EVALUATING ADHERENCE AND HEALTH OUTCOMES AMONG PATIENTS ON CONCOMITANT DIABETES, HYPERTENSION, & HYPERLIPIDEMIA TREATMENTS USING MARGINAL STRUCTURAL MODELING

By

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DEDICATION

To my beloved family who have been my strength, and my greatest support, without whom this journey would have been impossible.

ABSTRACT

Objective: Diabetes, hypertension, and hyperlipidemia have been identified as common modifiable risk factors of CVD, frequently occurring together, especially among the elderly. Medication adherence to concomitant triple therapy is of vital importance among this population. The objective of the current study was to examine adherence to concurrent oral antidiabetics, RAS antagonists, and statins (triple therapy) and evaluate the association between adherence to concomitant triple therapy and intermediate outcomes as well as cardiovascular outcomes among older adults under managed care

Methods: A retrospective cohort study with patients on concurrent triple therapy was conducted using a Texas Medicare Advantage database from January 2016 until December 2019. Medication adherence was measured using PDC during the follow-up periods to determine different adherence groups. A1C, LDL-C control and CV outcomes were also measured every 6 months. A multinomial logistic regression was conducted to determine various demographic and clinical factors associated with each adherence group. Lastly, a marginal structural model controlling for baseline covariates and time-varying confounders affected by prior adherence was conducted to evaluate the association.

Results: For aim 1 the final patient cohort was comprised of 7,847 patients. Of these 68.05% of patients were adherent to triple therapy, 21.43% of patients were adherent to double therapy and 10.51% of patients were adherent to monotherapy/none. Several socio-demographic and clinical predictors were associated with the different adherence groups. For aim 2, patients who were adherent to triple therapy and double therapy were more likely to have their LDL-C as well as A1C

under control as compared to patient's adherent to monotherapy/none. For aim 3, there was no significant associations between adherence to triple/double therapies and cardiovascular outcomes

Conclusion: Adherence to triple therapy among the elderly was sub-optimal. The study demonstrated the beneficial effects of adherence to concurrent oral antidiabetics, statins, and RAS antagonists among older adults in a real-world setting. Future studies should evaluate the association between adherence to triple therapy and CV outcomes using longer follow-up periods.

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1 Executive Summary

1.1 Background

According to CDC, cardiovascular disease (CVD) accounts for over 630,000 deaths and approximately $200 billion total annual costs in the United States. A leading cause of death, every 1 in 4 deaths is associated with CVD in the US.[1] Risk factors for CVD include various conditional and behavioral risks such as hypertension, hyperlipidemia, diabetes, smoking, obesity, and physical inactivity.[1] While the risk factors of CVD are multifactorial, they rarely occur in isolation.[2,3] Studies have reported that patients with more than one risk factor or those who exhibit risk factor clustering have an increased overall risk of CVD mortality, morbidity and medical-care costs.[4-6] Further, the clustering of CVD risk factors is highly prevalent among older adults.[2]

Diabetes, hypertension, and hyperlipidemia have been identified as common modifiable risk factors of cardiovascular disease, frequently occurring together.[1] The prevalence of concomitant hyperlipidemia, diabetes, and hypertension has been reported as 67.5% with higher prevalence reported among older adults.[2,3] Comorbid diabetes, hypertension, and hyperlipidemia is associated with an additive adverse effect on cardiovascular outcomes.[4,5] Management of glycemic control (A1C), blood pressure and low-density lipoprotein cholesterol (LDL-C) is necessary to manage all modifiable risk factors, commonly termed as the ABC (A1C, Blood Pressure, Cholesterol) goals, among these high-risk patients, to further reduce the risk of CVD morbidity and mortality.[6]

1.1.1 Medication Adherence:

Medication adherence defined as the extent to which patients take their medication as recommended by their physician serves as a crucial link between prescribing a medication and treatment success.[7-9] Reported rates of medication adherence vary between 50-60% across various chronic conditions.[10-15] The issue of non-adherence is highly prominent among older adults with a reported 40-86% remaining non-adherent.[7,16] Medication adherence is not only essential to achieve optimal treatment benefits, prevent morbidity, mortality, and reduce healthcare costs[15] but is also essential to the Medicare STAR program to evaluate quality of care for healthcare plans. The Medicare STAR program initiated by the Center for Medicare and Medicaid Services (CMS) provides considerable financial incentives to health plans that perform well on its star metrics.[17,18] Components of the star metrics include measuring adherence to Renin Angiotensin System (RAS) antagonists (antihypertensives), statins (lipid-lowering agents) and antidiabetics to achieve blood pressure control, LDL-C control, and A1C control respectively using Proportion of Days Covered (PDC).[19]

Maintaining adherence among patients with multiple chronic conditions is highly challenging, especially among older adults due to multiple comorbidities, polypharmacy, and cognitive decline.[20,21] Studies evaluating the effects of adherence to concomitant anti-hypertensive and lipid-lowering therapies have reported sub-optimal adherence with rates lower than 50% within one year.[22-24] Prior studies have reported that medication non-adherence is associated with reduced effectiveness of anti-hypertensive, lipid-lowering, and anti-diabetic treatments.[25,26] Further, independent studies have reported that poor adherence to statin monotherapy, oral hypoglycemic monotherapy, and anti-hypertensive monotherapy was associated with reduced LDL-C, A1C, and blood pressure control respectively.[20,27,28] Lastly, Chapman et al reported that adherence to concurrent antihypertensives and statins was associated with a lower risk of CV events.[19] Also, a

meta-analysis of 10 studies investigating the impact of medication adherence to concurrent cardio-protective agents on subsequent CV outcomes reported that optimum adherence to these medications was associated with reduced CV hospitalization and mortality.[20] However, literature investigating adherence to concurrent anti-diabetics, anti-hypertensives, and lipid-lowering therapies and intermediate (A1C and LDL-C) as well as CV outcomes is lacking.

1.1.2 Marginal Structural Modeling

In an observational study, the association between medication adherence and clinical outcomes can be confounded by selection bias which may vary over the follow-up period.[24,25] In this study CV events measured during the study period was considered as a time-dependent confounder affected by prior adherence. Prior CV events were considered as risk factors of subsequent adherence and CV outcomes as well as mediators between prior adherence and final CV outcomes. Further, adherence being a dynamic process may also vary over time, with changes in clinical outcome further affecting future adherence.[24] Marginal Structural Models (MSM) have been proposed to address this issue of time-dependent exposure and time-dependent confounders affected by prior exposure history, to further estimate unbiased causal effects.[26] MSMs produce unbiased estimates based on counterfactual outcomes using inverse-probability-of-treatment weights (IPTW). The weights create a pseudo population where exposure is no longer confounded producing causal estimates of the association between adherence and clinical outcomes.[26,27]

1.2 Objectives

Aim 1a: To examine adherence to concomitant oral antidiabetics, RAS antagonists, and statins (triple therapy) among older adults enrolled in a Medicare Advantage Plan (MAP).

Aim 1b: To evaluate predictors of adherence to concomitant triple therapy among older adults enrolled in a MAP.

Hypothesis: Adherence to concomitant therapy will be significantly associated with socio-demographic and clinical characteristics among older adults enrolled in a MAP.

Aim 2a: To examine the association between adherence to concomitant triple therapy and LDL-C among older adults enrolled in a MAP.

Hypothesis: Adherence to concomitant triple therapy will be significantly associated with LDL-C control among older adults enrolled in a MAP.

Aim 2b: To examine the association between adherence to concomitant triple therapy and A1C among elderly patients enrolled in a MAP.

Hypothesis: Adherence to concomitant triple therapy will be significantly associated with A1C control among older adults enrolled in a MAP.

Aim 3a: To examine the association between adherence to concomitant triple therapy and cardiovascular (CV) outcomes among older adults enrolled in a MAP.

Hypothesis: Adherence to concomitant triple therapy will be significantly associated with CV outcomes among older adults enrolled in a MAP.

Aim 3b: To examine the association between adherence to concomitant triple therapy and CV outcomes among older adults with prior CV events enrolled in a MAP.

Hypothesis: Adherence to concomitant triple therapy will be significantly associated with CV outcomes among older adults with prior CV events enrolled in a MAP.

1.3 Main findings

The final patient cohort comprised of 7,847 patients for aim 1. Of these 68.05% of patients were adherent to triple therapy, 21.43% of patients were adherent to double therapy and 10.51% of patients were adherent to monotherapy/none. Females had a higher likelihood of being in the triple therapy non-adherent groups while a refill of 90 days or more and prevalent use of triple therapy was associated with a lower likelihood of being in the triple therapy non-adherent groups. Elderly patients aged 65 or older were less likely to be in the adherent to monotherapy/none group. Patients who had more than one hospitalization were more likely to be in the adherent to monotherapy/none group as compared to the triple therapy adherent group. Lastly, patients with a higher number of total other medications were less likely to be in the adherent to monotherapy/none group as compared to the triple therapy adherent group.

For aim 2, the LDL-C cohort comprised of 4,803 patients on triple therapy while the A1C cohort comprised of 5,314 patients on triple therapy. Patients who were adherent to triple therapy and double therapy were more likely to have their LDL-C as well as A1C in control as compared to patient's adherent to monotherapy/none.

The final patient cohort comprised of 7,433 patients for aim 3. The MSM model revealed that there were no significant associations between adherence to triple/double therapies and cardiovascular outcomes. There were 471 patients with a prior CV event identified for the sub-analysis. Results of the sub-analysis MSM model revealed that there were no significant associations between adherence to triple/double therapies and CV outcomes among patients with prior CV events.

1.4 Summary

The study demonstrated that adherence to triple therapy among older adults was suboptimal. Given the greater risk of CVD among this population the results are excessively concerning. Several socio-demographic and clinical predictors were associated with adherence to triple therapy. Further, the study demonstrated that patients adherent to concurrent triple or double therapy were more likely to have A1C and LDL-C control as compared to patients adherent to monotherapy/none. Lastly, the study did not reveal any significant association between adherence to triple or double therapy and CV outcomes. Also, the sub-analysis conducted among patients with prior CV events did not reveal any significant association between adherence to triple or double therapy and CV outcomes. Implications of this study can help decision-makers and clinicians treating comorbid diabetes, hypertension, and hyperlipidemia identify patients at a higher risk of non-adherence early on to further improve adherence and CVD outcomes. Also, the results indicate the beneficial effects of medication adherence in controlling CVD risk factors among high-risk older adults and indicate that the ABC goals outlined by the ADA can be achieved if medication adherence is optimal.

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2 Manuscript 1

Title: Examining Adherence to Concomitant Diabetes, Hypertension, and Hyperlipidemia Treatments Among Older Adults Enrolled in a Medicare Advantage Plan

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2.1 Abstract:

Objective: Diabetes, hypertension, and hyperlipidemia have been identified as common modifiable risk factors of CVD, frequently occurring together, especially among the elderly. Medication adherence to concomitant triple therapy is of vital importance among this population. The objective of the current study was to examine adherence to concurrent oral antidiabetics, RAS antagonists, and statins (triple therapy) among older adults under managed care and further evaluate the predictors associated with concurrent triple therapy among older adults.

Methods: Patients on concurrent triple therapy were identified between July 2016 and December 2016 using a Texas Medicare Advantage dataset. Patients had to have an overlap of 30 days and a second prescription of each component of triple therapy within the identification period. Medication adherence was measured using PDC during the one-year follow-up period to determine different adherence groups. Patients were defined as adherent if they had ≥ 80% of days covered for all three therapies. A multinomial logistic regression was further conducted to determine various demographic and clinical factors associated with each adherence group.

Results: The final patient cohort was comprised of 7,847 patients. Of these 68.05% of patients were adherent to triple therapy, 21.43% of patients were adherent to double therapy and 10.51% of patients were adherent to monotherapy/none. Compared to the triple therapy adherent group, females had a higher likelihood of being in the triple therapy non-adherent groups while a refill of 90 days or more and prevalent use of triple therapy was associated with a lower likelihood of being in the triple therapy non-adherent groups. Lastly, predictors associated with the adherent to monotherapy/none group included age and total number of other medications.

Conclusion: Adherence to triple therapy among the elderly was sub-optimal. The demographic and clinical factors can help identify patients at a higher risk of non-adherence and intervene early on to improve adherence and outcomes.

