inform patients about the collaborative nature of this practice and

offered several opportunities for patients to opt out of this collaborative approach to care.

Through this process it was agreed that, as the pharmacist would join the practice at the Community Clinic for the duration of the study (in fact, the pharmacist was already employed there in advance of the project), she would become part of the care group and thus, a trustee of patients' health information according to the Health Information Protection Act. As a trustee, the pharmacist was subject to the same ethical considerations as any other healthcare professional (i.e. to access only information needed for a specific purpose with the reasonable expectation of benefiting the patient (74)).

Due to the before/after, all-inclusive methodology of CCARP II, it was ultimately deemed to be a quality improvement project, and an exemption was granted from the Biomedical Research Ethics Board at the University of Saskatchewan. Operational approval for the project was also granted from the Community Health Services Association at the Saskatoon Community Clinic.

3.4 Endpoints

Ideally, the evaluation of this clinical intervention would consider Economic, Clinical, and Humanistic outcomes. Due to time constraints, however, we focused our analysis of the intervention on clinical endpoints, as well as a brief assessment of the pharmacist human resources required for the project. Assessment of humanistic outcomes, such as patient and physician satisfaction, may be undertaken at a later date as part of a subsequent study; ethics approval for this would be sought at that time.

3.4.1 Primary Endpoint: Patient Screening

We determined the proportion of patients with uncontrolled risk factors (out of total number of patients screened), the number of patients with uncontrolled risk factors that were not previously identified, and the proportion of eligible patients who were enrolled and followed by the pharmacist.

3.4.2 Secondary Endpoints

3.4.2.1 Clinical Endpoints

We determined before and after changes in clinical endpoints (SBP, LDL-C, TC: HDL ratio, and HbA1c) as well as the proportion of patients achieving their targets in each risk factor that was uncontrolled at baseline.

We also determined the proportion of patients achieving Cardiovascular Risk Improvement index 20 (CRI-20): This endpoint is achieved by all subjects who exhibit $\geq 20\%$ reduction relative to target (or achievement of target) in at least one of SBP, LDL-C, or HbA1c, whichever risk factor(s) were uncontrolled at baseline. The CRI endpoint can be modified to identify greater levels of risk improvement (e.g. CRI-50 or CRI-75). We also explored the proportion of patients achieving target thresholds for each individual CV risk factor (SBP, LDL-C, and HbA1c) as well as changes in these risk factors from baseline until the end of follow up.

Appropriate utilization of antiplatelets, ACEI/ARBs, and beta-blockers in patients with compelling indications for these medications (according to guideline recommendations) was evaluated at baseline and at the end of follow up.

Compelling indications for antiplatelet therapy were the secondary prevention of

established CVD, such as previous stroke/TIA/MI, angina, CABG or stent, or peripheral vascular disease (75). Compelling indications for ACEI/ARB therapy were previous MI, heart failure with left ventricular systolic dysfunction (left ventricular ejection fraction (LVEF) <40%), or microalbuminuria (albumin to creatinine ratio (ACR) >2.0 for males or >2.8 for females on two or more measurements) (76,77). Compelling indications for beta-blocker therapy were previous MI/stent/CABG or history of heart failure with left ventricular systolic dysfunction (76-78).

Additionally, we evaluated the proportion of enrolled patients exhibiting primary non-adherence (defined as failure to fill a newly prescribed medication at all, as verified by PIP). We also determined the proportion of patients persistent with new CV medications prescribed over the study period. To be included in this analysis, patients must have had sufficient follow-up time on the new medication to warrant filling it more than once (i.e. > 68 days for regular medications and >200 days for 100-day list drugs). To be considered persistent with new drug therapies, patients' last fill of the new medication must have occurred within 45 days prior to the closing date for follow-up (June 17, 2011). For patients prescribed medications eligible for a 100-day fill, the drug must have been refilled within 110 days prior to the study close date. This information was also obtained from PIP.

3.4.2.2 Pharmacist Prescribing

In anticipation that physicians would delegate certain patients for the delegated prescribing protocol, we aimed to compare the demographics of patients

referred to the pharmacist for medication titration versus those who were not referred, in addition to the proportion of referred patients who declined to participate in this aspect of the intervention. We also planned to examine the clinical success of patients referred for prescribing by evaluating all clinical endpoints described above (CRI, SBP, LDL-C, TC: HDL-C, HbA1c, proportion receiving evidence-based therapies, etc). We also aimed to determine the number of prescriptions written by the pharmacist over the study period, including new prescriptions, titrations, and refills.

3.4.2.3 Human Resources

Finally, we aimed to crudely estimate the pharmacist human resources required to carry out this protocol. Thus, we recorded all pharmacist visits and contacts with each patient, including complete assessments (in-person), follow up appointments (in-person or telephone), contact with physicians or other health care professionals, as well as time dedicated to screening charts in preparation for incoming patients.

3.5 Statistical Analysis

Statistical analyses were conducted using SPSS version 19 for windows (SPSS Inc., Chicago, Ill). Patient screening, pharmacist prescribing, and human resources data were descriptive. Paired T-test was used to assess changes in clinical endpoints from baseline to the end of the study (LDL-C, SBP, HbA1c, TC: HDL ratio). To be conservative in our estimate of the benefit of the intervention, we used the patient's last observation carried forward for those that did not have repeat

measurements throughout the study period (79). Chi-square was used to compare the proportion of patients receiving evidence-based therapies before and after the intervention.

CHAPTER 4

4. Results

4.1 Primary Outcome: Patient Screening

Over 80 working days between October 21, 2010 and May 13, 2011, the pharmacist screened 566 male patients ≥ 40 years and female patients ≥ 50 years of age presenting for an appointment with one of the collaborating physicians (Figure 4.1). Of the 566 patients screened, 186 (32.9%) met the eligibility criteria of moderate or high cardiovascular risk with one or more cardiovascular risk factors (blood pressure, cholesterol levels, or HbA1c) above guideline-recommended target levels. The remaining 380 patients screened did not meet eligibility criteria: 176 of these patients were at low cardiovascular risk, and the remaining 204 patients classified as moderate (n=119) or high (n=85) cardiovascular risk were already meeting guideline-recommended targets for all risk factors.

Of the 186 patients identified as meeting the eligibility criteria, 113 (60.8%) were enrolled and followed by the pharmacist for the remainder of the study (see Figure 4.1). Of the 73 patients not enrolled for pharmacist follow-up, 18 were excluded because they were deemed not to be candidates for aggressive cardiovascular risk reduction: Ten of these patients had been diagnosed with dementia, and eight of these patients had a terminal illness. An additional 19 of the 186 patients identified did not arrive for their physician appointment, and thus were not able to be informed about the project or agree to participate. The remaining 36 patients out of the 186 potentially eligible were not enrolled because no pharmacist

follow-up was requested, either from the patient themselves or from the patient's physician.

The baseline characteristics of the 113 patients enrolled for pharmacist follow-up are outlined in Table 4.1. The mean age of these patients was 66.9 years, and 52.2% were female. Patients at high cardiovascular risk (those with a documented coronary heart disease risk equivalent or a calculated 10-year Framingham risk level of $\geq 20\%$) accounted for 70.8% of the patients enrolled, while 25.7% were at moderate cardiovascular risk (Framingham risk level of 10-19%). An additional four enrolled patients (3.5%) were unable to be classified according to cardiovascular risk level because they did not have their cholesterol levels measured as requested over the follow-up period.

Of the 113 enrolled patients, 25 (22.1%) had previously diagnosed diabetes mellitus, 88 (77.9%) had documented hypertension, and ten patients (8.8%) had documented chronic kidney disease. Four patients (3.5%) had a previous myocardial infarction, and six patients (5.3%) had a previous stroke or transient ischemic attack. Eighteen patients (15.9%) were smokers. Antiplatelet therapy was used in 28 (24.8%) of the patients enrolled, and seven patients (6.2%) were on anticoagulant therapy.

At baseline, mean blood pressure of all enrolled patients was $140.3 \pm 17.6 / 77.9 \pm 13.5$ mmHg while mean LDL cholesterol (most recent measurement up to 3 years prior to screening date) was 3.26 ± 0.98 mmol/L. For the 25 enrolled patients with diabetes, the mean HbA1c level (most recent measurement up to 6 months prior to screening date) was $6.68 \pm 0.61\%$.

Of the 113 enrolled patients, 48 (42.5%) had risk factors that had not been previously identified (had not been previously recorded in the chart). Four of these patients had previously undiagnosed hypertension (and hypertension was subsequently diagnosed by a physician during follow-up) and 44 patients had previously unidentified dyslipidemia.

Table 4.1: Baseline Characteristics of Enrolled Patients

Characteristic	Measurement n=113
Age – years (SD)	66.9 (11.03)
Female Sex – No. (%)	59 (52.2%)
Current Smoker* – No. (%)	18 (15.9%)
10-Year Cardiovascular Risk [^] - No. (%)	
Moderate (10-19%)	29 (25.7%)
High (\geq 20%)	80 (70.8%)
Unable to Calculate	4 (3.5%)
Hypertension* - No. (%)	99 (77.9%)
Diabetes Mellitus* – No. (%)	25 (22.1%)
Chronic Kidney Disease* – No. (%)	10 (8.8%)
Previous Myocardial Infarction* – No. (%)	4 (3.5%)
History of CAD* – No. (%)	8 (7.1%)
Previous Stroke* – No. (%)	6 (5.3%)
Antiplatelet Use* – no. (%)	28 (24.8%)
Anticoagulant Use* – no (%)	7 (6.2%)
Blood Pressure [†] – mmHg (SD)	
Systolic	140.3 (17.62)
Diastolic	77.9 (13.5)
Cholesterol Levels [‡] – mmol/L (SD)	
Total Cholesterol	5.33 (1.1)
HDL	1.26 (0.38)
TG	1.87 (1.03)
LDL	3.26 (0.98)
Ratio (TC:HDL)	4.45 (1.23)
Hemoglobin A1c (diabetics) [‡] – Percent (SD)	6.68 (0.81)
Duration of Follow-up – Months Mean (SD)	4.69 (1.8)

Range	1 – 8.5
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^ Per Framingham Risk Score (72)

