Pharmacist-Led Follow-Up Program for Rural Acute Coronary Syndrome Patients: The PLURAL-ACS Study

By

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A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

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University of Alberta

Abstract

Background: Rural patients have been shown to have reduced access to care, delayed discharge prescription fills, and frequent readmissions following acute coronary syndrome (ACS) compared to urban patients. While virtual and pharmacist-led programs have shown benefit in providing efficient care to cardiac patients, to our knowledge, their implementation in rural ACS-population have not been assessed. The purpose of this two-phase study was to implement a first-ever pharmacist-led virtual follow-up program for rural Canadian ACS patients and to determine the impact of the program as compared to a matched control group.

Methods: Consecutive rural ACS-patients discharged from the Mazankowski Alberta Heart Institute between March-May 2022 were included in the pharmacist-led follow-up pilot program. Structured telephone interviews were used to identify and resolve cardiac medication-related issues for each patient on day 1, 10, and 30 post discharge. Descriptive outcomes of the program were collected, which included the total number and type of cardiac medication-related issues identified and resolved by the program and change in cardiac medication knowledge using questionnaires adapted from prior studies. Program-patients were then compared to a control group, which included ACS patients with usual care (discharged November 2021-July 2022), matched for sex, zone of residence, and age within 10 years. Outcomes were collected from administrative databases and multivariable regression analyses were conducted for comparisons. In the retrospective analysis, the primary outcome was time to prescription fill of discharge ACS-medications within 30 days of discharge. Secondary outcomes included 30-day cardiac-related hospital readmissions, cardiac-related emergency department visits, and primary care practitioner (PCP)-visits.

Results: 40 patients entered the 15-week pilot-program and a total of 139 virtual visits were completed. Median time spent per visit was 60 (interquartile range [IQR], 50-80) minutes. A total of 255 cardiac medication-related issues (mean 6 per patient; IQR, 3.75-8.25) were identified, and 91% were resolved by the pharmacist. Discharge prescription errors, real adverse events, and therapy optimization were most common on day 1, 10, and 30 respectively. Cardiac medication knowledge was significantly increased in patients post program compared to their knowledge prior to program implementation (median score difference of 2.5 of 7; IQR, 2-4). When comparing the pilot program participants to matched control group (n=80), there was no significant differences in time to prescription fill (0.25 [IQR, 0.0-0.25] days vs 0 [IQR, 0.0-1.0] days; adjusted hazard ratio [aHR], 1.17; 95% confidence interval [CI], 0.80-1.74), cardiac-related hospital readmissions (8% vs 5%; aHR, 1.69; 95% CI, 0.36-7.96), or cardiac-related emergency department visits (10% vs 8%; HR 1.33; 95% CI, 0.38-4.73). PCP-visit was higher in the program patients (90% vs 73%; aHR, 2.99; 95% CI, 1.47-6.10).

Conclusion: Our study highlights that a high number of cardiac medication-related issues are encountered by ACS patients early post hospital discharge. A pharmacist-run post ACS follow-up program identified and resolved majority of medication issues, as well as enhancing patient safety and overall follow-up of care as outpatient. Longer duration studies, with adequate power, are required to confirm these findings and assess the impact of such a program on clinical outcomes.

Preface

This thesis is an original work by Hazal Babadagli. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "The PLURAL-ACS Outcomes Study" (Pro00120706) on August 28, 2022.

Phase one of this thesis has been accepted as a manuscript in a peer reviewed journal for publication and was presented at the 2022 Alberta Health Services Pharmacy Research Day. Phase two of the study was presented at the 2023 University of Alberta Cardiovascular Research Institute Research Day and accepted as a poster presentation at the Vascular 2023 Conference.

I was responsible for the pilot program design and implementation, phase one and phase two study design and analyses, and manuscript preparation. I also performed data abstraction in phase one of the study. Drs. Glen Pearson (co-supervisor), Sheri Koshman (co-supervisor), and Michelle Graham (committee member) conceived the research question, supervised pilot program design and implementation, along with supervising the study design and analyses, and manuscript preparation. Dr. Oleksandr Shlakter (Alberta Health Services data analyst) performed data abstraction in phase two of the study, along with assisting in statistical analyses in phase two of the study. Marnie Wang (Master of Public Health student) provided statistical analysis support for phase two of the study.

Dedication

This thesis is dedicated to my grandfather, Muammer Şatiroğlu, who was always my number one advocate in my academic career.

I would also like to dedicate this thesis to Luigi, for her unwavering loyalty and companionship in the many hours we spent together in completing my academic projects.

Acknowledgements

I would like to thank my supervisors and mentors, Drs. Glen Pearson, Sheri Koshman, and Michelle Graham, for their guidance and support. I am grateful for the initiative they took in creating this research opportunity and I have learned a tremendous amount under their supervision. I would also like to thank my colleague, Marnie Wang, for her selfless nature in supporting and contributing to our project.

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CHAPTER 1

INTRODUCTION

1. Introduction

1.1 Risk of Recurrence Post-Acute Coronary Syndrome (ACS)

ACS is the third most common reason for hospitalization in Canada.[1–3] Survivors of ACS face a substantial risk of further complications, including death, recurrent ACS, heart failure, arrhythmias, and stroke.[4–6] The first 30 days after an ACS are a particularly vulnerable period with the highest risk for recurrent ACS events.[5,7] Patients living in rural locations have been shown to have higher rates of repeat ACS compared to urban centers.[8] This has also been demonstrated in North and Central zone Alberta, where Alberta Health Services Cardiovascular Strategic Clinical Network (AHS CV SCN) data indicate that northern rural locations have up to double the 30-day ACS readmission rates compared to urban sites.[9]

One significant contributor to this disparity may be the reduced access to medical care in rural locations, which has been demonstrated in several studies. A study from rural Saskatchewan found that 15.4% of households experienced difficulties in getting routine or on-going medical care in the preceding 12 months, which was an independent predictor of combined cardiovascular disease.[10] Another study in Ontario demonstrated similar findings, as it found that rural patients had fewer total ambulatory physician visits and cardiology visits over one year, while emergency department utilization was higher.[11] Rural patients also had lower rates of follow-up cholesterol assessment, HbA_{1c} assessment, and statin use, compared to urban patients. These findings are comparable in Alberta; the AHS CV SCN found that 30-day cardiologist and 30-day family physician visit rates was almost double in urban locations compared to rural locations. [9]

1.2 Poor Prescription Fill Rates Post-ACS

Research has previously demonstrated that delayed outpatient follow-up after ACS results in reduced prescription fill rates and poorer medication adherence.[12,13] One study found that patients who had their first follow-up visit more than 6 weeks after being discharged had lower secondary prevention medication adherence rates.[12] Additionally, a population-based cohort study in Ontario found that one-fifth of patients did not fill at least 1 of their prescribed cardiac medications within a month of hospital discharge after having an ACS, with almost half of the patients not filling their antiplatelet therapy afterward.[14] Locally, AHS CV SCN data also demonstrated concerning results in Alberta, where the mean post-ACS discharge prescription-fill time was almost five days. Of concern, the time to prescription-fill was as high as 23 days in the North Zone.[9] These findings are significant, as the inability to obtain prescriptions following hospital discharge has been associated with an increased risk of adverse events, medication errors, and reutilization of the healthcare system.[15–17] In fact, a Quebec study showed that following a coronary stent implantation, a delay in clopidogrel prescription filling by at least one day was associated with a 34% relative increase in the risk of all-cause mortality.[17]

1.3 Lack of Post-ACS Programs for Rural Patients

There are a paucity of studies examining the impact of cardiac programs outside of urban settings. These studies have implemented general cardiac health awareness and diabetes management programs in primary prevention rural populations.[18–20] Other than a few cardiac rehabilitation programs, there have been no previous studies assessing post-ACS care programs for rural patients in Canada.[21,22] However, several secondary prevention programs have been implemented in urban post-ACS populations. Meta-analyses of such programs indicate an overall

reduction in ACS recurrence and rehospitalization by 12 months, as well as a reduction in all-cause mortality by 24 months.[23,24] These effects may also be sustained over time. Murphy et al. found a reduction in both all-cause mortality (relative risk [RR], 0.79; 95% confidence interval [CI], 0.66 - 0.93), and cardiac related mortality (RR, 0.74; 95% CI, 0.58 - 0.94) at about five years post-ACS care-program inititiation.[25]McAlister et al. also found that post-ACS programs lead to improvements in risk factor profiles, prescribing patterns, and patient-quality of life.[23]Numerous studies have also suggested that the benefit of secondary prevention programs were likely to be higher in settings where usual care is less accessible, such as rural locations.[23,26,27]

1.4 Virtual Post-ACS Care

While urban in-person post-ACS programs have shown significant clinical benefit, they are often limited by cost and lack of long-term sustainability. Following program effectiveness, sustaining and translating the program has been shown to be a challenge.[28] Considerable resources are spent on initiatives that are often discontinued soon after their initial funding ends.[28–30] Furthermore, given the limited number of health care workers and high staff-turnover in remote locations, implementing in-person secondary prevention programs in rural settings often has limited feasibility. Virtual care programs provide a potential promising solution to these challenges. Virtual care delivery (telephone, Zoom, mobile text messaging, web-based programs, or smart phone applications) allows for easier access for patients living outside of urban centers and have been shown to be successful in improving care-delivery for patients residing in remote locations.[31,32] Several meta-analyses for post-ACS virtual programs in urban locations have demonstrated improvements in medication adherence, life-style modifications, and risk factor

management, including smoking cessation and blood pressure reduction. [33–36] A meta-analysis by Jin et al. found that telehealth interventions, as adjunct care, resulted in a significantly lower risk of rehospitalization or cardiac events compared with non-intervention groups (RR, 0.56; 95% CI, 0.39-0.81).[35] A meta-analysis by Kotb and colleagues also found that telephone interventions for coronary artery disease patients were associated with significantly fewer hospitalizations than the control (odds ratio [OR], 0.62; 95% CI, 0.40-0.97).[37] An important feature of virtual interventions is also their efficiency for both the clinician and the patient, as they generally require less time and travelling. Several studies have also demonstrated consistent cost-savings.[33–36] In fact, Southard et al. demonstrated a net cost saving of US$965 per person with an estimated return of 213% on telehealth intervention.[38] Despite these benefits, the use of virtual programs for rural post-ACS patients in Canada has been limited.

1.5 Pharmacist Led Post-ACS Care

Studies assessing in-person and virtual post-ACS programs have not routinely included a pharmacist for providing care to post-ACS patients. As medication experts, pharmacists play a unique role by not only being able to assess pharmacotherapy and providing direct therapy interventions, but by also facilitating medication adherence and education. In particular, pharmacists in Alberta can order and interpret laboratory tests and prescribe medications, which have been shown to improve patient outcomes in various cardiovascular care settings.[39–41] In fact, a randomized controlled trial where community pharmacists provided dyslipidemia management resulted in greater than three-fold more patients achieving target cholesterol levels.[39] Specifically, pharmacist-led interventions (e.g. medication teaching, reconciliation, and therapy optimization) in post-ACS and ischemic heart disease patients have shown

improvements in cardiac disease management and medication adherence.[42–47] A systematic review by Kang et al., which included trials for both ACS and heart failure patients, found a significant improvement with pharmacy-intervention in all-cause hospitalization [OR, 0.74; 95% CI, 058–094] and in prescription rates for secondary cardiovascular prevention at 12 months.[44] Additionally, numerous economic studies have also demonstrated significant cost-reduction with pharmacist-led programs in various cardiac care settings. [48–53]

1.6 PLURAL-ACS Study Objectives

Disparities in both care and clinical outcomes are evident in rural post-ACS patients in Alberta. Lack of timely access to follow-up care, lower prescription fill-rates, and higher rates of recurrent-ACS and re-hospitalizations have been identified in various rural cohorts. While virtual programs have shown benefit in providing efficient care specifically to post-ACS patients, its implementation in rural Canadian populations have been limited. To our knowledge, pharmacists' role in a post-ACS virtual care program for Canadian rural patients have never been assessed, despite previously demonstrated benefits of improved clinical and cost-reduction outcomes with pharmacist-interventions.

We hypothesized that developing and implementing a pharmacist-led virtual follow-up pilot program for rural ACS patients in Alberta would lead to the efficient identification and resolution of cardiac medication-related issues and reduced discharge-prescription fill times. Given that delays in therapy as little as one day can have significant consequences, and that pharmacist-led medication assessments have been shown to lead to improved patient outcomes, we also hypothesized that our pilot program would lead to improvements in cardiac related hospitalizations and emergency visits.