2.2 Introduction

According to CDC, cardiovascular disease (CVD) accounts for over 630,000 deaths and approximately $200 billion total annual costs in the United States. A leading cause of death, every 1 in 4 deaths is associated with CVD in the US.[1] Risk factors for CVD include various conditional and behavioral risks such as hypertension, hyperlipidemia, diabetes, smoking, obesity, and physical inactivity.[1] While the risk factors of CVD are multifactorial, they rarely occur in isolation.[2,3] Studies have reported that patients with more than one risk factor or those who exhibit risk factor clustering have an increased overall risk of CVD mortality, morbidity and medical-care costs.[4-6] Further, the clustering of CVD risk factors is highly prevalent among older adults.[2]

Diabetes, hypertension, and hyperlipidemia have been identified as common modifiable risk factors of CVD, frequently occurring together.[7] Iglay et al reported the prevalence of concurrent diabetes, hypertension, and hyperlipidemia as 67.5%.[8] Further, older adults reported a higher

prevalence of these risk factors.[9] Comorbid diabetes, hypertension, and hyperlipidemia is associated with an additive adverse effect on CVD outcomes.[2,10] Thus, an aggressive, multifactorial risk factor modification addressing concurrent diabetes, hyperlipidemia, and hypertension is essential and of vital importance.[11] Adequate glycemic control as well as simultaneous management of blood pressure and low-density lipoprotein cholesterol (LDL-C) is necessary to manage all modifiable risk factors, commonly termed as the ABC goals, to further reduce the risk of CVD mortality and morbidity. A pooled analysis of the Multi-Ethnic Study of Atherosclerosis, Atherosclerosis Risk in Communities Study, and Jackson Heart Study demonstrated that diabetic patients who had an optimal blood pressure, target glycated hemoglobin (A1C), and LDL-C levels had a substantially lower risk of CVD and coronary heart disease.[12] However, several independent studies have reported that only a minority of patients with comorbid diabetes, hypertension, and hyperlipidemia achieve their target A1C, BP and lipid levels.[13-15]

Medication adherence defined as the extent to which patients take their medication as recommended by their physician, serves as a crucial link between prescribing a medication and treatment success.[16-18] Reported rates of adherence however vary between 50-60%, across a wide range of chronic conditions.[19-24] Consequences of poor medication adherence include increased health care utilization, worse health outcomes, and costs, leading to an approximated $68-105 billion avoidable healthcare costs per year in the US.[19,22,25] Among older adults, the issue of non-adherence is highly prominent with a reported 40-86% remaining non-adherent.[16,18,26] Plausible reasons include a higher medication burden and age-related cognitive decline.[17,27] The Medicare STAR program initiated by the Center for Medicare and Medicaid Services (CMS) uses an adherence metric to evaluate quality of care for healthcare plans. It provides considerable financial incentives to health plans that perform well on its Medicare STAR metrics.[28,29] Components of the

star metrics include measuring adherence to RAS antagonists (antihypertensives), statins (lipid-lowering agents) and antidiabetics for prevention of cardiovascular events using Proportion of Days Covered (PDC).[30]

Poor medication adherence has been identified as a key contributor in failure to achieve simultaneous A1C, BP and lipid levels.[13] Chapman et al reported that adherence to concurrent antihypertensive and lipid lowering therapy in older adults declined with time, with only 35.2% of patients remaining adherent at 36 months.[31] While there exists a plethora of literature assessing adherence to monotherapies, there is a dearth of literature evaluating adherence to concurrent antidiabetic, antihypertensive, and lipid lowering therapy (concurrent triple therapy) among older adults in a real-world setting. Thus, the objective of the current study was to evaluate adherence to concomitant oral antidiabetics, statins, and RAS antagonists among elderly patients enrolled in a Medicare Advantage Plan (MAP). The study evaluates components of the STAR metrics. Further it also aims to evaluate the predictors of concurrent triple therapy among older adults.

2.3 Methods

Study Design:

The study entails a longitudinal, retrospective cohort design using a Texas Medicare Advantage database from January 2016 until December 2017. The identification period was defined between July 1st, 2016 and December 31st, 2016. The baseline period was defined between January 1st, 2016 and June 30th, 2016, six months prior to the index date. The follow-up period was defined between January 1st, 2017 and December 31st, 2017, starting from the index-date. The study design is illustrated in Figure 1.

The study was approved by the institutional review board at the University of Houston.

Study Files:

The database contained multiple data files including member summary, institutional claims, professional claims, and pharmacy files. The member summary files include demographics, and CMS risk scores (severity scores). Institutional and professional claims include all inpatient and outpatient encounters respectively, as well as diagnostic information in the form of International Classification of Diseases, Tenth Revision (ICD-10) codes, date of admission and date of discharge. The pharmacy files include information on patient drug prescriptions, fill dates, days of supply, quantity dispensed, and dosing information of each prescription claimed.

Study Population:

Components of triple therapy: The study population included patients on concurrent triple therapy. Triple therapy was defined as components of the star metrics including RAS antagonists (antihypertensives), oral antidiabetics, and statins. Oral antidiabetic classes included biguanides, DPP-4 inhibitors, meglitinides, SGL2-inhibitors, sulfonylureas, and thiazolidinediones. RAS antagonist classes included Angiotensin Converting Enzyme Inhibitors (ACEs), Angiotensin Receptor Blockers (ARBs), and Direct Renin Inhibitors (DRIs).

Concurrent Triple Therapy: Concurrent triple therapy was defined as patients with at least one prescription of oral antidiabetics, statins, and RAS antagonists during the identification period (June 2016- December 2016). Further patients needed to have an overlap of at least one month of triple therapy with the first date of overlap defined as the index date.[32] Lastly continuation of triple therapy was indicated by a second prescription of each component of triple therapy after the index date.[33,34]

Inclusion Criteria: Patients were included in the study if they 1) had continuous enrollment over the study period from January 2016 until December 2017 2) were identified as concurrent triple therapy users during the identification period.

Exclusion criteria: Patients were excluded if they had a 1) diagnosis of dementia in the 6-month baseline period. 2) ACEI/ARB or statin contraindication like angioedema, hyperkalemia, renal artery stenosis as well as myopathy in the 6-month baseline period. 3) prescription of insulin throughout the study period. Patients on insulin were excluded as these patients might have uncontrolled A1Cs and were likely to be transitioning of oral anti-diabetic medications.

Adherence Measurement:

Medication adherence was measured using PDC during the 12-month follow-up period starting from the index date. The PDC was calculated as the total number of days on which medication was available (total days supplied) divided by the total number of days in the analysis period (12 months).[32]

Medication adherence was first calculated separately for each component of triple therapy and patients were considered adherent to monotherapy on a given day if any oral antidiabetic, any statin, and any RAS antagonist was available on that day.[31,35]

Patients were then considered adherent to concurrent triple therapy if they had 80% or more days covered for any oral antidiabetic, and any statin, and any RAS antagonist during the follow-up period.[31] Patients were further categorized as adherent to double therapy (Statin-RAS antagonists/statin-oral antidiabetics/ RAS antagonist- oral antidiabetics) and lastly adherent to monotherapy/none. The 80% cut off is used for measuring medication adherence in the Medicare

Star Ratings program, Centers of Medicare and Medicaid (CMS) quality measures and the National Committee for Quality Assurance.[20]

Conceptual Framework:

Variable selection was guided by the Andersen Behavioral Model for healthcare resource use behavior including predisposing, enabling and need factors as determined during the identification or the baseline period.

Predisposing factors included age (<65 years, 65-69 years, 70-74 years, ≥75 years), sex (male versus female), total number of other medications calculated during the identification period, and regimen complexity. Regimen complexity was defined as the mean doses taken per day multiplied by total number of medications determined during the identification period.[36,37]

Enabling factors included health plan (low income subsidy versus no subsidy).

Need factors included comorbidities such as depression, and end stage renal disease (ESRD), prior hospitalizations (none versus one or more than one), type of refill (≥90 days for all therapies versus not), prior history of CV events such as Myocardial Infarction (MI), angina, stroke, atherosclerosis, acute and chronic ischemic heart disease, prevalent users of triple therapy, and CMS risk score which accounts for medication burden and disease severity. The comorbidities, previous hospitalization, prevalent users of triple therapy, and prior history of CV events were determined during the baseline period.

Statistical Analysis:

Descriptive statistics were conducted to describe patient characteristics between different adherent groups using chi-square/fishers exact test for categorical variables and ANOVA for continuous variables.

To determine predictors associated with each adherence group, a multinomial logistic regression was conducted. The dependent variable was the different adherence groups. The predictors include those previously defined as *predisposing factors*: age, sex, regimen complexity, prevalent users, and number of other medications used, *enabling factors:* health plan, prescriber specialty and *need factors:* comorbidities, previous hospitalization, CMS risk score, type of refill and prior history of CV events. A correlation and interaction assessment were conducted among the major predictor variables. The correlation assessment was conducted by exploring the correlation matrix as well as the Variance Inflation Factor (VIF).

SAS version 9.4 (SAS Institute, Cary, NC) was used for statistical analysis at a 0.05 significance level.

Sub-Analysis:

A multinomial logistic regression to determine predictors associated with each adherence group was conducted among patients with a 90 days supply for all three therapies. The predictors and the dependent variable were similar to the main analysis.

2.4 Results

Study Cohort:

There were 13,394 patients identified with one prescription of triple therapy. After applying criteria for concurrent therapy 10,716 patients were identified on concomitant oral antidiabetics,

statins, and RAS antagonists. Further 10,242 patients were continuously enrolled throughout the study period. After applying exclusion criteria, the final cohort comprised of 7,847 patients on triple therapy as illustrated in Figure 2.

The patient characteristics are presented in Table 1. 52.49% of the patients were females and 35.01% were between the age of 65 and 69 years. Results of the correlation matrix revealed that all correlations were below 0.35, and the VIF below 1.5, indicating a lack of multicollinearity. Further, there were no significant interactions among the major predictor variables.

Adherence Groups & Multinomial Regression:

The study cohort comprised of 68.05% patient's adherent to triple therapy, 21.43% of patient's adherent to double therapy and 10.51% of patient's adherent to monotherapy/none. Individual adherence to statins, RAS antagonists, and oral anti-diabetics was above 80%. Results of the bivariate analysis are presented in Table 1. More elderly patients aged between 70-74 were adherent to triple therapy as compared to the other groups. More prevalent users of triple therapy were in the triple therapy adherent group as compared to other groups. Patients in the adherent to monotherapy/none group had on average the least number of other medications during the index period.

Results of the multinomial regression are presented in Table 2. Females had a higher likelihood of being in the triple therapy non-adherent groups as compared to the triple therapy adherent group (Adherent to Monotherapy/None, OR:1.25, 95% CI: 1.07-1.46; Adherent to Double Therapy, 1.16, 95% CI:1.03-1.30). Further, patients who had a refill of 90 days or more for all their triple therapies had a lower likelihood of being in the triple therapy non-adherent groups as compared to the triple therapy adherent group (Adherent to Monotherapy/None, OR:0.47, 95% CI: 0.39-0.57; Adherent

to Double Therapy, 0.60, 95% CI:0.52-0.71). Lastly, prevalent users of triple therapy were less likely to fall in the triple therapy non-adherent groups as compared to the triple therapy adherent group (Adherent to Monotherapy/None, OR:0.28, 95% CI: 0.23-0.33; Adherent to Double Therapy, 0.40, 95% CI:0.34-0.46).

Elderly patients aged 65 or older were less likely to be in the adherent to monotherapy/none group as compared to the triple therapy adherent group (65-69 years vs <65 years, OR: 0.62, 95% CI: 0.49-0.79; 70-74 years vs <65 years, OR: 0.59, 95% CI: 0.46-0.75, ≥75 years vs <65 years, OR: 0.72, 95% CI: 0.56-0.91). Patients who had more than one hospitalization were more likely to be in the adherent to monotherapy/none group as compared to the triple therapy adherent group (OR:1.51, 95% CI: 1.04-2.19). Lastly, patients with a higher number of total other medications were less likely to be in the adherent to monotherapy/none group as compared to the triple therapy adherent group (OR:0.96, 95% CI: 0.94-0.98).

Sub-Analysis:

There were 6,768 patients identified with a 90-days refill for all three therapies. The results of the sub-analysis were similar to the main analysis and are presented in Table 3. Among patients with a 90-days refill for all three therapies, females had a higher likelihood of being in the triple therapy non-adherent groups as compared to the triple therapy adherent group. Similarly, patients with one or more hospitalization were more likely to be in the adherent to monotherapy/none group as compared to the triple therapy adherent group.

Prevalent users of triple therapy were less likely to fall in the triple therapy non-adherent groups as compared to the triple therapy adherent group. Elderly patients aged 65 or older, and patients

with a higher number of total other medications were less likely to be in the adherent to monotherapy/none group as compared to the triple therapy adherent group.

2.5 Discussion

The current study, to our knowledge, is the first to investigate adherence behavior to concomitant oral antidiabetics, statins, and RAS antagonists among older adults enrolled in a Medicare Advantage Plan (MAP). The study findings revealed that adherence to triple therapy was sub-optimal among this high-risk elderly population. Further, several demographic and clinical characteristics were associated with each adherence group.

The Medicare STAR program reports adherence to RAS antagonist, oral antidiabetic, and statin monotherapies as a measure of a health plan. Heavy weights are placed on adherence ratings of each therapy signifying a greater emphasis in achieving these targets.[38] With a growing evidence of co-existing diabetes, hypertension, and hyperlipidemia among the elderly, it is essential to measure and report adherence to concurrent triple therapy rather than monotherapy since patients might be adherent to one therapy but non-adherent to another, thereby underestimating medication non-adherence. As exemplified from the current study, adherence to each monotherapy was adequate, however, adherence to concurrent triple therapy decreased significantly. Resources devoted towards building comprehensive adherence strategies targeted essentially towards improving concurrent triple therapy among older adults, should be encouraged in the future.

Prior studies have reported sub-optimal adherence to concurrent anti-hypertensive and lipid-lowering therapies ranging between 32-36%.[31,39,40] Similarly, a study conducted among patients on concurrent oral antidiabetic and hypertension medications reported a mean PDC of 0.53 for both therapies.[41] Lombardi et al evaluated adherence to concurrent cardiovascular medications

namely concurrent ACEIs, calcium-channel blockers (CCB) and statins as well as concurrent ACEIs, CCBs, and aspirin. The study reported an adherence rate of 47.9% and 49.4% respectively for patients on the above concurrent triple therapy combinations.[42] While the current study findings revealed that adherence to concurrent triple therapy was sub-optimal with only 68.17% of patients having a PDC of ≥0.8 for all three therapies, the adherence rate was considerably higher than the prior reported studies measuring adherence to various concurrent therapies. Plausible reasons could include different definitions of adherence, different definitions of concurrent therapy, a variable patient population, as well as effective interventions implemented by MAP to improve star ratings.

Evaluating various demographic and clinical characteristics associated with each group can help identify patients at a higher risk of non-adherence to concomitant triple therapy. This can further provide valuable insight to guide development of future interventions to enhance adherence and improve CVD outcomes among this high-risk elderly population. The current study identified several patient characteristics associated with each adherence group including sex, refill type, prevalent use, age, number of prior hospitalizations, and number of other medications.