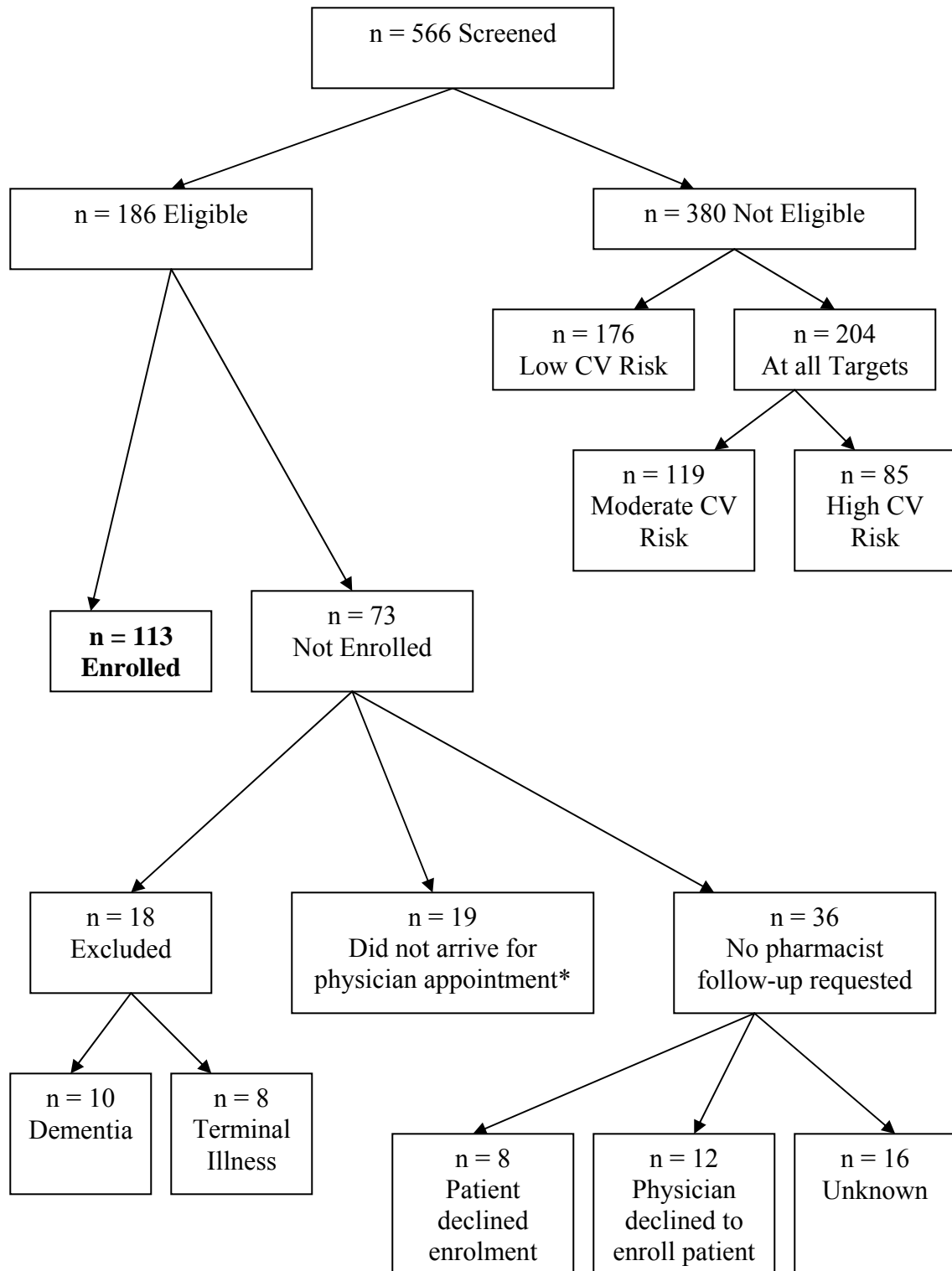
* As documented in the patient's chart

† Baseline blood pressure at first physician visit following pharmacist screening

‡ Most recent values as documented in patient chart (cholesterol level was measured at baseline or most recent measurement within 1 year of screening date was used; hemoglobin A1c was measured at baseline or the most recent measurement within 6 months prior to screening date was used).

CAD = Coronary artery disease; HDL = High-density lipoprotein; LDL = low-density lipoprotein;
SD = standard deviation; TG = triglycerides

Figure 4.1: Patient Screening Results



*Unable to consent to participate

4.2 Secondary Outcomes

4.2.1 Clinical Outcomes

4.2.1.1 Proportion of Patients Achieving CRI

The CRI-20 is achieved when a patient has achieved a minimum of 20% reduction in an uncontrolled risk factor relative to their target level (or achieved their target). Of all the patients enrolled and followed by the pharmacist, 78 (69.0%) achieved the CRI-20 endpoint (Table 4.2). Of these patients, 65.4% (51 / 78) achieved the CRI-20 due to reductions in SBP, 55.1% (43 / 78) due to reductions in LDL-C, 26.9% (21 / 78) due to reductions in the TC: HDL ratio, and 6.4% (5 / 78) due to reductions in HbA1c (note that patients may have had reductions in more than one risk factor to meet the CRI-20 criteria). The proportion of subjects achieving the CRI-20 was similar among the subgroup of subjects with at least 6 months follow-up (70.3%), but increased to 88.1% (52 / 59) when restricting the analysis to patients with at least one follow-up measurement for whichever risk factor(s) were uncontrolled.

The proportion of patients achieving the CRI-50 (a minimum of 50% reduction relative to target, or achievement of target, in at least one uncontrolled risk factor) was 65.5% (n=74). CRI-50 was reached by 70.3% (n=26) of those with at least 6 months follow-up and by 88.1% (n=52) of those with at least 1 follow-up measurement (Table 4.2).

Table 4.2: Proportion of Patients Achieving CRI

CRI	Patients	Number (%) Achieving	Number (%) Not Achieving
CRI-20	All† (n=109)	78 (69.0%)	31 (27.4%)
CRI-20	Minimum 6 months of follow-up (n=37)	26 (70.3%)	11 (29.7%)
CRI-20	At least one follow- up measurement (n=59)	52 (88.1%)	7 (11.9%)
CRI-50	All† (n=109)	74 (65.5%)	35 (30.9%)
CRI-50	Minimum 6 months of follow-up (n=37)	26 (70.3%)	11 (29.7%)
CRI-50	At least one follow- up measurement (n=59)	52 (88.1%)	7 (11.9%)

*CRI refers to a minimum percentage reduction (in this case, 20% or 50%) relative to target in an uncontrolled risk factor from baseline. Alternatively, CRI is considered achieved if the patient met their predetermined target for a risk factor that was uncontrolled at baseline.

†An additional 4 patients (3.5%) did not have sufficient baseline data to be included in the analysis.

4.2.1.2 Pre/Post Changes in Individual Risk Factors and Proportion of Patients Achieving Targets

4.2.1.2.1 Systolic Blood Pressure

There were 71 / 113 (62.8%) enrolled patients with baseline systolic blood pressure levels above their recommended target (Table 4.4). The mean baseline systolic blood pressure in this patient population was 150.0 mmHg. After the intervention period, the mean systolic blood pressure in this patient group was 137.3 mmHg, a reduction of 12.7 mmHg (SD 14.5) from baseline (p=0.017). Out of the 71 patients with systolic blood pressures above target at baseline, 32 (45.1%) had achieved their target SBP by the end of the follow-up period (Table 4.5). The

number of follow-up blood pressure measurements patients had throughout the study is listed in Table 4.3.

Table 4.3: Number of Blood Pressure Measurements during Study Period

n=71 patients with baseline BP above target

Number of BP Measurements During Study Period	Number (Percentage) of Patients
1 (Baseline BP only)	14 (19.7%)
2	11 (15.5%)
3	18 (25.4%)
4	8 (11.3%)
5 or more (including regular home BP monitoring by patient)	20 (28.2%)

BP = blood pressure

4.2.1.2.2 Cholesterol Levels

Baseline LDL cholesterol levels were above target in 83.2% (96 / 113) patients enrolled. The mean baseline LDL cholesterol in this patient population was 3.39 mmol/L. Following the intervention, the mean LDL cholesterol level in this patient group decreased to 3.03 mmol/L ($p < 0.001$) (Table 4.4). However, only 29.2% (28 / 96) had achieved their target LDL cholesterol at the end of the study period, partially as a result of 36 patients who had no follow up test completed after baseline (Table 4.5). Among the 60 patients who had a follow-up cholesterol panel completed during the follow up period, 26 (43.3%) had reached their target LDL-C levels by the end of the study period (Table 4.5).

In total, 54 / 113 patients (47.8%) had an above-target TC: HDL ratio at baseline. Mean TC: HDL ratio was reduced from 5.28 to 4.91 following the

intervention ($p < 0.001$) (Table 4.4). Of these patients, 20.4% (11 / 54) had achieved their target ratio by the end of the follow-up period (Table 4.5). In contrast, TG levels remained essentially unchanged (mean of 1.88 mmol/L at baseline to 1.84 mmol/L at the end of follow-up), as did HDL-cholesterol (mean of 1.25 mmol/L at baseline to 1.23 mmol/L at completion of follow-up).

4.2.1.2.3 HbA1c

There were eight diabetic patients enrolled with an elevated HbA1c at baseline (mean 7.51%) – see Table 4.4. Following the intervention, the mean HbA1c in this patient group was reduced to 7.16%; however, this absolute reduction of 0.35% from baseline did not achieve statistical significance ($p = 0.33$). Four of these patients (50%) had achieved their target HbA1c by the end of the study period (Table 4.5).

Table 4.4 Pre/Post Changes in Risk Factors in Patients Above Target for Each Risk Factor at Baseline

Parameter	n	Mean Pre +/- SD	Mean Post +/- SD	p-Value	Mean Difference (+/- SD) 95% CI
Systolic Blood Pressure (mmHg)	71	150.0 +/- 12.5	137.3 +/- 11.6	0.017	12.7 (+/- 14.5) 9.22 - 16.08
LDL-C (mmol/L)	96	3.39 +/- 0.93	3.03 +/- 0.96	<0.001	0.36 (+/- 0.66) 0.23 - 0.50
TC: HDL Ratio	54	5.28 +/- 1.06	4.91 +/- 1.18	<0.001	0.37 (+/- 0.78) 0.16 – 0.58
Hb A1c (%)	8	7.51 +/- 0.69	7.16 +/- 1.36	0.33	0.35 (+/- 1.76) -1.12 – 1.82

CI = Confidence Interval; SD = Standard Deviation

Table 4.5: Proportion of Patients Achieving Targets

Parameter	Patient Population	Number (%) At Target at Baseline	Number (%) Achieving Target	Number (%) Not Achieving Target
SBP	All* (n=113)	42 (37.2%)	71 (62.8%)	41 (36.3%)
	Baseline SBP Above Target (n=71)	-	32 (45.1%)	39 (54.9%)
	Minimum of 1 Follow-up SBP (n=93)	-	62 (66.7%)	31 (33.3%)
LDL-C	All† (n=109)	13 (11.9%)	36 (31.9%)	73 (64.6%)
	Baseline LDL-C Above Target (n=96)	-	28 (29.2%)	68 (70.8%)
	Minimum of 1 Follow-up LDL-C (n=60)	-	26 (43.3%)	34 (56.7%)
TC: HDL Ratio	All‡ (n=109)	55 (50.5%)	62 (54.9%)	47 (41.6%)
	Baseline Ratio Above Target (n=54)	-	11 (20.4%)	43 (79.1%)
	Minimum of 1 Follow-up Ratio (n=60)	-	36 (60.0%)	24 (40.0%)
HbA1c	All† (n=25)	17 (68.0%)	19 (76.0%)	6 (24.0%)
	Baseline HbA1c Above Target (n=8)	-	4 (50.0%)	4 (50.0%)
	Minimum of 1 Follow-up HbA1c (n=13)	-	10 (76.9%)	3 (23.1%)

* 1 patient (0.9%) did not have sufficient baseline data to be included in the analysis

‡ 4 patients (3.5%) did not have sufficient baseline data to be included in the analysis.

4.2.2 Medication Utilization

4.2.2.1 Evidence-Based Therapies

Results of pre-planned subgroup analyses focusing on patients with compelling indications for specific drug therapies was limited by small numbers (Table 4.6).