The Pharmacist-Led Follow-Up Program for Rural Acute Coronary Syndrome Patients (PLURAL-ACS) study and objectives were divided into two phases:

Phase One: Development and Implementation of the Pilot Program

The purpose of phase one was to develop and implement a first-ever pharmacist-led 30-day virtual follow-up pilot program for Central and North zone ACS patients in Alberta, as part of a quality improvement initiative. The focus of the program was to identify and resolve cardiac medication-related issues, which were collected as descriptive outcomes.

Phase Two: Retrospective Cohort Study

The purpose of phase two was to evaluate the clinical impact of the pilot program through a retrospective comparison of the clinical outcomes of the pilot participants to the clinical outcomes of the matched control group who had received usual care.

CHAPTER 2

PHASE ONE METHODS: PLURAL-ACS PROGRAM DESIGN, IMPLEMENTATION, AND DESCRIPTIVE OUTCOMES

2. Phase One Methods

2.1 Program Design and Setting

The PLURAL-ACS pilot program was a quality improvement initiative conducted at the Mazankowski Alberta Heart Institute, which is a tertiary cardiac care institution in Edmonton, Alberta. Discharged patients entered the program between March 9, 2022 to May 25, 2022 and were followed virtually for 30 days as outpatients.

2.2 Program Patients

Patients 18 years of age or older from Central and Northern Alberta zones who were admitted with ACS (i.e. ST- elevation myocardial infarction [STEMI], non-ST-elevation ACS) to the Mazankowski Alberta Heart Institute were eligible for the program. Patients were excluded if they did not have telephone access, were non-English speaking, had a diagnosis of dementia or significant cognitive dysfunction following anoxic brain injury during the index event, were discharged to a rehabilitation or long-term care facility, received coronary artery bypass surgery for the index event, admitted with myocardial infarction with non-obstructive coronary artery disease, or transferred back to home hospital. All patients received medication review and teaching by the inpatient unit pharmacist prior to discharge, as part of the unit protocol.

2.3 Program Service

The program pharmacist was an advanced year two cardiology pharmacy resident with prescribing authority who had prior clinical experience as a staff pharmacist in inpatient cardiology. Eligible patients were identified by the program pharmacist and members of the inpatient cardiology care teams prior to discharge. The program pharmacist introduced the

program to the patients in person, along with a handout detailing the program (Appendix 1 of the Supplementary Appendix). All patients who agreed to participate received three scheduled telephone visits by the program pharmacist, as follows: 24 hours, 10 days, and 30 days after discharge. The timeframes were chosen to trend the different type of issues encountered by patients over the course of 30 days post discharge. Specifically, early intervention with the 24-hour timeframe was chosen to ensure timely medication access, as the provincial data indicated delayed prescription fill times for rural ACS patients following hospital discharge.[9] Similarly, the 30-day timeframe was selected since the provincial data indicated an increased 30-day ACS-readmission rates following discharge for the same rural ACS patients and because this is a vulnerable period following ACS for high reoccurrence rates. The visits were structured and standardized. If the pharmacist failed to reach the patient for a scheduled visit, two additional contact attempts were made after which a telephone voice message was left. The program pharmacist also provided patients with a direct phone line access during weekdays (0800-1600 hours) and scheduled issue-focused follow-up telephone calls, as required, in addition to the scheduled protocol phone calls.

The program service follow-up visits focused on the identification and resolution of any barriers to medication-taking (e.g. drug unavailability in pharmacy, lack of patient knowledge) and cardiac medication-related issues (e.g. medication adverse events) in a timely manner, as well as cardiac medication and risk factor education. These services were chosen to address the delayed prescription fill of rural ACS patients that was identified in the province, as well as implement services that were used in prior successful pharmacy-led studies in urban cardiac patients. [44] Drug therapy optimization for cardiac medical issues was identified as a medication-related issue and patients were referred to their PCP; however, these issues were not addressed

during follow-up, unless it was urgent and medically necessary. Any medical issues that required further in-person assessment also led to the patient being referred to their PCP during the 30-day program. Patients were reminded and encouraged to see their PCP within one week of discharge or attain a PCP if they did not have one, consistent with the ACS discharge follow-up protocol established as the standard of care by the tertiary care site and recommended by guidelines on the management of ACS. [4,5] Figure 2.1 outlines the services provided by the program pharmacist during each visit. The first visit included a comprehensive review of patient's discharge medications, as well as assessment of their medication taking behaviors and baseline medication knowledge. Barriers to cardiac medication access were promptly addressed within 24 hours after discharge, while the identification and resolution of any cardiac medication-related issues were completed at each visit. Patients also received individualized education on cardiac medications and their cardiac risk factors based on the initial assessment of need to further improve their medication-taking. At the end of the 30-day follow-up, the program pharmacist provided a written discharge summary to patient's PCP, cardiologist, and community pharmacist outlining patient's cardiac-specific issues, details of care/interventions provided during the program, and any unresolved cardiac medication-related issues that required further follow-up for optimization. Medication knowledge assessment was repeated using the same questionnaire at the last visit to compare to assessment at the first visit. Full details of the clinical services, patient-assessment, and discharge summary templates are provided in the Supplementary Appendix.

2.4 Outcomes

During the PLURAL-ACS pilot program implementation, a number of descriptive outcomes were collected to assess the type of medication-related issues that were encountered in the program patients and the feasibility of program administration. The descriptive outcomes were collected from all the patients who entered the PLURAL-ACS pilot program during the implementation phase (March 9, 2022 - May 25, 2022). Patients were included in this phase one analysis up to each time point they completed the 30-day program but did not need to complete the entire program to be included in the analysis.

The primary outcome in phase one was the total number of cardiac medication-related issues identified by the program during the 30-day follow-up. Cardiac medication-related issues were defined as any medication-related issue (e.g. drug interactions, adverse events, medication non-adherence) that pertained to patients' post-ACS medications, as listed in the Supplementary Appendix. If patients failed to attend a scheduled visit, cardiac medication-related issues were not identified for that visit.

The secondary outcomes included the total number of cardiac medication-related issues that were resolved by the end of the 30-day program and the type of cardiac medication-related issues identified. Resolution of previously identified cardiac medication-related issues was determined at the next scheduled visit or marked as unresolved if this was indeterminate based on chart-review and patient-interview at the end of the program.

Cardiac medication-related issues and pharmacist action were determined and documented by the program pharmacist, using a prespecified categorization that was adapted from prior studies. [54,55] Specifically, cardiac medication-related issues were divided into three

separate categories, each comprising of subcategories (further definitions provided in Appendix 6 of the Supplementary Appendix):

1. General cardiac medication issues: adverse effects, patient-medication concerns, contraindicated therapy, drug or food interactions, assistance with medication adherence required, therapy optimization required, and follow-up on ordered blood work required.
2. Patient-level medication issues: non-intentional medication non-adherence, intentional medication non-adherence, continuation of discontinued preadmission medication, discharge medication not obtained from pharmacy, and discontinued medication by patient.
3. System-level medication issues: insufficient prescription duration, non-indicated therapy, omitted medication in discharge prescription, insufficient supply of pass-medications (supply of new medications provided to patient at discharge to ensure continuity of therapy until the patient is able to fill prescription in community pharmacy), drug cost creating a barrier to medication-taking, conflicting information between discharge documents, unavailable medication at pharmacy, and failure to reconcile home medication.

Secondary outcome also included patient's cardiac medication knowledge, which was assessed at the first visit prior to any medication counselling (i.e. medication knowledge pre-program implementation) and at the end of the last visit (i.e. medication knowledge post program implementation) using a questionnaire adapted from previous studies (Appendix 3). [56, 57] The questionnaire was a knowledge instrument that included 7 basic questions that is proposed to the patient to assess five key areas of medication knowledge (i.e. medication name, medication

indication, instructions on how to take the medication, important side effects of medication, and what to do if a dose is missed). Each question was worth a score of one, with the questionnaire providing a total score out of 7. Score of five or higher indicated high-medication knowledge. If patients failed to attend the last visit, their post-program medication knowledge was not assessed. Lastly, the time spent, including per visit and type of activity, was also recorded.

2.7 Data Sources

Baseline patient characteristics were collected from chart review by the program pharmacist. Other individual descriptive outcomes were collected by the program pharmacist from the electronic medical record.

2.8 Statistical Analysis

Given the descriptive nature of this analysis, outcomes were expressed as medians with interquartile ranges (IQR; 25^{th}-75^{th} percentile) or percentages (%). The small sample size and lack of normal distribution of certain outcomes necessitated that the data was expressed as medians.

2.9 Ethical Considerations

This project was a program evaluation/quality improvement initiative; therefore, ethics approval was not required for this component of the project.

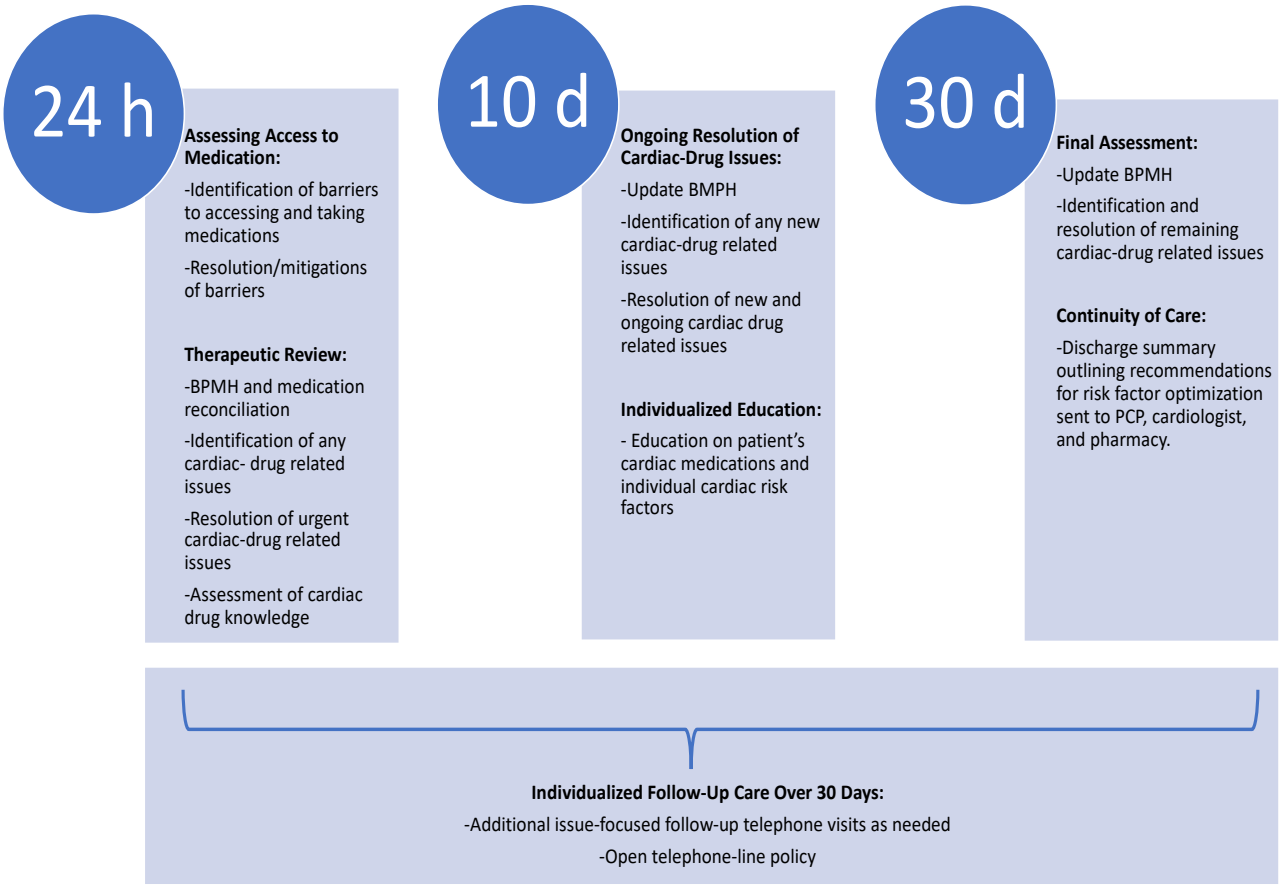

Figure 2.1. Overview of Pharmacist-Care in the PLURAL-ACS Pilot Program
Abbreviations: BMPH, best possible medication history; PCP, primary care provider

CHAPTER 3

PHASE TWO METHODS: RESTROSPECTIVE ANALYSIS OF PATIENT OUTCOMES IN PLURAL-ACS PILOT PROGRAM COMPARED TO OUTCOMES IN MATCHED ACS COHORT

3. Phase Two Methods

3.1 Design

Phase two was a retrospective cohort study. Once the PLURAL-ACS pilot program was implemented, clinical outcomes of the patients who participated in the pilot program (March 2022-May 2022) were compared to clinical outcomes of a matched control group who received usual care (November 2021-July 2022) to evaluate the program's impact on the outcomes of interest (Figure 3.1).