Findings from the current study reveal that females had a higher likelihood of being in the triple therapy non-adherent groups as compared to the triple therapy adherent group. These results are validated by a prior study which demonstrated that males were 14-27% more likely to be adherent to concurrent triple therapy than females.[42] Further a meta-analysis reported that females were 10% more likely to be non-adherent than males to their CV medications.[43] Lastly, studies have reported that lipophilic statins were associated with increased muscle symptoms among elderly women and 70% of females in this patient cohort were on lipophilic statins.[44] This might plausibly explain their increased non-adherence to triple therapy and indicate a greater need for health plans

to preferentially select less lipophilic statins to reduce adverse effects and improve adherence. Elderly patients who had a refill of 90 days or more for all their triple therapies had a lower likelihood of being in the triple therapy non-adherent groups as compared to the triple therapy adherent group. These findings are validated by a study conducted by Schmittdiel et al who evaluated the association between various system-level predictors and Medicare STAR adherence components individually and reported that a medication day's supply > 90 days for antihypertensives, statins, and oral hypoglycemic was strongly associated with medication adherence.[30] Plausible reasons could include increased access to medications[30] and reduced dispensing costs.[44] Lastly, prevalent users of triple therapy were less likely to fall in the triple therapy non-adherent groups as compared to the triple therapy adherent group. Barriers to adherence among new users could include lack of acceptance of a chronic disease[45] and could potentially be categorized as a modifiable factor, reflecting the urgency to monitor adherence among new diagnosed chronic illness users. Future studies are needed to understand the potential reasons of non-adherence to one or two therapies in the triple regimen.

Increasing age was associated with increased adherence to triple therapy among older adults Patients aged 65 or older were less likely to be in the adherent to monotherapy/none group as compared to the triple therapy adherent group. The study findings are consistent with prior literature reporting a positive association between medication adherence and increasing age (Paranjpe et al). Improved awareness of their health, an increased perceived risk of chronic illness due to an increased disease burden among older adults could lead to the higher adherence observed.[46,47] Similarly, patients who had more than one hospitalization were more likely to be in the adherent to monotherapy/none group as compared to the triple therapy adherent group. Implications of these findings indicate a greater need to monitor adherence among the elderly

during prior hospitalizations to further prevent future hospitalizations. Lastly patients with a higher number of total other medications were more likely to be adherent to the triple therapy group. Prior studies have reported mixed findings regarding the association between polypharmacy and medication adherence.[31,35,45] While patients with an increased pill burden might have a perceived higher need and improved medication taking behavior, they may also find it difficult to adhere to more medications due to an increased pill burden.[21]

2.6 Limitations

Adherence calculated through medication refills in a claims-based analysis might not truly indicate whether the patient actually took the prescription. However, prior studies have demonstrated the use of refill date to measure medication adherence and clinical outcomes.[17,48] Unmeasured confounders like education, race, and marital status might lead to some residual confounding. Since the study considered a patient adherent on a given day if any one oral antidiabetic, and any one statin, and any one RAS antagonists was available on that day, the study might have overestimated adherence to patients taking multiple drug regimens for each therapy. Also, patients with 90-day refills were assumed to have a 90 days continuous medication use without gaps which might overestimate adherence in comparison to those patients with a 30-day refill. However, results of the sub-analysis conducted only among patients with a 90-days refill reported similar predictors as the main analysis. Lastly the generalizability of the study might be limited to similar demographic populations since the study was conducted among a Texas Medicare Advantage population.

2.7 Conclusion

The study demonstrated that adherence to triple therapy among older adults was suboptimal. Given the greater risk of CVD among this population the results are excessively concerning. Several socio-demographic and clinical predictors were associated with adherence to triple therapy. Implications of this study can help decision-makers and clinicians treating comorbid diabetes, hypertension, and hyperlipidemia identify patients at a higher risk of non-adherence early on to further improve adherence and CVD outcomes.

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2.9 Figures and tables

Figure 1: Study Design

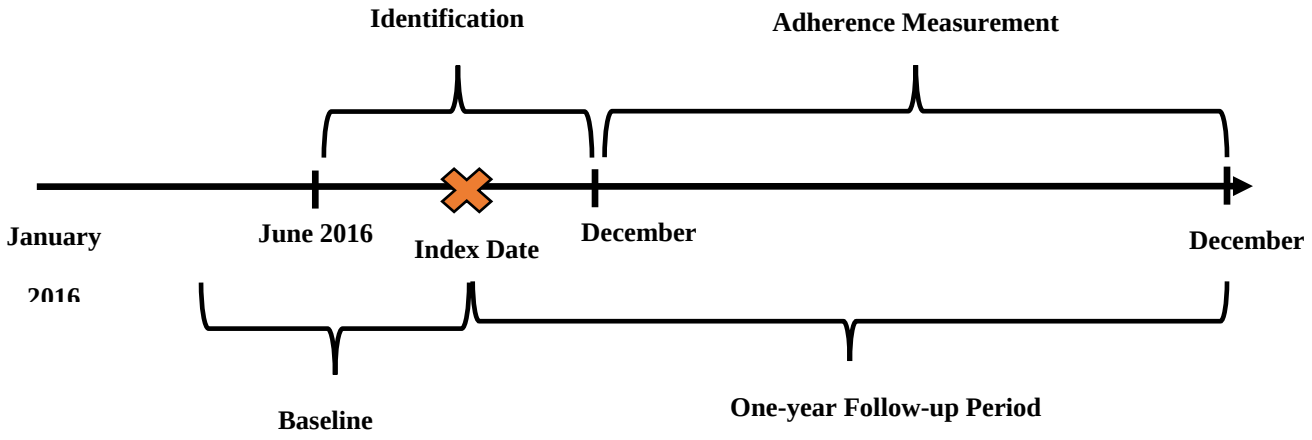

Figure 2: Patient Cohort Formation

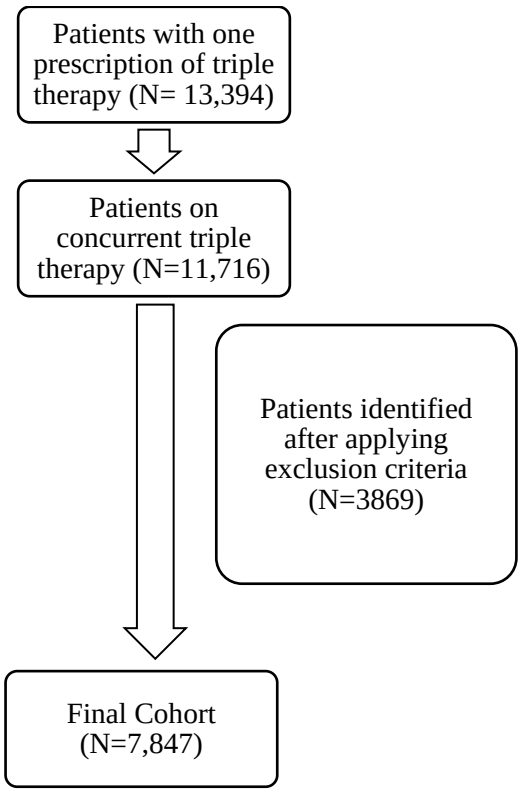

Table 1: Patient Demographics and Clinical Characteristics (N=7,847)

Variables	**Total Patients (%) N=7,847**	**Adherent to Monotherapy/ None (%) N= 825**	**Adherent to Double Therapy (%) N= 1682**	**Adherent to Triple Therapy (%) N= 5340**	**P-Value**
Sex					
Male	3728 (47.51)	375 (45.45)	759 (45.12)	2594 (48.58)	0.02*
Female	4119 (52.49)	450 (54.55)	923 (54.88)	2746 (51.42)	
Age					
<65 Years	1021 (13.01)	142 (17.21)	211 (12.54)	668 (12.51)	0.0008*
65-69 Years	2747 (35.01)	270 (32.73)	627 (37.28)	1850 (34.64)	
70-74 Years	2127 (27.11)	196 (23.76)	437 (25.98)	1494 (27.98)	
≥75 Years	1952 (24.88)	217 (26.30)	407 (24.20)	1328 (24.87)	
Health Plan					
No Subsidy	4153 (52.92)	460 (55.76)	894 (53.15)	2799 (52.42)	0.19
Low-Income Subsidy	3694 (47.08)	365 (44.24)	788(46.85)	2541 (47.58)	
Number of Prior Hospitalizations					
0	7560 (96.34)	780 (94.55)	1617 (96.02)	5165 (96.72)	0.0059*
≥1	287 (3.66)	45 (5.45)	67 (3.98)	175 (3.28)	
Depression					

No	7826 (99.73)	821 (99.52)	1683 (99.94)	5337 (99.85)	0.043
Yes	21 (0.27)	6 (0.73)	4 (0.24)	11 (0.21)	
90-Day Refill					
≥ 90 Days Supply for All/One/Two Therapies	1079 (13.75)	183 (22.18)	296 (17.60)	600 (11.24)	<0.0001*
All Three Therapies have 90 Day Supply	6768 (86.25)	642 (77.82)	1386 (82.40)	4740 (88.76)	
Prevalent Users of Triple Therapy					
No	1126 (14.35)	236 (28.61)	361 (21.46)	529 (9.91)	<0.0001*
Yes	6721 (85.65)	589 (71.39)	1321 (78.54)	4811 (90.09)	
CV Events					
No	7560 (96.34)	784 (95.03)	1619 (96.25)	5157 (96.57)	0.08
Yes	287 (3.66)	41 (4.97)	63 (3.75)	183 (3.43)	
CMS Risk Score Mean (SD)	1.29 (0.77)	1.27 (0.8)	1.32 (0.80)	1.29 (0.76)	0.27
Total Number of Other Medications Mean (SD)	6.53 (4.21)	6.13 (4.15)	6.77 (4.44)	6.52 (4.14)	0.0015*
Regimen Complexity Mean (SD)	21.12 (38.80)	20.82 (39.73)	22.74 (41.90)	20.65 (37.62)	0.15

***Significant P values from chi-square and anova<0.05; CMS: Centers for Medicare and Medicaid; SD: Standard Deviation.**

Table 2: Multinomial Logistic Regression to Assess Predictors Associated with Adherence Group (N=7,847).

	Adherent to Monotherapy/None vs Adherent to Triple Therapy		Adherent to Double Therapy vs Adherent to Triple Therapy	
Variables	**OR (95% CI)**	**P-Value**	**OR (95% CI)**	**P-Value**
Sex				
Female vs Male	1.25 (1.07-1.46)	0.004*	1.16 (1.03-1.30)	0.009*
Age				
65-69 Years vs <65 Years	0.62 (0.49-0.79)	<0.0001*	1.11 (0.92-1.34)	0.26
70-74 Years vs <65 Years	0.59 (0.46-0.75)	<0.0001*	0.96 (0.79-1.16)	0.69
≥75 Years vs <65 Years	0.72 (0.56-0.91)	0.008*	0.96 (0.79-1.18)	0.75
Health Plan				
Low-Income Subsidy vs No Subsidy	0.86 (0.73-1.00)	0.06	0.95 (0.85-1.07)	0.42
Number of Prior Hospitalizations				
≥1 vs 0	1.51 (1.04-2.19)	0.02*	1.09 (0.81-1.49)	0.54
Depression				

Yes vs No	3.18 (1.10-9.13)	0.03*	0.97 (0.30-3.12)	0.97
90-Day Refill				
Three Therapies have 90 Day Supply vs Not	0.47 (0.39-0.57)	<0.0001*	0.60 (0.52-0.71)	<0.0001*
Prevalent Users of Triple Therapy				
Yes vs No	0.28 (0.23-0.33)	<0.0001*	0.40 (0.34-0.46)	<0.0001*
CV Events				
Yes vs No	1.21 (0.83-1.77)	0.31	0.94 (0.69-1.28)	0.7
CMS Risk Score Mean (SD)	1.02 (0.92-1.13)	0.66	1.07 (0.99-1.15)	0.08
Total Number of Other Medications Mean (SD)	0.96 (0.94-0.98)	0.0001*	1.006 (0.99-1.02)	0.42
Regimen Complexity Mean (SD)	1.00 (0.99-1.003)	0.38	1.00 (1.00-1.002)	0.17

***Significant P<0.05; CI: confidence interval; OR: odds ratio.**

Table 3: Multinomial Logistic Regression to Assess Predictors Associated with Adherence Group Among Patients with a 90-Days Refill for All Therapies (N=6,768).

	Non-Adherent to Monotherapy/None vs Adherent to Triple Therapy		**Adherent to Double Therapy vs Adherent to Triple Therapy**	
Variables	**OR (95% CI)**	P-Value	**OR (95% CI)**	**P-Value**
Sex				

Female vs Male	1.25 (1.05-1.49)	0.004*	1.16 (1.03-1.32)	0.009*
Age				
65-69 Years vs <65 Years	0.65 (0.5-0.84)	0.0013*	1.17 (0.95-1.44)	0.13
70-74 Years vs <65 Years	0.57 (0.43-0.75)	<0.0001*	1.00 (0.81-1.25)	0.93
≥75 Years vs <65 Years	0.71 (0.54-0.93)	0.01*	1.02 (0.82-1.27)	0.83
Health Plan				
Low-Income Subsidy vs No Subsidy	0.89 (0.75-1.06)	0.21	0.97 (0.85-1.10)	0.67
Number of Prior Hospitalizations				
≥1 vs 0	1.68 (1.09-2.59)	0.01*	1.09 (0.77-1.55)	0.61
Depression				
Yes vs No	2.55 (0.72-9.04)	0.14	0.29 (0.03-2.30)	0.24
Prevalent Users of Triple Therapy				
Yes vs No	0.26 (0.22-0.32)	<0.0001*	0.39 (0.33-0.46)	<0.0001*
CV Events				
Yes vs No	0.95 (0.57-1.59)	0.85	1.04 (0.72-1.50)	0.81
CMS Risk Score Mean (SD)	1.01 (0.89-1.14)	0.85	1.06 (0.97-1.15)	0.14
Total Number of Other Medications Mean (SD)	0.96 (0.94-0.98)	0.003*	1.008 (0.99-1.02)	0.29
Regimen Complexity Mean (SD)	1.00 (0.99-1.003)	0.85	1.001 (1.00-1.003)	0.12

***Significant P<0.05; CI: confidence interval; OR: odds ratio.**

3 Manuscript 2

Title: Evaluating Adherence to Concomitant Diabetes, Hypertension, and Hyperlipidemia Treatments and Intermediate Outcomes Among Older Adults Using Marginal Structural Modeling.