Table 4.6 Utilization of Evidence-Based Therapies

Drug Class	No. (%) with Compelling Indication	No. (%) Receiving Drug at Baseline	No. (%) Receiving Drug at Follow-up Completion	p-value
Antiplatelet Therapy*	16 (14.2%)	16 / 16 (14.2%)	16 / 16 (14.2%)	NS
ACEI/ARB Therapy†	13 (11.5%)	10 / 13 (76.9%)	12 / 13 (92.3%)	NS
Beta-Blocker Therapy‡	10 (8.8%)	8 / 10 (80.0%)	8 / 10 (80.0%)	NS

* Compelling indications for antiplatelet therapy were secondary prevention of established CVD, such as previous stroke/TIA/MI, angina, CABG or stent, or peripheral vascular disease (75)

† Compelling indications for ACEI/ARB therapy were previous MI, heart failure with left ventricular systolic dysfunction (LVEF <40%), or microalbuminuria (ACR >2.0 for males or >2.8 for females on two or more measurements) (76,77).

‡ Compelling indications for beta-blocker therapy were previous MI/stent/CABG or history of heart failure with left ventricular systolic dysfunction (76-78).

NS = not statistically significant (p>0.05).

4.2.2.2 Changes in Medication Utilization

Of the 71 patients with baseline blood pressures above target, 29 (40.8%) had a new antihypertensive medication added throughout the study period, while 15 (21.1%) had a dosage increase of an antihypertensive they were already taking. Of the 96 patients with elevated LDL-C at baseline, 14 patients (14.6%) were prescribed new statin medications, while an additional 17 patients (17.7%) received

a new cholesterol lowering agent other than a statin (ezetimibe, fenofibrate, or niacin) or had a dosage increase of a cholesterol medication they had been taking previously. In the diabetic patients, three of the eight patients (37.5%) with elevated HbA1c levels at baseline were prescribed new medications, and two of these patients (25%) had dosage increases for antihyperglycemic medications they were already taking.

4.2.3 Medication Adherence

Of the 113 enrolled patients, 54 (47.8%) received a new cardiovascular medication or had a dose increase over the study period. All of these patients had their first prescription fill within 4 weeks of the prescription being written (information obtained from PIP). Thus, no patients were found to exhibit primary nonadherence (failure to fill a prescribed medication at least once) in this study.

We also determined whether patients' last fill of the new medication occurred within 45 days prior to the closing date for follow-up (June 17, 2011). The exception to this was patients prescribed medications eligible for a 100-day fill in Saskatchewan – these medications must have been filled within 110 days prior to the study close date for the patient to be considered adherent. Again, this information was obtained from PIP. To be included in this analysis, patients must have had sufficient follow-up time on the new medication to warrant filling it more than once (i.e. ≥ 68 days for regular medications and ≥ 200 days for 100-day list drugs).

Of the 41 patients receiving new medications requiring more than one fill by the end of the study period, 36 (87.8%) had filled the medication within the 45-day window prior to study closing. Additionally, six of these patients had received more

than one new medication or dose increase over the study period. All six of these patients met the criteria for adherence for the second medication, as did the three patients who had a third medication added or dose increased.

4.2.4 Pharmacist Prescribing

The initial study proposal had also aimed to examine several issues around pharmacist prescribing, such as the demographics of patients referred to the pharmacist for medication initiation or titration, the clinical success of patients receiving prescriptions from the pharmacists compared to the other patients, and the number of prescriptions written by the pharmacist. However, due to unforeseen circumstances, the legislation allowing pharmacists to prescribe in Saskatchewan did not come into effect until March 4, 2011. Thus, the majority of patients were already enrolled prior to this being an option.

Of the 23 patients enrolled after March 4, 10 patients (43.5%) were referred to the pharmacist for ongoing medication initiation and titration as needed (i.e., pharmacist prescribing). Due to the short follow-up time before the study close, only one prescription was written by the pharmacist (a new statin medication). The remaining 13 patients (56.5%) enrolled after this date were referred to the pharmacist for follow-up assessment but prescribing authority was not granted. Reasons were not provided when prescribing authority was not authorized so we cannot determine whether this was due to patient or physician preference.

4.2.5 Human Resources

In total, there were 80 working days throughout the study period where the pharmacist actively screened patients for eligibility to enrol in the study. During this time, 202 hours were spent on screening activities, and a total of 566 patients were screened. Thus, 2.5 hours of each working day were dedicated to patient screening, and each patient took a mean time of 21.4 minutes to screen. During the final month of the study, from May 13 until June 17, 2011, no further patients were screened or enrolled to ensure at least one month's follow-up for all patients.

The patient follow-up period ranged from October 21, 2010 (first patient enrolled) to June 17, 2011 (study close), and there were 97 working days within this timeframe. Patient follow-ups occurred either by phone or in-person for those requiring blood pressure checks, blood glucose log reviews, or more in-depth education. Fifteen in-person follow-up assessments were conducted by the pharmacist (mean duration 25 minutes) for a total of eight hours of the pharmacists' time over the study period (negligible on a daily basis). Follow-up assessments via telephone were the preferred method of contact for most patients. Over the study period, 207 phone follow-ups were conducted by the pharmacist. Time required for such assessments ranged from 5 to 20 minutes, with an average of 16.4 minutes per follow-up (including documentation time). The mean amount of time each day devoted to phone follow-ups was 48.7 minutes.

Additionally, tasks like pulling and reviewing patient charts took a mean of 16.3 minutes of the pharmacist's time on a daily basis. Consultations with

physicians were a minimal contributor to the pharmacist's time, accounting for a mean of 3.1 minutes daily (with a range of 1-15 minutes).

CHAPTER 5

5. Discussion

The purpose of CCARP II was to implement and evaluate a pharmacist-led collaboration to identify and manage uncontrolled CV risk factors in a family medicine setting. In total, the pharmacist undertook CV risk screening for 566 consecutive adult patients presenting for a physician appointment. Of the patients classified as moderate or high risk for CV events, 47.7% (186/390) had one or more above-target risk factors (SBP, LDL-C, TC: HDL ratio, or HbA1c). This patient subgroup represented 32.9% of all patients presenting for a physician appointment for any reason over the study period. This confirms our hypothesis that there is still a need for a systematic approach to identifying patients with uncontrolled risk factors. Of the patients identified, 113 (60.8%) were referred back to the pharmacist for ongoing monitoring and follow-up. At the end of the study period, we found statistically significant reductions in SBP, LDL-C, and TC: HDL ratio in this subset of patients. We also found a high rate of persistence with new medications (87.8%) over the follow-up period. Thus, we believe this initial pilot implementation project was successful in identifying patients with uncontrolled CV risk factors, and aiding in the reduction of these risk factors toward target levels. The next step would be to evaluate this intervention in a multi-site, randomized controlled trial to verify these findings.

5.1 Patient Screening

Our screening process discovered a high rate of uncontrolled CV risk factors among patients visiting the clinic for any reason. Although other pharmacist intervention studies have utilized screening in select patient populations, such as diabetes (15), CAD (14), or hypertension (13), this is the first study to our knowledge that incorporates systematic screening for CV risk factors in all patients presenting to a family medicine clinic. An important strength of this approach was that patients were screened prior to a physician appointment for any reason; thus, even patients who are not diligent about seeing their physician for regular preventive care were screened (39). Furthermore, physicians were provided with the relevant information at the time of an existing appointment so appropriate decisions could be made without delay.

This method of screening was useful for identifying patients with above-target CV risk factors, as well as for generating referrals for pharmacist assessment and follow-up. Although literature suggests that the management of CV risk factors has been improving over the last couple decades (27,35), our study showed that the presence of uncontrolled CV risk factors is still quite common. The first CCARP study, which relied on physicians to identify and refer patients for the pharmacist, resulted in a slow accrual of patients despite broader inclusion criteria and a longer period of patient enrolment (59). In this project, we could ensure a systematic process was used to identify patients. This illustrates the importance of proactive screening for pharmacist interventions, rather than relying on referrals to identify patients (59).

Of the 186 moderate to high risk patients with one or more risk factors above target, 113 (60.8%) were referred back to the pharmacist for ongoing follow-up. Of those patients not referred, 18 were excluded due to pre-existing dementia or a terminal illness, and therefore were not suitable candidates for aggressive CV risk reduction. An additional 19 patients did not arrive for their physician appointment, and were thus not able to be notified of the pharmacists' involvement in their care and were not able to be followed-up for ethical reasons. Excluding these patients increases the physician referral rate to over 75%, suggesting physicians were generally supportive of this collaborative intervention. Although a specific physician follow-up survey would have confirmed this inference, it was not part of the a-priori objectives of this project for practical reasons. The remaining 36 patients were not referred for pharmacist follow-up either at their request (8 patients) or due to the preference of their physician (12 patients); for the remaining 16 patients no reason was provided.

We believe the rate of uncontrolled risk factors may actually be higher in other primary care settings in Saskatchewan. The clinic where this intervention was implemented had already undertaken initiatives intended to improve chronic disease management among their patients. First, physicians employed by this clinic were paid by salary rather than fee-for-service. As outlined in the Action Plan for Primary Care (42), this payment structure is considered to be more appropriate to achieve optimal care of patients with chronic diseases. Also, this medical clinic had participated in Saskatchewan's Health Quality Council Chronic Disease Management Collaborative, a quality improvement initiative to improve care for

patients with established CAD or diabetes. Approximately 25% of family physicians in Saskatchewan were involved in this initiative (80). Notably, we identified very few patients with existing CAD or diabetes and at least one uncontrolled risk factor, suggesting these initiatives were successful in facilitating monitoring and follow-up of patients with these conditions. Despite the existence of these quality improvement systems, our intervention appeared to provide additional benefits to the overall control of CV risk among clinic patients.

Patient screening consumed approximately 70 minutes per eligible patient identified. This screening estimate takes into account that approximately 4 patients needed to be screened to identify one eligible patient. Included in the screening time estimate was also the time required to review upcoming appointment lists and confirm the patient had not been screened previously. Additionally, the time required to complete the CV risk profile form and formulate recommendations was also included in the time estimate for screening activities. One potential contributor to the time required for screening was the paper charting system employed by the clinic. Implementation of electronic health records would have undoubtedly streamlined the screening process. Also, it is possible that other staff members, such as clinical office assistants, could have carried out certain elements of the screening process. In this way, the charts of uncontrolled patients could be flagged for the pharmacist to review and provide recommendations to the physician. However, many clinics likely do not have the extra staff in place to do this, which is a gap that pharmacists could potentially fill in these settings.

5.2 Impact of the Study Design

The key advantage of our non-randomized, before - after study design was that all eligible patients could be included and managed under real-world conditions. The inclusive nature of this study design enhances the generalizability of our results to real-world practice settings, which was an important goal of CCARP II. Previously, our research group studied a similar pharmacist intervention with a RCT design (59). However, screening for patient recruitment was far slower due to the requirements for physician referral and patient consent. Additionally, this real-world design allowed us to avoid the potential for contamination, when physicians are treating patients in both the intervention and the control group in a single-site study (59).

The main disadvantage of the current study design was the lack of a concurrent control group. As a result, it is difficult to determine the extent to which ‘regression to the mean’ may have influenced the before-after changes in clinical outcomes observed. Regression to the mean refers to the fact that extreme values of a given variable tend to be closer to the population average on repeat measurement, even without intervention (81). As a result, the secondary analyses that examined before-after changes in clinical CV risk factors should be interpreted with caution. However, systematic screening of patients for uncontrolled CV risk factors uncovered many patients that may not have been detected without the support of this collaborative protocol.