3.2 Sample

Inclusion Criteria:

- 18 years or older
- Discharged diagnosis of ACS (as identified by the International Classification of Disease, Eleventh Revision (ICD-10 codes)
- Discharged home from the Mazankowski Alberta Heart Institute or Royal Alexandra Hospital
- Reside within either the North or Central zones of Alberta

Exclusion Criteria:

- Admitted for primary non-cardiac diagnosis who develop ACS as a secondary condition during index admission (e.g., perioperative MI)
- Admitted with myocardial infarction with non-obstructive disease
- Died in hospital
- Received coronary artery bypass grafting during the index admission

- Had a diagnosis of dementia or significant cognitive dysfunction following anoxic brain injury during index event
- Discharged to a rehabilitation facility or long-term care facility
- Transferred back to home hospital

Pilot program group:

Total number of patients who received care in the PLURAL-ACS program between March 9, 2022 and May 25, 2022 served as the active group and were identified by unique lifetime identifier.

Control group:

The control group were patients meeting the inclusion criteria but who received usual care. Control group was matched in a 2:1 fashion with the active comparator group. Matching variables included age ± 10 years, sex, and zone of residence (i.e. Central or North zone).

To ensure enough control-group patients were included to achieve the target sample size, control group patients were included from the Mazankowski Alberta Heart Institute and then the Royal Alexandra Hospital (both tertiary care hospitals with coronary catheterization labs) between November 1, 2021 and July 31, 2022. The pharmacy services provided at both hospitals were comparable: both sites had a full time, specialized cardiology trained pharmacist in the cardiology team that rounded with the team five days per week, as well as provide seamless care services, which included discharge medication reconciliation and teaching.

3.3 Outcomes

The primary outcome in phase two was the time to first discharge prescription fill of ACS medications, defined by prescription fill of any ACS medication within the first 30 days post hospital discharge. This included any prescription that was filled 48 hours prior to date of hospital discharge, to account for any prescriptions that were faxed to rural pharmacies ahead of time. ACS medications included: P2Y12 inhibitors, statins, ezetimibe, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor antagonists. For patients who did not fill any of the ACS discharge medications within 30 days, prescription fill of the ACS medications filled within 90 days prior to index admission were collected to determine if the potential cause was due to recent refills (e.g. already had a supply at home and refill was not required).

Secondary outcomes in phase two included the following: 30-day cardiac-related hospital readmissions, 30-day cardiac-related emergency department visits, and 30-day PCP-visits.

3.4 Data Sources

The outcome of time prescription fill of ACS medications was collected from the Pharmaceutical Information Network (PIN). Thirty day cardiac related hospital readmission, 30-day cardiac related ED visit, and 30-day PCP visits post discharge were collected from DAD, National Ambulatory Care Reporting System and Practitioner Claims respectively. Baseline characteristics were collected from DAD and Netcare PIN. The codes defining the cardiac medications were attained from Anatomical Therapeutic Chemical Classification, while codes defining cardiac related medical conditions were attained from ICD-10 Classification (Appendix 7 of the Supplementary Appendix).

3.5 Statistical Analysis

We calculated that 105 patients would provide the study with 90% power to detect a 2-day difference in the time to first discharge ACS prescription fill between the program patients and control patients at a two-tailed alpha of 0.05. This assumption was based on the 2019-2020 AHS SV SCN data, which showed a mean time to first discharge prescription fill time of 4.70 days and 4.3 days for North Zone and Central zone patients respectively. [9]

We presented continuous outcomes as means with standard deviation (SD) if data was normally distributed or as medians with interquartile ranges (IQR; 25^{th}-75^{th} percentile) when normality could not be assumed. Categorical outcomes were presented as proportions (%). Two-sample t-tests were performed for the analysis of normally distributed continuous outcomes; alternatively, Mann-Whitney U tests were used when normality could not be assumed. Preliminary hypothesis testing for categorical outcomes was conducted using Chi-squared tests of independence, or Fisher's exact test when expected cell frequencies were lower than five. To adjust for baseline differences, we used backward elimination to build multivariate logistic regression models: all variables in Table 4.1 were included in the initial model and individually subtracted until only variables that were significant at $p < 0.05$ remained.

To explicitly model for time-to-event and assess data from patients where the event of interest did not occur, we also calculated hazard ratios using Cox proportional hazards models. Adjustment was again performed through backward elimination model fitting.

All data management and statistical analyses were conducted using Stata 17.0 BE (College Station, TX: StataCorp LLC). $p < 0.05$ was considered significant in prespecified analyses.

3.6 Ethical Considerations

This retrospective cohort study received ethics approval from the University of Alberta Research Ethics Board, (Pro 00120706).

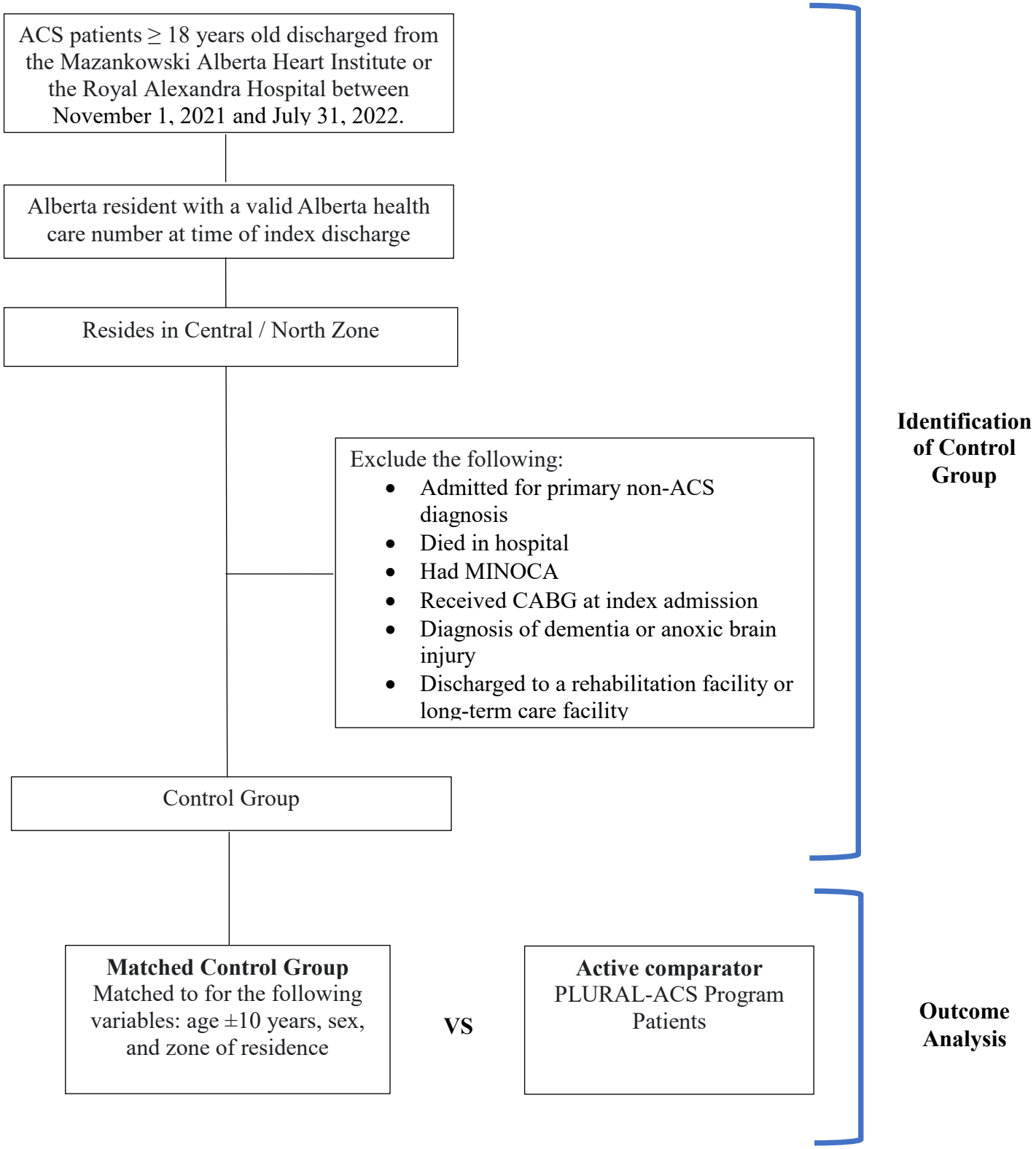

Figure 3.1 Cohort Derivation
Abbreviations: ACS, acute coronary syndrome; MINOCA, myocardial infarction with non-obstructive coronary arteries; CABG, coronary artery bypass surgery; PLURAL-ACS, Pharmacist-Led Follow-Up Program for Rural Acute Coronary Syndrome Patients

CHAPTER 4

PHASE ONE AND PHASE TWO RESULTS

4. Phase One and Phase Two Results

4.1 Program Patients (Phase One)

A total of 40 patients entered the PLURAL-ACS pilot program. Two patients did not complete the full 30-day program. One patient had a non-cardiac related readmission and passed several days after completing day-one visit, while the second patient could not be reached for the 30-day visit.

4.2 Matched Control Patients (Phase Two)

80 control patients (matched for age within 10 years, sex, and zone of residence) were included in the retrospective comparison. Although 105 patients total were required based on our sample size calculation, control group was matched in a 2:1 fashion, totaling 120 patients with the 40 program-patients in the active comparator group. Baseline characteristics of program and matching control patients are shown in Table 4.1. The mean age of patients was 66 years and 85% of the patients were male. Patients in the pilot program were more likely to be admitted with STEMI, receive percutaneous coronary intervention during the index admission, and be discharged with aspirin on top of a P2Y12 inhibitor. Every patient in the program was started on new cardiac medications during their index hospitalization.

4.3 Phase One: Descriptive Outcomes of PLURAL-ACS Program

4.3.1 Telephone Visits

Over the course of the 15-week program, a total of 139 telephone-visits were completed, including 117 scheduled standard visits, 12 patient-initiated visits, and 10 pharmacist-initiated visits. The patient-initiated visits were often due to patients experiencing a new adverse event or

having a drug-related question. Pharmacist-initiated visits were often to follow-up on patient's response to a recently modified therapy. Additional visits were unpredictable and were often dictated by the issues encountered, but generally occurred once every two weeks. The overall median time spent per visit was 60 (IQR, 50-80) minutes, which included the completion of any required chart reviews, patient care notes, and correspondence with other healthcare professionals. When averaging the time spent according to the visit, the median time was 80 (IQR, 70-95) minutes, 60 (IQR, 45-60) minutes, and 60 (IQR, 50-80) minutes for day 1, 10, and 30-visits respectively. Activities that required the largest amount of time were patient counselling and education (median 30 [IQR, 25-30] minutes), patient assessments (median 20 [IQR, 20-30] minutes), and completing discharge summaries (median 20 [IQR, 15-30] minutes).

4.3.2 Primary Outcome: Number of Identified Cardiac Medication-Related Issues

The total number of cardiac medication-related issues identified by the pharmacist during the program was 255 with a median of 6.0 (IQR, 3.75-8.25) per patient. Every patient had at least one issue identified. The median number of cardiac medication-related issues identified per patient was 3.5 (IQR, 2-5), 1 (IQR, 1-2), and 0.5 (IQR, 0-1.25) for day one, 10, and 30-visits respectively.

4.3.3 Secondary Outcomes

For the 255 cardiac medication-related issues identified during the program follow-up, 233 (91%) of them were resolved by the program. Overall, general cardiac medication-related issues were the most common, followed by patient-level medication issues and system-level medication issues (Figure 4.1). The absolute number and percentages of each

cardiac medication-related issue can be found in Table 4.2. The most commonly identified issues on day one, 10, and 30 were discharge prescription errors (21%), cardiac medication adverse events (47%), and therapy optimization being required (30%) respectively. Specifically, prescription errors included orders for less than the intended medication duration (e.g. one month as opposed to 12 months after ACS and PCI) or omitted medications (e.g. nitroglycerin spray). Medication adverse events often included symptomatic hypotension, drug rashes, or nuisance bleeding, such as nose bleeds or bleeding from hemorrhoids. Lastly, therapy optimization being required included the requirement of titration of therapy for patients who were consistently hypertensive, hyperglycemic or had heart failure. Lastly, patients' cardiac medication knowledge significantly increased post program implementation (Table 4.3).

