THE IMPACT OF COPAYMENT ELIMINATION AND A NOVEL SELF-MANAGEMENT EDUCATION AND SUPPORT PROGRAM, INCLUDING FACILITATED RELAY, ON ADHERENCE TO STATINS AND ACEI/ARB AMONG LOW INCOME INDIVIDUALS WITH HIGH CARDIOVACULAR RISK: A SECONDARY ANALYSIS FROM THE ACCESS TRIAL

Analytic plan

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Table of Contents

1. List of Abbreviations

ACEi - Angiotensin Convertase Enzyme inhibitors
ANOVA – Analysis of Variance
ASCVD - Atherosclerotic Cardiovascular Disease
ARBs - Angiotensin Receptor Blockers
CKD - Chronic Kidney Disease
REDCap - Research Electronic Data Capture

2. Introduction

Chronic diseases, also known as non-communicable diseases, affect many Canadians. In 2021, 45.1% of Canadians lived with at least one major chronic illness (1). Similarly, almost one-third of Albertans have at least one chronic disease (2). Among people over 65 years old, this percentage increases to more than 75% (2).

Adding to the high prevalence of chronic diseases, their management is a difficult task for both the patients and the providers. This is primarily due to the complexity of the diseases and the lack of integrated multidisciplinary approaches to address multiple issues of social determinants of health that people with chronic diseases face (3,4). Lack of these kinds of support leads to poor medication adherence and low self-efficacy (5). Furthermore, many patients do not receive the necessary medications and lifestyle recommendations that could improve their outcomes.

Studies suggest that medication adherence can be improved with education and by removing financial barriers. A randomized control trial conducted by Taibanguay et al. to enhance adherence in rheumatoid arthritis (RA) patients demonstrated that education substantially increased the pill count adherence rate 12 weeks after the interventions (6). In their study, they applied two interventions: a disease information pamphlet and counseling. In both groups, adherence increased from 92.21±14.05 to 97.59±10.07 in the multi-intervention group and from 88.60±19.66 to 92.42±14.27 in the single-intervention group.

Another randomized control trial that evaluated the impact of the elimination of copayments for drugs prescribed after Myocardial Infarction (MI) demonstrated adherence substantially improved after their intervention (7). The study showed a 6% increased adherence in the full-coverage group compared to the usual-coverage group.

Previously, we conducted the **A**ssessing Outcomes of Enhanced **C**hronic Disease **C**are through Patient **E**ducation and a value-ba**S**ed formulary **S**tudy (ACCESS) trial involving 4761 individuals with low income (8). This Randomized Control Trial applied interventions that address these two barriers in a Canadian context. We used a novel self-management education and self-management support, including facilitated relay of clinical information. Facilitated relay is clinical information transmitted by patients to their providers with the expectation that it will be used to manage their condition (9). We found that eliminating copayments modestly improved adherence to statins and ACEi/ARBs without reduced health care costs or improved clinical outcomes (10). There was a modest increase in adherence among participants who received self-management support and facilitated relay of clinical information, but this group also demonstrated reduced cardiovascular events (11).

3. Rationale

Medication non-adherence leads to poor health outcomes (12). One of the pillars of chronic disease management is improving self-efficacy, a capacity to perform behaviors desirable to improved health (13). Higher self-efficacy positively correlates with improved outcomes and reduced healthcare utilization (14).

Cost-related non-adherence in Canada is much higher than in other countries comparable to Canada (15). Copayments and deductibles associated with medications are some of the main reasons why people do not take their medication as prescribed (16).

With the exception of our findings from the ACCESs trial, there is a paucity of evidence on how interventions, including removing financial barriers, might lead to better adherence to medication among people with chronic illnesses in a Canadian context. Even after our initial study was published question remain regarding the mechanism of action of the changes observed. We seek to understand further how the interventions impacted adherence to statins and ACEi/ARBs by assessing and comparing adherence at specific periods after the interventions and how the interventions may have impacted several patient-reported measures related to medication adherence.

4. Objectives

This secondary outcome analysis aims:

4.1. To determine the effect of two interventions;

(a) Elimination of copayment for selected medications that are proven to prevent adverse outcomes such as stroke, heart attacks, and hospitalizations, and
(b) Comprehensive patient education program targeting lifestyle adjustment and optimal drug use in combination with facilitated relay of information about medication use on patients' beliefs about medication [concerns and needs] and self-efficacy.

4.2. To understand the dynamic changes in medication adherence through time by assessing whether there is a significant difference in adherence at different points during the study period.

5. Methodology

5.1. Trial Design

The trial was designed as a researcher-blinded, parallel, factorial 2x2 pragmatic randomized control trial. Participant blinding was not possible due to the nature of the interventions. The data from the trial will be used to analyze subjects of interest for this secondary outcome analysis paper.