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3.1 Abstract

Objective: Management of glycemic control (A1C), blood pressure and low-density lipoprotein cholesterol (LDL-C) is necessary to manage comorbid diabetes, hypertension, and hyperlipidemia to further reduce the risk of cardiovascular morbidity and mortality among the older adults. Medication adherence to concomitant oral antidiabetics, Renin Angiotensin System (RAS) Antagonists, and statins (triple therapy) is of vital importance to achieve optimal treatment benefits among this high-risk population. The objective of the current study was to evaluate the association between adherence to concomitant triple therapy and A1C as well as LDL-C, among older adults enrolled in a Medicare Advantage Plan (MAP) using marginal structural modeling.

Methods: A retrospective cohort study with patients on concurrent triple therapy was conducted using a Texas Medicare Advantage database from January 2016 until December 2019. Medication adherence to concurrent triple therapy was measured every 6 months using Proportion of Days Covered to determine the different adherence groups. A1C and LDL-C control was also measured every 6 months. A marginal structural model controlling for baseline covariates and time-varying confounders affected by prior adherence was conducted to evaluate the association.

Results: The LDL-C cohort was comprised of 4,803 patients on triple therapy while the A1C cohort was comprised of 5,314 patients on triple therapy. Patients who were adherent to triple therapy (OR:1.42, 95% CI: 1.24-1.62) and adherent to double therapy (OR:1.84, 95% CI: 1.62-2.10) were more likely to have their LDL-C in control as compared to patient's adherent to monotherapy/none. Similarly, patients who were adherent to triple therapy (OR:1.30, 95% CI: 1.11-1.52) and adherent to double therapy (OR:1.32, 95% CI: 1.12-1.55) were more likely to have their A1C in control as compared to patient's adherent to monotherapy/none.

Conclusion: The current study demonstrated the beneficial effects of adherence to concurrent oral antidiabetics, statins, and RAS antagonists among older adults in a real-world setting.

3.2 Background

Diabetes, hypertension, and hyperlipidemia have been identified as common modifiable risk factors of cardiovascular disease (CVD), frequently occurring together.[1] The prevalence of concomitant hyperlipidemia, diabetes, and hypertension has been reported as 67.5% with higher prevalence reported among older adults.[2,3] Comorbid diabetes, hypertension, and hyperlipidemia is associated with an additive adverse effect on cardiovascular outcomes.[4,5] Management of glycemic control (A1C), blood pressure and low-density lipoprotein cholesterol (LDL-C) is necessary to manage all modifiable risk factors, commonly termed as the ABC (A1C, Blood Pressure, Cholesterol) goals, among these high-risk patients, to further reduce the risk of CVD morbidity and mortality.[6]

Medication adherence defined as the extent to which patients take their medication as recommended by their physician serves as a crucial link between prescribing a medication and treatment success.[7-9] Reported rates of medication adherence vary between 50-60% across various chronic conditions.[10-15] The issue of non-adherence is highly prominent among older adults with a reported 40-86% remaining non-adherent.[7,16] Medication adherence is not only essential to achieve optimal treatment benefits, prevent morbidity, mortality, and reduce healthcare costs[15] but is also important to the Medicare STAR program to evaluate quality of care for healthcare plans. The Medicare STAR program initiated by the Center for Medicare and Medicaid Services (CMS) provides considerable financial incentives to health plans that perform well on its star metrics.[17,18] Components of the star metrics include measuring adherence to Renin Angiotensin System (RAS)

antagonists (antihypertensives), statins (lipid-lowering agents) and antidiabetics to achieve blood pressure control, LDL-C control, and A1C control respectively using Proportion of Days Covered (PDC).[19]

Maintaining adherence among patients with multiple chronic conditions is highly challenging, especially among older adults due to multiple comorbidities, polypharmacy, and cognitive decline.[20,21] Studies evaluating the effects of adherence to concomitant anti-hypertensive and lipid-lowering therapies have reported sub-optimal adherence with rates lower than 50% within one year.[22-24] Prior studies have reported that medication non-adherence is associated with reduced effectiveness of anti-hypertensive, lipid-lowering, and anti-diabetic treatments.[25,26] Further, independent studies have reported that poor adherence to statin monotherapy, oral hypoglycemic monotherapy, and anti-hypertensive monotherapy was associated with reduced LDL-C, A1C, and blood pressure control respectively.[20,27,28] There is, however, a considerable gap in knowledge regarding the clinical implications of medication non-adherence to concomitant oral antidiabetics, statins, and RAS antagonists among older adult patients.

In an observational study, the association between medication adherence and clinical outcomes can be confounded by selection bias which may vary over the follow-up period.[29,30] In this study LDL-C and A1C measured during the study period were considered as time-dependent confounders affected by prior adherence since prior LDL-C/A1C were risk factors of subsequent adherence and LDL-C/A1C outcomes as well as mediators between prior adherence and final LDL-C/A1C outcomes. Further, adherence being a dynamic process may also vary over time, with changes in clinical outcome further affecting future adherence.[29] To address this issue of time-dependent exposure and time-dependent confounders affected by prior exposure history, Marginal Structural Models (MSM) have been proposed to estimate unbiased causal effects.[31] While

standard methods of confounder adjustment produce biased estimates, MSMs produce unbiased estimates based on counterfactual outcomes using inverse-probability-of-treatment weights (IPTW). The weights create a pseudo population where exposure is no longer confounded producing causal estimates of the association between adherence and clinical outcomes.[31,32]

Thus, the objective of the current study was to evaluate the association between adherence to concomitant oral antidiabetics, statins, and RAS antagonists (triple therapy) and intermediate outcomes, particularly A1C and LDL-C, among older adults enrolled in a Medicare Advantage Plan (MAP) using marginal structural modeling.

3.3 Methods

Study Design:

A longitudinal, retrospective cohort study using a Texas Medicare Advantage database from January 2016 until December 2019 was conducted. The baseline period was defined between January 1st, 2016 and June 30th, 2016, six months prior to the index date. The identification period was defined between July 1st, 2016 and December 31st, 2016. The follow-up period was defined between January 1st, 2017 and December 31st, 2019. Further, the follow-up period was divided into 6 six-monthly time intervals (four time periods) to measure the time-dependent exposure, time dependent confounders, and the outcome, starting from the index-date as illustrated in Figure 1.

The study was approved by the institutional review board at the University of Houston.

Study Files:

The database contained multiple data files including member summary, institutional claims, professional claims, lab data, and pharmacy files. The member summary files included demographics, and CMS risk scores (severity scores). Institutional and professional claims included all inpatient and outpatient encounters respectively, as well as diagnostic information in the form of International Classification of Diseases, Tenth Revision (ICD-10) codes, date of admission and date of discharge. The lab data included A1C and LDL-C lab values. The pharmacy files included information on patient drug prescriptions, fill dates, days of supply, quantity dispensed, and dosing information of each prescription claimed.

Study Population:

Components of triple therapy were defined according to the star metric components namely oral antidiabetics, RAS antagonists, and statins. RAS antagonist classes included Angiotensin Converting Enzyme Inhibitors (ACEs), Angiotensin Receptor Blockers (ARBs), and Direct Renin Inhibitors (DRIs). Oral antidiabetic classes included biguanides, DPP-4 inhibitors, meglitinides, SGL2-inhibitors, sulfonylureas, and thiazolidinediones. Concurrent triple therapy was defined as patients with at least one prescription of oral antidiabetics, statins, and RAS antagonists during the identification period (June 2016- December 2016). Further patients needed to have an overlap of at least one month of triple therapy with the first date of overlap defined as the index date.[33] Lastly continuation of triple therapy was indicated by a second prescription of each component of triple therapy after the index date.[34,35]

Two study cohorts, one for LDL-C and one for A1C were created. Patients were included in each study cohort if they 1). were continuously enrollment from January 2016 until December 2019 2). were identified as concurrent triple therapy users during the index period 3). had a LDL-C/A1C

lab value in the baseline period. Patients were excluded from the study cohort if they had a 1) diagnosis of dementia in the 6-month baseline period. 2). ACEI/ARB or statin contraindication like angioedema, hyperkalemia, renal artery stenosis as well as myopathy in the 6-month baseline period. 3). prescription of insulin throughout the study period. Patients on insulin were excluded as these patients might have uncontrolled A1Cs and were likely to be transitioning of oral anti-diabetic medications.

Adherence Measurement (Exposure):

Medication adherence was measured every six months, starting from the index date using PDC. Patients were considered adherent to concurrent triple therapy if they had 80% or more days covered for any oral antidiabetic, and any statin, and any RAS antagonist during the follow-up period.[22] Patients were further categorized as adherent to double therapy (Statin-RAS antagonists/statin-oral antidiabetics/ RAS antagonist- oral antidiabetics) and lastly adherent to monotherapy/none. The 80% cutoff has been validated by the Medicare Star Ratings program, Centers of Medicare and Medicaid (CMS) quality measures and the National Committee for Quality Assurance.[11]

Medication adherence was measured at 6-, 12-, 18-, and 24-months starting from the index date and was denoted as AD2, AD3, AD4, and AD5, respectively. Further, adherence prior to each time interval (AD1-AD4) was also measured as a separate time-varying variable in the MSM model as illustrated in Figure 1.

Outcome Measure:

Two separate outcome measures, A1C and LDL-C control, were defined for this study.

A1C and LDL-C control were measured at 12-, 18-, 24-, and 30-months from index date and was denoted as LDL3, LDL4, LDL5, and LDL6, respectively as illustrated in Figure 1. If lab data was missing for a particular time period, then the lab values were imputed from the prior time period. A1C control was defined as per the American Diabetes Associations (ADA) recommendation of less than 8% for high risk patients.[36] Similarly, LDL-C control was defined as per the American Association of Clinical Endocrinologists/American College of Endocrinology guidelines recommendation of less than 70mg/dL for patients with a history of atherosclerosis and less than 100mg/dL for patients without a history of atherosclerosis.[37]

Conceptual Framework and Baseline Covariates:

The Andersen Behavioral Model for healthcare resource use guided variable selection. The model included predisposing, enabling and need factors as determined during the identification or the baseline period.

Predisposing factors included age (<65 years, 65-69 years, 70-74 years, ≥75 years), sex (male versus female), total number of other medications calculated during identification period, and regimen complexity. Regimen complexity was defined as the mean doses taken per day multiplied by total number of medications determined during the identification period.[38,39] Enabling factors included health plan (low income subsidy versus no subsidy). Need factors included prior hospitalizations (none versus one or more than one), type of refill (≥90 days for all therapies versus not), prevalent users of triple therapy, baseline LDL-C and A1C control (yes versus no), statin intensity (high intensity versus not) as well as CMS risk score which accounts for medication burden and disease severity. Previous hospitalization, baseline A1C, LDL-C, and prevalent users

of triple therapy were determined during the baseline period. Statin intensity was determined during the baseline and identification period.

Time-Dependent Covariates:

The time-dependent confounders affected by prior exposure for each model included prior LDL-C and A1C control measured during the first 6-, 12-, 18-, 24-, and 30-months starting from index date denoted as LDL1/A1C1- LDL4/A1C4 respectively. The time-dependent covariates included CMS risk score and total other medications which were measured at 6-, 12-, 18-, and 24-months post the index date as illustrated in Figure 1.

Statistical Analysis:

Descriptive statistics were conducted to describe patient characteristics between initial adherence groups (first six months starting index date) using chi-square for categorical variables and ANOVA for continuous variables. A correlation assessment was conducted among the major predictor variables. The correlation assessment was conducted by exploring the correlation matrix as well as the Variance Inflation Factor (VIF).

Marginal Structural Modeling:

Two separate MSM models, one for A1C and one for LDL-C as the outcome, were conducted. The follow-up period was divided into four time-intervals (T1-T4). The primary exposure was adherence to triple therapy measured at each time interval, and the covariates included both baseline and time-dependent variables.

MSM was conducted in a two-step process. In the first step, stabilized IPTW weights adjusting for adherence selection were calculated. These weights were calculated in the four 6-monthly time

periods (T1-T4) as the probability of falling into the observed adherence group given the prior adherence history and baseline covariates divided by the probability of falling into the observed adherence group given the prior adherence history, baseline covariates, and time-dependent confounders.[40] Separate multinomial logistic regression models for the numerator and the denominator with adherence as the dependent variable were conducted to fit the two pooled logistic regression models and obtain the stabilized weights. In the second step, a weighted repeated measures model using generalized estimating equations and an independent working correlation matrix was conducted to estimate unbiased estimates of the association between adherence to triple therapy and A1C/LDL-C control.[40]

SAS version 9.4 (SAS Institute, Cary, NC) was used for statistical analysis at a 0.05 significance level.

Sensitivity Analysis:

Two separate sensitivity analysis were conducted among patient's adherent to statin monotherapy and patient's adherent to oral antidiabetics, respectively. Among the statin adherent group, patient's adherent to triple therapy were compared to patient's non-adherent to triple therapy but adherent to statin monotherapy. Their effects on LDL-C were evaluated using MSM. Similarly, among the oral anti-diabetic adherent group, patient's adherent to triple therapy were compared to patient's non-adherent to triple therapy but adherent to oral antidiabetics. Their effects on A1C were evaluated using MSM.

3.4 Results

Study Cohort:

There were 13,394 patients identified with one prescription of triple therapy. After applying criteria for concurrent therapy 10,716 patients were identified on concomitant oral antidiabetics, statins, and RAS antagonists. Further 10,242 patients were continuously enrolled throughout the study period. After applying the exclusion criteria, the cohort comprised of 7,433 patients. Around 99% of patients had at least one A1C, LDL-C value in the follow-up period. After applying the baseline A1C and LDL-C inclusion criteria, the final LDL-C cohort comprised of 4,803 patients on triple therapy and 5,314 patients on triple therapy among the A1C cohort.