4.4 Phase Two: Retrospective Analysis of PLURAL-ACS Program Patients Compared to Matched ACS Control

4.4.1 Primary Outcome: Time to First Discharge Prescription Fill of ACS Medications

All (100%) of the pilot program and 95% of the matched control group filled their discharge ACS prescription within 30 days post discharge. Of the 5% of control patients who failed to fill their prescription, half of them had already filled their P2Y12 inhibitor within 90 days prior to hospital admission.

In both the unadjusted and adjusted analyses, there was no significant differences in time to ACS discharge prescription fill between program patients and matched control patients visits (HR, 1.24; 95% CI, 0.84-1.84 and adjusted HR [aHR], 1.17; 95% CI, 0.80-1.74) (Table 4.4).

4.4.2 Secondary Outcomes

In both the unadjusted and adjusted analyses, there was no significant difference in the 30-day cardiac related hospital readmissions or the 30-day cardiac-related emergency department (Table 4.4). However, in the adjusted analyses, the 30-day PCP visit was significantly higher in the program patients as compared to the outcome in matching control (HR,1.31; 95% CI, 0.86-1.98 and aHR, 2.99; 95% CI, 1.47-6.10).

Table 4.1 Baseline Characteristics of PLURAL-ACS Program Patients and Matched Control Group

Data point	**Pilot Program Patients (n=40)**	**Matched Control Group (n=80)**	***P* value**
Age, mean; yr (SD)	66 (11)	66 (11)	P=0.991
Male, no. (%)	34 (85)	68 (85)	N/A
AB Zone, no. (%):			
North	21 (53)	42 (53)	N/A
Central	19 (48)	38 (48)	N/A
Hospital of Discharge, no. (%):			
MAHI	40 (100)	21 (26)	<0.0001
RAH	0 (0)	59 (74)	<0.0001
Discharge diagnosis, no. (%):			
STEMI	25 (63)	34 (43)	0.039
NSTEMI	14 (35)	44 (55)	0.039

Unstable Angina	1 (3)	2 (3)	1.000
Length of inpatient stay-days, Median (Q1, Q3)	3.49 (2.82, 4.02)	2.61 (0.92, 3.62)	0.001
Received PCI during index admission, no. (%)	38 (95)	49 (61)	0.0001
Comorbidities During Index Admission, no. (%):			
Heart Failure	0 (0)	3 (4)	0.5450
Arrhythmia	1 (3)	5 (6)	0.662
Shock	0 (0)	2 (3)	0.552
Medical History, no. (%):			
Prior CAD	5 (13)	33 (41)	0.001
Dyslipidemia	6 (15)	19 (24)	0.266
Hypertension	29 (73)	61 (76)	0.655
Heart Failure	4 (10)	13 (16)	0.355
Atrial Fibrillation	1 (3)	13 (16)	0.033
Diabetes	15 (38)	34 (43)	0.599
CKD	0 (0)	4 (5)	0.300
COPD	6 (15)	13 (16)	0.860
Discharge Cardiac Medications, no. (%):			
Prescribed ASA*	29 (73)	38 (48)	0.009
P2Y12 Inhibitors	38 (95)	71 (89)	0.333

Lipid Therapy	36 (90)	67 (84)	0.355
RAASi	36 (90)	57 (71)	0.020
Beta Blocker	35 (88)	61 (76)	0.146
MRA	5 (13)	15 (19)	0.387

Abbreviations: MAHI, Mazankowski Alberta Heart Institute; RAH, Royal Alexandra Hospital; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ASA, acetylsalicylic acid; RAASi, renin-angiotensin aldosterone system inhibitors; MRA, mineralocorticoid receptor antagonist
*Only includes ASA that is prescribed, as over the counter ASA is not captured by the Pharmaceutical Information Network database

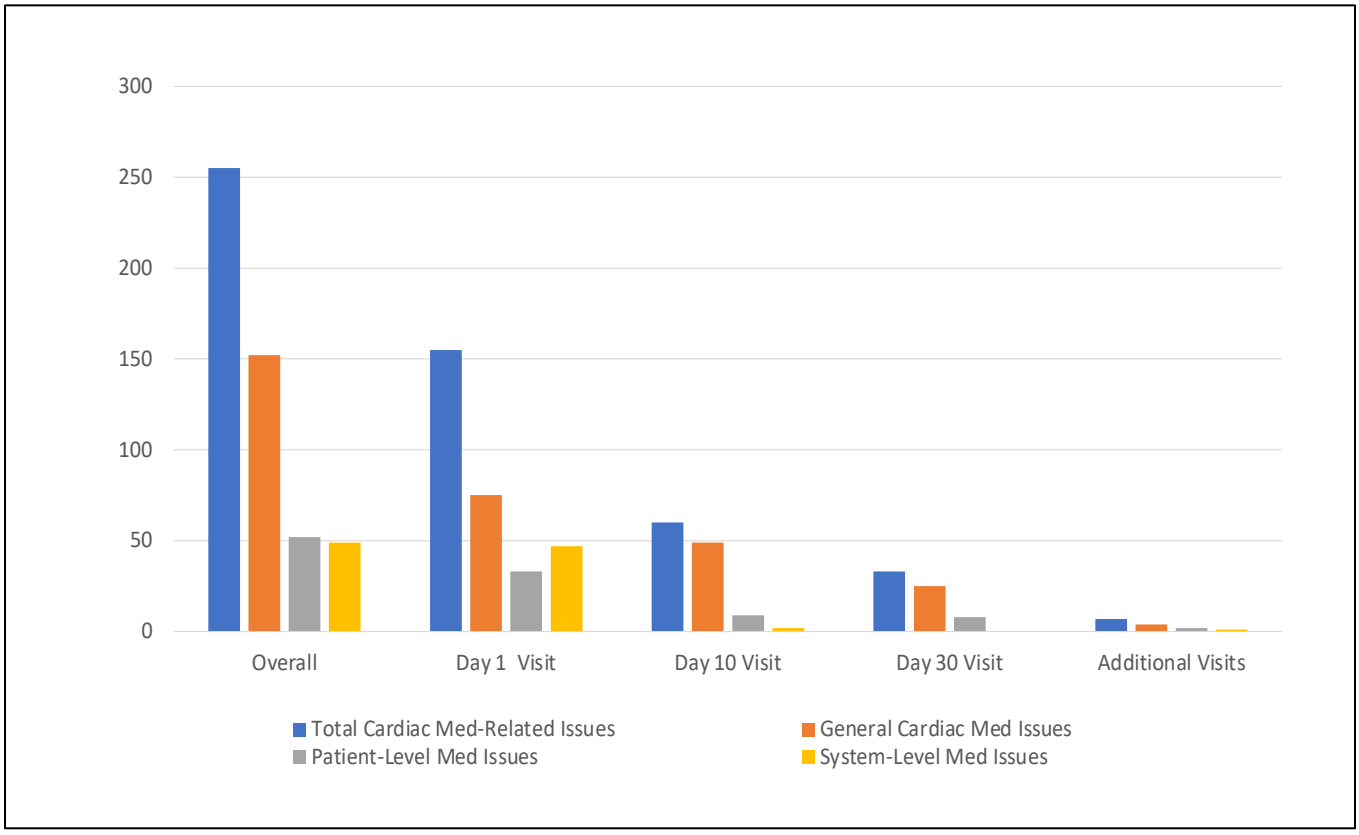

Figure 4.1 Type of Cardiac Medication-Related Issues Identified During the PLURAL-ACS Program
Abbreviations: Med, medication

Table 4.2 Number and Percentage of Cardiac Medication-Related Issues

	Day 1 Visit No. (%) of Issues *(n*=155)	**Day 10 Visit No. (%) of Issues *(n*=60)**	**Day 30 Visit No. (%) of Issues *(n*=33)**	**Additional Visits No. (%) of Issues *(n*=7)**	**Total No. (%) of Issues *(n*=255)**
General Cardiac Medication Issues					
Adverse Events	17 (11)	28 (47)	7 (21)	0	52 (20)
Therapy Optimization Required	8 (5)	12 (20)	10 (30)	0	30 (12)
Patient Medication-Concern	8 (5)	7 (12)	8 (24)	4 (57)	27 (11)
Assistance with Adherence	16 (10)	0	0	0	16 (6)
Contraindicated Medication	14 (9)	0	0	0	14 (5)
Drug/Food Interaction	12 (8)	1 (2)	0	0	13 (5)

Follow-up on Ordered Blood Work Required	0	1 (2)	0	0	1 (0.39)
Patient Level Medication Issues					
Non-intentional Non-adherence	13 (8)	5 (8)	4 (12)	2 (29)	24 (9)
Medication Not Picked Up	10 (6)	0	0	0	10 (4)
Continued Preadmission Medication	7 (5)	0	0	0	7 (3)
Intentional Non-adherence	2 (1)	2 (3)	2 (6)	0	6 (2)
Discontinued Medication	1 (1)	2 (3)	2 (6)	0	5 (2)
System Level Medication Issue					
Insufficient Prescription Duration	17 (11)	1 (2)	0	0	18 (7)
Omitted Medication from Prescription	15 (10)	0	0	0	15 (6)

Drug Cost a Barrier	6 (4)	0	0	0	6 (2)
Conflicting Information	2 (1)	0	0	1 (14)	3 (1)
Non-Indicated Therapy	2 (1)	0	0	0	2 (1)
Unavailable Medication at Pharmacy	1 (1)	1 (2)	0	0	2 (1)
Insufficient Pass-Med Supply	3 (2)	0	0	0	3 (1)
Failure to Reconcile Home Medication	1 (1)	0	0	0	1 (0.39)

Table 4.3 Cardiac-Medication Knowledge Score of Pilot Program Patients Pre and Post Program Implementation

	Pre-Program	**Post-Program**	**Difference**	***P* Value**
Knowledge Score*, median (IQR)	2 (1-3)	5 (4-6)	2.5 (2,4)	<0.0001

*Score is out of 7. High medication knowledge is considered a score of $\geq$5.

Table 4.4 Outcomes of the Retrospective Analysis of PLURAL-ACS Program Patients Compared to Matched Control Group

Outcome	Pilot Program (N=40)	Matched Control (N=80)	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)	Adjusted *P* value
Time to ACS discharge Rx fill median days, [IQR]	0.25 [IQR, 0.0-0.25]	0 [IQR, 0.0-1.0]	1.24 (0.84–1.84)	1.17 (0.80-1.74)[a]	0.418
CV hospital readmissions No. (%)	3 (8)	4 (5)	1.49 (0.33–6.66)	1.69 (0.36-7.96)[b]	0.510
CV ED visits no. (%)	4 (10)	6 (8)	1.33 (0.38-4.73)	N/A[c]	0.655
PCP visits No. (%)	36 (90)	58 (73)	1.31 (0.86-1.98)	2.99 (1.47-6.10)[d]	0.003

Abbreviations: ACS, acute coronary syndrome; Rx, prescription; CV, cardiac-related; ED, emergency department; PCP, primary care practitioner

[a]Adjusted for P2Y12 inhibitor prescribed at discharge
[b]Adjusted for age and type of acute coronary syndrome
[c]No statistically significant confounders were found to adjust for
[d]Adjusted for rate of mineralocorticoid receptor antagonist prescribed at discharge and hospital of discharge

CHAPTER 5

DISCUSSION

5. Discussion

This is a two-phase study that described the number and type of cardiac medication-related issues encountered by rural patients following discharge from a tertiary hospital after experiencing an ACS and retrospectively compared the 30-day clinical outcomes of rural ACS patients who received pharmacist-led follow-up care to the outcomes of matched control rural ACS patients with usual care. A large number of cardiac medication-related issues were identified and 91% of them were resolved by the program. Cardiac medication knowledge was also significantly enhanced for the program patients. Given the limited access to care in rural populations, this level of support could improve patient care post discharge for this vulnerable population. Time to discharge prescription was not statistically significantly different between the program patients and the control. However, 30-day PCP visits were significantly higher in the program patients compared to the matched control, also highlighting the potential benefit in enhancing overall follow-up of patients through the pilot program.