5.3 Clinical Outcomes

The majority of the patients enrolled for ongoing pharmacist follow-up in this study were at high CV risk (70.8%), as calculated by the Framingham risk score (72); however a relatively low proportion had a history of CAD or stroke (12.4%). The low proportion of patients with established CAD and above-target risk factor(s) is likely due to the Clinic's participation in the Health Quality Council Chronic Disease Management Collaborative, which promotes regular screening and follow-up of CV risk factors in patients with established CAD. Additionally, the proportion of diabetic patients with above-target risk factors identified was also quite low (22.1%), which is again likely due to the regular monitoring and follow-up these patients receive as part of the Collaborative. Thus, the intervention appeared to be most useful for identifying primary prevention patients at high risk for CV events. From a population perspective, the majority of CV events occur in patients considered as primary prevention (41) so identifying high risk, primary prevention patients in addition to those receiving secondary preventative care would appear to be a good strategy to address CV morbidity in a primary care clinic. The most common above-target CV risk factor identified in this study was LDL-C (83.2%) followed by SBP in 62.8% of the patients enrolled.

5.3.1 Systolic Blood Pressure

There was a significant reduction in SBP in patients with above-target SBP at baseline (-12.7 mmHg, $p=0.017$) over the follow-up period. Additionally, almost half of the patients (45.1%) with above-target SBP at baseline had achieved their target by the end of the follow-up period. New antihypertensive medications were

started during the follow up period in 40.8% of these patients, with an additional 21.1% receiving an increased dose of an antihypertensive they were already taking. The majority of these patients (64.8%) had two or more follow-up blood pressure assessments over the study period.

The magnitude of SBP reduction observed here is similar to what has been reported in previous pharmacist intervention studies to reduce global CV risk (8,10,15,57). Bunting and colleagues conducted a before/after analysis of a multi-pharmacist, multi-site medication therapy management program for hypertension and diabetes, and found a mean reduction in SBP of 11mmHg (8). Clifford and colleagues conducted a randomized controlled trial of a pharmacist intervention to reduce vascular risk in patients with diabetes. They found a significant 14mmHg reduction in SBP in the pharmaceutical care group after the intervention, and a 7mmHg reduction in the control group (10). Simpson and colleagues found a statistically significant reduction in SBP of 7.4mmHg in the intervention group but a non-significant reduction of 2.5mmHg in the control group in a randomized controlled trial of pharmacists' interventions on diabetes patients in primary care (15). In the study by Rothman and colleagues, patients in the pharmacist intervention group had a 7mmHg reduction in SBP while patients in the control group had a 2mmHg increase in SBP ($p=0.008$ for the difference) (57). Thus, in studies that had a concurrent control group, the change in SBP in these patients ranged from -7mmHg to 2mmHg; this provides a crude estimate of the impact regression to the mean may have had on our observed SBP reductions.

In our study, there was no standardized assessment of BP because of practical constraints on time and resources. As a result, the BP that was recorded in the patients' charts was used. This may be susceptible to errors in how or when blood pressure was measured, which could potentially affect these results. However, this is a limitation faced by clinicians making decisions in real-world clinical practice as well.

5.3.2 Cholesterol Levels

We also observed statistically significant reductions in LDL-C (0.36 mmol/L) and the total cholesterol: HDL ratio (0.37) over the study period, with 29.2% and 20.4% of patients achieving their targets, respectively. These reductions were similar, although slightly less marked than what has been reported in other studies; Al Mazroui and colleagues had an LDL-C reduction of 0.44 mmol/L in the intervention group after 4 months of follow-up (6), Bunting and colleagues found a 0.41 mmol/L reduction in LDL-C after one year of follow-up (8), and Johnson and colleagues found a 0.44 mmol/L reduction in LDL-C after one year of follow-up (22). Several other pharmacist intervention studies (15,57,59) did not show a statistically significant impact on lipid levels. In comparative studies, changes in LDL-C among patients allocated to control groups have ranged from +0.03 mmol/L to -0.24 mmol/L (6,17,25).

Our ability to assess changes in cholesterol levels was limited by the short duration of follow-up. In keeping with the real-world nature of CCARP II, laboratory assessments were ordered at the discretion of the participating physicians as clinically indicated during the study period; we did not obtain true baseline and

follow-up cholesterol panels for all patients. If the patient had had a cholesterol panel done within the last year, this was used as their baseline; if not, a baseline cholesterol test was recommended. Many patients (n=36) did not have both baseline and follow-up cholesterol panels done over the study period, so a baseline-observation-carried-forward (BOCF) approach was used in these patients (79). Despite the conservative nature of our analysis, however, a beneficial effect of the intervention was still observed on cholesterol levels.

Another potential reason for the low proportion of patients achieving their cholesterol targets post-intervention was an apparent reluctance to start statin therapy. Of the 96 patients with above-target LDL-C at baseline, only 14 (14.6%) received new statin prescriptions over the study period, while another 17 patients received other cholesterol-lowering agents or had a dosage increase in cholesterol medications they were already taking (including statins). An additional 27 patients with above-target LDL-C at baseline (28.1%) were recommended to start statin therapy, and either refused (12 patients) or wanted additional time to implement lifestyle changes first (15 patients). A longer-term intervention would be required to determine if greater improvements could be achieved in this subgroup of at-risk patients.

5.3.3 HbA1c

Overall, a small number (n=8) of the diabetic patients enrolled had above-target HbA1c at baseline. Although the reduction in HbA1c from baseline in this subset of patients did not reach statistical significance, 50% of these patients achieved their HbA1c target at the end of the study period.

5.3.4 CRI

Although CV risk factors tend to cluster within individual patients, there are few measures in the literature that capture improvements in CV risk from a global perspective. The Framingham Risk Score has been used to measure global CV risk change in previous studies (82); however, it only been validated in primary-prevention populations, it is not sensitive to small changes, and it does not register changes in HbA1c, a clinical endpoint that was of interest in our study.

Our research group has developed a new global CV risk endpoint, the CRI (Cardiovascular Risk Improvement index). The CRI is a binomial outcome that indicates a minimum reduction (relative to target), or achievement of target, in any risk factor (SBP, LDL-C, or HbA1c) that was uncontrolled at baseline. Thus, the CRI-20 refers to a minimum of 20% reduction relative to target, and the CRI-50 refers to a minimum of 50% reduction relative to target. We found that the majority of patients achieved both the CRI-20 (69.0%) and the CRI-50 (65.5%), indicating good progress towards achievement of CV risk reduction targets in an intention to treat analysis. Furthermore, when the analysis was restricted to those patients who completed at least one follow-up measurement of the target risk factor, 88.1% of patients achieved both the CRI-20 and the CRI-50. Again, a longer-term intervention would be required to determine if these initial improvements could be sustained.

5.4 Medication Adherence/Persistence

Primary non-adherence, where individuals fail to obtain the first prescription, has been reported in other clinical settings (83,84). However, all 54 patients who received new medications or had dosage increases over the study period had the medication filled for the first time within 4 weeks of the prescription being written. We also found a high rate of medication persistence in patients prescribed new medications requiring more than one fill before the end of the study period; 36/41 patients (87.8%) had refilled the medication within a 45-day window prior to the study end date. The short duration of follow-up for our study limited our ability to assess long-term adherence with new therapies; however, our results demonstrate a promising rate of early persistence and primary adherence with new medications started over the study period in a subgroup of patients considered at the highest risk (new-users) (69).

The Pharmaceutical Information Program (PIP) was used to assess medication adherence and persistence in this study. The main limitation to using administrative databases such as PIP to assess adherence is that these databases provide information on refill adherence, rather than actual medication consumption by the patient (85,86). However, studies have found a high rate of concordance between prescription claims data and pill counts (85), and suggest that administrative databases are a convenient, objective, and inexpensive way to assess medication adherence in health services research (86). Additionally, patient-reported adherence measures may overestimate adherence rates if they are the sole method used (87).

5.5 Pharmacist Prescribing

The legislation permitting collaborative prescribing by pharmacists in Saskatchewan did not come into effect until March 4, 2011, by which time the majority of patients had already been enrolled in our study. Thus, our ability to assess the utility of collaborative prescribing by the pharmacist was limited because our intervention was scheduled to be completed by June 2011. Despite the short time available to evaluate this tool, the preliminary data from our study suggest this strategy was well accepted by collaborating physicians. Of the 23 patients referred after pharmacist prescribing was an option, 10 (43.5%) were referred for this service. The only other study to examine this issue was conducted by Anaya and colleagues; they found that 110/579 patients (19.0%) were referred for collaborative prescribing by the pharmacist in an outpatient diabetes management clinic (7). However, only one prescription was written by the pharmacist over the study period, due in part to the short duration of follow-up for these patients.

The perceived acceptability of this option among physicians may be partially explainable by the steps we undertook prior to the beginning of the study. First, we consulted with each participating physician to provide input on the proposition for a collaborative prescribing agreement. Second, we developed prescribing algorithms on the basis of Canadian guidelines and obtained input from collaborating physicians so they were precisely aware how the management would be undertaken by the pharmacist (Appendices 4-10). Finally, we ensured that the decision to delegate prescribing for each patient was made by physicians on a case-by-case basis, so they could maintain control of the overall management of each patient's

care. We believe these steps helped to develop a true collaborative partnership. However, it should be noted that our study involved a select group of physicians who opted to participate in a collaborative initiative with a pharmacist; thus, these results may not be generalizable to all physicians. Further study on this issue is warranted.

5.6 Human Resources

A single pharmacist, working with four salaried family physicians, undertook the CCARP II intervention. Collectively, the four physicians involved with the project provided approximately 2.5 full-time equivalents of direct patient care. Routine physician appointments are booked for 15 minutes at this clinic.

Patient screening activities took approximately 2.5 hours of the pharmacist's time on a daily basis. As discussed previously, it may be possible to improve the efficiency of the screening procedures using electronic health records. Patient follow-up activities took approximately 65 minutes of the pharmacist's time on a daily basis, with just over 48 minutes daily devoted to telephone follow-ups with patients and just over 16 minutes daily spent reviewing charts for updated information.

Routine patient follow-ups were generally conducted by phone. In-person assessments by the pharmacist were reserved for patients requiring blood pressure checks or review of blood glucose logs for collaborative prescribing purposes, or those patients with more in-depth education needs (patients with known or suspected poor adherence, language barriers, or those requesting more information). The use of phone follow-ups for most routine issues helped enhance the efficiency of the

intervention; average time spent on phone follow-ups was 16.4 minutes, as compared to an average of 25 minutes when patients were seen in-person. If pharmacist prescribing had been an option earlier in the study, that may have increased the amount of time the pharmacist spent on in-person follow-up assessments. However, it is not clear if additional benefits to CV risk factors would have been achieved.

Time spent on patient follow-up assessments in other similar pharmacist interventions, when reported, has ranged from 15-60 minutes (6,8,10,12,14,16,23), with 30-minute follow-up appointments being the most common (8,12,14,16). Some studies had pre-specified intervals for patient follow-ups (10,24,25,59), while others had flexible follow-up schedules, tailored to the patient's needs at the discretion of the pharmacist (6-8,15). In our intervention, follow up visits were not protocol-driven. The pharmacist aimed to target patients at greatest need for ongoing support and triage their time appropriately. Although this approach is considered more difficult to quantify, we believe it is the most practical approach to a professional intervention that will be conducted in real-world settings (71).