The descriptive characteristics for the first six months are presented in Table 1 and Table 2 for A1C, and LDL-C cohorts, respectively. Among the A1C population, 53.05% of patients were female, and 24.93% were more than 75 years of age. Also, 84.59% had controlled A1C levels. Among the LDL-C population, 53.3% of patients were female, and 24.36% were more than 75 years of age. Also, 21.24% were on high intensity statins and 79.22% had controlled LDL-C levels. Results of the correlation matrix revealed that all correlations were below 0.3, and the VIF below 1.3, indicating a lack of multicollinearity. Further, there were no significant interactions among the major predictor variables.

Marginal Structural Modeling for A1C:

Results of the MSM model are demonstrated in Table 3. Patients who were adherent to triple therapy and adherent to double therapy were more likely to have their A1C in control as compared to patient's adherent to monotherapy/none (Adherence to triple therapy versus adherence to monotherapy/none, OR:1.30, 95% CI: 1.11-1.52, Adherence to double therapy versus adherence to monotherapy/none, OR:1.32, 95% CI: 1.12-1.55).

Females were more likely to have their A1C in control as compared to males (OR: 1.17, 95% CI: 1.02-1.34). Patients older than 70 years were more likely to have their A1C in control (70-74 years vs <65 years, OR: 1.41, 95% CI: 1.13-1.76; ≥75 years vs <65 years, OR: 1.69, 95% CI: 1.34-2.14). Patients who had a refill of 90 days or more for all their triple therapies were less likely to have their A1C in control as compared to patients who did not have a refill of 90 days for all their triple therapies (OR: 0.73, 95% CI: 0.59-0.89). Further, patients who had their A1C controlled in their baseline had a higher likelihood of A1C control (OR:7.7, 95% CI: 6.69-8.87). Patients with higher total other medications were more likely to have their A1C in control (OR: 1.04, 95% CI: 1.02-1.06). Lastly as the time period increased the likelihood of A1C control decreased (Time period 2 vs Time period 1, OR: 0.83, 95% CI: 0.79- 0.90; Time period 3 vs Time period 1, OR: 0.77, 95% CI: 0.7-0.85; Time period 4 vs Time period 1, OR: 0.69, 95% CI: 0.62- 0.77).

Marginal Structural Modeling for LDL-C:

Results of the MSM model are demonstrated in Table 3. Patients who were adherent to triple therapy and adherent to double therapy were more likely to have their LDL-C in control as compared to patient's adherent to monotherapy/none (Adherence to triple therapy versus adherence to monotherapy/none, OR:1.42, 95% CI: 1.24-1.62, Adherence to double therapy versus adherence to monotherapy/none, OR:1.84, 95% CI: 1.62-2.10).

Patients in the age group between 65-69 were more likely to have their LDL-C in control as compared to patients below 65 (OR: 1.26, 95% CI: 1.05-1.50). Patients with low income subsidy were more likely to have their LDL-C in control as compared to patients with no low subsidy (OR: 1.29, 95% CI: 1.15-1.45). Patients who had a refill of 90 days or more for all their triple therapies were more likely to have their LDL-C in control as compared to patients who did not have a refill

of 90 days for all their triple therapies (OR: 1.20, 95% CI: 1.03-1.39). Patients who had their LDL-C controlled in their baseline had a higher likelihood of LDL-C control (OR:3.6, 95% CI: 3.17-4.08). Further, patients who had received a high intensity statin were less likely to have their LDL-C controlled (OR: 0.83, 95%CI: 0.73-0.95). Patients with higher CMS risk score, and total other medications were less likely to have their LDL-C in control (CMS risk score, OR: 0.99, 95% CI: 0.99-0.99; Total other medications, OR: 0.96, 95% CI: 0.95-0.98). Lastly as the time period increased the likelihood of LDL-C control decreased (Time period 3 vs Time period 1, OR: 0.89, 95% CI: 0.83-0.96; Time period 4 vs Time period 1, OR: 0.87, 95% CI: 0.81- 0.94).

Sensitivity Analysis:

Results of sensitivity analysis are demonstrated in Table 4. There were 2,529 patient's adherent to statin monotherapy in all the time periods. Among the patient's adherent to statins, no significant difference in LDL-C control between the triple therapy adherent group and the triple therapy non-adherent group was observed (OR: 0.94, 95% CI: 0.81-1.19).

There were 3,583 patient's adherent to oral antidiabetics in all time periods. Among the patient's adherent to oral antidiabetics, the triple therapy adherent group had better A1C control than the triple therapy non-adherent group (OR: 1.16, 95% CI: 1.01-1.24).

3.5 **Discussion**

The current study demonstrated the beneficial effects of adherence to concurrent oral antidiabetics, statins, and RAS antagonists among older adults in a real-world setting. The study findings revealed that patients who were adherent to concurrent triple or double therapy were more likely to have A1C and LDL-C control as compared to patient's adherent to monotherapy/none.

Recent literature validates the use of MSM in several epidemiological studies controlling for time-dependent exposure and time-dependent confounding affected by prior exposure history.[29,30,32,41] Estimates closer to those obtained in randomized control trials where obtained with MSMs when both conventional methods and MSM were used.[41-43] Hernan et al demonstrated the clinical benefit of zidovudine on survival among human immunodeficiency virus (HIV)-positive patients controlling for CD4 lymphocyte count which was considered as the time-dependent confounder. While conventional methods reflected the presence of confounding effects, MSM demonstrated the beneficial effects of zidovudine.[32] Similarly, Desai et al compared the effectiveness of various angiotensin receptor blockers among patients with heart failure in a real-world setting and reported that the drugs had similar effectiveness in reducing the risk of mortality.[30]

The findings from the current study reveal that patients who were adherent to concurrent triple or double therapy were more likely to have A1C and LDL-C control as compared to patient's adherent to monotherapy/none. These findings are valuable since they indicate the beneficial effects of medication adherence in controlling CVD risk factors among this high-risk elderly population. The beneficial effects of adherence on health outcomes using MSM, among a cohort of diabetic patients were validated by a prior study. Yu et al demonstrated that medication adherence to hypoglycemic agents was associated with a decreased risk of microvascular complications among type 2 diabetic patients, and these results were consistent with prior clinical trials.[29] Further, Sugihara et al compared the effects of antihypertensive combination therapy versus antihypertensive monotherapy in reducing blood pressure using MSMs. The study reported that the combination therapy effectively reduced blood pressure than monotherapy.[41]

Results from the sensitivity analysis revealed that among patient's adherent to oral antidiabetics, the triple therapy adherent group had better A1C control than the triple therapy non-adherent

group. A plausible explanation could be a potential cumulative beneficial effect of triple therapy on A1C control. Literature suggests that ACEI/ARBs improve A1C control by reducing insulin resistance among diabetic patients.[44] Additional reports suggest that statins such as pitavastatin and simvastatin improve A1C control among diabetic patients.[45,46] Future studies should explore any potential pleotropic effects by non-glycemic medications on A1C control among this patient population. Further, according to the WHO, adherence to any therapeutic regimen is also a reflection of health-related behavior extending beyond, just taking medications.[44] Patients adherent to triple therapy could plausibly be adherent to several behavioral modifications including diet, exercise, and physician appointments as well as display higher perceived benefits regarding the therapy. This composite effect of several behavioral components may potentially explain the higher A1C control among the triple therapy adherent group. It could also be plausible that patients within the triple therapy group were on aggressive anti-diabetic therapy as compared to the non-adherent triple therapy group. These elements could further be explored in future studies. Among the patient's adherent to statins, no significant difference in LDL-C control was observed between the triple therapy adherent group and the triple therapy non-adherent group. These results may indicate that optimal LDL-C goals are achievable if patients are adherent to their statin medications.

Among the several significant predictors associated with LDL-C and A1C control, the most prominent were the baseline A1C and LDL-C control. Patients with a baseline LDL-C and A1C control were more likely to have their future LDL-C and A1C controlled. These results implicate that baseline A1C and LDL-C control can predict future A1C and LDL-C control and patients who do not achieve baseline A1C and LDL-C can be intervened early-on to help achieve future A1C and LDL-C goals to further reduce CVD. Further, patients who had received a high intensity statin

were less likely to have their LDL-C controlled. These findings are validated by a prior study which reported that a majority of high intensity statin users did not achieve their LDL-C goals with only 17-19% achieving treatment goals[45], reflecting an unmet need among these high-risk patients.

3.6 Limitations

The study includes some limitations. An assumption of MSM includes no unmeasured confounders, which is not testable. However, the study included as many relevant clinical and socio-demographic covariates as possible to ensure limited residual confounding. Other measures including blood pressure could be included as a time-varying confounder in future studies. Since the study considered a patient adherent on a given day if any one oral antidiabetic, and any one statin, and any one RAS antagonists was available on that day, the study might have overestimated adherence to patients taking multiple drug regimens for each therapy. The lab data was available for patients who used an in-network lab facility within the Medicare Managed plan which might create potential bias. However, on further analysis there was no significant difference in demographic characteristics among those patients who had a baseline lab value and were included in the study versus those who did not have a baseline lab value and were excluded from the study, thus minimizing any potential bias. Lastly the generalizability of the study might be limited to similar demographic, clinical, and geographic populations since the study was conducted among a Texas Medicare Advantage population.

3.7 Conclusion

The study demonstrated that patient's adherent to concurrent triple or double therapy were more likely to have A1C and LDL-C control as compared to patient's adherent to monotherapy/none. The study has valuable clinical implications since the results indicate the beneficial effects of

medication adherence in controlling CVD risk factors among high-risk elderly patients. Further, it also indicates that the ABC goals outlined by the ADA can be achieved if medication adherence is optimal. Lastly strengths of this study include an adequate representation of the patient population as seen in clinical practice, as well as estimation of adherence and clinical effects controlling for the unrecognized issue of time-dependent exposure and confounding.

3.8 References

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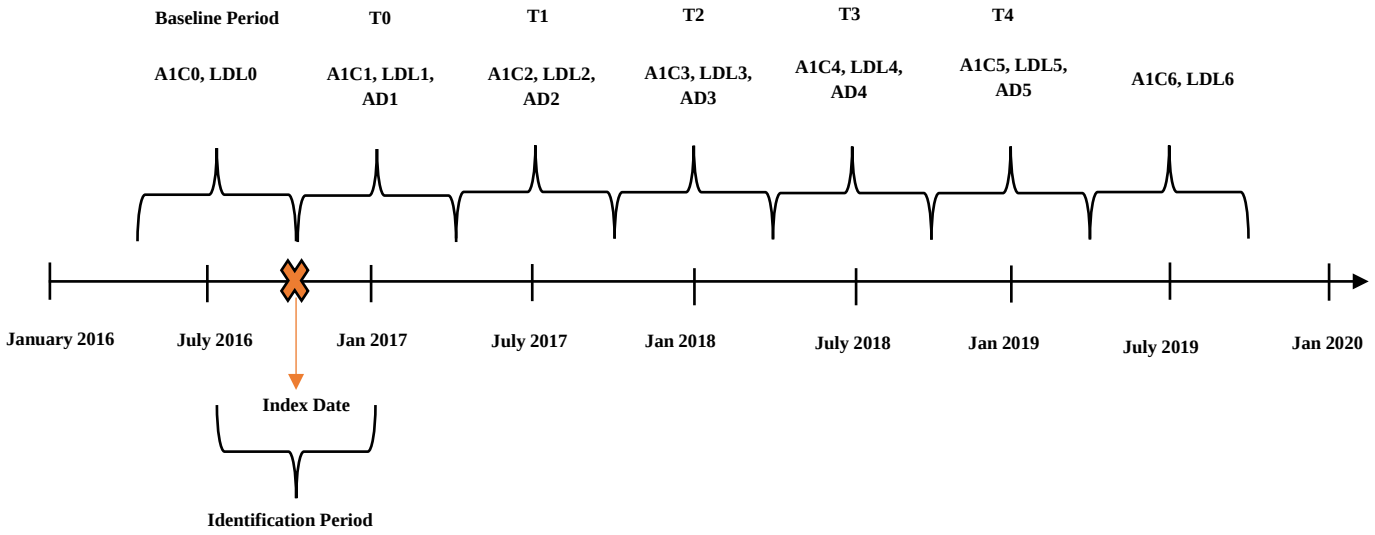
3.9 Figures and Tables

Figure 1: Study Design



Time Period	Exposure	LDL, A1C-Outcome	Time-Varying Confounder	Prior Exposure
T1	AD2	LDL3, A1C3	LDL1, A1C1	AD1
T2	AD3	LDL4, A1C4	LDL2, A1C2	AD2
T3	AD4	LDL5, A1C5	LDL3, A1C3	AD3
T4	AD5	LDL6, A1C6	LDL4, A1C4	AD4

Table 1: Patient Demographics and Clinical Characteristics for A1C Cohort (N=5,314)

Variables	Total Patients (%) N=5,314	Adherence to Mono Therapy/None (%) N= 356	Adherent to Double Therapy (%) N= 916	Adherent to Triple Therapy (%) N= 4042	P-Value
Sex					
Male	2495 (46.95)	168 (47.19)	422 (46.07)	1905 (47.13)	0.84
Female	2819 (53.05)	188 (52.81)	494 (53.93)	2137 (52.87)	
Age					
<65 Years	673 (12.66)	48 (13.48)	116 (12.66)	509 (12.59)	0.27
65-69 Years	1866 (35.11)	123 (34.55)	325 (35.48)	1418 (35.08)	
70-74 Years	1450 (27.29)	82 (23.03)	236 (25.76)	1132 (28.01)	
≥75 Years	1325 (24.93)	103 (28.93)	239 (26.09)	983 (24.32)	
Health Plan					
No Subsidy	2860 (53.82)	190 (53.37)	506 (55.24)	2164 (53.54)	0.63
Low-Income Subsidy	2454 (46.18)	166 (46.63)	410 (44.76)	1878 (46.46)	
Number of Prior Hospitalizations					
0	5130 (96.54)	342 (96.07)	879 (95.96)	3909 (96.71)	0.47
≥1	184 (3.46)	14 (3.93)	37 (4.04)	133 (3.29)	
90-Day Refill					