This study shows that a pharmacist-led virtual follow-up care program can help meet the care-gap that has been demonstrated in rural ACS patients. Rural patients have been shown to have reduced access to care, delayed discharge-prescription fills, and frequent readmissions following ACS compared to urban patients. [8–12] They are also associated with advanced age, lower socioeconomic status, and lower health literacy compared to urban populations. [58,59] Despite these factors, programs directed at providing post-ACS care to rural patients are very limited. To our knowledge, this is the first-ever pharmacist-led virtual follow-up program for rural ACS patients in Canada. The study confirms that post-ACS rural patients encounter a large number of cardiac-medication related issues after hospital discharge. Since these patients have reduced access to care in their remote locations, these medication issues often can go unnoticed,

which may contribute to their increased hospital readmissions. [8] Furthermore, when rural patients do access health care, they have poorer outcomes, potentially due to the delay in their care.[60] Therefore, establishing a program that is dedicated to providing timely and readily accessible care to this vulnerable population may help close this care gap.

Specifically, having virtual access to a pharmacist can enable the timely resolution of medication related issues and enhance patient education, as has been shown with phase one of our study, the majority of which happen within the first week of discharge. Pharmacists are ideally situated to provide virtual ACS follow-up care, as they play a substantial role as medication experts in assessing and optimizing medications, as well as facilitating patient education and medication-adherence. [42,61,62] However, studies assessing most post-ACS programs have not often included a pharmacist to provide care to post-ACS patients.[24,25] A large majority ACS patients are discharged with new therapies with the potential to encounter new adverse events, contributing to nonadherence of medications or worsening clinical outcomes. [63] Our study shows that not only did the program pharmacist identify a high number of similar medication-related issues per patient, but it resolved a large majority of them within the 30-day follow-up period. In addition to timely issue-resolution, the program also enhanced the medication knowledge of patients significantly. Furthermore, given that a score of five or greater is assessed to be a high medication knowledge score and that the median score pre-program increased from 2 to a median score of five post-program without the IQR overlapping, this was also a clinically significant finding. Lack of medication knowledge has been shown to increase medication non-adherence which is associated with worsening clinical outcomes. [64] Furthermore, rural patients can have poor medication knowledge compared to urban patients due to multitude of reasons, such as limited access to routine health care, lower socioeconomic status, and lower

health literacy. [10,11,65–67] Our study highlights that pharmacists can be ideal candidates to provide successful care to rural populations post ACS by targeting these issues directly.

In addition to the resolution of medication issues and medication knowledge improvement, virtual pharmacist-led programs can offer a sustainable and cost-effective form of care. In order to meet the medical therapy needs of the patients during this vulnerable time post ACS, 139 visits, on average 60 minutes each, was required. The program showed that a clinical pharmacist was able to provide this rather intensive follow-up care virtually, likely due to their expertise in therapy assessment and management. Finding a specialized clinician in rural settings is generally limited, so having a medication-expert to provide virtual outreach care can offer a sustainable solution to the issue of limited available care in rural locations. Virtual follow-up program can also offer a more accessible and efficient option to rural patients, as it does not require them to commit to long travel times to access specialty care that is often found urban, central locations. Lack of feasibility and sustainability have been limitations observed in many rural follow-up programs, primarily due to the cost of staffing and provision of in-person assessments. [68] While we did not assess the cost-effectiveness in our study, prior economic studies have also demonstrated significant cost-reduction with pharmacist-led programs in cardiac care. [48–53]

The type of cardiac medication-related issues identified in the program also highlights the need for a multifaceted follow-up approach. Similar to previous transition of care studies, seamless care issues were commonly identified within 24 hours after discharge in our program, despite the fact that each of the study patients were discharged from a tertiary cardiac care center that was supported by a large care team, including inpatient pharmacist and a transition of care nurse.[55,62] Drug therapy management issues, such as medication adverse events, were most

commonly observed on the day 10 follow-up, while drug therapy optimization was most commonly required on day 30. This finding may have been observed because newly prescribed medications would have likely reached steady state and patients would have had more time to recognize adverse effects by day 10 when settling back into their home routine. Conversely, by the 30-day mark, patients may have started to relapse in implementing lifestyle modifications and therapy-adherence, potentially leading to requirements in therapy optimization. [69] In addition, since every patient in the program was started on new cardiac medications during their index hospitalization, this therapy often required optimization during the outpatient follow-up period. To our knowledge, no other pharmacist-led follow-up program in rural ACS patients have categorized the type of cardiac medication-related issues over follow-up time. These findings could help delineate the type of services and time required for specific post-discharge services for successful program implementation and patient care optimization.

Although not all, many of the identified medication issues were also potentially clinically significant. Prescribing for less than the intended duration for P2Y12 inhibitors was identified as a prescription error could have led to increased risk of in-stent thrombosis following percutaneous coronary intervention. Patients were also experiencing significant adverse effects, such as full-body rashes, that required identification of cause and therapy modifications. Several of the encountered adverse events led to patients' request to stop their therapy, which required identification of the culprit therapy, regimen modifications, and education to the patient on the importance of ACS therapy continuation. Lastly, several patients remained hypertensive and hyperglycemic, which have been shown to be significant cardiovascular risk factors. Patients with heart failure following ACS also often did not have their heart failure therapy titrated,

despite evidence suggesting the reduction in all-cause death and heart failure hospitalization following timely titration of heart failure therapy. [70]

Despite the number of cardiac medication-related issues identified and resolved by the program, the primary outcome of time to discharge prescription-fill in phase two of our study was not significantly different between the two groups. This may have been because of the primary outcome selected. The time to prescription fill that was used in our sample size calculation was based on provincial data, which demonstrated that rural patients on average took five days to fill their discharge prescription. [9] However, in our study, control patients had a median time to prescription fill of zero days, which was a surprising finding, leading to an underpowered study. This difference could have been because all of our study patients were discharged from tertiary care sites as opposed to the rural secondary care sites which were included in the provincial data assessed; rural secondary sites typically have less transition of care support, which may lead to delayed prescription fills. Furthermore, transition of care staff at the tertiary care sites included our study often fax discharge prescriptions to the rural community pharmacy on the day of discharge. Therefore, this could have led to prescriptions being documented as filled on day zero in the Netcare PIN database, despite the fact that patients may not have actually picked up the prescriptions for use from the pharmacy.

Lastly, the clinical outcomes in program patients were not significantly different when compared to a matched control group in phase two of our study. However, our study was not powered to detect differences in these secondary outcomes, which were exploratory. Furthermore, the type of intervention used, the duration of intervention and follow-up could have impacted the findings. A systematic review by El Hajj et al. also found that pharmacy care (which included medication reconciliation, medication counselling, and adherence assessment)

to patients post-ACS led to mainly improvement in medication adherence but not improvement in the rates of rehospitalizations, emergency department visits, or mortality among ACS patients. [43] One major reason for this finding is that the intervention was typically provided for a few weeks post discharge and clinical outcomes were assessed on average at three months, which may not have been long enough to determine the potential clinical impact. On the other hand, a meta-analysis by Kang et al. found that trials implementing similar pharmacy interventions but over several months did lead to reduction in all cause hospitalization at 12 months. [44] In addition to longer duration of care and follow-up, programs that include medication optimization have also been shown to improve clinical outcomes in cardiac patients. Systematic reviews with such programs did find reductions in all-cause rehospitalization and mortality in 12 to 24 months.[23,24] Our study also found that medication optimization was the most common issue at 30 days post discharge. Given that this was not the goal of our program, future studies are required to examine if virtual medication optimization is a role pharmacist can play for rural ACS patients, as well as studies examining longer duration of care.

Despite the limited power, program-patients were still shown to have more visits with their PCP, resulting in closer follow-up of care. The program pharmacist not only provided education regarding the importance of PCP follow-up, but also provided prompts to the patient for PCP follow-up throughout the program, which may have contributed to the higher PCP follow-up rates. This finding is particularly impactful, as this population have been shown to have fewer total ambulatory physician visits and cardiac therapy assessments, which have been associated with worse clinical outcomes. [10–13,71] Therefore, ensuring timely PCP follow-up post discharge could potentially reduce the delayed care and hospital readmissions that have been so commonly documented in this population [8,10]

A major strength of this study was the collection and categorization of the different pharmacist-services required to resolve the encountered medication-related issues over the 30-day follow-up period. These are often insufficiently collected in similar studies, and it is critical for understanding a program's feasibility and reproducibility. Another strength of our study includes its external validity, given that the study population was not restricted to high-risk or referred-only ACS patients, which has been the case for many programs. [43,55] Since our pilot program included all-comers, this also limits potential referral-bias of the study. Phase one of the study had almost complete follow-up, with only one patient failing to attend the third follow-up visit. Lastly, our program's setting and target population was novel. To our knowledge, previous pharmacist-led post-ACS follow-up programs included in-person care in urban centers, which limit access to rural patients.

Our study has several limitations in both phase one and two. In phase one, patients may not have been forthcoming or accurate when the program pharmacist asked about certain medication-related issues (e.g. medication adherence), potentially introducing bias. While medication knowledge assessment questionnaire was adapted from prior studies, it was not validated. The data collection in phase one was completed by the program pharmacist who implemented the service, which could have led to assessment bias. In phase two of the study, the outcome of time to prescription fill as per Netcare PIN may not be truly indicative of medication-adherence, as pharmacies could have filled the prescription upon receival (particularly if prescription was faxed) without the patient picking up their medications from the pharmacy. This can therefore be misleading, as medications could have appeared to have been filled as per Netcare PIN database, despite the fact that patients may not have started taking their new therapies. This would particularly be the case if hospitals faxed discharge prescriptions to

patients' community pharmacies. However, this outcome would have likely occurred equally in both the program and control groups, as patients in both cohorts were discharged from tertiary care sites with similar discharge protocols. Lastly, as this is a small pilot study, further studies are required to confirm association between services and improvements in outcomes.

CHAPTER 6

CONCLUSION

6. Conclusion

This two-phase study revealed several important insights about rural post ACS population and the follow-up that is required to meet the needs of this vulnerable cohort. Firstly, the program showed that cardiac medication related issues are commonly encountered early post discharge and out to 30 days. Every patient in the program on average had 6 medication-related issues identified. Patients in our study were discharged from tertiary care sites with dedicated cardiac teams and transition of care support staff, highlighting that even well supported inpatients do encounter a large number of medication-related issues shortly after discharge.

Secondly, our study showed that it is feasible to provide virtual follow-up discharge program utilizing a clinical pharmacist to meet the therapy needs of rural patients post discharge. To our knowledge, this was the first pharmacist-led virtual post-ACS follow up program for rural patients in Canada and it showed very promising results. Specifically, phase one of the study demonstrated that the program pharmacist was able to identify a large number of cardiac medication-related issues and resolve 91% of these issues within 30 days post discharge virtually. Given the limited access to care in rural locations, this type of clinical support could drastically improve patient care provided to this vulnerable population. The type of issues encountered were varied, from transition of care issues to the need for therapy optimization. In addition to resolving the medication-related issues, the program was also able to enhance the medication knowledge of the patients virtually and may have contributed to higher PCP follow-up.

The program also showed that pharmacists are appropriate to provide virtual ACS follow-up care. Clinical pharmacists have the training and skills to be able to address the wide variety of issues encountered by the post ACS patients in our study. As medication experts, they are able to

assess drug intolerances and implement optimization of therapies, which were encountered to be the most common issues on day 10 and 30 post discharge respectively. With their clinical training, they are also able to identify and efficiently resolve barriers to accessing therapy, which was assessed to be a common issue shortly after hospital discharge. Lastly, pharmacists' medication-knowledge can also translate to optimum patient-education of ACS medications, which has been shown to improve adherence and clinical outcomes post ACS.[63–65] Given the limited access to care in rural locations, having a medication-expert to provide virtual care can offer a sustainable solution to meet this care gap.

Lastly, longer duration of care and therapy optimization could also be implemented in future programs, as these outcomes have been associated with improvements in clinical outcomes, including reduction in hospitalizations. [23,24,44] Given that our program was a pilot, we had a relatively small cohort with a short implementation phase of 30 days. However, previous studies implementing similar pharmacy services did find benefit in clinical outcomes after several months of program implementation. Furthermore, programs implementing therapy optimization post ACS also have found clinical benefit. While therapy optimization was also identified to be the most common issue at day 30 in our study, this service was not the goal of our program. Future studies incorporating these changes could show clinical benefit in rural post ACS patients.