5.2. Interventions

a. Elimination of copayments

We employed a new drug formulary plan that waived the 30% copayment for selected high-value medications. The formulary included statins, beta-blockers, ACE- inhibitors, ARBs, calcium channel blockers, diuretics, anti-platelet agents, anticoagulants, oral hypoglycemics, insulin, and smoking cessation aids.

b. Patient Education

We used a combined facilitated relay of information on patient medication use to their healthcare provider. To increase the prescription of beneficial medications, participants who were not on guideline-recommended medications were given a letter to be given to their usual clinicians.

Educational messages tailored to a specific patient's health information were sent through mail or accessed on a password-protected website portal to which they can log on. Patients' preference was requested before the beginning of the study.

The participants in the **control group** neither received the education messages nor had their copayments eliminated.

5.3. Outcomes

a. Beliefs About Medication Questionnaire (BMQ).

The mean score for BMQ will be calculated for each individual. Then, we will categorize it as 12 or below and over 12. We will also individually calculate the needs and concerns of subscales to localize further where issues arise.

b. Medication Adherence Self-Efficacy Score (MASES)

MASES score will be dichotomized and treated as a binary variable. We couldn't find a categorizing threshold from literatures a priori. Therefore, we will conduct a Receiver Operating Characteristic (ROC) analysis to determine a suitable threshold (17).

c. Medication Adherence (PDC)

Adherence to the high-value cardiovascular medications, including Angiotensin Convertase Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARBs), and statins, will be assessed by calculating the proportion of days covered (calculated using the formula below) (sum of days covered in the period of interest (POI)) ÷ (number of days in the POI) × 100% (18). Those with 80% or greater PDC are considered adherent, and vice versa.

5.4.Data source and collection

Data was collected at baseline, Eighteen months, and end of the study (Thirty-six months). Structured questionnaires were used to collect information about patient-reported outcomes. In addition, the pharmacy information network (PIN) is an objective dataset that will be used to assess medication adherence.

5.5.Randomization

Using a scheme developed within REDCap by the University of Calgary's clinical research unit, randomization was completed using random small (<8) variable permuted blocks. This method will ensure robust allocation concealment. Randomization was stratified based on age (</≥70 years), gender (man/woman), and low household income status (defined by household-size specific Low-Income Cut-offs).

5.6.Sample size

The calculated sample size was 4714, considering the annual 1% migration from Alberta for three years. We estimated the sample size required for Poisson regression analysis and assumed no interaction between our two interventions. The assumption of no interaction was verified by running simulations using 25% and 50% interactions that had negligible effect on the power.

6. Statistical principles

6.1.Confidence interval and P-values

We will calculate all analyses' 95% confidence interval and P-values using the appropriate statistical tests. We will consider findings as significant for P-values of 0.05 or lower.

7. Analysis Methods

7.1.Participant characteristics

We will conduct descriptive analyses to characterize the distribution of the study participants. We will use the mean, median, standard deviation, and interquartile range after the normality test for distribution (histogram and quantile-quantile (QQ) plots). We will also determine the baseline mean scores of the four outcomes in each intervention group.

7.2.Handling missing data

To deal with missing data, we will thoroughly evaluate the dataset to understand the extent and pattern of missingness. We will classify the pattern as either missing at random (MAR) or missing not at random (MNAR).

We will employ multiple imputations or other suitable techniques deemed appropriate for MAR (19). If the pattern is MNAR, then we will test different scenarios of assumptions using sensitivity analyses and report with the limitations.

Finally, to ensure the validity and reliability of our findings, we will conduct sensitivity analyses. The approaches we selected to deal with and the pattern of missing data will be reported in the final manuscript.

7.3. Covariates

Considering randomization was successful, only Age, Sex, and Income status will be used for adjustment because these were the variables upon which the randomization was stratified. The literature also recommends this practice to improve discriminatory power.

7.4.Subgroup analyses

We have specified the subgroups below to conduct analyses with stratifications. We will calculate the effect and confidence interval for each subset. We included subgroup analysis because there may be a subgroup that would benefit more from these interventions.

a. Age: >70 years vs 65-69 years
b. Income group: <30,000 vs >30,000
c. Financial barriers: Present vs Absent
d. Condition type: Diabetes // CKD // ASCVD // Risk factors only
e. Multimorbidity: 1-2 vs 3-4 indicated conditions
f. Primary Care Relational Continuity: Low/Medium vs High
g. Specialist Involvement in the Year Before Randomization: Yes vs No
h. On statin at baseline: Yes vs No
i. On ACE/ARB at baseline: Yes vs No
j. Living environment: supported living vs. Independent living
k. Urban / rural

7.5.Outcome analysis

Tests for Objective #1:

We will conduct log-binomial regression to estimate the effect of the two interventions on belief about medication and medication self-efficacy and needs concern. Similarly, medication adherence will be analyzed using Robust Poisson Regression.

Tests for Objective #2:

We will conduct Factorial ANOVA with or without a posthoc test to assess how medication adherence changes over time.

All analyses will be conducted using the intention to treat principle.

8. **Statistical software**

Data is collected and entered on REDCap, and we will import the data into and conduct the analysis using STATA version 18.

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