<90 Days Supply for All/One/Two Therapies	731 (13.76)	86 (24.16)	190 (20.74)	455 (11.26)	<0.0001*
All Three Therapies have 90 Day Supply	4583 (86.24)	270 (75.84)	726 (79.26)	3587 (88.74)	
Prevalent Users of Triple Therapy					
No	743 (13.98)	81 (22.75)	178 (19.43)	484 (11.97)	<0.0001*
Yes	4571 (86.02)	275 (77.25)	738 (80.57)	3558 (88.03)	
Baseline A1C Control					
No	819 (15.41)	67 (18.82)	134 (14.63)	618 (15.29)	0.16
Yes	4495 (84.59)	289 (81.18)	782 (85.37)	3424 (84.71)	
CMS Risk Score Mean (SD)	1.28 (0.78)	1.26 (0.88)	1.29 (0.76)	1.28 (0.77)	0.81
Total Number of Other Medications Mean (SD)	6.53 (4.18)	6.02 (4.05)	6.72 (4.21)	6.53 (4.8)	0.02*
Regimen Complexity Mean (SD)	21.19 (39.33)	18.89 (32.69)	21.09 (37.94)	21.41 (40.17)	0.51

***Significant P values from chi-square and anova<0.05; CMS: Centers for Medicare and Medicaid; SD: Standard Deviation. Descriptive statistics were compared among the initial adherence groups from time period T0.**

Table 2: Patient Demographics and Clinical Characteristics for LDL-C Cohort (N=4,803)

Variables	Total Patients (%) N=4,803	Adherence to Mono Therapy/None (%) N= 335	Adherent to Double Therapy (%) N= 838	Adherent to Triple Therapy (%) N= 3630	P-Value
Sex					
Male	2243 (46.70)	162 (48.36)	377 (44.99)	1704 (46.94)	0.48
Female	2560 (53.30)	173 (51.64)	461 (55.01)	1926 (53.06)	
Age					
<65 Years	619 (12.89)	57 (17.01)	114 (13.60)	448 (12.34)	0.02*
65-69 Years	1708 (35.56)	112 (33.43)	294 (35.08)	1302 (35.87)	
70-74 Years	1306 (27.19)	70 (20.90)	222 (26.49)	1014 (27.93)	
≥75 Years	1170 (24.36)	96 (28.66)	208 (24.82)	866 (23.86)	
Health Plan					
No Subsidy	2566 (53.42)	175 (52.24)	454 (54.18)	1937 (53.36)	0.82
Low-Income Subsidy	2237 (46.58)	160 (47.76)	384 (45.82)	1693 (46.64)	
Number of Prior Hospitalizations					
0	4635 (96.5)	321 (95.82)	806 (96.18)	3508 (96.64)	0.63
≥1	168 (3.50)	14 (4.18)	32 (3.82)	122 (3.36)	

90-Day Refill					
<90 Days Supply for All/One/Two Therapies	660 (13.74)	85 (25.37)	174 (20.76)	401 (11.05)	<0.0001*
All Three Therapies have 90 Day Supply	4143 (86.26)	250 (74.63)	664 (79.24)	3229 (88.95)	
Prevalent Users of Triple Therapy					
No	673 (14.01)	73 (21.79)	167 (19.93)	433 (11.93)	<0.0001*
Yes	4130 (85.99)	262 (78.21)	671 (80.07)	3197 (88.07)	
Baseline LDL Control					
No	998 (20.78)	112 (33.43)	203 (24.22)	683 (18.82)	<0.0001*
Yes	3805 (79.22)	223 (66.57)	635 (75.78)	2947 (81.18)	
Statin Intensity					
No	3783 (78.76)	264 (78.81)	629 (75.06)	2890 (79.61)	0.01*
Yes	1020 (21.24)	71 (21.19)	209 (24.94)	740 (20.39)	
CMS Risk Score Mean (SD)	1.27 (0.77)	1.29 (0.91)	1.31 (0.78)	1.26 (0.76)	0.23
Total Number of Other Medications Mean (SD)	6.54 (4.16)	6.21 (4.26)	6.81 (4.22)	6.51 (4.14)	0.05

Regimen Complexity Mean (SD)	20.90 (38.36)	19.04 (33.55)	23.60 (39.46)	20.91 (38.53)	0.59

***Significant P values from chi-square and anova<0.05; CMS: Centers for Medicare and Medicaid; SD: Standard Deviation. Descriptive statistics were compared among the initial adherence groups from time period T0.**

Table 3: Marginal Structural Modeling to Examine the Association Between Adherence to Triple Therapy and LDL-C as well as A1C.

Variables	**LDL-C (N=4,803)**		**A1C (N=5,314)**	
	Adjusted OR (95% Confidence Interval)	**P value**	**Adjusted OR (95% Confidence Interval)**	**P value**
Adherence Group				
Adherence to Double Therapy vs Adherence to Mono Therapy/None	1.42 (1.24-1.62)	<0.0001*	1.32 (1.12-1.55)	0.0009*
Adherence to Triple Therapy vs Adherence to Mono Therapy/None	1.84 (1.62-2.10)	<0.0001*	1.3 (1.11-1.52)	0.0009*
Sex				
Female vs Male	0.94 (0.84-1.05)	0.33	1.17 (1.02-1.34)	0.02*
Age				
65-69 Years vs <65 Years	1.25 (1.04-1.50)	0.01*	1.19 (0.97-1.48)	0.09
70-74 Years vs <65 Years	1.14 (0.95-1.37)	0.14	1.41 (1.13-1.76)	0.0018*
≥75 Years vs <65 Years	1.12 (0.93-1.36)	0.21	1.69 (1.34-2.14)	<0.0001*
Health Plan				

Low-Income Subsidy vs No Subsidy	1.3 (1.15-1.45)	<0.0001*	0.99 (0.99-1.00)	0.24
Number of Prior Hospitalizations				
≥1 vs 0	0.84 (0.63-1.13)	0.25	1.01 (0.68-1.51)	0.93
90-Day Refill				
Three Therapies have 90 Day Supply vs Not	1.2 (1.03-1.39)	0.01	0.73 (0.59-0.89)	0.0027*
Prevalent Users of Triple Therapy				
Yes vs No	0.88 (0.75-1.03)	0.13	1.07 (0.89-1.29)	0.45
Time Period				
2 vs 1	0.94 (0.88-1.00)	0.06	0.83 (0.76-0.9)	<0.0001*
3 vs 1	0.89 (0.83-0.96)	0.003*	0.77 (0.7-0.85)	<0.0001*
4 vs 1	0.87 (0.81-0.94)	0.001*	0.69 (0.62-0.77)	<0.0001*
Baseline LDL-C Control				
Yes vs No	3.6 (3.17-4.08)	<0.0001*	7.7 (6.69-8.87)	<0.0001*
Statin Intensity				
Yes vs No	0.83 (0.73-0.95)	0.007*		
CMS Risk Score Mean (SD)	0.92 (0.85-0.99)	0.04*	0.96 (0.88-1.05)	0.47

Total Number of Other Medications Mean (SD)	0.96 (0.95-0.98)	<0.0001*	1.04 (1.02-1.06)	<0.0001*
Regimen Complexity Mean (SD)	0.99 (0.996-0.999)	0.01	0.99 (0.99-1.00)	0.24

***Significant P<0.05; CI: confidence interval; OR: odds ratio.**

Table 4: Sensitivity Analysis to Examine the Association Between Adherence to Triple Therapy and LDL-C, A1C.

Variables	**LDL-C (N=2,529)**		**A1C (N=3,583)**	
	Adjusted OR (95% Confidence Interval)	**P value**	**Adjusted OR (95% Confidence Interval)**	**P value**
Adherence Group				
Adherence to Triple Therapy vs Adherence to Mono Therapy	0.94 (0.81-1.19)	0.9	1.16 (1.01-1.34)	0.02*
Sex				
Female vs Male	1.03 (0.87-1.22)	0.7	1.01 (0.86-1.19)	0.82
Age				
65-69 Years vs <65 Years	1.59 (1.21-2.10)	0.0009*	1.34 (1.06-1.71)	0.01*
70-74 Years vs <65 Years	1.24 (0.93-1.64)	0.12	1.51 (1.18-1.93)	0.0009*
≥75 Years vs <65 Years	1.47 (1.10-1.96)	0.0081*	1.8 (1.37-2.36)	<0.0001*
Health Plan				

Low-Income Subsidy vs No Subsidy	1.22 (1.02-1.46)	0.02*	1.1 (0.94-1.30)	0.19
Number of Prior Hospitalizations				
≥1 vs 0	0.65 (0.40-1.05)	0.07	0.96 (0.61-1.52)	0.89
90-Day Refill				
Three Therapies have 90 Day Supply vs Not	1.2 (1.03-1.4)	0.001*	0.69 (0.54-0.89)	0.0042*
Prevalent Users of Triple Therapy				
Yes vs No	0.78 (0.57-1.07)	0.12	1.12 (0.88-1.42)	0.35
Time Period				
2 vs 1	0.92 (0.81-1.04)	0.21	0.83 (0.75-0.91)	0.0003*
3 vs 1	0.7 (0.61-0.80)	<0.0001*	0.78 (0.70-0.88)	<0.0001*
4 vs 1	0.6 (0.52-0.69)	<0.0001*	0.68 (0.60-0.77)	<0.0001*
Baseline LDL-C Control				
Yes vs No	8.04 (6.62-9.78)	<0.0001*	6.64 (5.65-7.80)	<0.0001*
Statin Intensity				
Yes vs No	0.93 (0.75-1.16)	0.55		

CMS Risk Score Mean (SD)	0.9 (0.80-1.01)	0.07	0.91 (0.82-1.02)	0.11
Total Number of Other Medications Mean (SD)	0.97 (0.95-1.00)	0.053	1.04 (1.02-1.06)	0.0002*
Regimen Complexity Mean (SD)	0.99 (0.99-1.00)	0.31	0.99 (0.99-1.00)	0.26

***Significant P<0.05; CI: confidence interval; OR: odds ratio.**

4 Manuscript 3

Title: Evaluating Adherence to Concomitant Diabetes, Hypertension, and Hyperlipidemia Treatments and Cardiovascular Outcomes Among Older Adults Using Marginal Structural Modeling.

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4.1 Abstract

Objective: Diabetes, hypertension, and hyperlipidemia have been identified as common modifiable risk factors of cardiovascular disease, frequently occurring together. Comorbid diabetes, hypertension, and hyperlipidemia is associated with an additive adverse effect on cardiovascular (CV) outcomes. Medication adherence to concurrent anti-diabetics, anti-hypertensives, and lipid-lowering therapies is essential to achieve maximum treatment benefits. The objective of the current study was to evaluate the association between adherence to concomitant oral antidiabetics, statins, and Renin Angiotensin System (RAS) antagonists (triple therapy) and CV outcomes, among older adults enrolled in a Medicare Advantage Plan (MAP) using marginal structural modeling.

Methods: A retrospective cohort study with patients on concurrent triple therapy was conducted using a Texas Medicare Advantage database from January 2016 until December 2019. Medication adherence to concurrent triple therapy was measured every 6 months using Proportion of Days Covered to determine the different adherence groups. CV outcomes were also measured every 6

months. A marginal structural model (MSM) controlling for baseline covariates and time-varying confounders affected by prior adherence was conducted to evaluate the association. A sub-analysis was conducted among patients with prior CV events to evaluate the association between adherence to triple therapy and CV outcomes using MSMs.

Results: The final patient cohort was comprised of 7,433 patients. The MSM model revealed that there were no significant associations between adherence to triple/double therapies and cardiovascular outcomes. Various socio-demographic and clinical characteristics like sex, age, low-income subsidy, prior hospitalization, type of refill, statin intensity, CMS risk score, and total number of medications were associated with CV outcomes. There were 471 patients with a prior CV event identified for the sub-analysis. Results of the sub-analysis MSM model revealed that there were no significant associations between adherence to triple/double therapies and CV outcomes among patients with prior CV events.

Conclusion: Adherence to triple therapy was not associated with CV outcomes. Future studies should evaluate the association with longer follow-up periods.

4.2 Introduction

With an increasing disease burden among older adult patients, complex medication regimens are often essential to delay progression of disease.[1,2] According to the World Health Organization (WHO), medication adherence is defined as the extent to which a patient follows the agreed therapeutic regimen, life-style changes, and health-related behavior recommended by a provider.[3,4] However, suboptimal medication adherence remains a major public health issue among older adults .[5] The estimated prevalence of medication non-adherence is around 50% among the geriatric population.[5] Plausible reasons include increased comorbidities, polypharmacy, cognitive decline,

financial issues, and increased frailty.[1,6,7] Consequences of medication non-adherence among older adults include reduced therapeutic effectiveness, decreased quality of life, increased hospital readmissions and length of stay, and adverse events.[8]

Diabetes, hypertension, and hyperlipidemia have been identified as common modifiable risk factors of cardiovascular disease, frequently occurring together.[9] The prevalence of concomitant hyperlipidemia, diabetes, and hypertension has been reported as 67.5% with higher prevalence reported among older adults.[10,11] Comorbid diabetes, hypertension, and hyperlipidemia is associated with an additive adverse effect on cardiovascular (CV) outcomes.[12,13] Due to this increased risk, medication adherence to anti-diabetics, anti-hypertensives, and lipid-lowering therapies is essential to achieve maximum therapeutic benefits among older adults with comorbid diabetes, hypertension, and hyperlipidemia. However, studies evaluating the effects of adherence to concomitant anti-hypertensive and lipid-lowering therapies have reported sub-optimal adherence with rates lower than 50% within one year.[14-16] Further, prior studies have reported that medication non-adherence is associated with reduced effectiveness of anti-hypertensive, lipid-lowering, and anti-diabetic treatments.[17,18] Chapman et al reported that adherence to concurrent antihypertensives and statins was associated with a lower risk of CV events.[19] Lastly, a meta-analysis of 10 studies investigating the impact of medication adherence to concurrent cardio-protective agents on subsequent CV outcomes reported that optimum adherence to these medications was associated with reduced CV hospitalization and mortality.[20] However, literature investigating adherence to concurrent anti-diabetics, anti-hypertensives, and lipid-lowering therapies with CV outcomes is lacking.