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Supplementary Appendix

Appendix 1. Patient Information Handout

Discharge Medication Follow-Up

Information Sheet

Purpose:

Many people that have a heart attack feel a little overwhelmed when they are discharged from the hospital, especially when it comes to medications. Our goal is to help with your transition home and make taking your medicines as easy as possible.

How Will This Follow-Up Help You?

- We will assess all your medications when you are at home and make sure that they are safe to take with your heart condition
- We will help solve problems that can happen with your heart medications after discharge (interactions, side effects, problems with taking medications, problems with getting medications from your local pharmacy)
- Based on your need, we will offer teaching about your heart medications and heart condition and share educational websites and other resources to use at home
- You can call the cardiac pharmacist to ask any questions or concerns you may have about your heart medications

What You Can Expect from the Follow-Up?

1. A cardiac pharmacist (Hazal) will contact you by phone:
    - 24 hours, 10 days and 28 days after your discharge from the hospital
    - More phone calls can be scheduled based your needs
    - You can also call the pharmacist from 8 am to 4 pm weekdays, if you have any problems with your heart medicines
    - The pharmacist will work closely with your cardiologist as required
2. At the end of the one month of follow-up, the pharmacist will provide your family doctor, cardiologist, and community pharmacist with a letter that summarizes the follow-up and any other medication problems identified

Telephone number to call if you have problems with your heart medications: (780) 819-7960

Appendix 2. Details of Pharmacist-Care in the PLURAL-ACS Pilot Program

<table>
<tr><td colspan="2"><u>Medication-Taking Assessment and Identification of Barriers</u></td></tr>
<tr><td colspan="2">1. Identification and Resolution of Financial Barriers to Medication-Taking (at first telephone-call and then as needed)</td></tr>
<tr><td>Activity</td><td>Options for Resolution</td></tr>
<tr><td>• Identifying how patient pays for medications
• Identifying patient’s drug insurance
• Identifying any financial barriers to medication taking</td><td>• Assisting for applications for drug coverage authorizations for cardiac medications when indicated if issues identified (patient’s outpatient cardiologist may be contacted)
• Switching therapies to lowest-cost alternative
• Using half of double-strength tablet</td></tr>
<tr><td colspan="2">2. Identification and Resolution of Other Barriers to Medication-Taking (at first telephone-call and then as needed)</td></tr>
<tr><td>Activity</td><td>Options for Resolution</td></tr>
<tr><td>• Identifying barriers to accessing community pharmacy</td><td>• Identifying patient’s pharmacy and any other nearby pharmacy to access medications
• Contacting community pharmacy for delivery of medications to patient</td></tr>
</table>

	• Contacting a family member to pick up medications
• Identifying lack of medication-availability in the community pharmacy	• Contacting community pharmacy • Referring patient to an alternate community pharmacy that has medication in stock
• Identifying patient-factors that delay/prevent prescription fill and/or medication-adherence (e.g. intentional or nonintentional adherence, performance deficit)	• Providing education on therapy indication and consequences for medication-adherence (see below) • Providing strategies to help with medication-taking (e.g. setting-up blister packs, dosettes, alarms, medication-delivery, involving family member, sending letter to GP to apply for home-care med assist) • Intervening to solve AE/interactions (see below)
<u>Therapeutic Review</u>	
1. Medication Reconciliation (at first telephone call and then as needed)	

Activity	Options for Resolution
• Best possible medication history for all medications (at first telephone call) • Medication reconciliation performed by comparing discharge prescription and patient's current medication list. Patient's initial hospital admission medication list is also be assessed if there are any discrepancies identified between (at first telephone call)	• Resolution of medication discrepancies that poses a risk to patient's cardiac condition and/or immediate well-being. (at each telephone-call)
2. Identification of errors in discharge prescription (at first telephone call and then as needed)	
Activity	**Options for Resolution**
• Identifying missing medication, inadequate duration, duplicate therapies on discharge prescription	• Ensuring prescription for DAPT and other ACS medications has been correctly provided for at least 30 days (patient's discharging and/or outpatient cardiologist may be contacted)
3. Identification and resolution of adverse effects and/or patient-related concerns (at first telephone-call and then as needed).	
Activity	**Options for Resolution**

• Focused assessment and resolution of cardiac medication adverse effects and patient concerns of therapies • May include assessment for light-headedness, syncope, dyspnea	• Modify therapy to resolve a significant AE (e.g. change ticagrelor to clopidogrel if ticagrelor-induced dyspnea leads to medication non-adherence, change angiotensin converting enzyme inhibitor (ACEI) to an angiotensin II receptor antagonist (ARB) if dry cough likely due to ACEI hindering adherence) • Modify therapy to address significant patient concern (e.g. change statin to a different one if patient non adherent due to an AE or concern)
4. Identification of cardiac medication-related issues and therapy optimization (at first telephone-call and then as needed).	
Activity	**Options for Resolution**
• Identifying significant drug/food interactions • Ensuring relevant urgent therapy optimization	• Modify therapy to resolve drug interactions • Assess and address critically high BP, BG levels

• Identifying use of contraindicated medications	• Discontinuation of contraindicated medications (e.g. NSAIDs, oral decongestants)
5. Streamlined therapy counselling based on baseline medication knowledge (second telephone call and then as needed)	
Activity	**Options for Resolution**
2. Assessing baseline medication knowledge of ACS medications 3. Determining areas that require counselling (indication, dosing, duration, AEs)s	• Counselling on antiplatelet and oral anticoagulant o Indication, dosing, duration, AEs o Importance of medication-adherence o Notification of other health care professionals if potential need to hold therapy arises • Counselling on other ACS medications o Indication, duration of each ACS therapy • Importance of medication-adherence, not stopping therapy unless told by cardiologist

Final Assessment and Recommendations for Follow-Up

1. Identification and resolution of any remaining cardiac medication-related
2. Identification of any cardiac medication-related issues that require follow-up
3. Program discharge summary outlining patient's history, current list of medications, care provided during the program, and issues that require follow-up on sent at the end of the program to:
    a. GP
    b. Community pharmacy
    c. Cardiologist

Program Communication:

- Documentation of each telephone conversation in Connect Care
- Discharge summary routed to cardiologist, and faxed to patient's GP and community pharmacy. This discharge summary will include issues to follow-up at the end of the program (Part 3).
- Other documentation will be routed to cardiologist, GP and community pharmacy based on issues identified throughout the program.

Abbreviations: ACS = acute coronary syndrome, AE = adverse effect, BG = blood glucose, BP = blood pressure, DAPT = dual antiplatelet therapy, PCP = primary careprovider, NSAID = nonsteroidal anti-inflammatory drug.

Appendix 3. Patient Assessment Templates

Visit 1**:**

Part I: Medication Taking	
Access to Community Pharmacy	☐ Preferred community pharmacy updated ☐ Prescription has been taken to this pharmacy ☐ Nearby pharmacy needs to fill prescription Notes:
Discharge Prescription Pick-Up	☐ Picked-up prescription from the pharmacy Date:_____. Time to first new Rx Pick-Up:_____ ☐ Require family member to pick up prescription ☐ Require community pharmacy to deliver prescription Notes:
Medication Availability	☐ Medication not filled due to lack of stock in the community pharmacy ☐ Another pharmacy available to provide this medication Notes:
Financial Barriers	Insurance: ☐ Seniors Blue Cross ☐ Non-Group Blue Cross ☐ NIHB ☐ Third Party: ☐ No Drug Coverage

<table>
<tr><td></td><td>In the past 12 months, because of cost, did you decide not to fill a prescription, not to refill a prescription, or do anything to make a prescription last longer?
☐ Yes ☐ No
Other financial concerns / barriers:
Notes:</td></tr>
<tr><td></td><td>Special Authorization Application Required?
☐ Cardiac medication that requires application for special authorization
☐ Medications need to be switched to lowest-cost alternative
Notes:</td></tr>
<tr><td>Medication Experience</td><td>☐ New:
☐ Chronic:</td></tr>
<tr><td>Regimen Complexity</td><td></td></tr>
<tr><td>Functional Medication Management</td><td></td></tr>
<tr><td></td><td>
<table>
<tr><th></th><th>Self</th><th>Caregiver</th><th>Other</th></tr>
<tr><td>Ordering</td><td>☐</td><td>☐</td><td>☐</td></tr>
<tr><td>Pick-up</td><td>☐</td><td>☐</td><td>☐</td></tr>
<tr><td>Administer</td><td>☐</td><td>☐</td><td>☐ Homecare</td></tr>
<tr><td rowspan="2">Organize</td><td>☐</td><td>☐</td><td>☐</td></tr>
<tr><td colspan="3">Method:</td></tr>
</table>
</td></tr>
</table>

	☐ Vial supply ☐ Dosette - self ☐ Dosette - caregiver ☐ Blister pack -pharmacy ☐ Other:
Reminders	☐ Scheduled / combined with daily tasks ☐ Caregiver ☐ Alarm ☐ Phone App ☐ Other:

	No	**Yes** **Use of aid?**	**Impact on medications taking / comments**
Cognitive			
Visual			
Hearing			
Mobility			
Swallowing			
Dexterity			

Notes:

<table>
<tr><td>ACS Medication Knowledge</td><td></td></tr>
<tr><td></td><td>
<table>
<tr><th>Question</th><th></th></tr>
<tr><td>1. Can you list the names of all medications you are currently taking? ☐ No aids ☐ Uses Aids: (medication list, bottles)</td><td></td></tr>
<tr><td>2. Can you tell me why you are taking **?</td><td></td></tr>
<tr><td>3. Do you know how to take your **?</td><td></td></tr>
<tr><td>4. Do you know when to take your medicine?</td><td></td></tr>
<tr><td>5. Do you know the possible side effects of your medicine?</td><td></td></tr>
<tr><td>6. Do you know what to do if a side effect occurs?</td><td></td></tr>
<tr><td>7. Do you know what to do if you miss a dose?</td><td></td></tr>
<tr><td>Total Score</td><td></td></tr>
</table>
High medication knowledge is considered a score ≥ 5.
Notes:
</td></tr>
<tr><td>Medication Adherence</td><td>Method:
Adherence:</td></tr>
<tr><td></td><td>Which of the following categories best describes your use of prescribed heart medications?
☐ Take all of your pills
☐ Take 75-99% of your pills
☐ Take 50-74% of your pills</td></tr>
</table>

<table>
<tr><td></td><td>☐ Take less than 50% of your pills
☐ Take none of your pills
☐ Not applicable

Some people have difficulty taking their medications. Have you missed taking any of your medications in the past 2 weeks?
☐ No
☐ Yes
What is the most likely reason for patient to miss a medication?
<table><tr><td>☐ Forgetful</td><td>☐ Financial</td></tr><tr><td>☐ Busy schedule/work</td><td>☐ Medication working</td></tr><tr><td>☐ Non-routine day</td><td>☐ Side effect</td></tr><tr><td colspan="2">☐ Other:</td></tr></table>
When you feel better, do you ever stop taking or cut-back on your medications?
☐ No ☐ Yes</td></tr>
<tr><td>Other</td><td></td></tr>
<tr><td></td><td>☐ Social Supports -
☐ EtOH, Cannabis, Nicotine -</td></tr>
<tr><td colspan="2">Part II: Therapeutic Review</td></tr>
</table>

<table>
<tr><td>Allergies</td><td>☐ updated</td></tr>
<tr><td>BPMH</td><td>☐ updated</td></tr>
<tr><td>Medication Discrepancy</td><td>☐ patient-level contribution (e.g. performance deficit):_____
☐ system-level contribution (e.g. prescription missing medication): _____</td></tr>
<tr><td>Cardiac-Medication Considerations</td><td>☐ Contraindicated medication (e.g. NSAID, oral decongestant, herbals, supplements): _____
☐ Notable drug/food interaction: _____
☐ New AE reported by patient (e.g. dyspnea to ticagrelor, diarrhea to colchicine, cough to ACE-I, light-headedness, syncope): _____
☐ Medication-specific patient concerns: _____</td></tr>
<tr><td>Visit to ED/or Care Provider</td><td>☐ Patient visited ED
☐ Patient hospitalized
☐ Patient visited care-provider (e.g. GP, walk-in clinic)
Date: _____ Planned or Unplanned: _____</td></tr>
<tr><td>Pharmacokinetic/Dynamics</td><td><u>Renal Function:</u>
<table><tr><td></td><td>Scr</td><td>eGFR</td><td>K</td><td>Notes:</td></tr><tr><td>Current (Date)</td><td></td><td></td><td></td><td></td></tr><tr><td>Baseline (Date)</td><td></td><td></td><td></td><td></td></tr><tr><td colspan="5">☐ CKD
☐ updated labs required</td></tr></table></td></tr>
</table>