5.7 CCARP II Intervention

Overall, the duration of the CCARP II initiative was quite short (8.5 months) with no lead-in time for the pharmacist before the start of the study. Previous reports suggest that it may take approximately four months before pharmacists become comfortable with their role on a healthcare team and develop the necessary collaborative relationships (88,89). Despite the fact that no lead-in time was possible due to time constraints for CCARP II, we still found a benefit to the

collaborative intervention. Additionally, the physicians involved in the project did not have experience working with clinical pharmacists in this setting. Again, we believe our clearly defined roles and responsibilities that were mutually agreed upon with collaborating physicians from the beginning facilitated a relatively smooth transition to collaborative care.

CCARP II involved a combination of protocol-driven activities and activities that were tailored to the patients' clinical situations at the discretion of the pharmacist. The patient screening activities and documentation/recommendation procedures were consistently protocol-driven (provided in the same way to every patient), thus enhancing the internal validity and the reproducibility of our study (71). However, to ensure our study would also be applicable and feasible in a real-world clinical practice (71), patient follow-up activities were tailored to each patient's clinical situation, rather than using a standardized follow-up protocol for all patients (10,24,25). The use of protocol-driven clinical activities in a research study to ensure internal validity versus the need for clinical judgment to ensure external validity is a common dilemma in clinical research (71).

Pharmacist follow-up activities included patient counseling on cardiovascular risk and/or medications, promoting adherence to drug therapy or lifestyle changes, monitoring for target achievement, and making recommendations to physicians to facilitate target achievement. Thus, clinical judgment by the pharmacist was required to determine how best to follow-up with each patient. This flexibility in follow-up activities allowed for more efficient patient follow-ups (average of 16 minutes) compared with some studies using more structured

appointment-based follow-ups (8,12,14,16,17). However, this does slightly limit the reproducibility of the follow-up portion of this intervention.

5.8 Remaining Questions

There are a few remaining limitations of our initiative that warrant further discussion. First of all, the pharmacist was not able to follow-up with patients with uncontrolled risk factors who did not present for their scheduled physician appointment. This was due to ethical constraints of the study; because these patients were not able to be informed of the pharmacist's role in their care at their doctor appointment, the pharmacist was not able to contact these patients to follow-up. This is unfortunate, because this is a pool of patients that could potentially benefit from more persistent follow-up to ensure their cardiovascular risk factors are addressed (especially if these patients frequently miss medical appointments). Although the mean age of the patients not arriving for their appointment (62 years) was similar to those enrolled, as was the proportion with hypertension (75%), a higher proportion of these patients had diabetes (40%) compared to the patients that were enrolled (22.1%). Additionally, 83% of the patients with diabetes who did not arrive for their physician appointment had above-target HbA1c levels, compared with 32% of the diabetic patients that were enrolled for pharmacist follow-up, suggesting that these patients were not adherent with their regular physician follow-ups for diabetes every three months, as was the standard at the Clinic since participating in the Health Quality Council Chronic Disease Management Collaborative.

CCARP II was a single-centre pilot study conducted by a single pharmacist working with four family physicians who volunteered to participate in the project; this may limit the generalizability of our findings. Additionally, this initiative was conducted in a family medicine clinic with salaried family physicians; this may limit the generalizability of our findings to settings where physicians are paid on a fee-for-service basis. These issues warrant further study, preferably in a multi-center, randomized clinical trial involving several pharmacists. In addition, the primary investigator had to serve all major roles to carry out this study. She served as the clinical pharmacist, collected all data, and analyzed / synthesized all results. Ideally, these roles would have been performed by different, blinded individuals to minimize the risk of bias.

Due to time constraints with our study, we were not able to formally evaluate physician and patient satisfaction with this initiative. Such an evaluation would help give a more complete picture of the benefits and areas for improvement with the intervention, and will be conducted in the future as part of a separate study. However, similar studies suggest that physician and patient satisfaction are generally very high with these types of interventions (13,22,57,90,91). Anecdotally, physicians and patients in the clinic appeared very supportive and accepting of this new collaborative program.

CHAPTER 6

6. Conclusions and Perspectives

Despite improvements in CV risk factor identification and management over the last two decades (27,35), CCARP II showed that there are still opportunities for pharmacists to contribute to the care of patients with CVD or its risk factors. We found that approximately one third of adults presenting for a family physician appointment were at moderate or high risk of cardiovascular events and had at least one risk factor above guideline-recommended targets. Thus, it would appear that a systematic screening procedure is necessary to ensure CV risk management is consistently applied to all clinic patients. We also found significant reductions in SBP, LDL-C, and TC: HDL ratio in patients monitored and followed-up by the pharmacist on an ongoing basis. A high rate of persistence to new medications (87.7%) was observed in patients receiving pharmacist follow-up.

Two key aspects of the CCARP II intervention were the systematic approach to patient screening and identification, and the real-world, family medicine setting in which it was implemented. Further study is warranted to determine if the benefits observed in our pilot study can be reproduced with a multi-center, randomized controlled trial involving multiple pharmacists.

CHAPTER 7

7. References

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CHAPTER 8

8. Appendices

Appendix 1: Framingham Calculator for Estimating Cardiovascular Risk (71)

Estimation of 10-year risk of total cardiovascular disease in men (Framingham Heart Study)

POINTS	Age	HDL-C	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic
-2		>1.6		<120			
-1		1.3-1.6					
0	30-34	1.2-1.3	<4.1	120-129	<120	NO	NO
1		0.9-1.2	4.1-5.2	130-139			
2	35-39	<0.9	5.2-6.2	140-159	120-129		
3			6.2-7.2	160+	130-139		YES
4			>7.2		140-159	YES	
5	40-44				160+		
6							
7	45-49						
8	50-54						
9							
10	55-59						
11	60-64						
12							
13	65-69						
14	70-74						
15	75+						TOTAL POINTS
Points Allotted							

Adapted from reference 33. HDL-C High-density lipoprotein cholesterol; SBP Systolic blood pressure

SUPPLEMENTARY TABLE 4B Cardiovascular disease risk for men

Points	Risk, %	Points	Risk, %	Points	Risk, %
-3 or less	<1	5	3.9	13	15.6
-2	1.1	6	4.7	14	18.4
-1	1.4	7	5.8	15	21.6
0	1.6	8	6.7	16	25.3
1	1.9	9	7.9	17	29.4
2	2.3	10	9.4	18+	>30
3	2.8	11	11.2		
4	3.3	12	13.3		

SUPPLEMENTARY TABLE 5A
Estimation of 10-year risk of total cardiovascular disease in women (Framingham Heart Study)

POINTS	Age	HDL-C mmol/L	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic	
-3				<120				
-2		>1.6						
-1		1.3-1.6			<120			
0	30-34	1.2-1.3	<4.1	120-129		NO	NO	
1		0.9-1.2	4.1-5.2	130-139				
2	35-39	<0.9		140-149	120-129			
3			5.2-6.2		130-139	YES		
4	40-44		6.2-7.2	150-159			YES	
5	45-49		>7.2	>160	140-149			
6					150-159			
7	50-54				160+			
8	55-59							
9	60-64							
10	65-69							
11	70-74							
12	75+							TOTAL POINTS
Points Allotted								

Adapted from reference 33. HDL-C High-density lipoprotein cholesterol; SBP Systolic blood pressure

SUPPLEMENTARY INFORMATION – CONTINUED

SUPPLEMENTARY TABLE 5B
Cardiovascular disease risk for women

Points	Risk, %	Points	Risk, %	Points	Risk, %
-2 or less	<1	6	3.3	14	11.7
-1	1.0	7	3.9	15	13.7
0	1.2	8	4.5	16	15.9
1	1.5	9	5.3	17	18.51
2	1.7	10	6.3	18	21.5
3	2.0	11	7.3	19	24.8
4	2.4	12	8.6	20	27.5
5	2.8	13	10.0	21+	>30

Appendix 2: Cardiovascular Risk Profile Form

Cardiovascular Risk Profile

Completed by Erin Yakiwchuk: _____ For Dr. _____

Gender: M F **DOB:** _____

Smoking Status: Non-smoker Ex-smoker Current smoker (_____)

Estimated 10-Year Cardiovascular Risk: Moderate (10-20%) High ($\geq 20\%$)

Obtained from: Framingham CHD Risk Equivalent: _____

Diabetes: Yes No **Chronic Kidney Disease:** Yes No **Antiplatelet:**

Current Blood Pressure (): _____ Target Blood Pressure: _____

Hypertension Meds:

Cholesterol Levels ()

TC: _____
TG: _____
HDL: _____
LDL: _____
TC: HDL: _____

Target LDL: _____

Target TC: HDL (Ratio): _____

Cholesterol Meds:

If Diabetic: HbA1c (): _____ **Target A1c < 7%**
(A1c may be modified if high risk for hypoglycemia)

Diabetes Meds:

Pharmacist Recommendations:

Pharmacist to follow-up with patient? – PHYSICIAN TO SPECIFY:

<input type="checkbox"/> To provide medication and disease-state counseling, assess and promote adherence, and monitor for target achievement. All recommendations for drug therapy changes to be forwarded to physician.
<input type="checkbox"/> As above AND independently titrate medication(s) to achieve specified CV risk factor target(s) <i>per algorithm.</i>
<input type="checkbox"/> No patient follow-up required

Appendix 3 : Letter to Patients

Dear Patients,

I would like to inform you about a new member of the team at the Community Clinic, Erin Yakiwchuk. Erin is a licensed pharmacist who will be helping me look after your medications and risk factors for heart disease.

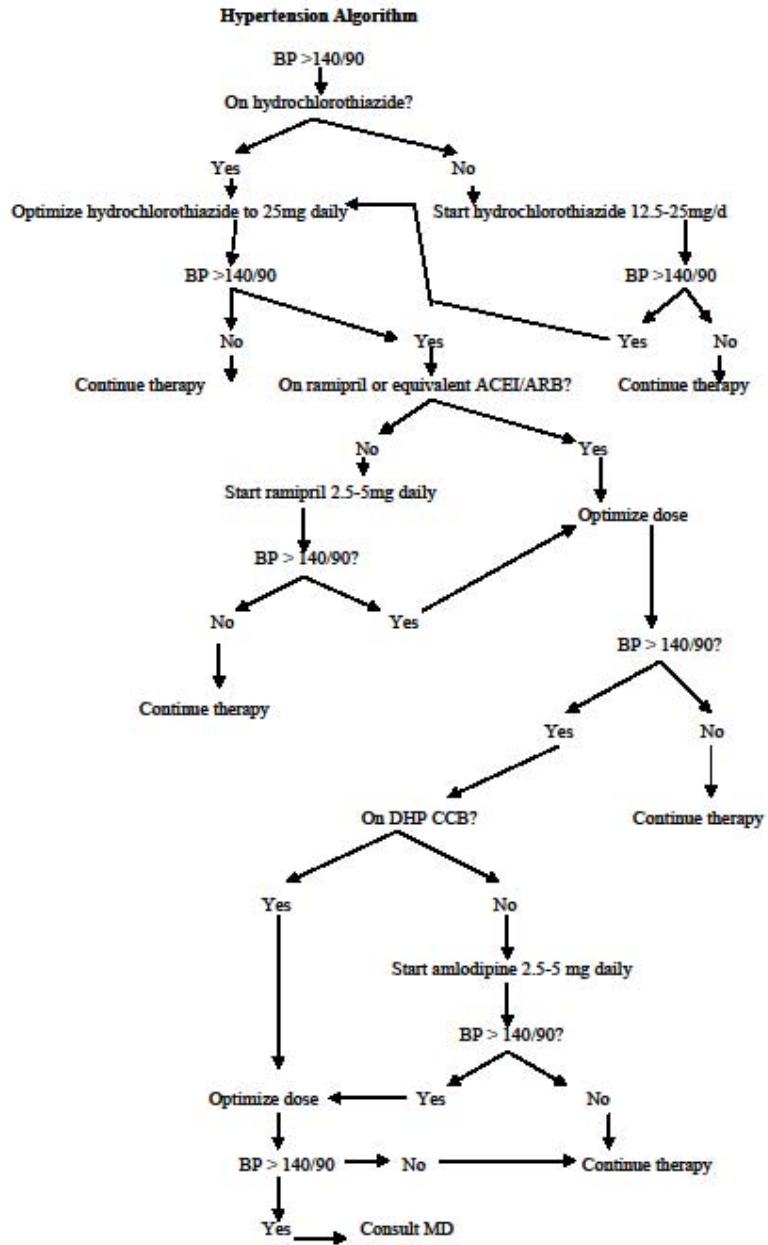
Part of her job will be to keep track of your blood pressure, cholesterol, and blood sugar on a regular basis by checking the results of your tests and updating me if your medications need to be reviewed.