Medication adherence to concurrent anti-diabetics, anti-hypertensives, and lipid-lowering therapies is not only essential to achieve maximum treatment benefits,[17,18] but is also important to

the Medicare STAR program to evaluate quality of care for healthcare plans. The Medicare STAR program initiated by the Center for Medicare and Medicaid Services (CMS) provides considerable financial incentives to health plans that perform well on its star metrics [21,22] including measuring adherence to Renin Angiotensin System (RAS) antagonists (antihypertensives), statins (lipid-lowering agents) and antidiabetics using Proportion of Days Covered (PDC).[23]

In an observational study, the association between medication adherence and clinical outcomes can be confounded by selection bias which may vary over the follow-up period.[24,25] In this study CV events measured during the study period was considered as a time-dependent confounder affected by prior adherence. Prior CV events were considered as risk factors of subsequent adherence and CV outcomes as well as mediators between prior adherence and final CV outcomes. Further, adherence being a dynamic process may also vary over time, with changes in clinical outcome further affecting future adherence.[24] Marginal Structural Models (MSM) have been proposed to address this issue of time-dependent exposure and time-dependent confounders affected by prior exposure history, to further estimate unbiased causal effects.[26] MSMs produce unbiased estimates based on counterfactual outcomes using inverse-probability-of-treatment weights (IPTW). The weights create a pseudo population where exposure is no longer confounded producing causal estimates of the association between adherence and clinical outcomes.[26,27]

Thus, the objective of the current study was to evaluate the association between adherence to concomitant oral antidiabetics, statins, and RAS antagonists (triple therapy) and CV outcomes, among older adults enrolled in a Medicare Advantage Plan (MAP) using marginal structural modeling.

4.3 Methods

Study Design:

A longitudinal, retrospective cohort study using a Texas Medicare Advantage database from January 2016 until December 2019 was conducted. The baseline period was defined between January 1st, 2016 and June 30th, 2016, six months prior to the index date. The identification period was defined between July 1st, 2016 and December 31st, 2016. The follow-up period was defined between January 1st, 2017 and December 31st, 2019. Further, the follow-up period was divided into four six-monthly time periods (T1-T4) to measure the time-dependent exposure, time dependent confounders, and the outcome, starting from the index-date as illustrated in Figure 1.

The study was approved by the institutional review board at the University of Houston.

Study Files:

The database contained multiple data files including member summary, institutional claims, professional claims, and pharmacy files. The member summary files include demographics, CMS risk scores (severity scores), and provider specialty data. Institutional and professional claims include all inpatient and outpatient encounters respectively, as well as diagnostic information in the form of International Classification of Diseases, Tenth Revision (ICD-10) codes, date of admission and date of discharge. The pharmacy files include information on patient drug prescriptions, fill dates, days of supply, quantity dispensed, and dosing information of each prescription claimed.

Study Population:

Triple therapy was defined according to the star metric components namely oral antidiabetics, RAS antagonists (antihypertensives), and statins. RAS antagonist classes included Angiotensin

Converting Enzyme Inhibitors (ACEs), Angiotensin Receptor Blockers (ARBs), and Direct Renin Inhibitors (DRIs). Oral antidiabetic classes included biguanides, DPP-4 inhibitors, meglitinides, SGL2-inhibitors, sulfonylureas, and thiazolidinediones. Concurrent triple therapy was defined as patients with at least one prescription of oral antidiabetics, statins, and RAS antagonists during the index period (June 2016- December 2016). Further patients needed to have an overlap of at least one month of triple therapy with the first date of overlap defined as the index date.[28] Lastly continuation of triple therapy was indicated by a second prescription of each component of triple therapy after the index date.[29,30]

The inclusion criteria included 1). continuous enrollment from January 2016 until December 2019 2). identified as concurrent triple therapy users during the index period. The exclusion criteria included 1). diagnosis of dementia in the 6-month pre-index period. 2). ACEI/ARB or statin contraindication like angioedema, hyperkalemia, renal artery stenosis as well as myopathy in the 6-month pre-index period. 3). prescription of insulin throughout the study period. Patients on insulin were excluded as these patients might have uncontrolled A1Cs and were likely to be transitioning of oral anti-diabetic medications.

Primary Exposure: Adherence Measurement

PDC was used to measure medication adherence every six months starting from the index date. Patients were considered adherent to concurrent triple therapy if they had 80% or more days covered for any RAS antagonist, and any statin, and any oral antidiabetic, during the follow-up period.[31] Patients were further categorized as adherent to double therapy (RAS antagonist-oral antidiabetics/ statin-RAS antagonists/ statin-oral antidiabetics) and lastly monotherapy/none. The

80% cutoff has been validated by the Medicare Star Ratings program, Centers of Medicare and Medicaid (CMS) quality measures and the National Committee for Quality Assurance.[32]

Medication adherence was measured in each time period (T1-T4) and was denoted as AD2, AD3, AD4, and AD5 respectively. Further, prior adherence measured between T0-T3 and denoted as AD1-AD4 respectively was also measured as a separate time-varying variable in the MSM model as illustrated in Figure 1.

Outcome Measure:

The outcome of the study was CV events measured every 6 months. The cardiovascular events included Myocardial Infarction (MI), angina, stroke, atherosclerosis, acute and chronic ischemic heart disease and were identified by ICD-10 codes. The cardiovascular events were measured in the corresponding time periods and were denoted as CV3-CV6 as illustrated in Figure 1.

Conceptual Framework and Baseline Covariates:

The Andersen Behavioral Model for healthcare resource use guided variable selection. The model included predisposing, enabling and need factors as determined during the identification or the baseline period.

Predisposing factors included sex (male versus female), age (<65 years, 65-69 years, 70-74 years, ≥75 years), total number of other medications calculated during identification period, and regimen complexity. Regimen complexity was defined as the mean doses taken per day multiplied by total number of medications determined during the identification period.[33,34] Enabling factors included health plan (low income subsidy versus no subsidy). Need factors included type of refill (≥90 days for all therapies versus not), prior hospitalizations (none versus one or more than one), prevalent

users of triple therapy (yes versus no), statin intensity (high intensity versus not), and CMS risk score which accounts for medication burden and disease severity. Previous hospitalization, prevalent users of triple therapy, and prior history of CV events were determined during the baseline period. Statin intensity was determined during the baseline and identification period.

Time-Dependent Covariates:

The cumulative prior CV events for each time period was defined as the time-dependent confounder affected by prior exposure while CMS risk score, and total other medications for each time-period were defined as the time-dependent covariates as illustrated in Figure 1.

Statistical Analysis:

Descriptive statistics were conducted to describe patient characteristics between initial adherence groups using chi-square for categorical variables and ANOVA for continuous variables. A correlation assessment was conducted among the major predictor variables. The correlation assessment was conducted by exploring the correlation matrix as well as the Variance Inflation Factor (VIF).

Marginal Structural Modeling:

The association between adherence to triple therapy and CV outcomes were evaluated using MSM controlling for both baseline and time-dependent variables.

MSM was conducted in a two-step process. In the first step, stabilized IPTW weights adjusting for adherence selection were calculated. These weights were calculated in the four 6-monthly time periods (T1-T4) as the probability of falling into the observed adherence group given the prior adherence history and baseline covariates divided by the probability of falling into the observed

adherence group given the prior adherence history, baseline covariates, and time-dependent confounders.[35] Separate multinomial logistic regression models for the numerator and the denominator with adherence as the dependent variable were conducted to fit the two pooled logistic regression models and obtain the stabilized weights. In the second step, a weighted repeated measures model using generalized estimating equations and an independent working correlation matrix was conducted to estimate unbiased estimates of the association between adherence to triple therapy and CV outcomes.[35]

SAS version 9.4 (SAS Institute, Cary, NC) was used for statistical analysis at a 0.05 significance level.

Sub-Analysis:

A sub-analysis was conducted among patients with prior CV events to evaluate the association between adherence to triple therapy and cardiovascular outcomes using MSMs. Prior CV events were identified during the baseline and identification period.

Sensitivity Analysis:

Two additional time-varying confounders, LDL-C and A1C were added to the MSM model to evaluate the association between adherence to triple therapy and CV outcomes. A1C and LDL-C control were measured during the first 6-, 12-, 18-, 24-, and 30-months from index date. If lab data was missing for a particular time period, then the lab values were imputed from the prior time period. A1C control was defined as per the American Diabetes Associations (ADA) recommendation of less than 8% for high risk patients.[36]. Similarly, LDL-C control was defined as per the American Association of Clinical Endocrinologists/American College of Endocrinology

guidelines recommendation of less than 70mg/dL for patients with a history of atherosclerosis and less than 100mg/dL for patients without a history of atherosclerosis.[37]

4.4 Results

Study Cohort:

There were 13,394 patients identified with one prescription of triple therapy. After applying criteria for concurrent therapy, 10,716 patients were identified on concomitant oral antidiabetics, statins, and RAS antagonists. Further 10,242 patients were continuously enrolled throughout the study period. After applying exclusion criteria, the final cohort comprised of 7,433 patients on triple therapy.

Adherence to triple therapy declined sharply in the first 12 months from 75.49% in the first 6 months to 64.93% in the next 6 months. It then remained consistent in the following time-periods. The sample characteristics are presented in Table 1. 52.62% of the patients were female, and 85.64% were prevalent users of triple therapy. 21.22% of the patients were on high intensity statins. Results of the correlation matrix revealed that all correlations were below 0.3, and the VIF below 1.3, indicating a lack of multicollinearity. Further, there were no significant interactions among the major predictor variables.

Marginal Structural Modeling:

Results of the MSM model are demonstrated in Table 2. The final model with stabilized weights, adjusting for various time-varying confounders, revealed that there were no significant associations between adherence to triple/double therapies and CV outcomes.

Females were less likely to have a CV event as compared to males (OR: 0.58; 95% CI: 0.52-0.65). Patients above the age of 70 years were more likely to have a CV event as compared to patients below the age of 65 (70-74 years vs <65 years, OR: 1.45; 95% CI: 1.20-1.75, ≥75 years vs <65 years, OR: 1.61, 95% CI: 1.34-1.94). Patients with a low-income subsidy were less likely to have a CV event as compared to patients without a subsidy (OR: 0.85; 95% CI: 0.76-0.95). Patients with one or more hospitalization were more likely to have a CV event as compared to patients with no hospitalization (OR: 1.57; 95% CI: 1.23-2.00). Patients who had a refill of 90 days or more for all their triple therapies were less likely to have a CV event as compared to patients who did not have a refill of 90 days for all their triple therapies (OR: 0.80, 95% CI: 0.69-0.93). Patients who received a high intensity statin were more likely to have a CV event as compared to patients who did not receive a high intensity statin. As the CMS risk score increased, the likelihood of a CV event increased (OR: 1.32; 95% CI: 1.24-1.41). Also, as the total number of medications increased the likelihood of a CV events increased (OR: 1.07; 95% CI: 1.05-1.08).

Sub-Analysis:

There were 471 patients with a prior CV event identified during the baseline and identification period. Results of the sub-analysis MSM model are demonstrated in Table 3. The final model revealed that there were no significant associations between adherence to triple/double therapies and CV outcomes among patients with prior CV events.

Sensitivity Analysis:

There were 4,435 patients identified with LDL-C and A1C lab values throughout the follow-up period. Results of the MSM model are demonstrated in Table 4. The final model revealed that

there were no significant associations between adherence to triple/double therapies and CV outcomes.

4.5 Discussion

The current study evaluated adherence to concomitant oral antidiabetics, statins, and RAS antagonists and CV outcomes among older adults enrolled in a MAP. The study findings did not reveal any significant association between adherence to triple or double therapy and CV outcomes. Further, the sub-analysis conducted among patients with prior CV events and the sensitivity analysis with A1C and LDL-C as additional time-varying confounders also did not reveal any significant association between adherence to triple or double therapy and CV outcomes.

In the current study, the adherence rate to concurrent triple therapy varied between 63-75% between different time periods, with an overall trend of decreasing adherence rates over time. While this finding is consistent with literature reporting a decline in adherence over time[14,31], this finding is equally valuable as it reflects an unmet need among this high-risk elderly population. It also highlights the need for early interventions to prevent potential future non-adherence among this population. A prior study evaluating adherence to concomitant cardiovascular medications namely calcium-channel blockers (CCB), ACEIs, and statins as well as concurrent CCBs, ACEIs, and aspirin reported an adherence rate of 47.9% and 49.4% respectively.[16] Other studies have reported adherence rates to concurrent lipid-lowering and anti-hypertensive therapies varying between 32-36%.[14,15,31] The adherence rates observed in the current study were higher than the previous reported studies and plausible reasons could include a higher motivation to remain adherent to therapy among this high-risk elderly population[31], as well as potential effectiveness of

ongoing interventions by the MAP since these therapies were components of the Medicare star metrics related to reimbursement.

While prior observational studies have reported a decreased risk of cardiovascular events associated with adherence to concomitant lipid-lowering and antihypertensive therapies[19,36], the current study did not report a significant association between adherence to triple or double therapy and CV outcomes. The results remained consistent in the sub-analysis conducted among patients with prior CV events and in the sensitivity analysis with additional time-varying confounders. While prior studies did not account for time-dependent exposure and time-dependent confounders affected by prior exposure, the current study accounted for both using MSM. Future studies should explore the association using longer follow-up periods and increased variables for controlling severity, as the relatively low follow up period, and residual confounding may have influenced the study findings. Since the population was a high-risk severe population to begin with, additional measures to control for severity of disease could be added to future MSM models to improve estimates. Future studies can also evaluate the association between adherence to triple therapy and intermediate outcomes such as glycemic control, blood-pressure, and low-density lipoprotein cholesterol using the current follow-up period.