	Hepatic Function:*
Risk Factor and Comorbidity Considerations	**Risk Factors:** ☐ HTN (BP=) ☐ Dyslipidemia (LDL=) Next Lipid Panel Due: ☐ Diabetes (A1C _%) ☐ Positive Family History ☐ Smoking ☐ ETOH ☐ Other: _____ **Comorbidities:** ☐ HF LVEF: _____ ☐ AFIB (CHADS2 = __); Anticoagulation regimen: Rate / rhythm control: ☐ VT ☐ Anemia Hgb: ____ ☐ Other: _____
Current ACS Regimen Hosp: PCI:	☐ ASA ☐ P2Y12 Inhibitor ☐ Warfarin ☐ DOAC

LV clot: EF: BNP:	☐ Statin Optimum dose?: ☐ Ezetimibe ☐ Beta Blocker ☐ ACEI/ARB ☐ MRA ☐ Other:
Patient Follow-Up	☐ Patient has follow-up with GP in 1-2 weeks Notes:

Visit 2 and 3:

Assessment and Follow-up	
Visit to ED/or Care Provider	☐ Patient visited ED ☐ Patient hospitalized ☐ Patient visited care-provider (e.g. GP, walk-in clinic) Date:_____ Planned or Unplanned: _____

Change in Medications	☐ Any new medication or change in regimen since last visit (e.g. prescribed, OTC, herbals): Date:_____ Prescriber/Initiator:_____
Cardiac-Medication Considerations	☐ Contraindicated medication (e.g. NSAID, oral decongestant, herbals, supplements): _____ ☐ Notable drug/food interaction: _____ ☐ New AE reported by patient (e.g. dyspnea to ticagrelor, diarrhea to colchicine, cough to ACE-I, light-headedness, syncope): _____ ☐ New medication-specific patient concerns: _____
Medication taking	☐ Missed any doses or delayed taking any doses: _____
Therapy Optimization Assessment	☐ Home BP readings: _____ ☐ Home BG readings: _____ ☐ Home weight: _____

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ACS = acute coronary syndrome, AE = adverse effect, AFIB = atrial fibrillation, ARB = angiotensin II receptor blocker, ASA = acetylsalicylic acid, BP = blood pressure, BG = blood glucose, BNP = B-type natriuretic peptide, BPMH = best possible medication history, CKD = chronic kidney disease, DOAC = direct oral anticoagulant, ED = emergency department, EF = ejection fraction, eGFR = estimated glomerular filtration rate, EtOH = alcohol,HF = heart failure, HTN = hypertension, K = potassium, LDL = low-density lipoprotein, LV = leftventricle, LVEF = left ventricular ejection fraction, MRA = mineralocorticoid receptor antagonist,NIHB = Non-Insured Health Benefit, OTC = over-the-counter medications, PCI = percutaneous coronary intervention, PCP = primary care provider, Rx = prescription, SCr = serum creatinine, VT = venous thrombosis

Appendix 4. Discharge Summary Template

PLURAL-ACS

Pilot

Program

Date:

Primary Care Provider:

Cardiologist:

Community Pharmacy:

Re: PLURAL-ACS Piot Program Discharge Summary

DOB:

ULI:

Please be advised that your patient,_____, was referred to the PLURAL-ACS Pilot Program, where _____ received pharmacist-led follow-up care after being discharged from the Mazankowski Albert Heart Institute on _____ following a _____.

Follow-up took place over the course of one month via scheduled telephone visits. A detailed review and assessment of _____'s medications was undertaken. A summary is provided below (please refer to hospital discharge summary for details regarding hospital stay).

Pertinent Cardiac History:

Cardiac Drug Therapy:

Clinical Issues Addressed During the Program:

Clinical Issues that Require Follow-Up:

I have identified the following concerns/issues as part of my review that require follow-up:

1. Medication Taking:

2. Cardiovascular Risk factors:

Risk Factor:		Comments:
☐ Hypertension	☐ treated ☐ controlled ☐ requires assessment	Home Blood Pressure:_____.

☐ Lipids	☐ treated ☐ controlled ☐ requires assessment	Requires a lipid panel in 2-4 weeks. If LDL-C remains above 1.8 mmol/L (or non-HDL above 2.4 mmol/L), patient would require further optimization of lipid therapy.
☐ Diabetes	☐ treated ☐ controlled ☐ requires assessment	A1C:_____. Home blood glucose:_____.
☐ Smoking	☐ treated ☐ controlled ☐ requires assessment	
☐ Overweight	☐ treated ☐ controlled ☐ requires assessment	BMI: ____. Education provided on role of lifestyle modifications and to initiate them under the recommendations of the cardiac rehab program.

3. Other:

Thank you for the opportunity to participate in the care of this patient.

Sincerely,

XXXXX

XXXXX

XXXXX

Appendix 5. List of Cardiac Medications

Category of Medication

- Acetylsalicylic acid
- P2Y12 inhibitors
- Oral anticoagulants
- Statins
- Ezetimibe
- Beta blockers
- Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers
- Mineralocorticoid receptor antagonists
- Nitroglycerin SL spray or topical patch
- Dihydropyridine calcium channel blockers
- Diabetic medications with cardiovascular benefit: metformin, SGLT-2 inhibitors, GLP-agonists

Abbreviations: GLP = glucagon-like peptide, SGLTI-2 = sodium-glucose transport protein2, SL = sublingual

Appendix 6. Definitions of Cardiac Medication-Related Issues

General Cardiac Medication Issues

- Adverse effects: any side effect that is assessed to be secondary to newly initiated or titrated cardiac medication (e.g. new nose bleeds after initiation of dual antiplatelet therapy)
- Patient medication-concern: apprehension or question regarding a cardiac medication brought forward by the patient that required pharmacist-intervention (e.g. patient asks which medication is safe to take with cardiac condition for gout)
- Contraindicated medication: any medication that is contraindicated to take with patient's cardiac condition (e.g. pseudoephedrine post-acute coronary syndrome)
- Therapy optimization required: when objective measurements of medication effect fail to meet guideline directed targets after program pharmacist confirmed patient adherence to therapy and after at least 5 drug-half lives have been achieved (e.g. average home blood pressure consistently above 135/85 mm Hg for patient with hypertension, fasting blood glucose consistently above 7 mmol/L for patient with diabetes mellitus, patient having cravings and relapsing with current smoking cessation regimen).
- Assistance with medication adherence: patient is assessed to be at high risk of medication non-adherence based on current medication administration and/or patient expresses need for assistance with adherence (e.g. establishment of blister packs after patient demonstrates confusion regarding administration and timing of current medications)
- Drug/Food interaction: any drug or food item that is categorized to be at least a level-C interaction based on Lexicomp with prescribed cardiac medications and that has not been

addressed prior (e.g. phosphodiesterase-5 inhibitor and nitroglycerin patch, omega-3 supplementation and antiplatelet therapy)

- Follow-up on ordered blood work required: outpatient blood work to assess the effects of a recently added medication (e.g. serum creatinine after addition of an ace-inhibitor, serum potassium after addition of spironolactone) that was ordered by the discharging cardiology team is not followed up on, leaving the patient at risk of potential harm

Patient Level Medication Issues

Note: the term "medication adherence" is the extent to which medication intake behavior corresponds with the recommendations of the health care provider. [1] Therefore, "non-adherence" in our study was defined as any situation since the last scheduled visit where medication was not taken as indicated in the discharge prescription (includes withholding of medication entirely, taking the incorrect dose, or changing the frequency of the medication taking). This includes any time that less than 100% of the pills were taken since the last scheduled visit.

- Nonintentional medication non-adherence: non-deliberately taking the prescribed cardiac medication differently than as prescribed (reasons include forgetfulness, confusion regarding therapy administration, performance deficit)
- Continued preadmission medication: patient continuing to take previously discontinued home cardiac medications or regimen that is changed at discharge, as confirmed with discharge prescription (e.g. continues to take amlodipine despite this being discontinued during hospitalization and at discharge)

- Intentional medication non-adherence: deliberately taking the prescribed cardiac medication differently than as prescribed (reasons can include patient's concern regarding cost of therapy or apprehension regarding therapy effects)
- Medication not picked up: patient fails to pick up new cardiac medication from the pharmacy after discharge despite not having any at home
- Discontinued medication: patient deliberately and permanently discontinues cardiac medication (e.g. permanently discontinues taking atorvastatin therapy due to concern of adverse event and refuses to restart atorvastatin therapy)

System Level Medication Issues

- Insufficient prescription duration: duration of medication inadvertently prescribed for a lesser-than intended duration on the discharge prescription, as confirmed with the discharge summary and directly with the discharging team (e.g. clopidogrel prescribed for 1 month despite discharging team decision to prescribe for the intended 12 months following ACS)
- Drug cost a barrier: patient unable to pick up cardiac medication(s) as he/she is unable to afford them
- Non-indicated therapy: medication that is not indicated (for patient's cardiac condition or any other reason) is inadvertently included in the discharge prescription, as confirmed with the discharge summary and directly with the discharging team (e.g. pantoprazole was included in discharge prescription after it was confirmed that patient's chest pain from ACS was incorrectly assessed to be acid reflux prior to admission)

- Insufficient pass-medication supply: supply of new medications provided to patient at discharge (to ensure continuity of therapy until patient call fill prescription in community pharmacy) does not last until patient can reach his/her community pharmacy
- Omitted medication: cardiac medication that patient has received during hospital stay and is prescribed to continue is inadvertently not included in the discharge prescription, as confirmed with the discharge summary and directly with the discharging team
- Conflicting information: information regarding cardiac medication regimen is conflicting between discharge prescription and discharge summary (e.g. discharge prescription includes rivaroxaban and clopidogrel for a patient's antithrombotic therapy while discharge summary includes aspirin and clopidogrel)
- Unavailable medication at pharmacy: newly prescribed discharge cardiac medication is not available at patient's community pharmacy, leading patient to not picking up the medication
- Failure to reconcile home medication: medication that patient was taking at home prior to hospital admission was not reconciled in the discharge prescription, leading to patient being unsure as to whether or not he/she should take it

Appendix 7. Codes Used to Identify Cardiac Medications and Cardiac-Related Conditions

1.0 Anatomical Therapeutic Chemical (ATC) Codes for Assessed Medications

1) ASA– B01AC06, N02BA01, N02BA51

2) Clopidogrel– B01AC04

3) Ticagrelor – B01AC24

4) Prasugrel – B01AC22

5) Statins:

Simvastatin- C10AA01

Lovastatin- C10AA02

Pravastatin- C10AA03

Fluvastatin- C10AA04

Atorvastatin- C10AA05

Rosuvastatin- C10AA07

6) Ezetimibe- C10AX09

7) ACE inhibitors:

Captopril- C09AA01

Enalapril- C09AA02

Lisinopril- C09AA03

Perindopril- C09AA04

Ramipril- C09AA05

Benazepril- C09AA07

Cilazapril- C09AA08

Fosinopril- C09AA09

Trandolapril- C09AA10

8) ARBs:

Losartan- C09CA01

Valsartan- C09CA03

Irbesartan0 C09CA04

Candesartan- C09CA06

Telmisartan- C09CA07

Olmesartan- C09CA08

9) Beta Blockers:

Pindolol - C07AA03

Propranolol - C07AA05

Timolol - C07AA06

Nadolol - C07AA12

Sotalol - C07AA07

Metoprolol – C07AB02

Atenolol – C07AB03

Acebutolol - C07AB04

Bisoprolol - C07AB07

Nebivolol - C07AB12

Labetalol - C07AG01

Carvedilol - C07AG02

Pindolol and other diuretics – C07CA03

Atenolol and other diuretics – C07CB03

10) Spironolactone- C03DA01

11) Eplerenone- C03DA04

2.0 International Classification of Disease, Tenth Revision (ICD-10) Codes for Cardiac-Related Hospital Readmission and ED Visits

1) Hypertension

I10-I15 Hypertensive diseases

- **I10** Essential (primary) hypertension
- **I11** Hypertensive heart disease
  - **I11.0** Hypertensive heart disease with (congestive) heart failure