If you have any questions or concerns about Erin's role at the clinic, you can talk to me during today's appointment or you can speak to Erin directly by calling the Community Clinic Pharmacy at 664-4277.

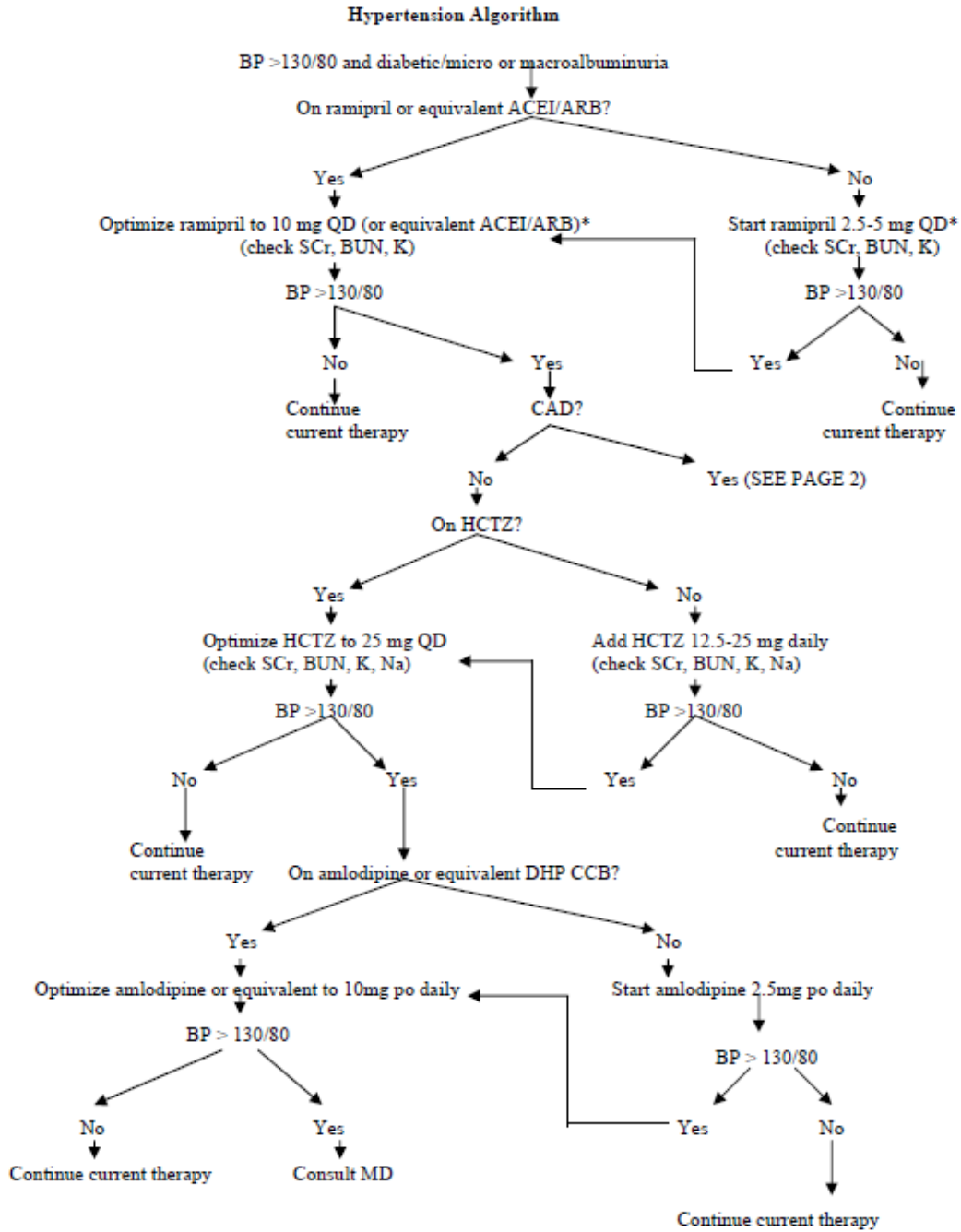
Sincerely,

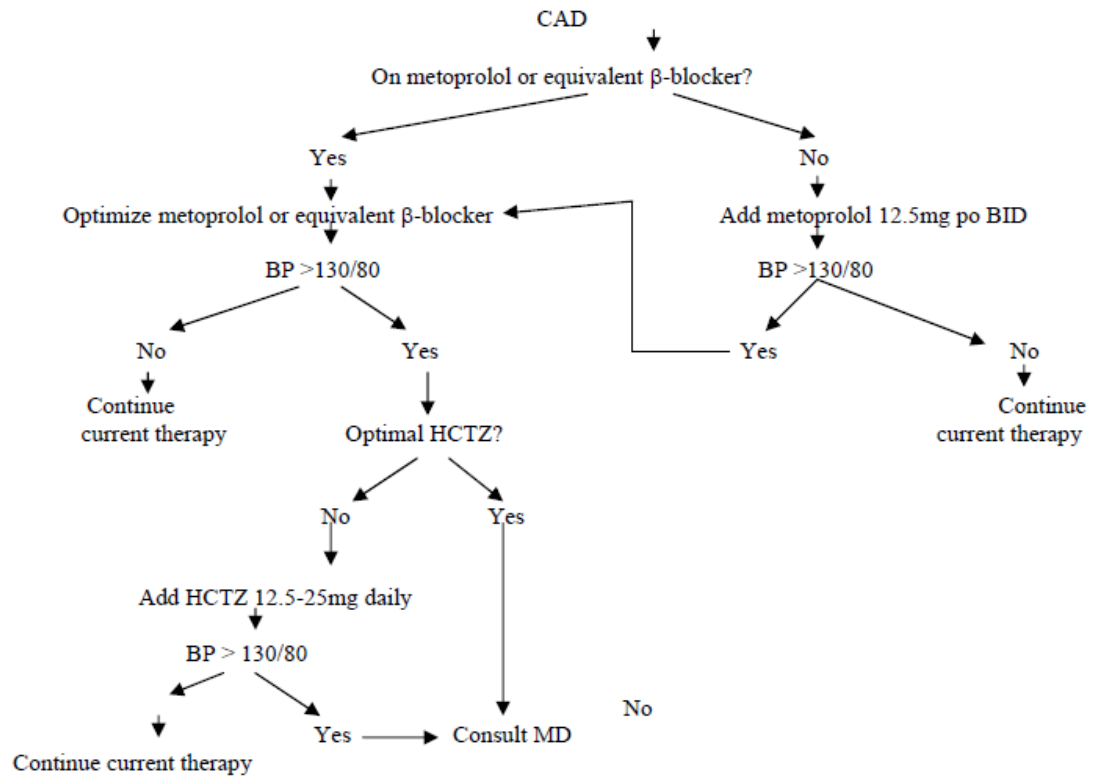
Dr. _____