Several socio-demographic predictors were associated with CV outcomes. Females were less likely to have a CV event as compared to males. Prior literature has highlighted the need to distinguish sex and gender, with gender being socially influenced, guiding lifestyle and health behavior, while sex including biological differences such as hormones and gene expression.[37,38] The study findings are consistent with previous reports of a lower risk of CV hospitalizations in females plausibly due to a lower CV disease prevalence and a higher onset age of CV disease among females as compared to males.[39,40] Further, gender determinants such as higher alcohol

consumption and smoking might explain these findings.[41] Older age was also associated with a higher risk of CV events. Identified as an independent non-modifiable risk of factor of CV disease, increasing age is also postulated to reflect the duration and intensity of exposure to other CV disease risk factors.[42] Studies have reported that the absence of other CV disease risk factors is associated with a reduced risk of age-related CV disease[43] thereby emphasizing the need to modify all other traditional risk factors of CV disease. These results may also further explain the observed increasing risk of CV disease over time.

Patients prescribed with a higher statin intensity were associated with a higher risk of CV events. A prior study reported that only 17-19% of patients on high intensity statins achieved LDL-C goals which might plausibly explain their associated high risk of CV events.[44] Further, these patients might comprise of a more severe population thereby having a higher risk of CV events to begin with. Prior hospitalization and a higher CMS risk score were associated with a higher risk of CV events. These findings imply that higher disease severity determine the risk of CV events which is consistent with literature.[45] Lastly, low-income subsidy and a 90-day refill were associated with reduced CV events. These findings are encouraging and reflect modifiable factors associated with a reduced risk of CV disease.

4.6 **Limitations**

The study includes some limitations. An assumption of MSM includes no unmeasured confounders, which is not testable. However, the study included as many relevant clinical and socio-demographic covariates as possible to ensure limited residual confounding. Since the study considered a patient adherent on a given day if any one oral antidiabetic, and any one statin, and any one RAS antagonists was available on that day, the study might have overestimated adherence

to patients taking multiple drug regimens for each therapy. The lab data was available for patients who used an in-network lab facility within the Medicare Managed plan which might create potential bias. However, on further analysis there was no significant difference in demographic characteristics among those patients who had a baseline lab value and were included in the study versus those who did not have a baseline lab value and were excluded from the study, thus minimizing any potential bias. Lastly the generalizability of the study might be limited to similar demographic, clinical, and geographic populations since the study was conducted among a Texas Medicare Advantage population.

4.7 Conclusion

The study did not reveal any significant association between adherence to triple or double therapy and CV outcomes. Further, the sub-analysis conducted among patients with prior CV events also did not reveal any significant association between adherence to triple or double therapy and CV outcomes. Future studies should evaluate the association using longer follow-up periods and increased measures for controlling severity.

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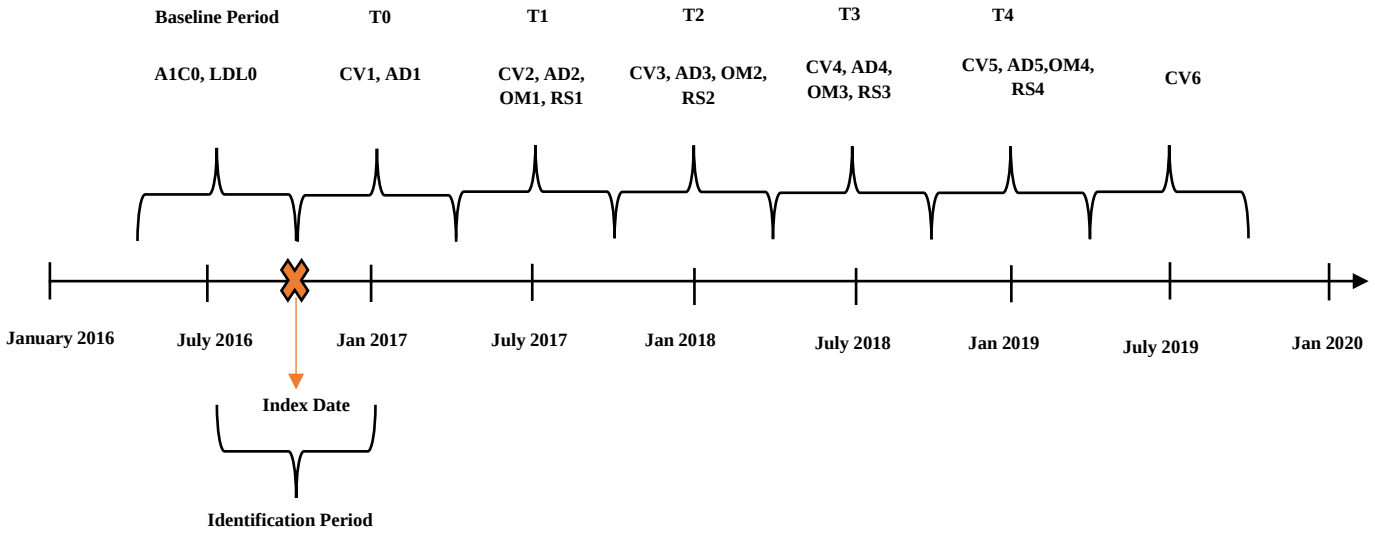
4.9 Figures and Tables

Figure 1: Study Design



Time Period	Exposure	CV-Outcome	Confounder 1 (Cumulative Prior CV Events)	Confounder 2 (Total Other Medications)	Confounder 3 (CMS Risk Score)	Prior Adherence
T1	AD2	CV3	Total CV1	OM2	RS2	AD1
T2	AD3	CV4	Total CV1+CV2	OM3	RS3	AD2
T3	AD4	CV5	Total CV1+CV2+ CV3	OM4	RS4	AD3
T4	AD5	CV6	Total CV1+CV2+ CV3+ CV4	OM5	RS5	AD4

Table 1: Patient Demographics and Clinical Characteristics (N=7,433)

Variables	Total Patients (%) N=7,433	Adherence to Mono Therapy/None (%) N= 534	Adherent to Double Therapy (%) N= 1288	Adherent to Triple Therapy (%) N= 5611	P-Value
Sex					
Male	3522 (47.38)	246 (46.07)	583 (45.26)	2693 (48.00)	0.17
Female	3911 (52.62)	288 (53.93)	705 (54.74)	2918 (52.00)	
Age					
<65 Years	936 (12.59)	86 (16.1)	160 (12.42)	690 (12.3)	0.01*
65-69 Years	2609 (35.10)	181 (33.9)	466 (36.18)	1962 (34.97)	
70-74 Years	2039 (27.43)	119 (22.28)	337 (26.16)	1583 (28.21)	
≥75 Years	1849 (24.88)	148 (27.72)	325 (25.23)	1376 (24.52)	
Health Plan					
No Subsidy	3953 (53.18)	283 (53.00)	704 (54.66)	2966 (52.86)	0.5
Low-Income Subsidy	3480 (46.82)	251 (47.00)	584 (45.34)	2645 (47.14)	
Number of Prior Hospitalizations					
0	7164 (96.38)	511 (95.69)	1231 (95.57)	5422 (96.63)	0.12
≥1	269 (3.62)	23 (4.31)	57 (4.43)	189 (3.37)	

90-Day Refill					
< 90 Days Supply for All/One/Two Therapies	1024 (13.78)	141 (26.40)	270 (20.96)	613 (10.92)	<0.0001*
All Three Therapies have 90 Day Supply	6409 (86.22)	393 (73.60)	1018 (79.04)	4998 (89.08)	
Prevalent Users of Triple Therapy					
No	1060 (14.26)	132 (24.72)	254 (19.72)	674 (12.01)	<0.0001*
Yes	6373 (85.64)	402 (75.28)	1034 (80.24)	4937 (87.99)	
Statin Intensity					
No	5856 (78.78)	398 (74.53)	989 (76.79)	4469 (79.65)	0.0034*
Yes	1577 (21.22)	136 (25.47)	299 (23.21)	1142 (20.35)	
CMS Risk Score Mean (SD)	1.28 (0.77)	1.26 (0.82)	1.30 (0.77)	1.28 (0.77)	0.44
Total Number of Other Medications Mean (SD)	6.49 (4.18)	6.16 (4.13)	6.66 (4.22)	6.48 (4.18)	0.06
Regimen Complexity Mean (SD)	20.96 (38.85)	20.27 (38.04)	20.75 (35.13)	21.07 (39.74)	0.87

***Significant P values from chi-square and anova<0.05; CMS: Centers for Medicare and Medicaid; SD: Standard Deviation.**

Table 2: Marginal Structural Modeling to Examine the Association Between Adherence to Triple Therapy and CV Events.

Variables	Adjusted OR	P value	95% Confidence Interval
Adherence Group			
Adherence to Double Therapy vs Adherence to Mono Therapy/None	1.09	0.23	0.94-1.27
Adherence to Triple Therapy vs Adherence to Mono Therapy/None	1.1	0.17	0.95-1.28
Sex			
Female vs Male	0.58	<0.0001*	0.52-0.65
Age			
65-69 Years vs <65 Years	1.11	0.25	0.92-1.34
70-74 Years vs <65 Years	1.45	<0.0001*	1.20-1.75
≥75 Years vs <65 Years	1.61	<0.0001*	1.34-1.94
Health Plan			
Low-Income Subsidy vs No Subsidy	0.85	0.0048*	0.76-0.95
Number of Prior Hospitalizations			
≥1 vs 0	1.57	0.0003*	1.23-2.00

90-Day Refill			
Three Therapies have 90 Day Supply vs Not	0.8	0.0039*	0.69-0.93
Prevalent Users of Triple Therapy			
Yes vs No	1.07	0.38	0.91-1.25
Time Period			
2 vs 1	1.11	0.01*	1.02-1.21
3 vs 1	1.19	<0.0001*	1.09-1.30
4 vs 1	1.23	<0.0001*	1.13-1.35
Statin Intensity			
Yes vs No	1.58	<0.0001*	1.4-1.79
CMS Risk Score Mean (SD)	1.32	<0.0001*	1.24-1.41
Total Number of Other Medications Mean (SD)	1.07	<0.0001*	1.05-1.08
Regimen Complexity Mean (SD)	1.0006	0.42	0.99-1.00

***Significant P<0.05; CI: confidence interval; OR: odds ratio.**

Table 3: Marginal Structural Modeling to Examine the Association Between Adherence to Triple Therapy and CV Events Among Patients with Prior CV Events.

Variables	**Adjusted OR**	**P value**	**95% Confidence Interval**

Adherence Group			
Adherence to Double Therapy vs Adherence to Mono Therapy/None	0.88	0.5	0.61-1.27
Adherence to Triple Therapy vs Adherence to Mono Therapy/None	0.9	0.57	0.63-1.28
Sex			
Female vs Male	0.79	0.11	0.6-1.05
Age			
65-69 Years vs <65 Years	0.93	0.77	0.57-1.5
70-74 Years vs <65 Years	1.53	0.07	0.95-2.46
≥75 Years vs <65 Years	1.03	0.89	0.63-1.66
Health Plan			
Low-Income Subsidy vs No Subsidy	0.84	0.23	0.63-1.11
Number of Prior Hospitalizations			
≥1 vs 0	0.88	0.48	0.63-1.24
90-Day Refill			
Three Therapies have 90 Day Supply vs Not	0.9	0.5	0.66-1.22

Prevalent Users of Triple Therapy			
Yes vs No	1.08	0.64	0.75-1.57
Time Period			
2 vs 1	1.04	0.67	0.85-1.28
3 vs 1	0.97	0.8	0.77-1.21
4 vs 1	1.16	0.19	0.92-1.47
Statin Intensity			
Yes vs No	1.76	<0.0001*	1.33-2.33
CMS Risk Score Mean (SD)	1.04	0.57	0.9-1.19
Total Number of Other Medications Mean (SD)	1.03	0.02*	1.004-1.07
Regimen Complexity Mean (SD)	0.99	0.76	0.99-1.00

***Significant P<0.05; CI: confidence interval; OR: odds ratio. 94**

5 Conclusion

The study demonstrated that adherence to triple therapy among older adults was suboptimal. Given the greater risk of CVD among this high-risk population, the results are concerning and underscore the need for designing and implementing interventions to enhance adherence among patients with concomitant therapy. Several socio-demographic and clinical predictors were associated with adherence to triple therapy. Implications of this study can help decision-makers and clinicians

treating comorbid diabetes, hypertension, and hyperlipidemia identify patients at a higher risk of non-adherence early on to further improve adherence and CVD outcomes.

The study also demonstrated that patients adherent to concurrent triple or double therapy were more likely to have A1C and LDL-C control as compared to patient's adherent to monotherapy/none. The study has valuable clinical implications since the results indicate the beneficial effects of medication adherence in controlling CVD risk factors among high-risk elderly patients. Further, it also indicates that the ABC goals outlined by the ADA can be achieved if medication adherence is optimal. Lastly strengths of this study include an adequate representation of the patient population as seen in clinical practice, as well as estimation of adherence and clinical effects controlling for the unrecognized issue of time-dependent exposure and confounding.

Lastly, the study did not reveal any significant association between adherence to triple or double therapy and CV outcomes. Further, the sub-analysis conducted among patients with prior CV events also did not reveal any significant association between adherence to triple or double therapy and CV outcomes. Future studies should evaluate the association using longer follow-up periods and increased measures for controlling severity.

In summary:

- Adherence to triple therapy among older adults was sub-optimal and several demographic and clinical factors were associated with the different adherence groups.
- The study demonstrated the beneficial effects of adherence to concurrent oral antidiabetics, statins, and RAS antagonists among older adults in a real-world setting.

- Adherence to triple therapy was not associated with CV outcomes. Future studies should evaluate the association with longer follow-up periods.