- **I11.9** Hypertensive heart disease without (congestive) heart failure
- **I12** Hypertensive renal disease
  - **I12.0** Hypertensive renal disease with renal failure
  - **I12.9** Hypertensive renal disease without renal failure
- **I13** Hypertensive heart and renal disease
  - **I13.0** Hypertensive heart and renal disease with (congestive) heart failure
  - **I13.1** Hypertensive heart and renal disease with renal failure
  - **I13.2** Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
  - **I13.9** Hypertensive heart and renal disease, unspecified
- **I15** Secondary hypertension
  - **I15.0** Renovascular hypertension
  - **I15.1** Hypertension secondary to other renal disorders
  - **I15.2** Hypertension secondary to endocrine disorders
  - **I15.8** Other secondary hypertension
  - **I15.9** Secondary hypertension, unspecified

2) **Ischemic Heart Disease**

I20-I25 Ischemic heart diseases

- **I20** Angina pectoris
  - **I20.0** Unstable angina
  - **I20.1** Angina pectoris with documented spasm
  - **I20.8** Other forms of angina pectoris
  - **I20.9** Angina pectoris, unspecified
- **I21** Acute myocardial infarction
  - **I21.0** Acute transmural myocardial infarction of anterior wall
  - **I21.1** Acute transmural myocardial infarction of inferior wall
  - **I21.2** Acute transmural myocardial infarction of other sites
  - **I21.3** Acute transmural myocardial infarction of unspecified site
  - **I21.4** Acute subendocardial myocardial infarction
  - **I21.9** Acute myocardial infarction, unspecified
- **I22** Subsequent myocardial infarction
  - **I22.0** Subsequent myocardial infarction of anterior wall

I22.1 Subsequent myocardial infarction of inferior wall

I22.8 Subsequent myocardial infarction of other sites

I22.9 Subsequent myocardial infarction of unspecified site

I23 Certain current complications following acute myocardial infarction

I23.0 Haemopericardium as current complication following acute myocardial infarction

I23.1 Atrial septal defect as current complication following acute myocardial infarction

I23.2 Ventricular septal defect as current complication following acute myocardial infarction

I23.3 Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction

I23.4 Rupture of chordae tendineae as current complication following acute myocardial infarction

- **I23.5** Rupture of papillary muscle as current complication following acute myocardial infarction
- **I23.6** Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction
- **I23.8** Other current complications following acute myocardial infarction

I24 Other acute ischaemic heart diseases

- **I24.0** Coronary thrombosis not resulting in myocardial infarction
- **I24.1** Dressler syndrome
- **I24.8** Other forms of acute ischaemic heart disease
- **I24.9** Acute ischaemic heart disease, unspecified

I25 Chronic ischaemic heart disease

- **I25.0** Atherosclerotic cardiovascular disease, so described
- **I25.1** Atherosclerotic heart disease
- **I25.2** Old myocardial infarction
- **I25.3** Aneurysm of heart
- **I25.4** Coronary artery aneurysm and dissection
- **I25.5** Ischemic cardiomyopathy

- **I25.6** Silent myocardial ischaemia
- **I25.8** Other forms of chronic ischaemic heart disease
- **I25.9** Chronic ischaemic heart disease, unspecified

3) Heart Failure

I50 Heart failure

- **I50.0** Congestive heart failure
- **I50.1** Left ventricular failure
- **I50.9** Heart failure, unspecified

I51 Complications and ill-defined descriptions of heart disease

- **I51.0** Cardiac septal defect, acquired
- **I51.1** Rupture of chordae tendineae, not elsewhere classified
- **I51.2** Rupture of papillary muscle, not elsewhere classified
- **I51.3** Intracardiac thrombosis, not elsewhere classified
- **I51.4** Myocarditis, unspecified
- **I51.5** Myocardial degeneration

- **I51.6** Cardiovascular disease, unspecified
- **I51.7** Cardiomegaly
- **I51.8** Other ill-defined heart diseases
- **I51.9** Heart disease, unspecified

I42 Cardiomyopathy

- **I42.0** Dilated cardiomyopathy
- **I42.1** Obstructive hypertrophic cardiomyopathy
- **I42.2** Other hypertrophic cardiomyopathy
- **I42.3** Endomyocardial (eosinophilic) disease
- **I42.4** Endocardial fibroelastosis
- **I42.5** Other restrictive cardiomyopathy
- **I42.6** Alcoholic cardiomyopathy
- **I42.7** Cardiomyopathy due to drugs and other external agents
- **I42.8** Other cardiomyopathies
- **I42.9** Cardiomyopathy, unspecified

4) Hypotension

I95 Hypotension

- **I95.0** Idiopathic hypotension
- **I95.1** Orthostatic hypotension

- **I95.2** Hypotension due to drugs
- **I95.8** Other hypotension
- **I95.9** Hypotension, unspecified

5) Pericarditis

I30-I52 Other forms of heart disease

- **I30** Acute pericarditis
  - **I30.0** Acute nonspecific idiopathic pericarditis
  - **I30.1** Infective pericarditis
  - **I30.8** Other forms of acute pericarditis
  - **I30.9** Acute pericarditis, unspecified
- **I31** Other diseases of pericardium
  - **I31.0** Chronic adhesive pericarditis
  - **I31.1** Chronic constrictive pericarditis
  - **I31.2** Haemopericardium, not elsewhere classified
  - **I31.3** Pericardial effusion (noninflammatory)
  - **I31.8** Other specified diseases of pericardium
  - **I31.9** Disease of pericardium, unspecified

6) Cardiac arrhythmia

I44 Atrioventricular and left bundle-branch block

- **I44.0** Atrioventricular block, first degree
- **I44.1** Atrioventricular block, second degree
- **I44.2** Atrioventricular block, complete
- **I44.3** Other and unspecified atrioventricular block
- **I44.4** Left anterior fascicular block
- **I44.5** Left posterior fascicular block
- **I44.6** Other and unspecified fascicular block
- **I44.7** Left bundle-branch block, unspecified

I45 Other conduction disorders

- **I45.0** Right fascicular block
- **I45.1** Other and unspecified right bundle-branch block
- **I45.2** Bifascicular block
- **I45.3** Trifascicular block
- **I45.4** Nonspecific intraventricular block
- **I45.5** Other specified heart block
- **I45.6** Pre-excitation syndrome
- **I45.8** Other specified conduction disorders
- **I45.9** Conduction disorder, unspecified

I46 Cardiac arrest

- **I46.0** Cardiac arrest with successful resuscitation

- **I46.1** Sudden cardiac death, so described
- **I46.9** Cardiac arrest, unspecified

I47 Paroxysmal tachycardia

- **I47.0** Re-entry ventricular arrhythmia
- **I47.1** Supraventricular tachycardia
- **I47.2** Ventricular tachycardia
- **I47.9** Paroxysmal tachycardia, unspecified

I48 Atrial fibrillation and flutter

- **I48.0** Paroxysmal atrial fibrillation
- **I48.1** Persistent atrial fibrillation
- **I48.2** Chronic atrial fibrillation
- **I48.3** Typical atrial flutter
- **I48.4** Atypical atrial flutter
- **I48.9** Atrial fibrillation and atrial flutter, unspecified

I49 Other cardiac arrhythmias

- **I49.0** Ventricular fibrillation and flutter
- **I49.1** Atrial premature depolarization
- **I49.2** Junctional premature depolarization
- **I49.3** Ventricular premature depolarization
- **I49.4** Other and unspecified premature depolarization
- **I49.5** Sick sinus syndrome

- **I49.8** Other specified cardiac arrhythmias
- **I49.9** Cardiac arrhythmia, unspecified

7) Convalescence following ACS

Z54 Convalescence

- **Z54.8** Convalescence following other treatment
- **Z54.9** Convalescence following unspecified treatment

8) Other Forms of Heart Disease

- **I34** Nonrheumatic mitral valve disorders
  - **I34.0** Mitral (valve) insufficiency
  - **I34.1** Mitral (valve) prolapse
  - **I34.2** Nonrheumatic mitral (valve) stenosis
  - **I34.8** Other nonrheumatic mitral valve disorders
  - **I34.9** Nonrheumatic mitral valve disorder, unspecified
- **I35** Nonrheumatic aortic valve disorders
  - **I35.0** Aortic (valve) stenosis
  - **I35.1** Aortic (valve) insufficiency
  - **I35.2** Aortic (valve) stenosis with insufficiency
  - **I35.8** Other aortic valve disorders

- **I35.9** Aortic valve disorder, unspecified

- **I36** Nonrheumatic tricuspid valve disorders
  - **I36.0** Nonrheumatic tricuspid (valve) stenosis
  - **I36.1** Nonrheumatic tricuspid (valve) insufficiency
  - **I36.2** Nonrheumatic tricuspid (valve) stenosis with insufficiency
  - **I36.8** Other nonrheumatic tricuspid valve disorders
  - **I36.9** Nonrheumatic tricuspid valve disorder, unspecified
- **I37** Pulmonary valve disorders
  - **I37.0** Pulmonary valve stenosis
  - **I37.1** Pulmonary valve insufficiency
  - **I37.2** Pulmonary valve stenosis with insufficiency
  - **I37.8** Other pulmonary valve disorders
  - **I37.9** Pulmonary valve disorder, unspecified

9) Cardiac complications after PCI or prior CABG

- **T82** Complications of cardiac and vascular prosthetic devices, implants and grafts

- **T82.2** Mechanical complication of coronary artery bypass and valve grafts
- **T82.3** Mechanical complication of other vascular grafts

- **T82.5** Mechanical complication of other cardiac and vascular devices and implants

- **T82.8** Other specified complications of cardiac and vascular prosthetic devices, implants and grafts
- **T82.9** Unspecified complication of cardiac and vascular prosthetic device, implant and graft

10) Follow up after cardiac care (e.g. follow up at ED rather than GP)

- **Z09** Follow-up examination after treatment for conditions other than malignant neoplasms
  - **Z09.7** Follow-up examination after combined treatment for other conditions
  - **Z09.8** Follow-up examination after other treatment for other conditions
  - **Z09.9** Follow-up examination after unspecified treatment for other conditions

11) Circulatory and Relevant Respiratory signs and symptoms (e.g. cardiac-drug AE)

XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified

R00-R09 Symptoms and signs involving the circulatory and respiratory systems

- **R00** Abnormalities of heart beat
  - **R00.0** Tachycardia, unspecified
  - **R00.1** Bradycardia, unspecified
  - **R00.2** Palpitations
  - **R00.3** Pulseless electrical activity, not elsewhere classified
  - **R00.8** Other and unspecified abnormalities of heart beat
- **R01** Cardiac murmurs and other cardiac sounds
  - **R01.0** Benign and innocent cardiac murmurs
  - **R01.1** Cardiac murmur, unspecified
  - **R01.2** Other cardiac sounds

- **R03** Abnormal blood-pressure reading, without diagnosis
  - **R03.0** Elevated blood-pressure reading, without diagnosis of hypertension
  - **R03.1** Nonspecific low blood-pressure reading

- **R04** Haemorrhage from respiratory passages
  - **R04.0** Epistaxis
  - **R04.1** Haemorrhage from throat
  - **R04.2** Haemoptysis
  - **R04.8** Haemorrhage from other sites in respiratory passages
  - **R04.9** Haemorrhage from respiratory passages, unspecified
- **R05** Cough
- **R06** Abnormalities of breathing
  - **R06.0** Dyspnoea
  - **R06.1** Stridor
  - **R06.2** Wheezing
  - **R06.3** Periodic breathing
  - **R06.4** Hyperventilation
  - **R06.5** Mouth breathing
  - **R06.8** Other and unspecified abnormalities of breathing
- **R07** Pain in throat and chest
  - **R07.0** Pain in throat
  - **R07.1** Chest pain on breathing
  - **R07.2** Precordial pain
  - **R07.3** Other chest pain

- **R07.4** Chest pain, unspecified

- **R42** Dizziness and giddiness

- **R53** Malaise and fatigue

12) Major Bleed (e.g. cardiac-drug AE)

-Intracranial bleed: **I60.0-I60.9, I61.0-I61.6, I61.8, I61.9, I62.0, I62.1, I62.9**

-Gastrointestinal bleed: **I85.0, I98.3, K22.1, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K.28.6, K29.0, K62.5, K66.1, K92.0, K92.1, K92.2**

-Pulmonary bleed: **R040, R041, R042, R048, R049**

-Urologic bleed: **N02.0-N02.9, R31.0, R31.1, R31.8**

-Other bleed: **R58, T810**

References for Supplementary Appendix

1.Hugtenburg JG, Timmers L, Elders PJ, Vervloet M, van Dijk L. Definitions, variants, and causes of nonadherence with medication: a challenge for tailored interventions. *Patient Prefer Adherence.* 2013; 10;7:675-82.