Appendix 4: Algorithm for Uncomplicated Hypertension

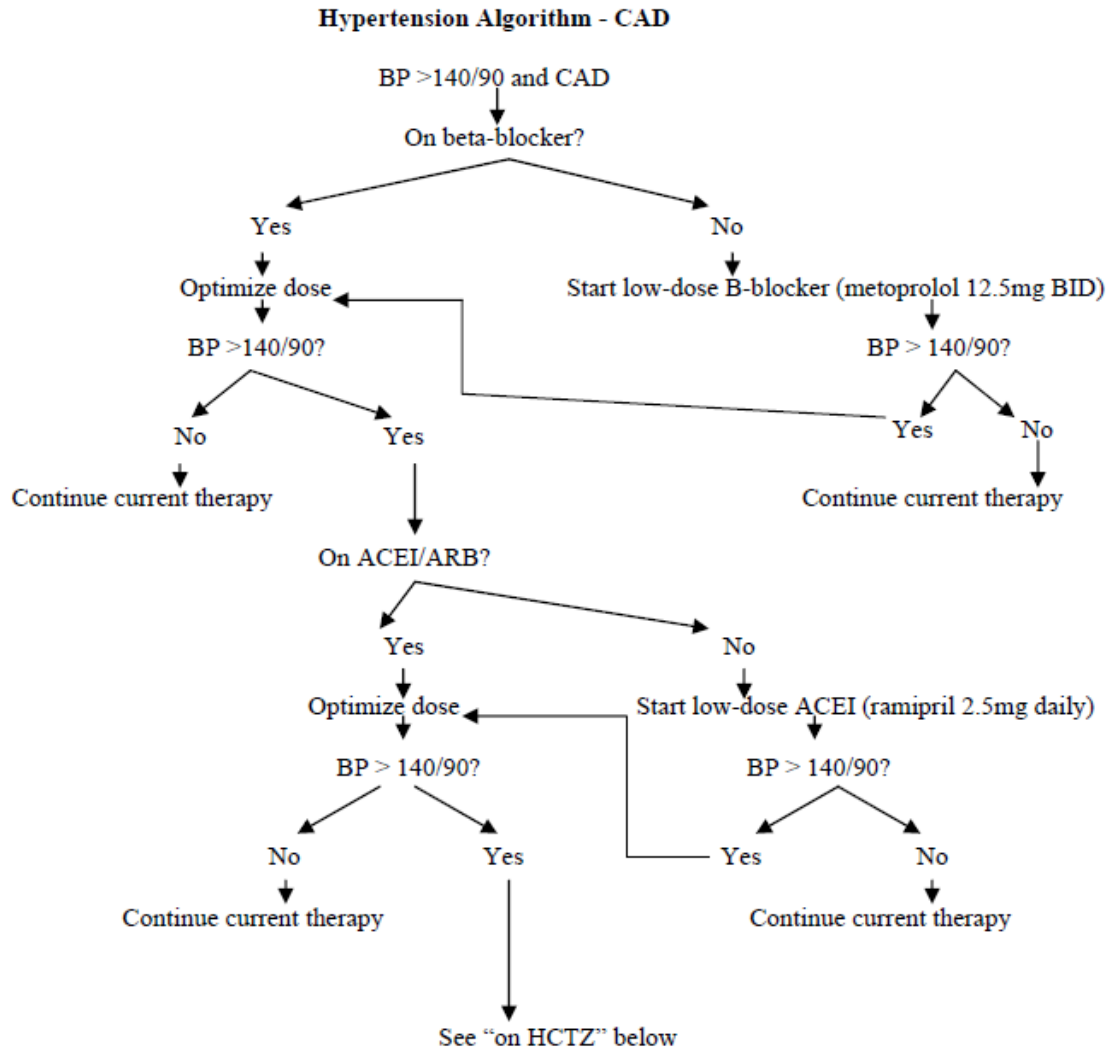


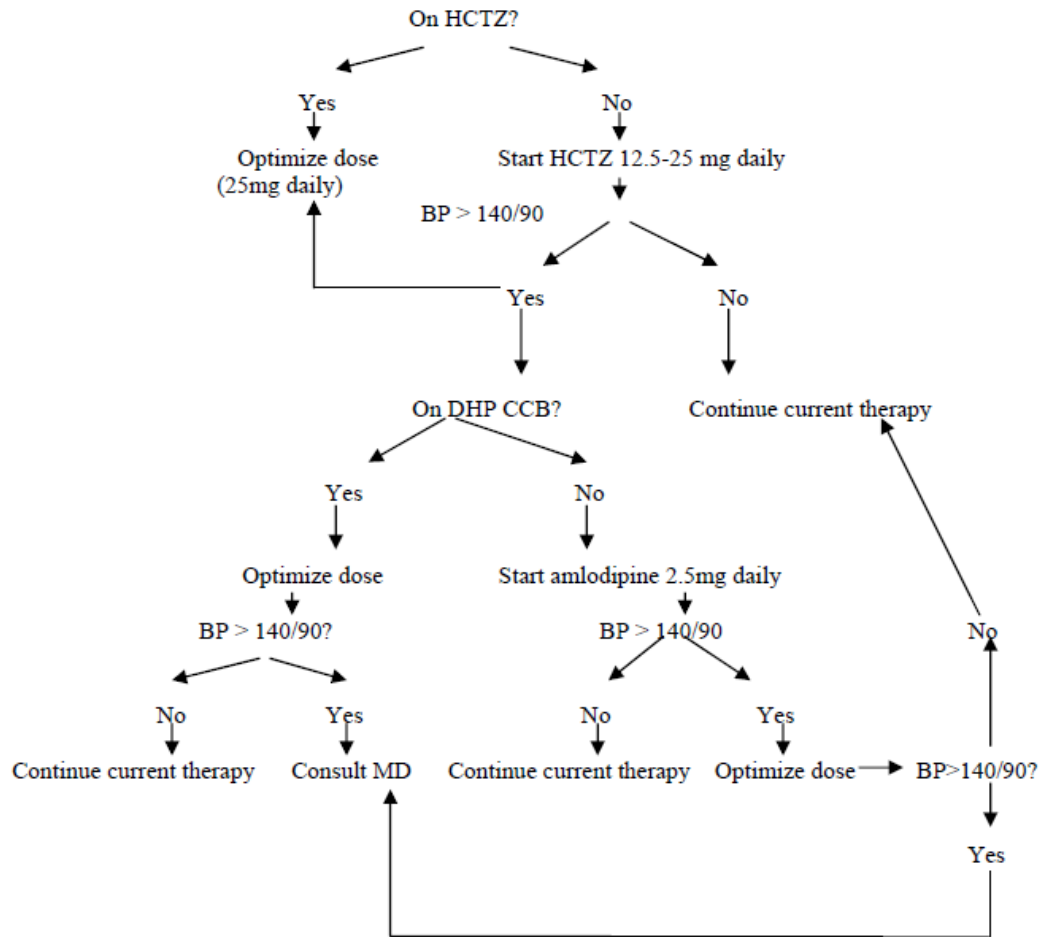
Appendix 5: Algorithm for Patients with Hypertension and Diabetes



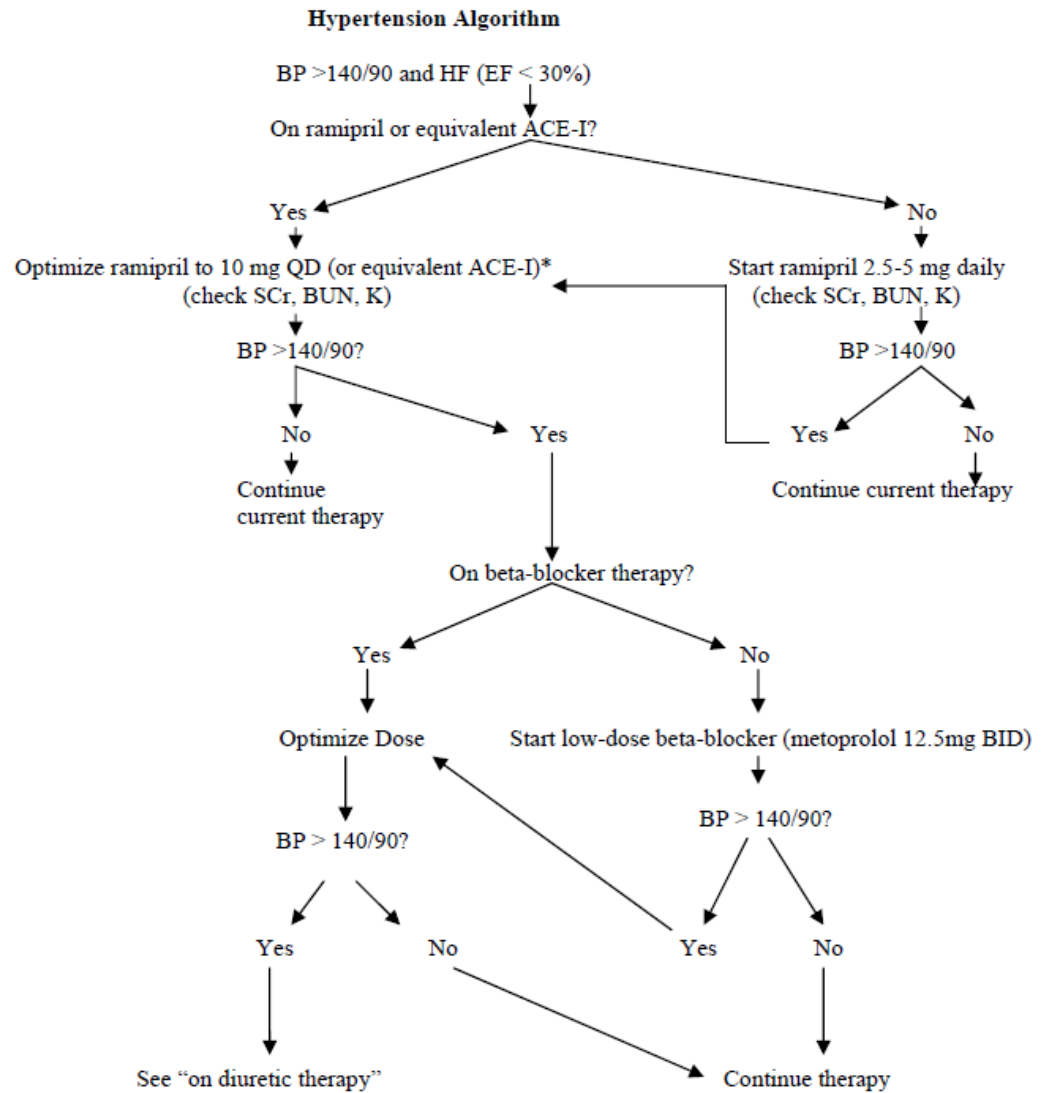


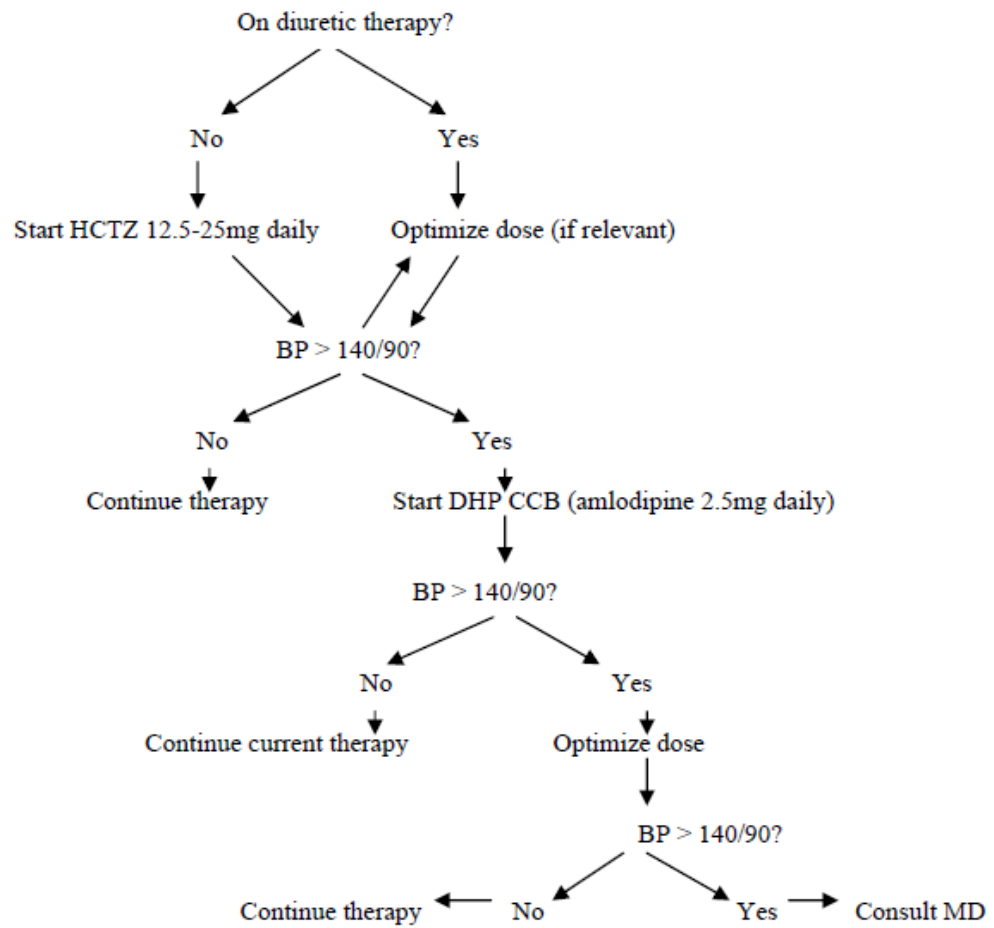
Appendix 6: Algorithm for Hypertension and Coronary Artery Disease





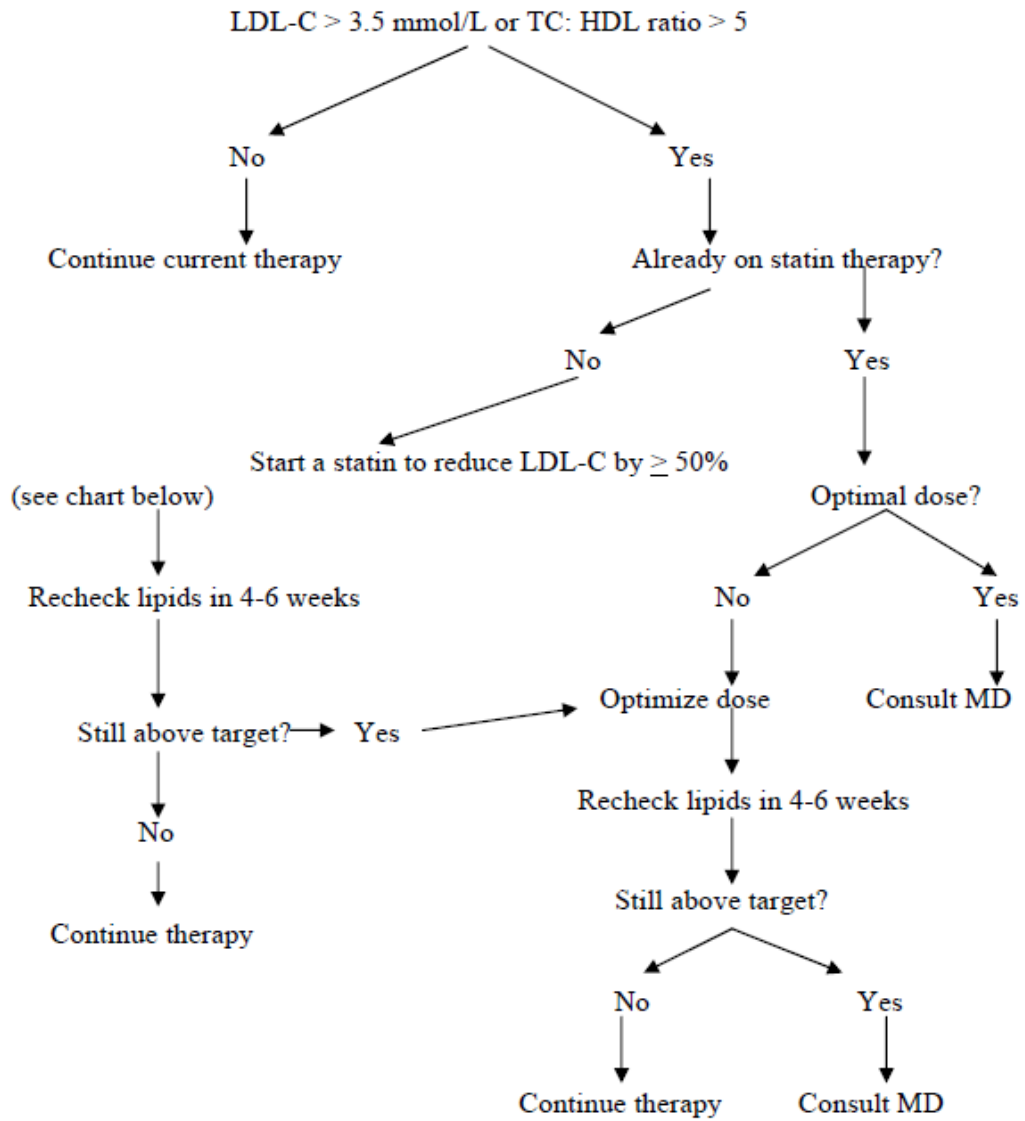
Appendix 7: Algorithm for Hypertension in Heart Failure





Appendix 8: Cholesterol Algorithm for Moderate Cardiovascular Risk

Dyslipidemia Algorithm – Patients at Moderate CV risk

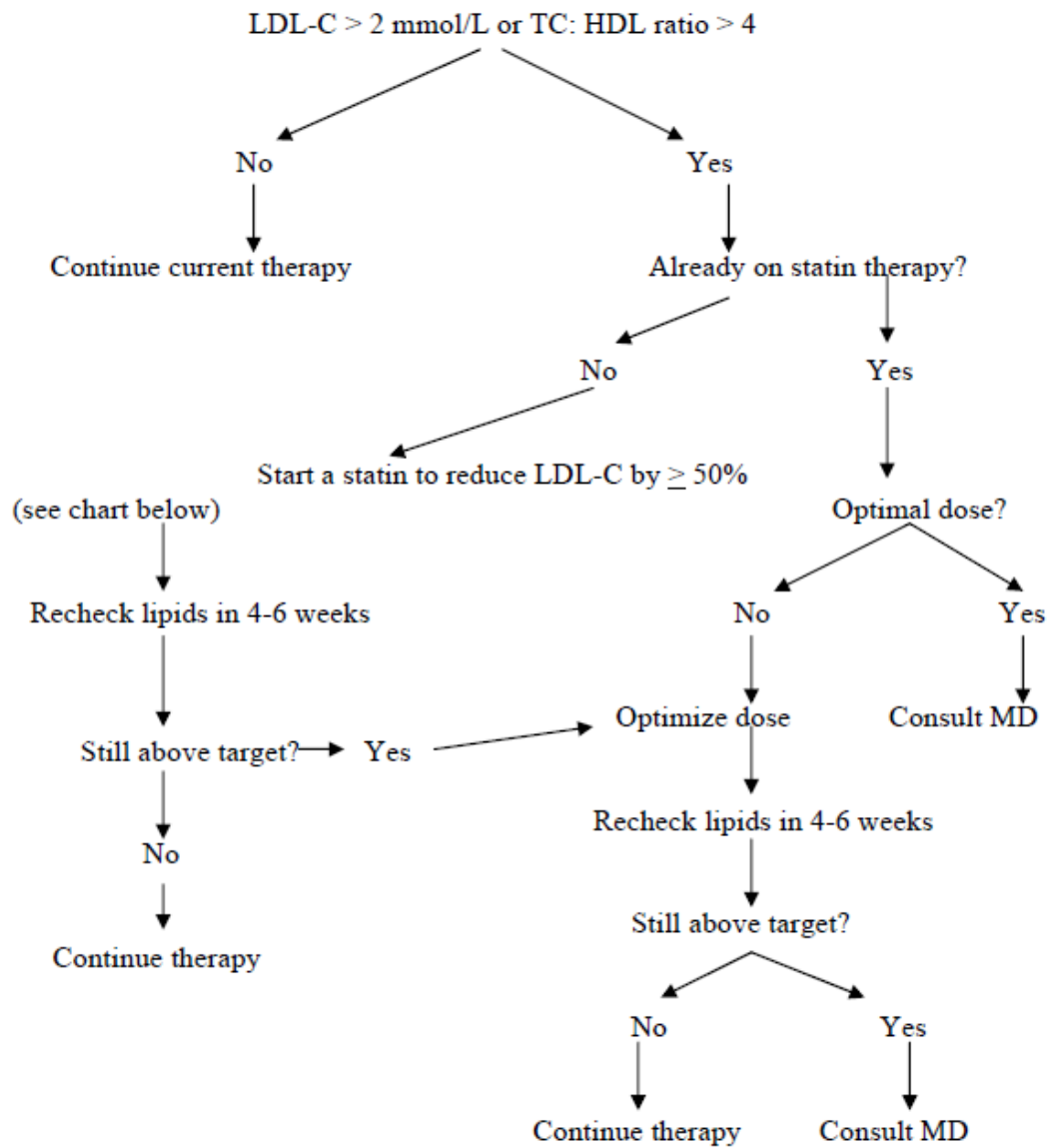


Statins to Decrease LDL-C by $\geq 50\%$ (92)

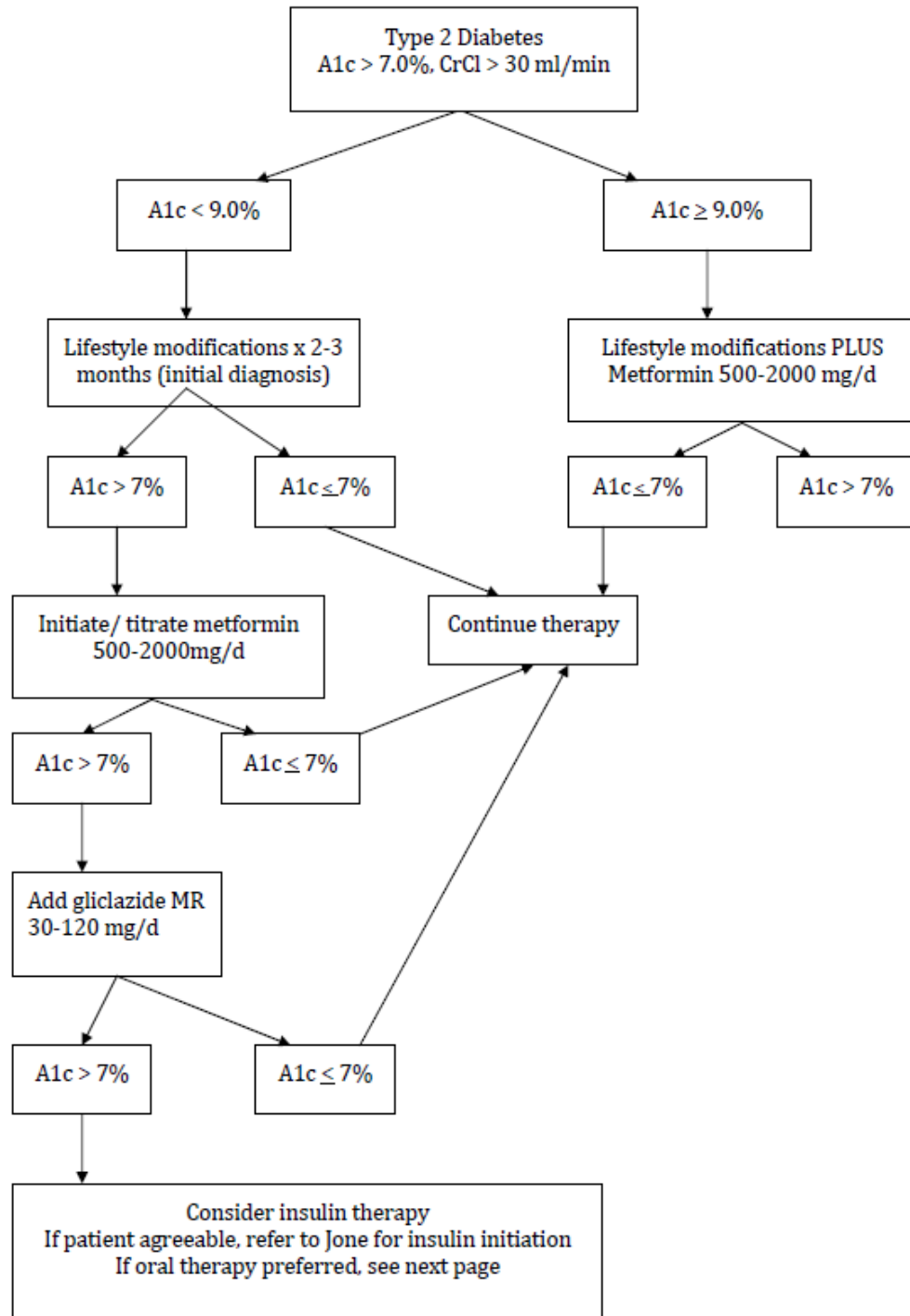
Simvastatin 80 mg (least expensive)
Atorvastatin 40 mg
Rosuvastatin 10 mg

Appendix 9: Cholesterol Algorithm for High Cardiovascular Risk

Dyslipidemia Algorithm – Patients at High CV risk



Appendix 10: Diabetes Algorithms



Jone = Jone Barry, Nurse Practitioner at the Community Clinic who initiates new patients on insulin

